Large Animal Internal Medicine

Sixth Edition







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Large Animal Internal Medicine

SIXTH EDITION

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Dedication

To study the phenomena of disease without books is to sail an uncharted sea,

while to study books without patients is not to go to sea at all.

Sir William Osler

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TO

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AND TO

the authors and consulting editors who worked so hard to advance large animal internal medicine to new levels.

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Esteemed colleague, wonderful human being. He will be missed by all.

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Preface

Large Animal Internal Medicine is an encyclopedic volume for the veterinary student or large animal veterinarian working with horses, cattle, sheep, or goats. Using the same popular format as the fifth edition, this edition provides the most current information available by utilizing more than 250 experts as authors. This edition contains additional pages of new color plates and more than 1210 figures, boxes, tables, color plates, and radiograph, ultrasound, computed tomography, and magnetic resonance images. The popular section on ultrasound of the equine abdomen has been updated and the ruminant abdominal ultrasound section completely rewritten by a new author. Many sections have been strengthened by the addition of outstanding new authors and new subjects, and chapters have been revised and improved with new references cited. Important new information regarding animal welfare is now included in Chapters 1 and 2 and new approaches to pain management described in Chapter 3. New genetic tests, which are rapidly developing, are described in Chapters 51 and 52. Many websites where important up-to-date information can be found are cited in this edition.

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Problem-Oriented Approach to Disease Diagnosis

The catch-22 of most textbooks is that the clinician must know the diagnosis to locate and read about a specific disease. *Large Animal Internal Medicine* is formatted such that the early sections allow the clinician to use the problem-oriented approach to create a differential diagnosis for a vast number of diseases of horses, cattle, sheep, and goats. More than 130 clinical signs or manifestations of disease are discussed. They are listed alphabetically in Parts 2 and 3; this list can be used to locate a particular manifestation of disease. These same manifestations are listed by organ system at the beginning of Chapters 3 through 20. A favorite feature of the previous editions is the differential diagnosis boxes. These were largely created using Cornell's Consultant program, found at www.vet.cornell.edu/consultant. We have retained these invaluable diagnostic tools in this edition. Throughout Part 2, complete lists of common, less common, and uncommon diseases associated with manifestations or signs of disease are shown in these easy-to-find boxes. The clinician is given an approach to each manifestation of disease and a method to work toward a diagnosis. The pathophysiology of a particular manifestation of disease is concisely summarized. Even if a final diagnosis is not reached, the animal with diarrhea, cough, or other problem can be treated symptomatically, a practice that is commonly used in the everyday world.

Similarly, abnormalities in laboratory test results are discussed in Part 4, and complete lists of diseases associated with a given laboratory abnormality are found in easy-to-read boxes. Interpretation of abnormalities in clinical chemistry, hematology, blood proteins, clotting tests, and bone marrow is facilitated. For example, if the problem is elevated serum calcium, the causes of hypercalcemia are discussed concisely, and diseases associated with this abnormality are listed. The clinician can then proceed to a rational approach to the particular laboratory abnormality. Many readers have found the table for conversion from “American” units to SI units extremely useful.

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Organization

The basic organization has not changed from the fifth edition. The book is divided into seven parts:

Part 1: History, Physical Examination, and Medical Records (with added material on welfare assessment)
Part 2: Manifestations of Disease
Part 3: Disorders and Management of the Neonate
Part 4: Collection of Samples and Interpretation of Laboratory Tests
Part 5: Disorders of the Organ Systems
Part 6: Preventive and Therapeutic Strategies
Part 7: Congenital, Hereditary, Immunologic, and Toxic Disorders

A neonatal disease section (Part 3), organized by presenting problem, includes everything from prepartum care, to care of the newborn, to solving problems ranging from diarrhea to septicemia of foals, calves, lambs, and kids. To aid the clinician in arriving at the proper diagnosis, lists of diseases are given for each manifestation of neonatal disease. Differences in approach to diagnosis or treatment of neonates and adult animals are cross-referenced throughout the text.

Part 5 is organized according to body system and includes internal medicine approaches. Diagnostic tests used in each system are described, including ultrasound (greatly expanded), endoscopy, radiography, thermography, computed tomography, magnetic resonance imaging, sample collection techniques, electrocardiography, cerebrospinal fluid collection, and biopsy of organs. Numerous illustrations include photographs, ultrasound images, radiographs, electrocardiogram tracings, and endoscopic views. Additional videos and images are available on the website. These chapters are written by experts in the field of large animal internal medicine and give details of the most up-to-date treatments available. *Large Animal Internal Medicine* complements existing texts dealing with current therapy.

Preventive and Therapeutic Strategies, Part 6, includes chapters with practical information on critical care and fluid therapy, antimicrobial therapy, infection control, prevention and detection of foreign animal diseases, vaccines and

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vaccination programs, and parasite control programs. Chapter 50 addresses nutrition of the sick animal and gives formulas for both enteral and parenteral support.

A detailed discussion of each disease is contained in Parts 5, 6, and 7 of *Large Animal Internal Medicine.* Once the reader has a list of diseases that fit the current problem, specific diseases can be found in these latter sections of the book. The organization is that of a traditional disease-oriented text:

Definition and Etiology
Clinical Signs and Differential Diagnosis
Clinical Pathology
Pathophysiology
Epidemiology
Necropsy Findings
Treatment and Prognosis
Prevention and Control

Chapters 51 and 52 deal with genetic disorders and genetic tests, most of which have only recently been developed.

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Popular Features Retained

Color Inserts

Chapter 28, Collection and Analysis of Bone Marrow, includes color plates that show various bone marrow biopsy techniques and results. Chapter 31, Diseases of the Respiratory System, features 11 color plates. Chapter 32, Diseases of the Alimentary Tract, includes color plates that feature endoscopic views of equine alimentary tract disorders. Chapter 39, Diseases of the Eye, contains color plates of ophthalmologic conditions that are best depicted in full color. Chapter 40, Diseases of the Skin, features color plates of some dermatologic disorders, and Chapter 54, Disorders Caused by Toxicants, includes new photographs that show several important toxic plants.

Printed Endsheets

The printed endsheets found in the front and back of the text provide information that is referred to frequently:

- Manifestations of Disease
- Disorders and Management of the Neonate
- Collection of Samples and Interpretation of Laboratory Tests
- Reference Intervals for Ruminants and Horses
- Normal Values for Leukogram Data (Adult Animals)
- Normal Serum Protein Values for Horses, Cows, Sheep, and Goats
- Clinical Chemistry: Normal Range for Large Animals

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New to This Edition

New Topics

The range of new topics is noteworthy. A sampling of new topics includes information on assessing animal welfare, the latest on pain management, additional information on colostrum supplements and substitutes, antigen detection tests and polymerase chain reaction, and new aspects of critical care. The neonatal chapters incorporate the latest in diagnostic and therapeutic modalities and techniques. The revised clinical pathology section includes four new experts as authors. The respiratory diseases chapter includes new findings on diagnosis and treatment options. Also included are new discussions on legal requirements for use of pharmaceuticals in food animals; infection control methods for a large animal hospital; and the prevention of, detection of, and response to foreign animal diseases. New genetic tests and the labs that perform them are included. Ultrasound images continue to be widely used, including a new section on the ruminant abdomen. National Research Council tables have been updated. Also included are advances in vaccines, diagnosing and treating temporohyoid osteopathy and bone fragility disease in horses, and advances in endocrine and muscle disorders. The section on snakebite has been expanded and the toxicology chapter completely rewritten.

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Index

The index of *Large Animal Internal Medicine* is thorough and extensive, making it an easy-to-use reference to find the answer to any question you may have.

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Acknowledgments

The motivation for undertaking *Large Animal Internal Medicine* came, in large part, from having been influenced in our professional careers by many teachers and colleagues with high standards. Our gratitude to them and respect for them runs deep. During our many years as teachers, we had the good fortune of working with many talented, inquisitive, and dedicated colleagues. Perhaps the individuals who have the greatest influence on a teacher are the students and residents who through their inquisitiveness keep us interested.

Many people worked hard to make *Large Animal Internal Medicine* the quality text that it is. More than 250 authors contributed in their area of expertise. This book would not be possible without them.

Special thanks to Jennifer Catando, Kathleen Nahm, Josh Rapplean, Rachel McMullen, Tara Delaney, and all the others at Elsevier who worked so hard on this project.

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Use of *Consultant* for Development of This Textbook

Maurice E. White

Each edition of *Large Animal Internal Medicine* has been facilitated by the online diagnostic system *Consultant.*

Consultant comprises the thousands of diseases described in the veterinary literature; for each disease there is a brief description, references with links to journal articles, and clinical signs. *Consultant*, which I developed and have maintained at Cornell University's College of Veterinary Medicine, has been used by millions; by modem and discs from 1985–1997, on the web at http://www.vet.cornell.edu/consultant/consult.asp since 1997, and by Android and Apple apps since 2017.

Two characteristics of *Consultant* are the keys to its use for this textbook. Online editing is rapid, and information from the literature appears in the database quickly; this rapid updating combined with the large number of information sources allows *Consultant* to contain a breadth of up-to-date material. The second important factor is the ability of the user to enter a clinical sign or signs (e.g., cough, colic, abortion) for a given species and be presented with a list of diseases for which they have been reported.

Much of this textbook is organized by clinical signs. *Consultant* provided a broad overview of possible causes for clinical signs that authors were encouraged to incorporate into their lists of differential diagnoses. Contributors were encouraged to compress, rank, and add to *Consultant*-generated lists on the basis of clinical experience. The use of the database in this fashion assisted in the organization of sign-based chapters.

Consultant and this textbook are symbiotic. The database can be thought of as a generalist that knows some up-to-date information on almost every disease in

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veterinary medicine. Despite that, it remains merely a tool for the clinician who uses it. For example, there are dozens of causes of epistaxis in the horse, and it is simple to get a complete list of them from *Consultant.* The clinician must take that list and decide which causes to pursue in an individual patient, in what order, by what means, at what cost, and to what treatment or prognostic end. When such decisions must be made, expert opinions such as those found in this book are of great help. Cooperation such as that between *Consultant* and *Large Animal Internal Medicine* allows practitioners and students to benefit from the linkage between the tireless memory and ease of retrieval of the computer and the convenience of expert knowledge in book form.

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CHAPTER 32

VIDEO 32.1

Focus on the biphasic contraction of the reticulum, which is recognized by its hyperechoic wall. Abomasal content and atrial wall of the rumen are observed when the reticulum is moving dorsally during contraction. (Courtesy Dr. Sébastien Buczinski.)

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Small intestine peristalsis in a healthy Holstein cow. The intestinal content is seen moving as well as intestinal loops. Large variation of small intestine diameter is seen during peristalsis. The shape of intestinal loop is highly variable during contraction and allows the progression of small intestine content. (Courtesy Dr. Sébastien Buczinski.)

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PART 1
History, Physical Examination, and Medical Records

OUTLINE

Introduction

• Chapter 1 Ruminant History, Physical Examination, Welfare Assessment, and Records

• Chapter 2 Equine History, Physical Examination, Records, and Recognizing Abuse or Neglect in Patients

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Introduction

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• CHAPTER 1

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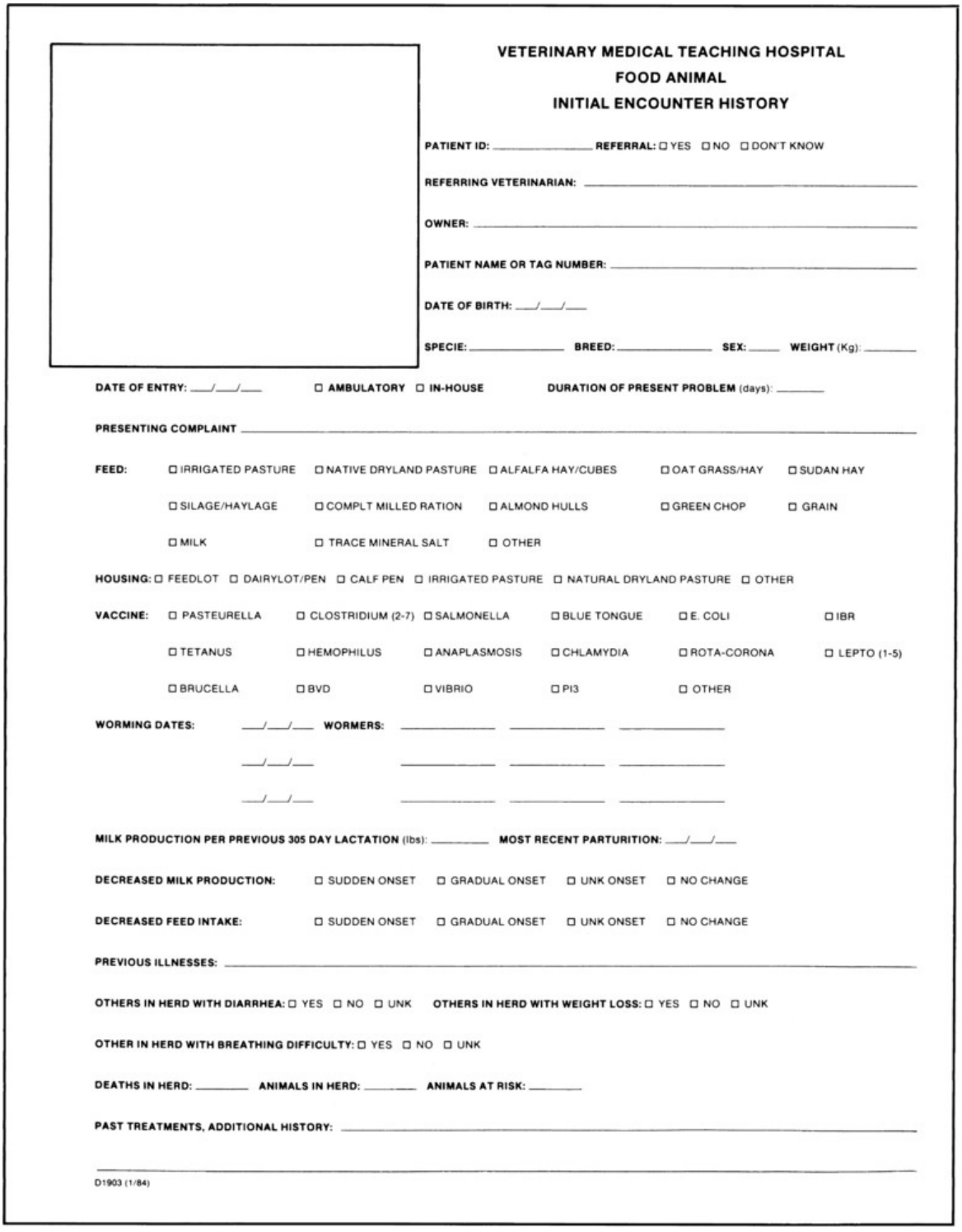
Ruminant History, Physical Examination, Welfare Assessment, and Records

Ronald L. Terra, James P. Reynolds, Consulting Editors

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Obtaining the History

Obtaining an anamnesis and performing a physical examination are the initial and often the most important diagnostic tests conducted in the diagnostic approach to the sick ruminant. The anamnesis can be performed before or during the physical examination and is accomplished by asking questions of the owner or manager. The signalment can be derived by either observation or questioning the owner. Information related to the chief, or presenting, complaint should be determined, especially the duration; whether the onset was gradual or sudden; and any associated signs that may have been noted. For females, one must know when the last parturition occurred, and for dairy cows, what the production parameters were in the previous lactation, as well as in the current lactation. With dairy cows a drop in milk production is often the only sign noted by the owner. Weight can be either approximated, via heart-girth measurements, or determined exactly if facilities exist. What and how the animal is fed are questions to be asked. Does the animal refuse any or all of the feed offered? Is there more than one ration or feeding regimen for this particular operation? If so, are these same signs noted in animals exposed to different feeding practices? The examiner also obtains vaccination and worming history and inquires about pasture or housing practices to determine the influence that management factors have on the incidence of the disease. Previous diseases noted in the herd, therapeutic regimens used, and resolutions of previous problems are pertinent aspects. Finally, the examiner should note the treatment history of the patient. An example of a history questionnaire that can be used for ruminants is included (Fig. 1.1). Specific problems that are noted in the history or physical examination can be found in the list at the beginning of Part Two: Manifestations of Disease, and lists of differential diagnoses can be considered. Alternatively, one can determine the pathophysiology(ies) that would present with the signs (problems) noted and then generate a list of diseases or disorders that would lead to that (those) pathophysiology(ies) noted.



VETERINARY MEDICAL TEACHING HOSPITAL
FOOD ANIMAL
INITIAL ENCOUNTER HISTORY

PATIENT ID: _____ **REFERRAL:** ☐ YES ☐ NO ☐ DON'T KNOW

REFERRING VETERINARIAN: _____

OWNER: _____

PATIENT NAME OR TAG NUMBER: _____

DATE OF BIRTH: ___/___/___

SPECIE: _____ **BREED:** _____ **SEX:** _____ **WEIGHT** (Kg): _____

DATE OF ENTRY: ___/___/___ ☐ **AMBULATORY** ☐ **IN-HOUSE** **DURATION OF PRESENT PROBLEM** (days): _____

PRESENTING COMPLAINT _____

FEED: ☐ IRRIGATED PASTURE ☐ NATIVE DRYLAND PASTURE ☐ ALFALFA HAY/CUBES ☐ OAT GRASS/HAY ☐ SUDAN HAY
☐ SILAGE/HAYLAGE ☐ COMPLT MILLED RATION ☐ ALMOND HULLS ☐ GREEN CHOP ☐ GRAIN
☐ MILK ☐ TRACE MINERAL SALT ☐ OTHER

HOUSING: ☐ FEEDLOT ☐ DAIRYLOT/PEN ☐ CALF PEN ☐ IRRIGATED PASTURE ☐ NATURAL DRYLAND PASTURE ☐ OTHER

VACCINE: ☐ PASTEURELLA ☐ CLOSTRIDIUM (2-7) ☐ SALMONELLA ☐ BLUE TONGUE ☐ E. COLI ☐ IBR
☐ TETANUS ☐ HEMOPHILUS ☐ ANAPLASMOSIS ☐ CHLAMYDIA ☐ ROTA-CORONA ☐ LEPTO (1-5)
☐ BRUCELLA ☐ BVD ☐ VIBRIO ☐ PI3 ☐ OTHER

WORMING DATES: ___/___/___ **WORMERS:** _____ _____ _____
___/___/___ _____ _____ _____
___/___/___ _____ _____ _____

MILK PRODUCTION PER PREVIOUS 305 DAY LACTATION (lbs): _____ **MOST RECENT PARTURITION:** ___/___/___

DECREASED MILK PRODUCTION: ☐ SUDDEN ONSET ☐ GRADUAL ONSET ☐ UNK ONSET ☐ NO CHANGE

DECREASED FEED INTAKE: ☐ SUDDEN ONSET ☐ GRADUAL ONSET ☐ UNK ONSET ☐ NO CHANGE

PREVIOUS ILLNESSES: _____

OTHERS IN HERD WITH DIARRHEA: ☐ YES ☐ NO ☐ UNK **OTHERS IN HERD WITH WEIGHT LOSS:** ☐ YES ☐ NO ☐ UNK

OTHER IN HERD WITH BREATHING DIFFICULTY: ☐ YES ☐ NO ☐ UNK

DEATHS IN HERD: _____ **ANIMALS IN HERD:** _____ **ANIMALS AT RISK:** _____

PAST TREATMENTS, ADDITIONAL HISTORY: _____

_____

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FIG. 1.1 Example of an initial encounter history form for use in ruminants.

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Examination

A complete examination should always be performed even if the presenting complaint is easily recognizable. The physical examination provides the veterinarian with information that is used to assess the health status of the patient. This information, combined with that obtained while taking the history, enables the practitioner to determine which specific signs of disease are present (i.e., what the problem[s] is/are) and aids in the localization of the disease process to specific organ systems. Performing a physical examination also helps determine which ancillary diagnostic tests should be performed. Additional information gathered during the examination may reveal disorders other than the presenting complaint that warrant further attention and may have a profound influence on the prognosis of the case. Realistically, economic and temporal constraints preclude full examinations in some cases. In these situations the veterinarian must be familiar enough with the complete physical examination to know which aspects can be excluded and which should be performed.

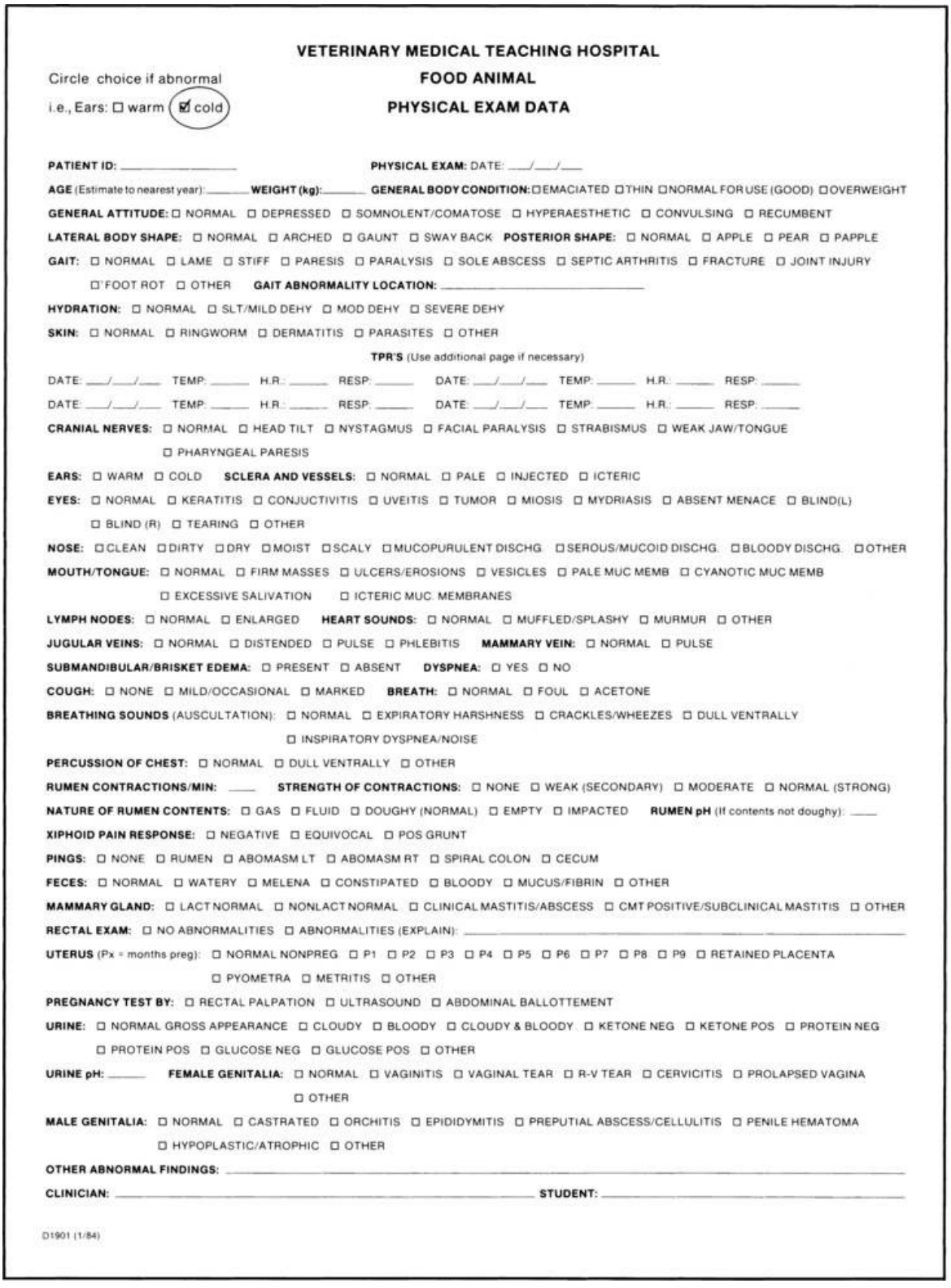
A systematic approach to the animal must be developed and used in every physical examination. The first step is to form an initial overall impression by observing the animal from a distance. The animal is then restrained and examined topographically, beginning on one side, moving to the other, and then evaluating the rear and finally the head and neck. Thus individual organs and systems are examined completely, although disjointedly, and the information gained is correlated to form the complete diagnosis.

Visual Examination

As observations are made and a physical examination is performed, it is important to follow a systematic approach and to record findings. A checklist has been found to be extremely useful (Fig. 1.2). While observing the animal from a distance, the examiner should assess its posture, gait, behavior, and physical condition. Observation of the other members of the flock or herd helps differentiate normal from abnormal characteristics under each particular management system, because normal may vary from farm to farm and because what is considered “normal” for a farm by the owner or herdsman might actually be abnormal; this information is valuable for assessing the incidence of a disease or disorder that is caused by management. As more animals in more herds are

observed, a background of knowledge is gained, allowing the practitioner to assess these management deficiencies more reliably.

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VETERINARY MEDICAL TEACHING HOSPITAL

FOOD ANIMAL

PHYSICAL EXAM DATA

Circle choice if abnormal

i.e., Ears: ☐ warm ☑ cold

PATIENT ID: _____ **PHYSICAL EXAM:** DATE: ___/___/___

AGE (Estimate to nearest year): _____ **WEIGHT (kg):** _____ **GENERAL BODY CONDITION:** ☐ EMACIATED ☐ THIN ☐ NORMAL FOR USE (GOOD) ☐ OVERWEIGHT

GENERAL ATTITUDE: ☐ NORMAL ☐ DEPRESSED ☐ SOMNOLENT/COMATOSE ☐ HYPERAESTHETIC ☐ CONVULSING ☐ RECUMBENT

LATERAL BODY SHAPE: ☐ NORMAL ☐ ARCHED ☐ GAUNT ☐ SWAY BACK **POSTERIOR SHAPE:** ☐ NORMAL ☐ APPLE ☐ PEAR ☐ PAPPLE

GAIT: ☐ NORMAL ☐ LAME ☐ STIFF ☐ PARESIS ☐ PARALYSIS ☐ SOLE ABSCESS ☐ SEPTIC ARTHRITIS ☐ FRACTURE ☐ JOINT INJURY ☐ FOOT ROT ☐ OTHER **GAIT ABNORMALITY LOCATION:** _____

HYDRATION: ☐ NORMAL ☐ SLT/MILD DEHY ☐ MOD DEHY ☐ SEVERE DEHY

SKIN: ☐ NORMAL ☐ RINGWORM ☐ DERMATITIS ☐ PARASITES ☐ OTHER

TPR'S (Use additional page if necessary)

DATE: ___/___/___ TEMP: _____ H.R.: _____ RESP: _____ DATE: ___/___/___ TEMP: _____ H.R.: _____ RESP: _____

DATE: ___/___/___ TEMP: _____ H.R.: _____ RESP: _____ DATE: ___/___/___ TEMP: _____ H.R.: _____ RESP: _____

CRANIAL NERVES: ☐ NORMAL ☐ HEAD TILT ☐ NYSTAGMUS ☐ FACIAL PARALYSIS ☐ STRABISMUS ☐ WEAK JAW/TONGUE ☐ PHARYNGEAL PARESIS

EARS: ☐ WARM ☐ COLD **SCLERA AND VESSELS:** ☐ NORMAL ☐ PALE ☐ INJECTED ☐ ICTERIC

EYES: ☐ NORMAL ☐ KERATITIS ☐ CONJUCTIVITIS ☐ UVEITIS ☐ TUMOR ☐ MIOSIS ☐ MYDRIASIS ☐ ABSENT MENACE ☐ BLIND(L) ☐ BLIND (R) ☐ TEARING ☐ OTHER

NOSE: ☐ CLEAN ☐ DIRTY ☐ DRY ☐ MOIST ☐ SCALY ☐ MUCOPURULENT DISCHG. ☐ SEROUS/MUCOID DISCHG. ☐ BLOODY DISCHG. ☐ OTHER

MOUTH/TONGUE: ☐ NORMAL ☐ FIRM MASSES ☐ ULCERS/EROSIONS ☐ VESICLES ☐ PALE MUC MEMB ☐ CYANOTIC MUC MEMB ☐ EXCESSIVE SALIVATION ☐ ICTERIC MUC. MEMBRANES

LYMPH NODES: ☐ NORMAL ☐ ENLARGED **HEART SOUNDS:** ☐ NORMAL ☐ MUFFLED/SPLASHY ☐ MURMUR ☐ OTHER

JUGULAR VEINS: ☐ NORMAL ☐ DISTENDED ☐ PULSE ☐ PHLEBITIS **MAMMARY VEIN:** ☐ NORMAL ☐ PULSE

SUBMANDIBULAR/BRISKET EDEMA: ☐ PRESENT ☐ ABSENT **DYSPNEA:** ☐ YES ☐ NO

COUGH: ☐ NONE ☐ MILD/OCCASIONAL ☐ MARKED **BREATH:** ☐ NORMAL ☐ FOUL ☐ ACETONE

BREATHING SOUNDS (AUSCULTATION): ☐ NORMAL ☐ EXPIRATORY HARSHNESS ☐ CRACKLES/WHEEZES ☐ DULL VENTRALLY ☐ INSPIRATORY DYSPNEA/NOISE

PERCUSSION OF CHEST: ☐ NORMAL ☐ DULL VENTRALLY ☐ OTHER

RUMEN CONTRACTIONS/MIN: ____ **STRENGTH OF CONTRACTIONS:** ☐ NONE ☐ WEAK (SECONDARY) ☐ MODERATE ☐ NORMAL (STRONG)

NATURE OF RUMEN CONTENTS: ☐ GAS ☐ FLUID ☐ DOUGHY (NORMAL) ☐ EMPTY ☐ IMPACTED **RUMEN pH** (If contents not doughy): ____

XIPHOID PAIN RESPONSE: ☐ NEGATIVE ☐ EQUIVOCAL ☐ POS GRUNT

PINGS: ☐ NONE ☐ RUMEN ☐ ABOMASM LT ☐ ABOMASM RT ☐ SPIRAL COLON ☐ CECUM

FECES: ☐ NORMAL ☐ WATERY ☐ MELENA ☐ CONSTIPATED ☐ BLOODY ☐ MUCUS/FIBRIN ☐ OTHER

MAMMARY GLAND: ☐ LACT NORMAL ☐ NONLACT NORMAL ☐ CLINICAL MASTITIS/ABSCESS ☐ CMT POSITIVE/SUBCLINICAL MASTITIS ☐ OTHER

RECTAL EXAM: ☐ NO ABNORMALITIES ☐ ABNORMALITIES (EXPLAIN): _____

UTERUS (Px = months preg): ☐ NORMAL NONPREG ☐ P1 ☐ P2 ☐ P3 ☐ P4 ☐ P5 ☐ P6 ☐ P7 ☐ P8 ☐ P9 ☐ RETAINED PLACENTA ☐ PYOMETRA ☐ METRITIS ☐ OTHER

PREGNANCY TEST BY: ☐ RECTAL PALPATION ☐ ULTRASOUND ☐ ABDOMINAL BALLOTTEMENT

URINE: ☐ NORMAL GROSS APPEARANCE ☐ CLOUDY ☐ BLOODY ☐ CLOUDY & BLOODY ☐ KETONE NEG ☐ KETONE POS ☐ PROTEIN NEG ☐ PROTEIN POS ☐ GLUCOSE NEG ☐ GLUCOSE POS ☐ OTHER

URINE pH: _____ **FEMALE GENITALIA:** ☐ NORMAL ☐ VAGINITIS ☐ VAGINAL TEAR ☐ R-V TEAR ☐ CERVICITIS ☐ PROLAPSED VAGINA ☐ OTHER

MALE GENITALIA: ☐ NORMAL ☐ CASTRATED ☐ ORCHITIS ☐ EPIDIDYMITIS ☐ PREPUTIAL ABSCESS/CELLULITIS ☐ PENILE HEMATOMA ☐ HYPOPLASTIC/ATROPHIC ☐ OTHER

OTHER ABNORMAL FINDINGS: _____

CLINICIAN: _____ **STUDENT:** _____

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FIG. 1.2 Example of a data sheet for the recording of the pertinent findings from the physical examination.

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The general appearance and conformation of the animal are included in determining posture. These are assessed in light of the age and breed of the patient. Determining abnormalities in posture can be difficult; however, noting these subtle changes can contribute greatly to the diagnosis of a disease process. Conformation is recognized by looking at the overall size and shape with particular regard to height, width, and relationship of the head, neck, and legs to the trunk. The general appearance of the patient in light of overall conformation can then be assessed. Determining a body condition score and correlating it with lifecycle stage or stage of lactation can offer insight into the course of the presenting complaint. Is the young, growing animal within breed standards for size and weight? (See Chapter 9.) The condition of the hair coat and evidence/presence of external parasites can be noted during the physical examination (e.g., frank hair loss, as seen in louse infestation, or dander and scruffiness of the hair coat, as seen in chronic debilitating diseases).

Observe the animal for signs of abdominal splinting or arching of the back, as can be seen with peritonitis. This posture can also be noted with other disease processes when these produce pain in the ventral abdomen. Lateral curvature of the spine could indicate a congenital defect or a chronic spinal lesion. Carrying the tail up away from the body is seen with conditions resulting in pain or irritation in the perineal region, vagina, or rectum. Standing with all four legs in the classic “saw-horse” stance with the neck and tail held erect is typical of tetanus. Abduction of the elbows is seen in disorders that cause thoracic pain. Lameness can be noted by observing unwillingness to bear weight fully on the affected limb while either standing or walking. Loss of extensor or flexor capabilities of the joints is seen in nerve paralysis or paresis; it can also be caused by tendon and/or joint contractures, in which case joints are rigid. Walking as if all four feet are sore may indicate laminitis. With bright and alert recumbent animals, a thorough examination to rule out fractures or severe joint trauma is essential. Once these have been ruled out, inability to stand may be indicative of generalized muscular paresis or paralysis. These can be of a primary nature, as with lesions within the spinal column causing cord compression, or secondary to mineral or electrolyte deficiencies (e.g., hypocalcemia, hypomagnesemia, hypokalemia).

To be able to judge the behavior of the animal as being normal or abnormal, the observer must call on a large amount of experience. Observing the animal from a distance allows assessment of eating and drinking behavior, as well as assessment of the subject as it is ruminating, urinating, and defecating. How the

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animal gets up or lies down and how it ambulates are important. Signs indicative of estrus or signs commonly seen with calving might be considered normal or abnormal, given the history and behavior of the animal during these events. Observing the patient during the milking process may also be beneficial. The influence of the manager on animal behavior is important, as is the overall temperament of the particular breed or herd in question. Normal animals react to the approach of a human being by moving away; however, those that have had extensive contact with people may be more inquisitive. Within a herd one can note animals that are more tolerant than others, more stubborn, more restless, and more anxious. These traits are not necessarily abnormal and need to be differentiated from behavior that would be considered secondary to disease. In general, one must determine whether the behavior is one of a depressed or apathetic animal or of a hyperexcitable or frenzied animal.

Nutritional status and physical condition are assessed by means of observation and palpation. Special attention is paid to the dewlap, the spinous processes of the thoracic and lumbar vertebrae, the transverse processes of the lumbar spine, the shoulder area, and the area around the tailhead. Determination of body condition will then result in a classification of the animal as being anywhere from severely emaciated or cachectic to extremely overconditioned or fat (see Chapter 9 for body scores). Next it must be determined whether the condition is of a primary or nutritional nature or the result of disease. Disease processes can influence or be influenced by the animal's body condition. Extremely thin animals are seen in primary undernutrition and also with chronic disease. Females carrying multiple fetuses and lactating animals with metabolic abnormalities secondary to abomasal displacements would also show signs of weight loss. Overconditioned animals are at greater risk for a wide variety of disorders primarily related to the accumulation of fat in the liver and excessive fat storage in the omentum.

Physical Examination

With the animal properly restrained, the physical examination can now progress to specific palpation, auscultation, and percussion. Obtaining a sample of urine for urinalysis is of great value if incorporated into the physical examination; it is easy to perform with the use of dipsticks such as N-Multistix (Bayer AG, Leverkusen, Germany). Stroking the perineal region can aid in eliciting urination in the female bovine; however, even this is futile if the animal is apprehensive.

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Consequently, it is recommended that this be done first, while the patient is still fairly relaxed. In the male, elicitation of urination is slightly more difficult and requires massaging of the preputial orifice. Another method is to wash the outside of the prepuce with warm water, but this is less successful. In the female sheep and goat, stroking the perineal area can be attempted, but positive results are rarely achieved. A method that has been reported but which causes the animal great stress is to prevent it from breathing until urination is stimulated. In male or castrated male sheep and goats, gentle massage of the prepuce sometimes results in urination. If that fails, the breath-holding technique can be used. Because of the extreme stress associated with this induced hypoxic state, the author cautions against using this technique and further recommends that it not be attempted on patients that are severely compromised because of any disease process. (See Chapter 22 for further information on interpretation of the urinalysis.)

Body temperature is then measured with a rectal thermometer. Normal values for each species are given in Table 1.1. There are no absolute values, and the upper and lower limits should be adjusted as needed to account for ambient temperature and housing. For example, if the ambient temperature is greater than 37.5° C (100° F), a body temperature of 39.5° C (103° F) may still be considered normal for the adult bovine, especially if the animal is not allowed access to shade. When body temperatures approach 41° C (106° F), as a result of high ambient temperatures, heat stroke may occur. Keep in mind that the animal tries to maintain its body temperature within these normal limits, and marked deviation from the norm would be indicative of a disease process. A markedly elevated temperature is seen in acute, severe inflammatory processes. Pathologic lowering of the body temperature is seen in disorders that cause an inhibition of metabolism such as postparturient paresis, neonatal hypoglycemia, the end stages of a chronic disease, or severe septicemia resulting from gram-negative bacteria. There is a normal diurnal variation in body temperature of as much as 0.5° to 1° C (1° to 2° F). In the female there can also be a slight increase in temperature in the days preceding estrus. Neonates are poor thermoregulators and often have a normal body temperature that is 0.5° to 1° C (1° to 2° F) higher than that of adults.

TABLE 1.1

Normal Values for Temperature in the Ruminant[1-3]

Animal	Degrees Celsius	Degrees Fahrenheit
Cattle		
Adult	38-39	100.5-102.5
Calf	39-40.5	101.5-103
Sheep		
Adult	39-40	102-103.5
Lamb	39.5-40.5	102.5-104
Goat		
Adult	38.5-39.5	101.5-103.5
Kid	39-40.5	102-104

In the evaluation of the thoracic and abdominal cavities, the initial step is the ballottement of the abdomen on the right side. Hearing “sloshing” sounds while performing this ballottement of the abdomen would be presumptive evidence of intraabdominal fluid. An increase in fluid being sequestered intraabdominally could be related to some degree of intestinal or ruminal stasis or associated with an increase in peritoneal fluid, as with peritonitis or ruptured bladder. Ballottement can also reveal whether any firm mass such as a fetus, impacted abomasum, abscess, or tumor is located in the abdomen. In goats the abdominal fat pad is quite prominent and tends to obscure any significant finding on ballottement. Deep palpation of the paralumbar fossa can sometimes reveal masses in this region, including lymphomas, fat necrosis, or abscesses. In goats, lambs, and calves, two hands are used to deeply palpate the abdomen; the normal freely movable left kidney is usually readily palpable. On the right side an enlarged or painful liver or kidney can be noted. Palpation of an abnormal swelling or firmness, especially with the elicitation of pain, indicates a problem that must be further evaluated.

The spinal column and ribcage are then palpated; the presence of fractures, enlargement of the costochondral junctions, or the elicitation of pain is noted. Enlargement or fractures of the costochondral junctions are commonly seen in young animals with deficiencies of calcium, copper, or vitamin D.

Auscultation with concurrent percussion by snapping the finger against the thoracic and abdominal walls is the next procedure. Gas trapped within abdominal viscera elicits a “pinging” sound that can be heard with the stethoscope. Localization of these gas pings to certain areas within the abdomen is helpful in determining which alimentary structure is involved (Figs. 1.3 to 1.5). If the cecum is enlarged and gas filled, an abdominal ping can be heard. This can extend caudally to the tuber coxae and cranially through the paralumbar fossa and under the ribcage on the right side (see Fig. 1.3). The diameter of this area can be variable and range from 6 inches (15 cm) in a cecal displacement to

3 feet (1 m) horizontally in cecal torsions. Spiral colon pings are generally localized to the right dorsocranial paralumbar fossa and rarely extend farther forward than the tenth intercostal space. They tend to be round areas 10 inches (25 cm) or less in diameter centered high under the last rib (see Fig. 1.3). Although commonly found in sick cattle that are anorectic, these spiral colon pings have no specific diagnostic significance and can be seen in normal cattle occasionally. Gas pings associated with a right-sided displacement or torsion of the abomasum can extend as far cranially as the ninth intercostal space and caudally into the paralumbar fossa (see Fig. 1.4). The diameter of displacements is usually 18 inches (45 cm), whereas that of torsions can be up to 3 feet (1 m). In cases of abomasal volvulus, the animal is usually exhibiting other systemic signs such as increased heart rate, dehydration, depression, scleral injection, and mild colic. In simple right-sided displacements or dilations of the abomasum, the only significant finding may be the small gas ping localized to the abomasum in a cow with depressed appetite and decreased milk production.

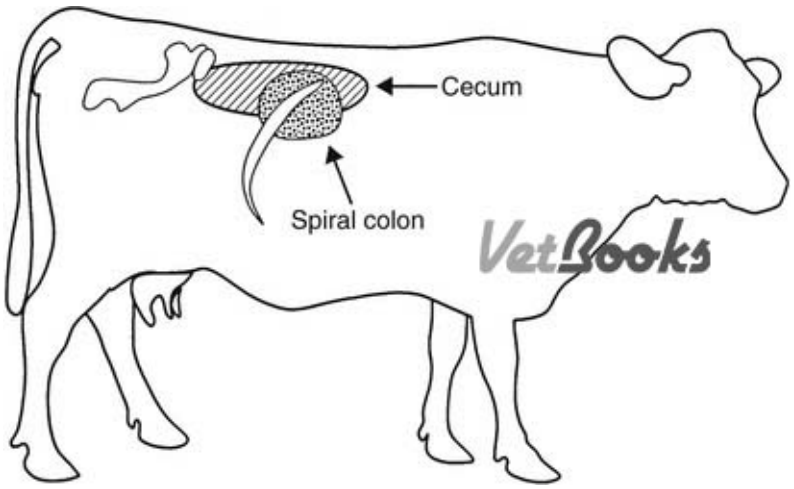


FIG. 1.3 Schematic representation of areas of gas pings elicited by percussion of the cecum and spiral colon.

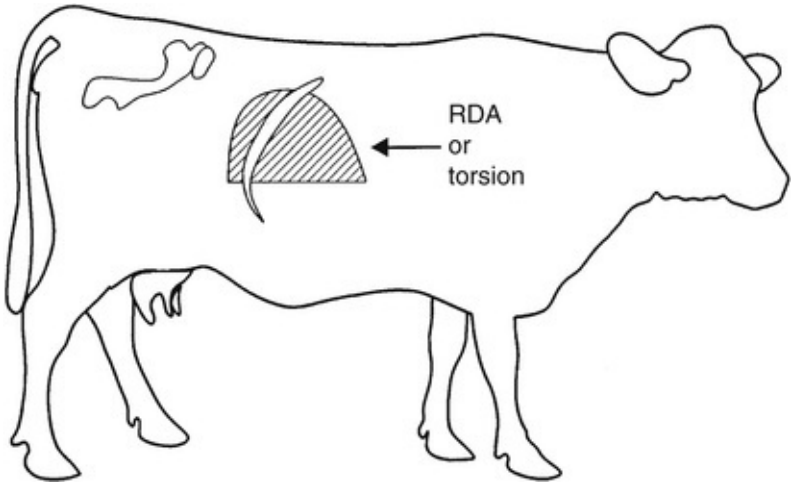


FIG. 1.4 Schematic representation of the area of the gas ping percussed in association with a right displaced abomasum *(RDA)* or abomasal torsion.

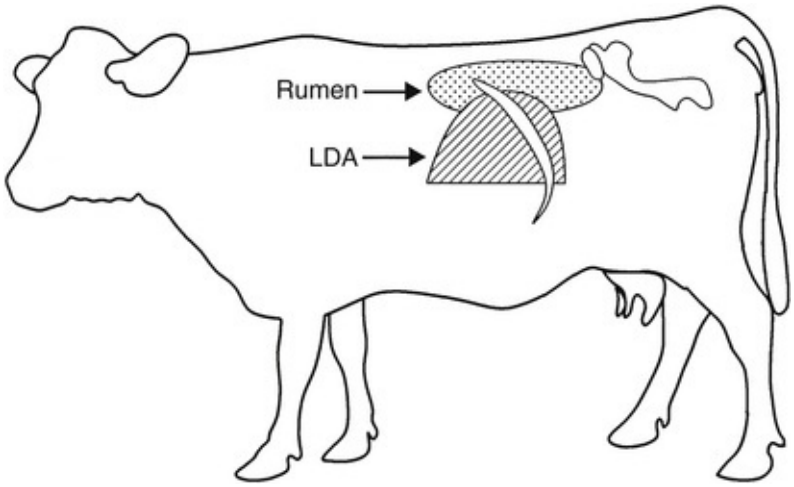


FIG. 1.5 Schematic representation of the area of the gas ping percussed in association with a left displaced abomasum *(LDA)* or gas ping in the rumen.

On the left side, gas pings can be noted as originating from the peritoneum, the rumen, or a left displaced abomasum (LDA). The auscultation of a gas ping that is primarily localized to the dorsal aspect of the paralumbar fossa and auscultable on both sides of the spinal column would be indicative of a pneumoperitoneum. The extent of these pings can be from the thoracolumbar junction caudally to the retroperitoneal space. Pings associated with ruminal tympany occupy the whole of the paralumbar fossa and can extend dorsally to the spinal column but generally do not extend over to the right side (see Fig.

1.5). LDA results in a gas ping that is localized, easily outlined, and approximately 12 to 18 inches (30 to 45 cm) in diameter. Caudal extent of the displacement is generally the 13th rib; however, it can extend into the paralumbar fossa, in which case the outline of the abomasum can be easily palpated. The LDA should ping over the 11th rib on a line from the hip to the elbow (see Fig. 1.5). Rumen gas associated with a left-sided ping will rarely ping at this location. Identification of a fluid line within the displacement can aid in diagnosis and is accomplished by balloting the left paralumbar fossa while auscultating the area of the gas ping concurrently, a process known as *succussion.* LDA often gives a pitch that changes in tone as it is percussed, as a result of movement of the rumen behind the abomasum. Often with LDA, intermittent gas bubbling or "sloshing fluid" sounds are heard. Rumen gas can be further differentiated from gas trapped in an LDA by rectal palpation of the rumen. One can also differentiate rumen gas from that trapped in an LDA by passage of a stomach tube into the rumen. Blowing into the rumen yields obviously auscultable sounds unless an LDA is present, in which case the sounds are muffled as the practitioner listens over the area of the ping. Performing a rumen or abomasal tap, the Liptac test, can further differentiate whether the ping originates from an LDA or the rumen. Fluid collected from an LDA would have a pH of less than 4, whereas that of the rumen should be 6 or higher, although cattle suffering from ruminal acidosis, or "grain overload," can have a ruminal pH approaching 4.

The rumen is examined by both auscultation and palpation. It should have a doughy texture with a small gas cap in its dorsal regions and usually is not distended above a plane formed by the coxofemoral joints. Increased accumulation of gas within the rumen would be seen with acute primary frothy bloat and also with free gas bloat. The rumen contractions should be counted, observed, and auscultated. Normally, primary ruminal contractions occur one and one-half to three times per minute, and the force of the contraction should displace the lateral body wall at least ½ to 1 inch (1 to 2 cm). When auscultated, the ruminal contraction sounds like a dull roar that starts quietly, rises to a peak, and dies away. Hypocalcemia and peritonitis are examples of disorders that result in weak or absent ruminal contractions. Hypermotility is rarely seen but can occur and has been described in association with vagal indigestion.

The cardiac region of the thorax is auscultated next. Heart rate and rhythm are determined at this time. Rate varies among species, and age differences within species are noted. In general, older or larger animals have a slower heart rate.

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Table 1.2 lists the ranges of heart rate that are considered normal for the ruminant species, depending on age. Tachycardia can be seen in animals that have been stressed or excited, as in the process of restraint. However, with time the rate should return to within a more normal range. Any deviation from the normal heart rate in a quiet, relaxed animal implies a general disturbance of the normal health of the animal. Increased heart rate can be seen with fever, inflammation, pain, hypocalcemia, or metabolic disturbances that result in hypovolemia. Bradycardia is seen with conduction disorders within the cardiac muscle and with some metabolic disorders (uremia, hypokalemia). The most common causes of arrhythmias are atrial fibrillation in adult cattle and hyperkalemia in diarrhetic neonates. Location and intensity of the heart sounds are also important to note, because muffling or displacement of the sounds can indicate space-occupying lesions within the thorax, pericardium, or mediastinum. With pericardial effusion the heart sounds are initially dull but develop splashy washing machine sounds as a gas-fluid interface develops. This often takes weeks. Normally the heart occupies a space on the ventral thorax between the third and sixth ribs. Most of the heart mass is located on the left side of the chest; thus the heart sounds should be louder on that side. However, if the heart is muffled on the left side and louder than normal on the right, one should consider the possibility of inflammation of the pericardium or lung lobes on the left side of the chest. Displacements of the heart sounds caudally are an indication of a space-occupying lesion in the anterior thorax or mediastinum, such as an abscess or neoplasm. Cranial displacements of the heart sounds would be noted with distention of the ruminoreticulum, eventration of abdominal viscera into the thorax through a diaphragmatic hernia, or other space-occupying lesions as noted previously. If any murmurs are noted on auscultation, an attempt should be made to localize the murmur to a specific heart valve. While the heart is auscultated, the pulse should also be palpated. The easiest point to find a pulse while the heart is being auscultated is at the vascular notch of the mandible where the facial artery is easily palpated. Pulse deficits in conjunction with an increase in heart rate are seen in atrial fibrillation and premature ventricular contractions. The heart rhythm is also noted. Dropped beats, gallop rhythm, and sinus arrhythmias should be compared with other clinical signs to determine importance.

TABLE 1.2

Normal Resting Heart Rates (Beats/Min) for Adult and Young (<30 Days of Age)

Normal Resting Heart Rates (Beats/Min) for Adult and Young (<30 Days of Age) Ruminants[1-3]

Animal	Average	Range
Cattle		
Adult	60	40-80
Calf	120	100-140
Sheep		
Adult	75	60-120
Lamb	140	120-160
Goat		
Adult	85	70-110
Kid	140	120-160

The prefemoral and prescapular lymph nodes are palpated. Enlargements would be seen with inflammatory processes occurring in the regions that they drain. The skin is then palpated, starting along the top line and moving down over the abdominal and chest walls to the ventral midline. The presence of subcutaneous gas or edema is noted, as is any elicitation of pain. Emphysema can have iatrogenic causes (e.g., be secondary to abdominal surgery) or result from pulmonary alveolar rupture, gas gangrene, or puncture wounds. Edema, if noted, is usually ventral and is the result of lowered plasma oncotic pressure or increased venous pressure. Right-sided heart failure, as seen in traumatic reticulopericarditis, pericarditis, mediastinal masses, or severe pulmonary disease, results in increased venous pressure. If this is the case, a distention of the jugular veins with jugular pulse should also be evident. Protein-losing enteropathies or nephropathies are causes of lowered oncotic pressure, as is liver failure, which results in a lack of synthesis of plasma proteins. Fluid and gas from subcutaneous injection of large volumes of medications such as calcium gluconate can sometimes be confusing.

The thorax is then auscultated and percussed. Respiratory rate (Table 1.3) and pattern are determined at this time, and the lungs are auscultated. If increased inspiratory or expiratory effort is noted, it should be correlated with auscultatory and percussive findings in an effort to determine lung pathology. Normal ruminant lung sounds vary greatly among species. In calves, sheep, and goats the relatively thin chest wall allows one to hear inspiratory sounds ventrally and over the large airways, whereas expiratory sounds are minimal (except in sheep, where they are frequently audible because of the large amount of mucus in sheep airways). In larger cattle, only faint inspiratory sounds are normally heard. Lung sounds can be classified as normal or harsh (tubular) or as wheezes or crackles. These sounds can vary over the different areas of the thorax or can be found singularly over the entire lung field. Significant pulmonary pathology may be

present in ruminants *without* any auscultatable abnormalities. Total absence of lung sounds ventrally indicates pleural effusion or pulmonary abscessation with loss of airways. When ventral consolidation of the lung occurs, airway sounds are transmitted well and easily heard ventrally as pipestem sounds similar to those heard over the trachea, whereas percussion reveals a marked increase in ventral lung density. The trachea should also be auscultated. Inspiratory dyspnea and stridor are usually the result of extrathoracic obstructions to airflow (nose, pharynx, larynx, extrathoracic trachea). Pneumothorax can also result in loss of auscultatable airway sounds, which may be absent dorsally or entirely over the entire side if the lung has collapsed completely.

TABLE 1.3

Normal Resting Respiratory Rates (Breaths/Min) for Adult and Young Ruminants[1-3]

Animal	Average	Range
Cattle		
Adult	24	12-36
Calf	48	30-60
Sheep		
Adult	36	12-72
Lamb	50	30-70
Goat		
Adult	28	15-40
Kid	50	40-65

Place the middle finger in the intercostal space and slap the finger with the opposite hand or use a tablespoon and rubber hammer to accomplish percussion of the chest wall to determine the ventral lung border. Percussion is most useful in goats and calves. In sheep the wool precludes effective use of the technique, and in adult cattle the chest wall is often too thick to effectively evaluate changes in percussion tones. The chest is percussed in a dorsal-to-ventral direction, moving caudal to cranial on the chest wall. A change in resonance is noted when the ventral border is reached; a line demarcating this change in resonance is the junction of the diaphragm to the thoracic wall. In the ruminant this line should be described by joining a point at the junction of the 11th rib and the epaxial musculature dorsally to a point at the middle of the 9th rib, then cranially to the point of the olecranon. The cranioventral portion of the percussed thorax is dull because of the heart field (≈3 inches [7.5 cm] above the olecranon in adult cattle; 1 to 2 inches [2.5 to 5 cm] in calves, sheep, and goats). Finding an increased area of dullness in the cranioventral lung field associated with harsh lung sounds

would be an indication of lung consolidation as seen in *Pasteurella* pneumonia. Pulmonary emphysema (atypical interstitial pneumonia) should be considered when the lung field is larger than expected, the animal is dyspneic, and airway sounds are minimal, whereas a ventral border that is markedly elevated and in a straight line could be an indication of pleural effusion. In this case auscultation would reveal decreased lung sounds ventrally and possibly the presence of pleural friction rubs. Acoustic percussion of the lung field can extend into the chest only to a depth of 2 to 2 and ½ inches (5 to 6 cm); therefore lesions within the thoracic cavity that lie deeper than this cannot be percussed.

The next step in the physical examination is to assess for evidence of pain in the ventral portion of the abdomen and thorax. This can be accomplished through the use of the withers pinch test or by ballottement of the xiphoid region. The withers pinch test involves auscultating the trachea while the withers are simultaneously squeezed and pushed ventrally. Painful lesions result in the ruminant resisting normal ventral movement of the spine and/or emitting a grunt or holding its breath when this test is performed. Ballottement of the xiphoid is also done while the trachea is auscultated. The xiphoid region is pushed with a knee or struck with a closed fist, and an elicitation of a grunt would indicate pain in this region. The examiner can then ballotte the remainder of the ventral abdomen and thorax to classify the lesion as localized or diffuse. If localized, the region affected should be identified. It should be noted that the animal may kick the examiner during the xiphoid ballottement test; thus proper precautions should be taken.

The subcutaneous abdominal veins are assessed next and palpated along their length for the presence of thickened walls, distention, or pulses. Distention and pulses may be abnormal if they correlate with other clinical evidence of right-sided heart failure. Thickening of the wall or evidence of thrombosis is often a consequence of faulty intravenous injection of irritating substances or of injuries that result in hematomas or abscesses.

If the animal is lame or has postural abnormalities, the feet and legs are palpated next. If the animal is uncooperative, it may be necessary to sedate and/or cast it. If sedation is necessary, it should be performed at the end of the physical examination. Care should be exercised for obvious reasons. The examination consists of comparing one foreleg with the other and then comparing both with the expected norm. The same procedure is followed for the hind legs. Abnormalities in the shape of the claw may be hereditary or may be caused by nutritional deficiencies, poor leg conformation, poor housing, or as a

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sequela to laminitis. The coronary bands should be palpated for evidence of pain or increased heat. An attempt should be made to pick up all four feet individually and observe the soles and interdigital regions for necrotic areas, areas of bruising or swelling, draining tracts, or presence of foreign bodies. The fetlock, carpal and tarsal, stifle, and elbow joints are all easily accessible and should be examined for swelling, tenderness, edema, heat, instability, and crepitation. Each joint should be tested over its full range of motion, and any elicitation of pain should be noted. Physical findings should be consolidated into a decision as to whether the joint problems are infectious or traumatic. Sheep or goats with acute polyarthritis most commonly have mycoplasma or chlamydial infection. Chronic joint pain in goats (often with soft tissue thickening and enlargement caused by synovitis) is frequently attributable to caprine arthritis encephalomyelitis. Conformation of the legs should be analyzed because this could contribute to a joint or foot problem. The pelvic girdle does not lend itself to extensive examination; however, one can note symmetry or asymmetry and further evaluate during the rectal examination. Fractures of the tuber coxae, subluxation of the sacroiliac junction, acetabular fractures, fractures of the head or neck of the femur, and dislocation of the coxofemoral joint may all be diagnosed by evidence gained during palpation and observation of the pelvic area. The dislocated or fractured limb is frequently shorter than the normal opposite limb. The tail can also be examined for evidence of fractures, paresis, or paralysis.

The perineal region is examined by noting the external condition of the genitals and rectum. Anal sphincter tone can be assessed, and the presence of vaginal discharge can be noted. In males the testicles, spermatic cord, and epididymis should be palpated for the presence of nodules or areas of fibrosis. The testicular circumference can be measured and compared with what is expected for age and breed. These measurements are noted in Tables 1.4 and 1.5. The perineal part of the penis can be palpated for the presence of hematoma or swelling and pain (cellulitis or abscess). In the female the supramammary lymph nodes can be felt at the attachment of the udder to the perineum. Enlargement of these nodes occurs with mastitis or lymphosarcoma. The udder is palpated for the presence of fibrotic areas, commonly seen secondary to staphylococcal mastitis or associated with *Trueperella pyogenes* (formerly called *Arcanobacterium [Actinomyces] pyogenes*) abscesses. The presence of a swollen quarter or quarters with pain and heat may be associated with mastitis caused by gram-negative bacteria. Cold damp areas of skin on the udder that are

discolored, necrotic, and possibly sloughing are evidence of gangrenous mastitis. In lactating animals, milk should be present in each quarter and some of this milk should be expressed for examination. The milk should be of normal color and consistency and should not have any appreciable smell. The presence of leukocytic flakes or clots (garget) is an indication that the udder is mounting an inflammatory response. This response can be measured qualitatively by using the California Mastitis Test (CMT). One should also collect individual quarter samples from those quarters showing garget or those that test positive on the CMT for bacterial culture and sensitivity.

TABLE 1.4

Expected Values for the Scrotal Circumference of the Bull at Different Ages[4]

Age (Months)	Scrotal Circumference (cm)
12-14	30-34
15-20	31-36
21-30	32-38
>31	34-39

TABLE 1.5

Expected Values for the Scrotal Circumference of the Ram at Different Body Weights[5]

Body Weight (kg)	Scrotal Circumference (cm)
<45	23-27
45-70	27-33
70-90	30-36
90-115	31-37
115-135	33-38
135-160	36-40

The next step is to evaluate the head and neck regions. The head should be symmetric in appearance, and any asymmetry should be evaluated to determine whether the deviation is caused by a neuromuscular or skeletal defect. Facial nerve paralysis results in one type of asymmetry, whereas a frontal sinusitis with concurrent displacement of the frontal bone appears differently. Discharges from the eyes, ears, nose, or mouth are noted and correlated with other physical findings. The oral cavity is examined by grasping the tongue with the hand and extending it out through the interdental space. Muscular tone of the tongue is evaluated at this time. The normal animal will resist extraction of the tongue and

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will quickly retract the tongue into the oral cavity when released. Increased ease of extraction and delayed retraction are indicative of diseases resulting in flaccid paralysis or paresis of skeletal muscle (e.g., as seen in botulism). The tongue and oral mucosa are examined for the presence of erosions, ulcerations, foreign bodies, or areas of necrosis. The dental arcade is evaluated for age of animal, absence of teeth, loose teeth, or necrotizing gingivitis. The color of the mucous membranes is noted. Icterus, pallor, hyperemia, cyanosis, excessive reddening, or brown “mud-colored” mucous membranes can all be noted, depending on the underlying disorder. Mucous membrane color is best evaluated in the eyes and/or vulva because of the presence of pigments in the oral mucosa of many ruminants. The smell of the breath is noted and, if fetid, might be an indication of a retropharyngeal abscess caused by trauma, lung abscess, or gangrenous pneumonia. If the breath is foul, deep palpation within the oral cavity for an abscess or necrotic area is indicated.

The mucous membranes of the nares are examined, and erosions and ulcerations are noted. Nasal discharges can be an indication of a pulmonic problem but can also be seen with sinusitis. Bilateral discharge is most commonly associated with pneumonia, and unilateral discharge is more often an indication of a sinus problem. However, percussion of the sinuses is necessary to fully evaluate the presence of a discharge. Normal sinuses percuss with a hollow sound, much like that of a hollow tree, and dullness on percussion might indicate sinusitis, sinus cyst, or other fluid or mass in the sinus.

The eyes are examined next. The sclera and mucous membranes are evaluated in much the same manner as the oral and nasal mucous membranes. The corneas are examined for the presence of opacities, discolorations, ulcerations, and lacerations. The position and size of the corneal opacities or ulcerations can be helpful in determining the cause. Foreign bodies such as plant awns and seeds beneath the third eyelid often cause opacity of the medial aspect of the cornea. Infectious bovine keratoconjunctivitis (pinkeye) is usually localized to the central cornea and causes severe corneal ulceration. When the mucosal diseases cause corneal opacities, they generally do so at the junction of the cornea and sclera and usually do not ulcerate the cornea. The anterior chamber should be examined for the presence of hyphema or hypopyon. These can sometimes be seen in animals with severe bacteremia, especially in neonates with failure of passive transfer. The animal should be evaluated for the presence of a menace reflex (absent in normal neonates for up to 2 weeks), and the pupillary light responses should be observed. Nystagmus and strabismus should be

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characterized, if present, because the direction is important in localizing the lesion. Nystagmus or strabismus or a deficit noted in the pupillary light reflex or menace reflex is indicative of underlying neurologic or ophthalmologic disease.

The ears should be palpated and evaluated as to their temperature and the presence of skin lesions. They should be warm to the touch. Ears that are cold are an indication that there is decreased blood flow to the periphery, as seen in hypocalcemic states, with decreased cardiac output, or in severe toxic states resulting in peripheral vasoconstriction. The presence of small crusty areas or erosions of the skin of the pinna is seen in some of the mucosal diseases such as bluetongue or bovine virus diarrhea. In sheep with acute bluetongue, edema of the face and ears sometimes occurs. If aural discharge or head tilt is present, the ear canal should be examined grossly and with the use of an otoscope for the presence of foreign body or parasites. Purulent discharge can be noted and is an indication of otitis externa. Noting that the eardrum has ruptured along with the purulent discharge is diagnostic of otitis media (and possibly otitis interna). Animals that have suffered trauma to the laryngeal or throat latch region and have a basisphenoid fracture can have bloody discharge from the aural canal. Correlation of the otoscopic findings with other clinical findings is necessary to arrive at a definitive diagnosis.

The palpable lymph nodes of the head and neck include the parotid, the submandibular, and the deep retropharyngeal. The deep retropharyngeal lymph nodes can be palpated externally, if enlarged, in the sheep, goat, and calf. They can be examined in the adult bovine by extending the hand through the mouth and palpating the pharynx. By keeping the animal's mouth open with one hand and guiding the other hand along the dorsum of the tongue to its base, the examiner can then extend the hand aborally into the pharynx. Enlargements of the deep retropharyngeals, abscesses, or other masses can then be palpated. The most common causes of masses or abscesses in the pharyngeal region are infectious or iatrogenic (e.g., secondary to trauma from a balling gun, paste wormer gun, or other instrument). The submandibular nodes are located in the intermandibular space and are identified by slipping the skin and underlying tissue through the fingers. These nodes are oval and about the size of a walnut, or 1 to 2 inches in diameter (2.5 to 5 cm). The parotid lymph nodes are almond shaped and are located just caudal to the ramus of the mandible and about 4 inches (10 cm) ventral to the ear. In overconditioned animals, the submandibular lymph nodes and the parotid lymph nodes are often impalpable due to the amount of fat deposited subcutaneously.

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The skin of the neck is palpated, with attention paid to the presence of abscesses, lacerations, or other lesions. Skin turgor can be assessed by tenting the skin and measuring the time it takes for the skin to return to normal shape. This is used to determine the state of hydration. In normal, hydrated animals the skin returns to normal position within 1 second. Using other factors such as sunken eyes, dryness of mucous membranes, abnormal heart rate, and degree of illness, an estimation of percent dehydration is made. Dehydration is first noted clinically when the animal is approximately 5% dehydrated, and death occurs at 12% to 15% dehydration.

The larynx should be palpated for enlargement and the presence of pain. The trachea should also be palpated for the presence of fractured tracheal rings, collapsed areas, and pain on palpation. The jugular veins are examined for the presence of distention and pulses. Thrombosed veins should also be noted because this condition may alter the desired course of therapy and often prevents placement of a catheter. The venous stasis test is performed on the jugular by holding off the vein in the midcervical region. Normally the vessel fills above the point of occlusion and remains collapsed below. With restricted venous blood flow, as seen in cases of right-sided heart failure, a positive stasis test can result. In these cases, the vessel below the occluded point fails to collapse or takes a prolonged time to do so and a jugular pulse is frequently present.

The final step in the physical examination is rectal palpation. This cannot be accomplished in small ruminants, so this section is directed primarily toward the bovine. The pelvic area is evaluated for the presence of retroperitoneal abscesses or fractures of the pelvic bones. The left kidney is more easily palpated than the right kidney because of its location within the abdominal cavity. Both kidneys are located to the right of midline, as the left kidney is displaced by the rumen and is located caudally to the right kidney. The kidney should be palpated for overall size and shape, which is normally lobulated in cattle, and the kidney can be gently squeezed to determine if pain is evident. The rumen should be palpated and the findings compared with those noted on percussion and auscultation. If there is any evidence of intraabdominal gas pings, an attempt should be made to palpate the suspected organ. This can provide information that may be helpful in determining therapeutic or diagnostic directions. The rectal palpation can reveal the presence of masses that were not palpable externally, such as fat necrosis or tumors. Adhesions and evidence of peritonitis can also be palpated rectally, and attempts should be made to localize them to a specific area of the abdomen to establish potential cause. The preiliac (or internal iliac) lymph nodes are located

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by sweeping the hand along the craniodorsal face of the ilium. These nodes normally have the size and shape of a walnut. Enlargements are noted with lymphosarcoma, peritonitis, and severe limb inflammation. The lymph nodes of the aortic bifurcation are small and not easily palpated. Their ability to be palpated would be evidence of abnormal enlargement. Palpation of the genital tract is directed toward establishing size, shape, and presence of abnormalities. These contents could be normal, as with a pregnant animal bearing a fetus, or abnormal, as seen with a pyometra. If it is determined that a cow is not pregnant, the ovaries and oviducts should be palpated for structures and abnormalities. In the bull, particular attention should be paid to the prostate, seminal vesicles, and bulbourethral gland.

Diagnostic imaging using an ultrasound probe in conjunction with rectal palpation can add to the information already gathered during the physical examination to further refine the problem and aid in prognostication and development of the therapeutic plan. Proper manipulation of the probe can allow for imaging the kidney, uterus, bladder, and rumen wall. Abnormal structures noted on palpation of the abdominal cavity can also be imaged. The accessory sex glands in the male can also be visualized.

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Medical Record

The information gathered by means of the physical examination (see Fig. 1.2) is compiled and correlated with the data obtained during the history (see Fig. 1.1). A problem list should be formulated through the physical examination and anamnesis, leading to the development of a differential diagnosis list, a specific diagnostic plan, and a proposed course of therapy (Fig. 1.6). Prognosis can also be assessed with the information now in the examiner's hands. Accurate recording of the abnormalities noted during the examination should become part of the medical record and can prove valuable in following the course of the case. In addition, with each complete and accurate physical examination performed, the practitioner becomes more skilled in the procedure, adapting it to fit his or her needs, and using his or her time more efficiently. With the number of diagnostic tests available to the profession today, the information gained from the physical examination will allow the examiner to pick the tests that are specific for those disorders suspected, which saves the practitioner time and the client money.

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DIAGNOSTIC AND TREATMENT SHEET

FARM OWNER _____ **DATE** _____

ANIMAL ID NUMBER _____ **PRODUCTION CLASS** _____
LACTATING COW/DRY COW/HEIFER/CALF/BULL

PHYSICAL EXAM

TEMPERATURE	NORMAL	FEVER	HYPOTHERMIA		
RUMEN MOTILITY	NORMAL	WEAK	ABSENT	BLOAT	COLLAPSED
ABDOMINAL PINGS/SPLASHES/PAIN	NORMAL	ABNORMAL	LDA/RDA/RTA	GRUNT	DIARRHEA
RECTAL PALPATION FINDINGS	NORMAL	ABNORMAL	DISTENDED BOWEL	KIDNEY	OTHER
MANURE	NORMAL	DIARRHEA	SCANT/NEG	FIRM	BLOOD/FIBRIN
URINE	NORMAL	KETONES	+ ++ +++	BLOOD/PUS	
REPRODUCTIVE TRACT	NORMAL	PREGNANT	METRITIS	PERIMETRITIS	ADHESIONS
LUNGS	NORMAL	PNEUMONIA	EMPHYSEMA	PLEURITIS	CHRONIC
HEART SOUNDS/RHYTHM	NORMAL	MURMUR	ARRHYTHMIA	SPLASHING	MUFFLED
LYMPH NODES/CNS	NORMAL	ENLARGED	DOWN COW	CNS SIGNS	
MAMMARY GLANDS	NORMAL	MASTITIS	TEAT ABNORMALITY		
EYES/MOUTH/MUCOUS MEMBRANES	NORMAL	ABNORMAL	PALE/JAUNDICE	SQUAMOUS CELL	LUMPY JAW
LIMBS/BODY EXTERIOR	NORMAL	ABNORMAL	SKIN LESIONS	LAMENESS	INJURY

Diagnosis 1. _____ **2.** _____ **3.** _____

TREATMENT

IV FLUIDS	CALCIUM	DEXTROSE	7.2% NA CL	K CL	ELECTROLYTES	PHOSPHAID
ANTIINFLAMMATORY	DEXAMETHASONE	PREDEF 2X	BANAMINE	PHENYLBUT	ASPIRIN	SOLUDELTA
ANTIBIOTICS	OXYTETRACYCLINE	ALBON	PENICILLIN G	POLYFLEX	NAXCEL	TRIBRISSEN
RUMENATORICS	LAXATIVE BOLUS	EPSOM SALTS	CHARCOAL	MINERAL OIL	NUTRADRENCH	NA HCO3
VITAMINS/MINERALS	MULTI B	B 12	D PANTHENOL	VIT E/SE	ORAL KCL	ORAL PO4
ANALGESICS	TORBUGESIC	VALIUM	EPIDURAL	SEDATION		
LONG ACTING ANTIBIOTICS	LA 200	MICOTIL	NUFLOR	LS 50	ERYTHROMYCIN	LA SULFA
HORMONES	OXYTOCIN	GNRH	LUTALYSE	ECP		
OTHER	EQUIPOISE	NA IODIDE	IU OXYTET BOL			

SURGERY **LDA** ☐ **RDA** ☐ **EXPLORATORY** ☐ **C-SECTION** ☐ **OTHER** ☐ _____

FOLLOW-UP THERAPY **PROGNOSIS** **EXC**☐ **GOOD**☐ **FAIR**☐ **POOR**☐

1. _____
2. _____
3. _____
4. _____

WITHDRAWAL INFORMATION

DRUG _____ **MILK** _____ **SLAUGHTER** _____

DOCTOR: _____

FIG. 1.6 Example of a diagnostic and treatment sheet. (Courtesy Lander Veterinary Clinic, Turlock, Calif.)

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As has been noted earlier, temporal and economic constraints sometimes preclude the performance of a complete physical examination. This is especially true when called to investigate a population-based disease/disorder case. In these instances, the practitioner needs to use aspects of the physical examination procedure outlined previously in order to arrive at a reliable presumptive diagnosis that can then be investigated further via the diagnostic plan. The affected population can be observed for signs of disease as previously described. The practitioner can look for evidence of pain, condition of the hair coat, body condition score, and variations in height or size or even shape of the affected animals along with their normal counterparts. Increased respiratory effort or rate can be noted from a distance, as can be discharges from body orifices. Mentation status can also be assessed. An effort should be made to try and determine the course of the disease on the basis of the signs of pain and/or disease noted. For example, in the case of a neonatal calf disease problem, the veterinarian would begin with the newborn and look for evidence of the disease/disorder while progressively observing older calves. Doing the investigation in this order would allow for determination of the onset of the disease (i.e., at what age group do you begin to see signs of the disease?), would allow one to determine progression of the disease as the calves age, and would allow one to get an idea of resolution of the disease process and allow for determination of any aftereffects of the disease. This same principle can also be applied to older ruminants, as one can begin with the animals that have just recently been through parturition and end with those that are approaching the end of gestation. While doing this, the veterinarian can also observe the feed bunks, the pens, the water troughs, etc. and gain great insight that could lead one to conclude that the disease process is primarily one that is management induced rather that pathogen induced.

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Diagnostic Tests That Can Be Applied in the Field

Laboratory procedures can be performed in the field, the results of which would prove beneficial in the development of a diagnostic plan. These include the CMT, partial urinalysis (dipsticks), ruminal pH determination, and milk or blood progesterone tests. In addition, some serum chemistries can be performed cowside with the use of the i-Stat Serum Chemistry Analyzer (i-Stat Corporation, Princeton, N.J.).

The CMT is a simple procedure that aids in the detection of clinical or subclinical mastitis (see Chapter 36). This procedure is done routinely during all physical examinations of lactating cows. Partial urinalysis is accomplished by collecting the urine and using any one of a number of urine dipsticks that can be commercially obtained. With a suspected case of lactic acidosis, a rumen sample can be collected through the stomach tube or via percutaneous needle puncture and rumen pH can be determined. Most drugstores carry pH paper that can be used for this procedure; however, confirm that the paper has a standard range, because certain papers are specific for the acidic or alkaline range. A rumen pH below 4.5 would be indicative of lactic acidosis. Numerous cowside progesterone assays that use either milk or blood as substrate have recently been developed. These can be relatively easy to use and interpret or they can be difficult, so discretion should be used when making initial purchases. These ancillary diagnostic procedures are explained in greater detail later in this text.

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Assessing the Welfare of the Individual Animal or the Herd

Health includes the mental and physical aspects of animals. The World Health Organization defined health as “a state of complete physical, mental and social well-being and not just the absence of disease or infirmity.”[6] Animal welfare is characterized by lives that are worth living.[7] This begins with providing for the physiologic needs of animals (housing, nutrition, disease, and injury prevention) and includes their mental/emotional well-being. The emotional status of animals has been termed *affective state*[8] and involves how animals are coping with their environments. Mental states of animals can be positive (enjoyment, comfort) or negative (anxiety, fear, or discomfort).

Welfare, including both physical and mental (emotional) components, is usually assessed using a combination of physical signs, behavioral observations, and sometimes references to the natural state of an animal. A physical examination for the health of an animal assesses each organ system to determine if the organ system is within normal limits or if abnormalities are found. An animal, or group of animals, is considered to be in ill health or to have disease when an observation or sign is outside the normal function or physiologic norm for that organ system. The same approach is applied to examining the welfare of animals: Understand what normal welfare is and assess the animals systematically to determine if welfare is compromised.

In some situations both welfare and health are compromised. Heat stress seriously affects physiology and thus both welfare and health. Animals are lame, an obvious health problem, because they have pain, a welfare problem.

Mastitis is a clinical health disease and can, in many cases, be painful. Poor nutrition not only makes an animal hungry but can result in compromised immune functions and increased risk of infection.

Welfare assessments often determine whether the Five Freedoms of Animal Welfare (Box 1.1) are being met. The Five Freedoms[9,10] categorize the basic elements of animal welfare and therefore allow determination of the state of an animal in each area. An animal has poor or compromised welfare if any of the Five Freedoms is not being met.

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BOX 1.1

Five Freedoms of Animal Welfare

1. Freedom from hunger and thirst
2. Freedom from discomfort
3. Freedom from pain, injury, or disease
4. Freedom to express normal behavior
5. Freedom from fear and distress

As a general example, nutrition is a basic need (food and water). Hunger or thirst for extended periods would be a compromise in this area. Overcrowding a pen could result in animals being unable to eat when they are hungry or drink when they are thirsty. Animals can experience distress with overcrowding from hindered access to feed and water, lack of ability to lie down when tired, or inability to avoid dominant or aggressive pen mates.

Assessing Welfare

The tools used to assess welfare in the field are mainly observation of animals for physical outcomes and behaviors that indicate affective states. A basic tenet of welfare is that housing should be clean, dry, and comfortable. The animals will show if that is the case: if the housing and lying areas are clean, then the areas they lie in are clean. If the housing and resting areas are comfortable, the animals will not have skin or leg lesions or abrasions from hard surfaces. Behaviors associated with compromised welfare include aggression, cannibalism, depression, and stereotypies. Stereotypies are what animals display to compensate for inabilities to express innate behaviors or for boredom. They include biting other animals, excessive licking or chewing, tongue rolling, and banging on enclosures. Scoring systems[11,12] have been developed or adapted to quantitatively assess four aspects of welfare (Table 1.6): body condition score, hygiene score, leg lesion score, and locomotion score.

TABLE 1.6

Animal Scoring Systems Used to Evaluate the Welfare of

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Dairy Cattle

Animal Observation	Score Range	Welfare Parameter	Conformance
Body condition score	1-5 (thin to fat)	Nutrition	2-4
Hygiene score	1-4 (clean to dirty)	Sanitation	1 and 2
Leg lesion score	1-3 (no lesion to swelling)	Comfort	1
Locomotion score	1-5 (sound to non–weight bearing)	Lameness	1 and 2

These scoring systems are used in formal welfare audits and evaluations of dairy cattle, and species-specific systems can be used for other animals. Body condition scoring of 1 to 5 is used to assess nutrition. Hygiene scoring (1 to 4) of animals is used to determine if housing and lying areas are clean and dry. In cattle, leg lesions on hocks and knees indicate comfort on lying areas and are scored 1 (no lesions), 2 (hair loss), or 3 (swelling). Locomotion scoring (1 to 5) is used to determine if the animal is lame and to what degree. These scoring systems can be used to determine the welfare of individual animals or applied to groups and herds as averages to assess the welfare of farms.

Some aspects of welfare are not readily assessed by observing animals. These encompass painful or distressing procedures such as dehorning, castration surgery, parturition, and treatments, including treatments for lameness. These procedures can affect welfare if not done humanely. Also included in this area are situations that are infrequent, such as handling disabled or nonambulatory animals and animals that require euthanasia. These areas are not often observed during a welfare assessment and are therefore evaluated by reviewing protocols and training for these tasks. Reviews of procedures that will cause pain must include assessment of pain management including postprocedure analgesia.

The behavioral aspects of welfare are assessed by understanding the species-specific behaviors of animals and determining if the animals observed have the ability to express the fundamental behaviors considered important. The abilities to move, associate with other animals when desired, and lie in comfortable positions are considered basic behaviors of livestock. Species have specific behavioral needs, such as cud-chewing in ruminants and rooting in pigs. Welfare evaluation of the housing and management of animals must consider the animals' ability to express normal behaviors.

Pain, anxiety, and distress are affective states that need to be minimized for animals to have good welfare. Signs of pain in animals include depression, vocalization, increased heart and respiratory rates, protection of body parts, lameness, and decreased activity. Signs of anxiety and distress include facial expressions (eyes open, ears up); restlessness; tail movements; feet stamping;

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and avoidance behavior. Recognition of negative affective states allows correct evaluation of the emotional aspects of animals' conditions and allows for appropriate medical and nursing care for sick or injured animals and management of animals in production systems.

In conclusion, evaluation or assessment of the welfare of an animal or a group of animals is similar. The most generic version of a welfare assessment is the FARM program (http://www.nationaldairyfarm.com/animal-care#standardsapp). It includes the FARM (Farmers Assuring Responsible Management) manual that details most of the points discussed. The practitioner must understand what normal, or good, welfare is, and then through systematic evaluation of each of the Five Freedoms determine if an animal's welfare is normal/acceptable for that species or is compromised.

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Insurance, Interstate, and Prepurchase Health Examinations

The complete physical examination as described in the preceding sections is necessary for a proper prepurchase or insurance examination. For insurance purposes a more complete accounting of the examination must be done. This means that all findings, whether normal or abnormal, have to be recorded. A specific form is generally provided by the insuring agent, and this should be used. Potential for future legal action also exists whenever an animal is insured; therefore it is in the practitioner's best interest to complete the insurance form accurately.

The prepurchase examination is similar to the insurance examination. The physical examination form (see Fig. 1.2) can be used to record findings. The prepurchase examination could be performed on the highly pedigreed female that is being consigned to sale, but it is more often performed on the male scheduled for use as an artificial insemination stud. Occasionally one could be asked to examine an animal under consideration for purchase. Experience indicates that the veterinarian should be employed by the potential buyer in these cases. This arrangement avoids any potential accusations of conflict of interest on the part of the examining veterinarian. A complete blood count and a chemistry panel should be run. Generally it is prudent to certify that the animal is healthy and to test for tuberculosis, brucellosis, and bovine leukosis (using agar gel immunodiffusion). Additional laboratory tests for anaplasmosis and bluetongue may be indicated. Often an animal being consigned to sale or one going into artificial insemination service is required to meet federal regulations for interstate shipment. This information can be obtained from the federal veterinarian in charge in your area or from the office of the state veterinarian in the state of destination.

A problem arises when the number of animals submitted for interstate health examination is large. Economic and temporal constraints usually preclude complete examination of all the animals presented. At such times the visual examination described earlier can prove helpful in determining which animals are to be singled out for the more complete physical examination. The examination of individuals is less complete than for prepurchase or insurance examinations because such factors as fertility are not at issue when filling out an

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interstate health certificate. Choosing animals with abnormalities in behavior, physical condition, gait, or posture allows the practitioner to concentrate on those that have the most potential to be diseased. Also, one can be fairly confident that if all the animals appear normal on the general examination, they are healthy and would be suitable for interstate shipment as long as the results of the intradermal tuberculosis test and required serologic tests prove negative. To sign an interstate health certificate, a veterinarian must be accredited and licensed in a state. It is essential that a veterinarian signing an interstate health certificate has examined the livestock sufficiently and diligently enough to be confident that no infectious or contagious diseases are present in the consigned group. A call should be placed to the office of the state veterinarian in the state of destination to be sure that all current requirements are fulfilled before shipment is scheduled.

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• CHAPTER 2

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Equine History, Physical Examination, Records, and Recognizing Abuse or Neglect in Patients*

Kathleen Casey Gonda, Consulting Editor

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▪ Section 1

The ideal purpose of the physical examination is to determine what or if a problem exists. The results should be used to establish a diagnostic plan, prepare a therapeutic approach, and develop a prognosis as rapidly and efficiently as possible.

The nature of an internal medicine problem does not always allow for each objective of the physical examination to spontaneously or quickly generate either a diagnosis or a prognosis. More realistically, the examination process dictates the specific laboratory tests or procedures to be performed that support the diagnostic or therapeutic effort. The clinician's self-discipline regarding the extent of the physical examination should be guided by experience, efficiency of time, and judicious selection of the ancillary diagnostic aids that are available. A complete and extensive examination of each patient may not always be practical, especially in busy private or academic practice situations. In these cases the clinician should provide for the client's concerns with an expedient history and a pertinent physical examination process that addresses the client's complaint (e.g., a rectal examination is not required for an evaluation of a pneumonia patient).

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Physical Examination Record

Preparation for the initial contact time with the client and patient should begin with a system of record keeping. Ambulatory records are usually more flexible than “in-house” hospital admission forms. Both field and clinic forms should include designated spaces for the client or agent's address and phone number. An area for the complete signalment (name, sex, breed, color, age, reproductive status), including an estimated weight, should be provided. If the patient is unnamed, as with foals, it should be listed in the dam's name with the year of birth (e.g., Curious ’06). The sire's name should not be used because more than one foal per year would be expected from a stallion's crop. Whenever surrogate mares produce multiple foals from a single embryo transfer dam, a new system of naming and identification will have to be incorporated. Additional identification of the patient may include a lip tattoo, freeze brand, or microchip number and, if available, should be noted in the horse's record. Thoroughbred racehorses are tattooed under the lip with a letter, denoting the year foaled, followed by four or five numbers. Thoroughbreds foaled in 1997 have “A” as the first character in their tattoo, followed by those foaled in 1998 with a “B” as the first letter, and so on. Once the end of the alphabet is reached, the process is repeated. Numbering and lettering schemes used for lip tattoos and freeze marks vary, depending on breed registry, so one should consider breed or discipline carefully when using the number for aging or identification purposes. As of 2013, horses competing in U.S. Equestrian Federation (USEF)–sanctioned events for the first time are required to have microchips as part of their passport identification. ISO 11784– and ISO 11785–compliant microchips (resQ, Bayer Healthcare, LLC, Shawnee Mission, Kan; HomeAgain, Merck Animal Health USA, Madison, NJ.), the same as those required by the U.S. Department of Agriculture's voluntary Animal Disease Traceability program (previously the National Animal Identification System), must be used.[1] Microchips should be located on the near side of the horse, in the nuchal ligament, approximately 3 to 4 cm below the crest, in the middle third of the neck.

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Equine Insurance

If the animal is insured, this should be documented, preferably with the insurer's telephone number. In addition, the type of insurance should be noted (e.g., mortality and/or surgical and medical). It is the client's or his or her agent's responsibility to notify the insurance company representative whenever an animal insured for full mortality contracts an illness or sustains an insult, life-threatening or not, that requires a veterinary examination. If the patient is insured, it is considered a professional courtesy for the veterinarian to also communicate directly with the insurance company, especially in the case of a life-threatening illness. Also, permission from the insurance company is required whenever a general anesthetic, surgical procedure, or euthanasia is to be performed. Whenever euthanasia is requested, the insurance company may require a second opinion from an adjusting veterinarian. If a direct representative from the insurance company cannot be contacted immediately, the clinician must exercise professional judgment in assuming the responsibility for a humane or critical decision. The client or agent should agree with the decision, and all communications and pertinent data should be documented in the medical record, including a signed euthanasia consent form, if applicable. If a necropsy is to be performed, it should preferably be done in the presence of another veterinarian from a different practice. The American Association of Equine Practitioners (AAEP) provides an insurance pamphlet as a guide to veterinarians.[2]

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History

The medical history should be directed to the clinical problem. The “herd health” of the stable or farm can be assessed briefly as depicted by the vaccination and parasite control program and visually by the condition of other horses residing on the premises. The patient's individual problems should be determined according to such factors as clinical history of onset, feed and water consumption, fevers, and decrease in performance. In essence, the clinician must effectively zero in on the problems at hand, which may affect multiple body systems.

The diet (e.g., supplements, grazing environment), stall or housing schedule, and medical problems concerning other animals on the premises, which may coincide with a group incidence of the client's complaint, should be determined. When contagious disease is a concern, travel history of the patient or stablemates, including recent additions to the farm, should also be considered.

When a veterinarian is dealing with neonates, the reproductive and foaling history of the mare may be important in establishing an early diagnosis. Any compromise during a mare's gestational period (e.g., systemic disease, general anesthesia, or administration of certain medications), foaling, or lactation; any placental abnormalities; and any problems that occurred during previous pregnancies should be questioned and considered to be important, pertinent historical data. In some circumstances, the foal's breed should be considered and the possibility of genetic disease transmission by the dam and/or sire should be investigated (e.g., combined immunodeficiency in Arabians).

A description of the types of medication used before hospitalization may aid in determining if “masking” agents have inadvertently been administered. Tranquilizers or sedatives, which can cause confounding clinical signs of hypotension, bradycardia, lethargy, weakness, and ataxia, are frequently given for the horse's safety during transport. In many instances a van driver or hauler is unaware of medications used or the patient's medical condition. Sedatives (e.g., xylazine) and analgesics such as flunixin meglumine, administered by owners or farm staff in the hours or days prior, may mask signs of pain or colic and alter interpretation of the severity of the horse's condition on arrival. Failure of such an analgesic to abolish clinical signs may necessitate hospital or clinic admission for further evaluation or surgical consultation. Conversely, the failure of other previous medical treatments can aid in the initial selection of more appropriate

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therapeutic planning. Knowledge of the quantity and interval of administered drugs is pertinent information as well, particularly in hypovolemic animals given drugs known to be nephrotoxic (e.g., phenylbutazone).

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Physical Examination

The extent of the physical examination will be subject to the condition of the patient, the environment where the examination is conducted (field vs. hospital), the equipment at hand, and the ancillary personnel available for restraint and procedural purposes. In a hospital setting the clinician should have immediate access to most of the equipment and diagnostic instrumentation listed in Box 2.1. The physical examination sheet should provide a systematic list of the organ systems being evaluated. Vital signs (temperature, pulse, and respiratory rate) should be documented in the “calm” animal, if possible (Table 2.1). Abnormal findings are described in an appropriate space provided, usually below the body systems checklist. Using the same numeral for each body system throughout the examination process and in problem identification is useful for future caseload recall, especially if a computer is used and codes can be applied to clinical findings and diagnosis. At the completion of the physical examination, the major problems identified are listed, and appropriate laboratory tests can be requested. The final diagnosis is seldom determined at the time of the initial examination; however, the final diagnosis represents the final assessment and should be filled in at the appropriate time (e.g., hospital discharge).

Box 2.1

Recommended Examination Room Equipment and Ancillary Services

Examination Room Equipment

Records (examination sheet, request forms, and euthanasia forms)
Thermometer
Clock with second hand
Stethoscope
Twitch
Rectal sleeves, sterile examination gloves and lubricants
Nasogastric tubes in various diameters/lengths

Hand pump
Hoof knife and testers
Ophthalmoscope/Otoscope
Dental speculum
Endoscope (1-, 2-, and 3-meter lengths)
Electrocardiogram (ECG) machine
Ultrasound (linear or sector scanner)
Sphygmomanometer and Doppler (tail or limb)
High-volume fluid pump
Refrigerator
Incubator
Oxygen (O_2) tank and foal mask
Culture swabs, transport media, blood culture bottles
Video equipment

Ancillary Services

Radiology and imaging services
Ultrasound consultation
Laboratory services

TABLE 2.1

Vital Signs in Normal Horses and Foals

	Adult Horses (Range)[a]	Foal (Range)[a]
Temperature (° F)	99-101	99-102
Heart rate (Beats/Min)	28-44	50-70
Respiration (Breaths/Min)	8-15	20-40

[a]Heart and respiratory rates vary depending on level of excitement and autonomic stimulation.

A general evaluation of the equine patient should be made from afar. This is particularly important for neonates at the side of their dams. The initial observations of body condition, posture, weakness, lethargy, incoordination, lameness, and musculoskeletal asymmetry are more easily observed at a slight distance from the patient. The integumentary system can usually be evaluated quickly as to the type, distribution, and number of lesions and site and layer of involvement. However, subtle lesions of petechia and ecchymosis cannot be

visualized in the integument because the hair coat and pigment hide lesions that are obvious in other species, such as purpura of nonpigmented humans and pigs. In these instances the mucous membranes must be examined as an extension of the integumentary system. If obvious multiple lesions of the skin are present, documentation is usually expedited by photographing or drawing a picture of the horse and indicating the distribution of the lesions on both sides (see Chapter 11). Gross generalized distortions (e.g., anasarca) may be viewed as lesions of possibly more than one body system (integumentary and circulatory).

Abnormalities in demeanor and mentation can be assessed by watching the horse's initial response to the environment and again once the physical examination and interaction with the patient begins. Whatever the approach, the physical examination should be systematic and orderly, so as not to miss subtle features in the face of obvious abnormalities. In general, most examinations start at the head, so as not to startle the horse or foal and to prevent possible injury to the veterinarian who may be unfamiliar with the horse's temperament or previous handling experience. Evaluation of facial symmetry and cranial nerve function can be accomplished with minimal handling or manipulation. The eyes can be examined by a rapid visual assessment using a penlight. The cornea and cranial and caudal lens capsules can be evaluated by horizontally moving the penlight and noting the crossing light reflexes. Pupillary constriction to light and the “menace” response should be observed, although these reflexes may be significantly slower or absent in the neonate. An ophthalmoscope retinal examination should be performed whenever the eyes represent the primary complaint, and fluorescein dye should be used to detect corneal ulcers before the installation of other ophthalmic agents. Blindfolding one eye at a time may aid in the assessment of unilateral blindness and should be conducted in a safe area with “blunt” devices contrived as an obstacle course.

Evaluation of the circulatory system starts with assessment of heart rate, rhythm, and any presence of murmurs. Mucous membrane color, capillary refill time, scleral injection, palpable changes in the temperature of the ears and extremities, jugular pulsation, and pitting subcutaneous edema are the most common obvious circulatory physical examination parameters. The heart should be auscultated bilaterally, and murmurs should be graded according to intensity (I to VI or I to V), character, valve site, and phase of the cardiac cycle. Cardiac arrhythmias usually necessitate an electrocardiogram (ECG), except in the case of type II atrioventricular block, a normal finding commonly observed in clinically asymptomatic horses. Type II heart block in normal horses can usually

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be obliterated by exciting the horse with a threatening gesture or trotting the horse a few steps to increase the heart rate. In addition to electrocardiography, transcutaneous ultrasound examination of the heart and pericardium and transrectal evaluation of the caudal aorta and iliac arteries for intraabdominal thrombotic lesions can be used.[3] If procedural assessments of blood pressure are necessary, a manometer for central venous pressure or a sphygmomanometer with Doppler ultrasound is used on the base of the tail in foals[4] and adults.[5]

The respiratory system is similar to the circulatory system in that the breathing rate and mucous membrane color are important assessments. A quick visual assessment of the alar folds may identify conformational abnormalities or indicate severe compromise (e.g., nostril flaring). Respiratory effort and the phase of increased work should be assessed (e.g., increased expiratory effort with “heaves”). Nasal airflow can be determined by wetting the hands and holding them gently over the nostrils so that both intensity and equality of air movement can be assessed. The color (e.g., blood tinged), character, and amount of any nasal discharge should be noted and indicated whether it is present in one or both nostrils. A penlight can be used to visualize the internal nares (septal mucosa). Smelling the breath for fetid or necrotic odors (ozena) is similarly important, and endoscopic evaluation of the upper airways should be an adjunct to abnormal clinical findings. Percussion of the sinuses should be performed for detection of dullness, suggesting a possible mass (e.g., ethmoid hematoma), sinusitis, or the presence of fluid within the sinus cavity. In addition, the head should be carefully examined ventrally and caudally for the presence of lymphadenopathy. Auscultation should be of both the upper (larynx and trachea) and the lower airways. In horses with equivocal lower airway findings, a rebreathing bag can be used to accentuate abnormal sounds by increasing the respiratory rate and volume of inspired air. The interpretation of lung sounds has been described elsewhere,[6] and the clinician should try to auscultate dorsal and ventral regions of the thorax bilaterally and document findings as to the location or absence of sounds and the phase of respirations involved. Coughing in horses with upper and lower respiratory disease is variable.

Percussion of the thorax is a reliable clinical tool and should be performed in cases of suspected abscess, tumor, or pleural effusion. A pleximeter and tablespoon are the only tools required, although some clinicians are adept at direct finger percussion of the chest. In foals, percussion can be performed by placing a stethoscope on one side of the chest and reaching over the back of the foal to manually percuss the opposite side. Fractured ribs may be recognized in

the neonatal foal as palpable asymmetry or a bony crepitus (“clicks”), often with edema of the sternum or elbow coinciding with the fractured side. Horses with pleuropneumonia may exhibit a reluctance to move (pleurodynia) similar to that seen in horses with laminitis, which is a possible sequela to endotoxemia caused by gram-negative bacterial pneumonia.[7]

Ultrasound has revolutionized the clinical evaluation of the thoracic cavity. Unfortunately, the familiarity of clinicians with thoracic interpretation is directly related to access to and frequency of ultrasound use. However, subtle pneumonia, abscess, and pleural effusion represent definitive objective findings and can be identified rapidly with little or no stress to the patient.[8] Because radiographic changes often lag behind clinical disease, serial examinations via ultrasound may be a more accurate way of monitoring response to treatment. In fact, ultrasound examinations may eliminate the need for chest radiographs in numerous cases, thereby increasing efficiency and decreasing client costs.

A systematic approach should always be used when examining the horse for gastrointestinal disease. Although most emergencies and referrals are related to colic or acute intestinal disease, the clinician should resist the temptation to focus only on the abdomen, so that important clinical signs relating to other problems (e.g., gastric ulceration, botulism) are not missed. If a clinical complaint involving the abdomen is present or in suspected cases of intestinal displacement, obstruction, or volvulus, the gastrointestinal system is initially examined with bilateral auscultation of intestinal sounds by dividing the abdomen into four quadrants. Intestinal borborygmi vary by location, and in the cecum and ascending colon propulsive contractions tend to occur in waves, with periods of quiescence, over several minutes. In general, small intestinal sounds are the least dramatic, heard in the area of the left flank. In addition, the abdomen should be auscultated ventrally for sounds similar to “ocean waves” or sand pouring on itself, indicative of the presence of sand within the gastrointestinal tract.[9] The presence of increased (hypermotile), reduced, or absent borborygmi (ileus) should be considered an important feature of the physical examination. It is helpful to document the activity or lack thereof in each of the four abdominal quadrants, especially in hospitalized patients where different clinicians may be monitoring the patient over several days. In cases in which the gastrointestinal tract is the site of the primary lesion, checking for gastric reflux and performing a rectal examination are required elements. Although only about 40% of the gastrointestinal tract can be reached by palpation, it is a valuable technique that can quickly identify surgical cases and

affect survival.[10] Clinicians should strive to become adept at rectal palpation and regard the procedure as a premier diagnostic skill while also respecting the risks involved for the patient and veterinarian.

The patient should be observed for the presence of normal prehension, eating, and drinking whenever dysphagia is present or neurologic dysfunction is suspected. A subjective assessment of tongue strength and tone can be made by carefully grasping the tongue. Normal horses will pull against the hand and, once the tongue is released, replace it immediately in the mouth. The evaluation of the gastrointestinal system should also include a dental examination for the presence of malocclusion and dental abnormalities (e.g., missing or damaged teeth, tooth root abscess) that can affect prehension or mastication. Use of a dental speculum is required for safe and complete examination of the dental arcade and adjacent soft tissues. Accurate notation of affected teeth should be made in the medical record using a universally accepted identification system such as a numeric system in which the horse's head is divided into four quadrants, with each tooth described by its own number (e.g., two central upper incisors on horse's right and left would be 101 and 201, respectively). Clinicians should also become adept at dental age determinations, albeit with an awareness of its limitations and subjectivity.[11] Nasogastric intubation is useful in evaluating dysphagia and esophageal blockage (choke) and determining the presence or absence of gastric reflux. In addition, the volume and character (e.g., color, pH, presence of blood or toxic plant material) of reflux obtained can be rapidly evaluated and may aid in the diagnosis.

The use of long endoscopes (e.g., 2 to 3 m) is valuable in the visual assessment of the esophagus and stomach with lesions such as esophageal stricture and gastric ulceration. For a diagnostic endoscopic examination of the stomach, it is recommended that the patient be muzzled or held off feed for at least 10 hours to allow complete visualization of the stomach.[12]

Ultrasound evaluation of the abdomen in conjunction with aspiration and analysis of visualized abdominal fluid may quickly reveal peritonitis, uroperitoneum, hemorrhage, ascites, visceral rupture, or abdominal masses. In adults, palpable abdominal masses and enlarged lymph nodes can usually be scanned transrectally.

The urogenital system can be examined by manual palpation, rectal palpation, vaginoscopic (speculum examination) viewing, endoscopy, and ultrasound. The caudal portion of the left kidney is easily palpated in most horses. Uterine and catheterized samples (e.g., cultures, urinalysis) should be obtained before any

contaminating invasive procedures (e.g., rectal palpation) are performed and before fluid therapy is initiated. Sphincter tone may be subjectively or objectively (urethral pressure profile) assessed in horses with urinary incontinence or stranguria. Horses with incontinence often demonstrate "scalding" of the perineum and hind legs, and foals with a patent urachus may dribble urine from a moist umbilical stump.

Examination of the neurologic system should involve a consistent procedure for all patients with nervous system disorders (see Chapters 8 and 35). The patient's attitude, posture, and head carriage should be assessed from afar. The cranial nerves should be evaluated, followed by examination of the spinal reflexes and tail tone. Sensory deficits should be noted at this time. Conscious proprioception and postural responses (e.g., placement, hemi-hopping, sway) can then be assessed before observing the patient in locomotion. Notes regarding symmetry, ambulation, paresis, muscle atrophy, and upper and lower motor neuron deficits should be documented to aid in determining the sites for any additional ancillary tests such as radiographs, cerebral spinal fluid collection, or myelogram. Blindfolding should be conducted in a safe area, especially for patients with vestibular disease. An area of incline is useful for evaluating the locomotor deficits, especially when the horse is led with the head elevated.

The lymphatic system is usually evaluated merely by recording any obvious lymphadenopathy. This can be regional or local (as in strangles) or generalized (cutaneous lymphosarcoma) and may be appreciated on rectal examination. Lymphangitis or the presence of edema should also be noted.

For the internist, evaluation of the musculoskeletal system usually involves a rudimentary examination of the site and appearance of the disease processes. Primary lameness is more commonly evaluated by clinicians familiar with diagnostic nerve blocks, arthrocentesis methods (e.g., septic arthritis in foals), and radiographic findings. It should be noted that acute (caused by fracture) or chronic lameness can coexist with primary neurologic disorders (e.g., equine protozoal myeloencephalitis). Therefore, when warranted, the patient should receive a cursory neurologic evaluation (see Chapter 8) in conjunction with the musculoskeletal examination. Conversely, all horses presenting with systemic illness (pneumonia, colitis) should also be evaluated for signs of laminitis in all four feet because this complication is often the limiting factor for the horse's survival. Visual inspection of the hoof wall and sole may indicate previous laminitic episodes and should be documented because this may increase the patient's risk and lower the threshold for repeat episodes. Careful palpation of

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the lower limbs may indicate increased intensity of digital pulses or changes in the coronary band that may be related to the “sinker” syndrome (distal phalangeal displacement).[13] If laminitis is present as a complicating factor, the clinician should be able to add to the clinical prognosis by using Obel grading (grades 1 to 4).

Once a patient has been admitted to the clinic or hospital, well-organized flow charts should be used for monitoring and assessing the patient.

Use of Ancillary Equipment in the Examination Procedure

Advancing technologies are allowing the practitioner or clinician to add to or replace many physical examination procedures with techniques capable of providing more rapid diagnostic information or direct therapeutic intervention. Ultrasound of the chest for the definitive diagnosis of a pleural effusion is an example of an objective procedure that may obviate many of the traditional physical examination procedures used for the clinical diagnosis of pleuropneumonia (e.g., auscultation, percussion). Though less commonly used by the internist, the advent of portable digital radiography has dramatically improved the efficiency of obtaining quality films without additional trips and repeated exposure of staff and patient.

The size of equipment is a determining factor in whether a diagnostic tool is suitable for the examination area. For example, equipment such as computerized axial tomography scanners, magnetic resonance imaging (MRI) units, and nuclear scintigraphy units do not currently fit in the spaces available in most hospital physical plants. Large, modular ultrasound machines can be cumbersome in small areas, although units for field reproductive use (linear or sector scanners) are appropriate for any area, including vehicle transport. The choice of ultrasound equipment is an individual decision based on need, budget, and availability. Security should also be a consideration in stocking an examination area with equipment and medications. The clinical examination areas of most facilities tend to be high-traffic regions; this may be a primary reason for not stocking certain pieces of equipment in both university practices and private facilities.

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Medical Record

In 1968 Lawrence Weed published on the use of the problem-oriented medical record. This system of record keeping emphasizes the justifications for daily decision making during hospitalization. Problems are defined by the history, physical examination, and laboratory findings. Daily (or more frequently for intensive care unit patients) *s*ubjective findings (e.g., appetite, attitude) are documented, and *o*bjective data (e.g., heart rate, temperature) are recorded. This information (e.g., patient is febrile) is then *a*ssessed by the clinician, and a *p*lan (e.g., resubmit laboratory tests, change antibiotic medications) is derived based on the assessment. The abbreviated form of this type of medical record is SOAP, and this method is applied to each problem identified. Although the system encourages medical judgment and accountability, it more directly serves as a teaching tool within institutions by which the student's clinical thinking can be evaluated by the in-charge clinician. In private practices the method of record keeping is more flexible and tends to document vital information that primarily serves as an accounting of services and provides a medicolegal record. Unfortunately, many medical records function only as invoices and do not record medical information regarding the patient. This is more often true of ambulatory records but can be found in certain hospital practices. State veterinary regulatory bodies have strict requirements regarding the patient medical record, with particular regard to the administration and cross-documentation of controlled substances (e.g., ketamine, butorphanol) and euthanasia solutions. Whichever system is used, the responsibly prepared medical record should provide medical information, justification for charges, a protection from liability, and adherence to state and federal regulations. A thorough medical record further allows for the retrieval of retrospective information. The accumulation of data is beneficial to the communication of clinical caseload experiences to other clinicians for the benefit of their patients.

Medical Record Filing

Two major systems of medical record filing exist: numeric and name filing. Numeric systems offer consistency of the record and avoid the confusion of patients with similar names. The problem of name similarity is primarily confined to the nonregistered breeds of horses. Breed registration requires name

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approval to avoid duplication, among other undesirable designations. Again, for record-keeping purposes, clinic or ambulatory records for unnamed young horses are best designated by the dam's name and the foal's year of birth (e.g., Curious ’06) and filed by month and year of examination. A “master” admission log should be maintained for record retrieval purposes, especially when a patient has been seen on multiple occasions. Color coding, along with numbering of the file folders, may be helpful in record retrieval. Computers offer the advantage that records can be retrieved through any one of several recall parameters (e.g., problem, client).

Computer-Generated Medical Records

Traditionally, patient medical records (PMRs) are maintained via a manual, paper-based, on-site system of data storage and retrieval as described previously. Before computerization and its acceptance by the medical community, all information regarding patient history, diagnostic testing, and treatment notes was handwritten and filed. Unfortunately, a number of problems coexist with a paper-based system, including illegible handwriting by practitioners or staff, poor integration of patient information (e.g., diagnostic test results and imaging studies filed separately from the PMR), and loss of or damage to files.[14] In addition, state veterinary boards require that all patient records and imaging studies be retained by a practice for a minimum period of time before they can legally be disposed of. Storage issues can be a problem for equine practices that do many prepurchase examinations, in which radiographs may be retained for 10 to 20 years. Although many veterinary facilities currently use computers for various tasks such as accounting and inventory, few have eliminated the paper-based PMR completely.

Computers offer the advantages of legibility, quick data retrieval, and immense archiving capacity. The need for rapid transfer of medical information from doctor to doctor or from doctor to referral facility is being met by advances in computer software and Internet access. Thus the current trend in human and veterinary medicine is the development and implementation of an electronic medical record (EMR) that is entirely computer generated. An EMR permits one or more individuals, simultaneously, to access laboratory results, imaging studies, and other pertinent patient information.[15] For the equine practitioner, the availability of real-time ultrasound imaging and digital radiography has revolutionized the production and transmission of high-quality diagnostic

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images, via computer, within moments after they have been taken. This has greatly increased the quality of medicine and efficiency of patient care, allowing general practitioners rapid access to the opinions of specialists at sites distant from the patient. Over time, acceptance of the EMR may result in the complete dissolution of the paper-based medical record.

Several software systems have been designed specifically for equine hospitals and include adaptations for ambulatory “off-site” data entry and retrieval (Henry Schein Veterinary Solutions, Piedmont, Mo.; Business Infusions, Calgary, Canada).

In addition to patient information, other applications such as client invoicing, inventory management, and payroll are included in certain software packages. Recently, voice recognition software has been adapted for use by veterinarians (Dragon Veterinary, Antigonish, Canada) and can be added to most software packages and implemented by using either a specialized microphone plugged into an in-house computer or a “cloud”-based mobile phone application. This system promises to improve efficiency and accuracy and save time by allowing ambulatory practitioners to enter data directly into the EMR through the app on their mobile phone at any time, either during the examination or while traveling between client locations.

Three basic types of systems are currently available to the equine practitioner: standalone and multiuser on-site systems; on-site systems with external synchronization; and Internet-based multiuser systems. The first and second types of systems are similar, but with the addition of external synchronization, patient information can be collected on handheld devices or laptop computers away from the main hospital (e.g., by ambulatory staff) and downloaded directly to an in-house computer. The third system is the most technologically advanced and offers not only greater efficiency but also the ability to continuously upgrade software. This system offers access to the Internet through either a hospital web page or a client Internet server and allows practitioners in the field the ability to transmit information such as digital radiographs immediately to other doctors, referral hospitals, or specialists throughout the world. These connections can be made via wireless (e.g., mobile phone) or direct Internet access (e.g., phone line, cable). Currently, IDEXX Laboratories in Westbrook, Maine, and VCA Antech, Inc. in Los Angeles can send test results directly to the PMR as soon as they are available. Another advantage of this system is that all information contained in the EMR can be stored on an off-site server and downloaded to the hard drives of in-house computers.

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This technology can be a cost-effective, important tool in modern practice management that increases efficiency and quality of patient care and dramatically reduces storage requirements.

Record Keeping for Special Purposes

The U.S. Drug Enforcement Administration (DEA) requires veterinary practices to maintain detailed inventory records for scheduled drugs. Drug inventory and use must be recorded in a readily retrievable medical record. Requirements may vary by state, so consultation with state regulatory agencies is prudent. Use should identify the patient, volume used/wasted, date, and authorized person who obtained the drug. The drug use should be further documented in the PMR to account for the volume having been depleted from the inventory. For scheduled drugs, states may vary as to the required timing and frequency of inventory accounting and/or inspection for veterinary practices, including ambulatory vehicles.

Occupational Safety and Health Administration (OSHA) records are comparable to the DEA ongoing inventory and use records and are stringent in terms of compliance with OSHA regulations.[16] Documentation regarding safety procedures (e.g., fire safety inspections) is required after an initial inspection for labeling and safety protocol. Upgrading of Material Safety Data Sheets (MSDSs) is a further requirement and should comply with current standards.

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▪ Section 2

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Recognizing Abuse and Neglect in Equine Patients

According to the American Horse Council statistics from 2005, approximately 9.2 million horses live in the United States. During the past decade, equine welfare has come to the forefront as one of the most important issues facing the equine industry. It is a complicated and emotionally charged subject that includes moral, ethical, and financial considerations. Catastrophic breakdowns that occur during high-profile televised events are seen by millions of non-horse-owning but horse-loving viewers. Often what follows is a powerful groundswell of public opinion that places pressure on participants and sponsors of such events to enact changes that satisfy the public's real or perceived concerns for the horse's welfare. Sadly, these changes are often made not simply to protect the horse but primarily to limit the financial impact such negative press has on that sector of the horse industry. Similarly, the 2007 federal ban on horse slaughter in the United States was not initiated by veterinarians or horse owners but, again, by the American public and their disdain for horsemeat. It is clear from these examples that protecting the welfare of horses is important to owners, investors, and the horse-loving public, but the ultimate responsibility must rest with the equine veterinarian, who understands the needs of horses and is in the best position to identify neglect or abuse and educate owners, caretakers, and policy makers.

What *Is* Equine Welfare?

Defining what constitutes acceptable welfare practice continues to be an evolving process that has yet to be conclusively agreed on among investigators.[17] Previous to the past decade, the emphasis focused on food animal confinement systems, with the improvements in welfare correlating positively with increased production. The modern concept of welfare attempts to merge scientific knowledge with the emotional state or “experience,” which has led to a greater emphasis on quality-of-life assessments.[18] Evaluating the health and welfare of horses can be a complex undertaking when one considers the number of contradictory ideas and opinions relating to husbandry and training practices. To circumvent these differences, surveys[19] and sophisticated

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methodologies[20] have been developed as tools to examine socioemotional issues such as welfare. Cruelty may be intentionally imposed or take the form of neglect due to ignorance, financial hardship, or poverty. Poor husbandry, unrecognized clinical and subclinical disease, improperly directed performance training, and work-related activities are examples of unintentional abuse and neglect that can also negatively affect a horse's quality of life.

As first responders, veterinarians are in the best position to not only recognize health issues that may be due to or affected by these practices but also educate clients who may be unaware of the harm they cause. To protect the welfare of horses, veterinarians must be equipped to recognize features that define abuse and neglect in patients. Unfortunately, social, moral, ethical, religious, and philosophical views affect how individuals, including veterinarians, approach the welfare of animals and ultimately react. Opinions vary widely as to exactly what constitutes “neglect” and “abuse,” and the sheer complexity of defining and quantifying the less tangible elements that affect a horse's welfare, such as pain, depression, and anxiety, is immense when attempting to construct a “one-size-fits-all” paradigm. As a result, developing universally agreed-on guidelines that accurately identify welfare cases in a way that protects all horses is not straightforward. In acting as the “voice” for the horse, clinicians are placed in a precarious and challenging position by these issues. The veterinarian is obligated to put the best interests of horses front and center but, to do so, must reconcile in his or her own mind what parameters will be used to identify cases of neglect or abuse. Unfortunately, few veterinary school curricula include courses dedicated solely to issues of animal welfare and behavior, which can be particularly challenging for new graduates who will be expected to recognize differing degrees of abuse or neglect and respond appropriately.

Spotting Cruelty or Neglect

Millions of horses and donkeys around the world live in the poorest, most underdeveloped countries, where their primary use is work related—transporting goods or working in factories, on farms, or as the sole source of transportation for their owners. Veterinary care and education in animal husbandry practices are often lacking or nonexistent, and sources of quality forage in many areas further affect general health and survival. Signs of abuse and neglect are usually obvious to even the untrained eye, as evidenced by open wounds, chronic sores, overt lameness, and a skeletal appearance. In a study by Pritchard and colleagues,[21]

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which examined nearly 5000 working donkeys, horses, and mules residing in Afghanistan, Egypt, India, Jordan, and Pakistan, 70% had a body condition score of 2 or less (scale of 1 to 5), and nearly 90% of the 2071 horses examined had obvious lameness or gait abnormalities, associated with limb and/or hoof deformities.

In contrast, horses residing in modern, industrialized nations such as the United States are, for the most part, considered companion animals. Depending on the circumstance, individuals with little or no knowledge of horses can recognize cases of abuse or neglect, yet signs often may be vague or equivocal, enough to escape detection by experienced horsemen and equine veterinarians. At first glance, such horses may appear well fed, well groomed, properly housed, and cared for with no obvious signs; however, closer inspection may uncover evidence of behavioral (e.g., stereotypic behaviors) or physical mistreatment, such as healed pastern scars from a previous “soring.” Even on commercially successful or well-managed farms that provide high-quality feeds, pasture, grooming, and regular veterinary care, owners or trainers may employ psychologically damaging or physically painful or abusive procedures and training techniques aimed at enhancing the horse's performance. Veterinarians should be cognizant of subtle signs of inhumane treatment in these environments that may escalate over time to negatively affect the horse's health and quality of life.

Unequivocal Cruelty or Neglect.

All practicing veterinarians will likely be confronted with some form of cruelty or neglect during their careers. Aside from being exposed to these issues in their own practices, veterinarians may be invited to render second opinions or act as agents for humane organizations or local authorities investigating cases of welfare. In the latter case, a veterinarian may act as both caregiver and advocate for the horses in question. The decision regarding when to intervene with clients may be complicated by several obstacles, including the relationship with the owner or trainer, the veterinarian's employment status, and personal convictions. Depending on the magnitude of the abuse or neglect, sharing concerns with and providing a plan to owners must be carefully thought out to prevent embarrassment or alienation. After showing empathy for the horse and owner, most clients are willing to be compliant and eager to share the responsibility of improving the situation. To provide the best plan of action, it is imperative that practitioners show flexibility and understanding regarding the owner's particular

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situation. In cases where a veterinarian is merely an employee without ownership in the practice, a practice manager or owner may attempt to pressure a colleague against proceeding with a welfare claim for more practical reasons such as the loss of an influential client or one who may contribute significantly to the financial interests of the practice. In certain cases, state or local laws and ordinances may apply, and it is the veterinarian's responsibility to be aware of such statutes, to not only protect his or her own interests but also remain in compliance. The American Veterinary Medical Association Model Veterinary Practice Act[22] guarantees immunity from liability in welfare cases, and most state and local laws ensure the protection of veterinarians who report cases of neglect or cruelty in good faith. In either case, evidence including accurate medical records, diagnostic tests, and photographic documentation is necessary to support a case of abuse and protect the veterinarian against liability claims. This becomes particularly important when a case proceeds before a regulating body or progresses toward criminal indictment. It is of the utmost importance that veterinarians choosing to assist in welfare cases understand the legal process, are experienced in equine medicine, and are confident in their skills to collect and provide clear and “irrefutable evidence” to the courts.[23] Because considerable variation may be present within groups of equally neglected horses, practitioners should have in place organized methodology to approach cases of neglect or abuse so that subtle features are not missed. Observation of behavior and general condition should include careful physical palpation to determine the magnitude of muscle mass and identify the presence of scars or lacerations that may be obscured by profuse or matted coats. Photos of the animals and areas of concern may prove useful.

Beyond an intensive physical examination and body condition assessment, additional diagnostic tests may be warranted and serve to support claims of subclinical, clinical, chronic, or terminal diseases such as gastric ulceration, pituitary pars intermedia dysfunction (PPID), laminitis, and neoplasia, respectively. The minimum database includes a complete blood count, chemistry profile, and fecal analysis. Several body condition scoring systems have been developed to determine body condition in horses and donkeys.[23] All are comparatively similar for horses but vary enough in the scoring number and description that all clinicians in a practice should agree to use the same numeric system to avoid any ambiguity that may occur with an already subjective assessment. Box 2.2 illustrates an example of a nine-point scoring system for horses. Because donkeys accumulate fat preferentially over localized areas,

scoring systems developed for horses should not be used to assess body condition in donkeys and mules.[24] The Donkey Sanctuary (www.thedonkeysanctuary.org.uk) has developed a body condition score chart specifically for donkeys.

Box 2.2

Body Condition Scoring[a,b]

1—POOR. Extremely emaciated. Spinous processes, ribs, tailhead, hip joints, and lower pelvic bones project prominently; bone in withers, shoulders, and neck are easily noticed. No fatty tissue can be felt.

2—VERY THIN. Emaciated. Slight fat covers base of spinous processes; transverse processes of lumbar vertebrae feel rounded. Spinous processes, ribs, tailhead, hip joints, and lower pelvic bones are prominent. Withers, shoulders, and neck structure faintly discernable.

3—THIN. Fat buildup about halfway on spinous processes. Transverse processes cannot be felt. Slight fat covers ribs. Spinous processes and ribs easily discernable; tailhead prominent but individual vertebrae cannot be identified visually. Hip joints appear rounded but easily discernable; lower pelvic bones not distinguishable. Withers, shoulders, and neck accentuated.

4—MODERATELY THIN. Slight ridge along back. Faint outline of ribs discernable. Tailhead prominence depends on conformation, but fat can be felt around it. Hip joints not discernable. Withers, shoulders, and neck not obviously thin.

5—MODERATE. Back is flat; ribs easily felt but not visually distinguishable. Fat around tailhead feels a bit spongy. Withers round over spinous processes; shoulders and neck blend smoothly into body.

6—MODERATELY FLESHY. May have slight crease down back. Fat over ribs spongy; fat around tailhead soft. Small fat deposits behind shoulders and along sides of neck and withers.

7—FLESHY. Might have slight crease down back. Individual ribs can be felt, but noticeable filling between ribs with fat. Fat around tailhead soft; fat deposited along withers, behind shoulders, and along neck.

8—FAT. Crease down back. Difficult to feel ribs. Fat around tailhead very soft; area along withers filled with fat. Area behind shoulder filled with fat; noticeable thickening of neck. Fat deposited along inner thighs.

9—EXTREMELY FAT. Obvious crease down back. Patchy fat appears over ribs. Bulging fat around tailhead, along withers, behind shoulders, and along neck. Fat along inner thighs may rub together. Flank filled with fat.

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[a]**Body condition scoring:** Body condition influences everything in your horse's life, from reproductive efficiency, to performance, to good health. By using Body Condition Scoring you can find out what kind of shape your horse is in and work to improve the score. Scoring focuses on critical areas of the body, based on palpable fat and visual appearance.

[b]**Ideal scores:** Most horses, including performance horses and growing horses, should be in a body score of 5 to 6. For optimum reproductive efficiency, broodmares should be a 5 to 7 and not allowed to lose condition such that they are below a 5 during breeding season. Horses over a condition score of 7 may be at greater risk for developing metabolic disorders such as insulin resistance.

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Impact of Husbandry on Well-Being and Behavior.

Regional (rural Western states vs. Eastern cities), cultural (Amish), political (animal rights activists), and religious differences strongly affect how societies and individuals view the treatment of horses and other animals. Husbandry practices vary widely and are also affected by location, property size, financial commitment, and an individual's personal background and exposure. Irregularities can affect the health and behavior of horses, leading to boredom, stall vices, training problems, and stereotypic behaviors. Problems usually result from misguided information or anthropomorphism, as most owners love their horses and do not set out to cause them harm. Paradoxically, veterinarians are often confronted with overzealous or ignorant owners who “over-care” for their horses and unnecessarily keep them covered in heavy blankets and hoods, ill-fitting tail sets, and tight leg bandages or with well-meaning owners who simply

overfeed and oversupplement their horses. These benign-appearing practices may seem harmless but should be monitored by the veterinarian because they can affect the horse's behavior, health, and well-being and can lead to systemic disease such as laminitis secondary to obesity, localized disease (bacterial/fungal skin infections, blanket sores), and physical discomfort (overheating, pruritus).

The natural environment from which horses have evolved is one of vast, uninterrupted space, nearly continuous grazing or food-seeking behavior, and close affiliation and bonding with herdmates. As prey, they have learned to be acutely sensitive to changes in their environment and to respond quickly, usually with avoidance or flight. What owners may assume to be disobedience or spookiness is merely a form of self-preservation. Stereotypic behaviors such as wood chewing, cribbing, weaving, pawing, stall walking, and self-mutilation are seen most often when horses are kept in confinement, though once manifested, many horses will continue the behavior to some degree even when turned out in a paddock or pasture. Facial abrasions (weaving), open wounds (self-mutilation), worn teeth (cribbing), orthopedic injury (repetitive turning), and bleeding hooves (weaving)[25] can occur secondarily as a result of these stereotypies. Several causes for these behaviors have been cited, including a diet low in fiber or nutrients[26] and solitary confinement and stress.[27] Impediments (muzzles, cribbing straps, head ties) imposed to prevent these behaviors can be painful or injurious and lead to greater frustration and anxiety, further affecting the horse's welfare and mental well-being.[26,27] Many owners and trainers believe that other horses can “learn” these stereotypic behaviors from stablemates, so they will often sequester horses with these behaviors, further compounding their anxiety and stress. Often the horse is brought directly to the veterinarian from a stall or paddock for examination, so unless previously disclosed by the owner or witnessed by the clinician, the veterinarian may be unaware that the horse possesses an undesirable behavior. In fact, under certain circumstances (e.g., prepurchase inspection), such information may be intentionally withheld from the clinician in the fear that it will be passed on to potential buyers and affect the value or sale of the horse.

Modern feeding practices such as time grazing, forage and concentrate selection, quantities fed, and feeding intervals are not in line with the horse's natural behavioral and gastrointestinal requirements. Ideally, horses kept in confinement should have access to pasture or turnout for extended periods and be allowed to socially interact with other horses, as this has been shown to reduce stress[26-28] and behavioral problems,[26-31] improve musculoskeletal

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health,[30,32] reduce the occurrence of gastric ulceration[29] and certain types of colic,[31,33] and improve quality of life.[18]

Patients suffering from chronic diseases such as recurrent airway obstruction ("heaves"), advanced PPID, or uncontrolled laminitis should be closely monitored, and every effort should be made to maintain a continuing dialogue with the horse's owner/trainer regarding effects of treatment and quality-of-life issues and to discuss euthanasia when appropriate. Further, clients should be made aware of the costs involved in maintaining chronically ill horses and the likelihood that such costs may be necessary for an extended period or possibly for the life of the patient. The subject of euthanasia is never an easy one but is necessary to discuss under certain circumstances.

Welfare and Training Practices.

Not every horse has the talent or mentality to excel at the discipline the owner has chosen, but many owners are unable to make this determination or refuse to accept such reality and will search for "shortcuts" designed to force the horse to succeed. Countless methods, training devices, and frightening contraptions have been developed over centuries to teach certain disciplines. Tying a horse's head in a fixed position for extended periods[34] and the use of severe bits, electric shock prods, and topical blisters are examples seen in modern training barns. In addition, surgical cosmetic alterations, systemic drugs or topical irritants, silicone injections, and alcohol tail blocks may be used in some breeds to enhance certain physical "breed" characteristics or change the horses' conformation to fit a show ring ideal. Physical and in some cases psychological effects resulting from such abusive practices can confound physical examination findings and delay diagnosis and timely intervention. This may be of particular concern for someone hired as an official horse show veterinarian who is inexperienced or unfamiliar with training practices related to a particular breed or discipline and is presented with an affected horse on emergency. For example, the ideal Western pleasure horse should carry the head and neck in a low, fixed, relaxed position while performing required gaits in the show ring. To maintain this unnatural head position[35] for the duration of the class, trainers suspend or "hang" the horse's head high above the withers for hours before the entered class. As a result, the neck muscles of these horses become fatigued and sore to the point that they will refuse to lift their heads above a horizontal plane, appearing compliant and well disciplined during the class. Clever

pharmaceutical intervention is also used by some to affect the horse's vision, particularly in an indoor show ring. Ophthalmic atropine is used occasionally in English show horses to alter the gait, the head and neck carriage, and how they "look" through the bridle. The resulting mydriasis can last for days to weeks.[36] Depending on the presenting complaint, it is clear from only two isolated examples how secondary signs from undisclosed intervention may lead to confusion on initial physical examination.

Owners frequently seek the advice of veterinarians for problems related to training and behavior, and clinicians should recognize the responsibility of such recommendations and not make them unless confident in their abilities. Aside from previously discussed stereotypies, most problems manifest as fear[25] (avoidance) or aggression expressed as ear pinning, rearing, bucking, bolting, biting, and kicking. Fear and aggressive responses are unpredictable and of particular concern for the veterinarian or staff that may be inadvertently exposed to injury when the owner or handler is inexperienced or afraid of the horse. Conversely, accidental injury of the horse or owner as a result of a confrontation may lead to liability claims against the veterinarian. These actions by the horse can be a result of pain associated with disease or abuse, evasion of a painful impulse such as a misdirected snap of a shank chain, or a learned behavior. The owner's attempt at behavior modification often involves doing nothing, applying positive reinforcement for the behavior, or wielding some form of punishment, which tends to make the problems worse and the horse even more anxious and unpredictable. A veterinarian should gain a feel for the experience and competency of clients and become adept at determining when such behaviors result from poor management by owners or if a physical problem or injury exists and may be causing the response. If the practitioner is uncomfortable giving advice, suitable professionals should be recommended to the owner for help in determining the underlying motivation for the behavior.[25,26] If not remedied, the horse or owner may be exposed to serious injury and the horse may be exposed to escalated physical abuse by a frustrated or fearful owner or passed on to an innocent party that is unaware of the possible dangers.

Musculoskeletal disease and lameness are common client complaints in equine practice. Numerous elements can contribute to lameness, including misadventure, overexertion, inappropriate footing, poor conditioning, abusive or inappropriate training techniques, lunging, poor riding skills, poor hoof care, and improper shoeing. These elements should always be evaluated when attempting to determine the cause of an injury or change in temperament. Poorly fitting

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tack, unbalanced or heavy-handed riders, and inappropriate use of training aids (spurs or whips) can result in avoidance or physical damage to the horse. To make a complete assessment, it is often advantageous to observe the horse under tack to determine what factors may be causing or contributing to musculoskeletal or behavior issues. Unsuccessfully managed lameness can result in chronic pain, spread to other areas such as the back,[30] and limit the horse's value and potential welfare. Practitioners should stress the importance of rest and rehabilitation after injury and carefully monitor the client's use and potential abuse of antiinflammatory drugs, over-the-counter medications, and supplements.

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Veterinarian's Responsibility to Patient Welfare

Concurrent with an increase in the number of nonprofit equine rescue organizations and politically powerful lobbying groups devoted to animal welfare, there has been a dramatic increase in the number of legal bills proposed and statutes imposed specific to the welfare of horses. The public's response after a series of high-profile breakdowns and abuses that occurred on Thoroughbred tracks and at other competitive horse events in the United States has placed veterinary practices engaged in servicing these sectors and others in the horse industry under intense scrutiny. As horse owners become more sensitive to these issues, veterinarians are expected to exercise careful handling of their patients so as not to cause undue pain or discomfort in the eyes of their owners or other onlookers.

Few veterinarians would challenge the idea that an abusive procedure such as “soring” of a Tennessee Walking Horse, used solely to improve show ring performance, is unacceptable. However, it could be argued that certain surgical and medical procedures performed with regularity in daily practice may be less obvious but equally suspect. Dispensing or administering steroidal and nonsteroidal medications locally or systemically to horses known to have underlying pathology, thereby enhancing the risk of further physical damage or catastrophic breakdown, could be viewed as a form of neglect of duty or malpractice. Castration in semiconscious horses without the use of local anesthetics[37] and postsurgical analgesics could also be looked upon critically. Surgical procedures such as distal limb neurectomies, done solely to remedy pain so that a horse may fulfill a career goal, can result in further bodily harm to the horse and affect the safety of current or future riders. The use or promotion of procedures such as internal blisters, injection of “off-label” or exotic substances (cobra venom), and electrocautery (pin firing), which not only lack the support of evidence-based medicine[38] but also may result in pain or long-term suffering for the patient, should be carefully evaluated. Requests for certain cosmetic procedures such as tail docking, which is currently illegal in several states, should be seriously justified. The American Association of Equine Practitioners (AAEP) has produced several guideline publications[39-44] specific to various breeds and disciplines to assist equine veterinarians in their management

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and care.

Veterinarians should strive to do the following:

- Achieve balance between protecting the health and welfare of their charges and satisfying the wishes of their clients
- Educate clients who may be unaware of the negative effects that husbandry or training practices impose on the horse's health and psychological well-being
- Direct owners to make informed decisions in the case of chronically ill animals, especially when financial constraints may affect appropriate treatment and quality of life

Horses are sensitive and incredibly compliant creatures. They are particularly vulnerable to many forms of continued physical and psychological abuse, whether done intentionally or unintentionally through ignorance or negligence. Equine veterinarians have a responsibility to protect horses and should make every effort to evaluate patients carefully for signs of inappropriate treatment or cruelty. Evidence of abuse or neglect may be blatantly obvious or less conspicuous initially, so constant surveillance is necessary to determine whether physical or behavioral problems challenge the horse's health and welfare.

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PART 2
Manifestations of Disease

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• CHAPTER 3

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Pain

Suzanne T. Millman, Johann (Hans) F. Coetzee, Consulting Editors

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Introduction

Addressing pain is a key expectation for animal welfare, and large animal practitioners have an important role in educating clients to recognize and respond to livestock pain. Pain is a subjective experience for humans and nonhuman animals; hence, we cannot truly know how it is felt by other individuals. Subjective experiences are challenging in medicine but not unique to veterinary practice. Some techniques used in human medicine, particularly with respect to nonverbal and preverbal patients, can be applied to animals to inform diagnosis and treatment of pain.

Veterinarians have important influence on the attitudes and behavior of livestock producers in regard to pain recognition and pain management. Dairy producers that involve veterinarians in their management decision for disbudding and dehorning protocols are more likely to provide analgesia,[1] and veterinarians that rate pain levels as high are more likely to provide analgesia.[2,3] However, there is little consensus among veterinary practitioners about appropriate pain management, with several surveys indicating that caesarian section and claw amputation are believed to be the most painful conditions in cattle, but opinions differ for severity of castration pain.[4,5] Female[6] and younger[3-5] practitioners rate pain higher than their male and older colleagues. The decision to use analgesics for particular conditions appears to have a dichotomous distribution, with practitioners choosing to use analgesics for all cases or for none.[1,3]

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Diagnosing Pain in Livestock

Pain processing includes sensation and perception. Sensation refers to the lower-level neurologic and biochemical components (nociception), whereas higher cognitive processing, such as interpretation, is associated with perception. A modification to the International Association for the Study of Pain definition of pain was suggested for application to animals: “an aversive sensory experience caused by actual or potential injury that elicits progressive motor and vegetative reactions, results in learned avoidance behavior, and may modify species-specific behavior, including social behavior.”[7] Three functions of nociception include (1) warning the animal of actual damage to its tissues, (2) predicting when tissue damage is likely to occur, and (3) warning conspecifics of the presence of danger.

Sensory information is communicated from nociceptors at tissue levels and modulated through spinal and supraspinal mechanisms. Integration of sensory and emotional components results in varied responses relative to species, ontogeny, and type of insult. Basic motor responses, such as withdrawal, occur in response to acute pain stimuli and are associated with protection from further tissue damage. However, simple withdrawal responses can occur consciously or unconsciously, in awake and anesthetized animals. More organized behavioral responses involving higher cognitive processing include aggression or escape attempts.

Increased pulse, respiratory rate, and tidal volume, pupil dilation, and other physiologic responses occur during pain, but these responses are nonspecific indicators because they also occur during arousal, such as during fear and excitement. Conversely, pain behaviors occur when pain is present versus absent and are absent or decrease when animals are provided with appropriate analgesia treatments versus placebo treatments, such as saline. These pain behaviors can be measured objectively or subjectively. Subjective assessments traditionally have been the most practical for clinical application, but advances in technology provide opportunities for objective assessments outside the laboratory. Pain assessment should be measured across multiple domains, including resting, movement, hyperalgesia, function, and quality of life.[8] Blurring of these constructs within a subjective pain scoring system can result in poor sensitivity and specificity, especially when observers are unclear about which construct is

driving an evaluation.

Clinical Scoring of Visual and Behavioral Indicators of Pain

Pain assessment in veterinary practice has typically relied on subjective global pain scales, with clinicians or animal caretakers providing proxy assessments for the animals in their care. Intangible measures, such as demeanor, attitude, or lethargy, are often cited for clinical scoring of pain but are poorly defined. Hence, challenges are likely to occur with interobserver and intraobserver reliability and interpretation. Subjective scoring systems may be improved when descriptions, photographic images (Fig. 3.1, *A* and *B*), or video clips of behaviors are provided for training clinicians and animal caretakers. A website developed by Dr. Joyce Kent and Dr. Vince Molony, Royal (Dick) School of Veterinary Studies, provides an excellent resource with photographic and video clips of pain responses in several livestock species to common clinical situations ("Guidelines for the Recognition & Assessment of Animal Pain", http://www.link.vet.ed.ac.uk/animalpain/Default.htm).

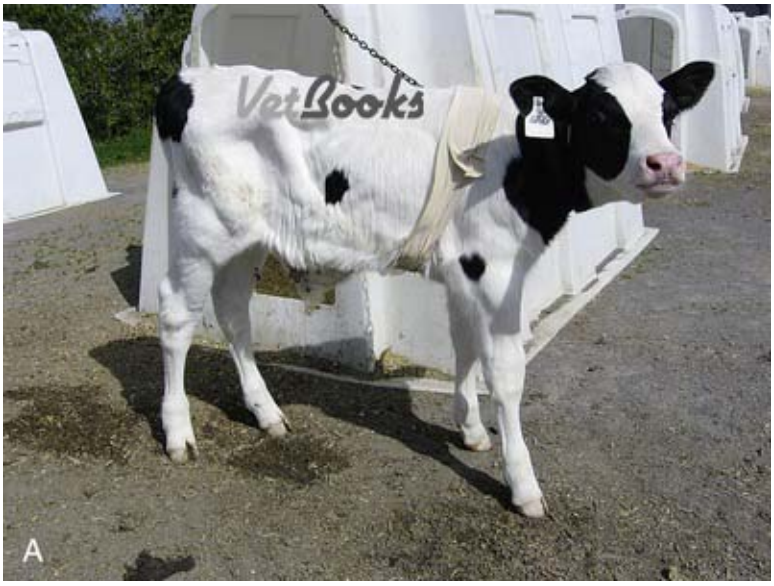




FIG. 3.1 Humans report severe abdominal pain associated with infection with *Cryptosporidium parvum*. Similarly, when compared with healthy calves **(A),** calves infected with *C. parvum* **(B)** display a dull eye, ear rotation, lower head carriage, and back arch postures characteristic of abdominal pain. (Courtesy Dr. Cynthia Todd, University of Guelph.)

Validation of subjective scoring systems for animal subjects is emerging and is a positive step in the evolution of pain research. A standardized facial grimace scale has been validated for assessing pain in mice, including distinct five components of which three are also observed in the human facial pain grimace.[9] Livestock may display similar facial grimace components, such as orbital tightening and ear position (horse,[10] sheep,[11] pig[12]). Since changes in posture are subtle and often characteristic of particular types of pain, it is wise to standardize the visual assessment of the animal, scoring sequentially from head to tail (Table 3.1). Furthermore, changes in motivation and motor patterns are also characteristic of the type and location of pain and should be scored systematically (Table 3.2). Effective pain scoring protocols are critical for evaluating the effectiveness of interventions and determination of humane endpoints when alleviation of pain cannot be achieved. Scoring of affective states, such as depression, can be refined with transparency regarding the responses recorded and use of specific tests to evoke behavioral responses (Table 3.3). Subjective pain scoring is most refined in terms of lameness and locomotion scoring, with excellent training resources available for bovine and equine practitioners and caretakers. Locomotion scoring systems that provide detailed descriptions of the observable changes in gait and allow observers to

score components of the gait separately have been validated for identifying cows with severe hoof lesions[13] and cows that have received a local anesthetic.[14]

TABLE 3.1

Postures Associated With Different Acute, Visceral, Abdominal Pain and Chronic, Somatic Lameness Pain in Livestock

Location	Abdominal Pain	Lameness Pain
Head	Dull, sunken eye (chronic) Wild, distracted eye (acute) Lip curl Wrinkled muzzle/grimace Contracted jaw tone Contracted ear position (acute) Drooped ear position (chronic)	
Neck/back	Lowered head carriage Neck extension Arched back	Arched back
Abdomen	Tucked abdomen Prolonged urination stance	
Limbs	Standing with hind limb extension Lying with hind limb extension Treading hind limbs	Uneven weight bearing Treading hind limbs Crossed forelimbs[a] Perching[b] Increased abduction/adduction of limbs
Tail	Tail tuck Prolonged urination stance	

[a]Standing with crossed forelimbs results in weight transferred from the inner claw to the outer claw.

[b]Perching occurs in dairy stalls when weight is transferred to the rear hooves, which are placed in the gutter anterior to the stall while fore hooves are placed in the stall.

TABLE 3.2

Behavior Changes Associated With Different Acute, Visceral, Abdominal Pain and Chronic, Somatic Lameness Pain in Livestock

Behavior	Abdominal Pain	Lameness Pain
Redirected and pain avoidance behaviors	Bruxism (teeth grinding) Wound licking Wound scratching Self-mutilation (equine) Rolling (equine) “Looking”—nose to flank Pawing, stamping (fore) Kicking, stamping (hind) Abnormal gait	Abnormal gait Crawling on knees Difficulty turning

	Crawling on knees Tail flicking	
Activity	Statue standing[a] Increased lying Increased standing inactive Hyperactivity, restlessness Frequent standing/lying transitions Reduced grooming Reduced exploration	Increased standing inactive Increased lying Reduced standing/lying transitions Abnormal standing/lying transitions Reduced exploration
Feeding	Anorexia (acute) Reduced feeding duration Intermittent eating Intermittent drinking Playing with water Cessation of rumination	Reduced feeding duration
Social interactions	Aggression Social isolation Reduced play	Reduced play
Vocalizations	Distress calls Groaning Grunting Snorting Sneezing (goats)	

[a]Standing immobile in a fixed, rigid posture.

TABLE 3.3

Example of Clinical Scoring Form for Transparency and Consistency in Subjective Assessment of "Demeanor" or "Depression"

Parameter	Yes	No	N/A	Comments
Does the animal orient toward handler entering pen?				
Does the animal approach a novel object placed in its pen?				
Does the animal approach the feed bunk when fresh feed is provided?				
Does the animal require encouragement to consume daily ration?				
Does the animal require encouragement to walk to the milking parlor?				
Etc.				

Pain behavior responses can also be measured objectively, particularly in experimental applications where detailed observations are collected during live observations or more frequently from video recordings. In ethology, the science of animal behavior, a key component of research methodology is development of an appropriate ethogram, which consists of a list of definitions for mutually exclusive behaviors.[15] For transparency and to avoid inherent bias associated with interpretation, definitions that focus on motor patterns or movements that

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an animal performs are preferred over those described in terms of an underlying motivation. Pain behaviors can then be quantified in terms of frequency and duration of occurrence. For example, head-related behaviors, such as head shaking, rubbing, and scratching, occur at greater frequencies following disbudding surgery[16] and ocular injury.[17] Experiments can also be designed to provoke behavior and quantified in terms of latency to respond and thresholds of stimulus required for response. Although pain-specific behaviors are relatively straightforward to observe and quantify when detailed definitions are provided, manual collection of behavior data is labor intensive and difficult to record because these behaviors occur at low frequencies even when the animal is undisturbed by activity in the barn.

New technologies are emerging for automated data collection, such as accelerometers for frequency and duration of activity and resting behavior (Fig. 3.2), and show promise for detecting behavioral changes associated with lameness.[18] Accelerometers are increasingly being incorporated into dairy management software programs, with changes in activity flagged for further investigation by the stockperson. Lameness detection can be aided by kinematic analysis during locomotion[19,20] and pressure-sensing equipment incorporated in stalls to detect differences in weight bearing during standing and locomotion.[20] During acutely painful procedures, livestock typically struggle or attempt to escape, and these behaviors can be quantified using exit velocity, latency for the animal to break an infrared beam, strain gauges to measure exertion forces on the restraint chute, or by software analysis of head movements captured with videoimages.[21]



FIG. 3.2 Accelerometers quantify activity when affixed to the limb and may provide useful data for identifying lame cows. The output includes duration and frequency of standing and lying bouts, as well as number of steps. For some devices, output is integrated into dairy management software to alert the stockperson when changes in activity patterns occur. (Courtesy Dr. Janet Higginson Cutler, University of Guelph.)

Similarly, in some livestock species distress calls are performed during painful procedures and can be discriminated from other vocalizations, such as contact calls, by the increase in rate, pitch, and volume.[22] Distress calls given during painful procedures are greater in intensity than other vocalizations, such as short calls at lower fundamental frequencies that are emitted from cattle when isolated.[23] However, vocalizations may not be a robust measure of pain for cattle, since they rarely vocalize, and propensity to vocalize is associated with breed, perhaps due to variations in excitability.[24] Conversely, goats are very expressive vocally, despite also being a prey species.

Nociceptive Threshold Tests

Several standard tests have been developed for assessing nociception in animal models for biomedical research, including von Frey filaments for mechanoreceptors and the Hargreaves' or plantar test for thermoreceptors. Increasingly, nociception tests are being modified or applied to livestock to ask about the sensory discriminatory perception of pain. To tease apart pain from other aversive experiences, such as fear or distress, attenuation of the response should occur when relevant analgesia is applied. Where possible, local

anesthesia is preferable to opioids or sedatives due to confounding that results from direct impacts of the latter on animal behavior.

Pressure algometry is an example of a mechanical nociception test that has proven useful for assessing pain in livestock (Fig. 3.3). This tool measures the amount of force applied to a surface, and painful thresholds are determined using a withdrawal response. When applied around the horn buds, calves display significantly lower nociception thresholds following disbudding when compared with pressure tolerated on the day before surgery. Furthermore, calves display less pressure sensitivity when treated with nonsteroidal antiinflammatory drugs (NSAIDs), including meloxicam,[16] firocoxib,[25] and carprofen.[26] Pressure algometry data suggest that the duration of postsurgical pain is greater than estimates using neuroendocrine markers because significantly lower nociception thresholds are observed for 3 days following surgery relative to baseline values.[16] Differences in mechanical nociceptive thresholds can also be used to identify lameness, with responses mitigated by NSAIDs.[27] Pressure algometry appears to be a robust tool, with potential for clinical application because it is cheap and easy to use and differences in response are often large.



FIG. 3.3 Mechanical nociception threshold test using pressure algometry to test pain sensitivity at a sole ulcer lesion. Cattle tolerate less pressure before displaying an avoidance (hoof withdrawal) response when the pressure algometer tip is applied to the sole ulcer compared with normal sole. (Courtesy Dr. Janet Higginson Cutler, University of Guelph.)

Thermal nociception threshold is quantified by the amount of time (latency) for an avoidance response to a radiant or laser thermal stimulus. A CO_2 laser thermal stimulator was found to provoke a foot lift or kicking withdrawal response when skin temperature reached 45°C to 55°C, and because CO_2 laser stimulators use a monochromatic, long-wavelength infrared source of radiation, absorption is not affected by pigmentation of the skin.[28] Standard operating procedures for all thermal nociception tests require the skin surface to be free of hair, manure, and moisture, and safety precautions, such as maximum duration of stimulus application, to avoid tissue damage on different skin surfaces.[29] A ceiling value of 20 seconds was successfully used as a safety precaution when a radiant thermal nociception stimulus (constant 80% beam intensity, 200C) was used during a lameness study in sows (Fig. 3.4).



FIG. 3.4 Thermal nociception threshold test using a radiant thermal stimulus to test pain sensitivity at the coronary band on a lame sow. Effective analgesia is evident by increased tolerance of the thermal stimulus and corresponding greater latency for an avoidance (leg withdrawal) response. (Courtesy Ms. Kathleen Tapper, Iowa State University.)

Pain Aversion Tests

Classical pain tests that quantify reflexive nociceptive withdrawal responses to mechanical or thermal stimuli provide information about the sensory-discriminatory aspects of pain, but not the affective (emotional) components. There is some evidence that some species, such as chickens and sheep, choose to

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self-medicate to avoid painful conditions. Conditioned avoidance tests are based on an animal's ability to recall an association of a stimulus, such as a location or a person, with a previous aversive experience. Conditioned place avoidance is commonly observed where livestock have previously experienced painful interventions, such as branding, dehorning, or castration. Similarly, cattle may associate the appearance or odor of a veterinary practitioner with previous aversive experience, resulting in difficulties with handling. However, it is often difficult to tease apart aversion arising due to experiences associated with pain versus fear. This is especially problematic with extensively managed livestock that are unfamiliar with handlers and equipment. In several species, electrical stimulation results in startle and withdrawal reflexive behaviors, as well as higher pain processes associated with aggression and avoidance behaviors. However, it is used in livestock to facilitate movement (electric prods), for restraint (electroimmobilization), and for semen collection (electroejaculation). Aversiveness of electroimmobilization is evident by conditioned aversion responses by livestock, resulting in reluctance to move through handling chutes or avoidance of particular handlers.[30] These results have been used to advise against the practice of electroimmobilization, such as animal welfare policies of the American Veterinary Medical Association and Canadian Veterinary Medical Association.

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Pharmacologic Interventions to Treat Livestock Pain

Negative public perception of pain associated with routine animal management practices such as dehorning and castration is mounting, with increasing call for the development of practices to relieve pain and suffering in livestock. Preemptive analgesia can be applied in advance of the painful stimulus, thereby reducing sensitization of the nervous system to subsequent stimuli that could amplify pain. Agents that could be used to provide preemptive analgesia include local anesthetics, NSAIDs, opioids, α2-agonists, and *N*-methyl *D*-aspartate receptor antagonists. However, less than 20% of U.S. veterinarians currently report using analgesia routinely at the time of dehorning and castration.[31]

The capacity to experience pain is considered to have a protective role by eliciting behavioral responses aimed at reducing further tissue damage and enhancing wound healing. However, persistent pain syndromes offer no biological advantage and are associated with suffering and distress. Pathologic pain states in cattle occur as a result of tissue damage, nerve damage, and inflammation and are frequently associated with pain hypersensitivity. Pain hypersensitivity manifests as hyperalgesia (exaggerated responses to painful stimuli) and allodynia (pain resulting from normally innocuous stimuli).

Hyperalgesia has been reported to persist in dairy cattle and lame sheep for at least 28 days after the causal lesion has resolved.[32,33] Consequently, chronic pain associated with lameness is considered one of the most significant welfare concerns in dairy cows. Inflammatory pain associated with lameness responds modestly to treatment with NSAIDs,[34,35] but neuropathic pain (due to nerve damage or neuronal dysfunction) is considered refractory to the effects of NSAIDs and many opioid analgesics. Therefore there is a need to identify novel drugs and drug targets for alleviating chronic pain of neuropathic origin in animals.

Challenges Associated With Providing Analgesia in Food Animals

Several challenges are associated with providing effective analgesia in food

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animals in the United States. Firstly, before July 2017, there were no analgesic drugs specifically approved for the alleviation of pain in livestock. At the time of writing this chapter, only one compound (Banamine Transdermal, Merck Animal Health) is approved in the United States for the control of pain associated with foot rot. Administration of any drug to alleviate pain associated with other conditions therefore constitutes extralabel drug use (ELDU).[36] Under the Animal Medicinal Drug Use Clarification Act of 1994 (AMDUCA), ELDU is permitted for relief of suffering in cattle provided specific conditions are met. These conditions include that (1) ELDU is allowed only by or under the supervision of a veterinarian, (2) ELDU is allowed only for U.S. Food and Drug Administration (FDA)-approved animal and human drugs, (3) ELDU is only permitted when the health of the animal is threatened and not for production purposes, (4) ELDU in feed is prohibited, and (5) ELDU is not permitted if it results in a violative drug residue in food intended for human consumption. Therefore use of an analgesic to alleviate pain associated with castration in calves in the United States would be required by law to comply with these regulations.

A second challenge to providing effective analgesia in cattle is that there is often a delay between the time of drug administration and the onset of analgesic activity. For example, local anesthetics require 2 to 5 minutes before a maximal effect is achieved. This may slow animal processing, as producers must wait for local anesthesia to take effect. This delay may serve as a disincentive for them to provide routine preemptive analgesia. Furthermore, the requirement for large numbers of animals to be processed quickly may result in procedures being initiated before optimal analgesia is achieved. A third challenge is that the route or method of analgesic drug administration may require specialized training and expertise or may be hazardous to the operator. Therefore administration requires the animal to be adequately restrained and the operator to be proficient in intravenous administration. Similar issues are encountered with epidural analgesic drug administration and administration of local anesthesia into the scrotum. The latter procedure is also considered especially hazardous by many livestock handlers. In addition, the majority of analgesic drugs that are available in the United States have a short elimination half-life, necessitating frequent administration in order to be effective.[36] This increases the stress on the individual animal and increases labor and drug costs.

In addition to the regulatory considerations discussed previously, certain drug classes such as the opioid and NMDA receptor antagonists are designated as Schedule 3 drugs and are subject to regulation by the U.S. Drug Enforcement

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Administration (DEA). Therefore administration of these compounds to provide preemptive analgesia is restricted to use by licensed veterinarians. Finally, the cost associated with providing preemptive analgesia contributes to the reluctance of producers to adopt these measures, especially because there is no perceived economic benefit for doing so. It may also be difficult for producers and veterinarians to determine if analgesic compounds are effective because cattle may not show overt signs of pain and distress. Thus determining the need for analgesia and the dose, route, duration, and frequency of drug administration in cattle can be especially challenging.

Analgesic Compounds and Their Effect in Cattle

Pain perception involves the transduction of chemical signals at the site of injury into electrical energy (Fig. 3.5). This is followed by transmission of the electrical signal via nerve fibers up the spinothalamic tracts where modulation may occur in the dorsal horn. Finally, the impulse is projected to the brain where pain perception occurs. The initial response to a noxious stimulus is typically brief, well localized, and somewhat proportional to the intensity of the insult. The second phase of the response is prolonged, diffuse, and often associated with hypersensitivity around the point where the initial stimulus was applied. This effect may lead to persistent postinjury changes in the central nervous system resulting in pain hypersensitivity or central sensitization (“wind-up”). These effects lead to hyperalgesia (increased pain from previously painful stimuli) and allodynia (a previously nonpainful stimulus now produces pain).

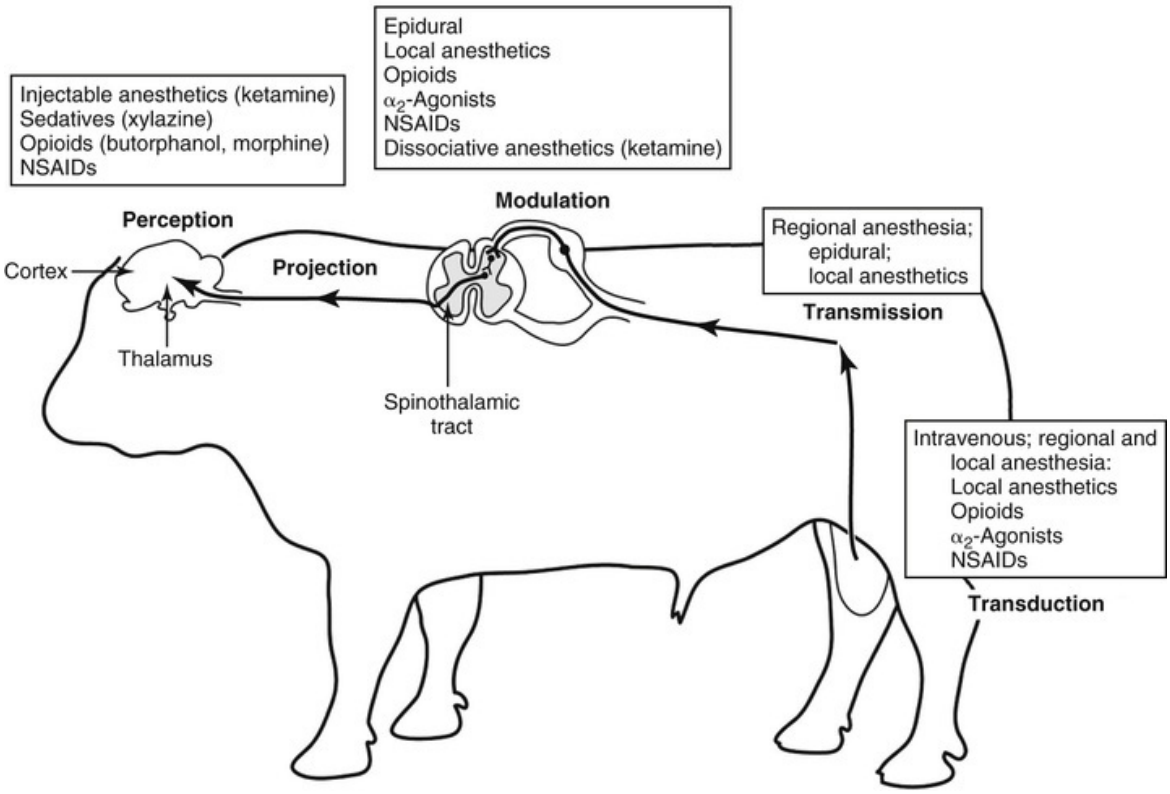


FIG. 3.5 Schematic representation of the nociceptive pathway in cattle indicating the anatomic location of target receptors for analgesic drug activity. (Courtesy of Mal Hoover, Kansas State University.)

Surgery-induced pain and central sensitization consist of two phases: an immediate incisional phase and a prolonged inflammatory phase that arises primarily due to tissue damage. The goal of administering analgesic compounds before castration is to mitigate both the incisional and inflammatory phase of the pain response. Effective analgesia therefore requires a multimodal approach using compounds that act on different receptor targets along the nociceptive pathway (Fig. 3.1). This can be achieved through a combination of local anesthesia, NSAIDs, and sedative-analgesic combinations of opioids, α2-agonists, and *N*-methyl *D*-aspartate receptor antagonists.

Local Anesthesia

Local anesthetics are the most commonly prescribed preemptive analgesic drugs used in food animal practice.[37] These compounds produce reversible loss of sensation in a localized area without causing loss of consciousness. Local anesthetics enter and block open sodium channels of nerve cells and prevent

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generation and propagation of nerve impulses. Repeatedly stimulated nerve cells are therefore more susceptible to the effects of local anesthetics. Furthermore, unmyelinated nerve fibers that transmit pain signals are preferentially blocked by local anesthetics compared with myelinated fibers that are responsible for pressure sensation and motor activity. The quality of local anesthesia in an acidic environment, such as infected tissues, is often poor because these compounds are weak bases that must dissociate in an alkaline environment to exert their effect. Lidocaine has a fairly rapid onset of activity (2 to 5 minutes) and an intermediate duration of action (90 minutes). Local anesthetic administration into the epidural space has also been shown to provide regional analgesia of the perineal region commencing 5 minutes after administration of 0.2 mg/kg lidocaine and lasting 10 to 115 minutes.[37]

Compounds That Potentiate Local Anesthesia

Magnesium Sulfate ($MgSO_4$).

Magnesium sulfate has been combined with lidocaine to potentiate the local anesthetic effects.[38] Magnesium competitively antagonizes NMDA receptors and their associated ion channels in the same manner as ketamine, thus reducing central sensitization caused by peripheral nociceptive stimulation. It was recently reported that the combination of lidocaine with magnesium sulfate produced epidural analgesia of longer duration than lidocaine with distilled water. In this experiment, local anesthesia with 2% lidocaine solution administered at 0.22 mg/kg was potentiated with 1 mL of 10% magnesium sulfate solution. Magnesium also reportedly has antinociceptive effects in animals and humans after systemic administration.[39] These effects are considered to be associated with the inhibition of calcium influx into the cell and antagonism of NMDA receptors. Further studies with respect to the safety and efficacy of magnesium augmentation of local anesthesia are needed before this technique can be recommended.

Sodium Bicarbonate.

Commercial preparations of lidocaine are prepared as acidic solutions to promote solubility and stability. The addition of sodium bicarbonate before administration significantly reduces pain produced by infiltration of lidocaine in humans, probably due to the reduced acidity of the commercial formulation. The

addition of sodium bicarbonate to lidocaine has also been found to reduce the time taken for the nerve block to take effect and enhance analgesia in humans. However, the addition of bicarbonate may decrease the duration of the block. A 10 : 1 ratio of 2% lidocaine with 8.4% sodium bicarbonate is recommended for optimal buffering of lidocaine. Thus 1 mL of commercially available 8.4% sodium bicarbonate solution can be added to 10 mL of 2% lidocaine immediately before administration in order to buffer the acidic effects of the formulation.

Alternatives to Local Anesthesia

Ethanol injection demyelinates nerve fibers and may be a promising long-acting local anesthetic for use at the time of disbudding.[40] When ethanol was administered as a corneal nerve block before disbudding, calves failed to display increased pain sensitivity in response to pressure algometry relative to their baseline values. Furthermore, ethanol-treated calves differed significantly from calves treated with the local anesthetic lidocaine at 1-hour post disbudding, when the lidocaine is assumed to be wearing off. Ethanol blocks appeared to desensitize the site of cautery dehorning for longer than 83 hours, at which time the experiment concluded. In this experiment, 2 mL of 100% ethanol were injected at the site of the corneal nerve block. However, more than half the calves subjected to ethanol anesthesia required a second injection to achieve complete loss of sensation in one or both horns. Further studies with respect to the safety and efficacy of ethanol blocks for local anesthesia are needed before this technique can be recommended.

Nonsteroidal AntiInflammatory Drugs.

NSAIDs produce analgesia and antiinflammatory effects by reducing prostaglandin (PG) synthesis through inhibition of the enzyme cyclo-oxygenase (COX) in the peripheral tissues and central nervous system. COX exists in two isoforms. COX-1 is constitutively expressed in both peripheral and central nervous systems, although expression is enhanced by pain and inflammatory mediators. COX-2 is ubiquitous in the CNS but only becomes the major enzyme for PG synthesis after induction by factors released during cell damage and death. It takes 2 to 8 hours for maximal COX-2 mRNA expression to occur in the peripheral tissues, therefore initial release of PG is primarily due to COX-1. PG in the peripheral tissues lowers the activation threshold of sensory neurons and may initiate nociceptive activity. PG also works in concert with substance P,

histamine, calcitonin gene-related peptide (CGRP), and bradykinin to lower the firing threshold of sensory nerves and produce inflammation. Therefore NSAIDs that inhibit COX-1 may have a more immediate impact on pain by inhibiting PG production in the periphery than COX-2 selective compounds. However, NSAIDs that inhibit COX-1 may be associated with increased risk for adverse gastrointestinal and renal effects.

Spinal PG, notably PGE_2, is responsible for increased excitability of the dorsal root ganglia leading to centrally mediated hyperalgesia. Given that COX-2 is constitutively expressed in the CNS, inhibition of spinal PGE_2 production by NSAIDs that inhibit COX-2 may be an important mechanism in preventing the establishment of hyperalgesia. The effect of NSAIDs on both central and peripheral PG synthesis suggests that these compounds have an important role in multimodal analgesic protocols.

The dose and pharmacokinetic parameters of the commonly used NSAIDs in the United States are summarized in Table 3.4.

TABLE 3.4

Nonsteroidal Antiinflammatory Compounds Available for Use in Cattle

Drug	Approved Species	Indications	Dose (Cattle)	$T_{1/2}$	Withhold Period
Flunixin meglumine	Cattle, horses, and pigs	NSAID—antipyretic, antiinflammatory	IV 2.2 mg/kg Topical 3.3 mg/kg	3-8 hours	IV Meat—4 days Milk—36 hours Topical Meat—8 days
Phenylbutazone	Horses and dogs	NSAID—anti-inflammatory	4 mg/kg IV ONLY!	40-55 hours	Not approved in cattle in the USA
Ketoprofen	Horses and dogs	NSAID—anti-inflammatory	3 mg/kg IV, IM	0.42 hours	Not approved in cattle in USA
Aspirin	No FDA approval Horses and cattle	NSAID—reduction of fever Relief of minor muscle aches and joint pain	50-100 mg/kg PO Oral F < 20%	0.5 hours (IV salicylate)	No formal FDA approval Not for use in

					lactating cattle
Carprofen	EU approval in cattle Dogs	NSAID—adjunctive therapy of acute respiratory disease and mastitis	1.4 mg/kg bodyweight IV or SC	Age Dependent <10 weeks: 49.7 ± 3.9 hours (R−) and 37.4 ± 2.4 hours (S+) Adult cows; 30.7 ± 2.3 hours	Not approved in cattle in USA
Meloxicam	EU and Canadian approval in cattle Dogs and cats	NSAID—adjunctive therapy of acute respiratory disease; diarrhea and acute mastitis (Europe)	0.5 IV, SC 0.5-1 mg/kg PO	27 hours (range: 19.97-43.29 hours)	Not approved in cattle in USA

IV, Intravenous; *PO,* per os/oral; *SC,* subcutaneous.

Flunixin Meglumine.

Flunixin is a highly substituted derivative of nicotinic acid. Currently flunixin meglumine is the only NSAID approved for use in cattle in the United States.[37] The plasma elimination half-life of flunixin after IV administration is reported to be 3 to 8 hours. Following a single intravenous dose of 2.2 mg per kg of body weight (mg/kg), plasma concentrations decreased from 16.16 ± 5.28 µg/mL to 1.22 ± 0.16 µg/mL in 2 hours and reached 0.5 ± 0.02 µg/mL by 30 hours.[41] A peak concentration (Cmax) of 0.9 ± 0.05 µg/mL occurred at 3.5 ± 1.0 hours (T_{max}) after a single oral dose of 2.2 mg/kg with an estimated half-life of 6.2 hours and bioavailability of 60%. Therefore once-daily administration is likely required to maintain effective plasma drug concentrations. Although this drug class is recognized as having analgesic properties, IV flunixin is only indicated for control of fever associated with respiratory disease or mastitis and fever and inflammation associated with endotoxemia, rather than for control of pain. Studies demonstrating the analgesic effects of flunixin administered alone at the approved dose of 2.2 mg/kg IV are deficient in the published literature. Use of flunixin meglumine is further complicated by the requirement for intravenous administration, which is more stressful on the animal and involves more skill and training on the part of the operator. Several reports have suggested that the IM administration of flunixin may result in significant myonecrosis and tissue residues.[37]

In July 2017, a formulation of flunixin meglumine for systemic absorption

following topical administration was granted FDA approval for the control of pain associated with foot rot in beef cattle. The mean bioavailability of topical flunixin is 48% (range: 34% to 61%).[42] It is noteworthy that the mean half-life for topical flunixin was 6.42 hours (range 5.22 to 9.76 hours) compared with 4.99 hours (range 4.37 to 5.82 hours) after IV administration. The C_{max} following topical application of flunixin was 1.17 µg/mL, and the time to maximum concentration was 2.14 hours. These data suggest that flunixin is rapidly absorbed and has longer plasma elimination half-life after topical administration compared with IV administration. It has also been reported that administration of flunixin meglumine significantly reduced PGE_2 concentrations in bovine exudate from 8 to 48 hours after treatment following an induced inflammation.[43]

Clinically, 6- to 8-week-old Holstein calves that were treated with topical flunixin meglumine without local anesthesia at the time of dehorning were found to tolerate more force applied to a site adjacent to the horn bud at 48 hours after treatment.[44] Furthermore, serum cortisol concentration was lower in treated calves compared with untreated dehorned calves at 90 minutes after the procedure. These data suggest that topical flunixin may be a convenient and effective analgesic when administered at the time of a painful procedure.

Phenylbutazone.

Phenylbutazone is not approved for use in cattle in the United States, although it has been used in veterinary medicine for more than 50 years.[45] The pharmacokinetics of phenylbutazone is characterized by a slow clearance and longer terminal half-life compared with other NSAIDs. The oral bioavailability of phenylbutazone ranges from 54% to 69% with peak plasma concentrations achieved in 8.9 to 10.5 hours.[46] Phenylbutazone has been associated with rare but fatal blood dyscrasias, including aplastic anemia, leukopenia, agranulocytosis, thrombocytopenia, and deaths in humans. In light of these potential adverse effects associated with exposure to phenylbutazone, the FDA has issued an order prohibiting the extralabel use of phenylbutazone animal and human drugs in female dairy cattle 20 months of age or older. There is also a zero tolerance for phenylbutazone residues in edible tissues from any class of animal. Use of phenylbutazone as an analgesic in food animals is therefore strongly discouraged.[36]

Ketoprofen.

Ketoprofen is a member of the propionic acid class of NSAIDs. Ketoprofen has a short plasma elimination half-life of 0.42 hours in adult cattle, making it less attractive for use as a preemptive analgesic.[47] Although it has been demonstrated that concentrations of ketoprofen are higher in inflammatory exudates than plasma, 80% of a parenteral dose is reportedly eliminated in the urine within 24 hours of administration.[48] Therefore multiple doses of ketoprofen will likely be required to maintain adequate analgesic concentrations.

Ketoprofen is approved in the European Union and Canada for the alleviation of inflammation and pain associated with arthritis and traumatic musculoskeletal injuries and as an adjunctive therapy for the alleviation of fever, pain, and inflammation associated with acute clinical mastitis.[48] The recommended dose in cattle is 3 mg per kg of body weight by intramuscular or intravenous injection, every 24 hours for up to 3 days. Ketoprofen is commonly used in small animal and equine medicine in the United States; however, there are currently no approved formulations for use in livestock.[36]

Salicylic Acid Derivatives.

Salicylic acid derivatives, including aspirin (acetylsalicylic acid) and sodium salicylate, were the first NSAIDs to be used in modern medicine and are still widely used for their analgesic, antipyretic, and anti-inflammatory properties. Although the veterinary forms of aspirin are extensively marketed with label indications for the treatment of fever, inflammation, and pain relief, these have never been approved by the FDA Center for Veterinary Medicine for such indications.[49] Therefore the legality of using salicylic acid derivatives in cattle is questionable because these are technically compounded products.

Aspirin elimination half-lives after oral administration range from approximately 4 hours after oral administration in cattle to approximately 38 hours in cats.[49] The slow absorption rate after oral administration demonstrated in adult dairy cows is evident in the difference between elimination half-times for IV sodium salicylate (0.54 ± 0.04 hours)[50] and oral acetylsalicylic acid (3.70 ± 0.44 hours).[51] The elimination half-life is longer after oral administration of aspirin because the rumen acts as a slow-release reservoir for aspirin absorption. The low volume of distribution (0.24 ± 0.02 L/kg) is indicative of limited distribution to tissues. It is noteworthy that salicylic acid derivatives are not

associated with clotting deficits in cattle.

Carprofen.

Carprofen is a member of the propionic acid class of NSAIDs.[52] The relative antiinflammatory, analgesic, and antipyretic activity of carprofen is reported to be greater than phenylbutazone or aspirin in calves.[53] Carprofen is approved in the European Union as an adjunct to antimicrobial therapy to reduce clinical signs in acute infectious respiratory disease and acute mastitis in cattle. The recommended dose for SC or IV administration is 1.4 mg/kg body weight. Carprofen is commonly used in small animal medicine in the United States, but there are currently no approved formulations for use in livestock.[36]

Meloxicam.

Meloxicam is an NSAID of the oxicam class that is approved in the European Union for adjunctive therapy of acute respiratory disease, diarrhea, and acute mastitis when administered at 0.5 mg/kg IM or SC.[54] It has been shown that 0.5 mg/kg meloxicam IM combined with a cornual nerve block reduced serum cortisol response for longer compared with calves receiving only local anesthesia before cautery dehorning.[16] Furthermore, calves receiving meloxicam had lower heart rates and respiratory rates than placebo-treated control calves over 24 hours post dehorning. It was recently reported that meloxicam administered IV at 0.5 mg/kg mitigated the onset of pain responses as measured by heart rate variability and eye temperature, compared with administration of a cornual nerve block alone.[55] We also observed that meloxicam administered at 0.5 mg/kg IV before dehorning in 16-week-old calves reduced plasma substance P concentrations and improved weight gain over 10 days compared with untreated controls.[56] These reports demonstrate that administration of meloxicam before dehorning at 0.5 mg/kg IV or IM may be effective at alleviating pain and distress associated with painful procedures in cattle.

Meloxicam (20 mg/mL) is approved for use in cattle in several European countries with a 15-day meat withdrawal time and a 5-day milk withdrawal time after administration of 0.5 mg/kg IM or SC.[54] An oral meloxicam suspension (1.5 mg/mL) and injectable formulation (5 mg/mL) are approved in the United States for the control of pain and inflammation associated with osteoarthritis in dogs. Furthermore, an injectable formulation (5 mg/mL) is approved for the

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control of postoperative pain and inflammation in cats. The pharmacokinetics of meloxicam after oral and IV administration to cattle have recently been described.[57] A mean peak plasma concentration (C_{max}) of 3.10 ug/mL (range: 2.64 to 3.79 ug/mL) was recorded at 11.64 hours (range: 10 to 12 hours) with a half-life ($T_{½}$ λz) of 27.54 hours (range: 19.97 to 43.29 hours) after oral meloxicam administration. The bioavailability (F) of oral meloxicam corrected for dose was 1.00 (range: 0.64 to 1.66). These findings indicate that oral meloxicam administration could be an effective and convenient means of providing long-lasting analgesia to ruminant calves. Several inexpensive generic tablet formulations containing meloxicam (7.5 and 15 mg) have recently been approved for relief of signs and symptoms of osteoarthritis in human medicine. In the absence of specific FDA analgesic approvals for conditions other than foot rot in cattle, use of oral meloxicam tablets for alleviation of pain could be considered under AMDUCA.

Sedative-Analgesic Drugs.

Opioids, α_2-adrenergic agonists, and *N*-methyl *D*-aspartate (NMDA) receptor antagonists are the most commonly used sedative analgesic compounds in veterinary medicine. These compounds may act synergistically and are therefore increasingly coadministered. A recent survey of Canadian veterinarians found that respondents who did use an analgesic at the time of castration used xylazine (>50% of respondents) more frequently than lidocaine (<30% of respondents).[3] Administration of local anesthetics into the testicles is considered by some to be dangerous and time consuming with unpredictable efficacy, especially when circumstances do not allow sufficient time for maximal anesthesia to take effect.[3] Sedative-analgesic compounds may replace the need for intratesticular anesthetic injection and thus enhance animal well-being and operator safety. A subanesthetic combination of xylazine, administered at 0.02 to 0.05 mg/kg and ketamine at 0.04 to 0.1 mg/kg given IV or IM (“Ketamine Stun”) is reported to provide mild sedation without recumbency in cattle.[58,59] Butorphanol (0.01 mg/kg) or morphine (0.05 mg/kg) may be included for enhanced analgesic effects.[58]

Opioid Analgesics.

The analgesic effects of opioids are associated with binding to spinal and

supraspinal mu (μ), kappa (κ), and sigma (δ) receptors. Drug binding decreases propagation of the nociceptive signal by activating receptor-linked potassium channels and inhibiting voltage-gated calcium channels. In addition to producing analgesia, μ receptor activation is associated with respiratory depression, decreased gastrointestinal motility, increased appetite, sedation, euphoria, and nausea. Therefore partial and mixed receptor opioids have been developed with fewer adverse effects and, in some cases, a lower abuse potential than pure μ agonists. There are currently no narcotic analgesics approved for use in cattle in the United States. Opioids are designated as Schedule 3 drugs in the United States and are subject to regulation by the DEA.

Butorphanol is a κ-opioid receptor agonist and either a partial μ agonist or antagonist. The potency of butorphanol is reported to be five to seven times that of morphine, although some authors dispute this. The efficacy of butorphanol is limited to mild and moderate pain, but it is one of the most common narcotic analgesics used in veterinary medicine. The half-life of butorphanol in dairy cows administered 0.25 mg/kg IV was 82 minutes.[60] Peak plasma concentration for butorphanol of 7.07 ± 0.55 ng/mL was observed at 9.5 ± 0.50 minutes after coadministration of 0.025 mg/kg butorphanol, 0.05 mg/kg xylazine, 0.1 mg/kg ketamine IM immediately before dehorning, and castration with a plasma elimination half-life of 71.28 ± 7.64 minutes.[61] In dogs a plasma concentration of 45 ng/mL is considered an effective analgesic concentration, but this has not been confirmed in cattle.

Nalbuphine is a synthetic opioid that is a κ-receptor agonist and a μ-receptor antagonist with similar pharmacologic effects as butorphanol. Nalbuphine has analgesic potency similar to morphine on a milligram basis. The onset of activity of nalbuphine reportedly occurs within 2 to 3 minutes after intravenous administration in humans with a plasma elimination half-life of 5 hours. Duration of activity of 3 to 6 hours has been reported after nalbuphine administration in human clinical studies. Nalbuphine injection may be associated with fewer adverse effects than morphine because κ agonists cause less respiratory depression compared with μ receptor agonists. Furthermore, κ agonists carry a significantly lower risk of dependency because opioid addiction is mediated primarily through activation of the μ receptor. As a result, nalbuphine is presently not scheduled as a controlled substance in most parts of the United States in accordance with the Controlled Substances Act (21 U.S.C. § 812) on the basis of the exclusion detailed in 21 C.F.R. § 1308.12. Therefore, special storage and record keeping are not necessary. The potential for fewer

adverse effects and reduced regulatory restrictions may make nalbuphine an attractive narcotic analgesic option for use in cattle if clinical efficacy were demonstrated.

α_2-Adrenergic Agonists.

α_2-Adrenergic agonists produce profound sedation, chemical restraint, and analgesia in cattle. Activation of α_2-adrenergic receptors inhibits the positive feedback mechanism for release of norepinephrine from the presynaptic nerve endings by reducing calcium conductance. Attenuation of norepinephrine release causes dose-dependent sedation and inhibits the afferent pain pathway. In addition, α_2-adrenergic agonists decrease cardiac output, cause a centrally mediated reduction in respiratory rate, produce muscle relaxation, and depress gastrointestinal motility. Epidural administration of α_2-adrenergic agonists can produce analgesia with minimal sedative and cardiovascular effects compared with IV administration.

Xylazine is the most commonly used α_2-adrenergic agonist used in cattle and is approved in the European Union for IM administration at 0.05 to 0.3 mg/kg. Administration of the lower dose is characterized by a slight decrease in muscle tone, but the ability to stand is maintained. Higher doses cause recumbency, deep sedation, and a degree of analgesia. It is recommended that cattle are fasted before systemic administration of higher doses of xylazine to reduce the risk of rumen tympany and aspiration of rumen contents.

Xylazine epidural has been shown to produce greater perineal analgesia than xylazine given intramuscularly.[62] Xylazine epidural has been proposed as a method of providing sedation and analgesia to facilitate castration in mature bulls.[63] The onset of analgesia following administration of xylazine alone was found to be significantly longer (11.7 ± 1 minute) than the combination of xylazine and lidocaine (5.1 ± 0.9 minutes) and lidocaine alone (4.8 ± 1.0 minutes).[64] The combination of lidocaine and xylazine produced analgesia of significantly longer duration (302.8 ± 11.0 minutes) than xylazine alone (252.9 ± 18.9 minutes) or lidocaine alone (81.8 ± 11.8 minutes). Xylazine induced mild to moderate sedation and ataxia. Ataxia was also noted in cattle receiving lidocaine alone.

N-Methyl *D*-Aspartate Receptor Antagonists.

Ketamine is an *N*-methyl *D*-aspartate (NMDA)-receptor antagonist that produces analgesia and dissociative anesthetic effects when administered at a dose of 2 to 4 mg/kg IV to calves.[65] Ketamine and its active metabolite, norketamine, also bind μ and κ opioid receptors producing analgesia. Data from rats suggest that norketamine contributes to the analgesic effect of ketamine, with a potency that is one third of the parent drug.

Subanesthetic ketamine administered at 0.1 to 1 mg/kg as an IV bolus is effective in managing acute postoperative pain in human medicine. In humans, plasma ketamine concentrations above 4 to 5 μmol/L (1000 ng/mL) are required to produce anesthetic effects, while analgesic effects are associated with plasma concentrations below 1 μmol/L (275 ng/mL) or $^{1}/_{10}$th to $^{1}/_{5}$th of the anesthetic dose. Plasma ketamine concentrations ranging from 40 to 150 ng/mL were associated with analgesia in humans. Our group previously demonstrated that mean plasma ketamine and norketamine concentrations in cattle decreased to below 40 ng/mL and 10 ng/mL after 30 and 60 minutes, respectively, after administration of a subanesthetic combination of xylazine (0.05 mg/kg) and ketamine (0.1 mg/kg).[66] NMDA receptor antagonists are designated as Schedule 3 drugs and are subject to regulation by the DEA.

Future Prospects for Treating Chronic Pain and Central Sensitization in Cattle

Gabapentin.

Gabapentin (1-[aminomethyl] cyclohexane acetic acid) is a γ-aminobutyric acid (GABA) analog originally developed for the treatment of spastic disorders and epilepsy. Studies have reported that gabapentin is also effective for the management of chronic pain of inflammatory neuropathic origin. Although the mechanism of action of gabapentin is poorly understood, it is thought to bind to the α_2-δ subunit of voltage-gated calcium channels acting presynaptically to decrease the release of excitatory neurotransmitters. Efficacy of gabapentin in humans is associated with 2 μg/mL plasma drug concentrations. It has also been reported that gabapentin can interact synergistically with NSAIDs to produce antihyperalgesic effects. We report a mean peak plasma gabapentin concentration (C_{max}) of 3.40 μg/mL (range: 1.70 to 4.60 μg/mL) at 7.20 hours (range: 6 to 10 hours) after oral gabapentin administration to calves at 15

mg/kg.[67] An elimination half-life ($T_{½}$) of 7.9 hours (range: 6.9 to 12.4 hours) was recorded. Oral administration of gabapentin at 15 mg/kg may be associated with plasma concentrations of greater than 2 µg/mL for up to 15 hours. The pharmacokinetics of gabapentin suggests that this compound may be useful in mitigating chronic neuropathic and inflammatory pain in ruminant cattle.

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Summary

The American Veterinary Medical Association veterinary oath was revised in 2011 to include emphasis in the protection of animal welfare and prevention and relief of animal suffering. In addition to diagnosis and treatment of pain discussed in this chapter, practitioners should explore opportunities to prevent and mitigate pain associated with routine surgical procedures through development of herd health protocols that include least painful techniques, training of stockpeople, and scheduling the surgeries to minimize stressors. In addition to pharmacologic interventions, thoughtful consideration of the hospital environment can aid convalescence by providing appropriate social groupings, a comfortable place to rest, and easy access to feed and water.

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• CHAPTER 4

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Alterations in Body Temperature

Marie-Eve Fecteau, Consulting Editor

MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Control of Body Temperature

In mammalian (homeotherm) species, the temperature of the deep tissues of the body—the *core*—remains within a narrow range (within ±1° F), even when exposed to extreme ambient temperature variations. In contrast, the *skin* temperature rises and falls with the temperature of the surroundings, giving it an important role in core temperature regulation. However, because the temperature regulatory mechanisms are not perfect, the core body temperature of even healthy animals can sometimes rise temporarily to as high as 104° F (40° C) when excessive body heat is produced (such as during a strenuous exercise) or, conversely, temporarily fall below 97° F (36° C) when the body is exposed to extreme cold. Maintenance of body temperature is under neuronal control in a negative feedback system. The first mechanism involves warm- and cold-sensitive neurons within the preoptic region of the anterior hypothalamus (POAH), which act similarly to a thermostat with a desired "set point."[1] Temperature sensors are also present in the skin and deep tissues of the body such as the abdominal viscera and around the great veins of the abdomen and thorax.[1] Most of the temperature-sensitive neurons in the skin respond to cold so that environmental temperature changes are detected before they threaten core temperature.[2] It is also for that reason that shivering occurs after exercise as the skin rapidly cools during sweat evaporation, despite the fact that core temperature may be normal or slightly elevated. Those temperature signals produced by the central and peripheral receptors are transmitted to the POAH, which then integrates them and initiates mechanisms to either increase or decrease heat loss or production (Fig. 4.1).[3] It is also important to note that the temperature "set point" varies between species and individuals and that fluctuations in body temperature occur normally throughout the day due to circadian rhythm.[1,4] For example, pigs have a higher temperature "set point" than do sheep, as the former lack hair or fiber. Conversely, dairy cattle that have a high milk production have a lower temperature "set point," as heat production increases with their increased metabolic demand. Temperature "set points" can also be affected by acclimatization to certain ambient temperatures. As such, with heat acclimatization, there is a lower body temperature threshold for sweating, and sweat gland sensitivity and capacity improve.[4]

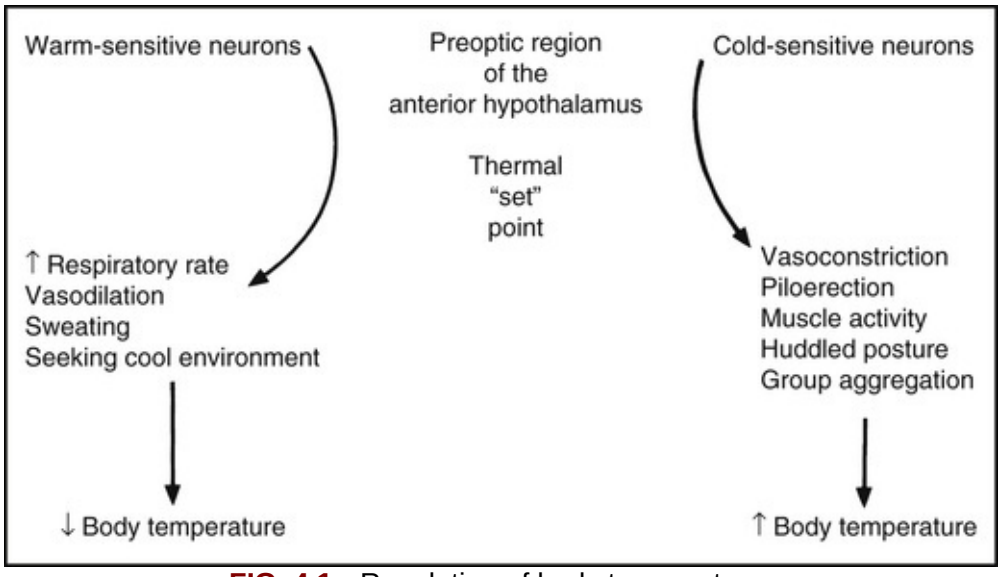


FIG. 4.1 Regulation of body temperature.

Most of the heat produced in the body is generated in the skeletal muscles and deep organs. Muscle activity may range from inapparent contractions to generalized shivering and vary according to the need. Digestion of food also contributes significantly to heat production, and the amount of heat produced per gram of food differs between food categories (carbohydrates, fat, and proteins), with fat producing more than twice as much heat as carbohydrates and proteins.[1] Heat conservation occurs from adrenergic autonomic stimuli to decrease peripheral circulation (vasoconstriction) and cause piloerection. Behavioral means of heat conservation include adopting a "huddled" posture, group aggregation, and seeking a sheltered environment.

Heat loss occurs from conduction, convection, and radiation from body surfaces and by evaporation. Sympathetic vasodilation of cutaneous vessels contributes to surface cooling. As ambient temperature rises, evaporative heat loss becomes more important. In ruminants, evaporative heat loss is mostly confined to the respiratory system, and respiratory rate increases concurrently with temperature. In horses, sweat production and subsequent evaporation have the most important role in heat loss, followed by respiratory tract evaporation. Behavioral responses that contribute to heat loss include seeking shade and wind currents and wading into water.

Conditions of Increased Body Temperature (Hyperthermia)

Body temperature disorders in which the core body temperature set point is unaltered can occur from increased heat production, absorption of heat, or impairment of heat loss. Central nervous system (CNS) disorders that disturb the hypothalamic regulatory center, certain drugs, and metabolic disorders may also cause temperature changes. Regardless of the triggering cause, hyperthermia should be considered a medical emergency, and severely hyperthermic patients require immediate total body cooling, as temperatures above 107° F (41.6° C) may lead to permanent organ damage or death. Cooling options for the hyperthermic patient are discussed later in the “Heat Stroke” section.

Malignant Hyperthermia

Malignant hyperthermia (MH) is a pharmacogenetic disorder of skeletal muscles that presents as a hypermetabolic response to potent volatile anesthetic gases such as halothane, sevoflurane, desflurane, and the depolarizing muscle relaxant succinylcholine and, rarely, in humans, to stresses such as vigorous exercise and heat.[5] The classical signs of MH include marked hyperthermia, tachycardia, tachypnea, increased end-expired carbon dioxide production, increased oxygen consumption, acidosis, hyperkalemia, and muscle rigidity.[5] The pathophysiology of MH involves an uncontrolled release of intracellular calcium from skeletal muscles’ sarcoplasmic reticulum, resulting in sustained muscle contractions, increased oxygen consumption and carbon dioxide production, adenosine triphosphate (ATP) breakdown, and increased glycogen metabolism, which in turn generates heat.[5] Although MH is most common in humans and pigs, it has been reported in horses.[6-9] Of note, MH has also been reported in pot-bellied pigs.[10] A dominant mutation of the ryanodine receptor 1 gene (*RYR1*), which is essential in skeletal muscle excitation-contraction coupling, is the basis of MH in humans, pigs, and dogs.[11] The mutation has also been documented in Quarter Horses with MH and has an estimated prevalence of 1.3% in a random sample of 225 Quarter Horses.[12-13] In all species, MH typically leads to death if it is not recognized and treated early (see also Malignant Hyperthermia, Chapter 42).

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Exercise

During sustained exercise, heat production may exceed the ability of heat loss mechanisms, leading to a stable increase in core body temperature proportional to the intensity and duration of exercise. The elevation in temperature often persists for several hours after exercise, but temperature returns to normal with rest as heat loss mechanisms remain activated. Body temperature increases of greater than 2° C (4° F) above normal during exercise, especially if reached early in exercise, are usually the result of severe environmental conditions and/or failure in heat loss mechanisms. In one study looking at the effect of age on thermoregulation during exercise, old horses reached higher body temperatures faster and had greater sweat losses when compared with young horses.[14] It is proposed that in horses, ageing affects the ability to handle the combined demand of exercise and thermoregulation in part due to a decrease in absolute preexercise plasma volume.[14] Peripheral cooling to augment heat loss should be used to lower body temperature because increases in temperature caused by exercise are unaffected by antipyretic drugs.[15-16]

The intense muscular activity associated with generalized tonic-clonic seizures may, like vigorous exercise, cause a rise in body temperature. If central heat regulatory systems are unaffected by the disease process, body temperatures return to normal no longer than 48 hours after the last seizure.[17] Elevated temperatures that persist for longer periods should prompt investigation into other causes for the increased temperature. Similarly, hyperkalemic periodic paralysis of horses has also been associated with episodes of hyperthermia.[18]

Heat Stroke

When animals are exposed to high ambient temperatures, intense solar radiation, and/or high humidity so that heat load increases at a rate faster than heat can be dissipated, heat stroke may develop.

Heat stroke is more common in ruminants because of their inability to sweat and thus their diminished evaporative ability for heat loss. Sheep with fleece and large dense cattle are especially prone to heat stroke when denied access to shade or adequate water and/or when physical activity is imposed on them. Rectal temperature will often exceed 107° F (41.5° C), and central body temperature may exceed 112° F (44.5° C). Heat stress is a recognized condition of llamas and alpacas that are exposed to high ambient temperature and high humidity.[19]

Normal camelids dissipate heat through evaporation of water through the respiratory system and sweat. In camelids, sweat glands are concentrated in the fleece-free areas of the axillary and inguinal regions. Camelids exposed to extreme heat conditions will seek out cool areas, decrease unnecessary physical activities, and stand or lie in a more upright position to improve sweating efficiency.[20] They can also increase their respiratory rate and open-mouth breathe to help with heat loss through the respiratory system. Risk factors that can predispose animals to develop heat stroke include primary disorders that will render an animal weak or recumbent and obesity.[20] With the peracute form of heat stroke, clinical findings include hyperthermia (often >105° F); tachycardia and/or tachyarrhythmia; recumbency; edema of the ventrum, perineum, and legs; and signs of respiratory distress including open-mouth breathing.[20] Thoracic auscultation typically reveals increased bronchovesicular sounds and crackles suggestive of pulmonary edema.[20] A frothy, blood-tinged oral or nasal discharge can be observed secondary to diffuse vasculitis.[20] Affected animals are likely to die of multiple organ failure if rapid and aggressive treatment is not undertaken.[20] With the more common subacute form (heat stress), affected animals are bright and alert but refuse to stand or have difficulties standing for long periods of time.[20] With this form, the hyperthermia may be only present briefly or intermittently, and affected camelids typically maintain a normal appetite and organ function. A neurologic examination may be difficult to interpret, and clinicians may often rely on the results of ancillary tests to rule out CNS disorders. A leukogram is typically nonspecific and reflective of stress response. Biochemistry will usually reveal increased muscle enzymes, azotemia, hypoproteinemia, hyperlactemia, and metabolic acidosis.[19-20]

Horses continuously exercised in high heat and humidity may also develop heat stroke. Evaporative heat loss from sweating is the most important means of heat loss as metabolic heat production increases during exercise, especially as ambient temperature and humidity increase.[21] Efficiency of evaporative heat loss diminishes when temperature and humidity are high and there is a significant radiation component resulting from strong sunshine.[22] Horses' susceptibility to heat stroke is enhanced if dehydration and electrolyte imbalances occur because of large losses of sweat (see also Exhaustion in Endurance Horses, Chapter 42). Adrenaline and noradrenaline may play a role in the adaptation of horses to thermal stress.[23]

As rectal temperature increases above 107° F (41.5° C), the homeostatic

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mechanisms of temperature regulation fail; peripheral vasoconstriction, decreased blood pressure, and decreased cardiac output occur. The animals are lethargic and have weak, flaccid muscles; prostration and shock occur rapidly. Disseminated intravascular coagulation, liver damage, renal failure, and myocardial necrosis are frequent complications.

The cornerstones of treatment of heat stroke are 1) to decrease the body temperature to normal levels and 2) to support the animal through its convalescent period.[20] First, the animal should be removed from the extreme condition and brought to a cool, shady, and well-ventilated environment. For animals with fleece or heavy hair coat, clipping away the fleece is helpful. Pools of water (such as down cow float tanks or water troughs) are useful in rapidly cooling down camelids and small ruminants. Topical alcohol and water (alcohol baths) are often ineffective at reducing body temperature as they may cause cutaneous vasoconstriction and can inhibit water evaporation from the skin. Administration of cool intravenous fluids may help with both decreasing body temperature and correcting hypovolemia and electrolyte losses. The rate of administration of intravenous fluids should be monitored closely, as animals with heat stroke (particularly camelids) can be prone to developing pulmonary edema. Other methods include administration of chilled water into the stomach or rectum and strategic placement of ice packs over areas with large vessels (neck, axilla, and inguinal regions). The administration of nonsteroidal antiinflammatory drugs is often useless at decreasing body temperature, as it is not a prostaglandin-mediated fever,[20] and may even be harmful to the kidneys of a severely dehydrated animal. Attempts should be made at diagnosing and treating primary disorders that may have predisposed the animal to developing heat stroke, such as a neurologic condition. It is not uncommon for camelids or small ruminants that have survived the acute phase of heat stroke to remain recumbent for an extended period of time following the acute stage of the disease. Basic supportive and nursing care is important for those animals in order to avoid pressure sores and limb contracture.

Anhidrosis

Up to 25% of horses in hot, humid environments lose their ability to sweat and subsequently suffer from hyperthermia as a result of impairment of heat loss.[24] In a more recent study that included more than 4500 horses from 500 Florida farms, the prevalence of anhidrosis was 11% at the farm level and 2% at the

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animal level.[25] Horses in training have been reported to have a higher frequency of anhidrosis, as are horses shipped to hot environments from more temperate regions; however, horses indigenous to hot, humid areas that perform less rigorously or not at all may also develop anhidrosis.[26-27] In addition to hyperthermia, clinical signs are poor performance, total or partial loss of ability to sweat, increased respiratory rates (three to five times normal), and dry, thin hair coats with areas of alopecia (see also Anhidrosis, Chapter 41).

Drugs and Toxins With Effect on Body Temperature

Phenothiazine tranquilizers are a recognized cause of loss of ability to control body temperature.[28] Conversely, α_2-adrenergic agonist sedatives (e.g., detomidine, xyalzine) have been shown to induce tachypnea and decrease body temperature in febrile horses.[29] The potential mechanism for the antipyrexic effect of α_2-adrenergic agonist drugs may be related to their ability to decrease prostaglandin E_2 production by the hypothalamus.[29-30] Erythromycin may induce hyperthermia during hot weather, particularly in foals.[31-32] This side effect has been attributed to a reaction to erythromycin itself or to an alteration of the foal's thermoregulatory system by mechanisms not yet described.[32] Other drugs that have been associated with increase in body temperature in large animals are summarized in Box 4.1. “Drug fever” should be a diagnosis of exclusion.[33] Helpful clues include the lack of fever pattern and the temporal association between initiation of a drug and the onset of fever or discontinuation of a suspected drug and resolution of fever.[33]

Box 4.1

Drugs Associated With Increased Temperature

Frequently

Penicillins
Sulfonamides

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Erythromycin
Antihistamines
Procainamide
Quinidine
Amphotericin B

Occasionally

Cephalosporins
Cimetidine
Ranitidine
Iodides
Rifampin
Ranitidine
Levamisole
Furazolidone

Rarely

Chloramphenicol
Tetracyclines
Phenothiazines
Salicylates
Herbal remedies
Others

Certain toxins and drugs may act to increase body temperature by causing an increase in metabolic work (Boxes 4.2 and 4.3). For example, chlorophenols and nitrophenols, used as herbicides and wood preservatives, cause uncoupling of oxidative phosphorylation within mitochondria and lead to rapid extreme rises in body temperature.[34] Chronic and/or low-level exposure to these compounds may manifest clinically as hyperthermia.

Box 4.2

Toxins Associated With Increased Temperature in the Horse

Blister beetle (cantharidin)
Selenium
Arsenic
Mercury
Chlorinated hydrocarbons
Dinitrophenol
Propylene glycol
Trichloroethylene extracted feed

Plant Toxins

Pyrrolizidine alkaloid–containing plants
Algae
Castor bean (Ricinus species)
Water hemlock (Cicuta species)
Jimson weed (Datura stramonium)
Mycotoxicosis

Box 4.3

Toxins Associated With Increased Temperature in Ruminants

Arsenic
Selenium
Mercury
Zinc
Crude oil, kerosine, coal oil
Organochlorine, chlorinated hydrocarbons
Iodine

Paraquat
Dinitrophenol
Propylene glycol
Trichloroethylene-extracted feeds
Halothane toxicity (C)

Plant Toxins

Fescue toxicosis (B)
Ergot (*Claviceps*) (B)
Pyrrolizidine alkaloid–containing plants, algae
Brassica species (mustards, crucifers, cress)
Bracken fern
Castor bean
Water hemlock
Milkweed (*Asclepias* species) (B, O)
Buttercup (*Caltha palustris* and *Ranunculus* species) (O)
Rhododendron (C, O)
Gossypol toxicity (B)
Jimson weed (*Datura stramonium*)

B, Bovine; *C,* caprine; *O,* ovine.

Tall fescue infected with the endophyte *Neotyphodium coenophialum* contains vasoactive ergopeptine alkaloids that cause vasoconstriction and reduced blood flow to the skin of ruminants.[35] These alkaloids also induce bronchoconstriction and pulmonary vasoconstriction, which further compromise ruminants' ability to lose heat, especially during hot environmental conditions.[35] Affected animals have a poor appetite and other indications of poor performance recognized as part of the syndrome of fescue toxicosis, or "summer slump."[35] A related endophyte infesting perennial ryegrass has been found to produce a similar hyperthermic condition in the western United States.[36] *Claviceps purpurea* infestations of annual or perennial ryegrass and of cereal grain heads have also been reported to produce a similar hyperthermic syndrome, which may lead to heat prostration and death when ambient temperatures are high.[37-39]

Cattle affected by any of these ergopeptine alkaloids have few to no clinical

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signs when environmental conditions are cool and heat loss mechanisms are not challenged. It is not yet known, however, if all of the effects of the alkaloids are peripheral or if they may also act within the CNS.[35]

Diseases of the Nervous System

CNS disorders that damage areas of the hypothalamus associated with temperature regulation may lead to either decreases or increases in body temperature, although hypothermia is most common. Hemorrhage, space-occupying masses (abscesses, tumors), infectious or inflammatory diseases, and degenerative disorders have all been implicated in hyperthermia. Hyperthermia is a common occurrence in humans with brain or spinal cord injury.[40] Central hyperthermia is usually characterized by lack of diurnal variation, absence of sweating, resistance to antipyretic drugs, and excessive response to external cooling.[3,28]

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Fever

True fever differs from other hyperthermic states in that the desired core body temperature or set point is elevated.[1] This new, higher set point is vigorously defended by the same mechanisms that maintain body temperature in health. Initiation of the febrile state can occur by a variety of infectious, inflammatory, immunologic, neoplastic, or injurious conditions. In the classic model of fever, these stimuli cause the production of multifunctional pyrogenic cytokines by a wide variety of cells, but primarily by fixed or circulating monocytes and macrophages[37] (Fig. 4.2). Currently at least 11 cytokines have been shown to induce the febrile response in humans and animals. Of these cytokines, interleukin 1 (IL-1α, IL-1β) and tumor necrosis factor alpha (TNF-α) are the most potent. Pyrogenic cytokines reach the POAH via the circulation and induce the production of arachidonic acid and its metabolism to prostaglandin E_2 (PGE_2), by the cyclooxygenase (COX)-2 pathway. This process will eventually result in a higher "set point" within the hypothalamic thermoregulatory center[41-42] (see Fig. 4.2). COX inhibitors, specifically COX-2 inhibitors, effectively reduce the febrile temperature to normal but have no effect on normal body temperature.[3,42] In addition, pyrogenic cytokines stimulate the activation and proliferation of T lymphocytes and of antibody-producing B lymphocytes, which, in turn, produce additional cytokines that both enhance and inhibit further production of pyrogenic cytokines.[43-44] Finally, pyrogenic cytokines, particularly IL-1 and TNF-α, cause membrane perturbation in a variety of body tissues, with a resultant increase in phospholipases and the production of arachidonic acid. Subsequent production of mediators is dependent on the metabolic pathways for arachidonic acid in the target tissue. Prostaglandins induced by pyrogenic cytokines have been shown to stimulate the muscle catabolism associated with fever and to induce collagenase synthesis from synovial cells.[45] These processes contribute to the muscle and joint pain associated with fevers that are relieved by COX inhibitors. Local tissue responses to IL-1β and TNF-α may stimulate afferent neural impulses that are responsible for many of the behavioral changes (increased sleep, decreased appetite, and loss of social behavior) associated with fever.

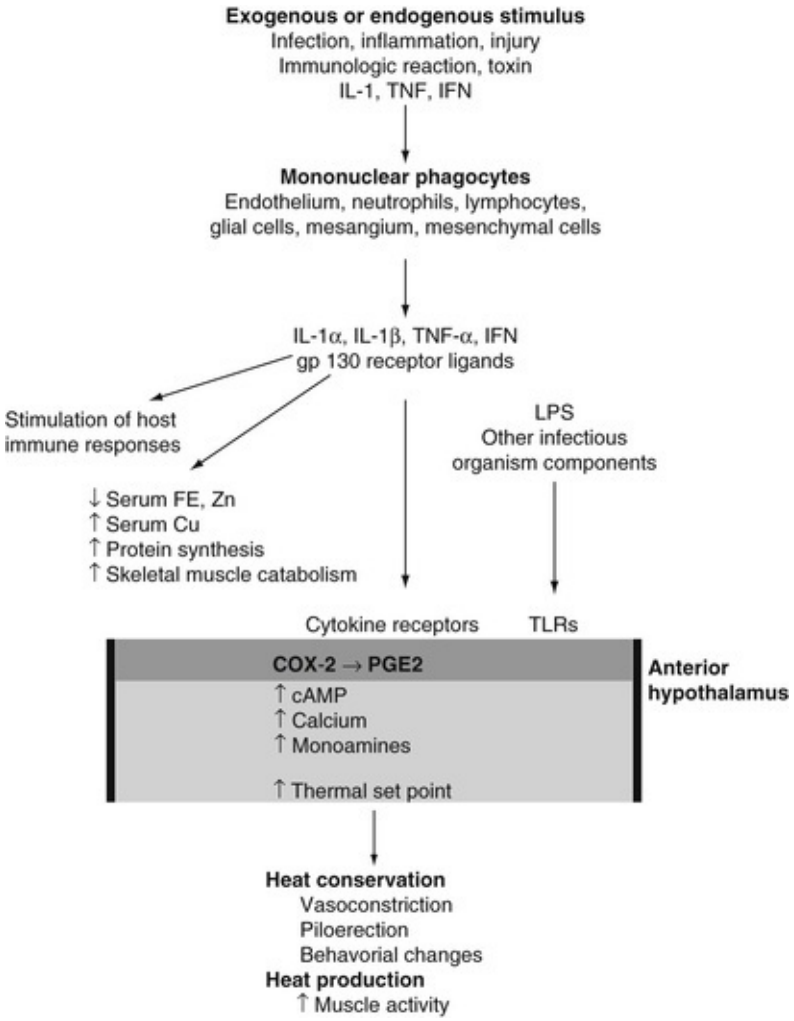


FIG. 4.2 Pathogenesis of fever. *OVLT,* Organum vasculosum laminae terminalis endothelium; *TLRs,* Toll-like receptors.

This model, however, does not fully explain the presence of fever, because specific blockade of IL-1 or TNF-α activity does not diminish the febrile response to lipopolysaccharide (LPS) or other microbial products in experimental studies or in patients with natural infections. Microbial products from a variety of agents bind to Toll-like receptors (TLRs) on the surface of cells. TLRs and IL-1 receptors share the same signaling areas and, along with other pyrogenic cytokines, a common pathway to activate nuclear factor (NF)-κB. Activated NF-κB in turn results in expression of COX-2 or COX-3 and PGE_2 synthesis. Mice deficient in COX-2 and injected with LPS, IL-1, TNF-α, or IL-6 either intravenously or within the CNS do not develop a fever.[42] Thus the induction of COX-2 and the subsequent production of PGE_2 provide a common pathway for divergent pyrogens to produce the febrile response (see Fig. 4.2).

There is also an apparent role for the vagal nerve in the production of the febrile response. Studies in laboratory animals in which the hepatic branch of the vagus nerve is severed have shown diminution of the febrile response to a relatively low dose of intraperitoneally injected LPS but not intramuscularly administered LPS or high-dose intraperitoneally injected LPS. Local production of cytokines may stimulate primary hepatic vagal receptors that, via vagal afferent fibers and A1/A2 noradrenergic cell groups in the brainstem, release noradrenaline, which subsequently induces the production of PGE_2 and fever.[46] Transection of the visceral vagal afferents has been shown to attenuate febrile behavioral responses, but not the associated temperature elevation, to high-dose intraperitoneal LPS injection in rats.[47]

In addition to a rise in body temperature, the febrile state is accompanied by a variety of metabolic, hematologic, and immunologic changes. IL-6 and IL-11, induced by IL-1α, IL-1β, and TNF-α, induce the synthesis of fibrinogen, C-reactive protein, haptoglobin, ceruloplasmin, and certain macroglobulins, known collectively as *acute phase proteins*, by hepatocytes.[42] In addition, these cytokines mediate the accompanying hypoferremia, hypozincemia, and hypercupremia of the acute-phase response.

Physiologic control of the febrile response is multifactorial and prevents extreme elevations in body temperature that are incompatible with life in most instances. TNF-α inhibits further production of itself. IL-1 and other inhibitory cytokines stimulate the production of IL-1 receptor agonist, which prevents further binding of IL-1. In addition, one of the receptors on cell surfaces for IL-1 (type II receptor) does not result in cell signaling and is thought to serve as a "decoy" receptor to decrease the concentration of IL-1.[48] IL-10, induced by pyrogenic cytokines, inhibits IL-1, TNF, and IL-6 production and suppresses the production of IL-2 and IFN-γ by T-helper cells.[48-49] Circulating pyrogenic cytokines may be bound to carrier molecules that reduce or prevent the interaction with receptors. For example, IL-1β has been shown to bind to α_2-macroglobulin, a protein increased during the acute phase response.[3] Glucocorticoids inhibit the transcription of numerous genes encoding the pyrogenic cytokines IL-1β, Il-6, and TNF-α. Within the brain, both arginine vasopressin (AVP) and alpha melanocyte stimulating hormone (αMSH) act as potent antipyretic agents. Receptors for AVP, which acts as a neurotransmitter within the brain, are found lateral to the POAH and decrease fever in both natural and experimentally induced fever, whereas injection of AVP receptor

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antagonist elevates fever and delays defervescence.[50-51] αMSH binds to local melanocortin receptors within the brain and on cell receptors of immune cells to decrease fever and inflammation. When administered systemically to humans, αMSH is 20,000 times more potent on a molar basis than acetaminophen in decreasing fever from endogenous pyrogens.[51] In the brain, nitric oxide (NO) participates in regulation of body temperature by activating soluble guanylate cyclase and increasing cyclic guanosine monophosphate (cGMP) levels. Intracerebral ventricular injection of NO donors depresses fever in rats, whereas inhibition of NO synthesis within the CNS enhances fever.[48]

In summary, the occurrence of fever during disease results from a complex interaction of multiple cytokines and microbial products that act locally (site of tissue injury), systemically (in the circulation), and in the POAH of the brain and affect the immune, endocrine, and nervous systems.

Beneficial Effects of Fever

It should be emphasized that fever is not an illness but is, in fact, a physiologic mechanism that has beneficial effects in fighting infection. Body temperature elevation in pyrogenic-mediated fevers, in contrast to hyperthermic states, rarely exceeds 5° F (2.5° C) above normal. Although the severity of some viral infections is decreased at these temperatures, most pathogens are not affected by a modest rise in temperature. Studies on bacterial infections in fish, lizards, rabbits, and humans, however, have shown an increase in survival correlated with the presence of fever.[3,52-53] One well-studied effect of fever on bacterial proliferation is the effect of hypoferremia. Bacteria, which require iron for multiplication, are inhibited by the reduced availability of iron during the acute phase reaction. This response is augmented by the increased susceptibility of bacteria to low iron at higher temperatures.[54-55] Certain neoplastic cells are inhibited during fever, although it is likely that inhibition of neoplastic cell division results from augmentation of immune responses.[56]

Literature on the effect of fever is conflicting owing to the multiple variables present in in vivo studies and the application of heat in temperature ranges exceeding those of natural fevers in in vitro studies. Enhancement of host defenses, however, appears to be the primary beneficial effect of fever. Fever or heat applied in in vitro studies within the physiologic range of natural fevers has a beneficial effect on multiple processes of the adaptive immune response.

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Neutrophils and monocytes have increased motility and emigration, enhanced phagocytosis, increased oxygen radical production, and enhanced killing of intracellular bacteria. IFN production increases, and its antiviral, antitumor, antiproliferative, and natural killer (NK) cell–stimulating properties are enhanced. Increased T-cell proliferative responses to nonspecific mitogens IL-1 and IL-2 and enhanced T-helper cell activation, expression, recruitment, and cytotoxicity have all been correlated with fever. Enhancement of B cells, with a subsequent increase in production of antibodies, and enhanced expression of Fc receptors occur during fever.[57]

Activity of pyrogenic cytokines is also influenced by temperatures achieved during fever. For example, in a mouse-endotoxin model, fever enhanced the early expression of TNF-α but limited the duration of its expression. Production of IL-1β was delayed, whereas that of IL-6 (which downregulates production of TNF-α and IL-1β) was enhanced, preventing the simultaneous expression of TNF-α and IL-1β and the potential harmful effects of their simultaneous expression.[58] Other studies have demonstrated that the effect of fever on various cytokines is specific for each cytokine and specific to body compartments. Thus fever is an important component of the coordinated and specific cytokine response of the host to various inflammatory stimuli.[3,45,57]

Adverse Effects of Fever

The beneficial effects of fever during bacterial infections in rabbits have been shown to reverse at temperatures >5° F (3° C) above normal. Cytokine dysregulation may result in prolonged or extreme fevers with adverse effects on a variety of body functions in addition to the immune response. Catabolic metabolic processes during fever are markedly different from catabolism of starvation. Protein loss occurs four times as rapidly in individuals with infectious or inflammatory diseases as compared with starvation-adapted individuals. Ketonemia is inhibited, resulting in the oxidation of large amounts of muscle-derived amino acids for energy. This cytokine-driven catabolism, combined with the decreased feeding behavior that accompanies fever, variable anorexia (even if feed is provided), and increased metabolic rate at higher temperatures, can result in rapid and severe muscle wasting, weakness, and atrophy. In humans, high fevers frequently cause seizures, especially in children,[59] but this is rare in animals unless temperatures reach 108° F (42° C) in neonates. Prolonged high fevers in debilitated animals may lead to failure of the cardiovascular system.

Fever is one of the earliest and most prominent manifestations of the acute phase reaction. Veterinarians have used the clinical thermometer to aid in diagnosis and to monitor the progress of illness in animals since 1770. With the increased knowledge of the pathogenesis of fever has come a better appreciation for the diverse causes of the febrile state. In ruminants and horses, however, infectious disease remains the most common reason for development of fever (Boxes 4.4 and 4.5). Careful evaluation for the presence of infectious disease is always indicated, especially when the onset of a fever is abrupt; the temperature is higher than 39.4° C (103° F); and the fever is accompanied by depression, variable loss of appetite, serous nasal exudate, epiphora, enlargement of lymph nodes, or diarrhea and a decreased or increased leukocyte count. Other causes of fever are neoplasia (Boxes 4.6 and 4.7), immune-mediated diseases (Boxes 4.8 and 4.9), noninfectious inflammation (Boxes 4.10 and 4.11), and certain drugs.

Box 4.4

Infectious Causes of Fever in Horses

Common Causes

Upper respiratory viral diseases
Strangles, *Streptococci equi*
Pneumonia, bacterial or viral
Pleuropneumonia
Gastrointestinal parasitic infections
Enteritis, *Clostridium difficile, Lawsonia,* or of unknown causes
Salmonellosis
Equine monocytic ehrlichiosis (Potomac horse fever)
Proximal duodenitis-jejunitis
Rotavirus diarrhea (foals)
Endotoxemia from gastrointestinal disorders
Septicemia, septic arthritis, osteomyelitis (foals)
Urachal abscess (foals)
Metritis (mares)
Peritonitis
Tetanus

Traumatic tenosynovitis, cellulitis
Localized occult abscesses (thorax, abdomen, upper respiratory system)
Tumors (see list in Box 4.6)

Less Common Causes

Equine encephalomyelitis (EEE, WEE)
West Nile virus
Osteomyelitis (adults)
Vesicular stomatitis
Tyzzer disease (foals)
Malignant edema
Bacterial endocarditis
Mastitis
Pyelonephritis
Equine infectious anemia
Equine viral arteritis
Otitis media and interna

Uncommon Causes

Pericarditis
Systemic or pneumonic aspergillosis, candidiasis
Pneumocystis carinii (renamed *P. jiroveci* in humans)
Brucellosis
Tularemia
Anthrax
Rabies
Lyme disease (*Borrelia burgdorferi*)
Nocardiosis
Coccidioidomycosis
Babesiosis, piroplasmosis
Toxoplasmosis

EEE, Eastern equine encephalitis; *WEE*, Western equine encephalitis.

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Box 4.5

Infectious Causes of Fever in Ruminants

Common Causes

- Mastitis
- Metritis
- Pneumonia: viral, mycoplasma, bacterial
- Traumatic reticuloperitonitis (B)
- Peritonitis (from other causes, e.g., ruptured abomasal ulcer, uterine tear)
- Septicemia, osteomyelitis, infectious arthritis, omphalophlebitis (neonates)
- Toxemia from gastrointestinal disorders
- Enteritis
- Abscesses
    - Liver
    - Pharyngeal/retropharyngeal
    - Internal lymph nodes (C, O)
    - Associated with foot
- Endocarditis
- Pericarditis (B)
- Listerosis
- Tetanus
- Bovine viral diarrhea (BVD), mucosal disease (B)
- Foot rot
- Otitis media, interna (*Mycoplasma bovis*) (B)
- Clostridial infections
    - Blackleg (*Clostridium chauvoei*)
    - Clostridium perfringens types D, A (C, O)
- Contagious ecthyma (C, O)
- *Histophilus somni* infection (thromboembolic meningoencephalomyelitis)
- *Mycoplasma* species arthritis, septicemia (C)
- *M. bovis* (B)
- Verminous pneumonia (B)

Less Common Causes

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Rabies
Anaplasmosis
Leptospirosis
Bluetongue (O)
Vesicular stomatitis
Malignant catarrhal fever (B)
Verminous pneumonia (C, O)
Cystitis, pyelonephritis
Epididymitis (C, O)
Balanoposthitis (O)
Enzootic abortion(C, O)
Epizootic abortion (B)
Caprine arthritis encephalomyelitis (C)

Uncommon Causes

Neoplasms (see list in Box 4.7)
Infectious necrotic hepatitis (*Clostridium novyi*)
Sarcocystosis (B)
Tuberculosis (B)
Systemic candidiasis, aspergillosis
Eperythrozoonosis
Brainstem, pituitary abscess
Systemic toxoplasmosis (C, O)
Tularemia
Pseudorabies
Brucellosis
Ovine progressive pneumonia
Chlamydial sporadic bovine encephalomyelitis

B, Bovine; *C*, caprine; *O*, ovine.

Box 4.6

Neoplastic Causes of Fever in Horses

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Common Causes

Metastatic melanomas
Lymphosarcoma
Squamous cell carcinoma
Fibrosarcoma

Less Common Causes

Granulosa cell tumors in mares
Undifferentiated reticuloendothelial cell sarcomas
Adenocarcinomas
Myeloproliferative diseases

Uncommon Causes

Hemangiosarcoma
Mesothelioma
Pheochromocytoma
Osteosarcoma
Myeloma of the gastrointestinal tract

Box 4.7

Neoplastic Causes of Fever in Ruminants

Common Causes

Lymphosarcoma

Less Common Causes

Adenocarcinoma
Metastatic melanoma (C)

Liver neoplasia
Mesothelioma

Uncommon Causes

Skeletal neoplasia
Malignant neuroblastoma

C, Caprine.

Box 4.8

Immunologic Causes of Fever in Horses

Common Causes

Purpura hemorrhagica
Urticaria
Drug-induced fever

Less Common Causes

Immune-mediated hemolytic anemia, thrombocytopenia
Combined immunodeficiency of foals
IgM deficiency
Pemphigus foliaceus
Chronic necrotizing vasculitis
Neonatal isoerythrolysis

Uncommon Causes

Connective tissue disorders, rheumatoid arthritis
Transient agammaglobulinemia of foals
Bullous pemphigoid

Common variable immunodeficiency

IgM, Immunoglobulin M.

Box 4.9

Immunologic Causes of Fever in Ruminants

Common Causes

Drug allergies
Urticaria (milk allergy in cattle)

Less Common Cause

Neonatal isoerythrolysis (B)

Uncommon Cause

Pemphigus foliaceus (C)

B, Bovine; *C*, caprine.

Box 4.10

Noninfectious Inflammatory and Miscellaneous Causes of Fever in Horses

Hepatic disorders
Hyperlipidemia, equine hepatic lipidosis
Acute hepatic necrosis (Theiler disease)
Chronic active hepatitis

Cholelithiasis
Hyperkalemic periodic paralysis
Foreign bodies
Nasal, oral, pharyngeal, tracheal, bronchial
Thrombophlebitis
Ocular trauma, recurrent uveitis
Burns, smoke inhalation
Snake bite
Acute renal failure
Idiopathic interstitial pneumonia

Box 4.11

Noninfectious Inflammatory and Miscellaneous Causes of Fever in the Ruminant

Phlebitis, thrombophlebitis
Salt toxicity, water deprivation
Acute bovine pulmonary emphysema
Fat necrosis (B)
Burn, smoke inhalation
Ocular trauma
Snake bite
Acute renal failure
Primary photosensitization
Cholelithiasis (B)
Postparturient hemoglobinuria (B)

B, Bovine.

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Fevers of Unknown Origin

Most febrile illnesses encountered in large animal practice are caused by infectious diseases that are readily diagnosed by careful evaluation of history and physical examination or are of short duration, run their course, and progress to complete recovery within 2 weeks without a specific etiologic diagnosis having been made. Some febrile conditions, however, continue for weeks or months, accompanied only by nonspecific signs of depression, variable anorexia, and weight loss, while the diagnosis remains obscure. Patients with prolonged febrile episodes of 3 weeks' duration or longer in which a diagnosis has not been made after a week of routine diagnostic efforts or after 3 days of hospitalization and diagnostic tests are considered to have fever of unknown origin (FUO). The majority of cases that meet the definition of FUO have infectious causes. Neoplastic diseases, immune-mediated vasculitides, and autoimmune diseases are the next most common causes. Adverse drug reactions and other miscellaneous diagnoses are the least common documented causes of FUO. Most cases of FUO are caused by common diseases with an unusual presentation; an ordered, problem-oriented approach to diagnosis will render a diagnosis in 90% of cases.[60-61] The following steps are suggested (Fig. 4.3).

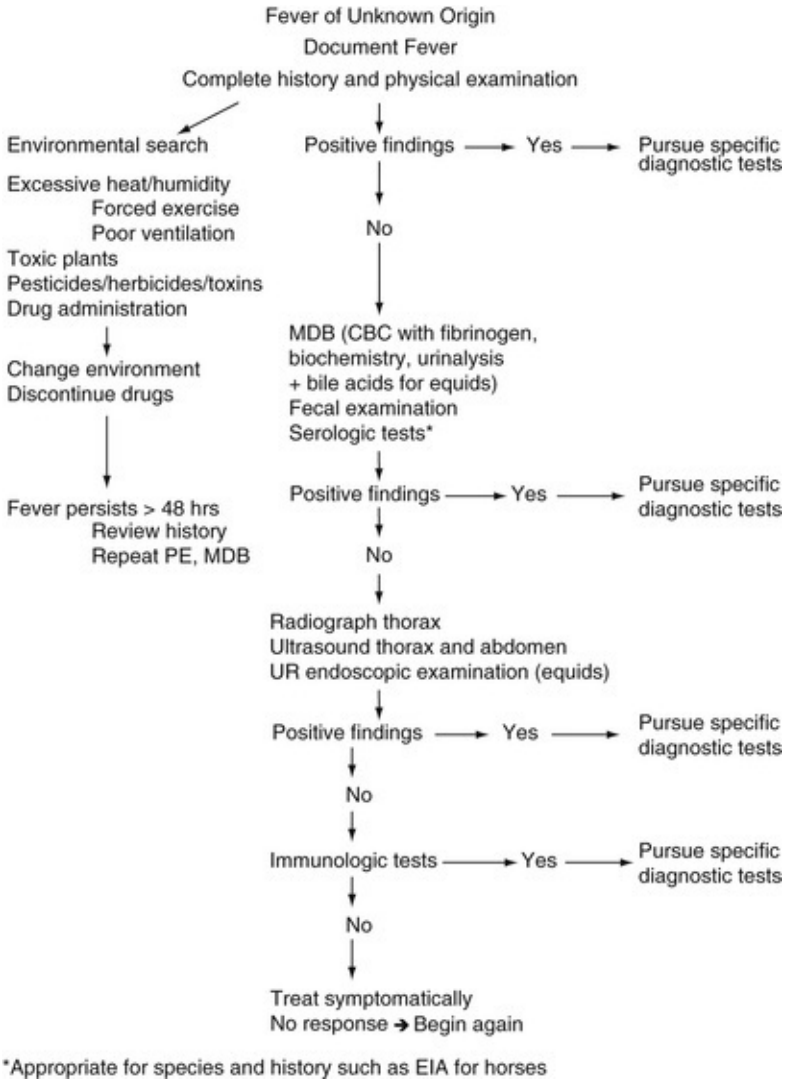


FIG. 4.3 Approach to fever of unknown origin. *CBC,* Complete blood count; *EIA,* equine infectious anemia; *MDB,* minimum database; *PE,* physical examination; *UR,* upper respiratory.

Document Fever

A temperature chart consisting of at least twice-daily determination of rectal temperature should be completed to characterize the fever pattern. *Intermittent fevers* are characterized by diurnal variation in which a peak elevation of temperature of higher than 1.5° F (0.75° C) occurs, followed by a decline in temperature, which in some patients falls within the normal range. Most intermittent fevers peak in late afternoon or evening, with the lowest temperatures occurring in the morning, but approximately 10% of cases will

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have a reverse pattern. Intermittent fever is most commonly associated with pyrogenic infections, although it may occur in neoplasia, especially if tissue necrosis and inflammation are concurrent. *Remittent fevers* are characterized by a period of days in which elevated temperatures occur, followed by several days of normal temperature, only to have the cycle repeat again. Brucellosis in ruminants, equine infectious anemia (EIA) in horses, and blood-borne protozoal diseases such as babesiosis may exhibit this type of pattern. *Sustained fevers* are characterized by a consistently raised temperature without variation and appear as a "flat line" on a temperature chart. Fevers caused by drug administration and certain toxins may be of this type, especially if the patient does not exhibit any other signs of illness.[3] Any pharmacologic agents being administered to the patient should be discontinued. Defervescence of fever from drug administration should occur in 48 hours.

Consideration of Epidemiology

Repeated efforts to obtain a complete history in chronologic order of development of clinical signs may be necessary to extract all the information pertaining to the individual animal. A knowledge of forage available, presence of nutrient deficiencies and excesses, toxic plants, and infectious organisms indigenous to the area, as well as the threat of exotic diseases, is necessary for the present and past geographic environment of the animal.

Physical Examination

A physical examination (see Chapters 1 and 2) should be carefully performed to evaluate all body systems as thoroughly as possible and repeated as often as practical, because it is unusual for a disease to cause a prolonged fever without the occurrence of some physical signs. Examination should include the following:

1. Horses
    a. Thorough auscultation of cardiopulmonary system at rest, with rebreathing bag, and following exercise; evaluation of peripheral perfusion before and after exercise
    b. Complete visual or manual oral examination; percussion of sinuses; endoscopic examination of upper airway structures

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(including the guttural pouches) and of the trachea and bronchi (if length of the endoscope allows)
c. Palpation of external lymph nodes, ballottement, and deep palpation of external abdomen for pain
d. Rectal examination
e. Fecal odor, consistency, volume; frequency of defecation
f. Complete ophthalmic examination
g. Evaluation of external genitalia and mammary gland
h. Evaluation of musculoskeletal conformation and gait analysis for lameness

2. Ruminants
a. Complete visual or manual oral examination; percussion of sinuses; eye examination
b. Check for abdominal pain by withers pinch or xiphoid pressure
c. Thorough auscultation of cardiopulmonary system, evaluation of peripheral perfusion
d. Palpation of all external lymph nodes
e. Rate and quality of rumen contractions, abdominal ping, and ballottement for rumen fill and pain
f. Complete udder examination and milk evaluation of lactating females
g. Testicular and penile palpation of males
h. Complete rectal examination (cattle) or external abdominal palpation (young cattle and small ruminants)
i. Fecal color, consistency, volume; frequency of defecation
j. Evaluation of musculoskeletal conformation and gait analysis for lameness, palpation of all joints

Diagnostic Aids (Table 4.1)

All cases of FUO should have a laboratory database consisting of a complete blood count (CBC), urinalysis, and biochemical profile. The CBC should include morphology of red blood cells and white blood cells (WBCs), WBC differential, and fibrinogen determination. Chronic inflammatory disease produces characteristic changes in the CBC (see Chapters 24 to 26), and morphologic evaluation of the blood smear may reveal blood-borne parasites.

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TABLE 4.1
Fever of Unknown Origin: Diagnostic Procedures

Procedure	Indications
Abdominocentesis	Abdominal pain
	Abnormal rectal examination (e.g., mass)
	Fluid wave on ballottement
	Abnormal ultrasound finding (e.g., fluid, mass)
Biopsy	Enlarged lymph nodes or other mass found
	Abnormal renal or liver function test results
	Vesicular or ulcerative skin lesions
Blood culture	Intermittent fever, especially in a neonate with failure of passive transfer
	Neutropenia or neutrophilia ± bands
	Increased fibrinogen
	Cardiac murmurs (bacterial endocarditis)
Radiography	Any musculoskeletal pain, heat, swelling
	Thorax, see transtracheal aspirate
	Abdomen: traumatic reticuloperitonitis (cattle), enterolith (horse)
Synovial fluid aspirate	Joint effusion, heat, pain
Thoracocentesis	Abnormal percussion of chest
	Fluid line thoracic radiographs
	Fluid found on ultrasonography
Transtracheal aspirate	Persistent cough or nasal exudate with normal upper respiratory tract
	Abnormal auscultation or percussion of thorax
	Persistent increased respiratory rate
Bronchial alveolar lavage	Exercise intolerance with normal cardiovascular system
Immunodiagnostic screening	
Serum protein electrophoresis	Abnormal serum protein
Serum protein immunoelectrophoresis	Hypergammaglobulinemia
	Hypogammaglobulinemia (horses)
Direct Coombs test	Hemolytic anemia
	RBC autoagglutination
Skin biopsy direct immunofluorescence	Vasculitis, purpura
	Bullous or ulcerative skin lesions
Antinuclear antibody	Multiple noninfectious arthritis
ECG	Dysrhythmia, congestive heart failure
Bone marrow aspiration	Anemia
	Thrombocytopenia
Gastrointestinal absorptive tests (horse)	Hypoproteinemia with normal kidney, liver
Serology	Persistent undiagnosed disease
Exploratory laparotomy	Abnormal rectal examination, ultrasonography
	Chronic abdominal pain
	Abnormal peritoneal fluid
Ultrasonography	Cardiac murmurs, dysrhythmias
	Abnormal liver or kidney function tests
	Abdominal mass—suspect fluid in thorax, pericardium, abdomen

ECG, Electrocardiogram; *RBC,* red blood cell.

Serum protein and albumin determinations characterize either

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hypoproteinemia or hyperproteinemia. Serum protein electrophoresis and immunoelectrophoresis further classify deficiencies or increased production of proteins. It is prudent to measure serum hepatocellular enzyme activities and serum bile acid concentration for evaluation of hepatocellular damage and function, respectively.

Because much of the abdomen is unavailable to rectal palpation, abdominocentesis and evaluation of peritoneal fluid for protein, cellularity, and cell morphology are justified. Peritoneal fluid is obtained more consistently in horses than in ruminants with abdominal disease because of the presence of the greater omentum and the rapid formation of fibrinous adhesions in ruminants with inflammatory abdominal disease. Peritoneal fluid evaluation is usually most helpful in inflammatory diseases, but it may be diagnostic in some cases of abdominal neoplasia. Bacterial culture and sensitivity of peritoneal fluid are indicated in inflammatory diseases when WBCs show degenerative or toxic changes but are rarely positive unless gross bowel contamination has occurred. Polymerase chain reaction (PCR) for *Streptococcus equi* and/or *R. equi* may be warranted in horses with evidence of chronic inflammation of the abdominal cavity.

Blood cultures are best used after characterization of a remittent fever and evidence of pyogenic inflammatory disease from the laboratory database. Any antimicrobial therapy should be discontinued 48 to 72 hours before sampling. Three to five samples should be collected at least 45 minutes apart and are best taken directly into culture media. Sampling just before and during a temperature rise is more likely to yield positive results than sampling at the temperature peak and decline.

Serologic evaluation for infectious diseases common in the geographic area and/or patient population should be performed. Single serologic determinations are usually of value only in those diseases in which one positive titer is significant and when the disease is characterized by persistent infection such as EIA, brucellosis, or Johne's disease. In many instances vaccination history and/or accompanying clinical signs must be correlated with titer determinations. Paired samples for toxoplasmosis, babesiosis, and various mycotic diseases (especially coccidioidomycosis) are indicated when the diagnosis remains obscure. Serologic determination of antibody titers to the SeM protein of *S. equi* can aid in the diagnosis of internal abscessation.[62] The synergistic hemolysis inhibition (SHI) test may be helpful in the diagnosis of *Corynebacterium pseudotuberculosis* infections in horses and small ruminants.[63-65] Virus isolation,

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PCR, and/or immunohistochemistry, particularly in persistent bovine viral diarrhea (BVD)-infected cattle, may be helpful.

Feces should be tested for the presence of occult blood. Suspicion of gastrointestinal blood or protein loss, intermittent/chronic diarrhea, and weight loss warrants fecal cultures and rectal biopsy for ruling out salmonella or infiltrative bowel disease in horses, whereas such signs in adult dairy cattle warrant ruling out abomasal lymphosarcoma and Johne's disease as the cause.

Also helpful are biopsies of enlarged lymph nodes, accessible abdominal masses, and the liver and kidney when laboratory data indicate abnormalities. Liver biopsies should be cultured and evaluated histologically, because bacterial cholangiohepatitis can be a cause of FUO. Evaluation of biopsies for the presence of immunoglobulins, particularly if skin lesions are present, may add in diagnosis of immune-mediated disorders. Antinuclear antibody determinations and a Coombs test are also indicated in suspected immune-mediated diseases.

Radiographic evaluation, particularly of the thorax, should be performed in horses and small ruminants and is often possible in dairy cattle. In cattle, radiographic evaluation of the cranioventral abdomen can help diagnose traumatic reticuloperitonitis. Ultrasonographic examination of the heart may definitively diagnose cardiac abnormalities and may provide more complete scrutiny of other organs in the thorax and abdomen, as well as deep structures of the musculoskeletal system. Ultrasonographic examination also aids in percutaneous biopsy of internal structures and may help the practitioner make the decision for exploratory laparotomy.

In equine patients, exploratory laparotomy should be performed only in patients that are becoming progressively debilitated and in which all other avenues of diagnosis have been exhausted. Blind exploratory laparotomies usually do not contribute to diagnosis, are costly, and are not without risk. Standing laparotomy or laparoscopy can be a useful alternative to ventral midline exploratory celiotomy because each of them is less expensive and does not involve general anesthesia. In ruminants, especially adult cattle, exploratory laparotomy is inexpensive and low risk and should therefore be used more routinely as an aid in the diagnosis of an FUO.

Nuclear imaging and imaging using autologous WBCs labeled with technetium-99m or indium-111 are increasingly used in human and small animal medicine.[66] These procedures may be helpful in localizing abscesses, particularly osteoarticular infections. These modalities may prove to be of benefit for large animals as the modalities’ availability increases. As a note, the

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use of nuclear imaging in food-producing animals is strongly discouraged.

The use of therapeutic trials of antimicrobials in FUO should be restricted to cases in which strong evidence of a bacterial infection exists. The therapeutic regimen should be as specific as possible and administered for a predetermined amount of time. Inappropriate use of broad-spectrum antimicrobials for all febrile diseases contributes to interference in accurate diagnosis.

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Hypothermia

Decreases in body temperature may occur when environmental stresses (cold, wet, wind) overwhelm the body's capability of heat production (especially when the body is weakened from disease), when CNS disease has resulted in damage to the regulatory centers within the hypothalamus, or when adrenergic or sympathetic effector systems have been damaged. Newborns, cachexic, and aged animals are most susceptible to heat loss caused by cold exposure (see Neonatal Sepsis and Weak Calf Syndrome, Chapter 20). Concurrent signs of septic disease in hypothermic animals signify a guarded prognosis, because the body's defense mechanisms are often overwhelmed when core body temperature declines. Severely hypothermic animals (core body temperature >30° C) are profoundly depressed and have marked reduction in ventilation, absence of muscle activity, and decreased reflexes. Decreased intravascular volume and depressed cardiac function lead to hypoxia, acidemia, and cardiac dysrhythmias. Newborns are often hypoglycemic and have potassium imbalances. These animals should be warmed by protecting them from wind or drafts, drying them, and providing a microenvironment of high ambient temperature. Applying thermal blankets and housing them in an insulated stall, with or without supplemental heat, is superior to using direct external heat from heat lamps or other sources. Direct external heat without environmental control causes cutaneous vasodilation, often exacerbates central hypothermia, and contributes to cardiovascular compromise.

Animals with severe hypothermia should be warmed gradually over 24 hours, with careful monitoring of body temperature and the cardiovascular system. Maintenance of adequate systemic perfusion is the most important means of preventing cardiac failure.[67-68] Acidosis and potassium imbalances are common and may fluctuate rapidly. Consequently, repeated measurements, especially when a patient's clinical condition worsens in the process of warming, are often necessary. Appropriate crystalloid fluids, warmed to body temperature, are usually necessary throughout the warming process. Evaluation of blood glucose and concurrent dextrose therapy, especially in neonates, should also be performed.

Warmed humidified oxygen therapy both as an aid in treatment of hypoxia and as a means of warming is helpful. Gastric (rumen) or rectal lavage with warmed fluids may also be used. However, care should be taken in rapid rewarming, because an imbalance in the basal metabolic rate (which is

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temperature dependent) and systemic perfusion may result in life-threatening cardiac dysrhythmias and worsening of metabolic acidosis and hypoxia. Hypothermia attenuates the inflammatory response by a multiplicity of effects on cytokines and other key signaling mechanisms.[69] Thus the adverse metabolic effects of disease are slowed at low body temperatures, and as body temperature elevates, signs of systemic disease become apparent.[70] In hypothermic animals in shock, particularly neonates, severe anoxic changes in the bowel wall may result in severe diarrhea, sloughing of mucosa, or clostridial growth in the bowel.

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• CHAPTER 5

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Alterations in Respiratory Function

Jeffrey Lakritz, Consulting Editor

MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Cough

W. David Wilson • Jeffrey Lakritz

■ Definition

Coughing, an important and normal respiratory defense mechanism, is the sudden, forceful, noisy expulsion of air through the glottis to clear mucus, particles, and other material from the tracheobronchial tree and glottis.

■ Pathophysiology

The mucociliary escalator and the cough reflex are the major protective mechanisms that function together to remove material from the respiratory tract.[1,2] Particles trapped in mucus are transported to the trachea by continuous waves of ciliary motion, starting at the level of the terminal bronchioles. Coughing is associated with development of increased intrathoracic pressure and generation of high-velocity airflow out of the respiratory system. This rapid expulsion of air removes secretions accumulating within the tracheobronchial tree proximal to the level of the segmental bronchi.[3] Coughing is thus a normal physiologic and protective response and a common clinical sign associated with a variety of cardiorespiratory disorders.

Neural Pathways Involved in the Cough Reflex.

Coughing is an involuntary reflex; however, this reflex may be voluntarily initiated or suppressed.[2,3] The reflex pathways involve sensory receptors present within the airway epithelia, from the larynx to the respiratory bronchioles, with nerve fibers conducting afferent impulses within vagal, glossopharyngeal, trigeminal, and phrenic nerves.[1,3,4,5] The receptors, mainly irritant receptors, are particularly numerous within the proximal airways (trachea and bronchi), especially around the hilus of the lung and bifurcation of the bronchi.[1,4] Other receptors capable of activating the cough reflex are found within lung parenchyma, the pleura, and elsewhere. Brainstem neuronal pathways for the cough reflex in the horse are not well characterized; however, in other species, afferent signals to the medulla oblongata are received and efferent fibers pass

back down to the respiratory system within the vagal, phrenic, intercostal, and lumbar nerves and motor portions of the trigeminal, facial, hypoglossal, and accessory nerves to supply striated and smooth muscles of the larynx, tracheobronchial tree, diaphragm, intercostal muscles, abdominal muscles, and secretory glands of the respiratory tract.[1,5-7]

Irritant receptors are stimulated by mechanical deformation induced by compressing the trachea; by bronchoconstriction, inert dusts such as carbon, irritant gases such as ammonia, and biological mediators such as histamine, prostaglandins, or bradykinins (Boxes 5.1 and 5.2).[2,4] Sensitivity to mechanical stimulation varies along the airway, and in horses the upper airway cough receptors appear to be less active than observed in many other species.[8] For example, a stomach tube inadvertently passed into the trachea frequently does not induce coughing until it reaches the carina. Similarly, endoscopic examinations often reveal large pools of exudate within the trachea of horses with limited history of coughing.[6] Foals with *Rhodococcus equi* pneumonia often develop a tracheal rattle, reflecting accumulation of exudates within the trachea, but may not cough. Repeated stimulation of irritant receptors over several hours does not appear to diminish sensitivity but may lead to changes in threshold.[4]

Box 5.1

Causes of Coughing in Horses

Common Causes

- Equine influenza A2 virus (H3N8)
- Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)
- Bacterial pneumonia
- Bacterial pleuropneumonia, pleuritis
- Recurrent airway obstruction (RAO or chronic obstructive pulmonary disease)
- Mechanical causes (e.g., nonspecific dust irritation)
- Pharyngitis (acute or chronic pharyngeal lymphoid hyperplasia)
- Postviral hyperreactive airways

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Less Common Causes

Strangles (*Streptococcus equi* infection)
Equine viral arteritis
Other viruses (equine rhinitis A and equine rhinitis B)
Parascaris equorum migration
Pharyngeal paresis
Guttural pouch empyema
Guttural pouch mycosis
Pharyngeal, laryngeal trauma or surgery
Postsurgical aspiration (e.g., after laryngeal prosthesis surgery)
Epiglottal entrapment
Subepiglottal cyst or abscess
Chondritis, chondromas of the arytenoid cartilages
Retropharyngeal abscess
Tracheal collapse (including scabbard trachea in ponies)
Tracheal stenosis, stricture
Choke, esophageal obstruction
Aspiration pneumonia (foreign bodies, feed material)
Inhalation pneumonia (smoke, thermal injury, noxious gases)
Lungworm infection *(Dictyocaulus arnfieldi)*
Pulmonary abscessation
Exercise-induced pulmonary hemorrhage (EIPH)
Pulmonary edema (smoke inhalation, acute renal failure, overhydration, septicemia, anaphylaxis)
Summer pasture–associated obstructive airway disease (SPOAD)
Left-sided heart failure
Congestive cardiac failure
Neonatal septicemia

Uncommon Causes

Tuberculosis
Pneumoconiosis or silicosis; other interstitial pneumonias
Eosinophilic interstitial pneumonia
Nocardiosis

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Coccidioidomycosis
Chlamydia psittaci pneumonia
Mycoplasma species pleuritis
Tularemia
Pulmonary hydatidosis
Tracheal perforation or rupture
Cryptococcosis
Dorsal displacement of the soft palate (laryngopalatal dislocation)
Rostral displacement of the palatopharyngeal arch
Idiopathic laryngeal hemiplegia
Guttural pouch neoplasia
Rectus capitis ventralis muscle rupture
Adenovirus infection
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Esophageal ectasia, dysfunction, stricture, perforation; esophagitis
Megaesophagus
Progressive ethmoidal hematoma
Nasal or paranasal sinus neoplasia
Fistula (pharyngeal, esophageal, esophagobronchial, esophagotracheal, bronchobiliary)
Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
Infarctive lobar pneumonia
Bronchopleural fistula
Pleural mesothelioma
Pneumothorax
Pulmonary tumor, primary or metastatic
Lymphosarcoma, lymphoma, leukemia
Pulmonary aspergillosis
Phycomycosis, pythiosis
Plant awn stomatitis
Anaphylaxis or acute drug reaction
Atrial fibrillation
Tetralogy of Fallot
Cor pulmonale
Endocarditis
Ruptured mitral chordae tendineae

Melioidosis, *Pseudomonas pseudomallei* (exotic)
Glanders (exotic)
African horse sickness (exotic)

Toxic Causes

Crofton weed *(Eupatorium adenophorum)*
α-Naphthyl thiourea (ANTU)
Pentachlorophenol
Organophosphate
Carbamate

Box 5.2

Causes of Coughing in Ruminants

Common Causes

Mannheimia haemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)
Histophilus somni pneumonia (B)
Lungworm infection, verminous pneumonia
Chronic bacterial pneumonia with abscessation or consolidation (*Arcanobacterium pyogenes* and other bacteria)
Infectious bovine rhinotracheitis (IBR; bovine herpesvirus type 1 [BHV-1]) (B, C)
Bovine respiratory syncytial virus (B)
Parainfluenza virus type 3
Mycoplasma species pneumonia
Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)
Necrotic laryngitis, calf diphtheria (B, O)
Abscess (oral, lingual, retropharyngeal, pharyngeal, laryngeal)
Trauma (pharyngeal, laryngeal, tracheal, bronchial, chest wall)
Esophageal obstruction, foreign body choke
Septicemia (neonates)

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Less Common Causes

Bovine rhinovirus (B)
Bovine adenovirus (B)
Bovine malignant catarrhal fever (B)
Bovine virus diarrhea (BVD-MD) (B)
Herpesvirus DN-599 (B)
Bovine herpesvirus type 4 (BHV-4) (B)
Bovine coronavirus (B)
Pulmonary adenomatosis (Jaagsiekte) (O)
Ovine adenovirus (O)
Ovine progressive pneumonia and arthritis, maedi (O)
Caprine respiratory syncytial virus (C)
Caprine arthritis-encephalomyelitis (CAE) pneumonia (C)
Aspiration, foreign body pneumonia
Foreign body (pharyngeal, laryngeal, tracheal, bronchial, pulmonary)
Inhalation pneumonia (smoke, noxious gases, thermal injury)
Pulmonary embolus from posterior vena cava thrombosis (B)
Anaphylaxis or adverse drug reaction
Reaction to death of parasites after anthelmintic treatment (B)
Milk allergy in cows (B)
Farmer's lung disease (hypersensitivity to *Faenia rectivirgula* and other mold spores) (B)
Atypical interstitial pneumonia (B)
Pleuritis, pleural effusion
Pneumothorax
Diffuse fibrosing alveolitis (B)
Left-sided heart failure (left atrioventricular [mitral] insufficiency, pericarditis, congenital cardiac defects, other causes)
High altitude disease (B)
Enzootic bovine leukosis (B)
Chlamydia psittaci pneumonia

Uncommon Causes

Diaphragmatic hernia

Pleural mesothelioma (B, C)
Sarcocystosis (B)
Sporadic bovine leukosis, thymic lymphosarcoma (B)
Tuberculosis
Tularemia (O)
Tracheal actinomycosis
Tracheal collapse, stricture, stenosis
Phycomycosis, pythiosis (B)
Pulmonary aspergillosis
Rhinosporidiosis
Zygomycosis, mucormycosis (B)
Pulmonary listeriosis (B)
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Cor pulmonale (C)
Neoplasia (nasopharyngeal, oropharyngeal, pulmonary)
Postpartum hemolytic-uremic syndrome (B)
Esophageal rupture, laceration, ulceration, megaesophagus, hiatal hernia
Neoplasia, skeletal (B, O)
Buss disease, chlamydial sporadic bovine encephalomyelitis (B)
Winter dysentery (B)
Ascaris suum migration in calves (B)
Rinderpest (exotic)
Theileriosis, East Coast fever (exotic)
Melioidosis, *Pseudomonas pseudomallei* (exotic)
Contagious bovine pleuropneumonia (exotic) (B)
African bovine malignant catarrhal fever (exotic) (B)
Virulent sheep and goat pox (exotic) (O, C)
Peste des petits ruminants (exotic) (O, C)
Contagious caprine pleuropneumonia (exotic) (C)
Viral dermatitis of goats (exotic) (C)
Ibaraki disease (exotic) (B)

Toxic Causes

Organophosphate, carbamate
Mercury (B)

Iodine (B, O)
Insect fogger (B)
Levamisole (O, C)
Nitrogen dioxide (B)
Hairy vetch *(Vicia villosa)* (B)
Sneezeweed (*Helenium* species)
Aflatoxicosis (C)

B, Bovine; *C*, caprine; *O*, ovine.

Bronchoconstriction is a consistent component of cough,[3,7,8] and stimuli resulting in a cough may also induce reflex bronchoconstriction through parasympathetic innervation.[4] However, cough and bronchoconstriction are separate airway reflexes.[7] Whereas stimulation of irritant receptors in large airways induces both cough and reflex bronchoconstriction independently, stimulation of nerve endings in smaller airways does not directly initiate coughing but does cause bronchoconstriction. Bronchoconstriction may then initiate coughing indirectly.[4] The role of bronchoconstriction in the induction of coughing is supported by studies in people demonstrating that administration of bronchodilators is associated with reduction in the frequency or severity of coughing in asthma.[9,10] These studies indicate that mediator release (blocked by cromolyn) causes bronchoconstriction (blocked by bronchodilators), which stimulates irritant receptors (blocked by local anesthetics) and causes coughing.[4] Much of the airflow obstruction in horses with recurrent airway obstruction (RAO) appears to be mediated through these pathways and is eliminated with atropine, a parasympatholytic bronchodilator.[4]

Mechanics of Coughing

The mechanical events that produce coughing occur during four phases: inspiration, compression, expression, and relaxation.[2-4] The first three phases are necessary to create the decreased airway cross-sectional area and high airflow rates needed for an effective cough. Coughing is a maximum expiratory flow maneuver that begins with deep inhalation to expand lung volume, increase elastic recoil, and dilate the airways through the tethering effect exerted by surrounding lung tissue.[11] Closure of the glottis is followed by forced expiratory

efforts involving the rib cage, abdomen, and diaphragm, which increase pressure in the abdominal, pleural, and alveolar spaces to more than 500 mm Hg.[4] The glottis then opens suddenly, allowing the elevated alveolar pressure to rapidly accelerate gas flow from the respiratory tree.[2,4,11] This high-velocity gas stream shears exudate from the airway walls and lumen and carries it to the nasopharynx, from which point it exits the respiratory tract as nasal discharge or is swallowed.[11] Airflow stops before the animal has exhaled to residual volume because the glottis closes or the driving force provided by the muscles abates.[4] The characteristic sound of coughing is produced by vibration of laryngeal and pharyngeal tissues, narrowing and deformation of airways, vibration of surrounding lung tissues, and turbulent gas flow vibration in the airway.[4,7]

During forced expiration such as occurs with coughing, the increased pleural pressure is transmitted to the intrathoracic airways and alveoli. Intraalveolar pressure exceeds pleural pressure by an amount equal to the elastic recoil pressure of the lung.[4,11] A pressure gradient thus exists between the alveoli and atmospheric pressure at the nostrils and mouth. At a point in the airways known as the *equal pressure point* (EPP), the pressure in the airway lumen equals the pleural pressure because the elastic recoil pressure has dissipated.[2-4,11] In the intrathoracic airways rostral to this point, the intraluminal pressure is lower than the pleural pressure; therefore a transmural pressure gradient exists, which causes dynamic compression or collapse of the more proximal airways.[2,4,11] The location of the EPP is determined by elastic recoil pressures, and thus indirectly by lung volumes and the frictional resistance to flow in the airways between the alveoli and the EPP.[4] At high lung volumes, elastic recoil pressure is high, resistance in peripheral airways is low, and the EPP is typically located in larger intrathoracic airways that resist collapse because they have cartilaginous support for their walls.[4] As lung volume decreases, elastic recoil forces decrease, airway resistance increases, and the EPP moves more peripherally, subjecting lower and less well-supported parts of the tracheobronchial tree to dynamic compression.[3,4,11] Dynamic compression reduces the cross-sectional area of intrathoracic airways and thus increases the velocity of airflow through the narrowed segment.[4] These spikes of accelerated airflow promote more effective shearing of mucus and debris from the airway wall and lumen during coughing.[11]

Dynamic compression also increases the resistance to airflow.[4] Once dynamic

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compression of peripheral (smaller) airways occurs, further increases in expiratory effort cause greater narrowing of the airway; thus the flow rate that can be generated at a given lung volume does not increase beyond a certain maximum point (maximum expiratory flow).[4] Maximum expiratory flow decreases progressively as the animal exhales because lung volume declines. Thus coughing beginning at high lung volumes achieves the highest airflows.[4] However, only the larger intrathoracic airways are compressed and subjected to these spikes of higher airflow velocity.[2,4,11] As lung volume falls or if cough is initiated at lower lung volumes, smaller airways are dynamically compressed and cleared of mucus.[2,3,11] The effectiveness of coughing can thus be improved by repeating it several times in succession, either in a progression from high to low lung volume during the same breath or by inhaling between breaths.[4]

Because maximum airflows are lower in smaller airways, coughing is probably less effective in clearing material from the smaller airways than from the larger ones.[4] In the alveolar regions of the lung, gas flow is too slow for coughing to be an effective means of clearance.[11] Because only intrathoracic airways are dynamically compressed and subjected to these spikes of higher flow velocity during forced expiration, the extrathoracic trachea should be less effectively cleared by coughing.[4] However, horses and other animals with long necks do not seem to have great difficulty in clearing their airways, although they do lower their heads and straighten their airways during coughing to assist the clearance process.

In diseases such as RAO that cause narrowing of the airway lumen, the increased resistance to airflow, especially in peripheral airways, causes the EPP to move more peripherally toward the alveoli, resulting in a reduction in the maximum expiratory flow rate.[2,4] In this situation the effectiveness of coughing in clearing the airways is reduced. Thus administration of a bronchodilator may greatly improve the effectiveness of coughing in patients with RAO.[4]

Cough Stimuli.

Cough may be stimulated by bronchoconstriction; excessive mucous production; deposition of inhaled particles in the airways; release of inflammatory mediators; infectious diseases; exposure to hot or cold air; intramural or extramural pressure or tension on the airways (tumor, granuloma, abscess, or decreased pulmonary compliance caused by restrictive disease such as interstitial fibrosis or pleural

effusion); sloughing of airway epithelial cells; and enhanced epithelial permeability (pulmonary edema).[12] Epithelial sloughing and enhanced epithelial permeability increase the accessibility of cough receptors to the mechanical or chemical agents that stimulate them. Loss of integrity of the epithelial lining of the respiratory tract is a common feature in many respiratory diseases associated with cough (infectious diseases); however, a cause-and-effect relationship between alterations in pulmonary epithelium and cough has not been established.[12] Diseases of the respiratory tract may alter the sensitivity of the cough reflex.[12] For example, viral infections may increase the responsiveness of cough receptors to stimuli.[7,12] Of the many causes of coughing in large animals, viral infections such as equine influenza and infectious bovine rhinotracheitis (IBR) are particularly important because they cause outbreaks of respiratory disease that have acute onset of coughing as a prominent feature and that are frequently associated with persistence of coughing for prolonged periods after signs of acute disease have abated. These features of viral infections reflect the decreased effectiveness of mucociliary clearance resulting from virus-induced injury to ciliated epithelial cells, together with exposure and sensitization of irritant airway receptors, which lead to persistent bronchial hyperreactivity.[4,13] Affected individuals show bronchoconstriction and coughing in response to mildly irritating stimuli such as dust, stable pollutants, cold air, dry air, and exercise that would not normally cause coughing. Coughing subsides only when the airway epithelium has healed, which may take up to 7 weeks.[4]

Although the role of mucus in coughing is not clear, normal amounts of mucus may have a protective effect by coating the epithelium with a layer that separates the receptors from irritants.[4] Conversely, excessive accumulation of mucus in the airways, such as occurs in horses with RAO, may mechanically stimulate irritant receptors and cause coughing.[4] Fluid flushed over the tracheobronchial epithelium stimulates irritant receptors, particularly if the fluid is hypertonic or hypotonic.[9,10,14] Coughing is also stimulated by fluid that lacks permeant anions (i.e., anions that have a hydrated size and membrane-penetrating characteristics similar to the chloride anion).[15]

Coughing is a prominent feature of cardiac disease in many species, although cardiac diseases are not often encountered in large domestic animals. Failure of the left side of the heart resulting from congenital defects, valvular stenosis or incompetence, conduction disturbances, myocardial disorders, or restrictive pericardial disease causes an increase in pressure in the pulmonary venous return

from the lung. This results in transudation of fluid from the pulmonary capillaries into the pulmonary parenchyma and airspaces (cardiogenic pulmonary edema) and causes swelling of the mucosal lining of small airways.[2] These changes stimulate cough receptors and initiate the cough reflex. Coughing that occurs secondary to cardiac disease is usually chronic, although acute-onset coughing may be observed with ruptured mitral chordae tendineae and bacterial endocarditis.[16]

Approach to Diagnosis of Coughing

History.

The history should include questioning relative to the patient, the cough, the environment, and management. The *age* of the affected animal is important because many conditions have a marked age incidence. For example, *R. equi* pneumonia occurs primarily in foals younger than 6 months of age, equine herpesvirus type 4 predominantly affects weanling and yearling horses, and RAO affects primarily mature stabled horses. The *use of the horse;* its state of fitness; the presence of vices such as crib biting; and any *history of contact with other horses* at shows, events, sales, racetracks, or breeding farms should be determined.

Recent stressors such as transportation, surgery, strenuous activity, or weaning should be determined because these are known risk factors for conditions such as pneumonia and pleuropneumonia. The duration of ownership of the animal, its previous health, and the geographic location of origin, if it was recently purchased, may help identify regional diseases not normally seen in the area (e.g., systemic mycosis, lungworms, or silicosis in horses) or indicate the degree of stress likely to have been experienced recently. For recently purchased feedlot cattle and sheep, it should be determined if the animals were preconditioned before sale, their place of origin, the number of sale yards through which they have passed, and the duration of transportation.

When evaluating the potential for contagious diseases or those related to common environmental conditions, the vaccination status of the affected animal and herdmates and the presence of similar clinical signs in other in-contact animals sharing common facilities or common airspaces should be determined. In nursing animals, the vaccination status of the dam is important. A history of other signs such as anorexia, nasal discharge, weight loss, exercise intolerance,

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stridor, lymphadenopathy, facial swelling, diarrhea, colic, and edema may provide important clues to the cause of the current problem. Weight loss occurs in many acute and chronic diseases, both infectious and noninfectious. Anorexia may indicate that eating is too painful for an animal, for example, because of a painful nasopharyngeal lesion or because the animal is devoting so much effort to breathing that it will not eat.

Environmental considerations such as the introduction of new animals into the environment or the return of animals from shows, sales, training centers, or breeding farms should increase the suspicion of infectious viral or bacterial diseases such as IBR in cattle or influenza in horses. For diseases such as *R. equi* pneumonia in foals, it is useful to know if similar cases have been seen on the premises in the past. The type of housing or pasturing facilities should be evaluated, particularly with regard to airspace, ventilation, sanitation, stocking density, dust, shade, and shelter. Equine stabling facilities that have enclosed barns, particularly when the stalls face a central arena or are located under a hay storage loft, promote the spread of contagious agents and almost invariably increase the concentration of dust, mold spores, and noxious gases such as ammonia and tractor exhaust fumes in the environment. The type of feed and bedding, storage facilities, and feeding arrangements should be evaluated, especially in chronically coughing horses suspected of having allergic lung disease. Quantitative measures of ventilation and environmental quality can be made and can prove helpful in case management and in monitoring the effectiveness of measures to reduce environmental dust and other pollutants.[17] Similarly, the sampling of air in barns or paddocks using special devices allowing quantitation of bacterial pathogens such as *R. equi* may prove useful for assessing risk of infection.

The quality of the feed should be evaluated visually and by smell, particularly with regard to the presence of mold spores. General management, pasture management, and parasite control measures should also be evaluated, especially if lungworm infection is suspected. Horses with lungworm infection almost invariably have a history of current or previous co-grazing with donkeys. The season and seasonal incidence of recurrence of the coughing can provide useful clues (e.g., marked seasonal worsening of signs in the late autumn when horses are stabled suggests chronic allergic respiratory disease). Similar to the conditions mentioned for horses, cattle pastured during the warmer months of the year and housed during the colder months may demonstrate recurrent episodes of respiratory dysfunction and cough associated with allergies to dusts

present in stored hay or bedding. The history should also include the nature of previous treatments and the response.

Important historical features of the cough include the time and speed of onset; frequency; duration (chronic if longer than 1 month); relation to feeding, housing, or weather; relation to exercise and timing during exercise; improvement, deterioration, or other change since onset; and the presence of and similarity to previous episodes of coughing or respiratory disease. Many coughs are exacerbated by exercise because exercise places greater stress on the respiratory tract. The resulting rapid airflow improves mobilization of secretions and irritates the airway directly. Coughs that occur during eating suggest specific or nonspecific sensitivity to molds, pollen, or other dusts in feed; inflammatory conditions of the larynx or pharyngeal region; laryngeal or pharyngeal problems, including complications of surgery, that interfere with swallowing or guarding of the lower airway; or esophageal obstruction (choke). The effort involved in coughing and associated pain may also give clues to the cause of the cough.

The character of the cough should be evaluated because certain features of a cough tend to point toward its origin and possible causes but are by no means pathognomonic for either. Coughs originating in the upper airway are usually of acute onset, loud, harsh, coarse, dry, hacking, and nonproductive in character. Painful upper airway conditions such as acute pharyngitis, strangles, or necrotizing laryngitis can make the cough more muted. Lower airway coughs are usually soft, deep, and productive (mucus, pus) and tend to be more persistent than coughs originating in the upper airway. However, chest pain frequently attenuates coughing in horses with pleuropneumonia. In horses the fixed position of the larynx within the nasopharynx usually precludes expectoration of sputum into the mouth; thus the productive nature of the cough is difficult to assess. Excess mucus or exudate that is coughed up into the pharynx is usually swallowed; thus a cough can be productive without evidence of a nasal discharge. Swallowing efforts that follow a cough generally indicate that the cough is productive.

Physical Examination.

The physical examination should include both distant and close evaluation of the patient and the environment. In addition to a detailed examination of the respiratory and cardiovascular systems, a general physical examination should also be completed so that diseases in other systems can be detected and systemic manifestations of cardiopulmonary disease can be evaluated. The attitude of the

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animal, the respiratory rate and character, the presence of excessive intercostal or abdominal respiratory effort or of a “heave line” or “barrel chest,” the presence and nature of respiratory distress or stridor at rest, and the presence and character of any nasal and ocular discharge should be noted before the animal is restrained. The following should then be determined: (1) rectal temperature, pulse rate, pulse rhythm and character, mucous membrane color, and capillary refill time; (2) symmetry of airflow from each nostril; (3) odor from the nostrils and mouth; (4) facial symmetry and swelling; (5) resonance or painful response on percussion of the maxillary and frontal sinuses; (6) enlargement of submandibular, parotid, retropharyngeal, prescapular, and other regional lymph nodes; (7) enlargement of the parotid salivary glands or thyroid gland; (8) swelling, pain, or palpable abnormalities in the retropharyngeal region; (9) palpable swelling or flattening of the cervical trachea; and (10) masses at the thoracic inlet and palpable turbulence such as a tracheal rattle in the extrathoracic airway. The oral cavity should also be examined. If spontaneous coughing is not heard during the physical examination, a cough should be induced after auscultation of the airways by pinching the larynx or trachea, and it should be ascertained whether the induced cough sounds like the animal's spontaneous cough. Pinching of the trachea generally causes normal animals to cough once or twice, whereas it often induces paroxysmal coughing in animals with lower airway disease. The laryngeal or tracheal cough reflexes show increased sensitivity in most infective and inflammatory airway diseases.[16]

The larynx, trachea, lungs, and heart should be carefully *auscultated,* as should both sides of the chest, in a quiet environment with the animal at rest and after the rate and depth of respiration have been increased by application of a rebreathing bag, by temporary occlusion of the nostrils, or by light exercise (see the Cyanosis section later). Auscultation of the trachea and larynx should be performed at an early point in the examination, before a rebreathing bag is applied, in order to assess the potential for upper airway obstruction during the examination of the thorax. Auscultation permits detection of turbulent airflow, increased or decreased bronchovesicular sounds, wheezes, crackles, pleural friction rubs, or pleural fluid splashes, all of which indicate disease of the airways, pulmonary parenchyma, or pleura. Wheezes and crackles reflect airway narrowing and dynamic airway collapse, respectively, and are both evidence of small airway disease.[16] A small (12 L) or medium-size (52 L) plastic trash bag makes an adequate rebreathing bag; a plastic rectal sleeve is satisfactory for foals or calves if the opening is stretched so that it does not occlude the nostrils. The

response to application of a rebreathing bag should also be noted. Most horses tolerate this procedure well and breathe more deeply, whereas animals with chest pain often do not. Normal horses do not cough when the bag is applied unless they have been eating recently, whereas horses with airway irritation caused by pneumonia or other conditions often cough paroxysmally in response to application of a rebreathing bag. The time taken to regain the normal respiratory rate and character after removal of the bag provides a reasonable, qualitative indicator of ventilatory reserve. Normal animals recover quickly, within a few breaths, whereas respiration may be altered for several minutes in animals with significant lung disease. On removal of the rebreathing bag, the expired air in the bag can be smelled to determine if odors suggestive of necrotic tissue are present.

The chest wall should be *palpated* to detect pleural friction rubs or lesions such as rib fractures, and the symmetry of chest expansion should be determined. Young calves with chest deformation (unilateral or bilateral) and severe inspiratory and expiratory respiratory distress should be evaluated for fractured ribs that are causing tracheal compression/stenosis (see Chapter 31 for horses and more on ruminants). Temporary tracheostomy does not relieve this respiratory embarrassment. Unilateral chest pain (pleurodynia) often reduces chest excursion on the affected side. Both sides of the chest should be *percussed* systematically to detect changes in resonance and chest pain. The caudoventral percussion border in the normal horse traces from the level of the tuber coxae at the seventeenth intercostal space (the horse normally has 18 pairs of ribs) to the level of the tuber ischii at the fifteenth intercostal space to the midthorax at the thirteenth intercostal space to the level of the point of the shoulder at the eleventh intercostal space; it continues as a curving line to a point 1 to 3 inches above the olecranon. The normal caudoventral percussion boundary in cattle and small ruminants traces from the eleventh intercostal space at the level of the lateral edge of the epaxial musculature to the ninth rib at a level halfway between the costochondral junction and the lateral edge of the epaxial musculature to the fifth rib at the olecranon (cattle, goats, and sheep normally have 13 pairs of ribs). Percussion is an important diagnostic tool in all large animals, but it is most useful in foals, calves, and goats. The precise percussion boundaries, degree of resonance, and auscultation findings are influenced by age, size, body condition, fitness, and hair coat, as well as by disease processes; a gas-filled abdominal viscus can also confuse interpretation. Hyporesonance (dullness) may indicate pulmonary consolidation, large mass lesions,

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cardiomegaly, pleural effusion, or other pleural disease. Free pleural fluid usually causes an abrupt change from normal resonance above a horizontal fluid line to hyporesonance below this line. Hyperinflation or pneumothorax may cause hyperresonance with or without expansion of the normal percussion boundaries. A painful response to percussion may indicate pleuritis or some other inflammatory process involving the parietal pleura. Painful responses may be dramatic and potentially injurious to the examiner.

In cattle the presence of thoracic or cranial abdominal pain should be ascertained by application of upward pressure to the xiphoid area with the knee or by application of downward pressure with both hands just caudal to the withers. Animals with cranial abdominal or thoracic pain resist these maneuvers and may make an audible or auscultatable grunting noise. Signs such as jugular distention or pulsation (or both) and peripheral edema, which may indicate heart failure, should be noted. As well, the heart should be auscultated to detect murmurs, dysrhythmias, muffling of heart sounds, or other abnormalities that would indicate the need for further cardiovascular diagnostic procedures.

Complete Blood Count.

A complete blood count including fibrinogen concentration usually reveals nonspecific findings but may be useful in the evaluation of cases in which primary or secondary inflammatory conditions are suspected and in conditions such as pulmonary thromboembolism secondary to caudal vena cava thrombosis (CVCT) in cattle and guttural pouch mycosis in horses in which blood-loss anemia is likely to be a complicating problem. Acute viral infections often induce a transient anemia and leukopenia, predominantly lymphopenia, followed by a monocytosis during recovery. Neutrophilia and hyperfibrinogenemia are features of many inflammatory conditions but are usually most marked when bacterial infection is involved. Some parasitic diseases (e.g., lungworm infection in cattle) may induce eosinophilia, as may allergic conditions, but eosinophilia is not a common feature of either lungworm infection or allergic RAO in the horse.

Nasal or Nasopharyngeal Swabbing.

Nasal or nasopharyngeal swabbing with direct cytologic examination and culture or molecular diagnostic testing are indicated for confirmation of viral or bacterial infections that involve the upper airway. Because a large number of bacteria normally inhabit the nasopharynx, only the presence of *Streptococcus*

equi or some other pathogen not considered part of the resident flora can be considered significant in horses. When clinical signs suggest a viral respiratory infection, especially when an outbreak of coughing occurs in several animals, *molecular detection* by polymerase chain reaction (PCR), *antigen detection* by antigen-capture enzyme-linked immunosorbent assay (ELISA), or *virus isolation* from nasal or nasopharyngeal swabs, tracheal wash, and/or buffy coat (ethylenediaminetetraacetic acid [EDTA] blood) samples collected during the acute phase of the disease is indicated, as may be *viral serologic tests* on acute and convalescent serum samples.[18] Under these circumstances, sampling as many of the most severely affected, often younger, animals as early as possible in the disease course maximizes the chances of establishing an etiologic diagnosis. Nasal swabs are slightly easier to collect than nasopharyngeal swabs and yield similar results when sensitive PCR tests are used[19]; however, nasopharyngeal swabs are preferred for virus isolation by many diagnostic laboratories. Nasal swabs are best collected using 6-inch Dacron or rayon (not cotton) swabs, whereas nasopharyngeal swabs are best collected using longer, larger swabs (e.g., Fox 16-inch Procto Swabs, Allegiance Health Care, Hayward, Calif.). Swabs should be placed in capped tubes for submission for PCR testing or into viral transport medium for immediate submission to the laboratory if virus isolation will be requested. It is best to use the transport medium supplied by the respective laboratory to ensure compatibility with viral culture systems. Antigen-capture ELISA (e.g., influenza Directigen Flu A test, Becton-Dickinson, Franklin Lakes, N.J.) and PCR tests are available for testing of nasal or nasopharyngeal swabs and other samples to confirm a diagnosis of viral infection.[18] These rapid-screening tests are sensitive and less cumbersome to perform than virus isolation, do not require such stringent conditions for handling and transporting samples, and provide results sufficiently quickly that specific control measures can be implemented. However, they do not yield an isolate that can be used to monitor genetic and antigenic evolution of the viral agent. Serologic testing often provides only retrospective information, but it can prove helpful in the formulation of future control measures, including vaccination. The larger the number of animals tested, the more informative are the results of serologic testing in a herd or flock. Serologic testing is also indicated when pneumonia caused by *Coccidioides immitis* or other fungal agents is suspected.

Endoscopic Examination.

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Endoscopic examination of the nasal passages, conchae (turbinates), pharynx, larynx, and trachea allows the presence, nature, and source of exudates and the presence of anatomic or functional abnormalities or mass lesions to be noted. Endoscopic examination of the upper airway of the horse to evaluate for partial airway obstruction is best performed without the use of sedatives or tranquilizers if possible because these alter the tone and function of the muscles supporting laryngeal and pharyngeal anatomy and function and may confuse interpretation of endoscopic findings. In the horse the interior of the guttural pouches may be examined by advancing the endoscope through the pharyngeal openings of each guttural pouch using a guidewire such as a closed biopsy instrument passed through the biopsy channel of the endoscope and into the pouch. Most coughing horses have lower airway disease, which may be reflected in accumulation of endoscopically visible exudate in the horizontal trachea, particularly after exercise. Lungworm larvae may be grossly visible in the trachea of horses with lungworm infection. Deeper bronchoscopic examination is necessary to determine whether exudate reflects diffuse airway disease or it arises from a specific area of the lung, such as would occur with a pulmonary abscess or a foreign body lodged in a bronchus. Sedation may or may not be necessary to permit endoscopic examination of the extrathoracic airways in the standing horse; however, sedation with xylazine (1.1 mg/kg IV), detomidine (0.04 mg/kg IV), or romifidine (0.04 to 0.12 mg/kg IV) supplemented with butorphanol (0.1 to 0.2 mg/kg IV) is recommended to facilitate bronchoscopy and to dampen the cough reflex, as is spraying of the carina and bronchial branches with 2% lidocaine via the biopsy channel of the endoscope to reduce coughing during the procedure. Tracheobronchial aspiration and bronchoalveolar lavage (BAL) can be performed by introducing appropriate catheters via the biopsy channel of the endoscope.

Tracheal Aspiration.

Tracheal aspiration with cytologic studies and quantitative or semiquantitative aerobic and anaerobic culture, or PCR testing, of collected samples is indicated in the evaluation of patients suspected of having disease of the lungs or pleura, particularly if an infectious cause is likely. Tracheal wash samples collected using the percutaneous transtracheal technique are preferred for bacterial culture because they are not contaminated by oropharyngeal organisms.[20,21] Collection of samples by introducing a sterile catheter through the biopsy channel of a presterilized endoscope inserted within a sterile sheath, or by introducing a

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double-sheathed catheter via the biopsy channel, is acceptable and less subject to complications than is the transtracheal technique, but samples obtained transendoscopically may be contaminated with *Pseudomonas* species and anaerobic bacteria despite the use of a guarded technique.[21] If tracheal aspiration will be performed percutaneously, the procedure should precede endoscopic examination of the lower airways to avoid contamination. Culture may fail to reveal the primary bacterial pathogen, especially in animals that have been treated with antibiotics. The diagnostic value of tracheal wash samples can be improved by discontinuing antibiotic therapy for at least 24 hours before collecting samples, rapidly processing samples, using antibiotic removal devices and selective culture media, and, if necessary, repeating sampling. Culture results should be evaluated in relation to the clinical signs, clinical experience (especially on the farm of origin of the patient), results of cytologic evaluation, and response to treatment. The trachea is not a sterile environment; therefore culture of small numbers of bacteria without cytologic evidence of infection is of questionable significance.

Bronchoalveolar Lavage.

Samples collected by BAL are less useful than those collected by tracheal aspiration for evaluating infectious lower airway diseases and focal pulmonary conditions because the technique samples secretions from only a limited area of the caudodorsal lung on one side and is subject to contamination during introduction of the BAL tube through the nasopharynx. However, BAL yields better samples for cytologic assessment and is therefore preferred for evaluation of patients with generalized, noninfectious lower airway diseases such as RAO or silicosis.[18] BAL samples can be collected under endoscopic guidance by means of catheters introduced through the biopsy channel of a suitable endoscope (<9 mm in diameter and longer than 180 cm) or by using commercially available BAL tubes. The advantage of collection via endoscopy is that specific areas of the lung can be sampled, although gaining access to the cranial lung lobes is difficult with any method. Differential cell counts in BAL fluid of normal horses vary depending on age, environment, activity, and other factors. In young horses (<6 years of age), the distribution of macrophages, lymphocytes, neutrophils, mast cells, and eosinophils is on average 65%, 30%, 3%, 0.5%, and 0%, respectively.[22] In horses older than 6 years of age, the neutrophil population may reach 15% in normal horses, with a corresponding

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decrease in the proportion of lymphocytes and macrophages.[22] The percentage of neutrophils in normal calves is generally within the range of 5% to 20% depending on calf age, type, health status, and sampling method.[23,24]

Neutrophils are usually the predominant cell type in BAL fluid or tracheal washes of horses with RAO and in animals with bacterial infections. The neutrophils usually show degenerative changes when significant bacterial infection is present. Large numbers of eosinophils are a feature of parasitic infections such as lungworms, some allergic conditions, and infiltrative eosinophilic interstitial pneumonia. The presence of hemosiderin-laden macrophages is an indication of recent pulmonary hemorrhage, and finding refractile intracytoplasmic granules in macrophages or giant cells should raise the suspicion of silicosis, especially in animals showing radiographic evidence of marked pulmonary interstitial disease. Noting the presence, number, location (intracellular or extracellular), and Gram stain characteristics of bacteria permits rational selection of antibiotics for treatment while awaiting the results of culture and susceptibility tests.

Ultrasound Examination.

Ultrasound examination is useful for examining externally visible lesions such as possible retropharyngeal abscesses impinging on the airway and causing the cough. Ultrasound examination of the chest is indicated to determine the presence and extent of pleural effusion, pleural roughening, pleural fluid with or without fibrin deposits, gas echoes in pleural fluid, pleural adhesions, and pulmonary lesions such as consolidation, atelectasis, or abscessation in animals with lesions in contact with the pleural surface or in animals in which sufficient pleural fluid has accumulated to allow evaluation of the underlying lung. The tissue-to-air interface at the visceral surface of the normal lung appears as a thin, smooth, bright echogenic line on ultrasound because it reflects the ultrasound beam, precluding visualization of deeper structures. Penetration of the ultrasound beam beyond the surface of the lung occurs only in the presence of lung pathology that extends to the visceral pleural surface of the lung in the area being scanned.

Blood Gas Analysis.

Blood gas analysis on arterial blood to determine oxygen (O_2) and carbon dioxide (CO_2) tensions is indicated in the evaluation and monitoring of patients

in which a history or clinical signs of coughing are accompanied by signs of respiratory distress or cyanosis (see the Respiratory Distress [Dyspnea] and Cyanosis sections later).

Thoracocentesis.

Thoracocentesis with culture and cytologic examination of collected samples is indicated in animals with clinical or ultrasonographic evidence of effusive pleural disease. Pleural fluid should be odorless, pale yellow to straw colored, and transparent and have a pH greater than 7.2, a protein concentration of less than 2.5 g/dL, and a total nucleated cell count of less than 10,000/µL cells, most of which should be mononuclear cells (macrophages and mesothelial cells).[18] Determination of the pH and concentrations of glucose, lactate, and lactate dehydrogenase (LDH) in pleural fluid collected into a heparinized tube or syringe helps differentiate septic from nonseptic effusions while awaiting culture results.[25] Septic effusions typically have a pH of less than 7.2, a low glucose concentration (<40 mg/dL), a high LDH concentration (>1000 IU/L), and a lactate concentration higher than that present in venous blood.[25-27] The best site for collecting pleural fluid can be confirmed by ultrasonography after auscultation and percussion of the chest. The sixth and seventh intercostal spaces at the level of the costochondral junction are commonly used sites in horses and cattle. The thorax should be penetrated in the part of the intercostal space immediately adjacent to the cranial border of the rib to avoid the intercostal vessels and nerves.

Pleuroscopy.

Pleuroscopy is a more invasive procedure with limited indications that include investigation of chronic pleural diseases such as abscesses, pleural adhesions, and possible primary or metastatic pulmonary or pleural neoplasia such as lymphosarcoma, gastric squamous cell carcinoma, or mesothelioma. The procedure can be performed in a standing, sedated patient by using a sterile rigid or fiberoptic endoscope. This procedure is indicated for patients in which large intrathoracic masses and adhesions have been demonstrated by ultrasonography or thoracic radiology and when less invasive techniques have failed to provide the necessary diagnostic information. Pleuroscopy allows direct visualization of affected structures and provides an opportunity to biopsy masses or aspirate fluid. The pleuroscopy procedure is associated with complications (e.g.,

pneumothorax, lung laceration, infection) that should be anticipated in advance.

Fecal Examination.

Fecal examination using the Baermann technique to detect lungworm larvae is indicated in ruminants suspected of having a lungworm infection. Because lungworm infection in the horse rarely becomes patent, larvae are not usually demonstrable by fecal examination. Pulmonary signs related to *Parascaris equorum* infection in foals occur during the prepatent (migratory) period; therefore the fecal flotation test for ascarid eggs often yields a negative result despite significant parasitic infection.

Radiographic Examination.

Radiography of the chest is indicated in patients suspected of having lower airway disease to determine the presence, severity, and pattern of disease changes involving the lungs, pleura, and mediastinum. Four overlapping lateral projections are usually required to evaluate the whole lung field in an adult horse. Because ventrodorsal projections are possible only in young large animals, lateral projections from each side may be necessary to lateralize lesions within the chest. Radiographs of the lungs are particularly useful for determining the prognosis and for monitoring the response to therapy of pulmonary diseases such as bacterial pneumonia and lung abscesses. The cardiac silhouette and the pattern and caliber of the aorta, vena cava, pulmonary artery, pulmonary veins, and other vessels should be evaluated for evidence of cardiac failure and pulmonary vascular disease. Radiographs of the pharynx, retropharyngeal area (including guttural pouches in the horse), larynx, and proximal trachea are indicated in some cases to confirm problems not definitively diagnosed by clinical examination and endoscopy.

Nuclear Scintigraphy.

Nuclear scintigraphy using aerosolized technetium-99m (^{99m}Tc)–labeled diethylenetriaminepentaacetic acid (DPTA) and intravenously injected ^{99m}Tc-labeled microaggregated albumin particles has been used to determine patterns of pulmonary ventilation, perfusion, and ventilation/perfusion ratios.[20,28] This technique requires special equipment and personnel but provides an objective assessment of pulmonary function and gas exchange capability.[28]

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Biopsy.

Biopsy, with histologic evaluation of samples, is indicated to diagnose certain mass lesions such as neoplasms, cysts, polyps, fungal granulomas, or foreign body granulomas in or surrounding the airway. Masses in the airway can be biopsied through the biopsy channel of an endoscope, but these samples inevitably are small. Biopsies can also be collected at the time of exploratory or corrective surgery from lesions in the upper airway. Lung biopsies can be collected blindly, using Tru-Cut, Biopty, or similar instruments, preferably from the peripheral areas of the lung to reduce the likelihood of serious hemorrhage (see Chapter 31). Focal lesions can be visualized ultrasonographically or radiographically during the percutaneous biopsy procedure to improve the likelihood of obtaining diagnostic specimens. Lung biopsy is most useful for diagnosing diffuse nonseptic conditions such as pneumoconiosis. The inherent risks associated with the procedure indicate that percutaneous lung biopsy should be reserved for circumstances in which the animal is not showing signs of marked respiratory distress, uncontrollable coughing, or bleeding disorders and a high likelihood exists that the procedure will yield significant diagnostic information. Open lung biopsy is possible, albeit rarely indicated.

Immunoglobulin Determinations.

Quantitative immunoglobulin determinations and possibly other *immune function tests* may be indicated in animals, especially the young, with chronic or recurrent respiratory tract infections or other indications of immune compromise.

Allergen Testing.

Intradermal testing (IDT) for allergens, a radioallergosorbent test (RAST), ELISA tests for immunoglobulin E (IgE) on serum, and inhaled challenge have been advocated to evaluate horses suspected of having allergic respiratory disease based on exacerbation of signs in certain environments or with certain feeding practices. Although there are anecdotal reports that horses with RAO have been hyposensitized successfully using allergens selected on the basis of these allergen tests, the authors are unaware of documentation in well-controlled studies. In addition, a recent study showed that compared with normal non-atopic horses, RAO-affected horses did not have a significantly greater number of positive reactions in IDT against any allergen group (molds, grasses, weeds, trees, and insects), leading the authors to conclude that reactions to individual

allergens in IDT should not be used to determine that horses have clinically relevant hypersensitivity.[29] Many normal horses show sensitivity to individual mold spores and other allergens, and there is poor correlation between the dermal and pulmonary reactivities to mold antigens.[13] Furthermore, when compared with the results of IDT, RAST and ELISA serum allergy tests have been shown to have low sensitivity in detecting allergen sensitivity.[30] Although the use of recombinant allergens rather than crude mold extracts in ELISA tests substantially improves sensitivity in detecting levels of allergen-specific IgE,[31] and significantly more RAO-affected horses than normal horses have high allergen-specific IgE levels, the degree of overlap of results precludes its use for diagnostic purposes.[32] The crude trial-and-error approach of adding or removing potential allergens from the environment is sometimes helpful diagnostically and therapeutically in RAO cases in which an allergic cause is suspected. Feeding of pellets instead of hay and using shredded paper, peat moss, or wood shavings instead of straw bedding are common examples of this approach (see the RAO section in Chapter 31). Allergen testing or serologic evaluation of adult cattle with historical evidence of recurrent, seasonal, respiratory disease (extrinsic allergic alveolitis) have not proven diagnostic of specific allergen-induced disease; rather, results merely suggest prior exposure to molds (see Chapter 31).

Pulmonary Function Testing.

Except for measurement of pleural pressure using an esophageal balloon catheter attached to a pneumotachograph, pulmonary function testing and evaluation of airway dynamics during exercise have until recently been largely research techniques that were not readily applicable to clinical patients. Development of the minimally invasive techniques of oscillometry (forced oscillatory mechanics [FOM]), forced expiratory maneuvers, and flow metrics now permits physiologic assessment of lung function in clinical patients.[33,34] When coupled with histamine provocation tests to assess airway reactivity and bronchodilator response tests, pulmonary function tests can provide a considerable amount of information to guide therapy and prognosis. Indications for pulmonary function testing might include evaluating horses with a history of poor performance or exercise intolerance but no other detectable abnormalities; assessing the degree of functional impairment in horses with known evidence of respiratory disease; assessing the efficacy of therapeutic regimens; determining if a horse has recovered from a diagnosed respiratory disorder and can be returned to training;

and ruling out functional pulmonary abnormalities in horses with upper airway conditions.

Bronchodilator Response Testing.

Bronchodilator response testing involves determining the response of measured pulmonary functions and pleural pressures to rapidly acting bronchodilator drugs such as albuterol (450 to 900 µg) or ipratropium bromide, administered by aerosol, or atropine administered parenterally.[33] Results are often helpful in determining the pathogenesis of RAO and the likely response to bronchodilator therapy. In the field setting, useful information can be gained by assessing the response of respiratory rate, respiratory character, and lung sounds to intravenous (IV) administration of a low dose of atropine (5 to 7 mg/450-kg horse). This test can be made more objective by measuring pleural pressures using a Ventigraph recorder (Boehringer Ingelheim Vetmedica, Inc., St Joseph, Mo.) attached to an esophageal catheter or flowmetric techniques.[13,33,35,36]

Differential Diagnosis of Coughing.

The differential diagnosis of coughing can be enhanced by arbitrarily categorizing it on the basis of *duration of signs* into acute or chronic (>1 month) and by the *presence or absence of fever.*[37] It should be kept in mind that some acute coughs become chronic and that, conversely, conditions that cause chronic coughing may be seen early in the disease course. Conditions typically associated with *acute coughing* include viral, bacterial, and parasitic infections of the upper and lower respiratory tract; acute allergic reactions or acute toxic injury to the lung; foreign bodies; choke; injuries to the larynx, trachea, or chest; pharyngeal or laryngeal dysfunction secondary to neurologic disorders or surgery; aspiration of food material or foreign bodies; smoke inhalation; and compressive upper airway lesions such as retropharyngeal abscesses or necrotic laryngitis. In most instances, outbreaks of sudden-onset coughing in groups of animals are the result of viral infection involving the upper and lower respiratory tract.[8,16]

Conditions typically associated with *chronic coughing* include chronic bacterial pneumonia; pulmonary abscess; chronic pleuritis; chronic allergic pulmonary diseases such as RAO in horses and farmer's lung disease of cattle; postviral bronchial hyperreactivity; chronic viral respiratory disease such as ovine progressive pneumonia; irritant airway disease caused by environmental

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irritants such as dust; lungworm infections, particularly in horses and small ruminants; functional or anatomic problems in the pharynx or larynx that interfere with guarding of the airway, including postsurgical problems; heart failure resulting in pulmonary edema; tumors or polyps in the upper airway or lung; mycotic infections of the upper airway, lung, or pleura; chronic guttural pouch infections in horses; tracheal collapse, especially in ponies; chronic interstitial disease such as pneumoconiosis caused by inhalation of particulate material; and so-called nuisance coughs. Nuisance coughs are common in horses, especially at the beginning of exercise, which emphasizes the fact that coughing is a normal airway-protective mechanism and not always evidence of disease. Nuisance coughs tend to bother the owner more than the horse and can result from habit; vices such as crib biting, wind sucking, or greedy eating; and environmental factors such as dust, ammonia, and cold air. Some nuisance coughs resolve after modifying the stabling or work environment.

Cough with fever usually indicates a primary infectious cause or a secondary infection superimposed on a noninfectious cause.[37] Fever is a typical but not invariable feature of aspiration pneumonia, bacterial pneumonia, pulmonary abscess, viral respiratory tract infection, strangles, fungal pneumonia, pleuropneumonia (bacterial, viral, or mycoplasmal), acute bronchointerstitial pneumonia, and thoracic neoplasia.[37]

Cough without fever is typically found in RAO, abnormalities of the larynx or pharynx, parasitic pneumonia, exercise-induced pulmonary hemorrhage (EIPH), tracheobronchial foreign body, tracheal collapse, and airway-oriented neoplasia (e.g., bronchial carcinoma).[37] Horses with chronic interstitial pneumonia such as silicosis or granulomatous pneumonia are usually afebrile but may have mild to moderate fever.[1]

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Nasal Discharge

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

■ Definition

Nasal discharge, which is any nongaseous material that exits the respiratory tract through the external nares, is described according to its *physical characteristics* (serous, mucoid, purulent, hemorrhagic [sanguineous], or a combination of these types with or without feed material); *acuteness of onset* (sudden or insidious); *origin* (unilateral or bilateral); *volume* (profuse or scant); and *association with activity* (spontaneous or intermittent).[38-40]

■ Pathophysiology

Normal Nasal Secretions.

The ciliated, pseudostratified columnar epithelium lining the respiratory tract from the nasal passages to the level of the respiratory bronchioles contains serous, mucous, and mixed tubuloalveolar glands in its lamina propria.[38] Goblet cells are present in large numbers throughout the nasal cavity and are present in the airway mucosa to the level of secondary and tertiary bronchi.[38] The secretions of these glands and goblet cells and the fluid transudated from serum together serve to warm and humidify inspired air, trap particulate matter, protect the respiratory epithelium from desiccation and infection, and provide the seromucous bilayer necessary for effective ciliary function.[11,41] The tracheobronchial fluid that constitutes the mucous blanket in the lower parts of the respiratory tract contains exfoliated epithelial cells, alveolar macrophages, other mononuclear cells, glycoproteins, bacteriostatic proteins (primarily lysozyme), lactoferrin, secretory IgA, IgG, IgM, and serum proteins (primarily albumin).[11,41] The cilia lining the pseudostratified columnar epithelium beat in coordinated waves to carry mucus, trapped particles, and cells from the lower respiratory tract to the nasopharynx. Material cleared from the tracheobronchial tree is normally swallowed on reaching the pharynx but may appear at the external nares as nasal discharge.[41]

Serous nasal secretions in normal animals are responsible for the moist appearance of the ventral portion of the external nares. In cattle, normal nasal secretions are more voluminous and more mucoid compared with other large animal species. Healthy cattle keep their external nares clean through frequent and repeated licking. Cattle that are systemically ill or otherwise debilitated often neglect to do this, and as a result mucoid secretions accumulate and crust around the external nares. On the other hand, a buildup of nasal discharge in cattle with respiratory disease can be removed by frequent nose licking, masking the presence of disease.

Lacrimal secretions also drain into the nasal passages through the nasolacrimal ducts and may appear at the external nares as a thin, watery, clear, nonviscous discharge, particularly in animals with conjunctival irritation or ocular inflammatory diseases that stimulate excessive lacrimation.[39]

Abnormal Nasal Secretions.

Inflammatory conditions involving the nasal cavity stimulate increased production of glandular secretions.[41] These secretions initially are serous but later become mucoid and purulent as secondary bacterial invasion induces an influx of neutrophils.[38] Serous nasal discharge generally indicates disease conditions affecting the nasal passages or upper respiratory tract.

Inflammation, irritation, and other pathologic states affecting the trachea and bronchi increase the production of mucous and serous secretions in the tracheobronchial tree[41] (Boxes 5.3 and 5.4). Initially the accompanying nasal discharge is mucoid (clear, colorless, thin, and elastic in consistency), but with chronicity and secondary bacterial invasion, neutrophils and other inflammatory cells accumulate in the tracheobronchial secretions and the nasal discharge becomes purulent, progressing from cloudy to opaque and then to viscous with a whitish cream color (Boxes 5.5 and 5.6).

Box 5.3

Causes of Serous and Mucoid Nasal Discharge in Horses

Common Causes

Influenza
Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)
Other viruses (e.g., rhinitis A and B viruses, adenovirus, reovirus, EHV-2)
Pharyngitis, chronic pharyngeal lymphoid hyperplasia
Nasal or paranasal sinus infection, cysts, polyps, tumors
Early bacterial pneumonia or pleuritis
Early strangles (*Streptococcus equi* infection)
Guttural pouch infection, mycosis
Overflow of nasolacrimal ducts
Recurrent airway obstruction (RAO or chronic obstructive pulmonary disease)

Less Common Causes

Equine viral arteritis
Burn (thermal, chemical)
Anaphylaxis or acute drug reaction
Aspiration or foreign body pneumonia, smoke inhalation
Foreign body (nasal, pharyngeal, guttural pouch, tracheal, or bronchial)
Summer pasture–associated obstructive airway disease (SPOAD)

Uncommon Causes

Nasal fungal infection (rhinophycomycosis), aspergillosis
Nasal amyloidosis
Coccidioidomycosis
Restrictive pulmonary disease, pneumoconiosis
Trauma to the skull or upper airway
Tuberculosis
Tularemia
Guttural pouch neoplasia
Chlamydia psittaci pneumonia
Nocardiosis
Cryptococcosis
Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, pythiosis
Lungworm infection *(Dictyocaulus arnfieldi)*

Ascarid migration
Cyst (pharyngeal, subepiglottal)
Progressive ethmoidal hematoma
Lymphosarcoma, lymphoma, leukemia
Halicephalobus (Micronema) deletrix granuloma
Pulmonary edema
Pulmonary aspergillosis
Stachybotryotoxicosis
Trichloroethylene-extracted feed toxicity
Pentachlorophenol toxicity
Organophosphate, carbamate toxicity
Ammonia toxicity
St. George disease (*Pimelea* species poisoning) (exotic)
Trypanosoma evansi, surra (exotic)
Trypanosoma equinum, mal de caderas (exotic)
Trypanosoma hippicum, murrina de caderas (exotic)
Besnoitiosis, globidiosis (exotic)
African horse sickness (exotic)
Getah virus (exotic)
Glanders (exotic)
Louping ill (exotic)

Box 5.4

Causes of Serous or Mucoid Nasal Discharge in Ruminants

Common Causes

Debilitating illnesses that reduce lingual nose cleaning in cattle (B)
Mannheimia haemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)
Histophilus somni pneumonia (B)
Nose bots *(Oestrus ovis)* (O, C)
Lungworm infection, verminous pneumonia

Atypical interstitial pneumonia (B)
Infectious bovine rhinotracheitis (IBR; BHV-1) (B, C)
Bovine respiratory syncytial virus (B)
Parainfluenza virus type 3
Mycoplasma species pneumonia
Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)
Caprine arthritis-encephalomyelitis (CAE) pneumonia (C)
Early bacterial pneumonia
Trauma (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial, chest wall)
Abscess (oral, pharyngeal, retropharyngeal)
Esophageal obstruction, foreign body, choke
Septicemia (neonates)

Less Common Causes

Paranasal sinus infection
Foreign body (oral, pharyngeal, laryngeal, tracheal, bronchial, pulmonary)
Aspiration, foreign body pneumonia
Ovine progressive pneumonia and arthritis, maedi (O)
Bluetongue
Bovine virus diarrhea (BVD-MD) (B)
Ovine adenovirus (O)
Caprine respiratory syncytial virus (C)
Bovine rhinovirus (B)
Bovine adenovirus (B)
Bovine malignant catarrhal fever, early (B)
Herpesvirus DN-599 (B)
Bovine herpesvirus type 4 (BHV-4) (B)
Pulmonary adenomatosis (Jaagsiekte) (O)
Inhalation pneumonia, smoke, noxious gases
Anaphylaxis or adverse drug reaction
Milk allergy in cows (B)
Farmer's lung disease (hypersensitivity to *Faenia rectivirgula, Aspergillus fumigatus,* and other mold spores) (B)
Chlamydia psittaci pneumonia
Burns (thermal, chemical)
Vagal indigestion, abomasal impaction

Nasal adenoma, adenopapilloma, adenocarcinoma, polyp (O, C)

Uncommon Causes

Familial allergic rhinitis (B)
Bovine nasal granuloma, atopic rhinitis, summer snuffles (B)
Fungal granuloma, maduromycosis, mycetoma, rhinosporidiosis
Nasal actinobacillosis (B)
Sarcocystosis (B)
Tularemia (O)
Phycomycosis, pythiosis (B)
Pulmonary aspergillosis
Bronchobiliary fistula (yellow froth) (B)
Zygomycosis, mucormycosis (B)
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Neoplasia (nasal, paranasal sinus, pharyngeal, pulmonary)
Buss disease, chlamydial sporadic bovine encephalomyelitis (B)
Winter dysentery (B)
Immunodeficiency states
Pregnancy toxemia (B)
Border disease (hairy shaker) (O, C)
Lymphosarcoma
Johne's disease
Listeriosis (C)
Tetanus
Rinderpest (exotic)
Theileriosis, East Coast fever (exotic)
Contagious bovine pleuropneumonia (exotic) (B)
African bovine malignant catarrhal fever, early (exotic) (B)
Virulent sheep and goat pox (exotic) (O, C)
Peste des petits ruminants (exotic) (O, C)
Contagious caprine pleuropneumonia (exotic) (C)
Rift Valley fever (exotic)
St. George disease (*Pimelea* species poisoning) (exotic)
Trypanosoma evansi, surra (exotic) (B)
Trypanosomiasis, nagana (exotic)

Jembrana disease (exotic) (B)
Sweating sickness (exotic) (B, O)
Cestrum poisoning (exotic)
Stinkweed poisoning (exotic) (B)
Endemic ethmoid carcinoma (exotic) (B)
Ephemeral fever (exotic) (B)
Lumpy skin disease (exotic) (B)
Nasal schistosomiasis (exotic)
Besnoitiosis, globidiosis (exotic)
Louping illness (exotic)
Theilezia rhodensis (exotic)
Cotyledon species poisoning, Krimpsiekte (exotic) (O, C)
Gedoelstia hasleri nasal bots (exotic) (O, C)
Nairobi sheep disease (exotic) (O, C)
Schistosoma nasale (exotic) (B)

Toxic Causes

Organophosphate or carbamate
Mercury (B)
Iodine (B, O)
Ammonia
Sodium hydroxide (caustic soda)
Trichloroethylene-extracted feed (B, O)
Formaldehyde irritation
Oxalate (B, O)
Thallium (O)
Furazolidone
Hairy vetch *(Vicia villosa)* (B)
Ergot *(Claviceps purpurea)*
Sneezeweed (*Helenium* species)
Aflatoxicosis (C)
Rubber weed (*Hymenoxys* species)
Acorn, oak (B, O)
Perennial broomweed (*Gutierrezia* species)
Chinese tallow *(Sapium sebiferum)* (B)
Stachybotryotoxicosis

Slender ice plant *(Mesembryanthemum nodiflorum)*

B, Bovine; *C*, caprine; *O*, ovine.

Box 5.5

Causes of Purulent Nasal Discharge in Horses

Common Causes

Postviral bacterial infection of the respiratory tract
Strangles (*Streptococcus equi* subsp. *equi* infection)
Bacterial rhinitis
Pharyngitis
Bacterial pneumonia
Bacterial pleuritis or pleuropneumonia
Guttural pouch empyema or chondroids
Guttural pouch mycosis
Lung abscess
Pharyngeal, retropharyngeal abscess
Paranasal sinus infection, cyst, tumor (unilateral discharge)

Less Common Causes

Fungal rhinitis (rhinophycomycosis), nasal granuloma, nasal aspergillosis (unilateral discharge)
Nasal foreign body (unilateral discharge)
Conchal necrosis (unilateral discharge)
Progressive ethmoidal hematoma (unilateral discharge)
Nasal tumor, polyp, cyst (unilateral discharge)
Trauma (nasal, skull, upper airway) (unilateral or bilateral discharge)
Burn (thermal, chemical)
Aspiration or foreign body pneumonia, smoke inhalation
Foreign body (pharyngeal, guttural pouch, tracheal, bronchial)
Esophageal obstruction, choke, stricture, ectasia, megaesophagus

Neurologic deficits affecting swallowing

Uncommon Causes

Coccidioidomycosis
Tuberculosis
Tularemia
Guttural pouch neoplasia
Chlamydia psittaci pneumonia
Nocardiosis
Cryptococcosis
Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, pythiosis
Ascarid migration
Lymphosarcoma, lymphoma, leukemia
Halicephalobus (Micronema) deletrix granulomas
Pulmonary aspergillosis
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Ammonia toxicity
Hendra virus (exotic)
Trypanosoma evansi, surra (exotic)
Besnoitiosis, globidiosis (exotic)
African horse sickness (exotic)
Glanders (exotic)
Melioidosis, *Pseudomonas pseudomallei* (exotic)

Box 5.6

Causes of Purulent Nasal Discharge in Ruminants

Common Causes

Debilitating illnesses that reduce lingual nose cleaning in cattle
Postviral bacterial infection of the respiratory tract

Mannheimia haemolytica or *Pasteurella multocida* pneumonia
Histophilus somni pneumonia (B)
Necrotic laryngitis, calf diphtheria (B)
Lungworm infection, verminous pneumonia
Mycoplasma species pneumonia
Caprine *Mycoplasma mycoides* subsp. *mycoides* infection (C)
Chronic bacterial pneumonia with consolidation or abscessation (*Arcanobacterium pyogenes* and other bacteria)
Esophageal obstruction, foreign body, choke
Nose bots *(Oestrus ovis)* (O, C)
Trauma (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial, chest wall)
Abscess (oral, pharyngeal, retropharyngeal)
Septicemia (neonates)

Less Common Causes

Foreign body (oral, pharyngeal, laryngeal, tracheal, bronchial, pulmonary)
Aspiration, foreign body pneumonia
Paranasal sinus infection
Pulmonary embolism from posterior vena cava thrombosis (B)
Ovine progressive pneumonia and arthritis, maedi (O)
Bovine malignant catarrhal fever (B)
Bluetongue
Pulmonary adenomatosis (Jaagsiekte) (O)
Inhalation pneumonia, smoke, noxious gases
Chlamydia psittaci pneumonia
Burns (thermal, chemical)
Vagal indigestion, abomasal impaction
Nasal adenoma, adenopapilloma, adenocarcinoma, polyp (O, C)

Uncommon Causes

Ovine nasal granuloma, atopic rhinitis, summer snuffles (B)
Fungal granuloma, maduromycosis, mycetoma, rhinosporidiosis
Nasal actinobacillosis (B)
Bovine salmonellosis (B)

Sarcocystosis (B)
Tularemia (O)
Tuberculosis
Phycomycosis, pythiosis (B)
Pulmonary aspergillosis
Bronchobiliary fistula (yellow froth) (B)
Zygomycosis, mucormycosis (B)
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Neoplasia (nasal, paranasal sinus, pharyngeal, pulmonary)
Immune deficiency states
Lymphosarcoma

Toxic and Exotic Causes

See Box 5.4.

B, Bovine; *C*, caprine; *O*, ovine.

Conditions such as chronic bronchitis and RAO cause goblet cell hyperplasia and increased mucous production, which may be reflected as a discharge at the external nares, depending on the efficiency with which the animal swallows these secretions. In some cases nasal discharge is evident only early in the morning or after a period of recumbence because in these situations secretions accumulate in the trachea and pharynx, drain into the nasal passages, and exit from the nares.

Hemorrhagic (sanguineous) nasal discharge, or epistaxis, occurs secondary to trauma, coagulopathies, and erosive or invasive conditions that insult the richly vascular nasal mucosa or secondary to conditions that invade regional blood vessels such as occurs when the internal carotid artery is eroded by a mycotic plaque in horses with guttural pouch mycosis. Pulmonary disorders such as infarctive pneumonia in horses and pulmonary thromboembolism secondary to posterior vena cava thrombosis in cattle may also induce epistaxis (see the Epistaxis and Hemoptysis section later).[38-40]

Foul odor (ozena) accompanying nasal discharge suggests an anaerobic infection, a necrotizing condition (e.g., fungal infection, neoplasia, turbinate

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necrosis, or necrotizing pneumonia), foreign body, or communication between the oral and nasal cavities (e.g., maxillary sinusitis secondary to tooth root infection in the horse).[40]

Food or water may drain from the external nares when there is communication between the oral and nasal cavities (e.g., cleft palate), in association with swallowing disorders (e.g., pharyngeal paresis secondary to botulism, cranial nerve damage secondary to guttural pouch mycosis in the horse), or in cases of obstructive dysphagia (e.g., severe pharyngitis, guttural pouch enlargement in horses, retropharyngeal abscesses, esophageal obstruction, obstructions of the gastrointestinal tract that lead to regurgitation of food from the stomach).[38-40] The respiratory position of the epiglottis dorsal to the soft palate in the horse means that except in cases of dorsal displacement of the soft palate (laryngopalatal dislocation), food regurgitated from the digestive tract enters the nasopharynx and appears at the external nares rather than at the mouth (see Chapter 7).

Chronic nasal discharges often cause scalding in the area ventral to the external nares.[39] Mucoid and purulent nasal discharges tend to dry and crust as an admixture with environmental dust and dirt around the external nares. In all large animal species but particularly in sheep and goats, tenacious exudates may obstruct the nasal passages and induce a snuffling noise. Horses with profuse nasal discharge often rub the nose on the dorsum of the front fetlock and cannon regions. During the physical examination, these areas should be inspected for mucoid exudate, dried crusts, or swarms of flies.

Acuteness of Onset.

Sudden-onset nasal discharge is usually associated with acute infection, trauma, or esophageal obstruction, whereas nasal discharge of insidious onset generally accompanies chronic infection, progressive neurologic disease that causes dysphagia, or neoplasia.[42]

Origin of Nasal Secretions.

Unilateral nasal discharge generally originates from structures located rostral to the caudal end of the nasal septum. Bilateral nasal discharge results from disease processes affecting structures caudal to the nasal septum or from conditions involving the nasal passages or paranasal sinuses bilaterally.[39,40] A discharge that appears from one nostril on some days and from the opposite nostril on

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others generally indicates a lesion or disease process caudal to the nasal septum.[40] The paired guttural pouches of the horse drain separately through ostia located dorsolaterally in the wall of the nasopharynx. Exudate draining from the guttural pouches may appear unilaterally at the ipsilateral nostril if the volume of drainage is small, but moderate to profuse guttural pouch drainage appears as a bilateral nasal discharge.[40]

Volume of Nasal Secretions.

The volume of nasal discharge frequently increases when the head is lowered, regardless of the source of the discharge, because of pooling of exudate in the trachea, pharynx, or nasal passages. However, the appearance of profuse, unilateral, purulent nasal discharge when the head is lowered generally indicates sinus empyema, and profuse bilateral nasal discharge under these circumstances suggests guttural pouch empyema.[21] This is attributed to accumulation of large volumes of exudate in the sinus cavities or guttural pouches when the head is elevated and to the fact that the ostia through which these structures drain are not located on the most dependent aspect of these cavities; thus significant drainage can occur only when the head is lowered. Nasal discharge observed only after exercise suggests an origin in the lower respiratory tract.[43]

Approach to Diagnosis of Nasal Discharge

Because many conditions, particularly those involving the lower respiratory tract, are associated with both nasal discharge and cough, the diagnostic approach used for large animal patients presented for evaluation of nasal discharge is similar to that used for large animals presented for evaluation of cough (see the Cough section earlier). Only the components of the history and diagnostic evaluation that differ substantially from those used in patients with cough are described in depth in this section.

History.

The patient history should include information about the rapidity of onset and duration of nasal discharge; whether the discharge is consistently unilateral, consistently bilateral, or intermittently bilateral; and the volume, color, consistency, and odor of the discharge.

The association of discharge with certain activities—such as initiation of exercise, when the animal is first disturbed in the morning, or when it is eating

with its head lowered—can provide useful clues to the origin or cause. It should be determined if the animal is showing other signs of respiratory disease (e.g., cough, respiratory distress, or exercise intolerance), dental disease (e.g., quidding or slow eating), or systemic disease (e.g., weight loss, depression, anorexia, fever, or lymphadenopathy).

It should also be determined if in-contact animals have exhibited nasal discharge or other signs of respiratory disease. The vaccination status of affected and in-contact animals should be ascertained. Recent transportation, surgery, or weaning should be noted as supportive of stress, and a history of contact with other animals at sales, shows, or other events should be established. Environmental quality and the overall management of the affected animal and the herd should be assessed (see the Cough section earlier). Progression or improvement in the signs, attempted therapy, and response to current or previous treatments should also be ascertained.

Physical Examination.

Physical examination of an animal showing nasal discharge should be complete and include inspection from a distance and close examination using *auscultation, palpation,* and *percussion* techniques (see Physical Examination in the Cough section earlier). The character and volume of the nasal discharge should be noted. Particular attention should be paid to whether:

- The nasal discharge is unilateral or bilateral
- The airflow from both nostrils is symmetric
- Odor emanates from the oral or nasal cavity
- Facial asymmetry is present
- Hyporesonance (dullness) or a painful response is elicited on percussion of the maxillary and frontal sinuses
- Enlargement of submandibular, parotid, retropharyngeal, or other regional lymph nodes is present

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- Palpable turbulence such as a tracheal rattle is present

The depth and symmetry of chest expansion should be assessed, and the rostral end of both nasal passages should be illuminated with a penlight and examined carefully.

The roots of the third through the sixth maxillary cheek teeth (108 to 111 and 208 to 211) in the horse are contained within the maxillary sinus; therefore infection of these teeth frequently leads to sinus empyema with drainage from the nasomaxillary opening into the middle nasal meatus and ultimately to a unilateral nasal discharge. Disease involving the paranasal sinuses should be considered in horses with unilateral nasal discharge, particularly when ozena is present. Under these circumstances a thorough *oral examination,* which should include probing of the occlusal surfaces of the maxillary cheek teeth with a fine dental pick, is indicated. Particular attention should be paid to detecting erosive periodontal disease, fractured maxillary cheek teeth, open pulp chambers, and patent infundibula. In cattle the oral examination should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx to determine whether mass lesions or swelling of the tongue are present.

Further diagnostic evaluation of nasal discharge may include a complete blood count with determination of the fibrinogen concentration, a serum biochemistry profile, endoscopy of the upper and lower airways and the esophagus, nasal or nasopharyngeal swabbing for molecular diagnostic testing or virus isolation, virus serologic testing, tracheal aspiration, BAL, ultrasonography, thoracentesis, radiography, blood gas analysis, nuclear scintigraphy, fecal examination, pulmonary function testing, and lung biopsy. For further information on diagnostic procedures not discussed in the following sections, see the Cough section earlier.

Endoscopic Examination.

Endoscopic examination of the upper and lower airways is a useful ancillary diagnostic procedure in all animals with nasal discharge. The nasal passages; the conchae (turbinates) including the ethmoidal conchae; the nasal septum; and the pharynx, larynx, and trachea should be examined through both nostrils. The presence, nature, and origin of exudates and the presence of anatomic or functional abnormalities or mass lesions should be noted. Although it is not

possible to introduce standard, 8- to 12-mm–diameter endoscopes into the paranasal sinuses via the nasal passages, drainage from the sinuses may be detected by examining the middle meatus.[40] Examination of the middle meatus may also reveal turbinate necrosis or mass lesions (e.g., tumors, fungal granulomas, nasal foreign bodies). Lesions such as progressive hematomas (expanding mass lesions of variable size on the ethmoid turbinates) can be visualized by advancing the endoscope slightly, after deflecting its tip dorsally through the common meatus, from a position in the caudal part of the ventral meatus just rostral to the choanae. In the horse the pharyngeal openings of the guttural pouches, which are located dorsolaterally on the wall of the pharynx, should be inspected for drainage. The interior of both guttural pouches can be examined for exudate, blood, mycotic plaques, and other proliferative lesions by advancing the endoscope through the pharyngeal openings of each guttural pouch. This procedure is facilitated by first introducing a biopsy instrument or similar guidewire into the guttural pouch via the biopsy channel of the endoscope.

Bronchoscopic examination may prove useful for identifying the bronchus of origin of pulmonary exudates and for facilitating appropriate BAL. In horses with intermittent bilateral nasal discharge, it may be helpful to repeat the endoscopic examination after exercise, which often mobilizes secretions from the lower respiratory tract and causes them to pool in the horizontal trachea. Endoscopic examination of the esophagus is indicated in patients with a history of dysphagia or return of ingesta through the nose (Boxes 5.7 and 5.8).

Box 5.7

Causes of Ingesta in Nasal Discharge in Horses

Common Causes

Esophageal obstruction, choke
Cleft palate, palatal hypoplasia (neonate)
Pharyngitis
Strangles (*Streptococcus equi* infection)

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Dorsal displacement of the soft palate
Guttural pouch infection, mycosis, neoplasia
Glossopharyngeal nerve damage
Botulism, shaker foal
Retropharyngeal abscess

Less Common Causes

Complications of laryngeal surgery
Laryngeal web defect
Epiglottal entrapment, subepiglottal abscess or cyst
Tetanus
Fistula (pharyngeal, esophageal, esophagobronchial, esophagotracheal)
Esophageal stricture, ectasia, diverticulum, megaesophagus, ulcer, rupture
Gastric, duodenal ulceration (foals)
Gastric dilation, rupture
Proximal enteritis, jejunitis
Small intestinal obstruction
Rabies
Other neurologic deficits affecting swallowing

Uncommon Causes

Persistent right aortic arch, vascular ring anomaly
Gastric tumor
Gastric stenosis
Rostral displacement of the palatopharyngeal arch
Hypoplasia of the soft palate
White muscle disease, nutritional myodegeneration
Rectus capitis ventralis muscle rupture
Lymphosarcoma, lymphoma, leukemia
Oleander poisoning
White snakeroot (tremetol) poisoning
Lead toxicity
Grass sickness (exotic)

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Box 5.8

Causes of Ingesta in Nasal Discharge in Ruminants

Common Causes

Esophageal obstruction, foreign body, choke
Pharyngeal, retropharyngeal abscess
Pharyngeal trauma, foreign body
Megaesophagus (B, C)

Less Common Causes

Rhododendron poisoning (O)
Diaphragmatic hernia
Water deprivation, salt toxicity (B, O)
Ruptured or lacerated esophagus
Tetanus
Cleft hard or soft palate
Glossopharyngeal nerve damage

Uncommon Causes

Neoplasia of the esophagus or rumen (B)
Persistent right aortic arch, vascular ring anomaly (B, O)
Listeriosis
Bronchobiliary fistula (yellow froth) (B)
Congenital defects of Kodiak Island calves (B)
Oleander poisoning
White snakeroot (tremetol) poisoning (B, O)
Crude oil toxicity (B)
Geigeria species poisoning
Sneezeweed (*Helenium* species) poisoning
Rubberweed (*Hymenoxys* species) poisoning

B, Bovine; *C*, caprine; *O*, ovine.

Radiography.

Radiography with lateral, dorsoventral, and oblique radiographic projections of the nasal passages, paranasal sinuses, pharynx, retropharyngeal area (including guttural pouches in the horse), larynx, and proximal trachea is indicated to confirm problems identified by clinical examination and endoscopy and to identify conditions not recognized by other diagnostic techniques. The demonstration of increases in tissue density, fluid lines, bony lysis or proliferation, distortion of normal architecture, or changes around tooth roots assists in the diagnosis and localization of disorders of the nasal passages, conchae, and paranasal sinuses. Space-occupying lesions in the oropharynx, nasopharynx, or larynx may also be demonstrated by radiographic examination of these areas. The presence of fluid lines, soft tissue densities, or thickening of the floor of the guttural pouches helps differentiate guttural pouch diseases (e.g., empyema) from other space-occupying lesions (e.g., abscesses) in the retropharyngeal region. Contrast radiographic studies such as barium swallows are indicated to evaluate aspiration during swallowing in horses suspected of having pharyngeal paresis. Carotid angiography under general anesthesia has been used to demonstrate aneurysms in the internal carotid artery of horses with guttural pouch mycosis.[44] Thoracic radiographs are indicated in patients suspected of having pulmonary, mediastinal, or pleural disease to determine the presence, pattern, and severity of radiographic changes.

Computed Tomography Scanning.

When a definitive diagnosis is not achieved using plain radiographs, computed tomography (CT) scanning under general anesthesia has proven valuable for more accurately defining the location, nature, and extent of lesions involving the nasal passages, paranasal sinuses, and cheek teeth.[45,46] Intracarotid or IV injection of contrast material further enhances the diagnostic utility of CT for evaluation of mass lesions.

Ultrasound Examination.

Ultrasound examination of externally visible lesions such as possible retropharyngeal abscesses or distended guttural pouches assists in characterization of lesions and collection of samples by aspiration or biopsy.

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Thoracic ultrasound is indicated when lower airway, pleural, or cardiac disease is the suspected cause of nasal discharge.

Percutaneous Aspiration.

Percutaneous aspiration, performed either blindly or with the assistance of ultrasound, followed by cytology and culture of aspirated material, is useful in the evaluation of masses such as submandibular or retropharyngeal abscesses that are also causing a nasal discharge.

Centesis.

Centesis of affected paranasal sinuses helps localize the source of exudates and provides samples for cytologic examination and culture in patients with chronic unilateral nasal discharge in which sinus percussion or radiographic examination (or both) suggests the presence of a sinus lesion. In the normal horse the rostral and caudal maxillary sinuses are separated by a thin osseous septum. This septum is often eroded in horses with septic sinusitis; therefore the caudal maxillary sinus is typically entered first. If no exudate can be aspirated, either directly or after lavage of the sinus, and if increased purulent drainage from the ipsilateral nostril is not accomplished during lavage, centesis of the rostral maxillary sinus is performed and the procedure is repeated. If the aspirated material is not malodorous and if there is no evidence of dental disease, there is a reasonable likelihood that primary (nondental) sinusitis is present. In the horse the rostral maxillary sinus can be entered at a site 2.5 cm dorsal and 2 to 3 cm caudal to the rostral end of the facial crest. The caudal maxillary sinus is entered at a point 2.5 cm dorsal to the facial crest and 2 cm rostral to the medial canthus of the eye. After shaving and surgical preparation of the skin and subcutaneous placement of a small volume of local anesthetic, a stab incision is created through the skin and extended down to the periosteum. A small hole is then drilled through the bone with a Steinmann pin in a handheld chuck or a 14-gauge needle. A 14-gauge cannula is introduced into the sinus and, if necessary, a 5-French catheter can be inserted through the cannula to facilitate sample collection and lavage (see the Diseases of the Paranasal Sinuses section in Chapter 31 for horses and the Diseases of the Sinuses section in Chapter 31 for ruminants).

Catheterization.

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Catheterization of the guttural pouches via the pharyngeal orifice, either blindly or under endoscopic guidance, followed by aspiration or lavage, culture, and cytologic examination of aspirated contents, is helpful in the evaluation of horses with chronic purulent nasal discharge in which guttural pouch empyema is suspected or has been confirmed by radiographic or endoscopic examination. In horses with large accumulations of fluid exudate, voluminous drainage of pus both through and around the catheter may occur when the pouch is first catheterized. In horses with chronic guttural pouch infection accompanied by tenacious or inspissated exudate, lavage with 250 to 400 mL of sterile saline or Ringer solution facilitates sample collection.

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Epistaxis and Hemoptysis

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

■ Definition

Epistaxis is defined as the presence of blood at the external nares[47]; the amount of blood at the nostrils can range from small flecks incorporated in serous nasal discharge to large volumes flowing freely from both nostrils. Hemoptysis is the coughing up of blood.[48]

■ Pathophysiology

Blood at the external nares originates from one or more of the following structures: nasal cavity, paranasal sinuses, guttural pouch (auditory tube diverticulum), oral cavity, pharynx, larynx, trachea, or lungs.[47] These respiratory structures may be affected by a primary disease process or may be one of many mucosal surfaces involved in a bleeding diathesis (Boxes 5.9 and 5.10). The actual disease condition, the affected structure, and the large animal species involved determine whether epistaxis is profuse or scant, unilateral or bilateral, induced by exercise, accompanied by hemoptysis, and/or associated with concurrent abnormal nasal discharge.

Box 5.9

Causes of Epistaxis in Horses

Common Causes

Exercise-induced pulmonary hemorrhage (EIPH)
Guttural pouch mycosis
Progressive ethmoidal hematoma
Nasal trauma
Pharyngeal or retropharyngeal trauma or abscess

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Nasal polyps
Tumors (nose, paranasal sinuses)
Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
Purpura hemorrhagica

Less Common Causes

Pleuropneumonia
Infarctive lobar pneumonia
Pulmonary neoplasia
Fungal granuloma (maduromycosis, aspergillosis, rhinosporidiosis, mycetoma)
Cryptococcal rhinitis
Coccidioidomycosis
Guttural pouch empyema
Guttural pouch neoplasia
Guttural pouch foreign body
Vesicular stomatitis
Atrial fibrillation
Idiopathic thrombocytopenic purpura
Immune-mediated thrombocytopenia
Lymphosarcoma
Myeloproliferative disease
Disseminated intravascular coagulation (DIC)
Toxic hepatic failure
Multiple clotting defects (foals)
Equine infectious anemia (EIA)
Skull fracture
Gunshot injury
Pharyngeal lymphoid hyperplasia

Uncommon Causes

Nasal amyloidosis
Rectus capitis ventralis rupture
Black disease *(Clostridium novyi)*

Snakebite
Retrobulbar neoplasia
Chronic hepatitis or cholangitis
Acute renal failure
Cardiac neoplasia
Laryngeal hemiplegia
Phycomycosis, pythiosis, zygomycosis
Thrombasthenia-like syndrome
Besnoitiosis, globidiosis (exotic)
Dacryohemorrhea (exotic)

Toxic Causes

Arsenic
Warfarin or dicumarol
Stachybotryotoxicosis (*Stachybotrys* species)
Plant toxins
Moldy sweet clover *(Melilotus alba)*
Pyrrolizidine alkaloid (e.g., common groundsel *[Senecio vulgaris]*, fiddleneck [*Amsinckia* species], tansy ragwort *[Senecio jacobaea]*)

Box 5.10

Causes of Epistaxis in Ruminants

Common Causes

Pharyngeal or retropharyngeal trauma or abscess
Lung embolus from caudal vena cava thrombosis (CVCT) (B)
Infection of paranasal sinuses
Nasal trauma
Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
Nasal bots *(Oestrus ovis)* (C, O)
Nasal adenoma, adenopapilloma, adenocarcinoma (C, O)
Dehorning of adult animals (B)

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Less Common Causes

Nasal granuloma, atopic rhinitis (B)
Fungal granuloma (maduromycosis, rhinosporidiosis, mycetoma) (B, C)
Neoplasia (nose, paranasal sinuses)
Skull fracture
Gunshot injury
Bluetongue (O)
Vesicular stomatitis
Bovine virus diarrhea (BVD-MD) (B)
Malignant catarrhal fever (B)
Infectious bovine rhinotracheitis (IBR; BHV-1) (B)

Uncommon Causes

Black disease *(Clostridium novyi)* (B, O)
Acute anthrax *(Bacillus anthracis)*
Bacillary hemoglobinuria *(Clostridium haemolyticum)* (B, O)
Snakebite
Acute renal failure
Endocarditis
Liver fluke disease
Pulmonary neoplasia
Pasteurella pneumonia or septicemia (C, O)
Xylazine-induced pulmonary edema (O)
Idiopathic granulocytopenia or thrombocytopenia (B)
Hemophilia A (factor VIII deficiency) (B)
Factor XI deficiency (B)
Hereditary platelet aggregating disorder in Simmentals (B)
Cardiomyopathy in polled Hereford calves (B)
Trypanosomiasis (exotic) (B, O)
Ondiri disease (exotic) (B, O)
Besnoitiosis, globidiosis (exotic) (B, O)
Endemic ethmoid carcinoma (exotic) (B)
Gedoelstia hasleri nasal bots (exotic) (O, C)
Nairobi sheep disease (exotic) (O, C)

Leech infestation (hirudiniasis) (exotic)

Toxic Causes

Mercury
Arsenic
Warfarin, diphacinone
Furazolidone
Trichloroethylene-extracted feed
Oak (acorn poisoning)
Bracken fern *(Pteridium aquilinum)*
Moldy sweet clover *(Melilotus alba)*
Phytogenous selenium poisoning (e.g., *Astragalus* species)
Oxalate poisoning (e.g., *Halogen* species, *Sarcobatus* species)
Stachybotryotoxicosis (*Stachybotrys* species)
Mycotoxicosis

B, Bovine; *C*, caprine; *O*, ovine.

Nasal Cavity or Paranasal Sinus Pathologic Conditions.

Epistaxis associated with diseased respiratory tract structures rostral to the caudal border of the nasal septum (e.g., nasal cavity, paranasal sinuses) is usually unilateral and appears spontaneously (i.e., occurs without exertion or lowering of the head). However, with profuse hemorrhage from these sites, blood may drain caudally, accumulate in the pharynx, and exit from both nostrils.

Nasal cavity structures are highly vascular and prone to injury. Bleeding can be caused by foreign bodies, fungal granulomas, or neoplasms that invade the nasal cavity; epistaxis associated with these lesions is commonly unilateral, scant, and evident only intermittently. Trauma induced by passage of a nasogastric tube or endoscope is the most common cause of profuse hemorrhage of nasal origin in horses.[47] Erosive diseases that affect the paranasal sinuses of horses (e.g., progressive ethmoidal hematoma)[47] or sheep (endemic nasal adenocarcinoma)[49] commonly cause a unilateral, serosanguineous nasal discharge preceded or accompanied by mucopurulent discharge. In the case of sinusitis the exudate is often malodorous, particularly when these processes

occur secondary to dental disease. Epistaxis resulting from fractures of the nasal bones or skull can be scant or profuse, depending on the extent of the fracture.

Pathologic Conditions of the Guttural Pouches of the Horse.

Spontaneous epistaxis that occurs at rest in a mature horse warrants consideration of the guttural pouch as the source of hemorrhage.[50] In the case of guttural pouch mycosis, epistaxis is typically caused by fungal erosion of the internal carotid artery in the roof of the medial compartment of the guttural pouch.[50-52] The horse initially experiences several episodes of minor hemorrhage characterized by a small amount of fresh blood at the external nares; this may be preceded by a unilateral catarrhal nasal discharge and followed by a seromucous nasal discharge. Ultimately, massive arterial bleeding associated with erosion of the internal carotid artery manifests as large volumes of blood gushing from both nostrils.[51] Epistaxis caused by bleeding from the guttural pouch is typically most pronounced on the ipsilateral side, but nasal bleeding is usually bilateral in this condition, especially if hemorrhage is profuse, because the nasopharynx drains into both nasal passages.[52]

Pulmonary Pathologic Conditions.

In horses, pulmonary hemorrhage manifests as bilateral epistaxis, most often during or immediately after strenuous exercise.[47] In many cases of pulmonary hemorrhage, however, epistaxis is not observed because blood originating from the lungs is swallowed when it reaches the pharynx. Hemoptysis, the hallmark of pulmonary hemorrhage in cattle, is rarely observed in horses because the position of the epiglottis dorsal to the soft palate prevents blood flow from the nasopharynx to the oropharynx and mouth. In contrast to humans and other animal species, where foaming of blood exiting the nares suggests pulmonary hemorrhage, foaming of the blood is rarely encountered in horses with pulmonary hemorrhage because the horizontal position of the major bronchi allows blood to pool and flow freely without having to be coughed up.

EIPH, a syndrome experienced by 40% to 75% of Thoroughbred racehorses and by horses of other breeds engaged in strenuous activity, is characterized by hemorrhage into the tracheobronchial tree during competitive exercise.[47,53,54] Although pulmonary hemorrhage can be identified by endoscopic examination of the trachea immediately after exercise in these horses, EIPH manifests as

frank epistaxis at the external nares in only a small percentage of cases.[53] Bleeding at the nares may range from a slight orange-tinged serous nasal discharge to a constant trickle of fresh blood that persists for several hours after exercise.[47,54] The exact source of hemorrhage in horses with EIPH has not been identified, but it is known that affected horses have proliferation of the bronchial arterial blood supply to the lungs.[55] Fatal massive epistaxis, an infrequent sequela to exercise, has been attributed to tearing of the lung in association with pleural adhesions or focal shear stress.[56] Other less common causes of postexercise pulmonary hemorrhage in horses include pulmonary abscesses or pleuropneumonia with pulmonary infarction; in these cases the odor of the breath may be fetid, and hemorrhage may occur spontaneously (without exercise), which aids in the differentiation of these conditions from EIPH.[47,57]

Caudal vena cava thrombosis (CVCT; also known as *pulmonary embolic aneurysm* or *pulmonary thromboembolism*) is the disease most likely to be associated with epistaxis and hemoptysis in cattle (Box 5.11).[58] This sporadic, fatal condition of feedlot cattle is the result of a four-step sequence of events that culminates with the rupture of a pulmonary artery aneurysm into a bronchus. Initially, affected cattle exhibit tachypnea, lethargy, painful cough, melena, and anemia. Terminally the disease is characterized by discharge of bright, foamy red blood from the nose and mouth, severe respiratory distress, and widespread pulmonary crackles.[58]

Box 5.11

Causes of Hemoptysis in Ruminants

Caudal vena cava thrombosis (CVCT)
Aspiration pneumonia
Pharyngeal or retropharyngeal abscess or trauma
Thoracic trauma (fractured ribs or sternum)
Foreign body (nasal, oropharyngeal, tracheal, bronchial)
Pulmonary aspergillosis

Pulmonary edema present in the terminal stages of left-sided heart failure may

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also be responsible for bilateral serosanguineous discharge at the external nares of large animals.[47]

Pathologic Conditions of the Oral Cavity, Pharynx, or Larynx.

Less often, epistaxis can result from bleeding from lesions in the oral cavity, pharynx, or larynx. Examples include oral cavity erosions associated with infectious diseases (e.g., mucosal form of bovine virus diarrhea infection in cattle, bluetongue in sheep), erosions associated with epiglottic entrapment in horses, foreign bodies wedged in the mouth or pharynx of large animals, and pharyngeal or retropharyngeal trauma caused by a “balling gun.”

Bleeding Diathesis.

Several inherited and acquired coagulation disorders of large animals manifest as epistaxis.[59] Inherited clotting factor deficiencies (usually deficiencies of factors VIII, IX, or XI) or acquired factor deficiencies (those caused by warfarin, sweet clover toxicosis, or advanced liver disease) cause bleeding from large vessels. In addition to epistaxis, subcutaneous hematomas, hemarthrosis, melena, hematuria, and prolonged bleeding from sites of injury may be observed. With conditions causing vasculitis (e.g., equine purpura hemorrhagica, equine viral arteritis), small vessel bleeding occurs. Vasculitis is characterized by mucous membrane petechiae and ecchymoses and demarcated areas of skin edema. Nasal mucous membrane petechiae associated with vasculitis may manifest as epistaxis. Similarly, thrombocytopenia (e.g., immune-mediated thrombocytopenia in horses, bracken fern toxicosis in cattle) is characterized by mucous membrane petechiae and occasionally epistaxis. In rare cases, disseminated intravascular coagulation (DIC) in large animals manifests as a consumptive coagulopathy with bleeding from mucous membranes and blood at the external nares.

Approach to Diagnosis of Epistaxis and Hemoptysis

History.

History information collected should closely follow that described for animals with nasal discharge and should include duration of ownership, time of first appearance of blood at the nares, number of times the animal has bled, volume

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and color of blood, presence of blood at one or both nostrils, association of epistaxis with exercise, swallowing motions or cough after exercise, concurrent hemoptysis, other signs of respiratory tract disease (e.g., stridor, cough, nasal discharge, respiratory distress), evidence of involvement of cranial nerves (e.g., feed particles at the nares, drooping of the lip or ear), possibility of recent trauma (e.g., nasogastric intubation, head injury), and exposure to toxic plants (e.g., bracken fern, sweet clover).

Physical Examination.

A complete physical examination should be performed to detect abnormalities indicative of systemic disease or disease affecting other body systems. This examination should include assessment of the attitude of the animal; determination of rectal temperature, pulse rate, and respiratory rate and character; evaluation of mucous membranes for color and petechiae; inspection of the animal to detect hematomas or prolonged bleeding from sites of injury or venipuncture; and neurologic examination to detect neurologic dysfunction (e.g., dysphagia, Horner's syndrome, facial paralysis, head tilt, nystagmus), which may accompany guttural pouch mycosis.

Evaluation of the Head and Respiratory System.

A complete evaluation of the head and respiratory system should also be carried out. The nasal bones and flat bones overlying the maxillary and frontal sinuses should be examined for asymmetry or deformation; the eyes should be evaluated for exophthalmos or epiphora; the nasal mucosae should be inspected with a light source to demonstrate erosive, ulcerative, or mass lesions; and the sinuses should be percussed to detect altered resonance or pain. On continuing the examination, the following should be evaluated: symmetry and amount of airflow through the nostrils and the effect of occluding each nostril independently, odor at the nose or mouth, presence of stridor, and the effect of applying pressure to the larynx or trachea. The oral cavity should be carefully inspected in animals in which epistaxis is accompanied by a necrotic breath odor. Special attention should be paid to the maxillary cheek teeth of horses and the base of the tongue and the oropharynx of all large animals. Structures in the external pharyngeal region (mandibular lymph nodes, Viborg's triangle, retropharyngeal lymph nodes, parotid salivary gland) should be observed and palpated for swelling, heat, or pain, and the trachea should be observed and

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palpated where exposed to detect any abnormalities. The larynx, trachea, and lungs should be carefully auscultated at rest and after application of a rebreathing bag for abnormally loud breath sounds, crackles, or wheezes, which may implicate pulmonary disease as the cause of epistaxis. Careful cardiac auscultation should be carried out to detect murmurs or dysrhythmias, which may be associated with left-sided heart failure and pulmonary edema. The chest wall should be palpated to detect rib fractures or pleural friction rubs, and the thorax should be percussed bilaterally to demonstrate large mass lesions, pleural effusion, or pleurodynia.

Complete Blood Count.

A complete blood count and assessment of fibrinogen concentration can be useful in the evaluation of animals with primary or secondary inflammatory conditions or those that have developed blood loss anemia as a sequela to epistaxis (e.g., horses with guttural pouch mycosis or cattle with pulmonary thromboembolism secondary to CVCT). The degree of anemia may give an indication of the severity and chronicity of the bleeding or, in cases of bracken fern poisoning, of the degree of bone marrow suppression.

Clotting Profile.

A clotting profile should be performed (platelet count, prothrombin time [PT], activated partial thromboplastin time [APTT], concentration of fibrin degradation products [FDPs], and plasma antithrombin III) if mucous membrane petechiae or a tendency to bleed was noted on the general physical examination or if the history suggests exposure to sweet clover, warfarin, or bracken fern.

Biochemistry Profile.

A biochemistry profile should be performed to detect disease processes in organ systems other than the lungs (e.g., increased liver enzyme activity in cattle with hemoptysis secondary to CVCT or animals with liver failure causing secondary clotting factor deficiency).

Occult Blood.

Feces should be tested for occult blood. Positive results may suggest swallowing of blood originating from the lungs or pharynx or gastrointestinal bleeding.

Endoscopic Evaluation.

Endoscopic evaluation is a useful diagnostic aid in cases of epistaxis. The nasal passages, nasomaxillary aperture in the middle meatus, turbinates (conchae), nasal septum, pharynx, guttural pouches, larynx, and tracheobronchial tree should be systematically evaluated through both nostrils at rest and after exercise if indicated to determine the presence, nature, and source of blood and the anatomic or mass lesion responsible for the bleeding. Care should be taken when endoscopy is performed in horses with guttural pouch mycosis because dislodging a clot of blood in the affected guttural pouch may result in fatal hemorrhage.[60] Similarly, the stress of endoscopy may prove fatal to cattle with pulmonary thromboembolism secondary to CVCT. If EIPH is suspected, endoscopy should be performed 30 to 120 minutes after strenuous exercise to allow time for the mucociliary escalator to transport blood to where it can be visualized[53]; this blood may persist from 6 hours to 4 days after exercise, depending on the severity of pulmonary hemorrhage. It is important to remember that EIPH may not be repeatable. In one study only 33% of Thoroughbred racehorses tested positive for EIPH on all subsequent endoscopic examinations after breezing.[61] Biopsy (with histologic evaluation and possibly culture of samples) is indicated when granulomas, polyps, erosions, or mass lesions are visualized through the endoscope.

Tracheal Aspiration, Bronchoalveolar Lavage, and Thoracocentesis.

Percutaneous transtracheal aspiration or endoscopic tracheal aspiration, BAL, or thoracocentesis with cytologic studies and culture of collected samples is indicated when pulmonary or pleural diseases are thought to be responsible for hemorrhage into the respiratory tract[20,21,62-64] (see the Cough section earlier). The presence of hemosiderophages in tracheobronchial aspirates or BAL fluid is generally considered indicative of previous pulmonary hemorrhage[53]; however, mucopolysaccharides engulfed by alveolar macrophages can bind plasma iron in the absence of pulmonary hemorrhage to form an iron pigment resembling hemosiderin.[64]

Radiographic Examination.

Radiographic examination of the nasal passages, paranasal sinuses, pharynx,

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retropharyngeal region (including the guttural pouches), larynx, and trachea is indicated if the source of nasal bleeding cannot be definitively diagnosed through physical examination and endoscopy. The nasal passages, turbinates, and paranasal sinuses should be evaluated for fluid lines, cystic structures, bony lysis or proliferation, distortion of normal architecture, or changes in the tooth roots. Space-occupying lesions in the pharynx and larynx may also be demonstrated by radiographic examination. Demonstration of a fluid-air interface in the guttural pouch may indicate guttural pouch hemorrhage or guttural pouch empyema.[47] New bone formation and sclerosis around the *temporohyoid articulation* (temporohyoid osteoarthropathy) may accompany mycotic infection of the guttural pouch but also occurs in the absence of mycotic infection.[47] CT examination may be indicated if the lesion in the head or neck causing hemorrhage cannot be defined adequately with plain radiographs. Thoracic radiographs using four overlapping lateral views in adult horses and cattle and lateral and ventrodorsal views in immature animals and small ruminants aid in identification and definition of diseases affecting the lungs, pleurae, and mediastinum.[20]

Ultrasound Examination.

See the Cough section earlier.

Paracentesis.

Paracentesis of the maxillary sinuses[20] can be performed if percussion and inspection indicate that a lesion in the maxillary sinus may be the cause of epistaxis (see the Nasal Discharge section earlier).

Pleuroscopic Examination.

Pleuroscopic examination[65] is rarely indicated in the evaluation of epistaxis and should be limited to cases in which a disease process involving the pleura (e.g., pleural neoplasia, pleuropneumonia with pulmonary infarctions) is strongly suspected based on the results of other diagnostic tests and a diagnosis cannot be reached by less invasive approaches (see the Cough section earlier).

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Tachypnea

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■ Definition

Tachypnea is the term used to describe an increase in the respiratory rate; the term *hyperpnea* is used when both the rate and the depth of respiration have increased.

The respiratory rate, which is assessed by counting rib or nostril movements or by thoracic or tracheal auscultation, is best determined before the patient is disturbed or restrained. Under average conditions of temperature and humidity, acceptable ranges for the respiratory rate in normal adult animals are as follows: cattle, 24 (range 12 to 36) breaths/min; horses, 12 (range 8 to 15) breaths/min; sheep, 36 (range 12 to 72) breaths/min; and goats, 28 (range 15 to 40) breaths/min. Resting respiratory rates in young animals are higher than those in adults. A neonatal foal has a resting respiratory rate of 60 to 80 breaths/min during the first 30 minutes of life, a rate that later falls to 20 to 40 breaths/min. A young calf has a respiratory rate of 20 to 60 breaths/min by 30 minutes of age.

■ Pathophysiology

Respiratory rate, depth, and rhythmicity are regulated by respiratory centers in the brainstem. Central chemoreceptors responding to increased levels of CO_2 (decreased cerebrospinal fluid pH) and peripheral chemoreceptors (carotid and aortic bodies) responding to hypoxemia (Pa_{O_2} below 60 mm Hg), increases in Pa_{CO_2}, and decreases in pH initiate increases in the respiratory rate. Mechanoreceptors in the lungs and joints also influence ventilation. Lung inflation stimulates stretch receptors in the airways, which decreases the inspiratory effort, whereas mechanoreceptors in the joints are thought to be partly responsible for the increases in ventilation that occur during exercise. Pulmonary chemoreceptors that influence the respiratory cycle include irritant receptors in the airways, which are stimulated by dust and histamine, and J receptors, which apparently detect levels of interstitial fluid and are thought to be responsible for the respiratory pattern observed in animals with pulmonary edema.

Tachypnea is classified as physiologic when it occurs in the absence of underlying disease and as pathologic when it is a manifestation of respiratory distress. Physiologic tachypnea is associated with pain, exertion, heat, fever, anxiety, and other stresses (Boxes 5.12 and 5.13). Factors predisposing to pathologic tachypnea are the same as those that cause respiratory distress: inadequate oxygenation of the blood (i.e., a need for additional oxygen); compensation for metabolic acidosis; excessive environmental heat; disorders that damage the central nervous system respiratory centers in the medulla (e.g., head trauma, inflammation, mass lesions) if they disrupt the control of breathing; disorders that cause dysfunction of motor nerves and/or weakness of respiratory muscles (e.g., botulism, hypocalcemia); and painful conditions involving the respiratory sensory nerves, muscles, pleurae, and ribs (e.g., chest trauma, pleural infection, neoplasia)[66] (see the Respiratory Distress [Dyspnea] section later).

Box 5.12

Causes of Tachypnea in Horses[a]

Common Respiratory Causes

- Bacterial pneumonia
- Pleuropneumonia, pleuritis
- Pulmonary abscessation
- Recurrent airway obstruction (RAO or chronic obstructive pulmonary disease)
- Viral pneumonia (equine influenza, adenovirus, equine rhinitis A and B, equine viral arteritis, others)
- Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)
- Aspiration pneumonia
- Prematurity, dysmaturity, or immaturity (foals)

Common Nonrespiratory Causes

- Hyperthermia (fever, postexhaustion syndrome, heatstroke, anhidrosis, other)

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Pain (abdominal crisis, laminitis, exertional myopathy, other)
Acidosis (acute enterocolitis, urinary bladder rupture, renal tubular acidosis, other)
Anaphylaxis
Blood transfusion reaction
Shock (hypovolemic, cardiac, septic)
Anemia (neonatal isoerythrolysis, blood loss, hemolytic anemia, iron deficiency, bone marrow suppression, ruptured middle uterine artery, other)
Cardiac disease (ruptured mitral chordae tendineae, ventricular septal defect, endocarditis, other)
Gastric dilation

Less Common Respiratory Causes

Smoke inhalation pneumonia
Parasitic pneumonia *(Dictyocaulus arnfieldi)*
Stenotic nares, choanal atresia
Nasal septum abnormalities
Neoplasia (nose, paranasal sinuses)
Fungal granuloma
Nasopharyngeal cicatrix
Paranasal sinus infection
Dorsal displacement of the soft palate
Pharyngeal or retropharyngeal abscess or trauma
Epiglottic entrapment
Chondroma of arytenoid cartilage
Guttural pouch empyema
Tracheal stenosis, collapse, stricture
Foreign body (nasal, nasopharyngeal, laryngeal, tracheal, bronchial)
Diaphragmatic hernia
Pneumothorax
Thoracic trauma

Less Common Nonrespiratory Causes

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Anaphylaxis
Air embolism
Intracarotid injections
Fluid therapy complications
Tetanus *(Clostridium tetani)*
Malignant edema *(Clostridium septicum)*
Malignant hyperthermia
Meningoencephalitis
Anemia (piroplasmosis, iron deficiency, hemolytic blood loss, other)
Cardiovascular anomalies (tetralogy of Fallot, tricuspid insufficiency, atrial septal defect, hypoplastic left heart, transposition of great vessels, persistent right aortic arch, patent ductus arteriosus)
Cor pulmonale
Pericarditis
Atrial fibrillation
Ventricular tachycardia, fibrillation, flutter

Uncommon Respiratory Causes

Pulmonary lobar hypertrophy
Branchial or thyroglossal duct cyst
Tracheal rupture
Fracture of laryngeal cartilage
Fracture of hyoid bone
Cutaneous or nasal amyloidosis
Pulmonary tuberculosis
Pulmonary nocardiosis
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia

Uncommon Nonrespiratory Causes

Lactation tetany
Hydroallantois or hydrops
Nutritional myodegeneration (foals)
Methemoglobin reductase deficiency

Acute hepatic insufficiency
Electrocution
Cardiac neoplasia
Embryonal mediastinal cyst

Toxic Causes

α-Naphthyl thiourea (ANTU)
Arsenic
Bromide
Sodium fluoroacetate
Cantharidin (blister beetle)
Ammonia
Amitraz
Propylene glycol
Dioctyl sodium sulfosuccinate
Iron
Selenium
Metaldehyde
Organophosphate
Organochlorine, chlorinated hydrocarbon
Phenothiazine
Potassium
Larkspur (*Delphinium* species)
Japanese yew *(Taxus cuspidata)*
White snakeroot *(Eupatorium rugosum)*
Water hemlock (*Cicuta* species)
Jimson weed *(Datura stramonium)*
Potato *(Solanum tuberosum)*
Cyanogenic plants
Onion (*Allium* species)
Red maple *(Acer rubrum)*

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[a]All causes of respiratory distress (see Box 5.14) are also causes of tachypnea.

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Box 5.13

Causes of Tachypnea in Ruminants

Common Respiratory Causes

Mannheimia haemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)
Histophilus somni pneumonia (B)
Visceral caseous lymphadenitis *(Corynebacterium pseudotuberculosis)* (C, O)
Chronic bacterial pneumonia with consolidation or abscessation (*Arcanobacterium pyogenes* and other bacteria)
Necrotic laryngitis *(Fusobacterium necrophorum)* (B)
Pulmonary embolus from posterior vena cava thrombosis (B)
Respiratory syncytial virus
Parainfluenza type 3 virus
Adenovirus (B, O)
Infectious bovine rhinotracheitis virus (IBR; BHV-1) (B)
Ovine progressive pneumonia virus (O)
Mycoplasma species
Caprine *Mycoplasma mycoides* subsp. *mycoides* infection
Mycoplasma ovipneumoniae (O)
Parasitic pneumonia (*Dictyocaulus viviparus* [B]; *Dictyocaulus filaria* [O, C]; *Müllerius capillaris* [O, C]; *Protostrongylus rufescens* [O, C])
Bovine atypical interstitial pneumonia (B)
Acute pulmonary edema and emphysema (B)
Farmer's lung (*Faenia rectivirgula* hypersensitivity pneumonitis) (B)
Aspiration or foreign body pneumonia

Common Nonrespiratory Causes

Hyperthermia (fever, heatstroke, rapid rise in ambient temperature, other)
Pain (abdominal crisis, urethral calculi, traumatic reticuloperitonitis, musculoskeletal injury, other)

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Acidosis (ruminal lactic acidosis, pregnancy toxemia, other)
Electrolyte aberrations (hypocalcemia, hypomagnesemia, other)
Shock (hypovolemic, cardiac, septic)
Anemia (iron deficiency, postparturient hemoglobinuria, blood loss, other)
Distended abdominal viscus (ruminal bloat, other)
Anaphylaxis
Blood transfusion reaction
White muscle disease

Less Common Respiratory Causes

Nasal trauma
Tumors of the nose and paranasal sinuses
Nasal granuloma (fungal granuloma, atopic rhinitis)
Congenital cystic nasal conchae
Laryngeal trauma, abscess
Tracheal stenosis, collapse, stricture
Bovine rhinovirus (B)
Bovine malignant catarrhal fever (B)
Ascaris suum migration (calves) (B)
Thoracic trauma, other causes of chest pain
Pneumothorax
Diaphragmatic hernia
Pleuritis or pleural effusion
Caprine arthritis-encephalitis (CAE) pneumonia (C)
Sheep pulmonary adenomatosis virus pneumonia (O)

Less Common Nonrespiratory Causes

Cardiac anomalies (ventricular septal defect, tetralogy of Fallot, other)
Endocarditis
Pericarditis
Central nervous system disease (meningoencephalitis, polioencephalomalacia, other)
Esophageal obstruction or foreign body
Clostridial diseases (Black disease, enterotoxemia, tetanus)

Anaphylaxis

Uncommon Respiratory Causes

Pleural mesothelioma
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Pulmonary aspergillosis
Pulmonary neoplasia
Cyst (branchial, cervical, thyroglossal duct) (B)
Bronchobiliary fistula
Contagious bovine pleuropneumonia (exotic) (B)
Endemic ethmoid carcinoma (exotic) (B)

Uncommon Nonrespiratory Causes

Bluetongue (B, O)
Thymic lymphosarcoma (B)
Retrobulbar neoplasia (B)
Calf lymphosarcoma (B)
Adult multicentric lymphosarcoma (B)
Embryonal mediastinal cyst
Dwarfism (B)
Anthrax

Toxic Causes

Sodium fluoroacetate
Strychnine
Sulfur
Propylene glycol
Urea or nonprotein nitrogen
Water deprivation or salt toxicity
Potassium
Nitrates
Bromide

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Iron
Selenium
Organophosphate
Organochlorine or chlorinated hydrocarbon
Larkspur (*Delphinium* species)
Japanese yew *(Taxus cuspidata)*
Sneezeweed *(Helenium autumnale)*
Hairy vetch *(Vicia villosa)*
Whitehead *(Sphenosciadium capitellatum)*
White snakeroot *(Eupatorium rugosum)*

B, Bovine; *C,* caprine; *O,* ovine.

Note: Tachypnea is a rather nonspecific sign and is associated with toxicity caused by a large number of plant species; only a few are listed in this box. See also Box 5.15.

Approach to Diagnosis of Tachypnea

Because tachypnea is a manifestation of respiratory distress, the approach used for evaluating patients with tachypnea is the same as that used for evaluation of respiratory distress (see the Respiratory Distress [Dyspnea] section later).

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Respiratory Distress (Dyspnea)

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

■ Definition

Respiratory distress indicates an inappropriate degree of effort to breathe based on an assessment of respiratory rate, rhythm, and character.[11,67]

Respiratory distress is a clinical sign that implies labored breathing, whereas dyspnea is a symptom that describes the subjective feeling of difficult, uncomfortable, or unpleasant breathing (shortness of breath) in human patients.[1,11,67] As such, the term *dyspnea* is not strictly applicable to animal patients, although it is widely used by veterinarians to describe respiratory distress.

Manifestations of respiratory distress include elevated respiratory rate (see the Tachypnea section earlier), extended head and neck position, mouth breathing (ruminants), nostril flaring (horses, sheep, and goats), abnormal respiratory noise (stridor or stertor), exercise intolerance, exaggerated intercostal or abdominal effort (or both), a double expiratory lift and a “heave line” (expiratory respiratory distress), abducted elbows, anxious expression, and inactivity. Animals in severe respiratory distress may show cyanosis (see the Cyanosis section later) and (especially those with severe RAO) may exert so much effort to breathe that the whole body rocks, the anus pumps in and out, and the animal does not move or eat because this diverts its energies from respiration.[67]

■ Pathophysiology

Normal respiratory rate and character are maintained by central and peripheral monitoring of blood gas and acid-base status, with resulting reflex adjustments that maintain carbon dioxide (CO_2), oxygen (O_2), and the blood hydrogen ion concentration (pH) within a narrow range.[8] Respiratory distress may occur for the following reasons[66]:

- Inadequate oxygenation of blood (i.e., a need for

additional oxygen)
• Compensation for metabolic acidosis
• Excessive environmental heat
• Disorders that damage the central nervous system respiratory centers in the medulla (e.g., head trauma, inflammation, mass lesions)
• Disorders that cause dysfunction of motor nerves or weakness of respiratory muscles (e.g., botulism, hypocalcemia)
• Painful conditions involving the respiratory sensory nerves, muscles, pleura, and ribs (e.g., chest trauma, pleural infection, neoplasia)

Inadequate oxygenation of blood leads to arterial hypoxemia (low partial pressure of oxygen in arterial blood [Pa_{O_2}]). This can be caused by a low partial pressure of inspired oxygen (Pi_{O_2}), such as occurs at high altitude; by disorders that interrupt the transfer of oxygen from the environment to the blood (e.g., upper and lower airway obstruction, pulmonary disease associated with alveolar flooding or collapse, pulmonary or intracardiac right-to-left shunting of blood); or by a decrease in the oxygen-carrying capacity of the blood, such as occurs in anemia, methemoglobinemia, and carboxyhemoglobinemia.[66] Primary or secondary disease conditions that affect the respiratory and cardiovascular systems induce arterial hypoxemia by causing alveolar hypoventilation, ventilation-perfusion mismatch, diffusion limitation, right-to-left shunting of blood, or combinations of these abnormalities (see the Cyanosis section later).[11,66]

Compensation for metabolic acidosis involves “blowing off” carbon dioxide, which may increase both the rate and the depth of respiration.[66] The resulting hyperventilation causes a decline in the partial pressure of arterial carbon dioxide (Pa_{CO_2}) in the face of clinical signs of respiratory distress.

Animals dissipate a considerable amount of heat through the respiratory tract. In ruminants, but not in horses, heat dissipation is further aided by the animals’

ability to mouth breathe and pant to increase evaporative cooling of blood passing through the tongue and other structures in the oral cavity and oropharynx. The need to dissipate heat when exposed to high environmental temperatures induces labored breathing (Boxes 5.14 and 5.15). Apparent respiratory distress also occurs when the weather is not excessively hot but the temperature has risen rapidly, such as occurs when cattle in cold climates are brought indoors in the winter. When the environmental temperature has been consistently low, cattle in feedlots may also experience respiratory distress if the temperature suddenly rises from 4.4° to 10° C (40° to 50° F).

Box 5.14

Causes of Respiratory Distress in Horses

Common Respiratory Causes

Bacterial pneumonia
Pleuropneumonia or pleuritis
Pulmonary abscessation
Recurrent airway obstruction (housing or pasture associated)
Strangles (*Streptococcus equi* infection)
Viral pneumonia (influenza, equine viral arteritis, other viruses)
Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)
Aspiration pneumonia
Prematurity, dysmaturity, immaturity (foals)
Neonatal septicemia (foals)
Pharyngeal, retropharyngeal abscess or trauma

Common Nonrespiratory Causes

Cardiac disease (e.g., congestive cardiac failure, mitral insufficiency, other cardiac diseases)
Shock (septic, cardiogenic, hypovolemic, acute blood loss)
Endotoxemia
Anemia (e.g., neonatal isoerythrolysis, autoimmune hemolytic anemia,

blood loss, other causes of acute anemia)
Pain (e.g., abdominal crisis, laminitis, myopathy, fracture, other lameness)
Hyperthermia (e.g., fever, postexhaustion syndrome, anhidrosis, heatstroke, erythromycin associated)

Less Common Respiratory Causes

Epiglottic entrapment with secondary infection or granulation
Arytenoid chondritis
Guttural pouch empyema, tympany, mycosis, neoplasia
Progressive ethmoid hematoma
Nasal polyps
Pharyngeal, subepiglottic cysts
Fungal rhinitis, cryptococcal rhinitis, equine nasal granuloma, nasal aspergillosis, rhinosporidiosis, rhinophycomycosis, maduromycosis, mycetoma
Cleft palate
Laryngeal or hyoid trauma, fractured laryngeal cartilages, laryngeal granuloma or scar
Paranasal sinus infection, cyst, trauma, tumor
Nasal trauma, nasal neoplasia
Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
Exercise-induced pulmonary hemorrhage (EIPH)
Parasitic pneumonia *(Dictyocaulus arnfieldi)*
Coccidioidomycosis, cryptococcosis, mycotic pneumonia
Inhalation pneumonia, smoke inhalation, drowning, water inhalation
Hyaline membrane disease (foals)
Acute bronchointerstitial pneumonia
Peripartum asphyxia syndrome
Fractured ribs or sternum, thoracic trauma
Pneumothorax
Diaphragmatic hernia
Mediastinal abscess

Less Common Nonrespiratory Causes

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Purpura hemorrhagica
Blood or plasma transfusion reaction
Complications of fluid therapy
Anaphylaxis
Intracarotid injection
Acidosis
Gastric distention (e.g., as in small intestinal obstruction)
Pulmonary edema
Malignant hyperthermia
Cardiovascular anomalies (ventricular septal defect, patent ductus arteriosus, tetralogy of Fallot, common ventricle, other anomalies)
Endocarditis
Pericarditis
Cardiac dysrhythmias (atrial fibrillation, heart block, ventricular premature beats, ventricular tachycardia, ventricular fibrillation)
Ruptured mitral chordae tendineae
Mitral insufficiency or stenosis
Clostridial infections (e.g., tetanus, malignant edema, injection abscess)
Procaine penicillin G reaction or intravascular administration
Hyperkalemic periodic paralysis (HYPP)

Uncommon Respiratory Causes

Stenotic external nares
Cutaneous, nasal amyloidosis
Cutaneous, nasal habronemiasis (summer sore)
Failure of closure of the false nostril
Abnormalities of the nasal septum
Choanal (posterior nares) atresia or stenosis (foals)
Nasopharyngeal cicatrix
Laryngopalatal dislocation (dorsal displacement of soft palate), soft palate hypoplasia
Rostral displacement of the palatopharyngeal folds
Pharyngeal hematoma
Laryngeal paralysis
Fistula (pharyngeal, esophageal, esophagobronchial, esophagotracheal)
Chondroma of the arytenoid cartilage

Laryngeal spasm
Hypertrophic ossification of the laryngeal cartilages, laryngeal chondropathy
Neoplasia of the upper airway
Tracheal stenosis, stricture, collapse, rupture
Phycomycosis, pythiosis
Pneumoconiosis (e.g., silicosis)
Interstitial pneumonia (restrictive pulmonary disease)
Pulmonary thromboembolism
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Pulmonary lobar hypertrophy (foals)
Infarctive lobar pneumonia
Chlamydia psittaci pneumonia
Pulmonary nocardiosis
Pulmonary tuberculosis
Pulmonary aspergillosis
Besnoitiosis *(Besnoitia besnoiti* and *Besnoitia jellisoni)*
Pulmonary neoplasia (primary or metastatic)
Pleural neoplasia (mesothelioma, lymphosarcoma)
Embryonic cyst (mediastinal, branchial, cervical, thyroglossal duct)
Hendra virus infection (exotic)

Uncommon Nonrespiratory Causes

Nutritional myodegeneration
Lactation tetany (eclampsia)
Hydroallantois or hydramnios
Methemoglobin reductase deficiency
Hemophilia A (factor VIII deficiency)
Acute hepatic insufficiency
Electrocution
Cor pulmonale
Neoplasia (all systems)
Snake or insect bite
Aortoiliofemoral thrombosis
Equine motor neuron disease

Cholesteremic granuloma

Toxic Causes

Vitamin D
Lead
Organophosphate-associated laryngeal paralysis
Monensin, lasalocid, salinomycin
Propylene glycol
Iron
Dinitrophenol
Selenium
Bromide
Sodium fluoroacetate
Strychnine
Ammonia
Theobromine, chocolate
Cantharidin (blister beetle)
α-Naphthyl thiourea (ANTU)
Red maple *(Acer rubrum)*
Water hemlock (*Cicuta* species)
Oleander *(Nerium oleander)*
Japanese yew *(Taxus cuspidata)*
Larkspur (*Delphinium* species)
Ryegrass (*Lolium* species)
White snakeroot *(Eupatorium rugosum)*
Crofton weed *(Eupatorium adenophorum)*
Pyrrolizidine alkaloid
Locoweeds (*Astragalus* species, *Oxytropis* species)
Avocado *(Persea americana)*
Hoary alyssum *(Berteroa incana)*
Coffee senna seed *(Cassia occidentalis)*
Rubber vine *(Cryptostegia grandiflora)*
Birdsville disease (*Indigofera* species) (exotic)
Trachyandra paralysis (exotic)

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Box 5.15

Causes of Respiratory Distress in Ruminants

Common Respiratory Causes

Mannheimia haemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia)
Bacterial pneumonia with consolidation or abscessation (*Arcanobacterium* and other bacteria)
Histophilus somni pneumonia (B)
Visceral caseous lymphadenitis *(Corynebacterium pseudotuberculosis)* (O, C)
Aspiration or foreign body pneumonia (especially after hypocalcemia)
Necrotic laryngitis *(Fusobacterium necrophorum)* (B, O)
Infectious bovine rhinotracheitis virus (IBR; BHV-1) (B)
Respiratory syncytial virus
Ovine progressive pneumonia virus (O)
Mycoplasma mycoides subsp. *mycoides*, *Mycoplasma agalactiae*, other *Mycoplasma* species (C)
Mycoplasma bovis (B)
Mycoplasma ovipneumoniae (O)
Parasitic pneumonia (*Dictyocaulus viviparus* [B], *Dictyocaulus filaria* [O, C], *Müllerius capillaris* [O, C], *Protostrongylus rufescens* [O, C])
Bovine atypical interstitial pneumonia (B)
Acute bovine pulmonary edema and emphysema (B)
Farmer's lung disease (*Faenia rectivirgula* hypersensitivity pneumonitis) (B)

Common Nonrespiratory Causes

Hyperthermia (fever, heatstroke, rapid rise in ambient temperature, other)
Pain (abdominal crisis, urethral calculi, traumatic reticuloperitonitis, other)
Distended abdominal viscus
Acidosis (ruminal lactic acidosis, pregnancy toxemia, other)

Electrolyte aberrations (hypocalcemia, hypomagnesemia, other)
Hypovolemic, cardiac, or septic shock
Fluid or electrolyte loss (acute diarrhea, gastrointestinal obstruction, other)
Endotoxemia (coliform mastitis, metritis, enteritis, salmonellosis, septicemia, other)
Neonatal septicemia
Anemia (iron deficiency, postparturient hemoglobinuria, hemolytic, anaplasmosis, eperythrozoonosis, other)
White muscle disease (nutritional myodegeneration)
Anaphylaxis or allergy, milk allergy

Less Common Respiratory Causes

Pulmonary embolus from posterior vena cava thrombosis (B)
Parainfluenza virus type 3
Adenovirus (B, O)
Nasal trauma
Tumors of the nose, paranasal sinuses, oral cavity
Nasal granulomas (fungal granuloma, atopic rhinitis)
Congenital cystic nasal conchae
Nose bots *(Oestrus ovis)*
Sinusitis (maxillary, frontal, postdehorning)
Laryngeal trauma or abscess
Trauma (oral, pharyngeal, retropharyngeal), abscess, hematoma
Tracheal stenosis, collapse, stricture
Bovine rhinovirus (B)
Bovine malignant catarrhal fever (B)
Bovine herpesvirus DN-599 (B)
Ascaris suum migration (calves) (B)
Thoracic trauma, rib fracture
Pneumothorax
Pleuritis or pleural effusion
Caprine arthritis-encephalitis (CAE) pneumonia (C)
Sheep pulmonary adenomatosis virus (Jaagsiekte) (O)
Smoke inhalation
Foreign body (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial)
Caprine herpesvirus (C)

Bluetongue
Peste des petits ruminants (C, O) (exotic)
Congenital cardiac anomalies (ventricular septal defect, tetralogy of Fallot, patent ductus arteriosus, transposition of the great vessels, other anomalies)
Acquired cardiac failure (bacterial endocarditis, valvular incompetence, valvular stenosis, cardiomyopathy, pericarditis, other causes)
Central nervous system disease (trauma, meningoencephalitis, encephalomalacia, abscess, louping ill, pseudorabies, other causes)
Esophageal obstruction, foreign body, laceration, rupture, megaesophagus
Clostridial diseases (Black disease, enterotoxemia, tetanus, blackleg, bacillary hemoglobinuria, others)
Anthrax
Complications of fluid therapy (pulmonary edema)
Water deprivation (salt poisoning) (B)
Blood transfusion reaction
Anaphylaxis
Burn, thermal injury, electrocution
Systemic toxoplasmosis (C, O)
Tick paralysis (C, O)
Bladder rupture
Bee or wasp sting, snakebite
Photosensitization

Uncommon Respiratory Causes

Actinobacillosis (wooden tongue)
Actinomycosis (lumpy jaw)
Diaphragmatic hernia
Pleural mesothelioma
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia
Pulmonary aspergillosis
Pulmonary neoplasia
Pulmonary tuberculosis
Chlamydia psittaci pneumonia
Cyst (branchial, cervical, salivary, thyroglossal duct)

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Bronchobiliary fistula
Contagious bovine pleuropneumonia (exotic) (B)
Endemic ethmoid carcinoma (exotic) (B)
Theileria annulata and *Theileria hirci* (exotic) (B)
Heartwater *(Cowdria ruminantium)* (exotic)

Uncommon Nonrespiratory Causes

Retrobulbar neoplasia (B)
Enzootic bovine leukosis (B)
Thymic lymphosarcoma or thymoma
Calf lymphosarcoma (B)
Adult multicentric lymphosarcoma (B)
Embryonal mediastinal cyst
Dwarfism (B)
Botulism
Vesicular stomatitis
High altitude (brisket) disease, cor pulmonale (B, C)
Procaine penicillin G reaction or intravascular administration
Liver disease (infectious, toxic, parasitic, other)
Border disease (hairy shaker) (C, O)

Toxic Causes

Sodium fluoroacetate
Strychnine
Sulfur (B, O)
Propylene glycol (B)
Oxalate, ethylene glycol (B, O)
Urea or nonprotein nitrogen
Potassium (B)
Nitrates
Bromide (B, C)
Lead
Mercury (C)
Iron (B, C)

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Selenium
Arsenic
Organophosphate or carbamate
Organochlorine or chlorinated hydrocarbon
Permethrin
Gossypol
Ergot *(Claviceps purpurea)*
Phosphate fertilizer (B, O)
Vitamin D_3 (B)
Warfarin, dicumarol, diphacinone
Metaldehyde
Formaldehyde
Ammonia
Hydrogen sulfide
Monensin, salinomycin
Dinitrophenol (B, O)
Copper (acute oral toxicity)
Insect fogger pneumonitis (B)
Aflatoxicosis (C)
Levamisole (C, O)
Polychlorinated biphenyl (PCB) (B)
Xylazine-induced pulmonary edema (O)
Carbolic dips (O)
Cyanogenic plants (arrow grass, Johnson grass, common sorghum, Sudan grass, chokecherry, acacia, other plants)
Avocado *(Persea americana)*
Moldy sweet clover (*Melilotus* species)
Moldy sweet potato *(Ipomoea batatas)* (B)
Brassica species
Ryegrass (*Lolium* species) (B, O)
Larkspur (*Delphinium* species)
Japanese yew *(Taxus cuspidata)*
Hairy vetch *(Vicia villosa)* (B)
Whitehead *(Sphenosciadium capitellatum)* (B)
White snakeroot *(Eupatorium rugosum)* (B, O)
Chinese tallow *(Sapium sebiferum)* (B)
Purple mint *(Perilla frutescens)* (B)

Oleander *(Nerium oleander)*
Nightshade (*Solanum* species) (B)
Cocklebur (*Xanthium* species) (B, O)
Locoweeds (*Astragalus* species, *Oxytropis* species) (B, O)
Foxglove *(Digitalis purpurea)* (B)
Water hemlock (*Cicuta* species)
Milkweed (*Asclepias* species) (B, O)
Hepatotoxic plants (*Senecio* species, *Amsinckia* species, others containing pyrrolizidine alkaloid)
Fescue summer poisoning (B)
Rubberweed (*Hymenoxys* species)
Sneezeweed *(Helenium autumnale)*
False hellebore (*Veratrum* species) (B, O)
Rhododendron (*Andromeda* species) (B, O)
Algae
Lupines (*Lupinus* species) (B, O)
Prickly paddy melon *(Cucumis myriocarpus)*

B, Bovine; *C*, caprine; *O*, ovine.
Note: Respiratory distress is a sign associated with toxicity caused by a large number of plant species. Not all have been listed here.

Observation of the nature of the respiratory distress may give important clues as to the functional characterization, and perhaps cause, of the underlying disease process. Obstructive diseases involving the intrathoracic airways (e.g., RAO in horses and farmer's lung in cattle) are more likely to cause flow limitation during expiration because of dynamic airway narrowing or collapse (see the Cough section earlier).[11,68,69] This results in expiratory respiratory distress and a pattern of respiration in which the expiratory phase occupies an increased proportion of the respiratory cycle as the patient attempts to expel air from the lungs.[68] In the extrathoracic airways, dynamic collapse occurs during inspiration because intraluminal pressures are subatmospheric at this time.[11,68,69] Therefore patients with upper airway obstructions, especially of the nonfixed type (e.g., laryngeal hemiplegia), generally show inspiratory respiratory distress and may have a prolonged inspiratory phase.[11,68] Fixed airway obstructions of either the upper or the lower airway (e.g., intraluminal mass,

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bronchoconstriction) are present during both phases of respiration and may lead to both inspiratory and expiratory distress.[11] However, the distress is likely to be accentuated during a particular phase of respiration, depending on the anatomic site of the obstruction (i.e., fixed upper airway obstructions cause more distress during inspiration, and fixed lower airway obstructions cause more distress during expiration). Restrictive diseases (e.g., pleural effusion, pneumoconiosis) inhibit expansion of the lungs and therefore generally lead to inspiratory respiratory distress.[11] Because an animal with restrictive disease has reduced compliance and must perform more respiratory work than normal to expand its lungs, a common strategy for maintaining adequate ventilation is to increase the respiratory rate and lower the tidal volume (i.e., rapid, shallow breathing).[11] Animals with obstructive diseases generally have a normal or even increased tidal volume.[11]

In many instances, respiratory distress is not apparent at rest but occurs in association with exercise. Under these circumstances the animal's capacity to exercise is impaired, and the owner may complain of exercise intolerance (see the Exercise Intolerance and Poor Performance in Horses section later).

Approach to Diagnosis of Respiratory Distress

History.

After ruling out environmental causes of respiratory distress (e.g., heat stress, high humidity, moving from outside into a heated barn in the winter, handling stress, relocation to high altitude) and attending to the immediate needs of the patient, a careful history should be taken that includes the following factors: time and speed of onset of the clinical signs of respiratory distress; progression of clinical signs; whether this is the first episode of respiratory distress or the animal is subject to recurrent attacks; whether signs are present at rest or only after exercise; the relationship of signs to environmental conditions and the response to environmental change; recent administration of pharmacologic or biological agents; the presence of an audible respiratory noise; or other signs of respiratory tract, oropharyngeal, or neurologic disease (e.g., nasal discharge, cough, dysphagia, facial paralysis, retropharyngeal swelling). A history of recent trauma or exposure to potentially toxic substances such as lead-containing paints, nitrate-accumulating plants or urea (ruminants), or carbon monoxide should be elicited. The animal's appetite and attitude and signs of disease in

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other systems (e.g., diarrhea) should be determined. In neonates the circumstances surrounding gestation and parturition should be ascertained because prematurity, dysmaturity, congenital infection, birth trauma (e.g., rib fracture) related to dystocia, prolonged parturition, and aspiration of amniotic fluid and meconium are all important causes of respiratory distress. However, it should be noted that tachypnea, with respiratory rates of 60 to 80 breaths/min, is normal in foals during the first 30 minutes after birth as they “blow off” carbon dioxide.

Physical Examination.

The physical examination should follow the same general approach as that described for cough. In particular, the following should be determined: rectal temperature, pulse rate, respiratory rate and character; regularity and pattern of breathing; presence of excessive intercostal or abdominal respiratory effort; synchrony and symmetry of chest excursion; presence of a “heave line”; presence of stridor at rest (the examiner listens at the nostrils); symmetry of airflow from each nostril; effect of occlusion of each nostril independently; odor from the nose or mouth (or both); presence and character of nasal discharge; swelling around the external nares, inside the nasal passages, or inside the false nostril; facial symmetry and swelling; ocular discharge; resonance or painful response on percussion of the maxillary and frontal sinuses; palpable abnormalities of the mandibles and hyoid apparatus; enlargement of submandibular, parotid, retropharyngeal, and other regional lymph nodes; enlargement of the parotid salivary glands or thyroid gland; swelling, pain, or palpable abnormalities in the retropharyngeal region; a palpable, left-sided pit on the dorsal surface of the larynx; accentuation of stridor, induction of a cough, or evidence of pain on application of pressure to the larynx and trachea; palpable swelling or flattening of the cervical trachea; masses at the thoracic inlet; and palpable turbulence in the extrathoracic airway.

The mucous membranes should be examined carefully for cyanosis, pallor, cherry red color, hemorrhages, congestion, or injection. The capillary refill time should be determined, and the peripheral pulse rate, rhythm, and character should be assessed. Other signs of heart failure (e.g., jugular distention or pulsation and peripheral edema) and signs of dehydration (e.g., delayed jugular filling, dry mucous membranes, altered skin turgor) should be noted. The larynx, trachea, and lungs should be carefully *auscultated* at rest and, after the rate and depth of respiration have been increased, if it is safe to do so, by application of a

rebreathing bag, by occlusion of the nostrils, or by exercising the animal, so that turbulent airflow and abnormal lung sounds may be detected. The heart should be auscultated to detect murmurs, cardiac dysrhythmias, muffling of heart sounds, or other abnormalities. The chest wall should be carefully *palpated* to detect rib fractures and other lesions, and both sides of the chest should be *percussed* to detect large mass lesions, lung consolidation, pleural effusion, hyperinflation, pneumothorax, or a painful response, which may indicate pleuritis. A thorough oral examination is important, and in cattle this should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx (see the Nasal Discharge section earlier).

A general physical examination should be completed so that diseases in systems other than the cardiovascular and respiratory systems (e.g., respiratory distress in cattle secondary to ruminal bloat and respiratory distress secondary to central nervous system trauma or severe metabolic acidosis) can be detected. Attempts should also be made to identify conditions that may cause severe acid-base disturbances and hemoconcentration (e.g., diarrhea, renal disease), pain (e.g., laminitis, trauma), or hyperthermia (e.g., infectious conditions, heatstroke).

Further diagnostic evaluation of respiratory distress may include a complete blood count with fibrinogen concentration; blood gas analysis; serum biochemistry determinations; endoscopy of the upper and lower airways and esophagus; nasal or nasopharyngeal swabbing or scraping; virus identification, isolation, and serologic testing; bronchodilator response testing; tracheal aspiration; BAL; ultrasound examination of the chest and of suspected mass lesions that impinge on the upper airway; thoracocentesis; radiography of the nasal passages, paranasal sinuses, pharynx, guttural pouches, larynx, trachea, and chest; fecal examination for lungworms and other parasites; CT scanning of the upper airway; nuclear scintigraphy; pulmonary function testing; and biopsy of externally visible or palpable lesions or those identified by ultrasound, endoscopy, or radiography as described for the evaluation of cough and nasal discharge (see the Cough and Nasal Discharge sections earlier). The examiner should exercise discretion in the selection of diagnostic tests for animals with respiratory distress because procedures such as BAL or endoscopy may prove to be excessively stressful and exacerbate the distress, with potentially fatal consequences.

Complete Blood Count.

A complete blood count including fibrinogen and plasma protein concentrations

helps evaluate the role of hemoconcentration, anemia, or leukocytosis and hyperfibrinogenemia, which may accompany pneumonia and other inflammatory conditions.

Endoscopic Examination.

Endoscopic examination of the upper and lower airways is particularly helpful in evaluating patients suspected of having obstructive disease[70] (see the Cough and Nasal Discharge sections earlier and the Abnormal Respiratory Noise [Stridor] section later). Endoscopic examination of the esophagus is indicated in patients with a history of bloat, dysphagia, or return of ingesta through the nose in addition to respiratory distress (see the Nasal Discharge section earlier and the Abnormal Respiratory Noise [Stridor] section later).

Blood Gas Analysis.

Blood gas analysis and acid-base determinations should be performed on arterial blood to determine O_2 and CO_2 tensions so that the contribution of hypoxemia or acidosis to the signs of respiratory distress can be ascertained. In foals and calves, arterial samples are usually obtained from the great metatarsal artery or the brachial artery as it crosses the medial aspect of the foreleg.[71] The auricular artery is also convenient in calves. The femoral artery can be used in neonates but is less convenient because it tends to roll. The facial artery can be used in adult horses, and the auricular or coccygeal artery can be used in mature ruminants.[72] During the sampling process, the patient should be quiet and not struggling, which can decrease the $PaCO_2$.[73] Local subcutaneous infiltration of 2% lidocaine without epinephrine over the artery being sampled minimizes needless struggling and facilitates sample collection. A heparinized syringe and a 22- to 26-gauge needle can be used. Any air bubbles should be removed after sample collection and the needle properly sealed. If the sample is kept on ice, the pH will remain unchanged for 3.5 hours and the blood gases for 6 hours.[74] The animal's temperature should be recorded at the time of sample collection so that it can be used in the calculation of actual blood gas concentrations.

The normal PaO_2 for the horse is 83.6 ± 1.7 mm Hg, and the normal $PaCO_2$ is 42.2 ± 0.8 mm Hg.[75] Hypoxemia is defined as a PaO_2 below 80 mm Hg.[75] Cyanosis is usually not evident until the PaO_2 is much lower than this (usually below 40 mm Hg).[75] Hypercarbia, or hypercapnia, is a condition of increased

Pa_{CO_2} (above 44 mm Hg).[75] Because CO_2 diffuses readily, considerable ventilatory dysfunction can occur before the Pa_{CO_2} rises; therefore severe hypoxemia can occur with a normal Pa_{CO_2}. An elevated Pa_{CO_2} generally indicates that hypoventilation or a severe pulmonic pathologic condition is present. Because venous blood samples reflect tissue metabolism, they are not considered adequate for evaluating pulmonary function. However, a partial pressure of carbon dioxide in venous blood (Pv_{CO_2}) above 60 mm Hg usually reflects arterial hypercapnia, and a partial pressure of oxygen in venous blood (Pv_{O_2}) below 20 mm Hg usually indicates arterial hypoxemia.[74]

Venous admixture is the term used to denote the ways that blood can pass from the right side to the left side of the circulation without being properly oxygenated and represents the efficiency with which the lung oxygenates blood. The magnitude of venous admixture (efficiency of oxygenation) can be assessed by calculating the Pa_{O_2}/Fi_{O_2} ratio or the alveolar-arterial P_{O_2} gradient. The Pa_{O_2}/Fi_{O_2} ratio is normally 500. Pa_{O_2}/Fi_{O_2} ratios between 300 and 400 reflect significant lung injury, values below 300 reflect profoundly inefficient lung function such as occurs with acute lung injury, and values below 200 reflect severe life-threatening lung disease typical of acute respiratory distress syndrome (ARDS). The alveolar-arterial (A-a) P_{O_2} gradient difference is the difference between calculated alveolar P_{O_2} and the measured arterial P_{O_2}. Alveolar P_{O_2} = Inspired P_{O_2} – Pa_{CO_2} (1.1), where inspired P_{O_2} = barometric pressure × 21% and 1.1 = 1/RQ, where RQ is the respiratory quotient and has an assumed value of 0.9. The A-a P_{O_2} difference is typically about 10 mm Hg in a normal horse breathing 21% oxygen (room air) at sea level and about 100 mm Hg when breathing 100% oxygen. The “120 rule” is a simplified version of the alveolar gas equation that can be applied to a patient breathing 21% oxygen at near sea level. The measured Pa_{O_2} and Pa_{CO_2} should add up to 140 ± 10. If the sum is less than 120, the patient has venous admixture; as well, the lower the value, the worse the admixture.

Insufflation of 100% Oxygen.

Insufflation of 100% oxygen causes a significant increase in Pa_{O_2} if hypoxemia is caused by hypoventilation or ventilation-perfusion mismatch, whereas little or no improvement in Pa_{O_2} occurs if hypoxemia is caused by anatomic or

physiologic right-to-left shunting.[11] Therefore measuring Pa_{O_2} 5 minutes after insufflation of 100% oxygen can help in determining the pathophysiologic processes contributing to arterial hypoxemia. In full-term neonates and adults, the Pa_{O_2} should exceed 200 mm Hg after 5 minutes of oxygen administration.[73] Continued cyanosis or inability to raise the Pa_{O_2} above 100 mm Hg is highly suggestive of a right-to-left shunt.

Detection of Abnormal Hemoglobin.

Blood samples should be evaluated for abnormal hemoglobin (e.g., methemoglobin) if exposure to nitrates or other intoxicants is suspected (see the Cyanosis section later).

Radiographic Examination.

Radiographic examination of the nasal passages, pharynx, larynx, and trachea permits detection and evaluation of obstructive lesions in the upper airway, especially if tachypnea is accompanied by inspiratory stridor, asymmetric nasal airflow, or other evidence of upper airway obstruction.

Radiographic examination of the trachea and thorax should include end-inspiratory phase radiographs to facilitate identification of pulmonary lesions and disorders such as dynamic collapse of the trachea that are visible only on inspiratory-phase radiographs. Chest radiographs help detect evidence of pneumonia, pleural effusion, pneumothorax, cardiomegaly, and mediastinal lesions. The cardiac silhouette and the pattern and caliber of the aorta, vena cava, pulmonary artery, pulmonary veins, and other vessels should also be evaluated for evidence of cardiac failure and pulmonary vascular disease. *Contrast angiography* and other diagnostic procedures such as *echocardiography, electrocardiography,* and *hemodynamic (pressure and flow) studies* may be indicated in patients with respiratory distress that has occurred secondary to cardiovascular disease.

Ultrasound Examination.

Ultrasound examination of the thorax is performed to detect pleural inflammation and effusion, pulmonary consolidation, pulmonary abscessation, and cardiac anomalies if the clinical examination suggests that pulmonary, pleural, or cardiac disease is the cause of the signs of respiratory distress.

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Cyanosis

Jeanne Lofstedt • W. David Wilson • Jeffrey Lakritz

■ Definition

Cyanosis is the bluish discoloration of skin, conjunctivae, and visible mucous membranes that results from an increase in the absolute amount of reduced hemoglobin in the blood.[76]

■ Pathophysiology

Oxygen is carried in blood in two forms, dissolved and in combination with hemoglobin (Hb). The amount of dissolved oxygen present in arterial blood is relatively small and is proportional to the Pa_{O_2}. Oxygen transport to tissues is facilitated by the ability of hemoglobin in erythrocytes to combine in a reversible manner with oxygen. When erythrocytes pass through the pulmonary circulation, oxygen binds to hemoglobin, forming oxyhemoglobin (HbO_2). As oxyhemoglobin passes through systemic capillaries, oxygen diffuses into tissues, and hemoglobin is once again formed.

The Bohr effect describes the ability of hemoglobin to bind to a number of different ligands (CO_2, H^+, and 2,3-diphosphoglycerate [2,3-DPG]), which results in modification of hemoglobin's affinity for oxygen. When tissue pH decreases, hemoglobin acts as a buffer and binds excess H^+, which decreases its affinity for oxygen. When the CO_2 concentration increases, some CO_2 is converted to bicarbonate and the remainder is bound to hemoglobin to form carbaminohemoglobin; this also decreases the affinity of hemoglobin for oxygen. Therefore the net effect of a decreased blood pH and increased blood CO_2 concentration is unloading of oxygen to the tissues. Conversely, as the CO_2 concentration in the pulmonary capillaries decreases and blood pH rises, the affinity of hemoglobin for oxygen increases; thus the net effect of elevated blood pH in pulmonary capillaries is increased uptake of oxygen by hemoglobin.

The affinity of hemoglobin for oxygen is also influenced by the concentration of 2,3-DPG, a metabolic intermediate of the Rapoport-Luebering shunt involved in erythrocyte glycolysis. An increase in the 2,3-DPG concentration may occur

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in association with chronic hypoxemia (high altitude, chronic lung disease), anemia, chronic alkalosis, phosphate retention, and red cell pyruvate kinase deficiency. When the 2,3-DPG concentration is increased, the affinity of hemoglobin for oxygen is decreased, resulting in improved unloading of oxygen to peripheral tissues. Conversely, a decreased 2,3-DPG level results in an increased affinity of hemoglobin for oxygen. A decrease in the 2,3-DPG concentration may occur in stored blood, in association with chronic acidosis, and with hypophosphatemia.

Cyanosis develops when the oxygen saturation of hemoglobin is below 80%. With a normal oxygen-hemoglobin dissociation curve, the Pa_{O_2} is usually below 40 mm Hg before cyanosis is noted in the patient.[77] The hemoglobin concentration of blood must be near normal for cyanosis to be clinically evident[78]; therefore patients with severe anemia and concomitant marked arterial oxygen desaturation may not show cyanosis. In contrast, patients with marked polycythemia may be cyanotic at higher arterial oxygen saturation than patients with normal hematocrit values.

Classification

Cyanosis can be classified as either *peripheral* or *central.*

Peripheral Cyanosis.

Peripheral cyanosis is caused by slowing of blood flow to an area, resulting in abnormally increased extraction of oxygen from normally saturated arterial blood. Decreased blood flow through the peripheral capillary bed may be caused by vasoconstriction of superficial vessels, obstruction of arteries or veins, or low cardiac output. Peripheral cyanosis is observed in the extremities, nose, and ears and is not usually associated with cyanosis of mucous membranes. Peripheral cyanosis is rarely recognized in large domestic animals because of their skin pigmentation and hair cover.

Central Cyanosis.

Central cyanosis results from either inadequate oxygenation of arterial blood or the presence of an abnormal hemoglobin derivative and is characterized by cyanosis of mucous membranes (Table 5.1). Causes of inadequate oxygenation of arterial blood are respiratory disease or congenital cardiac anomalies causing right-to-left shunting (Boxes 5.16 and 5.17). Acquired abnormalities of

hemoglobin function can be induced by a number of chemicals. Exposure to these chemicals results in the formation of methemoglobin or sulfhemoglobin, neither of which is capable of binding oxygen. Nitrites and nitrates are powerful reducing agents that produce methemoglobinemia by directly oxidizing hemoglobin to methemoglobin. Nitrate poisoning is most commonly associated with the incorporation of nitrate-accumulating plants (e.g., pigweed *[Amaranthus retroflexus]*, lamb's quarters *[Chenopodium album]*, and mintweed *[Salvia reflexa]*) in livestock forage. Nitrate intoxication is usually seen only in ruminants because rumen microorganisms reduce nitrate to the more toxic nitrite ion. Congenital defects in hemoglobin function have been reported in humans and may occur in large domestic animals. Examples of such defects are nicotinamide adenine dinucleotide methemoglobin reductase deficiency and familial methemoglobinemia.

TABLE 5.1

Pathophysiologic Classification of Central Cyanosis and Examples of Associated Conditions

Classification	Associated Condition
Decreased arterial oxygen saturation	Respiratory disease
	Ventilation-perfusion mismatch
	Alveolar hypoventilation
	Impaired oxygen diffusion
	Pulmonary arteriovenous shunting
	Cardiac disease
	Cardiac anomalies that cause right-to-left shunting (e.g., tetralogy of Fallot)
Abnormal hemoglobin derivative	Methemoglobinemia
	Sulfhemoglobinemia

Box 5.16

Causes of Central Cyanosis in Horses

Common Causes

Bacterial pneumonia, pleuritis, pulmonary abscessation (*Rhodococcus equi*, *Streptococcus* species, other bacteria)

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Recurrent airway obstruction (RAO or chronic obstructive pulmonary disease)
Aspiration pneumonia
Viral pneumonia (equine influenza, adenovirus, other viruses)
Equine herpesvirus types 1 and 4 (EHV-1, EHV-4)
Acute bronchointerstitial pneumonia
Prematurity, dysmaturity, immaturity (foals)
Ventricular septal defect with pulmonary hypertension
Tetralogy of Fallot
Toxic methemoglobinemia
Anaphylaxis
Shock (hypovolemic, cardiac, septic)

Less Common Causes

Stenotic nares or choanal atresia
Neoplasia (nose, paranasal sinuses)
Nasal granuloma
Nasopharyngeal cicatrix
Tracheal stenosis, collapse, stricture
Tracheal rupture or perforation
Diaphragmatic hernia
Pneumothorax
Pulmonary edema
Smoke inhalation pneumonia
Interstitial pneumonia
Pneumoconiosis
Atrial septal defect with pulmonary hypertension

Uncommon Causes

Pulmonary lobar hypertrophy (foals)
Embryonal mediastinal cyst
Pulmonary tuberculosis, nocardiosis
Pneumocystis carinii (renamed *Pneumocystis jiroveci* in humans) pneumonia

Air embolism
Pulmonary neoplasia
Transposition of great vessels
Tricuspid atresia
Aortic, pulmonary artery rupture
Interruption of aortic arch
Common ventricle with separate pulmonary outflow chamber
Multiple cardiac anomalies
Methemoglobin reductase deficiency
Lactation tetany
Clostridial diseases
Malignant hyperthermia

Toxic Causes

Sulfur, hydrogen sulfide
α-Naphthyl thiourea (ANTU)
Chlorinated hydrocarbon
Organophosphate, carbamate
Red maple *(Acer rubrum)*[a]
Redroot pigweed *(Amaranthus retroflexus)*[a]
Sudan grass *(Sorghum vulgare var. sudanensis)*[a]
Mintweed *(Salvia reflexa)*[a]
Lamb's quarters *(Chenopodium album)*[a]
Variegated thistle *(Silybum marianum)*[a]
Winged thistle *(Carduus tenuiflorus)*[a]

[a]Nitrate accumulator, which causes methemoglobinemia.

Box 5.17

Causes of Central Cyanosis in Ruminants

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Common Causes

Bacterial pneumonia, pulmonary abscessation (*Mannheimia haemolytica* [B], *Arcanobacterium pyogenes* [B], *Pasteurella multocida* [B], *Corynebacterium pseudotuberculosis* [O, C], other bacteria)
Viral pneumonia (respiratory syncytial virus [B], ovine progressive pneumonia [O], caprine arthritis-encephalomyelitis [C], other viruses)
Parasitic pneumonia (*Dictyocaulus viviparus* [B], *Dictyocaulus filaria* [O, C])
Aspiration pneumonia
Acute bovine pulmonary edema and emphysema (B)
Pulmonary edema
Ventricular septal defect with pulmonary hypertension
Tetralogy of Fallot
Toxic methemoglobinemia
Anaphylaxis
Shock (hypovolemic, cardiac, septic)
Rumen bloat

Less Common Causes

Obstruction of nasal passages or paranasal sinuses (neoplasm, granuloma, abscess, other)
Laryngeal abscess
Tracheal stenosis, collapse, stricture
Tracheal rupture, perforation
Diaphragmatic hernia
Prematurity, dysmaturity, immaturity
Inhalation pneumonia (smoke)
Pneumothorax
Hemothorax
Pulmonary contusion
Ventricular septal defect with pulmonic stenosis
Postparturient hemoglobinuria
Clostridial diseases (e.g., malignant edema, blackleg, tetanus)
Bluetongue (O)

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Obstructive urolithiasis, ruptured urethra

Uncommon Causes

Pleural mesothelioma (B)
Water inhalation (drowning)
Pulmonary adenomatosis (O)
Transposition of great vessels
Double-outlet right ventricle
Common ventricle with separate pulmonary outflow chamber
Acute anthrax
White liver disease (exotic) (O)
Sweating sickness (exotic) (B, O)

Toxic Causes

Strychnine
Arsenic
Metaldehyde
Hydrogen sulfide
Organochlorine, chlorinated hydrocarbon
Organophosphate, carbamate
Acute selenium toxicosis
Nitrate, nitrite
Perennial broomweed *(Gutierrezia microcephala)*
Oleander *(Nerium oleander)*
Whitehead *(Sphenosciadium capitellatum)*
Milkweed (*Asclepias* species) (O)
Rhododendron (*Andromeda* species)
Fireweed *(Kochia scoparia)*
Canary grass (*Phalaris* species)
Kikuyu poisoning (exotic) (B, O)
Albizia poisoning (exotic) (B, O)
Euphorbia, *Sarcostemma* poisoning (exotic) (B, O)
Acacia poisoning (exotic) (B, O)
Wild onion *(Allium validum)*[a] (O)

Variegated thistle *(Silybum marianum)*[a]
Redroot pigweed *(Amaranthus retroflexus)*
Sudan grass *(Sorghum vulgare var. sudanensis)*[a]
Winged thistle *(Carduus tenuiflorus)*[a]
Mintweed *(Salvia reflexa)*[a]
Lamb's quarters *(Chenopodium album)*[a]
Many pasture grasses fed during optimum growth conditions[a]
Locoweeds (*Astragalus* species, *Oxytropis* species)[a]

B, Bovine; *C*, caprine; *O*, ovine.

[a]Nitrate accumulator, which causes methemoglobinemia.

Conditions That Predispose to Hypoxemia and Central Cyanosis

The remainder of this section is confined to a discussion of respiratory conditions and cardiovascular anomalies that predispose to hypoxemia and central cyanosis. Impaired pulmonary function may cause hypoxemia and, in some circumstances, cyanosis. Mechanisms by which hypoxemia of pulmonary origin can arise include alveolar hypoventilation, reduced gas transfer or diffusion across the blood-gas barrier, ventilation-perfusion mismatch, pulmonary arteriovenous shunt, or a combination of these factors.[76,78] An additional cause of hypoxemia is the decrease in the partial pressure of alveolar oxygen that occurs at high altitudes.

Alveolar Hypoventilation.

Alveolar hypoventilation is defined as a reduced volume of inspired air reaching the alveoli per unit time. Alveolar hypoventilation is always associated with an increased Pa_{CO_2}. Conditions associated with alveolar hypoventilation are drug-induced respiratory depression (morphine, barbiturates), brainstem disease (encephalitis, trauma, hemorrhage, neoplasia), and transection of the cervical spinal cord. All these conditions prevent proper generation and transmission of signals from the respiratory center to respiratory muscles. Other possible causes

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of alveolar hypoventilation are abnormal respiratory muscle function (diaphragmatic hernia, botulism), thoracic cage abnormalities (rib fracture), increased airway resistance (e.g., stenotic nares, laryngeal stricture or paresis, foreign body obstruction, bronchitis, bronchiectasis), and pleural space disease (inflammatory or neoplastic effusions, pneumothorax, hydrothorax, chylothorax, pyothorax, hemothorax).

Impaired Diffusion.

Impaired diffusion, a second cause of hypoxemia, results from increased thickness of the blood-gas barrier. Equilibrium between alveolar oxygen and pulmonary blood oxygen is not reached because of increases in distance or resistance of barriers through which oxygen must pass to bind to hemoglobin. Because carbon dioxide diffuses more readily than oxygen, the Pa_{CO_2} is not usually increased in conditions that cause impaired diffusion. In fact, Pa_{CO_2} actually may be reduced because of compensatory hyperventilation stimulated by hypoxemia. Conditions that may result in impaired diffusion are pneumonia, pulmonary edema, atelectasis, pulmonary contusions, and pulmonary neoplasms.

Ventilation-Perfusion Mismatch.

Ventilation-perfusion mismatch occurs eventually in all generalized pulmonary diseases and is the predominant mechanism by which hypoxemia develops in respiratory conditions. Overall gas exchange is impaired by uneven ventilation and blood flow. Lung areas that are overperfused in relation to ventilation (low ventilation/perfusion ratio) contribute disproportionate amounts of blood with a low Pa_{O_2} to the systemic circulation. Examples of respiratory diseases that can cause low ventilation/perfusion ratios include bronchitis, bronchoconstriction, airway closure, pulmonary atelectasis or consolidation, and local restriction of lung movement. In the case of pulmonary embolization or decreased pulmonary arterial pressure, ventilation may exceed perfusion (high ventilation/perfusion ratio) and result in pathologic dead space. Pulmonary mechanisms can partly compensate for ventilation-perfusion inequalities. Alveolar hypoxia may lead to reflex pulmonary arterial constriction, which redirects blood flow to alveoli that are adequately ventilated. Airway hypocapnia can stimulate bronchoconstriction, resulting in redirection of airflow to better-perfused alveoli.

Shunting.

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Shunting is defined as any mechanism by which blood that has not passed through ventilated areas of the lung is added to arteries of the systemic circulation. The term *venous admixture* is used to describe venous blood that passes through the lungs without proper oxygenation. Animals with venous admixture often hyperventilate and present with normocapnia or hypocapnia in association with hypoxemia. The most common cause of shunting is congenital heart disease, which allows unoxygenated blood from the right heart to pass directly into the left heart without passing through the pulmonary circulation. Intrapulmonary anatomic shunts can result from pulmonary artery to pulmonary venous fistulae, or from prior to severe lung consolidation that results in large portions of the lung being well perfused but poorly ventilated. Cyanosis or hypoxemia unresponsive to oxygen administration suggests the presence of such congenital cardiac anomalies or intrapulmonary shunts.[79] Examples of common cyanotic congenital cardiac defects are tetralogy of Fallot, truncus arteriosus, transposition of the great arteries, tricuspid atresia, and hypoplastic left heart syndrome.[77,79] Aside from congenital defects, reversion to fetal circulation should be considered in any critically ill neonatal animal with hypoxemia that is unresponsive to oxygen insufflation.[79]

Approach to Diagnosis of Cyanosis

History.

The history should include questions about the duration of the cyanosis (e.g., cyanosis that has been present since birth or an early age may indicate congenital heart disease with right-to-left shunting); possible exposure to toxic plants or chemicals that may result in production of abnormal types of hemoglobin; evidence of an abnormal respiratory pattern (respiratory distress, inspiratory stridor, cough); and signs of episodic weakness or syncope that may be consistent with congenital cardiac anomalies or severe upper airway obstruction (e.g., tracheal collapse or severe laryngeal edema associated with necrotic laryngitis in calves).

Physical Examination.

A thorough physical examination should include visual *inspection* to detect abnormalities in the respiratory pattern (e.g., tachypnea, respiratory distress, stridor) and careful *auscultation* of the larynx, trachea, and lungs to provide

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information that helps further define the cause of respiratory dysfunction. Rebreathing bags (12- to 52-L capacity for adult horses and cattle; 6- to 12-L capacity for calves, foals, and small ruminants) cause temporary buildup of CO_2, stimulating the respiratory center, prompting deep breathing immediately after the bag is removed and the animal is allowed to inspire room air. Loud breath sounds, pulmonary crackles and wheezes, or pleural friction rubs may suggest cyanosis in association with pathologic respiratory conditions. Loud cardiac murmurs accompanied by precordial thrills point to congenital heart disease as the cause of cyanosis.

Palpation and *percussion* of the thorax are important examination procedures in animals with cyanosis. Chest palpation may reveal pleural friction rubs or the pain and crepitus associated with rib fractures. Increased resonance on percussion may indicate pneumothorax, whereas decreased resonance suggests pulmonary congestion or consolidation, pleural effusion, or a space-occupying lesion in the thorax.

Endoscopic Examination.

An endoscopic examination should be performed if upper airway obstruction or malformation is suspected (see the Cough, Nasal Discharge, and Respiratory Distress [Dyspnea] sections earlier).

Radiographic Examination.

Radiographs of the upper respiratory tract and thorax can be used to further characterize pathologic respiratory conditions. Abnormalities detected using these modalities include space-occupying lesions in the oropharynx, nasopharynx, or larynx; tracheal compression or collapse; enlargement or distortion of the cardiac silhouette; pulmonary consolidation; pneumothorax; pleural effusion; and pulmonary abscessation.

Ultrasound Examination.

Ultrasound examination of the chest and heart is indicated to characterize cardiac anomalies and to detect the presence and determine the extent of pleural effusion, pulmonary consolidation, and pulmonary abscessation.

Arterial Blood Gas Analysis.

Arterial blood gas analysis is indicated to determine O_2 and CO_2 tension (see the

Respiratory Distress [Dyspnea] section earlier).

Complete Blood Count.

A complete blood count should be performed to determine if polycythemia or inflammatory alterations in the leukogram are present. Polycythemia may develop secondary to chronic hypoxemia associated with long-standing pulmonary disease or right-to-left shunting. An inflammatory leukogram is consistent with a diagnosis of bacterial or aspiration pneumonia or other inflammatory respiratory condition.

Heparinized Blood.

A sample of heparinized blood should be shaken gently in the air for 15 minutes. Reduced hemoglobin (cardiovascular or respiratory disease) turns red on exposure to air, whereas methemoglobin remains chocolate brown after shaking.

Spectroscopic Examination.

Spectroscopic examination is necessary to determine if methemoglobin is present. Methemoglobin is stable in refrigerated heparinized blood for only a few hours. To preserve methemoglobin, 1 part of blood can be mixed with 20 parts of phosphate-buffered saline (pH 6.6) or diluted 1 : 20 in distilled water. These diluted samples can be refrigerated or frozen until they are analyzed.

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Abnormal Respiratory Noise (Stridor)

W. David Wilson • Jeanne Lofstedt • Jeffrey Lakritz

■ Definition

Stridor is an abnormal, intense respiratory sound (wheeze) that is audible without the use of a stethoscope. The sound is usually generated in the upper airway and is most often heard during inspiration.

■ Pathophysiology

The extrathoracic airway of the horse consists of segments that are relatively rigid (e.g., nasal passages, extrathoracic trachea) and others (e.g., nostrils, soft palate, larynx) that not only are elastic but also have valve-like actions that are further capable of modifying the cross-sectional area and therefore resistance to airflow.[68,80] Pressures in the extrathoracic airways are subatmospheric during inspiration,[68,70,80] which causes the less rigidly supported parts of the upper airway to narrow (dynamic narrowing or collapse) during inspiration.[68-70,80,81] A major function of the upper airway muscles and other supporting structures is to prevent this dynamic narrowing or collapse during periods of high inspiratory gas flow.[68] Disease in these structures or a more rostral obstructing lesion that causes a greater negative pressure during inspiration may make them incapable of resisting axial displacement.[68,70] The increased resistance to flow induced by static or dynamic obstructions increases the driving pressure and therefore the work needed to move a given volume of air.[80]

Approximately 80% of the total airway resistance to gas flow at rest and during exercise is in the upper airway rostral to the thoracic inlet.[70] Nasal resistance, most of which is caused by resistance just within the external nares, comprises more than 50% of the total upper airway resistance in the horse.[69,82] In most species, including ruminants, this resistance can be bypassed by mouth breathing to accommodate the high airflow rates that accompany strenuous exercise. The horse, in contrast, is limited to nasal breathing even during exercise[69,70,82,83] because the larynx is firmly maintained in the nasopharynx by the tight seal formed around it by the muscular palatopharyngeal ring

(intrapharyngeal osteum), except during swallowing.[83,84] Therefore mechanisms other than mouth breathing are necessary to reduce the energy cost of breathing in the horse.[68,81,83] These mechanisms include dilation of the distensible external nares by actively pulling the alar folds laterally, vasoconstriction in the erectile nasal vascular tissues to reduce congestion in the nasal mucosa, straightening of the respiratory tract, and dilation of the larynx by abduction of the vocal folds.[68,70,80-83,85,86]

The horse is capable of generating high respiratory rates during fast exercise. This is accomplished at the canter and gallop, but not at the trot, by locking respiration to locomotion so that the horse takes one breath for each stride.[84,87-89] Exhalation occurs each time the lead forelimb strikes the ground.[83,84,87] The horse can swallow during fast galloping exercise; the entire process is completed in exactly a two-stride sequence.[84,90]

At all levels of the respiratory tract, respiratory sounds are thought to result from vibrations in tissue and sudden changes in the pressure of gas moving in the airway lumen.[70,84] Airflow in the normal respiratory tract at rest occurs in a laminar fashion (i.e., the air closest to the wall of the airway is almost stationary, whereas succeeding layers toward the center of the lumen move progressively more rapidly).[84] Respiration in normal horses and in ruminants at rest does not generate easily audible sounds.

High rates of gas flow and airway narrowing increase both the tendency for dynamic collapse and the degree of turbulence and genesis of sounds. High peak flow rates of 125 mL/s/kg have been reported in galloping horses.[89] During exercise significant sound frequencies are generated and can be detected using sound spectrographs or radio stethoscopes, although most of these sounds are of frequencies and amplitudes not detectable by the human ear.[91,92] Deformities in the wall and masses in the lumen of the airway cause airway narrowing and further disturbances in laminar flow, resulting in more severe turbulence and sudden changes in the pressure of moving gas, which may generate audible sounds.[84] High airflow rates are necessary to induce audible stridor; therefore examination of the horse at exercise is an essential part of the physical examination.[83,84]

Stridor is best heard during inspiration in most cases because the usual source of origin, the upper airway, is subject to dynamic narrowing during the inspiratory phase of the respiratory cycle.[68,69,81] In particular, nonfixed

obstructions such as the paretic vocal folds of horses with idiopathic laryngeal hemiplegia (ILH) cause obstruction to airflow and turbulence only when dynamically drawn into the airway by the high inspiratory airflow rates that accompany fast exercise. Other obstructions such as arytenoid chondritis are fixed and obstruct airflow during both inspiration and expiration, which frequently result in audible stridor during both phases of respiration.

The pharynx is the site of greatest airway angulation because of flexion of the atlanto-occipital joint. At rest the horse's head is usually held at about 50 degrees to the horizontal plane.[84] At gallop the horse extends its head and neck and thus straightens the pharyngeal airway.[84] This maneuver also stretches and straightens the trachea, making it less compliant and less subject to dynamic narrowing during inspiration.[81] When ridden at a collected canter, the horse is forced to flex its poll so that its face is nearly vertical, thereby increasing the angulation of the pharyngeal airway and the obstruction to gas flow at this point.[84] Therefore abnormal respiratory sounds originating in the pharyngeal region are often more easily heard when the horse is ridden at a collected canter than when it is exercised at a full, extended gallop.[83,84]

Because food animals are not normally expected to perform fast exercise, signs of stridor are usually present at rest when the animals are presented to veterinarians for examination. Stridor in resting animals usually indicates moderate to severe upper airway obstruction of a fixed nature. In ruminants the epiglottis is relatively short and blunt, and the palatopharyngeal ring allows the laryngopalatal dislocation necessary for mouth breathing. In conditions that give rise to respiratory distress and mouth breathing, the turbulence produced is often sufficient to induce abnormal (grunting) expiratory sounds, which may be classified as expiratory stridor. The external nares of cattle are much less compliant than those of sheep, goats, and horses, which prevents dynamic collapse during inspiration; thus conditions such as paresis of the nares that cause stridor in sheep, goats, and horses do not cause stridor in cattle (Boxes 5.18 and 5.19).

Box 5.18

Causes of Stridor in Horses

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Common Causes

Idiopathic laryngeal hemiplegia (ILH, roaring)
Dorsal displacement of the soft palate (laryngopalatal dislocation)
Epiglottic entrapment
Retropharyngeal abscess
Strangles (*Streptococcus equi* infection)
Guttural pouch empyema
Chronic pharyngeal lymphoid hyperplasia
Arytenoid chondritis
Guttural pouch mycosis
Laxity of the alar cartilage

Less Common Causes

Arytenoid chondroma, chondropathy
Pharyngeal paresis
Botulism, shaker foal
Dynamic collapse of the pharynx
Subepiglottal, pharyngeal cyst
Subepiglottal abscess
Epiglottal retroversion
Guttural pouch tympany
Guttural pouch neoplasia
Rostral displacement of the palatopharyngeal arch
Nasal fungal infection (e.g., aspergillosis, rhinophycomycosis)
Nasal polyp
Nasal foreign body
Nasal trauma
Nasal tumor
Nasopharyngeal cicatrix
Progressive ethmoidal hematoma
Sinusitis (sinus empyema)
Sinus cyst
Sinus tumor
Atheroma

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Laryngeal trauma
Tracheal collapse (scabbard trachea)
Tracheal stricture, stenosis
Tracheal chondroma
Tracheal rupture, perforation
Stenotic nares
Laryngeal edema
Purpura hemorrhagica
Anaphylaxis or acute drug reaction
Chronic lead poisoning
Choanal (posterior nares) atresia, hypoplasia (foals)
Fracture of laryngeal cartilages
Laryngeal granuloma, scar tissue
Equine influenza
Exercise-induced pulmonary hemorrhage (EIPH)
Jugular thrombosis
Hyperkalemic periodic paralysis (HYPP)

Uncommon Causes

Amyloidosis (cutaneous, nasal)
Lymphosarcoma, lymphoma
Bee or wasp sting
Snakebite
Thyroid adenoma, adenocarcinoma
Vesicular stomatitis
Retrobulbar neoplasia
Dystrophic myodegeneration (white muscle disease)
Neoplasia (oral, mandibular, maxillary, laryngeal, pharyngeal, tracheal)
Coccidioidomycosis
Inhalation pneumonia, smoke inhalation
Burns (thermal, chemical)
Congestive cardiac failure
Cutaneous habronemiasis
Unilateral ventral displacement of the roof of the nasopharynx
Epiglottiditis
Hyoid bone injuries

Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma, cryptococcal rhinitis, equine nasal granuloma
Goiter
Hypertrophic ossification of the laryngeal cartilages
Abnormalities of the nasal septum
Intramural esophageal cyst
Foreign body (nasal, pharyngeal, laryngeal, tracheal, bronchial)
Hyperparathyroidism
Phycomycosis, pythiosis
Anaerobic abscesses (e.g., *Clostridium perfringens*)
Besnoitiosis, globidiosis (exotic)
Glanders (exotic)

Toxic Causes

Organophosphate-induced laryngeal paralysis
Lead-induced laryngeal paresis
Reserpine

Box 5.19

Causes of Stridor in Ruminants

Common Causes

Necrotic laryngitis (calf diphtheria) (B, O)
Abscess (pharyngeal, laryngeal, retropharyngeal, oral)
Nose bots *(Oestrus ovis)* (C, O)
Caseous lymphadenitis *(Corynebacterium pseudotuberculosis)* (C, O)
Actinobacillosis (wooden tongue, nasal actinobacillosis)
Nasal adenocarcinoma, adenoma, adenopapilloma, polyp (C, O)
Trauma (oral, nasal, pharyngeal, laryngeal, tracheal)
Anaphylaxis or drug reaction
Sinusitis
Foreign body (nasal, oral, pharyngeal, laryngeal, tracheal, bronchial)

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Less Common Causes

Actinomycosis (lumpy jaw)
Tracheal stenosis, collapse, stricture
Bovine leukosis (enzootic adult lymphosarcoma) (B)
Sporadic bovine leukosis (adult multicentric lymphosarcoma) (B)
Thymic lymphosarcoma (juvenile) (B)
Mannheimia haemolytica or *Pasteurella multocida* pneumonia (includes shipping fever and enzootic calf pneumonia) (B)
Infectious bovine rhinotracheitis (IBR; BHV-1) (B)
Atypical interstitial pneumonia (B)
Malignant catarrhal fever (B)
Vesicular stomatitis
Clostridial infection of the head (O)
Pulmonary embolism from posterior vena cava thrombosis (B)
Snakebite
Bee or wasp sting
Bovine nasal granuloma, atopic rhinitis (summer snuffles) (B)
Honker syndrome in feedlot cattle (B)
Neoplasia (nasal, paranasal sinus, oral, pharyngeal, laryngeal, tracheal, maxillary, mandibular, retrobulbar)
Congenital abnormalities
Inhalation pneumonia, smoke inhalation

Uncommon Causes

Tuberculosis (B)
Congenital cystic nasal conchae (B)
Choanal atresia (O)
Salivary cyst, mucocele, ranula, trauma (C)
Photosensitization in Southdown and Corriedale sheep (O)
Fungal granuloma, maduromycosis, rhinosporidiosis, mycetoma (B, C)
Phycomycosis, pythiosis (B)
Goiter, iodine deficiency
Hyperparathyroidism (B, C)
Enzootic ataxia, swayback (C, O)

Besnoitiosis, globidiosis (exotic)
Endemic ethmoid hematoma (exotic) (B)
African bovine malignant catarrhal fever (exotic) (B)
Lumpy skin disease (exotic) (B)
Nasal schistosomiasis (exotic)
Virulent sheep and goat pox (exotic) (C, O)
Peste des petits ruminants (exotic) (C, O)
Gedoelstia hasleri nasal bots (exotic) (C, O)

B, Bovine; *C*, caprine; *O*, ovine.

Approach to Diagnosis of Stridor

History.

The procedure for taking a history should follow that used in the evaluation of cough and nasal discharge (see the Cough and Nasal Discharge sections earlier). The history should also include the duration of ownership; time of onset of the clinical signs of stridor; progression of clinical signs; presence or absence of the noise at rest; relation of noise to fitness; relation of noise to speed, duration, and direction of work; relation of noise to head position during work; association of noise with poor performance or exercise intolerance; and other signs of respiratory tract, oropharyngeal, or neurologic disease (e.g., nasal discharge, cough, dysphagia, retropharyngeal swelling).

Physical Examination.

A physical examination of the entire respiratory tract at rest should be performed as described for cough and respiratory distress. In addition, the presence or absence of stridor at rest should be ascertained by listening at the nostrils, and digital pressure should be applied to the retropharyngeal region and to the larynx during palpation of these areas to evaluate whether stridor or pain (or both) can be induced easily or exacerbated. The dorsal surface of the larynx should be palpated with the fingertips with the horse relaxed and its head and neck in an extended position. This permits comparison of the prominence of the muscular process of the arytenoid cartilages and the thickness of the cricoarytenoideus dorsalis (CAD) muscle, both of which are affected in horses with atrophy of the CAD muscle in association with ILH. Air turbulence, flattening, swelling, and

pain should be assessed during palpation of the extrathoracic airway. The larynx, trachea, and lungs should be carefully auscultated, and the chest should be percussed. A thorough oral examination should be completed, particularly in ruminants; in cattle this should include palpation of the base of the tongue, the oropharynx, and, if possible, the larynx through the oral cavity.

Field Exercise Testing.[84]

In performance horses most examinations are carried out because the horse makes a noise only when worked, because of exercise intolerance or poor performance, or as part of a prepurchase examination. Unless a high-speed treadmill is available, the exercise testing should be completed under saddle with a competent rider, preferably with an intensity of work that matches the horse's normal activity.[70,83] It is less satisfactory but often necessary to work the horse on a lunge line, in which case it should be lunged in both directions.[83]

The horse should be worked in a circle about 30 yards in diameter so that it passes close to the observer on each circuit.[84] The observer should first identify the expiratory sound by its association with locomotion and then try to fit abnormal sounds into this base rhythm. At fast speeds, respiration is rapid; thus the observer should not stand too far away from the horse because the slow speed at which sound is transmitted confuses interpretation of whether the sound is inspiratory or expiratory.[84,90] In cold weather the visibility of exhaled breath aids interpretation. It is important to ride the horse in both directions because an abnormal sound is frequently heard more clearly when the horse is exercising in one direction than in the other.[83] If the presence or character of a respiratory noise remains in doubt after the horse has been exercised in a circle at a collected canter, the horse should be galloped until it is blowing hard and then ridden past the observer at a fast gallop.[83]

A satisfactory exercise test should include at least 5 minutes of work at the canter, after which the horse should immediately be brought over to the observer so that the character and sequence of abnormal sounds that persist can be determined. All horses that have been worked adequately make a loud expiratory blowing sound at this time. Turbulence of airflow in the larynx may be audible with a stethoscope.[84] Inducing adduction of the vocal fold, particularly on the right side, by applying gentle pressure in a rostromedial direction to the muscular process of the arytenoid cartilage often accentuates an inspiratory noise in horses with laryngeal hemiplegia. Noises originating from unilateral lesions in

the nasal passages are easily localized because the sound can be eliminated by alternately blocking off airflow through each nostril with the hand. Temporary occlusion of both nostrils simultaneously may provoke laryngopalatal dislocation and a loud gurgling sound in a susceptible horse.[83,84] The presence of nasal discharge or blood at the nostrils should be noted, and the time required for the heart and respiratory rates to return to preexercise values should be interpreted in light of the severity of the exercise test.[83]

Interpretation of Abnormal Sounds.

A normal horse makes no audible respiratory sound at rest and when exercised at a canter or slow gallop makes only a blowing expiratory sound.[70,83,84] In unfit horses, particularly overweight ones, an inspiratory sound is also frequently audible. This sound can be quite loud, and it may be difficult to differentiate from sounds caused by abnormalities of the respiratory tract.[82,83] Thus evaluation of the horse's “wind” is best carried out when the horse is in fit condition for its intended use. It takes at least 1 month for an older horse that has been turned out to pasture to regain a satisfactory level of fitness to perform a meaningful wind examination. Many normal horses produce a harsh expiratory “high blowing sound” of variable pitch, which results from resonance in the cavity of the false nostril during expiration.[83,84,90] If the source of the stridor remains in doubt, temporary suturing of the alar fold dorsal to the nostril can help localize noises suspected of being caused by vibration of the alar fold.

Horses with ILH make a rather characteristic biphasic sound, the inspiratory sound occurring between successive expiratory sounds. The pitch of the sound can vary from a whistle to a deep roar, the lower-pitched note giving rise to the so-called sawing wood sounds.[84] Sonographic and spectrographic analysis of the sounds produced by “roarers” indicates that the range of sound frequencies generated by these horses is the same as that produced by normal horses.[91,92] However, horses that make an audible whistle generate an intense band of frequencies centered on 1.9 kHz that are thought to result from amplification by the still-patent lateral ventricle of the frequency generated by vibration of the incompletely abducted left vocal fold.[92] In a normal horse the left vocal fold is fully abducted, and the cavity of the lateral ventricle is thus obliterated during strenuous exercise.[86]

The sounds generated by horses with laryngeal chondritis, severe proliferative pharyngeal lymphoid hyperplasia, epiglottic entrapment, and tracheal stenosis

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can be similar to those caused by ILH.[83,84] Laryngopalatal dislocation (dorsal displacement of the soft palate) gives rise to a transient, vibrant, gurgling sound.[69,83,84] In many instances a severe exercise test is required to induce this condition; thus this sound may be heard only during a race.[70,83,84] It is thought that the condition may occur when pharyngeal stimulation causes swallowing during fast exercise.[84] Instead of the horse completing the process and regaining the laryngopalatal seal consistent with the respiratory position of the larynx in the nasopharynx, the tip of the epiglottis disengages from the rostroventral aspect of the palatopharyngeal ring (the caudal free border of the soft palate), resulting in the entire epiglottis slipping ventral to the soft palate. At the subsequent inspiration the palatopharyngeal arch tends to be drawn into the rima glottis, and at expiration it is driven toward the roof of the pharynx by the airstream. The palatopharyngeal arch acts as an airway obstruction, and the tissue vibration and resulting turbulence generate a sound of varying pitch and intensity, often described as gurgling followed by swallowing.[84] The horse often slows suddenly or stops when this event occurs, and the jockey often reports that the horse stopped after “choking” or “swallowing its tongue.” If repeated swallowing is successful in relocating the normal laryngopalatal respiratory arrangement, the horse often continues to race after slowing or stopping.[70]

Gross obstruction of the airway by pressure from pus-filled guttural pouches, retropharyngeal abscesses, large subepiglottal cysts or abscesses, or large proliferative lesions (e.g., laryngeal tumors) produces loud, stertorous breathing (snoring) often heard at rest and readily so with exercise; both inspiratory and expiratory sounds are clearly audible.[84]

In a normal horse the pattern of respiratory sounds is regular and synchronized with the pace of the exercise. Laryngeal irritation caused by exudate from the upper or lower airway, pharyngeal lymphoid hyperplasia, or other inflammatory or space-occupying conditions causes the horse to swallow more frequently during exercise, which generates an irregular pattern of respiratory sounds characterized at the canter and gallop by a respiratory cycle of double the normal length.[84,90]

Interpretation of stridor in yearlings presented for sale is difficult because these animals are rarely fit and it is usually possible to exercise them only at a canter on a lunge line. It has been shown that resentment of restraint under such circumstances can significantly alter the linking of locomotion and respiration, which complicates recognition of the respiratory phasing of noise production.[86]

In addition, there is not always a close correlation between noise production, endoscopically visible abnormalities, and signs of exercise intolerance even in fit adult horses.[70, 83]

Endoscopic Examination.

Endoscopic examination of the upper airway is the most useful diagnostic procedure for investigating stridor. The examination should be performed at rest and, if possible, repeated during exercise in the field or on a high-speed treadmill. Endoscopic examination immediately after cessation of exercise is less satisfactory than endoscopy during exercise because dynamic collapse of the rima glottis terminates rapidly on cessation of exercise. The availability of self-contained portable videoendoscopy equipment allows visualization of the pharynx and larynx during over-the-ground exercise and permits digital video-image capture and analysis. Over-the-ground videoendoscopy has the distinct advantage of allowing the horse to be examined under the exact conditions under which the stridor occurs.

Because sedatives and tranquilizers may alter the tone and function of the muscles supporting laryngeal and pharyngeal anatomy, endoscopic examination should be performed without chemical restraint whenever possible.[70] The nasal passages, conchae (turbinates) (including the ethmoidal concha), nasal septum, pharynx, guttural pouches, larynx, and trachea should be examined through both nostrils so that the presence, nature, and source of exudates and the presence of anatomic or functional abnormalities or mass lesions can be determined. Because the nasal passages are not positioned on the midline, the larynx is viewed slightly obliquely when examined from the left or the right ventral meatus and may appear slightly asymmetric. Thus visually apparent asymmetry of the larynx should be confirmed by examining these structures through both nostrils.[70,83]

Interpretation of the findings of the endoscopic examination of the pharynx and larynx is by no means straightforward. The results can be influenced by the day the examination was done, the use of sedation, the side through which the endoscope was passed, and the observer's interpretation. The appearance of laryngeal symmetry or asymmetry in resting horses varies considerably and therefore is of limited clinical usefulness unless complete hemiparalysis is present. Many horses have asynchronous or asymmetric laryngeal movement at rest but not during exercise, whereas other horses have a normal-appearing

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larynx at rest but suffer dynamic collapse during exercise. Interpretation of findings is improved by use of an objective grading system, which includes assessment of the ratio of the areas of the left and right half of the rima glottis, and by correlating findings at rest with those observed on videoendoscopy performed during maximal exercise.[93] For evaluation of the larynx at rest, full abduction of the vocal folds should be induced by exercise or by temporary occlusion of the nostrils.[83] Contralateral adductory laryngeal movement should be stimulated by slapping the horse just behind the withers (slap test).[94] To induce the horse to swallow, the tip of the epiglottis should be touched with the endoscope, or water should be flushed through the endoscope. These maneuvers help to establish whether movement of the arytenoid cartilages is synchronous and symmetric and increase the predictive value of endoscopic observations, allowing laryngeal function to be graded as follows.[93]

- Grade 1: Synchronous, full adduction and abduction of the left and right arytenoid cartilages (considered normal).
- Grade 2: Asynchronous movement such as hesitation, fluttering, or adductor weakness of the left arytenoid cartilage during inspiration, expiration, or both, but full abduction of the left arytenoid cartilage, inducible by nasal occlusion or swallowing. Grade 2 findings are considered a normal variation and are not usually associated with dynamic airway collapse during exercise.
- Grade 3: Asynchronous movement of the left arytenoid cartilage during inspiration, expiration, or both, but full abduction is not inducible by nasal occlusion or induction of swallowing. The true functional significance of grade 3 findings can be

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determined only by performing endoscopic examination during maximal exercise, a procedure that has led to subclassification of grade 3 findings.[95] Some grade 3 horses (grade 3A) are able to achieve full abduction during exercise, whereas others maintain a partly abducted position similar to the resting position (grade 3B) or experience dynamic collapse (grade 3C).[95]

- Grade 4: Marked asymmetry of the larynx at rest and no substantial movement of the left arytenoid cartilage during any phase of respiration. These horses have complete left laryngeal hemiplegia, are true "roarers," and consistently experience dynamic collapse on inspiration during strenuous exercise.[93]

Performing an endoscopic examination during exercise over ground or on a high-speed treadmill makes it possible for a stationary observer to gain a good dynamic appreciation of the significance of upper airway abnormalities (i.e., dynamic endoscopy)[95-99] (see the Exercise Intolerance and Poor Performance in Horses section later). Dynamic changes in airway lumen diameter occur quickly during treadmill endoscopy and may be difficult to visualize; therefore the endoscopic examination should be videotaped for later playback in slow motion and freeze frame.[99] Racehorses should be exercised maximally and to exhaustion because some abnormalities are apparent only at maximal exercise toward the end of a race when pharyngeal or laryngeal muscles become fatigued and are no longer able to resist the transmural pressure gradient, which tends to induce dynamic collapse of the upper airway during inspiration.[95-99] Endoscopic identification of an upper respiratory tract abnormality in a resting horse does not necessarily mean that it is inducing a problem during exercise, and, conversely, the absence of an upper respiratory tract abnormality at rest does not rule out the possibility of intermittent airway obstruction during strenuous

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exercise. For example, dorsal displacement of the soft palate, epiglottic entrapment, dorsal displacement of the epiglottis, dynamic collapse of the left arytenoid cartilage or vocal fold (or both), and unilateral or bilateral ventral displacement of the roof of the pharynx (dynamic pharyngeal collapse) have been observed during treadmill exercise in horses with an endoscopically normal upper airway at rest.[95-99]

Radiographic Examination.

Radiographic examination of the nasal passages, paranasal sinuses, pharynx, retropharyngeal area (including guttural pouches), larynx, and proximal trachea is indicated to confirm anatomic or functional problems or space-occupying lesions not definitively diagnosed by clinical examination and endoscopy (see the Nasal Discharge and Respiratory Distress [Dyspnea] sections earlier). Radiography is particularly useful for visualizing subepiglottic masses such as cysts or abscesses and for evaluating the epiglottis of the horse when it is obscured from endoscopic view by dorsal displacement of the soft palate or other space-occupying lesions. An accurate assessment of epiglottic length can also be made from standardized true lateral radiographs of the larynx by measuring the distance from the body of the thyroid cartilage to the tip of the epiglottis (thyroepiglottic length).[100] The mean ± SD (standard deviation) thyroepiglottic length in normal Thoroughbreds is reported to be 8.76 ± 0.44 cm.[100] Significantly shortened thyroepiglottic lengths have been recorded in Thoroughbreds with dorsal displacement of the soft palate (laryngopalatal dislocation) and in those with entrapment of the epiglottis in the aryepiglottic folds.[100] Tracheal diseases such as chondroma or dynamic collapse may be visualized on radiographs of the trachea, particularly those made during the inspiratory phase.

Ultrasound Examination.

Ultrasound examination of externally visible lesions, such as possible retropharyngeal abscesses that may be impinging on the airway, helps to characterize lesions and assist in the collection of samples by aspiration or biopsy. Transcutaneous ultrasound examination of the larynx may also provide useful information.

Biopsy.

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Biopsy and histologic evaluation of samples are indicated to diagnose certain mass lesions such as neoplasms, cysts, polyps, fungal granulomas, or foreign body granulomas in or surrounding the airway. Masses in the airway can be biopsied through the biopsy channel of an endoscope, but these samples inevitably are small. Larger samples can be collected from lesions in the nares, nasal diverticulum, and nasal passages using uterine biopsy forceps, laparoscopy forceps, or curettes. Hemorrhage usually accompanies such procedures and should be anticipated before the procedure. Biopsies can also be collected at the time of exploratory or corrective surgery from lesions in the nasal passages, pharynx, larynx, and guttural pouches. Lesions such as habronemiasis involving the external nares and lesions in other accessible areas such as the parotid salivary gland can be biopsied percutaneously using Tru-Cut or similar instruments.

Aspiration.

Aspiration, performed either blindly or with the assistance of ultrasound, followed by cytologic examination and culture of aspirated material is useful in the evaluation of masses such as retropharyngeal abscesses that are causing stridor by impinging on the upper airway.

Swabbing or Scraping.

Nasal or nasopharyngeal swabbing or scraping followed by direct cytologic examination and culture is indicated for confirmation of nasal fungal infection and bacterial infections of the upper airway (e.g., strangles).

Complete Blood Count.

A complete blood count including fibrinogen concentration can be useful in evaluating patients suspected of having a primary or secondary inflammatory condition or conditions such as ethmoidal hematoma and guttural pouch mycosis in which blood-loss anemia is likely to be a complicating problem.

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Exercise Intolerance and Poor Performance in Horses

Stephanie J. Valberg • W. David Wilson

The popularity of performance horses has broadened our perspective on health beyond the conventional diagnosis of health or disease in a horse at rest. Sports medicine defines equine health as the optimum function of all body systems during the expected level of performance. Because many body systems function at only a small fraction of their maximum capacity in a resting athlete, a clearer understanding of exercise responses in the horse and new methods of evaluating horses during exercise are necessary.

Exercise Responses

As horses accelerate during exercise, motor units within active muscles fire in a coordinated fashion to produce the power necessary to drive the animal forward. Initially, slow-twitch type 1 muscle fibers are recruited, followed at increasing speed by recruitment of oxidative fast-twitch type 2A fibers and finally the fastest and most powerful muscle fibers, type 2X. The increased demand for adenosine triphosphate (ATP) to support muscle contractions during exercise can be met initially by small intracellular stores of creatine phosphate, but within seconds oxidative or glycolytic metabolism (or both) is activated. At submaximal speeds the major factors contributing to fatigue are motivation, total depletion of fuel reserves (glycogen), fluid and electrolyte losses, and hyperthermia.[101] Nociceptive input from muscle receptors to the brain may be a primary motivator to discontinue exercise in many horses, as in people.[102] Training increases the oxidative and endurance capacity of skeletal muscle by increasing the volume of mitochondria and the capillary density surrounding muscle fibers.[103] This delays the onset of fatigue by increasing the availability and metabolism of plasma free fatty acids and glucose, thus sparing muscle glycogen. Training also fine-tunes the motor unit recruitment pattern to provide the most efficient and coordinated pattern of movement.

When a horse accelerates toward a maximum speed, a peak in the total amount of oxygen consumed is realized ($\dot{V}O_{2max}$). Additional energy to produce speeds beyond $\dot{V}O_{2max}$ must be supplied by anaerobic glycolysis with lactic

acidosis as a consequence. The term *anaerobic threshold* has been used to describe the speed at which this exponential rise in lactate begins to occur. This inflection point is usually at a velocity producing a blood lactate of 4 mM (VLA_4). Fatigue with maximum (fast) exercise occurs when muscle pH falls so low that glycolysis and excitation contraction coupling are inhibited and muscle ATP concentrations fall.[104,105] Muscle (ATP) begins to decrease after muscle lactate exceeds 40 to 80 mmol/kg of dry muscle and muscle pH falls below 6.8. Overall muscle glycogen stores are not a limiting factor with maximum exercise.[106] Training over time increases the mitochondrial volume and the ratio of type 2A to type 2X muscle fibers.[103,107] As a result, the onset of anaerobic metabolism is delayed until a higher speed is reached and horses are able to maintain a higher speed over a given distance.

The cardiovascular system plays a central role in the oxygenation of blood by the lungs, the delivery of oxygen and other energy substrates to exercising muscles, and the removal of metabolic products from those muscles. Cardiac output increases with exercise in horses, largely as a function of an increase in heart rate.[108] As exercise begins, the heart rate quickly increases and then reaches a steady state within minutes at a submaximal speed. With increasing exercise intensity the heart rate shows a linear relationship with speed up to a maximum rate of 210 to 230 beats/min. The mean systemic arterial pressure does not change with submaximal exercise but rises with maximum exercise. Mean pulmonary arterial pressures increase with speed as the heart rate increases, reaching remarkably high levels that are four times resting values.[109] The oxygen-carrying capacity of the blood also rises with increasing speed through splenic contraction and a more than 50% increase in blood hemoglobin.[110] The increase in blood viscosity that occurs with splenic contraction is believed to contribute to the increase in blood pressure with exercise. Among the adaptive cardiovascular responses to training are a lowered heart rate and blood pressure at the same exercise intensity[111]; increased red cell volume[92]; and increased capillarization of muscle.[103]

After an initial abrupt rise, the respiratory rate increases linearly with the speed of trotting until, at a canter or gallop, respiration is linked to stride frequency on a 1 : 1 basis.[87,89] This leaves less time available for completing a respiratory cycle at faster speeds. To counter this, inspiratory and expiratory airflow velocities must increase to maintain or increase minute volume. As airflow rates increase, increased turbulence and an increased tendency for

dynamic narrowing of the airways causes an increased resistance to flow and increases the work (energy cost) of breathing.[70,81] A finite maximum flow rate is eventually achieved, beyond which the expiratory muscles and the physical characteristics of the respiratory tract do not permit further increases in flow rate.[81] In addition, a maximum stride frequency is reached, restricting the maximum respiratory rate to 140 to 150 breaths/min.[87,89] It has been suggested that beyond the finite maximum flow rate, the animal is forced to hypoventilate, which may result in arterial hypoxemia during maximal fast exercise.[112] The limitation placed on oxygen diffusion by blood hyperviscosity and the short transit time of blood through the pulmonary capillary bed at rapid heart rates also likely contribute to arterial hypoxemia.[113] The arterial hypoxemia and incomplete saturation of hemoglobin that occur during strenuous exercise do not necessarily limit delivery of oxygen to the tissues, however, because the decline in blood oxygen tension is offset by the increase in the total blood hemoglobin oxygen content resulting from splenic contraction. This fact and the horse's ability to sustain at least a sixfold increase in cardiac output between rest and the point of maximum oxygen uptake ($\dot{V}O_{2max}$)[114] are the major factors that contribute to the enormous aerobic capacity of the horse.

In contrast to the muscular and cardiovascular systems, the respiratory system shows little adaptation to training. Whether the apparent inability of the equine respiratory system either to adjust to training[115] or to compensate fully for the increased flow demands of heavy exercise limits athletic performance remains to be proven. However, it is likely that the maximally exercising horse is operating near the upper limit of ventilation and that even slight degrees of respiratory disease profoundly affect oxygen uptake and performance.[116] Any condition that causes increased resistance to airflow, decreased minute volume, decreased diffusion of gases, ventilation-perfusion mismatch, shunt, or increased oxygen cost of breathing constitutes a respiratory cause of exercise intolerance.

Approach to Diagnosis of Exercise Intolerance and Poor Performance

Top athletes arise from both a genetic background that emphasizes athletic ability and environmental influences that capitalize on this inherent potential. A coordinated, energy-efficient gait, muscular power and endurance, a large capacity for oxygen transport, and several intangible factors such as the horse's

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mental toughness and competitive spirit and the rider's skill all contribute to successful performance. *Poor performance* most often results from inadequate training, a lack of genetic potential, or both, or from a congenital or acquired dysfunction of the locomotor, cardiovascular, or respiratory systems. The term *exercise intolerance* is often used to describe this inability to perform to an expected or previously attained intensity of exercise.

History.

An accurate history is a fundamental part of the evaluation of exercise intolerance and should include the age, breed, and use of the horse and the training and feeding programs. The onset (time and rapidity) of the problem, previous performance history, activity level at which signs are observed, whether the horse performs well at first and then suffers tailing off of performance (no stamina), or whether performance is poor throughout the work period should be ascertained. If performance drops off during work, it should be established whether the drop-off is associated with the onset of other signs such as stridor. The presence of coughing, respiratory distress, stridor, excessive or lack of sweating associated with stress or exercise, or muscle stiffness should be noted. It should be ascertained whether the affected horse or in-contact horses have recently shown signs of respiratory disease, especially viral infections, and whether other horses are perceived to be performing poorly. It should be determined if the horse has shown lameness, gait abnormalities, or biting problems. Any medications or other treatments that have been used and their effects should be noted.

In particular, it is important from the history to distinguish between horses that have never been able to perform satisfactorily and horses that suddenly or gradually show a reduction in the level of performance after a background of satisfactory performance. The first scenario suggests a lack of genetic potential, congenital abnormalities, or inadequate training. Some horses do not have the genetic background to perform the expected work (e.g., racing Quarter Horses rarely make good endurance horses, and Thoroughbreds from sprinting families rarely excel at distances of more than 1¼ miles).

Clinical Examination.

Overt clinical diseases that cause exercise intolerance at moderate speeds usually can be diagnosed with a good history, physical examination, and selected

ancillary diagnostic techniques. The diagnostic procedures and specific diseases that can be identified at rest are detailed in subsequent chapters in this book (particularly Chapters 30, 31, 37, 38, 41, and 42). Problems that are subclinical at rest provide a greater diagnostic challenge. When testing procedures at rest fail to identify the cause of exercise intolerance, various types of ancillary diagnostic procedures including exercise tests may be used to further define the problem. Because the respiratory, cardiovascular, musculoskeletal, and hematopoietic systems are all important for competitive performance and because diseases in these systems are the most likely causes of exercise intolerance, these systems should receive particular attention in the detailed clinical examination of the horse at rest.

Hematologic Assessment.

Hematologic tests have historically been popular in the evaluation of fitness and performance because they are easy to perform and because of the important role of hemoglobin in oxygen transport.[117,118] Routine hematologic evaluation may be useful in monitoring the general health status and perhaps fitness of horses if the conditions of collection, particularly in relation to time of day and exercise, can be carefully controlled and if attention is paid to horses that become excited before or during sample collection.

Anemia can result in a decreased oxygen-carrying capacity during exercise. Veterinarians traditionally have regarded resting hematocrits below 35% as abnormal and likely to cause suboptimal racing performance, but values lower than this have been found in normal Thoroughbred racehorses.[119] Endurance horses and eventing horses usually have resting hematocrit values that are lower than those of racehorses.[119] However, the fact that a significant proportion of equine red blood cells and hemoglobin is contained in the splenic reserve makes interpretation of resting values for these parameters difficult (inaccurate). There is no correlation between the resting level of hemoglobin and the total body hemoglobin or red cell mass.[110,119] Consequently, even though total body hemoglobin does increase in response to training and may correlate with performance, this cannot be determined from a resting blood sample. Measurement of the total hemoglobin or total red cell mass requires collection of a blood sample after strenuous exercise or after administration of epinephrine to mobilize the red cell reserve and the determination of plasma volume using a technique such as Evans blue dye dilution.[110] These techniques have been used

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to document red cell hypervolemia in poorly performing, overtrained Standardbreds.[110]

Some veterinarians use the resting leukocyte count to monitor fitness, and particularly overtraining, in performance horses.[119] Decreases in the neutrophil/lymphocyte (N/L) ratio have been used to indicate overtraining (training off or adrenal exhaustion). However, the N/L ratio varies in individual horses, depending on when it is determined in relation to the timing and type of exercise and on factors such as age, stress, and disease. Reliable evidence indicates that the N/L ratio is not a good predictor of adrenal status.[120] Indeed, adrenal function in horses with “adrenal exhaustion syndrome” remains to be accurately characterized based on reproducible function tests.

Serum Biochemical Profiles.

Biochemistry profiles are commonly used to monitor performance horses and to evaluate those with performance problems. These profiles are useful, but interpretation must take into account that when many measurements are performed, there is a high statistical probability that one or two results will be outside the normal range (95% confidence).[119] If only one or two results on a profile are slightly abnormal, the tests are best repeated on a second sample before the true significance of the result is ascribed. Biochemistry profiles are most useful in detecting horses with subclinical muscle problems (either primary exertional rhabdomyolysis or muscular strain secondary to skeletal problems), liver diseases, renal diseases, and gross disturbances in electrolyte and acid-base regulation. Biochemical profiles usually include aspartate aminotransferase (AST), creatine kinase (CK), LDH, alkaline phosphatase (AP), γ-glutamyltransferase (GGT), sorbitol dehydrogenase (SDH), blood urea nitrogen (BUN), creatinine, sodium (Na), potassium (K), chloride (Cl), bicarbonate, phosphate, calcium (Ca), magnesium (Mg), glucose, and other parameters that are of variable clinical relevance. Studies of horses during training have failed to show any correlation between resting or exercising values for these parameters and fitness.[119] In endurance horses, evaluation of renal fractional excretions of electrolytes may provide better information regarding the horse's electrolyte balance than serum chemistry measurements alone.[121]

Evaluation of the Respiratory Tract.

Standard parameters of a routine examination, including rectal temperature,

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respiratory rate, respiratory character, mucous membrane color, and capillary refill time, should be carefully evaluated at rest. The presence of nasal discharge, cough, edema, jugular distention or pulsation, or other signs suggesting local or systemic disease should be noted. The larynx, muscular process of the arytenoid cartilages, retropharyngeal area, and trachea should be palpated for size and symmetry. The heart and lungs should be carefully auscultated and percussed at rest, and auscultation of the lungs should be repeated as the horse is induced to breathe more deeply by application of a rebreathing bag. When stridor is part of the history, the upper respiratory tract should receive particular attention in the diagnostic evaluation. Not only must the character of the noise be determined, but the extent of work the patient can tolerate before exhibiting diminished performance must be established, because this helps in the interpretation of abnormalities seen on the endoscopic examination (see the Abnormal Respiratory Noise [Stridor] section earlier). Often the onset and intensity of the stridor coincide with a decrease in work capacity that is typical of certain obstructive airway diseases. Endoscopy, including treadmill endoscopy if facilities permit or over-the-ground videoendoscopy, and radiography form an important part of the diagnostic evaluation of horses with upper airway abnormalities[122] (see the Respiratory Distress [Dyspnea] and Abnormal Respiratory Noise [Stridor] sections earlier). The most common abnormalities of the upper airway that cause poor performance include dorsal displacement of the soft palate, dynamic pharyngeal collapse, dynamic collapse of the left arytenoid cartilage in association with ILH, epiglottic entrapment, pharyngitis, and collapse of the alar folds.[97,99] Diminished performance in horses with mild or subclinical viral infection is probably mediated at least partly by abnormalities in the respiratory tract.[123] If no abnormalities are detected at rest, functional disturbances of airflow may occur during maximum exercise, and these disorders can best be identified by examining the upper airway using videoendoscopy on a treadmill during exercise or using over-the-ground videoendoscopy units. Slow-motion playback must be used because many abnormalities occur rapidly with each respiratory cycle. In particular, dorsal displacement of the soft palate and the extent of dynamic laryngeal obstruction with ILH can be more fully evaluated with videoendoscopy during exercise.[97,99,122,124] Over-the-ground videoendoscopy has the distinct advantage of allowing the horses to be examined under the exact conditions in which the problem occurs. The presence of inspiratory or expiratory obstruction can be further evaluated during treadmill exercise by introducing transducers via the

nostrils to measure airway pressures at the level of the pharynx and trachea.[99,122] During a treadmill exercise test, samples for blood gas analysis can be drawn from extension tubing connected to an 18-gauge, 2-inch catheter inserted into the transverse facial artery.

Further diagnostic evaluation of the lower airways is indicated in horses with an abnormal respiratory rate or character, cough, nasal discharge, abnormal lung sounds, prolonged recovery after application of a rebreathing bag, or with a history of EIPH, cough, or respiratory distress with exercise. Horses in which excess mucus or exudate can be demonstrated in the trachea during endoscopy performed after exercise are also candidates for further evaluation. Applicable tests include a complete blood count, tracheal wash or BAL, endoscopy, radiography, and ultrasound examination (see the Cough and Abnormal Respiratory Noise [Stridor] sections earlier). Tracheal wash samples collected after exercise are more likely to identify lower airway disease than those collected before exercise.[125] Respiratory viral infection, EIPH, bronchiolitis, hyperreactive airways, and RAO are all conditions that may not be apparent at rest but that constitute significant causes of exercise intolerance.

Evaluation of the Cardiovascular System.

A full evaluation of the mucous membranes, capillary refill time, pulse rate, pulse character and rhythm, heart rate and rhythm, and auscultatory findings is an important part of the evaluation of the performance horse. Failure to maintain cardiac output because of an inability to regulate either heart rate or stroke volume is the mechanism through which cardiac diseases induce exercise intolerance. Many cardiac dysrhythmias and valvular dysfunctions are apparent on auscultation of the resting horse. However, the contribution of mild abnormalities to exercise intolerance may require exercise testing. In addition, some arrhythmias and valvular or myocardial dysfunctions can be detected only during or shortly after exercise. Thus resting and exercising electrocardiography and echocardiography before and immediately after exercise are indicated.[99,122] The heart rate can be monitored during exercise using either telemetric electrocardiography or commercial heart rate monitors. Electrocardiograms (ECGs) provide the additional benefit of evaluating both heart rate and rhythm. Supraventricular tachyarrhythmias, the most important of which is atrial fibrillation (AF) in horses, can lead to heart rates exceeding 240 beats/min at submaximal exercise.[126] Under these circumstances, cardiac output may be

limited by the decreased time available for diastolic perfusion of the myocardium; the absence of atrial contraction; and the reduced time for passive ventricular filling, leading to reduced stroke volume. Many horses with AF maintain efficient circulation at rest and during light exercise but are intolerant to strenuous exercise because they are unable to increase cardiac output sufficiently at rapid heart rates.[127] Some horses show transient paroxysmal AF during exercise but not at rest.[127] These are often easiest to observe in ECG tracings obtained within 60 seconds after an exercise test. Conversion to sinus rhythm, either spontaneously with quinidine sulfate or with electroconversion,[128] usually leads to a return to normal performance in horses with AF.[129,130] The ability to maintain cardiac output can be compromised by other cardiac arrhythmias such as ventricular tachycardia and ventricular premature depolarization.[99,131] The frequency of premature depolarization can increase with exercise, and the timing of resultant abnormal extra systoles can reduce cardiac output even at submaximal heart rates.[131] Intraatrial block, second-degree atrioventricular (AV) block, and intraventricular block have also been documented in exercise-intolerant, poorly performing horses.[132,133] Horses with cardiac arrhythmias may show abnormal elevations in lactate concentration in response to exercise, indicating a lowered anaerobic threshold, which contributes to exercise intolerance.[111]

Electrocardiography is believed by some veterinarians to be of value in identifying myocarditis. T wave abnormalities (positive and peaked T waves, in contrast to the normal diphasic T waves) in multiple leads on resting ECG traces have been found in a high percentage of horses with a history of fading during the final portion of a race.[132] T waves are highly labile, affected by training status, and the mechanism by which abnormal T waves are generated is uncertain. However, T wave changes have been identified in some horses with myocarditis confirmed at necropsy.[119,133,134] Myocarditis may be more definitively documented by evaluating cardiac troponin I.[135] A positive correlation has been demonstrated between heart size and racing performance.[133] Electrocardiography has been used to assess performance potential by heart score measurement. The heart score represents the mean QRS duration in leads 1, 2, and 3 expressed in milliseconds and has been strongly correlated with heart weight and prize money won by racehorses.[119,133] The physiologic basis for heart score remains in dispute, and expertise is required to standardize leads and

measure QRS complexes.

An *echocardiogram* provides essential information in many cases in which clinical evidence of valvular or myocardial dysfunction is present. The pericardium, the size of the heart chambers, the presence of congenital defects, the function of valvular leaflets, and myocardial contractility all can be assessed (see Chapter 30). Decreased myocardial contractility, regurgitant leaks caused by valvular incompetence, left-to-right shunts, and increases in afterload such as occur in aortic stenosis result in systolic dysfunction and a drop in cardiac output.[136] A pulsed, continuous, or color flow Doppler technique may be necessary to determine the size and significance of any disturbances to flow. Cardiac conditions such as effusive pericarditis and myocardial fibrosis and peripheral vascular conditions that inhibit venous return may interfere with ventricular filling during diastole, resulting in decreased end-diastolic volume, stroke volume, and cardiac output.[136] Measurement of fractional shortening before and immediately after treadmill exercise, when pulse rates are above 100 beats/min, permits documentation of resting and exercise-induced myocardial dysfunction.[99] Contrast angiographic studies may be indicated if congenital or acquired cardiac outflow problems are suspected. Nuclear angiocardiography is also useful for evaluating myocardial contractility, cardiac chamber enlargement, outflow problems, and other abnormalities. Hemodynamic studies, which measure pulmonary capillary wedge pressure, pulmonary driving pressure, and pressure in the right side of the heart and pulmonary artery, have proven useful in detecting early cardiac and pulmonary failure in poorly performing trotting horses. These studies involve the introduction of flow directional balloon-tipped catheters through the jugular vein into awake horses.[137]

Evaluation of the Skeletal System.

A lameness examination including appropriate flexion tests and other stress tests should be completed to help rule out musculoskeletal problems. If lameness is observed, appropriate diagnostic nerve blocks, radiographs, scintigraphy, rectal examination of the bony pelvis and aortoiliofemoral arterial pulses, or ultrasound examinations are indicated to help localize the lameness and determine its cause, significance, and prognosis. Some lameness problems that are evident only at high speed may best be evaluated using treadmill exercise. For example, aortoiliofemoral thrombosis reduces peripheral perfusion but often causes only progressive hindlimb lameness with exercise. Foot balance should be carefully

assessed at rest and, if possible, during exercise, because gait changes and subtle lameness related to foot imbalance can adversely affect performance. Dynamic evaluation of hoof balance can be accomplished by examining videotapes recorded from behind the horse while it is exercising on a high-speed treadmill or by trotting the horse over force plates embedded in a firm level surface.[138]

Subtle lameness can increase the metabolic cost of locomotion by inducing changes in gait and coordination, which accelerate the onset of fatigue. In the same fashion, some horses may have an inefficient gait that reduces their performance capacity. Video imaging systems and gait analysis may play an increasingly important role in identifying these individuals in the future.

Evaluation of the Muscular System.

Primary skeletal muscular limitations on performance may occur as the result of painful conditions such as exertional rhabdomyolysis or weakness due to defects in energy generation or loss of muscle mass. In resting samples, high serum AST may indicate chronic rhabdomyolysis. Measurement of serum CK 4 to 6 hours after an exercise test is most useful in detecting horses with chronic or subclinical forms of exertional rhabdomyolysis. Serum muscle enzyme concentrations measured in blood samples collected immediately after exercise are often normal, but in horses with chronic exertional rhabdomyolysis significant abnormal elevations may be seen when CK peaks at 4 to 6 hours after completion of exercise. In the past it has been recommended that the exercise test be conducted at a speed and duration of exercise similar to that expected of the horse in competition. However, it has been shown that a 15- to 30-minute test at a slow trot more frequently produces abnormal elevations in serum CK (more than twofold to threefold) in susceptible horses.[139] Standardbreds and Thoroughbreds with histories of recent episodes of recurrent exertional rhabdomyolysis and horses with type 1 polysaccharide storage myopathy (PSSM) often show a greater than twofold increase over normal resting values in response to an exercise test.[139] Horses with type 2 PSSM may show exercise intolerance after 10 to 15 minutes under saddle, reluctance to pick up and maintain a canter, or inability to collect and maintain self-carriage under saddle without abnormal elevations in serum CK. Subtle loss of muscle mass and performance decline can occur with deficiencies in vitamin E, warranting assessment of serum alpha-tocopherol concentrations.

Muscle biopsy is a relatively simple procedure that can prove useful for

characterizing the nature of an identified exertional myopathy. However, the procedure is not widely used in the diagnostic assessment of poor performance because the evaluation of samples requires considerable histochemical expertise. Percutaneous techniques using a 6-mm–diameter needle (Bergstrom biopsy needle, Mortenson, Copenhagen, Denmark) and local anesthetic are routinely used. The middle gluteal muscle is most often sampled because it is relatively accessible and active at all intensities of exercise.[103,107,140] In adult horses a biopsy is collected at a depth of 2½ to 3 inches from a site 8 inches from the tuber coxae along a straight line connecting the point of the tuber coxae with the base of the tail. Open surgical biopsies are most easily obtained from the semimembranosus or semitendinosus muscle at a site approximately 3 inches below the tuber ischii. After the skin has been shaved and aseptically prepared, lidocaine is injected under the skin. A 2-inch–long incision is made through the skin and fascia, and two parallel incisions, 1 inch long and ½ inch apart, are made vertically in the muscle. The muscle is grasped in one place, to prevent handling artifacts, and the biopsy is first transected proximally, freed to a depth of ¼ inch, and then transected distally. The disadvantage of open surgical biopsies is that a recovery period of 1 week is often required, whereas horses can immediately begin to exercise when a needle biopsy is used. Muscle samples should be sent to a laboratory, where they will be frozen in isopentane that has first been chilled in liquid nitrogen. Commonly used histologic and histochemical stains include adenosine triphosphatase (ATPase) after alkaline and acid preincubations, nicotinamide dinucleotide diaphorase (NADH), periodic acid–Schiff (PAS), and hematoxylin and eosin.

An estimate of the state of training can be made by determining the percentage of type 1, type 2A, and type 2X muscle fibers, as well as the oxidative capacity of skeletal muscle in these small muscle samples. In general, horses suited for short-distance, fast exercise have a greater proportion of fast-twitch fibers in the middle gluteal muscles than horses suited for longer distance events, which have a higher proportion of slow-twitch type 1 fibers.[140] However, there are many successful athletes that do not follow this pattern. The proportion of type 1 relative to type 2 fibers is thought to be genetically based and cannot be manipulated to a great extent by training, whereas age and training increase the proportion of oxidative fast-twitch type 2A fibers relative to type 2X fibers.[103,107,139] Histochemical assessment of NADH staining or quantitative measurement of enzymes such as citrate synthase in biopsy samples frozen rapidly in liquid nitrogen may provide a guide to the state of aerobic fitness.[136]

The use of muscle biopsies in horses with poor performance has also aided in the identification of oxidative enzyme defects in Arabian horses and glycogen storage disorders in Quarter Horses that can markedly affect performance.[140,141]

Standardized Exercise Testing

Exercise intolerance is ultimately a neuromuscular phenomenon resulting from extreme metabolic stress at the level of the muscle fibers.[104] Under many circumstances premature muscle fatigue occurs secondary to disorders that affect oxygen transport (cardiopulmonary systems) or mechanical efficiency (lameness) (Box 5.20). Standardized treadmill exercise tests are often required to assess the function of these systems at high speeds to determine the primary cause of poor performance and to measure the metabolic response of skeletal muscle relative to work intensity. In a substantial number of cases, poor performance results from related or unrelated disorders in more than one body system, such as dynamic airway obstruction and cardiac dysrhythmia in the same horse.[99]

Box 5.20

Causes of Exercise Intolerance That Are Inapparent at Rest

Respiratory Causes

Obstructive Upper Airway Diseases

Common Causes

- Laryngopalatal dislocation (dorsal displacement of the soft palate)
- Dynamic pharyngeal collapse
- Dynamic collapse of the left arytenoid cartilage in association with idiopathic laryngeal hemiplegia
- Chronic pharyngeal lymphoid hyperplasia
- Epiglottic entrapment
- Axial deviation of the aryepiglottic folds
- Arytenoid chondritis

Paranasal sinus empyema
Paranasal sinus cysts
Guttural pouch infection

Uncommon Causes

Dynamic collapse of the alar folds
Nasal polyps
Progressive ethmoid hematoma
Subepiglottic cysts
Epiglottic retroversion
Chondroma of the arytenoid cartilages
Fractured laryngeal cartilages
Nasopharyngeal cicatrix

Congenital

Choanal (posterior nares) atresia or stenosis
Excessive alar folds
Stenotic nares
Abnormalities of the nasal septum
Rostral displacement of the palatopharyngeal arch
Tracheal stenosis, stricture, collapse

Lower Airway Diseases

Common Causes

Inflammatory lower airway disease
Exercise-induced pulmonary hemorrhage (EIPH)
Recurrent airway obstruction (RAO or chronic obstructive pulmonary disease)
Equine herpesvirus types 1 and 4 (EHV-1 and EHV-4)
Other viral infections (influenza, rhinitis A and B viruses, adenovirus, reovirus)
Bacterial pneumonia
Pleuropneumonia, pleuritis

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Uncommon Causes

- Pulmonary abscess
- Pneumoconiosis (e.g., silicosis)
- Interstitial pneumonia
- Diaphragmatic hernia

Cardiovascular Causes

Common Causes

- Atrial fibrillation
- Ventricular premature contractions
- Ventricular tachycardia
- Mitral insufficiency
- Aortic insufficiency
- Resting or exercise-induced myocardial dysfunction and reduced fractional shortening
- Pericarditis
- Aortoiliofemoral arteriosclerosis or thrombosis

Uncommon Causes

- Ventricular septal defects
- Monensin toxicity
- Heart block (intraatrial, second- and third-degree atrioventricular and intraventricular)
- Endocarditis
- Congestive cardiac failure
- Ruptured chordae tendineae
- Cor pulmonale
- Congenital defects

Musculoskeletal Causes

- Exertional rhabdomyolysis

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Lameness involving limbs, sacroiliac joint, back
Focal muscle strain

Metabolic and Systemic Causes

Anemia
Fluid and electrolyte imbalances
Anhidrosis
Heat exhaustion
Neoplasia
Liver disease (pyrrolizidine alkaloid)

General Causes

Obesity
Poorly trained horse
Poor genetic potential
Administration of illicit medications (doping)

Treadmill Tests.

Horses often need to be acclimated to a treadmill before representative exercise testing can be performed. Standardbred horses are typically exercised while wearing their usual racing tack, whereas horses of other breeds are typically exercised in a halter or bridle with a lead rope attached to each side. Most horses exercise comfortably on a treadmill after two to four training sessions at speeds that include all gaits to be tested. Breaking into a canter is an important skill to train horses to perform on the treadmill. During one of the training sessions, endoscopy of the upper airway can be performed to evaluate upper airway function during maximal speeds. Two types of standardized exercise tests can be used: a high-speed test, in which horses are accelerated to maximal speed for their normal racing distance, or an incremental test, in which speed is increased every 1 or 2 minutes until fatigue is reached. The incremental exercise test is used most commonly because it includes both submaximal and maximal intensities and is readily reproducible. Many exercise tests are performed with the treadmill set at a 6% to 10% slope to minimize the possibility of injury at top

speeds and to ensure that maximum exercise intensity is reached.

Several measurements are possible during treadmill exercise testing. In its simplest form, the heart rate can be monitored after 1 minute at each intensity of exercise using a heart rate monitor, although recording of an ECG during exercise provides additional information about exercise-associated dysrhythmias.[99] Blood samples can also be drawn from a jugular catheter during the final 15 seconds at each speed. A linear relationship between heart rate and speed is expected, with a plateau forming at the maximum heart rate. The maximum heart rate does not change with training, but the speed at which the maximum heart rate is reached should increase with training. As an alternative, a linear regression can be used to determine the horse's speed at a heart rate of 200 beats/min (V_{200}). V_{200} is close to the anaerobic threshold, may predict aerobic capacity, increases with increasing fitness, and has a high individual predictability that allows for early and valid detection of clinical disorders that limit performance.[111,119,142] The speed at which horses reach a maximum heart rate has been proposed as a better measure than V_{200} because it is an absolute rather than a relative measure; however, measurement of maximum heart rate requires a more strenuous exercise test. Parameters such as the velocity at which the whole blood lactate value reaches 4 mmol/L (V_{LA4}) and the heart rate at which blood lactate reaches 4 mmol/L (HR_{LA4}) can be calculated to evaluate the anaerobic threshold.[111,142] The rate of lactate accumulation may also provide valuable information.

Lactate concentrations can be determined in either whole blood or plasma. Recent studies suggest whole blood lactate may provide a more accurate reflection of lactate accumulation than plasma lactate[143] because red blood cells actively take up lactate and buffer it, and the type and number of red blood cell lactate transporters differ markedly among horses.

The value of V_{200}, V_{LA4}, HR_{LA4}, and other parameters is that they provide standards against which improvement or deterioration in fitness can be assessed, and individual horses can be objectively compared.[111,119,142] Hematocrit can also be easily determined from blood samples obtained at each speed to provide a rough estimate of the number of circulating red blood cells. Blood samples drawn before and 4 hours after exercise for measurement of CK activity can be used to screen for subclinical exertional rhabdomyolysis.

Further evaluation of the oxygen transport system can be obtained in laboratories where the sophisticated open-flow gas-collection system necessary

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to measure oxygen consumption ($\dot{V}O_2$) is available. During the incremental exercise test, a plateau in oxygen consumption eventually is reached, representing maximum oxygen uptake. $\dot{V}O_2$ can be used at submaximal speeds to calculate the oxygen cost of locomotion, and $\dot{V}O_{2max}$, a key indicator of aerobic capacity, can be determined. The cardiopulmonary system can be further evaluated during exercise by measuring arterial blood gases from the transverse facial artery using an 18-gauge indwelling catheter.[142] An accurate measure of the total red blood cell volume in a horse can be determined using an Evans blue dye dilution technique immediately after maximal exercise.

Field Tests.

Standardization of field exercise tests is difficult because weather, track conditions, and other factors influence the amount of work performed. The simplest form of exercise test involves timing a horse exercising maximally over a fixed distance and evaluating heart rate recovery rates at specific time points after exercise. Additional information can be obtained by measuring heart rate during exercise using a heart rate monitor or telemetric ECG.[119] As fitness improves, the heart rate for a given speed of exercise should be lower. Incremental field exercise tests have been used most successfully in Standardbred horses in which the heart rate and blood lactates were measured after several heats at predetermined increases in pace. At speeds above 450 m/min, lactate begins to accumulate in the blood during exercise; the precise kinetics of accumulation depends on the horse's fitness and exercise capacity. V_{LA4} has been used in field exercise tests to monitor responses to training. Fitness responses include a lower heart rate and lactate concentration for the same exercise speed. The value of these measurements is only as good as the standardization of the testing procedures used.

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• CHAPTER 6

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Alterations in Cardiovascular and Hemolymphatic Systems*

Virginia B. Reef, Joann Slack, Consulting Editors

MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Peripheral Edema, Pleural Effusion, and Ascites

Edema is an abnormal accumulation of extracellular fluid in the interstitial spaces of the tissues or in body cavities that can be generalized or localized. If the fluid accumulation occurs in the pleural cavity, it is referred to as *pleural effusion* or *hydrothorax;* if the fluid accumulation is in the abdominal cavity, it is referred to as *peritoneal effusion* or *ascites.*

Fluid accumulates more easily in those parts of the body where the connective tissue structure is relatively loose. The accumulated fluid tends to gravitate to the dependent areas of the body. In the cow, generalized edema is detected externally by swelling of the submandibular tissue, the brisket, the ventral abdomen, and occasionally the limbs (Fig. 6.1). External manifestation of generalized edema in the horse is frequently in the pectoral region between the front limbs, along the ventral abdomen, in the prepuce in stallions and geldings (Fig. 6.2), in the limbs, and sometimes in the head. Stocking up, or limb edema restricted to the lower limbs, is commonly detected in stabled horses with no underlying disease. Large amounts of fluid may accumulate before clinical signs become evident. External evidence of pulmonary edema (i.e., a frothy, possibly blood-tinged fluid in the nares or expectorated) is rarely detected in large animals (Fig. 6.3). Edema has numerous causes including congestive heart failure (CHF) (Boxes 6.1 and 6.2). Edema is a late sign of CHF; other subtle signs of failure may be present before edema appears.



FIG. 6.1 Cow with brisket, ventral, and udder edema.



FIG. 6.2 Gelding with ventral and preputial edema.



FIG. 6.3 Gelding with acute fulminant pulmonary edema.

Box 6.1

Causes of Peripheral Edema, Pleural Effusion, and Ascites in Horses

Common Causes

Chronic right-sided or biventricular heart failure
Pericarditis
Pleuritis/Pleuropneumonia

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Peritonitis
Pregnancy
Neoplasia: lymphosarcoma
Cranial mediastinal mass
Hypoproteinemia
Liver disease
Gastrointestinal malabsorption: inflammatory bowel disease, neoplasia, parasitism
Vasculitis
Equine infectious anemia
Purpura hemorrhagica
Equine granulocytic ehrlichiosis (*Anaplasma phagocytophilum*)
Equine viral arteritis
Thrombophlebitis
Lymphatic obstruction
Ulcerative lymphangitis
Lymphadenitis (*Corynebacterium pseudotuberculosis* abscesses)
Trauma

Uncommon Causes

Aortic cardiac fistula
Aortopulmonary fistula
Heart base tumor other than lymphosarcoma
Neoplasia: mesothelioma, melanoma, plasma cell myeloma, squamous cell carcinoma, fibrosarcoma
Starvation
Kidney disease: glomerulonephritis, amyloidosis
Ionophore toxicity
Copper deficiency
Counterirritant application
Hemodilution
Ruptured bladder
Cassia occidentalis toxicity

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Box 6.2

Causes of Peripheral Edema, Pleural Effusion, and Ascites in Ruminants

Common Causes

Chronic right-sided or biventricular heart failure due to mitral or tricuspid regurgitation, vegetative endocarditis, or congenital heart defects
High-altitude disease (brisket disease)
Cor pulmonale
Pericarditis (traumatic reticulopericarditis)
Pleuritis
Pregnancy (udder edema in heifers)
Cranial mediastinal mass: lymphosarcoma
Hypoproteinemia
Liver disease
Kidney disease: amyloidosis, glomerulonephritis
Gastrointestinal malabsorption: lymphosarcoma, Johne's disease, parasitism
Lymphatic obstruction (*Corynebacterium pseudotuberculosis*, lymphosarcoma)
Thrombophlebitis
Urolithiasis: ruptured urethra or bladder

Uncommon Causes

Mycoplasma (formerly Eperythrozoon) wenyoni (B)
Idiopathic hemorrhagic pericardial effusion
Chronic right-sided or biventricular heart failure due to cardiomyopathy, infectious myocarditis, ionophore toxicity
Starvation
Hemodilution
Copper deficiency
Vasculitis
Trauma

Caudal vena caval thrombosis
Anaplasmosis
Gossypol toxicity
Cassia occidentalis
Phalaris species toxicity
Oxytropis (locoweed) toxicity

B, Bovine.

Mechanisms of Edema

Edema is caused by an alteration in the equilibrium between capillary permeability and the forces that govern fluid movements at the capillary level. These forces are as follows:

1. Intravascular hydrostatic pressure
2. Interstitial fluid hydrostatic pressure, which exerts counterpressure to keep fluid within the capillary
3. Intravascular colloid oncotic pressure exerted by plasma proteins, which favors the resorption of interstitial fluid; the major determinant of colloid osmotic pressure in the capillary is albumin
4. Interstitial fluid colloid osmotic pressure exerted by some proteins in the interstitial fluid, which resists resorption of fluid from the interstitial space
5. Vascular surface area capable of fluid transport
6. Vascular permeability to proteins and water

Activation of complement and liberation of cytotoxic agents such as oxygen radicals, leukotrienes, hydrogen peroxide, platelet-activating factor, and lysosomal enzymes contribute to the endothelial and epithelial damage, causing permeability edema. Subsequent increase in colloid osmotic pressure causes fluid accumulation in the interstitial space. The most common causes of increased capillary permeability are trauma, infection, endotoxemia, and hypersensitivity (allergic) vasculitis. Topical administration of counterirritants can also cause local increase in capillary permeability. Equine purpura hemorrhagica, the most common vasculitic disease in horses, may in its mildest form have symptoms of mucosal petechiae and plaques of edema or, in severe

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cases, serum exudation from and necrosis of skin surfaces.

Increased hydrostatic pressure can cause either localized or generalized edema. In horses and ruminants the most common causes of increased hydrostatic pressure are CHF, venous thrombosis, liver disease causing obstruction of the portal venous system, lymphadenopathy, a cranial mediastinal mass, compression bandages, limb immobilization, and topical administration of counterirritants. CHF occurs when there is concomitant pulmonary and systemic vascular congestion. The compensatory salt and water retention increases ventricular diastolic, venous, and capillary pressures, which can result in the formation of generalized edema. Arteriolar vasodilation, caused by release of tissue mediators of inflammation or increased venous pressure resulting from obstruction to venous outflow, can also elevate capillary hydrostatic pressure and result in edema formation.

When the plasma protein concentration decreases from normal to values <5 g/dL or albumin concentration is <1.5 g/dL, generalized edema may occur. Hypoproteinemia can result from 1) decreased production of plasma proteins with starvation, liver disease, or severe heart failure or 2) augmented loss of plasma proteins resulting from kidney disease, protein-losing enteropathies (Johne's disease, chronic inflammatory bowel disease), peritonitis, or pleuritis. Hemodilution as a result of overzealous administration of fluids or decreased elimination of fluid can cause edema. Failure to excrete adequate water to maintain fluid balance can result from decreased glomerular filtration as a result of kidney disease or heart failure.

Increased tissue colloid osmotic pressure is rarely a cause of edema in horses and ruminants. Interstitial fluid has a lower plasma protein concentration than plasma. When capillary permeability is increased or when abnormal protein-like material is present in the interstitial space, edema can develop by this mechanism. The latter may occur with infection or after administration of topical counterirritants.

Lymphedema occurs when lymphatics are absent or obstructed. Congenital absence of lymphatics is extremely rare. Obstruction to lymphatic drainage can be caused by tumor, local inflammation (lymphangitis or lymphadenitis), or elevated central venous pressure as in heart failure.

Approach to Diagnosis of Peripheral Edema, Pleural Effusion, and Ascites

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1. Take history. Note especially history of deworming program, diet, and vitamin or mineral supplements. Determine onset, progression, and duration of the problem and whether other animals are affected. Ask about history of fever, signs of respiratory disease or difficulty, appetite, consistency of feces, and previous medications. Establish the function of the animal and whether there have been changes in performance capability. Compare growth and activity level with that of peers.
2. Perform a physical examination and record vital signs. Determine whether edema is localized or generalized. Palpate external lymph nodes. Palpate edematous areas to determine whether there is heat, pain, or fluid exudation. Edema is typically cool, nonpainful, and pitting, leaving an indentation when a finger is pushed against it. Carefully auscultate heart and lungs. Note abnormalities in cardiac rhythm, murmurs, or other sounds associated with the cardiac cycle. Palpate a peripheral pulse; observe mucous membranes for color, capillary refill time, and petechiae. Observe the jugular vein for distention and pulsations. Evaluate peripheral veins, including the mammary vein, for distention and pulsations. Perform a rectal examination to determine whether internal lymph nodes are enlarged. Palpate the aorta and iliac arteries for pulse strength and fremitus.
3. Obtain whole blood for the following:
    a. Complete blood count (CBC) (includes fibrinogen, serum amyloid A [SAA], and plasma protein concentration)
    b. Selenium concentrations if cardiomyopathy is suspected
    c. *Anaplasma phagocytophilum* (formerly *Anaplasma equi* or *Ehrlichia equi*) morula in granulocytes or *Anaplasma* DNA by polymerase chain reaction if edema, petechial hemorrhages, fever, icterus, or muscle stiffness is present
4. Test serum or plasma for the following:
    a. Total protein and albumin concentrations; measure or calculate globulin fraction
    b. Test for kidney function as follows: serum urea nitrogen (SUN) and creatinine concentrations, serum electrolyte (Ca, P, Na, K, Cl) concentrations, fractional excretion of electrolytes (see Chapter 34 for method), complete urinalysis; serum concentrations of Na may be decreased, and SUN may also be elevated in chronic heart failure

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   c. Liver enzyme concentrations and liver function (aspartate aminotransferase [AST], sorbitol dehydrogenase [SDH], alkaline phosphatase, γ-glutamyltransferase [GGT], bilirubin, and bile acid concentrations); values may be elevated in CHF
   d. Check for antibodies to equine infectious anemia virus by agar gel immunodiffusion (AGID) or Coggins test
   e. Check for antibodies against *Streptococcus equi* M protein if signs are compatible with purpura hemorrhagica
   f. Determine titers to equine viral arteritis by serum neutralization if there is ocular inflammation, nasal discharge, abortion, or fever with edema
   g. *A. phagocytophilum* antibodies as demonstrated by immunofluorescence if physical examination reveals icterus and fever with edema
   h. Vitamin E levels if cardiomyopathy suspected
5. Perform two-dimensional (2D), M-mode, and Doppler echocardiography if there is a cardiac murmur that is not localized to the left heart base, that radiates, is greater than 2/6 intensity, or is of significant duration.
6. Analyze fluid to rule out peritonitis, pleuritis, and pericarditis; if physical examination and CBC findings are compatible, examine:
   a. Pleural fluid
   b. Pericardial fluid
   c. Peritoneal fluid
7. Isolate virus from nasopharyngeal swabs, buffy coat, or semen for equine viral arteritis if clinical signs are compatible.
8. Oral D-xylose or glucose absorption test should be done in horses if there is hypoproteinemia and if starvation, renal disease, hepatic disease, pleuritis, peritonitis, infectious gastrointestinal disease, and hemodilution have been ruled out; these tests are not useful in ruminants unless intraabomasal instillation of D-xylose or glucose is accomplished.

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Cardiac Arrhythmias

Cardiac arrhythmias are abnormalities in the normal heart rate, rhythm, or conduction pattern. Arrhythmias result from abnormalities of impulse generation or impulse conduction or a combination of both. In the normal heart the impulse is generated in the sinus node because it has the highest rate of spontaneous depolarization. Atrial depolarization is followed shortly by ventricular depolarization. There is variability in reported normal ranges for heart rate in the large adult animal species, but there is general acceptance of the following ranges:

- Horses: 26 to 50 beats/min; 60 to 80 beats/min in foals
- Cattle: 49 to 84 beats/min
- Sheep and goats: 70 to 90 beats/min

Arrhythmias are more common in horses than in other domestic animal species. Up to 25% of horses that have no other signs of heart disease have cardiac arrhythmias during routine examination or electrocardiography.[1] During continuous 24-hour electrocardiography, 44% of normal horses had second-degree atrioventricular (AV) block, 10% had sinus arrhythmia, 3% had sinoatrial (SA) block, 27% had occasional supraventricular extrasystoles, and 15% had occasional ventricular arrhythmias.[2] Cardiac arrhythmias may be present in 40% of horses that have other signs of cardiac disease.[1] The horse may have arrhythmias at rest that are considered benign or functional. Benign, physiologic, or functional arrhythmias are usually bradyarrhythmias and are thought to be the result of increased vagal tone. These arrhythmias disappear at high heart rates (exercise or excitement) or with the administration of atropine 0.01 mg/kg intravenously (IV) or 0.02 mg/kg intramuscularly (IM) or glycopyrrolate (0.003 to 0.006 mg/kg SC or IM). Some examples of benign or functional arrhythmias are as follows:

- Second-degree AV block

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- Sinus arrhythmia
- Sinus bradycardia
- SA block
- SA arrest

Other arrhythmias are usually considered to be pathologic, even if there are no other overt signs of cardiac disease. Some examples of pathologic arrhythmias are:

- Atrial fibrillation/atrial flutter
- Frequent atrial and ventricular premature depolarizations
- Supraventricular or ventricular tachycardia
- Advanced second-degree or third-degree (complete) AV block

The most effective method of identifying the specific arrhythmia is by performing an electrocardiogram (ECG). Resting electrocardiography may not detect arrhythmias that are transient or intermittent. Continuous ECG recordings (Holter or telemetry) are useful for identifying transient arrhythmias and for characterizing the type, frequency, and severity of arrhythmias. Exercising electrocardiography may identify arrhythmias that are absent or clinically insignificant at rest but that may impair performance or affect safety of a rider or driver.

In general, cattle do not have benign arrhythmias like horses, but they are frequently found to have sinus bradycardia and sinus arrhythmia associated with lack of feed intake. These arrhythmias were previously thought to be abnormal and associated with vagal indigestion but have been shown to occur in normal cattle held off feed for 12 to 48 hours.[3] Cattle with gastrointestinal disease seem to have increased susceptibility to cardiac arrhythmias, especially atrial premature depolarizations and atrial fibrillation. Although the reason for the susceptibility is not established, abnormal electrolyte concentrations, acid-base disturbances, and aberrations in autonomic nervous system function have been

proposed.[4,5] Sinus arrhythmia in goats is considered to be a benign arrhythmia and is present in many normal animals. Normal camelids also frequently have sinus arrhythmia.

Mechanisms of Cardiac Arrhythmias

Arrhythmias result from abnormalities of impulse generation or impulse conduction or a combination of both. A variety of mechanisms can cause abnormal impulse generation or conduction (Boxes 6.3 and 6.4). Abnormal impulse generation occurs because of localized changes in ionic currents that flow across the membranes of single cells or groups of cells. Abnormal impulse generation can be seen as automaticity (normal and abnormal) or triggered activity.

Box 6.3

Causes of Cardiac Arrhythmias in Horses

Common Causes

- Excitement
- Autonomic imbalance
- Fever
- Sepsis
- Toxemia
- Hypoxemia
- Colic
- Disorders of acid-base or electrolyte homeostasis
- Congenital defects
- Myocarditis
- Valvular disease
- Idiopathic (presumptive myocardial fibrosis or fibrofatty infiltrate)

Uncommon Causes

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Ionophore toxicity
Zilpaterol toxicity
Anesthesia
Other drugs
Pericarditis
Cardiomyopathy
Cardiac or heart base tumor
Aortic root rupture
Aortopulmonary rupture
Atypical myopathy
Aortic regurgitation
Severe hemorrhage
Dynamic upper airway obstruction
Rattlesnake envenomation
Cardiotoxic plants
Hyperthyroidism (iatrogenic)

Box 6.4

Causes of Cardiac Arrhythmias in Ruminants

Common Causes

Gastrointestinal disease
Lymphosarcoma
Valvular heart disease
Myocardial diseases
Brisket disease
Pericarditis
Cor pulmonale
Excitement
Foot rot
Fever
Sepsis
Toxemia
Disorders of acid-base or electrolyte homeostasis

Myocarditis

Uncommon Causes

Ionophore toxicity
β-adrenergic agonist (zilpaterol) toxicity
Anesthesia
Hypoxemia
Cardiomyopathy
Autonomic imbalance
Cardiotoxic plants (*Rhododendron* and *Taxus* spp.)

Automaticity, the ability to initiate action potentials spontaneously, is a property of cells in the sinus node, some parts of the atria, AV junction, and His-Purkinje system. Cardiac disease can be responsible for the development of automaticity in cells that normally do not have this property. Normal automaticity develops when the membrane potential slowly falls (i.e., becomes less negative) during diastole. When the membrane reaches its threshold potential, an impulse is initiated. The most common clinical arrhythmias caused by the automaticity mechanism are sinus tachycardia and sinus bradycardia, which are the result of alterations in autonomic nervous system tone. Enhanced automaticity in another area of the heart that is capable of automaticity (spontaneous depolarization) may be responsible for atrial or ventricular premature beats. Atrial fibrillation is thought to be triggered by rapid firing from one or more foci (in humans, the foci are usually in the pulmonary vein region).

Under certain circumstances, conduction abnormalities allow a propagating impulse, which has already excited the heart, to persist and reexcite the atria or ventricles after the end of the refractory period. This can occur in an ordered or random fashion. Random reentry occurs over reentrant pathways that continuously change in size and location with time, whereas ordered reentry occurs over a relatively fixed reentrant pathway. Impulse propagation may be slow enough that reentrant circuits can be established in small areas of myocardium. In large animals the size of the myocardial circuit is large enough that relatively mild alterations in impulse propagation may make reentry feasible and may account for the relatively greater frequency of arrhythmias in these species. Both reentry and focal triggers are likely involved in the maintenance of

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atrial fibrillation. Atrial remodeling (electrical and structural) occurs with atrial fibrillation, which then perpetuates the arrhythmia. The mechanism of ventricular fibrillation is unknown, but reentry circuits are thought to be involved.

Under clinical conditions, cardiac arrhythmias may be associated with disturbances in electrolyte concentrations, especially potassium and calcium; in acid-base balance; and in autonomic nervous system function. These conditions can precipitate cellular changes conducive to the development of arrhythmias by any of the previously mentioned mechanisms.

Approach to Diagnosis of Cardiac Arrhythmias

It is important to distinguish between abnormal arrhythmias that are primary and those that are secondary. Most abnormal arrhythmias of horses and cattle are tachyarrhythmias. Primary arrhythmias are caused by pathologic conditions of the heart (myocarditis, valvular disease, conduction system abnormalities, and pericarditis). Secondary arrhythmias develop in the absence of heart disease and can be caused by excitement, fever, sepsis, hypoxemia, acid-base disorders, electrolyte homeostasis, gastrointestinal disturbances, anemia, severe hemorrhage, anesthesia, ionophores, other drugs, or toxemia. The treatment and prognosis for the two types of arrhythmias can be very different, and examination and laboratory tests are used to assist in making the distinction.

1. Take history. Determine the diet, feed additives, or medication (including thyroid hormone, furosemide, bicarbonate, or other prerace medications); note whether there has been exercise intolerance, syncope, fever, coughing, or edema; inquire about gastrointestinal problems, diarrhea, or colic; inquire about access to cattle feed (containing ionophores or beta adrenergic agonists), poultry feed (containing ionophores), or feed supplements (containing kelp) and about previous respiratory tract infections in this animal or stablemates.
2. Perform a physical examination to determine whether there is primary cardiac disease. Record the animal's vital signs. Determine whether this is a bradyarrhythmia or tachyarrhythmia. Careful auscultation should note which heart sounds are present and should characterize the arrhythmia. There may be irregularities in the basic rhythm, added sounds, or long pauses; classification of heart rate by regularity of

rhythm can distinguish one arrhythmia from another (see Chapter 30). Note whether a pulse deficit is present by simultaneous auscultation and palpation of the peripheral arterial pulse; note the strength of the peripheral arterial pulse; observe the jugular vein for pulsations and distention; examine peripheral veins for distention; and examine mucous membrane color and capillary refill time. Careful auscultation of the lungs with and without a rebreathing bag should be performed.

3. Record an ECG. The base-apex lead can be used to screen for arrhythmias; it is attached using positive, negative, and ground leads as follows:
    a. Positive lead is attached to skin over the left fifth intercostal space at the point of maximal intensity (PMI) of the apex beat; using lead I, this is the left arm electrode; using lead II or lead III, it is the left leg electrode.
    b. Negative lead is attached to the skin of the right jugular furrow two thirds of the distance from the ramus of the mandible to the thoracic inlet; using lead I or lead II, this is the right arm; using lead III, it is the left arm. ECG interpretation is discussed in Chapter 30.
4. If there is a cardiac murmur, perform an echocardiogram (including 2D, M-mode, and Doppler). Look for evidence of ventricular dysfunction, myocardial failure, chamber dilation, valvular abnormalities (such as prolapse, thickening, ruptured chordae tendineae, or endocarditis), congenital defects, aortocardiac fistula, aortopulmonary fistula (Friesian horse), pericardial effusion, and tumor.
5. Obtain feed for analysis if ionophore (monensin, lasalocid, salinomycin) or β-adrenergic agonist (zilpaterol) exposure is suspected.
6. Determine if horse is grazing on pasture containing seeds of *Acer pseudoplatanus* or *Acer negundo* species in the late fall or early spring[6] or other cardiotoxic plants.
7. Obtain whole blood for the following:
    a. CBC
    b. Selenium and vitamin E concentrations if cardiomyopathy suspected
    c. Blood gas determinations and acid-base status
7. Test serum or plasma for the following:
    a. Electrolyte (Na, K, Cl, Ca, Mg, P) concentrations

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   b. Vitamin E (α-tocopherol) concentration
   c. Cardiac troponin-I (cTnI) or cTnT[7] if myocardial inflammation, injury, or necrosis is suspected
8. Test urine for the following:
   a. Electrolyte (Na, K, Cl) concentrations
   b. Creatinine determination for fractional clearance calculations
   c. Myoglobin and hemoglobin
9. Calculate fractional excretion of potassium in the urine. This will be variable, depending on the diet, but a low value indicates the need for supplementation.
10. Treat the arrhythmia if:
   a. Patient is hemodynamically unstable (e.g., poor cardiac output, weak peripheral pulses, cold extremities, syncopal)
   b. There is ventricular tachycardia with a rapid rate (heart rate >120 beats/min)
   c. There are multifocal ventricular ectopic beats
   d. A QRS is detected in the preceding T wave (R on T)
   e. There is advanced second-degree or complete (third-degree) AV block
   f. The primary problem is cured or the condition is stabilized, and the patient is symptomatic with the cardiac arrhythmia
   g. If the arrhythmia is performance limiting, such as atrial fibrillation in horses performing high-intensity exercise

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Cardiac Murmurs

Throughout the cardiovascular system, blood has a laminar or streamlined flow, except in the heart and sometimes in the aorta. Occasionally conditions occur that cause turbulent flow that is sufficient to cause resonance in adjacent structures. This resonance may be heard as a murmur when a critical level of turbulence is reached (Boxes 6.5 and 6.6). The factors that determine whether blood flow is laminar or turbulent are related by the Reynolds number, which is the ratio of the inertial to viscous forces. When the Reynolds number exceeds a critical value (about 2000 in large vessels), turbulence occurs. Increased flow velocity or reduced blood viscosity (e.g., anemia) predisposes to murmur development. The characteristics of the murmur depend on the velocity of the blood flow and the nature of the structures that vibrate.

Box 6.5

Causes of Cardiac Murmurs in Horses

Common Causes

Valvular regurgitation
Congenital defects
Anemia
Excitement
Fever
Functional murmur
Exercise

Uncommon Causes

Aortic cardiac fistula
Aortopulmonary fistula
Cardiomyopathy
Pericarditis

Cranial mediastinal abscess

Box 6.6

Causes of Cardiac Murmurs in Ruminants

Common Causes

Anemia
Excitement
Fever
Functional murmur
Valvular regurgitation
Congenital defects
Lymphosarcoma
Pericarditis (usually traumatic reticulopericarditis)

Uncommon Causes

Cardiomyopathy
Myocarditis

It is useful to characterize murmurs with regard to timing in the cardiac cycle (systolic, diastolic, or continuous); duration in the cardiac cycle (early, mid, late, holo-, pan-); intensity (loudness); shape and quality or frequency; PMI; and radiation of the murmur. Systolic murmurs occur any time between the first and second heart sound. Diastolic murmurs occur between the second and first heart sounds. Continuous murmurs occur throughout the cardiac cycle (Fig. 6.4). The intensity of murmurs is frequently graded on a scale of 1 to 6[8]:

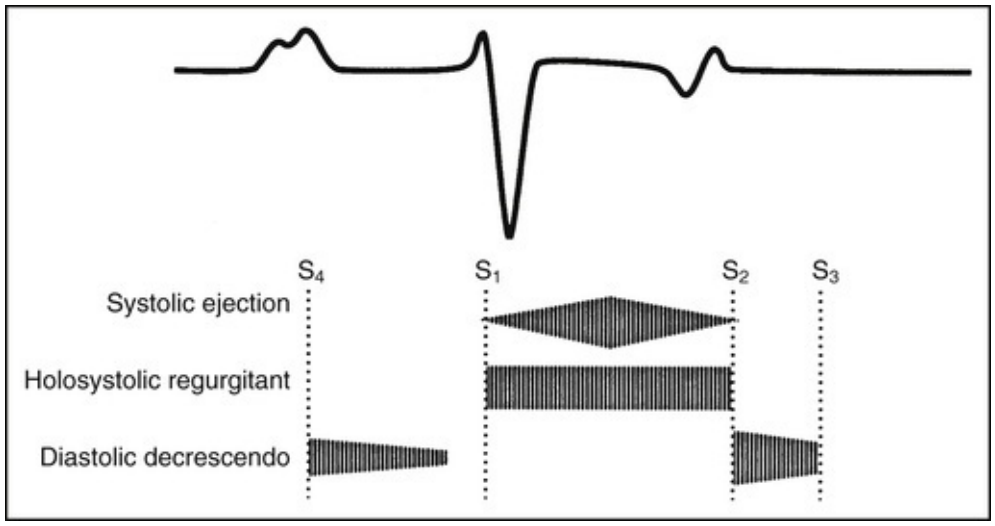


FIG. 6.4 Phonocardiographic characteristics of systolic ejection, holosystolic (pansystolic) regurgitant, and diastolic decrescendo cardiac murmurs.

- *Grade 1* is a soft murmur heard only after minutes of careful listening.
- *Grade 2* is a soft murmur heard immediately on auscultation.
- *Grade 3* is a murmur of moderate intensity.
- *Grade 4* is a loud murmur associated with a faint palpable thrill.
- *Grade 5* is a loud murmur with a palpable thrill but is not heard when the stethoscope is removed from the chest wall.
- *Grade 6* is a loud murmur with a palpable thrill and is audible with the entire stethoscope chest piece held away from the chest wall.

The PMI of a murmur usually corresponds to the location of one of the heart valves. Murmurs associated with the mitral valve will frequently be heard best in

the left fifth intercostal space just dorsal to the level of the elbow. These murmurs usually radiate dorsally or toward the aortic valve area. Pulmonic valve and aortic valve murmurs are best heard at the base of the heart. For this area to be accessed, the hand is moved under the left triceps muscle to the third (pulmonic) and fourth (aortic) intercostal spaces just below the level of the shoulder. Murmurs associated with the tricuspid valve are frequently located in the right third or fourth intercostal space between the shoulder and elbow.

Most systolic murmurs fall into one of two categories: ejection or regurgitant (see Fig. 6.4). Systolic ejection murmurs are caused by obstructed, increased, or turbulent blood flow across normal or damaged semilunar valves. Valvular obstruction is rare in large animals, but functional ejection murmurs are commonly found in healthy horses. The diagnostic considerations for systolic ejection murmurs are given in Box 6.7. The PMI of the innocent or functional murmur is typically at the pulmonic or aortic valve or just dorsal to them over the great vessels. It is a crescendo-decrescendo murmur that is audible in early to mid systole. The functional murmur may be distinguished from a pathologic murmur by being of lower and variable intensity, peaking in early to mid systole, ending well before the second heart sound, and having no radiation. The physiologic systolic ejection murmur may disappear or become louder after exercise. Diagnostic considerations for systolic regurgitant murmurs are listed in Box 6.7.

Box 6.7

Possible Causes of Ejection and Regurgitant Systolic Cardiac Murmurs

Ejection

Innocent murmur
Anemia
Fever
Aortic stenosis
Pulmonic stenosis
Atrial septal defect

Ventricular septal defect
Tetralogy of Fallot

Regurgitant

Mitral regurgitation
Tricuspid regurgitation
Ventricular septal defect
Tetralogy of Fallot

Regurgitant murmurs can be variable in duration and may occur in early, mid, or late systole or can be pansystolic or holosystolic. Location of the PMI and the direction of radiation of the systolic murmur distinguish mitral or tricuspid regurgitation from a ventricular septal defect (VSD). Systolic clicks are rare in horses and cattle but may indicate abnormalities of the chordae tendineae, AV valve prolapse, or dilation of the aorta. The presence of a musical murmur indicates vibration of a cardiac structure such as rupture of one of the chordae tendineae or a torn valve leaflet.

Diastolic murmurs can occur between S_4 and S_1 (atrial systolic murmurs), between S_2 and S_3 (ventricular filling murmurs), or from S_2 to S_1 (aortic regurgitation or, rarely, pulmonic regurgitation). Both the atrial systolic and ventricular filling murmurs are usually functional, can be heard over the left or right hemithorax, and can vary in intensity. They may have a musical or "squeaky" quality. The aortic regurgitation murmur is typically a decrescendo murmur with its PMI over the aortic valve that begins immediately after S_2 (see Fig. 6.4). Some aortic regurgitation murmurs can be harsh or musical, associated with high-frequency vibrations of an aortic valve leaflet, and they are often audible over the right thorax, although with lesser intensity.

Continuous murmurs are uncommon in horses and ruminants. Patent ductus arteriosus, a finding in normal foals for a short time after delivery, can be heard in the left third intercostal space. This murmur can be continuous, but more frequently only a residual systolic murmur is audible.[9] Continuous machinery murmurs are most frequently reported in adult horses with an aortic cardiac fistula secondary to rupture of the aortic root or of a sinus of Valsalva aneurysm. If both a systolic and diastolic murmur or a continuous murmur are heard in the aortic to pulmonic valve area in a Friesian horse, an aorticopulmonary fistula

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should be considered.[10] Most acquired systolic and diastolic murmurs in adult horses or cattle are usually the result of separate murmurs but can sometimes be confused. A continuous “washing machine” murmur/rub, which is most easily heard over the left cardiac area, is associated with traumatic pericarditis in cattle and is caused by the accumulation of fluid, gas, and fibrin within the pericardium.

Approach to Diagnosis of Cardiac Murmurs

1. Take a history. Note the age, onset, duration, and progression of the condition. Determine exercise capability, growth, and attitude; inquire about previous fever, illness, or medications.
2. Perform a physical examination. Record the animal's vital signs. Determine timing, duration, intensity, location of PMI, shape, and radiation of murmur. Palpate peripheral arterial pulse and observe the jugular vein for distention and pulsations. Carefully auscultate the lungs at rest and during deep inspiration.
3. Obtain blood for CBC (includes fibrinogen, SAA, and total plasma protein concentration).
4. Test serum or plasma for the following:
    a. Electrolyte concentrations
    b. Bovine leukosis virus (BLV), AGID status (cows)
    c. Cardiac troponin I or cTnT if myocardial inflammation, injury, or necrosis is suspected[7]
5. Record an ECG.
6. Perform an echocardiogram to look for valve abnormalities, abnormalities of the aortic root, congenital defects, chamber enlargement, and wall motion abnormalities; use pulsed wave and color flow Doppler echocardiography to localize the shunt, regurgitant blood flow, or stenosis (rare); use color flow and continuous wave Doppler echocardiography to estimate the severity of the jet associated with a shunt, valvular regurgitation, or stenosis (rare); estimate pulmonary artery pressure by applying the Bernoulli equation to tricuspid or pulmonic regurgitant jet velocities, if present. Contrast echocardiography can also be used for examination of congenital defects and detection of an aortic cardiac fistula and some valvular

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insufficiency. Tissue Doppler imaging and speckle tracking can be used to further assess myocardial function.[11]

7. Take radiographs or perform thoracic ultrasonography to find evidence of pulmonary edema or pleural effusion.
8. Catheterize the right heart to determine pulmonary artery and wedge pressures, which may complement data obtained noninvasively with Doppler echocardiography.

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Muffled Heart Sounds

Auscultation of heart sounds requires that the vibrations generated by the heart be transmitted through the tissues of the thorax to the outer chest wall with sufficient amplitude to be heard. Blood transmits sound well, whereas lung tissue strongly attenuates sound waves. The chest wall itself causes attenuation of the sound that is most significant at the interface between bone and muscle. Therefore physical factors in a normal patient, such as a large, thick chest or obesity, can cause heart sounds to be muffled. If the environment for auscultation is conducive to hearing heart sounds, other factors such as stethoscope quality may cause muffling of heart sounds in a normal patient. One should strive to have a stethoscope with comfortably fitting earpieces; thicker and shorter tubing; a rigid diaphragm to hear S_1, S_2, and higher-frequency sounds; and a bell piece for auscultation of S_3, S_4, low-frequency sounds, and murmurs. If the overlying hair coat is thick, clipping the hair may be necessary for optimal contact of the stethoscope to the skin.

Heart sounds are muffled primarily because of displacement of the heart from the thoracic wall by fluid (pericardial effusion), a soft tissue mass (abscess or tumor), or air (pneumothorax, pneumomediastinum, or emphysema) (Boxes 6.8 and 6.9). Rarely is muffling of heart sounds attributed to weak cardiac contractions alone, although this may be a finding in recumbent, hypocalcemic cows.

Box 6.8

Causes of Muffled Heart Sounds in Horses

Common Causes

Obesity
Large or thick chest wall
Pericarditis or pericardial effusion
Neoplasia: lymphosarcoma
Pleural abscess

Chronic heart failure

Uncommon Causes

Pulmonary emphysema
Pneumothorax
Neoplasia: mesothelioma, squamous cell carcinoma, fibrosarcoma

Box 6.9

Causes of Muffled Heart Sounds in Ruminants

Common Causes

Obesity
Large or thick chest wall
Pericarditis (traumatic reticulopericarditis)
Neoplasia: lymphosarcoma
Pleural abscess
Chronic heart failure
Emphysema

Uncommon Causes

Pneumothorax
Idiopathic hemorrhagic pericardial effusion

Approach to Diagnosis of Muffled Heart Sounds

1. Take a history. Inquire about any change in attitude, appetite, diet, or posture; determine whether a magnet has been administered to cattle; note any history of fever, weight loss, respiratory disease, colic, or diseases of other body systems and the deworming history; determine whether cattle are known to be BLV positive. Determine whether the

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horse had possible exposure to Eastern Tent caterpillars.[12]

2. Perform a physical examination and determine vital signs. Carefully auscultate the lungs to establish whether there is ventral dullness or evidence of increased or added sounds from pulmonary parenchymal compression; carefully auscultate the heart for pericardial friction rubs; determine whether there are signs of CHF (jugular venous distention, peripheral edema); percuss the thorax to determine whether there is emphysema, pleural fluid, or pneumothorax; note that pleural fluid in the absence of pericardial effusion causes radiating heart sounds but absence of airway sounds; determine whether there is thoracic and/or abdominal pain; and in cattle, check for the presence of a reticular magnet using a compass or stud finder.
3. Obtain blood for the following:
    a. CBC
    b. Fibrinogen concentration
    c. SAA concentration
    d. Plasma or serum protein concentration
    e. Liver enzymes and tests for liver function (AST, SDH, alkaline phosphatase, GGT, bilirubin, and bile acid concentration)
    f. Tests for kidney function (urinalysis, creatinine, blood urea nitrogen [BUN], Na, K, Cl, P concentrations, and fractional excretion of Na, Cl, P)
4. Test serum for BLV serology and for equine influenza, viral arteritis, and herpes virus.
5. Take radiographs of the thorax to determine whether there is pulmonary parenchymal and/or pleural or pericardial disease.
6. Perform an ECG.
7. Perform a thoracic ultrasound examination/echocardiogram to determine if there is pericardial or pleural fluid, a cardiac mass, or a mass in the cranial mediastinum compressing the heart. Determine the location and type of fluid present.
8. Analyze pericardial or pleural fluid, and perform culture and sensitivity testing if indicated.

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Cardiovascular Exercise Intolerance, Weakness, and Syncope

Exercise intolerance, weakness, or syncope can be a clinical sign associated with disease in many body systems. Exercise intolerance can be manifested as sudden deceleration or stopping, failure to perform at an expected level, a sudden change in the level of performance or production, lowered enthusiasm for work, cough on exertion, evidence of respiratory distress, or excessive sweating. Weakness can be manifested as recumbency, difficulty in rising from recumbency, muscle tremors or fasciculations, reluctance to move, or toe dragging. Syncope is a sudden collapse and loss of consciousness (fainting).

Mechanisms of Cardiovascular Exercise Intolerance, Weakness, and Collapse

The clinical signs of exercise intolerance, weakness, or collapse can be caused by cardiovascular disease (Boxes 6.10 and 6.11). They are the result of failure to maintain cardiac output, caused by inability to regulate either heart rate or stroke volume. A normal horse increases cardiac output at submaximal heart rates (<210 beats/min) primarily by tachycardia. At maximum heart rates (≈210 to 240 beats/min in horses), subsequent increments in cardiac output occur by increased stroke volume.[13] The maximum heart rate for cattle and small ruminants has not been published.

Box 6.10

Causes of Exercise Intolerance, Weakness, and Syncope in Horses*

Common Causes

Myocardial disease
Cardiac arrhythmias

Aortic or pulmonary artery rupture
Aortoiliac-femoral thrombosis
Congenital heart defects
Chronic heart failure
Pericardial disease
Hyperkalemic periodic paralysis

*See Chapters 8, 13, 31, 41 and 42 for additional noncardiac causes.

Box 6.11

Causes of Exercise Intolerance, Weakness, and Syncope in Ruminants*

Common Causes

Myocardial disease
Cardiac arrhythmias
Congenital heart defects
Chronic heart failure

*See Chapters 8, 13, 31, 41 and 42 for additional noncardiac causes.

Supraventricular arrhythmias, primarily atrial fibrillation in horses, can lead to heart rates greater than 240 beats/min with submaximal exercise.[14,15] Heart rates exceeding the maximum rate may limit cardiac output by decreasing the time for diastolic perfusion of the myocardium or by limiting stroke volume because the short diastolic intervals leave inadequate time for ventricular filling. The ability to maintain cardiac output can also be compromised by other cardiac arrhythmias such as ventricular premature systoles. The frequency of extrasystoles can increase with exercise, and the timing of the abnormal beats can reduce cardiac output even at submaximal heart rates.[16] Horses with cardiac

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arrhythmias can have abnormal elevations in lactate concentration in response to exercise, indicating a lower anaerobic threshold and leading to exercise intolerance.[17,18] Bradyarrhythmias cause exercise intolerance and/or collapse via failure to maintain an adequate heart rate at rest or by failing to adequately increase heart rate to meet the increased cardiac output demands during exercise. Complete heart block and advanced second-degree heart block are the most common bradyarrhythmias to cause clinical signs.

Cardiac output maintenance may also be compromised in animals by diseases affecting myocardial contractility or diseases that result in increased end-systolic volume despite a submaximal heart rate.[19] Diseases that result in decreased venous return (peripheral vascular disease) can also reduce cardiac output and cause signs of exercise intolerance, weakness, or collapse.

Exercise intolerance or weakness can also be caused by painful peripheral vascular conditions or conditions causing peripheral hypoxia or lactic acid accumulation. In horses, such conditions may exist with aortoiliac thrombosis. Sudden episodes of weakness and collapse without change in consciousness are associated with hyperkalemic period paralysis in horses (see Chapter 42).

Collapse may be associated with epilepsy, narcolepsy, or other central nervous system (CNS) disturbance. If cardiovascular and pulmonary function appear normal, the nervous system should be examined in detail (see Chapter 8). Collapse at rest may also be caused by sleep disorders or poorly defined mechanisms such as girth tightening. Collapse during exercise is most commonly caused by cardiovascular disease, whereas collapse at rest is usually associated with neurologic disease.

Approach to Diagnosis of Exercise Intolerance, Weakness, and Collapse

1. Note signalment and take history. Establish onset of problem, previous performance history, activity level, and whether there is loss of consciousness when clinical signs are observed. Determine whether there is coughing, dyspnea, or excessive sweating associated with stress or exercise. Determining whether the weakness or collapse primarily occurs with exercise or at rest will direct further workup.
2. Perform a physical examination and record vital signs. Of particular importance are heart rate at rest, peripheral arterial pulse characteristics,

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presence of pulse deficits, mucous membrane color, and appearance of jugular venous pulses. Lungs should be auscultated for evidence of pulmonary edema or pleural effusion. The chest should be percussed. Rectal examination should be performed to evaluate aortic and iliac arterial pulses; metatarsal artery pulses and saphenous vein refill should be evaluated.

3. Perform neurologic and lameness evaluations. Perform a rectal ultrasound examination if aortoiliac thrombosis is suspected, to document the disease and assess its severity.
4. Perform an echocardiogram (2D, M-mode, and Doppler) to evaluate the size of heart chambers; to look for congenital defects, acquired valvular heart disease, and pericardial disease; and to evaluate myocardial contractility and ventricular wall motion. Tissue Doppler imaging and speckle tracking can also be used to further evaluate atrial and ventricular wall motion.[11]
5. Record an ECG at rest. Record a continuous 24-hour ECG to determine the frequency of arrhythmias detected on the resting ECG or to look for infrequent or paroxysmal arrhythmias not detected at rest.
6. Simultaneous video monitoring and continuous ECG recording can help determine if episodes of collapse are associated with cardiac rhythm disturbances. Video surveillance can also help characterize the nature of the collapse episodes and aid in differentiation of seizure activity from sleep disorders.[20]
7. If collapse is associated with exercise and a definitive diagnosis cannot be made with resting diagnostics, an exercising stress test should be performed. Diagnostics may include resting and exercising upper airway endoscopy, an exercising ECG (preferably with real-time monitoring), stress echocardiogram before and immediately after exercise, resting and exercising lactic acid and arterial blood gas concentrations, resting and postexercise creatine kinase, and cTnI or cTnT concentrations and a postexercise bronchoalveolar lavage. Clinicians should be prepared to discontinue the test, treat life-threatening arrhythmias, and/or establish a patent airway (tracheostomy) in horses with a history suggestive of ventricular arrhythmias or upper airway obstruction, particularly pharyngeal collapse or laryngeal dysfunction.

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Venous Distention and Pulsations

The jugular venous pulsations observed in the neck are primarily a reflection of right atrial and right ventricular activity. There may be some small contribution from carotid arterial impact.[21] The jugular venous pulse reflects the right atrial or central venous pressure, which is influenced by blood volume, right ventricular cardiac output, and right atrial contractility (Boxes 6.12 and 6.13). Jugular venous pulsations are observed in normal animals, but the pulse seldom radiates more than one third of the distance from the thoracic inlet to the ramus of the mandible when the head is held in a normal, upright position.

Box 6.12

Causes of Jugular Venous Distention and Pulsation in Horses

Common Causes

Right-sided heart failure
Left-sided heart failure with pulmonary hypertension
Cardiomyopathy
Atrial fibrillation
Tricuspid regurgitation
Cranial mediastinal mass
Lymphosarcoma
Abscess
Jugular venous phlebitis and thrombosis

Uncommon Causes

Ionophore toxicity
Pericarditis
Myocarditis

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Ventricular tachycardia
Squamous cell carcinoma
Fibrosarcoma
Cor pulmonale
Chronic obstructive pulmonary disease
Overhydration

Box 6.13

Causes of Jugular Venous Distention and Pulsation in Ruminants

Common Causes

Right-sided heart failure
Left-sided heart failure with pulmonary hypertension
Vitamin E or selenium deficiency (white muscle disease)
Cardiomyopathy
Tricuspid regurgitation
Pericarditis
Jugular venous phlebitis and thrombosis
Heart base tumor: lymphosarcoma
Heart base abscess
Cor pulmonale caused by chronic pneumonia
Brisket disease

Uncommon Causes

Ionophore toxicity
Idiopathic hemorrhagic pericardial effusion
Overhydration
Cranial mediastinal mass

Mechanisms of Venous Distention and

Pulsations

The normal jugular venous pulse consists of three positive and two negative deflections (Fig. 6.5). The first and dominant positive wave is the A wave, produced by atrial contraction. During atrial relaxation the pressure declines until ventricular systole. The second positive deflection is the C wave, which is produced by the bulging of the tricuspid valve leaflets into the right atrium during early (isovolumetric) right ventricular systole. Carotid arterial impact on the jugular vein may also contribute to the C wave.[21] As the ventricle contracts, the plane of the tricuspid valve is pulled toward the apex of the heart and the atrial pressure declines, producing the X descent. The X descent is terminated by the V wave, which is associated with venous return, subsequent atrial filling, and a closed tricuspid valve. At the end of ventricular systole, the atrial pressure falls again as a result of tricuspid valve opening and rapid right ventricular filling. This is the Y descent. The Y descent is terminated as the pressure gradually rises with right-sided heart filling.

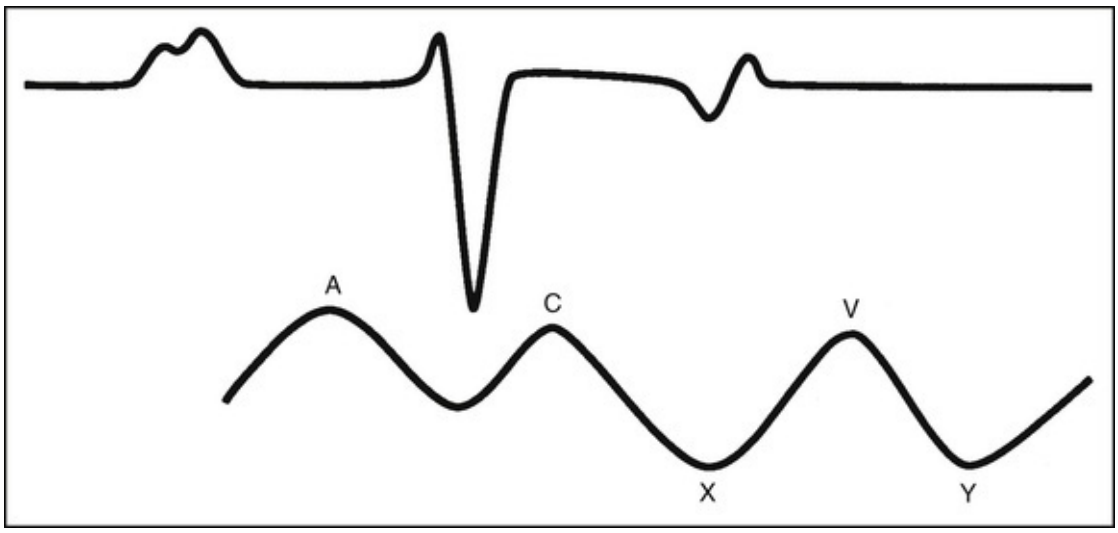


FIG. 6.5 Schematic illustration of a venous (jugular or atrial) pressure curve and its relationship to events of the electrocardiogram. *A,* Positive wave produced by atrial contraction; *C,* second positive deflection caused by bulging of the tricuspid valve during isovolumetric systole; *X,* first negative wave produced by the plane of the atrioventricular valve being pulled toward the apex of the heart during systole; *V,* positive pressure wave caused by venous return; *Y,* negative wave produced by AV valve opening.

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Abnormal pulsations occur with increased resistance to right ventricular filling, regardless of the cause. Distention and pulsations in the jugular vein are usually associated with an elevated right ventricular pressure such as occurs in right-sided heart failure, constrictive pericarditis, or, more rarely, cardiomyopathy. Prominent jugular pulsations are noted with tricuspid regurgitation and certain cardiac arrhythmias, especially those arrhythmias associated with atrial contraction against a closed AV valve. The carotid arterial pulse can mimic jugular venous pulsations. To distinguish among the causes of jugular venous pulsations, lightly compress but do not occlude the jugular vein at the thoracic inlet. The jugular vein will distend enough to eliminate carotid arterial pulsations. If pulsations are still present, tricuspid regurgitation, atrial arrhythmias, or right-sided heart failure should be considered. If the jugular vein is compressed near the ramus of the mandible and massaged toward the thoracic inlet, refilling is indicative of tricuspid regurgitation. Jugular venous distention without pulsations can occur with compression of the cranial vena cava from a cranial thoracic or mediastinal mass or from occlusion of the jugular vein with a thrombus.

Approach to Diagnosis of Venous Distention and Pulsations

1. Take history. Note especially history of respiratory disease, exposure to high altitude and locoweed, or ingestion of potential cardiotoxins. Determine whether other animals have been similarly affected, whether the BLV status of affected cattle is known, and whether a magnet has been administered.
2. Perform a physical examination. Determine whether there is tachypnea or tachycardia. Carefully auscultate for abnormal heart sounds, rhythm, or intensity of sounds; note whether jugular veins are patent. Look for jugular venous pulsations as described previously.
3. Obtain blood for the following:
    a. CBC
    b. Fibrinogen concentration
    c. SAA concentration
    d. Total protein concentration
    e. BLV status (bovine) and serology for equine influenza, viral

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arteritis, and herpes virus
   f. Vitamin E (serum) and selenium concentrations if cardiomyopathy suspected
4. Take radiographs of the thorax and abdomen to establish whether there is respiratory disease, a magnet, or a penetrating foreign body.
5. Record an ECG when there is an arrhythmia to look for atrial premature depolarizations.
6. Perform an echocardiogram to examine the following:
   a. Right ventricular size and function
   b. Right atrium, for abnormal size or structures
   c. Tricuspid valve
   d. Pulmonary artery diameter looking for evidence of pulmonary hypertension
   e. Left atrial size
   f. Left ventricular size and function
   g. Pericardium
   h. Interventricular septal thickness and motion
7. Perform Doppler echocardiogram to look for:
   a. Tricuspid regurgitation
   b. Pulmonic regurgitation
   c. If tricuspid or pulmonic regurgitation is detected, check for concurrent mitral and aortic regurgitation. Use velocity of tricuspid and/or pulmonic regurgitation to calculate/estimate pulmonary artery pressure.
8. Perform ultrasound examination of the cranial thorax and cranial mediastinum.
9. Performing jugular venous catheterization may be useful to determine right atrial (central venous), right ventricular, and pulmonary arterial pressures.

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Painful Peripheral Swellings

Close inspection of the skin and extremities of patients can reveal evidence of peripheral vascular or lymphatic system disease. These diseases can be manifested by diffuse swelling; localized swelling (papules, nodules, macules, or wheals); or subcutaneous edema of the extremities. Frequently there is necrosis, ulceration of the skin, and exudation as the disease progresses. Animals may be lame, have heat in the involved area, or exhibit a painful response to palpation of the area (Boxes 6.14 and 6.15), which helps to differentiate these conditions from nonpainful peripheral edema. Swellings in the neck may cause dyspnea or abnormal carriage of the head. In light of the zoonotic potential of certain infectious agents (e.g., glanders, sporotrichosis), donning of appropriate personal protective equipment should be considered.

Box 6.14

Causes of Painful Peripheral Swellings in Horses

Common Causes

Thrombophlebitis
Abscess (*Corynebacterium pseudotuberculosis* in western United States)
Cellulitis
Hypersensitivity vasculitis (complicated by skin necrosis and secondary infection)
Equine viral arteritis
Equine granulocytic ehrlichiosis *(Anaplasma phagocytophilum,* formerly *Anaplasma equi* or *Ehrlichia equi)*
Equine infectious anemia
Purpura hemorrhagica
Clostridium species myositis
Septic tenosynovitis
Bursitis

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Muscle disruption/hematoma
Fracture
Insect bite
Application of topical counterirritants, firing, or soring

Uncommon Causes

Frostbite
Piroplasmosis
Ulcerative lymphangitis
Epizootic lymphangitis
Glanders
Melioidosis
Sporotrichosis
Immune vasculitis
Aortoiliac thrombosis
Sporadic lymphangitis
Congenital lymph node and lymphatic dysgenesis
Hemangiosarcoma
Snakebite

Box 6.15

Causes of Painful Peripheral Swellings in Ruminants

Common Causes

Thrombophlebitis
Abscess
Clostridial myositis
Malignant edema
Blackleg
Muscle disruption/trauma/hematoma
Carpal hygroma

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Fescue foot
Ergotism
Cellulitis (injection site or wound)
Fracture
Insect bite
Frostbite

Uncommon Causes

Disseminated hemangiosarcoma
Heartwater disease (*Ehrlichia ruminantium*, exotic)
Snakebite
Septic tenosynovitis
Bursitis

Approach to Diagnosis of Painful Peripheral Swellings

1. Take history. Establish whether there is a history of a wound or trauma to the area or previous drainage; inquire about previous infections, particularly those referable to the respiratory system, in this animal or others; determine vaccination, deworming, and drug administration history.
2. Perform a physical examination. Determine vital signs. Note whether the animal is febrile; examine extremities for wounds, dilated lymphatic channels, ulcers, focal swellings, and edema; determine the temperature and sensitivity of the swollen area; examine mucous membranes for color and presence of hemorrhages; perform a rectal examination and palpate aortic quadrifurcation in horses for vessel size, firmness, pain, fremitus, and strength of pulse; evaluate these vessels before and after exercise, if indicated; test saphenous refill by holding off the saphenous vein distally over the hock, stripping the vein proximally, and releasing the pressure over the vein at the level of the hock.
3. Obtain blood for the following:
    a. CBC (includes examination of red blood cells, neutrophils,

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and eosinophils for inclusion bodies or morula and determination of platelet count)
   b. Fibrinogen concentration
   c. SAA concentration
   d. Total protein concentration
   e. Coombs or direct immunofluorescence test
   f. Appropriate tests for equine ehrlichiosis (immunofluorescence assay), piroplasmosis (complement fixation), or viral arteritis (serum neutralization), if indicated
4. Take radiographs of swollen extremities, if appropriate.
5. Perform an ultrasound examination of the swelling, if appropriate. Perform transrectal ultrasound examination of terminal aorta and iliac arteries of horse if palpation or physical examination findings suggest thrombus.
6. Obtain Gram stain and bacterial and fungal culture of ulcerated area or exudate.
7. Perform a biopsy of granulomas and submit for histopathology and culture and sensitivity testing, if appropriate.
8. Analyze and culture fluid obtained from dilated lymphatic channels or localized edematous areas.
9. Analyze urine to look for hemoglobinuria or hematuria.
10. Test feces for fecal occult blood.

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Enlarged Lymph Nodes

Diffuse or single lymph node enlargement occurs with infectious (bacterial, viral, fungal) conditions, neoplasia, and, rarely, immune-mediated causes in large animals (Boxes 6.16 and 6.17). Lymphadenopathy may cause obstruction to lymphatic drainage, leading to peripheral edema, pleural effusion, or ascites. The peripheral lymph nodes that are most readily accessible for examination are the submandibular (horses), superficial cervical (ruminants), and superficial inguinal (ruminants) lymph nodes. When there is generalized lymphadenopathy, internal lymph nodes may be enlarged, causing clinical signs such as dyspnea, esophageal obstruction, diarrhea, or other signs of organ dysfunction.

Box 6.16

Causes of Enlarged Lymph Nodes in Horses

Common Causes

Strangles
Lymphosarcoma
Upper respiratory infection
Corynebacterium pseudotuberculosis lymphadenitis

Uncommon Causes

Ulcerative lymphangitis
Epizootic lymphangitis
Sporadic lymphangitis
Glanders
Melioidosis
Granulomatous lymphadenitis
Plasma cell myeloma
Tuberculosis
Hemolytic uremic-like syndrome

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Box 6.17

Causes of Enlarged Lymph Nodes in Ruminants

Common Causes

Caseous lymphadenitis (*Corynebacterium pseudotuberculosis*)
Lymphosarcoma (including bovine leukosis virus)
Abscess or cellulitis of area drained

Uncommon Causes

Tuberculosis
Sporadic bovine encephalomyelitis
Malignant catarrhal fever

Approach to Diagnosis of Enlarged Lymph Nodes

1. Take history. Note especially history of weight loss, inappetence, depression, lethargy, or lymph node enlargement; inquire about previous illness or wounds; for cattle, determine whether there is a history of lymphosarcoma in the family or herd and whether the cow has a positive BLV test result; for sheep and goats, determine whether there is a history of *Corynebacterium pseudotuberculosis* abscesses in the flock or herd.
2. Perform a physical examination. Determine vital signs. Examine peripheral lymph nodes or other swellings, perform a rectal examination to palpate accessible internal lymph nodes, and, when appropriate, examine the uterus in cattle; carefully inspect the skin over the area drained by the lymph node for pain, swelling, or exudate; check mucous membranes for pallor or icterus; determine whether there is jugular venous distention or pulsations or whether there is evidence of pleural or pericardial effusion or ascites.

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3. Obtain blood for the following:
    a. CBC to examine for anemia or leukemic changes; note inclusions, morula, or abnormal appearance of cells
    b. Serum chemistry profile to determine if there are signs of other organ dysfunction (e.g., gastrointestinal [hypoproteinemia], liver, or kidney)
4. Test feces for occult blood, if indicated.
5. Perform ultrasonographic examination of the lymph node or swelling.
6. Obtain lymph node or swelling aspirate and biopsy sample for culture and histopathologic examination.
7. Obtain a bone marrow sample for cytologic examination.

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Abnormal Peripheral Pulse

Palpation of the arterial pulse is an important aspect of the examination of the patient with cardiovascular disease. Arterial pulse strength and contour (how fast pressure rises and falls) are the objectives of the examination and are determined by the cardiac output, heart rate, and vascular impedance. The arterial pressure pulse begins with the opening of the aortic valve and ventricular ejection and rises rapidly in early systole. The pulse pressure reaches a peak and then declines as ventricular ejection slows. During isovolumic relaxation (before AV valve opening), there is a transient reversal of flow in the arterial system, and an incisura or dicrotic notch (Fig. 6.6) is inscribed on the descending limb of the pressure curve. Following the incisura, there is a small positive wave that is attributed to elastic recoil of the aorta and the aortic valve and the summation of reflected waves from more distal arteries.[19] After the positive wave, the pulse pressure declines because there is peripheral runoff of blood in diastole. The incisura and secondary positive wave are not usually palpable. Palpation of peripheral arteries (facial, transverse facial, and digital arteries in the horse and median and coccygeal arteries in ruminants) normally reveals a smooth, rapid upstroke, a dome-shaped summit, and a downstroke that is slightly more prolonged than the upstroke.

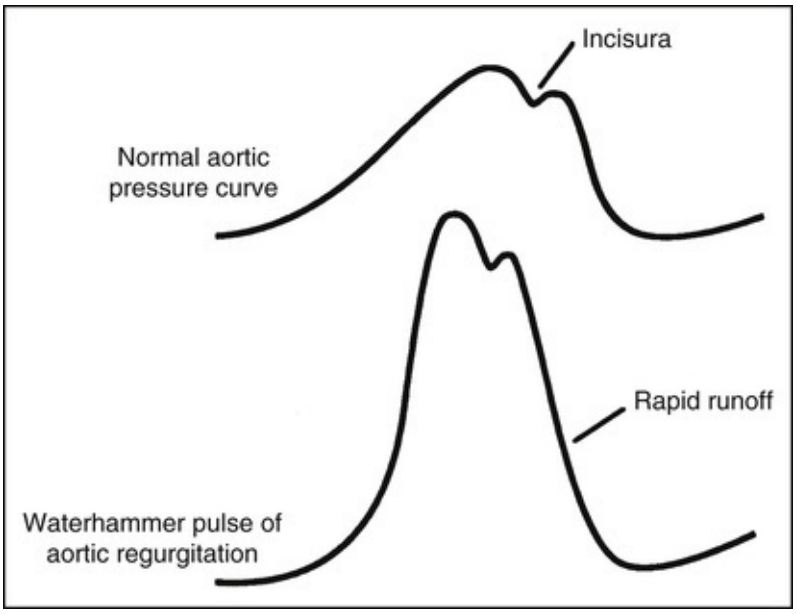


FIG. 6.6 Schematic illustration of the normal arterial pressure pulse. The incisura that occurs during the descending limb is caused by a transient reversal in flow during isovolumic relaxation. Compared with the normal arterial pressure pulse, the waterhammer pulse of aortic regurgitation builds rapidly and has a rapid runoff.

Pressure values and pulse wave configurations are altered as the pressure waves are transmitted through the peripheral arterial tree. With increasing distance from the heart, the dicrotic notch and second positive wave disappear, the systolic pressure gets higher (loss of distensibility in the distal arteries and summation of reflected pulse waves from the distal vascular bed), and the diastolic pressure gets lower. The difference between the systolic and diastolic pressure determines pulse pressure and can be evaluated by an impression of pulse strength. Pulse pressure increases as one moves to more peripheral arterial sites. The mean arterial pressure changes little but decreases slightly as one moves downstream in the arterial system from the pressure source. Systolic blood pressure, as measured indirectly at the tail or on a limb, is higher than that measured in the ascending aorta. In smaller arterial beds (e.g., arteries of the ear), the pulse wave is gradually dampened and pulsatile characteristics are lost on the capillaries and small veins.

Mechanisms of Abnormal Peripheral Pulse

Hyperkinetic arterial pulses occur in patients with increased cardiac output (e.g., fever, exercise, excitement), increased stroke volume, or bradycardia (Boxes 6.18 and 6.19). They may also occur when there is rapid runoff of blood in the arterial system, as occurs with aortic valve regurgitation, patent ductus arteriosus, aortic cardiac fistulas, or aortopulmonary fistulas. In aortic valve regurgitation the rapidly rising, hyperdynamic pulse is caused by increased stroke volume (regurgitated blood in the left ventricle), followed by a rapid runoff of pressure later in systole as a result of regurgitation (see Fig. 6.6).

Box 6.18

Causes of Abnormal Peripheral Pulse in Horses

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Common Causes

- Dehydration
- Shock
- Toxemia
- Congestive heart failure
- Electrolyte imbalances
- Acid-base disorders
- Hypertension
- Hypotension
- Exercise
- Fever
- Laminitis
- Aortic regurgitation
- Cardiac arrhythmias

Uncommon Causes

- Aortic cardiac fistula
- Aortopulmonary fistula
- Peripheral arteriovenous shunt
- Patent ductus arteriosus

Box 6.19

Causes of Abnormal Peripheral Pulse in Ruminants

Common Causes

- Dehydration
- Shock
- Toxemia
- Congestive heart failure
- Electrolyte imbalances

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Acid-base disorders
Fever
Cardiac arrhythmias

Uncommon Causes

Patent ductus arteriosus
Aortic regurgitation
Peripheral arteriovenous shunt

Hypokinetic pulses are present in patients with diminished stroke volume caused by hypovolemia, left ventricular failure, or, rarely in large animals, mitral or aortic valve stenosis.

Abnormal peripheral pulses are detected in patients with cardiac arrhythmias. With premature ventricular complexes (PVCs), the compensatory pause that occurs after the PVC allows a longer period of time for ventricular filling, which results in a greater end-diastolic volume, increased contractile force, and a stronger pulse in the beat that follows the PVC. The strength of the peripheral pulse is variable in arrhythmias such as atrial fibrillation because the irregular rhythm is associated with variable time for ventricular filling. Certain arrhythmias, particularly tachyarrhythmias, allow inadequate ventricular filling to generate a peripheral arterial pulse, and a pulse deficit is palpated. This is particularly likely with ventricular tachycardia at high heart rates.

Approach to Diagnosis of Abnormal Peripheral Pulse

1. Take history. Note changes in appetite, attitude, milk production, or ability to exercise; determine whether there have been signs of previous illness and duration and progression of the problem.
2. Perform a physical examination. Determine vital signs. Note whether there is a cardiac arrhythmia, murmur, or other evidence of heart disease (e.g., jugular venous distention or pulsation, edema). Palpate the pulse in multiple sites and bilaterally to rule out occlusive arterial disease; check patient's hydration. Evaluate for potential causes of hypovolemia (e.g.,

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diarrhea, blood loss) and sepsis/toxemia.

3. Obtain blood for the following:
    a. CBC; look for evidence of toxemia or anemia
    b. Blood gases to determine acid-base balance
    c. Electrolyte concentration, especially Ca and K
4. Record an ECG to characterize any arrhythmia.
5. Determine blood pressure. The site for indirect blood pressure measurement in the standing animal is the tail over the coccygeal artery; a limb can be used in a recumbent animal. Take the mean of several (minimum of three) readings in which the blood pressure cuff is gradually inflated and deflated at approximately 2 to 4 mm Hg/sec; values obtained should be corrected for the difference in height between the site measured and the heart, which is considered to be at the level of the shoulder; the difference in height (centimeters) between the heart and the site of pressure measurement is multiplied by 0.77 (constant used to convert centimeters of blood to millimeters of mercury). In standing horses, approximately 27 mm Hg is added to the indirectly measured coccygeal artery pressure to give the corrected value[22]; no correction factor is necessary if the measurement is made in a recumbent animal. An appropriately sized blood pressure cuff is considered to be one fourth of the tail circumference[23]; in horses a 4.5- to 5.6-cm cuff has been recommended for electronic oscillometric devices, and a 10.6-cm cuff is used for ultrasonic flowmeters.[22] Values for normal horses by blood flow detection methods are 79/49 to 145/106 mm Hg (uncorrected for the height of the tail).[21] Mean arterial blood pressure (MAP) obtained noninvasively (NIBP) correlates well with invasive blood pressure (IBP) measurements in normotensive horses but not in hypotensive or hypertensive horses.[24,25]
6. Blood pressure can be evaluated by Doppler scan, or measurements can be recorded by direct cardiac catheterization (see Chapter 30).
7. Perform an echocardiogram to evaluate size of chambers, myocardial function, presence of valvular or pericardial disease, or congenital defects.

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• CHAPTER 7

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Alterations in Alimentary and Hepatic Function

Bradford P. Smith, K. Gary Magdesian, Consulting Editors

MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

Diarrhea, 95
Colic (abdominal pain), 102
Melena, 105
Blood, fibrin, and/or mucus in feces (dysentery), 106
Abdominal distention and constipation, 106
Regurgitation and vomiting, 108
Dysphagia, 110
Oral vesicles, erosions, ulcers, or growths, 111
- **Dental abnormalities,** 113
- **Icterus (jaundice),** 113

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Diarrhea

K. Gary Magdesian • Bradford P. Smith

Diarrhea is an increase in the frequency, fluidity, or volume of feces. Diarrhea may be a sign of a primary gastrointestinal (GI) disease or a nonspecific response to sepsis, toxemia, or disease of another organ system.

Under normal circumstances a large volume of essentially isotonic fluid enters the proximal GI tract daily. Most of this fluid is resorbed, and only a small percentage is ultimately passed with the feces. The fluid comes from dietary intake and from endogenous secretions of the upper digestive tract. The total daily volume exchanged exceeds that of the animal's total extracellular fluid volume. Normally absorption just exceeds secretion; therefore small changes in rate of absorption or secretion can result in diarrhea. In the horse most water resorption occurs in the cecum and large colon, and diarrhea in the horse (other than neonates) usually involves some abnormality in the lumen or wall of the large intestine.

Normal fecal color is tan, brown, or greenish, depending on diet. The adult horse normally produces 11 to 13 kg of fecal material per day (24 to 29 lbs of body weight per day) while on a diet of grass hay and 3 lb of oats.[1] Fecal output is as high as 20 kg/day (44 lbs/day) in horses fed a mixture of alfalfa and orchard grass ad libitum.[2] Horses with chronic watery diarrhea can produce up to 214 g/kg of body weight per day,[1] which is >90 L of diarrhea in a 450-kg horse.

Cattle normally produce 15 to 28 kg of feces per day with a water content of about 75% to 85% on a diet of grass hay.[3] Fluidity of cattle feces can increase markedly in animals on lush green feed. Sheep and goat feces contain only 50% to 60% water.[3] Fluid feces in the cow and unformed feces in the horse, goat, and sheep are nonspecific signs that often accompany sepsis or illness other than a primary gastrointestinal disease.

Animals with chronic diarrhea rarely develop severe dehydration because they compensate for increased fecal water losses by increasing water consumption by an equivalent amount. Normal water consumption in the horse on a hay diet in a mild ambient temperature environment is about 24 to 30 L/day, whereas cattle consume 30 to 60 L/day based on 10 kg of dry matter feed intake. Water and feed intake do not increase linearly with increasing body size, but by multiplying body weight in kilograms to the 0.75th power (BW $kg^{0.75}$) by a base factor

(≈200 mL for water). Thus a 500-kg horse requires 21 L of water. The effect of temperature on water intake is dramatic and not linear; as ambient temperatures rise close to 37° C (98° F), water intake per kilogram of dry matter increases much more rapidly than at lower temperatures. Exercise and loss through sweat, particularly in the horse, can dramatically increase salt and water requirements.

Mechanisms of Diarrhea

The following six major mechanisms produce diarrhea (Box 7.1):

Box 7.1

Mechanisms of Diarrhea

Malabsorption (villous atrophy)
Osmotic overload
Secretion
Abnormal motility
Increased blood-to-lumen hydraulic pressure
Inflammation
Decreased transit time

- Decreased or damaged absorptive surface area (malabsorption)
- Increased numbers of osmotically active particles within the intestinal lumen
- Increased volume of secretion of solutes and water
- Abnormal intestinal motility resulting in decreased transit time, as with systemic inflammatory response syndrome (SIRS)
- Increased blood-to-lumen pressure as in heart failure or acute or chronic inflammatory bowel diseases

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- Gastrointestinal inflammation, as occurs with peritonitis

The common net result is an increase in fecal water.

Decreased surface area is mainly a result of villous blunting (atrophy) and/or microvillous damage in the small intestine, which lead to malabsorption. Both occur to some degree with most enteric diseases, and regeneration of surface area from crypt cells with healing is accompanied by a gradual decrease in the volume of diarrhea. Diseases in which this is a major mechanism include neonatal diseases such as rotavirus and coronavirus enteritis,[4] cryptosporidiosis, acute inflammatory disease such as salmonellosis, and chronic diseases such as Johne's disease and other granulomatous bowel diseases. The finding of villous atrophy is so nonspecific that it is not diagnostic in itself. It can also occur in advanced cases of secondary copper deficiency (molybdenosis) with diarrhea. Loss of villous epithelial cells can result in maldigestion because these cells produce important enzymes such as lactase. Many neonates with enteritis develop temporary lactose intolerance as a result, especially with rotaviral and clostridial infections. Damaged surface area occurs in such diseases as salmonellosis, where the mucosa of the large colon and cecum may be severely disrupted.

Inflammation can be accompanied by increased mucous production and increases in size of membrane pores, through which tissue fluids and serum proteins leak into the lumen. This is associated with increased capillary and lymphatic hydraulic pressures. Both acute (salmonellosis) and chronic (Johne's) inflammatory bowel diseases are protein-losing enteropathies. Low plasma protein concentrations, particularly low albumin, are often found (unless hypovolemia and hemoconcentration are present). Bowel inflammation often results in transudation and exudation of serum proteins, blood, and/or mucus, resulting in dysentery (bloody diarrhea). In addition to salmonellosis, dysentery may also commonly be seen with enterotoxemia caused by *Clostridium perfringens*, types A, B, or C; *Clostridium difficile; Lawsonia intracellularis*[5]; attaching effacing *Escherichia coli; Campylobacter jejuni;* coccidiosis; malignant catarrhal fever (MCF); arsenic toxicity; and oak toxicity. Inflammation results in malabsorption, maldigestion, osmotic effects, and, in acute disease, changes in intestinal motility. Because most water absorption in the horse occurs in the cecum and colon, inflammatory typhlitis and colitis are

the major causes of diarrhea in the adult horse (Boxes 7.2 and 7.3). The neonatal foal commonly develops small intestinal enteritis.

Box 7.2

Causes of Diarrhea in Horses[a]

Common Causes

Colitis or typhlitis
Salmonellosis
Enteritis, unknown cause
Potomac horse fever (equine monocytic ehrlichiosis)
Endotoxemia or gram-negative sepsis
Overfeeding or sudden change in diet
Clostridium difficile
Clostridium perfringens
Parasites (ascarids, large and small strongyles)

Less Common Causes

Eosinophilic gastroenteritis
Renal failure, uremia
Necrotizing enterocolitis
Heart failure
Enterotoxemia (*C. perfringens*, mainly type A)
Lawsonia intracellularis (mainly foals and weanlings), proliferative enteropathy
Intestinal lymphosarcoma
Cathartics or laxatives
Parasympathomimetics
Chronic granulomatous bowel disease
Proximal enteritis
Peritonitis
Intussusception

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Sand, gravel, or enterolith in gut lumen
Gut stenosis
Antibiotic use
Gastroduodenal ulcers
Rhodococcus equi, gut infection (mainly foals)
Cryptosporidiosis (mainly foals)
Giardiasis (mainly foals)
Toxins or poisonous plants (see Box 7.3)

Uncommon Causes

Hepatic failure
Cholelithiasis
Vascular aneurysm
Combined immunodeficiency
Agammaglobulinemia
Lactose intolerance (mainly foals)
Campylobacter jejuni (mainly foals)
Colorectal polyps
Anaphylaxis
Vitamin A deficiency
Tularemia
Snake bite, insect or spider sting or bite
Histoplasmosis
Hydroallantois
Hyperlipidemia
Internal abdominal abscess
Pheochromocytoma
Viral arteritis
Sarcoidosis
Addison disease
Malignancy
Grass sickness (exotic)
Glanders (exotic)
Besnoitiosis (globidiosis) (exotic)

[a]See Chapter 17 for information on neonates.

Box 7.3

Toxic Causes of Diarrhea in Horses[a]

Phenylbutazone or other nonsteroidal antiinflammatory drug toxicity
Blister beetle toxicity (cantharidin)
Salt poisoning
Selenium toxicity
Slaframine toxicity (slobber factor)
Amitraz toxicity
Propylene glycol toxicity
Dioctyl sodium sulfosuccinate toxicity
Sulfur toxicity
Phosphorus toxicity
Nicotine (Black Leaf 40) toxicity
Reserpine toxicity
Arsenic toxicity
Mercury toxicity
Monensin, lasalocid, or salinomycin toxicity
Organophosphate toxicity
Iron

Plant Toxins

Oleander poisoning
Japanese yew *(Taxus cuspidata)* poisoning
Castor bean poisoning
Avocado poisoning
Thorn apple *(Datura stramonium)* toxicity
Potato poisoning
Heath *(Ericaceae)* poisoning
Algae poisoning
Acorn or oak poisoning

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Hypericum (St. John's wort, Klamath weed) poisoning
Agrostemma githago (corn cockle) poisoning
Mycotoxicosis
Pimelea poisoning (St. George disease) (exotic)
Monkshood
Buttercup
Death camas
Datura
Foxglove
Hoary alyssum

[a]See additional lists at www.vet.cornell.edu/consultant.

Irritation of the bowel with a foreign body such as sand may result in either low-grade recurrent colic or diarrhea or both. Weight loss may also be evident with a large amount of sand. Sand accumulation in the large bowel of the horse may be suspected when there is evidence of a significant amount of sand in the feces or when sand can be auscultated with a stethoscope or detected via ultrasound over the ventral abdomen. Irritation probably causes diarrhea through creation of an inflammatory response and altered motility.

Osmotic diarrhea results from any disease causing maldigestion and/or malabsorption. Any osmotically active solute can produce diarrhea in normal animals if given in quantities sufficient to surpass the intestinal capacity for digestion or absorption. Disaccharides are natural examples. Osmotic cathartics such as dioctyl sodium sulfosuccinate (DSS) hold water in the intestine and act as fecal softeners. Magnesium phosphates and sulfates and other divalent and trivalent cations and anions are poorly absorbed and thus are effective laxatives and cathartics.

Osmotic diarrhea can be associated with ingestion of osmotically active and poorly absorbed solutes, overloading of the intestine with carbohydrates or lipids beyond the amount that can be digested and absorbed, sudden dietary changes resulting in marked shifts in gut flora and resulting bacterial action on ingested substrate (e.g., grain overload), or bowel disease in which surface area is diminished or digestion interfered with in some manner. Lactase deficiency, secondary to rotavirus or *C. difficile* infections, may result in osmotic diarrhea in

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foals[6] and probably also in neonatal ruminants. This results in increased concentration of undigested and/or unabsorbed nutrients entering the lower bowel, increased bacterial fermentation, and an increase in the concentration of osmotically active particles. Unfavorable electrochemical gradients prevent resorption of water. Mucosal digestive enzyme levels are often decreased with any disease involving the small intestine, resulting in maldigestion. When osmotic diarrhea is suspected in mature animals, dietary modification to basic roughage should be tried as part of the nonspecific therapy. Sodium and potassium are normally present in roughly equal amounts in feces and (with small concentrations of ammonium) make up the vast majority of cations in the feces. Concentrations of sodium and potassium in feces and osmotically active nonelectrolytes influence fecal water. In general, osmotic diarrheas diminish when the animal is fasted. When the offending substance is reintroduced, diarrhea occurs.

Secretory diarrheas are most important in neonates[4] (e.g., enteropathogenic *E. coli*), but many strains of *Salmonella* that are associated with colitis in large animals may also produce enterotoxins that stimulate secretion. Enterotoxins act by stimulating cyclic adenosine monophosphate (AMP) or other intracellular messengers to promote secretion of chloride, sodium, and other electrolytes into the gut lumen. Water is carried with these electrolytes and osmotically retained. The hallmark of secretory diarrheas is the large volume of feces produced.

Examples of secretory diarrheas are enterotoxigenic *E. coli,* many strains of *Salmonella*, and *C. perfringens. Salmonella* and other invasive microorganisms produce inflammation that may induce prostaglandin-mediated secretion as well. *Salmonella typhimurium* translocates Salmonella effector proteins into epithelial cells and causes diarrhea.[7] Secretion may occur with viral diarrhea by a different mechanism, as damaged mature (absorbing) villous cells are replaced by immature (secreting) crypt cells.[8] An example of viral secretory enteritis is rotavirus.

Decreased intestinal transit time, associated with increased peristalsis and/or decreased segmentation, appears to occur in many bowel diseases because of bowel irritation. Peritonitis is a major cause of bowel inflammation and should always be explored as a contributing cause of diarrhea, especially when fecal output volume is scant. Abnormal motor patterns have been demonstrated to occur with many infectious diarrheas and may be a bowel response to irritation and/or increased intraluminal volume. Elimination of gut contents thus appears to be a normal gut defense mechanism against infection and should not be

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pharmacologically alleviated in acute infectious diarrheas. Primary motility disorders of animals are not well recognized; diarrhea associated with nervous or excited animals may be the best example of this type. In general, fecal volume associated with motility disorders is not great.

Increased hydraulic or hydrostatic pressure, from the blood to the intestinal lumen, also decreases net fluid absorption. These can result from decreased oncotic pressure (hypoalbuminemia), increased capillary hydrostatic pressure (heart failure or portal hypertension as with liver disease), or decreased lymphatic drainage associated with inflamed or blocked lymph vessels or nodes (lymphosarcoma). These mechanisms are most commonly associated with chronic diarrhea, but acute inflammation can also result in diarrhea associated with this mechanism.

Two or more of these mechanisms are probably at work in most diarrheal diseases. Therapy of diarrhea is therefore nonspecific and supportive, except when the actual causative agent can be identified and is treatable. Diagnosis of a specific causative agent is most important when diarrhea is caused by an infectious agent so that appropriate therapeutic steps can be taken before chronicity develops, spread of disease can be prevented, and an accurate prognosis can be made.

In mature horses, small intestinal diseases such as granulomatous bowel disease or duodenitis/proximal jejunitis (anterior enteritis) may not be associated with diarrhea, and diseases of the stomach almost never cause diarrhea. Most significant diarrheal disease in adult horses involves the large colon because this is the principal site of water absorption. The exception to this is the neonatal foal, in which primarily small intestinal diseases such as rotavirus infection and cryptosporidiosis may cause severe diarrhea.

The frequency of defecation is usually increased when diarrhea is present, and defecation frequency is highest when the colon or rectum is irritated. When these areas are involved, tenesmus (straining) may result. Tenesmus can also occur with hepatic failure in ruminants and in horses and ruminants with rectal tears or strictures, vaginitis, retained placenta, dystocia, intussusception, urolithiasis, perirectal abscesses, rabies, and diseases involving the nervous system when there is retention of feces or urine. Severe rectal irritation can lead to straining and rectal prolapse.

In **ruminants,** abnormalities such as grain overload (toxic indigestion) resulting in ruminal osmotic changes can produce diarrhea, as can changes in abomasal pH such as occur with type II ostertagiasis. Diarrhea in ruminants is

frequently caused by forestomach problems (Boxes 7.4 and 7.5). The colon and remainder of the distal bowel are involved in diseases such as salmonellosis. Gram-negative infections and resulting endotoxemia, found in conditions such as coliform mastitis and septic metritis, are relatively common causes of nonspecific diarrhea.

Box 7.4

Causes of Diarrhea in Ruminants (Except Neonates; See Chapter 20 for Neonates)

Common Causes

Parasitism, worms
Coccidiosis
Salmonellosis
Colitis or typhlitis
Enteritis, unknown cause
Indigestion (spoiled feed, overfeeding, or sudden change)
Displaced abomasum (B)
Abomasal torsion (B)
Peritonitis
Intussusception
Sepsis or toxemia
Johne's disease
Enterotoxemia
Grain overload (rumen acidosis)
Bovine viral diarrhea (B)
Winter dysentery (B)
Liver failure
Malignant catarrhal fever (B)
Molybdenosis or copper deficiency
Heart failure
Uremia, renal failure
Xylazine, following large doses

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Cathartics or laxatives
Parasympathomimetics
Toxins or poisonous plants (see Box 7.5)

Less Common Causes

Amyloidosis
Giardiasis (mainly calves)
Intestinal obstruction, partial
Intestinal neoplasia
Traumatic reticuloperitonitis (hardware)
Vagal indigestion
Selenium deficiency (white muscle disease)
Cecal dilation (B)
Liver abscess
Brisket disease (high-altitude disease) (B)
Sarcocystosis (B)
Bluetongue (O)
Bovine leukosis (BLV) (B)
Hemorrhagic bowel syndrome (B)

Uncommon Causes

Fat necrosis (B)
Abomasal impaction
Duodenal ulcers
Systemic candidiasis
Vitamin A deficiency
Volvulus, root of mesentery
Water intoxication (B)
Cholelithiasis
Cobalt deficiency
Zinc deficiency (baldy calf) (B)
Hydrops allantois (B)
Lethal trait A 46, keratogenesis imperfecta (parakeratosis) (B)
Zygomycosis, mucormycosis

Pregnancy toxemia
Bacillary hemoglobinuria
Rumen flukes, paramphistomosis
Pancreatic adenocarcinoma
Bee or wasp sting
Pseudorabies
Hemochromatosis of Salers cattle (B)
Rift Valley fever (exotic)
Rinderpest (exotic)[a]
Schistosomiasis (exotic)
Theileriosis (East Coast fever) (exotic)
Wesselsbron disease (exotic) (B, O)
Heartwater (exotic)

B, Bovine; *O*, ovine.

[a]Rinderpest was a cause of diarrhea in ruminants until 2011, when it was eradicated worldwide.

Box 7.5

Toxic Causes of Diarrhea in Ruminants[a]

Arsenic poisoning
Sulfur poisoning
Salt poisoning
Propylene glycol
Levamisole
Monensin, salinomycin, lasalocid (ionophores)
Polybrominated biphenyl
Sodium bicarbonate
Aflatoxin
Herbicide

Zinc
Lead
Phosphorus toxicity
Nicotine (Black Leaf 40) toxicity
Copper
Chlorpyrifos (Dursban)
Organophosphates
Phosphate fertilizer
Lincomycin
Trichothecene (T-2 toxin)
Plant toxins
Oak (acorn poisoning)
Senna occidentalis (coffee weed)
Selenium accumulators
Slaframine (blackpatch-diseased legumes, slobber factor)
Mycotoxicoses
Helenium (sneezeweed, bitterweed)
Solanum (nightshade)
Pyrrolizidine alkaloid (*Senecio, Crotalaria, Amsinckia* species)
Brassica (mustards, crucifers, cress)
Oleander poisoning
Japanese yew *(Taxuscuspidata)* poisoning
Whitehead *(Sphenosciadium capitellatum)*
Pokeweed *(Phytolaccaamericana)*
Mushroom
Inkweed *(Drymariapachyphylla)*
Tung tree (aleurites)
Chinese tallow tree
Kalanchoe (crassulaceae)
Fungal toxicity
Sesbania (rattlebox)
Gutierrezia (broomweed, snakeweed)
Hypericum (St. John's wort; Klamath weed) poisoning
Agrostemma githago (corn cockle) poisoning
Monkshood
Buttercup
Castor bean (ricin)

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Foxglove (digitalis)
Larkspur

[a]See additional lists at www.vet.cornell.edu/consultant.

Foals with septicemia also commonly develop nonspecific diarrhea associated with SIRS.

Diarrhea may be 1) a manifestation of a primary disease (bovine viral diarrhea [BVD]; Johne's disease; *C. difficile*, salmonellosis); 2) one of the signs of a generalized disease (MCF, uremia); or 3) secondary to toxemia (coliform mastitis, septic metritis, septicemia, salmonellosis).

Nonspecific Fluid Therapy for Diarrhea

Dehydration, electrolyte losses, and acid-base abnormalities can occur rapidly when diarrhea is present. Treatment to correct these problems is an important component of nonspecific therapy in animals with diarrhea. Often the cause of diarrhea remains undetermined, yet correction of hypovolemia, dehydration, and acid-base and electrolyte abnormalities can result in a return to normal systemic function, particularly if the diarrhea is acute and severe. Fluids and electrolytes can be given orally or parenterally. Oral fluids can be given rapidly and inexpensively but only if dysmotility is not present. Oral fluids should be isotonic or hypotonic. The degree of dehydration should be estimated as a percentage of body weight. Mild dehydration is usually considered less than 5%; moderate, 5% to 8%; and severe, over 8%. Thus a severely dehydrated 450-kg patient with an estimated 10% dehydration (weakness, cold extremities, sunken eyes, decreased urine output, decreased elastic skin rebound, weak pulse, rapid heart rate) may require up to 45 L of fluids over time. Boluses of 10 to 20 mL/kg of isotonic crystalloid can be administered IV until signs of shock abate or plateau.

The optimal means of determining electrolyte status is to analyze a plasma or serum sample before initiating fluid therapy. Electrolyte requirements can be estimated; with diarrhea, mixed water and electrolyte losses occur, so sodium-containing fluids are usually required to replace lost sodium and improve blood volume (see also Critical Care and Fluid Therapy, Chapter 44). Unless the acid-base status can be measured, the safest sodium-containing fluids are balanced

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polyionic fluids such as PlasmaLyte A, PlasmaLyte 148, Hartmann's solution, or lactated Ringer's solution. Normal saline is a satisfactory alternative in many cases, but the relatively high concentration of chloride ions in saline can aggravate a preexisting metabolic acidosis through raising chloride concentration, producing a hyperchloremic metabolic acidosis (HCMA), and therefore saline should be used sparingly. In calves with severe metabolic acidosis, use of fluids containing sodium bicarbonate is indicated. In horses, it is best not to include large quantities of sodium bicarbonate in fluids unless there is laboratory evidence that a significant strong ion metabolic acidosis exists (such as hyperchloremia). Flow rates for administering isotonic intravenous fluids should be monitored, with close attention to perfusion parameters, in order to avoid fluid overload, pulmonary edema, and excessive diuresis. When the patient is shocky, flow rates close to 20 mL/kg/h or faster may be required for the initial administration of isotonic crystalloid fluids, but in general rates below 5 to 10 mL/kg/h are desirable, especially once hypovolemic shock has been addressed. Fluid overload is detrimental, and therefore frequent reassessment of the patient should be made. Hypertonic saline (7% NaCl) may be given rapidly intravenously at a dose of 4 to 5 mL/kg once. When a colloid fluid is required to combat low plasma protein concentrations, hetastarch or plasma can be used. Hetastarch is available as 6% hetastarch in a balanced electrolyte or normal saline solution. A dose of 10 mL/kg should not be exceeded for hetastarch because of development of dose-dependent coagulopathies. The use of hetastarch in human critical care has recently been questioned. A meta-analysis has suggested an increase in renal disease and mortality in patients treated with hetastarch.[9] How this applies to large animals is unknown, but creatinine should be monitored closely. See Neonatal Diarrhea, Chapters 17 (section on Neonatal Foals) and 20 (section on Neonatal Ruminants); Fluid and Electrolyte Balance, Chapter 22; and Fluid Therapy, Chapter 44 for more details on fluids and acid-base balance.

Approach to Diagnosis of Diarrhea in the Horse (for Neonates, See Chapter 17)

1. Take history. Especially note change in diet, deworming program, housing and management, and whether diarrhea is acute or chronic. Note appetite, whether animal is drinking an adequate volume of water, and whether salt is available. Note whether it is a single or multiple case,

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if there are concurrent diseases, or if other medications or exposure to toxins are involved. Most antimicrobials have been associated with diarrhea in horses at times, but especially lincomycin and erythromycin. Antimicrobials should be discontinued if diarrhea develops during administration. Most pathogenic bacterial and protozoal agents rely on altered intestinal microflora to proliferate in the gut and cause diarrhea. Note whether nonsteroidal antiinflammatory drugs such as phenylbutazone were used before the development of diarrhea. Many causes of diarrhea can be eliminated from consideration on the basis of history. Find out about housing and whether animals have access to pasture or natural water sources or are stall confined. For example, Potomac horse fever would be considered in horses with access to or living near water sources in endemic areas.

2. Perform physical examination. Take vital signs (these are often normal in chronic cases). Perform rectal examination unless an infectious contagious agent is suspected, especially if diarrhea is scant in volume. Note body condition score (see Chapter 9). Systemic signs of endotoxemia, SIRS, hypovolemia, and dehydration often accompany acute colitis, including salmonellosis, equine monocytic ehrlichiosis (Potomac horse fever), clostridiosis, and many other acute diseases.
3. Examine feces. Perform gross inspection; note whether blood or fibrin is present (see list of causes of dysentery).
    a. Gram stain of feces. A predominance of gram-positive rods may indicate an anaerobic overgrowth such as occurs with *C. difficile* infections, although this is not highly sensitive or specific. Perform microscopic examination for ova and protozoa, especially for chronic cases.
    b. Perform multiple cultures for *Salmonella, C. difficile,*[10] and *C. perfringens* if onset is acute, if animal is febrile, or if feces contain fibrin and mucus. A commercial polymerase chain reaction (PCR) test can be used as an aid to evaluate for the presence of salmonellosis.[11] Cultures for *C. difficile* should be performed on selective media (cycloserine-cefoxitin-fructose agar). Recently *Brachyspira pilosicoli* has been isolated from the feces of weanlings with chronic diarrhea.[12] This agent warrants further investigation as a cause of diarrhea and failure to thrive in young horses. Fecal PCR and

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serology for *Lawsonia intracellularis* should be performed on young horses (including young adults) with hypoproteinemia, unthriftiness, and variable diarrhea.

c. An evaluation for *C. difficile* and *C. perfringens* toxins (with fecal enzyme-linked immunosorbent assays [ELISAs] or a stool cytotoxin assay for *C. difficile*) should be made if the diarrhea is temporally associated with antibiotic administration. Several ELISA kits are available for identification of toxins A (enterotoxin) and B (cytotoxin) of *C. difficile* in feces. A stool cytotoxin cell culture is available for toxin B.[13,14] Toxin B cell culture testing is considered the gold standard.[15]

d. Isolates of *C. perfringens* should be examined for the ability to produce alpha, beta, epsilon, and beta 2–toxins because certain strains may be associated with gastrointestinal disease.[16,17] Type C *C. perfringens* isolates have been associated with the most severe disease in horses and foals and elaborate both alpha and beta toxin. Gene sequences for these toxins are found by PCR once the isolates are cultured. Commercial veterinary diagnostic laboratories now offer PCR for the *C. perfringens* gene sequences directly in horse feces as part of diarrhea PCR panels. In addition, a commercial fecal ELISA is available for detection of alpha-toxin, beta-toxin, and epsilon-toxin in feces directly at the California Animal Health and Food Safety Laboratory (San Bernardino). This allows diagnosis of *C. perfringens*, types A (alpha toxin) and C (alpha and beta toxins). Recently, NetFtoxin-producing type A *C. perfringens* isolates have been linked to severe, necrotizing enterocolitis in foals.[18]

e. Fecal occult *blood* (if positive, see list of causes of melena and blood in feces).

f. Fecal osmolality, sodium, and potassium concentrations (optional). Electrolyte concentration in feces is roughly twice the sodium plus potassium. When this value is much lower than the measured osmolality of the feces, the difference is an osmolar gap caused by osmotically active nonelectrolytes such as lactose, and osmotic diarrhea is confirmed.

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g. Check for sand by placing some feces in a bucket of water or rectal palpation sleeve, mixing thoroughly, and decanting the water or inspecting the bottom for sedimentation of sand. If a radiographic unit with the appropriate power capability is available, abdominal radiographs should be taken to detect the presence and amount of sand. Ultrasound of the ventral abdomen can be used to diagnose the presence of sand, although this requires considerable expertise.

A PCR test for feces is available at University of Minnesota Diagnostic Laboratory at www.vdl.umn.edu and the University of California Molecular Laboratory at www.vetmed.ucdavis.edu/vme/taqmanservice/ (see Chapter 29 for complete list) for detection of *L. intracellularis*, organisms in weanlings and yearlings with diarrhea, weight loss, general malaise, and hypoalbuminemia.[19] Also see serum test described later. Young adult horses can also develop disease from *Lawsonia*.[20]

h. *Rhodococcusequi* can cause diarrhea in 3-week to 6-month-old foals. Diagnostic tests include cultures of transtracheal aspirates, abdominal fluid cytology and culture, abdominal ultrasonography, and ruling out other etiologies of diarrhea. Fecal PCR should also be performed.[21]

i. If all other cultures are negative and an infectious cause of diarrhea is suspected, the feces should be cultured for *Aeromonas* species and *C. perfringens* (see earlier).[22,23]

4. Obtain blood for the following database:

a. Complete blood count (CBC; includes fibrinogen and plasma protein concentrations). Increased fibrinogen concentration indicates inflammation. Decreased protein concentrations indicate protein-losing enteropathy. Thrombocytopenia may indicate a coagulopathy. Neutropenia with or without a toxic, left shift (immature neutrophilia) is often present with infectious and inflammatory causes of acute colitis, indicating SIRS. Increases in packed cell volume (PCV) and red cell mass are often present, indicating hemoconcentration and/or splenic contraction in horses.

b. Acid-base analysis should be performed if the condition is

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acute and the horse is dehydrated or toxic. Although acid-base values are not useful diagnostically in terms of specific etiology, they allow for initiation of proper acid base and electrolyte supportive therapy.

5. Test serum for the following:
    a. Electrolyte (Na, K, Cl, Mg, Ca, HCO_3) concentrations, including ionized calcium.
    b. Serum creatinine and blood urea nitrogen (BUN) concentrations—prerenal azotemia is common as a result of dehydration; check again after rehydration. Acute kidney injury is also common. Serum chemistries should be evaluated for liver and other organ disease. Liver enzymes are frequently elevated during and for a period following acute toxic diarrhea.
    c. Albumin and globulin concentrations; hypoalbuminemia is seen with chronic protein-losing enteropathies such as inflammatory bowel disease (e.g., granulomatous enteritis), phenylbutazone toxicity (right dorsal colitis), hypobiotic cyathostomiasis, *Lawsonia intracellularis* infection, and acute colitis conditions (such as salmonellosis).
    d. Specific immunoglobulin (Ig) A, IgM, and IgG concentrations; immunodeficient individuals may have chronic diarrhea. Specific immunoglobulin concentrations may be altered with lymphoma or multiple myeloma. Elevated globulins may indicate the presence of chronic disease.
    e. PCR for *Neorickettsia risticii* (Potomac horse fever) in whole blood and feces samples. Both blood and feces should be tested, in order to increase the sensitivity of detection. Paired sera for *Neorickettsia risticii* titer following acute diarrhea with fever can also be performed, but this is rarely performed since availability of PCR testing.
    f. Clotting times (prothrombin time [PT] and partial thromboplastin time [PTT] or activated clotting time [ACT]) should be monitored as indicators of coagulopathies such as disseminated intravascular coagulation (DIC) in horses with acute typhlocolitis. Antithrombin concentrations can be

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monitored for the risk of thromboses, particularly in horses with hypoproteinemia.

6. Perform abdominocentesis, especially if signs of colic are present. Evaluate cytology, protein, and fibrinogen values in chronic cases to rule out peritonitis, tumors, and mesenteric abscess.
7. Perform function and absorption tests in chronic diarrhea cases, especially when weight loss is present.
    a. Oral glucose or xylose small intestine absorption tests (see Chapter 32) for chronic cases, particularly if a high index of suspicion of malabsorption exists because of hypoalbuminemia. If tests indicate malabsorption, either biopsy the gut (duodenum through duodenoscopy) or rectum or assess the response to treatment following larvicidal anthelmintic treatment.
    b. Perform liver function tests such as measurement of serum bile acid concentrations if liver involvement is suspected as a result of increased liver enzyme concentrations and/or hypoalbuminemia. Liver enzymes are increased in many cases of enterocolitis and in these cases do not necessarily indicate primary liver disease (see Chapter 33). Secondary liver disease may occur secondary to endotoxemia or altered hemodynamics, as well as cholangiohepatitis.
8. Examine tissue.
    a. Rectal or intestinal (duodenal) biopsy for microscopic examination and fluorescent antibody for immune-mediated diseases (also culture for *Salmonella*). Rectal mucosal histopathology is particularly useful in horses with hypoalbuminemia or weight loss.[24]
    b. Detection of *C. perfringens* beta 2–toxin from type A or beta toxin from type C isolates can be performed by immunohistochemistry of gut mucosa and is diagnostic on biopsy or postmortem specimens.[25] NetF toxin is a recently recognized virulence factor in some type A isolates[18].
    c. Liver biopsy if indication of significant or persistent liver disease, especially in chronic cases.
9. Toxicology.
    a. Blood lead, liver lead, and liver arsenic concentrations can be

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measured if toxicity is suspected.[26]

b. High-pressure liquid chromatography or gas chromatography-mass spectrometry can be used to detect cantharidin (blister beetle toxin) in urine or gastrointestinal contents in endemic areas or when hay is imported from those areas.[23,27]

c. Urine, serum, and gastrointestinal contents can be evaluated for the presence of oleandrin toxins using thin-layer chromatography. Oleander toxicity should be suspected in animals with diarrhea, colic, arrhythmias, and renal disease.[28]

10. Evaluate response to treatment with undiagnosed chronic diarrhea.

a. Alter diet to simple grass hay. Alternatively, a complete pelleted diet can be tried, especially if right dorsal colitis or maldigestion/malabsorption is suspected, as well as in horses that are normal clinically and have normal clinicopathologic results, but that have increased fecal water. Psyllium mucilloid (4 oz), and 1 to 2 cups of corn oil can be added to the daily diets of horses with right dorsal colitis.[29,30]

b. Stop nonsteroidal drugs such as phenylbutazone if right dorsal colitis is a possible cause of loose feces.

c. Transfaunation with fecal (or colon or cecum if available) contents from a healthy animal that has been tested negative for Salmonella and other fecal pathogens can be tried, especially when dysbiosis of the microbiome is suspected.

d. Attempt to classify by rectal biopsy; many changes are nonspecific.

If lymphocytic, lymphoplasmacytic, or granulomatous enteritis is diagnosed: Administer 0.04 to 0.06 mg/kg IM or IV dexamethasone per day, tapering down to 0.02 mg/kg in 5 to 7 days; if response is favorable, continue with 1 to 1.5 mg/kg prednisolone PO per day, taper over 2 months.

Eosinophilic infiltrate: Administer larvicidal anthelmintic dose of fenbendazole plus corticosteroids.

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e. Transfusion with plasma (1 to 2 mL/kg) in young horses 2 to 12 months of age that may need some additional proteins, antithrombin, or immunoglobulin. Synthetic colloids such as hetastarch can be used in animals with reduced colloid osmotic pressure (hypoalbuminemia); check especially if edema is present. Hetastarch (6%) has been used at 10 mL/kg, and this dose should not be exceeded daily because of risks of dose-dependent coagulopathies.[31] Hetastarch has been associated with adverse effects in human patients, including renal injury and mortality in some studies.[9]

f. Horses with Potomac horse fever often respond favorably to systemic treatment with tetracycline.

g. Metronidazole (15 mg/kg PO q 8 h) can be used empirically, especially if an anaerobic overgrowth is suspected, *C. difficile* or *perfringens* has been diagnosed, or when the diarrhea is secondary to antibiotic use.[32] Metronidazole can be administered intravenously in horses with reflux.

Approach to Diagnosis of Diarrhea in Ruminants (for Neonates, See Chapter 20)

1. Take history. Especially note diet, appetite, previous deworming and vaccinations, and whether it is an individual or herd problem. In animals younger than 1 year of age, *Coccidia, Ostertagia,* or other helminths should be strongly considered. Determine if onset is acute or chronic. If chronic, first consider diseases such as parasitism, Johne's disease, copper deficiency (molybdenosis), selenium deficiency, liver failure, and other diseases of individual cows such as bovine leukosis virus (BLV), amyloidosis, heart failure, or uremia.
2. Perform physical examination. Especially note weight loss, fever, systemic signs, rumen activity, and oral lesions. Perform rectal examination. In most acute-onset diseases, vital signs are abnormal and systemic involvement or oral lesions (especially with BVD) may be obvious.
3. Examine feces.
    a. Gross inspection

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   b. Microscopic examination for ova and parasites
   c. Culture for *Salmonella* if animal is febrile or feces appear inflammatory (fibrin or mucus)
   d. Check for fecal occult blood
   e. Culture or other diagnostic test for *Mycobacterium avium* subsp. paratuberculosis, if weight loss is a problem (especially if a herd problem in animals older than 2 years of age)
4. Take rectal scrapings of mucous if weight loss and chronic diarrhea are present.
   a. Make thin smear on glass slide for acid-fast staining for *M. avium* subsp. paratuberculosis. Examine under oil immersion lens
5. Test for BVD if any oral lesions or other relevant clinical signs. See Chapter 32 for available tests.
6. Obtain blood for the following:
   a. Plasma proteins
   b. Fibrinogen
   c. In acute cases, electrolytes and acid-base status
   d. If a herd problem, copper and selenium status
7. Test serum for the following:
   a. BUN
   b. Liver enzymes (γ-glutamyltransferase [GGT] and sorbitol dehydrogenase [SDH])
   c. Albumin and globulin values
   d. Agar gel immunodiffusion (AGID) for BLV (single animals); request gp51 and p24 antibody status (see Chapter 37).
   e. If Johne's disease is suspected, perform ELISA test or other relevant test (see Chapter 32).
8. Perform paracentesis. Paracentesis rules out gross peritonitis, but many false-negatives are possible as a result of focal or fibrinous peritonitis.
9. Perform urinalysis for protein to rule out consideration of amyloidosis or other multisystemic immune-mediated disease. Because ruminants normally have a urine pH of 8 or higher, most dipstick tests will give a trace or a 1+ positive reading for urine protein even when the animal's urine is normal.
10. Examine tissue. Perform rectal, intestinal, or mesenteric lymph node

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biopsy for acid-fast stain for Johne's disease, for culture for *Salmonella*, BVD, and for presence of lymphosarcoma.

11. Perform feed analysis (herd problem only); check copper, molybdenum, and selenium levels.
    a. Toxins suspected (e.g., mercury, arsenic)
12. Tap abomasum for increased pH; rule out type II ostertagiasis.
13. Perform necropsy (herd problem only).
    a. Pick severely affected individual to examine thoroughly.

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Colic

K. Gary Magdesian • Bradford P. Smith

Colic is defined as the manifestation of visceral abdominal pain. Colic may be the result of nongastrointestinal pain such as urinary tract obstruction (Boxes 7.6 and 7.7). This section discusses colic of gastrointestinal origin. Pain may be acute, chronic, or recurrent. Gas distention or recognizable organic problems such as displacements are most frequently associated with acute colic. Five basic causes of colic in large animals are as follows:

Box 7.6

Gastrointestinal Causes of Colic in Horses[a]

Common Causes

Accumulation of intestinal, cecal, or colonic gas
Hypermotility and intestinal spasms
Feed impaction, constipation
Meconium impaction (newborn)
Gastric ulcers (foal)

Less Common Causes

Thromboembolism
Intestinal foreign body (sand; enterolith; phytobezoar)
Volvulus of small intestine
Pedunculated lipoma with bowel strangulation
Hernia, inguinal, epiploic, umbilical, diaphragmatic
Nephrosplenic ligament bowel entrapment
Ascarid impaction
Massive strongyle infection
Gastric dilation
Anterior enteritis (duodenitis or proximal jejunitis)

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Enteritis, impending or active
Peritonitis
Parasympathomimetic drugs
Irritant cathartics
Necrotizing enterocolitis
Psychogenic colic
Rectal tear
Volvulus or displacement of large bowel
Rupture of stomach or intestine
Ileus
Intussusception

Uncommon Causes

Abdominal adhesions
Intramural hematomas of stomach or intestine
Stenosis or stricture of bowel lumen
Botulism
Tetanus
Potomac fever
Exhaustion
Anaphylaxis
Rhodococcus equi, gut abscesses
Cribbing or wind sucking
Abdominal fibroma
Segmental ischemic necrosis following mesocolic tearing
Equine viral arteritis
Anthrax with bleeding
Malignant edema (*Clostridium* species)
Malignant mesothelioma
Gastric or intestinal tumor
Atropine
Vitamin K3 deficiency (moldy sweet clover)

Toxins

(See also toxins listed under Diarrhea)
Cantharidin toxicity
Dioxin
Trichloroethylene-extracted feed toxicity
Warfarin (dicumarol)
Herbicides
Lead
Nitrophenyl urea (vacor)
Phenylbutazone or other nonsteroidal antiinflammatory drugs
Poison plants (many of those that produce diarrhea also produce colic; see plant toxins listed under Diarrhea)
African horse sickness (exotic)
Grass sickness (exotic)

[a]See additional lists at www.vet.cornell.edu/consultant.

Box 7.7

Causes of Colic in Ruminants[a]

Common Causes

Increased intestinal gas
Intussusception
Torsion or volvulus of the mesenteric root
Peritonitis
Intestinal foreign body or obstruction
Urolithiasis
Ruptured bladder
Acute pyelonephritis
Abomasal torsion
Abomasal ulcer
Cecal dilation or volvulus
Severe bloat

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Less Common Causes

Cystitis or urinary tract disease
Abomasal bloat (neonates)
Uterine torsion or rupture
Hernia
Parturition, impending
Hypermotility and spasms of gut
Feed impaction
Right displaced abomasum
Acute traumatic reticulitis, abomasitis, or duodenitis
Acute liver disease
Vagal indigestion
Hemorrhagic bowel syndrome
Atresia coli (neonates)

Uncommon Causes

Rabies
Rectal tear
Rectal prolapse
Diaphragmatic hernia
Grain overload
Water intoxication
Winter dysentery
Ovarian abscess
Fat necrosis
Cholelithiasis
Intestinal adhesions
Enterotoxemia
Ileus
Intestinal strangulation
Inversion of uterine horn
Malignant edema
Malignant mesothelioma
Ruptured uterine artery

Intestinal neoplasia
Aortic, iliac, or femoral thrombosis
Anaphylaxis
Renal cysts
Ruptured prepubic tendon
Vaginal laceration
Torsion of descending colon
Rinderpest (exotic)[b]

Toxins

Plant poisonings (many of those that cause diarrhea also produce colic; see plant toxins listed under Diarrhea)

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[a]See additional lists at www.vet.cornell.edu/consultant.

[b]Rinderpest was a cause of colic in ruminants until 2011, when it was eradicated worldwide.

- Distention of gut with fluid, gas, or ingesta
- Pulling on the root of the mesentery (mesenteric tension)
- Ischemia or infarction
- Deep ulcers in the stomach or bowel
- Peritoneal pain (peritonitis)

Signs of colic in the horse include restlessness, lying down and getting up, groaning, grunting, rolling, sweating, kicking at the abdomen, or suddenly dropping to the ground in pain. Anorexia and depression often accompany these signs. Horses may develop hypovolemic or endotoxic shock characterized by tachycardia with weak pulse quality and prolonged capillary refill time, cold extremities, and bright red (vasodilatory phase) followed by dark or pale (vasoconstrictive phase or low cardiac output state) mucous membranes if the

problem is severe and affects cardiovascular integrity.

Evidence of shock is usually present only when the disease condition is severe and involves ischemic or infarctive disease (volvulus, torsion, thromboembolism) or advanced visceral distention (extreme flatulence, impaction, or dilation). Foreign bodies such as sand or enteroliths in the large colon may result in low-grade recurrent colic. When an enterolith is passed into the transverse colon where it obstructs the bowel, signs of complete obstruction and acute colic ensue. These signs are manifestations of visceral pain, mediated by the sympathetic nervous system. External palpation and pushing on the abdomen of adult horses do not usually elicit pain unless the affected inflamed or dilated viscus is contacted.

In contrast, parietal pain associated with peritonitis is sometimes responsive to external palpation. Whereas the animal with visceral pain shows active signs of colic, the animal with parietal pain is usually reluctant to move and has a splinted abdomen. Acute peritonitis occurs within minutes after rupture of the stomach or perforation of an ulcer as a result of immediate irritation of serosal surfaces by the acid contents, whereas with rupture of the colon or rectum it may take several hours or more before peritonitis is clinically apparent.

Ruminants exhibit colic less frequently than horses, probably because of a higher threshold for pain and because dietary shifts principally affect the rumen; thus intestinal gas pains occur less frequently. Colic with visceral pain (including urinary tract) is manifested by grinding the teeth (odontoprisis or bruxism), grunting or groaning, treading with the hind feet, kicking at the abdomen, restlessness, repeatedly lying down and getting up, anorexia, and depression. With parietal pain caused by peritonitis, ruminants demonstrate abdominal pain by arching the back, splinting, and exhibiting pain on deep palpation of the area. These signs are seen most commonly with traumatic reticuloperitonitis and perforating abomasal ulcers; rarely are these diseases associated with the colic signs described previously.

Diagnosis and Management of Colic in the Horse (for Neonates, See Chapter 17)

1. Take history. Because colic is a common problem in horses, mild to moderate degrees of abdominal pain are often initially treated symptomatically with analgesics and/or laxatives before major diagnostic efforts are undertaken. Most colic of mild to moderate

severity responds favorably to symptomatic treatment. In general, severe pain or pain that is unresponsive to analgesics indicates a more serious condition for which more aggressive medical management or surgical correction may be indicated. Recurrent mild-to-moderate colic may be an indication of a more serious problem such as bowel entrapment or displacement, thromboembolism, internal abscess, enterolith, sand or other foreign body, tumor, gastric ulcers, hypobiotic cyathostomiasis, *Strongylus vulgaris* larval migration, heavy burden of ascarids, abdominal adhesions, cholangiohepatitis, biliary stones, strictured bowel, or urinary tract disease.

2. Perform physical examination. Intestinal causes of colic can often be differentiated from colic associated with other organ systems (Box 7.8) by physical examination findings and laboratory data. Although extraintestinal origins of acute colic are relatively uncommon in the horse, they include abdominal abscesses, tumors, cholelithiasis or cholestatic disease, and genitourinary tract disease and can be recurrent. It is important to note the presence or absence of normal intestinal borborygmi and whether or not feces are being passed in determining whether the problem is extraintestinal. Careful auscultation of the thorax should be performed to evaluate for the presence of diaphragmatic hernias or pleural disease. The testicles should be palpated on all stallions to screen for scrotal hernias or testicular torsions. Rectal examination findings often help to determine anatomic location within gut or other site. Abdominal tumors, abscesses, and other masses may be palpable. Although mild to moderate chronic intermittent colic may be of extraintestinal or intestinal origin, most cases of severe, unremitting colic indicate gut involvement, often with anatomic displacement or ischemia.

Box 7.8

Extraintestinal Causes of Colic in Horses

Common Causes

Mesenteric abscess
Ovarian tumor, abscess, or hematoma
Parturition
Acute hepatitis (massive necrosis) or hepatic lipidosis
Diaphragmatic hernia

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Ruptured bladder (foal)
Uterine torsion

Less Common Causes

Urinary tract or renal disease, including urolithiasis
Pleuritis or pericarditis (referred pain)
Retained placenta
Uterine rupture or retroflexion
Spermatic cord thrombosis or torsion
Hypocalcemia

Uncommon Causes

Perirectal abscess
Pheochromocytoma
Purpura hemorrhagica
Biliary atresia
Vaginal or vulvar tear
Cholelithiasis
White muscle disease
Atypical myopathy
Rabies
Rupture of prepubic tendon
Splenitis, splenic abscess, splenomegaly
Cauda equina neuritis with retention of feces or urine

3. Ultrasound and radiology. Ultrasound may help in locating masses, adhesions, or enlarged liver (see Abdominal Ultrasonography, Chapter 32). It may also be helpful in the diagnosis of gastrointestinal disease including nephrosplenic entrapment of the large colon, right dorsal displacement, and small intestinal distention. Detection of sand from the ventral abdomen may be possible. Ultrasound can be particularly useful in foals and small ruminants because of their size. Radiology can also be useful in detecting enteroliths or sand in adult horses and in some gastrointestinal conditions of foals, such as meconium impaction or sand enteropathy, provided powerful units are available. Rarely is radiology useful in diagnosing the cause of colic in ruminants, except for urethrographs in sheep and goats to locate a urethral stone.
4. Examine feces. Gross examination of feces should be performed. The presence of sand can often be detected by mixing feces with water in a bucket, then pouring off the water and looking for sediment. If no feces are passed, a more serious condition is usually indicated, particularly if intestinal sounds are absent.
5. Use laboratory aids. Laboratory aids of immediate benefit in diagnosis and management include measurement of PCV and plasma protein

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concentration to aid in assessing hydration and vascular integrity, as well as an abdominal paracentesis to evaluate abdominal fluid grossly and microscopically. Pain and excitement alone can increase the PCV in horses, but some studies indicate that there is a correlation of increased PCV (>55%) and nonsurvival in colic cases. Plasma proteins are not increased acutely unless blood volume is decreased through shifts in compartmental distribution of body fluids. In colic cases these fluid shifts usually mean that an increased and abnormal amount of extracellular fluid is in the gut lumen, a “third space” where it is not available for maintaining blood volume. Blood lactate concentration measurement has become routine in evaluation of horses with acute abdominal disease. It is useful in monitoring as an end point to fluid therapy, as well as of systemic inflammation and cell metabolic health. Some studies have suggested a prognostic role of lactate in horses with colic, although there is marked overlap between survivors and nonsurvivors. An increase in peritoneal lactate concentration over time has been predictive of strangulating lesions in horses with colic.[33]

6. Abdominal fluid is normally present in small volume (a few drops to 50 mL); is clear and colorless to yellow; and has a total protein concentration below 2.5 g/dL, specific gravity less than 1.015, little or no fibrinogen (<100 mg/dL), and fewer than 5000 white blood cells (WBCs) per microliter. Increases in these parameters often indicate inflammation on serosal surfaces (including colitis), strangulating lesions or ischemic compromise in colic cases. Comparisons of abdominal fluid glucose with serum glucose (>50 mg/dL difference is abnormal) and evaluation of abdominal fluid pH, lactate (as compared with blood lactate), and lactate dehydrogenase (LDH) concentrations can aid in the diagnosis of septic peritonitis.[34] Grossly, fluid changes to cloudy yellow, then to blood-tinged with fibrin clots, and finally to black in color as bowel necrosis and hemolysis of extravasated red blood cells (RBCs) occur. Increased levels of peritoneal fluid protein concentrations are consistently found in anterior enteritis (duodenitis and proximal jejunitis) and often disproportionate to the increase in white blood cell concentration; in these cases it therefore provides a useful differential aid, although this finding is nonspecific and observed with other conditions, such as in cantharidin poisoning. Increased protein levels are present in peritonitis but are accompanied by increased numbers of

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neutrophils as well. If peritoneal fluid is grossly contaminated with feed material, rupture of a viscus should be considered. Another peritoneal tap in a different location should be undertaken if the possibility of bowel penetration during paracentesis cannot be ruled out. It is not necessary to have abnormal peritoneal fluid before consideration of surgical correction of colic is contemplated. Recently, abdominal fluid lactate has been shown to be predictive of intestinal ischemia secondary to strangulating obstruction in colic cases and may aid in early detection of intestinal strangulation, rupture, and septic peritonitis.[35]

7. Plasma fibrinogen, as well as peripheral leukocyte counts, can aid in the differentiation of enterocolitis or anterior enteritis from strangulating lesions. Serum electrolyte concentrations and acid-base status are important from a therapeutic standpoint. Serum biochemistries including liver enzymes, creatinine, and BUN are important in evaluating for liver and renal compromise. Hyperglobulinemia may be indicative of chronic disease.
8. Evaluate response to treatment. The approach to diagnosis of colic signs is often tied in with management because if the animal's pain cannot be alleviated, surgical intervention and specific diagnosis of displacements, torsions or volvulus, internal hernias, masses, and adhesions are the next steps. The initial diagnosis considers the history of deworming and feeding. The findings of the physical examination including rectal examination and evaluation of the degree of pain determine whether additional laboratory workup is indicated. In many cases with mild to moderate pain and no evidence of shock, standard treatment includes parenteral administration of an analgesic agent such as flunixin meglumine (as long as the patient is hydrated) or butylscopolamine (see Chapter 3) and oral administration of a mild laxative such as mineral oil (4 to 8 mL/kg). When a nasogastric tube is passed, the stomach should be checked for reflux and decompressed as needed. The pH of the gastric reflux may indicate primary gastric dilation if acidic, or small intestinal blockage or ileus if alkaline. Dark brown, foul-smelling, and alkaline reflux is often associated with anterior enteritis (duodenitis and proximal jejunitis). If a significant amount of reflux is present, oral medications should be withheld. If cardiovascular function is impaired (poor mucous membrane color and capillary refill, weak pulse, cold extremities, impending shock), balanced, polyionic, and isotonic

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crystalloid fluids should be given intravenously at a rate of 10 to 20 mL/kg boluses until signs of shock abate or plateau. In addition, 4 mL/kg hypertonic saline can be administered as a rapid but transient treatment of shock. Large amounts of apparently painful gas that is auscultable in the right flank can be tapped and drawn off with cecal trocharization, although the risk for peritonitis should be considered and this technique should be reserved for when surgical exploration is not an option or is delayed. The principles of colic management include 1) control of pain, 2) relief of distention, 3) relief of obstruction, and 4) treatment of shock.

9. Perform exploratory surgery. In making a decision concerning management of colic, it is important to separate impending enteritis and peritonitis from bowel disease requiring surgical intervention. Anterior or proximal enteritis can result in prolonged moderate pain and requires constant or frequently repeated analgesic administration and gastric decompression of the foul-smelling, dark reddish-to-brownish stomach contents. However, pain often subsides and is replaced with depression after gastric decompression in horses with anterior enteritis, whereas horses with strangulating lesions often remain in pain. The presence of fever or decreased total WBC count (with neutropenia) may be an indication of impending or ongoing enteritis, in which case surgery may not be indicated.

   Surgery is indicated in the following situations:

   a. Pain is severe and intractable or nonresponsive/poorly responsive to analgesics.
   b. Pulse is weak and rate is over 70 beats/min, and oleander or other cardiotoxicity and acute enterocolitis are ruled out.
   c. Perfusion is poor, as evidenced by cold extremities, off-color mucous membranes, and poor capillary refill, and enterocolitis or toxicities are ruled out.
   d. No gut sounds are auscultated (a lack of fecal production).
   e. Bowel is markedly distended on rectal palpation or abdominal ultrasound.
   f. Large volumes of yellowish alkaline gastric reflux are present.
   g. Abdominocentesis indicates damaged bowel (blood tinged, increased protein, increased WBCs). When proximal enteritis

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remains a possibility, surgery should be avoided unless it is indicated to decompress bowel.

Surgery may be contraindicated in the following situations:

a. Fever
b. Neutropenia or marked neutrophilia
c. Severe icterus or marked enzyme abnormalities indicating primary liver disease
d. Foul-smelling, brownish-red gastric reflux characteristic of proximal enteritis (duodenitis/jejunitis), especially when removal of reflux results in discontinuation of signs of pain
e. Evidence of an extraintestinal cause not amenable to surgical correction (such as severe pyelonephritis) or hyperammonemia
f. Colitis, enterocolitis, or diarrhea
g. Abnormal behavior or neurologic signs (look for neurologic diseases and recent fluphenazine administration, and check blood ammonia concentrations)

Diagnosis and Management of Colic in Ruminants

1. Take history. Colic in neonates is most often associated with increased abomasal or intestinal gas and is discussed in Chapter 20. Perforating ulcers are not uncommon as a cause of colic in calves 1 to 6 months of age. It should be determined whether the onset of colic was acute or whether the colic is chronically recurrent. Few diseases cause recurrent colic in ruminants. Urolithiasis is the most common cause of colic in

male or neutered male goats and sheep and occurs under varied dietary and environmental conditions. Urolithiasis in cattle occurs most frequently in bulls or steers eating high-grain diets, but silicate stones can occur in very young animals and animals on pasture diet.

2. Perform a physical examination. Take vital signs; with torsion or severe peritonitis, shock signs such as rapid heart rate (>90 beats/min), cold extremities, and weakness may be seen. Tympany can be detected by simultaneous auscultation and percussion. Such causes of colic as cecal dilation, bloat, free gas in the peritoneal cavity, and severe abomasal dilation can be diagnosed in this way (see Figs. 1.3 to 1.5). Rectal examination detects such abnormalities as gas in the cecum, uterine abnormalities, urinary tract disease, and intussusception. Observe animal urinating to rule out obstructive urolithiasis. Ultrasound examination of the abdomen is also useful (see Abdominal Ultrasonography, Chapter 32).
3. Examine feces. Observe grossly; intussusception usually has scant dark red (almost black) feces. Black tarry feces may also be seen with bleeding abomasal ulcer of some duration. Scant feces are seen with cecal dilation or displacement.
4. Check preputial hairs and urethral process for sediment and stones. Grit on the preputial hairs is often associated with urolithiasis. Observe animal urinating and check urine for abnormalities. Rule out pyelonephritis. Radiology and ultrasound can be useful in sheep and goats when urolithiasis is a consideration. Ultrasound can detect a distended bladder, and stones may sometimes be detected. Radiology (lateral view) may detect a stone in the urethra or stones in the bladder. A contrast urethrogram may also be diagnostic.
5. Perform paracentesis to look for peritonitis caused by perforated abomasal ulcer, serosal devitalization, intussusception, or ruptured bladder. Interpret as earlier for horses, except that normal peritoneal fluid protein concentration can go as high as 5 g/dL in ruminants.
6. Other laboratory aids such as CBC and clinical chemistries are seldom diagnostic in ruminant colic. If grossly abnormal, they may be grounds for formulating a poor prognosis. Intussusception may be associated with neutrophilia (as well as dark feces and colic) in cases where peritonitis is occurring.
7. Symptomatic treatment of colic includes analgesics and, if heart rate is

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over 90 beats/min, intravenous fluid therapy with a sodium-containing fluid. Take a blood sample for electrolytes and acid-base status before initiating fluid therapy.

8. Surgical exploration is indicated if colic is persistent, abdominal distention occurs, the heart rate is over 100 beats/min, feces are scant (especially those that are dark red and indicative of intussusception), there are pings indicating abomasal or cecal displacement or torsion, or the peritoneal fluid indicates bowel devitalization (blood-tinged fluid with elevated protein and WBCs). If surgical exploration is indicated, an important consideration is whether the animal will remain standing under local anesthesia during surgery. It is often best to perform abdominal surgery on animals with colic in left lateral or dorsal recumbency, aided by sedation and restraint, to avoid sudden collapse when painful surgical manipulations are performed. If the left lateral position is selected, use padding to raise the hip and shoulder so that the abdominal viscera can sit in a depression.

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Melena

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Melena (dark, tarry feces) is caused by blood in the lumen of the stomach or proximal intestinal tract, resulting in black (digested) blood appearing in the feces (Boxes 7.9 and 7.10). Usually blood is a result of a bleeding ulcer in the stomach or abomasum but may also result from ingestion, oral or pharyngeal bleeding, or coughing up blood that is then swallowed. In ruminants the presence of dark red feces from an intussusception is the main differential to be considered. Blood must stay in the intestinal tract for hours before the hemoglobin is altered and turns black. Small amounts of hemoglobin can be detected by using one of the tests for occult blood. In general, fairly large volumes of blood (1 to 2 L) are required to produce a positive fecal occult blood test in the horse (Carlson G, personal communication, 1990). A 24- to 48-hour time period is necessary for orally administered blood to reach the rectum in the horse. In ruminants, smaller volumes of blood are necessary to produce a positive fecal occult test, and a faster transit time is expected (Carlson G, personal communication, 1990).

Box 7.9

Causes of Melena in Horses

Common Causes

Gastric or duodenal ulcer
Gastric squamous cell carcinoma
Coughing up and swallowing blood

Less Common Causes

Phenylbutazone toxicity (nonsteroidal antiinflammatory drugs [NSAIDs])
Purpura hemorrhagica
Gastroenteritis with bleeding

Warfarin toxicity or other coagulation disorder
Colonic hematomas
Disseminated intravascular coagulation with mucosal hemorrhage
Anterior or proximal enteritis (duodenitis or proximal jejunitis)
Arsenic toxicity
Hepatic failure with hemolysis
NSAID toxicity

Uncommon Causes

Lupus erythematosus
Factor VIII deficiency, hemophilia A
Histoplasmosis
Hemangiosarcoma
Snake bite

Box 7.10

Causes of Melena in Ruminants

Common Causes

Abomasal ulcer
Intussusception

Less Common Causes

Lung abscess with ruptured blood vessel
Oak toxicity
Coccidiosis
Gastroenteritis with bleeding
Arsenic toxicity
Ingestion of blood after parturition
Intestinal parasites
Toxicity from nonsteroidal antiinflammatory drugs

Abomasal torsion or volvulus
Hemorrhagic bowel syndrome

Uncommon Causes

Duodenal ulcers
Hemophilia A, factor VIII deficiency
Bacillary hemoglobinuria
Sulfur toxicity
Warfarin poisoning or other coagulation disorder
Snake bite
Bovine viral diarrhea
Malignant catarrhal fever
Winter dysentery
Narthecium asiaticum maxim poisoning (exotic)

In approaching a diagnosis, rule out pulmonary, oral, or pharyngeal bleeding. Bleeding of gastrointestinal origin can be determined to be caused by mucosal disease or full-thickness bowel disease (such as an intussusception or neoplasia) by examining peritoneal fluid for abnormalities. Abnormalities in peritoneal fluid are usually present in the case of serosal involvement. Bleeding abomasal ulcers are probably the leading cause of melena in ruminants. They can be silent except for the dark feces and weakness if severe anemia develops. In older horses, gastric squamous cell carcinoma is a frequent cause of gastric hemorrhage. Significant bleeding is much less common in foals and calves with gastric ulcers, and melena is rare in foals and calves with gastric ulcers.

Consideration should be given to whether or not the melena is the result of clotting abnormalities associated with such diseases as DIC or warfarin poisoning. In cattle with colic and dark red-to-black feces, intussusception should be considered likely.

When severe anemia develops, there is evidence of blood loss because the decrease in PCV and RBCs is accompanied by a decrease in plasma proteins. Nonspecific therapy for melena consists principally of blood transfusions in life-threatening cases. Sudden, massive gastric or abomasal bleeding may result in anemia and collapse before melena has appeared.

In the foal, gastric ulcers may be treated with histamine-2 (H2) blockers such

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as ranitidine or cimetidine, or with hydrogen pump blockers. The H2 blockers are probably less effective in ruminants. Their benefit in ruminants with abomasal ulcers is not well understood at present. Drugs such as the hydrogen pump blocker omeprazole are useful and potent gastric pH effectors. Therapy with protectants such as sucralfate (which coats the ulcer) is a viable and clinically useful therapy in the horse. In ruminants, orally administered protectants and antacids are so diluted by the time they reach the abomasum that they are probably of limited benefit.

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Blood, Fibrin, and/or Mucus in Feces (Dysentery)

Bradford P. Smith

Bloody diarrhea is termed *dysentery.* The presence of fresh blood or clots in the feces is termed *hematochezia* and is the result of bleeding into the distal intestinal tract. Occasionally blood from the female reproductive tract may appear in or on the feces. Fibrin indicates severe inflammatory bowel disease. Fibrin appears as casts, chunks of yellow-gray material, or mucosa-like sheets. Mucus in feces increases with inflammatory bowel diseases such as salmonellosis. It is often seen when fecal volume is small in animals that are anorectic, in which case the feces are often coated with mucus. This mucous coating can become obvious in the horse and is not a sign of bowel disease in this case.

Frank blood in feces without diarrhea and other evidence of gastrointestinal dysfunction or systemic illness may be a result of a bleeding disorder, a traumatic foreign body, rectal examination trauma, sadistic rectal trauma, or rectal trauma in a mare from a stallion penetrating the rectum (Boxes 7.11 and 7.12). Many of the diseases listed as causes of melena may also result in gastrointestinal hemorrhage and are therefore listed in both places. If the bleeding is in the distal gastrointestinal tract, fresh blood may be seen in the feces. With diseases midway down the tract, such as intussusception, fecal material is dark red and may appear black until a sample is examined closely and spread on a white surface.

Box 7.11

Causes of Blood, Fibrin, or Mucus in Feces of the Horse

Common Causes

Foreign body

Rectal tear or trauma
Intussusception
Blister beetle (cantharidin) toxicity
Colitis, unknown cause
Salmonellosis

Less Common Causes

Purpura hemorrhagica
Small strongyle infection (cyathostomiasis)
Colorectal polyps
Eosinophilic gastroenteritis
Acorn or oak poisoning
Arsenic toxicity
Organophosphate toxicity
Warfarin poisoning or other coagulation disorder
Mycotoxicoses
Besnoitiosis (globidiosis) (exotic)

Box 7.12

Causes of Blood, Fibrin, or Mucus in Feces of Ruminants

Common Causes

Foreign body
Intussusception
Coccidiosis
Salmonellosis

Less Common Causes

Rectal tear or trauma

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Rectal examination trauma
Volvulus, root of mesentery
Malignant catarrhal fever
Enterotoxemia
Bovine viral diarrhea
Arsenic toxicity
Abomasal torsion
Warfarin poisoning or other coagulation disorder
Castor bean *(Ricinus)* poisoning
Tung tree *(Aleurites)* poisoning
Solanum (nightshade, potato) poisoning
Sesbania (rattlebox) poisoning
Bracken fern

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Abdominal Distention and Constipation

Bradford P. Smith

Abdominal distention may be caused by feed, fluid, gas, feces, or a neoplasm (Boxes 7.13 and 7.14). Pregnancy or extreme obesity may also result in an enlarged abdomen. The physical examination should determine which of these is the most likely cause. Often in ruminants the distention can be seen as primarily left sided, right sided, or bilateral. For example, bloat in ruminants results in a characteristic high left-sided gas distention. It may be primary or associated with vagal indigestion, tetanus, or hypocalcemia. With vagal indigestion the rumen becomes enlarged and fluid filled, often giving a pear shape to the abdomen as it is viewed from the rear, or a pear shape on the right and an apple shape on the left (“papple” shape) if some degree of bloat is also present. Hypocalcemia and hypokalemia contribute to ileus and may result in constipation and abdominal enlargement. In sheep, abomasal impaction and enlargement associated with abomasal emptying defects can result in an enlarged abdomen with decreased food intake. When a mass (most commonly an abscess, a tumor, or fat necrosis [cattle only]) obstructs fecal passage, abdominal enlargement can become severe. With obstructive disease, some degree of colic is almost always present. A ruptured bladder results in a large fluid-filled abdomen, but constipation is not an obvious sign.

Box 7.13

Causes of Abdominal Distention and Constipation in Horses

Common Causes

Ileus impaction
Intestinal foreign body such as enterolith (see Colic)
Peritonitis
Intestinal obstruction, impaction, or gas (see Colic)
Necrotizing enterocolitis (foals)

Torsion or volvulus of gut (see Colic)
Sudden decrease in exercise

Less Common Causes

Pregnancy
Pelvic mass (abscess, tumor)
Cecal tympany (see Colic)
Hernia, obstructive (see Colic)
Intussusception (see Colic)

Uncommon Causes

Anticholinergics
Opiates
Intrinsic colonic nerve dysfunction
Anorectal pain
Perineal hernia
Hypokalemia
Tetanus
Hypocalcemic tetany
Intramural hematomas on gut
Propylene glycol toxicity
Grass sickness (exotic)

Box 7.14

Causes of Abdominal Distention and Constipation in Ruminants

Common Causes

Pregnancy
Obesity

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Vagal indigestion
Grain overload
Bloat
Ileus
Cecal volvulus or dilation with ileus
Peritonitis, traumatic or other cause
Fat necrosis involving rectum or colon
Ruptured bladder (uroperitoneum)
Intestinal obstruction
Pelvic mass (abscess, tumor)
Hypocalcemia
Omasal obstruction or foreign body

Less Common Causes

Anticholinergics
Intussusception
Abomasal volvulus
Abomasal impaction
Tetanus
Abomasal bloat (calf)
Necrotizing enterocolitis (calf)

Uncommon Causes

Hydrops
Ascites
Torsion of descending colon
Internal herniation, especially diaphragmatic hernia involving reticulum
Displacement of intestine to left of rumen
Stenosis of duodenum
Adhesions of intestine
Bovine leucosis
Intestinal volvulus
Atresia of anus, colon, rectum, or intestine
Abomasal adenocarcinoma

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Omental bursitis
Perforated abomasal ulcer
Zinc toxicity
Crude oil toxicity
Diesel fuel toxicity
Propylene glycol toxicity
Larkspur poisoning

The most common causes of decreased fecal output in ruminants and horses are decreased feed intake and dehydration. In such cases the animal will appear gaunt or have a relatively empty abdomen or rumen. Horse feces in cases of prolonged transit are often covered with a layer of tenacious, thick, yellow mucus. When a functional obstruction (ileus, vagal indigestion) or physical obstruction (impaction, foreign body, displaced intestine, fat necrosis) occurs as a cause of constipation, the abdomen is more likely to appear normally full or to become distended. Rectal examination is of great help in determining whether a mass or an obstruction exists because loops of distended small bowel can sometimes be palpated in the latter case.

Radiographs and ultrasound may be valuable to help determine the cause of abdominal distention in foals, calves, and small ruminants. Increased gastrointestinal gas may result in abdominal distention. Abomasal bloat and necrotizing enterocolitis in young animals may best be confirmed with lateral abdominal radiographs.

Dehydration may also result in dry feces but not in abdominal enlargement. When constipation is present and feces are drier than normal, rehydration and correction of hypocalcemia, hypokalemia, and any existing acid-base abnormalities are important parts of correction of the constipation. Other nonspecific therapies for functional constipation include laxatives, cathartics, and cholinergic drugs. When treating constipation, which is usually a secondary problem, it is important to simultaneously attempt to diagnose the primary disease.

In ruminants, when abdominal distention involves the rumen or is caused by pregnancy or obesity, colic is absent. When abdominal distention is the result of obstruction from the pylorus distal, colic is usually present. Abdominal distention and constipation are frequently accompanied by colic in the horse, regardless of anatomic site involved (review the approach to colic).

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Regurgitation and Vomiting

Bradford P. Smith

Regurgitation is the reflux of esophageal, gastric, or rumen contents into the mouth or nose. This may be caused by malfunction of the esophagus or, in ruminants, as part of the normal physiology for rechewing ingested plant fiber (Boxes 7.15 and 7.16). Vomiting is a coordinated, centrally (medulla) mediated event, usually preceded by nausea (inappetence), increased salivation, or retching. In vomiting the abdominal musculature contracts, the diaphragm is pushed caudally and the cardia relaxes. The medullary vomiting center can be stimulated by visceral afferent stimuli or through the chemoreceptor trigger zone. Most toxins and drugs that cause vomiting act by directly affecting the chemoreceptor trigger zone. Other than with toxins, most cases of feed returning to the mouth in large animals are examples of regurgitation rather than true vomiting. Vomiting is unusual in both ruminants and horses.

Box 7.15

Causes of Regurgitation and Reflux in Horses

Common Causes

Choke
Damaged esophagus, foreign body, or diverticulum
Megaesophagus
Foreign body in pharynx, trachea, or nose
Guttural pouch infection and pharyngeal paresis with nerve involvement
Gastric dilation, impaction
Gastric rupture

Less Common Causes

Snake bite
Tetanus

Tick paralysis
Anterior enteritis (duodenitis or proximal jejunitis)
Gastric stenosis, ulcers
Hydrocephalus, meningitis, encephalitis
Central nervous system trauma
Polyneuritis
Peritonitis
Persistent right aortic arch
Grass sickness (exotic)

Toxins

Phosphorus
α-Naphthylthiourea (ANTU)
Cyanide
Herbicides
Arsenic
Lead
Nitrophenyl urea (vacor)
Organochlorine

Plant Toxins

Oleander
Castor bean
Death camas (*Zigandenus* species)
Algae
Heath *(Ericaceae)*

Box 7.16

Causes of Regurgitation and Vomiting in Ruminants

Common Causes

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Esophageal trauma or foreign body
Oral or pharyngeal foreign body, abscess, or trauma
Salt toxicity (water deprivation/access)
Tumor, papilloma, or other mass in rumen or esophagus
Toxins and poisonous plants

Less Common Causes

Megaesophagus
Hiatal or diaphragmatic hernia
Esophageal diverticulum
Esophageal reaction to *Hypoderma lineatum* (B)
Hydrocephalus
Meningitis, meningoencephalitis
Central nervous system trauma
Hypomagnesemia

Uncommon Causes

Intestinal neoplasia
Traumatic reticulitis
Tick paralysis
Tetanus
Bluetongue (O)
Peritonitis
Persistent right aortic arch
Pseudorabies
Rift Valley fever (exotic)

Toxins

Methanol or ethanol
Acute oral copper
Phosphorus
Arsenic
Nitrates

Crude oil
Diesel fuel
Snake bite

Plant Toxins

Solanum species
Melia (chinaberry)
Larkspur *(Delphinium)*
Cyanogenic plants
Nitrate accumulators
Death camas (*Zigandenus* species)
Castor bean
Oleander
Cocklebur
Tremorgenic toxins
Heath *(Ericaceae)*
Helenium (sneezeweed, bitterweed)
Hymenoxys (rubberweed, bitterweed)
Veratrum (hellabore)
Amianthium (stagger grass)
Haplopappus (burroweed)
Psilostrophe (paper flowers) (O)
Agrostemma githago (corn cockle)
Kalmia (laurel)
Kikuyu grass, *Pennisetum clandestinum* (exotic)
Ibaraki disease (exotic)
Geigeria (exotic)
Yellow-wood (exotic)

B, Bovine; *O*, ovine.

Although regurgitation is a normal phenomenon in ruminants, it is unusual to find excessive regurgitation as a sign of disease. Physical blockage of ruminoreticular outflow by a foreign body, warts, actinobacillosis, granulomas, or diaphragmatic hernia can cause rumen distention and excessive regurgitation

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after eating. An esophageal foreign body can cause irritation and result in regurgitation. Animals with facial paralysis may drool feed and saliva on the affected side; this should be differentiated from animals with excessive or abnormal regurgitation. Vomiting or forced regurgitation in ruminants is rare and is seen principally with the toxins listed.

Horses have such a marked tone at the cardiac sphincter that vomiting occurs only when extreme intragastric pressures develop, usually in small intestinal obstructive diseases or proximal enteritis. Vomiting in the horse thus often occurs with gastric rupture or terminally with shock. Stomach contents are usually pH 5 or below. Because it is a terminal event, vomiting in the horse is often grounds for rendering a poor prognosis. Abdominocentesis should be performed on a horse after vomiting to rule out gastric rupture. To avoid this sequence of events, decompression using a nasogastric tube should be performed in any horse with evidence of gastric distention (see approach to colic). Regurgitation and vomiting in horses most commonly occur from the nose rather than into the mouth because of the anatomy of the soft palate. With choke (esophageal obstruction), esophageal regurgitation from the nares consists of mixed feed and saliva.

In foals a few weeks to several months of age, milk returning from the nares is often associated with gastric ulceration, along with signs of colic, lying in dorsal recumbency, hypersalivation, and champing movements of the mouth. In advanced cases with duodenal ulcers, pyloric outflow can be obstructed by scarring, resulting in more pronounced signs. Foals 1 to 6 months of age are most susceptible to gastric ulceration.

Occasionally, neonatal foals without cleft palate have some mild degree of dysphagia with milk regurgitation from the nose for the first 24 to 48 hours of life, which spontaneously corrects. The cause of this is unknown, but it would appear to be a failure of normal swallowing events to be sufficiently strong or coordinated in the newborn. The major ruleout in these cases is cleft palate.

Approach to Diagnosis of Regurgitation and Vomiting

Evaluation of regurgitation or vomiting should include a history to determine possible exposure to toxins or poison plants, which is most likely when multiple animals are affected. Age of the animal limits some considerations; young animals are more prone to meningitis and central nervous system (CNS) trauma, and congenital problems such as esophageal diverticula and persistent right aortic arch are found only in neonates and may not manifest as choke or

regurgitation until solid food intake is increased.

The physical examination can determine whether the problem is vomiting or regurgitation. In ruminants, regurgitation often occurs as a result of distention and overfilling of the rumen, resulting in an obviously distended abdomen. Painful pharyngeal lesions can also cause pharyngeal paresis, which results in gagging and regurgitating. In horses the most common causes of feed coming from the nares are spontaneous choke and pharyngeal paresis associated with guttural pouch lesions (see the dysphagia section later).

Physical examination should also include passing a stomach tube to determine whether any impediment to passage of ingesta is present (Box 7.17). Endoscopy is useful to visualize esophageal defects. Many endoscopes currently in use are not long enough to reach the stomach of the adult horse. Endoscopy of the rumen is rarely diagnostic because it is almost impossible to empty it adequately to allow for visualization of a lesion. Ultrasound of the cervical esophagus may also be useful.

Box 7.17

Useful Techniques in Diagnosing Cause of Regurgitation

- Passing of stomach tube
- Endoscopy of pharynx, guttural pouches, esophagus, and stomach
- Ultrasound examination of the cervical esophagus may be helpful
- Radiographs; plain films of pharynx, guttural pouches, esophagus, and stomach
- Radiographs, barium swallows, checking gastric emptying time in horse

In horses and small ruminants, radiography, particularly barium contrast studies, can be useful in detecting esophageal abnormalities. In foals, prolonged gastric emptying time may be diagnosed from contrast studies. Normal emptying and movement of contrast media into the small bowel occur in less than 2 hours; contrast media reach the large bowel by 3 hours. Radiography may also be useful in detecting diaphragmatic hernia.

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The most significant complications of regurgitation and vomiting include aspiration pneumonia, dehydration, and electrolyte imbalances. The marked hypochloremic alkalosis common to most monogastrics is rare in horses and occurs in ruminants mainly with internal vomiting (one type of vagal indigestion) associated with reflux of abomasal contents back into the rumen.

Vomiting, like diarrhea, is often an attempt by the body to rid itself of a noxious or toxic substance. Antiemetics are therefore rarely indicated in vomiting of central origin and rarely effective in regurgitation in large animals.

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Dysphagia (Including Feed From Nares and Excessive Salivation)

Bradford P. Smith

Dysphagia is used here to refer to abnormalities of prehension, mastication, or swallowing. It is associated with diseases of the mouth, lips, teeth, pharynx, esophagus, mandible, or masseter muscles or, in the case of neurologic problems, with central or peripheral lesions resulting in malfunction in these areas. Diseases resulting in erosions, ulcers, swellings, crusts, or growths in or on the lips, mouth, or pharynx are discussed under a separate heading. Painful causes of dysphagia such as dental problems require differentiation from oral lesions such as ulcers.

The causes of dysphagia can be divided into three clinical categories: 1) pain induced, 2) neurologic, and 3) obstructive (Boxes 7.18 and 7.19). A fourth category is mechanical interference with prehension and swallowing, but this usually manifests in a manner resembling the manifestation of painful lesions. Particularly in horses, worn, missing, capped, abscessed, overgrown, or broken teeth often result in mechanical interference with chewing, resulting in half-chewed feed being dropped from the mouth (quidding). Observation of the animal as it attempts to eat and a good physical examination including oral inspection and passage of a stomach tube to rule out choke are essential in determining the cause of dysphagia. Use of a fiberoptic endoscope to visualize the pharynx, guttural pouches, and esophagus may be helpful. Plain film radiographs and barium swallows may also be indicated to see functional abnormalities in the guttural pouches, pharynx, and esophagus during swallowing and to rule out fractures of the hyoid or mandible. Ultrasound should also be employed.

Box 7.18

Causes of Dysphagia in Horses

Pain

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Tooth root abscess or periodontal disease
Worn, missing, capped, overgrown, or broken teeth
Foreign body in mouth, pharynx, nose
Oral vesicles, erosions, ulcers, or growths
Pharyngeal abscess, cellulitis, trauma, fistula, or neoplasia
Esophageal choke, trauma
Strangles
Rupture of rectus capitus ventralis muscle
Snake bite
Oral, mandibular, or maxillary fracture, neoplasia, or granulomas
White muscle disease
Epiglottiditis, epiglottic cysts
Trauma or excessive traction to tongue
Hyoid bone injury
Nasal mass (granuloma)
Neurogenic dysphagia

Obstruction

Pharyngeal abscess, cellulitis, trauma, fistula, or neoplasia
Esophageal choke, trauma, megaesophagus
Strangles
Rostral displacement of palatopharyngeal arch
Damaged or abnormal esophagus
Cleft palate
Dorsal displacement of soft palate
Epiglottiditis, epiglottic cysts
Nasal mass (granuloma)
Lymphosarcoma
Purpura hemorrhagica

Neurologic, Neuromuscular

Yellow star thistle (nigropallidal encephalomalacia)
Guttural pouch mycosis, infection, or tympany
Megaesophagus

Botulism
Lead toxicity
Rabies
Snake bite
Tetanus
Tick paralysis
Encephalitis, meningitis
Encephalopathy, hepatic
White muscle disease
Cerebrospinal nematodiasis
Electrocution
Transit or lactation tetany
Lymphosarcoma
Myeloproliferative disease
Myotonia
Otitis interna and media
Pontomedullary, brainstem neoplasia, pituitary abscess, trauma, neoplasm
Postanesthetic myasthenia
Herbicide toxicity
White snakeroot (tremetol) toxicity
Moldy corn poisoning
Locoweed *(Astragalus, Oxytropis)* toxicity
West Nile fever
Borna disease, Near East encephalitis (exotic)
Grass sickness (exotic)

Box 7.19

Causes of Dysphagia in Ruminants

Pain

Oral vesicles, erosions, ulcers, growths (see following section)
Foreign body
Pharyngeal abscesses, cellulitis, or tumor
Traumatic or irritant stomatitis

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Snake bite
White muscle disease
Actinobacillosis
Actinomycosis
Worn, missing, overgrown, or broken teeth
Periodontal disease or tooth root abscesses
Oral, maxillary, or mandibular neoplasia
Fractured mandible or maxilla
Stomatitis
Necrotic laryngitis (calf diphtheria)
Ruptured or damaged esophagus

Obstruction

Foreign body
Pharyngeal abscess, cellulitis, or tumor
Choke
Snake bite
Actinobacillosis
Oral, maxillary, or mandibular neoplasia
Megaesophagus
Hiatal or diaphragmatic hernia
Cleft palate
Bovine leukosis

Neuromuscular

Listeriosis
Rabies
Tetanus
Botulism
Tick paralysis
Encephalitis, encephalopathy
Brain abscess
White muscle disease
Megaesophagus

Paresis of masseter muscles (mandibular branch of trigeminal)
Bovine leukosis
GM1 gangliosidosis in Friesian cattle
Meningitis
Encephalitis or encephalopathy
Atlantoaxial subluxation or occipitoatlantoaxial malformation
Hypocalcemia
Otitis media and interna
Pontomedullary brainstem neoplasia, trauma, infection, inflammation
Pituitary abscess
Pseudorabies
White snakeroot (tremetol) poisoning
Fireweed *(Kochia scoparia)* poisoning
Locoweed *(Astragalus, Oxytropis)* poisoning
Mercury poisoning
Kikuyu grass *(Pennisetum clandestinum)* poisoning (exotic)
Ibaraki disease (exotic) (B)
Geigeria poisoning (exotic)
Ephemeral fever (exotic) (B)

B, Bovine.

Pain is probably the most frequent cause of dysphagia in ruminants and horses. Oral lesions, oral foreign bodies, and poor teeth result in decreased feed intake, in increased salivation, and often in dropping feed from the mouth while attempting to chew. Dental problems are relatively common in sheep and goats. In cattle, pharyngeal injuries from balling guns and paste wormers can result in severe pharyngeal cellulitis, which is manifested by an extended head, ptyalism, foul breath, and a painful, externally palpable pharyngeal swelling. Mandibular fractures must be ruled out by careful examination because even nondisplaced unilateral mandibular fractures can result in weak jaw tone, reluctance to eat, and drooling.

When dysphagia is associated with loss of large amounts of saliva, metabolic acid-base and electrolyte disorders may develop. Cattle and sheep have saliva high in sodium (136 to 201 mEq/L) and bicarbonate (108 mEq/L), with potassium and chloride values in the 14 to 15 mEq/L range.[36,37] As a result, losses of large amounts of saliva can result in hypovolemia and severe metabolic

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acidosis. In contrast, horses have relatively high levels of salivary chloride (48 to 82 mEq/L) with relatively low salivary bicarbonate (44 to 52 mEq/L). Equine salivary potassium is 14 to 18 mEq/L, and sodium is 54 to 90 mEq/L.[38,39] As a result, horses with esophageal fistulas that have lost saliva have a transient metabolic alkalosis.[38]

In the horse a common cause of acute dysphagia is choke (esophageal obstruction), followed in frequency by pharyngeal paresis (neurologic) resulting from lesions in the guttural pouch that affect the pharyngeal nerves. Feed coming from the nose is the most obvious sign of both conditions. In choked horses, as a result of the length and position of the soft palate, feed comes mainly from the nares rather than coming back into the mouth. Choke and other obstructive diseases can be easily identified by using a nasogastric tube, whereas pharyngeal paresis may be associated with a number of neurologic or neuromuscular conditions, such as botulism or guttural pouch mycosis, which require careful differentiation. The most frequent serious problem associated with choke or pharyngeal paresis is inhalation (aspiration, foreign body) pneumonia. Mineral oil or other material that is particularly damaging if it gains entry into the lung should never be used in choke for this reason. In any animal with dysphagia, care must be taken to prevent aspiration pneumonia and to evaluate the thorax periodically.

Animals with facial paralysis often drool from the affected side and may pack feed into the cheek on the affected side. Listeriosis in ruminants is frequently associated with facial paralysis. In horses facial paralysis is usually caused by halter trauma or a blow to the head.

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Oral Vesicles, Erosions, Ulcers, or Growths

Bradford P. Smith

Oral lesions are found with many conditions (Boxes 7.20 and 7.21). In general, they result in some degree of dysphagia or reluctance to eat because of pain. The lesions include vesicles, erosions, ulcers, crusts, or growths in or on the lips, tongue, gums, palate, or pharynx. Oral lesions are often associated with champing and increased amounts of saliva being observed on the lips or running from the mouth. When the volume of saliva is increased, the condition is called *ptyalism* and the animal may be observed swallowing repeatedly. Pseudoptyalism refers to a normal volume of saliva that, because it is not swallowed, is visible to the observer and may be confused with dysphagia (see previous section).

Box 7.20

Conditions Accompanied by Oral Vesicles, Erosions, Ulcers, or Growths in Horses

Common Causes

Vesicular stomatitis
Phenylbutazone toxicity
Yellow bristle grass (*Setaria lutescens* or *Setaria glauca*) ulcers
Other plant awn stomatitis
Oral foreign body

Less Common Causes

Irritant or caustic chemical stomatitis
Periodontal gingivitis
Blister beetle (cantharidin) toxicity

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Uremia
Drug eruption
Oral neoplasia

Box 7.21

Conditions Accompanied by Oral Vesicles, Erosions, Ulcers, or Growths in Ruminants

Common Causes

Bluetongue (O)
Contagious ecthyma (Orf virus) (O, C)
Bovine viral diarrhea/mucosal disease (B)
Bovine papular stomatitis (B)
Traumatic or irritant stomatitis
Bristle grass (*Setaria lutescens* or *Setaria glauca*) ulcers
Other plant awn stomatitis
Oral foreign body
Actinobacillosis (woody tongue)
Vesicular stomatitis

Less Common Causes

Actinomycosis (lumpy jaw)
Cheek abscess
Periodontal gingivitis
Oak or acorn toxicity
Malignant catarrhal fever (B)
Irritant or caustic chemicals

Uncommon Causes

Caprine herpesvirus (C)

Blister beetle (cantharidin toxicity)
Necrotic stomatitis
Epidermolysis bullosa
Familial acantholysis (B)
Oral neoplasia
Epitheliogenesis imperfecta
Hereditary zinc deficiency (baldy calf) (B)
Electrical injury
Bovine herpes 2 mammillitis (B)
Elaeophorosis (O)
Chlorinated naphthalene toxicity (B)
Thallium toxicity (O)
Giant hogweed *(Heracleum mantegazzianum)* toxicity
Lead toxicity
Mycotoxicoses
Ibaraki disease (exotic) (B)
Lumpy skin disease (exotic) (B)
Sweating sickness (exotic) (B)
Sheep and goat pox (exotic) (O, C)
Peste des petits ruminants (exotic) (O, C)

B, Bovine; *C*, caprine; *O*, ovine.

The approach to determining the cause of oral lesions is based on first determining whether the cause is likely to be an infectious disease (Table 7.1). Essentially all these infectious diseases are associated with a fever, although it is short lived and moderate in the case of bovine papular stomatitis (BPS) and actinobacillosis. Papular stomatitis rarely causes illness and is usually an incidental finding in calves with a different clinical problem, although BPS can cause severe lesions and illness. Most of the infectious diseases are associated with additional lesions or symptoms. They can be conveniently grouped into those causing diarrhea and those not usually associated with diarrhea. Of those not associated with diarrhea in North America, BPS, actinobacillosis, and vesicular stomatitis (VS) are most common in cattle; VS in horses; bluetongue in sheep; and contagious ecthyma (CE) in sheep and goats. CE can be readily differentiated from bluetongue because it involves primarily lips and gums and is proliferative, whereas bluetongue involves the tongue and dental pad most

severely, is erosive, and is associated with other signs of generalized vasculitis. Laboratory diagnosis in acute cases of VS is done by working with state and federal veterinarians. Because VS is highly contagious and similar in clinical appearance to foot-and-mouth disease, quarantine and proper diagnosis are essential. CE can be diagnosed serologically, by fluorescent antibody on the impression smear or biopsy of a lesion, and by isolation. Bluetongue is diagnosed by ELISA, serology (AGID), PCR, and virus isolation. Asymptomatic seroconversion to bluetongue is common where *Culicoides* vectors are active. Congenital defects can result from bluetongue infection of the fetus in sheep, goats, and cattle.

TABLE 7.1

Infectious Diseases Associated With Oral Lesions in Cattle, Sheep, Goats, and Horses

Disease	Natural Species	Oral Lesions	Other Lesions
Vesicular stomatitis (VS)	Cattle Horse Sheep (rare)	Vesicles for short time, then large ulcers; tongue usually severely involved	Teats and feet may be involved
Bluetongue	Sheep Goat (rare) Cattle (rare)	Large oral ulcers; dental pad and tongue most affected; generalized vasculitis	Coronitis, muscle degeneration, lameness, pulmonary edema, edema of face and ears
Contagious ecthyma (CE; Orf)*	Sheep Goat	Proliferative scabby lesion on lips to fleshy growth on gums	Occasionally on teats of nursing dams
Bovine papular stomatitis*	Cattle	Round, dark red, raised papules on muzzle and on hard palate	Occasionally in esophagus
Foot-and-mouth (exotic)	Cattle Sheep Goat	Vesicles for short time, then large ulcers	Teats and coronary bands often involved
Bovine viral diarrhea/ mucosal disease (BVD/MD)	Cattle	Ulcers in mouth, particularly on hard palate; erosive stomatitis	May have skin lesions; a few have corneal edema or enlarged lymph nodes; pneumonia and lesions in esophagus and gastrointestinal tract common; severe diarrhea
Malignant catarrhal fever (MCF)	Cattle (Bison)	Erosive stomatitis with ulcers; generalized vasculitis	Purulent nasal discharge, corneal edema, enlarged lymph nodes, ± cracking skin, ± central nervous system signs; severe diarrhea; high fever
Rinderpest (exotic)†	Cattle	Erosive stomatitis	Blepharospasm, severe intestinal involvement, and diarrhea
Peste des petits ruminants (PPR)	Sheep Goat	Erosive stomatitis	Severe diarrhea, purulent ocular and nasal discharge

Alimentary form of infectious bovine rhinotracheitis (IBR) in calves	Cattle	Gray pinpoint pustules on soft palate and occasionally in nares; minimal oral lesions	Rhinotracheitis, conjunctivitis, pneumonia

*Infectious to humans.

†Rinderpest was eradicated worldwide in 2011.

The two most common North American infectious diseases associated with oral lesions and diarrhea in cattle are bovine viral diarrhea/mucosal disease (BVD/MD) and malignant catarrhal fever (MCF). MCF can usually be differentiated because it most commonly occurs sporadically in single animals and has signs of generalized vasculitis such as bilateral corneal opacity, mucopurulent nasal discharge, enlarged lymph nodes, and high fever. Dysentery is common in MCF, and some animals exhibit CNS signs or have thickened and cracking skin. See Chapter 32 for more on diagnosis of MCF. Laboratory diagnosis in acute cases of BVD (see the Bovine Viral Diarrhea section in Chapter 32) involves fluorescent antibody testing of slides made from ear notch biopsies, lesion swabs, buffy coat, or tissue. Virus isolation from swabs, serum, or blood or a rise in serum titer from acute to convalescent samples is also diagnostic. Asymptomatic seroconversion is also common, and infection of the fetus may result in congenital anomalies including cerebellar hypoplasia in cattle.

In animals without fever and other signs of systemic involvement, irritants and caustic chemicals should be considered as possible causes of oral lesions. Horses and young calves are susceptible to severe ulceration when consuming hay contaminated with yellow bristle grass, which is armed with barbed bristles.[40] Horses sometimes develop gingivitis or oral ulcers associated with dry plant awns called foxtails, which become embedded into the gums around teeth. Foals and ponies are most susceptible to phenylbutazone toxicity, which can produce oral ulceration. In cattle the surfaces of masses produced by actinobacillosis and actinomycosis sometimes ulcerate. Many cattle without significant disease have one or more small ulcers of traumatic origin from plant awns on the hard palate and in the cleft (sulcus lingualis) where the base and shaft of the tongue meet.

Dental Abnormalities

Chronic fluorosis is a cause of a variety of dental abnormalities in young animals with developing teeth (Boxes 7.22 and 7.23). Although cattle are most frequently

involved, all large animals are susceptible. The teeth may appear mottled, striated, chalky, or hypoplastic or may have defective calcification. In severe cases teeth may be yellow, brown, or black and have multiple caries. Animals of any age may also develop bone lesions associated with chronic fluorosis.

Box 7.22

Causes of Dental Cavities, Abnormalities of Tooth Color, and Loose Teeth in Horses

Periodontal disease
Chronic fluoride toxicity
Dental decay
Fractured teeth
Osteomalacia, osteodystrophy
Halicephalobus (Micronema) deletrix, granulomas of mandible or maxilla
Skeletal neoplasia of mandible or maxilla
Hyperparathyroidism
Tooth root abscess with osteomyelitis, secondary to open infundibulum
Ameloblastoma (odontoma)
Dental stain (black walnut hull ingestion or other compound)

Box 7.23

Causes of Dental Cavities, Abnormalities of Tooth Color, and Loose Teeth in Ruminants

Chronic fluoride toxicity
Bovine erythropoietic porphyria
Fractured teeth
Osteogenesis imperfecta in Holstein Friesians
Osteomalacia, osteodystrophy
Actinomycosis

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Skeletal neoplasia of mandible or maxilla
Lymphosarcoma (goat and sheep)
Periodontal disease
Broken mouth (old worn teeth)
Tooth root abscess with osteomyelitis
Ingestion of black walnut hulls or other dental stain
Ingestion of sweet potato cannery waste (B)

B, Bovine.

Porphyria is a rare congenital condition of cattle transmitted by a simple autosomal-recessive gene. The teeth often appear pink because of the presence of porphyrins and fluoresce pink, purple, or red when exposed to ultraviolet light. Affected calves often develop photosensitization and anemia. This condition must be differentiated from superficial staining caused by ingestion of black walnut hulls or other compounds with staining properties. Cattle fed sweet potato cannery waste develop dental erosions and tooth discoloration.

Excessive or uneven wear or loss of teeth is often seen in horses and ruminants as they age. Tooth wear, particularly of incisors, is more rapid in animals on sandy range. Periodontal disease can cause premature loss of teeth (broken mouth) and tends to be most common in sheep in some geographic areas; the cause of this is unknown.[41]

The most common dental disease in horses has been described as periodontal disease.[42] In horses fractured teeth or teeth with a small tract into the root through an open infundibulum often result in tooth root abscesses. This dental decay is a result of hypoplasia of the cementum of the enamel lakes and occurs most frequently in the second and third lower cheek teeth and third and fourth upper cheek teeth.[43] These can cause sinusitis and foul-smelling unilateral nasal discharge if upper cheek teeth are involved or draining tracts to the exterior skin surface if lower cheek teeth are involved.

Most of the other causes of dental abnormalities listed here are bone abnormalities that cause secondary loss of teeth. See dental sections of Chapter 32 for more details.

Icterus (Jaundice)

Icterus and *jaundice* are synonymous terms referring to the expression of a yellow coloration in the sclera and mucous membranes resulting from increased amounts of bilirubin in tissues and increased serum bilirubin levels (Boxes 7.24 and 7.25). Bilirubin especially stains elastic tissues and is thus most visible in the sclera and vulva. Icterus usually indicates decreased excretion of bilirubin with liver or biliary tract diseases or increased production of bilirubin with hemolytic anemia.

Box 7.24

Causes of Icterus in Horses

Liver

Common Causes

Pyrrolizidine alkaloid toxicity
Serum-associated hepatitis
Acute hepatitis
Chronic active hepatitis
Cholangitis or cholangiohepatitis
Bile stones, other biliary obstruction
Fasting hyperbilirubinemia

Less Common Causes

Aflatoxicosis with liver failure
Tyzzer disease (foals)
Hepatic lipidosis
Hepatic abscess

Uncommon Causes

Infectious necrotic hepatitis (black disease)
Hemangioma, hemangiosarcoma, angiosarcoma
Cardiac neoplasm

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Viral arteritis
Gastric or duodenal ulcers
Severe ascarid infection
Lymphosarcoma

Hemolytic Anemia

Common Causes

Immune-mediated hemolytic anemia
Equine granulocytic ehrlichiosis (*Anaplasma phagocytophilum*, formerly *Ehrlichia equi*)
Neonatal isoerythrolysis

Less Common Causes

Piroplasmosis (babesiosis)
Equine infectious anemia
Snake bite
Blood transfusion
Erythrocytosis

Uncommon Causes

Equine viral arteritis
Leptospirosis
Hemochromatosis
Bee or wasp sting
Sulfur toxicity
Trichloroethylene-extracted feed
Iron toxicity
Phosphorus toxicity
Herbicide toxicity
Phenothiazine toxicity
White snakeroot poisoning (tremetol)
Onion poisoning
Red maple *(Acer rubrum)*

Pentachlorophenol toxicity
Oak toxicity
Mycotoxicosis
Surra, *Trypanosoma evansi* (exotic)
Mal de caderas, *Trypanosoma equinum* (exotic)
Murrina de caderas, *Trypanosoma hippicum* (exotic)

Box 7.25

Causes of Icterus in Ruminants

Liver

Common Causes

Pyrrolizidine alkaloid toxicity
Aflatoxicosis
Fat cow syndrome (fatty liver)

Less Common Causes

Acute hepatitis
Liver flukes
Infectious necrotic hepatitis (black disease)
Liver abscess
Cholangiohepatitis

Uncommon Causes

Sarcocystosis
Hepatic neoplasia
Ruptured gallbladder
Cholelithiasis
Biliary obstruction
Nolina (beargrass) toxicity
Lantana, toxicity

Agave, toxicity
Wesselsbron disease (exotic) (B, O)

Hemolytic Anemia

Common Causes

Leptospirosis
Anaplasmosis
Bacillary hemoglobinuria *(Clostridium hemolyticum)*
Piroplasmosis, babesiosis (exotic)

Less Common Causes

Snake bite
Oak (acorn) toxicity
Immune-mediated hemolytic anemia
Transfusion reaction
Postparturient hemolytic anemia
Copper toxicity (especially sheep)
Neonatal isoerythrolysis
Yellow lamb disease (*Clostridium perfringens*, type A) (O)

Uncommon Causes

Anaplasma ovis
Eperythrozoonosis
Bee or wasp sting
Brassica species toxicity
Trichloroethylene-extracted feed toxicity
Iron toxicity
Onion poisoning
Zinc poisoning
Phosphorus poisoning
Mercury poisoning
Fireweed *(Kochia scoparia)* poisoning
Mycotic lupinosis

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Mycotoxicosis
Theileriosis (East Coast fever) (exotic)

B, Bovine; *O,* ovine.

The accumulation of conjugated bilirubin results in more pronounced jaundice than does a similar amount of unconjugated bilirubin, with the result that the most pronounced jaundice is usually seen with hepatic or biliary obstructive disease. Laboratory examination of serum for relative amounts of unconjugated (indirect reacting) and conjugated (direct reacting) bilirubin is essential in determining the cause of the icterus. Generally, mainly unconjugated bilirubin levels are elevated with hemolytic anemia. Anorectic horses may have a plasma unconjugated bilirubin of 5 or 6 mg/dL without any evidence of hemolytic anemia or liver disease. Anorectic ruminants also experience a rise in plasma unconjugated bilirubin, often to a level between 0.5 and 2 mg/dL.

In determining the cause of icterus, laboratory tests including PCV, RBC count, and the liver enzymes SDH and GGT should be determined. In horses, alkaline phosphatase (AP) may also be useful, although it is not liver specific.

When active hepatocellular damage is occurring, SDH, which is liver specific, and aspartate aminotransferase (AST [SGOT]), which is not liver specific, are found in serum in elevated levels. GGT and AP are more indicative of biliary tract disease or proliferation and tend to rise more slowly but also remain elevated for a longer period than SDH, which has a short half-life. Elevated levels of GGT or AP are often associated with chronic liver disease, cholangitis, cholelithiasis, or liver flukes. It is possible to have liver disease without icterus. Production and elimination of bilirubin are often equal in chronic liver disease, but acute liver disease or liver failure is usually associated with icterus. Although liver function tests such as BSP half-time can be run to determine the extent of liver damage, in most cases a liver biopsy must be taken for histopathologic examination to make a specific etiologic diagnosis of the cause of liver disease.

Liver abscesses rarely result in icterus because they rarely damage a sufficient percentage of liver to impair bilirubin clearance. They do cause multifocal hepatic damage and therefore are often associated with increased levels of SDH and AST when in the acute stages of formation.

Hemolytic anemia is characterized by destruction of RBCs either intravascularly or in the reticuloendothelial organs. This increased destruction

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results in production of bilirubin more rapidly than it can be removed by the liver, resulting in icterus. The specific cause of hemolytic anemia may sometimes be evident, as when autoagglutination is seen (autoimmune hemolytic anemia). *Anaplasma* bodies are visible in stained RBCs of cattle, or *Anaplasma phagocytophilum* (formerly *Ehrlichia equi*) blue cytoplasmic inclusion bodies are seen in stained neutrophils from horses.

In mature sheep, the most common cause of severe icterus is copper toxicity. In lambs, yellow lamb disease caused by *C. perfringens*, type A is a leading cause.

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• CHAPTER 8

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Localization and Differentiation of Neurologic Diseases

David C. Van Metre, Robert J. MacKay, Consulting Editors

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Terminology and Description of Clinical Signs of Neurologic Disease (See Table 8.1)

TABLE 8.1

Localization of Central Nervous System Lesions According to Major Signs Encountered

Sign or Problem Encountered	Lesion Location
Changes in Gait and Locomotion	
Ataxia	Spinocerebellar tracts, spinal cord, and brainstem; vestibular system; cerebellum
Conscious proprioceptive deficit	Fasciculus gracilis and fasciculus cuneatus and connections, spinal cord, brainstem, forebrain
Knuckling	Usually LMN, ventral horn gray matter, spinal cord; occasionally UMN, spinal cord, brainstem
Abduction or adduction	Spinocerebellar tracts, spinal cord, brainstem, cerebellum
Abnormal postural placement	Spinocerebellar tracts, spinal cord, and brainstem; gracilis and fasciculus cuneatus and connections, spinal cord and brain
Hypermetria	Cerebellum, cerebellar peduncles, spinocerebellar tracts
Circling, or falling to one side	Forebrain, vestibular nuclei and connections, cerebellum
Paraplegia	UMN, T2 to S2, or LMN, L3 to S2
Hemiplegia	Ipsilateral brainstem or spinal cord, cranial to T3
Changes in Sensorium and Behavior	
Coma or semicoma	ARAS; diffuse forebrain
Obtundation	ARAS; forebrain
Seizures	Forebrain
Head pressing, compulsive walking	Forebrain
Aggression or rage	Forebrain
Inappropriate sexuality	Forebrain
Hyperphagia or hypophagia	Hypothalamus
Diabetes insipidus	Hypothalamus

Headshaking	Unknown, probably peripheral trigeminal neuralgia
Changes in Head Posture	
Stiff neck	Meninges, cervical spine
Head tilt	Vestibular nuclei and connections (medulla oblongata, cerebellum)
Head tremor	Cerebellum, basal ganglia
Opisthotonos	Cerebellum (rostral vermis), rostral brainstem, cerebrum, cranial nerve VIII
Cranial Nerve Dysfunction	
Blindness	Cerebral cortex, internal capsule, optic tracts, optic chiasm, optic nerve, eye
Anisocoria	Cervical spinal cord (tectotegmentospinal tract), cranial thoracic nerve roots, vagosympathetic trunk, midbrain (oculomotor nerve nucleus), cranial cervical ganglion, ciliary ganglion, oculomotor nerve, optic nerve
Mydriasis	Oculomotor nerve, midbrain, optic nerve, eye
Miosis	Vagosympathetic trunk, ciliary ganglia, tectum, brainstem, cervical spinal cord
Ptosis	Facial nerve, vagosympathetic trunk, cranial cervical ganglion, midbrain, oculomotor nerve, cervical spinal cord (tectotegmentospinal tract)
Strabismus	
Ventrolateral	Cerebellum, vestibular nucleus, oculomotor nerve
Dorsomedial	Trochlear nerve
Medial	Abducent nerve
Nystagmus	
Horizontal	Nerve VIII (peripheral)
Vertical or rotatory	Vestibular nuclei, peripheral vestibular receptor, cerebellum, vestibulocochlear nerve
Jaw drop	Trigeminal motor nucleus (pons), trigeminal nerve
Flaccid tongue	Hypoglossal nucleus (medulla oblongata), hypoglossal nerve, lingual muscle
Facial paralysis	Facial nucleus (medulla oblongata), facial nerve, facial muscles
Facial analgesia	Trigeminal nerve (sensory component), pons, forebrain
Dry eye	Cranial nerve VII before exiting petrous temporal bone
Changes in Reflexes	
Patellar	L3-L6 spinal cord, femoral nerve, quadriceps femoris muscle
Flexors (thoracic limbs)	C5-T2 spinal cord segments, radial, ulnar, musculocutaneous and median nerves, and innervated muscles
Flexors (pelvic limbs)	L6-S2 spinal cord segments (pelvic limbs); sciatic, peroneal, and tibial nerves; flexor muscles of the limbs
Triceps	C6-T1 spinal cord segments, radial nerve, triceps muscle
Cutaneous trunci	C8-T1 spinal cord segments, lateral thoracic nerve, white matter of thoracic spinal cord
Anal	S1-S5 sacral spinal cord segments, pudendal nerve
Cervicofacial	Dorsal columns of cervical spinal cord segments; facial nucleus (medulla oblongata), nerve, facial nucleus, muscles of ear; connections between cervical plexus and facial nerve
Dysuria (dribbling urine)	Spinal cord, S1-S5, sacral nerves, bladder wall

ARAS, Ascending reticular activating system; *LMN,* lower motor neuron; *UMN,* upper motor neuron.

Telencephalon (cerebrum, basal ganglia) and diencephalon (thalamus)

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- Changes in behavior
- Changes in the level of consciousness
  - Dullness, obtundation
  - Stupor
  - Coma
  - Excitement, mania
  - Seizures (convulsions)
  - Narcolepsy
- Vision disturbance
  - Blindness in both visual fields (amaurosis)
  - Blindness in the contralateral visual field (hemianopsia)
  - Menace reflex deficit
  - Change in pupil size: small to pinpoint pupils
- Circling (toward the side of the lesion)
- Head turn (toward the side of the lesion)
- Gait usually normal
- Abnormal postural reactions (contralateral)
  - Decreased or absent conscious proprioception
  - Noticeable ataxia, paresis (weakness), and paralysis are uncommon
- Abnormal spinal reflexes
  - Normal to increased (hyperreflexic) myotatic reflexes
- Altered muscle tone
- Normal to increased muscle tone (spasticity)
- Urinary incontinence (upper motor neuron)
- Tremors

Mesencephalon (midbrain)

- Changes in the level of consciousness
  - Dullness (depression)
  - Stupor
  - Coma
  - Narcolepsy
- Abnormal posture
  - Opisthotonos
  - Decerebrate posture

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- Abnormal visual or ocular function
  - Blindness in both visual fields (amaurosis)
  - Blindness in the contralateral visual field (hemianopsia)
  - Change in pupil size
  - Small pupils in early, mild lesions
  - Dilated, nonresponsive pupils in severe lesions
  - Menace reflex deficit (ipsilateral)
  - Anisocoria (asymmetric lesions)
- Circling (toward the side of the lesion—ipsiversive)
- Head turn (toward the side of the lesion—ipsiversive)
- Abnormalities of gait (usually contralateral to lesion)
  - Decreased or absent conscious proprioception
  - Ataxia
  - Paresis (weakness)
  - Paralysis
- Abnormal spinal reflexes
  - Normal to increased (hyperreflexic) myotatic reflexes
- Altered muscle tone
  - Spasticity
- Urinary incontinence (upper motor neuron)

Metencephalon (pons, cerebellum)

- Abnormal posture
  - Head tilt
  - Decerebellate posture
- Circling (usually away from side of lesion—paradoxical signs)
- Head turn (usually away from side of lesion—paradoxical signs)
- Nystagmus (variable—may be constant, positional, direction changing, or disconjugate and may occur in any direction)
- Abnormalities of gait
  - Ataxia
  - Dysmetria—typically, hypermetria
- Abnormal spinal reflexes (occasional)
  - Normal to increased myotatic reflexes (hyperreflexia)
- Altered muscle tone

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- Normal to increased muscle tone on the opposite side of the body (contralateral spasticity)
- Normal to decreased muscle tone on the same side of the body (ipsilateral hypotonus)
- Urinary incontinence (upper motor neuron) (rare)

Medulla oblongata

- Changes in the level of consciousness
  - Dullness, obtundation
- Abnormal posture
  - Head tilt (toward side of lesion—ipsiversive)
  - Circling (toward side of lesion—ipsiversive)
  - Head turn occasionally (toward side of lesion)
- Strabismus—variable
- Nystagmus—spontaneous, abnormal (variable—may be constant, positional, direction changing, or disconjugate and may occur in any direction)
- Dysphagia
- Facial analgesia
- Facial paresis or paralysis
- Menace reflex deficit
- Jaw weakness
- Roaring, snoring, dysphonia
- Tongue weakness, deviation, or paralysis
- Abnormalities of gait—ipsilateral
  - Decreased or absent conscious proprioception
  - Ataxia
  - Paresis (weakness)
  - Paralysis
- Abnormal spinal reflexes
  - Normal to increased (hyperreflexic) myotatic reflexes
- Altered muscle tone
  - Normal to increased muscle tone
- Urinary incontinence (upper motor neuron)

Spinal cord C1-C5

- Abnormalities of gait in thoracic and pelvic limbs—ipsilateral
  - Decreased or absent conscious proprioception

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- Ataxia
- Paresis (weakness)
- Paralysis

- Abnormal spinal reflexes—ipsilateral
  - Hyperreflexia in both thoracic and pelvic limbs
  - Decreased to absent caudal cervical and auricular reflexes
  - Decreased to absent slap test (horses)
- Altered muscle tone
  - Normal to increased muscle tone
- Urinary incontinence (upper motor neuron)

Spinal cord C6-T2

- Abnormalities of gait in thoracic and pelvic limbs—ipsilateral
  - Decreased or absent conscious proprioception
  - Ataxia
  - Paresis (weakness)
  - Paralysis
- Abnormal spinal reflexes—ipsilateral
  - Hyporeflexia in thoracic limbs
  - Hyperreflexia in pelvic limbs
  - Decreased to absent caudal cervical and auricular reflexes
  - Decreased to absent slap test (thoracolaryngeal reflex, horses)
  - Absent panniculus reflex
- Horner's syndrome (ipsilateral)
- Altered muscle tone
  - Decreased muscle tone in thoracic limbs
  - Normal to increased muscle tone in pelvic limbs
- Urinary incontinence (upper motor neuron)

Spinal cord T3-L2

- Abnormalities of gait in pelvic limbs only—ipsilateral
  - Decreased or absent conscious proprioception
  - Ataxia
  - Paresis (weakness)
  - Paralysis
- Abnormal spinal reflexes—ipsilateral

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- Hyperreflexia in pelvic limbs only
- Decreased panniculus reflex caudal to lesion
- Altered muscle tone—ipsilateral
- Normal to increased muscle tone in pelvic limbs
- Urinary incontinence (upper motor neuron)

Spinal cord L3-S3

- Abnormalities of gait in pelvic limbs only—ipsilateral
- Decreased or absent conscious proprioception
- Ataxia
- Paresis (weakness)
- Paralysis
- Abnormal spinal reflexes—ipsilateral
- Hyporeflexia in pelvic limbs only
- Altered muscle tone
- Decreased muscle tone in pelvic limbs
- Flaccidity of the tail
- Urinary incontinence (lower motor neuron)
- Fecal incontinence (lower motor neuron)

Peripheral nerve and muscle

- Abnormalities of gait
- Paresis to paralysis
- Decreased or absent conscious proprioception
- Ataxia
- Paresis (weakness)
- Paralysis
- Abnormal spinal reflexes—ipsilateral
- Hyporeflexia
- Altered muscle tone
- Decreased muscle tone
- Muscle atrophy
- Flaccidity of the tail
- Urinary incontinence (lower motor neuron)
- Fecal incontinence (lower motor neuron)

The clinical signs of neurologic disease depend on the location of the disease process within the nervous system (Table 8.1). Widely varying disease entities may produce similar or identical clinical signs. Seizures, for example, may be

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the result of metabolic, toxic, traumatic, neoplastic, or other causes. Definitive diagnosis of neurologic disease, therefore, cannot be made based on clinical signs alone. Localization of lesions within the nervous system by meticulous physical and neurologic examination is the first and key step in developing a differential diagnosis list and a rational diagnostic and therapeutic plan.

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Diagnosis of Neurologic Diseases

Signalment

The species, breed, age, and pedigree of an animal are important considerations in the differential diagnosis of neurologic disease. Many diseases are species specific, particularly in the case of infectious and genetic diseases. Some diseases are not only species specific but also have higher incidence in certain breeds and ages of that species.[1-13]

Some diseases are found in the neonate at birth. A large number of congenital disorders of the central nervous system (CNS) can affect domestic livestock. These diseases have a variable clinical course, depending on the nature of the disorder. Congenital disorders of myelin metabolism worsen with age, whereas other developmental conditions may remain stable throughout the animal's life.[14-19] Examples of these disorders that have genetic tests available are listed in Chapter 52.

History

Many disorders of the CNS produce characteristic patterns of onset and progression. Some CNS diseases occur acutely, developing the full range of clinical signs within hours. If the disease is not fatal, the signs either stabilize by 24 hours and remain constant thereafter or improve. Diseases that may display this clinical course include traumatic injuries and some types of toxic, infectious, and metabolic diseases. Diseases with degenerative, neoplastic, and certain viral causes may develop more slowly, requiring days to weeks for development of characteristic clinical signs.[2,20,21]

Diet

The diet of patients with neurologic disease should be evaluated[20-25] (Table 8.2). Equine motor neuron disease is seen mainly in horses that are housed without access to pasture and whose diet is deficient in vitamin E.[26] Copper deficiency occurs in ruminants pastured in areas with shale or volcanic soils, which are either deficient in copper or contain high concentrations of molybdenum and sulfur; demyelination of the spinal cord in newborn small ruminants may result,

as can vertebral fractures in calves. Overfeeding of protein and energy, as well as imbalance of certain trace minerals, has been linked to cervical vertebral stenotic myelopathy in horses (wobbler).[27,28]

TABLE 8.2

Dietary Deficiencies Associated With Neurologic Disorders of Livestock

Dietary Deficiency	Disease Produced	Neurologic Sign
Copper	Demyelination, pathologic vertebral fractures	Ataxia, recumbency
Vitamin E	Demyelination	Ataxia, recumbency
Vitamin A	Encephalopathy	Convulsions, blindness
Magnesium	Grass tetany, transport tetany, milk tremors	Convulsions, tremors, ataxia
Potassium	Weakness	Postpartum recumbency
Calcium or phosphorus	Milk fever, pathologic vertebral fractures, tetany	Weakness, ataxia, recumbency, tetany
Vitamin E or selenium	Nutritional myodegeneration	Weakness, ataxia, recumbency, sudden death

Environment

Examination of the patient's environment may provide valuable information about the cause of CNS disease. Outbreaks of botulism and listeriosis have been associated with ingestion of rotting vegetation around haystacks, silos, and feed bunks.[29,30] Plant poisonings are common in livestock, and identification of neurotoxic plants is important whenever multiple animals are affected simultaneously[30-32] (Table 8.3). Nonplant neurotoxicants of livestock include lead, ethylene glycol, organic mercurials, chlorinated hydrocarbons, organophosphates, salt, sulfur, petroleum distillates, and many others. Dose of the neurotoxicant may be important, with different clinical signs appearing depending on the level of exposure. For example, ingestion of high concentrations of organophosphates or carbamates produces marked ataxia, coma, muscle tremors, salivation, and miotic pupils. When low doses of organophosphates are ingested chronically, however, the result is an axonopathy of spinal cord and medullary neurons, resulting in pelvic limb paresis and ataxia, which may progress to tetraparesis and recumbency.[33] Therapeutic and dietary interventions also may result in toxicoses when improperly administered. Overdosing of cattle with propylene glycol produces profound ataxia, depression, and coma.[34] Ingestion of urea or ammoniated feedstuff produces hyperesthesia, excitability, coma, and convulsions. High concentrations of salt in

drinking water or, more commonly, lack of fresh water or interruption of the water supply followed by unlimited access to water can result in laminar necrosis of the cerebral cortex or eosinophilic meningitis.[33] The clinical signs are those of forebrain dysfunction, including blindness, dullness, seizures, coma, and death.[35-37] Geographic area also may be important in the differential diagnosis of neurologic disease. Certain infectious diseases may be more common in particular areas of the country or even regions within a single state where the conditions for disease vectors are optimal.[38] The travel history of the animal must be considered, as well as the animal's location at the time clinical signs appeared. Travel also may result in increased contact with other animals and greater risk of exposure to infectious diseases. Intermingling of horses from different premises is a potential risk for equine herpesvirus myeloencephalopathy (EHM).[39]

TABLE 8.3

Selected Poisonous Plants Producing Neurologic Signs (Also See Chapter 54)

Plant Poisoning	Clinical Signs
Blue green algae *(Aphanizomenon, Anabaena flos-aquae)*	Sudden death, tremors, salivation, miosis, bradycardia
Bracken fern *(Pteridium aquilinum)*	Ataxia, weight loss, strip sweating (horses only)
Buckeye (*Aesculus* species)	Incoordination, twitching, sluggishness
Catsear *(Hypochaeris radicata)*	Hyperflexion of the hock during movement (stringhalt)
Cheesewood *(Malva)*	Tremors, worsened by forced exercise, hyperflexion of the hock during movement (stringhalt)
Creeping indigo *(Indigofera spicata)* and Birdsville indigo *(Indigofera linnaei)*	Ataxia, obtundation, blepharospasm, corneal edema, lingual ulcers, seizures
Dandelion *(Taraxacum officinale)*	Hyperflexion of the hock during movement (stringhalt)
Death camus (*Zigadenus* species)	Trembling, uncontrolled running, recumbency, opisthotonos, convulsions, vomiting, salivation
Dutchman's breeches *(Dicentra)*	Trembling, uncontrolled running, recumbency, opisthotonos
Fiddleneck *(Amsinckia intermedia)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Horse tail *(Equisetum arvense)*	Ataxia, weight loss, strip sweating (horses only)
Laburnum *(Laburnum anagyroides)*	Excitement, incoordination, convulsions, death
Larkspur *(Delphinium)*	Ataxia, collapse, recumbency, inability to lift head, tremors of face, flank, and hip; vomiting
Locoweed (*Astragalus* species)	Ataxia, weight loss, recumbency, hyperesthesia
Lupine *(Lupinus)*	Tremors, hyperexcitability, depression
Milkweed (*Asclepias* species)	Tremors, salivation, ataxia
Monkshood *(Aconitum)*	Restlessness, salivation, paresthesia, irregular heartbeat, recumbency, coma
Nightshades (*Atropa* species, *Solanum* species)	Tremors, ataxia, recumbency, convulsions
Poison hemlock *(Conium maculatum)*	Tremors, vomiting, ataxia, sudden death, abortions, pupillary dilation, bradycardia, coma

Rape *(Brassica napus)*	Blindness, ataxia, aggressiveness
Rattlebox *(Crotalaria spectabilis)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Rayless goldenrod *(Haplopappus heterophyllus)*	Lassitude, obtundation, arched back, stiff-legged gait, tremors, weakness, collapse
Russian knapweed *(Rhaponticum repens, Acroptilon repens)*	Facial rigidity and dystonia, lack of prehension, ataxia, depression (horses only)
Tansy ragwort *(Senecio jacobaea)* and common groundsel *(Senecio vulgaris)*	Ataxia, obtundation, somnolence, excitability, head pressing (hepatic encephalopathy)
Tobacco (*Nicotiana* species)	Tremors, salivation, ataxia, convulsions, birth defects
Water hemlock *(Cicuta maculata)*	Tremors, vomiting, ataxia, sudden death, convulsions, odontoprisis, pupillary dilation, abortions, bloat
White snakeroot *(Eupatorium rugosum)*	Tremors, salivation, convulsions
Yellow star thistle *(Centaurea solstitialis)*	Facial rigidity and dystonia, lack of prehension, ataxia, depression (horses only)

Vaccination and Disease History

When a neurologic problem is evaluated, the vaccination history and previous herd or individual disease problems should be noted. Some vaccines are highly protective, such as those for rabies and tetanus. Neurologic disease may be a secondary complication of disease in another organ system. Foals and calves with severe diarrhea, for example, may convulse secondary to hypokalemia, hypernatremia, hyponatremia, or hypoglycemia. Preexisting diseases in the population should be determined. For example, outbreaks of EHM are sometimes preceded by respiratory disease or abortions in herdmates.[39] Historical evidence of limited colostral intake may be important in the diagnosis of bacterial meningitis of neonates. Bloody diarrhea often precedes the onset of nervous coccidiosis of calves.[40]

Gestational Stage

Hypomagnesemia, eclampsia (hypocalcemia), hypokalemia, hypophosphatemia, and nervous ketosis are common causes of recumbency, convulsions, and tremors in adult livestock. These diseases usually occur between the beginning of the last trimester and the first 2 months after parturition.

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Nervous System Examination

General Comments

A thorough physical examination should always precede or be performed concurrently with the neurologic examination. In some instances disease of organ systems other than the nervous system may take precedence for diagnosis and treatment. Such may be the case with animals that are in shock or suffering from other life-threatening cardiovascular or respiratory disturbances.

The neurologic examination should be carried out in a systematic fashion. The exact order of the examination is not important in itself, but procedures that may cause discomfort or pain, such as palpation of the spine, should be left until last. A common system used by many neurologists is to start at the head and progress to the tail.[41] Some clinicians prefer to examine the animal standing in the stall initially and then observe the gait. Because large animals are less amenable to handling than the typical cat or dog, another system for the neurologic examination is to begin with procedures that require minimal handling of the animal, such as observation of mental status, posture, and gait, and proceed to those that require greater manipulation.

Neurologic examination alone rarely leads to definitive diagnosis but rather helps to answer the questions “Does the animal have neurologic disease?” and “What is the location of the neurologic lesion?” Once these questions are answered, a list of differential diagnoses can be made in light of other information such as the signalment of the animal and the history of the current problem. The diagnostic plan is based on the location of the lesion and the most likely differential diagnoses.

Mentation and Behavior

Initial examination should be done from a distance. The examiner observes the animal's mental state and whether its responses to its surroundings are appropriate. This is done ideally in the animal's usual environment, where it would be expected to be calmest. When this is not possible, the influence of factors such as the stress and excitement of previous travel and the animal's natural fear of unfamiliar surroundings, sounds, and smells must be taken into account. The animal's usual handler may help to discern subtle changes in an

individual animal's behavior. All livestock should recognize and fear strangers and should show awareness of the examiner's position. Normal animals change the posture of the head, ears, and eyes as the examiner moves. Depending on previous conditioning, normal behavior may include cautionary moves, avoidance, belligerence, or affection. Animals with decreased mental alertness (obtunded, dull, depressed) have reduced responses to examination, lassitude, lack of recognition, unwillingness to rise or lift the head from the ground, lack of appetite, drooped ears, stupor, or coma (Fig. 8.1). Systemic illnesses also may cause dull mentation; thorough physical examination and appropriate diagnostic tests facilitate detection of these diseases.



FIG. 8.1 Dull mentation in a horse with cerebral toxicosis caused by sage toxicity (*Salvia* species).

Changes in behavior are consequences of diseases affecting the forebrain: the cerebrum or the relay areas of the diencephalon. Abnormal behavior caused by forebrain dysfunction can be termed *dementia*. Some common examples of dementia include head pressing, compulsive walking (often around the inside of an enclosure), frequent yawning, loss or absence of innate behaviors such as

udder seeking by neonates and mutual affinity of dams and offspring, and loss of learned behaviors such as the ability to be led by a lead rope and halter. Hyperexcitability, rage, mania, exaggerated fear, or frantic motor activities are suggestive of a lesion of the limbic system of the forebrain, an assembly of interconnected neurons in the brain that is involved in emotional responses and patterns of behavior. Animals so affected may strike or kick at inappropriate times, demolish their stalls, bellow, show belligerence, or, if recumbent, struggle violently.

Maintenance of mental alertness is the role of the ascending reticular activating system (ARAS) of the brainstem, which repetitively signals the forebrain to maintain consciousness. The ARAS is important in maintaining the animal's level of consciousness and arousal. The relationship between the cerebral cortex and the ARAS is sometimes described as follows: The cerebral cortex determines the *content* (external display) of consciousness, and the ARAS determines the *level* of consciousness. Diseases affecting the ARAS tend to produce profound depression of consciousness. The forebrain is the “seat of consciousness”: Conscious perception of both external stimuli (e.g., vision, hearing, touch) and internal stimuli (e.g., abdominal pain) depends on its integrity. In general, level of consciousness is *not* substantially altered by forebrain diseases unless the injury is diffuse and severe.

A seizure (convulsion, ictus) is a manifestation of forebrain dysfunction characterized by involuntary somatic and autonomic motor activities and/or loss of consciousness. Seizures may be generalized or focal (partial). Generalized seizures are characterized by recumbency, loss of consciousness, flailing or galloping motions of the limbs, elimination of feces and urine, and nystagmus. Localized involuntary movements with or without obvious alterations of consciousness characterize focal seizures. Alternatively, focal seizures may result in episodes of abnormal or bizarre behavior or momentary lapses of consciousness without collapse or significant motor activity. A third form of seizure is focal with secondary generalization. The onset of the seizure is focal within the forebrain, but seizure activity subsequently spreads throughout the brain, resulting in a generalized seizure. Animals with this form of seizure activity exhibit initial focal signs such as head turning, bellowing, and focal tremors followed by loss of consciousness and generalized seizure signs. Rarely, seizures in large animals may be preceded by an aura, a period in which the animal exhibits anxiety or restless behavior shortly before the onset of the seizure itself. A postictal phase, a period subsequent to the seizure during which

the animal is obtunded or, occasionally, restless and anxious, is common after seizures in most animals. The postictal phase usually lasts a few minutes to hours but may last as long as several days. The postictal phase may be the only stage of the seizure observed by the animal's handler. Thus seizures should be considered as a possible cause in any animal with a history of episodes of abnormal behavior. The typical history is that the animal is found in a dull or excited state, without the handler observing the onset of this change of behavior. Additional signs of postictal forebrain dysfunction may include blindness, absent menace responses, and insensitivity to cutaneous noxious stimulation. Additional supporting evidence includes physical injuries such as scrapes and cuts that may have been incurred during the seizure.

Abnormalities of forebrain dysfunction are the ultimate cause of seizure activity. During a seizure, neurons in the cerebral cortex exhibit spontaneous electrical activity, beginning either focally or simultaneously throughout the cortex, resulting in the clinical manifestations of focal or generalized seizures. Causes of seizures are legion, including alterations in the neuronal environment resulting from metabolic disturbances or toxicities and the effects of structural brain diseases such as congenital or developmental disorders, traumatic injuries, neoplasia, and inflammatory conditions. Diagnosis of seizures and other states of altered mentation must include a thorough physical examination and screening for metabolic diseases such as electrolyte imbalances and hepatic or renal failure.

Abnormalities in the neurologic examination found between seizures (interictal period) support a diagnosis of primary brain disease and are an indication for diagnostic procedures such as cerebrospinal fluid (CSF) tap. Some toxins cause additional systemic signs such as neuromuscular involvement (tremors, weakness) or parenchymal organ failure (icterus, uremia). Such signs, combined with clinical history and inspection of the environment, will help to direct specific tests for toxins.

Narcolepsy is a condition reported in cattle and horses wherein the normal mechanisms of sleep are disturbed.[42-45] Although sudden onset of sleep is one manifestation of narcolepsy, the acute onset of cataplexy—complete paralysis of striated muscles—is usually a more prominent clinical feature. Animals may be observed to collapse to the ground suddenly or to buckle at the knees. Cardiac and respiratory muscles are not affected. Narcoleptic attacks may be difficult to distinguish from seizures but are not accompanied by the involuntary motor activity that characterizes most generalized seizures. In some cases, traumatic

injuries to the head, face, and limbs can result.

Gait

Gait should be evaluated by moving the animal in a straight line, moving it in a tight circle, backing up, and moving it over obstacles such as a curb. Having the patient walk up and down a slope with varying steepness and with the head elevated may reveal subtler abnormalities. The examination may need to be modified depending on the species of the patient, amenability to handling, and consideration of safety concerns.

Quadrupeds begin walking by protracting the pelvic limb, followed by the thoracic limb of the same side, then the opposite pelvic limb, and finally the opposite thoracic limb. Gait on a level surface requires integrity of the musculature, motor and sensory components of the peripheral nerves, local spinal reflexes, ascending and descending pathways in the spinal cord, and centers within the brainstem. Dysfunction of ascending pathways (spinocerebellar tracts) results in mild to severe proprioceptive disturbances when standing or walking, which are exacerbated by turning the animal in a circle or stepping it on and off a curb. Animals with cerebral disease are usually able to perform simple motor activities such as walking along a straight path without obvious deficits but may exhibit decreased proprioception when they are required to perform complex motor activities such as walking on slopes or negotiating obstacles such as curbs or ground poles.

Subtle gait deficits may be elicited by walking and then trotting the patient or by walking or trotting the patient briskly and then stopping suddenly. While a helper is walking the animal in a straight line on a level surface, the examiner should take hold of the tail on the same side and pull the animal firmly to one side during the stance phase of the stride. The normal animal will move toward the pull but should not stumble or fall. If the tension on the tail is maintained, strength can be assessed. Animals with lesions anywhere within the ascending or descending pathways controlling gait may be weak and/or show decreased proprioception in the form of stumbling, tripping, or crossing the limbs. The same test can be performed in the patient at rest. Resistance to lateral pressure at rest is provided by the antigravity myotatic reflex. Because this reflex uses peripheral nerves and spinal cord segments of the lumbosacral intumescence, inability to resist the tail-pull test at rest is suggestive of lower motor neuron (spinal cord gray matter, nerve roots, or peripheral nerves) of the L3 to S2 spinal

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cord segments on the side being tested. Circling the patient in a wide circle and then a tight circle also may elicit deficits, such as knuckling, stumbling, interference between feet, pivoting on one foot, or wide movements in the outside limb (circumduction), that are not observed when the animal is walked in a straight line. Assessment of gait is facilitated when animals are halterbroken and can be led. This is not the case in many ruminants, so the clinician must rely more on observing the animal in its usual environment or in a confined area such as a pen. A handler may drive animals that are not halterbroken, but this should be done with due consideration of animal and handler safety.

A grading system for gait deficits has been described elsewhere,[46] as follows:

Grade 0:	Normal gait
Grade 1:	Very subtle deficits, observed only by an experienced clinician
Grade 2:	Deficits apparent to an inexperienced clinician
Grade 3:	Deficits apparent to laypersons
Grade 4:	Severe deficits, including stumbling, knuckling at the fetlock, falling
Grade 5:	Recumbency and inability to rise

Proprioception is the sense of body position in space. Proprioceptive information is collected by receptors in the skin, joints, muscles, and vestibular system. General proprioceptive pathways run mainly in the lateral (spinocerebellar) and dorsal (conscious perception) funiculi of the spinal cord, relaying information to centers in the brainstem, cerebellum, and cerebral cortex. The vestibular system and pathways in the spinal cord to the vestibular centers in the medulla oblongata and cerebellum also help to control proprioception. Abnormalities of proprioception include stumbling, adduction or abduction of the limbs, circumduction, and interference between limbs (Fig. 8.2). Animals with proprioceptive deficits often slap down the feet hard, rather like the gait of a person walking down stairs in the dark, unsure of where the next step is. Walking the animal off a curb or step or down a slope exaggerates this appearance. When spun in a tight circle, normal animals lift the inside forefoot as the weight shifts. The outside rear leg is put down within a line demarcated by the lateral margin of the trunk. When spun in a tight circle, patients with abnormal proprioception may pivot on the inner hindfoot rather than lifting it and replacing it into a normal position. The outside foot may circumduct widely, knuckle, or buckle, and the inside foot may step on the outside foot. Animals with abnormal proprioception worsen when they are required to climb hills or lift the foot over a curb or are walked with the head elevated. The gait of noncompliant cattle may be assessed by observation of maneuvers through

corrals, alleys, or a squeeze chute.

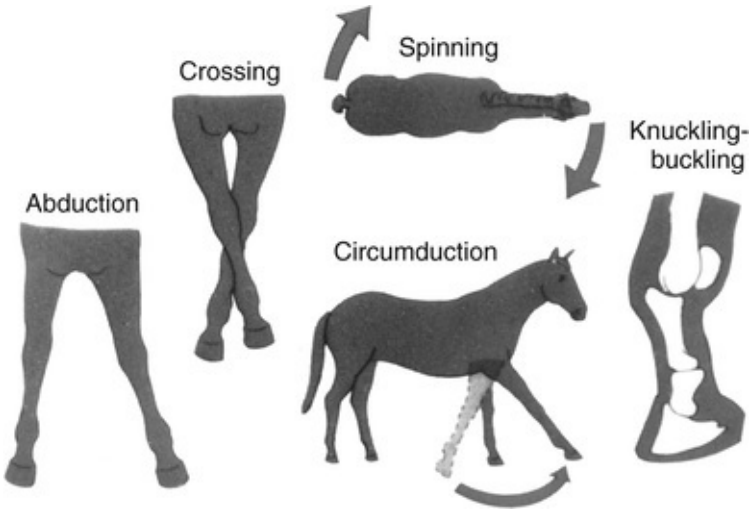


FIG. 8.2 Examples of conscious proprioceptive deficits in a horse. The signs of proprioceptive deficits in ruminants are similar.

Having the animal walk backward also tests proprioception. The normal subject should be able to do so in a smooth, coordinated fashion, with conjugate movement of diagonally opposite limbs. Animals with lesions of upper motor neurons in the descending motor pathways may exhibit abnormalities such as foot dragging and weakness, sometimes to the point of “dog-sitting”; others may be reluctant to move straight backward and will try avoidance maneuvers such as circling to one side or the other to avoid it. Such tactics should raise the index of suspicion of a neurologic deficit. Care should be taken when backing an animal with severe neurologic deficits because some animals could fall backward during the procedure. Animals that are uncooperative or that have been little handled may exhibit a reluctance to walk backward that is not caused by neurologic disease. Observing the patient's general level of cooperation and having a behavioral history will help the examiner determine whether the problem is caused by neurologic disease or the animal's lack of compliance.

Cerebellar disease causes errors in the rate, range, and force of voluntary movements; there is generalized ataxia with a rolling, drunken gait. Protraction of the limbs is delayed and limb movements are exaggerated, characterized either by excessive flexion during protraction, a condition known as *hypermetria,* or by *hypometria,* characterized by reduced joint flexion. There are often coarse bobbing movements of the head when the patient is walking; an

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intention tremor (most notable in the head) occurs when the animal initiates purposeful movements, such as reaching out to take food. Intention tremors may disappear when the animal is relaxed or recumbent. Cerebellar diseases may also result in opisthotonos or seizure-like fits.

Spontaneous circling is seen in diseases of the vestibular system and forebrain. Circling varies from a mild tendency to move in one direction to spinning and staggering in tight circles. Circling most often occurs *toward* the side of the lesion, except in paradoxical vestibular disease (caused by lesions in the vestibular components of the cerebellum) and with some asymmetric forebrain lesions, in which the animal circles *away* from the side of the lesion. Localization of the neurologic lesion in animals that circle is made based on other neurologic abnormalities such as dementia, seizures, central blindness (forebrain disease) or proprioceptive deficits, head tilt, spontaneous nystagmus, obtundation, and other cranial nerve deficits (vestibular disease).

Conscious Proprioception and Postural Reactions

The integrity of conscious proprioceptive pathways may be tested by means of the postural reactions. Normal animals stand at rest with the limbs in line with the abaxial boundaries of the trunk. Normal alert animals do not permit the limbs to be placed outside of the body axis or across the midline. After the examiner places the limbs in an abnormal position, the neurologically intact animal returns to a normal stance within a few seconds. Animals with conscious proprioceptive deficits allow the limb to remain in the abnormal position for longer than the usual period. This can vary from animals in which replacement of the limb into a normal position is slightly slowed to animals that do not try to replace the limb at all. The examiner should cross one of the animal's limbs over the opposite limb or abduct one limb; the normal response is for the limb to be placed back into the resting position. Normal animals often strongly resist attempts to place the limbs in abnormal positions. It should be noted that normal animals are extremely variable in their responses to this maneuver, so undue reliance should not be placed on its results, particularly if there are no other signs of ataxia. Animals with proprioceptive deficits may spontaneously place the limbs in abnormal positions: excessively adducted, abducted, or even crossed. Abnormalities of proprioception alone are poorly localizing signs, although a couple of generalities may be stated. Unilateral lesions rostral to the medulla

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oblongata produce mild to moderate proprioceptive and postural deficits in the *contralateral* limbs. Unilateral lesions in the medulla oblongata or spinal cord produce more severe proprioceptive and postural deficits in the *ipsilateral* limbs. Lesions of the cerebellum rarely result in postural deficits.

Additional postural reactions such as hopping, hemiwalking, and wheelbarrowing can be tested in small ruminants, calves, and some foals. Hopping is tested in the thoracic limbs by lifting the pelvic limbs a few inches off the ground by means of a hand and arm placed around the abdomen, flexing one thoracic limb slightly, and moving the animal away from the side of the flexed thoracic limb so that it must hop laterally on the thoracic limb still in contact with the ground. It is easiest if the examiner stands in one place and turns clockwise when testing the animal's right thoracic limb and counterclockwise when testing the left thoracic limb. Hopping in the pelvic limbs can be tested similarly, supporting both thoracic limbs off the ground with an arm around the chest. Hemiwalking is done by supporting both limbs on one side of the body in a slightly flexed position and pushing the animal toward the opposite side so that it must walk laterally on the two limbs still in contact with the ground. Both hopping and hemiwalking should be done with care not to push the patient over. Adult horses can be made to hop on one thoracic limb by picking up the opposite limb and firmly pushing the head and shoulders laterally. Hopping and hemiwalking involve the same ascending and descending motor tracts involved in gait on a level surface but also require input from the forebrain. These maneuvers are abnormal on the ipsilateral side in animals with lesions in the skeletal muscles, peripheral nerves, spinal cord, and medulla oblongata and on the contralateral side in animals with lesions in the midbrain or forebrain. Animals with forebrain lesions have normal gait on a level surface but subtle deficits in hemiwalking and hopping.

Abnormalities of Posture and the Righting Response

Posture refers to the position of the body and head in space, in relationship to gravity and to each other. Animals adopt slightly different postures when on a sloped or uneven surface compared with posture on a level surface. However, sustained asymmetric postures such as head tilt (Fig. 8.3), in which one ear is closer to the ground than the other, and head turn (Fig. 8.4), in which the nose is turned back toward the trunk, are abnormal. Circling often accompanies head tilt

and head turn in asymmetric vestibular disease, and all tend to be toward the direction of the lesion. The exception to this rule occurs in paradoxical vestibular syndrome, in which head tilt and circling occur in a direction away from the side of the lesion.



FIG. 8.3 Head tilt caused by vestibular dysfunction in a horse that sustained head trauma.

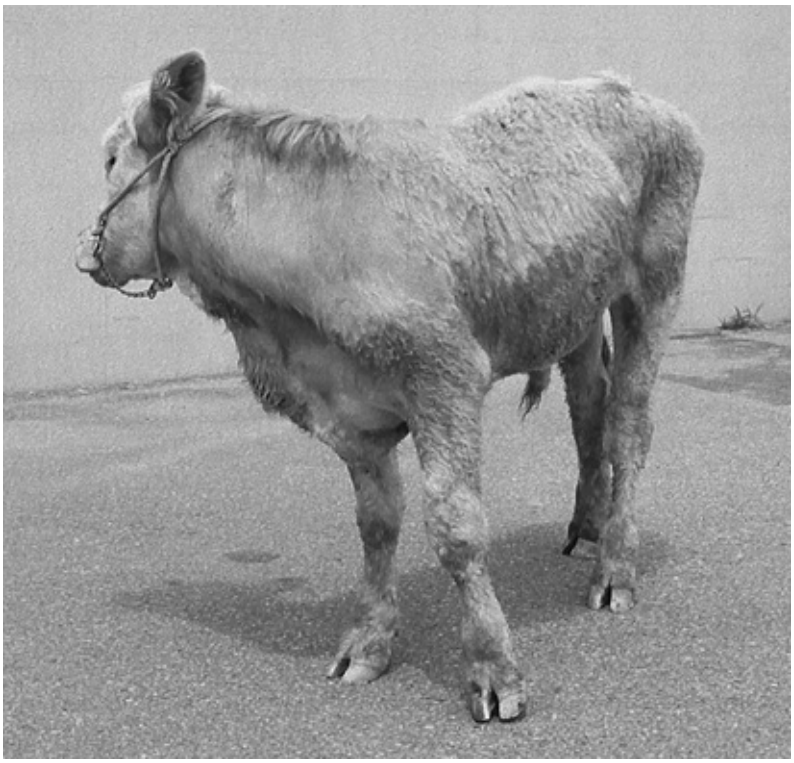


FIG. 8.4 Head turn in a steer with polioencephalomalacia.

The righting response is most easily tested in small ruminants and in recumbent large animals (Fig. 8.5). The response is initiated by receptors in the eyes and vestibular labyrinths and by proprioceptive receptors in the joints, tendons, and muscles. Information regarding limb position and balance is relayed ultimately to the cerebral cortex. Descending impulses are initiated in the motor cortex and relayed via the brainstem, cerebellum, and spinal cord to the appendicular musculature. The normal response to stimulation is to lift the head, assume sternal recumbency, and rise. The normal horse rises on the thoracic limbs first, whereas the normal ruminant rises on the pelvic limbs first. Animals that are in lateral recumbency and unable to lift the head from the ground may have lesions in the peripheral or brainstem vestibular centers or in the cervical spinal cord cranial to the C4 spinal cord segment. Unilateral lesions in this area result in an inability to lift the head from the ground when the lesion side is up. When the lesion side is down, the animal can raise the head slightly. Animals with incomplete lesions of the C7 to T2 spinal cord segments can lift the head and neck but cannot rotate the thorax into a prone position, and they may remain recumbent. Animals with lesions of the thoracolumbar and lumbosacral spinal cord (T3 to S3 spinal cord segments) can usually lift the head and neck, arise on the thoracic limbs, and assume a dog-sitting position.

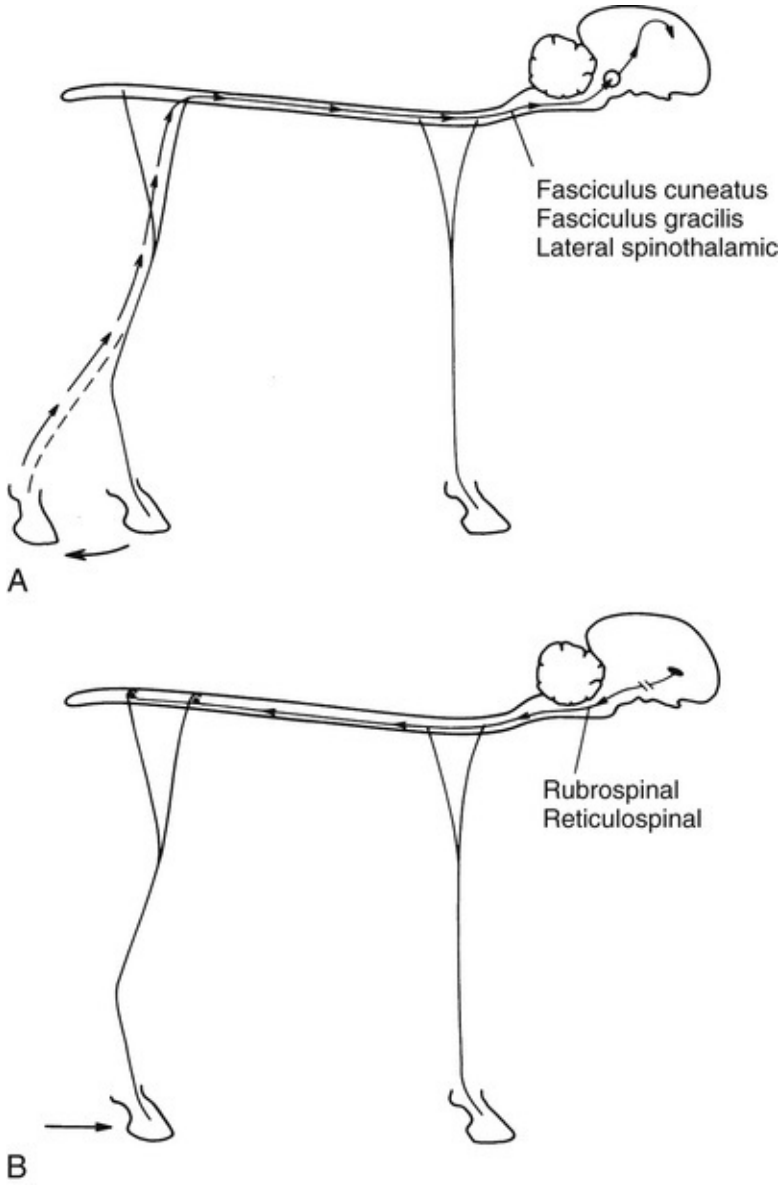


FIG. 8.5 **A,** Afferent pathways responsible for providing proprioceptive information to the brainstem and higher centers. **B,** Efferent pathways responsible for providing motor activities to the motor neurons.

Spinal Reflexes

The spinal reflexes are stereotyped responses to specific stimuli. They include the myotatic or tendon reflexes, the cutaneous trunci reflex (incorrectly called the “panniculus reflex”), the perineal reflex, and several others. As their names imply, spinal reflexes depend on the integrity of local spinal cord segments; dorsal and ventral nerve roots; and peripheral nerves, neuromuscular junctions,

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and muscles. Lesions of descending pathways in the spinal cord that are located cranial to the spinal components of the peripheral nerves to the limbs being tested result in *normal to increased* spinal reflexes and are commonly referred to as *upper motor neuron lesions.* Lesions in the gray matter of the spinal cord segments at the level of the reflex arc, the ventral roots, or peripheral motor nerves cause *diminished* spinal reflexes and are commonly referred to as *lower motor neuron lesions.*

It is appropriate at this point to define the terms *upper motor neuron* and *lower motor neuron.* Upper motor neurons are nerve cells contained completely within the CNS, with cell bodies in the brain and axons that terminate at synapses within the brain or spinal cord. Diseases affecting upper motor neurons result in normal to increased spinal reflexes, variable severity of weakness, and variably increased muscle tone (spasticity). The nerve cell bodies of somatic lower motor neurons lie in the nuclei of cranial nerves in the brainstem or in the ventral horn gray matter of the spinal cord. The axons exit the CNS, course within the peripheral or cranial nerves, and terminate at neuromuscular junctions. Diseases affecting lower motor neurons result in decreased spinal reflexes, ataxia, moderate to severe weakness, decreased muscle tone (flaccidity), and rapid, pronounced atrophy of the denervated muscles.

Myotatic Reflexes

Myotatic or tendon reflexes are tested by sharply striking the tendon of a specific muscle (or sometimes the muscle itself) and evaluating the strength of the reflex contraction. The afferent component of the reflex arc involves the muscle spindles, which are stretch detectors; sensory fibers in the peripheral nerve; the dorsal nerve root and its ganglion; and the connection from the sensory nerve fiber to the lower motor neuron in the ventral horn of the same spinal cord segment (Fig. 8.6). The efferent component of the reflex arc involves the lower motor neuron, ventral nerve root, motor fibers in the peripheral nerve, the neuromuscular junction, and the muscle being tested. Lesions in the spinal cord cranial to the level of the reflex arc and lesions of the brain result in *normal to increased* myotatic reflexes after a period of several days. Lesions in either the afferent or the efferent components of the reflex arc result in *decreased to absent* myotatic reflexes.

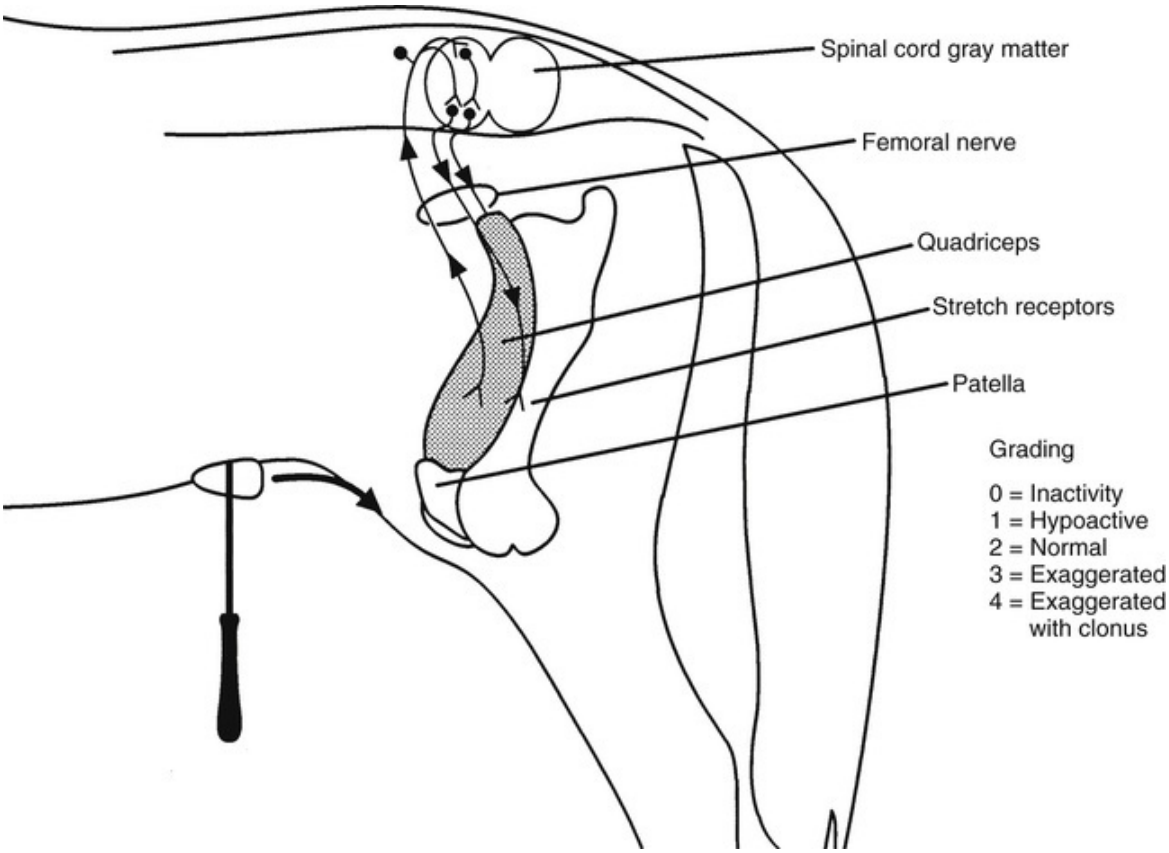


FIG. 8.6 Pathways governing patellar tendon reflex.

In adult horses and many adult cattle, myotatic reflexes can be tested only in recumbent animals. Some cattle can be cast with ropes for this purpose, and young animals and small ruminants can be placed in lateral recumbency for testing. These reflexes should be tested only in the limbs that are uppermost when the animal is lying on one side. The animal must be turned over to test the limbs on the opposite side; however, reflexes are often diminished in limbs that have been laid upon for prolonged periods of time (hours). In adult horses and cattle, only patellar reflexes can be reliably tested. The reflex responses are assigned a qualitative clinical score as follows:

0—No reflex activity
1—Hypoactive
2—Normal
3—Hyperactive
4—Hyperactive and clonic

Clonus is a phenomenon observed with severe upper motor neuron lesions: the response of the muscle being tested is a series of rapid, repeated contractions rather than a single contraction. The innervation of the limbs is listed in Tables 8.4 and 8.5.

TABLE 8.4

Innervation of the Thoracic Limbs of Large Animals

Spinal Cord Segment	Peripheral Nerve	Muscle(s)
C7	Suprascapular	Supraspinatus, infraspinatus
C6, C7	Subscapular	Subscapularis
C7, C8, T1	Pectoral	Subscapularis, pectoral muscles
C6[a], C7, C8	Musculocutaneous	Biceps brachii, coracobrachialis, brachialis
C8, T1, T2	Median	Flexor carpi radialis, deep digital flexor, superficial digital flexor
C8[a], T1, T2	Ulnar	Flexor carpi ulnaris, deep digital flexor, superficial digital flexor
C7, C8, T1	Radial	Triceps, extensor carpi radialis, ulnaris lateralis, lateral and common digital extensors
C6[b], C7, C8	Axillary	Deltoideus, teres minor, subscapularis, cleidobrachialis
C7, C8	Long thoracic	Serratus ventralis
C8, T1, T2[b]	Thoracodorsal	Latissimus dorsi
C8, T1	Lateral thoracic	Cutaneous trunci

[a]Contributes innervation in the ruminant only.

[b]Contributes innervation in the horse only.

TABLE 8.5

Innervation of the Pelvic Limbs of Large Animals

Spinal Cord Segment	Peripheral Nerve	Muscle(s)
L3[a], L4, L5, L6[b]	Femoral	Quadriceps
L5[a], L6, S1	Cranial gluteal	Gluteals, tensor fascia lata
S1-S5	Caudal gluteal, pudendal	Biceps femoris, middle and superficial gluteals
L5[a], L6, S1, S2	Sciatic, peroneal	Lateral digital extensor, long digital extensor, short digital extensor, cranial tibial
L5[a], L6, S1, S2	Tibial	Gastrocnemius, popliteus, superficial and deep digital flexor, interosseus
L5[a], L6, S1, S2	Pudendal	Retractor penis
S3-Cd5	Caudal rectal	Rectum, anal sphincter, bladder

[a]Contributes innervation in the horse only.

[b]Contributes innervation in the ruminant only.

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Thoracic Limb Myotatic Reflexes

Triceps Reflex.

Hold the limb moderately flexed at the elbow, and percuss the triceps tendon just above the olecranon using a heavy instrument. The normal response is a contraction of the triceps muscle, leading to retraction of the upper limb and extension of the elbow. The triceps reflex measures the integrity of the radial nerve and the C7 to T1 spinal segments.

Biceps Reflex.

Hold the limb moderately extended at the elbow and place the supporting hand over the attachment of the biceps muscle on the dorsomedial aspect of the limb at the level of the elbow joint. Percuss the biceps tendon or the taut biceps muscle with a heavy instrument. Contraction of the muscle may be perceived visually or by palpation. A slight flexion of the elbow and extension of the carpus is normal. The test measures the function of the musculocutaneous nerve and spinal cord segments C6 to C8 in ruminants and C7 and C8 in horses.

Lesions cranial to C6 result, within several days from the time of injury, in general hyperreflexia of both thoracic limbs and pelvic limbs. Lesions located in spinal segments C5 to T2 result in immediate hyporeflexia to areflexia of the thoracic limbs and, within several days, hyperreflexia of the pelvic limbs.

Pelvic Limb Myotatic Reflexes

Patellar Reflex.

Flex the stifle moderately, and sharply percuss the middle patellar ligament with a heavy instrument. The normal reflex is a sharp contraction of the quadriceps femoris muscle resulting in extension of the stifle and a forward jerk of the lower part of the limb. The patellar reflex measures the function of the femoral nerve, the quadriceps femoris muscle, and L3 to L5 and L4 to L6 spinal cord segments in horses and cattle, respectively.

Cranial Tibial Reflex.

The cranial tibial reflex is elicited by flexing the hock and sharply striking the belly of the cranial tibial muscle. The reflex consists of a slight extension of the

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digit. The cranial tibial reflex is mediated through the peroneal and sciatic nerves and spinal cord segments L5 to S2 and L6 to S2 in the horse and the ruminant, respectively. Lesions of the spinal cord anterior to L3 segments result in hyperreflexia, whereas lesions of L3 to L6 spinal segments result in hyporeflexia or areflexia.

Flexor (Withdrawal) Reflexes.

The flexor reflexes are elicited on the upside front and hind limb in the recumbent large animal. For safety, the examiner should be positioned on the dorsal side of the animal or well cranial to the limb being tested. A painful stimulus is applied to the uppermost foot or distal limb. The normal response consists of two phases: (1) rapid reflex limb flexion, and (2) slower conscious perception of and response to the stimulus, characterized by attempts to assume sternal recumbency, vocalization, ear and eye movements, and/or kicking. The thoracic limb flexor reflex tests the integrity of the axillary, median, and musculocutaneous nerves and spinal cord segments C5 through T2, as well as the flexor muscles of the limb. The pelvic limb flexor reflex is mediated by the sciatic, peroneal, and tibial nerves; the pelvic limb flexor muscles; and spinal cord segments L6 to S2.

Spinal cord and peripheral nerve lesions may be localized further by testing the integrity of the sensory innervation of the skin of the limbs. Areas of decreased or absent cutaneous sensation reflect lesions of the peripheral nerves innervating the regions of the skin or of the spinal cord segments in which those sensory nerves terminate. The skin over the trunk and much of the limbs is innervated by more than one peripheral nerve. Some areas of the limbs derive sensory innervation from a single peripheral nerve. These areas are termed the *autonomous zones* for those peripheral nerves. Damage to a peripheral nerve innervating the skin of a limb therefore will result in decreased to absent cutaneous sensation in the autonomous zone for that nerve. This information can be used to localize lesions. Decrease in or loss of sensation to an entire limb or to limbs on both sides of the body suggests a lesion affecting several local spinal cord segments or a transverse spinal cord lesion rostral to the affected limbs.

Other Spinal Reflexes

Perineal Reflex.

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The perineal reflex is elicited by pinching the mucocutaneous junction of the anus. The normal reflex includes tightening of the sphincter muscle and contraction of the ventral tail muscles. Conscious perception of the stimulus produces avoidance or protective responses that may range from a slight movement of the pelvic limbs and pelvis to a violent kick. The reflex is mediated by the pudendal nerve and spinal cord segments S1 to S5. Lesions in the nerve or in the sacral spinal cord result in a dilated, atonic rectal sphincter that fails to respond to noxious stimuli. Additional signs of sacral spinal cord injury may include fecal impaction in the rectum and a dilated urinary bladder. The bladder is full of urine and dribbles whenever digital pressure is applied through the rectum or vagina. The perineum remains wet and may become irritated from constant contact with urine.

Cutaneous Trunci Reflex.

The cutaneous trunci reflex (also known incorrectly as the “panniculus reflex”) is a shrugging or flinching of the skin over the thorax when it is stimulated by light touch or by pinching. Tap the skin with an extended thumb (in adult horses) or with a hemostat. The normal reflex response is a skin twitch often followed by a conscious avoidance maneuver such as moving away from the stimulus. The afferent part of the cutaneous trunci reflex is mediated by the segmental spinal nerves and dorsal nerve roots in the territory of the reflex. The tracts ascend in the dorsal funiculi of the spinal cord and synapse on efferent neurons in spinal segments C8 to T1 in ruminants and C8 to T2 in horses. The efferent axons exit in the ventral roots and form the lateral thoracic nerve, which innervates the cutaneous trunci muscle. The degree of reflex responsiveness varies among the large animal species. Sheep, goats, and many cattle possess a poor cutaneous trunci reflex. Horses and Zebu cattle have a well-developed reflex.

Cervical Reflexes.

Two reflexes have been described in the cervical area of the horse.[47] The cervical reflex is tested by tapping or pinching the skin of the cervical region over the brachiocephalicus muscle and behind the second cervical vertebra. The expected response is contraction of the brachiocephalicus muscle and twitching of the skin. The pathway is believed to involve the cervical segmental spinal nerves and the local spinal cord segments. The cervicofacial reflex is elicited in

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horses by tapping the skin as described for the cervical reflex. As the skin is stimulated in normal horses, the ear reflexively twitches rostrally and ventrally, and the commissure of the lip retracts. This test measures the integrity of the dorsal funiculi of cervical spinal cord segments and the facial nerve in the medulla oblongata. The diagnostic usefulness of this test in ruminants is unknown.

Both reflexes may be abnormal in animals with lesions affecting the cervical spinal cord, such as cervical vertebral stenotic myelopathy in horses. The cervicofacial reflex also may be diminished or absent in animals with caudal brainstem lesions involving the facial nerve or with peripheral facial nerve lesions.

“Slap” Test (Laryngeal Adductor Reflex).

A sharp slap applied in the saddle region on one side of a horse's thorax results in adduction of the vocal folds of the larynx on the opposite side.[48] Standing on one side of the animal, the examiner curls his or her fingers around the dorsolateral aspect of the larynx on the opposite side. A slap is applied to the saddle region on the side on which the examiner is standing. The response is palpated as a small movement of the arytenoid cartilage felt under the fingertips on the opposite side of the larynx. The laryngeal adduction elicited in this test can also be observed endoscopically. The pathway for the reflex is only partially understood. Sensory information from the skin and/or pleural stretch receptors is relayed to the spinal cord in the segmental spinal nerves. The ascending pathways cross the spinal cord and run cranially in the spinal cord to the origin of the vagus nerve in the medulla oblongata. The efferent part of the reflex runs in the cervical vagosympathetic trunk and thence to the recurrent laryngeal nerve, which branches from the vagus in the cranial thorax. The recurrent laryngeal nerve courses cranially alongside the trachea to the larynx. Reduced or absent laryngeal adductor reflexes are found in animals that have lesions of the cervical spinal cord but also in those with caudal brainstem lesions, vagus nerve lesions, and lesions of the left recurrent laryngeal nerve (some of which are clinical “roarers”). The test's accuracy may be limited. In one study there was poor correlation when predicting the presence or absence of cervical spinal cord or brainstem disease.[49]

Muscle Mass and Tone

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Normal mass and tone of the musculature depends on an intact nerve supply. Primary diseases of muscle and loss of use of a limb secondary to orthopedic disease are often associated with mild to moderate muscle atrophy that develops over weeks to months. Atrophy caused by denervation, however, is more severe and rapid in onset. Visible loss of mass of specific muscles or groups of muscles is most likely caused by damage to the nerve supply to those muscles, either by direct injury to peripheral nerves or by injury to the cell bodies of those nerves in the ventral horn of the gray matter of the spinal cord (Fig. 8.7). Knowledge of the central origins of the nerves to the limbs and the course of those nerves in the periphery can be used to specifically localize neurologic lesions (see Tables 8.4 and 8.5). Electromyography and nerve conduction testing can further be used to help identify muscle denervation and peripheral neuropathies (see Chapter 35).



FIG. 8.7 Muscle atrophy in the gluteal muscles in a horse with equine protozoal myeloencephalitis.

Muscle tone can be evaluated in the recumbent animal by passively flexing the limbs. Evaluation is not accurate in the standing animal or in animals supported in slings because of resistance from taut bands of connective tissue. In normal animals repeated flexion is accompanied by an increase in the tone in the flexed limb. The limbs of animals with a lower motor neuron deficit remain flaccid.

The tone of the thoracic limbs is controlled through spinal cord segments C6 to T2 and the radial, musculocutaneous, median, ulnar, axillary, and long thoracic nerves. The motor tone of the pelvic limbs is controlled through spinal

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cord segments L3 to S2 and the femoral, cranial and caudal gluteal, and sciatic nerves. The lower motor neurons to the anus originate in spinal cord segments S1 to S5, via the pudendal nerve. The tail is innervated by the coccygeal segmental spinal nerves.

Examination of Cranial Nerves

Examination of the cranial nerves is most easily carried out by examining the functions of groups of nerves that innervate particular regions of the head rather than by performing the examination in a strictly numeric order. For example, examination of vision and other ocular functions such as the menace response, pupillary light reflexes, and physiologic nystagmus reveals the integrity of several cranial nerves, not only II, III, IV, and VI but also V (sensory to the cornea), VII (motor to the eyelids), and VIII (providing vestibular input to control the functions of III, IV, and VI), as well as centers within the brain.

Cranial Nerve I—Olfactory Nerve.

Reliable and specific testing of the sense of smell is difficult in animals. Large animals require an intact sense of smell to eat properly, so it can be inferred that animals with good appetites possess an adequate sense of smell. Having a blindfolded animal track food moved from side to side in front of the nose may be helpful. Irritating substances such as ammonia should not be used for evaluation of olfactory nerve function; such compounds stimulate nociceptors in the nasal mucosa, which are the dendrites of the maxillary nerve (cranial nerve V), rather than stimulating olfactory receptors innervated by the olfactory nerve. Loss of the sense of smell is more likely to be caused by disease within the nasal passages than by a primary neurologic disease.

Cranial Nerve II—Optic Nerve.

Vision and light perception are the functions of cranial nerve II, the optic nerve. Observing the animal's response to its environment provides a good initial assessment. Does it respond to visual cues such as movement or does it walk into objects? Noise may cause the animal to turn its head toward the sound, so the observer must be careful to distinguish such responses from those made in response to visual cues. A maze can be set up using straw bales or other objects, and then the animal can be gently driven through the maze. Normal animals will avoid colliding with objects. Animals that are severely obtunded, however, may

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walk into objects even when they can see. Thorough evaluation of the complete neurologic examination is necessary to distinguish this from true blindness.

The menace response measures the integrity of the entire visual pathway. The afferent pathway runs from the retina via the optic nerves and internal capsule to the visual areas in the occipital lobe of the cerebrum. Information from the visual cortex is processed and relayed to the ipsilateral motor cortex. The efferent pathway of the menace response runs from the motor cortex via the pons to the nucleus of the facial nerve in the medulla oblongata and thence via the facial nerve to the orbicularis oculi muscle. It is not known whether this pathway passes through the cerebellum, but it is clear that the ipsilateral cerebellar cortex is required for a competent menace response. The menace test is performed by rapidly advancing the hand toward the eye and observing closure of the eyelid. In addition to closure of the eyelid, some animals display a generalized avoidance response characterized by coordinated movement of the head and neck away from the stimulus. The opposite eye may be covered to ensure that only one eye is being stimulated. Care must be taken not to touch the face or eyelashes or create air currents near the face. Separate menacing gestures must be directed from both the nasal and the temporal aspects, in order to cover the entire visual arc. The menace response measures the integrity of the retina, optic nerve, optic chiasm, optic tracts, thalamus, internal capsule, and occipital cortex. There is approximately 90% crossing over of optic nerve fibers in the optic chiasm of livestock. Unilateral lesions central to the optic chiasm—in the optic tract, internal capsule, thalamus, or occipital lobe—cause loss of vision in the opposite eye, with apparently normal vision in the ipsilateral eye. It should be noted that normal neonatal animals may not display a response to a menace gesture because this is a learned response.

Menace deficit may be the result of facial nerve paralysis. In such cases the animal does not blink but shows avoidance of the stimulus by pulling the head away. Facial nerve deficits will be apparent in these animals by their inability to close the eyelids in response to cutaneous stimulation around the lid margins (palpebral reflex) and by other signs such as drooping of the lip and ear on the same side. Animals with cerebellar disease may also display a menace deficit yet possess normal vision. Menace deficits resulting from facial nerve or cerebellar disease may be differentiated from deficits in other areas by maze testing. Animals with cerebellar or facial nerve disease retain visual acuity and maneuver through the course successfully. In addition to the optic pathways, the test measures the integrative pathways in the frontal and parietal lobes of the

brain, the motor neurons, and the proprioceptive pathways (Table 8.6). Myasthenic diseases (e.g., botulism, hypocalcemia, hypomagnesemia) result in bilaterally decreased menace and palpebral responses but do not produce blindness.

TABLE 8.6
Guide to Neuro-Ophthalmologic Lesion Location

	Menace Response		Pupillary Light Reflex		
Lesion Location	**Ipsilateral**	**Contralateral**	**Ipsilateral**	**Contralateral**	**Maze Test[a]**
Unilateral retina, optic nerve	Absent	Present	Absent (direct), slightly dilated	Normal	Abnormal
Bilateral retina, optic nerve, optic chiasm	Absent	Absent	Fixed	Fixed	Abnormal
Unilateral oculomotor nerve	Absent	Present	Dilated nonresponsive	Normal	Normal
Unilateral occipital cortex	Present	Absent	Normal[b]	Normal[b]	Abnormal
Bilateral occipital cortex	Absent	Absent	Normal[b]	Normal[b]	Abnormal
Bilateral vagosympathetic trunk	Present	Present	Miotic	Normal	Normal
Bilateral cerebellar cortex	Absent	Absent	Normal	Normal	Normal[c]

[a]In unilateral cases, assumes that contralateral eye is blindfolded.

[b]Assuming that no cortical swelling has occurred.

[c]Animals walk abnormally but recognize and generally avoid obstacles.

The pupillary light reflex measures the integrity of the retina, optic nerves, optic chiasm, pretectal and oculomotor nuclei in the midbrain, oculomotor nerve, ciliary ganglia, and constrictor pupillae muscle. The test is performed by shining a bright light into each eye and observing constriction of the pupil in the ipsilateral eye (direct reflex) and the contralateral eye (indirect reflex). Lowering the ambient light level may facilitate this test by causing the pupils to dilate. The reflex in large animals is considerably slower than those observed in cats and dogs. A “swinging light” test has been recommended in large animals to reduce the dazzle and startle responses elicited by suddenly shining a bright light into the eyes.[46] From a position directly in front of the animal, a strong light is slowly swung from one eye to the other while bringing the light closer and closer to the head and observing the responses in each pupil. The effects on the pupillary light reflex of lesions at various levels along the visual pathway are shown in Table 8.6.

Unilateral lesions in the forebrain may result in blindness of the opposite eye.

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With forebrain lesions, the pupillary light reflexes are usually normal. If the forebrain disease is accompanied by increased intracranial pressure, the oculomotor nerve or nucleus may be compressed in the midbrain, resulting in ipsilateral mydriasis.

Cranial Nerves III, IV, and VI—Oculomotor, Trochlear, and Abducent Nerves.

The position of the globe in the orbit is governed by the activities of the oculomotor, trochlear, and abducent nerves. Dysfunctions of these nerves result in deviation of the globe that is constant in all head positions. Loss of oculomotor nerve function results in ventrolateral strabismus. Trochlear nerve dysfunction results in rotation of the dorsal aspect of the globe away from the midline (dorsomedial strabismus). Loss of abducent nerve function results in medial strabismus and inability to retract the globe, which is best demonstrated by closing the eyelid and then pushing on the globe through the eyelid. The normal reflex is a retraction of the globe.

Competent function of the oculomotor, trochlear, and abducent nerves is also required for the oculocephalic reflexes. When the head is turned from side to side in a horizontal plane, physiologic horizontal nystagmus is observed, with the fast phase of the nystagmus in the direction of head movement. The sensory receptors for this reflex lie within the semicircular canals of the inner ear, and they detect angular acceleration of the head. Input from the semicircular canals is transferred to the vestibular centers in the medulla oblongata and the cerebellum and then to the nuclei of cranial nerves III, IV, and VI. Lesions of the peripheral or central components of the vestibular system can also result in abnormal eye position (strabismus) and movement (nystagmus), described in more detail later. With peripheral or central vestibular lesions, however, eye position typically changes when the head and neck are moved, in contrast to the constant deviation of the globe seen with direct lesions to the oculomotor, trochlear, and abducent nerves.

The oculomotor nerve is motor to the levator palpebrae superioris muscle, the most important of the muscles responsible for elevation of the upper eyelid. Lesions of the nerve cause ptosis (drooping of the upper eyelid) in addition to the signs described previously. Ptosis can also be induced by lesions of the sympathetic nerve supply to the eye because of paralysis of the superior tarsal (Müller's) muscle and, in the horse only, by lesions of the facial nerve, which

innervates the levator anguli oculi medialis muscle (see later).[50]

Cranial Nerve V—Trigeminal Nerve.

The trigeminal nerve is sensory to the face and motor to the muscles of mastication. The sensory functions of the trigeminal nerve are tested by lightly stimulating the forehead, upper and lower jaws, and muzzle using the tip of a closed hemostat or a finger. The normal response is one of avoidance using neck, facial, and appendicular musculature; the animal usually pulls the head away and blinks simultaneously. Some areas such as the cheeks, forehead, and chin are normally less sensitive, whereas the periorbital region, nasal planum, nasal septum, and lips are sensitive. The test evaluates the function of the sensory part of the trigeminal nerve, the trigeminal ganglion, the nucleus and spinal tract of the trigeminal nerve, the pontine sensory tract nucleus of cranial nerve V, the thalamus, and the sensorimotor cortex. After the trigeminal nerve enters the lateral aspect of the pons, axons both ascend and descend through the medulla as the spinal tract of the trigeminal nerve. Ascending information ultimately reaches the sensorimotor cortex via the thalamus, where it is consciously perceived. Descending information projects to the nucleus of the facial nerve in the medulla and also into the first cervical spinal segment. Unilateral loss of facial perception of touch most commonly results from damage to the peripheral portion of the trigeminal nerve, the trigeminal ganglion in the petrosal bone of the skull, or the contralateral forebrain (i.e., thalamus or cerebrum). Lesions affecting the spinal tract of the trigeminal nerve in the medulla and midbrain would likely be fatal because they also would affect adjacent respiratory and cardiovascular centers in the brainstem. Patients with bilateral facial hypalgesia most often have bilateral forebrain disease.

The palpebral reflex is elicited by lightly touching the periorbital area (both above and below the eye) and observing a brisk closure of the eyelid. This reflex reflects the sensory function of the trigeminal nerve and the motor function of the facial nerve and orbicularis oculi muscle. Simultaneous loss of the menace response and the palpebral reflex suggests a lesion in the facial nerve or the orbicularis oculi muscle. Loss of the palpebral reflex with normal menace responses suggests a lesion in the trigeminal nerve or ganglion. Loss of menace response with preservation of the palpebral reflex and pupillary light reflex suggests the presence of either contralateral forebrain disease or ipsilateral cerebellar cortical disease.

The jaw should be opened to assess the strength of the masticatory muscles.

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This measures both the sensory (proprioceptive) fibers of the trigeminal nerve and the motor component of the nerve. Bilateral lesions of the motor component of the trigeminal nerve result in a dropped jaw. Affected animals may protrude the tongue but can retract it normally when stimulated. Animals with dropped jaws may drool because they cannot hold saliva within the oral cavity. Unilateral lesions of the trigeminal nerve produce asymmetric jaw closure, with deviation of the mandible away from the affected side, and neurogenic atrophy of the visible masticatory muscles (i.e., masseter and temporalis).

Cranial Nerve VII—Facial Nerve.

The motor nucleus of cranial nerve VII (the facial nerve) originates in the middle and ventral part of the medulla oblongata. The motor fibers are distributed to muscles of facial expression. Just as the motor fibers are exiting from the lateral aspect of the brainstem, they merge with axons from the parasympathetic facial nucleus. These autonomic fibers innervate the lacrimal and salivary glands and separate from the motor component of the facial nerve as it traverses the petrous temporal bone. Lesions of cranial nerve VII located between the brainstem and this separation usually result in “dry eye.” More distal lesions, however, have no effect on tear production. The tone of the facial musculature is examined by palpation of the ears, lips, eyelids, and muzzle. Clinical signs of facial nerve dysfunction include drooped ear and lips, drooling saliva, and retention of food in the cheek pouch on the denervated side (Fig. 8.8). Closure of the eyelids is weak in partial facial nerve lesions and absent in severe lesions. Despite this, there is slight drooping of the upper eyelid (ptosis) because of paralysis of the levator anguli oculi medialis muscle, which contributes to eyelid retraction. In species with a soft muzzle (e.g., horses, sheep, goats), there is a marked deviation of the nasal filtrum *away* from the side with the lesion after unilateral loss of facial nerve function. The filtrum of affected cattle is not deviated because of the large amount of fibrous tissue in the planum nasale. In *chronic* facial paralysis the face may be deviated *toward* the affected side because of atrophy and contracture of the denervated musculature of the face. In horses neurogenic atrophy of the parotidoauricularis muscle is evident as a groove behind the vertical ramus of the mandible.

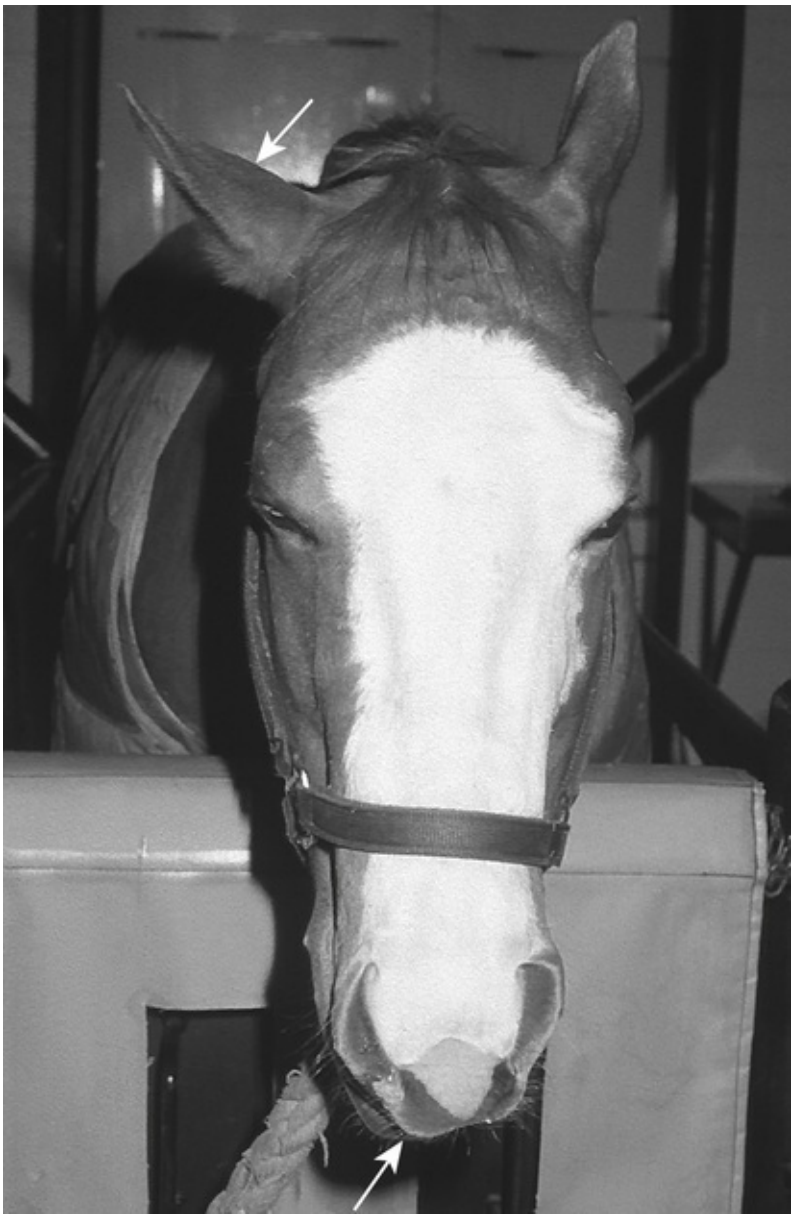


FIG. 8.8 Acute right facial paralysis in a horse with guttural pouch mycosis. Note the drooped right ear and deviation of the muzzle toward the left side *(arrows)*.

Cranial Nerve VIII—Vestibulocochlear Nerve

Vestibular System.

The function of the vestibular system—which is composed of the sensory structures in the inner ear (semicircular canals, utriculus, saccule), the vestibular portion of cranial nerve VIII, and the central components of the vestibular

system in the medulla oblongata and cerebellum—is tested by assessment of gait, extensor tone, head posture, and eye movements. Signs of vestibular dysfunction include a staggering gait, circling, falling, rolling, head tilt, and spontaneous nystagmus. Lesions can be classified as peripheral or central. Diseases affecting the inner ear or cranial nerve VIII result in signs of peripheral vestibular disease. Lesions affecting vestibular structures in the medulla oblongata result in central vestibular signs, and lesions affecting vestibular structures in the cerebellum result in paradoxical vestibular signs. Blindfolding affected patients results in a worsening of clinical signs because of elimination of visual compensatory mechanisms. Recumbent animals with vestibular lesions tend to lie with the side of the vestibular lesion downward. When turned, these animals spontaneously rotate back to the lesion-down position and may strongly resist attempts to turn them over. Animals with unilateral vestibular disorders typically have ventral strabismus in the ipsilateral eye and dorsal strabismus in the contralateral eye. Bilateral, symmetric lesions of the vestibular system are rare. Bilateral vestibular dysfunction does not cause head tilt, nystagmus, or strabismus. Affected animals are reluctant to move. They stand with a basewide posture, with the head held low, and fall easily when forced to move.

Cranial Nerves IX, X, and XI—Glossopharyngeal, Vagus, and Spinal Accessory Nerves.

Cranial nerves IX, X, and XI originate in the nucleus ambiguus, a column of motor neurons in the medulla oblongata. They provide motor control to the muscles of the neck, pharynx, and palate. The vagus nerve contains efferent fibers that stimulate the secretions of glands of the visceral and respiratory mucosa and control forestomach motility in ruminants. The glossopharyngeal and accessory nerves carry afferent fibers from the mucosa of the tongue, larynx, and pharynx.

The signs of glossopharyngeal and vagus nerve dysfunction include dysphonia (roaring, snoring), dysphagia, and regurgitation. Animals with pharyngeal paralysis regurgitate food and saliva from the nose. Roaring is a characteristic stridor emanating from the larynx. The abnormal sound may be heard only during exercise. Functional examination of these nerves should include auscultation of the larynx for stridor, observation of the animal as it swallows, passage of a nasogastric tube to evaluate deglutition, endoscopic examination to evaluate pharyngeal and laryngeal movements, and palpation of the larynx for muscle atrophy. The slap test, described earlier, is a test for function of the vagal

innervation of the larynx via the recurrent laryngeal nerve. Specific descriptions of the endoscopic appearance of pharyngeal paralysis and roaring are presented elsewhere (see Chapter 31).

Signs of spinal accessory nerve dysfunction are extremely rare and include atrophy of the trapezius, sternocephalicus, and brachiocephalicus muscles.

Sympathetic Innervation of the Head—Horner's Syndrome.

Preganglionic sympathetic motor fibers that innervate structures of the head originate from the first three thoracic spinal cord segments. These fibers ascend the neck in the vagosympathetic trunk to the cranial cervical ganglion under the tympanic bulla, where they synapse with postganglionic sympathetic fibers. The postganglionic fibers are distributed to the smooth muscles of the head via the ciliary nerves, passing through the petrous temporal bone area. Lesions anywhere along the course of the preganglionic or postganglionic sympathetic nerves, in spinal cord segments T1 to T3, or, rarely, in the upper motor neuron component of the sympathetic pathway in the cervical spinal cord or brainstem (tectotegmentospinal tract) cause a characteristic constellation of clinical signs known as *Horner's syndrome.* Signs include miosis, ptosis, and increased warmth on the ipsilateral side of the face. In cattle there is a loss of sweating on the ipsilateral half of the planum nasale, whereas in horses there is excessive sweating on the affected side of the head and upper neck. Miosis is produced by lack of sympathetic tone to the affected pupil. Diseases that could produce Horner's syndrome in large animals include lesions of the T1 to T3 spinal cord segments, mediastinal or thoracic abscesses or neoplasia, trauma or infection involving the cervical sympathetic trunk, esophageal perforations, guttural pouch mycosis in horses, otitis media and interna, and retrobulbar abscesses. Lesions of the midbrain may produce miotic pupils without other signs of Horner's syndrome.

Cranial Nerve XII—Hypoglossal Nerve.

The hypoglossal nerve supplies motor innervation to the muscles of the tongue and the geniohyoideus muscle. The nucleus is located in the caudal medulla oblongata. Hypoglossal nerve function is tested by pulling the tongue out of the mouth. Normal animals should have forceful resistance to passive manipulation of the tongue. Lesions of the hypoglossal nerve result in flaccidity and atrophy of the tongue. Acute lesions result in deviation of the tongue away from the side

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of the lesion; with time the tongue may deviate toward the affected side because of muscle atrophy and contracture.

Other Aspects of Physical Examination of the Patient With Neurologic Disease

Diagnosis of a neurologic disease can often be facilitated by the observation of physical abnormalities in other systems. When one examines animals with limb ataxia or tetraparesis, the head, neck, and back should be gently manipulated while the spine is palpated for pain, crepitation, or swelling. These findings could indicate the presence of a fracture, malformation, or luxation of one or more cervical vertebrae, vertebral osteomyelitis, diskospondylitis, or osteoarthritis of intervertebral joints. Do not manipulate the neck when there is evidence of acute cervical vertebral trauma. Swelling, bruising, or hair loss on the skin around the head or bleeding from the ears or nose could signify cranial trauma. Hair loss and dermatitis around the perineum and medial thigh may indicate urinary incontinence. In neonates a hairless patch over the dorsum of the spine or skull could indicate a meningomyelocele or meningoencephalocele. Crepitation over coxofemoral or stifle joints of recumbent cattle could indicate a luxation or fracture. The pelvic limb and pelvis should be examined in all recumbent large animals to detect displacement of the hip joint into the obturator foramen or fractures through the shaft of the ilium. All joints should be passively manipulated to detect dislocations or fractures. The heart should be auscultated for murmurs that could suggest left-sided endocarditis because such lesions can shower bacteria into the meninges. Odors on the breath such as ammonia, ketones, or petroleum distillates could provide clues about possible toxic causes. The ocular fundus should be examined ophthalmoscopically to detect retinal hemorrhages (trauma), papilledema (increased intracranial pressure), or vasculitis.

Examination of the Neonate

Most of the physical diagnostic techniques described in the preceding paragraphs for the adult may be applied to examination of the neonate. Most spinal reflexes of livestock are well developed after birth. In the normal foal younger than 3 weeks of age, the limbs are hypertonic and hyperreflexic, with occasional myoclonus occurring after percussion of the patellar or triceps tendons. This

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hyperreflexia is most pronounced in the pelvic limbs. A lack of menace response for up to 2 weeks after delivery is expected because the menace response must be learned. When restrained, the newborn foal relaxes into a trancelike state, periodically awakening and struggling violently before becoming passive again.

Bottle-reared calves aggressively attempt to suck while being examined, including vigorously head-butting the handler. Beef calves attempt to escape restraint and do not attempt to suck. See Chapter 17 for more on foals and Chapter 20 for more on neonatal ruminants.

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Localization of Central Nervous System Lesions

Localization of a CNS lesion based on clinical signs is vital because many specific diseases are restricted to particular regions of the CNS. Lesions can be localized to one of seven regions of the CNS: forebrain, midbrain, cerebellum, medulla oblongata, spinal cord, peripheral nerve (either cranial nerves or spinal nerves), and muscle. Once the clinician has located the anatomic site of a neurologic lesion, a list of rule-out diagnoses may be formulated. Additional tests, including CSF analysis, radiography, magnetic resonance imaging (MRI), computed tomography (CT), serology, electroencephalography, brainstem auditory evoked response (BAER), and myelography, can be performed to further characterize the disease.

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Localization of Neurologic Diseases by Major Clinical Signs

Abnormal Mentation and Behavior and Seizures

Decreased mental alertness (dullness, obtundation, stupor, coma) is the most common change of mental status in animals with neurologic disease, although increased responsiveness to external stimuli (anxiety, mania, aggression) sometimes occurs. Altered mentation results from lesions in the ARAS or after diffuse severe forebrain disease. Diseases affecting the ARAS tend to produce severe changes in mentation (stupor, coma), whereas those affecting the forebrain tend to produce mild obtundation with concurrent behavioral abnormalities (i.e., dementia). In order of worsening severity, decreased mental status in animals can be categorized as follows.

Letha gy.

Animals respond to normal stimuli but are duller than normal.

Stupor.

Animals appear to be asleep and will respond only to vigorous and painful stimuli. Responses are blunted even to these stimuli. Semicoma is a severe form of stupor wherein patients are too obtunded to remain standing.

Coma.

Animals are unconscious and will not respond even to the most painful stimuli. Animals in coma are recumbent.

Dementia.

Animals with dementia exhibit abnormal reactions and responses to their environments, including to inanimate objects, humans, and other animals within those environments. Signs are extremely variable, from head pressing and yawning to compulsive walking, bellowing, rearing, self-mutilation, and aggression.

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Seizures, Collapse.

Episodic abnormalities of behavior or consciousness are usually the result of seizure activity, narcolepsy or cataplexy, or syncopal attacks caused by cardiovascular or respiratory dysfunction. Intermittent toxicities or fluctuating metabolic abnormalities such as occasionally occur with hepatic encephalopathy may also cause episodic changes in mentation and behavior. Animals with a history of episodic collapse should undergo a thorough physical examination to determine whether disease of the cardiovascular system (e.g., cardiac arrhythmias, intermittent hemorrhage) or respiratory system (e.g., laryngeal paralysis) is present. Animals that have seizures usually have a period of abnormal behavior after the seizure (postictal phase of the seizure), whereas those with narcolepsy, cataplexy, or nonneurologic causes of collapse usually do not.

Diffuse forebrain disease often results from metabolic, toxic, or infectious diseases. Increased intracranial pressure, the consequence of early acquired hydrocephalus, mass lesions within the cranial vault, inflammatory diseases, or cerebral edema, tends to produce signs of diffuse forebrain dysfunction, which can range from mild to severe. Mild to moderate forebrain dysfunction usually results in an animal with decreased mental awareness or, more rarely, excitement and overreaction. Diffuse disease does not result in circling, and gait on a level surface may appear normal, or almost so. Gait may be abnormal, however, when the animal is challenged to ascend or descend slopes, step over objects on the ground, step onto and off curbs, circle, or back up. Postural and proprioceptive reflexes and reactions similarly may be abnormal. When an animal is walking at normal speed on a level surface, local reflexes in the spinal cord and regulatory information from the red and reticular nuclei in the brainstem control simple gait patterns. Movements that require visual input or complex limb and body integration of movements are initiated in motor centers of the cerebral cortex and regulated by the cerebellum. The combination of normal gait on a level surface with obvious proprioceptive and postural deficits should immediately alert the examiner to the likelihood of forebrain disease.

Vision and the menace response may be defective (see Blindness and Ocular Abnormalities, later). Pupillary light reflexes and oculocephalic reflexes are usually normal in animals with forebrain disease. Responses to noxious tactile stimuli, especially around the head, are reduced.

The hypothalamus regulates primitive functions such as eating, drinking, cardiovascular function, and sexual behavior. Lesions of the hypothalamus may

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cause behavioral changes ranging from profound depression, rage, and inappropriate sexual activities to unusual affection, as well as polydipsia, polyuria, bradycardia, and abnormal appetite (pica).

Seizures are the physical manifestations of spontaneous paroxysmal electrical activity arising in the forebrain. When seizure activity is limited to a small area of the cerebral cortex, the seizure is focal, resulting in localized abnormal motor activity such as muscular twitching in the face or in one limb or episodes of lateralizing abnormal behavior. More commonly the seizure is generalized or starts focally and becomes generalized to the entire cerebral cortex. Generalized seizures cause loss of consciousness, collapse, and generalized tonic-clonic motor activity. The presence of seizures indicates forebrain dysfunction, but the initiating cause may lie elsewhere in the brain; the origin may even be extracranial. *Epilepsy* is a term that means repeated seizures of any cause, although it is often used to indicate seizures of unknown cause. The nature of the seizure, whether focal or generalized, is not a reliable indicator of the underlying cause. Congenital, familial, or idiopathic epilepsy syndromes such as benign epilepsy of Arabian foals are usually characterized by generalized seizures. Partial or focal seizures more commonly indicate an acquired cause. Animals with seizures should undergo a complete physical examination, together with diagnostic testing for suspected toxins and underlying metabolic diseases, as well as a thorough neurologic examination to localize any interictal neurologic signs. Further diagnostics such as CSF analysis and MRI are performed as indicated after this initial work-up.

When forebrain disease is unilateral or asymmetric, asymmetry of clinical signs becomes apparent. Circling often occurs, ranging from a tendency to drift toward one side to obvious and compulsive circling around the inside of an enclosure. It is usually possible to stop the circling, although the animal may be reluctant to turn in the opposite direction. Proprioceptive and postural reaction deficits may be present in the limbs on the side of the body opposite to the lesion (contralateral) and vary in severity with the severity of the underlying neurologic disease. The head and neck may be turned to one side (usually toward the side of the lesion), but the head tilt characteristic of vestibular disease is not seen. The absence of signs such as head tilt, nystagmus, and strabismus, together with the presence of contralateral proprioceptive and postural reaction deficits, distinguishes forebrain lesions from those affecting the vestibular system.

Specific diseases associated with the forebrain of ruminants and horses are given in Tables 8.7 and 8.8, respectively.

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TABLE 8.7

Diseases of Ruminants That May Produce Forebrain Signs

Disease	Predominant Clinical Signs	Species Affected
Ammoniated feed toxicosis	Trembling, fear, uncontrolled running, crashing through objects, coma, convulsion	Cattle
Babesiosis (exotic)	Odontoprisis, ataxia, conscious proprioceptive deficits, coma, convulsions	Cattle
Border disease	Ataxia, tremors, bunny-hopping	Sheep, goat
Borna disease (exotic)	Head tremors, hyperesthesia, ataxia, anorexia, compulsive walking, coma, convulsions	Cattle, sheep, goat
Bovine spongiform encephalopathy	Aggression, weight loss, milk production, ataxia, recumbency, coma	Cattle
Brain abscess, meningitis	Recumbency, opisthotonos, blindness, hyperesthesia, stiff neck, proprioceptive deficit, ataxia, head pressing, depression, coma	Cattle, sheep, goat
Brain tumor	Obtundation, facial paresis or paralysis, facial analgesia, head tilt, strabismus, nystagmus, loss of menace, hypermetria, ataxia	Cattle
Caprine arthritis-encephalitis	Obtundation, ataxia, head pressing, convulsions, coma	Goat
Ceroid lipofuscinosis	Blindness, ataxia, weight loss, coma, convulsions	Cattle
Citrullinemia	Recumbency, coma, convulsions, death by 4 days of age	Cattle
Coenurus cerebralis	Blindness, circling, ataxia, conscious proprioceptive deficit, head tilt, recumbency, coma, convulsions	Sheep
Ethylene glycol poisoning	Obtundation, somnolence, blindness, ataxia, facial analgesia, weak tongue, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cattle, sheep, goat
Globoid cell leukodystrophy	Ataxia, proprioceptive deficits, hyperreflexia, depression, coma	Sheep
Grass staggers	Tremor, ataxia that worsens with excitement or exercise	Cattle, sheep, goat
Heartwater (exotic)	Hyperesthesia, behavioral changes, muscular fasciculations, hypermetria, ataxia, head pressing	Cattle, sheep, goat
Hepatic encephalopathy	Hyperexcitability, aggression, rage, odontoprisis, ataxia, head pressing, coma, convulsions, semicoma, blindness, tenesmus, rectal prolapse	Cattle, sheep, goat
Hydrocephalus, hydranencephaly, microcephaly, anencephaly	Blindness, ataxia, proprioceptive deficit, ventrolateral strabismus, failure to suckle, dysphonia	Cattle, sheep, goat
Hypocalcemia	Cattle, doe: weakness, ataxia, inappetence, bloat, proprioceptive deficit, cool extremities, weak pulse, bizarre head posture, dysuria	Cattle, goat
Hypoglycemia	Coma, semicoma, convulsions, blindness, hyperesthesia, cold extremities	Cattle, sheep, goat
Hypomagnesemia	Stiffness, hyperexcitability, recumbency, ataxia, muscle tremors	Cattle
Idiopathic epilepsy	Intermittent psychomotor seizures	Cattle, goat

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Infectious bovine rhinotracheitis	Fever, bellowing, coma, convulsions, somnolence, hyperexcitability, hyperesthesia, proprioceptive deficit, recumbency	Cattle
Insecticide poisoning (organophosphate carbamate)	Salivation, vaginal discharge, diarrhea, tremors, coma, convulsions, ataxia, recumbency	Cattle, sheep, goat
Lead poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial analgesia, weak tongue, anisocoria (late), head pressing, opisthotonos, odontoprisis, convulsions, decerebrate rigidity	Cattle, sheep, goat
Louping ill (exotic)	Fever, anorexia, obtundation, constipation, muscular tremors, head tremors, hypermetria, ataxia, proprioceptive deficits, hyperexcitability, incoordination, rabbit-hopping gait, recumbency, convulsions, coma	Sheep, cattle
Maedi-visna	Obtundation, ataxia, head pressing, convulsions, coma	Sheep
Malignant catarrhal fever	Aggression, rage, ataxia, depression, head pressing, blindness, nystagmus, bellowing, mucosal and skin erosions, lymphadenopathy, diarrhea	Cattle
Narcolepsy	Sleep state, recumbency, loss of consciousness, loss of motor activity, rapid eye movement	Cattle
Nervous coccidiosis	Diarrhea, recumbency, obtundation, somnolence, blindness, ataxia, compulsive walking, head pressing	Cattle
Nervous ketosis	Aggressiveness, tremors, ataxia, paresthesia, recumbency, hyperesthesia, bellowing	Cattle
Nitrofurazone poisoning	Obtundation, proprioceptive deficit, recumbency, convulsions, coma	Cattle, sheep, goat
Nitrofurazone toxicosis	Hyperirritability, compulsive running, muscular tremors, blindness, convulsions	Cattle
Organochlorine poisoning	Tremors, hyperesthesia, recumbency, coma, convulsions	Cattle, sheep, goat
Plant poisonings	Convulsions, blindness, ataxia, compulsive walking, head pressing, odontoprisis, hyperexcitability, salivation, proprioceptive deficit, sudden death, vomiting, fetal malformations	Cattle, sheep, goat
Polioencephalomalacia	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, facial analgesia, weak tongue, anisocoria (late), dorsomedial strabismus, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cattle, sheep, goat
Propylene glycol poisoning	Depression, bloat, ataxia, recumbency	Cattle, sheep, goat
Propylene glycol toxicosis	Ataxia, obtundation, bloat, characteristic garlic-like odor	Cattle, sheep, goat
Pseudorabies	Obtundation, ataxia, hyperesthesia, paresthesia, self-mutilation, aggressiveness, fear, head pressing, compulsive walking, hypersexuality, salivation, coma, convulsions, recumbency, conscious proprioceptive deficit	Cattle, sheep, goat
Rabies	Obtundation, excitement, aggressiveness, hyperesthesia, analgesia, anesthesia, proprioceptive deficits, recumbency, compulsive walking, head pressing, tenesmus, hypersexuality, salivation	Cattle, sheep, goat
Salt poisoning	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, opisthotonos, facial analgesia, weak tongue, convulsions, anisocoria (late), head tilt, head pressing, decerebrate rigidity	Cattle, sheep, goat
Sarcocystis	Fever, weight loss, tremors, weakness, diarrhea, loss of hair on the tail switch, abortions	Cattle
Sarcocystis species infection	Seizures, blindness, opisthotonos, nystagmus, ataxia, muscular weakness, tremors, hyperexcitability, hypersalivation, recumbency	Cattle
Scrapie	Chewing, licking, wool break, depression, weight loss, ataxia, reduced	Sheep,

	menace, hypertonicity, hyperreflexia, proprioceptive deficit, recumbency, coma	goat
Sporadic bovine encephalomyelitis	Blindness, circling, ataxia, proprioceptive deficits, pleural friction rubs, pericardial friction rubs, abdominal tenderness	Cattle
Theileriosis (central nervous system form, exotic)	Depression, hypersensitivity, ataxia, circling, paralysis, convulsions	Cattle
Trauma, hematoma, brain edema	Obtundation, somnolence, blindness, ataxia, proprioceptive deficits, opisthotonos, facial analgesia, weak tongue, convulsions, anisocoria (late), head tilt, head pressing, blood from ears or nose, decerebrate rigidity	Cattle, sheep, goat
Trypanosomiasis (exotic)	Ataxia, somnolence, circling, head pressing	Cattle
Urea poisoning	Muscle tremor, bloat, salivation, incoordination, struggling, ataxia, proprioceptive deficit, recumbency, bellowing, coma, convulsion	Cattle
Vitamin A deficiency	Obtundation, somnolence, blindness with fixed pupils, ataxia, facial analgesia, weak tongue, head pressing, opisthotonos, convulsions, odontoprisis, decerebrate rigidity	Cattle, sheep, goat

TABLE 8.8

Diseases of the Horse That Produce Forebrain Disease

Disease	Predominant Clinical Signs
Brain abscess, meningitis	Head pressing, blindness, conscious proprioceptive deficit, ataxia, circling, depression, convulsions, hyperexcitability, stiff neck, rigid legs, fever, compulsive walking
Brain tumor	Depression, facial paresis or paralysis, facial analgesia, head tilt, strabismus, nystagmus, loss of menace, hypermetria, ataxia
Hepatoencephalopathy, gastrointestinal hyperammonemia	Aggression, rage, hyperexcitability, odontoprisis, ataxia, head pressing, convulsions, obtundation, coma, semicoma, blindness, fear, red urine (hemolysis), icterus
Hydrocephalus	Coma, semicoma, blindness, somnolence, head pressing, dysphonia, ataxia, weak tongue
Idiopathic epilepsy	Intermittent psychomotor seizures, normal interictal periods
Leukoencephalomalacia	Recumbency, ataxia, aggression, obtundation, coma, semicoma, head pressing, circling, compulsive walking, mydriasis, tenesmus, fear, continual chewing
Rabies	Recumbency, ataxia, aggression, depression, coma, semicoma, head pressing, circling, compulsive walking, mydriasis, tenesmus, fear, continual chewing
Trauma, hematoma	Head pressing, blindness, ataxia, circling, depression, convulsions, hyperexcitability, stiff neck, rigid legs, fever, compulsive walking, blood from ear or nose
Verminous encephalitis	Head tilt, hyperexcitability, odontoprisis, ataxia, head pressing, circling, coma, semicoma, blindness, anisocoria, convulsion, tongue dystonia
Viral encephalomyelitis (nonrabies) Eastern equine encephalomyelitis Western equine encephalomyelitis Venezuelan equine encephalomyelitis Borna disease	Head pressing, blindness, ataxia, circling, depression, coma, convulsions, recumbency, hyperexcitability, stiff neck, rigid legs, fever, compulsive walking

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Blindness and Ocular Abnormalities

Blindness may be the result of lesions in the eye, optic nerve, optic chiasm, optic tracts, or central projections of the visual pathways. Ophthalmic examination, including fundic examination, should be part of the routine physical examination. Animals presented with the complaint of blindness should receive a more detailed ophthalmic examination to determine whether primary ocular disease is the cause of the problem (see Chapter 39). Sophisticated diagnostics such as electroretinography (ERG) may be indicated in some animals. When no ocular disease can be found to account for blindness, a lesion in the nervous system is likely to be responsible. Observing the animal's ability to negotiate its environment, particularly in unfamiliar surroundings, and testing the menace responses are the primary methods of determining visual function. Further testing can be performed by setting up a maze of objects for the animal to negotiate, by using different light levels and assessing vision in bright versus dim light, and by blindfolding each eye in turn when unilateral deficits are suspected. About 90% of optic nerve fibers (i.e., axons of retinal ganglion cells) cross to the opposite side of the brain in the optic chiasm of ungulates; thus central representation of vision in these species is predominantly *contralateral*. Fibers that remain uncrossed originate from the temporal extreme of the retina. Lesions in the visual apparatus distal to the optic chiasm (i.e., lesions of the globe, the retina, or the optic nerve) produce ipsilateral visual deficits. Lesions proximal or central to the optic chiasm produce lesions in the opposite visual field.

The following discussion refers to severe or complete lesions because these are most easily understood and described. Partial lesions will produce similar but milder signs (e.g., reduced visual acuity rather than complete blindness). Absent or reduced menace response can be caused by lesions of the facial nerve (cranial nerve VII), the cerebellum, or the forebrain. Animals with facial nerve lesions can see, but palpebral reflexes cannot be elicited. Animals with cerebellar disease can see and have normal palpebral reflexes. Forebrain disease causes defective menace responses with intact pupillary light and palpebral reflexes. Localization of lesions causing blindness is summarized in Table 8.6.

Pupillary size and movement of the globes are affected by cranial nerves II, III, IV, and VI and the sympathetic innervation of the eye. Clinical signs of diseases affecting these nerves are described earlier.

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Circling

Circling is a sign of lateralized disease in the forebrain or vestibular system. Circling associated with forebrain disease is usually toward the side of the lesion. Animals that circle secondary to cerebral disease often also keep the head and neck turned toward the side of the lesion. Whereas gait may appear normal on a level surface, there are proprioceptive and postural reaction deficits on the side of the body contralateral to the lesion. Head tilt and spontaneous nystagmus are not observed. Physiologic nystagmus is normal. The severity of circling seen with lateralized cerebral disease is variable, from a subtle tendency to marked compulsive circling.

Head Tilt and Nystagmus

The presence of a head tilt, wherein the head is rotated so that one ear is held closer to the ground than the other, indicates dysfunction of the vestibular system. Head tilt is usually accompanied by spontaneous or positional (abnormal) nystagmus and a variety of other clinical signs. Vestibular disease can be classified as peripheral or central. Peripheral vestibular disease occurs with lesions of the vestibular apparatus of the inner ear (utricle, saccule, semicircular canals) or vestibulocochlear nerve (cranial nerve VIII) or, theoretically, when there is involvement of vestibular afferents from the proximal part of the neck. Animals with peripheral vestibular lesions have normal mentation but may be extremely disoriented, making assessment of mentation difficult. The head tilt (i.e., the lower ear) in animals with peripheral vestibular disease is toward the side of the lesion. Unilateral peripheral vestibular dysfunction causes decreased extensor tone in the limbs ipsilateral to the lesion and increased extensor tone in the contralateral limbs, resulting in the clinical signs of leaning, falling, curling, and rolling toward the affected side. Asymmetric peripheral vestibular lesions produce horizontal or rotatory conjugate nystagmus, with the fast phase directed *away* from the side of the lesion. The direction of the nystagmus in relation to the head is unchanged no matter what the position of the head. Physiologic nystagmus may be absent or decreased, particularly when the head is moved in a horizontal plane toward the side of the lesion. The facial nerve is closely associated with the vestibulocochlear nerve within the skull, and there may be facial paralysis along with peripheral vestibular disease when the facial nerve is also damaged by the

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underlying cause such as may occur in skull trauma, temporohyoid osteoarthropathy of horses, or severe otitis media or interna. Rarely, involvement of the postganglionic sympathetic nerve to the eye as it courses through the petrous temporal bone results in ipsilateral Horner's syndrome (ptosis, miosis, facial sweating in horses, reduced sweating on the nasal planum in cattle).

Lesions within the vestibular centers in the medulla oblongata and cerebellum also cause signs of vestibular dysfunction. Head tilt in central vestibular disease is usually toward the side of the lesion but may be in the opposite direction when the underlying disease involves the cerebellum (i.e., paradoxical vestibular syndrome). Similarly, nystagmus may be horizontal or rotatory as in peripheral vestibular disease but also may be vertical, diagonal, or different in each eye (disconjugate nystagmus); may change in direction when the position of the head is changed (positional nystagmus); or may be horizontal or rotatory with the fast phase toward the side of the lesion (paradoxical vestibular syndrome). Signs of involvement of the motor and sensory tracts to and from the limbs as they course through the medulla usually accompany central vestibular disease. Proprioceptive and postural reaction deficits are present in the ipsilateral limbs, together with mild hyperreflexia. Obtundation and signs of other cranial nerve dysfunctions may accompany central vestibular disease and can be used diagnostically to distinguish central from peripheral lesions.

Animals with either peripheral or central vestibular lesions tend to lean against walls and may fall when forced to perform a complex motor maneuver. They may adopt recumbency with the lesion side directed down and have poor righting responses, particularly from lesion-side-down recumbency. When positioned so that the lesion side is directed up, they often will roll to a lesion-down position. Blindfolding the patient eliminates visual compensatory mechanisms and therefore increases the severity of the clinical signs (Romberg's test). Blindfolding may help reveal subtle dysfunction but should be done with caution. Animals with vestibular disease occasionally may have slight ventral strabismus in the ipsilateral eye and slight dorsal strabismus in the contralateral eye. These deviations are exaggerated when the head is held in the median plane and the chin is lifted. This *vestibular* strabismus can be differentiated from the ventrolateral *true* strabismus seen with lesions of the oculomotor nerve because the former changes when the head is rotated, whereas the latter does not.

Animals with bilateral vestibular lesions do not have strabismus, head tilt, or nystagmus. The animal stands with the legs basewide and may fall to either side when head position is rapidly altered. Affected animals may show a coarse side-

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to-side head tremor. Bilateral vestibular lesions are usually peripheral and are rarely encountered in clinical practice. Central lesions extensive enough to cause bilateral vestibular disease are likely to be fatal.

Incoordination, Hypermetria, Hypometria, Dysmetria, and Intention Tremor

Clinical signs that occur in animals with cerebellar disorders include hypermetria, hypometria, intention tremor, and truncal ataxia (excessive body sway during movement along a straight path). Conscious proprioceptive fibers do not pass through the cerebellum. Consequently, postural placement of the limbs is normal. Animals with cerebellar disease move the limbs with imprecise and variable rate, range, and force. There is a slight delay in lifting the limb from the ground. At the peak of protraction the limbs are lifted too high and too far anteriorly. The legs then hit the ground with excessive force. During the exaggerated protraction, thoracic limbs may flex excessively, termed *hypermetria,* or may appear stiff because of reduced flexion, termed *hypometria* or *spasticity.* The animal may violently thrust the outside pelvic limb backward and laterally when turned. The thoracic limbs and the pelvic limbs occasionally collide during the turn (interference). At rest the animal stands with the legs abducted, in a basewide stance. This is not a conscious proprioceptive deficit, however, because the animal consciously returns the limbs to the basewide posture if the leg position is manually corrected. There is intention tremor, most marked in the head. When the animal attempts to reposition the head, it overshoots the intended position, corrects, and then overshoots again. The sequence of overcompensation and overcorrection results in a coarse oscillation or bobbing of the head. The head tremor is most conspicuous when the animal is alert, especially when eating. Intention tremor disappears when the animal is recumbent and the musculature is relaxed. In animals with cerebellar disorders, the extensor muscles of the limbs may be hypertonic, and spinal reflexes occasionally are exaggerated. Lesions of the rostral cerebellum can result in opisthotonos. Animals with cerebellar cortical disease may lack a menace response but retain their vision and can negotiate around obstacles. Animals with pure cerebellar dysfunction remain bright, alert, and responsive to external stimuli. Animals with severe lesions of the cerebellum may be recumbent and unable to rise and show opisthotonos. Cerebellar disease is often bilaterally symmetric, but lateralized lesions cause signs on the ipsilateral side of the body.

Diseases that cause spasticity or tremors in livestock are listed in Table 8.9.

TABLE 8.9

Diseases of Spasticity or Tremors in Horses and Ruminants

Disease	Clinical Manifestations	Affected Species
Cerebellar hypoplasia Bovine viral diarrhea Bluetongue Akabane Border disease Wesselsbron disease Hereditary	Intentional head tremor, basewide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos	Cattle, sheep, goats
Cerebellar abiotrophy	Intentional head tremor, basewide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos	Cattle, horses, goats
Grass staggers	Hypermetria, hyperreflexia, truncal ataxia, head tremors, basewide stance, recumbency, ptyalism, hyperexcitability, hyperesthesia	
Bermuda staggers		Cattle, horses
Paspalum staggers		Horses
Perennial ryegrass staggers		All species
Other fungal tremorgens		All species
Annual ryegrass toxicity		All species
Kikuyu grass		Cattle, sheep
Phalaris (canarygrass)		Sheep
Hypomagnesemia	Hypermetria, hyperreflexia, truncal ataxia, recumbency, hyperesthesia, menace deficit, opisthotonos, aggressiveness, hypertonia	Cattle, horses
Lysosomal storage disease	Intentional head tremor, basewide stance, hypermetria, hypertonia, hyperreflexia, truncal ataxia, menace deficit, opisthotonos, blindness, aggressiveness	Cattle, goats
Locoism and *Swainsona* poisoning	Ataxia, obtundation, intentional head tremor, loss of herd instinct, maniacal behavior, flaccidity of the nose and lips, basewide stance	All species
Aspergillus clavatus toxicosis	Ataxia, weakness, muscle tremors, hypersalivation, altered behavior, recumbency, opisthotonos, death	Cattle, sheep
Hereditary neuraxial edema	Recumbency, head tremor, good appetite, hyperesthesia, nystagmus, strabismus, muscular fasciculations	Cattle
Bovine familial convulsions and ataxia	Tetaniform seizures, ataxia, hypermetria, hyperreflexia, head tremors, truncal ataxia	Cattle
Maple syrup urine disease	Obtundation, recumbency, opisthotonos, stimulus-induced tetanic spasms, convulsions, generalized decrease of spinal reflexes	Cattle

Solanum spp. storage disease	Head tremors, hypermetria, hypertonia, hyperesthesia, weight loss, opisthotonos, recumbency, and convulsions	Cattle, goats

Involvement of the vestibular components of the cerebellum (caudal cerebellar peduncle, flocculonodular lobe, and fastigial nucleus) results in signs of paradoxical vestibular syndrome, described earlier.

Abnormalities of Cranial Nerve Function

The normal functions of the cranial nerves were described earlier, in the discussion of the neurologic examination. Cranial nerve dysfunction may be central or peripheral in type, depending on whether the neurologic lesion lies within the central components of the cranial nerves within the brain or in the peripheral portions of the nerves. Clinical signs of cranial nerve dysfunction are ipsilateral to the lesions that cause them.

Blindness, Strabismus, Ocular Paresis or Paralysis, Abnormalities of Pupil Size or Pupillary Light Reflexes.

Lesions involving cranial nerves II, III, IV, and VI were described earlier, in the discussion of blindness and other visual dysfunctions.

Facial Hypalgesia or Analgesia, Deviated or Dropped Jaw.

Loss of or reduced sensory perception on the face, including the inside of the mouth, the nasal planum, the nasal septum, the cornea, and the lower jaw area, occurs with lesions of the trigeminal nerve. It is important to distinguish this from the signs of contralateral forebrain disease. Unilateral loss of facial sensation may result from damage to the peripheral portion of the trigeminal nerve or the trigeminal ganglion in the petrosal bone of the skull, or its connections in the pons, or from contralateral forebrain disease. Bilateral facial hypalgesia is most likely caused by diffuse forebrain dysfunction rather than trigeminal nerve disease. The mandibular branch of the trigeminal nerve also carries motor innervation to the muscles of mastication from the pontine motor nucleus of the trigeminal nerve. Bilateral involvement of the motor component of the nerve results in a dropped jaw and inability to prehend and chew food, together with drooling saliva. The muscles of mastication atrophy rapidly over a few weeks, most obviously in the masseter and temporalis muscles. Unilateral disease causes atrophy of the denervated muscles, and mild jaw weakness may be appreciated, but the animal can still eat and close the jaw. Usually the

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mandible is deviated away from the side of the trigeminal nerve lesion. Central lesions in the trigeminal nerve may also involve adjacent structures in the brainstem, such as the facial nerve, the vestibular system, and the long motor and sensory tracts to and from the limbs.

Facial Paresis or Paralysis.

Lesions of the facial nerve result in ipsilateral atonia or hypotonia of the facial muscles. The clinical signs of facial nerve paralysis in all large animals include ptosis, dropped ear, and absence of the menace response and palpebral reflex. There is accumulation of food in the cheek pouch and commissure of the lips on the ipsilateral side. Affected animals frequently drool saliva from the lip commissure on the affected side. The animal is unable to open the nostril on the affected side during inspiration. The muzzle of the horse, goat, and sheep deviates away from the direction of the neurologic lesion. Deviation of the muzzle is not seen in cattle because of the normal rigidity of the planum nasale. If the neurologic lesion is located between the medulla oblongata and the stylomastoid foramen, the ipsilateral eye may be dry because of loss of innervation from the parasympathetic nucleus of cranial nerve VII. Lesions of the central components of the facial nerve in the medulla oblongata also destroy upper motor neurons, proprioceptive tracts, and reticular activating system (RAS) neurons, resulting in limb weakness, ataxia, and sometimes obtundation. Lesions of the peripheral component of cranial nerve VII cause facial atonia or hypotonia but do not produce obtundation or ataxia.

Head Tilt, Spontaneous Nystagmus, Deafness.

Lesions involving cranial nerve VIII, the vestibulocochlear nerve, produce signs of vestibular dysfunction, as described previously. Deafness may also be a consequence of vestibulocochlear nerve disease. Bilateral deafness has been reported in Paint horses,[51] where it may be a heritable defect associated with the gene for white coat color, similar to the situation that exists in a number of breeds of dogs with white or merle coat color. Deafness can also result from severe aural disease. Although bilateral deafness is fairly easy to recognize clinically, unilateral deafness may be less obvious. Inability to localize sound occurs when animals have unilateral deafness and may be suspected when animals alert to sound but do not turn toward the sound. Auditory evoked potentials can be used to determine the integrity of the auditory pathway in the

inner ear and medulla oblongata.[51,52]

Dysphagia, Dysphonia, Stridor.

Lesions in the nuclei of cranial nerves IX, X, and XI in the medulla oblongata produce dysphonia, inspiratory dyspnea, dysphagia, and neurogenic atrophy of the trapezius, sternocephalicus, and brachiocephalicus muscles. The inspiratory dyspnea is characterized by roaring and stridor. Roaring is a stridor that is made during peak inspiratory flow in horses with idiopathic left recurrent laryngeal neuropathy. It is caused by paralysis of the left cricoarytenoideus dorsalis muscle, resulting in failure to abduct the arytenoid cartilages during inspiration. Additional evidence of paralysis of cranial nerves IX and X may be obtained by endoscopic examination of the pharynx. Other signs of paralysis of cranial nerves IX and X include failure to abduct the vocal folds, collapse of the pharynx, dorsal displacement of the soft palate, and inability to swallow a nasogastric tube. Animals with peripheral nerve deficits remain alert and appetent and do not show conscious proprioceptive deficits, whereas animals with centrally located lesions may be depressed and inappetent and may have ataxia and limb weakness. Animals with bilateral lesions in the peripheral nerves are unable to open the glottis during inspiration and display extreme respiratory distress. Peripheral lesions of the accessory nerve that have been present for longer than 1 month may produce neurogenic atrophy of the trapezius, brachiocephalicus, and sternocephalicus muscles. This is frequently accompanied by aspiration pneumonia. Lesions of the visceral efferent component of cranial nerve X in ruminants produce vagal indigestion, which is characterized by ruminal distention with fluid, ruminal tympany, abomasal stasis, and sometimes a hypochloremic, hypokalemic metabolic alkalosis.

Hypoglossal nerve lesions produce a weak or flaccid tongue. In animals with unilateral lesions, the tongue deviates away from the side with the lesion and is flaccid when it is manually extended from the mouth. After prolonged denervation (2 weeks or more) the ipsilateral side of the tongue atrophies and the tongue deviates toward the affected side. Horses with lesions in the forebrain may also fail to retract the tongue normally; however, the lingual musculature is normal, the tone is variable, and the animal can retract the tongue if it receives sufficient stimulation. In comparison, the tongue tone is consistently weak in cases of hypoglossal paralysis.

Signs of cranial nerve dysfunction, together with the central origins or projections of the nerves, are summarized in Table 8.10. Diseases that involve

the brainstem and cranial nerves are summarized in Table 8.11.

TABLE 8.10
Clinical Signs of Cranial Nerve Dysfunction

Cranial Nerve	Central Origin or Projection	Clinical Signs of Dysfunction	Comments
I—Olfactory	Olfactory bulb, limbic system (behavior and emotion centers), cerebral cortex	Loss of sense of smell (anosmia)	Olfactory nerve lesions are rare and difficult to detect clinically.
II—Optic	Optic chiasm, optic tract, lateral geniculate nucleus, optic radiation, occipital cortex	Blindness	See text for additional comments (blindness).
III—Oculomotor	Midbrain somatic and parasympathetic nuclei	Ventrolateral strabismus, ptosis (somatic component); dilated, nonresponsive pupil (parasympathetic component)	
IV—Trochlear	Midbrain	Dorsomedial strabismus	Trochlear nerve lesions are rare and usually accompanied by other signs of midbrain dysfunction.
V—Trigeminal	Pons (motor nucleus), medulla, and rostral cervical spinal cord (sensory tract)	Dropped jaw in bilateral motor paralysis; deviated jaw in unilateral paralysis; decrease or loss of sensation to most of the structures of the head and face in sensory nerve disease	Rabies is an important differential diagnosis in animals with a dropped jaw.
VI—Abducent	Rostral medulla oblongata	Medial strabismus (paralysis of the lateral rectus muscle)	
VII—Facial	Medulla oblongata (rostral to middle); motor, sensory, and parasympathetic components	Facial paralysis (motor component); loss of sense of taste to rostral two thirds of the tongue; decreased tear production (dry eye) and decreased salivation (parasympathetic components)	The facial nerve is particularly susceptible to damage in its peripheral course because of its proximity to the middle ear and to the guttural pouch in horses and its superficial location on the face.
VIII—Vestibulocochlear	Medulla oblongata (middle)	Decreased hearing or deafness; vestibular signs (head tilt, nystagmus, falling, rolling)	See description of vestibular disease in text.
IX, X, XI—Glossopharyngeal, vagus, accessory	Medulla oblongata (nucleus ambiguus in middle to caudal medulla and rostral cervical spinal cord)	Dysphagia (IX and X), laryngeal paresis to paralysis (X), atrophy of sternocephalicus, brachiocephalicus, and trapezius muscles (XI)	Rabies is an important differential diagnosis in animals with dysphagia or choke.
XII—Hypoglossal	Medulla	Paralysis of the tongue	Acute unilateral lesions result in the

	oblongata (caudal)		tongue being deviated away from the side of the lesion. In chronic disease, atrophy and contracture of the affected side of the tongue result in deviation toward the affected side.

TABLE 8.11

Diseases of the Brainstem and Cranial Nerves

Disease	Location	Clinical Signs and Laboratory Findings
Nonrabies viral encephalomyelitis, rabies, malignant catarrhal fever (cattle only)	Multifocal brainstem, particularly medulla oblongata	Head tilt, nystagmus, circling, ataxia, tongue paralysis, anisocoria, dilated nonresponsive pupils, strabismus, lingual paralysis, dysphonia, dysphagia; CSF may show pleocytosis (mainly mononuclear cells) and high protein concentration
Listeriosis (ruminants, horses [rare])	Multifocal brainstem, particularly basal ganglia, metencephalon, and medulla oblongata	Circling, head tilt, facial paralysis, stridor, stertor, dysphagia, obtundation, coma, convulsions, ataxia; CSF shows pleocytosis (mainly mononuclear) and a high protein concentration
Thromboembolic meningoencephalomyelitis (cattle)	Multifocal brainstem	Circling, nystagmus, head tilt, strabismus, tongue paralysis, dysphagia, facial paralysis, coma, convulsions, obtundation; xanthochromic CSF with increased neutrophils and protein concentration
Peripheral vestibular disease	Petrous temporal bone, membranous labyrinths, vestibulocochlear nerve, often accompanied by facial nerve paralysis	Head tilt, circling, or leaning toward lesion side; ventrolateral strabismus on ipsilateral side; dorsomedial strabismus on contralateral side; nystagmus (usually horizontal and constant)
Verminous encephalitis	Multifocal brainstem, most commonly thalamus	Circling, nystagmus, head tilt, strabismus, tongue paralysis, facial paralysis, obtundation, coma, convulsions, depression, proprioceptive deficit, bradycardia, salivation, head pressing, blindness; high protein concentration and increased nucleated cell count in CSF
West Nile virus	Multifocal brainstem	Fasciculations of neck and facial muscles in addition to the other signs
Equine protozoal myeloencephalitis	Multifocal brainstem and cerebrum	Seizures, head tilt, facial paralysis, circling, nystagmus, dysphagia, facial paralysis, blindness, ataxia, paresis, hyporeflexia, hyperreflexia
Space-occupying mass Tumor, abscess	Cerebellopontine angle; cranial nerves V, VII, and VIII	Head tilt, strabismus, proprioceptive deficit, facial analgesia, jaw drop, obtundation, coma, strabismus, nystagmus, hyperreflexia, hypertonia, falling or circling toward affected side, blindness on contralateral side, tongue paralysis, hemianopsia, bradycardia, coma, convulsion
Horner's syndrome	T1 to T3 motor neurons (gray matter), spinal roots, vagosympathetic trunk, sympathetic UMN of spinal cord (tectotegmentospinal), periorbita	Miosis, lack of nasal sweat (cattle only), ipsilateral facial swelling (horses only)
Guttural pouch mycosis	Guttural pouch	Dysphagia, head shyness, headshaking, roaring,

(horses)		dysphonia, protrusion of the tongue from the mouth, epistaxis, head tilt, nystagmus, facial sweating, shivering, Horner's syndrome, colic, facial paralysis

CSF, Cerebrospinal fluid; *UMN,* upper motor neuron.

Lesions of the medulla oblongata can produce severe obtundation, somnolence, or coma as a result of ARAS dysfunction in addition to signs of vestibular dysfunction and functional deficits in cranial nerves V to XII. Other clinical signs of medullary lesions include ipsilateral paresis and proprioceptive deficits. The spinal reflexes of the ipsilateral limbs are exaggerated, and the extensor muscle tone is increased. Further details are given later in the discussion of quadriparesis and hemiparesis.

Measurement of Brainstem Function Using Auditory Evoked Potentials

The integrity of the vestibulocochlear apparatus can be examined using brainstem auditory evoked potentials.[51-54] This method examines the averaged brain waveform that is generated after an auditory click in the ear. Ablation of the entire cochlear apparatus and vestibular nerve, as might occur with otitis interna, results in a loss or attenuation of waveform activity after the click stimulus. Injury to the brainstem vestibular nuclei or pons results in specific losses of certain waveforms.

Paresis and Ataxia in Two or Four Limbs

Quadriparesis and hemiparesis are seen with lesions affecting the mid to caudal brainstem (midbrain, pons, medulla oblongata) or the cervical spinal cord (C1 to T2 spinal cord segments). Quadriparesis can also be seen in generalized peripheral nerve or muscle disease, discussed later. Paraparesis results from disease lesions of the spinal cord affecting segments T3 to S2 or the peripheral nerves to the pelvic limbs. Disease of the forebrain does not produce appreciable paresis and ataxia when the animal is walking in a straight line on a level surface, but these signs may become apparent in the limbs contralateral to the lesion when the animal is asked to circle, back, step over obstacles, or walk on a slope. Localization of the lesion when signs of paresis and ataxia are present depends on the assessment of muscle mass and tone, spinal reflexes, and evaluation of brainstem function; the last is determined by the presence or

absence of signs such as altered mentation and cranial nerve deficits.

Quadriparesis and ataxia with normal muscle mass and tone and normal to increased spinal reflexes can be explained by a lesion of the descending and ascending tracts in the brainstem or spinal cord segments C1 to C5. Note that such a finding does not exclude multifocal lesions within the same areas of the CNS. Presence of clinical signs of brain disease indicates that the lesion (if singular) is in the brainstem, as described earlier. Lesions in the midbrain cause contralateral postural and proprioceptive deficits, whereas those in the medulla oblongata cause ipsilateral signs. Cerebellar disease causes head, neck, truncal, and limb ataxia, without limb weakness. Lesions of the forebrain (thalamus and cerebrum) cause minimal to no paresis or ataxia when the animal moves on a level surface, but contralateral subtle proprioceptive and postural reaction deficits are present. Altered mentation and other signs of forebrain disease such as compulsive circling or central blindness are expected. Animals with spinal cord disease have normal mentation. The clinical signs shown by such patients depend on the location of the lesion and the relative amount of damage to gray (cell bodies) and white (myelinated spinal cord tracts) matter. Loss of white matter affects upper motor neurons and proprioceptive and other sensory pathways, whereas gray matter damage produces lower motor neuron deficits. The sensory losses manifest as either proprioceptive deficits or loss of cutaneous sensation. Spinal cord diseases may be localized to one of the following five regions: high cervical (C1 to C5), cervicothoracic (C6 to T2), thoracolumbar (T3 to L2), lumbosacral (L3 to S2), and sacrococcygeal (S3 to Cd5) regions. Tables 8.4 and 8.5 list the peripheral nerves and the spinal segments that innervate them.

Cervical Spinal Cord

Animals with incomplete section of the cervical region of the spinal cord display hemiparesis or tetraparesis. The clinical signs include knuckling, stumbling, failure to lift the inside feet when turned in a tight circle, circumduction of the outside pelvic limb during circling, interference, hypometria or hypermetria, abnormal postural placement responses, crossing over midline when turned, and excessive truncal sway. Animals with more severe lesions of the cervical spinal cord become recumbent and are unable to lift the head from the ground. There is an asymmetric righting response in animals with unilateral lesions. They can raise the head and neck to a variable distance only when lying with the lesion

side facing down. Within several days of the time of spinal cord injury, muscle tone and spinal reflexes in the limbs of recumbent animals are exaggerated. The urinary bladder is distended. Affected animals have difficulty posturing and urinating, and afterward the bladder contains a large amount of residual urine and sediment. Animals with complete spinal cord transection anterior to C5 die suddenly from respiratory failure because of paralysis of the intercostal muscles and diaphragm.

Lesions from C6 to T2 spinal segments (i.e., brachial intumescence) result in proprioceptive deficits in all four limbs and tetraparesis or tetraplegia (recumbency). There is flaccidity and hyporeflexia of the thoracic limbs and hypertonia and hyperreflexia of the pelvic limbs. Unilateral lesions result in ipsilateral signs. Lesions of C6 to T2 segments involving white but not gray matter do not produce thoracic limb hypotonia. Perception of painful stimuli over all four limbs may be reduced. Flexor reflexes in the thoracic limbs may be depressed but are normal in the pelvic limbs. The righting responses of the head and neck are normal, but the animal may have difficulty rolling onto its sternum from a laterally recumbent position. Voluntary control of urination is poor or absent, posturing for urination is difficult, and the urinary bladder is distended and has a large residual volume. After 2 weeks or more, lesions of the gray matter of the spinal cord or the peripheral nerves may result in neurogenic atrophy of one or more muscle groups of the thoracic limbs. Gray matter lesions of T1 to T3 spinal segments may cause Horner's syndrome, which is characterized by miosis and ptosis in all species. Unilateral facial sweating occurs in horses; lack of sweating on the planum nasale occurs in cattle. Differentiation of high (C1 to C5) and low (C6 to T2) cervical spinal cord lesions may be difficult in horses, especially when signs are fairly mild.

Lesions of the thoracolumbar region (T3 to L3 inclusive) cause paraparesis and ataxia in the pelvic limbs but usually do not affect the thoracic limbs. There may be knuckling, stumbling, abduction, adduction, interference, excessive truncal sway, circumduction of the outside limb, and failure to lift the inside foot when pivoted in a tight turn. With complete lesions, the animal becomes recumbent but intermittently assumes a dog-sitting position, with the thoracic limbs extended and weight bearing and the pelvic limbs flexed. Muscle tone and spinal reflexes are exaggerated in the pelvic limbs. The urinary bladder is distended and, because of poor coordination of bladder filling with detrusor and sphincter tone (dyssynergia), residual volume is large. The tone of the urethral sphincter is normal. Rarely, animals with severe spinal cord lesions between T2

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and L2 display transient hypertonia of the thoracic limbs (Schiff-Sherrington syndrome).[55] This condition is caused by interference with inhibitory fibers ascending from the lumbar segments in the dorsal funiculi to the lower motor neurons of the thoracic limbs.[55] These fibers synapse on the lower motor neurons of the brachial intumescence. Hypertonia from this deficit may be differentiated from cervical cord lesions by the lack of conscious proprioceptive deficits in the thoracic limbs of animals with thoracolumbar lesions.

The lumbosacral region (L3 to S2) of the spinal cord contains lower motor neuron efferents to and general proprioceptive afferents from the pelvic limbs. Lesions in this area result in paraparesis or paraplegia. Affected animals are ataxic and have conscious proprioceptive deficits of the pelvic limbs. Patients with complete spinal cord lesions of L3 to S2 exhibit flaccid paraplegia, which is accompanied by hyporeflexia or areflexia of the pelvic limbs. With prolonged denervation, there is neurogenic atrophy of the pelvic limb musculature.

Lesions located between L3 and L6 spinal cord segments result in urinary bladder distention and maintenance of a large residual volume. The sphincter tone is intact, but urine is not voided unless the intravesicular pressure exceeds that of the sphincter. These animals usually have contact dermatitis of the perineum and preputial area because of urine scalding. Lesions located around the S1 and S2 segments result in bladder distention and flaccidity. Urine may drip continuously from the urethral orifice, and perineal or preputial scalding can be present. The rate of flow may be increased by manually pressing on the bladder during a rectal examination.

Lesions of the sacrococcygeal (S3 to Cd5) spinal cord segments or cauda equina produce flaccidity and muscular atrophy of the tail and anus and, in males, penile paralysis (paraphimosis). Lesions in this area also result in desensitization of the tail, penis, vulva, rectum, anus, and perineum. The urethral sphincter is dilated, and urine constantly drips from the urethral orifice. The animal does not evacuate the bladder and is unable to defecate, resulting in a large dilated urinary bladder and distention of the rectum with feces (obstipation).

If the entire neurologic lesion is located caudal to S2, ataxia or limb weakness is not seen. The combination of flaccidity of the tail and anus and the constant urine leakage produces contact dermatitis of the perineum and pelvic limbs. Perineal scalding is characteristic of lesions of the cauda equina. Specific diseases of the spinal cord, peripheral nerves, and motor end plate are listed in Table 8.12.

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TABLE 8.12

Diseases of the Spinal Cord, Peripheral Nerve, and Motor End Plate of Large Animals

Disease	Signs	Species Affected
Occipitoatlantoaxial malformation	Ataxia, spasticity, hyperreflexia, crepitation or pain with neck flexion, head tilt, torticollis, ataxia, visible swelling or asymmetry	All species
Fractures and dislocations	Tetraparesis, tetraplegia, paraparesis, paraplegia, hyperreflexia, stiff neck, recumbency, ataxia, acute death, crepitation, pain, swelling	All species
Cervical spinal abscesses	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, ataxia, sudden death, crepitation, pain, swelling	All species
Cervical vertebral stenotic myelopathy	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, ataxia, strip sweating	Horse
Spinal tumor (lymphosarcoma, neurofibroma)	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia	All species
Equine herpesvirus myeloencephalopathy	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia, flaccid anus, flaccid tail, dysuria, distended bladder, impacted rectum, urine scalding	Horse
Copper deficiency	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia	Sheep, goat
Cauda equina neuritis	Pruritus in perineum, hair loss in perineum, analgesia in perineum, flaccid tail, flaccid anus, paraphimosis, dysuria, facial palsy, head tilt, leaning, nystagmus	Horse
Ischemic myelopathy (fibrocartilaginous embolism)	Paraplegia, tetraplegia, flaccid tail, flaccid anus, areflexia at site of lesion, hyperreflexia distal to site of lesion, ataxia	Horse, sheep
Postanesthetic myelopathy	Paraparesis to paraplegia, ataxia, hypalgesia, scoliosis	Horse, cattle
Caprine arthritis-encephalitis virus	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia	Goat
Segmental myelitis	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, stiff neck, ataxia, strip sweating, hyporeflexia, areflexia, lower motor neuron deficit, facial nerve paralysis, jaw drop	Horse
Developmental defects (spina bifida, Arnold-Chiari syndrome, syringomyelia, hemivertebrae, spinal cysts)	Paraplegia, paraparesis, tetraplegia, tetraparesis, hypotonia, atonia, neurogenic atrophy, torticollis, scoliosis, kyphoscoliosis, misshapen tail, absence of skin over dorsal midline	All species
Verminous encephalitis	Tetraparesis, tetraplegia, paraparesis, paraplegia, recumbency, ataxia, head tilt, hyporeflexia, areflexia, hyperreflexia, hypertonia, hypotonia	All species
Tetanus	Stiffness, normal reflexes, flashing third eyelid, trismus, bloat, convulsions, coma, raised tailhead	All species
Botulism	Flaccidity, ataxia, dysphagia, hyporeflexia, pupillary dilation, facial hypotonia, flaccid tail, flaccid anus	All species
Progressive ataxia	Ataxia, recumbency	Charolais cattle
Locoism	Ataxia, recumbency, bizarre behavior	All species
Dying back axonopathies	Hypermetria, hyperreflexia, ataxia, flaccid tail, flaccid anus, fecal and urine retention, urine scalding, recumbency	All species
Elso heel (spastic paresis)	Affected pelvic limb is hyperextended and swings in pendulum	Cattle

	fashion; tailhead is elevated	
Bovine spastic syndrome	Episodic hyperextension of the pelvic limb, extension of the limb behind the cattle, head and neck extension	Cattle
Peripheral nerve injuries	Areflexia, hypotonia, hyporeflexia, atonia, anesthesia, analgesia of a specific area of limbs or trunk, inability to support weight, normal function of limbs distal to denervated site	All species
Ionophore toxicosis (salinomycin, lasalocid, monensin)	Tetraparesis, tetraplegia, ataxia, colic, cardiac dysrhythmia, sudden death	All species
Periodic hyperkalemia (HYPP)	Episodic tremors, weakness, spasticity during episodes, recumbency	Horse
Myotonia congenital	Episodic weakness, spasticity during episodes	All species
Bromide intoxication	Weakness, ataxia, stumbling, closed eyelids, drooped head and neck, paraphimosis	Horse
Coyotillo poisoning	Progressive weakness, hypermetria, areflexia	Goat
Neosporosis	Recumbency, ataxia, neurogenic atrophy	Calf
Cycad palm poisoning	Posterior paresis, elevated tailhead, paraparesis, paraplegia	Cattle
Acquired torticollis	Abnormally positioned head and neck	All species
Sorghum toxicosis	Ataxia, paraparesis, paraplegia, rabbit-hopping gait, ataxia, recumbency, weight loss	Horse, cattle
Stringhalt	Normal at rest, involuntary hyperflexion of the hock and stifle	Horse
Tick paralysis	Progressive generalized paresis, ataxia, recumbency, flaccid tail, flaccid anus, weak facial muscles	All species

Muscle Atrophy, Reduced Muscle Tone, Flaccid Paresis, Focal Analgesia

Reduced muscle tone, muscle atrophy, and flaccid paresis are characteristic of peripheral nerve, muscle, or neuromuscular diseases. Signs may be localized to a single limb, as in the case of traumatic peripheral nerve injury; generalized, as in botulism and many myopathies; or multifocal, as in equine protozoal myeloencephalitis and other diseases that attack multiple areas of the CNS. Details of neuromuscular diseases and the use of ancillary diagnostic testing to localize peripheral nerve, muscle, and neuromuscular disease are described in Chapter 35. Muscle disorders are discussed in Chapter 42.

Peripheral nerve lesions, whether of the central components of the nerves in the spinal cord and brainstem or along their peripheral course in the limbs and head, can also result in focal hypalgesia or analgesia. Knowledge of the autonomous zones for the peripheral nerves innervating the limbs can be used to localize such peripheral nerve lesions.[56]

Urinary Incontinence and Urine Retention

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The clinical signs of urinary bladder denervation are variable and depend on the lesion location. Lesions of the sacral segments of the spinal cord produce a flaccid bladder, which distends with a large residual volume. Spontaneous urine leakage occurs continuously through the paralyzed atonic urethral sphincter. Additional urine flow occurs when the abdominal pressure is increased. Lesions of the brainstem or spinal cord anterior to S1 produce reflex dyssynergia, a disturbance in coordination of micturition, wherein the facilitatory influence of the bladder stretch receptor (afferents) maintains tonic activity on the efferents of the urethral sphincter. The lack of inhibition of these reflexes from the upper motor neuron pathways produces hypertonicity of the urethral sphincters and results in an impediment to urine flow. There is a high intravesicular pressure and a large postvoiding urine volume. The urine escapes paroxysmally only when the intravesicular pressure exceeds the sphincter pressure. After approximately 1 month of denervation, local spinal reflexes between the sacral afferent and efferent neurons develop in the S1 to S5 segments, and incomplete voiding occurs. In these cases the residual volume remains large, and the normal urination posture is not attained.

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• CHAPTER 9

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Alterations in Body Weight or Size

Alexandra Hund, Consulting Editor, Shannon E. Pratt-Philips

MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Slowed growth and below-normal weight gain usually happen at the same time, although occasionally they develop separately. By definition a decrease in growth and weight gain is limited to the growing animal. Similar pathogenic mechanisms cause weight loss or an emaciated condition in an adult patient. This arbitrary age division allows the clinician to consider possible causes that are more or less common for a given age group.

Potential growth and weight gain are genetically and partially environmentally determined.[1] They differ according to species, breed, and sex, and marked differences in potential growth exist within a breed. In ruminants the size is greater in the offspring of multiparous females than in those from primiparous females at birth, but the potential for growth may not differ overall.[2-5] The normal or minimum growth and weight gain rates for common breeds of the various large animal species are outlined in the section on assessment of growth

and weight gains.

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Mechanisms of Decreased Growth and Decreased Weight Gain

Major pathogenic mechanisms that result in decreased growth and decreased weight gain include the following:

- Inadequate dietary intake of essential nutrients
- Infections or inflammation
- Parasitism
- Genetic errors in metabolism or physiologic function
- Concurrent toxicosis
- Environmental causes
- Multiple causes

Inadequate intake of one or more essential nutrients is an important cause of decreased growth. In many cases growing animals are not provided with a sufficient volume of feed to meet their nutrient requirements. Young animals rely on a highly digestible diet that provides energy and essential nutrients for growth. Even animals fed an appropriate volume of a poor-quality milk replacer could suffer from poor growth. Milk replacers formulated with sources of protein, fat, vitamins, and minerals that have limited nutrient digestibility may induce a state of energy, protein, vitamin, or mineral malnutrition. The process of weaning may pose substantial challenges for the growing animal, especially in dairy calves when performed abruptly, and may lead to a depression in growth.[6] Weaned foals and ruminants rely on forages and cereal grains to provide essential nutrients.

Hay that has been harvested at a late stage of growth usually has a lower nutrient digestibility compared with young forages. Diets low in digestible energy or protein or both reduce total daily intake in ruminants because of the decreased turnover time ($T_{1/2}$) in the gastrointestinal tract and subsequent

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decreased throughput. This compounds the problems caused by an inadequate intake of digestible nutrients. The digestibility of forages is even lower for horses than for ruminants.

Protein-calorie malnutrition (PCM) is the most common clinical cause of decreased growth and decreased weight gain in young animals. It is characterized by smaller size and lower weight than the normal minimums for age, breed, and sex. Inadequate intake of digestible energy and protein (or essential fatty acids in the neonate primarily adapted to a milk diet) results in inadequate levels of amino acids, fats, and carbohydrates for normal metabolism and growth. Diets that lack any of the other essential nutrients (essential fatty acids, vitamins, macrominerals, or trace minerals) can also decrease growth. Deficiencies of calcium, phosphorus, and magnesium result in improper skeletal formation. Deficiencies in other macrominerals (e.g., sodium, chloride, potassium), trace minerals (e.g., copper, zinc, manganese, cobalt, iron), and vitamins (e.g., A, D, E, thiamin) cause biochemical dysfunctions that lead to inefficient metabolism and growth. Large animal patients that grow slowly as a result of inadequate diets often have normal or increased appetites until they are terminally ill. Physical findings and clinical chemistry profiles from animals with PCM are often within the normal range until the disease process is well advanced.

Infections or inflammatory processes are important causes of decreased growth and decreased weight gain in young horses and ruminants. The decrease in growth can be of short duration followed by recovery and compensatory gain (cryptosporidiosis) or can persist (chronic bronchopneumonia). Infections or inflammatory processes can also result in nutrient malabsorption (chronic salmonellosis, acute rotavirus diarrhea, equine proliferative enteropathy), anorexia (pharyngeal abscesses, systemic disease), increased nitrogen turnover, and direct protein losses (gastrointestinal disease). Both energy and protein requirements may be increased as a result of infection and inflammation.

Parasitism often affects young horses and ruminants and results in decreased growth and decreased weight gain by increasing nutrient requirements, increasing nutrient losses, and/or decreasing nutrient absorption. The animal's metabolic rate and nutrient requirements may also increase as a result of inflammatory and immune reactions that arise secondary to parasitism.

Genetic diseases (α-mannosidosis, dwarfism) result in decreased growth through generalized errors in the genetic code or interference with strategic reactions in one or more metabolic pathways. Congenital cardiac malformations

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(tetralogy of Fallot, ventricular septal defect) create physiologic inefficiencies that require energy beyond the body's ability to supply it. Congenital renal disease (agenesis, dysplasia, hypoplasia, polycystic kidney disease) affects homeostatic mechanisms that regulate electrolyte and acid-base balance, results in the production of uremic toxins, and often results in partial anorexia and PCM. Digestive tract malformations, especially oral and dental defects such as cleft palate, parrot and monkey mouth, megaesophagus, and brachygnathism, can reduce nutrient ingestion and impair growth.

Toxicities, although rare in growing animals, result in decreased weight gain by interfering with metabolic pathways (e.g., ammonia toxicity, zinc-induced copper deficiency with abnormal skeletal development in foals) by causing loss of body reserves (e.g., thiamin deficiency in horses, bone marrow hypoplasia and associated bleeding diatheses in ruminants associated with bracken fern toxicity), inducing anorexia, or a combination of mechanisms. The pathogenic mechanisms of many toxins are not yet known.

Tall fescue *(Festuca arundinacea)* is a popular pasture grass (marketed as “Kentucky 31”) for both cattle and horses. Tall fescue is typically infected with an endophyte *(Neotyphodium coenophialum)* that causes ergot alkaloid toxicity problems in animals. In cattle, tall fescue consumption can decrease feed intake and weight gain. In both cattle and horses, the toxins produced by the endophyte decrease serum dopamine and prolactin, which affects reproduction in these animals. Consumption of endophyte-infected fescue in the last trimester results in late-term abortion, prolonged gestation periods, thickened and/or retained placentas, and agalactia, a decreased ability to produce milk. While foals of mares fed fescue tend to be larger in size at birth (due to a longer gestation), decreased milk production and thus consumption by the foals can greatly affect growth rate and potential. It is recommended that pregnant animals be removed from endophyte-infected pastures for their third trimester. Alternatives are other pasture grasses, or the endophyte-free fescue varietals. In horses, domperidone paste (a dopamine antagonist) may be administered to mitigate the effects of endophyte-infected pasture on mares.

Environmental factors including extreme heat or cold or high humidity result in decreased growth and decreased weight gain. Extremely cold conditions increase an animal's daily energy requirements. During extremely hot weather feed intake often decreases, which may contribute to decreased growth. Often, environmental conditions influence the development of disease, resulting in a subsequent increase in nutrient requirements in a growing animal (e.g., calves

with PCM housed in poorly ventilated or overly humid conditions become much more susceptible to infectious pneumonia).

In many cases a combination of these diverse factors may influence the growth and weight gain of young animals. A period of increased growth rate and weight gain, called *compensatory gain,* often occurs after a period of restricted growth once adequate dietary energy and protein are available. In growing foals, compensatory gain should be closely monitored to prevent rapid growth and abnormal skeletal development, which could lead to developmental orthopedic disease.

Boxes 9.1 and 9.2 list many of the possible causes of decreased growth and decreased weight gain in horses and ruminants, respectively.

Box 9.1

Causes of Decreased Growth and Decreased Weight Gain in Horses

Common Causes

Protein-calorie malnutrition (PCM), inadequate nutrient intake
Extreme environmental factors (cold, heat)
Diarrhea (*Clostridia* species, *Salmonella* species, rotavirus, sand enteropathy, other causes)
Parasitism (*Parascaris equorum,* small strongyles, large strongyles, tapeworms, threadworms, bots)
Gastric ulcers
Bacterial pneumonia (*Rhodococcus equi, Streptococcus zooepidemicus,* other)
Viral pneumonia (equine herpesvirus, equine influenza)
Lameness (e.g., physitis, osteochondritis dissecans, contracted tendons, osteomyelitis)
Prematurity, dysmaturity

Less Common Causes

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Jaw pain (fracture, dental abnormality)
Esophageal stricture, megaesophagus (idiopathic, acquired)
Campylobacter jejuni
Cryptosporidium parvum
Equine proliferative enteropathy
Fungal pneumonia
Congenital cardiac and great vessel anomalies
Endocarditis
Ventricular septal defect
Abdominal abscess
Peritonitis
Osteodystrophy
Goiter
Calcium deficiency
Copper deficiency
Phosphorus deficiency
Selenium deficiency
Zinc deficiency
Vitamin A deficiency

Uncommon Causes

Hydrocephalus
Biliary atresia
Hepatic portosystemic shunt
Congenital renal abnormalities (hypoplasia, dysplasia, agenesis, polycystic kidney disease)
Wound myiasis
Agammaglobulinemia
Fell Pony syndrome
Selective IgM deficiency
Severe combined immunodeficiency
Transient hypogammaglobulinemia
Congenital hypothyroidism
Gonadal dysgenesis, intersex (XO, XXY)
Thiamine deficiency
Vitamin D deficiency

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Toxins

Ammonia toxicity
Fluorosis
Phenylbutazone, flunixin meglumine, and other nonsteroidal antiinflammatory drugs
Lead toxicity
Zinc toxicity

Box 9.2

Causes of Decreased Growth and Decreased Weight Gain in Ruminants

Common Causes

Protein-calorie malnutrition (PCM)
Extreme environmental factors (cold, heat)
Diarrhea (Enterotoxigenic *Escherichia coli*, attaching and effacing *E. coli*, *Shiga* toxin-producing *E. coli*, *Salmonella*, bovine virus diarrhea, coronavirus, rotavirus infection, *Cryptosporidium parvum*, coccidiosis, other causes)
Ostertagiasis I and II
Parasitism (flukes, gastrointestinal worms, lungworms)
Bacterial bronchopneumonia
Viral bronchopneumonia
Umbilical infections (omphaloarteritis, omphalourachitis, omphalophlebitis, hepatic abscessation)
Hepatic abscessation
Sarcoptic mange
Lameness (infectious and claw horn lesions, bovine digital dermatitis, sole ulcers, white line disease, etc.), osteomyelitis, septic arthritis)
Agammaglobulinemia (failure of passive transfer) in neonates
Copper deficiency (molybdenosis)
Selenium deficiency

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Less Common Causes

Pharyngeal abscess, injury
Severe bovine papular stomatitis
Abomasal ulcers
Peritonitis
Urachal or bladder abscess
Osteodystrophy, rickets
Immune-mediated anemia
Neonatal isoerythrolysis
Sarcocystosis
Myiasis
Tick infestation
Goiter
Cobalt deficiency
Vitamin A deficiency
Zinc deficiency

Uncommon Causes

Brisket disease
Calf lymphosarcoma
Mucormycosis
Zygomycosis
α-Mannosidosis[31]
Hypersensitivity to soy protein
Phosphorus deficiency

Congenital Abnormalities

Hydrocephalus
Cardiac or great vessel anomalies
Arthrogryposis
Osteogenesis imperfecta in Friesians
Congenital porphyria

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Granulocytopathy[32]
Epidermolysis bullosa
Generalized glycogenosis (GM1 gangliosidosis, type II glycogenosis)[33]
Gonadal dysgenesis, intersex
Familial acantholysis[34]
Bovine leukocyte adhesion deficiency (BLAD)[32]
α-Mannosidosis (B)[31]
Bovine hereditary zinc deficiency (lethal trait A-46)[35]

Toxins

Aflatoxicosis
Ammonia (urea) toxicity
Fluorosis
Herbicide toxicity
Iodine toxicity
Selenium toxicity
Zinc toxicity

Plant Toxins

Bracken fern *(Pteridium aquilinum)*
Cassia spp.
Fescue toxicity
Oxalate toxicity
Pyrrolizidine alkaloid toxicosis (*Senecio* spp., *Amsinckia* spp., *Crotolaria* spp., and others)
White leadtree *(Leucaena leucocephala)*

Exotic Diseases

Babesiosis *(Babesia bigemina, Babesia bovis)*
Schistosomiasis
Trypanosomiasis (*Trypanosoma* spp.)

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Approach to Diagnosis and Management of Decreased Growth and Decreased Weight Gain in Horses

1. Take a general history and a diet history.
    a. General history
        i. Foal factors: What is the patient's age? Was the foal born prematurely? Were any congenital defects identified during the initial examination of the foal after birth? Did the foal have any complications from sepsis? What is the vaccination history of the mare and the foal? Has the foal shown any evidence of systemic illness (diarrhea, nasal discharge, cough, pyrexia)?
        ii. Environmental factors: How is the foal housed? What type of protection is provided from adverse weather conditions? Has the foal experienced any extreme weather conditions (cold, heat, humidity)? Does the foal have access to a pasture or dry lot? Are there any toxins in the foal's environment? What is the stocking density of the herd? Is the foal exposed to a high parasite load in the environment? What is the foal's deworming history? Have there been previous problems with gastrointestinal parasitism on the farm? Does the farm have a history of infectious disease agents (*Rhodococcusequi, Streptococcus equi* subsp. *equi, Clostridium difficile*)? Are there any sick horses on the same farm? If so, what age cohort is sick?
    b. Diet history
        i. Foal: If the foal is nursing, is the mare at an ideal body weight? Is the mare producing a sufficient amount of milk for the foal? Has the mare had access to endophyte-infected tall fescue? If the

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foal is an orphan, what type of milk replacer is the owner using? What is the daily energy and protein intake of the foal? Is the owner mixing the milk replacer properly? Does the foal have access to a creep feed? What is the owner using as a creep feed? How much of the creep feed does the foal consume daily?

ii. Weaning: When was the foal weaned? Does the foal compete with other foals for feed? Has the owner changed the foal's diet recently? If yes, what changes were made? Does the foal have a good appetite? Has the foal's appetite changed recently?

(1) Forage: What type of forage is fed to the foal? Does the foal have access to pasture? How long is the foal turned out in the pasture? What is the nutritional quality of the hay or pasture? Is there gross evidence of dirt, mold, or weed contamination in the hay? Has a hay analysis been performed? Is the nutrient density of the hay/pasture appropriate for a growing horse? How much hay is offered to the foal (in weight) daily? How much forage (in weight) does the foal eat each day?

(2) Supplemental feeds and grain: What type of supplemental feed or grain is fed to the foal? Is the feed of high quality and indicated for a growing foal? What is the nutrient composition of the supplemental feed? Does it contain appropriate protein

quality, vitamins, and minerals? How much of the supplemental feed or grain (in weight) does the foal eat each day?

(3) Vitamins and minerals: If the foal is consuming commercial feed designed for a growing foal, it should not need supplemental vitamins or minerals. However, if the foal is being fed whole grains and hay/pasture, vitamin/mineral supplementation is warranted. Is the foal offered a vitamin and mineral supplement? Is the vitamin and mineral supplement appropriate for a growing foal? Is the vitamin and mineral supplement offered free choice? How much of the supplement (in weight) does the foal eat each day? Could any nutrients be consumed in a toxic amount? Has the owner provided any supplemental parenteral vitamins or minerals to the foal?

2. Perform a physical examination.

a. What is the body weight of the foal (measured by using either a scale or weight tape if the foal is 3 months of age or older)? What is the body condition score (BCS) of the foal (see Table 9.1)? Is the foal small, thin, or underweight according to growth charts (Tables 9.2 and 9.3; Fig. 9.1)?

TABLE 9.1

Body Condition Scoring System for Horses

Score	Description
1	Poor. Animal is extremely emaciated. Spinous processes, ribs, tailhead,

	tuber coxae, and tuber ischii project prominently. Bone structure of the withers, shoulders, and neck is noticeable. No fatty tissue can be felt.
2	Very thin. Animal is emaciated. There is a slight fat covering over the base of the spinous processes; the transverse processes of the lumbar vertebrae feel rounded. Spinous processes, ribs, tailhead, tuber coxae, and tuber ischii are prominent. Bone structure of the withers, shoulders, and neck is faintly discernible.
3	Thin. Fat buildup is present about halfway on the spinous processes; the transverse processes cannot be felt. There is a slight fat cover over the ribs. Spinous processes and ribs are easily discernible. Tailhead is prominent, but individual vertebrae cannot be visually identified. Tuber coxae appear rounded but are easily discernible; tuber ischii are not distinguishable. Bone structure of the withers, shoulders, and neck is accentuated.
4	Moderately thin. Negative crease can be seen along the back. Faint outline of ribs is discernible. Tailhead prominence depends on conformation; fat can be felt around tailhead. Tuber coxae are not discernible. Withers, shoulders, and neck are not obviously thin.
5	Moderate. Back is level. Ribs cannot be visually distinguished but can be felt easily. Fat around tailhead is somewhat spongy. Withers appear rounded over spinous processes, and shoulders and neck blend smoothly into the body.
6	Moderately fleshy. Slight crease may be seen down the back. Fat over ribs is spongy, and fat around tailhead is soft. Fat is beginning to be deposited along withers, behind shoulders, and along neck.
7	Fleshy. Crease may be seen down the back. Individual ribs can be felt, but there is noticeable filling of fat between ribs. Fat around tailhead is soft. Fat is deposited along withers, behind shoulders, and along neck.
8	Fat. Crease is seen down the back. Ribs are difficult to feel. Fat around tailhead is very soft. Areas along withers and behind shoulders are filled with fat, and neck is noticeably thickened. Fat is deposited along inner thighs.
9	Extremely fat. Obvious crease is seen down the back. Patchy fat appears over ribs. Bulging fat is seen around tailhead along withers, behind shoulders, and along neck. Fat along inner thighs may cause thighs to rub together. Flank is filled with fat.

From Henneke GD, Potter GD, Kreider JL, et al. Relationship between condition score, physical measurements and body fat percentage in mares. *Equine Vet J* 15:371, 1983.

TABLE 9.2

Weight as Percentage of Mature Body Weight in Horses

Age (Months)	Ponies[4] (%)	Light Horses[1-3,5] (%)	Draft Horses (%)
6	55	46	40
12	75	67	57
18	84	80	75

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TABLE 9.3

Body Weight Predicted by Equation 1 and Expected Mature Body Weight and Body Weight Estimated in the Previous NRC (1989) for Growing Horses

Mature Wt	Age (months)	NRC (1989)	Equation 1
200 kg	4	75 (37.5%)	67.4 (33.7%)
	6	95	86.4
	12	140	128.5
	18	170	155
	24	185 (92.5%)	172 (86%)
	36	No value	189
400 kg	4	145 (36.3%)	134.8 (33.6%)
	6	180	173
	12	265	257
	18	330	310
	24	365 (91.2%)	343.4 (85.9%)
	36	No value	379
500 kg	4	175 (35%)	168.5 (33.7%)
	6	215	215.9
	12	325	321.2
	18	400	387.5
	24	450 (90%)	429.2 (86%)
	36	No value	472
600 kg	4	200 (33.3%)	202.1 (33.7%)
	6	245	259
	12	375	385.5
	18	475	465
	24	540 (90%)	515 (86%)
	36	No value	566.4
900 kg	4	275 (30.6%)	303.2 (33.7%)
	6	335	388.6
	12	500	578.2
	18	665	697.5
	24	760 (84.4%)	773 (85.9%)
	36	No value	850

Values in parentheses represent % of mature body weight. Equation (1) $Y = 9.7 + (100 - 9.7) \times (1 - (e(-0.0772 \times X))$ (R2 = 0.99); Y = percent mature body weight; X = months of age.

From National Research Council [NRC]. 2007. Nutrient requirements of horses. National Academies Press, Washington DC.

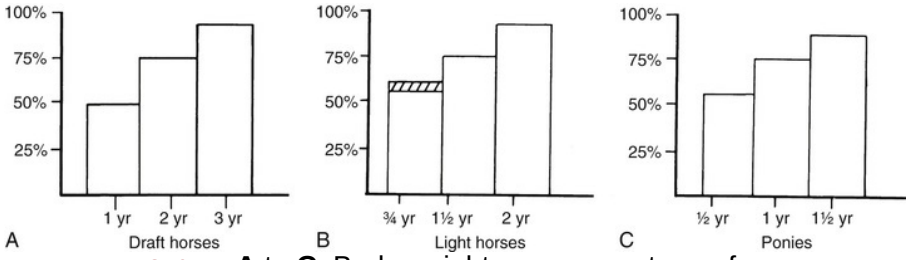


FIG. 9.1 **A** to **C,** Body weight as a percentage of mature body weight for horses at a given age. (**A** modified from Crampton EW. Rate of growth of draft colts. *J AgricHortic* 26:172, 1923; **B** modified from Lewis LD. *Feeding and care of the horse*. Philadelphia, 1982, Lea & Febiger; **C** modified from Hintz HF. *Factors affecting the growth rate of horses. Horse Short Course Proceedings*. College Station, Tex., 1979, Texas A&M Animal Agriculture Conference.)

b. Does the foal have evidence of a congenital abnormality (cardiac, renal, gastrointestinal, oral)?
c. Does the foal show any signs of infectious disease (current or resolved)?
d. Does the foal have any musculoskeletal abnormalities?

3. Examine the feces. What is the consistency of the feces? Refer to Chapter 17 for the diagnosis and management of neonatal diarrhea; refer to Chapter 7 if the foal is older and has evidence of diarrhea. Is there evidence of sand in the manure? If yes, the foal should be treated with psyllium. Perform a fecal egg count. If the foal has a positive fecal egg count, follow the parasite control program recommendations in Chapter 49. If a negative fecal egg count is reported but parasitic infestation is still suspected, repeat the test in 2 to 3 weeks or follow the deworming protocols in Chapter 49. Evaluate the feces for occult blood. If the foal has a positive fecal occult blood test, review the medical management for melena in Chapter 7.
4. Perform blood analyses.
    a. Perform a complete blood count (CBC) and include a plasma protein and fibrinogen concentration. If the foal is anemic, determine the cause of the anemia following the guidelines in Chapter 24. If the foal's CBC indicates inflammation, review Chapters 25 and Chapter 26 and select appropriate ancillary diagnostic tests to identify the source of the infection or inflammation.
    b. Perform a serum biochemical analysis. Evaluate the results for evidence of systemic disease. Serum albumin is usually

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within normal limits with PCM until the condition is terminal. Serum glucose is usually normal, but it may be decreased in neonatal foals with sepsis. Serum glucose may be elevated in stressed animals. Serum urea nitrogen and creatinine concentrations are elevated in foals with renal disease. Serum urea nitrogen decreases in cases of chronic protein malnutrition.

c. If the foal has evidence of systemic disease, perform ancillary diagnostic tests to identify the source of the illness and then manage the case with appropriate medical or surgical intervention.

5. Analyze the diet and improve the feeding program.
    a. Determine whether the energy, protein, mineral, and vitamin content of the diet meets the requirements of the growing foal (Table 9.4). Use the Nutrient Requirements of Horses free companion computer program as a reference for all essential nutrients (www.nap.edu/catalog/11653/nutrient-requirements-of-horses-sixth-revised-edition).
        i. Dietary protein and essential amino acids are especially important in young growing horses. Lysine is the first, and threonine is the second limiting amino acid in the equine. Growing foals should consume 4.3% of their crude protein requirement as lysine (multiply the crude protein requirement by 4.3%).[7] Growing foals should also consume at least 0.5% threonine dry matter (DM) in their diet. Soybean meal and alfalfa hay contain approximately 3.3% and 0.9% lysine (DM), respectively. Cereal grains are poor sources of lysine. Commercial feeds typically designed for growing horses should have sufficient lysine and threonine content, either via the inclusion of soybean meal as an ingredient, and/or direct addition of lysine and threonine as ingredients.
        ii. Milk replacer: If the foal is consuming a milk replacer, review the guaranteed analysis and

ingredient list of the product. Review the mixing instructions with the owner or farm manager. Develop a feeding program appropriate for the foal's age.

iii. Forage: Determine the nutrient content of forage or pasture with an analysis. Equi-Analytical forage laboratory service (www.equi-analytical.com) can analyze for major energy, protein, and major and some minor minerals. NP Analytical Laboratories (https://www.npal.com) can analyze feeds further for amino acids and vitamins if warranted. Forage sampling instructions and forage analysis companies are listed in Boxes 9.3 and 9.4. University extension services often provide a forage analysis service. If the client does not purchase a large volume of hay, or if analysis cannot be performed, forage tables from the Nutrient Requirement Council reference books (www.nap.edu) and nutrient tables from the Equi-Analytical Laboratories forage laboratory database can be referenced to estimate the concentration of different nutrients in common forages and supplemental feeds; however, if nutrient deficiency/toxicity are suspected, forage analysis should be conducted. Use the daily nutrient requirements (see Table 9.4) to recommend the type and amount of forage the foal should consume on the basis of the nutrient content of the forage.

Box 9.3

Forage and Large Animal Feed Sampling Instructions

Sampling Pasture

1. Collect pasture samples from a 1-foot-square area. Sample only the same type of forage that the horses are grazing. Sample 10 to 20 sites.

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2. Using scissors, cut the pasture to within 1 inch of the ground. Do not collect soil-contaminated pasture. Cut all samples to a length of 1 inch, and place all samples into a clean bucket.
3. After sampling is complete, mix the samples well and place the forage into a plastic sealable bag (1-gallon Ziplock). Label the bag with the date of sampling, the collection site, and the owner's name.
4. If the sugar and starch content of the sample is of special interest, the sample should be frozen and shipped on ice to the analysis company.

Sampling Hay Using a Core Hay Sampler

1. Choose 10 to 20 bales randomly from the hay shipment. Only one type of forage should be submitted for analysis in the same container. If more than one type of hay is analyzed, each should be placed into a separate, labeled plastic bag.
2. Use the core hay sampler with a ratchet brace or drill to collect two samples from each bale. Square bales should be sampled from the long end of the bale. Round bales should be sampled along a horizontal line at the curve of the bale. Place all samples into a plastic sealable bag (1-gallon Ziplock), and label the bag with the date, type of hay, and owner's name.

Sampling Hay by Hand

1. Choose 10 to 20 bales randomly from the hay shipment. Only one type of forage should be submitted for analysis in the same container. If more than one type of hay is analyzed, each should be placed into a separate, labeled plastic bag.
2. Open the bale, and divide the bale in thirds. Collect a handful of hay from the center of the bale at each site (two samples per bale). Include everything that you have grabbed (including weeds and other plants) in the sample. Cut all samples to a length of 1 inch, and place all samples into a clean bucket. Thoroughly mix the cut hay samples, place the forage into a plastic sealable bag (1-gallon Ziplock), and label the bag with the date, type of hay, and owner's name. Ensure that all parts of the sample (leaves and stems) are included in the final sample.

Sampling Grain or Pelleted Feed

1. Analysis of two to four samples from 10 bags is recommended to obtain a representative sample of feed. Only one type of feed should be submitted for analysis in the same container. If more than one type of grain or pelleted feed is analyzed, each should be placed into a separate, labeled plastic bag.

2. Open a bag or a bin, and obtain a 2- to 4-oz sample from two to four locations in the bag or bin. A sample should be obtained from the bottom of the bin or bag to ensure that a sample of the settled feed is analyzed. When multiple bags or bins are sampled, samples from each bin or bag should be placed into a clean plastic bucket. Once all sampling has been completed, the feed sample should be mixed well, and approximately 1 lb of the feed should be placed into a plastic sealable bag (1-gallon Ziplock). Label the bag with the date, type of feed, and owner's name.

Box 9.4

Feed Analysis Companies

Submission forms are available online.

1. Equi-Analytical Laboratories
   http://equi-analytical.com
2. Cumberland Valley Analytical Services
   www.foragelab.com
3. NP Analytical Laboratories
   www.npal.com
4. Eurofins
   www.eurofinsus.com

iv. Commercial feeds and grain mixes: The guaranteed analysis on the feed tag label provides the nutrient content of certain ingredients. Contact commercial feed companies for the energy content of their product and nutrients not required for the guaranteed analysis tag. Make recommendations about the appropriate use of commercial equine feeds, grain, or grain mixes to complement the forage-based ration for growing foals on the basis of the clinical health of the foal.

v. Vitamins and minerals: Ensure that the ration meets the vitamin and mineral requirements of the foal and that proper mineral ratios are maintained in the ration. Supplement the ration if necessary.

TABLE 9.4

Daily Nutrient Requirements for Growth in Equines of Various Mature Body Weights

Mature Body Weight (kg/lb)	Category	Weight		Daily Gain		Digestible Energy (Mcal)	Crude Protein (g)	Lysine (g)	Calci (g)
		(kg)	(lb)	(kg)	(lb)				
Ponies 200 kg (440 lb)	Nursing foal (4 mo old)	67	147	0.34	0.75	5.3	268	11.5	15.6
	Weanling (6 mo old)	86	189	0.29	0.64	6.2	270	11.6	15.5
	Yearling (12 mo old)	128	282	0.18	0.40	7.5	338	14.5	15.1
	Long yearling (18 mo old)	155	341	0.11	0.242	7.7	320	13.7	14.8
	2-year-old (24 mo old)	172	378	0.07	0.154	7.5	308	13.2	14.7
Horses 400 kg (880 lb)	Nursing foal (4 mo old)	135	297	0.67	1.47	10.6	535	23.0	31.3
	Weanling (6 mo old)	173	381	0.58	1.28	12.4	541	23.3	30.9
	Yearling (12 mo old)	257	565	0.36	0.79	15.0	677	29.1	30.1
	Long yearling (18 mo old)	310	682	0.23	0.51	15.4	639	27.5	29.6
	2-year-old (24 mo old)	343	755	0.14	0.31	15.0	616	26.5	29.3
Horses 500 kg (1100 lb)	Nursing foal (4 mo old)	168	370	0.84	1.85	13.3	669	28.8	39.1
	Weanling (6 mo old)	216	475	0.72	1.58	15.5	676	29.1	38.6
	Yearling (12 mo old)	321	706	0.45	1.0	18.8	846	36.4	37.7

	Long yearling (18 mo old)	387	851	0.29	0.64	19.2	799	34.4	37.0
	2-year-old (24 mo old)	429	944	0.18	0.40	18.7	770	33.1	36.7
Horses 600 kg (1320 lb)	Nursing foal (4 mo old)	202	444	1.01	2.22	15.9	803	34.5	46.9
	Weanling (6 mo old)	259	570	0.87	1.91	18.6	811	34.9	46.4
	Yearling (12 mo old)	385	847	0.54	1.19	22.5	1015	43.6	45.2
	Long yearling (18 mo old)	465	1023	0.34	0.75	23.1	959	41.2	44.5
	2-year-old (24 mo old)	515	1133	0.22	0.48	22.4	924	39.7	44.0
Horses 900 kg (1980 lb)	Nursing foal (4 mo old)	303	667	1.52	3.34	23.9	1204	51.8	70.3
	Weanling (6 mo old)	389	856	1.30	2.86	28.0	1217	52.3	69.5
	Yearling (12 mo old)	578	1272	0.82	1.80	33.8	1522	65.5	67.8
	Long yearling (18 mo old)	697	1533	0.51	1.12	34.6	1438	61.8	66.7
	2-year-old (24 mo old)	773	1701	0.32	0.70	33.7	1386	59.6	66.0

Modified from National Research Council. *Nutrient requirements of horses.* Washington, D.C., 2007, National Academies Press.

b. If the foal or weanling has a nutrient deficiency, the problem should be corrected by a change in the ration or through appropriate parenteral supplementation.
c. If the diet history indicates that nutrients for maintenance and growth have been available and steadily consumed, the

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search for another cause of decreased growth and decreased weight gain should continue.

6. Perform ancillary diagnostic tests. If the cause of the decreased growth and/or poor weight gain has not been determined, additional diagnostic tests should be performed. Possible tests include, but are not limited to, ultrasound, radiographs, serum or whole blood trace mineral analysis, and carbohydrate absorption tests (oral D-glucose, D-xylose).

Approach to the Diagnosis and Management of Decreased Growth and Decreased Weight Gain in Ruminants

1. Take a general history and a diet history.
    a. General history
        i. What is the age of the animal? When was a decrease in growth observed? How many animals in the herd are affected? What are the ages of the affected animals? Has the herd had historical problems with growth of the young?
        ii. Identify the problem as acute, subacute, or chronic.
        iii. Check for signs or history of previous infectious disease in the herd.
        iv. Determine the parasite control procedures for the animal or herd.
        v. Examine the environment, including feed preparation areas and equipment, for possible toxic substances (e.g., zinc from galvanized buckets). Ensure cleanliness of bottles and equipment used with nursing animals.
    b. Diet history
        i. Obtain an accurate diet history, including diet information when milk or a milk replacer is being fed (birth to 2 or 3 months of age). Note the age and condition of the dam if patient was suckled before weaning. An accurate

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postweaning dietary history is essential. Suckled animals are developed ruminants at weaning, but hand-reared animals (dairy calves, bummer lambs, and dairy kids) are usually not fully developed ruminants at the time they are weaned from milk.

ii. Inspect all forages and concentrates for quality, signs of spoilage, or abnormal color or odor. Has an analysis been performed on the forage or feed? Is the feed formulated appropriately for a young growing animal? Is the feed stored appropriately?

iii. Because ruminants are often fed in groups, note whether all animals have adequate space to eat simultaneously.

2. Perform a physical examination.

a. Determine the patient's age, weight, and body condition score. Is the patient growing appropriately? The growth curve depends on multiple factors including genetic and environmental factors and can be predicted using a number of different equations, each being adequate for different species or breeds.[8-10] One example is the Brody growth curve[11]

(1) $Wt = A(1 - B\ e^{-kt})$

(Wt: body weight at age t; A: mature weight; B: initial weight; k: growth rate; t: age in days)

Targets for growth in dairy heifers are shown in Box 9.5.

Box 9.5

Targets for Growth in Dairy Heifers[27]

- Target weight first bred = mature shrunk body weight (SBW) × 0.55
- Target shrunk weight gain (SWG) before first pregnancy = (Target weight first bred – current SBW)/(Target age for first pregnancy – current age)
- Target first calving weight = mature SBW × 0.82
- Target second calving weight = mature SBW × 0.92
- Target third calving weight = mature SBW × 1.00
- First pregnant SWG = (Target first calving weight – Target weight first

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	bred)/280

Modified from National Research Council. *Nutrient requirements of dairy cattle*, 7th revised ed. Washington, DC, 2001, National Academies Press.

b. Does the animal show any signs of infectious or parasitic disease?
c. Does the animal show any signs of congenital abnormalities?

3. Examine the feces. Perform flotation, sedimentation, and Baermann's procedures to detect patent parasitic infestation. Perform a fecal occult blood test; if the result is positive or if there is evidence of diarrhea, see the section on melena or diarrhea in Chapter 7. If diarrhea is noted in neonatal calves, refer to Chapter 20 for diagnostic and therapeutic management.
4. Perform blood analysis.
    a. Perform a CBC, including plasma protein and fibrinogen. Use the erythrocytic indices to document and characterize the anemia if present. If a herd problem exists in a selenium-deficient region, measure the whole blood selenium concentration or glutathione peroxidase activity.
    b. Perform a serum biochemical analysis. Serum albumin is decreased late in PCM. Albumin is normally lower in neonates (≈1 g/dL less) than in adults. The blood urea nitrogen (BUN) level is often low in ruminants as a result of urea recycling through saliva. Total serum calcium may be decreased with hypoalbuminemia (ionized serum calcium remains normal), anorexia, or hypocalcemic syndromes (milk fever). Serum phosphorus may be increased during severe starvation or decreased with anorexia. Hypophosphatemia may be the result of dietary deficiency or *Brassica* feeding, or it may be associated with copper deficiency. Measure serum (plasma) copper if a herd problem exists in a copper-deficient region (or a region with excess molybdenum or sulfate or both). Copper (serum or plasma) concentrations below 0.5 µg/mL (ppm) indicate deficiency. The concentration of copper in the liver is even more indicative of status. Serum glucose may be increased with stress or decreased or normal near death.

5. Analyze the diet and improve the feeding program. Compare nutrient intake with the requirements for maintenance and growth of the various ruminant species (Tables 9.5 to 9.11). If the neonate is being fed a milk diet, evaluate the quality of the product and ensure that the animal's intake meets the dietary requirements (see Tables 9.5 and 9.6). Requirements for other breeds and life stages can be found in the nutrient requirement textbooks for dairy cattle, beef cattle, and small ruminants. Ensure that the milk replacer is mixed properly. If the ruminant is consuming a grain mix or forage, ensure that the quantity and quality of the feed are adequate to allow sufficient intake in developed ruminants. Equations to predict dry matter intake are available; some examples are listed in Table 9.12. Forage sampling instructions are listed in Box 9.3. If anorexia is present, look for more specific signs of a primary disease process. If the diet supplies adequate nutrients for maintenance and growth, consider decreased growth and decreased weight gain to be caused by a primary disease condition.

TABLE 9.5

Daily Energy and Protein Requirements of Young Dairy Replacement Calves Fed Only Milk or Milk Replacer

			Energy				Protein		
Live Weight (kg)	**Gain (g)**	**Dry Matter Intake[a] (kg)**	**NE_M (Mcal)**	**NE_C (Mcal)**	**ME (Mcal)**	**DE (Mcal)**	**ADP (g)**	**CP (g)**	**Vitamin A (IU)**
25	0	0.24	0.96	0	1.12	1.17	18	20	2,750
	200	0.32	0.96	0.26	1.50	1.56	65	70	2,750
	400	0.42	0.96	0.60	2.00	2.08	113	121	2,750
30	0	0.27	1.10	0	1.28	1.34	21	23	3,300
	200	0.36	1.10	0.28	1.69	1.76	68	73	3,300
	400	0.47	1.10	0.65	2.22	2.31	115	124	3,300
40	0	0.34	1.37	0	1.59	1.66	26	28	4,400
	200	0.43	1.37	0.31	2.04	2.13	73	79	4,400
	400	0.55	1.37	0.72	2.63	2.74	120	129	4,400
	600	0.69	1.37	1.16	3.28	3.41	168	180	4,400
45	0	0.37	1.49	0	1.74	1.81	28	30	4,950
	200	0.46	1.49	0.32	2.21	2.30	76	81	4,950
	400	0.59	1.49	0.75	2.82	2.94	123	123	4,950
	600	0.74	1.49	1.21	3.50	3.64	170	183	4,950
50	0	0.40	1.62	0	1.88	1.96	31	33	5,500
	200	0.45	1.62	0.34	2.37	2.47	78	84	5,500
	400	0.63	1.62	0.77	3.00	3.13	125	135	5,500

	600	0.78	1.62	1.26	3.70	3.86	173	185	5,500

[a]Dry matter intake necessary to meet ME requirements for calves fed milk replacer composed primarily of milk proteins and containing ME at 4.75 Mcal/kg of dry matter.

ADP, Apparent digestible protein, g/d); *CP (crude protein),* ADP/0.93; *DE (Mcal),* ME/0.96; *ME (Mcal),* 0.1 $LW^{0.75}$ × (0.84 $LW^{0.355}$ × $LWG^{1.2}$), where LW and LWG are in kilograms; NE_G *(Mcal)*, (0.84 $LW^{0.355}$ × $LWG^{1.2}$) × 0.69, where LW and LWG (live weight gain) are in kilograms; NE_M *(Mcal),* 0.086 $LW^{0.75}$, where LW is live weight in kilograms. The digestibility of undenatured milk proteins is assumed to be 93%; *Vitamin A (IU),* 110 IU/kg of LW.

Modified from National Research Council. *Nutrient requirements of dairy cattle,* ed 7. Washington, D.C., 2001, National Academies Press.

TABLE 9.6

Net Energy Requirements of Young Lambs on Milk-Replacer Diets[a]

Body Weight in Kilograms (Pounds)					
Average Daily Gain (g)	**5 (11)**	**7.5 (16.5)**	**10 (22)**	**12.5 (27.6)**	**15 (33)**
NE_m Required, kcal/day					
	359	487	603	712	817
NE_g Required, kcal/day					
100	127	172	214	253	290
150	193	262	325	383	440
200	261	353	438	518	594
250	330	447	555	355	751
300	401	543	674	796	913
350	473	641	796	940	1078
400	547	742	921	1088	1247

[a]Protein requirements for young lambs on milk-replacer diets are approximately 20 g, 40 g, and 60 g for weight gains of 0, 100, and 200 g/day, respectively.

NE_g, Net energy of gain; NE_m, net energy of maintenance.

From Chiou PWS, Jordan RM. Ewe milk replacer diets for young lambs. IV. Protein and energy requirements of young lambs. *J Anim Sci* 37:581, 1973.

TABLE 9.7

Net Energy Requirements for Growth of Beef Cattle (Mcal/day)

Shrunk Body Weight (kg); (NE_m Required)						
Daily Gain (kg)	250 (4.8)	300 (5.6)	350 (6.2)	400 (6.9)	450 (7.5)	500 (8.1)
Growing and Finishing Cattle NE_g Required						
0.4	1.2	1.3	1.5	1.6	1.8	1.9
0.8	2.5	2.8	3.2	3.5	3.8	4.1

1.2	3.8	4.4	5	5.5	6	6.5
1.6	5.3	6.1	6.8	7.5	8.2	8.9
2	6.7	7.7	8.7	9.6	10.5	11.3
	Body Weight (kg); (NE_m Required)					
Daily Gain (kg)	300 (6.4)	400 (7.9)	500 (9.4)	600 (10.7)	700 (12.1)	800 (13.3)
Growing Bulls NE_g Required						
0.4	0.9	1.1	1.3	1.5	1.7	1.9
0.8	2	2.4	2.9	3.3	3.7	4.1
1.2	3.1	3.8	4.5	5.1	5.8	6.4
1.6	4.2	5.2	6.1	7	7.9	8.7
2	5.3	6.6	7.8	9	10.1	11.1

NE_g, Net energy of gain; *NE_m*, net energy of maintenance.

Modified from National Research Council. *Nutrient requirements of beef cattle,* ed 8. Washington, D.C., 2016, National Academy of Sciences.

TABLE 9.8

Protein Requirements for Growth of Beef Cattle[a]

Shrunk Body Weight (kg); (MP Required)						
Daily Gain (kg)	250 (239)	300 (274)	350 (307)	400 (340)	450 (371)	500 (402)
Growing and Finishing Cattle MP Required						
0.4	149	139	129	120	111	102
0.8	288	267	246	226	207	188
1.2	423	390	358	326	296	267
1.6	556	510	466	423	381	341
2	686	627	571	516	463	412
	Body Weight (kg); (MP Required)					
Daily Gain (kg)	300 (274)	400 (340)	500 (402)	600 (461)	700 (517)	800 (572)
Growing Bulls MP Required						
0.4	163	150	138	126	115	104
0.8	319	291	264	239	215	192
1.2	471	427	386	347	310	273
1.6	622	561	505	451	400	350
2	770	693	621	553	487	423

[a]Metabolizable protein g/day.

Modified from National Research Council. *Nutrient requirements of beef cattle,* ed 8. Washington, D.C., 2016, National Academy Press.

TABLE 9.9

Calcium (Ca) and Phosphorus (P) Requirements for Growth of Beef Cattle (g/day)

Shrunk Body Weight (kg) (Ca and P Required)							

Daily Gain (kg)	Mineral	250 (7.7, 5.9)	300 (9.2, 7.1)	350 (10.8, 8.2)	400 (12.3, 9.4)	450 (13.9, 10.6)	500 (15.4, 11.8)
	Growing and Finishing Cattle						
0.4	Ca	10.4	9.7	9	8.4	7.7	7.1
	P	4.2	3.9	3.6	3.4	3.1	2.9
0.8	Ca	20.1	18.6	17.2	15.8	14.4	13.1
	P	8.1	7.5	6.9	6.4	5.8	5.3
1.2	Ca	29.6	27.2	25	22.8	20.7	18.6
	P	12	11	10.1	9.2	8.4	7.5
1.6	Ca	38.9	35.6	32.5	29.5	26.6	23.8
	P	15.7	14.4	13.1	11.9	10.8	9.6
2	Ca	48	43.8	39.9	36.1	32.4	28.8
	P	19.4	17.7	16.1	14.6	13.1	11.6
		Body Weight (kg) (Ca and P Required)					
Daily Gain (kg)		300 (9.2, 7.1)	400 (12.3, 9.4)	500 (15.4, 11.8)	600 (18.5, 14.1)	700 (21.6, 16.5)	800 (24.6, 18.8)
	Growing Bulls						
0.4	Ca	11.4	10.5	9.6	8.8	8	7.3
	P	4.6	4.2	3.9	3.6	3.2	2.9
0.8	Ca	22.3	20.3	18.5	16.5	15	13.4
	P	9	8.2	7.5	6.8	6.1	5.4
1.2	Ca	32.9	29.9	27	24.2	21.6	19.1
	P	13.3	12.1	10.9	9.8	8.7	7.7
1.6	Ca	43.4	39.2	35.3	31.5	27.9	24.5
	P	17.5	15.8	14.2	12.7	11.3	9.9
2	Ca	53.8	48.4	43.4	38.6	34	29.6
	P	21.7	19.6	17.5	15.6	13.7	11.9

Modified from National Research Council. *Nutrient requirements of beef cattle,* ed 8. Washington, D.C., 2016, National Academy Press.

TABLE 9.10

Daily Nutrient Requirements of Sheep (Growing Lambs, Growing Rams, and Yearlings)

Body Weight		Daily Body Weight Gain	Metabolizable Energy (ME) (Mcal)	Total Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)
(kg)	(lb)	(g)					
Growing Lambs and Yearlings; Late Maturing; 4 Mo Old/8 Mo Old							

20	44	100	1.09/1.41	300/390	51/49	2.3/2.2	1.5/1.5
		150	1.50/1.81	410/500	70/65	3.1/3.0	2.2/2.1
200			1.42/1.99	390/550	78/75	3.7/3.5	2.5/2.6
300			1.74/2.69	480/750	104/105	5.1/5.0	3.5/3.8
40	88	250	2.53/3.10	700/860	115/108	5.0/4.7	3.7/3.6
		300	2.94/3.53	820/980	134/124	5.9/5.5	4.4/4.3
400			2.78/3.9	770/1080	150/144	7.0/6.7	5.1/5.2
500			3.35/4.62	930/1280	182/174	8.6/8.2	6.3/6.4
60	132	250	2.74/4.44	760/1230	122/140	5.1/5.7	3.8/4.6
		300	3.15/3.95	870/1100	141/134	6.0/5.7	4.5/4.5
400			3.98/4.82	1100/1340	179/167	7.8/7.3	5.9/5.8
500			3.57/5.69	990/1580	190/199	8.7/8.9	6.4/7.2
600			4.15/5.83	1150/1620	222/214	10.3/9.9	7.6/7.8
80	176	150	2.08/3.58	580/990	92/109	3.4/4.0	2.5/3.2
		200	2.50/4.21	690/1170	111/130	4.3/4.9	3.2/4.0
300			3.34/5.48	930/1520	149/171	6.1/6.8	4.6/5.6
400			4.19/5.24	1160/1450	186/176	7.9/7.5	6.0/6.0
500			5.03/6.13	1390/1700	224/209	9.7/9.1	7.5/7.3
Growing Rams; Late Maturing; 4 Mo Old/8 Mo Old							
20	44	100	1.14/1.5	320/420	52/50	2.3/2.2	1.5/1.5
		150	1.18/1.91	330/530	62/66	2.9/3.0	1.9/2.2
200			1.47/2.09	410/580	78/76	3.7/3.6	2.5/2.6
300			1.79/2.8	500/780	105/106	5.1/5.1	3.5/3.8
40	88	250	2.62/3.28	730/910	116/110	5.1/4.8	3.7/3.7
		300	3.03/3.71	840/1030	135/126	6.0/5.6	4.5/4.4
400			2.87/4.08	800/1130	151/146	7.0/6.8	5.1/5.2
500			3.45/4.81	960/1340	184/176	8.6/8.3	6.3/6.5
60	132	250	2.85/3.76	790/1040	124/120	5.2/5.0	3.9/3.9
		300	3.27/4.2	910/1160	143/137	6.1/5.8	4.6/4.6
400			4.11/5.08	1140/1410	181/170	7.9/7.4	6.0/5.9
500			3.7/5.34	1020/1480	191/187	8.7/8.5	6.4/6.7
600			4.28/6.1	1190/1690	224/217	10.3/10	7.7/7.9
80	176	150	2.22/3.87	620/1070	94/114	3.5/4.1	2.5/3.3
		200	2.65/4.51	730/1250	113/134	4.4/5.1	3.3/4.2
300			3.49/5.81	970/1610	151/176	6.2/7.0	4.7/5.8
400			4.34/5.56	1200/1540	189/180	8.0/7.6	6.1/6.1
500			5.19/6.47	1440/1790	227/214	9.8/9.2	7.6/7.5

Modified from National Research Council. *Nutrient requirements of small ruminants.* Washington, D.C., 2007, National Academies Press

TABLE 9.11

Daily Nutrient Requirements of Goats (Growing Goat Kids)

Body	Daily Body	Total

Weight		Weight Gain	Metabolizable Energy (ME) (Mcal)	Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)
(kg)	(lb)	(g)					
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
10	22	0	0.72/0.61	200/170	17/17	0.9/1.0	0.5/0.6
		25	0.86/0.75	240/210	25/27	1.6/1.5	0.8/0.8
100			1.27/1.16	350/320	46/58	3.5/3.5	1.6/1.5
150			1.55/1.44	430/400	61/78	4.8/4.8	2.2/2.1
200			1.82/1.71	510/470	75/98	6.2/6.1	2.7/2.7
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
20	44	0	1.21/1.02	340/280	29/29	1.4/1.3	1.0/0.9
		25	1.35/1.16	370/320	36/39	2.2/2.0	1.4/1.2
100			1.76/1.57	490/440	58/69	4.0/3.9	2.0/1.9
150			2.04/1.85	570/510	73/90	5.1/5.2	2.4/2.6
200			2.31/2.13	640/590	87/110	6.4/6.3	3.0/2.9
		250	2.59/2.4	720/670	102/130	7.7/7.6	3.5/3.4
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
30	66	0	1.64/1.38	460/380	39/39	1.8/1.6	1.4/1.2
		25	1.78/1.52	490/420	47/49	2.5/2.3	1.7/1.5
100			2.19/1.94	610/540	68/80	4.2/4.5	2.3/2.5
150			2.47/2.21	680/610	83/100	5.6/5.4	2.9/2.8
200			2.74/2.49	760/690	97/120	7.0/6.8	3.5/3.4
		250	3.02/2.76	840/770	112/140	7.9/8.2	3.7/4.0
		300	3.30/3.04	910/840	126/161	9.3/9.1	4.3/4.2
Growing Kids; Doelings and Male Castrates; Dairy/Boer							
40	88	0	2.04/1.72	560/480	49/49	2.1/1.8	1.7/1.4
		25	2.17/1.86	600/510	56/59	2.8/2.6	2.0/1.8
100			2.59/2.27	720/630	78/89	5.0/4.7	3.0/2.8
150			2.86/2.55	790/710	92/109	5.8/6.2	3.1/3.5
200			3.14/2.82	870/780	107/130	7.2/7.0	3.7/3.6
		250	3.42/3.10	950/860	121/150	8.6/8.4	4.4/4.2
		300	3.69/3.37	1020/940	136/170	10.0/9.8	5.0/4.8

Modified from National Research Council. *Nutrient requirements of small ruminants.* Washington, D.C., 2007, National Academies Press.

TABLE 9.12

Examples of Equations for Predicting Dry Matter Intake (DMI) in Different Kinds of Cattle

DMI of	Equation	Abbreviations
Lactating Holstein cows[a]	DMI (kg/d) = $(0.372 \times FCM + 0.0968 \times BW^{0.75}) \times (1 - e^{[-0.192 \times \{WOL + 3.67\}]})$	FCM: 4% fat corrected milk (kg/day), BW: body weight (kg), WOL: week of lactation

Growing-finishing beef cattle[b]	DMI (% BW) = 1.2425 + 1.9218 × NEm – 0.7259 × NEm^2	NEm: Net energy required for maintenance, can be obtained from [28]
Feedlot steers fed high-grain diets[b]	DMI (kg/d) = 3.830 + 0.0143 × ISBW	ISBW: Initial shrunk body weight (kg)

[a]Modified from National Research Council. *Nutrient requirements of dairy cattle*, 7th revised ed. Washington, DC, 2001, National Academies Press.

[b]National Academies of Sciences EM, Studies DEL, Resources BAN, Cattle CNRB. *Nutrient requirements of beef cattle:* ed 8. Washington, D.C., 2016, National Academies Press.

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Weight Loss

The clinical problem of weight loss suggests that an individual large animal patient or a herd has lost weight over a known period of time. It may also suggest that the patient has reached a subnormal adult weight and size (see section on decreased growth and decreased weight gain, earlier). Late pregnancy, early lactation, and intense exercise are normal physiologic conditions commonly accompanied by mild to moderate weight loss. Late pregnancy can be associated with decreased body condition (Fig. 9.2) without actual weight loss because weight is gained with the conceptus. During pregnancy and lactation the loss of body condition may be mild, resulting in a low normal BCS, or the loss may be severe and can threaten the health of both the dam and neonate.

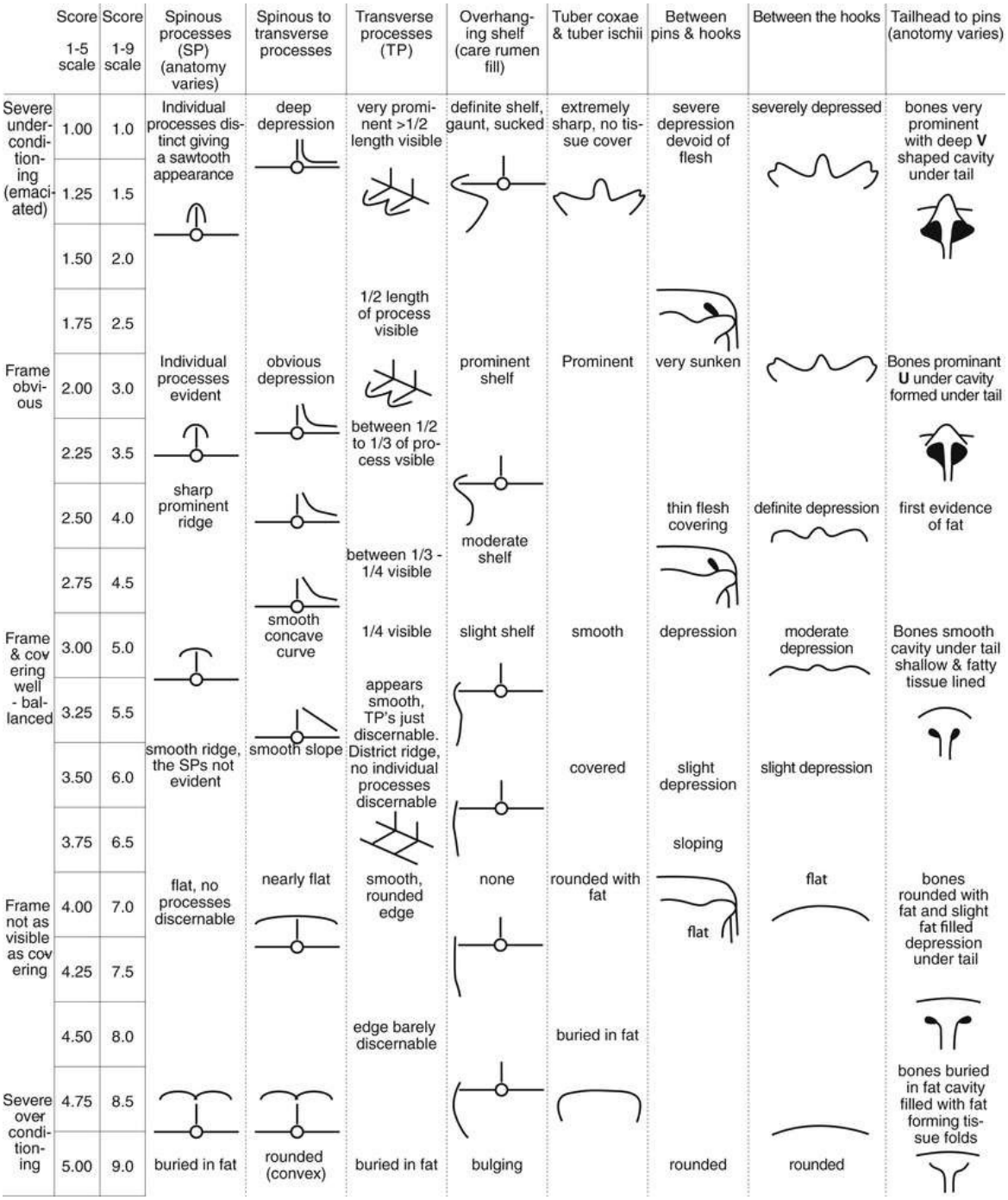


FIG. 9.2 Body condition scoring system for dairy cows. (From Edmonson AJ, Lean IJ, Weaver LD, et al: A body condition scoring chart for Holstein dairy cows. *J Dairy Science*. 72(1)68–78, 1989.)

Weight loss in adult animals is most commonly associated with one or more of the following circumstances (other causes are listed in Boxes 9.6 and 9.7):

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Box 9.6

Causes of Weight Loss in Horses

Common Causes

Protein-calorie malnutrition (PCM)
Dental disease
Jaw abnormalities
Gastric ulcers
Right dorsal colitis
Parasitism (small strongyles, large strongyles, tapeworms, bots)
Sand enteropathy
Pneumonia (bacterial, viral)
Pleuritis, pleuropneumonia, pulmonary abscessation
Recurrent airway obstruction
Internal abdominal abscess
Peritonitis
Streptococcus equi (lymph node abscessation, pulmonary or mesenteric abscessation)
Acute renal failure
Chronic renal failure
Pituitary pars intermedia dysfunction
Neoplasia (alimentary tract)

Less Common Causes

Equine herpes myeloencephalopathy
Equine motor neuron disease
Oral foreign body
Guttural pouch infection
Otitis media, interna
Paranasal sinus infection
Esophageal abnormalities (esophagitis, diverticula)
Vesicular stomatitis

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Gastric impaction
Gastric squamous cell carcinoma
Duodenal ulcers
Inflammatory bowel disease (basophilic enterocolitis, eosinophilic enterocolitis, granulomatous enteritis, lymphocytic-plasmacytic enteritis, multisystemic eosinophilic epitheliotropic enterocolitis)
Chronic colonic impaction
Idiopathic diarrhea
Giardiasis
Fungal pneumonia
Pneumoconiosis (silicosis)
Tuberculosis
Cholelithiasis
Chronic hepatitis
Toxic hepatopathy
Atrial fibrillation
Cardiac or great vessel anomalies
Congestive heart failure
Endocarditis, pericarditis
Splenic rupture, abscess
Amyloidosis
Glomerulonephritis
Pyelonephritis
Renal neoplasia
Renal tubular acidosis
Urinary bladder neoplasia
Urolithiasis
Infectious arthritis
Osteomyelitis
Granulosa cell tumor
Lymphoma, lymphosarcoma
Malignant melanoma
Autoimmune anemia or thrombocytopenia
Purpura hemorrhagica
Coccidioidomycosis
Cryptococcosis
Nocardiosis

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Agammaglobulinemia
Equine adenovirus
Equine infectious anemia
Equine viral arteritis
Anhidrosis

Uncommon Causes

Botulism
Micronema deletrix, infection of the central nervous system
Nigropallidal encephalomalacia
Nutritional rhabdomyolysis
Rabies
Rectus capitus ventralis muscle rupture
Spinal abscessation
Prognathia, brachygnathia
Pyloric stenosis
Basophilic enterocolitis
Colonic fistula
Ileal hypertrophy
Strongylus vulgaris, thromboembolism
Micropolyspora faeni, hypersensitivity pneumonitis
Pleural mesothelioma
Rhodococcus equi, infection
Tuberculosis
Mammary carcinoma
Malignant mesothelioma
Ovarian adenoma
Pancreatic neoplasia
Pulmonary neoplasia
Skeletal or vertebral neoplasia
Testicular neoplasia
Portal vein shunt
Liver fluke
Theiler's disease-associated virus (TDAV)
Enzootic cystitis
Polycystic disease

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Diabetes mellitus
Hyperparathyroidism
Pheochromocytoma
Steatitis
Brucellosis
Multiple cartilaginous exostoses
Bullous pemphigoid
Eosinophilic dermatitis
Fungal granuloma
Horsefly-deerfly infestation
Lupus erythematosus
Panniculitis
Pemphigus foliaceous
Seborrhea
Wound myiasis
Babesiosis
Erythrocytosis
Histoplasmosis
Myeloproliferative disease
Phycomycosis
Tularemia
Goiter
Phosphorus deficiency
Thiamine deficiency
Vitamin A deficiency

Toxins

4-Aminopyridine
Aflatoxicosis
Arsenic toxicity
Dioxin
Fluorosis
Mercury toxicity
Pentachlorophenol
Phenylbutazone, flunixin meglumine, and other nonsteroidal antiinflammatory drugs

Selenium toxicity
Vitamin D calcinosis
Vitamin K_3 toxicity
Zinc toxicity

Plant Toxins

Crofton weed *(Ageratina adenophora)*
Plant calcinosis (*Cestrum diurnum*, *Trisetum flavescens*, others)
Pyrrolizidine alkaloid toxicosis (*Senecio* spp., *Amsinckia* spp., *Crotolaria* spp., others)
Red maple leaf *(Acer rubrum)*
Jimsonweed (*Datura* spp.)
White snakeroot *(Eupatorium rugosum)*
Yellow star thistle *(Centaurea solstitialis)*, Russian knapweed *(Centaurea repens)*

Exotic Diseases

Besnoitiosis *(Besnoitia bennetti)*
Burkholderia pseudomallei
Dourine *(Trypanosoma equiperdum)*
Equine dysautonomia (grass sickness)
Glanders *(Burkholderia mallei)*
Mal de caderas *(Trypanosoma equinum)*
Nagana (*Trypanosoma* spp.)
Stachybotryotoxicosis
Surra *(Trypanosoma evansi)*
Trombiculiasis
Trypanosoma hippicum

Box 9.7

Causes of Weight Loss in Ruminants

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Common Causes

Protein-calorie malnutrition (PCM)
Dental abnormalities
Pharyngeal, retropharyngeal abscess
Actinobacillosis
Actinomycosis
Diarrhea (Enterotoxigenic *Escherichia coli, Salmonella*, bovine virus diarrhea, coronavirus, rotavirus infection, *Cryptosporidium parvum*, coccidiosis, winter dysentery [B], other causes)
Johne's disease (paratuberculosis)
Parasitism (lungworms, gastrointestinal parasites)
Abomasal ulcer
Displaced abomasum
Subacute ruminal acidosis
Vagal indigestion
Bacterial pneumonia, pulmonary abscessation
Infectious bovine rhinotracheitis
Traumatic reticuloperitonitis, pericarditis
Hepatic abscess
Liver fluke infestation
Ketosis
Fat necrosis (B)
Leptospirosis
Pyelonephritis, cystitis
Urolithiasis
Mammary abscess
Mastitis
Anaplasmosis (B)
Bovine leukosis
Septic arthritis
Lameness (infectious and claw horn lesions [bovine digital dermatitis, sole ulcers, white line disease, etc.], pedal osteomyelitis)
Lice or ked infestation
Sarcoptic mange
Wound myiasis
Copper deficiency

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Selenium deficiency
Bluetongue (O)

Less Common Causes

Coenurosis (gid)
Sarcocystis
Mandible, maxilla fracture
Loss of teeth, periodontal disease
Lingual injury, abscess
Otitis media, externa
Sinusitis
Esophageal malfunctions
Omasal impaction
Abomasal impaction
Colonic obstruction
Aspiration pneumonia
Micropolyspora faeni hypersensitivity pneumonitis
Pleuritis
Tuberculosis
Brisket disease
Endocarditis
Vena caval thrombosis
Thymic lymphosarcoma (B)
Stomatitis (ulcerative, vesicular, papular [B])
Glomerulonephritis
Urachal abscess, bladder abscess
Postparturient hemoglobinuria
Renal amyloidosis
Eperythrozoonosis
Sarcocystosis (B)
Dermatophilosis
Psoroptic mange
Goiter
Cobalt deficiency
Sodium chloride deficiency
Water deprivation

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Uncommon Causes

Bovine spongiform encephalopathy
Sporadic bovine encephalomyelitis
Omental bursitis (B)
Bronchobiliary fistula (B)
Pulmonary listeriosis
Endocardial fibroelastosis (B)
Cholelithiasis
Neoplasia (other than bovine leukemia virus)
Ulcerative posthitis, vulvitis (B)
Local and systemic mycoses
Fungal granuloma
Systemic candidiasis
Mycoplasma, arthritis
Polycythemia (B)
Idiopathic granulocytopenia or thrombocytopenia
Hypersensitivity to soy or milk replacer
Phosphorus deficiency
Vitamin A deficiency
Zinc deficiency

Toxins

4-Aminopyridine
Aflatoxicosis
Arsenic
Chlorpyrifos
Cobalt
Crude oil
Diesel fuel
Ergotism
Ethylene glycol
Fluorosis
Furazolidone
Herbicides

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Kerosine
Lead toxicity
Mercury toxicity
Polybrominated biphenyls
Selenium toxicity
Sodium chloride toxicity
Trichothecene (T-2)
Vitamin D_3 toxicity
Zinc toxicity
Stachybotryotoxicosis (exotic)

Plant Toxins

Acorn, oak (*Quercus* spp.)
Bermuda grass (prussic acid)
Bracken fern *(Pteridium aquilinum)*
Cocklebur (*Xanthium* spp.)
Fescue (B)
Fireweed *(Kochia scoparia)*
Geigeria spp. (exotic)
Gossypol (cottonseed) (*Gossypium* spp.)
Grass staggers (*Phalaris* spp.)
Hairy vetch (Vicia villosa)
Leucaena leucocephala (exotic)
Locoweed *(Oxytropis, Astragalus)*
Mushroom (*Amanita* spp.)
Perennial broomweed *(Gutierrezia sarothrae)*
Pimelea spp. (exotic)
Pyrrolizidine alkaloid toxicosis (*Senecio* spp., *Amsinckia* spp., *Crotolaria* spp., and others)
Sneezeweed *(Helenium hoopesii)*
Tung tree (*Aleurites fordii* Hemsl.)
White snakeroot *(Eupatorium rugosum)*
Yellow-wood (*Terminalia oblongata* spp. oblongata) (exotic)

Exotic Diseases

Malignant catarrhal fever
Babesiosis *(Babesia bigemina, Babesia bovis)*
Besnoitiosis *(Besnoitia besnoiti)*
Bovine petechial fever *(Ehrlichiaondiri)* (B)
Burkholderia pseudomallei
Contagious bovine pleuropneumonia *(Mycoplasma mycoides mycoides)* (B)
East Coast fever (theileriosis)
Echinococcosis
Foot-and-mouth disease *(Aphtae epizooticae)*
Ibaraki disease (epizootic hemorrhagic disease) (B)
Ovine encephalomyelitis (O)
Schistosomiasis
Surra *(Trypanosoma evansi)*
Trypanosomiasis (*Trypanosoma* spp.)

B, Bovine; *O*, ovine.

- Anorexia
- Increased nutrient demands
- PCM
- Micronutrient deficiencies
- Parasitism

Anorexia usually occurs secondary to a primary disease. A decrease in DMI occurs in dairy cows when temperature and humidity (Temperature Humidity Index, THI) exceed the coping mechanisms of the animals.[12] Increased nutrient requirements are associated with normal physiologic conditions (e.g., pregnancy, lactation, exercise, cold weather) and pathologic processes (e.g., sepsis, trauma, parasitism, burns). Mild to severe PCM is often associated with inadequate feed quality or quantity but can also be caused by increased energy requirements resulting from adverse environmental conditions. Weight loss can also occur with a deficiency of essential micronutrients such as copper, cobalt (vitamin B_{12}), or vitamin A. Parasitism should always be on the differential list in an

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animal that has lost weight.

Mechanisms of Weight Loss

Anorexia is the loss of appetite or lack of desire for food; it may be complete or partial. It is a primary mechanism for weight loss of short or intermediate duration. Weight loss results from decreased nutrient intake. When partial anorexia occurs over a long period, the weight loss may be subtle and go unrecognized. Acute, complete anorexia results in more dramatic rapid weight loss.

In domestic species, anorexia is usually associated with a primary disease condition and is regulated by cytokines including interleukin (IL-1) and tumor necrosis factor alpha (TNF-α), released during an inflammatory response.[13] Resolution of the primary disease process usually results in a return to voluntary food consumption. Anorexia must be differentiated from dysphagia by observation. The distinction between the conditions that cause anorexia and those that control hunger and satiety is not clear; however, many diseases that cause anorexia also result in dehydration, electrolyte imbalances, and/or acid-base disorders.

In addition to causing anorexia, many disease processes cause an increase in the nutrient requirements for basal metabolism. Nutrient requirements for maintenance, growth, pregnancy, lactation, and exercise have been well defined for many large animal species. Nutrient requirements in disease have not been adequately evaluated in large animals, and most information is currently extrapolated from humans, laboratory animals, and small animal species. In human patients, published estimates indicate that requirements for energy and protein increase approximately 10% after elective surgery, 20% with fractures, 30% to 60% with severe infection or sepsis, 40% with peritonitis, and 50% to 110% with major burns.[14,15] In humans, the resting energy expenditure is estimated to increase by 14% for each degree Celsius increase in body temperature.[16] Extrapolation of these data directly to equine and ruminant patients is probably not possible; however, the figures do indicate the degree of change in nutrient requirements as a result of disease. The stress of many disease processes results in an increase in serum cortisol and glucagon. The decreased insulin/glucagon ratio alters the production of glucose and results in hyperglycemia because of enhanced hepatic gluconeogenesis. An increase in sympathetic activity appears to regulate fat oxidation, the increased release of

fatty acids from cellular lipid stores, and the development of hypertriglyceridemia in many patients with sepsis. Protein degradation and a negative nitrogen balance are also hallmarks of the acute response to infection. Weight loss resulting from protein and lipid catabolism is often observed in large animal patients with sepsis, owing to altered metabolic activity and nutrient requirements. In horses, particularly obese ponies or donkeys or pregnant mares, who may be stressed, the increased cortisol coupled with innate insulin resistance may predispose these animals to the development of hyperlipemia and/or hyperlipidemia.

In conditions such as burns, peritonitis, pleuritis, colitis, and granulomatous bowel disease, nutrients (particularly proteins) are lost. In many disease conditions, concurrent anorexia and increased nutrient requirements greatly increase the risk of PCM and weight loss. Certain conditions such as Johne's disease in ruminants and granulomatous enteritis in horses are also associated with a malabsorption or malassimilation syndrome. In these types of diseases, nutrients are not efficiently digested and absorbed; anorexia may be absent, and dietary intake may appear normal, but weight loss still occurs.

PCM continues to be a persistent problem in domestic animals. Inadequate ingestion of energy and protein obviously results in weight loss, but PCM and associated weight loss can occur through several other mechanisms. The most direct cause is that the animals receive an inadequate volume of feed to meet their dietary requirements. This can occur as frank underfeeding of all animals or as a consequence of inadequate feeding facilities that create competition among animals for available feed. The latter circumstance occurs most dramatically when animals of varying ages are mixed; the younger animals with the highest requirements are often pushed away by older, dominant individuals.

The quality of the diet, particularly dietary forages such as hay and pasture, is an important factor in the development of PCM and total nutrient intake. Table 9.1 lists guidelines for estimating the maximum daily intake by cattle. It is evident that as forage quality (digestibility) decreases, maximum daily intake decreases because poor-quality feed must remain in the rumen for an increased period of time before it is sufficiently digested to allow passage through the reticuloomasal orifice. Maximum dry matter intake (DMI) as a percentage of body weight is somewhat higher in small ruminants than in cattle. However, the energy requirement per kilogram of body weight is higher in small ruminants than in cattle. Similar estimates for maximum DMI in horses related to forage quality are not available, yet horses will consume on average 2% of their body

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weight as DMI, with some studies reporting intakes as high as 4% of body weight. Horses do not have a pregastric fermentation organ (rumen) and can ingest slightly more of the same quality forage than cattle. Low-quality forages are often the cause of PCM, even when an unlimited quantity is available. The best way to determine the nutrient content of forage, grain, and pelleted feeds is to have the feed analyzed by a forage laboratory. Feed analysis instructions are provided in Box 9.3. Feed tag labels or forage databases can be referenced if an analysis is not performed.

Environmental factors can have a major influence on nutrient requirements and can increase the subsequent risk for PCM and weight loss. The most important environmental factor is the ambient temperature. Nutrient requirements for maintenance change with a decreasing ambient temperature as follows:

- *Adult horses:* Estimated increase in digestible energy (DE) requirements by 2.5% for every degree Celsius below the lower critical temperature (LCT). The LCT for adult horses ranges from 5° C to −15° C, depending on the horse's adaptation to the environment. In cold temperatures, when the hair coat is wet, the maintenance DE requirement may be increased by as much as 50%.[7]
- *Beef cattle:* 1% increase in maintenance energy requirements (total digestible nutrients [TDN], net energy of maintenance [NE_m], digestible energy [DE], and metabolizable energy [ME]) for each 1° C drop below 20° C (68° F).
- *Dairy cattle (lactating):* 25% increase in energy requirements (TDN, net energy of lactation [NE_L]) as ambient temperature drops from 20° C (68° F) to

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−10° C (14° F).
• *Sheep with 10-cm wool:* 1% increase in energy requirements (TDN, ME, DE) for each 1° C drop below lower critical temperature (approximately −10° C).

There are also additive effects of wind and rain that increase energy requirements in large animal species. As nutrient requirements increase, the dietary intake must also increase to prevent weight loss associated with PCM. Horses in inclement weather may not be able to consume enough forage to meet their increased energy requirements, and for these animals, dietary fat and limited grain supplementation may be required.

Deficiencies of micronutrients (trace minerals, B vitamins) often result in inefficiencies in basic biochemical pathways. These inefficiencies, if marked, can be associated with weight loss. Genetic errors in metabolism can cause similar disturbances, but these usually manifest as decreased growth and even death in young animals.

Parasitism is a common cause of weight loss in adult domestic animals. The mechanisms by which parasite infestation can result in weight loss include a loss of body fluid and tissues resulting in increased nutrient requirements, competition for nutrients in the gastrointestinal tract, malassimilation and malabsorption, inflammation resulting in increased nutrient requirements, micronutrient deficiencies, and organ or vascular damage from migrating parasite larvae. Anorexia may also develop in the advanced stages of severe parasitism.

Approach to the Diagnosis and Management of Weight Loss in Adult Horses

Use the flow sheet in Fig. 9.3 to aid in decision making.

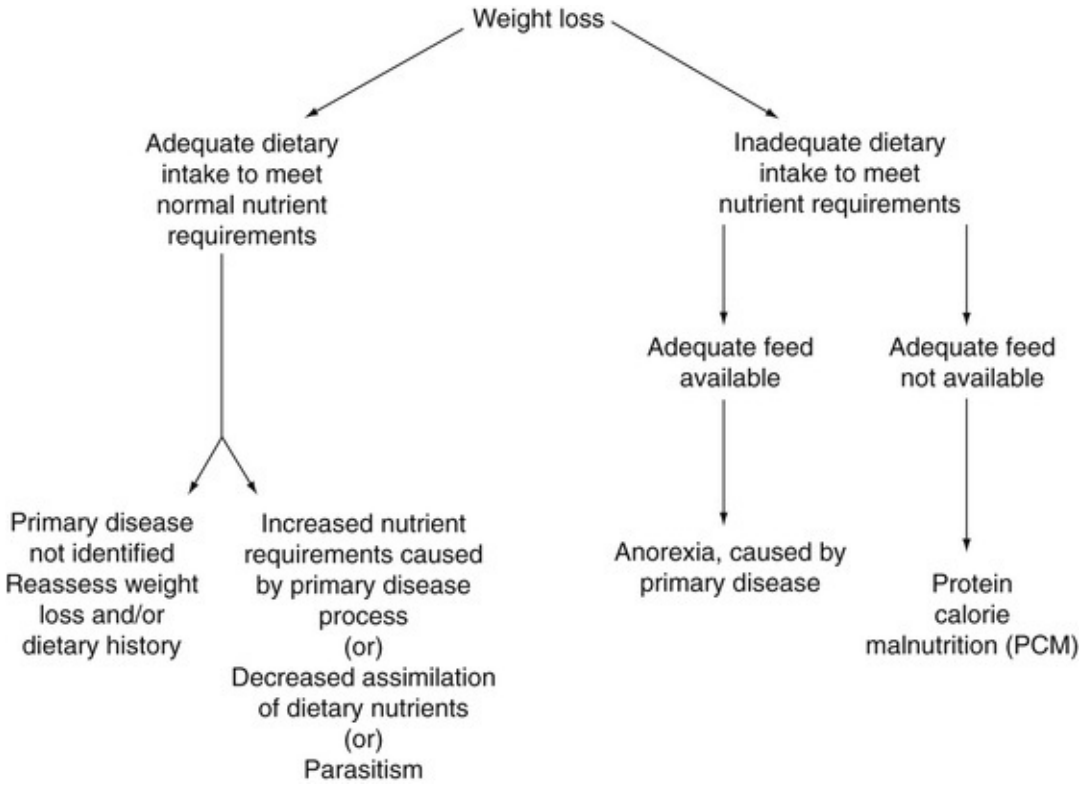


FIG. 9.3 Flow sheet for classifying conditions associated with weight loss.

1. Take a general history and a diet history.
    a. General history
        i. Is the weight loss affecting one animal or many animals? If many horses are affected, what is the age range of the affected animals? How long has the caretaker noticed the weight loss? Has the diet been changed to manage the weight loss? What is the change in BCS of the horse(s)? How much weight has been lost? Is this an estimate of weight loss, or has the horse(s) been monitored on a scale or with a weight tape? Weight loss is often suspected but not documented in the initial complaint or history. Acute weight loss of 5% to 10% is significant. If a weight tape will not fit around the girth of the horse or if the horse has a BCS of 1 to 3, a rough estimate of body weight can be made using measurements of the length

and girth of the horse.[17,18] Length is measured from the tuber ischium to the point of the shoulder, and girth is measured at the withers, behind the elbows, at the end of expiration.

$$\text{Body weight (kg)} = \frac{\text{Chest girth (cm)}^2 \times \text{Length (cm)}}{11,877}$$

The weight of miniature horses should be obtained using a small animal clinic scale. If a scale is not available to weigh a miniature horse, then the following equation can be used to estimate the weight of the miniature horse.[19]

$$\text{Body weight (kg)} = \frac{(3.7 \times \text{Chest girth in cm}) + (2 \times \text{Length in cm}) - 348.5}{2.2}$$

ii. Is there any past or current clinical disease in the horse or herd? If so, when was the disease first diagnosed? How many animals were affected? What type of treatment was administered? Was the diet changed during this period of time? Question the caretaker closely about any clinical signs of diarrhea, coughing, dysphagia, or polyuria. What is the deworming history of the horse and herd? Has the deworming protocol been changed lately?

b. Diet history

i. Type of feed. Obtain an *accurate* dietary history including the type and amount of feed offered (in pounds, ounces) and the amount of feed refused by the horse(s). It is essential that feeds are weighed accurately. What type and volume of forage is available? Inspect the pasture and all feeds for gross quality, evidence of spoilage,

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abnormal color or odor, presence of weeds and mold, and quantity of feed the owner has at the facility. Has an analysis been performed on the forage (pasture grass and/or hay)? If yes, obtain a copy of the analysis for the patient record. How much time does the horse have to graze in a pasture? What type of grass is available in the pasture? Is the pasture overgrazed? Are there any plant toxins in the pasture or environment? Have there been any changes in the type of forage offered to the horse(s)? Hay quality is often not consistent between shipments. If grain or other supplemental feeds are used, what volume is fed and consumed by the horse(s)? Are any diet supplements fed to the horse? If so, what amount is fed? Does the horse have access to a salt or trace mineral block? How long has this diet been fed? Nutrient requirements of adult ponies and horses are listed in Table 9.13 and can also be calculated using the Nutrient Requirements of Horses free companion computer program (www.nap.edu/catalog/11653/nutrient-requirements-of-horses-sixth-revised-edition).

TABLE 9.13

Daily Nutrient Requirements of Ponies and Horses of Mature Body Weight

Category	Digestible Energy (Mcal)	Crude Protein (g)	Calcium (g)	Phosphorus (g)
Mature Ponies, 200 kg (440 lb) of Mature Body Weight				
Maintenance, average activity	6.7	252	8	5.6
Mares, last 90 days of gestation	7.7-8.6	319-357	14.4	10.5
Lactation, first	12.7-12.2	614-587	23.6-	15.3-14.4

3 mo			22.4	
Mature Horses, 400 kg (880 lb) of Mature Body Weight				
Maintenance, average activity	13.3	504	16	11.2
Mares, last 90 days of gestation	15.4-17.1	637-714	28.8	21
Lactation, first 3 mo	25.4-24.5	1228-1174	47.3-44.7	30.6-28.8
Mature Horses, 500 kg (1100 lb) of Mature Body Weight				
Maintenance, average activity	16.7	630	20	14
Mares, last 90 days of gestation	19.2-21.4	797-893	36	26.3
Lactation, first 3 mo	31.7-30.6	1535-1468	59.1-55.9	38.3-36
Mature Horses, 600 kg (1320 lb) of Mature Body Weight				
Maintenance, average activity	20	756	24	16.8
Mares, last 90 days of gestation	23.1-25.7	956-1072	43.2	31.5
Lactation, first 3 m	38.1-36.7	1842-1761	70.9-67.1	45.9-43.2
Mature Horses, 900 kg (1980 lb) of Mature Body Weight				
Maintenance, average activity	30	1134	36	25.2
Mares, last 90 days of gestation	34.6-38.5	1434-1607	64.8	47.3
Lactation, first 3 mo	54.4-52.4	2763-2642	106.4-100.6	68.9-64.9

Modified from National Research Council. *Nutrient requirements of horses.* Washington, D.C., 2007, National Academies Press.

ii. Feeding management. How often are the horses fed? What type of feeder is used? Are mats placed under the feeders to reduce sand and dirt ingestion? Is there competition among the horses for food? Are there any toxic substances in the horse's environment? What is the water source

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for the horses? How many water sources are available? Is the water clean?

2. Perform a physical examination.
    a. Observe the horse while it is eating. Can the horse prehend, masticate, and swallow food normally? Is the horse dysphagic? Does the horse have a good appetite? Is the horse hungry? Are there any signs of neurologic disease?
    b. Examine the patient closely to identify signs of concurrent disease (e.g., pyrexia, diarrhea, melena, dysphagia, abnormal dentition, icterus, nasal discharge, cough, dyspnea, tachycardia, cardiac murmur, dysuria).
    c. What is the horse's body weight (scale or weight tape) and BCS (see Table 9.1)?
3. Examine the feces. What is the consistency of the feces? If the horse has evidence of diarrhea, review the section on diarrhea in Chapter 7. How long are the fibers in the feces? Perform a glove test. Is there evidence of sand in the feces? Horses can have a significant volume of sand in the large intestine while having negative fecal sand test results. Perform a fecal egg count. An enzyme-linked immunosorbent assay (ELISA) may be useful in diagnosing a tapeworm infection. Follow the parasite control program in Chapter 49 if the horse has evidence of fecal parasites or if a parasite infection is suspected despite a negative fecal egg count. Perform a fecal occult blood test; if the result is positive, see the section on melena in Chapter 7.
4. Perform blood analyses.
    a. Perform a CBC including plasma protein and fibrinogen. Examine the results closely for indication of an inflammatory process (e.g., leukocytosis, neutrophilia, leukopenia, neutropenia, hyperfibrinogenemia, decreased plasma protein/fibrinogen ratio [below 10]). Calculate the erythrocytic indices, and characterize anemia, if present.
    b. Perform a serum biochemical analysis. The serum albumin half-life is approximately 19 days in horses. Hypoalbuminemia may be associated with colitis, internal abscessation, PCM, liver disease, renal disease, and granulomatous bowel disease, among other conditions. Albumin is often within normal limits in PCM until the

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patient is near death. Globulin (particularly γ-globulins) may be increased with inflammation, and the albumin/globulin ratio may be decreased. The glucose concentration is usually normal or elevated as a result of stress and may also be elevated in horses with pituitary pars intermedia dysfunction (PPID) and equine metabolic syndrome. Hyperlipidemia (serum triglyceride between 100 and 500 mg/dL) is commonly associated with early anorexia and can be present in horses with PPID. Hyperlipemia (serum triglyceride above 500 mg/dL) is a serious condition associated with prolonged anorexia and hepatic lipidosis and is often found in miniature horses, ponies, and donkeys under severe physiologic stress (PCM and lactation). Unconjugated bilirubin levels can rise to 6 or 7 mg/dL with anorexia or decreased food intake. An elevated γ-glutamyltransferase (GGT) (above 25 IU/L) may indicate hepatic disease. Horses with PCM may have a low serum urea nitrogen if the protein malnutrition is prolonged and severe.

5. Analyze the diet and improve the feeding program.
    a. Determine if the energy, protein, mineral, and vitamin content of the diet meets the nutrient requirements of the horse at its current metabolic state and activity level (see Table 9.13). Include pertinent environmental and management factors in the nutrient requirement calculations. The quality of the feeds should be assessed.
        i. Forage. Determine the nutrient content of forage or pasture with an analysis (see Boxes 9.3 and 9.4). A university extension service often can assist with a forage analysis. If the client does not purchase a large volume of hay, or if analysis cannot be performed, forage tables from the Nutrient Requirement Council reference books (www.nap.edu) or nutrient tables from the Equi-Analytical Laboratories forage laboratory database (www.equi-analytical.com) can be used to estimate the concentration of different nutrients in common forages and supplemental

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feeds.

ii. Grain, commercial feeds, and other supplemental feeds. Review the feed tag label to determine the nutrient concentration of protein and other essential nutrients. Contact commercial feed companies for the energy content of their products. Use nutrient databases to estimate the nutrient content of other feeds.

iii. Vitamins, minerals, and other dietary supplements. Review all products used on the horse(s). Ensure adequacy of all essential nutrients. Are there any nutrient toxicities? Are all products necessary? If botanical ingredients are fed, are there any nutrient-drug interactions or contraindications in feeding the botanicals?

b. If the horse has a dietary deficiency, the problem should be corrected by a change in the diet or through appropriate supplementation. Contact an equine clinical nutritionist for guidance on ration formulation.

c. If the dietary history indicates that adequate nutrients for maintenance, or the appropriate life stage, or performance have been steadily consumed, continue to search for another cause of the weight loss.

6. Perform ancillary diagnostic tests. If the weight loss is not caused by inadequate or poor-quality feed, additional diagnostic tests should be performed. Possible tests include but are not limited to ultrasound, gastric endoscopy, radiographs, serum or whole blood trace mineral analysis, serum insulin concentration, carbohydrate absorption tests (oral D-glucose, D-xylose [see Chapter 32]), and appropriate organ biopsy.

Approach to the Diagnosis and Management of Weight Loss in Adult Ruminants

1. Take a general history and a diet history.

a. General history: Question the caretaker closely about any clinical signs that might indicate a primary disease (e.g.,

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diarrhea, coughing, dysphagia, polyuria, depression, agalactia). Note if body condition is less than desired. Quantitate the weight loss or BCS if possible. Acute weight loss of 5% to 10% is quite significant. Carefully note the production level of the animal or herd (e.g., pregnancy [single, twins, triplets], lactation [level of milk production]). Evaluate the parasite control program. Does the herd have a history of chronic or recurrent disease (Johne's disease, bovine virus diarrhea, subacute ruminal acidosis, mastitis, pneumonia)?

b. Diet history: Obtain an *accurate* dietary history, particularly when signs of a primary disease are absent. Inspect all forages, concentrates, and feed additives for quality, signs of spoilage, abnormal color or odor, and quantity on hand. Be sure the feeding system allows for adequate consumption by all animals and that competition for feedstuffs does not occur, for example, due to a lack of bunk space in freestall barns. Check to see if the feeding program was changed before the onset of observed weight loss or loss of body condition. The history should include the *weight* of each feedstuff and supplement fed and consumed per day. The maximum DMI can be predicted for different types of cattle using the equations given in Table 9.1.

c. Determine or estimate the nutrient analysis of the feedstuffs being fed. Examine the environment for possible toxic plants or substances.

2. Perform a physical examination. Examine patients carefully for signs of concurrent disease (e.g., diarrhea, decreased ruminal motility, pyrexia, dysphagia, abnormal dentition, melena, icterus, mastitis, metritis, dyspnea, tachycardia). Is the patient hungry? Weigh the patient (or use a heart-girth measurement) and note the BCS (see Tables 9.14 and 9.15 and Fig. 9.2). Observe the patient for signs of muscle wasting and the presence or absence of subcutaneous fat. Test the milk with nitroprusside powder (a positive reaction indicates an acetoacetate concentrate above 5 mg/dL and is diagnostic of ketonlactia and ketonemia), or measure the ketone concentration in the urine. In order to detect subclinical ketosis with higher accuracy, it is beneficial to use

hand-held devices that measure β-hydroxybutyrate (BHB) in whole blood.[20] The level of nonesterified fatty acids is a good indicator for excessive body fat mobilization, especially in close-up cows. Measure the ruminal pH (pH above 7 is indicative of anorexia). Examine the skin for evidence of lice or keds.

TABLE 9.14

Body Conditioning Scoring System for Beef Cows

Group	Score	Definition
Thin condition	1	Emaciated (body fat = 3.8%)
		The cow is severely emaciated and physically weak. Bone structure of shoulder, ribs, spinous processes, transverse processes, hooks, and pins are sharp to the touch and easily visible. No evidence of fat deposits or normal muscling. Cattle in this score are extremely rare and are usually inflicted with a disease and/or parasitism.
	2	Very thin (body fat = 7.5%)
		The cow appears emaciated, similar to 1, above, but not weak. Muscle atrophy is significant in the shoulder, over the loin and rump, and through the hindquarters. The spinous and transverse processes, hooks, and pins feel sharp to the touch and are easily seen. Ribs can be easily identified.
	3	Thin (body fat = 11.3%)
		The cow appears thin with no fat in the brisket. There is evidence of muscle atrophy over the shoulder, lion, and rump and through the hindquarter, but there is the beginning of some fat deposition over the shoulder, loin, and rump. The foreribs have slight evidence of fat deposition, but the last 3 or more ribs (11th, 12th, and 13th) are visible. Vertebrae of the spine are easily visible and can be identified individually by touch. Spaces between the processes have some evidence of some fat infiltration. Bone structure of the hooks and pins are evident under the hide.
Borderline condition	4	Borderline (body fat = 15.1%)
		The cow appears thin, with the last 2 ribs (12th and 13th) easily visible, especially in mature cows with a big spring of rib and broad, flat ribs. Muscle atrophy over the shoulders and loin and through the hindquarters is evident but approaching normal. Movement of the muscles in the shoulder is prominent just under the hide as the animal moves. Individual spinous processes along the topline, and transverse processes along the edge of the loin between the hooks and last rib, are not visible, but can be easily palpated with minimal pressure and feel rounded rather than sharp. The hooks and pins are covered in minimal fat and easily identified.
Optimum moderate condition	5	Moderate (body fat = 18.8%)
		There is a slight evidence of fat deposition in the brisket. Muscle expression in the shoulder, loin, rump, and hindquarters are normal. A thin layer of fat covers the muscles in the shoulder, and when the animal is in motion; the muscle and scapula movement under the hide are not prominent. The last 2 ribs can only be seen if the cow has less than normal gut fill. Individual

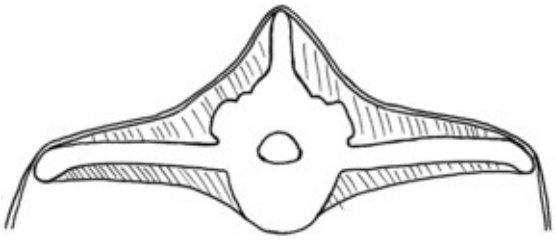
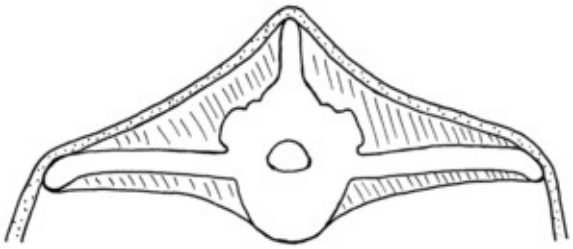
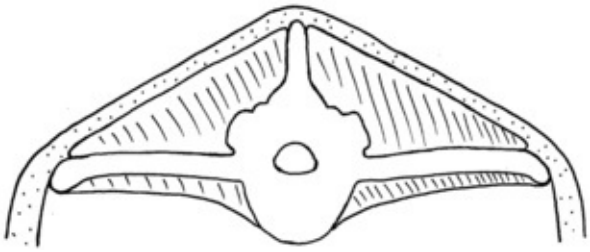
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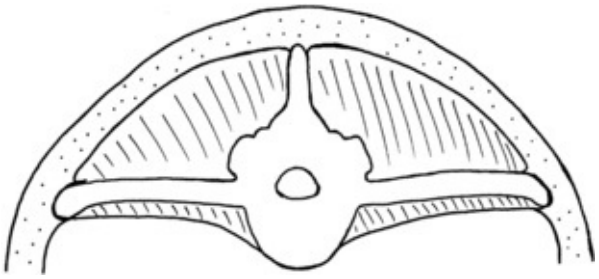
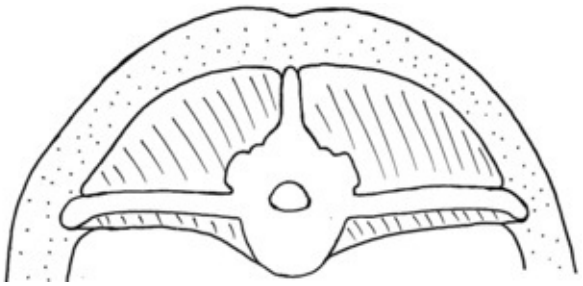
		spinous processes along the topline and transverse processes along the loin edge between the hooks and last rib appear smooth and are not visible, but they can be palpated with firm pressure. The hooks and pins are covered with a layer of fat, but still distinguishable. Areas on each side of the tail head are fairly smooth, but not mounded.
	6	Good (body fat = 22.6%)
		Some fat deposition in the brisket is evident. The cow exhibits a smooth appearance throughout without any evidence of muscle atrophy. A layer of fat covers the muscles in the shoulder, and shoulder movement visually takes on a fluid motion. There is noticeable sponginess over the foreribs just behind the shoulder. The ribs on young cows are fully covered by fat and cannot be detected visually. Flat, wide ribs on older cows may be seen. The spinous processes along the topline and transverse processes between the hooks and last rib are embedded in muscle and fat and can only be felt with firm pressure. The hooks are embedded in fat and appear round and smooth. The pins are embedded in fat, and there is noticeable sponginess on each side of the tail head.
	7	Fleshy (body fat = 26.4%)
		The brisket is full but not distended. A layer of fat covers the muscles in the shoulder, and the movement appears fluid. The ribs appear smooth, and there is a uniform layer of fat from the forerib to the last rib. The spinous processes along the topline and transverse processes between the hooks and last rib are embedded in fat, and the topline is beginning to take on a square appearance. The pins are embedded in a layer of spongy fat, and there are pones of fat forming on either side of the tail head.
Fat condition	8	Obese (body fat = 30.2%)
		The neck appears short and thick and the brisket is distended with fat. There is no evidence of bone structure in the shoulder, along the topline, hooks, or pins. A thick layer of fat covers the shoulder, and shoulder muscle movement under the hide is not evident. The animal appears very square and blocky over the topline and smooth along the sides. Fat cover over the shoulder, topline, and ribs appear spongy both visually and by touch. The pins are embedded in pones of fat on both sides of the tail head. There is evidence of fat deposition in the udder. Animal movement may be somewhat impaired due to excess fat.
	9	Very obese (body fat = 33.9%)
		These cows are very obese and are rarely seen. The animal appears very square and blocky over the topline, smooth along the sides, and spongy throughout. Bone structures are difficult to identify, and the animal appears short necked with a full, distended brisket. The pins are embedded in patchy pone fat on both sides and over the top of the tailhead. There is evidence of significant fat deposition in the udder. Animal mobility may be seriously impaired due to excess fat.

Modified from National Research Council (NRC). 2016. Nutrient requirements of beef cattle, ed 8. National Academy Press, Washington, DC.

TABLE 9.15

Body Condition Scoring System for Sheep

Score	Description	Illustration
1	The spinous processes are prominent and sharp. The transverse processes are also sharp, with fingers passing easily under the end of this process. The eye muscle areas are shallow with little to no fat cover.	
2	The spinous processes are smooth but still prominent. The individual processes can still be felt but only as fine corrugations. The transverse processes are smooth and rounded. However, it is still possible to pass the fingers under the ends of the processes with some pressure. The eye muscle areas are of moderate depth, but have sparse fat cover.	
3	The spinous processes are smooth and rounded, and individual bones can only be felt with some pressure applied. The transverse processes are also smooth and well covered. Firm pressure is required to feel over the ends. Eye muscle area is full and	

	covered by a moderate degree of fat.	
4	With pressure applied, the spinous processes can just be detected, although the ends of the transverse processes cannot. Eye muscle areas are full with a thick covering of fat.	
5	Even with firm pressure applied, the spinous processes cannot be detected. Due to a high level of fat adjacent to the spinous process, a depression directly above where the spinous processes would normally be felt may be present. It is not possible to detect the transverse processes. The eye muscle areas are very full with very thick fat cover. It is possible to have significant deposits of fat cover over the rump and tail.	

From Kenyon PR, Maloney SK, Blache D. Review of sheep body condition score in relation to production characteristics. *N Z J Ag Res* 57:38-64, 2014.

3. Examine the feces. Perform flotation, sedimentation, and Baermann's procedures to detect patent parasitic infestations. If the feces test positive for occult blood or are dark, see the section on melena in Chapter 7. If there is evidence of or apparent diarrhea, see the section on diarrhea in Chapter 7.
4. Perform blood analysis.
    a. Perform a CBC including plasma protein and fibrinogen.

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Interpret for evidence of inflammation, and characterize the anemia if present. Analyze for blood selenium concentration or glutathione peroxidase activity if a herd problem of weight loss exists in a selenium-deficient region.

b. Perform a serum chemistry analysis. The serum albumin half-life is approximately 16.5 days in cattle and 14 days in sheep and goats. Hypoalbuminemia is associated with internal abscessation, PCM, liver disease, renal disease, and Johne's disease, among other conditions. In the first two of these conditions, albumin is often normal until the patient is near death, whereas with protein-losing renal or gastrointestinal disease or with failure to make albumin in severe hepatic disease, hypoalbuminemia is often seen by the time noticeable weight loss occurs. Globulins, particularly γ-globulins, may be increased with inflammation, and the albumin/globulin ratio may be decreased. The serum glucose concentration is usually not helpful in determining the cause or causes of weight loss. An elevated serum GGT (>25 IU/L) may indicate hepatic disease or, in rare cases, pancreatic disease. Serum BUN is often low with PCM in ruminants because of salivary urea recycling. Serum (total) calcium may be decreased with hypoalbuminemia, anorexia, or periparturient hypocalcemia. Serum phosphorus may be increased during severe starvation or Johne's disease or decreased with anorexia. The serum (plasma) copper concentration may be decreased if a herd problem of copper deficiency exists. Weight loss is particularly associated with copper deficiency when diarrhea is present in a region known to be copper deficient or in a region with excess dietary molybdenum or sulfates or both. A low serum copper concentration (below 0.5 µg/mL or ppm) indicates deficiency. Ketonemia may be associated with anorexia. Hand-held meters measuring BHB concentrations have been reported to be a useful tool in diagnosing pregnancy toxemia in pregnant sheep.[21] BHB concentrations ≥1.0 mmol/L indicate that the animals are at greater risk to develop severe hyperketonemia.[22]

5. Analyze the diet and improve the feeding program. Is the feed quantity and quality adequate to allow sufficient intake of nutrients? Compare the nutrient intake from the diet with the requirements for the appropriate species (Tables 9.16 to 9.20). Consider any important environmental and management factors in the daily nutrient requirements. Review nutrient analysis profiles on the feeds and total mixed ration (TMR) ingredients. Is the TMR mixed properly? Are grain rations mixed properly? Is too much grain being fed to the animal or herd? Analyze the pasture, forage, or concentrate rations (see Box 9.3). Make appropriate recommendations to optimize the ration. Determine if the patient or patients have a normal appetite. Is anorexia present? If the dietary history and analysis indicate that adequate nutrients have been steadily consumed, the search for a primary cause for the weight loss should be resumed.

TABLE 9.16

Daily Nutrient Requirements for Lactating Dairy Cows at Various Production Levels

Daily Milk Production (3.5% Butterfat)		NE_L (Mcal)	Total Digestible Nutrients (kg)	Crude Protein (kg)	Calcium (g)	Phosphorus (g)
(kg)	(lb)					
400 kg of Body Weight						
20	44	21	9.23	2	67	48
30	66	28	12.27	2.83	96	66
40	88	34.80	15.31	3.65	116	83
500 kg of Body Weight						
20	44	22.26	9.80	2.07	70	50
30	66	29	12.84	2.9	96	68
40	88	36	15.88	3.71	119	85
600 kg of Body Weight						
20	44	23.5	10.35	2.2	73	52
30	66	30.4	13.39	2.95	99	70
40	88	37.3	16.43	3.77	125	87
700 kg of Body Weight						
20	44	24.69	10.87	2.2	59	54
30	66	31.59	13.91	3	77	72
40	88	38.49	16.95	3.82	94	89

NE_L, Net energy of lactation. Maintenance requirements can be calculated by the following formula: Maintenance $NE_L = 0.080$ Mcal/kg $BW^{0.75}$. The energy requirement for milk production when only the butterfat content of the milk is known by the following formula: NE_L (Mcal/kg milk) + 0.360 + (0.0969 [fat%]).

Modified from National Research Council (NRC). *Nutrient requirements of dairy cattle.* Washington, DC, 2001, National Academy of Sciences, NRC.

TABLE 9.17

Daily Nutrient Requirements for Mature Beef Cows

Reproductive Status	Total Gain (kg)	NE_M (Mcal/day)	Metabolizable Protein (g/d)	Calcium (g)	Phosphorus (g)
Mature 550-kg Beef Cow					
Nonpregnant, maintenance	0	10.5	432	16.9	12.9
Pregnant, third trimester	29–64 kg[a]	22.4	0.73	25	20
Lactating, 20 lb milk per day	0	29	1.18	38	27

[a]This gain represents only the weight of the gravid uterus.

Modified from National Research Council. *Nutrient requirements of beef cattle,* ed 8. Washington, D.C., 2016, National Academy Press.

TABLE 9.18

Daily Nutrient Requirements for Growing Bulls: Maintenance and Growth (900-kg mature SBW)

Weight (kg)	Daily Gain (kg)	Net Energy (Mcal/day)	Metabolizable Protein (g/d)	Calcium (g/d)	Phosphorus (g/d)
600	0	10.7	461	18.5	14.1
600	0.8	14	700	35.2	20.9
600	2	19.7	1014	57.1	29.7
700	0	12.1	517	21.6	16.5
700	0.8	15.8	732	36.6	22.6
700	2	22.2	1004	55.6	30.2
800	0	13.3	572	24.6	18.8
800	0.8	17.4	764	38	24.2
800	2	24.4	995	54.2	30.7

Modified from National Research Council. *Nutrient requirements of beef cattle,* ed 8. Washington, DC, 2016, National Academy Press.

TABLE 9.19

Daily Nutrient Requirements of Sheep

Body Weight	Metabolizable Energy (ME) (Mcal)	Total Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)

(kg)	(lb)					
Maintenance, Mature Ewes						
60	132	2.01	560	53	2.2	1.8
80	176	2.49	690	66	2.6	2.2
100	220	2.94	820	78	3.0	2.7
120	264	3.37	940	90	3.3	3.1
Breeding, Mature Ewes						
60	132	2.21	610	62	2.6	2.1
80	176	2.74	760	77	3.1	2.7
100	220	3.24	900	92	3.6	3.2
120	264	3.71	1030	106	4.0	3.7
Early Gestation, Mature Ewes, Twin Lambs; BW = 3.4-6.6 kg						
60	132	2.89	800	87	5.9	4.2
80	176	3.52	980	105	7.0	5.1
100	220	4.10	1140	123	7.9	5.9
120	264	4.66	1290	139	8.7	6.6
Late Gestation, Mature Ewes, Twin Lambs; BW = 3.4-6.6 kg						
60	132	3.94	1090	116	8.1	4.8
80	176	4.75	1320	139	9.4	5.8
100	220	5.48	1520	173	11.3	7.7
120	264	6.19	1720	196	12.5	8.6
Early Lactation, Mature Ewes, Twin Lambs; Milk Yield = 1.18-2.21 kg/day						
60	132	4.31	1200	189	7.3	6.3
80	176	5.15	1430	222	8.5	7.4
100	220	5.92	1640	253	9.5	8.5
120	264	6.63	1840	296	11.3	10.7
Early Lactation, Mature Ewes, Parlor Production; Milk Yield = 2.37-3.97 kg/day						
60	132	6.14	1700	291	11.4	9.4
80	176	7.26	2010	351	13.8	12.0
100	220	8.27	2290	396	15.5	13.5
120	264	9.22	2560	438	17.0	14.9
Maintenance, Rams						
100	220	3.38	940	86	3.3	3.1
125	275	4.00	1110	102	3.8	3.7
150	330	4.58	1270	118	4.3	4.3
200	440	5.69	1580	148	5.2	5.3

Modified from National Research Council. *Nutrient requirements of small ruminants.* Washington, D.C., 2007, National Academies Press.

TABLE 9.20

Daily Nutrient Requirements of Milk and Meat Goats

Body Weight		Metabolizable Energy (ME) (Mcal)	Total Digestible Nutrients (g)	Metabolizable Protein (g)	Calcium (g)	Phosphorus (g)

(kg)	(lb)					
Maintenance, Mature Does (Dairy/Nondairy)						
20	44	1.13/0.96	310/260	27/24	1.3/1.2	0.9/0.8
40	88	1.91/1.61	530/450	45/41	1.9/1.7	1.5/1.3
60	132	2.58/2.18	720/600	61/55	2.4/2.1	2.0/1.7
80	176	3.2/2.7	890/750	75/68	2.8/2.5	2.4/2.0
Late Gestation, Mature Does (Dairy/Nondairy), Twin Kids; BW = 2.6/2.11-4.8 kg						
20	44	1.96/1.78	540/490	70/69	5.0/4.9	2.4/2.3
40	88	3.07/2.77	850/770	111/107	5.8/5.6	3.2/3.0
60	132	4.05/3.64	1120/1010	143/139	6.4/6.1	3.7/3.5
80	176	4.93/4.43	1370/1230	172/179	6.9/7.2	4.3/4.6
Early Lactation, Mature Does (Dairy), Twin Kids; Milk Yield = 2.06-3.22 kg/day						
40	88	3.77	1050	178	9.5	5.9
60	132	4.98	1380	230	10.3	6.7
80	176	6.09	1690	275	11.1	7.5
Early Lactation, Mature Does (Dairy), Parlor Production; Milk Yield = 5.82-8.04 kg/day						
50	110	7.62	2110	398	19.7	11.4
70	154	9.54	2640	487	20.7	12.3
90	198	11.27	3130	566	21.5	13.1
Early Lactation, Mature Does (Nondairy), Twin Kids; Milk Yield = 0.91-2.08 kg/day						
20	44	1.59	444	73	7.6	4.1
40	88	2.53	700	118	8.6	5.0
60	132	3.34	930	152	9.2	5.6
80	176	4.04	1120	181	9.7	6.1
Maintenance, Mature Bucks (Dairy/Nondairy)						
50	110	2.59/2.18	720/610	58/52	2.4/2.1	2.0/1.7
75	165	3.51/2.96	970/820	78/70	3.0/2.7	2.6/2.2
100	220	4.36/3.67	1210/1020	97/87	3.7/3.2	3.2/2.7
125	275	5.15/4.34	1430/1200	114/103	4.2/3.7	3.8/3.2
150	330	5.91/4.98	1640/1380	131/118	4.8/4.1	4.3/3.7
Prebreeding, Mature Bucks (Dairy/Nondairy)						
50	110	2.85/2.40	790/670	63/57	2.6/2.2	2.1/1.8
75	165	3.86/3.26	1070/900	86/77	3.3/2.9	2.9/2.4
100	220	4.79/4.04	1330/1120	106/96	4.0/3.4	3.5/3.0
125	275	5.67/4.78	1570/1320	126/113	4.6/4.0	4.1/3.5
150	330	6.50/5.48	1800/1520	144/130	5.2/4.5	4.7/4.0

Modified from National Research Council. *Nutrient requirements of small ruminants.* Washington, D.C., 2007, National Academies Press.

6. Perform ancillary diagnostic tests.
    a. If the weight loss is not related to the diet, additional diagnostic tests should be performed on the animal or on a number of animals in the herd. Possible tests include but are not limited to trace mineral analyses, ultrasound, and appropriate organ biopsy.

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b. Pathologic findings of affected ruminants often provide evidence of the effects of a systemic disease or of chronic malnutrition. Ruminants with PCM exhibit serous atrophy of fat in the coronary grooves of the heart and bone marrow at necropsy. Subcutaneous, abdominal, and perirenal fat are not present.

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Obesity

Mechanisms of Obesity

Obesity is a common problem in domestic large animal species, especially in horses, and in ruminants raised as companion animals. In ruminants, obesity increases the risk of metabolic disease, reproductive failure, and health complications during late pregnancy and lactation. The risk of obstructive urolithiasis increases in overweight bucks and rams, especially wethers. In horses, obesity is related to a variety of diseases including insulin resistance, equine metabolic syndrome, laminitis, and colic associated with strangulating lipomas. Obese horses and ponies that have increased metabolic energy demands (late pregnancy, lactation) that are rapidly losing weight or that are anorexic are particularly susceptible to hyperlipidemia and hyperlipemia.

Obesity results from the consumption of more calories than are required by an animal based on its stage of life and level of activity. Individual animals and certain breeds appear to be predisposed to obesity even if they are fed to meet their maintenance energy requirements. Obesity frequently occurs in horses fed high-energy feeds including grain and energy-dense commercial feeds and in horses grazing highly digestible pasture. Even horses that are only fed hay may gain weight if they consume an excess amount of energy. Purebred or pet sheep and goats (particularly wethers) tend to be overfed. In dairy cattle, obesity occurs when cattle are fed well above requirements for maintenance and milk production. Poor reproductive performance is often associated with the initiation of obesity in ruminants and is also a common sequela to obesity. Feeding for high milk production for lengthy periods in production groups predisposes infertile cows to become fat cows. Dairy cows dried off with a body condition above target are also predisposed to hepatic lipidosis, increasing the risk for periparturient diseases. The systemic complications associated with hepatic lipidosis, as well as its diagnosis and treatment, are described in Chapter 33.

Diagnosis of Obesity in Horses and Ruminants

Obesity is diagnosed by measuring the animal's body weight and assigning a subjective BCS number on the basis of muscle mass and external fat deposits. The clinical description of obesity provided by the BCS system is

straightforward (see Figs. 9.2 and 9.3, Tables 9.1, 9.14, and 9.15). Overweight and obese animals have an elevated BCS (7 to 9/9 for horses; 8 to 9/9 for beef cattle; 4 to 5/5 for dairy cattle, sheep, and goats). Palpation of the back, gluteal area, and ribs should be included in the physical examination of sheep and camelids with long wool or fiber and of horses with a long winter hair coat so that a BCS can be determined. In some animals, external signs of fat deposition may be subtle. In horses, a BCS greater than 5 to 6/9 does not accurately predict the total body fat mass of the animal in a linear fashion as may be expected using the linear BCS system.[23] Instead, body fat shows an exponential increase in horses with moderate to obese BCS.[23] Other measurements of body fat deposition including abdominal girth and fat depth (subcutaneous and retroperitoneal) measured by ultrasound may provide a better assessment of obesity in horses when the BCS is greater than 5.[23,24] Assessment of back fat thickness in dairy and beef cattle can also be evaluated with an ultrasound examination and has been shown to correspond well with total body fat.[25]

In some animals, obesity can be mistaken for the normal physiologic condition of pregnancy. In other cases, obesity could be mistaken for a distended abdomen from acute pathologic disease conditions including uroabdomen and peritonitis. A CBC and serum biochemical analysis can identify many subclinical diseases in an obese animal. A full physical examination should always be performed on a large animal patient before a weight loss ration is fed.

Treatment of Obesity

Overweight and obese horses and ruminants should lose weight to improve their health, extend life span, and improve production efficiency. In many cases a reduction in energy intake can be achieved by simply eliminating excess calories in the ration. Animals that fail to lose weight after 1 to 2 months after removing high-calorie feeds often require a more aggressive weight loss program with a therapeutic ration and a gradual implementation of an exercise program. Voluntary activity in animals that are turned out in pasture is rarely high enough to promote weight loss. Obese laminitic horses present a difficult challenge because exercise may not be practical, and weight loss must rely solely on dietary energy restriction.

Horses and companion ruminants that require a managed weight loss program should have the energy content of their diet evaluated by the veterinarian or nutritionist. The actual energy intake should be compared against the energy

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requirement for the animal's current life stage (see Tables 9.10, 9.11, 9.13, 9.16 to 9.20). The animal's current calorie intake should be reduced by 10% to 20% at the start of the weight loss program. This can typically be achieved in horses by decreasing forage intake to 1.5% of body weight and removing supplemental concentrates. Decreasing forage to 1% of body weight may be required under veterinarian care for some horses resistant to weight loss. Dietary protein should not be restricted, and adequate protein intake can be met by ensuring the forage available has appropriate protein content, or through the addition of soybean meal. Supplemental feeds and treats should be reduced or eliminated from the diet; however, a vitamin and mineral supplement should be fed with a weight loss ration to ensure all nutrient requirements other than energy are met. For horses, a concentrated vitamin-mineral supplement (typically offered in amounts <100 g, or about 4 oz) is often sufficient. A forage analysis can be used to select feeds that are low in nonstructural carbohydrates, as these may exacerbate any conditions associated with glucose metabolism.

Feeding straw to horses increases the risk of impaction colic and other gastrointestinal complications and should be avoided. To prevent boredom and improve the regulation of glucose, small amounts of forage should be fed in multiple small meals throughout the day. Horses can be fed hay in a hay bag, in doubled hay nets, in a NibbleNet, or with a mechanical feeder (Stable Grazer, The Grazer Hay Feeding Machine) as long as the horse can safely tolerate this equipment in its stall. The target weight loss goal is between 0.5% and 1% body weight each week. A weight tape should be used to assess the horse's weight if a scale is not available. Abdominal girth measurements, ultrasonographic evaluation of subcutaneous fat at the 12th intercostal space, and BCS measurements can be made to monitor weight loss every month.[23,24]

Owner compliance is essential during a weight loss program for horses and companion large animals. Owners should be encouraged to keep a journal of their animal's ration, body weight, and BCS. Horse owners can also monitor the horse's abdominal circumference, measured around the widest part of the abdomen.[24] Digital photos can help document physical changes over time. Excessive, rapid weight loss should be avoided. Weight loss programs should be approached with caution in animals that are either pregnant or lactating. Once the animal has achieved the ideal body weight and BCS, it should be placed on a maintenance ration and exercise program that will ensure the ideal weight is maintained.

In a production management setting the ration should be evaluated and revised

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to reduce calories while maintaining sufficient energy intake to maximize reproduction or milk production. Care should be taken to ensure the animals consume an adequate concentration of vitamins and minerals to meet their requirements when they are fed an energy-restricted ration.

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Pica

Pica (geophagia) is defined as a depraved or abnormal appetite. It is usually associated with animals that chew or eat wood (fences, trees, buildings); dirt; bones; or other inanimate objects not usually considered feedstuffs. The mechanism or mechanisms of pica are not yet understood. Pica has been associated with PCM, parasitism, obesity, and deficiencies of phosphorus, salt, protein (kwashiorkor), and micronutrients. Diagnosis is by observation or history or both. The main emphasis must be placed on identification and resolution of the primary problem. Pica must be differentiated from abnormal behavior associated with central nervous system diseases, bovine ketosis, and equine behavioral abnormalities associated with boredom.

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• CHAPTER 10

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Alterations in Urinary Function

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MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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Dysuria, Stranguria, and Incontinence

Dysuria is defined as difficult or painful urination. *Stranguria* is defined as straining to urinate, with the normal rate of voiding and urine egress being decreased and the effort required to void increased. Because these signs are often difficult to distinguish from each other and often present concurrently, they are considered together in this section. The most common causes of dysuria and stranguria are urethral obstruction, inflammation of the urethra and/or bladder, and neurologic conditions that prevent normal emptying of the bladder. Adhesions between the bladder and other structures in the abdominal or pelvic cavities can create mechanical interference with bladder emptying, resulting in dysuria and stranguria.

The horse voids urine actively and forcefully. Both male and female adult horses may briefly groan and strain slightly during normal urination. This should not be misinterpreted as dysuria or stranguria. In ruminants, urination is more passive, and straining or groaning is not normally observed, although vocalization during urination may signal dysuria. Conditions in which the horse may spuriously appear to have dysuria include lower urinary tract (LUT) disease, abdominal pain, peritonitis, pleuritis, severe musculoskeletal disease, or neurologic disease. With any of these conditions, the horse may attempt to posture and urinate but may not be able to sufficiently increase intraabdominal pressure to allow complete voiding. Owners of horses frequently misinterpret abdominal pain (colic) as “straining to urinate.”

Signs of dysuria and stranguria include treading, repetitive switching or flagging of the tail, pollakiuria (frequent voiding of small amounts of urine), flatulence during voiding, and retention of the urination posture after voiding has ceased. Urine scalding of the perineal region or rear legs may be noted in large animals with dysuria or stranguria. While straining to void, forceful contractions of the abdominal musculature may be seen. Male horses and ruminants experiencing dysuria or stranguria typically stand with the back slightly extended (mild lordosis), with the front legs held farther ahead of the body and the hind feet positioned farther behind the body than normal (Fig. 10.1).



FIG. 10.1 Lordosis and stranguria in a steer with urethral obstruction.

Dysuria or stranguria may be confused with rectal tenesmus (straining to defecate). This is most frequently a dilemma in neonatal foals when trying to distinguish a ruptured bladder from meconium impaction. However, with tenesmus the rear feet of the foal tend to be positioned slightly more anteriorly than with stranguria or dysuria. Stranguria may be severe enough in some cases to induce secondary rectal prolapse; therefore when examining an animal with rectal prolapse, the clinician must establish whether the underlying cause might be urinary tract disease. Conversely, animals with tenesmus may strain to defecate with sufficient force to void small amounts of urine, and the problem may be mistakenly attributed to primary urinary tract disease.

Urinary *incontinence* is the involuntary voiding of urine. It is most frequently indicative of impaired neuromuscular control of urination. Concurrent fecal incontinence is commonly found if disease or trauma to the sacral segments of the spinal cord is present. Urinary incontinence may also occur with severe cases of LUT trauma and inflammation. In young animals, congenital abnormalities such as ectopic ureter must be considered in the differential diagnosis for urinary incontinence. Causes of dysuria, stranguria, and urinary incontinence are shown in Box 10.1.

Box 10.1

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Causes of Dysuria, Stranguria, and Urinary Incontinence in Horses and Ruminants

Adhesions of the bladder
Balanitis, posthitis, vulvitis, vaginitis
Bracken fern intoxication (R)
Botulism
Cobalt toxicosis (E)
Cantharidin (blister beetle) toxicosis (E)
Ectopic ureter
Equine dysautonomia (grass sickness) (E)
Equine herpesvirus myeloencephalopathy (E)
Equine protozoal myeloencephalitis (E)
Equine neonatal maladjustment (E)
Estrogen-responsive dysuria (E)
Everted bladder
Habronemiasis (E)
Hemorrhage into the urinary tract
Hendra virus (E, Australia and Southeast Asia)
Laminitis
Lumbosacral spinal cord trauma, inflammation, or neoplasia
Lumpy skin disease virus (R, Africa)
Myopathy
Neoplasia of the urinary tract or accessory sex glands
Painful conditions of the abdominal organs or abdominal wall
Painful conditions of the thoracic organs or thoracic wall
Parturition
Penile, vaginal, urethral, or preputial trauma
Penile masses or encircling hair rings
Pelvic entrapment of the bladder
Pelvic, sacral, or vertebral fracture
Polyneuritis equi (Cauda equina neuritis)
Prolapsed bladder
Prolonged recumbency
Rabies
Rectovaginal fistula

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Ruptured urethra, bladder, or ureter
Seminal vesiculitis
Smegma accumulation (E)
Sorghum intoxication
Squamous cell carcinoma (penis, prepuce, or vulva)
Tetanus
Ulcerative posthitis and vulvovaginitis (pizzle rot) (R)
Urachal infection or abscesses
Urinary calculi (urolithiasis)
Urinary tract infection
Vaginal prolapse
Vertebral or spinal malformation

E, Found only in horses; *R*, found only in ruminants.

Approach to Diagnosis of Dysuria, Stranguria, and Incontinence

Initially, the signalment, dietary and environmental history, onset of signs, duration, progression, and response to treatment should be established. Urethral calculi should be considered a top differential in castrated ruminants on high-grain diets. A history of one or more horses showing clinical signs of spinal cord disease, respiratory disease, fever, stranguria, or urinary incontinence should immediately lead the practitioner to consider equine herpesvirus myeloencephalopathy. A history of dysuria or stranguria that develops after parturition usually indicates an injury to the LUT; such injuries can increase the female's risk of subsequent urinary tract infection (UTI). For safety's sake, the clinician should consider the potential for rabies as a primary cause before initiating the examination. A full physical examination should be performed because abnormal urination may be a sign of disease in other body systems, such as those characterized by diffuse muscular weakness.

When possible, the animal should be observed urinating, and a sample of urine should be collected for dipstick urinalysis, measurement of specific gravity, and sediment examination; urine can be collected in a separate, sterile container for culture, if indicated. Urination can be induced in cows by gently rubbing the perineum immediately ventral to the vulva. In male cattle, the examiner may induce urination by placing a finger into the preputial cavity and

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gently rubbing the preputial mucosa. In ewes, urination can be induced by holding off the nose until the ewe struggles; urination typically occurs at this point. This procedure should not be performed on weak ewes or those in shock or with poor cardiac or respiratory function. In horses, goats, and male sheep, the examiner simply must wait until the animal is ready to void, although urination may be encouraged by placing the animal in a freshly bedded stall. Recumbent animals will often void soon after standing. Horses will often cease urinating midstream if approached quickly; thus, a urine collection cup taped to a long stick or straightened wire coat hanger affords the clinician a better chance of catching urine quickly and safely. In some species, urinary catheterization is possible and sometimes required to obtain a sample. The vulva or penis should be cleaned with dilute chlorhexidine solution, and aseptic technique should be maintained. In female horses and ruminants the urethral opening is located under the suburethral diverticulum, a mucosal flap on the floor of the vagina. A lightly lubricated stiff urinary catheter can be passed blindly into the urethra by sliding it gently along the ventral floor of the vagina, taking care to stay exactly on the midline. Alternately it can be located by placing a hand in the vagina. In male horses sedation is required to relax and exteriorize the penis, which then should be grasped firmly and extended; then a lubricated flexible catheter can be passed. Acepromazine sedation should be avoided in stallions due to the risk of paraphimosis. Normal equine urine is variably turbid owing to the presence of mucus and calcium-based crystals (Fig. 10.2).



FIG. 10.2 Normal equine urine *(left)* and urine with severe myoglobinuria *(right).* Urine containing myoglobin is not always so markedly discolored. (Photo courtesy Paul S. Morley.)

The male's preputial hairs and the female's perineal region should be closely inspected for the presence of blood, exudate, or crystalline debris (Fig. 10.3). Sedation and/or epidural anesthesia may be necessary to induce sufficient relaxation of the retractor penis muscles to enable examination of the penis. In prepubescent ruminants the frenulum often prevents complete exteriorization of the penis for examination of the urethral orifice; general anesthesia may be necessary to induce sufficient relaxation. In bulls and steers transrectal massage of the pelvic segment of the urethra may stimulate penile relaxation and visualization. The glans penis and urethral orifice should be carefully examined for masses such as papillomas, evidence of trauma, encircling hair rings, and embedded foreign bodies (e.g., grass awns). Penile examination is particularly important in the dysuric or stranguric small ruminant because urinary calculi frequently become lodged in the urethral process (see the Urolithiasis in the Ruminant Renal System section in Chapter 34).

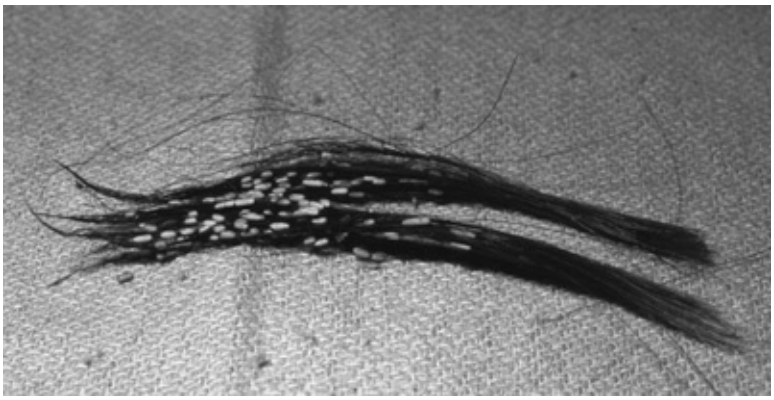


FIG. 10.3 Crystals adherent to the preputial hairs of a steer with urolithiasis. The crystals were analyzed and found to be composed of struvite (magnesium ammonium phosphate).

An accumulation of smegma, composed of mucus and cellular debris, may cause preputial swelling and dysuria in adult male horses. Smegma can usually be found as a hard, waxy mass in the urethral diverticulum. Preputial swelling without urinary dysfunction may be seen with equine metabolic syndrome, and in equine pituitary pars intermedia dysfunction.[1,2]

In the male the penis and the urethra should be palpated percutaneously from the perineum distally to the sheath. Swelling, pain, abnormal urethral pulsations, and calculi lodged in the urethra may be detected. Urethral calculi are most commonly lodged just below the anus in male horses, and these can occasionally be palpated on the midline of the perineum. Marked swelling along the prepuce and ventral body wall in a bull or steer with active or recent dysuria or stranguria can indicate urethral rupture.

The vulva, caudal vagina, and urethral orifice should be visualized and palpated in females. Sacrocaudal epidural anesthesia may facilitate examination if painful lesions are present. In females of breeding age the cervix should be visualized or palpated and the uterus evaluated by palpation or ultrasonography because the pollakiuria and apparent dysuria that may occur at the onset of parturition may be the primary complaint of a novice observer. Previous dystocia can result in sufficient soft tissue trauma, laceration, swelling, and pelvic neuropraxia to induce dysuria or stranguria. The ventrum of the tail, perineum, udder, and hindlimbs should be examined for adherent blood or exudate originating from the female's reproductive or urinary tract.

In adult horses and cattle rectal palpation should be performed when dysuria and stranguria are present. Before examination the clinician should take careful note of the tail and anal tone of the animal; reduction of either or both may

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indicate underlying neurologic or muscular disease. Introduction of the examiner's hand and wrist into the rectum is usually sufficient for palpation of the pelvic segment of the urethra and bladder trigone. The caudal extent of the pelvic cavity should be carefully palpated for masses that might mechanically interfere with voiding. The bladder is typically located on the midline at the level of the pubic brim. Its presence in the caudal pelvic cavity, particularly in the standing animal, may suggest pelvic entrapment of the bladder.

Bladder distention is commonly found in persistently recumbent horses and cattle, and on rectal examination the bladder is often positioned farther caudally than in standing animals. In the horse bladder distention may also be found with abdominal or thoracic pain. Apparently the abdominal pressure necessary to empty the bladder incites sufficient pain of diseased structures to cause reluctance to void. Musculoskeletal and neurologic disease may also result in bladder distention. These other possibilities should be carefully investigated when bladder distention is detected yet no primary disease is found in the urinary tract.

A careful rectal examination of the bladder and the proximal urethra of the horse might allow identification of urethral or cystic calculi. Most cystic calculi in the horse are singular, located in the trigone of the bladder, and are palpable with the examiner's arm inserted to the level of the wrist. If there is a large amount of urine in the bladder, the stone may not be palpable; in such cases, transrectal ultrasound examination may enable visualization of the stone. Detection of calculi in the bladder or urethra should prompt consideration of concurrent nephrolithiasis.

If bladder dysfunction is not caused by structural abnormalities, trauma, or infectious disease, a thorough neurologic examination should be conducted. If neurologic dysfunction is suspected, an attempt should be made to determine whether the primary lesion is affecting the detrusor muscle (lower motor neuron [LMN]) or the urethral sphincter muscles (upper motor neuron [UMN]) of the bladder. This determination is often helpful in localizing the lesion and is important when selecting treatment.

When bladder paralysis is caused by UMN dysfunction, signs of UMN dysfunction may be evident in the rear limbs. The animal frequently postures and strains to urinate but voids only a small amount of urine because the striated urethral muscles are disinhibited from higher centers and their resultant increased tone impedes urine outflow from the bladder. Frequent, small-volume urine egress from the distended bladder occurs when the animal responds to the

urge to void or when the bladder undergoes reflex contraction.

With severe disease of the sacral spinal cord or sacral nerve plexus, LMN input to the detrusor muscle is impaired or absent. Urinary incontinence is often the predominant clinical sign (e.g., cauda equina neuritis in horses, spinal cord lymphoma in cattle). The bladder is usually moderately to severely distended, and urine can be expressed easily if pressure is applied to the bladder during rectal examination. With LMN dysfunction, urine may also be voided as the animal walks. Voluntary or involuntary voiding is often incomplete, leading to retention of urine in the bladder. This, in turn, increases the patient's risk of UTI. In horses with bladder paralysis, sabulous accumulations may form a doughy sludge in the ventral bladder, and on rectal examination the clinician may interpret the palpation findings as a bladder tumor.[3] Other neurologic signs involving the sacral and coccygeal nerves may be apparent, such as decreased tail and anal tone and atrophy of the gluteal or tailhead musculature. Ataxia or weakness of the rear limbs may or may not be present with bladder paralysis due to LMN dysfunction. Urethral and bladder pressure profiles can be determined to better assess the location of the lesion.[4-6]

In small ruminants and neonates, transabdominal palpation is useful for evaluation of the urinary tract. In these animals a distended bladder can usually be palpated by simultaneously placing one hand on each side of the caudal ventral abdomen at the level of the pelvic brim and pressing the fingers of each hand toward the abdominal midline. If the bladder has been ruptured, it will be difficult to identify by palpation, but ascites due to uroperitoneum can be detected. Digital rectal palpation of the pelvic segment of the urethra can be performed in neonatal cattle and horses and in small ruminants. The umbilicus should be carefully palpated in neonates with dysuria or stranguria because urachal abscesses and adhesions to the bladder may impair voiding. An infected urachus will occasionally communicate with the bladder lumen, creating concurrent septic cystitis.

Ectopic ureter(s) should be considered in young animals with persistent urinary incontinence; stranguria and dysuria are less common primary complaints. In affected females vaginal urine pooling is often present. Vaginoscopic or cystoscopic examination can be performed, but the opening of the ectopic ureter can be difficult to locate during routine examination. Location of the ectopic ureter(s) often requires intravenous contrast urography or intravenous administration of a dye that is excreted in the urine, such as fluorescein. As for all congenital defects, a careful assessment for defects in

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other organs should be performed in confirmed cases.

If physical examination and urinalysis do not reveal the source of dysuria, stranguria, or incontinence, transabdominal and/or transrectal ultrasonographic evaluation of the urogenital tract should be performed. Transrectal ultrasound can be performed in geldings to evaluate the accessory sex glands, caudal ureters, and pelvic urethra.[7] An endoscope can be used to visualize the vaginal vault or preputial cavity and penis; air insufflation can be used to expand the walls and achieve a clear view of these structures. When advanced retrograde into the urethra, the urethral wall, bladder, and ureteral openings can be visualized. In neonates and small ruminants, plain abdominal radiographs, positive contrast urethrocystography, and intravenous contrast urography are additional options.[8]

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Hematuria and Pigmenturia

Hematuria is defined as blood in the urine. It may appear as occult blood detected during urinalysis, as uniformly red-colored urine throughout urination, or as blood clots passed at any phase of urination. If large clots are present, obstruction of the urinary tract may occur, resulting in concurrent stranguria and dysuria. *Pigmenturia* is defined as the presence of abnormal pigment in the urine; in large animals such pigments are usually limited to hemoglobin or myoglobin. Hemoglobin, myoglobin, and blood all cause a positive reaction for blood and protein on an ortho-toluidine–based urine dipstick test. Certain oxidizing disinfectants can also trigger a positive reaction for blood on these strips. In addition, contamination of the urine with blood from the reproductive organs can result in hematuria, as can admixture of fecal blood with voided urine in females. Blood from penile or preputial injuries can contaminate the urine of males.

When clots of blood are visible in the urine, the presence of hematuria is confirmed. Also, when scattered spots of color change are evident on the blood reagent pad of the urine dipstick, the reaction pattern reflects the presence of small aggregates of red cells deposited on the pad. Otherwise, differentiation of hematuria from hemoglobinuria and myoglobinuria requires that the discolored urine be centrifuged and the sediment examined. Hematuria is characterized by red-, pink-, or brown-colored urine that clears partially or entirely after centrifugation, resulting in a pigmented sediment pellet. With hematuria, red cells or red cell “ghosts” (red cells devoid of pigment) are visible on microscopic examination of urine sediment.

Urine containing hemoglobin is clear to dark red in color, depending on the concentration of hemoglobin in the sample. If visibly discolored, the urine sample with hemoglobinuria does not clear when centrifuged. Animals with hemoglobinuria may be experiencing intravascular hemolysis, which leads to passage of hemoglobin from the plasma into the tubular fluid of the nephrons. The serum or plasma of these animals may be pink in color. Mucous membrane pallor or icterus may be evident, and tachycardia and tachypnea are present when red cell destruction is rapid and extensive. The packed cell volume (PCV) may be decreased at the time of initial examination, or it may decrease progressively during subsequent measurement. Intravascular hemolysis may result in elevation of the plasma and serum total protein concentration. The

clinician should note that hemoglobin is potentially nephrotoxic; renal function and hydration should be monitored. Sediment findings vary according to the underlying disease, and hyaline or cellular casts may be seen if pigment nephropathy is present.

Urine containing myoglobin may be of normal color; if present in high concentrations in a sample, it imparts a dark red to brown color to the urine (see Fig. 10.2). If visibly discolored, urine containing myoglobin does not clear when centrifuged. Sediment findings are variable but can include hyaline or cellular casts if pigment nephropathy is present. Myoglobin can be differentiated from hemoglobin in urine through ammonium sulfate precipitation, electrophoresis, or spectroscopy. Animals with myoglobinuria have muscle necrosis or injury, which leads to release of myoglobin from damaged muscle cells into the plasma and renal tubular fluid. Extensive muscle trauma (e.g., dog attacks, trailer accidents) or primary myopathies can induce myoglobinuria. Affected animals may show abnormal stance, gait, or other evidence of muscle swelling, pain, or weakness. The serum activity of the enzymes creatine phosphokinase (CPK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) is variably increased, depending on the duration and severity of muscle injury. As for hemoglobin, the persistence of myoglobin in the tubular fluid of the nephrons is nephrotoxic and can induce renal tubular necrosis. Causes of hematuria and pigmenturia are listed in Box 10.2.

Box 10.2

Causes of Hematuria and Pigmenturia in Horses and Ruminants

Hematuria

Aberrant parasite migration within the urinary tract
Admixture of fecal blood with urine
Admixture of blood from the reproductive organs with urine (e.g., metritis, orchitis, seminal vesiculitis)
Arsenic toxicosis
Bleeding diatheses (e.g., warfarin, disseminated intravascular coagulation

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[DIC])
Cantharidin (blister beetle) poisoning (E)
Cobalt toxicosis (E)
Contamination of urine with oxidant disinfectants
Enzootic hematuria (R)
Exercise-induced hematuria (E)
Habronemiasis (E)
Leptospirosis
Neoplasia of the urogenital tract
Penile, vaginal, preputial, or urethral trauma
Penile masses or encircling hair rings
Renal papillary necrosis (e.g., related to nonsteroidal antiinflammatory drugs [NSAIDs])
Ulcerative cystitis
Urinary calculi (urolithiasis)
Urinary tract infection
Vascular anomaly, corpus cavernosum rupture (proximal dorsal urethral hemorrhage in males) (E)

Hemoglobinuria

Burns (severe)
Clostridium haemolyticum infection (redwater) (R)
Copper intoxication
Ethylene glycol toxicosis (severe)
Excess water intake, water intoxication
Hepatic failure
Intravenous (IV) hypotonic fluid administration (e.g., 0.45% saline or water)
IV hypertonic fluid administration (e.g., dimethyl sulfoxide [DMSO])
Leptospirosis
Onion and *Brassica* species (rapeseed, kale, mustard, etc.) intoxication
Neonatal isoerythrolysis
Postparturient hemoglobinuria (combined phosphorus/selenium and/or copper deficiency) (R)
Red maple intoxication (E)

Myoglobinuria

Clostridial myonecrosis
Compartment syndrome, down cow syndrome
Exertional or capture rhabdomyolysis
Hereditary or congenital myopathies
Infarctive purpura hemorrhagica (E)
Muscle trauma
Myopathy associated with streptococcal infections (E)
Nutritional myodegeneration
Postanesthetic myoneuropathy
Toxic myopathies (e.g., *Acer* species, *Cassia* species, ionophores, gossypol)
Viral myopathies (influenza, equine herpesvirus [EHV], bluetongue)

E, Found only in horses; *R*, found only in ruminants.

Approach to Diagnosis of Hematuria and Pigmenturia

The history should include data on recent infectious diseases, exercise, diet, and treatment, and a full physical examination should be conducted. Hematuria after exercise may indicate the presence of erosions in the urinary tract mucosa, anomalous vascular structures, or mucosal trauma from uroliths. Ingestion of certain toxins (e.g., cantharidin, bracken fern) can create hematuria. Geldings and stallions may develop spontaneous hematuria associated with a vascular fistula or cavernosal rupture in the most proximal urethra.[9-11] Hemoglobinuria can result from exposure to hemolytic toxins such as red maple leaves, copper, onions, and certain bacterial hemolysins. Intravenous infusion of markedly hypotonic (e.g., water) or hypertonic (e.g., undiluted dimethyl sulfoxide [DMSO]) fluids can also result in intravascular hemolysis and hemoglobinuria. In dehydrated animals, ingestion of large volumes of water (water intoxication) can reduce intravascular osmolality to the point of causing hemolysis, with resultant hemoglobinuria.

Hemolysis should be investigated through examination of the serum or plasma, serum total protein measurement, and/or a complete blood count (CBC).

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A urine sample should be obtained for full urinalysis, centrifugation, and sediment examination. The patient with potential hematuria should be carefully examined for clinical signs suggestive of impaired coagulation. Severe vulvitis often develops in females with diarrhea because of prolonged contact of the vulvar mucosa with fecal contents, and a trace reaction for blood is often evident in the urine. However, the possibility of hemorrhage from tubular injury caused by hypovolemia should also be considered.

Lesions of the urethra most often produce hematuria at the beginning of urination. Hematuria that originates from the bladder is most likely to be seen or appear more pronounced at the end of urination. Hemorrhage originating from the upper urinary tract is likely to be more pronounced at the end of urination. It should be noted, however, that it is not always possible to accurately localize the source of urinary tract hemorrhage by the timing of the appearance of blood in the voided sample. If the urine discoloration appears uniform throughout urination and no clots are obvious, it must be determined that the discoloration is hematuria and not hemoglobinuria, bilirubinuria, or myoglobinuria. This can be accomplished by routine dipstick urinalysis; urine sediment examination; assessment of the patient's PCV, plasma protein concentration, and serum muscle enzyme activities; and visualization of the color of the plasma and mucous membranes.

Hematuria often accompanies pyuria and bacteriuria UTI. If hematuria is confirmed and UTI or genital or perineal trauma is *not* the cause, rectal examination may reveal calculi or tumors in the proximal urethra or bladder. Endoscopic examination of the urethra and bladder is necessary if the lesion cannot be detected during rectal or physical examination. During endoscopic examination of the urethra and bladder, if the source of hemorrhage is not apparent, the openings of the ureters and the color of the urine coming from both of them should be visualized. This is best performed after suctioning urine from the bladder and then distending the bladder with air, taking care that bubbling of the urine does not occur. The two openings can be visualized simultaneously by passing the scope farther into the bladder and retroflexing the scope caudally until the entire trigone area is visualized. If hemorrhage is seen to originate from one or both ureteral openings, ultrasound examination of the kidneys and ureters should be performed, as the hemorrhage has now been localized to the upper urinary tract (UUT).

When myoglobinuria is present, the potential for exposure to gossypol and ionophores should be investigated. Certain viral and bacterial infections, such as

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streptococcal infections in horses, can induce myopathy and myoglobinuria. A recent history of heavy exertion or very high ambient temperature (heatstroke) may exist in cases of myopathy with myoglobinuria. The potential for nutritional myodegeneration from vitamin E and/or selenium deficiency should be considered in light of the animal's diet and the regional soil selenium content. A previous history of recurrent exercise intolerance or muscle dysfunction may be evident in certain inherited, idiopathic, or diet-associated cases of rhabdomyolysis. Prolonged recumbency (e.g., general anesthesia, downer animals) can induce sufficient pressure myopathy to cause myoglobinuria. Rarely, idiosyncratic responses to medications can induce hemolysis or muscle injury, resulting in hemoglobinuria and myoglobinuria, respectively.

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Pyuria

Pyuria is defined as gross or microscopic evidence of inflammatory cells in the urine. Dysuria, stranguria, pollakiuria, crystalluria, urine scalding, and hematuria can accompany it. Pyuria may result from systemic septic inflammatory disease, localized microbial UTI, or nonseptic inflammation (sterile pyuria; see Fig. 10.2). In horses, the normal variable turbidity of equine urine should be considered when assessing gross pyuria. Causes of pyuria are listed in Box 10.3.

Box 10.3

Causes of Pyuria in Horses and Ruminants

- Admixture of inflammatory exudate from the reproductive tract (spurious pyuria)
- Calculi (uroliths, nephroliths)
- Ectopic ureter
- Encircling hair rings of the penis
- Infection of the urinary tract (urethritis, cystitis, ureteritis, and/or pyelonephritis), including Leptospirosis
- Neoplasia
- Nephritis (sterile)
- Penile, preputial, or urethral trauma
- Rectovaginal fistula
- Ulcerative posthitis (small ruminants) and vulvovaginitis
- Viral infections of the genitalia
- Vulvar, vaginal, or urethral trauma or neoplasia

Approach to Diagnosis of Pyuria

A complete examination of the urinary tract should be performed, including rectal palpation or transabdominal palpation of the bladder. Cystitis may be characterized by a thickened bladder wall, but this is often difficult to detect during rectal palpation and ultrasonographic examination may be necessary.

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Predisposing factors for UTI such as urinary calculi, dystocia, abnormal urethral or genital structure, and neurologic diseases should always be considered.

Pyuria is confirmed by obtaining a midstream (free catch) or catheterized urine sample and by quantitating the number of white blood cells (WBCs) and bacteria in the urine sediment. Evaluation of urine sediment within 30 to 60 minutes of collection enables preservation of the greatest cytologic detail. In human medicine, pyuria is defined as the presence of more than 10 WBCs per mm^3 urine, 3 or more WBCs per microscopic high-power field (HPF) or positive Gram staining on unspun urine, or leukocyte esterase positive on a urinary dipstick.[12] In horses, to the authors' knowledge, no peer-reviewed study has specifically assessed the cellular content of urine in healthy horses. Pyuria is generally considered to be the presence of more than 10 WBCs per HPF of a midstream-voided or catheterized sample, and the urine of normal horses and cattle generally is said to have fewer than 5 WBCs per HPF.[13,14] However, a study assessing quantitative cultures in free catch urine from healthy horses found that no horse had a WBC count of more than 1 per HPF.[15] This suggests that the generally accepted number of more than 10 WBCs per HPF to diagnose pyuria may be too high for horses and that pyuria should be suspected if more than 5 WBCs per HPF are seen, providing collection is aseptic and there is clinical suspicion. When bacterial infection is the cause of pyuria, there are typically more than 20 organisms visible per HPF. The cytologic features of urine sediment and quantitative culture are influenced by the method of collection, rigor of aseptic technique, and degree of contamination of the prepuce, vulva, and urethral orifice. Catheterization can be used to obtain urine from the bladder of most male and female horses and female ruminants. If adequate quantity is obtained, the first 20 mL collected should be discarded and analysis done on the subsequent 20 mL.[15] In male ruminants, the urethral recess (diverticulum) prevents retrograde catheterization of the bladder, and collection of a midstream sample is usually the sole option. Cystocentesis of a large animal with a UTI carries the risk of induction of septic peritonitis.

Urine samples should be refrigerated and quantitative culture performed as soon after collection as possible to avoid false increases in the colony count that can occur from bacterial proliferation in the sample during storage. The results of quantitative culture are greatly influenced by the method of collection and the degree of contamination of the prepuce and vulva. In specimens collected by midstream free catch, bacterial counts greater than 1×10^4 bacteria/mL of urine

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are indicative of UTI if compatible dipstick and sediment examination findings are present. Normal equine urine has fewer than 20,000 colony-forming units (CFUs)/mL in a free catch sample and fewer than 500 CFUs/mL in a catheterized sample.[15] In free catch urine samples from horses, mean CFU/mL bacterial counts are significantly higher in females (6054 CFU/mL) than in males (490 CFU/mL).[15] A culture that yields a large number of a variety of bacterial species may reflect heavy contamination of the vulva or penis, fecal admixture, a UTI involving multiple bacterial species (rare), or delay before culture was initiated, especially if the urine sample was not kept refrigerated.

Once pyuria is confirmed, its location or origin, inciting cause(s), and any predisposing conditions should be determined. In males, the accessory sex glands should be carefully examined because inflammatory exudate from these structures may be admixed with urine, resulting in a spurious diagnosis of pyuria. In females, mixing of urine and inflammatory exudate in the urethra and vestibule may also result in spurious pyuria. Trauma or inflammation of the glans penis or prepuce can also result in admixture of exudate with urine, as often occurs in ulcerative posthitis in rams and bucks. Endoscopic examination of the vaginal vault or preputial cavity may be helpful, using air insufflation to aid in visualization of the mucosa. Inflammatory diseases of the LUT usually produce obvious clinical signs of dysuria but minimal to no signs of systemic disease. Low-grade fever is occasionally present in cases of localized cystitis, although affected animals are often not apparently systemically ill.

If the pyuria originates from the UUT, the animal is usually persistently or intermittently febrile and shows systemic signs of disease, and changes suggestive of inflammation are often present on a CBC. Inflammation of the ureter(s) and kidney(s) may result in colic. Rectal examination may reveal enlargement of one or both ureters, pain on palpation, and possibly enlargement and/or abnormal shape of the left kidney. If grossly enlarged, the right kidney can occasionally be palpated per rectum in horses or cattle. In cows and heifers, thickening and pain of one or both ureters is often more readily identified during vaginal palpation than rectal palpation. Casts of blood, protein, or cellular debris may be seen in the urine sediment in cases of pyelonephritis. An ultrasonographic examination of both kidneys and ureters should be performed in all animals with evidence of upper UTI. The technique for ultrasound examination of the urinary tract is described in Equine Abdominal Ultrasonography and Ruminant Abdominal Ultrasonography in Chapter 32.

If *Leptospira interrogans* serotype Pomona is suspected as a cause of pyuria

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(cattle), urine sediment should be placed on a microscope slide, air-dried, and examined by fluorescent antibody for *Leptospira* antigen.[16] Polymerase chain reaction testing for *Leptospira* species can be performed on urine sediment in cattle, goats, and horses; in cattle, greater sensitivity may be achieved by obtaining a urine sample after administration of furosemide.[17-19]

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Crystalluria

Crystalluria is defined as the presence of crystals in the urine. Calcium carbonate and calcium phosphate crystals are abundant in normal equine urine. These, along with mucus, impart a turbid, slightly opaque quality to normal equine urine (see Fig. 10.2). Herbivore urine is normally alkaline, which reduces the solubility of certain calcium- and phosphate-based compounds in urine, inducing crystal development. Therefore calcium phosphate, calcium carbonate, or calcium oxalate crystals may be present as an incidental finding in highly concentrated ruminant urine if the animal is healthy and free from signs of urinary tract disease. However, in male ruminants, heavy or persistent crystalluria may be a risk factor for urolithiasis because the combination of highly concentrated urine and urinary mineral precipitation is considered instrumental in calculogenesis. A precautionary review of diet, salt intake, and water management may be indicated in such cases.

Crystalluria presents a medical problem when crystals enlarge through precipitation, causing microscopic or gross traumatic injury to the urinary epithelium and urinary tract obstruction. When crystals coalesce and enlarge to form calculi (uroliths), the calculi may remain occult or cause disease through trauma to and obstruction of the urinary tract.[20-22] As a result, the clinician usually detects crystalluria in these animals during the diagnostic work-up for hematuria, dysuria, stranguria, pyuria, or signs of urinary tract obstruction. It is critical to note that the *absence* of crystalluria does not indicate that the urinary tract is free of calculi or renal mineralization, just as the presence of crystalluria does not necessarily indicate disease.[23,24] Causes of crystalluria are listed in Box 10.4.

Box 10.4

Causes of Crystalluria in Horses and Ruminants

Alkaline urine

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Calcium-based crystalluria of horses (normal)
Concentrated urine
Ethylene glycol intoxication
Oxalate intoxication
Urinary tract infection
Urolithiasis
Vitamin C intoxication

Approach to Diagnosis of Crystalluria

Toxins such as oxalic acid and ethylene glycol can induce calcium oxalate crystalluria, so access to oxalate-containing plants and storage areas or garages should be investigated.[23,25] High doses of parenteral vitamin C can induce calcium oxalate deposition in the urinary tract, and there is also a suggestion that primary hyperoxaluria may be related to inherited metabolic defects.[25,26] Previous urinary tract surgery, dystocia, or genital trauma may indirectly contribute to crystalluria, as abnormal structure of the urinary tract, suture material inadvertently placed in the tract, or loss of uroepithelial integrity can promote crystal precipitation into calculi.

The hairs surrounding the preputial orifice or vulva should be carefully examined for visible crystals that cling to the hair, indicating heavy crystalluria (see Fig. 10.3). In males, given that urolithiasis is an important diagnosis to investigate, urinary tract patency should be determined.

Crystalluria and calculus formation can be caused by UTI because urease-producing bacteria may increase the pH of urine to the point of inducing precipitation of certain minerals suspended in the urine into calculi.[27] In addition, inflammatory exudation into the urinary tract provides nidi for deposition of urinary minerals.[27]

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Polyuria

Polyuria can be defined as the passage of abnormally large amounts of urine. This may be a normal response when excessive fluid, electrolytes, or both are presented to the tubules of a healthy kidney. It may also occur with renal failure when tubular function is impaired or when sufficient nephron loss overwhelms the remaining nephrons with excess fluid and/or solute. Polyuria is also present in central or neurogenic diabetes insipidus (DI) (caused by insufficient secretion of antidiuretic hormone [ADH]), nephrogenic DI (caused by diminished effect of ADH on receptors in the kidney), renal medullary washout (caused by an insufficient interstitial concentration gradient), excessive drinking (polydipsia), liver failure, and certain electrolyte abnormalities. A phenomenon termed *postobstructive diuresis* results in polyuria after relief of urinary tract obstruction. Common causes of polyuria are listed in Box 10.5.

Box 10.5

Causes of Anuria, Oliguria, and Polyuria in Horses and Ruminants

Anuria and Oliguria

Acute or chronic renal failure (multiple causes)
Blood loss
Cardiac failure
Dehydration
Rupture of the urethra, bladder, or ureter(s)
Septic or toxic shock
Urinary tract obstruction (e.g., urinary calculi)

Apparent Anuria or Oliguria

Bladder paralysis or atony
Botulism

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Dysautonomia (grass sickness) (E)
Ectopic ureter(s)
Encephalopathies
Equine herpesvirus myeloencephalopathy (E)
Neonatal maladjustment syndrome
Painful diseases of the abdomen or abdominal wall
Painful diseases of the thorax or thoracic wall
Patent urachus
Prolonged recumbency
Ruminal acidosis/grain overload
Severe spinal cord disease

Polyuria

Acute or chronic renal failure (multiple causes)
Cantharidin intoxication
Diabetes insipidus (central or nephrogenic)
Diabetes mellitus
Drugs: diuretics, xylazine, corticosteroids
Encephalopathies
Excessive intravenous fluid therapy
Excessive water or salt ingestion
Hepatic failure
Hypercalcemia (including iatrogenic)
Hyperglycemia (including iatrogenic)
Medullary washout
Organophosphate intoxication
Pituitary pars intermedia dysfunction (PPID) (E)
Postobstructive diuresis
Psychogenic polydipsia
Renal amyloidosis
Salt deficiency
Vitamin D intoxication

E, Equine.

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Approach to Diagnosis of Polyuria

Evaluation should begin with careful inquiry about any history of recent disease, drug administration (e.g., diuretics, corticosteroids, xylazine), fluid therapy, change in diet, change in water quality or availability (e.g., drought, frozen water), or known laboratory evidence of renal disease. The next step is to collect a urine sample to measure the osmolality or specific gravity (UspG). If the osmolality is close to the isosthenuric range (UspG of 1.008 to 1.014) in the face of dehydration, primary renal disease should be considered. This is typically confirmed by measuring the serum creatinine and blood urea nitrogen (BUN) concentrations, although radionuclide clearance studies and/or 12- or 24-hour urinary creatinine clearance can also be performed. If evidence of renal failure is not present on these tests (see Polyuria and Polydipsia in the Equine Renal System section, Chapter 34), a water deprivation test may be necessary to determine the tubules' ability to concentrate urine. This should be performed in a normovolemic patient with careful monitoring of patient status because the mild dehydration induced during this test may exacerbate preexisting, occult renal disease.

As an alternative to the water deprivation test used to identify tubular disease and dysfunction as the cause of polyuria, the fractional clearance (fractional excretion) of sodium in the urine can be measured. This test is performed by collecting urine and plasma samples at exactly the same time, then measuring the creatinine and sodium in both samples. The fractional clearance of sodium (Fc_{Na} [%]) is then determined using the following formula:

$$Fc_{Na}(\%) = \frac{[Na_u]}{[Na_p]} \times \frac{[Cr_p]}{[Cr_u]} \times 100$$

where Na_u is the urine sodium concentration, Na_p is the plasma sodium concentration, Cr_u is the urine creatinine concentration, and Cr_p is the plasma creatinine concentration. A fractional sodium clearance value above 1% in adult horses is suggestive of primary tubular disease, particularly if the animal's diet and physiologic state are such that avid sodium conservation is expected.[28] Fractional clearance of sodium values of up to 4% have been measured in healthy, lactating dairy cattle.[29] For this test to be valid, salt intake must be

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normal and the animal must not be given diuretics, parenteral fluids, or fluids administered orally other than what is drunk voluntarily.

If the UspG or osmolality is less than that of the plasma (1.007), DI, psychogenic polydipsia, and renal medullary washout should be considered. Although rare, DI has been reported in the horse and may be the result of inadequate secretion of vasopressin (neurogenic DI) or inadequate response to vasopressin in the kidney (nephrogenic DI).[30,31] However, the patient may simply be ingesting large amounts of water in response to exercise or a high ambient temperature, so interpretation of low UspG requires due consideration of the animal's physiologic state.

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Anuria and Oliguria

Anuria is defined as the absence of urine production, and *oliguria* is defined as scant or subnormal urine production. These two disease conditions are often difficult to distinguish at the onset of evaluation. Furthermore, the difficulties associated with maintaining urine collection devices in large animals make an accurate measurement of urine production difficult. Causes of anuria and oliguria are listed in Box 10.5.

Volume of urine produced by healthy animals varies tremendously according to breed, age, physiologic status, exercise, diet, and environmental factors. In 1961 Altman determined normal urine output for the large animal species to be as follows: horses, 3 to 18 mL/kg/day; cattle, 17 to 45 mL/kg/day; and sheep and goats, 10 to 40 mL/kg/day.[32] Neonates urinate more frequently than adults and often directly after nursing. Anuria and oliguria frequently become apparent to the clinician when an azotemic animal is diagnosed with a primary disease in which renal function is commonly threatened (e.g., severe diarrhea, congestive heart failure) and urine output after initiation of fluid therapy is subnormal or absent.

If urine collection and measurement cannot be performed, the adult animal with potential anuria or oliguria can be closely watched or placed in a stall with no or minimal bedding or fine, fresh bedding (e.g., sawdust) to facilitate detection of urine on the floor. When indicated, fluid therapy should be initiated and expectations for urine output predicted based on the rate and route of fluid administration. Animals with painful thoracic or abdominal disease may refrain from urination, and the clinician must remember to evaluate *bladder filling* by transrectal or transabdominal ultrasonography, and not just the volume of urine voided. Recumbent, obtunded foals, particularly males, may not reliably void urine; monitoring bladder fill by ultrasound or directly monitoring urine output by placement of an indwelling urinary catheter is recommended to avoid bladder rupture. The same applies for some recumbent neurologic horses and cattle. Urachal leakage of urine must be considered in neonates with suspected anuria or oliguria because they may void less frequently than normal. Animals with encephalopathies (again, rabies warrants mention) or severe spinal cord disease may not be capable of voluntary voiding.

When evidence for anuria mounts, the clinician must determine whether the urinary tract is patent and rule out the presence of rupture of the bladder, urethra,

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or ureters. Repeat physical examination and ultrasonography of the upper and lower urinary tract and abdominal cavity is warranted in such instances. Obstructive diseases of the LUT are typically accompanied by signs of colic and stranguria. However, these signs will not be present if the patient has a preexisting rent in the urinary tract or if the animal is severely obtunded from uremia.

Oliguria is a physiologic adaptation to dehydration and can be expected in animals with prerenal azotemia. Assessment of UspG is critical in determining the presence of renal failure in such cases. If urine cannot be collected from the dehydrated animal, fluid therapy should be initiated and the azotemia monitored. Oliguria is a relatively common feature of acute renal failure, particularly if the disease process involves obstruction of the nephron lumen with crystals, cellular debris, or proteinaceous casts. However, volume of urine produced by a patient in renal failure can vary greatly according to hydration status, diet, and the inciting cause. Urine production can be normal, increased, or decreased in renal failure. Renal failure is covered in detail in Chapter 34.

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Uremia

Uremia is defined as the constellation of clinical signs, impaired metabolic processes, and alteration of organ function that occurs as a result of failure to excrete waste products from the body via the kidneys and urine. Uremia may be the result of either acute or chronic renal failure, retention of urine in the body because of urinary tract leakage (e.g., bladder rupture), or both. In humans more than 100 retained toxins, including urea, guanidine, phenolic compounds, and phosphorus, are associated with the uremic process, and it can be assumed that similar magnitudes of toxins are present in uremic large animals.[33] The predominant clinical signs of uremia seen in large animals are depression and anorexia, along with progressive weight loss, polyuria, polydipsia, melena, and diarrhea. Oral erosions or ulcers, gingivitis, diffuse stomatitis, dental tartar, and halitosis may be evident on examination of the oral cavity. Gastroscopy may reveal gastric ulceration. Coagulopathy and platelet dysfunction make uremic patients prone to gastrointestinal hemorrhage and impaired clotting. Pulmonary edema and uremic encephalopathy may develop in severe cases. Uremia and renal failure are discussed in further detail in Chapter 34.

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• CHAPTER 11

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Alterations in the Skin*

Stephen D. White, Consulting Editor

MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

Pruritus, 179
Nodules, tumors, and swellings, 181
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General Approach to Diseases That Alter the Skin

It is important to remember that the skin has a limited repertoire with regard to its presentation; many diseases with various causes may manifest with similar lesions. However, certain patterns of response to disease are also recognized. In order to manage skin problems successfully, the veterinarian must use a systematic approach by obtaining a complete history, performing a thorough physical examination, and, when appropriate, using one or more simple diagnostic techniques.[1] The following sections discuss the materials and methods necessary to perform techniques commonly used to diagnose large animal skin disease.

History

To obtain a differential diagnosis list, the questions listed on the sample history form (Fig. 11.1) should be answered. Often it is helpful to repeat the questions to the owners at a later time or to give them a history form to complete at their leisure, which allows them greater opportunity to remember details relevant to the skin disease. The goals should be to determine the initial features of the skin disease, how the problem has progressed, and what factors have influenced its progression to the present state.

DERMATOLOGY HISTORY FORM

Owner_____ Date_____

Animal's name_____ Case #_____

Age of animal_____

Age when purchased_____ Age when skin problem started_____

Where on the body did the problem start?_____

What did the skin problem look like initially?_____

How has it spread or changed?_____

What season did the problem start?_____

Is the problem seasonal or year round?_____

If seasonal, what seasons is the disease present?_____

Does the animal itch?_____ If so, where?_____

Do any animals contacting the affected animal have skin problems?_____

Do any people in contact with the animal have skin problems?_____

Is fly control used?_____ If so, describe_____

Do any relatives of this animal have skin problems?_____ If yes, explain_____

List injectable, oral, or topical medications that have been used before and after onset of the disorder_____

Which medications were of benefit?_____

Which medications aggravated the condition?_____

Describe the environment where the animal is kept, including bedding_____

What is the animal fed?_____

Any additional information you feel is relevant to the skin disease_____

FIG. 11.1 Sample dermatology history form.

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Physical Examination

The diagrams and terms listed on the sample form (Fig. 11.2) may serve as a useful guide for recording the physical findings. The animal's overall condition should be assessed, and a general physical examination should be performed to determine if the disease is limited to the skin or if systemic signs of disease are also present. The distribution, morphology (e.g., papules, nodules, wheals, patches of alopecia), and size of skin lesions should be noted. Mucous membranes should also be examined, and the skin surface should be palpated to determine features not readily noted visually (e.g., crusts beneath the hair, dryness, ability to epilate hairs, presence of peripheral lymphadenopathy).

DERMATOLOGY PHYSICAL EXAMINATION FORM

Date_____

Distribution of lesions:

_____

_____

_____

Primary lesions (circle):

Macule	Patch	Papule
Pustule	Vesicle	Bulla
Wheal	Nodule	Tumor

Secondary lesions (circle):

Scale	Erosion	Excoriation
Fissure	Ulcer	Lichenification
Erythema	Alopecia	Hyperpigmentation
Crust	Comedone	

Pruritus_____ Epilation_____

Skin thickness_____ Skin tone_____

Hair coat_____ External parasites_____

Diagnostic workup:

Skin scrapings_____

KOH preparation_____

Dermatophyte culture_____

Acetate tape prep_____

Dermatophilus prep _____

Histopathology_____

Immunofluorescence_____

Microfilarial prep_____

Bacterial culture & sensitivity_____

Differential diagnosis:_____

Initial therapy:_____

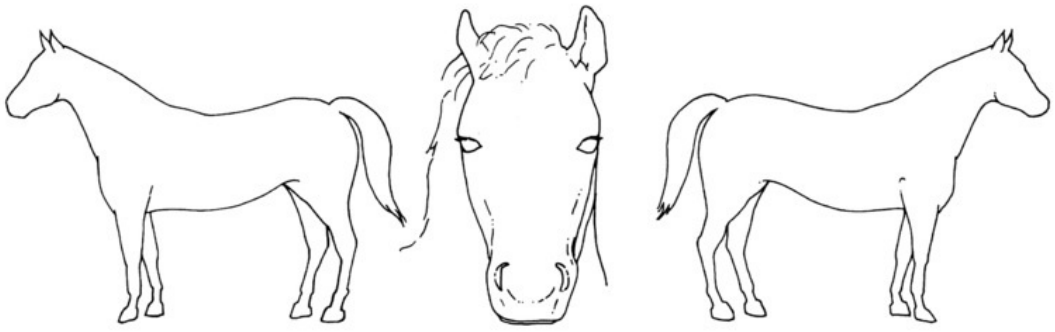


FIG. 11.2 Sample dermatology physical examination form.

The practitioner's goal should be to describe accurately the animal's clinical appearance in a written record for future reference.

Diagnostic Techniques

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For most of the techniques that follow, a good-quality microscope equipped with ×4, ×10, ×40, and ×100 (oil immersion) objectives is recommended.

Skin Scrapings.

Skin scrapings are used primarily to demonstrate microscopic ectoparasites, specifically mites. Scraping is a quick, simple, inexpensive diagnostic technique that is more useful in ruminants than in horses because equine mite infestations are relatively uncommon. The materials needed to perform a skin scraping are a sterile container, mineral oil, a medical-grade spatula (Fisherbrand Microspatula with Flat-Ended Blade, catalogue no. 21-401-20, Fisher Scientific, Pittsburgh, Pa.; www.fisherscientific.com), glass slides, and cover slips. Although a No. 10 scalpel blade may be used, a medical-grade spatula will not cut the skin in cases of sudden movement of the animal yet is just fine enough to be able to scrape deep enough to find *Demodex* species mites, if indicated. If the hair coat is thick, a small area should be clipped before scraping. Multiple superficial scrapings that cover large surface areas should be performed, as well as several scrapings covering a small area that are deep enough to create capillary oozing. The collected material should be placed in a container until it can be examined microscopically. Some of the sample can then be placed on a glass slide and finely dispersed in enough mineral oil to provide a confluent layer without air bubbles beneath a cover slip. The slide should be scanned systematically with the ×10 objective. If something of importance is noted, the ×40 objective can be used to examine the specimen in more detail.

Dermatophyte Culture.

The materials necessary to perform a dermatophyte culture include dermatophyte test medium, mosquito forceps, a medical-grade spatula, and sterile empty containers such as evacuated blood collection tubes. The forceps should be sterile, and each lesion to be sampled should be wiped gently with either water or isopropyl alcohol (there is some controversy as to which is better; the author uses water out of concern that the alcohol may inhibit fungal growth on the culture medium) to remove as many bacterial and fungal contaminants as possible and allow them to dry. Multiple small, scaling, and slightly crusted lesions should be sampled; the samples should be stored in individual containers. Broken hairs, scales, and crusts from the periphery of the lesions are collected (because dermatophytes cause peripherally expanding lesions). A spatula may be

useful for scraping scales and debris from the skin surface. The forceps are used to pluck broken hairs.

If the clinician's practice performs its own fungal cultures, the samples should be removed from the containers with a sterile forceps in a clean working area and gently pressed onto, but not buried beneath, the culture medium. The top of the culture dish or vial should be loosely replaced to allow sufficient ventilation for the culture to grow. Most dermatophytes grow at room temperature, except for some strains of *Trichophyton verrucosum* that require incubation at 37° C (98.6° F). The colony usually first appears in 5 to 7 days, although all cultures should be allowed to incubate for 3 weeks before a negative result is declared.

Dermatophyte test medium is an amber-colored Sabouraud's dextrose agar containing phenol red, a pH indicator, and several antibacterial and antifungal agents to inhibit growth of contaminant organisms. Dermatophytes preferentially use the protein in the medium as they begin to grow, producing alkaline metabolites that cause the medium to turn red. The dermatophyte colony is typically a white to beige, powdery to fluffy growth; the colonies are never dark colored. Most saprophytic (contaminant) fungi metabolize the carbohydrates first, producing acidic metabolites that do not change the color of the medium. It should be stressed that after the carbohydrate source has been depleted, saprophytes use the proteins and produce a red color change.

Positive identification of a dermatophyte is made in most instances if a white to beige, powdery to fluffy colony begins to appear on the medium at the same time or within 24 hours of the appearance of a red color change in the medium (Fig. 11.3, shown as the darker area in the figure). An infrequently encountered exception to this rule is growth of the saprophyte *Scopulariopsis brevicaulis,* a tan to light brown, smooth or mealy colony that produces a concurrent red color change in the medium. It is essential to check the cultures daily to determine if the red color change and colony growth occur nearly simultaneously. If any doubt exists about the type of colony growth, the sample should be submitted to a diagnostic laboratory for specific identification.

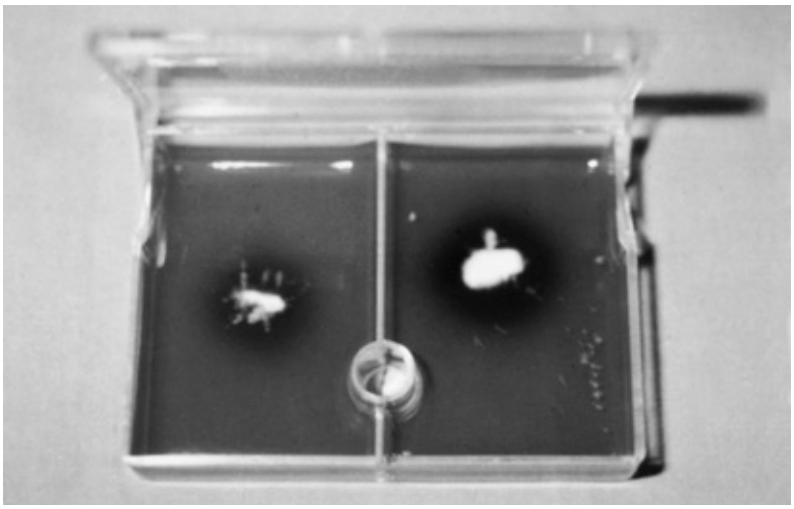


FIG. 11.3 **Positive result on dermatophyte culture. Growth of light-colored colony and simultaneous red color change are shown on dermatophyte test medium (right half of culture plate). Growth of dermatophyte on rapid-sporulating medium is shown on left half of culture plate.**

Potassium Hydroxide Preparation.

A potassium hydroxide (KOH) preparation may permit immediate diagnosis of dermatophytosis. However, examination of KOH preparations requires considerable experience because fungal elements may be easily overlooked (false-negative result) and numerous artifacts such as fibers, cholesterol crystals, or oil droplets may be mistaken for fungal elements (false-positive result). It is always advisable to perform a dermatophyte culture in conjunction with a KOH preparation.

The materials necessary to perform a KOH preparation include mosquito forceps, a medical-grade spatula, a sterile empty container, glass microscope slides, cover slips, a Bunsen burner, and clearing solution. As with a dermatophyte culture, it is important to sample several lesions to increase the chances of obtaining a diagnostic sample. Hairs and scales are collected from the periphery of the lesions with the mosquito forceps and the spatula. The samples are stored in the sterile container until a microscopic examination can be performed. A drop of the KOH clearing solution is placed on a glass slide, hairs and scales are added to the solution, and a cover slip is placed over the material. The slide should be scanned systematically with the ×10 objective for abnormal-appearing hairs with a fuzzy internal structure. If these features are noted, a higher-powered objective should be used for more detailed examination. A positive result with a KOH preparation demonstrates hyphae, which are usually

uniform in width and septate. Beadlike chains of arthroconidia may be seen as well (Fig. 11.4).

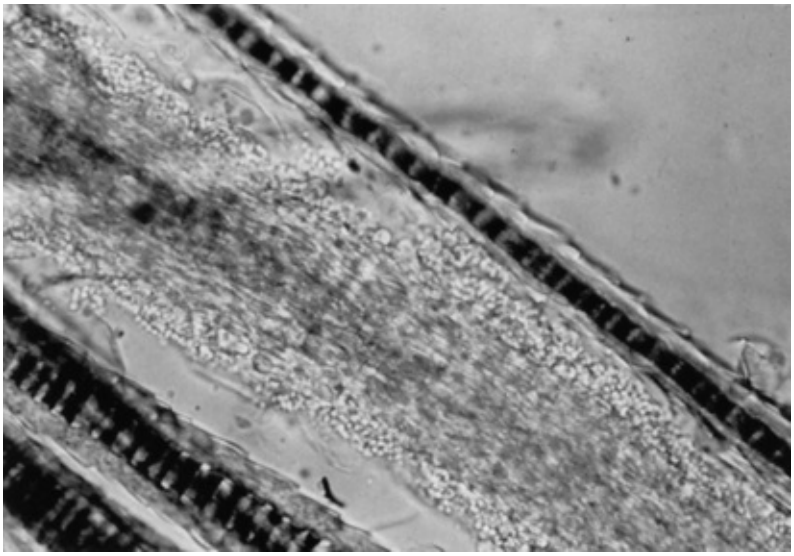


FIG. 11.4 **Positive result on potassium hydroxide (KOH) preparation. Note the small, spheric fungal elements (arthroconidia) on the hair shaft.**

The purpose of the clearing solution is to dissolve the hard keratin and bleach the melanin of the hair shaft so that the fungal hyphae and arthroconidia can be identified more readily. Care should be taken not to spill any clearing solution on the microscope because it can damage the lenses. Several types of clearing solutions are available. If 15% KOH is used, the slide should be heated for 15 to 20 seconds to facilitate clearing before examination. As an alternative, the preparation can be allowed to stand at room temperature for 30 minutes before viewing.

Acetate Tape Preparation.

Acetate tape preparations for parasites are used primarily to diagnose infection with *Oxyuris equi,* although they may also be used to diagnose *Chorioptes* species. The materials required to perform an acetate tape preparation include acetate (nonfrosted) tape, mineral oil, and glass microscope slides. A piece of the tape is pressed over several areas in the anal and perianal region when looking for *O. equi* or over an affected region that has been lightly clipped when looking for *Chorioptes* species. The tape is then placed with the adhesive side down on a line of mineral oil that was placed lengthwise on a glass microscope slide. The

purpose of the oil is to help clear the debris and facilitate examination of the preparation for parasites. The preparation is scanned with the ×10 objective for organisms.

Dermatophilus Preparation.

This test is used as an aid in identification of *Dermatophilus congolensis.* Crusts should be removed from the patient, and the excess hair should be carefully trimmed from the crusts with a small pair of scissors. The crusts are minced with the scissors and mixed with several drops of saline on a glass slide. After the crusts have softened in the saline for several minutes, they should be crushed with the tip of an applicator stick. The excess debris is removed, and the slide is allowed to air dry. The slide should then be heat fixed; stained with Gram, Giemsa, or Wright stain; and examined for the characteristic bacteria. *D. congolensis* organisms are gram-positive, branching, filamentous bacteria that divide horizontally and longitudinally, forming parallel rows of cocci (zoospores) that are commonly described as resembling “railroad tracks” (Fig. 11.5).

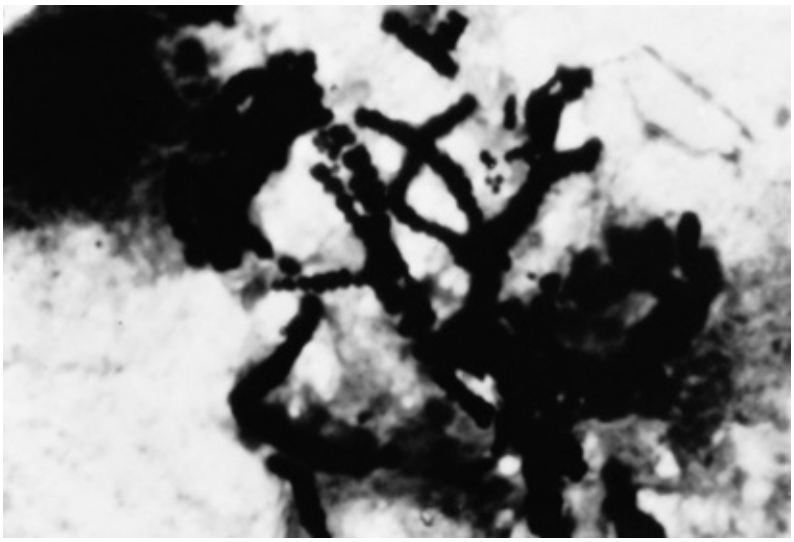


FIG. 11.5 Positive result on *Dermatophilus* preparation. *D. congolensis* is a large, gram-positive, filamentous bacterium that divides horizontally and longitudinally, forming parallel rows of cocci (zoospores) that are commonly described as “railroad tracks.”

Cytologic Studies.

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Cytologic studies are of value when dealing with crusts, scales, pustules, vesicles, nodules, or tumors. They can quickly indicate the presence of infectious organisms and provide a rough assessment of the spectrum of cell types present in a lesion (e.g., neoplastic, acantholytic, or inflammatory). The surface of the lesion should be gently shaved (if necessary); particular care must be taken not to rupture fragile pustules and vesicles or remove crusts. Crusts and scales may be evaluated by performing a superficial scrape with a spatula, placing the material on a dry (i.e., no mineral oil) microscope slide, heat fixing, and then staining with Gram, Giemsa, or Wright stain. Alternatively, acetate tape may be used to collect the material, and instead of placing the tape on a slide that has mineral oil (as is done when looking for parasites), the tape is placed on a slide on which several drops of the “blue” solution from the Wright stain have been placed. With either of these methods, the slide is scanned for areas of sufficient stain with the ×4 objective and then examined using the ×100 objective with immersion oil.

Cytologic evaluation of intact pustules and vesicles is best accomplished by gently opening an intact lesion with the tip of a sterile No. 15 scalpel blade or 25-gauge needle and smearing the contents on the surface of a glass slide. The slide should be air dried, heat fixed, stained with one of the previously mentioned stains, and examined. Nodules, tumors, and swellings are best evaluated by fine-needle aspiration. A 25- or 22-gauge needle on a 12-mL syringe is introduced into the mass, and negative pressure is applied. Several passes through the mass at different angles should be performed. After negative pressure has been released, the needle is removed from the mass. The needle is then removed from the syringe, the syringe is filled with air, and the needle is reattached. Alternatively, just the needle is introduced into the mass in several places and then attached to a syringe filled with air. The contents of the needle are pushed out onto glass slides, which are subsequently dried, fixed, and stained as described previously.

Biopsy for Routine Histopathologic Examination.

The following materials are necessary to perform a skin biopsy:

- 6-mm and 4-mm biopsy punches
- No. 15 scalpel blade

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- Sharp scissors
- Curved mosquito forceps
- Needle holders
- No. 2-0 or 3-0 nonabsorbable suture
- 2% lidocaine
- 3-mL syringe with a 22- to 25-gauge needle
- Tongue depressor or cardboard
- Gauze
- 10% buffered formalin

It is important *not* to surgically prepare a lesion that is going to be biopsied for histopathologic examination. Shaving and scrubbing remove crusts and epithelial tissue that may be important in reaching a diagnosis. Cutaneous infections caused by biopsies taken in this manner are extremely uncommon. If the clinician is concerned about infections, surgically prepare the site *after* the biopsy has been taken, before suturing.

Local anesthesia is sufficient for obtaining most skin biopsies. A 22- to 25-gauge needle is inserted at the margin of the lesion until the bevel is buried in the subcutaneous tissue beneath the lesion. The 2% lidocaine (0.5 to 1 mL) is injected, allowing 1 to 2 minutes for the anesthetic to take effect. Infiltration of the dermal or epidermal tissue with lidocaine should be avoided because this causes artifactual changes in the specimen.

Four techniques can be used to biopsy skin: the excisional, wedge, punch, and elliptic techniques. When the lesion to be sampled is a single nodule, the ideal biopsy technique is excisional because the lesion can be eliminated at the same time the histologic diagnosis is made. If the lesion is a tumor and too large to be excised, a generous wedge biopsy should be performed, which ideally extends from the margin to the center and includes the full depth of the lesion.

Most lesions can be sampled with a 6-mm biopsy punch. A disposable biopsy punch (Baker's Biopsy Punch, Chester A. Baker Laboratories, Miami, Fla.) can usually be used to obtain two or three biopsies before its edge is dulled and it must be discarded. The punch is placed directly over the lesion and rotated in a continuous circular motion while pressure is applied until the blade of the punch

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is in the subcutaneous tissue. If the punch has cut to a sufficient depth, when it is removed the tissue sample is free of the adjacent dermis and remains only loosely attached to the underlying subcutaneous tissue by a thread of connective tissue. A small pair of curved mosquito forceps is used to gently grasp the subcutaneous part of the biopsy and elevate it from the surrounding tissue. The specimen is then cut free with a pair of sharp scissors. It is important to avoid handling the epidermal and dermal parts of the sample during this procedure to minimize artifactual changes in the tissue sample. The sample is *gently* blotted to remove any surface hemorrhage and immediately placed in 10% buffered formalin for fixation. The site from which the sample was taken may then be cleaned with an antiseptic solution and closed with either two simple interrupted sutures or a cruciate stitch using No. 2-0 or 3-0 nonabsorbable sutures.

Although punch biopsies are convenient and easy to use, they are not appropriate for vesicular, bullous, and ulcerative lesions (unless the first two are small enough to be completely enclosed within the biopsy punch). For these lesions the method of choice is a surgical elliptical biopsy. The biopsy of vesicular and bullous lesions should encompass the entire lesion. Biopsy of samples of ulcerations should include abnormal tissue, the leading edge of the lesion, and normal tissue. Because an ulcer lacks epithelial tissue, the leading edge where epithelium remains may be the most rewarding in providing a histologic diagnosis. Thus the skin is biopsied so that the long axis of the ellipse crosses perpendicular to the leading edge of the ulcer (Fig. 11.6). It is important to mount surgical elliptical biopsies before placing them in formalin or they will curl during fixation, resulting in distortion of the histologic features during sectioning. To mount the specimen, the subcutaneous surface is placed on a small piece of a wooden tongue depressor or cardboard while gentle pressure is applied to the tissue so that it adheres to the surface. Then the specimen is placed in the formalin.

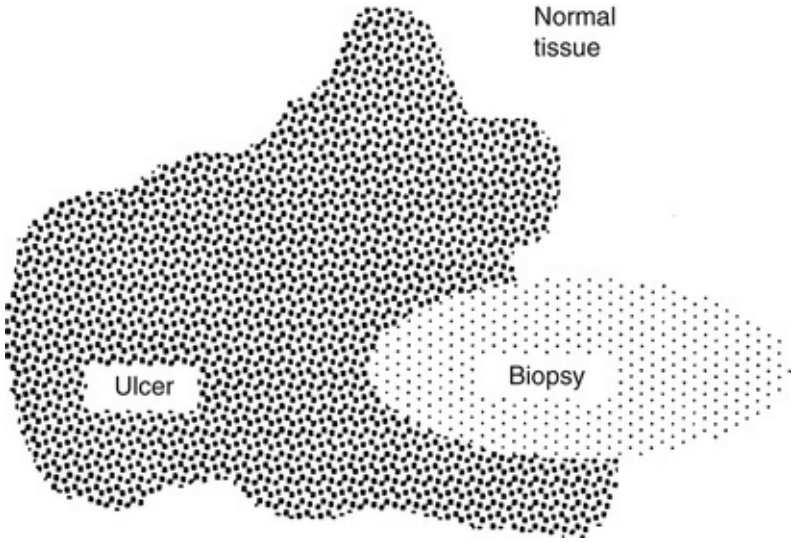


FIG. 11.6 An ulcerative lesion should be biopsied in an elliptical fashion, using a No. 15 scalpel blade, so that the long axis of the ellipse crosses perpendicular to the leading edge of the lesion.

Ideally biopsy specimens should be submitted to a veterinary histopathologist with special interest and training in dermatopathology. Submission of adequately biopsied specimens of properly chosen lesions is the clinician's responsibility. To further increase the chances of securing clinically valuable information from the biopsy samples, the clinician must also provide the pathologist with a concise history of the skin problem, physical findings, a description of the morphology and location of the lesions (and, if possible, images of the lesions), and a list of differential diagnoses. When the suspected clinical diagnoses are provided, the pathologist's efforts can be directed specifically toward confirming or ruling out those diagnoses.

Biopsy for Immunopathology.

Immunopathology may be used as an adjunct to conventional histologic testing when the clinician suspects that the patient has an immune-mediated skin disease. The two methods used are direct immunofluorescence, which requires a special medium for fixation (Michel's fixative), and immunoperoxidase techniques, which may be performed on the paraffin block prepared for the histopathologic study (i.e., the formalinized tissue section). The materials and the technique for biopsy for immunopathology are essentially identical to those for a routine histologic examination. Administration of corticosteroid medications within 3 weeks of testing may be associated with false-negative test results. It is advisable to bisect biopsy samples along their long axis, submitting

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half for direct immunopathology and half for histopathologic examination. It should be borne in mind that histopathology of the lesions, rather than immunopathology, is often the more accurate of the two methods in the diagnosis of autoimmune diseases; thus if faced with the choice (because of financial reasons or paucity of lesions), the clinician should always choose the former.

Microfilarial Preparation.

The microfilarial preparation technique is applicable to the diagnosis of cutaneous onchocerciasis in horses, stephanofilariasis in cattle, and elaeophorosis and parelaphostrongylosis of sheep and goats. After selecting the lesion to be sampled, a 6-mm punch biopsy is used to obtain the tissue sample in the same manner as for the histopathologic biopsy. The tissue should be split and half preserved in 10% buffered formalin for routine histologic studies. The other half is placed on a dampened gauze sponge in a tightly closed container until the preparation can be performed. A small piece of the tissue that includes the dermis is placed on a glass slide and minced with a razor blade; a few drops of nonbacteriostatic saline are added. Bacteriostatic saline should not be used because it kills the microfilaria and thus makes their identification more difficult. The specimen is incubated at room temperature for 15 minutes. The slide is then scanned with the ×4 objective along the margins of the tissue debris while the clinician searches for indication of motion in the saline. If the characteristic whiplash movement of the parasite is noted, a higher-powered objective should be used. If the preparation result is negative, a small amount of water is added to a Petri dish, the glass slide is rested on two wooden sticks above the water, and the cover is replaced on the dish. The preparation should be incubated for several hours or overnight and reexamined. The Petri dish helps prevent the sample from drying out.

Bacterial Culture.

The method of bacterial culture depends on the type of lesion. All haired lesions should be gently shaved. Nodules and tumors should be cultured by aseptically excising the lesion or by obtaining a generous wedge of the tissue. To prevent culture contamination by surface bacteria, the nodules should be gently shaved, washed with an antiseptic soap, and dried with a sterile gauze pad. A perilesional injection of 2% lidocaine is used to anesthetize the tissue. The sample is placed

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in a transport medium and sent to a microbiology laboratory for culture. A papular eruption (rash) is best cultured by obtaining a sterile 6-mm punch biopsy of skin. Crusts may be lifted up, and the underside should be cultured via a sterile culturette. Ulcerative lesions should not be cultured because any bacteria isolated are more likely to be opportunistic rather than primary pathogens. If the lesions are fluctuant (vesicles, pustules), the overlying skin can be opened gently with a No. 15 blade and some of the contents of the lesion transferred with the blade to the tip of a sterile culture swab. Although some older literature recommends not using sterile culturettes directly on the skin surface, due to concerns that nonpathogenic bacteria from the skin surface may be cultured,[1] the author has used this method of culturing papular eruptions or scale when a biopsy is not feasible.

Subcutaneous and Deep Fungal Culture.

Subcutaneous and deep fungal cultures should be performed on nodules, tumors, and swellings. The technique is identical to that described for bacterial culture of these lesions.

Polymerase Chain Reaction.

This molecular test has been shown to be helpful in diagnosing bacterial, mycobacterial, fungal, and viral infections, as well as determining the precise causative organism.[2-5] Further details on this method are found in Chapter 29.

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Pruritus

Definition

Pruritus is an unpleasant sensation that provokes the desire to scratch. It is designated a primary cutaneous sensation, along with heat, cold, pain, and touch. There are two broad categories of pruritus. Physiologic or spontaneous itch is a sharp, well-defined, pruritic sensation that is sufficiently intense to prompt scratching but does not result in significant irritation of the skin; this is a frequent daily occurrence in normal individuals. Pathologic itch is the less well-defined pruritus that occurs in a variety of primary and secondary skin disorders and in systemic diseases. It is an intense cutaneous discomfort that provokes vigorous scratching.[6]

Mechanisms of Pruritus

The investigation of the mechanism of pruritus has been primarily in laboratory animals and humans. It is presumed that much of this knowledge is applicable to other animal species. Pruritus is a distinct sensory quality transmitted from an arborizing network of nerve endings situated at or near the dermoepidermal junction. The sensation is carried to the spinal cord through small, unmyelinated C fibers. The fibers enter the dorsal root of the spinal cord and ascend in the ventrolateral spinothalamic tract through the posterior ventral nucleus of the thalamus to the sensory cortex. The pruritic sensation may be modified in the sensory cortex by behavioral factors or competing stimuli.[7,8]

Many physical and chemical stimuli can evoke pruritus, and many substances have been implicated as mediating pruritus in humans. Examples of these mediators, which are assumed to have importance in domestic animals as well, include the following[8]:

- *Histamine*. Histamine has been regarded as the classic mediator of pruritus. Histamine is present in mast cells in the dermis and in blood basophils. An intradermal injection of histamine produces pruritus

within 20 to 50 seconds. Because many pruritic disorders respond poorly to antihistamines given either therapeutically or prophylactically, histamine is not believed to be the sole mediator of pruritus.

• *Endopeptidases.* Examples include trypsin, papain, and kallikrein.

• *Prostaglandins (E series* and *endoperoxidases).* Prostaglandins induce pruritus by potentiating the release of proteases from keratinocytes and leukocytes and by lowering the threshold and increasing the duration of histamine-induced pruritus.

• *Endogenous opioid peptides.* Opiates may potentiate preexisting pruritus. The opiate antagonist naloxone hydrochloride has an attenuating effect on the histamine-induced component of pruritus.

• *Substance P.* Substance P is a neurotransmitter found in the central and peripheral nervous systems. When introduced intradermally, it elicits a pruritic response.

Many factors can potentiate existing pruritus. Neurologic factors such as boredom and fatigue can potentiate a pathologic itch and possibly transform a physiologic itch into a pathologic itch. Local axonal reflexes can potentiate pruritus; that is, if a second stimulus is applied to an area close to one that is pruritic, the second stimulus, irrespective of its type, is perceived as an itch. In addition, skin with chronic dermatitis has limited perception of stimuli, and any stimulus applied to the affected region may be perceived as either a burning sensation or an itch. This phenomenon is known as “conversion itch.” Secondary bacterial infections, vasodilatation, and inflammation result in a local increase in proteases that potentiate pruritus.[7]

Pruritus can be diminished by several nonpharmacologic mechanisms, the

most common being application of competing stimuli. Pruritus is a minor sensation compared with the other primary sensations of heat, cold, touch, and pain; thus local application of a competing stimulus to a pruritic area often suppresses the pruritic sensation. Scratching is an example of a competing stimulus. Scratching may relieve pruritus by disturbing the rhythm of afferent impulses traveling toward the central nervous system. An alternative theory is that scratching may cause transient damage to nerve fibers that convey the pruritic sensation. Unfortunately, the effect is short lived because the epidermal damage induced by scratching causes the release of epidermal proteases that may later increase the degree of pruritus. Centrally acting factors such as diversions or distractions can also diminish the perception of pruritus by providing competing stimuli directly to the cortex rather than locally to the skin.[7]

Approach to Diagnosis of Pruritus

Pruritus is the most common sign of cutaneous disease. Most often in large animals, it is caused by ectoparasites or a hypersensitivity reaction, or both (e.g., *Culicoides* hypersensitivity); it may also be caused by cutaneous bacterial or fungal infections (e.g., dermatophytes, *Malassezia* species) (Box 11.1). Because pruritus may be a feature of a more generalized disease process, it is important to take the patient's general health into account. Hypersensitivity reactions, which are commonly pruritic, may or may not be limited to the skin. For example, anaphylaxis is a life-threatening hypersensitivity reaction that may manifest as pruritus in its early stages. Other pruritic skin diseases include immune-mediated diseases such as atopic dermatitis or pemphigus foliaceus; direct irritation by chemicals; and photoactivated dermatoses. It is helpful to formulate a differential diagnosis by considering each of these broad categories of diseases and using historic information, other cutaneous signs, and appropriate diagnostic tests to narrow the list of differential diagnoses.

Box 11.1

Most Common Causes of Pruritus in Horses and Ruminants

Ectoparasites

Culicoides species (horses)
Other flying insects
Lice
Psoroptes cuniculi (goats)
Psoroptes ovis (sheep)
Sarcoptes scabiei (ruminants)
Chorioptes species (horses and cattle)

Hypersensitivity (Horses)

Atopic dermatitis

Infectious

Staphylococcal pyoderma (horses)
Dermatophytes

The following steps are a guide to the diagnosis of pruritus in the horse and ruminant:

1. History and physical examination (see Fig. 11.1).
    a. Determine if the pruritus is a seasonal or year-round problem. A seasonally recurrent pruritic disease tends to suggest either seasonal exposure to a parasite (e.g., lice in the winter, flies in the summer) or a seasonal environmental allergen (e.g., pollens) as the cause. Determine the level of fly exposure for the animal that is pruritic in the warmer months.
    b. Determine if the pruritus is generalized or localized and, if localized, what areas of the body are affected. For example, photoactivated dermatoses are limited to the white-haired regions.
    c. Determine if contact animals of the same and/or different species are affected or unaffected. The presence of multiple pruritic animals is suggestive of a contagious disease (e.g., dermatophytes, ectoparasites) or a disease of common exposure *(Culicoides).* A single pruritic animal among a

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group of unaffected animals is more likely to be experiencing a hypersensitivity reaction (drug or environmental).

d. Determine what topical and systemic medications were given to the animal both before and after the onset of the problem. Medications given before onset may be the cause of the pruritus, and those given after onset may interfere with the results of diagnostic tests.

e. Determine whether all the cutaneous lesions can be attributed to self-trauma or if primary cutaneous changes are present (e.g., wheals, nodules, pigmentary changes).

f. Determine whether, on close inspection, the coat shows evidence of small but grossly visible parasites such as lice or their eggs.

2. The most useful diagnostic tests are skin scrapings, acetate tape preparations, dermatophyte culture plus KOH preparation, *Dermatophilus* preparation, microfilarial preparation, biopsy for routine histopathologic examination, and intradermal testing (see Chapter 40).

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Nodules, Tumors, and Swellings

Definition

A *nodule* is a circumscribed, solid elevation larger than 1 cm in diameter that does not deform when palpated. Nodules extend into the deeper layers of the skin and are usually the result of cellular infiltrates in the dermis or subcutis. *Tumor* is a less precise term that usually refers to a neoplastic, nodular enlargement of the skin or subcutaneous tissue.[7] The term *tumor* is most commonly used to describe large nodular neoplasms. In addition to nodules and tumors, *swellings* include elevated lesions that pit with pressure (wheals) and fluctuant lesions (cysts and abscesses).

Mechanisms of Nodule, Tumor, and Swelling Formation

Nodular lesions can be subdivided into inflammatory and neoplastic lesions. Inflammatory nodules are composed of a massive mixed cellular infiltrate involving the dermis, the subcutis, or both. The inflammatory infiltrate may contain variable numbers of neutrophils, histiocytes, lymphocytes, plasma cells, and eosinophils. Cellular infiltration is usually stimulated by the presence of foreign material, and the nature of that material influences the composition of the inflammatory infiltrate. The foreign material may be infectious (parasite, bacteria, or fungi) or noninfectious (fibrin, crystalline material, or other inert substances). Grossly visible nodules develop as the masses of inflammatory cells accumulate in the tissues to phagocytize or “wall off” the foreign material. As the lesion enlarges, the dermis and subcutis are obliterated by the inflammatory infiltrate and the overlying epidermis may become atrophic, resulting in ulceration of the nodule's surface.

Most cutaneous and subcutaneous neoplasms form nodular lesions. Cutaneous and subcutaneous neoplasms may either arise from a cell type of the epidermis, dermis, or subcutis or less commonly metastasize from another tissue of origin. Cytologically and histologically, neoplasms are composed of a uniform population of pleomorphic cells with variable atypia. Neoplasms may stimulate a secondary inflammatory reaction.

Swellings include solid lesions such as nodules and tumors, as well as

urticaria, cysts, and abscesses. Urticarial lesions (wheals, hives) are often transient, localized, inflammatory lesions caused by a vascular reaction in the dermis in which vasodilatation results in fluid transudation with or without erythema. The fluid is not compartmentalized but dispersed evenly throughout the dermal tissue. The result is an elevated lesion that, unlike a nodule, pits with pressure and often dissipates within minutes to hours as the fluid is resorbed. Typically a sparse, perivascular infiltrate that is usually lymphocytic is seen, although the infiltrate may be dense and intermingled with eosinophils. Urticaria is usually well circumscribed, although with confluence the edema may assume geometric shapes.

A cyst (Latin for *sac*) is an epithelium-lined cavity containing fluid or semisolid material.[7] A cyst usually presents as an elevated, smooth, well-circumscribed, fluctuant mass. Cutaneous cysts are usually lined by adnexal epithelium (hair follicle, sebaceous or apocrine epithelium) and are filled with cornified cellular debris and sebaceous or apocrine secretions.

An abscess is a localized, fluid-filled, fluctuant lesion; if large enough, it may be ballotted. It results from a dermal or subcutaneous accumulation of the debris of dead cells and tissue elements liquefied by the proteolytic and histolytic enzymes elaborated by polymorphonuclear cells (e.g., pus). Abscesses most commonly result from localized infection, although they occasionally result from septicemia or may be sterile.

Approach to Diagnosis of Nodules, Tumors, and Swellings

Nodules, tumors, and swellings may arise from a variety of cutaneous disorders and, in rare cases, are signs of a systemic disease. The major categories of diseases that should be considered when forming a differential diagnosis include hypersensitivity reactions, infectious diseases, sterile inflammatory diseases, and neoplasia (Box 11.2). The primary systemic diseases that should be considered are amyloidosis, lymphosarcoma, and anaphylaxis.

Box 11.2

Most Common Causes of Nodules, Tumors, or

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Swellings in Horses and Ruminants

Horses

Infectious

Corynebacterium pseudotuberculosis
Habronema species
Sporotrichosis

Neoplasia

Sarcoid
Squamous cell carcinoma
Melanoma

Sterile, Nonneoplastic

Eosinophilic granuloma
Exuberant granulation tissue (proud flesh)
Urticaria (hives)

Ruminants

Infectious

C. pseudotuberculosis
Hypoderma species (warbles)
Sporotrichosis
Actinobacillosis
Actinomycosis

Neoplasia

Squamous cell carcinoma
Fibroma or fibrosarcoma
Epidermal inclusion cysts

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Sterile, Nonneoplastic

Urticaria (hives)

The following steps are a guide to the diagnosis of nodules, tumors, and swellings in horses and ruminants:

1. History (see Fig. 11.1). Pay particular attention to:
    a. Signalment. Older animals are at greater risk for cutaneous neoplasia (e.g., gray horses and melanomas). However, neoplasia is not restricted to older animals; equine sarcoids are frequently recognized in horses as young as 3 years of age.
    b. Number and progression of lesions. If one or only a few lesions are present, hypersensitivity to arthropod bites should be considered, particularly if there is rapid onset of the lesion. Rapid onset of generalized lesions such as urticaria suggests a differential diagnosis of drug, flying insect, environmental (pollen), or (rarely) food allergies.
    c. A recent history of systemic illness, which might suggest that the lesion is a bacterial abscess.
2. Physical examination (see Fig. 11.2). In particular:
    a. Determine by palpation if the cutaneous lesions are nodules or swellings.
    b. Inspect the lesion or lesions closely for evidence of cutaneous parasitism (ticks, breathing pores associated with *Hypoderma* larvae, yellow granules associated with cutaneous habronemiasis).
    c. Determine if the lesions are painful or pruritic (e.g., evidence of excoriations).
3. Perform fine-needle aspiration for cytologic studies.
4. Perform biopsy for histopathologic examination.
5. Perform bacterial culture and sensitivity.
6. Perform subcutaneous and deep fungal cultures.
7. Perform dermatophyte culture and KOH preparation.

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Ulcerations and Erosions

Definition

An *ulcer* is a cutaneous defect that results from a complete loss of the epidermis and usually part of the underlying dermis.[7] Ulcers often heal with scarring that is caused by destruction of dermal collagen. An *erosion* is a cutaneous defect that results from a partial loss of the epidermis that does not penetrate beneath the basal laminar zone. Because an erosion does not involve the dermis, it heals without leaving a scar. Because the epidermis is a cutaneous barrier to invading microorganisms, ulcers and erosions are often secondarily infected.

Mechanisms of Ulcer and Erosion Formation

Ulcers and erosions are secondary lesions. Primary lesions develop spontaneously and are a direct reflection of underlying disease. Secondary lesions evolve from primary lesions or are artifacts induced by excoriation or external trauma. Primary lesions that may lead to the formation of ulcers and erosions include fluid-filled lesions such as pustules and vesicles. Rupture of these fragile lesions results in epidermal destruction and erosion or ulcer formation. Swellings such as abscesses and cysts may also rupture, resulting in ulceration, but these primary lesions are more stable and often remain intact. Nodules and tumors may become secondarily eroded or ulcerated. As the nodule or tumor enlarges, the mass exerts pressure on the overlying epidermis, leading to epidermal atrophy and ultimately a break in epidermal confluence, resulting in ulceration and erosion. The most common cause of ulceration and erosion is pruritus, which induces excoriation and hence epidermal destruction. Ulcers and erosions may also result from external trauma such as epidermal destruction arising from mechanical, thermal, or chemical causes (Box 11.3).

Box 11.3

Most Common Causes of Ulcerations and Erosions in Horses and Ruminants

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Immune-Mediated

Adverse drug reaction
Contact irritant or hypersensitivity
Photosensitivity
Purpura hemorrhagica (horses)
Vasculitis

Infectious

Dermatophilus congolensis
Habronema species (horses)
Viral diseases (in ruminants; e.g., infectious bovine rhinotracheitis, vesicular stomatitis, bovine herpes mammillitis)

Neoplasia

Squamous cell carcinoma

Approach to the Diagnosis of Ulcerations and Erosions

To diagnose the cause of an ulcer or erosion, the clinician must first determine the primary lesion that resulted in ulceration and erosion. Ulcers and erosions occurring secondary to pustules and vesicles, to swellings such as abscesses and cysts, to nodules and tumors, to pruritus, and to external trauma must be differentiated. The list of differential diagnoses relevant to each of these groups of primary lesions is then considered.

The following steps are a guide to the diagnosis of ulcerations and erosions in horses and ruminants:

1. History (see Fig. 11.2)
    a. Determine if the animal is pruritic.
    b. Determine if the animal has been subjected to external trauma (mechanical, thermal, or chemical).

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   c. Determine what topical and systemic medications were given to or used on the patient before the onset of the problem. Use of certain topical agents may suggest a diagnosis of contact dermatitis, whereas administration of systemic medications may suggest a drug hypersensitivity.

2. Physical examination (see Fig. 11.2)
   a. Examine the oral cavity and mucocutaneous junctions for lesions. Oral or mucocutaneous lesions (or both) in the horse might suggest accidental ingestion of a vesicant or the rare diagnosis of bullous pemphigoid or pemphigus vulgaris. In a ruminant these lesions are often seen with viral infections.
   b. Look for evidence of excoriation, suggesting that the ulcerations and erosions have occurred secondary to pruritus.
   c. Look for evidence of primary lesions such as pustules, vesicles, nodules, tumors, or swellings, which may have preceded the ulcerations and erosions.
3. Biopsy for routine histopathologic examination
4. Biopsy for direct immunofluorescence testing

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Papules, Pustules, and Vesicles

Definition

A *papule* is a solid, circumscribed, elevated lesion up to 1 cm in diameter. Papules are essentially small nodules that do not extend beneath the dermis. A *pustule* is a fluctuant, circumscribed, elevated accumulation of pus (inflammatory cells and often necrotic debris) up to 1 cm in diameter (e.g., a small abscess). Pustules are frequently associated with infectious diseases, although sterile pustular diseases (such as pemphigus foliaceus) exist. A *vesicle* is a fluid-filled, acellular, circumscribed, elevated lesion up to 1 cm in diameter. A *bulla* is a vesicle that is larger than 1 cm in diameter. All these lesions can be either follicular or nonfollicular in orientation, depending on the underlying cause. Pustules and vesicles are rarely seen clinically because of their fragility and hence their susceptibility to rupture. Because papules are solid lesions, they are more stable and therefore more commonly encountered.

Mechanisms of Papule, Pustule, and Vesicle Formation

Papules usually form as a result of an infiltrate in the dermis, either cellular or noncellular. Cellular infiltrates may include inflammatory or neoplastic cells, although neoplastic papular lesions are relatively uncommon in large animals. Inflammatory infiltrates may be mixed, containing variable numbers of neutrophils, histiocytes, lymphocytes, plasma cells, and eosinophils, or one cell type may predominate. The composition of the inflammatory cells is influenced by the underlying cause of the papule, and the possible causes are extensive. Noncellular papular infiltrates include substances such as edema fluid, amyloid, and proliferative collagen, although these are relatively rare.

Pustules form as the result of an intraepidermal, subcorneal, or, less commonly, subepidermal accumulation of inflammatory cells. Infiltration of inflammatory cells, particularly polymorphonuclear leukocytes, leads to the release of proteolytic enzymes that liquefy tissue elements and result in the formation of a fluctuant lesion. Eosinophils, acantholytic cells, and infectious organisms may also be noted in a pustule, depending on the underlying cause. The stimulus leading to pustule formation is most commonly infectious,

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although pustules can result from noninfectious causes such as hypersensitivity reactions and autoimmune disease.

Vesicles form either at the dermoepidermal junction (subepidermal) or in the epidermis (intraepidermal) as a result of malformation or destruction of the basement membrane zone, or confluence of intercellular edema (spongiosis). Clinically, these types of vesicles are indistinguishable. Vesicles form as the result of certain viral diseases, during severe inflammatory reactions (allergic contact dermatitis), or with cutaneous physical damage (mechanical, chemical, or thermal). In pemphigus foliaceus or pemphigus vulgaris, autoantibodies bind to transmembrane proteins between the epidermal cells, causing disruption of epidermal intercellular attachments. The result is intraepidermal cleft formation that leads to vesiculation. In bullous pemphigoid, complement-activating antibodies bind to antigens in the basement membrane zone, causing degranulation of mast cells, chemotaxis of neutrophils and eosinophils, and release of tissue-destructive enzymes that injure the basement membrane zone. The result is loss of dermoepidermal adherence and vesicle formation.[7] Vesicles are transient, fragile lesions and therefore are rarely recognized clinically. If they are not destroyed by surface trauma, rapid infiltration by inflammatory cells often transforms a vesicle into a pustule.

Approach to Diagnosis of Papules, Pustules, and Vesicles

Although papules, pustules, and vesicles may look somewhat similar on a cursory physical examination, the clinician must differentiate among the three and determine which of the lesions are present. Examination with a hand lens may help. The differential diagnoses relevant to papules, pustules, and vesicles are not necessarily the same (Box 11.4). In all cases it is important to determine if disease is limited to the skin or if the animal's general health is compromised as well.

Box 11.4

Most Common Causes of Papules, Pustules, and Vesicles in Horses and Ruminants

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Horses

Hypersensitivity—Usually Papules

Culicoides species
Other flying insects

Infectious—Papules or Pustules

Staphylococcal pyoderma
Dermatophilus congolensis

Immune-Mediated

Pemphigus foliaceus—papules or pustules
Bullous pemphigoid—vesicles

Ruminants

Ectoparasites—Usually Papules

Sarcoptes scabiei
Psoroptes cuniculi (goats)
Lice

Infectious

Viral diseases (e.g., vesicular stomatitis)—vesicles
Staphylococcal pyoderma (goats)—pustules or papules

Papular lesions have the most extensive differential diagnoses:

- *Hypersensitivity reactions.* Parasitic hypersensitivities are the most common (e.g., *Culicoides* hypersensitivity), although drug and

(rarely) food hypersensitivities should also be considered. Many hypersensitivity reactions are pruritic.

• *Parasites.* Some species simply irritate the skin with their bites (e.g., horn fly [*Haematobia irritans*]) without inducing a hypersensitivity reaction.

• *Infectious diseases (bacterial, fungal, and viral).* Typically papules caused by infections have a follicular orientation.

• *Certain neoplastic diseases (papillomas or sarcoids).*

• *Uncommon causes* including autoimmune diseases such as pemphigus foliaceus and diseases of uncertain cause such as equine sarcoidosis.

Pustules are most commonly associated with bacterial infections, although fungi and, in rare cases, parasites (*Demodex* species) can cause pustule formation. Sterile pustular diseases are less frequently seen (drug eruptions, sterile eosinophilic folliculitis of cattle)[9] but should be included in the differential diagnoses. Vesicles are rapidly infiltrated by inflammatory cells and transformed into pustules. Diseases commonly associated with vesicles include viral diseases of ruminants, autoimmune diseases, contact dermatoses, and burns.

The following steps are a guide to the diagnosis of papules, pustules, and vesicles in horses and ruminants:

1. History (see Fig. 11.1)
    a. In particular, determine whether the lesions are pruritic, painful, or asymptomatic.
    b. Determine if contact animals of the same and/or different species are affected or unaffected. If contact animals are

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affected, a contagious problem should be considered: fungal (dermatophytosis), bacterial (dermatophilosis), viral (contagious ecthyma), or parasitic (*Culicoides* hypersensitivity).

c. Trace the temporal course of development. Rapid onset of lesions may suggest a hypersensitivity reaction.

d. Check for seasonality. A seasonal problem suggests a parasitic or hypersensitivity (pollens) cause. Lice are a problem in the winter, trombiculidiasis tends to occur in the fall, and most of the flying insects are present in the spring, summer, and early fall.

e. Determine what topical and systemic medications were given to or used on the animal before the onset of the problem. Use of certain topical agents may suggest a diagnosis of contact dermatitis, whereas administration of systemic medications may suggest drug hypersensitivity.

f. Determine if the animal has been subjected to external trauma (thermal or chemical).

2. Physical examination (see Fig. 11.2)

a. Gently palpate the lesions to determine if they are solid (papules) or fluctuant (pustules or vesicles).

b. Note if the lesions have a follicular orientation, suggesting an infectious cause.

c. Check for lesions involving the oral cavity and mucocutaneous junctions.

d. Look for evidence of excoriation, suggesting that pruritus is a feature of the disease.

e. Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.

f. Inspect contact animals for evidence of disease.

3. Skin scrapings of papular lesions
4. Cytologic studies
5. Dermatophyte culture and KOH preparation
6. *Dermatophilus* preparation
7. Bacterial culture and sensitivity
8. Microfilarial preparation
9. Biopsy for routine histopathologic examination

10. Biopsy for direct immunofluorescence testing

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Scaling and Crusting

Definition

Scale is a visible accumulation of fragments of the horny layer of the skin (stratum corneum); it represents the final product of epidermal keratinization.[7] The process of forming the stratum corneum is termed *cornification.* Histologically, scale is recognized as hyperkeratosis and can be subdivided into parakeratosis (cornification with nuclear retention) or orthokeratosis (cornification without nuclear retention). In some conditions parakeratosis and orthokeratosis may be present together. Grossly the scale varies in appearance. The color may be white, silver, yellow, brown, or gray. The consistency may be like that of bran flakes or powdery, coarse, greasy, or dry. Scale can be either loose or adherent to the skin or hair shafts.

Crusts are composed of variable amounts of serum; cells (leukocytes, erythrocytes, keratinocytes); fibrin; infectious agents (bacteria and fungi); debris; and/or medications. They often cover erosions or ulcerations. Heaped-up crusts are referred to as *vegetations.* On the basis of their histologic composition, crusts may be subdivided into cellular, serocellular, serous, and hemorrhagic types.

Mechanisms of Scale and Crust Formation

Scaling results from increased desquamation (exfoliation) of the stratum corneum. Exfoliation is the final stage of keratinization, the process by which the permanent population of cells of the basal layer of the epidermis divides, undergoes specific patterns of differentiation, and progresses toward the surface, where it is shed.[7,9] Excessive exfoliation and scale formation occur when the rate of keratinization is accelerated; when trauma to the surface of the epidermis (chemical, mechanical, or thermal) loosens the stratum corneum; or when the structures sustaining epidermal intercellular cohesion (such as transmembrane proteins) are destroyed, resulting in a loss of cohesion between epidermal cells.

Because crusts are composed primarily of serum and cells, their presence on the skin surface implies that vascular and epidermal permeability has increased to permit their formation. Serum and inflammatory cells are released into the tissues from the dermal vasculature and then cross the epidermis to the skin

surface either through erosions or ulcerations or by permeating between the intercellular spaces. The exudate dries on the skin surface, in combination with any medication or debris that was already present on the hair or skin, to form the visible crust. Desquamating keratinocytes may be swept up in the exudate and become part of the crusts. Bacteria frequently invade crusts after they have formed and will be noted on histologic examination, even though they may not be a factor in the pathogenesis. Fungal organisms, when present, are more likely to be important to the pathogenesis of the underlying disease process.

Approach to Diagnosis of Scaling and Crusting

The most important factor in determining the underlying cause of scale or crust formation in either a horse or a ruminant is to determine if the patient is pruritic and if some or all of the lesions are induced by self-trauma. If pruritus is a feature, the approach to diagnosis of pruritus should be used because all pruritic diseases can cause scale and crust formation. If the patient is not pruritic, the most important differential diagnoses include infectious diseases (particularly dermatophilosis and dermatophytosis), nutritional disorders, toxicities, autoimmune disease (pemphigus foliaceus), cutaneous filariasis, photosensitization, irritant contact reactions or burns, and diseases of uncertain cause (e.g., in equine patients, sarcoidosis, aural plaques, and primary seborrhea) (Box 11.5).[7,10] Viral diseases are important nonpruritic causes of scaling and crusting in ruminants, although they are usually associated with ulceration and erosion with involvement of the oral cavity and mucocutaneous regions. Rarely, congenital genetic diseases such as ichthyosis may cause excessive crusts and scale, as has been reported in cattle and sheep.

Box 11.5

Most Common Causes of Scaling and Crusting in Horses and Ruminants

Ectoparasites

Sarcoptes scabiei (ruminants)

Psoroptes cuniculi (goats)
Psoroptes ovis (sheep)
Lice
Chorioptes species (horses and cattle)

Infectious

Dermatophilus congolensis
Staphylococcal pyoderma
Dermatophytosis

Immune-Mediated

Pemphigus foliaceus (horses and goats)
Photosensitization (horses)

Nutritional

Zinc deficiency (ruminants)

The following steps are a guide to the diagnosis of scaling and crusting in horses and ruminants:

1. History (see Fig. 11.1)
    a. In particular, determine if the patient is pruritic.
    b. Determine if contact animals of the same and/or different species are affected. If they are, a contagious problem should be considered: fungal (dermatophytosis), bacterial (dermatophilosis), viral, or parasitic.
2. Physical examination (see Fig. 11.2)
    a. Look for evidence of excoriation, suggesting that pruritus is a feature.
    b. Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.
    c. Inspect contact animals for evidence of disease, suggesting a

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contagious cause.

3. Skin scrapings
4. Acetate tape preparations
5. Dermatophyte culture and KOH preparation
6. *Dermatophilus* preparation
7. Biopsy for routine histopathologic examination (careful histologic examination of scale and crusts is essential to the search for the underlying cause of their formation)
8. Microfilarial preparation
9. Biopsy for direct immunofluorescence testing
10. Bacterial culture and sensitivity

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Abnormal Coat Length and Density

Definition

Abnormalities in coat length and density can be subdivided into decreased coat length and density (alopecia, hypotrichosis) and increased coat length and density (hirsutism, hypertrichosis). *Hirsutism*, or excessive body hair, is far less common than alopecia, which is an absence of hair from areas where hair is normally present. *Alopecias* are usually classified as scarring (cicatricial) or nonscarring (noncicatricial). In cicatricial alopecias the hair follicles are destroyed, and hair loss is permanent because neogenesis of the hair follicle does not occur in an adult mammal. In nonscarring alopecias the hair follicles are retained; therefore the potential for regrowth remains. Both alopecia and hirsutism may be complete or partial, diffuse or focal, and congenital or acquired.

Mechanisms of Development of Abnormal Coat Length and Density

A basic understanding of the dynamics of hair structure and development is essential to an understanding of the mechanisms associated with pathologic changes in coat length and density.

The hair follicle and the sebaceous and apocrine glands are epidermal appendages. The hair follicle forms during fetal development as a downgrowth of epidermal cells toward a group of mesenchymal cells that ultimately become the dermal papillae. The sebaceous and apocrine glands begin as buds of epithelium from the sides of the developing hair follicle.

Hair is composed of keratin and is the product of the hair follicle. The hair shaft is the part of the hair that emerges from the skin surface. The hair root is the part of the hair in the follicle. The hair bulb is a knob of epidermal cells that attaches the follicle to the dermal papilla. Both the hair follicle and the shaft have distinct layers. There are two types of hair follicles: simple and compound. A simple hair follicle produces a single hair. A compound hair follicle produces multiple hairs with bundles of hairs sharing a common skin opening and a single follicle down to the level of the sebaceous gland. Below the sebaceous gland the follicle branches so that each hair has its own hair bulb. Horses and cattle have

only simple follicles. Goats and sheep have a mixture of simple and compound hair follicles (Fig. 11.7).[7,9]

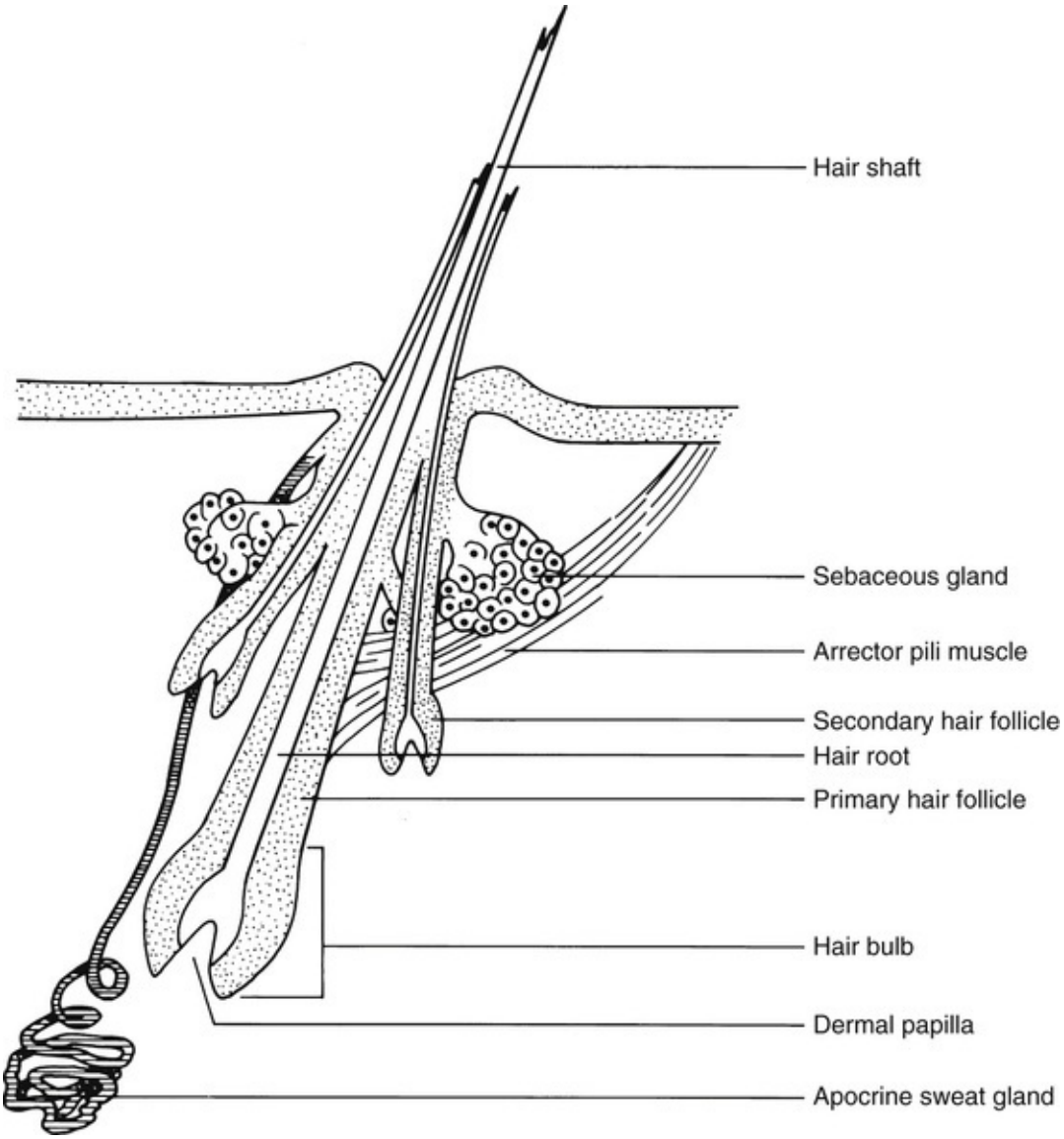


FIG. 11.7 Longitudinal section of a compound hair follicle.

The normal hair growth cycle is divided into repeating stages: anagen, catagen, telogen, and exogen, with the size and shape of the follicle changing during each stage (Fig. 11.8). The amount of time a follicle spends in each phase varies with the species, breed, individual, and body region. In addition, it is influenced by factors such as photoperiod, stress, and disease. Anagen is the active phase of hair growth. Catagen is the transition stage from the growing to

the resting state. Catagen is short, and the hair quickly enters the telogen phase, in which hair growth stops. As the follicle reenters anagen, a new hair grows up beside the old and dislodges it (exogen). The signal that stimulates progression from telogen to anagen is unknown.

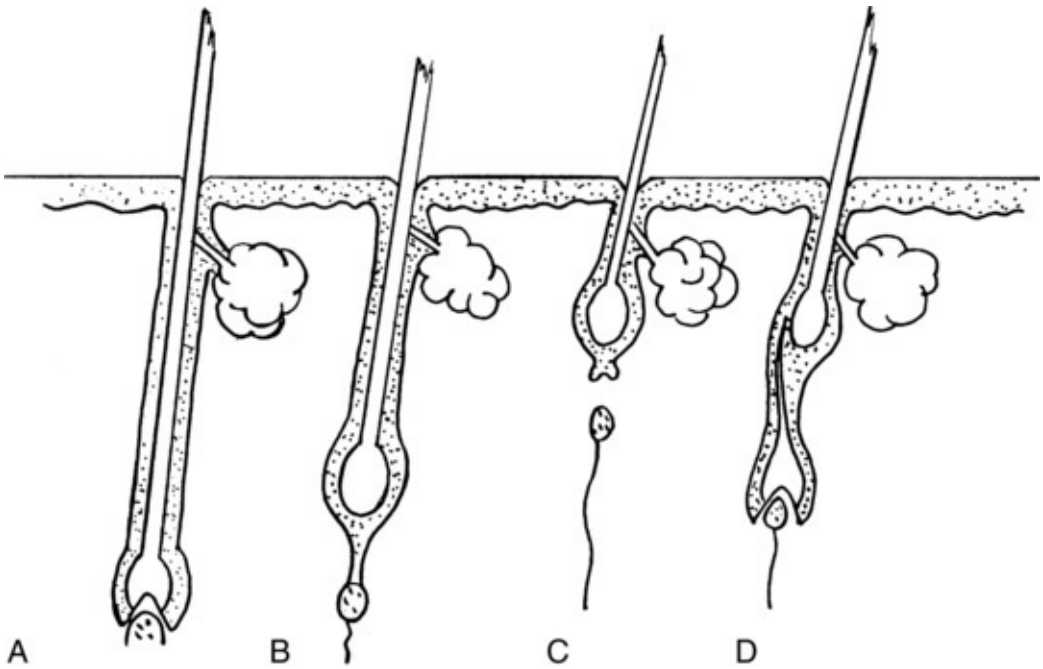


FIG. 11.8 **Stages of the hair growth cycle. A, Anagen. B, Catagen. C, Telogen. D, Early anagen/exogen.**

Coat abnormalities may result from a multitude of endogenous and exogenous factors that can modify the normal pattern of hair growth and development.

The length, density, and texture of the coat of a normal animal are determined genetically, and a variety of hereditary defects result in coat abnormalities. These defects may cause changes in hair length, density, or quality. Coat quality may be abnormal at birth or may become apparent sometime before 6 months of age. A given defect may alter the number of follicles present in the skin, or the number of follicles present may be normal but there may be genetic alterations in the way the hair is produced. Altered hair production may manifest as an increased or a decreased growth rate or as structural deformities that result in weak hair shafts that break easily.

Nutritional imbalances can affect growth and maintenance of the coat in various ways, depending on the species. Nutritional deficiencies may result in a shift of greater numbers of follicles into telogen, thus increasing shedding.

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Dietary carbohydrate and protein deficiencies reduce the length, diameter, and strength of hair. Supplementing the diet with carbohydrate and protein releases protein for keratin formation, provides energy to use protein, and maintains mitotic activity in the hair matrix. Fatty acid deficiencies affect lipid production in the skin, leading to a dry coat with increased fragility. A variety of vitamin and mineral deficiencies may also result in poor hair growth or quality.

Inflammatory skin diseases frequently result in hair loss. Infectious inflammatory processes such as dermatophytosis and pyoderma are usually directed specifically at the hair or hair follicle. Inflammatory processes directed elsewhere may still affect the hair follicle by sweeping it up as an “innocent bystander.”

Hormonal effects on hair growth are complex. Thyroid hormones, corticosteroids, sex hormones, melanocyte-stimulating hormone (MSH), adrenocorticotropic hormone (ACTH), growth hormone, and prolactin all affect hair growth. The effect of a single hormone may be modified in the presence of other hormones, and the importance or effect of any one hormone on hair growth may differ from species to species. Hormonal variations affect the hair coat quality and length by altering the period of time that hair follicles spend in any given part of the cycle, by influencing the rate of hair growth, and by inducing follicular atrophy. External factors such as changes in the photoperiod influence hair growth by altering hormonal levels.

Trauma to the skin is a frequent secondary cause of hair loss. Self-trauma induced by pruritus is the most common cause of alopecia. Hairs may be lost either from trauma to the hair shaft, resulting in breakage, or from trauma to the dermis, resulting in destruction of the hair follicle. In the former case, the hair regrows once the source of trauma has been removed. In the latter case, hair loss is permanent.

A variety of factors can result in hair loss by causing an abrupt shift of hairs into the telogen phase. Recognized causes of telogen effluvium include stress from high fever or severe illness and parturition.

Approach to Diagnosis of Abnormal Coat Length and Density

The differential diagnosis of abnormalities resulting in *increased* coat length and density is relatively limited and does not provide much of a diagnostic dilemma for the clinician. In the horse increased coat length and density is an acquired

abnormality associated with equine hyperadrenocorticism.[7] In ruminants defects are congenital and are the result of either an in utero infection (border disease) or a breed-specific hereditary defect.[9,11]

The differential diagnoses of *decreased* coat length and density are extensive. The initial step is to determine if the alopecia is congenital, implying a hereditary defect, or acquired. If the abnormality is acquired, the clinician must determine if it is a primary alopecia or secondary to another cutaneous abnormality such as pruritus or ulceration. If alopecia is the result of another primary cutaneous abnormality, the clinician should focus on the differential associated with that primary abnormality. Finally, to help provide a prognosis for hair regrowth, the clinician should biopsy to determine if the alopecia is scarring (cicatricial) or nonscarring (noncicatricial). Regardless of the underlying cause and its resolution, hair will not regrow with a cicatricial alopecia because by definition the hair follicle has been destroyed. In a noncicatricial alopecia the potential for hair regrowth remains if the underlying cause for hair loss can be identified and resolved (Box 11.6).

Box 11.6

Most Common Causes of Abnormal Coat Length and Density in Horses and Ruminants

Alopecia[a]

Dermatophytosis
Staphylococcal pyoderma (horses)
Alopecia areata (horses, cattle)
Drug reaction
Congenital hypotrichosis (cattle)
Onchocerciasis (horses)

Increased Coat Length

Pars intermedia pituitary dysfunction (horses)
Congenital hypertrichosis

[a]Alopecia without pruritus, crusts, or other clinical signs.

The following steps are a guide to the diagnosis of decreased coat length and density in horses and ruminants:

1. History (see Fig. 11.1)
    a. Determine whether the lesions are congenital or acquired. If they are congenital, determine if any related animals are affected and if the lesions have progressed since birth.
    b. If the alopecia is acquired, determine if the animal is pruritic and if other cutaneous lesions have been observed.
    c. Determine if the animal's diet is nutritionally complete.
    d. Determine if the animal has been exposed to any toxic substances.
    e. Determine if contact animals of the same and/or different species are affected. If contact animals are affected, a contagious problem such as dermatophytosis or dermatophilosis should be considered. Because feed and environment are also shared, dietary deficiencies and toxicities should be included in the differential diagnosis.
    f. Determine what medications have been given systemically or applied topically to the patient. Use of certain topical agents, along with a history of an inflammatory stage preceding or coincident with the alopecia, may suggest a diagnosis of contact dermatitis. Administration of systemic medications may suggest that the cause is a drug hypersensitivity.
    g. Determine if the animal has been subjected to any stresses that might provoke a telogen effluvium.
2. Physical examination (see Fig. 11.2)
    a. Check for evidence of disease in organ systems other than the skin. Does the animal appear thin and malnourished, suggesting hair loss related to a dietary deficiency? Is it febrile or suffering from a severe systemic disease, suggesting a telogen effluvium?
    b. Can the hairs be epilated readily from the coat? If not, hair loss may be caused by trauma (self-induced or external). If

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so, underlying nutritional, hormonal, or stress-related causes of alopecia are more likely.

c. Look for evidence of excoriation, suggesting that self-trauma is the cause of the hair loss.
d. Determine whether the lesions are generalized or localized, either to particular areas of the body or to certain hair colors (e.g., black hair follicle dystrophy). Note if the hair loss has a symmetric pattern.
e. Inspect the coat closely for small but grossly visible parasites such as lice or their eggs.
f. Inspect contact animals for evidence of disease.

3. Microscopic examination of the ends of affected hairs (squared or broken ends suggest that the hair loss is traumatically induced; tapered ends suggest an abnormality in the hair follicle, growth cycle, or an inflammatory process such as dermatophytosis)
4. Skin scrapings
5. Acetate tape preparations
6. Dermatophyte culture and KOH preparation
7. Microfilarial preparation
8. Biopsy for routine histopathologic examination (sagittal sections should be evaluated to determine the proportion of hairs in the various phases; for the presence or absence of inflammation and infectious organisms; and for evidence of scarring, which suggests a poor prognosis for hair regrowth; cross-sections of the biopsy specimen should be evaluated in noninflammatory alopecias to determine the number of hair follicles present per given area)

The following steps are a guide to the diagnosis of increased coat length and density in horses and ruminants:

1. Horses demonstrating increased coat length and density should be evaluated with appropriate laboratory tests for hyperadrenocorticism.
2. Lambs with increased coat length and density should be evaluated for evidence of border disease.
3. Cattle with increased coat length and density probably have hereditary hypertrichosis.

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Abnormal Pigmentation

Definition

The following terms are used when discussing pigmentation and pigmentary abnormalities.[7]

- *Melanin* is a brown-black, light-absorbing, insoluble pigment formed in many organisms by specialized cells called *melanocytes*.
- *Hyperpigmentation* is an excessive tissue deposition of pigment, usually melanin.
- *Hypopigmentation* refers to less than normal pigmentation and can be congenital or acquired.
- *Leukoderma (hypomelanosis)* is a partial or total acquired loss of melanin pigment from the skin. The term *vitiligo* also refers to an acquired loss of melanin from the skin but is often reserved for a specific type of leukoderma found in humans.
- *Leukotrichia* is an acquired loss of pigment from the hair.
- *Albinism* is a congenital lack of pigment in all tissues.

Mechanisms of Pigmentation Abnormalities

Cutaneous pigmentation results from the interaction of melanocytes and keratinocytes. The degree of “baseline” pigmentation observed in an animal is genetically controlled. Melanocytes are of neural crest origin and migrate from this site during embryologic development. They are present in nearly all tissues

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but occur in the highest numbers in the epidermis, mucous membrane epithelium, dermis, hair follicles, leptomeninges, uveal tract, and retina. Epidermal melanocytes are found in the basal cell layer, and each melanocyte is presumed to supply melanin to 10 to 20 keratinocytes. Melanin is usually found in the deeper layers of the epidermis, although darkly pigmented animals may have melanin throughout the epidermal layers.

Melanocytes produce membrane-bound organelles called *melanosomes* that fuse with vesicles containing the enzyme tyrosinase. Melanin, a black-brown pigment, is produced from tyrosine in the presence of tyrosinase and copper. It is deposited on the protein matrix in the melanosomes. Once melanosomes are fully melanized, they disperse to the periphery of the dendrites of the epidermal melanocytes and the dendritic tips are phagocytized by keratinocytes. Melanin is also synthesized and transferred to cells of the hair shaft during the anagen phase.[7]

In general, mechanisms associated with pathologic pigmentary disturbances in large animals are poorly understood. Hyperpigmentation results from increased amounts of melanin in the epidermis or dermis or both. The melanin may be present in melanocytes, keratinocytes, or melanophages (dermal macrophages that have phagocytized melanin pigment). Hyperpigmentation is an uncommon problem in horses because most normally have darkly pigmented skin. Hyperpigmentation may be reversible: with removal of the pigment-promoting stimulus, it tends to decline over time to the baseline level.

MSH may stimulate hyperpigmentation. MSH acts by affecting the levels of cyclic adenosine monophosphate (cAMP), resulting in increased tyrosinase activity. MSH also causes increased dispersion of melanosomes into melanocyte dendritic processes, where they are phagocytized by keratinocytes. Increased levels of ACTH, estrogens, progesterones, and androgens may also affect pigmentation, although the importance and mode of action in large animals are not clear.

Inflammation from a variety of causes and persistent cutaneous trauma from friction induce hyperpigmentation. Stimuli that may be factors in large animals include physical cutaneous damage (trauma, friction); chemicals (primary irritants, allergic sensitizers, photosensitizers); infectious agents; and nutritional disturbances.

Hypopigmentation is the result of a decreased amount of melanin in the epidermis or dermis (or both) and may be congenital or acquired (depigmentation). Possible mechanisms include decreased melanin production

(defects in melanocyte migration during embryogenesis or disorders of melanin synthesis), decreased dispersion of melanin granules (defective transfer of melanin to keratinocytes), and increased loss of melanin (accelerated desquamation of epidermal melanin, epidermal pigment loss caused by disruption of the basement membrane with resultant pigmentary incontinence, or immunologic destruction of melanin or melanocytes).

Several congenital genetic abnormalities that result in partial or total hypopigmentation have been identified in large animals. Albinism is a recessive condition in which a normal complement of melanocytes is present but a biochemical defect results in lack of ability to synthesize tyrosinase, so melanin is not produced. There is complete lack of melanin in all tissues in a true albino. Pseudoalbinism, in which there is ocular pigmentation, may be more common. Other genetic disorders include abnormal melanosome production and abnormalities in melanocyte development and migration from the neural crest (piebaldism).[7,9]

Acquired hypopigmentation (leukoderma) may be caused by several factors, including genetic abnormalities, trauma, inflammation, dietary imbalances, hormonal influences, and immunologic disorders. In some cases acquired hypopigmentation is idiopathic. Juvenile Arabian leukoderma appears to have a genetic basis because of the predilection for the Arabian breed and the occurrence of the disease in young animals.[10] Trauma and inflammation are the most common factors associated with depigmentation, particularly in the horse. The intensity of the inflammatory reaction may bear little relation to the degree of postinflammatory leukoderma. Dietary abnormalities, particularly molybdenum toxicity and copper deficiency, are associated with faded or washed-out coat color in food animals. Severe protein deficiency, such as occurs in kwashiorkor in humans, can lead to deficient melanin pigmentation. Melatonin is a hormone produced by the pineal gland that antagonizes MSH, thus causing decreased pigmentation, although an association with pathologic hypopigmentation in large animals has not been documented. Immunologic destruction of melanocytes has been documented in humans and is suspected of being a factor in acquired hypopigmentation in the dog but has not yet been documented in large animals. Idiopathic leukodermas are noted in all species.

Leukotrichia is the result of decreased amounts of melanin in the hair shaft. In most cases the pathogenesis is speculative, and the actual factors are unknown. Melanocytes in the hair bulbs can be affected independently of melanocytes in the epidermis, and leukotrichia without a coexistent leukoderma is common.

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Leukoderma, however, is usually accompanied by leukotrichia; thus when the two conditions are seen in combination, their pathogenesis is the same. Several leukotrichias that occur independently of leukoderma appear to be genetically induced because of breed predilections (e.g., reticulated leukotrichia of Quarter Horses).

Approach to Diagnosis of Pigmentation Abnormalities

The initial approach to diagnosis of pigmentary abnormalities is to determine whether the defect is congenital or acquired. Congenital pigmentary abnormalities are almost always caused by a genetic defect, whereas acquired abnormalities most commonly do not have a hereditary basis. If the abnormality is acquired, the clinician must determine if it is a primary pigmentary abnormality or if it is associated with some other pathologic change such as inflammation or trauma. If associated changes are a feature of the disease, differential diagnosis should focus on the initial pathologic changes (Box 11.7).

Box 11.7

Most Common Causes of Abnormal Pigmentation in Horses and Ruminants

Loss of Pigmentation

Burns and other trauma
Idiopathic leukotrichia and leukoderma (horses)
Copper deficiency (ruminants)

Increase in Pigmentation

Pruritus
Melanoma

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The following steps are a guide to the diagnosis of pigmentation abnormalities in horses and ruminants:

1. History (see Fig. 11.1)
    a. If the pigmentary change is congenital, determine if related animals are affected and if the lesions have progressed or regressed since birth. Take note of the patient's signalment and determine if that breed has been documented to have congenital pigmentary abnormalities.
    b. If the pigmentary change is acquired, determine if the animal has been subjected to cutaneous trauma that could result in posttraumatic pigmentary change. Determine if other cutaneous lesions in addition to the pigmentary changes have been observed (e.g., inflammation, ulceration).
    c. Determine if the animal's diet is nutritionally complete and balanced.
    d. Determine if the animal has been exposed to any toxic substances.
    e. Determine if contact animals of the same or different species are affected. Because feed and environment are shared, if contact animals are affected, dietary imbalances and toxicities should be included in the differential diagnosis.
    f. If the affected animal is a horse, determine what parasiticidal agents have been administered and if they are effective in the treatment or prevention of onchocerciasis.
2. Physical examination (see Fig. 11.2)
    a. Check for evidence of disease in organ systems other than the skin. Does the animal appear thin and malnourished, suggesting a pigmentary change secondary to a dietary deficiency or toxicity?
    b. If the patient's problem is hypopigmentation, examine the coat closely to determine if leukoderma, leukotrichia, or both are present.
    c. Look for evidence of other cutaneous lesions (inflammation, ulceration) that could result in postinflammatory pigmentary changes.
3. Microfilarial preparation

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4. Biopsy for routine histopathologic examination (affected, unaffected, and marginally affected areas should all be biopsied and labeled appropriately for histologic comparison).

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• CHAPTER 12

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Alterations in Sexual Function

Mats H.T. Troedsson, Bruce W. Christensen, Consulting Editors, Claudia Klein, Karen McDowell

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Alterations in Male Sexual Function

Stallions, bulls, rams, and bucks intended to be used as breeding animals need to

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have 1) normal genital organs, 2) the libido necessary to tease females and gain an erection, 3) the physical ability to mount and intromit the penis into the female's vagina, and 4) an adequate number of morphologically normal, motile spermatozoa in each ejaculate to be considered as satisfactory breeders under natural service conditions. Digression from normal sexual function in males is usually recognized clinically by changes in sexual behavior, abnormalities or diseases of the genital organs, or by a decreased pregnancy rate in dams bred. Subfertile males may be responsible for significant economic loss in the livestock industry.

Mechanisms of Altered Male Sexual Function

Sexual function may be altered by any of four major mechanisms: general physical abnormalities, abnormalities of the genital organs, decreased libido, and poor semen quality (Boxes 12.1 and 12.2).

Box 12.1

Causes of Altered Sexual Function in Stallions

Abnormalities of Penis

Balanoposthitis
Paraphimosis
Phimosis
Trauma
Hematoma, seroma
Abscess
Urolithiasis
Equine coital exanthema
Tumor (squamous cell carcinoma)
Cutaneous habronemiasis (equine summer sores)
Improper use of stallion rings

Abnormalities of the Prepuce

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Trauma
Foreign body
Preputial stenosis
Balanoposthitis
Tumor (squamous cell carcinoma, sarcoid)
Hematoma
Abscess
Cutaneous habronemiasis
Varicosities of the preputial vein
Equine viral arteritis

Abnormalities of Testicles, Spermatic Cord, and Scrotum

Testicular hypoplasia, atrophy
Testicular degeneration
Segmental aplasia
Testicular, scrotal neoplasia
Thrombosis of the spermatic cord
Torsion of the spermatic cord
Orchitis, epididymitis
Sperm, parasitic granuloma
Trauma
Hematoma, hematocele
Inguinal, scrotal hernia
Androgen, anabolic steroid effects
Cryptorchidism
Pseudohermaphrodism
Actinomycosis
Chemical irritation of the scrotum
Equine viral arteritis

Lack of Libido

Malnutrition, protein-calorie starvation
Testicular neoplasia
Lameness

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Trauma, foreign body of the prepuce
Overuse
Equine coital exanthema
Iodine deficiency
Penile trauma, hematoma, abscess
Neurologic dysfunction
Ocular deficiencies
Psychological impotence

Infertility

Segmental aplasia of the reproductive tract
Seminal vesiculitis
Blocked ampullae
Malnutrition, protein-calorie starvation
Testicular degeneration
Testicular hypoplasia, atrophy
Testicular neoplasia
Thrombosis of spermatic cord
Torsion of the spermatic cord
Urolithiasis
Vitamin A deficiency
Hemospermia
Lameness
Iatrogenic causes, including artificial insemination–associated infertility
Bacterial contamination of the semen
Trauma, foreign body of the prepuce
Balanoposthitis
Paraphimosis
Orchitis, epididymitis
Sperm, parasitic granuloma
Androgen, anabolic steroid use
Testicular trauma, hematoma, hematocele
Chromosomal abnormalities
Hermaphrodism, pseudohermaphrodism
Cryptorchidism
Ejaculation failure

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Frostbite
Abnormalities of spermatogenesis
Sperm storage dysfunction
Iodine deficiency
Heat stress, heat stroke
Inguinal, scrotal hernia
Psychological impotence

Box 12.2

Causes of Altered Male Sexual Function in Ruminants

Abnormalities of the Penis

Penile deviation (B)
Balanoposthitis
Paraphimosis
Phimosis
Penile-preputial adhesions (B)
Penile hair ring (B)
Penile trauma, hematoma, abscess
Urethral calculi
Ruptured urethra
Persistent penile frenulum (B)
Papillomatosis
Infectious bovine pustular vulvovaginitis (B)
Herpes vulvovaginitis (C)
Ovine ulcerative dermatosis (O)

Abnormalities of Prepuce

Abscess, cellulitis
Balanoposthitis
Trauma

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Foreign body
Preputial stenosis
Prolapsed prepuce
Ulcerative posthitis (pizzle rot)
Ovine ulcerative dermatosis (O)

Abnormalities of Testicles, Spermatic Cords, and Scrotum

Scrotal abscess (O)
Orchitis, epididymitis
Segmental granuloma, spermatocele
Testicular degeneration
Testicular hypoplasia, atrophy
Varicocele
Zinc deficiency
Testicular tumors
Brucellosis (B, O)
Testicular trauma, hematoma, hematocele
Inguinal, scrotal hernia
Cryptorchidism
Actinomycosis
Intersex in polled goats (C)
Pseudohermaphrodism (C)
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)

Lack of Libido

Malnutrition, protein-calorie starvation
Ulcerative posthitis
Vertebral osteophytosis, spondylosis (B)
Zinc deficiency
Lameness
Trauma, foreign body of prepuce
Prolapsed prepuce (B, O)
Loss of penile sensation (B)
Penile hair ring (B)

Corpus cavernosum vascular shunts (B)
Iodine deficiency
Psychological impotence
Penile trauma, hematoma, abscess
Persistent penile frenulum (B)
Epididymitis, orchitis (O, C)
Intersex in polled goats (C)
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)
Obesity
Spondylosis (B)

Infertility

Testicular degeneration
Orchitis, epididymitis
Trauma, foreign body of the prepuce
Paraphimosis
Heat stress, heat stroke
Penile trauma, hematoma, abscess
Segmental aplasia
Vesicular gland adenitis
Sperm granuloma, spermatocele
Malnutrition, protein-calorie starvation
Testicular hypoplasia, atrophy
Ulcerative posthitis (pizzle rot)
Urolithiasis
Varicocele
Vitamin A deficiency
Zinc deficiency
Manganese deficiency
Iodine deficiency
Hemospermia
Lameness
Iatrogenic, including artificial insemination–associated infertility
Balanoposthitis
Testicular trauma, hematoma, hematocele
Cryptorchidism

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Dermatophilosis
Frostbite
Inguinal, scrotal hernia
Psychological impotence
Hermaphrodism, pseudohermaphrodism
Short retractor penis muscle in Dutch Friesian bulls (B)
Abscess of scrotum (O)
Prolapsed prepuce (B, O)
Penile deviation (B)
Penile-preputial adhesions (B)
Vertebral osteophytosis, spondylosis (B)
Testicular tumors (B, O)
Bulls born co-twin with freemartins (B)
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)
Infectious bovine rhinotracheitis–contaminated semen (B)
Infectious bovine rhinotracheitis–associated dermatitis (B)
Bovine virus diarrhea–contaminated semen (B)
Chromosomal abnormalities (B, O)
Loss of penile sensation (B)
Penile hair ring (B)
Bovine herpesvirus type 1
Brucellosis
Corpus cavernosum vascular shunt (B)
Urethral fistula (B)
Cold weather–associated infertility (B)
Papillomatosis, warts (B)
Abnormalities of spermatogenesis
Micropenis, penile hypoplasia (B)
Persistent penile frenulum (B)
Ovine ulcerative dermatosis (O)
Congenital phimosis (O)
Overuse
Chorioptic mange (O, C)
Hexachlorophene toxicity
Gynecomastia (C)

B, Bovine; *C*, caprine; *O*, ovine.

The male must be mobile enough, especially in a pasture breeding program, to locate, tease, mount, and breed estrual females successfully. Musculoskeletal abnormalities may limit reproductive ability or desire. Hindlimb conformation defects in bulls and rams, degenerative joint disease involving the hock in stallions, and foot problems in rams are examples of conditions that may cause enough discomfort to interfere with the normal breeding process or prevent normal mobility, impairing reproductive performance.[1–3]

Congenital or acquired abnormalities of the genital organs, including the penis, prepuce, scrotum, testicles, spermatic cords, or accessory sex glands, can lead to altered sexual function or infertility. Congenital abnormalities such as persistent penile frenulum and penile deviations in bulls may prevent normal intromission.[4] Acquired lesions such as a penile hematoma caused by rupture of the tunica albuginea of bulls at time of service may limit sexual function by causing paraphimosis, adhesions, or sensory nerve damage.[5]

Libido is an essential component of breeding performance but may be difficult to measure during a breeding soundness examination and cannot be evaluated if semen is collected by electroejaculation. Libido has been demonstrated to be an inherited behavioral trait in bulls.[6]

Semen volume, concentration of spermatozoa, percentage of progressive motility, and percentage of morphologically normal spermatozoa are semen parameters commonly measured during a breeding soundness examination. Fertility in stallions can be predicted with high accuracy using a combination of motility, morphology, viability, oxidation level, acrosome integrity, DNA integrity, and hypoosmotic resistance.[7,8] Abnormalities of semen quality associated with decreased fertility in bulls include spermatozoa morphology and, to a lesser degree, motility.[2,4,9]

Approach to Diagnosis of Altered Male Sexual Function

A complete breeding soundness examination and history should be obtained, including number of females bred each year, conception rates, breeding methods (natural service or artificial insemination), and results of previous breeding soundness examinations (Box 12.3). A medical or health history, including medications, vaccinations, and previous illnesses, should be obtained. The animal should be given a general physical examination. Hindlimb conformation and the presence of degenerative joint disease, laminitis, foot abscesses, abnormal foot wear, corkscrew claw defect, weak pasterns, postleggedness,

sickle hock, interdigital fibromas (bulls), foot rot, ulcerative dermatitis and pizzle rot (rams), and caprine arthritis-encephalitis (CAE) (bucks) should be noted. An ophthalmologic examination should be done to ensure that the animal has adequate vision and that no significant pathologic condition is present. A special emphasis is placed on identification of squamous cell carcinoma and pinkeye *(Moraxella bovis)* and corneal lesions in bulls. Range animals showing weight loss and a decline in reproductive performance should be given an oral examination, and the parasite control program should be evaluated.

Box 12.3

Outline of Breeding Soundness Examination for Diagnosis of Male Infertility

1. Species, breed
2. Age
3. Month of evaluation
4. Breeding history
5. Physical examination
    a. General
    b. External genital organs
        (1) Penis
        (2) Prepuce
        (3) Testes
        (4) Scrotum
        (5) Epididymides
    c. Internal accessory organs
        (1) Ampullae
        (2) Seminal vesicles
6. Libido
7. Mating ability
8. Semen evaluation
    a. Motility
    b. Concentration
    c. Morphology

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    d. Volume
    e. Viability
    f. Additional fluorescent markers
9. Microbiologic culture
10. Serologic tests

The external genital organs should be examined carefully. The penis of the stallion is easiest to examine after an erection is obtained by teasing to an estrual female. In ruminants manual palpation of the penis per rectum or by use of an electroejaculator is suitable in many cases. The penis should be normal in size and shape and free of lesions. In bulls, deviations or other abnormal configurations such as corkscrew penis may occur with use of an electroejaculator and therefore cannot be considered abnormal.[5] Rams and bucks should be carefully examined for abnormalities of the urethral process, including the presence of calculi.[10] The lesions most often observed on the penises of stallions are squamous cell carcinoma and cutaneous habronemiasis.[11,12]

The prepuce should also be examined for lesions. Strictures of the preputial orifice may increase the risk of phimosis or paraphimosis. Bulls of the *Bos indicus* breeds often have a pendulous prepuce that is predisposed to traumatic injury, abscessation, stricture formation, and eversion.[5,13] Ulcerative posthitis (pizzle rot) caused by *Corynebacterium renale* in rams on a high-protein diet is the most common lesion of the prepuce.[14]

The scrotum, testicles, and spermatic cords should be examined for size, consistency, symmetry, and presence of lesions. Two scrotal testicles should be present, each smooth, resilient on palpation, and freely movable. Testes volume and consequently the amount of testicular parenchyma present are highly correlated with daily sperm production in all species. Each gram of testicular tissue should produce 15 to 20 million sperm per day. In ruminants, scrotal circumference has been determined to be highly correlated with testes weight or volume. Yearling beef bulls should have a scrotal circumference of 30 cm or more, depending on the animal's age and breed.[9] In stallions, measurements of total scrotal width or, more accurately, testicular volume have been evaluated and correlated to potential daily sperm production. Mature stallions should have a scrotal width of at least 8 cm. Testicular volume in stallions can be determined by the following steps[15]:

1. Measure the length (L), width (W), and height (H) of each testicle.
2. Volume of each testicle can be determined using the formula:

$$\text{Testicular volume } (\text{cm}^3) = 0.5233 \times \text{L} \times \text{W} \times \text{H}$$

3. Add the volume of each testicle to obtain total testicular volume.
4. Expected daily sperm production (DSP) (in billions of sperm per day) can be calculated using the formula:

$$\text{Expected DSP} = 0.024\ (\text{Total testicular volume in } \text{cm}^3) - 1.26$$

The epididymides should be palpated for position, size, and presence of lesions. The most common palpable abnormality in rams is epididymitis caused by infection with *Brucella ovis*, *Actinobacillus seminis*, or *Histophilus ovis*.[10,14,16] A definitive diagnosis is obtained by isolation of bacterial organisms in the semen and serologic testing.

Diseases of the accessory sex glands are diagnosed most frequently in bulls and stallions. Vesicular gland adenitis in both species is clinically recognized by the presence of leukocytes in the semen and enlargement, induration, and loss of lobulation noted during palpation and ultrasonographic examination of the glands per rectum.[17,18] Culture of the ejaculate is indicated to guide antibiotic treatment. Medications in the stallion may be delivered directly into the glands via urethroscopy. In stallions, azoospermia can be caused by bilateral sperm granuloma blockage of the ampullae. Lower than normal levels of alkaline phosphatase in the clear ejaculate will indicate a lack of epididymal contribution to the ejaculate. Transrectal ultrasound evaluation of the ampullae will demonstrate dilated ampullae, filled with hypoechoic fluid or mixed echogenicity. Treatment involves a combination of gentle transrectal massage, low-dose prostaglandin or oxytocin administration, and frequent semen collections in an effort to dislodge the granuloma. When the blockage is cleared, the first ejaculate will contain a large number of dead sperm with abnormal morphology. Subsequent semen collections should show improved semen quality. Frequent continuing semen collections will likely be necessary to prevent recurrence.

Libido and the ability to mate should be assessed after the physical examination. The male should be teased to a female in estrus. Interest in and

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interactions with the female and ability to gain an erection, mount, intromit the penis into the vagina (or into an artificial vagina), and ejaculate are noted. Libido and mating ability cannot be evaluated when using an electroejaculator to collect semen from ruminants. Tests for “serving capacity” have been described for bulls.

The evaluation of semen quality is a major part of the breeding soundness examination. Semen from stallions is collected into an artificial vagina. Semen from ruminants may be collected into an artificial vagina or obtained by use of an electroejaculator. Semen collected by electroejaculation usually has a higher volume and a lower concentration of spermatozoa than semen collected by an artificial vagina. Semen quality in ruminants is scored primarily on the basis of motility and morphology.[9] Evaluation of semen from stallions should include determination of volume, concentration, motility, and morphology. The motility of the spermatozoa should be evaluated microscopically on raw and extended semen immediately after collection. In ruminants, bright-field microscopy at ×40 to ×125 magnification is used to detect mass motion or swirling to evaluate gross motility. Changes in sperm concentration, progressive motility, or speed of progression of spermatozoa will decrease or eliminate the swirling effect. Phase contrast microscopy at ×200 to ×500 is used to evaluate motility of individual spermatozoa. Computer-assisted semen analysis (CASA) is commonly used at larger reproduction facilities.

Concentration can be measured by use of a hemocytometer, calibrated spectrophotometer or densimeter, CASA system, or image cytometry (e.g., NucleoCounter, ChemoMetec, Allerod, Denmark). Morphology can be evaluated microscopically, using stained semen samples (e.g., eosin-nigrosin stain or a variety of bright-field stains), phase-contrast, or differential interference contrast microscopy.

Ejaculates from stallions may be collected once daily for 5 to 10 days until daily sperm output (DSO) is achieved to fully evaluate potential fertility.[19] However, this is time consuming, labor intensive, and expensive. Consequently, most stallions are evaluated by the collection of two ejaculates 1 hour apart, with the total number of progressively motile, morphologically normal spermatozoa in the second ejaculate most critically evaluated.

The age of the stallion or male ruminant being evaluated for potential fertility may influence the semen parameters, measurements of the testicular size, mating ability, and libido. Puberty is attained in the stallion at 18 months, in the bull at 9 to 12 months, and in the ram and buck at 7 to 8 months.[20] Semen parameters and

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testicular size continue to increase until sexual maturity is reached. The season of the year in which the fertility evaluation is done may affect semen parameters in the stallion, ram, and buck.

Microbiological samples should be routinely collected when evaluating infertility in the stallion and when evaluating high-risk populations of bulls. Smegma samples should be collected from the prepuce of bulls and cultured for *Trichomonas foetus* and *Campylobacter fetus.* Swabs from the preejaculate and postejaculate urethra, semen, fossa glandis, and prepuce of stallions should be cultured for potentially pathogenic bacterial organisms, especially *Taylorella equigenitalis* (requires specific culture techniques), *Escherichia coli, Streptococcus zooepidemicus equi, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae.*[11] The semen of rams should be cultured for *B. ovis, A. seminis,* and *H. ovis.*[10,14,16] Serologic testing for exposure to equine arteritis virus (EAV), the causative agent of equine viral arteritis (EVA), is important for breeding stallions. Determination of negative serologic status should be required before vaccination against the virus may be performed.

Other tests that are occasionally performed to evaluate male reproductive function, health, or pathology include hormone analysis, chemical evaluation of seminal plasma, transmission electron microscopy of semen, karyotype, sperm chromatin structure assay, urethral endoscopy (stallion), and testicular biopsy.

After summarizing the results of the entire breeding soundness evaluation, stallions and male ruminants may be categorized into classifications such as satisfactory, questionable, or unsatisfactory. In bulls a fourth category of "decision deferred" may be used for young prepubertal bulls or mature bulls that have recently experienced a transient disturbance in spermatogenesis.

It must be emphasized that the breeding soundness examination is a measure of potential fertility.[21] True fertility can be determined only by the results of breeding trials or by conception and live birthrates in dams bred.

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Cyclic Irregularity

Claudia Klein

Cyclic irregularities become evident in the display of irregular estrous cycles (i.e., an abnormal interval from one estrus to the subsequent estrus). Irregular estrous cycles can be physiologic, such as during the transition period in seasonal breeders; can be pathologic such as a sequel to endometritis; or may be an artifact, such as failure in estrus detection (Box 12.4).

Box 12.4

Causes of Cyclic Irregularity in Mares

Common Causes

- Transition season
- Erroneous heat detection
- Diestrus ovulation
- Intrauterine therapy
- Diestral endometrial biopsy
- Pneumovagina
- Endometritis
- Pubertal cycles
- Early embryonic death
- Spontaneous corpus luteum prolongation
- Endophyte-infested fescue
- Cervical dilation

Less Common Causes

- Urovagina
- Rectovaginal fistula
- Ovarian tumors
- Pyometra

Persistent follicles
Split heats
Endotoxemia
Hemorrhagic anovulatory follicles
Old age
Use of Deslorelin implant

Uncommon Causes

Contagious equine metritis
Corpus luteum inadequacy
Anabolic steroids
Progesterone therapy
Phosphorus deficiency
Sex chromosome anomalies
Administration of oxytocin during days 7 to 14 of the estrous cycle

Cattle

Irregular estrous cycles in the cow may result from a number of factors (Box 12.5). Detection of heat in cattle is challenging given that the average duration of estrus is 18 hours and in many cows may be appreciably shorter. Failure to detect heat in intensively managed herds bred by artificial insemination is common and is one of the most important management factors contributing to a perceived abnormal estrus interval.[22] Missed heats should be expected if the heat intervals approximate multiples of 21 days, the normal cycle length. Errors in estrus detection are further indicated when 1) more than 10% of the interestrus intervals are 3 to 17 days or 25 to 35 days long, 2) more than 5% of the cows have two artificial inseminations within 3 days, or 3) cows are calving early or are further in gestation than predicted from the last breeding when examined for pregnancy. Seventy percent of cows should have an interestrus interval of fewer than 30 days, and 60% should be in the range of 18 to 24 days. The ratio of 18- to 24-day cycles to 38- to 46-day cycles should be 5 : 1.[23] Evaluation of heat detection methods is important in artificial insemination programs. Cows need to be observed at least twice daily for signs of estrous behavior. Heat detection aids such as tailhead chalking (will be rubbed off), adhesive heat pads (will change color), and pedometry (record an increase in activity) are indispensable tools for

efficient estrus detection. Especially pedometry can detect estrus accurately, is least labor intensive, and through a software program generates daily lists of cattle with increased activity.[24]

Box 12.5

Causes of Cyclic Irregularity in Ruminants

Common Causes

Erroneous heat detection
Endometritis
Intrauterine therapy
Cystic ovaries
Heat stress
Leptospirosis
Infectious bovine rhinotracheitis (IBR) (B)
Bovine virus diarrhea (BVD) (B)
Campylobacteriosis
Trichomoniasis
Embryonic death after maternal recognition of pregnancy

Uncommon Causes

IBR- or BVD-infected semen
Bluetongue-infected semen
Zearalenone toxicity
Ovarian neoplasia
Corpus luteum inadequacy
Copper deficiency (O, C)
Molybdenum deficiency (O, C)
Iodine deficiency
Phytoestrogen toxicity
Segmental aplasia of the uterus

B, Bovine; *C*, caprine; *O*, ovine.

Silent heat, which is the lack of cycling cows to express estrous behavior (silent ovulation), occurs most commonly in the immediate postpartum period. More than 50% of cattle display a silent heat on their first ovulation postpartum with the incidence declining thereafter.[25] This may be related to insufficient progesterone priming of the behavior center for optimum expression of estrus. Lameness or general disease impairing an animal's ability to move will mask signs of heat independently from its reproductive status. Silent heat can be diagnosed only through rectal palpation of the ovaries or the use of progesterone assay in milk or plasma.

While the cow cycles normally in the face of failure in heat detection or silent heat, true, irregular cyclicity does occur. Endometritis, through the release of prostaglandin, can result in premature lysis of the corpus luteum (CL) and therefore a shortened diestrus phase.[26] Cystic ovarian follicles, either in the form of follicular or luteal cysts, interfere with regular cyclic ovarian activity. This condition is mainly observed in high-yielding dairy cows during the first months postpartum. Estrogen-producing follicular cysts may result in nymphomania, a state of persistent or frequent heats. Progesterone-producing luteal cysts result in absence of estrous behavior and prolonged interestrus interval.[27] Early embryonic death occurring after the time period of maternal recognition of pregnancy will prevent lysis of the CL, and the cow will undergo a prolonged interestrus interval due to the action of progesterone.[28] A less common cause for prolonged diestrus is segmental aplasia of the uterine tract.[29] If ovulation occurs ipsilateral to a missing uterine horn, the CL will persist due to the lack of exposure to prostaglandin.

Mares

Irregular estrous cycles in the mare are most commonly encountered during the transitional period and are considered physiologic then. Follicles will initiate growth during the transition from winter anestrus to spring reproductive activity, resulting in estrous behavior. Due to inadequate gonadotropin, support follicles may fail to ovulate and eventually regress after a varying period of time leading to irregular estrus intervals.[30] Mares that have been artificially induced to develop a follicle and ovulate during seasonal anestrus using gonadotropin-releasing hormone (GnRH) or recombinant follicle-stimulating (FSH) usually do

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not display regular estrous cyclicity following the artificially induced ovulation till the onset of breeding season. Likewise, mares foaling during the nonbreeding season may display foal heat, which may be followed by a variable period of anestrus. Mares older than 20 years of age may experience irregular estrous cycles independent of the time of the year, and it is not unusual for mares older than 25 years of age to stop cycling altogether. During the regular breeding season, prolonged interestrus intervals may occur in association with diestrous ovulations.[31] Follicles developing during diestrus may either regress or, less commonly, ovulate. If this ovulation occurs on or after day 10 of diestrus, the newly resulting CL will be refractory to the actions of prostaglandin released from the endometrium around day 14 of the cycle. This becomes evident in a prolonged interestrus interval. Prolonged diestrus may also be observed following early embryonic death occurring after the time of maternal recognition of pregnancy. If a pregnancy is lost following formation of endometrial cups, the mare may not display regular cyclic activity during the remainder of that breeding season. Ovulation failures such as hemorrhagic luteinized follicles or anovulatory persistent follicles interfere with regular cyclicity. Anovulatory hemorrhagic follicles that luteinize may persist for more than a month without treatment, which is reflected in a prolonged diestrus phase. Anovulatory persistent follicles may or may not interfere with cyclic activity. Some mares will develop a new dominant follicle despite the presence of this abnormal structure, whereas other mares will not show signs of heat as long as these structures are present.[32] Persistent estrous or stallion-like behavior is commonly described as a sequel to the presence of a granulosa cell tumor.[33] Following unilateral ovariectomy, mares usually return to regular cyclicity within 6 months. Endometrial irritation such as endometritis or uterine lavage can result in shortened intervals between heats due to the release of prostaglandin.[34] A less commonly encountered cause of irregular cyclicity in mares is chromosomal abnormalities such as XO genotype.[35] Iatrogenic causes of irregular cyclicity are the accidental administration of prostaglandin (shortened luteal phase) or the twice-daily administration of oxytocin during days 7 to 14 (prolonged luteal phase).[36]

Sheep and Goat

The first ovulation at the beginning of the breeding season is often not accompanied by overt signs of estrus due to the absence of progesterone

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priming. The corpora lutea arising from these ovulations often regress prematurely, again because of the inadequate progesterone priming. A pathologic cause of irregular or prolonged estrous cycles is the consumption of phytoestrogens from plants such as clover and alfalfa, which may lead to signs of irregular and prolonged estrous cycles.

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Anestrus

Claudia Klein

Anestrus is the absence of estrous behavior and can be a physiologic state during pregnancy, lactation, or seasonal anestrus, or it may be a pathologic condition (Boxes 12.6 and 12.7). Anestrus can occur either in the face of or the absence of ovarian activity; in the case of the latter, acyclicity is present. Causes underlying anestrus can be subdivided into physiologic and pathologic. The lack of estrous behavior due to ovarian inactivity is physiologic in seasonal species and is mediated via melatonin levels, which vary with day length. The mare is a long-day breeder, whereas the ewe and doe are short-day breeders, although breed variations occur in small ruminants.[37] Certain breeds of sheep are less affected by the season and can have longer breeding seasons or practically cycle year-round. Some sheep and goats near the equator have cycles throughout the year presumably because of the consistency of the photoperiod. Prepubertal animals naturally do not show signs of estrus, as do some dams during lactation. The most common physiologic cause for the lack of estrous behavior is pregnancy; mares, however, are an exception because some of them may display signs of heat despite being pregnant. In intensively managed cattle herds bred by artificial insemination, failure in heat detection is a major contributor to perceived cases of anestrus.[38] A plethora of pathologic conditions can lead to anestrus, and a thorough examination of the history and evaluation of the reproductive tract is required for a definite identification of the underlying cause. Congenital conditions such as ovarian aplasia, chromosomal abnormalities, or freemartinism in cattle; intersex conditions that occur in polled goats; and gonadal dysgenesis in the mare are accompanied by the lack of estrous behavior. These animals frequently have rudimentary or hypoplastic ovaries.[39] Uterus unicornis will lead to persistence of the ipsilateral CL and subsequently interfere with regular estrous behavior.[40] Nutritional anestrus due to a negative energy balance during times of high milk production can lead to anestrus in cattle.[41] In mares, anestrus due to nutritional deficiencies is less commonly observed than in cattle. In beef cattle nursing their offspring, a delayed resumption in ovarian activity is frequently observed.[42] This is related to both the physical act of the calf nursing and olfactory and auditory cues received by the dam from the calf. Anestrus related to lactation is not observed in mares. Mares foaling during the

short day–length period that have not been kept under lights for 2 months preceding parturition may show a first ovulation within the first 2 weeks postpartum (i.e., foal heat) but then revert to an anestrous state with cyclic activity not resuming until increasing day length. Persistent endometrial cups, a rare condition in mares, may also lead to the failure of presenting regular estrous activity in the period postfoaling.[43] Both conditions may easily be misinterpreted as cases of lactational anestrus. In mares, psychogenic factors have to be considered in the differential diagnosis for anestrus. A mare being overly protective of her foal or of nervous constitution may not show signs of heat. Teasing with a stallion may be necessary to elicit estrous behavior in these animals.

Box 12.6

Causes of Anestrus in Mares

Common Causes

Season (fall, winter)
Poor heat detection
Corpus luteum persistence
Diestrus ovulation
Pregnancy
Early embryonic death after recognition of pregnancy
Fetal death after endometrial cup formation
Psychological impediments
Maternal behavior

Less Common Causes

Ovarian tumors
Pituitary tumors
Pyometra
Weight loss
Chronic disease

Lactation
Old age

Uncommon Causes

Gonadal dysgenesis
Intersex conditions
Progesterone therapy
Nonsteroidal antiinflammatory drugs (NSAIDs)
Phosphorus deficiency
Ovarian hypoplasia
Anabolic steroids
Zearalenone toxicity
Chromosomal abnormalities
Persistent endometrial cups
GnRH immunization
Deslorelin implants

Box 12.7

Causes of Anestrus in Ruminants

Common Cause

Season (C, O)
Pregnancy
Poor heat detection
Luteal cysts (B, C)
Pyometra
Poor nutrition, energy
Heat stress
Foot and leg problems
Poor footing (B)
Nursing beef cows and ewes (B, O)
Lactation (O)

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Freemartinism (B, C)
Intersex conditions (C)
Postpartum period
Heavy lactation
Primiparity
Periparturient disease

Less Common Causes

Mucometra
Hydrometra
Macerated fetus
Mummified fetus
Trichomoniasis pyometra
Anaplasmosis
Johne's disease
Caprine arthritis-encephalitis (C)
Pseudopregnancy (C)
Insufficient number of cycling herdmates

Uncommon Causes

Ovarian tumor
Segmental aplasia
Uterine foreign body
Ovarian hypoplasia
Zearalenone toxicity
Phytoestrogenism
Phosphorus deficiency
Copper deficiency
Cobalt deficiency
Manganese deficiency
Molybdenum toxicity
Progesterone implants
Schistosomiasis (exotic)
Lumpy skin disease (exotic)

B, Bovine; *C*, caprine; *O*, ovine.

A variety of conditions can lead to hypothalamic or pituitary suppression, preventing the release of GnRH from the hypothalamus, in turn resulting in a lack of FSH and luteinizing hormone (LH) released by the pituitary. Consequent ovarian inactivity results in the absence of behavioral estrus. Most common underlying conditions are poor nutrition, heavy lactation, periparturient disease, weight loss, or idiopathic condition.

Any condition discussed in the Cyclic Irregularity section that results in prolonged luteal function will result in absence of overt estrous signs. Differential diagnoses further include the presence of cystic ovarian disease in cattle and anovulatory follicles in mares. Uterine abnormalities such as mucometra, hydrometra, and pyometra prevent the release of $PGF_{2\alpha}$ in ruminants.[44] Thus the CL persists and perceived anestrus results. Pyometra in the mare may result in anestrus if the endometrial damage is severe enough to prevent production of $PGF_{2\alpha}$. The presence of a mummified or macerated fetus in the ruminant uterus prevents release of $PGF_{2\alpha}$ and results in a persistent CL and perceived anestrus.[45] Ovarian atrophy leading to persistent anestrus can be seen in high-producing dairy cattle as a sequel to nutritional problems or can be occasionally encountered as an idiopathic condition in mares.[41] If no overt reason for ovarian atrophy can be identified, dysfunction at the hypothalamic-pituitary-ovarian axis has to be considered as a potential underlying cause. Iatrogenic causes of anestrus in mares, such as previous immunizations with GnRH or the application of a deslorelin implant, have to be considered, especially if the reproductive history of the mare is unknown.[46] Mares exposed to a deslorelin implant used to hasten ovulation can display pituitary downregulation induced by constant high GnRH input. Older mares undergo reproductive senescence, which is accompanied by atrophying ovaries and lack of cyclicity. Anecdotally, some mares coming off the race track show anestrous behavior and small ovaries on examination. No studies have been undertaken to determine the cause for this, but stress and possible medications during the racing career have been suspected.

Knowledge of the reproductive physiology of the species involved is essential to understanding the cause of anestrus. Determining the cause of anestrus relies on an in-depth general and reproductive history, a thorough physical examination, and evaluation of estrus detection programs involved. Pregnancy

must be ruled out when dealing with any case of anestrus.

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Repeat Breeder

Bruce W. Christensen

Managing repeat breeders is often frustrating and expensive. The repeat breeder is an animal that has been bred during three or more successive heat periods without being diagnosed pregnant.[47] An incidence of 10% to 15% repeat breeders is considered acceptable for dairies.[48] The incidence increases with the herd size and the level of milk production and with the use of artificial insemination.[48] This may be an even greater problem in the horse because pregnancy rates per cycle are normally between 60% and 70%, and 5% to 8% of mares lose their pregnancy in the first 4 months of gestation.[49] The use of ultrasonography and embryo collection indicates that the incidence of early embryonic death (EED) in the mare is likely even higher.[50] The syndrome of repeat breeders in mares is completely different from that in cows. In mares it is often associated with persistent endometritis. This is discussed in detail in Chapter 43.

The causes of repeat breeding are numerous and are related to male, female, and management factors (Boxes 12.8 and 12.9). The pathogenesis of repeat breeding involves either a failure of fertilization or EED.[48] Some etiologies, such as heat stress in the herd, may involve both mechanisms. Fertilization rates are normal in heat-stressed cows that are bred artificially, but heat stress increases the rate of EED. Heat stress can cause failure of fertilization by affecting spermatogenesis in males used in a natural breeding program.[51] When dealing with an individual repeat breeder, it is often wise to begin with the female. When several females are affected, the male should be eliminated as a source of the problem before proceeding. Management errors may be related to either male or female factors.

Box 12.8

Causes of Repeat Breeding in Mares

Common Causes

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- Transition season
- Endometritis
- Poor timing of artificial insemination
- Pneumovagina
- Metritis
- Endometrial fibrosis
- Poor heat detection
- Ovulation failure
- Twins
- Uterine lymphatic lacunae
- Endometrial cysts
- Early foal heat breed
- Poor uterine clearance
- Ventral uterine sacculation

Less Common Causes

- Diestrus breeding
- Urovagina
- Rectovaginal fistula
- Malnutrition
- Pyometra
- Heat stress
- Poor semen quality
- Old age
- Endophyte-infested fescue

Uncommon Causes

- Salpingitis
- Hydrosalpinx
- Oviductal adhesions
- Oophoritis
- Uterine neoplasia
- Cervical neoplasia
- Ovarian neoplasia

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Parovarian cysts
Contagious equine metritis
Iodine deficiency
True hypothyroidism
Phosphorus deficiency
Zearalenone toxicity
Intersexuality
Gonadal dysgenesis, sex reversal, trisomy
Other karyotype abnormalities
Teratogenic factors
Vitamin A deficiency
Cervical trauma
Luteal insufficiency

Box 12.9

Causes of Repeat Breeding in Ruminants

Common Causes

Heat detection
Poor timing of artificial insemination
Inadequate or delayed luteinizing hormone surge
Poor artificial insemination technique
Malnutrition
Follicular cysts
Endometritis
Heat stress
Trichomoniasis
Campylobacteriosis
Leptospirosis
Inadequate uterine involution

Less Common Causes

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Poor semen quality
Inadequate male power (not enough males)
Infectious bovine rhinotracheitis (IBR) (B)
Bovine virus diarrhea (BVD) (B)
Bluetongue
Brucellosis
Anaplasmosis
Toxoplasmosis (C, O)
Border disease (C, O)
Selenium deficiency
Phosphorus deficiency
Ureaplasmosis
Urine pooling
Pneumovagina, pneumouterus
Oviductal bursal adhesions
Segmental aplasia
Rectovaginal fistula
Parovarian cysts
Zearalenone toxicity (B, O)
Fescue toxicity
Uterine tumors
Defective embryos
Dietary protein toxicity

Uncommon Causes

Johne's disease
Tuberculosis
Vitamin A deficiency
Zinc deficiency
Manganese deficiency
Cobalt deficiency
Copper deficiency
Molybdenum toxicity
Selenium toxicity
Iodine deficiency
Iodine toxicity (B, O)

Oophoritis
Fat necrosis (B)
Brasilia, toxicity
Ovarian tumors
Progressive degenerative myeloencephalopathy of Brown Swiss cattle (B)
Polybrominated biphenyl toxicity (B)
Phytoestrogen toxicity (B, O)
Hydrosalpinx
Salpingitis
Cervical anomalies and cysts
Chromosomal abnormalities (1/29 or 14/20 centric fusions)
Fluoride toxicosis
Segmental aplasia
Uridine monophosphate synthase deficiency
Delayed ovulation
Schistosomiasis (exotic)
Tick-borne fever (exotic)
Epivag (exotic)
Leucaena leucocephala (exotic)
Besnoitiosis (exotic)
Maedi, visna (exotic)
Lumpy skin disease (exotic)
Onion grass toxicity (exotic)

B, Bovine; *C*, caprine; *O*, ovine.

Fertilization failure is often the cause of repeat breeder syndrome. Studies have demonstrated delayed or inadequate release of LH, as well as consequent delayed ovulation, in repeat breeder cows compared with those cows showing normal fertility rates.[52] This observation has led to the investigation of GnRH (or its analogs) and prostaglandins as treatment options for repeat breeders, with some success.[53,54] In addition to LH abnormalities, repeat breeder cows showed prolonged duration of estrus, prolonged lifespan of the preovulatory follicle, and a late postovulatory rise in progesterone.[52] These changes negatively contribute to final oocyte maturation and competence in repeat breeder cows compared with unaffected cows.[55] Insulin has been shown to be an important mediator of

follicular development, steroidogenesis, oocyte maturation, and subsequent embryo development,[56] and treatment with insulin has been shown to increase fertility in repeat breeder cows.[57] Workers in Japan have linked the repeat breeder syndrome with abnormal profiles of endometrial epidermal growth factor (EGF). Assays of EGF have been suggested as diagnostic tools, and EGF treatment has been suggested to restore fertility.[58,59]

Early embryonic death also contributes as a cause of infertility in repeat breeders.[48,50] The interval between heats may help distinguish between EED and failure of fertilization. Failure of fertilization usually does not affect the interestrus interval. However, EED may prolong the interestrus interval if the fetal wastage occurs after the time of maternal recognition of pregnancy. Maternal recognition of pregnancy occurs at approximately days 15 to 17 after estrus in the cow, days 11 to 14 in the mare, and days 12 to 13 in the ewe.[60] Animals experiencing EED after pregnancy recognition often have interestrus intervals corresponding to multiples of a normal cycle length. Luteal insufficiency is suspected to cause EED in some repeat breeder cows, and trials of exogenous progesterone supplementation have shown promise for maintaining pregnancy in young late-lactation repeat breeders.[61]

Approach to Diagnosis

Clinical differentiation of EED from failure of fertilization is difficult. In addition to evaluation of heat detection and breeding techniques, it is important to obtain a detailed history. When dealing with a herd problem, the clinician begins by evaluating the male or males used or assessing the semen quality and techniques used for artificial insemination. When dealing with an individual repeat breeder, evaluation of the female is the first step.

Evaluation of the male should include evaluation of the animal's physical condition, including the genitalia. The quality of the semen should be checked. The male's libido and ability to mount should be determined by observation or through historic information. Examination of the male for venereally transmitted diseases, such as trichomoniasis and campylobacteriosis in the bull and contagious equine metritis in the stallion, may be warranted if other factors are ruled out. When dealing with an artificial insemination program, the semen quality should be evaluated and the thawing, transporting, timing, and deposition techniques should be evaluated.

Errors in heat detection and the timing of breeding are major management

causes of repeat breeding. Discussing and observing the methods used to determine when an animal should be bred are important in dealing with both the individual animal and the herd. Milk or serum progesterone determinations at the time of breeding have proved helpful in determining the accuracy of heat detection and timing of insemination. In some dairies 40% to 50% of the cows are bred at the wrong time.

Examination of the female or females should begin with evaluation of the body condition. Poor nutrition has been associated with repeat breeding.[62] The reproductive examination should include evaluation of the vulva, vagina, cervix, uterus, oviducts, and ovaries. Poor vulvar conformation may lead to pneumovagina and endometritis, resulting in EED. The spermicidal effect of urine may cause failure of fertilization in the mare or cow that pools urine in the vagina. Cervical canal occlusion can prevent fertilization. An abnormal uterine environment may also lead to repeat breeding. Endometritis with minimal intraluminal pus may cause failure of fertilization but often results in EED. Unlike ruminants, the mare may continue to display estrus while experiencing pyometra. The volume of pus present in the uterus will cause failure of fertilization. Hydrosalpinx or salpingitis may lead to failure of fertilization by blocking sperm or ovum passage. Ovulation abnormalities such as delayed ovulation or ovarian cyst formation may result in failure of fertilization. Whenever possible, including a uterine culture, cytologic smear, and endometrial biopsy as part of the examination is likely to help determine the cause of the infertility.

Differentiation of EED from failure of fertilization in repeat breeders has been facilitated by the use of embryo flushing techniques and ultrasonography. Collection of unfertilized ova indicates failure of fertilization; collection of degenerating embryos indicates early embryonic death. In ruminants, failure to collect ova or embryos may indicate oviductal blockage resulting in failure of fertilization. This is not the case for mares because they usually retain unfertilized ova in the oviducts.

Ultrasonic determination of pregnancy in the mare and cow has made early detection of pregnancy possible. Loss of an embryo after detecting it with ultrasound at 10 days of gestation confirms EED. Pregnancy wastage can be confirmed later in gestation with sequential rectal palpations of the reproductive tract or ultrasonic evaluation. Hormone assays are also helpful for confirming embryo or fetal loss.

An assay for eCG, previously called *pregnant mare serum gonadotropin*

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(PMSG), can be used to determine if a mare was pregnant long enough to stimulate formation of the endometrial cups and eCG production. eCG can be detected at about 40 days of gestation with these kits. The endometrial cups continue to produce eCG until 120 to 150 days of gestation even if the fetus dies. Therefore eCG can be used to confirm EED but not failure of fertilization. Progesterone determination cannot be used to confirm pregnancy in the mare or ruminants. However, it can be used to confirm nonpregnancy if the progesterone level is low early in the expected gestation. A bovine early conception factor test can be used to confirm fertilization, but it does not rule out EED later.

The fetally derived hormone-metabolite estrone sulfate has been used to determine the presence of a live fetus. It is detectable in the serum or urine of the dam if the fetus is alive after 45 days of gestation in the doe, 70 days of gestation in the ewe, 100 days of gestation in the mare, and 120 days of gestation in the cow.[63,64] Thus a decline in estrone sulfate indicates death of the fetus. Estrone sulfate is probably most helpful in confirming fetal loss in the doe and ewe because other techniques are available in the larger species.

Boxes 12.8 and 12.9 list the causes of repeat breeding in mares and ruminants. The causes have been divided into expected frequencies of occurrence.

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Pregnancy Loss

Mats H.T. Troedsson

Pregnancy loss refers to the failure of a conceptus to be maintained successfully to term. Pregnancy loss may be classified as early embryonic death (EED), abortion, or stillbirth, depending on the gestational stage when the pregnancy loss occurred. *EED* is the death of a conceptus before organogenesis is complete (≈55 days in horses, 45 days in cattle, and 34 days in sheep).[65] *Abortion* refers to pregnancy loss after the completion of organogenesis. *Stillbirth* refers to the delivery of a nonviable fetus at or near term.

Early Embryonic Death

The exact incidence of EED in any species is difficult to determine because most losses occur before pregnancy can be routinely diagnosed. Embryonic death early in pregnancy usually results in reabsorption of the embryonic tissues and fluids. Consequently, EED cannot be distinguished from failure of fertilization in most instances. However, despite the lack of clinical evidence, EED probably accounts for the largest percentage of reproductive wastage in large animals. The incidence of EED has been estimated at 5% to 24% in mares,[66] 30% to 35% in cows,[67] and 20% to 30% in ewes.[68] The rate of EED is generally higher in subfertile or repeat breeder females and in older females.

Loss of the embryo before maternal endocrine recognition of the pregnancy (i.e., days 11 to 14 in the mare, days 15 to 17 in the cow, and day 12 in the ewe and doe) results in return to estrus at the normal time. Embryonic loss after this critical period may result in persistence of the CL in horses, pseudopregnancy in goats, or irregular returns to estrus in cattle.

Chromosomal and genetic defects of the oocyte, sperm, or embryo; a poor oviductal or uterine environment; endocrine dysfunction; and maternal stress are all considered important factors in the pathogenesis of EED.[66,69] Infectious agents such as *T. foetus* and *C. fetus* subsp. *venerealis* in cattle[69] and *Streptococcus zooepidemicus* and other bacteria in horses[70] can cause EED. Endogenous release of $PGF_{2\alpha}$ during the CL-dependent stage of gestation may result in luteolysis and subsequent embryonic loss or abortion in any large animal species. Primary luteal insufficiency associated with low plasma

progesterone concentrations has been suggested as a possible cause of EED in horses, cattle, and sheep, although scientific evidence is limited.[67,71,72]

Abortion

The rate of abortion after pregnancy diagnosis at 60 days of gestation has been estimated to be approximately 10% in horses[73] and 3% to 4% in cattle.[74] Fetal death may result in abortion (expulsion of the fetus from the uterus) or retention of the fetus in the uterine lumen, with subsequent fetal maceration or mummification. In animals with a CL-dependent pregnancy for all or most of gestation (cows, goats, llamas), death of the fetus usually results in the abortion of an autolyzed fetus because of a delay between the time of fetal death and lysis of the CL. In species that do not depend on a CL for maintenance of pregnancy for most of gestation (e.g., mares and ewes), fetal death causes an immediate decrease in placental progestogen production and rapid expulsion of a relatively nonautolyzed fetus. *Mummification* is characterized by fluid reabsorption from a fetus retained in a sterile uterine environment. Fetal mummification is most common in multiparous species with a CL-dependent pregnancy (e.g., sows) and is rare in uniparous species that are CL independent for most of gestation (e.g., mares). *Maceration* refers to the degenerative changes that occur in a fetus after retention in a nonsterile uterine environment. Fetal maceration may be associated with significant maternal endometrial damage.

Horses.

Equine abortions may be characterized as infectious or noninfectious in origin. Most equine abortions occur secondary to placental dysfunction. One of the most commonly diagnosed infectious causes of abortion in horses is equine herpesvirus type 1 (EHV-1).[73] Abortion caused by EHV-1 usually occurs after 7 months of gestation as a result of exposure to the virus with subsequent viremia and damage to the placental vasculature. Exposure of pregnant mares to EAV may lead to abortion within 1 to 3 weeks after initial viral exposure. Abortion may be caused by vasculitis, edema, and necrosis in the endometrium and allantochorion.[75] Exposure to EAV at breeding will not cause a mare to abort later in gestation. Abortion rates may range from 10% to 70% during an outbreak.

Consumption of eastern tent caterpillars (larva of *Malacosoma americanum*) by mares causes abortion. The syndrome has been named *mare reproductive loss*

syndrome (MRLS). Pregnancy loss before 150 days of gestation is characterized by hyperechoic amniotic and allantoic fluids on ultrasonographic examination along with a dead or dying fetus.[76,77] Near-term abortions are characterized by histologic lesions in the placenta and umbilical cord. In many cases, endometrial cultures are positive for non–beta-hemolytic streptococci and *Actinobacillus* species. Diagnosis of MRLS is based on four variable factors: placental lesions, culture of characteristic bacteria from fetal tissues, conformation of increased caterpillar exposure, and diagnostic elimination of other known causes of abortion (John Roberts, personal communication). The microscopic lesions observed in natural late-term MRLS cases are primarily the result of host response to bacterial infection, with the most common isolates being non–beta-hemolytic streptococci and actinobacilli.

During an outbreak in central Kentucky in 2001 and 2002, a variety of nonspecific lesions were reported that included placental edema, fetal pneumonia, and hemorrhages in the heart and placenta. During this outbreak, inflammation of the umbilical cord (funisitis), specifically the amniotic segment, was observed in 78% of cases.[78] Funisitis was also observed in necropsied cases during a 2006 Florida outbreak.[79] The lesion is initiated as a suppurative to pyogranulomatous response between the outer circumferential stroma and the outer tunica adventitia of major umbilical vessels and progresses outward to involve or ulcerate the amniotic surface of the umbilical cord.[79,80] Other causes of equine abortion such as noninfectious umbilical cord lesions, leptospirosis, and EHV should be ruled out by appropriate diagnostic tests. In addition, if a horse farm encounters unilateral endophthalmitis or pericarditis in the general population, MRLS should be elevated as a differential diagnosis for unsolved abortions.[81,82]

Crosiella equi, *Amycolatopsis* spp., and *Streptomyces* spp. have been associated with chronic placentitis and subsequent late-term abortion, stillbirth, and premature birth.[83,84] The condition is often termed *nocardioform placentitis* due to similarities of the causative agents to the *Nocardia* species. The pathogenesis, route of infection, or risk factors have not been identified for the disease. Lesions are typically located in the ventral aspect of the uterine body and base of the uterine horns. Gross lesions are easily recognized as a brownish, thick, and tenacious exudate on the chorionic surface. The causative bacteria have been isolated only from clinical cases and not from the environment.[85]

Leptospira species have also been identified as a significant cause of equine

abortion in Kentucky.[86] *Leptospira interrogans* serovar Pomna type *Kennewicki* is most commonly causing abortion in horses in North America, but other serovars such as Grippotyphosa and Hardjo have also been implemented in equine abortions.[87,88] Environmental wet conditions are considered important to dissemination of *Leptospira* from wildlife to horses.

Bacterial and fungal abortions in mares are primarily caused by infections that ascend through the cervix, causing placentitis and subsequent fetal infection. The bacterial organisms most commonly cultured from aborted fetuses include *Streptococcus* species, *Escherichia coli*, *Pseudomonas* species, *Klebsiella* species, and *Staphylococcus* species. The most frequently recovered fungi are *Aspergillus* species.

The most common noninfectious cause of equine abortion is twin pregnancy.[73] Inability of the uterus to support two fetuses to term because of insufficient placental support may result in abortion at any stage of gestation but is most common after 7 months. Early diagnosis of pregnancy using ultrasonography allows for highly successful manual reduction of one twin if done before day 16 of pregnancy. This technique has significantly reduced the incidence of abortion caused by twin pregnancies.

Ruminants.

Infectious bovine rhinotracheitis–infectious pustular vulvovaginitis (IBR-IPV) virus and bovine virus diarrhea–mucosal disease (BVD-MD) virus are two of the most common viral causes of abortion in cattle.[89] Bacterial abortions caused by Brucella abortus, Arcanobacterium (Actinomyces) pyogenes, Bacillus species, Listeria monocytogenes, E. coli, Leptospira species, and Pasteurella haemolytica and fungal abortions caused by Aspergillus species and Mucor species usually result from hematogenous spread and localization in the placenta.[90] Protozoal abortion, caused by Neospora organisms, has been recognized as a significant cause of abortion in cattle worldwide.[91] Epizootic bovine abortion (EBA) is a common cause of third-trimester abortion in susceptible heifers and cows inhabiting the foothills of the Sierra Nevada mountain range of California, Nevada, and Oregon.[92] The Pajaroello tick, Ornithodoros coriaceus, is responsible for transmitting the causative agent, which has been

identified as a delta proteobacteria, unofficially named Pajaroellobacter abortibovis when it feeds on pregnant cows.[93,94]
Campylobacteriosis (vibriosis), caused by *C. fetus* and *C. fetus* subsp. *jejuni*, and enzootic abortion of ewes, caused by *Chlamydia psittaci*, are the most common infectious causes of abortion in sheep.[95] They are characterized by abortion in the last 4 to 6 weeks of gestation, premature births, stillbirths, and birth of weak, infected lambs. *C. psittaci* is also the most common cause of infectious abortion in goats in the United States.[96]

Noninfectious causes of large animal abortion include genetic or chromosomal factors, maternal stress, inadequate nutrition, vitamin or mineral deficiencies, ingestion of poisonous plants or other toxins, hormonal factors, environmental factors, physical factors, and certain medications.

Approach to Diagnosis of Abortion

A definitive diagnosis is reached in 20% to 40% of bovine abortions,[65] 50% to 60% of equine abortions,[73] and 30% to 40% of sheep abortions.[97] The generally low diagnostic success is a result of the complexity of the condition (Boxes 12.10 and 12.11). Abortion involves disease in the maternal, placental, and fetal compartments individually or together, and all these compartments have to be examined thoroughly. In addition, a "triad" of determinants for animal disease has to be considered: 1) the presence of a pathogenic organism, 2) the environment in which a host lives, and 3) the susceptibility of the host to the disease.[98] To enhance diagnostic success, information and samples must be collected from the fetus, placenta, dam, and herd. A thorough history should be obtained, including the gestational age of the fetus; reproductive, medical, and vaccination history of the dam and other individuals in the herd; previous abortions and diagnoses; new arrivals to the herd and contacts of the animal with other herds; potential causes of maternal stress; possible access to toxins and poisonous plants; and sources of water and nutrition.

Box 12.10

Causes of Pregnancy Loss in Mares

Common Causes

Impaired oviductal and uterine environment (EED)
Chronic endometritis (EED, Ab)
Embryonic defects (EED)
Endometrial fibrosis (EED, Ab)
Twinning (Ab)
Equine herpesvirus type 1 (EHV-1) (Ab)
Bacterial placentitis (*Streptococcus* species, *Escherichia coli*, *Pseudomonas* species, *Klebsiella* species, *Staphylococcus* species, *Crosiella equi*, *Amycolatopsis* species, *Streptomyces* species) (Ab)
Fungal placentitis (Ab)
Umbilical cord abnormalities (Ab)

Less Common Causes

Endotoxemia (EED, Ab)
Leptospirosis (Ab)
Mare reproductive loss syndrome (MRLS) (EED, Ab)
Fetal anomalies (Ab)
Maternal stress, other disease (EED, Ab)
Chromosomal abnormalities (Ab, EED)
Fescue toxicity (EED, Ab)
Advanced maternal age (EED)
Equine viral arteritis (Ab)
Equine infectious anemia (Ab)
Uterine torsion (Ab)
Endocrine factors (EED)
Malnutrition (EED, Ab)
Drug-induced causes (EED, Ab)
Premature separation of the placenta (Ab)
Fetal asphyxia (Ab)
Placental insufficiency (Ab)

Uncommon Causes

Ehrlichia risticii (Potomac horse fever) (Ab)
Uterine body pregnancy (Ab)

Endometrial adhesions (EED)
Taylorella equigenitalis (contagious equine metritis) (EED)
Uterine lymphatic lacunae, cysts (EED, Ab)
Hyperlipemia (Ab)
Lymphosarcoma (Ab)
Iatrogenic causes (EED, Ab)
Fetal diarrhea syndrome (Ab)
Ergot toxicity (EED, Ab)
Brucellosis (Ab)
Mycobacterium infection (Ab)
Corynebacterium pseudotuberculosis (Ab)
Rhodococcus equi (Ab)
Mycoplasma infection (Ab)
Coccidioidomycosis (Ab)
Histoplasmosis (Ab)
Babesiosis (Ab)
Vitamin A deficiency (Ab)
Iodine deficiency (EED, Ab)
Granulosa theca cell tumors (Ab)
Cryptococcosis (Ab)
Sorghum, Sudan grass (Ab)
Locoweed *(Astragalus)* species
Hoary alyssum poisoning (Ab)
Salmonella abortus equi (Ab)
Gonadal stromal tumors (Ab)
Trauma (Ab)

Ab, Abortion; *EED,* early embryonic death.

Box 12.11

Causes of Pregnancy Loss in Ruminants

Common Causes

Campylobacter infection (B: EED; O, C: Ab)

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Epizootic bovine abortion (B: Ab)
Arcanobacterium (Actinomyces) pyogenes (B: Ab)
Bacillus species (B: Ab)
Bovine protozoal abortion (*Neospora* species) (B, C: Ab)
Infectious bovine rhinotracheitis—infectious pustular vulvovaginitis (IBR-IPV) virus (B: EED, Ab)
Leptospirosis (B, O, C: Ab)
Trichomoniasis (B: EED, Ab)
Brucellosis (B, O, C: Ab)
Bovine virus diarrhea (BVD) (B: EED, Ab)
Toxoplasmosis (O, C: EED, Ab)
Border disease (O, C: EED, Ab)
Chlamydiosis (O, C: Ab)
Embryonic defects (B, O, C: EED)
Bacterial abortion (B, O, C: Ab)

Less Common Causes

Twinning (B: Ab)
Prenatal asphyxia (B, O, C: Ab)
Akabane virus (B, O, C: Ab)
Q fever *(Coxiella burnetii)* (O, C: Ab)
Mycotoxicosis (B, O, C: Ab)
Anaplasmosis (B, O, C: Ab)
Ureaplasma infection (B, O: EED, Ab)
Mycoplasma infection (B, C: Ab)
Chromosomal abnormalities (B, O, C: EED, Ab)
Malnutrition, protein-calorie starvation (B, O, C: EED, Ab)
Bluetongue (B, O: EED, Ab)
Histophilus (Haemophilus) somni (B: Ab)
Tuberculosis (B: Ab)
Uterine torsion (B: Ab)
Water deprivation–salt toxicity (B, O, C: Ab)
Selenium deficiency (B, O, C: Ab)
Mycotic, fungal abortion (B, O, C: Ab)
Salmonellosis (B, O, C: EED, Ab)
Nitrate-nitrite poisoning (B, O: Ab)

Drug-induced causes (B, O, C: EED, Ab)
Endotoxemia (B, O, C: EED, Ab)
Cache Valley virus (B, O: EED, Ab)
Maternal stress (O, C: Ab)
Pregnancy toxemia (O, C: Ab)
Umbilical cord, placental abnormalities (B, O, C: Ab)
Fetal anomalies (B, O, C: Ab)
Deficiency of uridine monophosphate synthase (DUMPS) (B: EED)
Listeria (B, O, C: Ab)

Uncommon Causes

Pine needle poisoning (B: Ab)
Chlorinated naphthalene toxicity (B: Ab)
Osteopetrosis (B: Ab)
Lathyrus, poisoning (B, O, C: Ab)
Cobalt deficiency (B: EED, Ab)
Yersinia pseudotuberculosis (B, O, C: Ab)
Death camas (*Zigadenus* species) (O: Ab)
Foxglove (B: Ab)
Phosphate fertilizer toxicity (O: Ab)
α-Mannosidosis (B, O, C: Ab)
Ergot toxicity (B, O: EED, Ab)
Iodine deficiency (O, C: EED, Ab)
Hydrops fetalis (B, O: Ab)
Iatrogenic causes (B, O, C: EED, Ab)
Lead toxicity (B, O: EED, Ab)
Liver fluke disease (B, O, C: Ab)
Locoweed (*Astragalus*, *Oxytropis* species) (B, O, C: EED, Ab)
Ryegrass poisoning (B, O: Ab)
Sarcocystis infection (B, O, C: Ab)
Veratrum poisoning (O, C: EED, Ab)
Vitamin A deficiency (B, O, C: Ab)
Polybrominated biphenyl toxicity (B: EED, Ab)
Broomweed (*Gutierrezia* species) (B, O, C: Ab)
Bacillary hemoglobinuria (B, O: Ab)
Tetraglymia glabrata (O: Ab)

Copper deficiency (O, C: Ab)
Caprine herpesvirus infection (C: Ab)
Habitual abortion in Angora goats (C: Ab)

Ab, Abortion; *B*, bovine; *C*, caprine; *EED*, early embryonic death; *O*, ovine.

A physical examination that includes all body systems should be performed on the aborting dam. Examination of the reproductive system should include palpation or ultrasonography of the reproductive tract per rectum, speculum examination of the vagina, and digital examination of the cervix. Samples should be collected from the vagina, uterus, or both, for culture and cytologic studies. Paired serum samples from the dam and other females in the herd (10 animals or 10% of the herd, whichever is greater) may also help demonstrate an immunologic response to an infectious agent. Maternal serologic testing is generally most useful if paired samples are submitted, combined with accurate information about the animal's vaccination history. However, postabortion titers from cows that aborted can be compared with titers from unaffected cows in the herd at a similar stage of lactation. Demonstration of a fourfold rise in titer between acute and convalescent serum samples suggests recent exposure to an agent, but the presence of antibodies does not necessarily indicate that the agent caused the abortion. An exception can be made for brucellosis, for which a high titer from a single sample can be diagnostic.

For optimal diagnostic efficiency, the entire aborted fetus and placenta should be submitted to a diagnostic laboratory for necropsy. If this cannot be done, a prompt necropsy should be performed and collections of fetal, placental, and maternal samples should be submitted to a diagnostic laboratory (Table 12.1).

TABLE 12.1

Tissue Samples to Be Submitted for Diagnosis of Cause of Abortion

Source	Preservation Method	
	Chilled or Frozen	Fixed[a]
Aborted fetus	Lung, liver, kidney, spleen, thymus, skeletal muscle, heart, heart blood, abomasum, and stomach contents	Lung, liver, kidney, spleen, thymus, skeletal muscle (diaphragm), heart, adrenal gland, lymph node, thyroid, brain, gonads
Placenta	Allantochorion (ruminants: cotyledons and intercotyledonary areas), allantoamnion,	Allantochorion (ruminants: cotyledons and intercotyledonary areas), allantoamnion, umbilical

	amniotic fluid, cord blood	cord
Dam or herd	Paired serum samples, vaginal or uterine swabs	

[a]10% Formalin or Bouin fixative should be used.

A systematic necropsy must be performed on the aborted fetus. Fetal age and development may be assessed by measuring crown-rump length, hair patterns, and color. Meconium staining of the skin suggests uterine fetal distress. The condition of the fetus, including the degree of autolysis, should be noted. A careful examination for fetal anomalies (e.g., cerebellar hypoplasia, hydrocephalus, cleft palate, cardiac anomalies) should be performed. Histopathologic samples should be immersed in a volume of 10% buffered formalin (or Bouin fixative) equivalent to 10 times the volume of tissue. Samples for culture, virus isolation, and fluorescent antibody tests should be submitted on ice in separate sterile containers. A sample of abomasum and stomach contents should be aseptically collected for culture. Fetal heart blood or thoracic fluid may be collected for serologic evaluation. A late-term fetus is immunologically competent, and high titers may indicate activity of a pathogenic agent. Serologic testing of fetal fluids can be useful both in detecting a nonspecific active fetal immune response (total immunoglobulin [IgG]) and for titers against a specific antigen.

The fetal membranes should be examined for size, weight, degree of autolysis, condition, and completeness. Samples of placental tissue, especially areas with lesions, should be collected for histologic examination, impression smears, bacterial culture, virus isolation, and fluorescent antibody tests. The equine placenta should be examined for integrity, lesions, and distribution of chorionic villi. The normal equine placenta is everted after expulsion, with the allantoic surface presented outward and chorioallantois ruptured at the site of the cervical star. Blood may be collected from the free end of the cord. The allantoic surface should be examined for abnormalities such as multiple allantoic pouches that may indicate compromised fetal circulation.[99] The chorionic surface of the placenta should be examined for lesions and distribution of chorionic villi. Areas of avillous chorion are normally observed in association with the cervical star, narrow folds over large vessels, and areas opposing endometrial cups. Absence of chorionic villi over a circumscribed area is characteristic of twins and represents the region where two placentas were in contact. The region of the placenta adjacent to the cervix should be examined for loss of chorionic villi and the presence of inflammatory exudate, a hallmark of ascending infection. In

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cases of nocardioform placentitis, a characteristic thick and sticky exudate often covers an avillous area of the chorion at the ventral part of the site of the uterine body and base of the horn.

The cotyledons and intercotyledonary spaces of the ruminant placenta should be carefully examined for lesions. Autolytic changes of the placenta may be difficult to interpret. Some normal features of the bovine placenta must be kept in mind.[73] Amniotic plaques are present on the inner surface of the amnion and on the umbilical cord. They are most prominent at 3 to 7 months of gestation. Necrotic areas of the chorioallantois in the tips of the uterine horns are also normal and caused by insufficient vascularization to that area. Mineralization of the placenta is normal during the first months of gestation but may reflect placental injury associated with infection at the end of gestation.

All aborted fetuses and placental tissues should be handled with care, and tissues not submitted to a diagnostic laboratory should be burned or buried. Dams that have aborted should be isolated from the remainder of the herd.

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Fescue Toxicosis

Karen McDowell

Tall fescue (*Lolium arundinaceum* [Schreb.] Darbysh.) is one of the most widely grown perennial grasses in the world and covers approximately 14 million ha in the United States alone. It can be infected with an endophytic fungus, *Epichloë coenophiala* (previously classified as *Neotyphodium coenophialum* or *Acremonium coenophialum*), which, in a symbiotic relationship with the plant, produces a variety of potentially toxic alkaloids that may adversely affect grazing livestock.[100,101] It is the ergot alkaloids, a class of compounds including ergopeptines, lysergic acid amines, and clavines, that are the principle toxins responsible for fescue toxicosis in livestock.[102–104] Perennial ryegrass (*Lolium perenne* L.) may be infected with a similar endophyte, *N. Lolli*, and also produce ergot alkaloids, resulting in a toxicosis in livestock that is similar to fescue toxicosis.[105] Tall fescue toxicosis is the major grass-induced toxicosis in the United States,[106] and ergovaline is the most abundant ergot alkaloid in tall fescue.[103]

Clinical Signs of Fescue Toxicosis

Ergot alkaloids have an ergoline ring structure with a molecular architecture similar to various biogenic amines, including dopamine, serotonin, norepinephrine, and epinephrine, and this structural similarity allows them to bind to the respective biogenic amine receptors.[103] Clinical signs of fescue toxicosis in livestock have been well documented.[106–112]

Historically, the endocrine hallmark of fescue toxicosis in several species has been a decrease in circulating concentrations of prolactin.[112,113] Prolactin is secreted from the lactotrophs of the anterior pituitary gland, and control of its secretion is complex and not completely understood. However, inhibition by dopamine (from the hypothalamus) is a major regulator of its release.[114] Dopamine exerts inhibition of prolactin by interacting with the dopamine type-2 receptors (DRD2) of the lactotroph.[112] Ergovaline is a dopaminergic agonist, and it is through interaction with this DRD2 receptor that it inhibits release of prolactin. Dopamine receptors in ovarian tissues, including the CL, have been

reported for a number of species, including horses[115] and cattle,[116] but the role of those receptors in fescue toxicosis, if any, has not been fully elucidated.

A second hallmark of fescue toxicosis is vasoconstriction, which has been reported in cattle,[117–119] sheep,[120,121] goats,[122] and horses,[123–126] and this vasoconstriction may adversely affect reproductive performance.

Horses

In horses the most frequently reported problems associated with endophyte infected (E+) fescue consumption are in late pregnancy and include altered hormone concentrations, extended gestation, thickened placenta, premature placental separation, placental retention, dystocia, birth of dysmature foals, increased foal and placental weights, and agalactia.[109,113,127] Pregnancy may be prolonged as much as 2 to 4 weeks.[109,127,128] For pregnant mares grazing E+ versus E− (endophyte negative) fescue, Monroe[109] reported significantly reduced circulating prolactin concentrations throughout gestation, as well as reduced progesterone and estrogen concentrations at foaling. Gestation length averaged 360 days for mares on E+ fescue and 333 days for mares on E− fescue, and more mares grazing E+ fescue had retained and thickened placentas than in mares grazing E− fescue. Similarly, Cross[113] reported increased gestation length, agalactia, and weak and dysmature foals, as well as reduced concentrations of progesterone in pregnant mares grazing E+ versus E− fescue.

In addition to lactogenesis,[129] prolactin also exerts effects on steroidogenesis (estrogens, progesterone and testosterone)[130,131]; hair growth and shedding[132]; libido; and synthesis of surfactant by the fetal lungs,[133] so perturbations in prolactin secretion may affect a variety of systems. Importantly, prolactin may also exert an effect on the feto-placental unit by altering steroid synthesis and/or metabolism and maturation of the fetal adrenal-pituitary axis necessary for parturition.[107] Placental lactogens have not been identified in mares, and as such physiological effects related to inhibition of pituitary prolactin release associated with fescue toxicosis in pregnant mares may be severe.

Normally progestins in the maternal circulation of pregnant mares increase and estrogens tend to decrease in the last 60 days of gestation. Approximately 24 to 48 hours before parturition progestins decrease dramatically, thus causing an increase in the estrogen-to-progestin ratio.[134] However, studies have shown that late-gestation mares consuming E+ fescue do not have the decreased estrogens

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or increased progestins at the expected time of parturition.[107,109] In addition, the placental hormone relaxin tends to be lowered when pregnant mares graze E+ fescue.[135] Alterations in these hormone concentrations, along with the possibility that the ergot alkaloids from E+ fescue may interfere with the maturation of the fetal hypothalamic-pituitary-adrenal axis and the ability of the fetus to produce cortisol and thyroid hormone,[113,136,137] may contribute to the extended gestation exhibited by mares consuming E+ fescue.

Youngblood and coworkers[138] fed pregnant mares, between 65 and 100 days gestation, either E+ or E− fescue seed, added to their diet, for 10 days. Serum concentrations of prolactin were not different between the treatment groups. Mean concentrations of progesterone were greater in the mares fed E+ fescue seed, but there was no change in progesterone concentrations over time compared with pretreatment values, and there were no incidences of pregnancy loss. There was, however, a significant decrease in plasma concentrations of endogenous catecholamine activity (3,4-dihydroxyphenyl acetic acid) that occurred in the E+ treated mares, suggesting an endocrine disruptive effect of hypothalamic origin.

Recently, McDowell and coworkers (unpublished) allowed pregnant mares to graze and foal on pastures planted in a novel endophyte (NE) fescue versus those planted in a mixture of orchard grass and Kentucky bluegrass (OGBG). There were no differences in prolactin, progesterone, or estradiol concentrations; foaling rates; or placental weights among the mares on the different pasture types. In addition, foals from the mares grew at comparable rates regardless of pasture. The NE fescue pastures contained negligible ergovaline. Novel endophyte fescues have been developed to retain alkaloids that confer benefit to the plants but not those that are deleterious to grazing animals.[139,140]

Reports of the effect of E+ fescue on estrous cycles and/or early pregnancy rates in mares differ. Arns[141] reported no differences in pregnancy rates, cycles per pregnancy, or estrous cycle lengths in mares consuming E+ versus E− fescue seed, whereas Brendamuehl[142] reported prolonged luteal function, decreased pregnancy rates, and higher early embryonic death rates in mares grazing E+ versus E− fescue pastures. The Arns study reported decreased prolactin in the mares receiving E+ fescue seed, whereas when Hestad and McDowell[124] compared cycling, nonbred mares fed either E+ or E− fescue seed, the E+ seed resulted in reduced serum prolactin concentrations only associated with the periovulatory prolactin surge, but not during diestrus. Hestad also reported

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decreased blood flow to the corpus luteum (CL) in the mares receiving the E+ seed compared with mares receiving E− seed.

For pregnant mares, it is generally recommended that animals be removed from E+ fescue pastures 30 to 90 days before expected parturition. Both horses and cattle respond well to treatment with a DRD2 receptor antagonist, such as domperidone.[113,143,144] Further discussions and dosing recommendations have been given by Cross,[113,145] Evans,[107] and Jones.[146]

That E+ fescue causes vasoconstriction in horses has been demonstrated both in vivo[124,126,147] and in vitro.[123,148] This vasoconstriction likely contributed to the decreased blood flow in the CL in cycling mares reported by Hestad.[124] Decreased blood flow in the CL, while not affecting interovulatory intervals in the Hestad study, might have contributed to increased lengths of diestrus in the 1994 Brendemuehl study, by contributing to CL resistance to $PGF_{2\alpha}$.[149]

Responses of individual horses grazing the same pastures are variable, and there are currently no convenient and inexpensive laboratory assays to determine fescue alkaloid concentrations in the circulation of horses grazing E+ pastures. Even if there were, the minimal amounts of alkaloids necessary for an animal to develop premonitory signs of fescue toxicosis have not been established. It has frequently been reported that pastures with ergovaline concentrations below approximately 300 ppb do not cause detrimental effects in horses.[150] However, minimal “safe” levels of ergot alkaloids that do not result in fescue toxicosis in horses are not known, and animals grazing in the same pastures likely consume different amounts of fescue grasses. Thus a sensitive measure of biological responses to fescue toxicosis is necessary. To that end, McDowell and coworkers[124,126,147] proposed that monitoring vasoconstriction of the palmar artery in horses can provide a convenient, noninvasive, and satisfactory biomarker to determine premonitory signs of fescue toxicosis.

Ruminants

The most consistent deleterious health effects associated with fescue toxicosis in ruminants are due to vasoconstrictive properties of the ergot alkaloids. The vasoconstrictive effects of ergot alkaloids are well documented in cattle[151–153] and sheep.[154] Fescue toxicosis in ruminants is best characterized by the two maladies of “summer slump” in warm climates and “fescue foot” in cold climates.[110–112] Summer slump is associated with decreased weight gain,

elevated body temperature and respiration rates, shade-seeking behavior, rough hair coat, excessive salivation, and reduced milk production. Fescue foot is characterized by tenderness and/or swelling around the fetlock, lameness, tissue necrosis, and potential sloughing of the hoof, tips of ears, or tail switch. Clearly the previously described conditions may directly and indirectly affect reproductive performance, particularly elevated body temperatures and decreased weight gain associated with summer slump.

Fescue toxicosis associated with decreased reproductive performance in ruminants has been reported.[111,155] Cattle grazing E+ fescue pastures, compared with nontoxic forages, typically have reduced dry matter intake, reduced body condition scores, and reduced calving rates.[155–158] However, reports of reduced reproductive performance have not been consistent. Pregnancy rates for cows consuming E+ fescue were reduced 7% to 39% compared with control cows,[159,160] but other reports showed no reduction in pregnancy rates.[161,162] Serum progesterone concentrations may be reduced in heifers[143] and ewes,[163] and age of the animal may influence the effect of E+ fescue consumption on reproductive performance in cattle.[162] Jones[143] reported that heifers consuming E+ diets had shorter estrous cycle lengths and lower midcycle progesterone concentrations than heifers on E− and commented that vasoconstriction in the ovary may result in decreased peripheral progesterone concentrations.

Consumption of E+ fescue causes decreased concentrations of prolactin in cattle and sheep. This decrease in prolactin causes a decrease in milk production,[164] but rarely complete agalactia, as ruminants have placental lactogens that are thought not to be affected by fescue toxicosis. In addition to decreased prolactin production, cattle grazing E+ fescue also have altered expression of over 500 different genes in the pituitary gland, including genes controlling growth hormone, GnRH and ACTH,[165] decreased glutamatergic neurotransmission capacity,[166] and altered expression of several liver genes, including those involved in immune responses, oxidative phosphorylation, and ATP synthesis.[167]

Male Reproductive Function

E+ fescue may negatively impact reproductive performance in bulls and rams. Looper[156] reported that bulls grazing toxic E+ fescue pastures had reduced sperm motility and morphology compared with bulls grazing NE (nontoxic)

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pastures and that semen quality in bulls grazing E+ pastures was decreased as ambient temperature increased. In other studies, ergot alkoids inhibited sperm motility[168] and reduced IVF embryo cleavage rates.[169] Jones[170] reported that bulls fed a diet containing E+ fescue seed had increased scrotal temperature, reduced scrotal circumference, and increased sperm concentration compared with bulls fed a control diet. In addition, studies using Doppler ultrasonography demonstrated constriction of blood flow to the testes of bulls fed E+ fescue seed or allowed to graze E+ fescue pastures.[171] However, it is difficult to differentiate between direct effects of fescue toxicosis on male fertility versus effects of increased core and/or testicular temperatures due to vasoconstriction.

There is little information on the effects of E+ fescue on stallion fertility. One study showed no adverse effects of E+ fescue seed consumption on sperm motility, number, morphology, or testicular size, but it did result in reduced gel-free semen volume compared with control stallions.[172] Clearly, much more information on potential effects of fescue toxicosis on male fertility is necessary.

Mitigating Fescue Toxicosis in Grazing Livestock

Approaches to ameliorating adverse effects of fescue toxicosis have been reviewed[113,145,173–175] and include, among other things, renovation to remove or reduce the amount of E+ fescue in pastures; chemical suppression of seedheads in fescue; removal of animals from E+ infected pastures during times of growth or reproductive performance that may be affected by E+ fescue, using NE or E− tall fescues; and treating the animals with domperidone. Interestingly, clover isoflavones have been demonstrated to relieve alkaloid-induced vasoconstriction in goats,[122] and a single polymorphism in the *DRD2* receptor gene has been associated with resistance to fescue toxicosis in cattle.[176,177]

Ergotism in Human Populations—in Medicine and Disease

For interesting discussions on ergotism in human populations, see Strickland,[112] van Dongen and Groot,[178] and Schiff.[179]

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Approach to Diagnosis of Fescue Toxicosis

James P. Brendemuehl

Definitive diagnosis of fescue toxicosis involves identification of the causative endophytic fungus in forage or seed samples by microscopic examination (Boxes 12.12 and 12.13). Ergopeptine concentrations may additionally be determined by high-pressure liquid chromatography analysis or specific enzyme-linked immunosorbent assay (ELISA). A presumptive diagnosis of fescue toxicosis can be made in cattle on the basis of expression of the characteristic clinical signs of hyperthermia; excessive salivation; long, rough hair coat; necrosis of the tail and ear tips; and fat necrosis in association with consuming fescue forage. Hypoprolactinemia is supportive of the diagnosis, but the assay is not commercially available.

Box 12.12

Manifestations of Fescue Toxicity in Mares

Agalactia, hypogalactia
Hypoprolactinemia
Decreased relaxin prepartum
Prolonged gestation
Early embryonic death
Cyclic irregularity
Dystocia
Premature allantochorion separation
Allantochorion edema
Increased placental weight
Retained placenta
Corpus luteum persistence
Decreased pregnancy rates
Decreased total progestagens prepartum
Poor neonatal viability
Reduced colostral immunoglobulin G (IgG) absorption
Neonatal hypoadrenalism
Neonatal hypopituitarism

Neonatal hypothyroidism
Fetal oversize
Hirsutism
Hyperhidrosis

Box 12.13

Manifestations of Fescue Toxicity in Ruminants

Agalactia, hypogalactia
Reduced calf birth weight
Hypoprolactinemia
Reduced serum cholesterol
Reduced conception rates
Reduced pregnancy rates
Early embryonic death
Cyclic irregularity
Delayed return to cyclicity postpartum
Dystocia
Hyperthermia
Hyperpnea
Hirsutism
Reduced weight gain
Photosensitization
Necrosis of the digits
Necrosis of the ears and tail
Fat necrosis

A presumptive diagnosis of fescue toxicity in the pregnant mare is based on the observation of failure of normal mammary development for gestational stage. Prolongation of gestation is commonly reported as well. An accurate breeding history should include dates of breeding, dates of confirmed pregnancy diagnosis, and absence of parturition at the anticipated time. A history of recent exposure to fescue pasture or hay is supportive. In tall fescue–endemic areas,

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pastures that contain tall fescue grass should be considered infected with the endophyte unless specific testing has confirmed otherwise. Determination of total plasma progestogen concentrations is a sensitive indicator of endophyte exposure after 300 days of gestation.[180]

Management of a mare suspected of endophyte exposure should consist of removing the mare from the suspected pasture or hay source and maintaining the mare in a stall or dry lot under close observation. High-quality hay, preferably legume, should be provided. Because of the increased incidence of dystocia in mares grazing endophyte-infected tall fescue, close monitoring of the mare and attendance at parturition is critical to minimize risk to the mare and loss of the foal. Removal of mares from infected fescue by day 300 of gestation has been demonstrated to alleviate the toxic effects on the mare and foal. Removal after day 300 carries an increased risk of prolonged gestation, agalactia, dystocia, and neonatal death. Induction of parturition is not recommended because of the high incidence of fetal dysmaturity, fetal oversize, and failure of pelvic relaxation associated with endophyte exposure. Elective cesarean section deliveries of postdate gestation mares have resulted in significantly higher foal survival rates than spontaneous deliveries.

Where removal of pregnant mares from infected fescue is not practical or mares are inadvertently grazed on endophyte-infected fescue beyond the recommended stage of gestation for removal, pharmacologic intervention is warranted. Several DA_2 dopamine receptor antagonists—perphenazine,[181] fluphenazine,[182] and domperidone[183]—and the dopamine depleter reserpine[184] have been investigated prophylactically to prevent or therapeutically to treat clinical fescue toxicosis. Perphenazine[181] and fluphenazine[182] have demonstrated mixed success in preventing toxicosis in restricted clinical trials. Reserpine[184] was ineffective in preventing prepartum agalactia and prolonged gestation but was sufficient to resolve postpartum agalactia. Domperidone[185] has demonstrated efficacy in both the prevention and treatment of clinical fescue toxicosis in clinical trials involving large numbers of mares in numerous locations.

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Prolonged Gestation

Bruce W. Christensen

Many factors influence the duration of gestation in horses and ruminants. Normal variations in length of gestation have been attributed to genetic, nutritional, and environmental factors.[186,187] The species, breed, and sex of the fetus; ambient temperature; and length of photoperiod are among factors that, within normal variations, affect the duration of gestation.[20,186–188] The duration of pregnancy in Thoroughbred mares ranges from 310 to 374 days,[188] in dairy cows from 275 to 292 days, in beef cows from 271 to 310 days, in ewes from 143 to 155 days, and in does from 146 to 155 days.[189] Prolonged gestation periods are those that exceed the normal gestational variation attributable to genetic, nutritional, and environmental factors. In pathologic prolonged gestation there is an impediment to the mechanisms that terminate gestation and initiate parturition. Pathologically prolonged gestation has been attributed to genetic, infectious, and toxic factors,[190] as well as to manipulation of the embryo.[191,192]

Of the several forms of prolonged gestation with genetic causes in cattle, the best described forms have been observed in Guernsey and Holstein cattle.[20,187,190,193] In each the fetus fails to initiate parturition at term because of fetal adrenal hypoplasia. Prolonged gestation, from 3 weeks to 3 months beyond normal term, has been observed in a number of dairy cattle breeds.[194] Graves, Hansel, and Krook[193] described a Holstein fetus of 441 days' gestation in which the pituitary pars distalis was aplastic and the adrenal and thyroid glands were severely hypoplastic. Two different types of fetuses have been associated with prolonged gestation in cattle.[186] In the first type, fetuses had a large skeleton and excessive growth of epidermal organ structures such as hair and hooves but no obvious deformities. The second type of fetus was mature or immature and exhibited cranial and central nervous system anomalies; growth ceased at about 7 months of gestation. Both types of calves had hypoplastic or absent adrenal glands. These anomalies have been observed to be inherited as an autosomal recessive trait.[187,190]

Several infectious agents have been incriminated in prolonged gestation in ruminants. Bluetongue virus, bovine diarrhea virus, and border disease virus may cause severe cerebral lesions in the fetus, resulting in the absence of a

hypothalamus and pituitary stalk. Again, by virtue of the lack of adrenocorticotropic hormone, the sequence of events necessary for parturition does not occur.[190]

The use of assisted reproductive techniques in cattle in the form of in vitro procedures and somatic cell nuclear transfer ("cloning") offers advantages for reproducing important genetic lines, but they have many accompanying complications that have yet to be overcome. Besides increased pregnancy loss, increased birthweight of calves, and increased incidence of dystocia and perinatal losses, another complication is prolonged gestation in recipient cows compared with embryo transfer recipient and artificially inseminated cows.[191] This technology has great potential for manipulating and preserving superior genetic potential.[195] The cow has been the most successfully cloned animal to date, but such cloning still has a low success rate.[196–198] This is an active area of research, and it is still hopeful that with further understanding the current pitfalls surrounding in vitro procedures and nuclear transfer will be overcome and use of the techniques will become more commonplace.[197]

Veratrum californicum contains the teratogenic agent cyclopamine. When pregnant ewes ingest cyclopamine on the 14th day of gestation, their fetuses lack a pituitary gland or have a malformed hypothalamic stalk. These defects result in prolonged gestation by virtue of secondary adrenal hypoplasia.[190]

Prolonged gestation in mares has been cited as an indication for induction of parturition.[199,200] However, the clinical significance of prolonged gestation in mares is undetermined because there is no apparent correlation between duration of gestation and readiness for birth. Dysmature neonatal foals have resulted from gestations of normal and longer than normal durations; alternatively, 399 days' gestation resulted in births of normal twin foals.[201] Prolonged gestation in the mare has not generally been associated with excessively large foals and dystocia.[202] Therefore in the absence of clinical signs that warrant induction of parturition in a high-risk pregnancy and the fulfillment of criteria for induced parturition, there is no reason to perform elective parturition induction in mares in which gestation is prolonged.

Approach to Diagnosis of Prolonged Gestation

Approach to the diagnosis of prolonged gestation in mares and ruminants is essentially similar (Boxes 12.14 and 12.15). If the client is concerned about what is apparently prolonged gestation in an otherwise normal dam, an accurate

breeding history should be obtained. Because no pathognomonic clinical or laboratory findings are associated with prolonged gestation, the diagnosis is predicated on the history and a general physical examination of the dam. The overall condition of the dam should be determined. In addition to the reproductive history, exposure to infectious agents and toxic plants should be determined. The most important anamnestic factors are breeding dates, dates of confirmed pregnancy examinations, and absence of parturition at the expected time. The reproductive tract should be examined for the gravid uterus and evidence, although tenuous, of the term or near-term fetus. Diagnostic ultrasonography can be incorporated into the workup to enhance the assessment of viability and fetal well-being by determination of fetal heart rates, fetal size and movement, uteroplacental thickness, and estimation of allantoic fluid volume.[203,204] Parturition should not be induced unless the objective is fetal survival in the face of a high-risk pregnancy.[205] Otherwise, the mare should be examined and, if appropriate, the owner assured that the gestation is probably normal and that patience will likely result in a normal foal with adequate colostrum and passive immunity.[206]

Box 12.14

Causes of Prolonged Gestation in Mares

Fescue toxicity
Fetal mummification
Delayed embryonic development

Box 12.15

Causes of Prolonged Gestation in Ruminants

Fetal mummification
Fetal hypothalamic-hypophysial-adrenal axis disorder
Autosomal recessive genetic disorder affecting Holstein and Guernsey

cattle (B)
Vitamin A deficiency (B)
Veratrum album toxicity (B)
Veratrum californicum toxicity (cyclopamine) (O)
High environmental temperature (B)
Fescue toxicity
Hydrops amnii (B, O)
Bluetongue (B, O)
Bovine virus diarrhea (B)
Border disease (O)
Salsola tuberculata toxicity (Grootlamsiekte [exotic]) (O)
Akabane virus (exotic) (B, O)
Somatic cell nuclear transfer (B)

B, Bovine; *O*, ovine; *C*, caprine.

Dystocia

Mats H.T. Troedsson

Dystocia is defined as difficult parturition; it may be a sign of either maternal or fetal conditions that impede fetal passage through the birth canal.[20] Dystocia in mares and ruminants is more likely to be attributable to fetal causes such as malpresentation, malposition, and malposture than to maternal conditions[20,207] (Boxes 12.16 and 12.17). The overall incidence of dystocia and incidences of types of dystocia vary among the species and breeds within a species.[208] Cattle, especially first-calving heifers and larger breeds, are more commonly affected by dystocia; the overall incidence of bovine dystocia ranges from 3% to 25%.[20] The incidence of dystocia among Thoroughbred mares is 4%,[207] and in does it is 3% to 5%.[209] The incidence of dystocia is generally greater in sheep than in goats.[95] Dystocia represents an emergency situation that commands prompt resolution to afford the optimum prognosis for dam and fetus. Reposition, traction, fetotomy, and cesarean section are the obstetric procedures available for the management of dystocia.[210] The economics of large animal practice often play a significant role in determining which course to pursue in resolving dystocia. The lives of the dam and the fetus may be at risk. Although the objective should be the survival of both, unless otherwise advised by the owner and if conditions are not

prohibitive, the well-being of the dam and her reproductive potential should have priority over the fetus.

Box 12.16

Causes of Dystocia in Mares

Common Causes

Malpresentation
Malposition
Malposture
Abortion
Arthrogryposis
Twinning

Less Common Causes

Fescue toxicity
Preterm parturition
Torticollis
Vaginal, vulvar obstructions (hematoma, callus, abscess, tumor)
Pelvic injury, fracture

Uncommon Causes

Fetopelvic disproportion
Congenital defects
Hydrocephalus
Uterine dorsoretroflexion
Uterine torsion
Hydrops of fetal membranes
Rupture of prepubic tendon
Fetal mummification, maceration
Vaginal prolapse

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Abdominal, inguinal hernia
Uterine inertia
Induction of parturition
Premature separation of chorioallantois from endometrium
Uterine laceration

Box 12.17

Causes of Dystocia in Ruminants

Common Causes

Fetopelvic disproportion (B, common; C, O, uncommon)
Malpresentation
Malposition
Malposture
Twins, triplets (B)
Uterine torsion
Periparturient hypocalcemia (B)
Failure of cervix to dilate (B, O; rare in C)
Lymphedema

Less Common Causes

Preterm parturition
Abortion
Congenital defects (fetal monsters)
Hydrops of fetal membranes (B, O)
Emphysematous fetus
Hydrocephalus (more common in B than O, C)
Extremity ankylosis (more common in B than O, C)
Breeding immature, young, small-for-age females
Obesity (B)
Pregnancy toxemia (O, C)
Uterine inertia

Fetal mummification, maceration
Uterine, cervical, vaginal obstruction
Retained fetus
Pelvic fracture
Vaginal prolapse

Uncommon Causes

Phytoestrogen toxicity (B, O)
Rectovaginal constriction of Jersey cattle (B)
Uterine rupture
Abdominal, inguinal hernias
Lipomatosis (B)
Lupine poisoning, arthrogryposis (B)
Polybrominated biphenyl toxicity
Bovine fetal tumors
Rupture of prepubic tendon (B)
Hereditary edema, lymphedema in Ayrshire calves
Prolonged gestation (B, O)
Chlorinated naphthalene toxicity

B, Bovine; *C,* caprine; *O,* ovine.

Although parturition has been divided into three distinct stages for descriptive purposes, the stages overlap clinically and normal parturition is observed as a continuous process.[207] The equine fetus is lying in a ventral or ventrolateral position with head and forelimbs flexed during late gestation.[211] During the first stage of parturition the fetus plays an active role, along with myometrial contractions, in assuming correct extremity posture as it positions itself for delivery through the birth canal. The second stage of parturition commences with rupture of the chorioallantois and culminates in delivery of the fetus. Myometrial contractions continue during third-stage parturition, which ends with the expulsion of the placenta. In the mare, parturition is a forceful, explosive act. The time between rupture of the chorioallantoic membrane and delivery of the fetus is normally about 20 minutes.[20] Separation of the fetal membranes from the endometrium may occur within 1 to 2 hours after the second stage of parturition

commences; therefore the retained fetus must be delivered quickly or it will asphyxiate. Fetal expulsion in the ruminant is not quite as explosive as in the mare; second-stage parturition in the bovine usually requires ½ hour to 4 hours.[20] Ewes and does require a range of ½ hour to 2 hours to complete the second stage, or slightly longer if twins or triplets are present.[20] Primiparous animals generally require a longer time to expel the fetus than do multiparous dams.

Dystocia in large animals is often accompanied by forceful straining. The dam may attempt to lie down and stand repeatedly. This is characteristic of dams with dystocia that is caused by fetopelvic disproportion, malposture, or fetal impaction. Alternatively, the dam may stand quietly with minimal or no straining, as in cases of uterine inertia, uterine rupture, or exhaustion associated with prolonged dystocia of any cause. Whatever the presentation of the dam, the attending veterinarian must be prepared for unexpected behavior when attempting to perform obstetric examinations and procedures. General anesthesia followed by elevation of the hindquarter will facilitate safe manipulation and vaginal delivery of a foal in mares with dystocia. This technique, if applied correctly, will likely result in less damage to the mare's reproductive tract. If general anesthesia is not an option, the dam, fetus, attendants, and veterinarians must be protected from injury. The dam should be placed in open-ended stocks with movable sides or a straw-bedded box stall. During obstetric examination and manipulation, mares and cows may attempt to get up and lie down, or they may suddenly collapse. Such sudden movements may injure the dam and veterinarian if rigid, closed-end stocks are used. Minimum physical restraint should be used; however, restraint should be sufficient to permit completion of the obstetric examination and procedures with efficiency and safety.

Little is known about the pharmacokinetics of drugs in pregnant domestic animals. Accordingly, it must be assumed that sedative and anesthetic drugs will depress neonatal and fetal functions at least as much as those of the mare. The effects on myometrial activity of drugs administered to dams experiencing dystocia must also be considered. Acepromazine has little effect on the fetus and is generally considered safe for use in the pregnant mare. However, acepromazine was shown to have a suppressive effect on myometrial activity in cycling mares.[212] Xylazine causes significant fetal cardiovascular compromise in horses and has been reported to stimulate myometrial activity in cows and mares.[212–214] The fetal and myometrial effects of detomidine are similar but of

longer duration compared with those of xylazine.[212,213] The effects of detomidine on myoelectrical activity in the uteri of cows and mares treated during the last trimester of pregnancy were dose dependent.[215,216]

As equipment is being organized and the process of evaluating the dam begins, a pertinent reproductive history should be obtained, including the dam's age, her previous breeding history, and the outcomes of previous pregnancies (i.e., abortion, normal parturition, dystocia). Her present gestational status should be determined; has parturition commenced at term, or is it a preterm or postterm delivery? Her udder should be examined to determine the stage of development. Information about the progress of the current parturition should be obtained. The time since rupture of the chorioallantoic membrane, the duration and intensity of labor, whether fetal membranes or parts have appeared at the vulva, and previous attempts to assist in delivery should be noted. If the dam is recumbent, the veterinarian should determine if she has attempted to or been able to rise. Although a complete examination of the dam is optimum, it should be postponed until after the delivery of the fetus. However, in obtaining the dam's reproductive history, questions about her current physical condition should be included. Such predisposing factors as recent weight loss, systemic disease, and trauma should be considered. She should be assessed for signs of hemorrhage, dehydration, and shock.

After the tail has been wrapped, the perineal area should be thoroughly and gently washed and rinsed. Examination of the dam's reproductive tract may cause some discomfort or pain. Caudal epidural anesthesia (1 to 1.25 mL/100 kg of 2% lidocaine or other anesthetic) is often an excellent means of facilitating examination and resolution of dystocia and at the same time minimizing trauma to the dam, fetus, and operator. Lidocaine epidural anesthesia, however, may cause hindlimb weakness and ataxia. Safe and effective analgesia can also be induced by epidural administration of xylazine (0.17 mg/kg diluted in 10 mL physiologic saline). A combination of lidocaine (0.22 mg/kg) and xylazine (0.17 mg/kg) resulted in an onset of analgesia within a few minutes and a duration of over 5½ hours.[217] Although both vaginal sensitivity and the Ferguson reflex are reduced by epidural anesthesia, myometrial contractions and abdominal press are not totally eliminated unless the dam is put under general anesthesia. This approach has to be combined with an elevation of the hindquarter of the dam, in order to provide sufficient space for safe manipulation of the fetus. Great care must be taken during the examination of the genitalia and fetus. In addition to the viability of fetus and dam, the dam's future reproductive potential is at risk

and must be preserved. The vulva, vestibule, vagina, and cervix should be carefully examined. The location of the fetus in the birth canal, as well as its viability, presentation, position, and posture, should be determined. Schuijt and Ball[218] described a procedure to manually dilate the bovine birth canal before forced extraction is attempted. In the management of dystocia in any species, forced extraction should proceed only after maximal dilation of the caudal reproductive tract in order to minimize the potential for injuries to the dam during parturition (i.e., cervical, vaginal, and vulvar lacerations; hematomas; postparturient vaginal necrosis; and obturator, perineal, and gluteal paralyses).[20,219] Mares are especially susceptible to cervical lacerations, which may have detrimental consequences on the dam's future reproductive performance. Slow traction with continuous palpation of cervical stretching by the attending obstetrician is therefore recommended in equine dystocias.

The integrity of the birth canal, fluids, and fetal membranes serves as an indicator of the length of time the dystocia has persisted and the well-being of the fetus. Generous lubrication is required in all cases of dystocia and should be applied continuously during the management of dystocia to prevent damage to the dam's birth canal. Lubricating preparations consisting of methyl cellulose are superior to those consisting of mineral oil or soaps. Several liters of lubricants should be infused into the bovine and equine uterus by the use of a nasogastric tube.

Traction or forced extraction can usually be successfully implemented after correction of malpresentation, malposition, or malposture. Because of the length of the extremities of the foal, manipulation is more difficult in the mare than in the cow and requires extensive repulsion to provide adequate room for manipulation. Examination and manipulation can be greatly facilitated by elevating the mare's hindquarters under general anesthesia, enabling the fetus and viscera to recede cranially into the mare's abdominal cavity, thereby allowing more room for the operator.[220] If a nonviable fetus cannot be delivered by traction or forced extraction or if the owner is unwilling to select cesarean section, fetotomy can be performed.[210,220] Beyond the delivery of the nonviable fetus, fetotomy is indicated to save the mare and her subsequent fertility.[210] The advantages of fetotomy include avoiding major abdominal surgery (cesarean section) and its complications and preserving the birth canal because excessively large parts are not forced through it.[20,219–221] At the same time, the primary disadvantage of fetotomy, particularly if not properly performed by an

experienced obstetrician, is trauma to the birth canal by instruments, wire, or bone.[20] The indications, equipment, procedures, and complications of fetotomy have been reviewed in several publications.[20,210,219–221]

Cesarean section is indicated for a dam with dystocia when attempts to deliver the fetus by reposition, traction, and fetotomy are unsuccessful or contraindicated, and continued attempts may compromise the fetus, the dam, or her subsequent fertility.[20,95,201,205,208,222–227] Cesarean section may be the only rational procedure for delivery of some fetuses (e.g., emphysematous fetuses, deformed fetuses, bicornuate fetuses). In addition, high-risk pregnancies caused by maternal conditions can be effectively and efficiently managed by cesarean section.[205] The specific indications, procedures, and complications of cesarean section have been reviewed in a number of publications.[20,201,205,208,222–227]

Management of a case of dystocia is not complete until a systematic examination, focusing on the dam's reproductive tract, has been conducted. Complications during dystocia involving the reproductive tract and other body systems can affect the outcome of the case.[20,202,228,229] As much as possible, examination of the dam's reproductive tract should rule out the presence of another fetus in the uterus or abdominal cavity.[20] The most common reproductive injuries incurred by dams during parturition include cervical, vaginal, and vulvar lacerations; hematomas; postparturient vaginal necrosis; and uterine hemorrhage.[206,219,229] Gastrointestinal complications, such as constipation associated with unwillingness to defecate, postpartum perineal inflammation, and bruising or rupture of entrapped or compressed segments of the gastrointestinal tract, can follow parturition in the mare.[229] Musculoskeletal and neurologic complications have been reported after parturition in cows and mares.[20] Retained placenta, delayed uterine involution, metritis, and laminitis may result from normal parturition but are more likely sequelae of dystocia.[20,229,230]

The signs associated with normal progression of each of the stages of parturition must be explained carefully to clients and farm managers. It is only through understanding the clinical signs associated with events of normal parturition that clients become proficient at recognizing abnormal events and know when to seek professional assistance.

Retained Fetal Membranes

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Mats H.T. Troedsson

Retained fetal membranes represent the failure of the entire or partial placenta to be expelled within physiologic time limits. Although variation exists among species regarding the duration of time that must pass before a placenta is considered retained, the condition is one of the most common complications occurring in animals after parturition.

Retained Fetal Membranes in Mares

The anatomic structure of the equine placenta is described as diffuse, epitheliochorial, and microcotyledonary. It is composed of the allantochorion, the allantoamnion, and the umbilical cord.[231] During most normal foalings, the separation of fetal membranes from the endometrium and their subsequent expulsion occur within ½ hour to 3 hours of the delivery.[210,232,233] The incidence of retained fetal membranes is 2% to 10% in the mare, with a higher incidence in draft horses than in lighter horse breeds.[234] The cause of retained fetal membranes remains unclear, but it is believed that allantochorionic microcotyledons near the tip of the nongravid uterine horn have failed to separate as a result of an endocrine unbalance, a disturbance in normal myometrial contractions, or any swelling at the site of microcotyledons[235] (Box 12.18). Diagnosis of retained fetal membranes in the mare is straightforward when it is based on the observation of membranes hanging from the vulva beyond 3 hours after foaling. However, if the fetal membranes fall cranially over the pelvis, they remain within the uterus without being visible, and the diagnosis must be made using vaginoscopy or ultrasonography or by digital intrauterine examination. If an early diagnosis of complete or partial retention of fetal membranes has been missed, the diagnosis may be made 1 to 2 days after foaling. At this time, clinical signs indicative of metritis are often present (i.e., fever, depression, colic, and/or laminitis).

Box 12.18

Causes of Retained Fetal Membranes in Mares

Common Causes

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Dystocia
Preterm parturition
Abortion
Endometritis, metritis
Twinning
Induced parturition
Stillbirth

Less Common Causes

Fetotomy
Cesarean section
Placental edema at uterine horn tip
Placentitis
Drugs
Prolonged gestation
Fescue toxicity
Poor condition, poor environment, fatigue, increasing age, and other debilitating conditions
Hypocalcemia
Dropsy of fetal membranes
Entrapped placenta

After their expulsion, the fetal membranes should be stored until they can be scrutinized to determine if they are complete. The clinician should rinse the fetal membranes with water and, on a flat surface, thoroughly examine them for completeness.[236] Evidence that a part of the placenta is retained in the uterus or that an area of microvilli has been sheared off and retained in the endometrial crypts is an indication for digital endometrial examination or ultrasonographic examination and institution of appropriate therapy (see Chapter 43).

Approach to Diagnosis of Retained Fetal Membranes in Mares

History.

Many cases of retained fetal membranes follow episodes of dystocia, cesarean

section, and fetotomy. An increased incidence of retained fetal membranes has been reported in mares that abort after the seventh month of gestation.[234] However, no increase in the incidence of retained fetal membranes associated with abortion, stillbirth, twinning, and delivery of a weak or diseased foal was observed if it occurred without dystocia.[237]

Physical Examination.

Fetal membranes must be examined after their expulsion to determine their entirety and integrity. Tears, missing areas of tissue, and areas of chorionic surface devoid of microvilli should be considered evidence of partly retained fetal membranes, and immediate action should be taken to enhance expulsion of retained tissue and minimize complications.

Vital signs may be normal early in cases of retained fetal membranes. A rectal examination should be performed to determine the degree of uterine involution. Aseptic intrauterine palpation can be performed to determine the area and extent of retention and the integrity of involved tissues and fluid.[236] Systemic signs of dehydration, septicemia, toxemia, and laminitis may accompany fetal membranes retained for 24 to 36 hours.[229] Occasionally mares with retained fetal membranes show signs of colic. Therapeutic approaches for retained fetal membranes in mares are discussed in Chapter 43.

Retained Fetal Membranes in Ruminants

The anatomic structure of the ruminant placenta is described as cotyledonary and epitheliochorial.[233] It is composed of the allantochorion, allantoamnion, and umbilical cord. Fetal membranes are considered pathologically retained in the cow if they are not expelled by 8 to 12 hours after calving.[232,233] The incidence of retained fetal membranes in dairy cattle is 3% to 12% after normal parturition.[238] Dairy cows are more commonly affected than beef cows.[238] The incidence of retained fetal membranes may exceed 50% after abnormal parturition or abortion and in brucellosis-infected herds.[238] The retained placenta itself is relatively innocuous, but the condition is important because cows with retained fetal membranes experience an increased incidence of postpartum complications such as metritis, pyometra, ketosis, mastitis, delayed conception, and abortion.[214,239] The principal cause of retained placenta in cattle is a disturbance in the loosening process between the fetal cotyledons and maternal

caruncles[240] (Box 12.19). The processes that lead to successful loosening and separation of the placentome occur during the months preceding parturition. Many infectious and noninfectious factors are believed to disrupt the separation and expulsion processes. An endocrine causal relationship does not appear to exist.[241]

Box 12.19

Causes of Retained Fetal Membranes in Ruminants

Common Causes

- Multiple births
- Induced parturition
- Placentitis (bacterial, fungal infection)
- Hypocalcemia
- Abortion
- Stillbirth
- Dystocia
- Abnormal gestation length

Less Common Causes

- Injury, inflammation, or edema of placentome
- Cesarean section
- Uterine torsion
- Necrotic placentome secondary to uterine and systemic disease
- Excessive weight gain during dry period
- Uterine atony
- Dropsy of fetal membranes
- Entrapment of separated placenta
- Prostaglandin $F_{2\alpha}$ deficiency
- Trace mineral deficiencies (selenium and iodine)
- Vitamin deficiencies (carotene, vitamins A and E)

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Mineral deficiencies, imbalances (calcium and phosphorus)
Heat stress
Increasing age
Nitrate toxicity
High milk production

Clinical signs of retained fetal membranes in the doe and ewe are similar to those in the cow. The placenta of the ewe and doe is considered retained if it is not expelled within 24 hours after parturition.[95] The incidence of retained placentas in does is 6.4%.[242] Placental retention for longer than 24 hours may cause metritis in ewes and does. Inadequate dietary selenium and inadequate nutrition and exercise during gestation have been seen as factors predisposing does to retained placentas.[242] There have been several reports on factors that predispose to retained fetal membranes.[210,232,233,238,240,243,244] Many infectious and noninfectious factors apparently contribute to the disruption of the process of loosening and separation of the placentome. Accordingly, it has been suggested that a retained placenta should be considered to be a sign of an underlying disease.[245]

Approach to Diagnosis of Retained Fetal Membranes in Ruminants

History.

A review of accurate breeding records correlates retention of fetal membranes with the duration of pregnancy. Gestational periods of abnormal lengths result in a higher incidence of retained placenta than do normal-term parturitions. Induced parturition, twinning, and late-term abortions have been associated with retained fetal membranes in cows. Many periparturient diseases and conditions affect the incidence of retained fetal membranes.[210,232,233,238,240,243,244]

Physical Examination.

In cows that have calved spontaneously and without problem after a normal gestation period, little illness tends to be associated with retained fetal membranes, and treatment may be unnecessary. Transient decreases in appetite and milk production may be observed.[238] However, metritis, toxemia, and

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septicemia may be observed when retention of fetal membranes is associated with gestation of abnormal length, dystocia, nutritional deficiencies, or certain infectious diseases. Metritis affects up to 90% of cows with retained fetal membranes.[243] For considerations for the treatment of retained fetal membranes in cows, see Chapter 43.

Alterations in Lactation

Bruce W. Christensen

The mammary glands are modified cutaneous glandular structures considered accessory reproductive organs that function to secrete milk for the nourishment of the young.[246] The mammary glands are located in the prepubic region in the mare, cow, ewe, and doe. The cow's udder is composed of four mammary glands, whereas in the doe, ewe, and mare the udder has two mammary glands. One teat serves each mammary gland, and in the cow, ewe, and doe each teat has one streak canal. The mare has two streak canals per teat.

The mammary glands are ectodermal in origin, and most of their fetal development occurs during the first half of gestation.[247] Except for growth that occurs in association with some of the anomalous conditions of the mammary gland or as a result of the deposition of fat, there is little growth of mammary tissue between birth and puberty. Further mammary gland development occurs with each estrous cycle after the onset of puberty. Development of the duct system is primarily attributable to estrogen. Progesterone is the principal stimulant to development of secretory tissue. However, neither estrogen nor progesterone alone or in combination can cause optimum mammary gland growth and development.[248] Insulin, cortisol, thyroxine, prolactin, and growth hormone are necessary for full mammary gland development. During pregnancy the mammary gland attains maximum development under the control of pituitary, ovarian, adrenal, and placental hormones.[249] During parturition a process of interrelated neuroendocrine processes initiates lactogenesis, the production of milk. The secretion of milk and its release from the mammary gland after parturition depend on the availability of appropriate amounts of the hormones named previously, especially prolactin and oxytocin.

In addition to mastitis, conditions that manifest themselves as alterations in the mammary gland and lactation are fairly common in ruminants and horses. Problems caused by conditions that affect the mammary gland are often multifactorial in that they compromise the well-being of the patient, the nutrition

of the offspring, and ultimately the economics, especially in commercial dairies.

Enlarged Mammary Gland

Many conditions and diseases of the mammary gland cause swelling or enlarging of the gland[250] (Boxes 12.20 and 12.21). Enlargement may involve one or more of the glands of the udder. However, the enlarged mammary gland is not necessarily inflamed. Several anomalies of the mammary gland cause noninflammatory enlargement of the gland (e.g., gynecomastia, precocious udder development).[250–252] It is important to determine whether the enlargement of the gland is attributable to an infectious or a noninfectious cause. Trauma is probably the most likely cause of noninfectious inflammation of the mammary gland. Mastitis, with which a large number of organisms have been associated, is the most common cause of mammary gland inflammation (see Chapter 36).

Box 12.20

Causes of Enlarged Mammary Glands in Mares

Common Causes

Mastitis
Abscessation
Periparturient udder edema (physiologic)
Gland distention associated with weaning

Less Common Causes

Trauma (contusion, hematoma, seroma, laceration)
Neoplasia (malignant melanoma, carcinoma)
Cutaneous histoplasmosis *(Histoplasma farciminosus)*

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Box 12.21

Causes of Enlarged Mammary Glands in Ruminants

Common Causes

Mastitis
Periparturient udder edema
Abscessation
Trauma (contusion, hematoma, seroma, laceration)
Pendulous udder (B, C)
Blind quarters (aplastic duct) (B)

Less Common Causes

Eczema
Urticaria (irritants, caustic chemicals; contact dermatitis; insect bites)
Sarcoptic and psoroptic mange
Primordial mammarian tissue swelling (accompanies witch's milk)
Photosensitization
Sunburn
Frostbite
Cowpox (B)
Pseudocowpox (B)
Goat pox
Contagious ecthyma (orf) (C, O)
Furunculosis, abscesses
Staphylococcal folliculitis
Papillomatosis, warts
Caprine arthritis-encephalitis (C, O)
Zearalenone toxicity
Neoplasia (lymphosarcoma, malignant melanoma [C], squamous cell carcinoma [C])
Milk allergy (B)
Tuberculosis (B)

Ovarian neoplasia
Caseous lymphadenitis (O, C)
Cutaneous lipomatosis
Enzootic mycobacterial nodular-ulcerative mammillitis (B)
Bovine herpesvirus mammillitis (BHV-2) (B)
Precocious udder development (B, C)
Udder cysts (C)
Gynecomastia (C)
Pseudopregnancy (C)
Foot-and-mouth disease (exotic)

B, Bovine; *C*, caprine; *O*, ovine.

Evaluation of a patient with an enlarged mammary gland should include the medical and reproductive histories. The age and sex of the animal may limit the considerations. Gynecomastia is seen in young bucks, rarely in rams and bulls, and never in stallions.[250,252] Congenital anomalies such as stenotic or absent teat canals are not determined until parturition occurs and lactation commences.[250] The animal should be given a complete physical examination, with emphasis on the affected mammary gland. Examination of the gland should include observation, palpation, and expression of its contents. Cytologic and bacteriologic examination of the secretion from the mammary gland may be helpful in determining the cause and establishing the prognosis of enlarged mammary glands. In postpartum cows the most common causes of enlarged mammary glands are periparturient udder edema and mastitis. Mastitis occurs most often in mares after weaning. Trauma to the udder is more likely to be problematic in cows and goats than in ewes and mares because the udder is more pendulous in the former.[250] Undesirable udder traits of genetic origin occur in the goat (e.g., hanging or saclike udder, polythelia, blocked teat).[253] Lacerations, superficial contusions, and seromas are detected by close examination of the affected gland. Diagnoses of other injuries may rely on examination of the gland's secretion for evidence of increased cellularity and hemorrhage. Mammary gland neoplasia is rare in mares, cows, and small ruminants.[250,254–256]

Udder Edema

Udder edema, one of the most common causes of enlarged mammary glands,

results from the excessive accumulation of intercellular fluid in the mammary gland (Box 12.22). The disorder is observed during the late gestation and early postpartum periods and is common in both horses and ruminants, but it is probably more frequently seen in dairy cattle. One study reported an udder edema incidence of 18% in dairy cattle, of which less than 1% required veterinary treatment.[257]

Box 12.22

Causes of Udder Edema

Mares

Periparturient udder edema (physiologic)

Ruminants

Periparturient udder edema (physiologic)
Hereditary predisposition
Overfeeding of grain prepartum
Excess dietary protein
Obesity
Excess dietary sodium, potassium
Hypomagnesemia (chronic udder edema)
Disturbances in udder blood and lymph circulations
Excessively long dry period
Anemia

Two forms of udder edema are seen in cattle.[258] In the physiologic or acute form, there is edema of the mammary gland during the late gestation and early postpartum periods.[258] The entire udder is usually symmetrically involved, and the edema may involve adjacent abdominal and perineal areas.[258] The condition is usually not obviously painful but may cause the cow some difficulty in lying down and walking because of the mammarian swelling. Chronic bovine udder edema differs from the acute form in that affected cows develop udder edema

within 6 weeks after calving, and the edema may persist for several months.[258] The swelling may be localized in the form of plaques on the ventral aspect of the rear of the udder, or it may involve the ventral abdominal wall.[258]

Udder edema is a relatively common condition of dairy goats.[259] Two-year-old does kidding for the first time are most commonly affected; however, all ages can be affected. Affected does usually have colostrum at parturition, but within a few hours the udder is warm, hard, and agalactic.

Broodmares affected with udder edema have generalized ventral edema during the last 1 to 2 weeks of gestation and for as long as 2 to 3 days after foaling. The extent of ventral edema varies, ranging from local swelling of the udder and immediately adjacent subcutaneous tissues to a generalized swelling that may extend from posterior to the mammary glands forward, along the ventral abdomen and thorax, to the axillary or pectoral area. In the mare such edematous accumulations are referred to as *plaques of edema.* Affected broodmares seem to be uncomfortable and reluctant to move. Younger broodmares, especially primiparous mares affected with udder edema, appear to be in more pain than older mares, and some of the mares so affected refuse to allow their foals to suckle.

Agalactia

Any disease or condition that adversely affects the dam has the potential to compromise lactation. Agalactia, the failure of lactation after parturition, may be attributable to a primary endocrinologic or mammary gland problem, or it may be secondary to any of a multitude of systemic conditions and diseases (Boxes 12.23 and 12.24). True agalactia may be attributable to mammary gland anomalies or inadequacies among the numerous endocrinologic factors of development and pregnancy. Agalactia may be a complication of many conditions. In some animals the conditions to which agalactia is secondary manifest as alterations in a specific system, whereas other animals with agalactia may demonstrate such signs as fever, weight loss, anorexia, and anemia. Inadequate nutrition is rarely the cause of clinically observed agalactia. Fescue grass toxicity, caused by ingestion of the ergot alkaloid–producing *Acremonium coenophialum,* is an important cause of agalactia and hypogalactia[260,261] (see Clinical Signs of Fescue Toxicosis earlier).

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Box 12.23

Causes of Agalactia and Hypogalactia in Mares

Common Causes

Mammary aplasia, hypoplasia
Abscessation
Mastitis
Abortion
Premature birth
Postpartum complication

Less Common Causes

Endocrine dysfunction
Nutritional deficiencies, malnutrition
Neoplasia
Squamous cell carcinoma
Malignant melanoma
Pituitary adenoma
Lymphosarcoma
Other tumors
Fescue toxicity
Trauma to mammary gland
Periparturient disease
Dystocia
Anemias
Severe toxicity

Box 12.24

Causes of Agalactia and Hypogalactia in Ruminants

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Common Causes

Mammary aplasia, hypoplasia
Mastitis
Abscessation
Caseous lymphadenitis (udder involvement) (C, O)
Caprine arthritis-encephalitis (CAE; hard udder) (C, O)

Less Common Causes

Endocrine dysfunction
Malnutrition
Water deprivation
Self-sucking (B, C)
Trauma
Chapped teats; teat dip irritation (B, C)
Milk allergy
Neoplasia
Malignant melanoma (C)
Lymphosarcoma
Squamous cell carcinoma
Carcinomas
Fescue toxicity
Papillomatosis
Mycoplasmal agalactia (C, O)
Anemias
Severe toxicity

B, Bovine; *C*, caprine; *O*, ovine.

Agalactia should not be confused with failure of milk ejection (milk letdown). Administration of oxytocin may enhance milk letdown but does not affect milk production. Oxytocin stimulates a release phenomenon that acts on previously secreted and stored milk. Although somatotropin may increase milk production in a normally lactating cow, its effect on agalactia has not been adequately studied.

Inexperienced or nervous mares with adequate milk are often reluctant to allow their offspring to nurse, in part because of the mare's inexperience. Such nervous mares need not necessarily be primiparous mares. Although not allowing their offspring to nurse is usually a manageable behavior problem, the mare's udder should be examined for evidence of periparturient edema, inflammation, and painful conditions.

Approach to Diagnosis of Agalactia.

An accurate reproductive history should be obtained. It should be determined whether the dam is primiparous or multiparous. If primiparous, is she manifesting anxiety in the presence of her offspring? If multiparous, has she been agalactic at previous parturitions? Has she sustained recent trauma, perhaps during parturition, or was there exposure during gestation to infectious diseases or toxic plants? After a history has been determined and the dam and neonate have been observed, attempts to facilitate the youngster's suckling might be indicated. Is the dam agalactic, or does she simply refuse to let the neonate suckle? Such measures as twitching or tranquilizing the nervous and inexperienced mare may resolve that problem. If assessing the dam's behavior toward her offspring does not resolve the problem, a thorough physical examination should be initiated. The objective now should be to rule out or incriminate infectious and inflammatory conditions contributing to the agalactic state. The dam herself may be systemically affected, or the problem may be localized in the udder or a mammary gland.

In listing causes of agalactia and hypogalactia in Boxes 12.23 and 12.24, the authors included only those that have a direct effect on the anatomic integrity of the mammary gland or its function. Abnormalities involving any system may compromise lactation.

Galactorrhea and Precocious Mammary Gland Development

Galactorrhea, the abnormal manifestation of lactation (not the secretion of true milk), occurs occasionally from the primordial mammary gland of young foals and ruminants, including neonates.[250] The secretion is popularly known as *witch's milk.*

Precocious mammary gland development and galactorrhea occur in pregnant and nonpregnant mares and in some of the ruminant species (Box 12.25). Such

premature udder development and subsequent lactation have been observed in nonpregnant and nonsuckled doelings and heifers.[250,262] Udder development and subsequent lactation have been observed in young nonpregnant heifers and does being suckled by other young animals.[250] In addition to the continued stimulation of suckling, other causes of premature mammarian development and lactation may be trauma and diseases of the pituitary, ovarian, and adrenal glands.[250] Zearalenone toxicity has been implicated in precocious mammary gland development and lactation in heifers.[263] Milk production is nonphysiologic in that it is of insufficient quality and quantity and does not justify milking the affected animals. There is no evidence that such abnormal development compromises normal lactation after parturition.[250]

Box 12.25

Causes of Galactorrhea and Precocious Mammary Gland Development in Horses and Ruminants

Impending abortion
In utero death of one twin fetus
Spontaneous (inappropriate prolactin secretion)
Placental separation
Zearalenone toxicity
Pregnancy (especially multiple fetuses)
Suckling
Pseudopregnancy (caprine)
Ascending infection during pregnancy, placentitis
Ovarian tumors

Inappropriate lactation has been observed at various stages of pregnancy in most domestic species.[250] The most common cause of galactorrhea is abortion. Lactation may commence before or even without expulsion of the dead fetus. Lactation during pregnancy has also been observed in association with multiple fetuses, placentitis, and ovarian tumors. Accordingly, premature mammary gland

development during gestation should be considered a warning of impending abortion, and the dam should be examined. Occasionally, pregnant mares develop mammarian enlargement during middle to late gestation that spontaneously regresses.[261] Some of these mares begin to lactate before parturition. It must be kept in mind that premature lactation and subsequent loss of colostrum is one of the most important causes of failure of passive transfer of immunoglobulins.[264]

Gynecomastia, the abnormal development of the male's mammary glands, has been observed in bucks in which rudimentary mammary glands and associated teats underwent development.[250,262] The aberrant structures, located on both sides of the buck's scrotum, can secrete up to 1 L daily of a substance that resembles milk. The cause is presumed to be endocrine imbalance but has not been determined. Lofstedt and colleagues[265] reported adrenal neoplasia as a cause of lactation in a wether.

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• CHAPTER 13

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Musculoskeletal Abnormalities

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▪ Major Clinical Signs or Problems Encountered

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Lameness and Stiffness

Randall B. Eggleston • John Maas • Carter E. Judy

Lameness is the term used to describe a condition in which an animal is incapable of normal locomotion. Generally, lameness is characterized by an inability to maintain a normal gait, manifested by asymmetry in movement, apparent incoordination or weakness, and inefficient or ineffective motion of the limbs. Lameness can usually be assessed only when the animal is moving under its own power, although lameness severe enough to cause an inability to bear weight can be assumed at a standstill. The onset of lameness can be acute (e.g., fracture), chronic (e.g., degenerative joint disease), or acute on chronic (e.g., catastrophic fracture secondary to stress fractures).

Mechanisms of Lameness and Stiffness

The ultimate effects of any cause of lameness are restricted movement of the limbs or body, reduced performance, and abnormal gait. Causes of lameness are generally associated with conditions of the musculoskeletal system or nervous system. Most causes of lameness have both a musculoskeletal component (e.g., atrophy of the supraspinatus and infraspinatus muscles) and a neurologic component (e.g., suprascapular neurapraxia). Some causes of lameness have only a musculoskeletal component (e.g., upward fixation of the patella) and are not principally associated with either afferent nerve signs (i.e., pain) or efferent nerve signs (i.e., motor dysfunction). Similarly, other causes of lameness are solely related to a motor nerve deficit (e.g., radial neurapraxia).

Unlike the usual definition of lameness, *stiffness* refers to a generalized restriction in freedom of movement in a limb, the neck, or back. Stiffness is manifested by a limited range of motion by a joint, reduced length of stride, or decreased flexibility during bending or turning. For example, cellulitis and soft tissue swelling in the area of the tarsocrural joint can cause restricted freedom of movement of the hind limb and an apparent lameness, yet there may be no specific musculoskeletal or neurologic cause. Stiffness may have either congenital or acquired causes, and the clinical signs may be mild and transient or severe and persistent. Stiffness may or may not be associated with pain.

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Approach to Diagnosis of Lameness and Stiffness in Horses

The lameness examination is the most commonly performed assessment of the musculoskeletal system in the horse. The examination should be well planned, consistent, and thorough. Knowledge of all diseases capable of causing lameness is not required, as long as the examiner maintains an open mind and objectivity during the examination (Box 13.1). The goals of the lameness examination are to determine which limbs are affected, differentiate between supporting limb and swinging limb lameness, and establish the musculoskeletal and/or neurologic components producing the lameness.

Box 13.1

Causes of Lameness and Stiffness in Horses

Common Causes

Infections of the foot
Bruised or punctured sole
Hoof wall defects
Fractures
Septic (infectious) arthritis
Laminitis
Secondary (degenerative) joint disease
Navicular disease
Osteomyelitis
Fibrotic or ossifying myopathy
Rhabdomyopathy (tying up)
Sprain
Strain
Tenosynovitis
Contracted tendons (flexural deformity)
Ankylosis or arthrogryposis
Osteochondrosis or bone cyst
Cruciate or meniscal rupture

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Luxation or subluxation (dislocations)
Upward fixation of the patella (locking patella)
Sesamoiditis
Muscle injury, soreness, bruise, trauma, compartment syndrome
Subcutaneous abscess, cellulitis
Angular limb deformities
Disruption of the suspensory apparatus (broken down)
Postanesthetic equine myasthenia
Tendon rupture, damage, tendonitis (bowed tendon)
Osteomalacia, osteodystrophy (rickets)
Bucked shins
Epiphysitis (physeal injuries)
Purpura hemorrhagica

Less Common Causes

Shivers (shivering)
Borreliosis (Lyme disease)
Equine monocytic ehrlichiosis (Potomac fever)
Chronic selenium toxicity
Hemangioma, hemangiosarcoma, angiosarcoma
Skeletal neoplasia
Rabies
Spondylitis, diskospondylitis
Spinal or vertebral neoplasia
Vertical column malformation
White muscle disease (nutritional myodegeneration)
Gunshot injury
Corynebacterium pseudotuberculosis
Hypothyroidism (goiter)
Actinobacillosis
Hyperparathyroidism
Ulcerative lymphangitis
Myotonia congenita
Vesicular stomatitis
Fistulous withers (*Brucella abortus* or other organisms)
Sporadic equine lymphangitis

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Acute necrotizing equine vasculitis (with or without thrombocytopenia)
Peripheral arteriovenous fistula
Hypertrophic osteopathy or osteodystrophy

Uncommon Causes

Nocardiosis
Cutaneous blastomycosis
Pemphigus foliaceus
Tuberculosis
Multisystemic postexhaustion syndrome
Generalized steatitis
Cutaneous vasculitis
Sterile nodular panniculitis
Multiple clotting defects in ill foals
Salmonellosis
Factor VIII deficiency (hemophilia A)
Idiopathic equine aplastic anemia
Idiopathic equine thrombocytopenia
Hemimelia (radial, tibial, ulnar hypoplasia, agenesis)
Lupus erythematosus (rheumatoid arthritis)
Phycomycosis
Bone fragility disorder

Poisons, Toxins, Deficiencies, and Excesses

Moldy sweet clover poisoning
Strychnine toxicity
Tetrachlorodibenzodioxin (dioxin) toxicity
Warfarin (dicumarol) toxicity
Vitamin K–induced renal toxicity
Calcinosis resulting from plant poisoning
Zinc toxicity
Phosphorus toxicity
Phosphorus deficiency
Vitamin D toxicity

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Locoweed-associated limb deformities or stringhalt-like gait
Chronic fluoride toxicity

1. History. The lameness examination begins with the client interview. A summary of the important historical features of the lameness should include answers to basic questions about the following:
    - Onset (e.g., When was the last time the horse was seen sound? Was the lameness acute in onset, or did it have a slow, insidious onset?)
    - Characteristics of the lameness (e.g., Is the lameness seen more in hand, at the lunge, or under saddle?)
    - Associated or inciting factors (e.g., injury) that may have contributed to or caused the lameness.
    - Changes in the characteristics, intensity, and duration of the lameness.
    - Responsiveness to treatment (e.g., Has the horse received any type of treatment, and, if so, what was the response?)
    - Time since the last hoof trimming and shoeing, and whether or not the horse's shoeing was changed.
    - In addition, the signalment and activity that the horse undertakes (e.g., jumping vs. racing) should be ascertained and may be a guide in determining potential causes of the lameness (e.g., stress fractures are more common in racing Thoroughbreds, and osteochondrosis is more commonly diagnosed in young animals).
2. Observe from a distance—stationary phase. Observing the horse from a distance while it is stationary permits an assessment of the horse's conformation, position, and posture. The horse should be viewed from the front, from behind, and from both sides. Special note should be made of any abnormality in the following:
    - Conformation. A number of conformational abnormalities have been associated with lameness. For example, upright pastern conformation predisposes to pastern disease and foot lameness; offset or bench knees predispose to carpal disease; and straight through the hocks or post-legged conformation predisposes to upward fixation of the patella, suspensory desmitis, and fetlock disease. Poor conformation can affect

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the young horse when it is put into training or can cause a slow insidious onset of lameness. Recognizing these conformational abnormalities at the time of examination can be helpful in diagnosing potential causes of lameness. When a horse is evaluated for purchase, recognition of poor conformation should be noted and discussed as a source of future lameness problems.

- Position of the head (e.g., tilted, turned).
- Distribution and equality of muscle mass along the neck and trunk.
- Topographic symmetry of the front limbs, from the dorsal region of each scapula to the hoof. From the rear, the height and mass of the hip musculature and the symmetry between the hindlimbs should be assessed. From each side, abnormalities in stance (e.g., camped out in front) or load bearing (e.g., dropped elbow) and the position of the head and neck (e.g., hyperflexed poll) should be compared.

3. Physical examination and palpation. Palpation enables a closer inspection of the horse and identification of abnormalities that may or may not otherwise be noticed. A thorough examination of the musculoskeletal system allows for identification of palpable abnormalities and also offers the opportunity for the practitioner to refine the identification of normal structures; subtle abnormalities cannot be appreciated unless the examiner is skilled at recognizing normal anatomy. There are also many instances in which normal structures palpate abnormally but are not necessarily associated with lameness (e.g., flexor tendon sheath [windpuffs, windgalls] and palmar or plantar metacarpophalangeal joint [MCPJ] pouch effusion [wind puffs]). The examination should be conducted consistently and thoroughly starting with the cervical neck and concluding at the tail. Abnormal findings should be described to identify their location on the limb, their size, and their orientation relative to normal anatomic landmarks. Palpation of the upper limb is often limited to the overlying muscle mass, with identification of any atrophy, hypertrophy, pain, or fibrosis. Articular structures and surrounding ligamentous structures can be difficult to palpate because of the overlying muscle. Deep palpation of the thoracolumbar and gluteal musculature can provide clues to potential

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hindlimb lameness and tack or rider issues. The pelvis, iliac arteries, and sublumbar musculature can be evaluated by rectal palpation while the horse is standing quietly; movement or crepitation can be assessed while swaying the horse from side to side.

Particular attention should be directed toward palpation of the limbs. The majority of lameness will originate from the carpus distally in the front limb. Common sources of lameness in the hindlimb can be identified from the stifle distally. All palpable structures should be evaluated, including skeletal structures, synovial structures, and soft tissue structures (tendons and ligaments). This portion of the examination can be performed using different methods, by either palpating each tissue in one pass of the limb or making multiple passes of the limb, palpating each tissue structure separately. Regardless of the preferred technique, a consistent and complete examination should be performed. Once the limbs have been palpated in the weight-bearing position, the examiner should palpate them in the non–weight-bearing position. This allows for separation of the soft tissue structures and facilitates deep palpation of the suspensory apparatus. Comparing limbs is often useful for distinguishing an abnormality from an unusual or unique conformation.

The relative size, shape, and condition of the feet (e.g., contracted heel, scuffed toe); length of heel; and pattern of shoe wear (e.g., thinner branch on the outside of the shoe than on the inside) give clinically significant but often overlooked clues to the site and cause of lameness. Evaluation of the feet with hoof testers is mandatory; most lameness arises from problems in the forefeet.

Certain signs indicating trauma (e.g., wounds, swelling, hair loss, pain) may lead to more important findings such as underlying evidence of a fracture (e.g., bony crepitus, warm or cold areas, bony protuberance). Observe from a distance—the mobile phase. Observations made from a distance while the horse is moving can be evaluated critically once clues provided by the history, as well as observations made of any postural deformities, direct the practitioner's attention to a specific area of the horse's body. This part of the examination is conducted while the horse is moving in at least two gaits, the walk and the trot. Sometimes it is also helpful diagnostically to observe the horse move at other gaits (e.g., canter) or while under saddle. It may also be beneficial to observe the horse on different surfaces to amplify different lameness issues. If possible, the horse should be evaluated under conditions similar to those under which it performs. At a walk, the horse should be observed moving toward and away from the

examiner. The breakover point of the foot at the toe, the arc of the foot flight, the distance covered by the foot in the swing phase, and the placement of the foot should be evaluated for each limb and should be compared between pairs of limbs. Although many abnormalities can often be observed only during a trot, some conditions may cause a subtle alteration in gait that can be observed only at a walk (e.g., fibrotic myopathy, stringhalt).

If a fracture is suspected or if there is the possibility of exacerbating preexisting trauma, this part of the examination should either be abbreviated or not performed at all to preclude further damage or trauma. In such cases, immediate radiographic or other definitive diagnostic tests should be performed (Box 13.2).

Box 13.2

Causes of Spontaneous Fractures in Horses and Ruminants

- Pathologic fractures
- Subclinical stress fractures
- Tumors
- Infection
- Inflammation
- Osteoporosis
- Copper deficiency
- Molybdenum excess
- Phosphorus deficiency
- Protein deficiency
- Osteomalacia
- Osteodystrophy (rickets)
- Rapid growth
- Lactation
- Advanced pregnancy
- Bone fragility disorder

Recognizing the asymmetric movement of the head and neck for frontlimb

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lameness and the asymmetric movement of the pelvis for hindlimb lameness is a common method of lameness identification. Hindlimb lameness issues often present the greatest diagnostic challenge.

Sound horses at a trot show a perfect sinusoidal pattern for all midline body locations, including the head, withers, and tubera sacrale. The height of these structures falls from the beginning of the diagonal stance phase, reaching the lowest position at midstance, and then rising to the highest level at or shortly after the end of the stance phase (suspension). Correlating head and neck movement with the correct frontlimb lameness is relatively easy. It is well recognized that the head is elevated during the stance phase of the lame limb, with an increase in downward motion during the stance phase of the sound limb —"down on sound." Lameness can also be recognized by changes in the distal limb, including changes in the motion of the MCPJ. During the stance phase, the hyperextension of the MCPJ is decreased with increasing lameness in the lame limb, whereas in the contralateral sound limb an increase is seen. With respect to stride length and foot flight, with forelimb lameness the caudal phase of both the lame and the sound limbs becomes shortened, whereas the cranial phase remains unchanged. In the hindlimbs the opposite is seen; the cranial phase is shortened and the caudal phase remains unchanged. This may be explained by the significantly decreased suspension phase following the lame diagonal. In the forelimbs the arc of the lame front foot is unchanged, but there is an increase in the arc of the sound front foot. In the hindlimbs, the arc of the foot flight in the lame hindlimb is lower than the sound limb in most cases. The change in maximal hoof height during the swing phase appears to be the result of changes in trunk height and is no indication for reduced flexion in the upper joints or an effort to reduce the pain when the hoof lands. Medial (winging) or lateral (paddling) deviation of the distal limb during the flight phase can result in interference and trauma to other limbs and potential lameness. Conformational abnormalities, most commonly toeing in or toeing out, give rise to an alteration in the point of breakover and a change in the flight of the distal limb. Poor foot balance caused by either poor conformation or poor trimming can result in similar flight patterns.

Plaiting describes adduction of the lame limb directly in front of or lateral to the opposite limb. In the front limbs, plaiting is commonly the result of faulty conformation, but in the hindlimbs it is more commonly associated with lameness. This pattern of travel is often associated with upper limb lameness but can also be seen with distal hock or proximal metacarpal disease.

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A dampening effect also appears to occur as an adaptation to lameness. This effect is more pronounced in the hindlimb than the frontlimb. Flexion of the shoulder and hock joints actually increases during weight bearing in the lame limb. This is probably an increase in the function of the shock-absorbing mechanism. The increased flexion cannot be related to increased loadings but has to be attributed to a gentler braking of the flexion by the extensor muscles. In such a way the loading of the lame limb with the body weight occurs more gradually, reducing the peak forces in the hoof.

The tubera coxae are typically the landmark of choice in evaluating hindlimb lameness. Because the tubera coxae are more laterally located, the pattern is different from that seen in the head. Also, because the hindlimbs lack closely located segments, such as the neck and head, an enhancement of the vertical movements must be found in a rotation of the back around a longitudinal axis. Such a rotation is indicated by different vertical displacements of one tuber coxae during both stance phases. The vertical movement of the tuber coxae exhibits a characteristic pattern of a double-waved, slightly asymmetric line during one stride. The lowest point of the hip is reached in the middle of the stance phase of the contralateral limb. The highest point of the hip is reached shortly after the stance phase of the contralateral limb.

Kinematic studies have more clearly defined the notion of “hip hike” and “hip drop” and have recorded regular patterns of pelvic movement in lame horses. Consistent findings in the overall pelvic movement in the lame horse include less downward movement during the midstance phase and less upward movement at the end of and after the stance phase of the lame limb. This can give the appearance of an overall pelvic elevation during the stance phase of the lame limb as compared with pelvic height during stance of the sound limb; a similar exaggerated pattern is seen in the tubera coxae. The tubera coxae also exhibit less downward movement during the midstance phase and less upward movement at the end of the stance phase in the lame limb. More notably, there is more downward movement during midstance of the sound limb (midflight of the lame limb) and more upward movement at the end of stance of the sound limb (impact of the lame limb), giving rise to the notion of a “hip hike.” These changes result in an increase in the overall vertical movement of the tuber coxae on the lame side as compared with the sound side. Clinically, many find it easier to identify the exaggerated excursion of a tuber coxae to identify the side of the lameness.

Lateral movement or drifting of the hind end can also be seen in horses with

unilateral hind limb lameness. Horses tend to drift or move away from the side of the lameness. Subtle lameness with an absence of asymmetric pelvic movement may present with a consistent drifting to one side or the other.

Thorough and useful systems for grading the severity of lameness are available. Most systems are designed to enable the practitioner to compare how lameness changes with time, assess the characteristic of lameness among horses, and accurately record information and communicate information to other veterinarians. Simple and consistent schemes that are easy to remember and modify can be developed (Table 13.1).

TABLE 13.1

Five-Grade Lameness Scheme

Grade	Description
1	An inconsistently observable lameness visible under special circumstances (e.g., in a circle, flexion tests, hard surface)
2	A consistently observable lameness visible only under special circumstances (e.g., in a circle, flexion test, hard surface)
3	A consistently observable lameness at a trot in a straight line
4	A consistently observable lameness at a walk
5	A non–weight-bearing lameness; horse is unable to use the leg

Modified from the *Am Assoc Equine Pract Newsl*, March 12, 1983.

Once the initial standing and mobile examinations are completed, the affected limb is identified, and the lameness is graded, identification of the specific region of the limb is the next goal. Manipulative tests or stressing of articulations and associated soft tissue structures can provide additional information as to the location of the source of lameness. Flexion and extension tests are designed to stress selective regions of the limb and observe the effects of the manipulation on the lameness. These tests are also commonly performed on the sound horse to reveal potential areas of concern, particularly during prepurchase examinations. Flexion and extension manipulations also enable an assessment of range of motion. Interpretation of these tests should be approached with caution. They are seldom specific for one particular joint. For example, the fetlock flexion test not only stresses the fetlock joint but also places stress on the proximal and distal interphalangeal joints; the hock flexion test also flexes and stresses the stifle joint because of the presence of the stay apparatus. If a flexion test results in a positive response, the horse should be walked out of the response and observed before additional manipulations. Occasionally exacerbation of the lameness will

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persist for an extended period of time, which changes the baseline lameness and clouds the interpretation of additional manipulations.

It is common for horses to be presented with multiple lameness issues. Secondary lameness or compensatory lameness is the result of increased stress or overloading of the other limbs in response to the primary lameness. This most commonly occurs in the contralateral limb but can also occur between frontlimbs and hindlimbs. The secondary lameness can also be the result of shifts in body mass that produce an apparent or phantom lameness. Phantom lameness is less severe than the primary lameness. The following guidelines can be used to aid in the differentiation between a real or compensatory and an apparent or phantom lameness.

- Address the most severe lameness first.
- Horses with primary hindlimb lameness and apparent or phantom contralateral frontlimb lameness: Each lameness should be considered as real.
- Horses with a primary forelimb lameness and apparent or phantom ipsilateral hindlimb lameness: Each lameness should be considered as real.
- Primary forelimb lameness may produce asymmetric pelvic movement causing the perception of a contralateral hindlimb lameness. Example: left foreleg lameness (head elevation) causing apparent or phantom right hindleg lameness (hip drop).
- Horses with a primary forelimb lameness and apparent contralateral hindlimb lameness: Isolate out the front limb lameness first.
- Primary hindlimb lameness (>3 to 5/5) can mimic ipsilateral forelimb lameness. Example: A horse shows a cranial load shift during the stance phase of

the lame limb that causes the head and neck to shift forward and nod down, giving the perception of ipsilateral forelimb lameness—"down on sound."
• Horses with a primary hindlimb lameness and apparent ipsilateral forelimb lameness: Isolate the hindlimb lameness first.

Assumptions as to the cause of a horse's lameness based solely on the physical examination and visual inspection should be avoided unless obvious signs are present, such as severe swelling or crepitus. After the physical and visual examination, evaluation of the horse with perineural analgesia is mandatory for accurate isolation and diagnosis. The clinician must possess a thorough knowledge of anatomy and the structures desensitized by blockade of the appropriate peripheral nerves or synovial structures (Table 13.2). *When performing perineural analgesia, it is important to remember to block from distal to proximal.* Perineural anesthesia of proximal structures first may inadvertently anesthetize more distal pathology, resulting in misinterpretation of the region of pain affected. An improvement in gait indicates a favorable response to a nerve or joint anesthesia; complete elimination of gait asymmetry is unusual and generally should not be expected after intraarticular or peripheral nerve analgesia. If necessary, improvement in gait can be confirmed by repeating the successful block the next day. By that time residual effects from multiple blocks performed previously should be absent.

TABLE 13.2

Structures Desensitized by Commonly Performed Nerve Blocks

Nerve Block	Nerve(s) Affected	Structures Desensitized[a]
Palmar (plantar) digital	Palmar (plantar) digital	Heel bulbs; frog; bars; navicular bone and bursa; palmar regions of the third phalanx, distal interphalangeal joint, sole, and soft tissues
Abaxial sesamoid	Palmar (plantar)	Coronary band, interphalangeal joints, lamellar and solar corium
Low palmar (volar)	Palmar, palmar metacarpal[b]	Skin of medial and lateral pastern, metacarpophalangeal joint, proximal sesamoids, flexor tendons, tendon sheath
High palmar	Palmar, palmar	Skin and deep structures of palmar cannon region (flexor tendons, suspensory

(volar)	metacarpal[b]	ligament except origin, interosseous ligaments of splint bones)
High 2-point	Lateral palmar, medial palmar	Origin of suspensory ligament

[a]Includes all structures listed up to and including the particular block; first structure listed in each block is also the area that can be tested with point pressure to evaluate the effectiveness of the block.

[b]For hindlimbs, additional anesthetic (i.e., ring block) is necessary at the level of the particular perineural block to achieve the desired effect.

Common local anesthetics used in horses include solutions of lidocaine, mepivacaine, and bupivacaine. These solutions all share a common mechanism of action, specifically the ability to block or inhibit nociceptive nerve conduction by preventing the increase in membrane permeability to sodium ions. Lidocaine and mepivacaine are considered to be fast acting and have a duration of action of ½ to 3 hours and 2 to 3 hours, respectively. Bupivacaine, on the other hand, is intermediate in onset and has a much longer duration of action of 3 to 6 hours. Mepivacaine is reportedly less irritating to tissues than lidocaine.

Intrasynovial analgesia can be used to more specifically isolate lameness to a joint, tendon sheath, or bursa. It can be used in combination with perineural analgesia or alone depending on the suspected source of the lameness. Proper patient restraint and strict aseptic technique, including aseptic preparation of the skin, wearing sterile gloves, and use of a new bottle of anesthetic, are imperative to avoid iatrogenic synovial sepsis. Lameness may be erroneously associated with a joint if intraarticular analgesia of several joints is performed within a short period of time; ample time (30 to 60 minutes) must be allowed between joint blocks to allow for adequate articular desensitization. Some intraarticular and intrasynovial anesthetic techniques may mimic the results of perineural anesthesia. An example is that of the coffin joint, where intraarticular anesthesia of the joint has the same regions of anesthesia as that of the palmar digital nerve block. It is important not to overinterpret the results in such cases.

When performing intrasynovial analgesia, it is not necessary to follow the distal-to-proximal rule. If intraarticular analgesia of a proximal joint results in no improvement in the lameness, immediate follow-up with distal limb perineural blocks is still possible. Exceptions to this rule exist with intrasynovial analgesia to the foot. When performing intrasynovial analgesia of the distal interphalangeal joint (DIPJ) or navicular bursa, it is important to take into consideration the volume of anesthetic used and the timing at which the

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lameness is reevaluated. The recommended volume of anesthetic for the DIPJ is 4 to 5 mL, and for the navicular bursa 3 to 4 mL. Once injections into these structures have been performed, the horse should be evaluated at 5-minute intervals to help with the interpretation of the response to the block because they may result in inadvertent anesthesia similar to the palmar digital nerve block.

Significant improvement in experimentally induced lameness to the navicular bursa can be seen at 5 minutes after intraarticular anesthesia of the DIPJ with 5 mL of 2% mepivacaine hydrochloride. Amelioration of bursal lameness is most likely caused by diffusion of the anesthetic into the bursa via an indirect or functional communication, or by diffusion of anesthetic into the periarticular tissues. The proximal palmar pouch of the DIPJ lies in close proximity to the palmar digital (PD) neurovascular bundles as they course along the medial aspects of the collateral cartilages, making it possible for anesthetic diffusion to block nerve conduction at that level.

Experimentally induced solar toe pain can also be ameliorated by intraarticular blockade of the DIPJ with 10 mL of 2% mepivacaine hydrochloride. The structures innervated by the deep branch of the PD nerves include the DIPJ, navicular bursa, distal navicular ligament, laminar corium, and corium of the sole. The DIPJ capsule contacts the PD neurovascular bundle, and a local anesthetic injected into the DIPJ likely desensitizes the PD nerves below the level of the coronary band, as well as the structures innervated by them.

Variable responses are also seen with blockade of the DIPJ when different volumes of anesthetic are used. Blocking the DIPJ with 6 mL of 2% mepivacaine results in significant improvement in lameness originating from the dorsal margin of the sole; however, lameness originating from the palmar sole shows no improvement. Using 10 mL of mepivacaine reduces lameness originating from the dorsal margin of the sole, as well as the palmar heel regions of the sole, but only after 30 minutes. The difference in response to analgesia of the DIPJ in attenuating pain at the dorsal margin of the sole versus the angles of the sole may be because these regions are innervated by different branches of the PD nerve. This may help distinguish between pain arising from the DIPJ or the navicular apparatus and palmar solar pain.

In contrast to the responses seen with blocking the DIPJ in the presence of navicular bursa disease, blocking the navicular bursa with 3.5 mL of mepivacaine hydrochloride in the presence of experimentally induced DIPJ lameness results in a significant improvement in lameness but only after 30 minutes. Experimentally induced lameness from the dorsal sole is improved by

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blockade of the navicular bursa; lameness originating from the palmar sole does not show significant improvement.

Knowledge of the previously described responses to intrasynovial analgesia of the DIPJ and the navicular bursa is helpful in localizing and interpreting lameness commonly seen in the horse. Similar responses can be encountered with intraarticular analgesia of the carpus and distal tarsal joints. Instillation of anesthetic into the middle carpal joint and the tarsometatarsal joints can result in desensitization of the proximal suspensory ligament, a common site for soft tissue injury and lameness in the horse.

Recently, objective methods of lameness evaluation have become prevalent in equine veterinary practice. The development of a body-mounted inertial sensor system using accelerometers and gyroscopes to measure acceleration and angular velocity of the head and torso during locomotion has been shown to facilitate lameness evaluation. Results of a recent study indicated that lameness evaluation of horses obtained by use of a body-mounted inertial sensor system was significantly associated with results obtained via subjective lameness evaluation by expert clinicians. The objective measurements provided by this system may be beneficial for evaluation of horses with mild, intermittent lameness; difficult, multi-limb involvement; and for documentation of response to regional or intraarticular anesthetic blocks.

Once the lameness has been described and localized, a radiographic or ultrasonographic examination can be performed as the next step to confirm a clinical diagnosis. Radiography should be performed using proper technique, an ideal film/screen combination, and multiple views to construct a thorough study (Table 13.3). Comparing radiographs of affected and unaffected limbs can help confirm or refute a suspected abnormality, evaluate the severity of the disease, and identify possible bilateral limb involvement.

TABLE 13.3

Recommended Radiographic Views of Extremities

Radiographic Series	Minimum Radiographic Views
Distal extremity (navicular)	45 degrees DP, 65 degrees DP (2), LM, flexor tangential[a]
Pastern	45 degrees DP, LO, MO, LM
Fetlock	45 degrees DP, LO, MO, LM, flexed LM
Metacarpal or metatarsal	DP, LO, MO, LM
Carpus	DP, LO, MO, LM, flexed LM, flexed skylines (distal radius, proximal and distal rows of

	carpal bones)
Tarsus	0 degrees DP, 10 degrees DP, LO, MO, LM
Radius-ulna or tibia-fibula	Cr-Cd, LO, MO, LM
Elbow	Cd-Cr, LO, LM
Shoulder	ML
Stifle	Cd-Cr, LM, flexed LM, Cd 30° L-CMO, patellar skyline

[a]View to highlight the flexor cortical margin of the navicular bone (50 degrees proximal palmarodistal oblique).

Cd-Cr, Caudocranial; *Cd 30° L-CMO,* caudal 30-degree lateral-craniomedial oblique; *Cr-Cd,* craniocaudal; *DP,* dorsopalmar (dorsoplantar); *LM,* lateromedial; *LO,* lateral oblique; *ML,* mediolateral; *MO,* medial oblique.

Although standard radiographic techniques are well documented and described, ultrasound examination has become a mainstay in musculoskeletal imaging. Indications for ultrasonographic evaluation of a lameness include diagnosis of soft tissue injuries, including muscular, vascular, tendon, tendon sheath, ligament, joint capsule, or bursal defects; evaluation of articular surfaces (articular cartilage thickness, osteochondritis dissecans lesions); assessment of fluid accumulation (synovial effusions, seromas, or infection); evaluation of bony surfaces; monitoring of the progression of healing; and monitoring of the effects of training on soft tissue injuries such as tendonitis or desmitis.

When radiographic or ultrasonographic techniques are nondiagnostic, other methods such as thermography, nuclear scintigraphy, treadmill evaluation, computerized videographic gait analysis, force plate evaluation, body-mounted inertial sensors examination, computed axial tomography (CAT), or magnetic resonance imaging (MRI) may be useful.

Approach to Diagnosis of Stiffness, Lameness, and Abnormal Gait and Posture in Ruminants

Sarel R. Van Amstel • Jan K. Shearer

Clinical signs can be caused by neurologic deficits, pain, and muscular or skeletal disorders. Diagnosis requires a complete history, including review of information on lameness in dairy records; careful observation during standing and walking, including locomotion scoring; and examination and palpation of the foot and upper limb.

History

Historical details should be obtained in terms of duration, severity, onset of clinical signs, and previous treatment. Past history may help establish if the condition is acquired or congenital. This is particularly important in order to distinguish among conditions with similar signs such as spastic paresis, upward patella fixation, and spastic syndrome. History should also include information regarding management and housing such as free stall size and bedding; evidence of overcrowding; types of walking surfaces; number of times a day milking; and accumulation of mud, manure, gravel, and stones on tracks in cases of pastured cattle. Finally, historical information regarding nutrition including the use of supplements, water source, and potential toxin exposure should be included.

Observation

Detection of lameness may present a challenge because cows are adept at disguising discomfort. Therefore careful observation both during standing and walking is important. Changes in weight bearing, posture, and conformation may be indicative of both the presence and type of lameness. Nearly 90% of lameness involves the foot; thus particular attention should be paid to alterations in weight bearing between claws. Observation is best conducted on a flat, hard surface because subtle lameness may not show when the animal is walking on a softer earthen surface. Stiffness and rigidity may be major components of altered gait and posture. Common causes in which stiffness may be an important component are shown in Box 13.3.

Box 13.3

Alterations in Gait in Ruminants in Which Stiffness Can Be a Major Component

Chronic hypophosphatemia
Chronic fluorosis
Tetanus
Lupine alkaloid intoxication
Copper deficiency or molybdenosis
Acute laminitis
Nutritional myodegeneration (white muscle disease)

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Locoweed toxicity
Sweet clover poisoning
Rickets, osteomalacia, osteodystrophy
Bovine virus diarrhea (coronitis and cerebellar atrophy) (B)
Sarcocystis
Vesicular stomatitis (B)
Overgrown claws
Bluetongue (coronitis) (O)
Degenerative joint disease
Muscle trauma
Ionophore toxicity
Hemlock poisoning
Generalized calcinosis
Fescue intoxication (fescue foot)
Frostbite
Contracted tendons
Selenium toxicosis
Clostridial myositis
Claviceps spp. mycotoxicosis (ergotism; Bahia grass and Dallis grass staggers)
Mycoplasma bovis polyarthritis and tenosynovitis (B)
Mycoplasma mycoides subsp. *mycoides* polyarthritis (C)
Caprine arthritis encephalitis virus (CAE) (C)
Muscle abscess
Ruptured anterior cruciate ligament or torn collateral ligament of stifle
Luxations and subluxations
Upward fixation of the patella
Epiphysitis

Palpation

For upper leg conditions, hands-on examination includes palpation during standing and walking, as well as manipulation of the leg with the animal in lateral recumbency. For examination of the hip, the examiner attempts to detect crepitation in the joint by placing both hands over the greater trochanter while an assistant abducts, adducts, and rotates the affected limb. For the stifle, examination in the standing animal involves palpation of the joint for fluid

effusion and stability. Stability of the joint can be assessed in the following ways: (1) Standing behind the animal, the examiner reaches around the leg with both hands locking the fingers over the tibial crest while leaning into the back of the thigh. The leg is stabilized against that of the examiner while the tibia is pulled caudally (Video 13.1). (2) Alternatively, the examiner stands in front of the affected leg and attempts to demonstrate laxity by pushing on the tibial crest. It is important to stabilize the foot during this procedure. Distention of the joint capsule can cause swelling between the patellar ligaments despite the presence of the fat pad (see Video 13.1). One should also note that there are extensions of the joint capsule between the quadriceps femoris muscle and the femur and distally around the tendons of the peroneus tertius and the long digital extensor muscle.

When evaluating the tarsus or hock, one should always assess the degree of flexion possible in this joint. Overflexion of the hock indicates gastrocnemius rupture, whereas overextension may be indicative of rupture of the peroneus tertius.

Swelling of joints and legs should be palpated for heat, pain, and consistency. Peritarsal bursitis causes a soft, nonpainful swelling on the lateral side of the hock, whereas a hard, painful swelling may be associated with septic arthritis or degenerative joint changes. In cases of septic arthritis, a discharging tract may also be present.

In some cases it may be difficult to distinguish upper from lower leg problems. This can be done by placing a tourniquet at or slightly above the level of the fetlock joint followed by an intravenous injection of 20 mL of 2% lidocaine into a vein below the tourniquet (Video 13.2). Remove the tourniquet after a few minutes or so, and immediately allow the animal to walk. In cases of an upper leg problem, the lameness will persist. Pain and lameness associated with upper leg problems tend to become worse after a period of flexion.

Foot and claw conditions are diagnosed by visual appearance after appropriate restraint. The claw including the interdigital space is thoroughly cleaned. Claw horn and foot lesions should be identified, taking into consideration the location and the claw zone affected (Fig. 13.1). The presence of pain should be investigated if no lesions are visible. This can be done with a hoof tester. Important areas in which to apply pressure include the sole ulcer site in the axial region of zone 4 and the toe ulcer site in zone 5. Sole hemorrhages occurring in zone 4 should also be tested for pain.

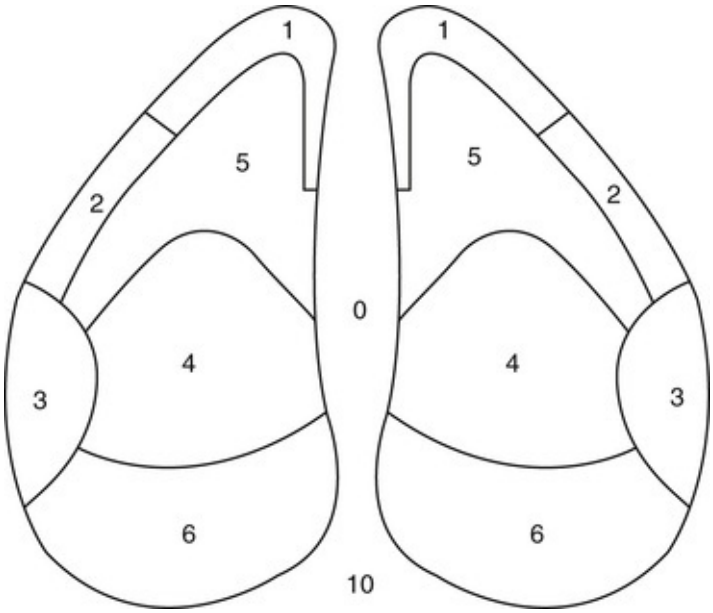


FIG. 13.1 Zones of ruminant claw.

The skin of the interdigital space and interdigital cleft (zones 0 and 10, respectively) should also be carefully examined for evidence of fissures or lesions indicative of digital dermatitis.

Postural Deformities

Carter E. Judy • John Maas

A postural deformity in horses or ruminants is an abnormal stance caused by neurologic deficit, pain, or a musculoskeletal problem. Postural deformities can range from subtle conformational faults such as broken forward foot axis to severe and unusual positions, such as when the animal is camped out in front. Inability to bear weight on a limb, asymmetric angles between joints, and lateral or medial deviations in the alignment of limbs are examples of postural deformities. Often the postural deformity itself is specific for certain diseases and conditions (Table 13.4).

TABLE 13.4

Examples of Postural Deformities and Possible Origins for Horses

Postural Defect	Likely Site of Origin
Contracted heels	Foot; flexor tendons
Bucked knees	Suspensory ligament
Dropped elbow	Motor nerves to forelimb; olecranon
Tiptoe stance	Foot; flexor tendons; interphalangeal joints
Non–weight bearing	Foot; any long bone; any limb articulation
Broken down (hyperextension) fetlock; dropped fetlock	Suspensory apparatus
Toe-out hindlimb and elevated hip	Coxofemoral joint; femoral neck
Basewide behind	Coxofemoral joint; femoral neck
Hyperextension of stifle and hock	Patella
Camped out in front	Bilateral forefeet
Carpal valgus	Distal metaphysis, physis, epiphysis, or carpal bones
Stiffly elevated head	Withers; cervical spine
Shifting weight between forefeet	Bilateral forefeet
Recumbency	Any long bone; feet; spinal cord; myopathy

Mechanisms of Postural Deformities

Postural deformities can be either congenital or acquired and result from maldevelopment, trauma, or disease. Congenital deformities may be caused by tendon contracture or laxity, osseous malformation, and hypoplasia or aplasia of osseous structures or soft tissues. Acquired deformities are most often caused by trauma or disease. Disuse atrophy secondary to an unrelated musculoskeletal abnormality can result in abnormal posture. Occasionally diseases affecting

proprioception and consciousness may cause an abnormal stance that appears as a postural deformity (e.g., head pressing) but is unrelated to neurologic pain or a musculoskeletal problem.

Approach to Diagnosis of Postural Deformities in Horses

A history can help the examiner determine if a postural deformity is congenital, as with arthrogryposis, or acquired. Because most postural deformities in horses (Box 13.4) arise from traumatic injuries or overuse, a complete lameness examination is essential. Occasionally a postural deformity does not cause lameness; in these instances the veterinarian must consider nontraumatic causes associated with abnormal development, improper nutrition, and seemingly unrelated disease such as carpal valgus deformity.

Box 13.4

Causes of Postural Deformities in Horses

Common Causes

Infections of the foot
Hoof wall defects
Fractures
Septic (infectious) arthritis
Secondary (degenerative) joint disease
Laminitis
Angular limb deformities
Osteomyelitis
Sprain
Strain
Tenosynovitis
Contracted tendons (flexural deformity)
Laxity of flexor tendons in foals
Tendon rupture, damage, tendonitis (bowed tendon)
Upward fixation of the patella (locking patella)

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Epiphysitis
Septic tenosynovitis
Muscle injury, soreness, bruise, trauma, compartment syndrome
Navicular disease
Cuboidal bone hypoplasia

Less Common Causes

Disruption of the suspensory apparatus (broken down)
Lateral or medial patellar luxation
White muscle disease (nutritional myodegeneration)
Brucellosis
Sesamoiditis
Hypertrophic osteopathy or osteodystrophy
Ankylosis or arthrogryposis
Luxation or subluxation
Snakebite
Equine monocytic ehrlichiosis (Potomac fever)
Spondylitis, diskospondylitis
Spinal or vertebral neoplasia
Tick paralysis
Vertebral column malformation
Nigropallidal encephalomalacia (star thistle poisoning)
Postanesthetic equine myasthenia
Abscess caused by *Clostridium perfringens*
Hyperparathyroidism
Osteomalacia, osteodystrophy (rickets)

Uncommon Causes

Lupus erythematosus (rheumatoid arthritis)
Osteochondrosis
Cruciate or meniscal rupture
Patellar ligament injury
Malnutrition
Splenic rupture

Neonatal maladjustment
Subcutaneous abscess, cellulitis, foreign body
Vesicular stomatitis
Bucked shins (dorsal metacarpal disease)
Hemimelia (radial, tibial, ulnar hypoplasia, agenesis)
Botulism (shaker foal)
Myotonia congenita
Skeletal neoplasia
Shivers (shivering)
Borreliosis (Lyme disease)

Diagnosis of the cause of a postural deformity begins with a detailed description of the deformity and assessment of the position and asymmetry of the anatomic structures involved. If the nature and severity of the deformity cannot be determined by direct observation, palpation and manipulation of the affected structure are required. Radiography and ultrasonography can also assist in the diagnosis and provide information on which to base treatment recommendations and prognosis.

Approach to Postural Deformities in Ruminants

Sarel R. Van Amstel • Jan K. Shearer

The causes of postural deformities in cattle vary widely and may be congenital, nutritional, environmental, traumatic, and infectious. History, visual inspection, manipulation, and palpation are important in the diagnosis of postural deformities in ruminants. Postural deformities in ruminants including the origin are shown in Box 13.5.

Box 13.5

Causes of Postural Deformities in Ruminants

Common Causes

Congenital

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Contracted tendons
Hemimelia (radial, tibial, ulnar hypoplasia)
Dactylomegaly in Shorthorns
Angular limb deformity
Syndactyly
Osteogenesis imperfecta
Dactylomegaly

Nutritional, Toxic

Rickets
Fluorosis
Crooked calf syndrome (lupinosis)
Osteomalacia
Locoweed-associated limb deformities
Epiphysitis
Chronic selenosis
Primary/secondary copper deficiency
Calcinosis caused by plant poisoning

Acquired

Secondary contracted tendons
Fractures
Degenerative joint disease
Ruptured gastrocnemius
Septic tenosynovitis
Peroneal neuropathy
Radial neuropathy
Suprascapular neuropathy
Obturator neuropathy
Severed or ruptured tendons
Luxations
Arthritis (septic)
Ruptured peroneus tertius
Muscle atrophy caused by denervation

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Tibial neuropathy
Femoral neuropathy
Sciatic neuropathy
Myopathies

Overall symmetry of the limbs may be changed because of swellings originating from muscle, bones, or joints and muscle atrophy. Swellings could be caused by dislocations of joints or fractures of any long bone caused by trauma or metabolic bone disease. Other swellings of joints include septic arthritis in which the joint is swollen and painful and there is a palpable effusion in the joint. In cases of degenerative joint disease, the swelling is hard and often not painful to pressure. Swellings of the muscle could be hard (vitamin E/selenium deficiency); soft and fluctuant, such as with subcutaneous hematoma or abscesses; or crepitant, such as with subcutaneous emphysema or gangrenous myositis (e.g., blackleg).

Leg Angles

Straight hocks in excess of 175 degrees may predispose to degenerative joint disease. Bilateral excessive hock angle (sickle hock) is often associated with shallow toe angles and low heels. Cow hocks (inward hock rotation), on the other hand, are often associated with unbalanced weight bearing and overgrowth of the outer claws. Abduction of a single leg usually indicates pain in the outer claw, whereas a basewide stance in the front legs is indicative of pain in the outer claws. In the rear legs, a basewide stance may also be due to obturator nerve paralysis, which affects the adductor muscles of the inner thigh of the rear legs. Apart from a basewide stance, animals affected by obturator nerve paralysis appear ataxic and are predisposed to splaying their back legs. With a "camped under" posture, more weight is shifted to the rear legs and is often associated with pain in the front feet due to laminitis. Laminitis and pain may also cause the animal to cross the front legs in an effort to remove weight from the medial claws. Partial flexion of the front leg with inability or difficulty in advancing the leg may be associated with suprascapular or radial nerve injury or bicipital bursitis. The leg is held in

semiflexion, and the elbow is dropped in case of damage to the radial nerve at the level of the brachial plexus.

Postural Changes Associated With Stifle Joint.

Instability within the stifle joint associated with cranial cruciate rupture is often seen when the animal is walking and may be accompanied by an audible sound (Video 13.3). This is caused by sliding of the femoral condyles over the tibial plateau. The animal tends to stand with the fetlock slightly flexed and the heel raised. Weight bearing is on the tip of the toe. In cases of medial collateral ligament instability, the leg is held in an abducted position to relieve weight bearing on the medial side of the stifle and weight is placed on the medial claw when walking. With upward fixation of the patella the limb will “lock” while in full extension. This is followed by a stringhalt-type exaggerated motion during flexion. The animal may have a normal gait in between steps. Rarely the leg may become locked in extension.

Postural Changes Associated With Hock Joint.

Dropping (overflexion) of the hock during standing, but more so during walking, is often indicative of gastrocnemius rupture (Video 13.4). Tibial nerve paralysis also results in a dropped hock and slight knuckling of the fetlock. The hock remains dropped while the animal is walking but does not sink during weight bearing, in contrast to rupture of the gastrocnemius muscle. Overextension of the hock is associated with peroneal nerve damage, peroneus tertius rupture, upward fixation of the patella, flexor tendon contracture, and advanced degenerative joint disease. Intermittent spastic contracture of both legs with flexion of the hocks is caused by spastic (spasmotic) syndrome (Video 13.5). In contrast, spastic contracture of one or both hind legs with overextension of the hock is due to spastic paresis. Cattle with damage to the peroneal nerve will stand with the foot knuckled over onto the dorsum of the pastern and fetlock joint. At the same time the hock joint will appear to be overextended. In mild cases, the fetlock tends to knuckle over intermittently when the cow walks.

Postural Changes Associated With Fetlock and Interphalangeal Joints.

Knuckling of the fetlock joint is associated with neuropathy of the sciatic nerve and its branches, the peroneal and tibial. Other causes include lesions of the

palmar or plantar aspect of the foot or sole, as well as conditions of the spinal cord (e.g., lymphosarcoma) or vertebral column.

Postural Changes Associated With Nerves, Tendons, and Joints of Front Legs.

Postural changes and clinical signs of suprascapular nerve injury include stumbling, inability to support weight in severe cases, inability to support and extend the shoulder, a shortened stride, and abduction of the leg. Reflexes and sensation in the lower limb remain normal if the suprascapular is the only nerve affected, and atrophy of the supraspinatus and infraspinatus muscles can become visible in 5 to 7 days after injury.

In calves, contracture of the flexors may cause flexion of both the carpus and fetlock. In such cases, the leg usually cannot be straightened. Semiflexion of the knee can also be due to abnormal conformation or metabolic bone disease. Depending on the level of contracture of the flexors, only the fetlock may be affected. In more severe cases, the carpus may also be affected because of contracture of the flexor carpi radialis and ulnaris or, additionally, because of fibrosis of the joint capsule. In milder cases, the animal may be able to walk on its toes and knuckle forward during weight bearing. In more severe cases, the animal bears weight on the dorsum of the foot or is unable to walk.

Postural Changes Associated With Conditions of Foot (Defined as Part of Limb Below Fetlock).

A symmetric swelling of the foot sometimes extending to and above the fetlock is usually associated with foot rot, whereas a unilateral swelling of the digit is more often associated with a septic tenosynovitis, retroarticular space abscess formation, or sepsis of the distal interphalangeal joint. This can be confirmed through an aspirate of the distal interphalangeal joint and ultrasound of the flexor tendons and structures in the heel. Toe ulcers may cause a heel-first foot placement or weight bearing toward the heel when standing; these can be seen in the apex of zone 5 (see Fig. 13.1). The proximal interphalangeal joint may become subluxated with superficial flexor tendon contracture, resulting in knuckling of the joint.

Septic arthritis of the distal interphalangeal joint results in severe lameness with little to no weight bearing during both standing and walking. White line disease in zone 3 of the rear outer claw often prompts the animal to abduct the

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limb to move weight bearing to the medial claw. Ulcers or hemorrhage in zones 4 and 6 could also be responsible for changes in gait and posture, which may include inward rotation of the hocks to reduce weight bearing on the outer claws of the rear legs, knuckling of the fetlock, crossing of the front legs, and abduction or adduction of the leg. White line disease in zones 1, 2, and 3 could also result in postural change.

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Swellings and Enlargements (Soft and Hard Tissue)

Carter E. Judy • John Maas

Swellings and enlargements consist of soft tissue (e.g., tendon) or hard tissue (e.g., osseous) and can occur anywhere on an animal's body. Typically, swellings and enlargements that are clinically relevant are located on the limbs.

Swellings and enlargements can be further divided into two principal groups: those associated with a specific musculoskeletal anatomic structure and those that are not. For example, a soft fluctuant swelling in the region of the left carpus may be caused by an abnormality of the antebrachialcarpal joint (e.g., septic synovial effusion) or may not involve the joint at all (e.g., subcutaneous abscess). Although lameness can be associated with such a swelling, clearly it is important to determine the cause of the abnormality because the one involving the joint may require the more immediate treatment.

Mechanisms of Swellings and Enlargements

The mechanism by which swelling or enlargement develops depends on the tissue involved. Soft tissue swelling is often produced by trauma, inflammation, infection, or neoplasia; it can consist of interstitial fluid (e.g., edema), fluid within an open space (e.g., synovial hernia), or a localized accumulation of cells or fibrous tissue. Localized edematous swelling is commonly caused by inflammation and/or obstruction of venous blood or lymph flow. Generalized edema is usually the result of increased hydrostatic pressure caused by circulatory failure or an altered capillary-tissue osmotic gradient stemming from hypoalbuminemia. Fluctuant swellings such as hematoma, synovial effusion, a purulent abscess, or a plasma-filled cyst contain free fluid. Granulation tissue, fibrous scar tissue, and tumor cells are the most common constituents of firm soft tissue swellings. Rupture of supporting or confining structures (e.g., prepubic tendon rupture) can result in unusual forms of soft tissue swelling caused by herniation of internal organs.

Many factors influence new bone formation. Trauma and infections initiate bony enlargement (e.g., callus) by disrupting the periosteum, producing inflammation and eventually ossification. The extent of periosteal new bone

formation depends on the cause of the stimulus and size of the affected area. Remodeled bone may also arise from nontraumatic events, usually associated with altered metabolism or neoplasia. Bony enlargements associated with the metaphysis and physis in young, growing animals are usually secondary to a combination of nutritional and traumatic factors. For example, dietary calcium, phosphorus, and vitamin D imbalance can lead to abnormal bone growth. A bony swelling develops gradually and may become noticeable only after it enlarges, interferes with normal function, or becomes a source of lameness.

Approach to Diagnosis of Swellings and Enlargements in Horses

For causes of swellings and enlargements in horses see Box 13.6.

Box 13.6

Causes of Swellings and Enlargements in Horses

Soft Tissue

Septic (infectious) arthritis
Secondary (degenerative) joint disease
Sprain
Strain
Hygroma
Tenosynovitis
Osteochondrosis
Suspensory desmitis or sesamoiditis
Infections of the foot
Insect bites or snakebites
Cellulitis
Abscess
Herniation
Neoplasia

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Capped hock
Hematoma
Phycomycosis

Hard Tissue

Secondary (degenerative) joint disease
Fracture
Sequestrum
Osteomyelitis (periosteal new bone formation)
Epiphysitis
Luxation or subluxation
Osteochondroma
Osteomalacia (rickets)
Bucked shins (dorsal metacarpal disease)
Hypertrophic osteopathy
Ankylosis or arthrogryposis
Calcinosis caused by plant poisoning
Selenium toxicity

1. History. A history should determine the number of horses involved, duration of clinical signs, and possibility that traumatic events or environmental factors are responsible for causing a swelling or enlargement. In addition, changes over time in the appearance and size of the swelling or enlargement can be informative.
2. Inspection and palpation. The location of the swelling and its proximity to anatomic structures often reveal the tissue involved and the probable cause of the condition. For example, swelling around a joint may indicate arthritis, periarthritis, or hygromas. Tendon swelling may indicate tendonitis or ruptured tendons. Swelling over ligaments may indicate rupture, subluxation, or inflammation around a ligament. Muscle swelling results from abscesses or fascial tears. Subcutaneous swelling may indicate hematomas, edema from inflammation around a ligament, or cellulitis. Bony enlargements can often be localized to the shaft of a bone (e.g., periosteal callus) or ends of a bone (e.g., metaphyseal flaring). Periarticular new bone may be readily apparent

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(e.g., ringbone) or may not be found even on deep palpation. New bone formation can also be found associated with the axial skeleton and head. Palpation of a swelling can determine its consistency and association with anatomic structures. Osseous swelling indicates calcification, proliferation of bone, or fracture. Firm soft tissue swelling indicates inflammation, abnormal proliferation of soft tissue (e.g., granulation, tumor), or herniation. Warmth, redness, and pain associated with swelling indicate active inflammation. While new bone is forming, the swelling may be soft and sensitive to palpation. Cold and insensitivity to palpation suggest inadequate blood supply and possibly ischemia (e.g., gangrene). Lameness caused by an injury or condition that results in a hard swelling or enlargement may be accentuated by performing a stress test, such as trotting the horse in hand after direct pressure on the swelling. Intraarticular anesthesia may substantially reduce lameness caused by joint effusion associated with periarticular new bone.

3. Radiography, ultrasonography, and alternative imaging techniques. In addition to identifying definitively the nature of an osseous swelling or enlargement, radiography can gauge the severity and progression of the disease and help establish a therapeutic plan and prognosis. Ultrasound can often determine the position (e.g., depth, area) and volume of a soft tissue swelling and the optimum site for aspiration or biopsy. Thermography may help identify subtle heat production secondary to inflammation and increased blood flow, before onset of a swelling, allowing for early treatment. Nuclear scintigraphy may help localize the cause of swellings and identify whether they are bony or soft tissue in origin. CAT scanning is useful for evaluating bony swellings, especially of the head when swellings of the mandible and maxilla may be related to infected teeth. MRI may prove useful for accurate imaging of soft tissue masses that cannot be accurately characterized with other diagnostic techniques.
4. Cytology, microbiology, and histology. A fine-needle aspiration, using aseptic techniques, should be performed to obtain samples for microbiologic culture (e.g., bacterial and fungal) of soft tissue swellings. If the material is very viscous, a large-gauge needle may be required. Fluid collected for cytology should be placed in tubes containing ethylenediaminetetraacetic acid (EDTA) to prevent clotting before analysis. Tissue samples obtained by biopsy should be placed in 10%

buffered formalin.

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Swellings and Enlargements in Ruminants

Sarel R. Van Amstel • Jan K. Shearer

Swellings and enlargements can originate from soft tissue (muscle or tendons) or hard tissue (bone). Those associated with lameness usually occur on the limbs.

Approach to Swellings and Enlargements in Ruminants

History

History will indicate whether it is congenital or acquired, as well as the duration. Historical information should also include type of pasture, presence of lameness, and progression of the lameness signs, possibility of trauma, vaccination history, appetite, and presence of systemic signs, as well as the number of animals affected.

Examination Including Palpation

The anatomic location of the swelling may give an indication as to its origin. Palpation will provide information about the nature and possible cause of the swelling. Soft fluctuant swellings on the upper leg are usually due to abscess formation following a small penetrating wound, or they may occur after an intramuscular injection. Cattle on sweet clover may develop hematomas due to the presence of warfarin sodium, which inhibits vitamin K and thus vitamin K–dependent factors.[2,7,9,10] Fluid effusion into a joint capsule will result in a soft fluctuant swelling. Those associated with septic joints are usually less fluctuant and warm and painful on palpation. Joint swelling associated with degenerative joint disease may be hard on palpation due to new bone formation and nonpainful. Fluid effusion into the joint space is usually present. Degenerative joint disease may be hereditary, typically incited by abnormal conformation. Acquired degenerative joint disease is common after traumatic injury to supporting ligaments or menisci. Unilateral swelling of the foot is often associated with sepsis of the distal interphalangeal joint and sheath of the flexor

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tendons. Bilateral swelling of the foot is typically associated with foot rot. Swelling immediately above the dew claws may be due to tenosynovitis, septic inflammation of the fetlock joint, rupture of the flexor tendons, or suspensory ligament. Generalized soft and nonpainful swelling of the leg that pits on pressure may be due to lymphatic obstruction, increased hydrostatic pressure, decreased oncotic pressure, or increased capillary permeability.

Radiology, Ultrasonography, and Cytology

Carpal Joint.

Ultrasound carried out in the longitudinal plane over the dorsal surface of the joint will facilitate arthrocentesis. Individual joint recesses that can be visualized include the radiocarpal, intercarpal, and carpometacarpal joints. In the absence of ultrasound, joint fluid can usually be obtained from the radiocarpal pouch with the carpus in slight flexion. A high white cell count in the presence of degenerate neutrophils confirms septic arthritis. Bacteria may not always be visible on cytologic examination. In chronic cases of septic arthritis, the joint looks and feels thicker with a reduced range of motion. In such cases, chronic degenerative changes will be visible radiographically. These changes can first be detected over the cranial surfaces of the proximal carpal row. The radiocarpal joint space is widened, and subchondral bone destruction may be present, which is eventually followed by new bone formation.

Coxofemoral Joint.

Ultrasound-guided arthrocentesis can be carried out in cases where an increase in joint fluid can be visualized. Radiographs are useful in establishing the cause of lameness and may be accomplished by anesthetizing the animal and positioning it in dorsal recumbency for a ventrodorsal radiograph. The size of the musculature will greatly influence the detail visible in the radiograph.

Stifle Joint.

The following should be considered with arthrocentesis of the stifle. There is communication between the femoropatellar and medial femorotibial joint cavities. These compartments do not always communicate with the lateral femorotibial space. To enter this compartment, a needle is introduced behind the lateral patellar ligament and directed caudally. To enter the femoropatellar and

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the femorotibial compartments, the needle is inserted between the medial and middle patellar ligaments and directed slightly down and toward the medial lip of the trochlea. Use of ultrasound will confirm the presence of increased joint fluid and facilitate collection.

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Paresis and Weakness

Richard Andrew LeCouteur

Paresis may be defined as a deficit of voluntary movement. It may be monoparesis (paresis of a single limb), paraparesis (paresis of both pelvic limbs), tetraparesis (paresis of all four limbs), or hemiparesis (paresis of a thoracic and pelvic limb on the same side). Paresis results from disruption of the voluntary motor pathways that extend from the cerebral cortex, through the brainstem and spinal cord, to the motor unit (peripheral nerve, neuromuscular junctions, and muscle fibers). Complete loss of voluntary movement is referred to as *paralysis (plegia).* Voluntary movements must be differentiated from reflex movements on the basis of neurologic examination findings.

Weakness may be defined as impairment of strength and power. Most authors use the terms *paresis* and *weakness* synonymously; however, this may be confusing in some circumstances. For example, weakness may occur in the absence of paresis in some disorders of the nervous system, and weakness may result from many disease processes that do not primarily involve the nervous system (e.g., heart failure, respiratory insufficiency). The clinical signs of weakness may vary considerably and may include paresis, gait abnormalities, dysphagia, regurgitation, dyspnea, and dysphonia. Weakness may be present at rest or may occur after exercise. The distribution of involvement may be local, regional, or generalized. In addition, there may be gross deformities of muscle mass (e.g., atrophy, hypertrophy, skeletal deformities) associated with weakness.

This section focuses on paresis and weakness caused by conditions that affect the motor unit (Box 13.7). Diseases of other systems (e.g., respiratory and cardiovascular diseases or central nervous system disorders) that may result in paresis and weakness are discussed separately in other sections.

Box 13.7

Causes of Paresis and Generalized Weakness in Horses and Ruminants

Anemia

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Cardiovascular disease
Chronic inflammatory disease
Drug-related conditions
Electrolyte disorders
Endocrine or metabolic disorders
Exhaustion
Fever or sepsis
Gastrointestinal disease
Motor unit disease
Neoplasia
Nervous system disease
Nutritional disorders
Respiratory system disease
Trauma
Toxicities

Mechanisms of Paresis and Weakness

Voluntary movement is initiated by the cerebral cortex. Muscular activity occurs subconsciously after activation of successively lower levels of the nervous system: basal nuclei, midbrain, pons and medulla, cerebellum, brainstem, spinal cord, and motor unit. The function of these lower levels is vital, and without their input voluntary movements become impossible.

Monoparesis (or monoplegia) is a common problem in horses and ruminants. It may be caused by dysfunction of the lower motor neuron or neuromuscular junction. Monoparesis is commonly caused by trauma to a nerve or plexus, although neoplasia (e.g., lymphoma, neurofibroma) and inflammation or infection (e.g., early stages of rabies) of peripheral nerves have been reported to cause monoparesis.

Bilateral pelvic limb paresis, ataxia, or paralysis may occur as a result of a neurologic disorder localized to the spinal cord caudal to the T2 spinal cord segment. Various congenital vertebral and spinal cord malformations may result in pelvic limb paresis. Equine protozoal myeloencephalitis and equine degenerative myeloencephalopathy may result in lameness, weakness, and ataxia that may progress to tetraparesis. Musculoskeletal disorders resulting only in bilateral pelvic limb weakness and paresis are unusual. Possible causes include trauma (e.g., postcalving or postfoaling paralyses caused by lumbosacral nerve

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root compression or contusion), vascular disorders (e.g., thrombosis), and early stages of an infectious disorder that may progress to tetraparesis.

The causes of tetraparesis are numerous and include progression of many of the disorders mentioned previously. Outbreaks of intoxication with *Clostridium botulinum* occur sporadically in horses and ruminants; the condition results in a flaccid paralysis that starts with the pelvic limbs and progresses cranially. Depending on the amount of toxin involved, large numbers of animals may be affected. Polyneuropathies (congenital and acquired) and polymyopathies (congenital, metabolic, infectious, and immune-mediated) are causes of tetraparesis.

Muscle weakness may result either from a primary neuromuscular disease or disorders that affect muscle secondarily. In the latter category, problems of horses and ruminants that commonly result in weakness include poor diet, underfeeding, toxicoses, and anorexia. Systemic diseases and disorders such as dehydration, low circulating blood volume, anemia, and metabolic abnormalities (e.g., acidosis or alkalosis) also may result in weakness. Disorders of bones and joints affecting one limb also may affect the contralateral limb through overuse or misuse, and weakness of the contralateral limb may result.

Primary neuromuscular diseases are usually classified on the basis of the anatomic component of the motor unit that is involved. Such diseases are broadly subdivided into neuropathies (disorders of the neuron, its cell body, axon, and/or Schwann cells [myelin]); junctionopathies (disorders of the neuromuscular junction); myopathies (disorders of muscle fibers); and neuromyopathies (disorders of both neurons and muscle fibers).

Dysfunction of the motor unit results in lower motor neuron signs, seen clinically as muscle weakness. The expression of this weakness may vary considerably, and the distribution of involvement may be local, regional, or generalized. Atrophy, hypertrophy, and skeletal deformities may accompany the muscle weakness. Any patient with some form of clinical weakness should be viewed as potentially having a motor unit disorder. That the patient is “weak merely because it is sick” should not be readily assumed without meticulous evaluation of the motor unit.

Approach to Diagnosis of Paresis and Weakness in Horses

Establishing a diagnosis requires an informed and coordinated approach to

defining a problem list through associations and direct observations (i.e., a diagnostic plan) (Box 13.8).

Box 13.8

Causes of Paresis and Weakness in Horses

Degenerative

Equine degenerative myeloencephalopathy

Anomalous or Congenital

Hydrocephalus
Vertebral and spinal cord malformations

Metabolic

Exertional rhabdomyolysis
Hyperkalemic periodic paralysis
Hypothyroidism
Hyperthermia
Hypocalcemia
Hypokalemia
Equine hepatic lipidosis
Vitamin A deficiency

Nutritional

Macronutrient malnutrition
Vitamin E (selenium) deficiency

Neoplastic

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Brain or spinal cord tumor
Lymphosarcoma
Melanoma
Leukemia

Infectious or Inflammatory

Encephalitis, myelitis
Equine protozoal myeloencephalitis
Diskospondylitis
Botulism
Rabies
Ehrlichiosis
Tuberculosis
Rhinopneumonitis
Hepatoencephalopathy
Tick paralysis
Cerebrospinal nematodiasis
Equine protozoal myeloencephalitis

Toxic

Snakebite
Plant poisons (star thistle poisoning, oleander, moldy corn poisoning, white snakeroot, locoweed, larkspur, delphinium, onion, moldy sweet clover)
Vitamin D
Phosphorus
Heavy metals (lead, arsenic)

Traumatic

Vertebral fracture or luxation

Vascular

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Postanesthetic hemorrhagic myelopathy

1. Signalment. Breed, age, sex, and use of the horse.
2. History. Feeding program, vaccination and deworming schedules, course of complaint, response to treatment, and possibility of exposure to toxins or trauma.
3. Physical examination. The clinician must rely on clinical signs of abnormal function to identify the location of the neurologic dysfunction. The first step in locating a neurologic lesion is to determine the level of the abnormality along the longitudinal plane of the neuraxis (i.e., brain, spinal cord, or motor unit). The second step is to further localize the lesion within an anatomic region (e.g., motor unit should be further localized to peripheral nerve, neuromuscular junction, or muscle). The third step is to determine the location of the lesion in the transverse plane at the appropriate longitudinal level (e.g., left or right side).
4. Minimum database. Complete blood count, serum biochemistry panel (including electrolyte determinations), fecal analysis, and urinalysis may be considered. Measurement of muscle-specific serum enzymes such as creatine kinase (CK), as well as aspartate aminotransferase (AST) and lactic dehydrogenase (LDH), may be helpful in identifying neuromuscular disorders in which myonecrosis is a principal pathologic feature. Urine can be tested for the presence of myoglobin released from damaged skeletal or cardiac muscle.
5. Specific diagnostic tests: Electrodiagnostic testing. Electromyography (EMG) involves the detection and characterization of electrical activity (potentials) recorded from a patient's muscles. A systematic study of individual muscles permits an accurate determination of the distribution of muscles affected by a pathologic process.
6. Nerve and muscle biopsy examination. This procedure evaluates the morphology of portions of the motor unit and may differentiate neuropathies, junctionopathies, and myopathies. In some instances, results of muscle biopsy analysis may provide a definitive diagnosis (e.g., polysaccharide storage myopathy of horses).

Approach to Diagnosis of Paresis and Weakness in Ruminants

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Sarel R. Van Amstel • Jan K. Shearer

The approach to the diagnosis of disorders causing paresis and weakness in ruminants (Box 13.9) is essentially the same as that for horses. The following should be included:

Box 13.9

Causes of Paresis and Weakness in Ruminants

Anomalous or Congenital

Progressive degenerative myeloencephalopathy of Brown Swiss cattle
Progressive ataxia of Charolais cattle
Inherited progressive spinal myelinopathy of Murray Grey cattle
Inherited myophosphorylase deficiency in Charolais cattle
Heart disease
Hydrocephalus

Metabolic

Hypoglycemia
Hypocalcemia
Hypokalemia
Hypomagnesemia
Rumen acidosis
Anemia
Hypothermia
Hepatic encephalopathy

Infectious or Inflammatory

Infectious diarrhea; for example, *Salmonella*
Tick paralysis
Botulism
Rabies

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Parasitism
Pneumonia
Spinal abscess
Sepsis
Bovine spongiform encephalopathy
Severe mastitis
Endotoxemia
Encephalomyelitis

Nutritional

Starvation
Vitamin E/selenium
Polioencephalomalacia
Diarrhea
Water intoxication/salt poisoning
Copper deficiency

Neoplastic

Spinal lymphoma

Traumatic

Vertebral fracture or luxation
Calving paresis

Parasitic

Parelaphostrongylus tenuis

Toxic

Lead poisoning
Ionophore toxicity

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Signalment

Age, sex, breed, use (pet, dairy, beef)

History

Feed composition and storage, calving difficulty, exposure to trauma or toxins, recent purchase of new animals or new introductions into an established social group, vaccinations, housing

Physical Examination

Observe the animal from a distance to evaluate posture, signs of weakness or neurologic signs such as stumbling, and ataxia. Observe for knuckling, muscle fasciculation, and limb dragging. Look at mucous membrane color (conjunctiva or vulva). Look at the position of the eye (degree of retraction) and skin elasticity above the eye, the presence of dry mucous membranes, and capillary refill time to assess degree of dehydration. Palpate the rumen to assess rumen filling. In cases of acute rumen acidosis, the rumen is usually fluid filled. Take a rumen sample to measure pH. Do a rectal examination and palpate the spine and pelvic bones to determine the presence of fractures or any bony prominences or lymph node enlargements.

Other Diagnostic Tests

A hematocrit and total protein will give an indication of the degree of anemia or dehydration. A complete blood count including fibrinogen may indicate the presence of inflammatory disease. A blood smear should be examined for the presence of blood parasites and type of anemia present. Blood chemistry including electrolytes and the animal's blood gas status should be evaluated. A neurologic examination should be carried out. Reduced lower jaw and tongue tone, as well as dysphagia, may be indicative of botulism, rabies, polioencephalomalacia, or listeria. Other common cranial signs may include ptosis, anisocoria, delayed or absent pupil light response, dropped ears, facial asymmetry, delayed or absent sensory response to the face, head tremors, blindness, and star gazing. Intension tremors may indicate cerebellar disease, whereas head pressing may indicate problems with the cerebral cortex.

The degree of ataxia and weakness can be tested by walking the animal in a tight circle and observing the proprioceptive response or pulling the tail (laterally) while walking next to it. Spinal reflexes can be done if the animal is

recumbent. Box 13.9 lists causes of paresis and weakness in ruminants. A spinal tap should be considered, particularly in small ruminants including camelids where an eosinophilic pleocytosis is suggestive of meningeal worm infestation.

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Muscle Spasms and Myoclonus

Richard Andrew LeCouteur

Muscle spasms are sudden, transient, and involuntary contractions of a single muscle or group of muscles, attended by pain and loss of function. Often all the muscles affected by a spasm are supplied by a single nerve. A painful, tonic, spasmodic muscular contraction is often referred to as a *cramp*.

Myoclonus may be defined as a disturbance of neuromuscular activity characterized by abrupt, brief, rapid, jerky, arrhythmic, asynergic, involuntary contractions involving portions of muscles, entire muscles, or groups of muscles, regardless of their functional association. The movements may be single or repetitive (10 to 50 per minute) and are similar to those that follow stimulation of a muscle. Myoclonus is seen primarily in muscles of the limbs, where involvement is often diffuse or widespread. Myoclonus may also be present in facial or masticatory muscles and muscles of the tongue, larynx, and pharynx. Myoclonus usually disappears during sleep.

This section describes muscle spasm and myoclonus as specific clinical signs associated with dysfunction of the musculoskeletal system.

Mechanisms of Muscle Spasms and Myoclonus

Spasms are usually of reflex origin and may result from irritation or stimulation at any level of the nervous system from the cerebral cortex to the muscle fibers. In most cases, however, spasms are caused by peripheral irritation affecting either muscles or nerves. Pain may cause either tonic or clonic spasms of muscles, especially if the painful stimulus is focal or discrete. Mechanical irritation may cause a localized spasm. There may be prolonged and characteristic muscle spasm associated with hyperirritability of nerves and muscles in tetany or tetanus. Spasms may follow injury or irritation of peripheral nerves, particularly during the process of regeneration. Spasms may also result from irritation or diseases affecting cortical centers in the brain, motor nuclei in the brainstem, or descending motor pathways in the spinal cord.

There has been much discussion regarding the pathologic process underlying myoclonic movements. Although it was originally thought that the neural discharge that excites the muscular contraction of myoclonus was confined to the motor unit, it is now known that myoclonus may also result from dysfunction of

the brain (e.g., cerebral cortex, brainstem, basal nuclei, thalamus), spinal cord, peripheral nerve, neuromuscular junction, or the muscle itself, alone or in combination. A variety of processes evidently lead to hyperexcitability of the cerebral cortex, subcortical structures, or even the lower motor neurons alone. Myoclonic movements or muscle spasms may occur in a variety of conditions. They have been observed in association with encephalitis, meningitis, toxic and postanoxic states, metabolic disorders, degenerative diseases, and vascular and neoplastic conditions. Myoclonus has also been reported in association with lesions of peripheral nerves, nerve roots, and spinal cord.

Specifically, disturbances in plasma electrolyte concentrations, certain drugs, and toxins may elicit involuntary muscle activity. In general, the mechanism that is common to all causes of spasm or myoclonus involves inappropriate stimulation of a nerve or muscle cell, causing the cell to fire a series of action potentials, resulting in muscle contraction. For example, toxins may act directly on the muscle cell membrane to stimulate the release of calcium into the cell from the sarcoplasmic reticulum, thereby causing involuntary muscle contraction. Alternatively, some toxins may cause efferent neurons to release neurotransmitter across the neuromuscular junctions, thereby stimulating receptors on the muscle cell membrane.

Approach to Diagnosis of Muscle Spasms and Myoclonus in Horses

A broad spectrum of diseases may be associated with muscle spasms or myoclonus in horses (Box 13.10). A thorough investigation is necessary to achieve an accurate diagnosis.

Box 13.10

Causes of Muscle Spasms and Myoclonus in Horses

Anomalous or Congenital

Myotonia congenita

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Metabolic

Hyperkalemic periodic paralysis
Hypocalcemia
Hypoglycemia
Hypothermia
Exhaustion
Shivering

Neoplastic

Insulinoma

Infectious or Inflammatory

Tetanus
Rabies
Equine influenza
Tick-borne encephalitis
Meningitis
Muscle cramps associated with ear ticks *(Otobius megnini)*

Idiopathic

Neonatal maladjustment syndrome

Toxic

Strychnine
Organochlorines
Chlorinated hydrocarbons

1. History. A comprehensive history should include evaluation of the environment and stablemates, description of any traumatic episodes, and any potential drug or toxin exposure.

2. Physical examination. Complete lameness and neurologic examinations should be done as extensions of a thorough physical examination.
3. Minimum database. Complete blood count, serum biochemistry panel (including muscle enzyme determinations), and cerebrospinal fluid analysis should be considered. In the case of muscle spasm and myoclonus, elevation in muscle enzymes may indicate secondary muscle damage rather than a primary muscle disease. A tetany panel, including serum calcium, phosphorus, and magnesium determinations, may be completed. Hypocalcemia may be a cause of muscle spasms in lactating horses, exhausted endurance horses, or horses transported long distances.
4. Specific diagnostic tests: Electrodiagnostic testing. A systematic study of individual muscles using EMG permits an accurate determination of the distribution of muscles affected by a pathologic process.
5. Nerve and muscle biopsy examination. This procedure evaluates the morphology of portions of the motor unit and may differentiate neuropathies, junctionopathies, and myopathies.

Approach to Diagnosis of Muscle Spasms and Myoclonus in Ruminants

The approach to diagnosis of muscle spasms and myoclonus in ruminants is essentially the same as that described for horses. The cause and pathogenesis of muscle spasms in ruminants are outlined in Table 13.5). In ruminants a tetany panel (consisting of serum calcium, phosphorus, and magnesium determinations) should be completed in any animal exhibiting these signs. In lactating cattle on grass pasture and in sheep transported long distances, hypomagnesemia and hypocalcemia are likely. Several infectious (e.g., rabies, pseudorabies), toxic, and inherited causes of muscle spasms and myoclonus should be suspected in ruminants. In postparturient animals and animals with wounds or bites, or animals recently castrated or tail docked, tetanus should be considered as a possible cause of muscle spasms and myoclonus.

TABLE 13.5

Causes and Pathogenesis of Muscle Spasms in Ruminants

Sign	Pathogenesis

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Posterior paralysis of Danish Red calves	Single Mendelian recessive factor from 1 bull
Inherited congenital myoclonus of polled Herefords and their crossbreeds	Decrease in inhibitory glycine receptors
Maple syrup urine disease in polled Herefords and their cross breeds	Deficiency of activity of mitochondrial enzyme branched-chain alpha-keto acid dehydrogenase
Lethal spasms in Jersey and Hereford calves	Autosomal recessive gene from 1 bull
Congenital brain edema in Herefords	Autosomal recessive gene
Hypomagnesemia (lactation tetany; grass tetany; grass staggers; wheat pasture poisoning)	Stress; transport; dietary deficiency (lush pasture, high potassium and nitrogen); inclement weather; lactation and pregnancy; individual susceptibility
Hypocalcemia	Onset of lactation, vitamin D deficiency, starvation, metabolic alkalosis, stress (sheep and goats), prepartum diets high in calcium, individual and breed susceptibility, IV oxytetracycline administration
Hypoglycemia	Failure to nurse, sepsis, bacterial meningitis, enterotoxigenic colibacillosis, cold exposure, twin or triplet lambs
Tetanus	Disinhibition of gamma motor neurons
Rabies	Encephalitis
Pseudorabies	Encephalitis
Meningitis	Bacterial infections, viral encephalitides
Coccidiosis	Possible labile neurotoxin
Chlorinated hydrocarbons	Cause repetitive discharge of motor and sensory neurons
Strychnine	Antagonist of glycine and acetylcholine and mainly affects the motor nerves in the spine
Organophosphates	Inactivation of cholinesterase
Cocklebur	Carboxyatractyloside (CAT)
Buckeye	Glycoside saponin (aesculin)

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• CHAPTER 14

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Collapse and Sudden Death

Stan W. Casteel, Consulting Editor, Philip J. Johnson

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Collapse Versus Sudden Death

Collapse is easily identified as a state of extreme prostration and depression. However, sudden death has a somewhat tenuous meaning, lending itself to subjective impression. The timing parameter used to define sudden death ranges from 1 to 24 hours from the onset of the fatal episode. Some veterinarians restrict the definition to a narrower time span. The 12- to 24-hour interval is sometimes selected to coincide with the frequency of owner observation of the livestock. For our purposes, sudden death means clinically unanticipated, rapid death (12 to 24 hours) occurring during normal activity in animals that had been regarded as healthy. As a rule, a condition of this nature results from fatal dysfunction of the cardiovascular, nervous, respiratory, or gastrointestinal (GI) systems. In addition, disruption of cellular metabolism (such as is associated with cyanide or hydrogen sulfide intoxication) may result in peracute death.

Approach to Diagnosis of Sudden Death

The causes of sudden death are investigated in much the same way as for any disease. The accompanying tables of differential diagnoses include infectious, metabolic, nutritional, physical, cardiovascular, toxic, and miscellaneous causes of sudden death. Diagnostic laboratories provide an array of tests and analytic procedures on the basis of veterinarians' needs in their service areas. Use of these facilities to support a definitive diagnosis is essential in sudden death cases.

Recently, a specific postmortem examination protocol intended to identify etiology in instances of sudden death and exercise-associated sudden death (EASD) in racehorses was developed and described by the California Animal Health and Food Safety Laboratory System–University of California, Davis.[1] The three principal goals of that protocol include performance of a complete postmortem examination for each case to attempt to establish the cause of EASD, standardization of histopathologic examination of the heart in cases of EASD (so that results would be compared over time and between institutions), and description of the toxicology screens performed at that institution for cases of EASD.[1]

Diagnosis is rarely based on a single item of evidence and usually requires input from multiple testing procedures. Unless the cause of death is apparent,

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some important considerations required for effective use of a diagnostic laboratory include the following:

1. A detailed history, which consists of the herd incidence, management changes, past medical problems, vaccination records, new additions to the herd, a complete description of the environment (e.g., recent lightning, flooding?), and assessment of the frequency of animal observations. Owners and managers may not be candid for fear of being considered negligent. Inconsistencies among involved parties should be carefully evaluated. Recent changes in management practices should be scrutinized, including feeding habits and whether there have been any illnesses in comingled animals. Animals trailed or transported for long distances or introduced onto unfamiliar ranges may be poisoned by plant species normally avoided by indigenous livestock or infected by a novel locally endemic infectious agent against which the animal had insufficient immunity. The likelihood of foul play should be considered without creating undue alarm. Assigning blame should be left to the discretion of owners. Consideration of disgruntled former employees and equine insurance claims are particularly critical situations that may have legal implications. The precise cause of death is crucial for insured livestock (mostly horses) because of exclusion clauses in many insurance policies. Heavily insured horses should be subjected to a detailed, documented, and witnessed diagnostic evaluation by an unbiased specialist, wherever possible. Toxicologic testing is especially critical in these cases. Scrutiny of the environment before the carcass is moved is necessary to eliminate questionable procedures in insurance claim cases. Evidence of struggling in the immediate area indicates a more protracted illness in contrast to collapse and death without a struggle. Suspicions should be aroused when evidence suggests that the carcass may have been dragged or carried to the current location.
2. Communication with the diagnostic laboratory before specimen collection should be undertaken to ensure that necessary samples are identified, correctly handled, and transported in accordance with the laboratory's current standard operating procedures. In light of the fact that many cases of sudden death result from central nervous system dysfunction, it is necessary to remove the brain for examination. Busy practitioners frequently do not take the time to remove this organ.

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Furthermore, there is a higher-than-normal probability of a poison being involved in sudden death cases, especially in equine insurance claims. For toxicologic examination, toxicants remaining in the GI tract must be considered, together with those in the major excretory organs, liver, and kidneys. Again, an active dialogue with laboratory personnel should facilitate appropriate specimen collection and handling in order to maximize the probability of a positive diagnostic outcome.

3. The correct quantity and method of preservation of the sample depends on the specific test. Medicolegal cases demand that stringent photographic and written documentation, witnessing, and chain-of-custody protocol be followed during necropsy and sample collection. The quantity of the sample is particularly important for chemical analysis. Sending insufficient quantities of sample may preclude multiple testing procedures. In general, 100 to 200 g of tissue or ingesta, 50 mL of urine, all fluid from both eyes, and 5 to 10 mL of blood or serum suffice for most analytic procedures. A midsagittal cut through the brain is performed to allow freezing of one half for chemical analysis and formalin preservation of the other. When poisoning is suspected, samples from possible sources such as feed, water, baits, poisonous plants, and suspect materials should be submitted. Usually 1 kg of each is adequate. Samples submitted for chemical analysis should be frozen in individual containers and labeled with patient identification data, date, location, and specific identity of the specimen (type of tissue). Specimens for bacteriology and virology must be packaged separately and chilled. Dry ice should be avoided because gaseous carbon dioxide may kill some infectious agents. Tissues for histopathologic examination require fixing in 10% formalin with tissue slices only 4 to 5 mm thick (excessively large blocks of tissue will not be properly fixed in 10% formalin). Suspected poisonous plants are properly preserved by placing them in a plastic bag with wet paper towels or drying them between sheets of paper.

Causes of Collapse and Sudden Death

Infectious Causes of Sudden Death in Horses

Foal actinobacillosis is an acute fulminant septicemia caused by *Actinobacillus equuli*, a gram-negative bacterial pathogen found in the upper respiratory tract, feces, and genital tract of normal adult horses (Box 14.1). Many other bacteria can also cause bacteremia/septicemia. Predisposing factors to foal septicemia with any agent include prematurity/dysmaturity, failure of passive transfer, maladjustment, dam malnourishment/illness during gestation, and adverse environmental conditions. A characteristic histopathologic finding is multiple bacterial emboli in renal glomerular capillaries without inflammatory infiltrate in neonatal foals. Acute hemorrhagic necrotizing enterocolitis, sometimes associated with Clostridial infection, may cause sudden death in foals in the absence of other clinical signs.

Box 14.1

Infectious Causes of Collapse and Sudden Death in Horses

Peracute typhlocolitis (any cause)
Babesiosis/Theileriasis
Botulism[a]
Clostridial myopathy
Clostridium difficile enterocolitis
Clostridium perfringens enterotoxemia
Clostridium sordellii dysentery
Guttural pouch mycosis
Hemorrhagic enterotoxemia in foals
Neonatal septicemia
Neonatal diarrhea
Neorickettsia risticii infection (Potomac horse fever)
Salmonellosis[a]

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	Theiler disease (serum hepatitis)
	Tyzzer disease

[a]Likely to involve several animals.

Acute anthrax may be rapidly fatal to horses (following a period of excitement, depression, convulsions, and coma). Isolating the causative agent from blood confirms the diagnosis. Babesiosis/Theileriasis is caused by an intraerythrocytic parasite that may cause death within 24 hours. Identification of the organism in blood smears, complement fixation testing for parasite antibodies, or polymerase chain reaction (PCR) testing confirms the diagnosis.

Death may result from clostridial myonecrosis associated with infection at intramuscular injection sites by *Clostridium septicum, Clostridium chauvoei, Clostridium novyi,* or *Clostridium perfringens;* various parenteral agents such as ivermectin, vitamin B complex, vitamin E, prostaglandin, antihistamines, and flunixin meglumine have been implicated in this regard. Clostridial myopathies are also associated with deep stab or puncture wounds. Toxicoinfectious botulism (shaker foal syndrome) is caused by *Clostridium botulinum* (usually type B or C) and is more common in specific (endemic) geographic locations. *Clostridium botulinum* spores can be identified in approximately 80% of affected foals. The neurotoxin may sometimes be demonstrated in gut contents. Although rapid death (within a few hours) was attributed to *Clostridium sordellii* enteritis in foals with colic and bloody diarrhea in one study,[2] *C. perfringens* type C is a more common cause of hemorrhagic enteritis, enterotoxemia, and peracute death in foals as young as 4 days.[3] Diagnosis may be supported by bacteriologic culturing, the demonstration of alpha and beta toxins in fresh intestinal samples, and identification of large numbers of clostridia (large gram-positive bacilli) in smears of intestinal contents. *C. perfringens* type D also induces sudden death in the most aggressive foals in group-feeding situations. Similar enterotoxemia has also been associated with toxin-producing *Clostridium difficile*[4] and *Bacteroides fragilis.*[5] Death of foals resulting from hemorrhagic necrotizing enterocolitis as a result of infection by *C. difficile* has been increasingly reported in recent years.

Peracute death may result from severe disease associated with infection by *Neorickettsia risticii* (Potomac horse fever or Shasta River Crud). More commonly, *N. risticii* infection results in severe colitis, fever, systemic

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inflammation, diarrhea, dehydration, ileus, colic, and laminitis in adult horses. Diagnosis of *N. risticii* infection is based on PCR testing to demonstrate *N. risticii* DNA in whole blood and feces. Salmonellosis is responsible for many cases of acute enterocolitis, especially when several animals are involved. Peracutely affected horses may die within 6 to 12 hours. Horses may die before signs of colic or diarrhea are recognized. Confirmatory postmortem diagnosis is based on characteristic histopathologic findings, microbiological isolation of *Salmonella* spp. from bowel contents, bowel wall, and/or associated lymph nodes, or demonstration of Salmonella deoxyribonucleic acid using PCR. Tyzzer disease is a rapidly developing fatal hepatitis of foals caused by *Clostridium piliforme*. The incidence is sporadic, and, because of the peracute development, clinical signs may not be observed before death. Diagnosis is based on histopathologic demonstration of bacilli in bundles within hepatocytes surrounding necrotic areas using a silver stain (such as Warthin-Starry) or PCR.

Guttural pouch mycosis often results in nonfatal intermittent unilateral epistaxis or dysphagia. Occasionally a single episode of severe epistaxis from hemorrhage from the internal carotid artery may result in unanticipated death from exsanguination. Necropsy reveals blood in the nasal passages and guttural pouch with fungal plaques on the surface of the affected artery, usually at the dorsocaudal aspect of the medial compartment. In fatal cases, the local exterior environment of the carcass will be contaminated with blood that has clearly issued from one or both nostrils.

Acute infection of the central nervous system by either West Nile virus (WNV) or equine herpesvirus 1 (EHV-1) may simply present as unexpected death in susceptible individuals. Diagnostic corroboration for these conditions is based on histopathologic characterizations, immunohistochemistry (WNV), and PCR testing.

Infectious and Parasitic Causes of Sudden Death in Ruminants

Infectious causes of sudden death range from acute septicemia and toxemia to rupture and release of abscess contents into the systemic circulation (Box 14.2). A liver abscess rupturing into the caudal vena cava; endocarditis, especially of the right atrioventricular valve, with subsequent pulmonary thromboembolism; and the rupture of a pituitary abscess are occasional causes of sudden death in individual animals. Acute anthrax and the clostridial infections, as well as

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ingestion of their preformed toxins, are more common causes of sudden death in ruminants. Anaplasmosis may cause sudden death in mature cattle under stress, without apparent icterus. In these cases, anthrax may be mistaken for anaplasmosis because of the gross enlargement of the spleen. *Anaplasma* organisms may be demonstrated in blood smears, whereas newer diagnostic methods involve indirect fluorescent antibody and PCR testing. Of all domestic animals, cattle are the most susceptible to clostridial infections in which tissue invasion is present (blackleg). Therefore it is important to ascertain the vaccination status of affected animals. In addition, a fluorescent antibody test and isolation of the bacterium confirm the diagnosis. *C. perfringens* of various types is responsible for heavy losses caused by enterotoxemia in calves, lambs, kids, and feedlot cattle in apparent good health and on full feed. *C. perfringens* type D has been associated with focal symmetric encephalomalacia in lambs.[6] Coliform mastitis may result in peracute systemic disease and rapid death if not treated early. Diagnosis is based on culture of the organism from the affected gland. *Leptospirae* may cause an acute septicemia with hemolytic anemia and rapid death in young ruminants. Demonstration of leptospires in fresh urine, immunohistochemical staining of tissues, or PCR testing may assist in making the diagnosis. The course of listeriosis in sheep and goats is rapid, and death may occur in 4 to 48 hours after the appearance of clinical signs.[7] Bacteriologic culture (isolation) or immunohistochemical staining of the organism in tissues is diagnostic. Acute fascioliasis *(Fasciola hepatica)* occurs seasonally in sheep and may cause sudden death within 6 weeks of initial infection. Anaerobic conditions induced by flukes in hepatic parenchyma predispose ruminants to the highly fatal clostridial hepatopathies such as *Clostridium hemolyticum* infection. Evidence of fluke infection is grossly visible. Individual animals with chronic or severe endoparasitism may present as acute collapse or sudden death if they are maintained in a herd/flock. This is especially true for South American camelids. Peracute malignant catarrhal fever (MCF) is a sporadic cause of sudden death in cattle that is usually associated with contacting ovine carriers, but most animals with MCF have diarrhea, keratitis, and other obvious clinical signs for days before death occurs. A septicemic form of mycoplasmosis was reported to cause rapid death in kids.[8] Isolation of the causative organism is diagnostic. Sudden death is the usual manifestation of septicemic pasteurellosis in lambs. Pseudorabies is a consideration in sudden death cases of ruminants having contact with infected swineherds and feral hogs in the Midwestern United States. Brain for microscopic examination and virus isolation should be submitted to

confirm the diagnosis. Acute septicemic salmonellosis mainly affects young ruminants and may result in death within 24 hours. Acute septic metritis usually occurs secondary to complications of parturition. Endotoxic shock and rapid death may occur in severe cases. Thromboembolic meningoencephalomyelitis caused by *Histophilus somni* is a peracute septicemic disease of young calves. Many cattle die without showing clinical signs. It may be associated with prior respiratory problems in the herd or feedlot. Typical lesions or isolation of the causative organism is diagnostic. Adult lymphosarcoma associated with bovine leukemia virus can be a cause of sudden cardiac death when neoplastic cells infiltrate the cardiac conduction system.

Box 14.2

Infectious and Parasitic Causes of Collapse and Sudden Death in Ruminants

Abscess rupture at liver hilus or pituitary
Anaplasmosis[a] (B)
Anthrax[a]
Black disease, infectious necrotic hepatitis
Blackleg
Botulism[a]
Bovine lymphosarcoma
Clostridium hemolyticum, bacillary hemoglobinuria, redwater[a]
Clostridium perfringens, enterotoxemia
Coliform mastitis
Endocarditis
Leptospirosis
Listeriosis (C, O)
Liver flukes (O)
Malignant catarrhal fever (B)
Mycoplasmosis (C)
Neonatal septicemia
Neonatal diarrhea

Pasteurellosis, septicemic[a] (O)
Pseudorabies
Salmonellosis[a]
Septic metritis
Thromboembolic meningoencephalomyelitis[a] caused by *Histophilus somni* (B)

B, Bovine; *C*, caprine; *O*, ovine.

[a]Likely to involve several animals.

Metabolic and Nutritional Causes of Sudden Death in Horses

Hypocalcemia is commonly associated with lactation (“lactation tetany”), transport (“transit tetany”), and exhaustion during or following endurance work. Affected animals develop tetany, synchronous diaphragmatic flutter (“thumps”), muscle tremors, sweating, and ileus. Diagnosis is based on demonstration of hypocalcemia in the face of typical clinical signs. White muscle disease (nutritional myodegeneration) is associated with selenium and vitamin E deficiency. Sudden death in affected adult horses after severe exercise may be attributed to degenerative lesions in cardiac and skeletal musculature. Death in foals may occur within hours of birth as a result of heart failure and pulmonary edema. Diagnosis of nutritional myodegeneration is based on histopathologic findings and measurement of whole blood and/or liver selenium and vitamin E concentrations. Unanticipated death may result from cardiotoxic hyperkalemia in Quarter Horses (and related breeds) affected with hyperkalemic periodic paralysis (HyPP). HyPP is a genetic disease that more commonly results in episodes of muscle weakness and/or stertorous breathing. Diagnosis of HyPP status (unaffected/heterozygous/homozygous) is straightforward and based on genetic testing. However, the determination as to whether unexpected death resulted specifically from hyperkalemia is less straightforward and may be based on a combination of genetic testing (tissue obtained postmortem), ruling out other plausible etiologies (including postmortem examination), and the demonstration of elevated potassium concentration in ocular fluids (compared

with controls).[9]

Metabolic and Nutritional Causes of Sudden Death in Ruminants

Metabolic and nutritional diseases are not often considered in cases of sudden death. The primary lesion in a disorder of cattle known as “falling disease” is progressive fibrosis of the myocardium. Sudden deaths characteristic of the disease are attributed to exercise-induced heart failure.[10] Rapid development of hypocalcemia is usually associated with the onset of lactation in cattle, with stressful circumstances in older lactating ewes, or with transport associated with fasting and weather stress. Hypomagnesemia may also develop under similar conditions, especially in ewes and cows in heavy lactation and on lush grass pastures. Polioencephalomalacia occurs most commonly in animals raised under intensive production techniques and can sometimes be traced to excessive sulfates in the diet and/or water. The clinical course tends to be most rapid in sheep. Severe cases of ruminal lactic acidosis, especially in animals unaccustomed to high levels of soluble carbohydrate in the diet, may induce death within 24 hours. Nutritional myodegeneration of the heart is a frequent cause of sudden death in young ruminants born to dams fed selenium-deficient diets during gestation. Diagnosis is based on histopathology and measurement of liver selenium concentration. Some cases of sudden death associated with myocardial necrosis are idiopathic.[11]

Cardiovascular Causes of Sudden Death in Horses

As a category, cardiovascular conditions likely represent the most common cause of unanticipated death in horses. Diagnosis of sudden death caused by cardiovascular failure depends on a careful and organized methodological approach (Box 14.3).[1] In most instances, a single animal is affected. Necropsy is necessary to identify the location and characteristics of the lesion, and further analysis may be necessary to establish the exact cause of death.

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Box 14.3

Cardiovascular Causes of Collapse and Sudden Death in Horses

Aortic ring (root) rupture
Central nervous system embolism
Coronary occlusion
Endocarditis
Massive abdominal or thoracic hemorrhage
Myocarditis
Pericardial rupture
Splenic rupture
Thrombi of verminous origin
Uterine arterial rupture

Disorders of the equine cardiovascular system that might lead to unanticipated death may be categorized into those conditions in which death results from a fatal rhythm disturbance (ventricular tachycardia, ventricular flutter, ventricular fibrillation, complete atrioventricular block, or asystole); conditions in which death results from acute myocardial failure (acute decompensation of chronic heart failure, acute onset of severe valvular insufficiency [e.g., chordal rupture], or acute myocardial ischemia/necrosis); and conditions in which heart function is compromised by tamponade (viral, bacterial, or idiopathic pericarditis, trauma).[12] Cardiac-related death may result suddenly from several intoxications (myocardial plant toxicities including yew (*Taxus* spp.), oleander *(Nerium oleander),* foxglove (*Digitalis* spp.), summer pheasant's eye *(Adonis aestivalis),* box elder (*Acer* spp.), and marsh mallow *(Malva parviflora).* Cardiac death may also result from intoxication by ionophore antibiotics (as contaminants from the bovine feed industry), cantharidin toxicity (blister beetle poisoning), and snake envenomation (*Crotalus* spp. *Viperidae*).[12] In rare instances, marked hyperkalemia (hyperkalemic cardiotoxicity) may be responsible for death in horses affected with HyPP. Penetrating chest wounds or iatrogenic damage to the equine heart (cardiac catheterization) may provoke fatal arrhythmia or cause severe hemorrhage with fatal outcomes. External or internal exsanguination represents an important cause of unanticipated death, and several specific

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syndromes have been described: cardiac rupture (with cardiac tamponade); rupture of either the pulmonary artery or aorta (with or without tamponade); carotid artery rupture in the guttural pouch may lead to the unanticipated death of horses affected with guttural pouch mycosis; and rupture of the cranial mesenteric artery at its origin consequent to damage resulting from *Strongylus vulgaris* larval migration is presently a rare cause of fatal internal hemorrhage following widespread use of ivermectin. Peripartum uterine arterial rupture involving ovarian, utero-ovarian, uterine, or external iliac arteries is sometimes observed in older mares, with death ensuing in 30 minutes to 20 hours. Pulmonary artery rupture may lead to death in horses that are affected with exercise-induced pulmonary hemorrhage or pulmonary hypertension for any cause. Brain hemorrhage may cause death, especially in horses that have "flipped over backwards" and fractured the basioccipital/basisphenoid bones at the base of the skull.

Aortic sinus of Valsalva aneurysms or tears in the aortic root are well-recognized conditions in breeding stallions, often leading to sudden death, especially early in the breeding season, often occurring immediately after servicing a mare.[12] Rupture of the aorta may occur just distal to the aortic valve, resulting in cardiac tamponade and rapid death. Aortopulmonary fistulation in conjunction with aortic rupture is quite common in the Friesian breed; aortic rupture and aortopulmonary fistulation should be included in the differential diagnosis when Friesian horses are presented with a history of recurrent false colic, coughing, sustained tachycardia, and/or peripheral edema.[12,13] Cardiovascular diseases including myocardial lesions (hemorrhage, swelling, fibrosis, and infarction), aortic root rupture, and abdominal large artery rupture were identified as common explanations for sudden/unexpected death in Japanese stallions.[14]

Acute central nervous system embolism results from detached thromboemboli originating from vegetative lesions on heart valves affected with bacterial endocarditis or from accidental intracarotid injection. Cerebral hematoma may also result from inadvertent intracarotid injections. Endocarditis, especially of the aortic valve, may result in coronary thromboembolism and myocardial infarction, albeit rarely. Coronary artery occlusion resulting from damage induced by migrating *S. vulgaris* larvae is diagnosed by the presence of the larvae in the coronary thrombus. Massive abdominal or thoracic hemorrhage is found at necropsy, and the cause may be difficult to ascertain.[15] Myocarditis in horses up to 4 years of age resulting from recent respiratory infection may be

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diagnosed with histopathologic examination. Pericardial rupture and the associated heart damage may result from violent trauma. Splenic rupture with fatal hemorrhage occurs rarely because of the protection afforded by the thoracic wall. Massive thrombi of verminous origin have been observed in young horses that die suddenly while exercising.

Physical Causes of Sudden Death in Horses

Fatal air embolism can result from any open vein above the heart. Open needles or catheters and severe head wounds involving teeth and sinuses have resulted in sudden death from air emboli. Air is aspirated into the vein by the *Venturi* effect from blood surging past a portal and creating the necessary negative pressure to aspirate air into the vein. Between 700 and 6000 mL of air may produce a fatal air embolus in the right ventricle, where it obstructs the pulmonary artery. Cecal or colonic rupture in periparturient mares may lead to death within 8 hours.[16]

Physical Causes of Sudden Death in Ruminants

Physical causes of sudden death typically display gross evidence indicative of the diagnosis. Abomasal bloat occurs in calves and lambs drinking excessive quantities of warm milk replacer at infrequent intervals. Abomasal ulcers may occasionally perforate and cause rapid death in calves or adult cattle. Ruminal bloat is one of the more common physical causes of sudden death in intensively raised ruminants. When differentiating postmortem from *antemortem* bloat, note that bloat is the primary cause of death when there is congestion and hemorrhage in the anterior parts of the carcass and edema in the scrotal and ventral perineal areas. Bloat and hypersalivation are the most consistent clinical signs seen in cases of choke. Attempts to swallow firm fruits, tubers, or green ears of corn may occlude the esophagus and result in rapid ruminal tympany and death.

Sudden death is a major concern in feedlots because most such deaths occur in cattle near market weight. GI disturbances are seen with a high frequency in cattle in the late stages of the feeding program. Sudden death is the result of interactions among factors such as rumen acidosis, bloat, and endotoxemia.

Exposure to high-voltage currents in the form of lightning or electrical transmission wires may cause instantaneous death. The diagnosis of lightning strike is based on a history of an electrical storm, linear singe marks, food in the mouth, several animals being found dead in the vicinity, and evidence of

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lightning damage in the immediate environment. Gunshot wounds may be deliberate or accidental; death resulting from gunshot injury typically involves either the head or heart. Bullets may pass through or lodge in obscure locations, making retrieval difficult. Radiography can assist in confirming and locating a bullet. Heatstroke is a sporadic condition characterized by hyperthermia and collapse. High humidity, dehydration, obesity, and poor heat tolerance associated with young or old age are all factors that predispose animals to overheating. Fleeced animals such as sheep and South American camelids often succumb to heatstroke if the time of shearing is not appropriate. “Summer slump” induced by consumption of endophyte-infected fescue potentiates the heat intolerance. Internal bleeding may cause sudden death when a uterine artery is ruptured during parturition. This is readily apparent on necropsy. Tracheal edema, or “honker” syndrome, of feeder cattle is seen sporadically in feedlot cattle of the southern plains during hot weather. The pathoanatomic basis of this syndrome is extensive edema of the mucosa and submucosa of the lower trachea, with attendant dyspnea and obstructive asphyxiation. Increased respiratory movements stimulated by hot weather or exercise trigger the clinical illness, especially in heavy cattle during the latter part of the feeding period.[17] Traumatic reticuloperitonitis or reticulopericarditis result from poor oral discrimination behavior in cattle. Sudden death in these cases may result from acute hemorrhage or dysrhythmia if the heart is affected by foreign body migration (cardiac puncture may occur).

Toxic Causes of Sudden Death in Horses

Toxic causes of sudden death are frequently related to management practices. An increase in specific disease syndromes or sudden death in a population of livestock with common potential exposures suggests involvement of a toxicant. Investigation of the premises and a familiarity with poisonous plants and pesticides used in the practice area should help narrow the list of possible causative agents (Box 14.4).

Box 14.4

Toxic Causes of Collapse and Sudden Death in

Horses[a]

4-Aminopyridine (Avitrol), an avicide
Arsenic
Black flies
Cantharidin*
Ferrous fumarate
Fusarium moniliforme–associated mycotoxicosis
Insulin and potassium
Monensin[a]
Nitrogen dioxide
Organophosphate and carbamate insecticides
Toxic plants
- *Acer rubrum* (red maple)
- *Acer negundo* (female box elder)
- Blue-green algae[a]
- *Cicuta* spp. (water hemlock)
- *Conium maculatum* (poison hemlock)
- Cyanogenic plants
- *Melilotus* spp. (sweet clover)
- *Nerium* spp. (oleander)
- *Nicotiana* spp. (tobacco)
- *Ricinus communis* (castor bean)
- *Taxus* spp. (Japanese yew)

[a]Likely to involve several animals.

Horses ingesting a lethal dose of the avicide 4-aminopyridine have died within 2 hours of the onset of clinical signs. Diagnosis is based on chemical analysis of stomach contents. Fatal doses of arsenic-containing pesticides may induce cardiovascular collapse and death in horses within hours of ingestion. The presence of edema and fluid in the GI tract suggests arsenic toxicosis, and chemical analysis of GI tract contents, liver, or kidney confirms it. Black flies swarm where swiftly flowing water provides the aeration necessary for the

development of larvae. Massive attacks of these blood-sucking insects can rapidly kill livestock because a toxin present in the saliva of the flies increases capillary permeability.[18] Cantharidin poisoning can occur after ingestion of 4 to 5 g of blister beetles. Lesions suggestive of cantharidin toxicosis include blistering and ulceration of mucous membranes of the GI and urinary tracts and myocardial degeneration and necrosis. Sustained hypocalcemia and hypomagnesemia are features of the clinical pathology consistent with blister beetle poisoning. Identification of blister beetles in the hay and chemical analysis of urine and GI contents are suitable for diagnostic confirmation. In the past, ferrous fumarate, present in digestive inoculate and administered to foals immediately after birth, resulted in death in some cases in 12 to 96 hours. This illustrates the acute toxicity of iron to young animals in particular. Lesions induced were those of gross liver damage. *Fusarium moniliforme*–contaminated corn causes rapid death in horses after the sudden onset of bizarre neurologic deficits and behavioral effects. The lesion of this mycotoxin-induced leukoencephalomalacia is liquefactive necrosis in the subcortical white matter.

High intravenous doses of insulin[19] and potassium[9] induce sudden death without significant lesions. Chemical detection is often overlooked and difficult to perform and interpret in cases of deliberate poisoning. Immediate analysis of blood and circumstantial evidence of needle punctures (blood stains) in the jugular furrow may be of diagnostic value. Monensin is quite toxic to horses, and fatal poisoning can occur within 12 hours of ingestion of poultry feed containing 100 g/ton or cattle premixes containing 300 g/ton. Lesions related to heart failure are seen on postmortem examination. Tissues collected for microscopic examination should include heart and diaphragm. Chemical analysis of feed samples and stomach contents will confirm exposure. Toxic gases such as nitrogen dioxide, hydrogen sulfide, and carbon monoxide may be responsible for sudden death in horses housed in poorly ventilated buildings with associated gas sources nearby. Organophosphate and carbamate insecticides may induce acute intoxication and death within hours. Diagnosis is based on a history of exposure, determination of acetylcholinesterase activity in the caudate nucleus of the brain, and chemical detection of specific compounds in gut contents.

Circumstances surrounding toxic plant ingestion and diagnosis of intoxication are described in the ruminant section of this chapter. Ingestion of wilted *Acer rubrum* (red maple) leaves and other *Acer* spp. may induce massive methemoglobinemia, causing marked tissue anoxia and death.[20] Red maple poisoning usually occurs during the late summer and early fall when trees are in

full leaf. Ready access to wilted leaves follows windstorms. *Ricinus communis*, or castor bean, is also unique. Seeds of this plant contain a phytotoxin called *ricin*, which causes severe enteritis and rapid death in horses. About 150 beans (50 g) are sufficient to kill a 450-kg horse. Diagnosis can be verified by finding a toxic amount of ingested seeds in the gut contents.

Toxic Causes of Sudden Death in Ruminants

Intoxication of livestock is frequently suggested as a simple explanation for complex situations involving sudden death. Suspicions are warranted when a large number of animals die suddenly within a short time. Toxicants should be considered when the appearance of a disease or sudden death is temporally associated with a change in the environment (Box 14.5). An accurate diagnosis in many of these cases requires qualitative and quantitative analyses for suspect poisons. Selecting toxicants for which to analyze requires reasoned judgment supported by an extensive investigation of the environment and postmortem findings.

Box 14.5

Toxic Causes of Collapse and Sudden Death in Ruminants[a]

4-Aminopyridine (Avitrol), an avicide
Anticoagulants
Arsenic
Botulism[a]
Carbamates
Carbon monoxide
Chlorinated hydrocarbons
Copper (B, O)
Crude oil
Gossypol[a]
Hydrogen sulfide gas[a]
Ionophores[a]

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- Lead[a]
- Metaldehyde
- 4-Methyl-imidazole, bovine bonkers syndrome (B, O)
- Nicotine sulfate
- Nitrogen dioxide gas[a]
- Organophosphates
- Selenium, parenteral overdose
- Strychnine
- Urea, nonprotein nitrogen[a]
- Water deprivation, sodium ion toxicity
- Toxic plants
    - *Aconium* spp. (monkshood)
    - *Asclepias* spp. (milkweed)
    - Blue-green algae[a]
    - *Calycanthus fertilis* (bubby bush) (B)
    - *Cicuta* spp. (water hemlock)
    - *Conium maculatum* (poison hemlock)
    - Cyanogenic plants
    - *Delphinium* spp. (larkspur) (B)
    - *Drymaria pachyphylla* (inkweed)
    - *Halogeton glomeratus* (halogeton) (O, B)
    - *Kalmia* spp. (laurels)
    - *Kochia scoparia* (summer cypress)
    - *Laburnum anagyroides* (golden chain tree)
    - *Lupinus* spp. (lupine) (O)
    - *Melilotus* spp. (sweet clover)
    - *Nerium* spp. (oleander)
    - *Nicotiana* spp. (tobacco)
    - Nitrate-accumulating plants
    - *Perilla frutescens* (perilla mint)
    - *Phalaris* spp. (canary grass) (O)
    - *Sarcobatus vermiculata* (greasewood) (B, O)
    - *Solanum* spp. (nightshades)
    - *Taxus* spp. (Japanese yew)
    - *Xanthium* spp. (cocklebur) (B, O)
    - *Zigadenus* spp. (death camas) (O)

B, Bovine; *O*, ovine.

[a]Likely to involve several animals.

The avicide 4-aminopyridine is usually formulated with corn, making it a palatable poison for nontarget herbivorous livestock. Diagnosis is confirmed by chemical analysis of rumen contents or urine. Anticoagulant intoxication may induce sudden death when hemorrhage occurs in the cranial vault, abdominal cavity, pericardial sac, mediastinum, or thorax. The antemortem or postmortem sample for chemical analysis is whole blood or liver. Failure to detect an anticoagulant is not unusual because of the time lag between consumption and presence of the clotting defects, as well as the metabolism of the compound. Arsenic derivatives are a significant hazard to ruminants, especially in areas where such chemicals are widely used as cotton desiccants. Postmortem findings are consistent with microvascular injury to the GI tract. Diagnosis is confirmed by chemical analysis of rumen contents, liver, or kidney. In rare cases, large doses of botulinum toxin may cause sudden death in ruminants. Sources of the toxin include the bones of dead animals eaten by osteophagic livestock, poultry carcasses in manure fed to cattle, stagnant pond water, animal tissues in silage or baled hay, and improperly ensiled silage or haylage.

Acetylcholinesterase-inhibiting agents such as the carbamate and organophosphate pesticides can kill livestock within hours. When agricultural strategy results in the deployment of these pesticides in close proximity to livestock, the situation may be disastrous. Acetylcholinesterase activity in the caudate nucleus of the brain is readily determined and interpreted, and specific compounds may be identified in rumen contents. Toxic gases such as carbon monoxide, hydrogen sulfide, and nitrogen dioxide become important differentials for sudden death in ruminants housed in poorly ventilated buildings, particularly over waste pits. Chlorinated hydrocarbon pesticides do not enjoy the widespread use they once did; however, old containers remain in obscure locations on many farms. When acute intoxication with these compounds is suspected, samples for analysis should include liver, brain, and rumen contents. In subacute cases, fat and milk are appropriate samples. Copper toxicosis is a frequent cause of sudden death in sheep and has been reported in cattle fed chicken litter.[21] Cattle feeds normally contain twice as much copper as sheep

feeds and may cause copper toxicosis in sheep. Copper from treated fence posts also may poison sheep that either chew the posts or ingest contaminated forage in the vicinity. Samples required for chemical confirmation consist of whole blood or serum and liver. Close proximity of livestock to petroleum exploration and production activities in the major oil-producing states results in a variety of clinical problems, including sudden death.[22] Consumption of the more volatile petroleum constituents may induce rapid bloating and coating of the respiratory membrane when these substances are aspirated into the lungs. Gossypol toxicosis reportedly causes death without premonitory signs in calves (occasionally cows) and lambs fed cottonseed products containing this toxic pigment.[23,24] Poisoning appears abruptly after livestock have been fed the gossypol-containing ration for a period of weeks to months. Sudden death is attributed to heart failure. Postmortem examination reveals edema, centrilobular hepatic necrosis, and an enlarged heart. Ionophores may induce sudden death in species exposed to large overdoses, but delayed death is the usual course. Conditions conducive to lethal overdose include insufficient mixing or top dressing with monensin- or lasalocid-supplemented mineral. Degenerative-to-necrotic lesions in the heart are compatible with a diagnosis of ionophore poisoning.

Acute lead intoxication is another differential from the list of possibilities in sudden death cases. Lead poisoning is the most common toxicosis in cattle. Blood, liver, and kidneys are suitable specimens for lead analysis. Metaldehyde is an uncommon poison for ruminants; however, intoxication in cattle has occurred in low wetland areas where the chemical is used as a molluscicide. The palatability of metaldehyde baits promotes ingestion. Ammoniation of high-quality forage such as forage sorghum and Sudan grass, cereal grain, brome, and fescue hays is responsible for bovine bonkers syndrome, reportedly caused by the formation of 4-methyl-imidazole.[25] This sporadic intoxication causes central nervous system derangement and rapid death in cows and nursing calves. Ruminants may be poisoned by nicotine sulfate from ingestion of solution, treated foliage, and food or water from contaminated containers. The onset and progression of the syndrome are rapid, and death may occur within hours. Detection of nicotine in urine is easily performed by most toxicology laboratories. Iatrogenic selenium toxicosis and death in young ruminants can result from parenteral administration of excess doses. Rapid onset of violent tetanic seizures ending in death characterizes strychnine toxicosis. Samples suitable for chemical analysis include rumen contents, liver, and urine.

Urea toxicosis is a frequent cause of sudden death in feedlot livestock. In one particular case, 48 feedlot steers died within 2 days of delivery of a new lot of feed supplemented with urea.[26] Unusually high rumen pH, excess ammonia in serum, rumen contents, and eyeball fluid support the diagnosis. Water deprivation, with attendant sodium ion intoxication, is a known cause of sudden death in ruminants.[27] Some cases occur in hot weather, but frozen water supplies in cold weather can be equally as devastating.

Poisonous plant problems frequently present a unique set of circumstances associated with their ingestion. Overgrazing of pastures is probably the most significant factor affecting the ingestion of toxic plants. Other situations conducive to poisonous plant ingestion include lack of suitable forage in periods of drought and the incorporation of toxic forbs in hay or green chop. Plants normally avoided because of poor palatability may become acceptable when frosted or sprayed with herbicide. Toxic plants may also be the first green plant available early in the spring, when livestock are hungry for anything green and succulent. Livestock trailed or transported for long distances without food or water and then suddenly introduced to new pasture may fail to avoid toxic plants and often will eat anything within immediate reach. In general, diagnosis of plant poisoning is based on availability, grazing evidence or presence in the hay, and the existence of plant parts in the rumen contents. Diagnostic lesions are usually lacking, and analytic methods for toxic components are severely limited.

Aconitum spp. (monkshood) are rarely a cause of sudden death because of their limited availability. *Delphinium* spp. (larkspur), however, are closely related to monkshood and are responsible for more cattle losses in the western United States than any other poisonous plant. Larkspur grows in dense stands in the mountainous West and is readily consumed, especially during an early stage of growth. Mature stands are less palatable and not as toxic. Cattle poisoned by larkspur are often found close to a stand, collapsed, and bloated. Death from the cardiotoxic and neuromuscular blocking effects may occur within a few hours of ingestion. Sheep are less susceptible to larkspur and are seldom poisoned by it, partly because of their different grazing habits.[28] *Asclepias* spp. (milkweed) contain either cardioactive glycosides or neurotoxic compounds.[29] The most toxic species reside in the western and southwestern United States. These plants are not very palatable but are somewhat less objectionable when dried. Livestock will graze them in a drought, but the biggest problem is contamination of hay or green chop. Blue-green algae may cause sudden death in all classes of livestock within minutes of ingestion of toxins from certain neurotoxic species. Toxins

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from other hepatotoxic species may require 24 hours to induce death. Toxic blooms occur sporadically during certain environmental conditions of late summer and fall. Diagnosis is usually based on a history of exposure to a concentrated bloom, but some laboratories perform chemical and biological assays.

Calycanthus spp. (bubby bush) contain an alkaloid similar in structure and mechanism of action to strychnine. These species are of minor importance to the livestock industry in the Southeast and West but have induced death in cattle. Seeds and other plant parts may be identified in rumen contents. *Cicuta* spp. (water hemlock) may induce violent convulsions and death within an hour of consumption. Intoxication is most common in early spring, when plants growing along waterways are easily uprooted and the tuberous parts are eaten. A single root system from a large plant can kill a cow. This is one of the most toxic plants in North America, and it has been responsible for the deaths of numerous livestock and humans. *Conium maculatum* (poison hemlock) grows throughout the United States. Cattle are most sensitive, and sheep are relatively resistant. Poisoning is usually associated with heavily grazed pastures.

Cyanogenic glycosides are present at toxic concentrations in more than 250 plant genera, including *Sorghum, Prunus, Triglochin,* and *Linum.* Ruminants are especially susceptible to these glycosides because they possess the microorganism enzyme systems necessary for rapid liberation of hydrocyanic acid. Death may occur within 15 to 30 minutes of ingestion. Hyperoxygenated venous blood will be cherry red and slow to clot, and rumen contents may have the odor of almond extract. Samples of forage, blood, and rumen contents should be collected immediately, placed in airtight containers, and frozen for analysis. Negative results are often questionable because of the highly volatile nature of hydrogen cyanide. *Drymaria pachyphylla* (inkweed) has caused sudden death in cattle in the southwestern United States. The differential diagnosis in this part of the country includes anthrax. Diagnosis is based on examination of rumen contents for plant parts.

Halogeton glomeratus is a soluble oxalate-containing plant that grows best in disturbed soil along roadsides in the western intermountain states. *Sarcobatus vermiculata* (greasewood) grows in semiarid regions of the West. It also contains toxic levels of soluble oxalate. Unadapted sheep are most frequently intoxicated by these plants, and death may occur within 9 to 11 hours of onset of intoxication. Sudden death results from hypocalcemia and inhibition of cellular respiration. Postmortem findings include hemorrhagic rumenitis, hydrothorax,

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ascites, and the presence of oxalate crystals in the kidney and rumen wall. *Kalmia* spp. (laurel) are an occasional problem in winter or early spring, when they are the only conspicuously green plant available. Laurel grows in the wild in the eastern and western regions of the United States. Death may occur in 12 to 14 hours. Fragments of glossy, leathery leaves may be visible in rumen contents. *Kochia scoparia* (summer cypress or burning bush) sporadically causes a thiamine-responsive polioencephalomalacia in cattle. *Laburnum anagyroides* (golden chain tree) is a large ornamental shrub considered to be the second most poisonous plant in Great Britain. It also grows in much of the United States. The shrub contains quinolizidine alkaloids that may induce rapid death from respiratory failure. *Lupinus* is a genus with about 200 species in North America. There is considerable seasonal variation in toxicity, with the toxic species presenting a problem when plants are immature or when they have reached the seedpod stage. Acute intoxication and rapid death are likely only when large quantities of seeds are ingested within a short time. Toxic species cause more deaths in sheep than any other plant in Montana, Idaho, and Utah. Improperly cured hay and silage derived from *Melilotus* spp. (white and yellow sweet clover) may cause sudden death in cattle when hemorrhage occurs in the cranial vault, pericardial sac, mediastinum, or thorax. Induction of the disease requires consumption of the moldy forage for several weeks to allow sufficient depletion of vitamin K–dependent clotting factors. *Nerium* spp. (oleander) are widely cultivated in the South and West. Toxic in the green or dry state, these plants may border hay fields, and significant mortality of livestock may occur when dropped leaves or trimmings are incorporated into forage. Livestock are often poisoned when prunings are mixed with grass clippings and the bitter taste is disguised. Diagnosis is based on evidence of consumption and identification of plant parts in rumen contents.

The genus *Nicotiana* contains toxic species of wild and cultivated tobacco. Poor palatability usually hinders consumption; however, opportunities for intoxication and death sometimes occur in areas of the West where forage is scarce and in parts of the country where tobacco is cultivated. Nitrate-accumulating plants include certain annuals, weeds, and cool-season crops and grasses. Notable examples include pigweed, lamb's quarters, Sudan grass, and oat hay. Under the right environmental conditions most plants can accumulate toxic concentrations of nitrate. Plant-associated nitrate poisoning is a serious problem only in ruminants because of the nitrate-reducing ability of rumen microbes. Onset of nitrate intoxication is rapid, and death may result within 6 to

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24 hours of rapid ingestion of a toxic dose. Diagnosis is based on a brownish cast to the viscera and blood, together with chemical analysis of serum, aqueous humor, and forage for nitrate concentration.

Acute bovine pulmonary emphysema is associated with an abrupt change from dry range forage to lush green pasture high in L-tryptophan concentration. Less commonly, the pulmonary toxins of *Perilla frutescens* (perilla mint) can induce dyspnea and death in a few hours. Necropsy reveals incomplete collapse of lungs that are heavy and firm, with froth-filled airways. Histologic examination shows a proliferation of type II pneumocytes. *Phalaris* spp. (canary grass) have been reported to have caused sudden collapse and death of sheep in California.[30] Sheep that had been grazing a field containing canary grass were herded a short distance when six ewes collapsed and died. Bilaterally symmetric, greenish-gray discoloration was seen in the midbrain. The same gross discoloration was also seen in the renal cortex. Microscopic examination confirmed the presence of intracytoplasmic accumulation of this granular pigment. *Solanum* spp. (nightshades) grow throughout the United States, especially in waste areas and overgrazed pastures. Rapid ingestion of large quantities of highly toxic fruit can result in coma and rapid death. *Taxus* spp. (yew) poisoning in ruminants commonly results in sudden death. Poisoning is most likely to occur when ruminants are pastured adjacent to residential areas where yew is a common ornamental shrub. Diagnosis is based on evidence of exposure and identification of yew leaves in rumen contents. *Xanthium* spp. (cocklebur) are most toxic at the cotyledonary stage of growth. These species may induce death in calves within 12 hours of onset of clinical intoxication. Hypoglycemia and centrilobular hepatic necrosis are consistent findings. *Zigadenus* spp. (death camas) are of major importance to sheep grazing on western ranges. These plants begin growth in early spring, presenting a significant hazard at this time.[31]

Miscellaneous Causes of Sudden Death in Horses

Allergic reactions capable of causing sudden death include rupture of warble fly larvae. Warble fly larvae are seldom able to penetrate equine skin, and the fully matured larvae either die or are killed when the horse is saddled or harnessed. The ruptured larvae induce anaphylactic shock and pulmonary edema. Foam in the airways is found on necropsy. Penicillin or other antibiotics may cause an

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anaphylactic reaction with a similar outcome.

Perinatal sudden death may occur in foals as a result of meningeal hemorrhage caused by birth trauma. The sudden onset of profuse, watery diarrhea and rapid development of hypovolemic shock characterize colitis-X. A severe necrotic typhlitis is seen at necropsy, with destruction of colonic and cecal mucosa. Diaphragmatic rupture and hernia are associated with violent exercise or trauma, with or without bowel herniation. Electrocution occurs when a horse chews through or comes into contact with an uninsulated hot wire while well grounded. Death is instantaneous, usually with negative necropsy findings. Lightning strike may reveal burning or singeing of skin, hair, or underlying tissue. GI conditions that may cause sudden death include volvulus, intussusception, torsion, strangulation, tympany, and small intestine rupture from ascarid impaction (in foals). Gastric rupture may cause sudden and unexpected death; in one study, rupture of the stomach was predominantly attributed to either idiopathic causes or as a complication of gastric impaction.[32]

Gunshot wounds may be another cause of sudden death that is surprisingly difficult to verify, because bullet retrieval is necessary to establish the diagnosis. Tracking and finding a small metal object lodged in tissue is a time-consuming task at best. Heat or work stress is seen in horses in hot, poorly ventilated quarters, or in poorly conditioned horses overworked in hot, humid weather. Collapse and coma are followed by death in a few hours. Necropsy reveals skeletal and cardiac muscle damage, GI ulceration, and renal necrosis. In pregnancy, unrecognized and untreated torsion of the gravid uterus may result in sudden death.

Exercise-induced respiratory tract injury may cause sudden death in well-conditioned horses.[33] Exercise-induced pulmonary hemorrhage occurs during race training or competition, with most cases being of little acute concern. In severe cases, horses may die during or immediately after exercise with extensive hemorrhage (especially the caudal lung lobes) evident at necropsy.

Serum hepatitis (Theiler disease, viral hepatitis) may result from administration of biologics of equine origin 50 to 90 days before the onset of clinical signs, including fever, jaundice, and hepatoencephalopathy. In severe cases, death may occur within 12 to 48 hours. The main lesion seen is liver necrosis with discoloration and accentuation of the lobular pattern on the cut surface. Recently, several viral pathogens have been implicated in the etiology of Theiler disease.[34,35] Fracture of the junction between the basisphenoid and the basioccipital bone usually results from rearing over backward and striking the

poll on the ground.

Sudden and Unexpected Death in Equine Athletes

Emphasis placed on the postmortem diagnosis of cause of death and risk factors for death in racehorse communities has led to several retrospective studies on this topic in recent years.[36-38] Consistently, most racehorse deaths result from catastrophic musculoskeletal injuries (serious accidents) with limb fracture being the most common circumstance leading to death among all racehorses. Other fatalities are classified as unexpected or sudden death, in association with exercise (racing or training) or occurring spontaneously in the absence of physical exertion. The pathologist may or may not be able to conclude definitively that any observed lesions are necessarily the cause of death (e.g., observed abnormalities may represent unrelated comorbidities or could even result from agonal breathing). Although often presumed to result from acute cardiac, cardiovascular, or cardiorespiratory failure, the importance of a complete and structured postmortem examination cannot be overstated.[1] Results and conclusions from postmortem examinations at different institutions (and over time within the same institution) will be easier to compare if a recently described standardized protocol gains broad acceptance.[1]

In one recent study, postmortem findings and cause of death were retrospectively reported over a 13-year period for 963 horses examined for the Ontario Racing Commission Death Registry.[36] In that study, unexpected or sudden death that occurred during or immediately following exercise accounted for 31% of performance-related deaths, most commonly resulting from cardiopulmonary lesions (pulmonary hemorrhage was the most common explanation). The most frequent causes of death or significant postmortem findings in horses dying suddenly during exercise were classified as respiratory (50%), cardiovascular (22%), and undetermined (20%). Less frequently, skull fracture, sepsis, encephalitis, dyshemostasis, and hemorrhage were reported in a handful of cases. Pulmonary hemorrhage (such as exercise-induced pulmonary hemorrhage) represented 93% of respiratory explanations. Acute heart failure and pulmonary hypertension resulting from postexercise arrhythmia may lead to pulmonary hemorrhage, cardiopulmonary failure, and sudden death in racehorses.[39] Hemopericardium (pericardial tamponade), hemothorax, and

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hemoabdomen represented 82% of cardiovascular cases. For example, aortic rupture is a well-recognized cause of sudden death in this species and likely results from increased aortic pressure during strenuous physical activity, as reported previously.[40]

As mentioned earlier, a cause of death was not established for 20% of sudden death cases because explanatory lesions could not be identified postmortem. In those cases, it was speculated that cardiac arrhythmia may have led to death. Injection-associated death was identified in 4% of the study population.[36] The proportional mortality rate for exercise-associated sudden death among all breeds was 9% (157 of 1708). Death resulting from injected drugs occurred in 38 of 377 horses (10%) whose deaths were unrelated to exercise and in 38 of 963 of all horses (4%) horses in that study.[36] In most instances, collapse followed by seizure or death occurred *during or immediately following* the injection. Untoward clinical reactions led to euthanasia for a number of other injected horses that died. Various drugs and combinations of drugs were implicated in this study and included amino acid supplements; antibiotics (penicillin, trimethoprim–sulfadiazine, gentamicin); unspecified iron preparations; dimethyl sulfoxide (DMSO); mannitol; vitamin E–selenium preparations; other nonspecified vitamins; testosterone; other anabolic steroids; estrogen; calcium; pentosane polysulfate; Sarapin; trichlormethiazide–dexamethasone acetate; n-butyl alcohol; and prednisone.[36] Although specific necropsy-identified lesions that satisfactorily explained death in these cases were not identified, both pulmonary edema and/or congestion with variable hemorrhage were often identified. Suspicion of an inadvertent intracarotid injection was based on the presence of cerebral edema, malacia, and vasculitis in one case. Furthermore, evidence of sepsis identified during postmortem examination implied that death may have resulted from the intravenous administration of contaminated solutions in three additional cases.

Bit-induced asphyxia (partial or complete) was recently suggested to contribute to the risk of sudden death in racehorses.[41] In that work, the author contended that both sudden/unexpected death and catastrophic musculoskeletal injury result from bit-induced asphyxia, a potentially preventable situation in racehorses.[41]

Miscellaneous Causes of Sudden Death in

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Ruminants

Fatal anaphylaxis occurs in sensitized animals after parenteral administration of drugs or vaccines. This is most common with the penicillins. Vaccines containing gram-negative bacteria or cell walls may cause an endotoxemic reaction that looks similar to anaphylaxis. Anaphylactic shock may also be an outcome of blood transfusion reactions. Immune-mediated hemolytic anemia (neonatal isoerythrolysis) from ingestion of colostrum-containing alloantibodies against a neonate's erythrocytes may induce sudden death if the specific antibody concentration is sufficiently high. A sudden death syndrome occurs in feeder cattle on high-concentrate diets. It usually occurs in warmer months and is limited to cattle fed high-concentrate rations for several weeks.[42] A malignant tumor that has been associated with sudden death is the thymoma, or thymic lymphosarcoma, seen most commonly in old goats. It appears as a large, pale, fleshy mass in the cranial mediastinum.[43]

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PART 3
Disorders and Management of the Neonate

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• CHAPTER 15

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The Equine Peripartum Period

Guy D. Lester, Consulting Editor

DISORDERS AND MANAGEMENT OF THE NEONATE

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Assessment of the Mare During Late Gestation

The per-cycle pregnancy rate in mares has been reported between 60% and 69%, with increasing mare age, breeding at foal heat, and overuse of stallions reported as negative factors at one Thoroughbred stud.[1] Approximately 79% and 87% of pregnancies detected at days 15 and 40, respectively, result in a live foal.[2] With additional losses in the perinatal period, it has been estimated that between 22% and 40% of mares that are bred do not produce a live foal.[2–5] Factors that contribute to this outcome include mare age, infertility, early fetal loss, abortion, and perinatal death.[1,4] During late gestation, common causes of reproductive loss are fetoplacental infection, placental dysfunction, maternal illness, and complications of delivery.[4,6,7] As mares age, their pregnancy and foaling rates decline and their foals experience higher morbidity and mortality rates and decreased athletic ability.[1–3,5]

The 2015 National Animal Health Monitoring System (NAHMS) reported that 3.3% of foals died within the first 48 hours after birth. This compares to the 1998 and 2005 NAHMS studies, where mortality rates of 1.7% and a 2.6% were reported, respectively.[8] This includes an estimate of euthanasia and spontaneous deaths. Sepsis, asphyxia, and dysmaturity, including prematurity and postmaturity syndromes, are the leading causes of neonatal foal mortality during the first 2 weeks of life.[9] Despite advances in neonatal intensive care, many foals still die, not because their primary problem is untreatable, but because veterinary intervention was delayed, delivery was unattended, neonatal compromise was not recognized in a timely fashion, or critical care was unavailable or not economically feasible. Foals surviving severe peripartum illness often experience increased morbidity associated with chronic infections, suboptimal growth, or developmental orthopedic disease. The three periparturient events that have the most devastating effect on neonatal survival are hypoxia, infection, and derangement of in utero development.

Many of the periparturient events associated with increased fetal/neonatal morbidity and mortality have been identified in the mare (Box 15.1).

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Box 15.1

Common Causes of Abortion, Stillbirth, and Perinatal Death in Horses

- Infectious problems (in order of frequency)
  - Fetoplacental infection
    - Bacterial
    - Viral
    - Fungal
    - Unidentified
- Noninfectious problems (in order of frequency)
  - Neonatal asphyxia not associated with dystocia
  - Neonatal asphyxia associated with dystocia
  - Placental edema
  - Premature placental separation
  - Twin pregnancies
  - Contracted foal syndrome
  - Other congenital malformations
  - Umbilical cord abnormalities
  - Placental villous atrophy
- Eastern Tent *(Malacosoma americanum)* or Processionary caterpillars *(Ochrogaster lunifer)* ingestion

From Giles RC, Donahue JM, Hong CB, et al: Causes of abortion, stillbirth, and perinatal death in horses: 3527 cases (1986-1991). *J Am Vet Med Assoc* 203:1170, 1993.

There are several clinical indications for evaluating the late-term fetus, including a larger than expected maternal abdomen, premature lactation, vaginal discharge, maternal illness, or prolonged gestation.[7] Mares that have a history of reproductive failure in late gestation are also candidates for close monitoring in future pregnancies. Biochemical and biophysical techniques for monitoring fetoplacental well-being have been developed for use in the pregnant mare.[10–14] Mares with high-risk pregnancies should be identified early, treated

appropriately, and monitored closely through the perinatal period. Accurate assessment of fetal well-being is complicated and handicapped by the size of the dam and fetus.

Mares experiencing problem pregnancies can be assigned to one of three categories: (1) mares with histories of abnormal pregnancies, deliveries, or newborn foals; (2) mares at risk for a problem with the current pregnancy due to systemic illness or reproductive abnormality; and (3) mares with no apparent risk factor, which experience an abnormal periparturient event.[13] A list of important risk perinatal risk factors is presented in Box 15.2. Ideally, mares with high-risk pregnancies should receive some type of late-gestation fetal monitoring or at least be carefully watched during late gestation and attended at the delivery. Personnel attending the delivery of a high-risk foal should be trained in resuscitation techniques (see later).

Box 15.2

Conditions Associated With the High-Risk Foal

Maternal Conditions

- Past history of:
  - Foals with neonatal isoerythrolysis, perinatal asphyxia syndrome, congenital malformations
  - Prematurely born, post-term foals that appear premature or asphyxiated foals
  - Dystocia or premature placental separation
  - Foal rejection
  - Recent exposure to infectious diseases associated with abortion and stillbirths, such as equine herpesvirus, viral arteritis, *Leptospira* spp.
- Systemic problems such as:
  - Fever
  - Anemia or hypoproteinemia
  - Endotoxemia

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- Gastrointestinal crisis, such as large bowel torsion
- Malnutrition
- Severe systemic infection
- Laminitis
- Prolonged recumbency from a variety of neurologic or musculoskeletal problems
- Excessive medication administration
- Prolonged transport before parturition

Reproductive, mammary gland, or localized problems, such as:

- Severe endometrial fibrosis
- Hydrops allantois or amnii
- Purulent vaginal discharge
- Prepubic tendon rupture
- Pelvic injuries
- Agalactia, such as from grazing on fescue pastures
- Failure to produce good-quality colostrum
- Premature lactation

Abnormalities of Labor or Delivery in Current Pregnancy

Premature parturition
Abnormally long gestation
Prolonged labor
Induction of labor
Dystocia
Early umbilical cord rupture, umbilical cord abnormality
Cesarean section
Premature placental separation

Neonatal Abnormalities

Meconium-stained fluid or neonate
Placental disease (e.g., placentitis, villous atrophy, edema)
Twins
Orphan
Delay in or lack of intake of colostrum

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Dysmaturity or prematurity
Exposure to infectious diseases, such as influenza
Trauma (birth, predators, mother)
Adverse environmental conditions
Failure to be up and nursing by 2 to 3 hours of age
Congenital abnormalities
Weakness, poor appetite

The hormones associated with pregnancy and fetal well-being can be divided into several categories.[15] These include hormones that control uterine myometrial activity, including quiescent and contractile states, and those that induce fetal maturation. Progestagens, including progesterone and its metabolites, are important in maintaining uterine quiescence during pregnancy. Progesterone is produced by the ovary until days 120 to 150 of gestation. After this time progestagens are synthesized by the uteroplacental tissues from pregnenolone, which is derived from fetal adrenal glands.[16] Pregnenolone is metabolized to progesterone in the placenta, which is further converted to 5 α-pregnane,3,20,-dione (5 α-DHP) in the endometrium. 5 α-DHP is metabolized to other progestins in the fetus, while some is passed into the maternal circulation, where it can be measured using commercial progesterone assays, due to endogenous progestagen cross-reactivity with progesterone antibodies. Maternal progestagen concentrations are relatively low and stable between days 150 and 315 of gestation, with concentrations typically between 2 and 12 ng/mL, depending on the assay used. These values rise sharply over the final 15 to 21 days of the pregnancy, before a large fall in the last 1 to 2 days before parturition. The rise is associated with mammary gland development and changes in the electrolyte concentrations of mammary secretions.[15]

Monitoring progestagen concentrations can provide useful insight into fetoplacental abnormalities, although maternal changes typically lag the early stages of disease. Measurement of progestagens may therefore be indicated to determine the need for progestin supplementation.[17] Three abnormal progestagen patterns have been described, and multiple samples collected at 48- to 72-hour intervals are recommended in high-risk mares.[18–21] Precipitous falls in progestagen concentration are seen in circumstances of fetal death and/or imminent expulsion.[22] In acute maternal illnesses, such as colic or uterine torsion, the progestagen concentration declines hours to days before abortion. In

these mares the concentration may fall to less than 2 ng/mL.[21] A premature rise in the plasma progestagen concentration can occur in response to fetal stress and/or placental pathology and can persist for days or weeks before abortion or premature delivery.[18] A premature increase in maternal progestagens could reflect hastened or precocious fetal maturation. Removal of the initiating stressful event can lead to normalization in progestagen concentrations and the subsequent delivery of a healthy full-term foal. A third abnormal maternal progestagen profile is found in mares exposed to tall fescue grass infected with an endophyte fungus, where there is a failure in the concentration rise seen in normal mares.

Relaxin is a marker of fetoplacental well-being and periparturient complications in the mare.[23] The placenta is the sole source of circulating relaxin in mares.[24] In healthy pregnant mares, relaxin concentrations increase from about day 80 to a peak of 80 to 100 ng/mL at day 175, which persists until birth.[25,26] There are breed differences in relaxin concentrations during normal pregnancy.[27] A study of mares with normal pregnancies reported slightly lower values over the final 7 weeks of gestation.[23] Plasma values drop at delivery and are cleared within 48 hours of passage of the fetal membranes. In mares with problematic pregnancies, low relaxin levels during late pregnancy have been indicative of placental insufficiency associated with a variety of causes including twinning, fescue toxicosis, oligohydramnios, placentitis, and pituitary disease.[23] The variability in values and breed differences make it difficult to rely on relaxin concentration as a marker of treatment efficacy in problem pregnancies.[23]

Estrogens regulate contractile properties of the myometrium. The precursors for estrogen formation are derived from fetal gonads, and metabolism takes place in the placenta. Precursors include estrone, estradiol-17α and estradiol-17β, and the equine-unique compounds equilin and equilenin.[15] Removal of the fetal gonads does not affect gestational length, implying that estrogens are not required for maintenance of pregnancy. However, labor is lengthened, foals are growth restricted, and maternal concentrations of prostaglandin F are decreased. It is likely that a prepartum increase in estrogens is associated with increased prostaglandin production and increases in oxytocin receptors, similar to that of other species.[15] Measurement of total maternal estrogens may reflect fetal health, with low concentrations associated with fetal compromise or death, but clinical data are lacking.

Several studies have demonstrated that ultrasound-guided transabdominal and

allantocentesis can be used relatively safely in the late-gestation mare as long as the procedure is performed aseptically and multiple attempts are not made.[13,28,29] However, the clinical usefulness of fetal fluid analysis in the horse remains to be determined. Studies attempting to relate the phospholipid profile in amniotic fluid with equine fetal lung maturation have been inconclusive.[13,30,31] Transabdominal-guided ultrasound amniocentesis has also been used to detect experimentally induced equine herpes virus (EHV-1) fetal infection in utero.[32] The technique holds promise as a diagnostic aid to detect specific fetal diseases and as a potential therapeutic avenue to deliver medication in utero. Preliminary data demonstrated that mares that delivered healthy foals had a significantly higher amniotic fluid lactate concentration at the time of delivery than mares that delivered sick foals.[33] The significance of this finding is not known.

Electrolyte concentrations in prepartum mammary secretions may be monitored to predict impending parturition in the mare. As parturition approaches, the mammary concentration of sodium decreases and concentrations of potassium and calcium increase. An elevation in calcium concentration to over 40 mg/dL (400 µg/mL; 10 mmol/L) is a reliable indicator of readiness for birth and can be used to help determine whether elective induction or cesarean section should be performed. The increase in calcium occurs over the last 72 hours of gestation.[34,35] Test strips are commercially available to measure calcium and magnesium concentrations in a field setting (Predict-A-Foal Kit [Animal Health Care Products, Vernon, Calif.] and FoalWatch Kit [Chemetrics, Calverton, Calif.]). The milk calcium test better predicts mares that are not likely to foal rather than accurately determining the timing of foaling.

There are increases in the mammary concentration of potassium and a decrease in the mammary sodium concentration over the final 7 days of the gestational period. The mammary concentration of potassium typically exceeds that of sodium between 1 and 5 days before foaling. This has been used by some as a predictor of birth, although a recent study concluded that the use of mammary electrolyte concentrations was not reliable due to individual variability in both raw concentrations and percent changes.[36] The reversal of the milk sodium-to-potassium ratio was more accurate at predicting the day of birth than the milk calcium concentration in Martina Franc jennies, a breed that has longer mean gestational length.[37] The ratio reliably reversed 48 to 24 hours before parturition.

An arbitrary scoring system using calcium, sodium, and potassium

concentration in the mammary secretions to assess fetal maturity has been described.[35] False-positive results (i.e., a value that inaccurately predicts imminent foaling) have been associated with vaginal discharge, placentitis, and premature lactation. False negatives occur commonly in mares with systemic illness or animals that have undergone general anesthesia. In many mares the changes in the electrolytes occur only within hours of delivery, so if monitoring is not performed frequently, the changes will be missed.[36,38] Recently, a comparison was made among milk calcium carbonate concentration, refractometry index, and pH with respect to prediction of foaling in healthy Thoroughbred mares.[39] Milk pH declines from a mean of approximately 7.4 to 6.4 over the final week of parturition. The positive predictive value (PPV) of foaling within 72 hours and the negative predictive value (NPV) of foaling within 24 hours for calcium carbonate concentration (using a water hardness test kit) were 93.8% and 98.3%, respectively. The PPV with 72 hours and NPV within 24 hours for mammary secretion pH (using pH paper 6.2 to 7.6) were 97.9% and 99.4%, respectively. Both techniques were superior to handheld refractometry. The authors used cutoff values of 400 µg/g for calcium and 6.4 for pH. The decision on whether or not to induce parturition in a mare should not be based solely on the results of this type of testing.

Fetal heart rate (FHR) and fetal heart rate variability (FHRV) are useful tools to assess fetal well-being. The most commonly used technique for assessing FHR is M-mode echocardiography (Fig. 15.1). This requires access to suitable ultrasound equipment including a low-frequency probe and appropriate software. This technique does have several limitations, including difficulty in locating the fetal heart in some cases due to maternal and fetal movement. Also, the heart rate at any time point is influenced by fetal activity, and a single time point observation may not accurately reflect the upper and lower FHR extremes.[40]

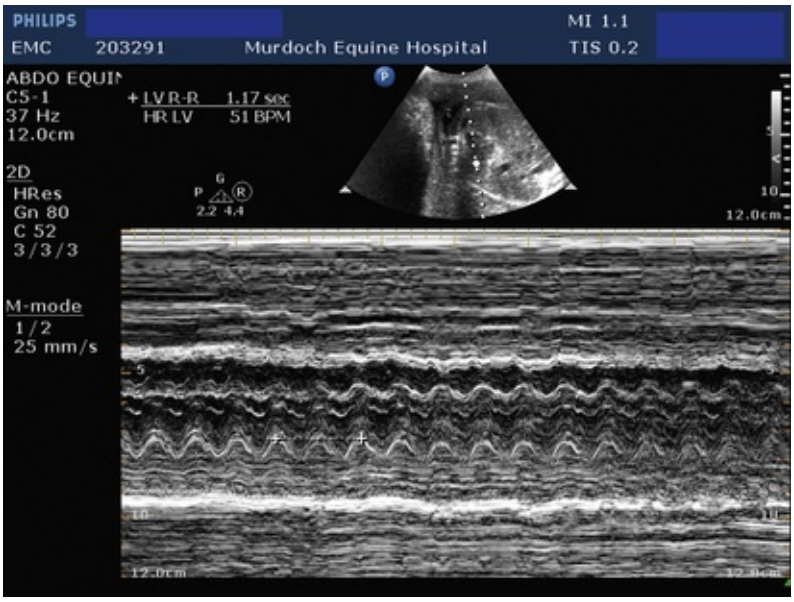


FIG. 15.1 M-mode assessment of a fetal heart to determine fetal heart rate. In this example the rate was calculated using two successive heart beats, resulting in a rate of approximately 102 beats per minute. (Courtesy Dr. Emma McConnell.)

A fetal electrocardiogram (ECG) can be used to assess FHR and FHRV after day 150 of gestation.[40–44] The left arm electrode is placed on the dorsal midline of the mare at the lumbar region, and the left leg electrode is placed 15 to 20 cm cranial to the udder on the ventral midline. The hair should be clipped, and ample gel or alcohol should be placed to ensure good contact of the electrodes. Poor fetal signals may result from poor electrode contact or placement, fetal movement, or electrical interference. An alternative method involves placement of the left leg lead on the left neck, the left arm lead in the left flank at the height of the hip, the neutral lead on the mare's croup, and the right arm lead over the linea alba cranial to the udder and then connecting the leads to a Televet 100 Holter ECG (Engel Engineering Services GmbH, Heusenstamm, Germany) recording system. This configuration allows for simultaneous determination of the maternal and fetal ECG. Calculation of the fetal HRV has merits but remains essentially a research tool. It requires acquisition of a minimum of 5 minutes of good-quality recording and export of an R-R interval file, which is then processed using a dedicated software product (Kubios HRV software [Biosignal Analysis and Medical Imaging Group, Kuopio, Finland]). From a practical perspective, gross examination of the beat-to-beat variability can be done using a standard ECG trace; an absence of variability is a concerning sign, assuming no maternal sedation.

The fetal heart rate peaks around 196 beats per minute at 3 months' gestation, before decreasing over the reminder of the gestational period.[11] Heart rate decreases from greater than 120 beats per minute before day 160 of gestation to between 60 and 90 in late gestation.[12,40–43,45,46] In late gestation FHRs below 60 bpm are common and are not of concern unless they persist and occur without accelerations.[47] Conversely, rates greater than 120 bpm are also common in active foals and are normal unless they do not return to healthy baseline levels. Cardiac accelerations in response to fetal movement are an indicator of fetal well-being. An early study reported an average of 10 heart rate accelerations (25 to 40 beats per minute) in a 10-minute period; 95% of these were associated with fetal movement.[48] Another study reported that the number and duration of cardiac accelerations and decelerations remained relatively constant over the last 2 months of pregnancy. There were approximately 22 accelerations per hour lasting around 29 to 42 heart beats and around 24 decelerations per hour lasting 24 to 60 heart beats.[43]

There is an increase in FHRV over gestation.[43,46] HRV describes the variability in R-R intervals between successive beats and reflects the influence of the neuroendocrine system. A frequency-domain analysis, reported as a low frequency (LF)/high frequency (HF) ratio, is an indicator of sympathetic activity and is used as a marker of stress. In stressful states the HF component decreases, producing a lower LF/HF ratio.[43] Therefore a healthy state is typically associated with a high HRV.[40] The FHV and FHRV are relatively constant over the final 10 days of gestation and are not useful indicators of foaling.[43]

The fetal response to hypoxia is persistent bradycardia and a reduction in movement. If reduced oxygen delivery persists or worsens, tachycardia and arrhythmias result, again with an absence of movement. Ultimately myocardial exhaustion leads to a return of persistent bradycardia immediately before fetal death. Although persistent fetal tachycardia and bradycardia suggest fetal compromise, a normal FHR alone does not guarantee that the fetus is healthy. Prolonged periods of fetal inactivity, in the absence of maternal sedation, are also suggestive of poor fetal health.

Transabdominal ultrasonography allows noninvasive evaluation of the intrauterine environment and fetal well-being. In the mare, transabdominal ultrasonography can be used to evaluate the equine fetus after day 90, when the gravid uterus contacts the ventral abdominal wall. This technique is used more commonly during the second and third trimesters. After 9 months of gestation,

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most fetuses are in an anterior presentation and are unlikely to change that presentation before delivery.[49]

Transabdominal scanning has been used to detect twins, document fetal position, estimate fetal size using fetal aortic diameter, evaluate fetal activity, evaluate placental integrity, determine fetal fluid clarity and volume, and monitor FHR and fetal breathing. Phased array or convex transducers with lower frequencies (2 to 4 MHz) are required due to the deep tissue penetration needed (up to 25- to 30-cm depth). Higher-frequency probes provide a clearer assessment of the uteroplacental unit, with depths less than 10 cm typically required. The mare's ventral midline must be cleaned from the level of the umbilicus (xiphoid in late pregnant mares) caudally to the mammary gland, and isopropyl alcohol is applied with or without coupling gel. Clipping provides a better image but is usually not required. Chemical sedation should be avoided because drugs such as xylazine and detomidine induce fetal bradycardia and retard fetal movement. The abdomen should be scanned in both sagittal and transverse planes. The examination typically begins at the front of the udder, moving cranially to detect the characteristic shadowing of the fetal ribs (Fig. 15.2) The aorta is identified and measured as close to the heart as possible (Fig. 15.3). A fetal heart rate is typically calculated using M-mode ultrasound. The position of the foal is verified, and as discussed earlier, after 9 months' gestation the head is directed toward the pelvis and the fetus lies in dorsal recumbency with vertebrae closest to the ventral abdominal wall.[12] Abnormal positioning after this time heightens the risk of dystocia. Fluid depths are assessed for both the allantoic and amniotic fluid compartments using multiple measurements from the lateral aspect of the ventral abdomen of the mare.[14] The most prominent region of fetal fluid is around the thorax in the area of the elbows.[12] In healthy mares the maximum depth of the allantoic fluid has been reported as 13.4 ± 4.4 cm, and the maximal depth of the amniotic fluid as 7.9 ± 3.5 cm. The amniotic membrane is a thin, hyperechoic structure that appears to float freely in between the amniotic and allantoic sacs.



FIG. 15.2 Characteristic rib markings overlying the thorax in a 5-month gestational age pony fetus.



FIG. 15.3 Measurement of the aortic diameter is ideally made close to the heart.

Biophysical profiles that use several parameters to establish an idea of the size and overall health of the equine fetus have been developed.[10,11,14,45,48] There is evidence that these profiles are important in high-risk mare pregnancies[50] but

fall short of similar profiles in human medicine in predicting outcome.[14,47] The six parameters typically assessed using transabdominal ultrasonography include fetal weight, as estimated by the fetal aortic diameter in relationship to the mare's weight (mean 2.1 cm at 300 days' gestation to 2.7 cm at full term), FHR (decreases with advancing gestational age), fetal activity (increases with advancing age; graded from 0 to 3), uteroplacental contact and thickness, and maximal amniotic and allantoic fluid depth. Similar to human biophysical profiles, a maximum score of 2 is given to each parameter if it is normal. Low scores predict poor outcomes, but high scores do not guarantee a healthy foal.

Qualitative assessment of the fluid appearance is also useful. The fluid within the allantoic and amniotic spaces is characteristically anechoic, although small floating particles can be observed in the allantoic compartment in late-term mares.[45] During late gestation the equine fetus should demonstrate moderate activity (grade 2 to 3/3) with only brief episodes of inactivity (<20 minutes). Assessment of fetal breathing should be an important component on any biophysical profile, but it is difficult to assess in mares.[47] Breathing is characterized by excursion of the diaphragm between the thorax and the abdomen with accompanying rib cage expansion. Regular breathing movements are observed intermittently in most late-term fetuses. It can be difficult to differentiate fetal from maternal breathing movements. Ideally, a minimum of 20 seconds of continuous breathing is observed.

Assessment of the combined thickness of the uteroplacental (CTUP) unit is limited to ventral and lateral views using transabdominal ultrasound (Fig. 15.4). Combined measurements are used because it is difficult to accurately demarcate the junction of the placenta and uterus. The average CTUP viewed transabdominally ranges between 8 and 15 mm.[11] One study reported mean values across normal Paints, Quarter Horses, and Thoroughbreds between 270 and 330 days' gestation of 8 to 12 mm.[51] Measurements may vary between breeds with reports of mean CTUP values of 12.7 ± 3.1 mm in Lipizzaner mares between 280 and 315 days.[14] Thicker measurements may indicate placental edema, hemorrhage, or placentitis. Areas of separation between the uterus and chorion appear as black anechoic areas. The maximum ventral fetal fluid pocket depths average 8 cm for amniotic fluid and 13 cm for allantoic fluid.[11] Excessive fetal fluid accumulation is observed in cases of hydrops. Markedly decreased amounts of fetal fluids have been associated with placental dysfunction and the birth of a dysmature, hypoxic foal. As gestation advances, fetal fluids increase in

turbidity. Sudden increases in turbidity may be associated with meconium passage, hemorrhage, or inflammatory debris. Given the frequency of ascending placentitis, transrectal ultrasonography has been added to the assessment of mid- and late-term pregnant mares.[51]

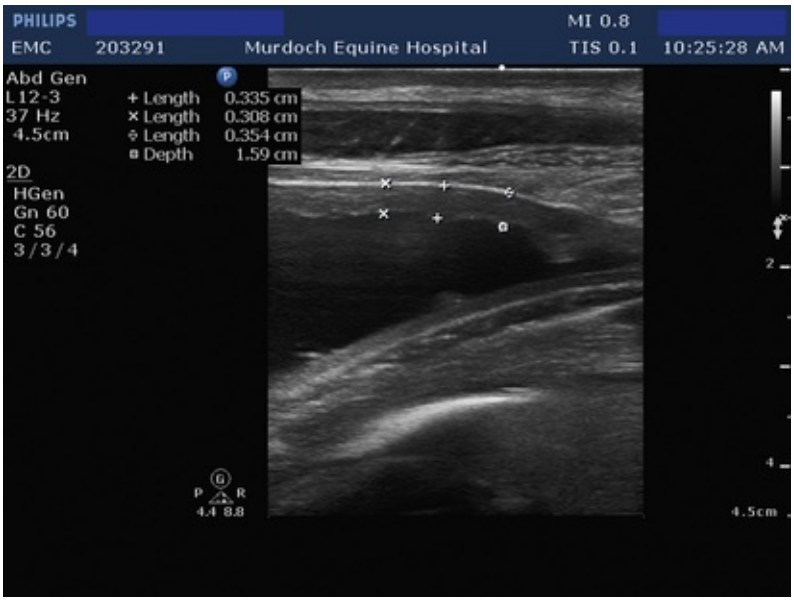


FIG. 15.4 Measurement of the combined thickness of uteroplacental unit. This measurement is taken from a 150-day gestation age pony fetus.

Uterine blood flow changes can by assessed with rectal ultrasound using pulsed wave and color flow Doppler settings.[52] Monitoring changes in uterine artery diameter, blood flow (pulsatility index, blood flow volume), and the presence of an early diastolic notch may have a role in monitoring high-risk mares, although evidence is currently lacking.

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Effects of Placental Insufficiency

The effects of uteroplacental vascular insufficiency on the newborn depend on the severity of placental compromise and the severity and duration of prenatal and perinatal asphyxia. Conditions associated with chronic asphyxia include chronic placentitis, villous atrophy, twin and post-term pregnancies, and ingestion of endophyte-infected fescue grass. If decreased uteroplacental blood flow is long-standing, growth is concomitantly inhibited in the fetus. The pattern of growth retardation associated with chronic placental insufficiency is usually asymmetric, characterized by visceral wasting with relative preservation of fetal length and head circumference. It has long been recognized that twin equine neonates and other abnormally small foals tend to have heads that are disproportionately large for their small bodies.[53]

In placental vascular insufficiency, the fetus has the ability to avoid overgrowing its nutrient supply and to maximize organ growth. Under metabolic stress, there is a fetal anti-insulin response with loss of fat and glycogen stores and muscle mass. Associated with the decrease in uteroplacental blood flow is an increase in uterine and fetal vascular resistance and redistribution of cardiac output, with a greater percentage of blood flow going to organs such as the brain and heart. Unless uteroplacental insufficiency is severe, brain growth continues at a relatively normal rate. In the human fetus, the redistribution of cardiac output also results in decreased blood flow to the lung and kidney and decreased production of fetal urine and lung liquid, two major components of amniotic fluid. A decrease in amniotic fluid volume is therefore associated with chronic fetal asphyxia.[54,55]

Repeated episodes of hypoxemia during gestation slowly deplete cardiac glycogen stores and impair the ability of the heart to effectively pump blood during subsequent hypoxemic episodes, such as during labor. The newborn with depleted glycogen stores may also be at increased risk of developing hypoglycemia and hypothermia. Meconium aspiration and persistent arterial hypertension in the newborn period are secondary to chronic fetal hypoxia. Immature skeletal ossification, particularly of the carpal and tarsal bones, has also been associated with growth retardation in the foal.[53]

There are certain advantages associated with adaptation to chronic placental insufficiency. Growth-retarded premature human infants have a lower incidence

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of hyaline membrane disease than babies of the same gestational age that are appropriately sized.[56] Presumably, fetal hormones, such as the corticosteroids and catecholamines that are released in response to nutrient deprivation, stimulate early maturation of the lung and surfactant system. Accelerated neurologic maturity has also been documented along with accelerated pulmonary maturity.[57] Therefore the fetus that has been chronically exposed to an adverse in utero environment may be in some ways more tolerant of premature delivery and independent life outside the uterus than the “normal” fetus that is abruptly displaced through induction of labor or cesarean section. The low-birth-weight fetus therefore represents a successful adaptation to a nutrient-deprived environment. Its smaller size, decreased metabolic needs, and early organ maturation actually place it at lower risk of hypoxic injury at birth and aid its transition to independent life after delivery.[55] Further discussion of the characteristics, treatment, and prognosis of growth-retarded premature foals may be found in Chapter 17.

Premature lactation, purulent vaginal discharge, previous history of growth-retarded foals, advanced maternal age, and prolonged gestation are problems that should raise the suspicion of chronic uteroplacental insufficiency. The birth should be attended to minimize the chances of acute asphyxia. The newborn animal should be examined for evidence of growth retardation; infection, particularly in utero–acquired pneumonia secondary to placentitis; and metabolic and acid-base derangements. Ample colostrum should be administered, and body temperature and blood glucose should be monitored closely.

Human infants that display characteristics of asymmetric growth retardation commonly “catch up” by late infancy or early childhood. Similar observations have been made in the foal. Many mildly to moderately growth-retarded newborn foals have also done well following discharge from the hospital and have grown to a normal size. Problems secondary to an immature musculoskeletal system are the most common complications noted in these individuals, but careful orthopedic management can result in a successful outcome.

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Placentitis

Placentitis is a common cause of reproductive losses in horses, with an estimated 30% of pregnancy losses attributable to the disease.[4] The most common cause of placentitis is ascending infection from the lower urogenital tract via a relaxing cervix. This leads to thickening of the fetal membranes and separation from the uterus. Infection via this route is typically localized to the cervical star region. A far less common route of infection is the hematogenous avenue resulting in a diffuse or multifocal placentitis.

Mares with ascending placentitis are typically pluriparous, and many have anatomic defects, including vestibule-vaginal reflux, pneumovagina, and damage to the cervix, including fibrosis, tears and adhesions.[15] Most cases of placentitis are the result of bacterial infection caused by typical equine pathogens including *Streptococcus equi* subspecies *zooepidemicus, Escherichia coli, Enterobacter agglomerans, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*. In some regions a slightly different form of placentitis has been recognized and is characterized by focally extensive placentitis located predominantly at the base of the placental horns at the junction of the horns and body of the placenta.[58] The affected area is covered with thick, tenacious brown mucoid exudate, and the underlying chorionic villi are necrotic and absent or reduced in size. This form is associated with infection by a group of gram-positive, branching, filamentous Nocardioform actinomycetes, including *Crossiella equi, Amycolatopsis* species, and less commonly *Cellulosimicrobium cellulans* and *Streptomyces* species.[59] There is link between some of these bacteria, which are part of the normal intestinal flora, and ingestion of Eastern Tent caterpillars *(Malacosoma americanum)* or Processionary caterpillars *(Ochrogaster lunifer).*[60,61] The Eastern Tent caterpillar is linked to Mare Reproductive Loss Syndrome (MRLS) in the United States, and the Processionary caterpillar is a causal agent of Equine Amnionitis and Fetal Loss (EAFL) syndrome in Australia.[62] It is likely that the barbed setae (hairs) penetrate the intestinal mucosa, thereby facilitating bacterial translocation.

*Chlamydophila (*formerly *Chlamydia) psittaci* infects a wide range of wild bird and poultry species around the world. The organism has been documented as a cause of placentitis in mares with associated foal mortality.[63] It has the potential to spill over into humans, with clusters of human cases documented

after handling of diseased fetal membranes.[63,64] The likely modes of transmission in these cases from fetal membranes to humans are either via the airborne route or direct inoculation of the eyes or nose. There is some limited evidence that respiratory protection (P3 mask) and eye protection reduces the risk of disease.[65] The potential avian reservoir for equine chlamydiosis is not known, but a pigeon-like variant was isolated in New South Wales.[66]

Clinical signs of placentitis include vaginal discharge, premature udder development, and precocious lactation. The discharge may be evident on the vulva, tail, or inner thighs. Premature udder development is the result of placental compromise, fetal stress, a precocious increase in maternal progestagen concentration, and enhanced fetal adrenocortical activity. Despite even voluminous vaginal discharge, most mares with placentitis do not become febrile and do maintain a normal appetite. The dam's hematology and fibrinogen concentration usually remain within normal limits. Untreated mares with experimental placentitis due to *S. equi* subsp. *zooepidemicus* had significant increases in serum amyloid A (SAA) within 96 hours of inoculation that persisted through to birth or abortion.[67] The increase in SAA was prevented in most treated mares.

Transrectal ultrasound is used to identify placental separation and utero-placental thickening of the caudal uterine body. This region is most commonly involved in mares with ascending placental infection. Measurement of the combined thickness of the uterus and placenta (CTUP) is established. The rectal transducer is placed at the cervical-placental junction, where a branch of the uterine artery is seen between the uterus and bladder. This measurement increases from around 4 to 6 mm at 7 months' gestation to 10 to 12 mm at term.[45,51] Mare parity has an impact on CTUP during midpregnancy (100 to 250 days), with primiparous mares having a greater thickness than multiparous mares.[68] The difference is lost in late pregnancy. A measurement greater than 12 mm at 9 months, or greater than 15 mm at 11 months, is consistent with placental pathology.[45,69] Measurement of CTUP alone can be misleading, and monitoring of the CTUP by ultrasound along with determination of the maternal progestagen concentrations has been recommended.[18] Fetal membranes commonly disunite from the uterus, separated by fluid of variable echodensity.

Transabdominal ultrasonography is used to evaluate other areas of the placenta to detect loss of placental integrity or increased uteroplacental thickening. Using transabdominal ultrasound, the uteroplacental unit should be

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less than 16 mm during late gestation. Other signs suggestive of placentitis include increased fetal fluid echogenicity, which might result from hemorrhage or purulent exudate. If placentitis is severe enough to alter placental function, reduced fetal movement, loss of heart rate variability, and absolute fetal bradycardia collectively indicate fetal compromise.

Samples of vaginal discharge should be cultured, and Gram stains should be performed. The goal of maternal therapy is to treat the placental infection and maintain the pregnancy, provided there is no evidence of severe fetal distress or demise. In many cases, because the infection is of long duration, the fetus has been chronically stressed and therefore is relatively mature for its gestational age and better prepared to tolerate preterm birth. If placentitis is suspected, following delivery, the foal should be considered a high-risk individual. Commonly encountered problems in the newborn foal that was exposed to placentitis are pneumonia, uveitis, growth retardation, incompletely ossified bones, and sometimes systemic sepsis.

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Systemic Disease in the Mare

Colic and colic surgery are risk factors for fetal death or premature delivery. Foal survival rates after medical colic are superior to rates after colic surgery, which are reported as between 54% and 80%.[70–73] Specific risk factors have varied among studies but have included the duration of anesthesia, intraoperative hypotension, intraoperative hypoxemia, perioperative toxemia, stage of gestation, and age of the mare. A retrospective study reported that pregnant mares older than 15 years of age undergoing colic surgery were less likely to produce a live foal than mares aged 15 years or younger.[72] In the same study mares that had colic surgery at 16 to 39 days of pregnancy were less likely to produce a live foal (49%) than mares that were older than 40 days in foal. The management of mares postoperatively typically includes supplementation with a progestin, although no clear benefit has been reported.[71] Likewise, the tocolytic agent clenbuterol hydrochloride has been recommended, but again without significant evidence.

In acute colic, the progestagen concentration declines hours to days before abortion. The concentration may fall to less than 2 ng/mL.[21]

Laminitis is often a chronic condition that is exacerbated in pregnant mares because of added body weight. The condition is associated systemic hypertension, and a recent study of pregnant laminitic mares reported hypertension, shorter gestational periods, and lower placental and foal birth weights than a control group of normal mares.[74] The authors reported a number of vascular abnormalities in the placenta, including reduced vascular lumen and capillary area in microcotyledons, and thickened vascular walls.

There have been several retrospective studies of uterine torsion in mares. Survival rates of mares have varied between 60% and 90.5%.[75] Survival of the mare and the foal is determined, in part, by gestational age at the time of the torsion, degree of rotation, and method used for correction. Foal survival is also related to the interval from torsion to correction. A multicenter retrospective study reported an overall foal survival rate of 82.3%; positive foal outcomes were highest when torsion occurred before 320 days' gestation (90.6%) and when corrected by standing flank laparotomy (88%).[75] The authors suggested that improved outcomes at earlier stages of gestation were likely due to lighter foals exerting less pressure on uterine vessels by crossed broad ligaments. This

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is coupled with reduced oxygen demands in younger fetuses. Avoidance of general anesthesia and dorsal recumbency must also have comparatively less impact on placental blood flow.

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Management of the High-Risk Late-Gestation Mare

Each mare should receive a complete physical examination, and foaling histories should be obtained. Signs of impending parturition (sacroiliac ligament and perineal relaxation, mammary development, and mammary secretion electrolyte concentration) should be assessed daily. The reproductive tract may be evaluated by rectal palpation, and transabdominal ultrasonography may be performed at regular intervals to detect changes in the fetus, fetal fluids, or placenta. Prolonged periods of feed restriction should be avoided to prevent maternal hypoglycemia.[13] Estimation of progestin concentrations in the maternal circulation, using a commercial progesterone assay, is recommended.[18]

When treating a pregnant mare for any medical or surgical condition, consideration must also be given to the fetus. Any illness or disease that affects the mare's cardiovascular system has the potential to affect placental perfusion and the integrity of the fetoplacental unit. Hypotension, toxemia, and hypoxemia are examples of conditions that can alter uteroplacental blood flow and jeopardize the pregnancy. Diseases that stimulate prostaglandin production have the potential to initiate labor and delivery. Illnesses that produce prolonged periods of anorexia in the late-term mare can also contribute to premature delivery. The effect of various drugs on the placenta and fetus should be considered when treating the pregnant mare. If delivery is not imminent, then many drugs will pass through the placental and fetal circulation and be cleared by the maternal liver and kidneys. Due to the epitheliochorial nature of the equine placenta, some drugs will not cross the placental barrier at all. If drugs are administered to the mare and the fetus is delivered shortly thereafter, then the neonate must rely on its renal and hepatic function to process, degrade, and excrete those drugs. In most instances, as long as fetal well-being and placental integrity are closely monitored, the goal of most therapies is to treat the maternal condition and maintain the pregnancy as long as possible to achieve an acceptable degree of fetal maturation.

The use of antibiotics in placentitis should be based on knowledge of common pathogens and the likelihood of achieving therapeutic concentrations at the site of infection. Studies using microdialysis probes inserted into the allantoic fluid of normal mares reported therapeutic concentrations of penicillin and gentamicin

in the allantoic fluid after 22,000 IU/kg of potassium penicillin G (IV q6h) and 6.6 mg/kg gentamicin (IV q24h), albeit with peak concentrations in allantoic fluid 80% of that achieved in maternal serum.[76] Studies in two mares with experimentally induced bacterial placentitis again confirmed passage of both drugs across the placenta. The combination of trimethoprim and sulfadiazine (30 mg/kg PO bid) and the phosphodiesterase inhibitor pentoxifylline (8.5 to 10 mg/kg PO bid) also readily crosses the fetal membranes in both healthy mares and in animals with experimental placentitis.[17] In many cases, medical treatment of the placental infection and prolongation of pregnancy is associated with a good outcome. Maternal treatment includes systemic antibiotics, flunixin meglumine, pentoxifylline, and altrenogest.[13,77] In an experimental model of placentitis, induced through inoculation of *S. equi* subspecies *zooepidemicus*, the combination of trimethoprim sulfamethoxazole, pentoxifylline, and altrenogest was highly effective at prolonging gestation and improving foal viability when contrasted with mares that received no treatment.[77] Because of the usual presence of mixed gram-positive and gram-negative placental and fetal infections, a broad-spectrum antibiotic that reaches therapeutic levels in the fetus and fetal fluids should be selected. Therapeutic options include penicillin and gentamicin, trimethoprim-sulfonamide, or ceftiofur. Trimethoprim-sulfonamide combinations or doxycycline have in vitro activity against several nocardioform actinomycetes.[59] Low doses of flunixin can be administered to decrease inflammation and prevent prostaglandin-mediated induction of delivery.

Altrenogest (Regu-Mate, 0.044 to 0.088 mg/kg, 10 to 20 mL of 0.22% solution for 500-kg mare, PO q24h) is commonly used in late pregnancy to prevent preterm delivery, possibly through interference with prostaglandin regulation and oxytocin receptors.[17] The rationale for altrenogest use in late pregnancy has been questioned, as plasma progestagen concentrations are typically raised in mares with placental disease.[78] The evidence for altrenogest use in mares with placentitis is not strong, with studies using a model of experimental placentitis failing to document an advantage of the drug over antimicrobials alone.[79,80] Altrenogest readily crosses the placenta and reaches relatively high concentrations in the fetal fluids and the newborn foal.[81] Concentrations in the healthy foal decline rapidly over the first 6 hours postpartum. The effects of altrenogest on the foal are largely unknown, but a reduced neutrophil-to-lymphocyte ratio in foal blood has been reported.[82] It has been recommended to withdraw altrenogest after 320 days' gestation.

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In a group of mares with experimentally induced ascending placentitis after inoculation with *S. equi* subspecies *zooepidemicus*, the authors reported that estrogen supplementation (estradiol cypionate 10 mg IM q3d for 3 treatments), coupled with trimethoprim sulfamethoxazole (30 mg/kg IV q12h for 10d) and flunixin meglumine (1.1 mg/kg IV q24h for 10 days), resulted in a normal gestation period and foal survival rates similar to control animals.[79] This was a superior result than that of mares treated with antibiotics, flunixin, and altrenogest.

If there are large areas of placental thickening, IV DMSO (0.5 to 1 gm/kg) can be administered to decrease placental edema, although direct evidence is lacking. Pentoxifylline has also been administered in attempts to improve placental perfusion.

If premature delivery appears unavoidable, then one to three doses of maternal corticosteroids can be used with the hope of stimulating and accelerating fetal lung maturation through enhanced surfactant production. This is done with the knowledge that corticosteroids are anecdotally associated with a heightened risk of laminitis, particularly in mares with underlying disease. Normal Thoroughbred mares given 100 mg of dexamethasone intramuscularly on gestation days 315, 316, and 317 delivered foals around 2 weeks earlier than saline-treated control mares.[83] The interval between the last dose and parturition was only 1 to 8 days. Resultant foals were smaller but appeared mature and had normal neutrophil-to-lymphocyte ratios. There was evidence of lingering adrenal suppression in some foals.

In the high-risk mare, it is important that the delivery be attended by knowledgeable personnel and that all supplies, drugs, and equipment required for diagnosing and correcting a dystocia and stabilizing the mare and foal be organized and close at hand. A spontaneous, vaginal delivery is generally preferred in the high-risk mare, both because of the profound problems associated with the untimely delivery of a premature foal and the complications sometimes associated with induced labor or cesarean section. (See the Maturity section in Chapter 17). There are instances, however, when an induced birth or cesarean section is indicated or preferred.

Induction of parturition should be considered with the following:

- Severe fetal distress noted on prenatal assessment
- Evidence of premature placental separation or a

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history of premature placental separation associated with dead or asphyxiated foals
- Hydrops allantois and/or amnion
- Unproductive stage I labor
- Uterine inertia
- Impending prepubic tendon rupture
- Life-threatening maternal illness

Indications for cesarean section may include the following:

- Pelvic injury or abnormality resulting in obstruction of the birth canal
- Gastrointestinal crisis requiring surgery
- Severe dystocia
- Insufficient, thickened placenta associated with fescue toxicity in the mare
- Catastrophic and terminal illness or injury in the mare, such as gut rupture or fractured limbs

If induction of parturition or cesarean section is elected, every effort should be made to ensure that the fetus is mature and ready to be born; the usual result of induction at an inappropriate time is a nonviable newborn. Three essential criteria are a gestation of longer than 330 days, good-quality colostrum in the udder, and softening of the cervix.[84] The scheduling needs of the veterinarian or owner should never be the only criterion used for determining the timing of delivery. A slow, continuous oxytocin infusion administered at a rate of 1 unit/minute usually results in delivery within 20 to 40 minutes.[13] Alternatively, multiple intravenous or intramuscular injections of 10 to 20 units of oxytocin every 10 minutes have been recommended.[84,85] Other investigators have shown that smaller intravenous doses of oxytocin (2.5 IU administered every 15 to 20

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minutes until rupture of the chorioallantois or a total of 20 IU of oxytocin has been administered) is an effective, and perhaps more physiologic, method of induction.[86]

Induction of parturition in the mare has been associated with more violent, painful contractions than spontaneous labor and a higher incidence of premature placental separation and neonatal asphyxiation. Cesarean section also predisposes to neonatal peripartum asphyxia. Maternal hypotension secondary to general anesthesia and the weight of the maternal abdominal contents on the aorta and vena cava both compromise uteroplacental circulation. For further details concerning anesthesia of the late-term mare, the reader is referred to other texts.[87] Abdominal support with nonsteroidal antiinflammatory drugs and altrenogest has been used to maintain the pregnancy in a mare with hydrous amnion until day 321, when spontaneous delivery occurred.[88] The delivery was complicated by uterine inertia, maternal postpartum hypovolemic shock, and cardiac arrhythmia, but both mare and foal survived.

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Foal Resuscitation

The veterinarian attending or assisting in the birth should be prepared in the event that cardiopulmonary cerebral resuscitation (CPCR) of the foal is required. Detailed descriptions of CPCR are published elsewhere.[89–92] Foals born by Cesarean section or assisted vaginal delivery are at increased risk of cardiac or pulmonary arrest. Mares suffering from systemic illness, hydrops, prepubic tendon rupture, placentitis, placental insufficiency, or premature placental separation are also at heightened risk for delivering foals with serious complications.

After delivery the at-risk foal should be positioned on a firm, flat surface with the withers against a wall to prevent movement if thoracic compressions are needed.[92] Quickly palpate the thorax for evidence of rib shaft fractures or costochondral dislocations. If fractures are detected, the affected side should be in contact with the ground. Initially place a nasal insufflation tube into one nasal passage to the level of medial canthus of the eye, and deliver oxygen at 10 L/min. Assess the foal's breathing and circulation over the following 30 seconds, noting rates and effectiveness. The nasal passages should be examined for meconium staining, and any fetal membranes should be removed. Remaining fluid can be cleared using gentle postural drainage and a bulb syringe and soft catheter. Hanging foals from their pelvic limbs must be avoided.

Spontaneous breathing is stimulated by vigorous rubbing of the body and head with a dry towel. Gentle thoracic compression is also helpful. Other techniques used to improve breathing include tactile stimulation of the nasal mucosa or the ear canal. In other species, pouring of cold water into the ear canal or application of acupuncture needles to the nasal philtrum (absent in the foal) has been suggested.[93] If the foal fails to breathe or is making irregular gasping movements, then positive pressure is urgently required.

The attendant can provide positive pressure using mouth-to-nostril resuscitation. The opposite nostril is occluded along with gentle pressure over the proximal esophagus, and breaths are delivered with the foal's head in extension. During each forced breath, the rise in thoracic wall should be observed to ensure an appropriate tidal volume is delivered. Exhaled air is only 16% to 18% oxygen, but this is considered adequate in the face of failing perfusion.[92] Alternatively, a pump and face mask resuscitator can be used

(McCulloch Medical Products, Glenfield, New Zealand). This device can be connected to a nasotracheal tube or a face mask and delivers a set volume of 780 mL, thereby avoiding volutrauma. The resuscitator device can also be easily adapted to suction the airway.

Cuffed nasotracheal tubes (7-mm, 9-mm, and 12-mm diameter; 55 cm long) should be available as part of the resuscitation kit, along with a self-inflating resuscitation bag (the bag component of a commercial air mask bag unit [AMBU; Ambu Inc., Linthicum Heights, Md.). Intubation provides the most effective method for ventilation support. A 9-mm tube will suit most foals, although a large tube may be needed in foals larger than 55 kg. Passage of the nasotracheal tube is facilitated by keeping the head in extension. The tube is passed through the ventral meatus into the nasopharynx to the larynx. Rotation of the tube can aid in passage through the arytenoid cartilages and into the trachea. The tube is inserted fully to reduce dead space, such that the tube end is positioned in the midtracheal region and the cuff is inflated. An adult resuscitation bag (typically 1600-mL capacity with 2600-mL oxygen reservoir bag) is connected to the tube and manually compressed to provide positive-pressure ventilation at an initial rate of 10 breaths/minute. The bag has an adjustable escape valve that prevents barotrauma. The valve is typically set at 35 to 45 cm H_2O.[90] The thoracic wall should rise appropriately without air leaks around the cuff. Ideally, the bag is connected to an oxygen cylinder using a flow rate of 8 L/min, but ventilation with room air is acceptable. The oxygen flow rate can be adjusted on the basis of the minute volume that is delivered.[92] Assisted ventilation should be ceased every 3 minutes to monitor for spontaneous ventilation. The use of chemical respiratory stimulants, such as doxapram hydrochloride, is no longer indicated in the treatment of secondary apnea.

If there is asystole or the heart rate is persistently less than 40 beats per second, then cardiac compressions are indicated without delay. It has been recommended that compressions occur at a rate between 100 and 120 per minute, with complete thoracic wall recoil between each compression.[89,91] The compressions should be forceful and contribute around 25% to 30% of normal cardiac output. Ideally, compressions are continuous and there should be a compression-to-ventilation ratio of 30 : 2.[91]

Drugs are indicated if the heart rate fails to increase with supported ventilation and thoracic compressions. The drugs can be administered intravenously via the jugular vein or intraosseously, using a 12-gauge intraosseous infusion needle.[89]

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The most popular medications for cardiovascular resuscitation include epinephrine and vasopressin. Epinephrine can initially be administered using a bolus dose of 0.01 to 0.02 mg/kg (1 mg/mL, 0.5 to 1.0 mL/50-kg foal), repeated every 3 to 5 minutes due to a short half-life. A higher dose is recommended if the foal fails to respond to other therapies (0.1 mg/kg; 1 mg/mL, 5 mL/50-kg foal). Vasopressin is a peripheral vasoconstricting agent that can be administered at a bolus dose of 0.6 U/kg IV.[92] It can be used alone or in combination with epinephrine.[91] The effects last approximately 10 to 20 minutes. The use of sodium bicarbonate in CPCR continues to be controversial, but evidence indicates a potentially deleterious effect of myocardial function, and in the absence of any positive survival data it is no longer recommended in human CPCR.[91,94]

Defibrillation is indicated in ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia without palpable pulse pressure.[90] The technique should not be used in the management of bradyarrhythmias or asystole. Recommendations include an initial defibrillation of 2 J/kg, followed by a discharge of 4 J/kg 30 to 60 seconds after treatment with epinephrine or 1.5 mg/kg, repeated in 5 minutes for lidocaine, and continued cardiac compressions.[89] Amiodarone has been used in adult horses with refractory ventricular tachycardia; the recommended dose is 5 mg amiodarone/kg/h for 1 hour, followed by 0.83 mg amiodarone/kg/h during 23 hours, although boluses over 2 minutes have been used safely in normal adult horses.[95,96]

Resuscitation should be discontinued in the absence of spontaneous cardiac output within 10 minutes of initiating CPCR. Successful resuscitation is associated with spontaneous ventilation at a normal rate, depth, and effort and a regular cardiac rhythm with a rate greater than 60 beats/min. The foal should be monitored closely over the following 60 minutes and then at a lower level for a further 48 hours, as there is a heightened risk of postasphyxia complications.

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Perinatal Asphyxia Syndrome

Perinatal asphyxia syndrome (PAS), also termed *hypoxic ischemic syndrome* (HIS), describes the clinical consequences of reduced oxygen delivery to tissues. The clinical effects of asphyxia can be widespread and can involve many systems including the nervous system, kidneys, gastrointestinal tract, and cardiopulmonary system. The nervous system is the most commonly affected. The pathophysiology and clinical features of nervous system disease can be found in the Neonatal Encephalopathy section in Chapter 17. The renal system is the second most common system affected by asphyxia. In most affected foals the impact is relatively small, with reduced glomerular filtration and mild tubular disease, resulting in few abnormal clinical or laboratory findings. The most common laboratory derangement is persistent elevation in creatinine concentration or an increased level that is slow to normalize. In a small number of animals there is significant acute tubular necrosis resulting in anuria or oliguria, widespread edema, persistent and worsening elevation in serum creatinine concentration, and abnormal fractional excretion of electrolytes. Tissue edema can develop quickly, particularly if high rates of sodium-rich fluids are used. It is recommended to err on the side of fluid restriction rather than fluid excess when managing foals at risk for complications from PAS.[97] See Chapter 17 for fluid therapy guidelines in neonatal foals. Nephrotoxic drugs such as gentamicin or amikacin should be avoided if possible, unless therapeutic drug monitoring is available.

The management of oliguria or anuria can be difficult. Strategies to promote diuresis include a constant rate infusion (CRI) of dopamine at a rate of 2 to 5 µg/kg/min or furosemide at a CRI (0.25 to 2.0 mg/kg/h) or frequent boluses (1 mg/kg). The two treatments can be used concurrently.[98] Use of mannitol remains controversial but can be considered if oliguria persists. Once urine flow is established, the use of diuretics and vasoactive drugs should be revised and serum electrolyte concentrations and blood pH monitored. Overuse of diuretics can promote excessive fluid and electrolyte losses.

The gastrointestinal tract is another common target for asphyxial injury. The clinical signs are often related to gastroparesis and intestinal ileus. These include colic, recurrent gastric reflux, abdominal distention due to accumulation of intestinal gas and fluid, intestinal impaction, and diarrhea. In severe cases there

is marked edema of the bowel wall, epithelial necrosis, and hemorrhage into the lumen. Damage to mucosal integrity can lead to translocation of bacteria with generalized peritonitis and systemic sepsis. The syndrome of necrotizing enterocolitis (NEC) is a significant cause of morbidity and mortality in preterm human infants.[99] The disease involves intestinal coagulative necrosis, bacterial overgrowth, *Pneumatosis intestinalis*, and a marked inflammatory response. Although controversial, intestinal hypoxia or ischemia and infection with certain bacteria, such as *Clostridium perfringens*, may be important contributing factors.[99] A similar syndrome has been reported in foals associated with birth hypoxia and *Clostridium* species.[100,101]

The recognition that intestinal complications of asphyxia should promote preventative strategies, including avoidance of overfeeding, monitoring of gastric and intestinal volume and wall movement with ultrasound, monitoring for increases in abdominal circumference using a soft tape measure, and avoidance of antiacid medications. Decreased gastric acidity may be a partial explanation as to why preterm human infants are at heightened risk of NEC.[99] A small volume of milk is often fed to at-risk foals to promote intestinal health (so-called “trophic feeding”), but this falls short of what is required in terms of minimal caloric requirements.[102] Trophic feeding is often around 12 to 24 mL/kg/day in human neonates, with full enteral feeding described as 150 to 180 mL/kg/day.[103,104] Other strategies that have been used to reduce the risk of NEC in human preterm infants include recombinant erythropoietin (rEPO), probiotics, and lactoferrin[105]; none of these have been described in at-risk foals. Recombinant EPO was originally used to treat anemia of prematurity but also exerts a trophic effect on the intestine.[105] Calorie supplementation of foals with parenteral nutrition is strongly recommended, particularly when gastric reflux or hemorrhagic diarrhea is present and no enteral feeding can be used.

Foals that have experienced an episode of hypoxia or ischemia are at increased for secondary infection and should be on broad-spectrum antibiotics. The use of aminoglycosides should be reconsidered if therapeutic monitoring is not available due to likely altered renal function. Immunoglobulin prophylaxis is recommended when serum IgG concentration is less than 800 gm/dL (8 gm/L), although there are no data that document decreased infection or improved survival with plasma therapy in at-risk foals. Plasma does have benefits in addition to immunotherapy, including improvement of osmotic pressure and provision of coagulation factors and a buffer base.[97] Glucose homeostasis is

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commonly disturbed in postasphyxiated foals, and concentrations should be monitored frequently. Hypoglycemia is frequently noted at the time of admission, but hyperglycemia is also common in responsive to modest replacement therapy. In some foals glucose intolerance can be managed by insulin therapy (see Chapter 17).

Respiratory failure is uncommon in PAS foals, but periods of hypoxemia and/or hypercapnia are not uncommon. Intranasal delivery of humidified oxygen is often helpful in the early stages of treatment. Rates of 2 to 5 L/min are commonly used with the goal of raising the arterial oxygen concentration (PaO_2) above 80 mm Hg. This should be achieved along with maintenance of tissue perfusion, using judicious fluid therapy and vasopressive agents as needed. Hypercapnia should be treated only if there is a poorly compensated respiratory acidosis. This can be managed using positive pressure ventilation or respiratory stimulants, such as doxapram or caffeine.

The short-term prognosis for foals with PAS is dependent on several factors, including the degree and duration of oxygen deprivation, as well as the organ systems involved, and the preparedness and training of attending personnel. The prognosis for most foals is good to excellent with survival rates commonly reported around 75%.[106,107]

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• CHAPTER 16

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Assessment of the Newborn Foal

Guy D. Lester, Consulting Editor, Jane E. Axon

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Neonatal Behavior

Most spontaneous births (≈80%) occur between 8 p.m. and 6 a.m., with a peak foaling time between 10 and 11 p.m.[1] A normal foal should have righting reflexes and sufficient muscle tone to be able to right itself to sternal recumbency within 2 to 3 minutes of birth. By 5 minutes the foal should be bright, alert, and responsive to visual, auditory, and tactile stimuli. Over the next 20 to 25 minutes the normal foal will be restless, alternating periods of sternal recumbency with lateral recumbency before beginning lurching attempts to stand. During this period the foal will often vocalize in response to maternal sounds or contact. Once standing, the initial posture is an unsteady basewide rocking stance, but this slowly improves such that by 60 minutes most foals should be standing securely without assistance. The mean time to stand in a recent study of Thoroughbred foals was 52 minutes (±30 minutes standard deviation).[1] Colts typically take slightly longer to stand than fillies. The suckle reflex is present within minutes of birth in most foals and should be present in all foals by 30 minutes. Once standing, the foal will seek the udder, a process that is initially very clumsy but improves once the foal has successfully sucked. There will be repeated nudges of the udder in order to facilitate milk letdown. The foal should be nursing from the mare by around 2 hours (mean reported times of 111 and 125 minutes; ranges 35 to 420 minutes and 30 to 600 minutes), and most have nursed twice by 2.5 hours of age.[1,2] Sucking periods vary in duration between 1 and 5 minutes and are interspersed with periods of sleep that last around 7 minutes. It is important to watch the foal during sucking to confirm appropriate teat contact and swallowing movements. A foal that spends long periods at the udder may do so because of inability to nurse from the mare or inadequate milk from the mare. The daily milk consumption of most newborn foals is estimated between 21% and 25% of their body weight.[3] This equates to around 12 to 12.5 L/day for a 50-kg foal. On the basis of the caloric density of milk, this reflects a daily intake of 120 to 150 kcal/kg body weight, half used for basal metabolism and thermoregulation and half for growth.

Sleep periods first occur between 90 minutes and 4 hours after birth and last for about 7 minutes.[4] The foal spends one-third of its time lying down during the first 2 months of life, compared with 5% to 10% for adults, most of which occurs overnight. Foals do not learn to follow their dams to the exclusion of any

other moving object for the first 1 to 2 weeks of life. Foals identify their dams by sight and smell and during the first week of life spend 85% of the time within 1 m of the dam, 94% to 99% within 5 m, and only rarely more than 10 m away from the dam.[5] Loss of affinity for the mare in a foal that seems otherwise healthy may be an early sign of the neurologic form of hypoxic ischemic syndrome.

Recommendations to clients as to when veterinary intervention should be sought vary from practice to practice. The “1-2-3” rule states that foals should be standing unassisted by 1 hour, sucking from the mare by 2 hours, and the mare should have passed her fetal membranes by 3 hours. Clients may adopt a similar “2-4-6” rule to seek veterinary attendance, where intervention should be sought if the foal has not stood by 2 hours, not sucked by 4 hours, or the fetal membranes are still in place by 6 hours. These recommendations are only used as a rough guide and will obviously be influenced by peripartum conditions and client experience. A recent study from New Zealand reported that 95% of mares had passed the fetal membranes within 4 hours of parturition.[1]

A modified Apgar score (Table 16.1) has been used in foals to semiquantitate the severity of signs that occur in response to peripartum asphyxia.[6] The acronym used in equine practice differs from that used in human medicine and refers to appearance, pulse, grimace, activity, and respiration. Appearance refers to oral mucous membrane color; pulse uses 60 beats per minute (bpm) as a cutoff; grimace is assessed in response to stimulation of the nasal mucosa, inside of the pinnae, and over the thoracolumbar area adjacent to the spine; attitude reflects the degree of muscle tone; and respiration refers to ventilation rate and rhythm with 30 breaths/min as the cutoff. Each category is scored from 0 to 2 points with a score of 10 being optimal. A score of 0 to 3 indicates marked depression; 4 to 6, moderate depression; 7 to 8 reflects mild asphyxial injury; and normal foals have a score of 9 or 10. Ideally the modified Apgar calculation should be made within the first minute after birth, but certainly within 15 minutes of delivery. Repeating the score 4 minutes later is recommended. Foals with low scores typically require aggressive resuscitation, whereas mildly affected foals may respond to vigorous rubbing, stimulation of the nasal mucosa, and limb movement.

TABLE 16.1

Apgar Score: Assessment of Neonatal Asphyxia

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Parameter	0 Points	1 Point	2 Points
Appearance	Gray or blue mucous membranes	Pale pink mucous membranes	Pink mucous membranes
Pulse (beats per minute)	Absent	<60, irregular	>60, regular
Grimace			
Nasal stimulation	No response	Grimace	Strong grimace, sneeze
Ear tickle	No response	Head and neck motion	Ear tickle, head shake
Thoracolumbar stimulus	No response	Head and neck motion	Attempt to stand with head, neck, limb motion
Activity (muscle tone)	Limp, lateral recumbency	Semisternal, some limb flexion	Sternal
Respiration (breaths per minute)	Absent	<30, irregular	>30, regular, can whinny

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Maternal Behavior

The mare's behavior is critical and must be closely monitored. A good dam will pay close attention to its foal, avoiding stepping or lying on it, protecting it from real or perceived threats, and facilitating the nursing process. The mare and foal will be in close contact over the first few days of life, within 5 m of each other for more than 95% of the time. Signs of concern are mares that are ambivalent about the foal, avoid or fear their foal, do not allow the foal to nurse, demonstrate extreme protection (“foal proud”), or are outwardly aggressive toward the foal.[7,8] Some mare behavior may be viewed as aggressive but may actually be normal. This may occur in response to excessive bumping of the udder or overly enthusiastic sucking. It has been reported that maiden mares, older mares, mares with a history of rejecting foals, and Arabian mares of Egyptian lineage are at greatest risk of rejecting their foals.[9] The health of either the foal or mare can contribute to a failure to bond. For example, foals that are unable to stand or suck are less likely to form a normal bond, and mares with painful mammary glands or that are experiencing strong postpartum uterine contractions are less tolerant of foals trying to suck. The benzodiazepine drug alprazolam has been used to treat maternal aggression with apparent success.[10] A dose rate of 0.035 mg/kg, PO, q8-12h has been recommended. Some cautions are recognized, including slight mare sedation at q8h dosing; the likelihood that the drug is passed in milk (although no foal sedation has been observed); and there may be increased risk of congenital defects when used in the first trimester by pregnant women.[10]

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Physical Assessment

Numerous factors influence a foal's body weight at birth, including breed, gender, gestational age, and intrauterine environment. Estimates of body weight for newborn Thoroughbred foals for the purpose of drug calculation range between 40 and 55 kg, although many healthy foals may well exceed this range. Birthweight of Thoroughbred foals was positively correlated with mare body condition score.[11] The average daily weight gain for healthy foals is breed dependent but is typically between 1.3 and 1.7 kg/day for Thoroughbred-type foals.[12] Daily weight gain in hospitalized foals is determined by disease, calorie intake, and a lack of exercise and is almost always less than that of healthy, active foals.

The degree of physical development should be considered in relation to the estimated gestational age. This assessment should be made in light of the variable gestational length in horses. Typically gestational length is calculated from the time of insemination through birth, a figure that overestimates the true gestational period by as much as 7 days. The mean gestational period in Thoroughbreds is around 340 to 342 days with 95% of mares foaling between 327 and 357 days.[13] A number of factors influence this period, including breed, gender, and time of year. Colts on average have a gestational length that is approximately 1.5 to 2.5 days longer than that of fillies; they are slightly heavier, slower to stand, and have a heavier placenta.[14] Mares that conceive early in the breeding season have pregnancies that may be up to 10 days longer than those that become pregnant late in the season.[13,15] The role of dam, sire, and the dam's sire in determining gestational period has been suggested in some but not all breeds.[16]

Physical characteristics of immaturity include low birth weight, small body size, short and shiny hair coat, doming of the head, periarticular laxity, and droopy ears. Foals with a shortened gestational period and signs of physical immaturity are termed *premature*, while foals that are physically immature in the face of an appropriate gestational length are termed *dysmature*. Foals born after 356 days should be regarded as post-term. This is distinguished from foals that are post-mature, a condition of increased morbidity as a consequence of failing placental function.[16] Post-mature foals tend to have a lean and lanky physical appearance.

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Rectal Temperature

Rectal temperature in normal foals ranges between 99° F and 102° F (37.2° C and 38.9° C) during the first 4 days after birth.[2] The upper end of the normal range, which is around 1° F (0.6° C) above the upper end of the adult range, is strongly influenced by environment and exercise. Temperature can be variable in foals with systemic sepsis; in the early stages of sepsis the rectal temperature is commonly within the normal range or mildly elevated. Foals in septic shock will usually have a low rectal temperature, and those with localized infection will often be afebrile.

Ears

The ears of a normal foal are typically erect at the time of birth. Drooping of the ear pinnae is most commonly associated with prematurity or dysmaturity and, as such, is often accompanied by other physical signs of immaturity, such as small body size, short silky hair coat, and a domed head. Examine inside the ear pinnae for evidence of dermal hemorrhages. These can be a manifestation of systemic sepsis (see Chapter 17) or thrombocytopenia caused by disseminated intravascular coagulation (DIC) or alloimmune thrombocytopenia.

Eyes

The neonatal foal may not be able to close its eyelids completely (lagophthalmos), has reduced production of tears, and lacks a menace response. The menace response is a learned one and is usually acquired in the first 14 days of life. The pupil is oval-shaped, and pupillary light reflexes are present from birth but are slower. Other normal ocular findings include persistence of the hyaline artery remnants, the blood supply to the developing lens, and a pale pink to red optic disc with smooth margins. Newborn foals also have very prominent lens “Y” sutures. Lens suture lines are apparent in most foals and can persist into adulthood. An ophthalmic survey of healthy Standardbred foals conducted within 48 hours of birth reported abnormalities in 36% of foals.[17] Most were acquired and included retinal and subconjunctival hemorrhages; these had resolved in all foals by 1 (retinal) and 2 weeks (subconjunctival) of age. All foals in that study had hyaloid system remnants of various degrees.[17] In an ophthalmic survey of older foals (mean age of 9.4 weeks), suture lines were observed in

95% of animals.[18] The anterior suture was predominately Y-shaped, but the authors reported that posterior sutures were more variable, from “Y-shaped to sawhorse, to stellate.” Posterior lens sutures are reportedly more difficult to recognize in Thoroughbred foals. The suture patterns are not consistently symmetric between eyes. Prominent lens sutures can be confused with congenital cataracts. Congenital cataracts are amenable to surgery in the absence of uveal tract inflammation, a normal retina, and an appropriate demeanor. Other abnormalities that can occur include atresia of the nasolacrimal system, dermoids, retinal dysplasia, and optic nerve hypoplasia.

The neonatal foal may have significant corneal ulceration without tearing, blepharospasm, or photophobia due to reduced corneal sensitivity when compared with older foals and adult horses.[19] Consequently, special attention is required to monitor for ocular disease. It is recommended to fluorescein stain the cornea daily in sick recumbent neonatal foals. The combination of lagophthalmos, recumbency, and seizure predisposes foals with encephalopathy to a high incidence of corneal ulceration.

Entropion (inward rolling of the eyelid margin) is a common ocular problem of newborn foals. This usually occurs as a complication of dehydration and/or malnutrition and may lead to corneal abrasion and ulceration. Treatment is placement of vertical mattress sutures or staples to evert the offending lid while the primary condition is corrected. An alternative strategy is to inject procaine penicillin G subcutaneously into the lower lid to cause temporary eversion. It is extremely rare that surgery is required to correct entropion.

Examine the conjunctiva and sclera for signs of hemorrhage. This is commonly associated with birth trauma, and affected foals should be monitored closely for development of more classical postasphyxia complications. These hemorrhages resolve by week 2 of postnatal life.[17] Episcleral injection (engorgement and proliferation of scleral vessels) is a prominent feature of systemic sepsis. Iridocyclitis is usually associated with systemic sepsis and can include hyphema, hypopyon, and fibrin. These changes are not uncommon in foals with in utero–acquired infection and may be present at birth. Iridocyclitis is also seen in older foals with *Salmonella* or *Rhodococcus equi* infection.

Oral Cavity

Oral mucous membranes in healthy newborn foals should be pink and moist and have a capillary refill time (CRT) of 1 to 2 seconds. Bright pink to red mucous

membranes, accompanied with injected scleral vessels and hyperemia of the coronary bands, are consistent with the early stages of sepsis. During this early hyperdynamic phase the CRT may be shorter than normal. Darkening of mucous membranes with a delay in the CRT may indicate sustained sepsis. In severe cases this is accompanied by petechial or ecchymotic hemorrhages.

Icteric mucous membranes are most commonly associated with systemic sepsis but are also a feature of neonatal isoerythrolysis, liver disease, internal hemorrhage, meconium retention, or infection with equine herpesvirus type 1. Pale membranes suggest anemia and can occur with external umbilical cord hemorrhage, internal hemorrhage from torn umbilical vessels, fractured ribs, or hemorrhage within gastrointestinal or urinary tracts. Pallor with icterus would normally indicate neonatal isoerythrolysis or internal hemorrhage. Petechial or ecchymotic mucosal hemorrhages suggest advanced sepsis when associated with darkened membranes and a prolonged capillary refill time, or alloimmune thrombocytopenia when the membranes are pink (Fig. 16.1). Blue to gray discoloration of the membranes is consistent with hypoxemic circulatory shock. Overt cyanosis is uncommon and should prompt close examination of the cardiovascular and respiratory systems.



FIG. 16.1 Spontaneous mucosal hemorrhages and ulceration in a foal with alloimmune neonatal thrombocytopenia.

In term foals the central incisors usually erupt during the first 5 to 7 days of

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postnatal life. The middle incisors rise between 4 and 6 weeks of age, but the corner incisors do not erupt until around 6 to 9 months. In miniature horses and ponies the eruption of the middle and corner incisors is delayed at 4 months and 12 to 18 months, respectively. The 12 temporary molars are present at birth or erupt within the first week of life. These teeth are replaced by permanent premolars at 2.5, 3, and 4 years of age. The three molar teeth do not erupt until 1, 2, and 3.5 years of age for molars 1, 2, and 3, respectively.

Dental problems are uncommon in foals with the exception of those associated with facial deformities such as maxillary prognathism, mandibular prognathism, and campylorrhinus. Maxillary prognathism (parrot mouth; bird face; overbite; brachygnathism; brachygnathia) describes the condition where the mandible is shorter than the maxilla, producing an overjet or overbite. The condition may affect the incisors, cheek teeth, or both, and is the most common congenital oral malformation of foals. The majority of foals with maxillary prognathism suffer little impact to their quality of life, and the defect simply represents a cosmetic problem. In moderate to severely affected foals the lack of incisor contact results in excessive growth of the lower teeth and secondary soft tissue trauma to the palate caudal to the upper incisors. The premaxilla and incisive bones tend to bend forward and downward as growth continues due to the lack of an opposing force, normally provided by the mandible. This can lead to difficulty in grazing. Mandibular prognathism (sow mouth; monkey mouth; brachygnathia superior; underbite) describes the condition where the maxilla is shorter than the mandible, producing an underbite. The condition occurs much less commonly than the maxillary equivalent and is most frequently seen in pony and small horse breeds. The defect in its most severe form can be associated with deformity of the nasal passages and nares, and there may be difficulty in breathing and an inspiratory stridor. Mandibular prognathism is commonly associated with congenital hypothydroidism.[20] Campylorrhinus lateralis (wry nose, wry face) describes the condition where the premaxilla and nasal septum are deviated laterally. It may occur singularly or in combination with other deformities, such as wry neck, cleft palate, and maxillary or mandibular prognathism. If the deviation is severe, the foal may have great difficulty in sucking from the mare. There may also be problems with breathing. In most foals the deviation is mild and represents a simple but obvious cosmetic defect. Close attention must be paid to dental wear as maxillomandibular malocclusion occurs commonly.

Cleft palate is an uncommon congenital defect of foals that results from

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incomplete fusion of the lip and/or secondary palate during the early gestational period. Previous reports estimate the incidence between 0.1% and 0.2% of all horse births.[21] Almost all clefts occur in the secondary palate, the horizontal partition dividing oral and nasal cavities. The secondary palate includes all of the soft palate and most of the hard palate, with the majority of defects restricted to the soft palate. The basis of this congenital defect is not known but could include a heritable component and/or exposure of the developing fetus to infection, toxins, or nutritional disturbances. The diagnosis is usually straightforward and centers on an appropriate history and signalment. Confirmation is through palpation using the third finger of an upturned hand or by direct inspection of the oral cavity. It is important that the hand is clean before direct palpation. Endoscopic examination of the nasal passages or through the oral cavity under anesthesia may be required to detect small defects. Oral palpation is recommended for all sick neonatal foals before commencing potentially costly treatment. A cleft in the secondary palate permits the oral contents to pass directly into the nasopharynx and nasal passages. Consequently, the most common complaint is nasal regurgitation of milk immediately after sucking. As the foal matures, feed particles will also appear at the nares. Foals with small palate defects may have intermittent milk drainage from the nostril and consequently escape diagnosis during the neonatal period. Rarely, cases are initially diagnosed in adult horses. Most will develop an aspiration pneumonia, which can be difficult to identify in its early stages due to immaturity of cough receptors. Surviving foals will typically be poorly grown and ill-thrifty. The presence of milk at the nares after feeding does not definitively indicate that a cleft is present and is more commonly associated with pharyngeal/laryngeal weakness or incoordination. The tongue should be examined for evidence of candidiasis, appearing from small white plaques up to a diffuse tan coloration of the tongue. The condition can be local or systemic and is common in debilitated foals and those that have been on chronic antibiotic therapy. In severe cases the condition will cause reduced nursing and salivation.

Thyroid Gland

Hypertrophy of the thyroid gland (goiter) can occur in response to deficient or excess dietary iodine. One of the more common reasons for thyroid gland enlargement in neonatal foals is excess iodine supplementation during pregnancy.[22] There are reports of neonatal goiter when seaweed was

incorporated into the diet of broodmares or when pellets were fed to mares that had been formulated with excessive iodine.[23,24] Dysmature foals with thyroid hyperplasia and concurrent musculoskeletal problems have been identified in Western Canada and northwest United States.[25,26] The syndrome results in hypothyroidism and may be related to the feeding of diets that are high in nitrate or low in iodine to mares during pregnancy. Thyroid hormone is an important cofactor in maturation of the respiratory system, and hypothyroidism has been linked to respiratory failure in a newborn foal.[27] In older foals enlargement of the thyroid has been associated with dietary iodine deficiency and low circulating levels of T4.[22] Newborn foals have baseline T3 and T4 levels that are considerably greater than that of adult horses.[28,29] These levels decline over the first 12 days after birth.

Neck and Back

A number of congenital anomalies affect the alignment of the vertebral column. These include atlantoaxial malformations, scoliosis, kyphosis, lordosis, and combined anomalies, such as kyphoscoliosis. Atlantoaxial malformations may occur with or without cervical scoliosis or signs of spinal cord compression. Arabian foals are most commonly affected, and a familial predisposition has been suggested.[30] There may be palpable abnormalities of the atlas and axis and altered head carriage. The diagnosis is confirmed using radiography where a range of abnormalities is seen, including atlantooccipital fusion, hypoplasia of the dens, and axis malformation. Prognosis is poor as many have signs of ataxia and paresis involving all four limbs at birth. Some animals may have normal neurologic function. Foals with severe kyphosis or kyphoscoliosis often have underlying malformation of the thoracic vertebrae.[31]

Gastrointestinal System

Most foals display abdominal straining within a few hours of birth and pass most of the meconium within the first 1 to 4 hours after delivery, but passage may be delayed without concern for up to 12 hours. Differentiating straining to defecate from straining to pass urine can be difficult in some foals. Typically foals straining to pass feces will have an arched appearance to their hindquarters (Fig. 16.2). A change in the color and consistency of the feces from a dark brown to

black pasty material to a lighter brown, less tenacious material indicates that the meconium has been passed. The routine administration of an enema is performed commonly in healthy newborn foals in an attempt to reduce the straining associated with passage of meconium. A variety of methods are used, with commercial glycerine phosphate−based products the most common. These are relatively easy to administer, although care should be taken to avoid direct trauma to the rectal mucosa with the applicator tip. Many veterinary practices probably use gravity enemas using 400 to 800 mL of warm soapy water delivered through a soft tube, such as a canine stomach tube or male urinary catheter. Acetylcysteine retention enemas are not administered routinely, but rather in foals with resistant meconium impactions.



FIG. 16.2 A foal demonstrating a classical hunched appearance while straining to pass feces.

Auscultation of the abdomen can provide an indirect assessment of intestinal contractility. The technique should be interpreted with caution as the presence of borborygmi does not equate to propulsive motility or ingesta transit. The changes in gastrointestinal sounds over time may be more useful in determining a diagnosis. For example, a silent abdomen that progresses to a hyperactive one could be indicative of inflammatory intestinal disease, whereas an abdomen with normal sounds that changes to silent could be consistent with a surgical lesion. Percussion and ballottement are used to differentiate abdominal distention

caused by gas or fluid accumulation. A tympanic sound on percussion is consistent with intraluminal or free peritoneal gas, and ballottement can detect waves of free abdominal fluid. Progressive abdominal distention, irrespective of the underlying cause, can be monitored using a soft measuring tape repeatedly positioned over small clipper marks. Gastric distention can cause a “sprung rib,” a swelling that projects beyond the 18th rib.

Firm structures can be detected using transcutaneous abdominal palpation, assuming the foal is suitably relaxed. It is possible to palpate bowel impacted with meconium, fecoliths, intussusceptions, the urinary bladder, or enlargement of the internal umbilical remnants caused by infection or hemorrhage. The external umbilicus should also be palpated for enlargement or herniation, and, in colts, the inguinal rings and scrotum should be assessed for bowel herniation. These are typically soft and fluctuant swellings that are easily reduced when the foal is placed on its back and are managed by manual reduction and strapping. Incarceration is rare, but bowel integrity can be assessed using ultrasound; devitalized bowel lacks motility and has thickened and edematous wall. In some colts the intestine can protrude through a rent in the parietal vaginal tunic and migrate subcutaneously in what is described as a direct inguinal hernia[32] (Fig. 16.3). This is often associated with preputial swelling and requires surgical intervention.

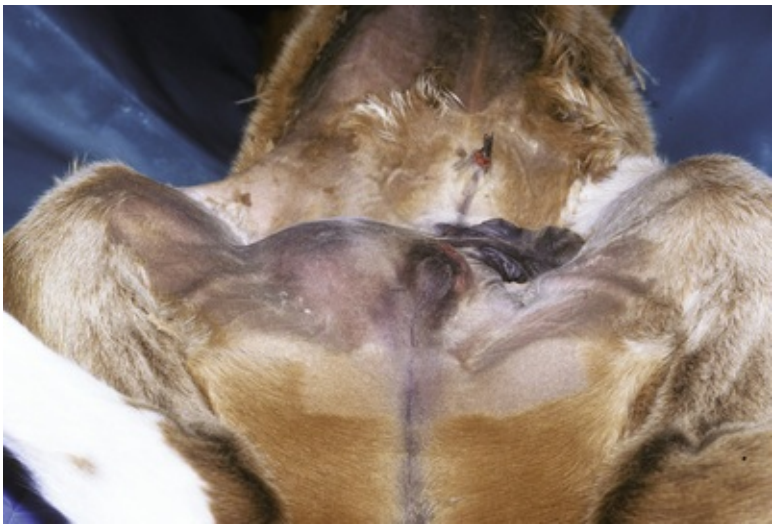


FIG. 16.3 A dissecting scrotal hernia before surgical repair.

Digital rectal examination is indicated in a colicky foal or in any foal where

meconium passage has not been observed. Distal meconium impaction is typically apparent on rectal examination, but high impactions are not. Intestinal atresia should be suspected if there is no history of fecal passage and there is clear or white mucous on the glove.

Passage of a nasogastric tube is an often-overlooked diagnostic procedure in colicky neonatal foals. Removal of gastric fluid can reduce or eliminate colic signs, as well aid in the localization of disease. Gastric distention may also be present in sick neonates showing no signs of colic. The condition occurs with primary gastric outflow problems or mechanical or functional small intestinal obstruction. Functional obstruction caused by small intestinal ileus occurs more commonly in neonates secondary to a range of diseases including hypoxic ischemic syndrome, sepsis, prematurity, enteritis, electrolyte derangements, and overfeeding.

Coprophagy is observed in normal foals from birth through 5 to 6 months of age.[33–35] Most foals demonstrate coprophagy by 7 days of age (Fig. 16.4). The consumption of feces is not driven by hunger, and foals have a selective preference to consume feces of their dams. The most likely basis for coprophagy is as a mechanism to populate the intestinal tract with bacteria, fungi, and protozoa essential for digestion of a herbivorous diet. Coprophagy precedes the passage of protozoa in foal feces and the development of the syndrome known as “foal heat diarrhea.” This is a benign diarrheal disease of newborn foals and should not require treatment.



FIG. 16.4 Coprophagy is an important behavior in establishing hindgut flora.

Abdominal Ultrasound

Ultrasound is a key component in the examination of a foal abdomen. Numerous conditions are recognized on ultrasound, including uroperitoneum, bacterial peritonitis, hemoperitoneum, strangulating intestinal obstructions, meconium impaction, gastric enlargement, enteritis, necrotizing enterocolitis, and hernias. The foal can be scanned in lateral recumbency or standing; the latter is preferred as thickened or heavy structures will move to the dependent region of the abdomen, gas-filled structures will migrate dorsally, and visualization of peritoneal fluid is improved. Clipping is not essential if the hair is dampened with alcohol. The stomach is identified in the mid to ventral abdomen on the left side between the 6th and 12th intercostal spaces and lies medial to the spleen. In contrast to adults, the stomach is commonly in contact with the ventral body wall during the first week of life and the contents are readily imaged.[36] Gastric wall thickness is typically around 2.0 mm during the first week of life. The duodenum is readily located in normal foals on the right side of the abdomen between the ventral and caudal aspect of the liver and the dorsal margin of the right dorsal colon, as well as ventral to the caudal pole of the right kidney. The remainder of the small intestine is also easily identified throughout the abdomen and should have a wall thickness less than 2.5 mm. The large intestine is differentiated from the small intestine by increased luminal diameter, bowel sacculations, and greater likelihood of gas. The colon wall should be less than 2.8 mm during the first week of life. The neonate with acute colic should be assessed with ultrasound for small intestinal intussusception. These are readily identified, are typically jejunojejunal, and are often located in the ventral abdomen when the foal is standing. They have a characteristic appearance with the intussusceptum surrounded by fluid and the intussuscipiens creating a “target” sign. Some will resolve spontaneously, but most require surgical reduction. Meconium impactions have an echogenic ball or log appearance when in the small colon or a more varied appearance when present in the large colon, a hypoechoic to hyperechoic mass that may be surrounded by fluid.[37] Thickening of the wall with intramural gas echoes is consistent with a strangulated obstruction or necrotizing enterocolitis. Abdominal hemorrhage results in a classical “smoke

swirl” appearance to the peritoneal fluid.

Abdominal Radiography

Radiography has been displaced as the principle imaging modality of the foal abdomen but still can provide essential information.[38] Contrast radiography remains an important technique to assess gastric outflow problems, intestinal transit, intestinal atresia, and high meconium impaction. The abdomen of most neonatal foals can be captured on a 35 cm × 43 cm cassette. A grid should be used to minimize film fogging. For a standing foal weighing around 50 kg, using a 400-speed film-screen system, a grid with a 10 : 1 grid ratio, and a focal spot-film distance of 100 cm, the appropriate technique should be in the range of 80 to 90 kV (peak) and 15 to 20 mA. This technique can be reduced slightly lateral projections in the recumbent foal. The beam should be centered on the last rib. For upper gastrointestinal contrast studies, 5 mL/kg of 30% wt/vol barium suspension is administered through a nasogastric tube; ideally foals are fasted for 4 hours before the procedure and should not be sedated. Barium typically empties rapidly from the stomach, allowing examination of the stomach and duodenum on initial films. The contrast should clear the small intestine by 3 hours and be completely cleared by 36 hours. The cecum should be visible by 1 to 2 hours post administration. A barium enema can be used to evaluate the lower intestinal tract, specifically intraluminal obstruction and atresia. Sedation can be used as the procedure is not defining a dynamic problem. A 30-French Foley catheter with a 30-cm^3 balloon is inserted 6 to 10 cm into the rectum, the cuff is inflated, and 300 to 500 mL of 30% wt/vol barium sulfate suspension are infused. Volumes up to 20 mL/kg have been described; colonic or rectal rupture is a rare but fatal complication of the procedure. Computed tomography (CT) is an underused tool in the assessment of the foal abdomen, with most applications involving examination of limbs, head, or neck.[39]

Abdominocentesis

Peritoneal fluid can also be evaluated by abdominocentesis. The technique has a greater complication rate in neonates, and ultrasound should be used to identify pockets of fluid for sampling. Most complications arise due to a combination of hypodermic needles, a moving patient, and a relatively thin bowel wall. If no fluid is identified, then the procedure should not be performed. For small

volumes it is recommended to use a blunt, small bovine teat cannula; for larger volumes a hypodermic needle can be used. Peritoneal fluid nucleated cell counts are lower in foals than in adult horses.[40] Nucleated cell counts above 1.5×10^9/L may be considered abnormal in foals up to 4 months of age,[41] although another study suggested a value of 3.0×10^9/L as a cutoff for foals younger than 75 days of age.[42] Cytologic evaluation is similar to adults with a predominance of large mononuclear cells (macrophages and mesothelial cells) with smaller numbers of lymphocytes and neutrophils. The relative percentage of neutrophils (15%) may be less than that seen in normal adult peritoneal fluid. The protein concentration of foal peritoneal fluid is similar to that of adults, below 20 gm/L, and therefore values above this are considered abnormal. An increased total nucleated cell count, increase in the percentage of neutrophils with cell degeneration, and intracellular and extracellular bacteria would be expected in foals with septic peritonitis. This would be accompanied by a low pH (<7.2), increased lactate concentration, and a discrepancy between serum and peritoneal glucose concentrations (>2.7 mmol/L).[40]

Cardiovascular System

Physical assessment of the cardiovascular system includes examination of visible mucous membranes, palpation of peripheral arterial pulses, assessment of extremities for warmth, detection of limb or ventral edema, and cardiac auscultation. The heart rate in newborn foals in the minutes after birth is influenced by vagal tone and varies between 36 and 80 bpm. As the foal becomes active and struggles to stand, the heart rate will increase to 120 to 150 bpm before stabilizing in a range of 80 to 100 bpm over the first week of life.[43] Tachycardia is an important mechanism in neonates to improve cardiac output and blood pressure, and it is expected during periods of asphyxia and in response to hypovolemia, sepsis, anemia, or hypoxemia. A sustained increase in heart rate may also accompany pain or stress or reflect a primary cardiac problem. Bradycardia can be due to hypothermia, electrolyte abnormalities, or hypoglycemia.

Cardiac arrhythmias are rarely recognized but occur in most foals during the immediate postpartum period with supraventricular premature contractions and sinus arrhythmia predominating.[44,45] Other arrhythmias include supraventricular (atrial) tachycardia, atrial fibrillation, second-degree atrioventricular block,

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ventricular premature contractions, ventricular tachycardia, and idioventricular rhythm. These rhythm disturbances typically only last for 5 minutes and in most foals have disappeared by 15 minutes of age. Rarely they may persist up to 2 hours of age. The more severe arrhythmias are associated with a lower arterial oxygen concentration, suggesting a role for hypoxemia in the pathophysiology of these events. Arrhythmias that persist beyond this timeframe should be investigated by electrocardiogram. Causes include electrolyte abnormalities, persistent hypoxemia, and sepsis. Foals with sustained and rapid ventricular tachycardia need treatment with intravenous quinidine, gluconate, lignocaine, or propranolol.[46]

Cardiac murmurs are expected in the early neonatal period. A patent ductus arteriosus (DA) can result in a continuous machinery murmur with a point of maximal intensity high over the left heart base in the third intercostal space.[46,47] These are typically audible up until 3 to 4 days of age.[48] As the DA begins to close, the systolic component of the murmur often remains audible. Low-intensity, left-sided systolic murmurs are commonly heard through the first months of postnatal life. Some may be associated with flow across the foramen ovale, but most are likely due to turbulence in the great vessels created during left ventricular ejection.[46] Others have suggested that flow through the DA may persist for weeks to months.[49] Loud murmurs that persist beyond 7 days of age or any murmur that is accompanied by signs of cardiac disease, such as poor growth, cyanosis, lethargy, or exercise intolerance, should be referred for echocardiography. Auscultation of both sides of the thorax is important as right-sided cardiac murmurs are a feature of several congenital cardiac anomalies. Occasionally serious cardiac defects may not be associated with audible murmurs. Although most congenital cardiac diseases are detected in foals or young horses, some defects do not become apparent until the horse is required to perform or may occur simply as incidental findings in older horses.

Distal extremities should be free of edema and warm to the touch. Limb edema can occur for several reasons, but most commonly secondary to asphyxia or in response to inappropriate fluid therapy in oliguric or anuric foals. Limbs that are cool or cold are poorly perfused and will typically have weak arterial pulses. However, the relationship between peripheral pulse pressure and hypotension is not consistent; hypotension is not always associated with weak pulses and, conversely, weak pulses do not always indicate hypotension.[50] Arterial thrombosis should be suspected if a single limb is cold, although an

aortic thrombosis could result in decreased perfusion to both hind limbs.[51] Pulse quality can be assessed in the distal limbs using the great or dorsal metatarsal arteries on the lateral aspect of the hind cannon bone. In the forelimbs the brachial artery can be palpated at the level of the medial collateral ligament of the elbow joint. Several methods are available to assess arterial blood pressure. Direct blood pressure monitoring is ideal because it is accurate and continuous, but it is invasive and difficult to maintain and can be complicated by vessel thrombosis or sepsis. More commonly, blood pressure is monitored indirectly using oscillometry or Doppler-based devices over the coccygeal, brachial, or great metatarsal arteries. An infant-sized inflatable cuff (bladder 52 mm) placed snuggly around the base of the tail yields data that are comparable to mean arterial measurements taken directly from a catheterized great metatarsal artery in a day-old foal weighing between 44 and 69 kg.[52] The technique tended to underestimate systolic and overestimate diastolic values, although the differences were not large. The mean arterial pressure of a healthy Thoroughbred foal using an oscillometric device was reported to be 95, 100, and 101 mm Hg at days 1, 2, and 3, respectively.[53] Other noninvasive methods to measure cardiac output, such as volumetric echocardiography, have shown good correlation with more robust but invasive techniques in anesthetized foals. The question remains if this correlation will be sustained in critically ill foals.

Respiratory Tract

In newborn foals the nasal passages are examined for meconium staining and, if present, the passages should be suctioned using a dose syringe and soft catheter or other portable or fixed suction device. The early stages of pulmonary disease are difficult to recognize, as cough and nasal discharge are typically absent. Immature cough receptors also contribute to a lack of awareness of ongoing milk aspiration into the major airways. Auscultation of the lung fields can also be misleading in young foals. Fluid sounds are normally present immediately after birth, as are end-inspiratory crackles due to simple atelectasis of the dependent lung during or after lateral recumbency. These crackles should resolve when the foal has been standing for several minutes. Conversely, foals with bronchopneumonia may have minimal abnormal lung sounds until the pathology becomes severe. In the absence of advanced diagnostics the clinician must rely on clinical signs, such as restlessness and agitation, increased respiratory rate and depth, or respiratory distress, to diagnose lower airway disease.

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The normal response after delivery is an increase in minute ventilation, with elevations in both rate and tidal volume. The respiratory rate is usually rapid for the first hour of life, around 60 to 80 breaths/min, but should decline to a steady rate of 30 breaths/min thereafter in normal foals. Persistent elevations in the respiratory rate can be caused by a range of pulmonary and extrapulmonary causes. Pulmonary causes include meconium aspiration, bacterial or viral pneumonia, atelectasis due to recumbency, congenital pulmonary disease, rib fracture or dislocation, or pleural effusion. Nonpulmonary causes include fever, pain, excitement, exercise, brain disease, a compensatory response to metabolic acidosis, or idiopathic or transient tachypnea syndrome. An increase in the effort of breathing may be the first sign of respiratory disease. As the disease progresses, the foal can develop paradoxical thoracic wall motion due to muscular fatigue where the thoracic wall paradoxically moves inwards during inspiration and outwards during expiration. This is more commonly seen in premature foals with lung disease and is a sign of impending respiratory failure. Another sign of failure is an expiratory “grunt”; foals will keep their glottis closed until the end of the breathing cycle in order to maintain sufficient pressure in the respiratory tract to prevent airway collapse.

Respiratory rhythm should be regular in awake foals but may be irregular in normal foals during rapid eye movement (REM) sleep. This can also include body and limb movements and vocalization. Irregular or erratic breathing patterns in conscious foals, or in foals that are in coma or semicoma, are consistent with central nervous system disease or, less commonly, metabolic or electrolyte disorders, hypothermia, or prematurity or dysmaturity. Patterns include periodic breathing, ataxic breathing, tachypnea, hypopnea or intermittent apnea, and apneustic breathing. Hypopnea or apnea in foals with central nervous system disease may result in severe respiratory acidosis, prompting the use of respiratory stimulants or mechanical ventilation. Doxapram administered as a constant rate infusion was more effective than oral caffeine at reducing the arterial carbon dioxide concentration ($PaCO_2$) in affected foals.[54]

Respiratory distress or stertorous breathing can be caused by several uncommon conditions in the newborn foal. A range of congenital cardiac or respiratory tract malformations should be considered if abnormalities are present at or shortly after birth. Those involving the respiratory system include stenotic nares, choanal atresia, subepiglottic cysts, collapsing trachea, and lung lobe agenesis. Tearing of the diaphragm during birth with herniation of abdominal contents can also result in immediate respiratory distress. Similar distress can be

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seen with a dorsally displaced soft palate caused by neurologic or anatomic dysfunction. Soft fluctuant swelling in the parotid region could be consistent with guttural pouch tympany. The condition is more commonly seen in older foals but has been reported in the early neonatal period, often associated with pharyngeal/laryngeal weakness and altered ostia function. This may also result in milk entering the pouch. There is a reported predisposition in fillies and certain breeds, including Arabians and Paints.[55]

Localized or widespread crepitus of the subcutaneous tissues could be consistent with air leakage from respiratory tissues, most commonly from ruptured pulmonary bullae.[56] The thoracic wall should be palpated for evidence of rib shaft fractures or costochondral dislocation. Thoracic trauma and rib fracture occur most commonly as a complication of the birthing process. They are identified by observation of thoracic wall symmetry and synchrony, palpable crepitus, and localized edema. In addition, there may be an audible “click” on auscultation of the thorax. Affected foals may grunt on expiration and prefer to lie on the unaffected side. Diagnosis is confirmed by ultrasound or radiographic examination. On ultrasound examination there is disruption of the cortical surface and associated soft tissue edema. Management includes recognition and treatment of potential complications and avoidance of further thoracic trauma. Potential clinical complications of rib fracture include hemothorax, lung laceration and pneumothorax, and pericardial/myocardial puncture.

Arterial Blood Gas Collection and Analysis

Due to the limitations of physical examination in accurately assessing the respiratory system, arterial blood gas (ABG) analysis is commonly performed at referral practices during the initial assessment. It is a sensitive indicator of respiratory function.[57] The sample is usually collected from the dorsal metatarsal artery. Alternative sites include the brachial artery, located at the level of the medial collateral ligament of the elbow joint, or the carotid artery, but hematoma formation is a common sequel to aspiration from this site. The sample will remain useful for up to 90 minutes in a capped plastic syringe at room temperature. Contamination of the sample with room air will artificially increase the arterial oxygen concentration (PaO_2) and decrease the $PaCO_2$. Interpretation of blood gas values of venous blood can be deceptive and should be restricted to evaluation of metabolic conditions and not pulmonary gas exchange.

Normal ABG values for neonates of different postnatal and gestational ages

are presented in Table 16.2. Interpretation of the ABG sample involves consideration of the amount of struggling and position of the foal during sample collection. Foals that require considerable restraint to obtain a sample probably do not require sampling. Lateral recumbency can reduce the PaO_2 by as much as 30 mm Hg. Supplemental oxygen affects ABG values; a flow rate of 10 L per minute (lpm) delivered by nasal insufflation increased the PaO_2 from 84 ± 6 mm Hg to 298 ± 69 mm Hg in healthy, full-term newborn foals.[58] This flow rate approximates to a fraction of inspired oxygen (FiO_2) of 1.0.[59] If the respiratory rate is rapid and the depth shallow, supplemental oxygen will be diluted by room air because of the large quantity of room air entering the upper respiratory tract, and the concentration of alveolar oxygen will be less than expected. A general guide for supplemental oxygen use is to set an initial flow rate of 5 lpm. Oxygen should be humidified if delivered at high flow rates or for long periods of time.

TABLE 16.2

Normal Blood Gas Values for Foals[a]

	Arterial					Venous			
Age Group	**O_2 (mm Hg)**	**CO_2 (mm Hg)**	**pH**	**Base Excess**	**HC^-_3 (mEq/L)**	**O_2 (mm Hg)**	**CO_2 (mm Hg)**	**pH**	**HC^-_3 (mEq/L)**
Immediate post foaling[b]	40-50	52-60	7.2-7.3	+2	24-26	—	—	—	—
2 hours[b]	68 ± 10	49 ± 2	7.37 ± 0.01	+4	26 ± 2	42 ± 2	56 ± 2	7.33 ± 0.01	28 ± 2
4-12 hours[c]	75 ± 5	47 ± 2	7.39 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 2
24 hours[c]	81 ± 6	48 ± 2	7.4 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 3
1-3 days[c]	90 ± 6	148 ± 2	7.4 ± 0.01	+6	28 ± 2	43 ± 2	52 ± 2	7.38 ± 0.01	29 ± 2
4-14 days[c]	86 ± 5	45 ± 2	7.41 ± 0.01	+6	28 ± 1	38 ± 2	53 ± 2	7.38 ± 0.01	31 ± 2
Premature[b] birth	39 ± 5	55 ± 4	7.27	−.274 ± 1	—	—	—	—	
(320-330 days' gestation)—1 hour	52 ± 4	48 ± 3	7.33	−.33	25 ± 1	—	—	—	—

[a] Lateral recumbency.

[b] *Data from Rose RJ, Rossdale PD, Leadon DP: Blood gas and acid-base status in spontaneously delivered, term-induced and induced premature foals. J Reprod Fertility 32:521, 1982.*

[c] *Data from Stewart JH, Rose RJ, Barko AM: Response to oxygen administration in foals: effect of age, duration and method of administration on arterial blood gas values. Equine Vet J 16:329,*

1984.

Hypoxemia (PaO_2 < 70 mm Hg) can occur with hypoventilation, ventilation/perfusion mismatching, or right-to-left shunting of blood.[57] The two most common respiratory-derived derangements are hypoxemia with normocapnia or hypocapnia and hypoxemia with hypercapnia. Treatment of the former involves supplemental oxygen. The latter is usually indicative of severe respiratory disease but could reflect primary hypoventilation, as may occur in cases of botulism. Acute hypercapnia is associated with a more substantial drop in blood pH and may lead to circulatory collapse and coma, particularly if accompanied by hypoxemia. Chronic exposure to elevated CO_2 permits adaptation and subtle clinical effects. The change in pH is less dramatic because of enhanced bicarbonate reabsorption in the proximal tubules of the kidney, a process that begins within 6 to 12 hours and is maximal by 4 days. Hypercapnia can be exacerbated by fever or the administration of carbohydrates or bicarbonate. The latter is often clinically relevant and highlights the danger of giving large amounts of sodium bicarbonate to foals with pulmonary disease, potentially taking a primary metabolic acidosis and creating a more severe respiratory or mixed acidosis. Hypercapnia is also an expected response to metabolic alkalosis.[60]

Airway sampling either by transtracheal aspiration (TTA) or bronchoalveolar lavage is rarely performed in sick neonates, as the added stress of the procedures on an already compromised neonate can have fatal consequences. The TTA procedure is more likely to cause additional complications in foals with high ventilation rates, including pneumomediastinum and subcutaneous emphysema.

Pulmonary Imaging

Radiography can provide additional information that can assist in establishing a diagnosis, assessing the type and distribution of disease, and monitoring the response to treatment.[38] Radiographs are particularly useful in the diagnosis of rib shaft fractures, pneumothorax, pleural effusion, and diaphragmatic hernia. Radiographic changes associated with pulmonary disease tend to lag behind clinical changes, and it is difficult to differentiate atelectasis from pneumonia. Infiltrate tends to settle or move ventrally as the foal becomes ambulatory. Unfortunately, capturing diagnostic thoracic images in the field is difficult because of the amperage of portable machines and the limitation in plate size.

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The relatively low amperage results in long exposure times, which in a poorly compliant patient with high respiratory rate leads to motion artifact and a false interpretation of disease. Images tend to be limited to standing or recumbent lateral projections as positioning for ventrodorsal views can further compromise the cardiopulmonary system. Pleural and parenchymal diseases have a similar ultrasonographic appearance in newborn foals to that seen in adults. Anechoic pleural fluid can be seen with some infectious processes, in foals with uroperitoneum, or with some congenital anomalies. Echogenic or cellular fluid is seen with other infectious processes, and in hemothorax cases there will be characteristic “smoke whirls” present.

Urogenital System

As the foal begins to move after birth, it causes stretch and breakage of the umbilical cord, typically around 3 cm beneath the abdomen. This can also occur when the mare rises after foaling.[61] Early separation of the cord has no detrimental effect, provided the cord is severed by stretch rather than sharp dissection. The volume of placental blood available for transfer to the foal under normal circumstances is relatively small, typically well below 200 mL.[62] Greater volumes may be lost if the cord is cut, preventing contraction of vascular smooth muscle. Hemorrhage should therefore be controlled with a commercial clamp or umbilical tape. Prolonged attachment of the cord is unlikely to be a significant problem, although blood flow between the placental membranes and the foal is partly gravity dependent, such that blood could flow preferentially from foal to membranes if the foal is above the level of the placenta. Manual breakage of the umbilical cord is recommended if it remains attached for more than 8 minutes. The preferred method for manual cord breakage is to grasp the placental side of the cord while holding the foal side of the cord with your other hand to prevent excessive traction on the abdominal wall. Gently twist and pull from the placental side such that the breakage will occur at the natural site of detachment. Intraabdominal umbilical arteries may continue to pulse for several days after delivery; this may result in a palpable pulse in the umbilical stump, but it is not associated with blood flow.[62] The umbilical stump should be treated once or twice daily until it becomes dried and sealed. A 0.5% chlorhexidine solution is preferred; however, it may cause delayed drying of the stump. Iodine solutions can also be used, but the concentration should be limited to 2% to prevent tissue necrosis.

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Urine is one of the most important indicators of health in foals. As a consequence of a milk diet, normal neonatal foals produce a large volume of urine relative to their body weight, estimated at 148 mL/kg/day, or 7.4 L for a 50-kg foal. This value is approximately 5-fold to 10-fold greater than that of a healthy adult horse on a per-kg body weight basis.[63] The first passage of urine after birth occurs around 12 hours of age in normal foals, with colts passing urine earlier than fillies. The first urination in normal foals is concentrated with a specific gravity greater than 1.030, which will gradually decrease with subsequent urinations. The urine will become light in color and be very low in specific gravity, typically 1.001 to 1.008. Any foal observed to pass thick, concentrated urine should be assessed closely. Disruption to the urinary tract occurs relatively commonly and can be difficult to diagnose early in the clinical course. Rupture of the urinary bladder during delivery occurs more commonly in colts than fillies, although postpartum disruption to the tract in sick or hospitalized foals has no gender bias.[64,65] Signs often include prolonged straining, passage of small volumes of urine, progressive abdominal distention, lethargy, and weakness. Patency of the urachus is a common complication in sick newborn foals. Surgery is rarely required as most will close spontaneously by 2 weeks of age. Techniques to hasten closure generally involve chemical cautery, such as application of silver nitrate around the external opening. However, some believe that the resultant inflammation could predispose to infection or damage to internal structures and therefore limit their therapy to local disinfectants and systemic antibiotic therapy. Surgery would generally be recommended if the urachal leakage continued beyond 3 weeks of age.

In male foals the inguinal and scrotal region should be palpated for swelling and testicular descent. Inguinal and scrotal hernias occur relatively commonly but rarely result in clinical signs. Preputial edema may be present. Most congenital hernias are indirect, unilateral, and easily reducible and spontaneously resolve by 3 to 4 months of age. Positioning the foal on its back facilitates manual reduction. A figure-8 support wrap can assist in keeping the hernia reduced. Surgical correction is recommended if spontaneous resolution is delayed, if the hernia increases in size, or if signs of colic develop. Certain breeds appear to be at increased risk for herniation, including Tennessee Walking Horses and Standardbreds. A rent in the parietal vaginal tunic can lead to subcutaneous dissection of intestinal loops; this requires surgical reduction, herniorrhaphy, and unilateral castration.[66] Although extremely uncommon in foals, signs of colic can occur if herniated loops of intestine strangulate.

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At the time of birth most testes lie within the inguinal canal. The extraabdominal gubernaculum, which can be easily mistaken for a testicle, typically limits movement into the scrotum. Monorchidism has been reported in foals, and affected colts are usually mistaken as cryptorchids.[67] Congenital abnormalities of the penis are rare. Failure to drop the penis during urination can occur as a consequence to preputial edema, a common complication in colts that are straining to defecate or urinate. The free part of the penis is normally fused to the internal lamina of the prepuce for up to 1 month of age. This can make exteriorization of the penis difficult. “Kinking” of the penis has been described, resulting in stranguria or pollakiuria.[68] Correction was achieved through manual straightening of the penis.

Umbilical Hernias

Umbilical hernias occur commonly in foals. The condition is generally considered to be a congenital defect with a likely hereditary basis, although umbilical infection may be an important postnatal predisposing factor. In a study of Dutch Warmblood foals, 19 of 44 had a palpable abdominal wall defect between 2 and 6 cm at the time of birth.[69] In all but one of these foals the defect had closed by 4 days of age; however, 28% of the foals developed a defect between 5 and 8 weeks of age. These were considered to be true umbilical hernias in that a hernial sac with contents was palpable in addition to the abdominal wall defect. The group included both foals with or without a palpable abnormality at birth. In a study of hospitalized foals it was concluded that the defect was more likely to occur in fillies than males and that the condition was more common in Thoroughbreds than Standardbreds.[70] Most clinicians recommend delay in treatment, as some defects will close spontaneously. Several techniques have been described for repair and vary from external clamps to surgical herniorrhaphy. Rarely, complications associated with umbilical hernias or their repair occur. These include colic, enterocutaneous fistulae, umbilical abscessation, and intestinal incarceration.[71]

Ultrasound Examination of Umbilical and Related Structures

The examination can be performed with the foal either standing or in lateral

recumbency using a mid- to high-frequency linear transducer. The preferred probe is a high-frequency (10 to 14 MHz) linear transducer, although diagnostic scans can be performed with a 5- to 7.5-MHz linear rectal probe. Dorsal recumbency affords the best access, but care should be taken as this positioning has an adverse effect on ventilation. Clipping is helpful but not necessary, and most examinations are adequately performed using alcohol with or without coupling gel. Images are obtained in the transverse (short-axis) plane with the probe orientated perpendicular to the vertebral column and in a long-axis (sagittal) plane with the probe parallel to the spine. The external umbilical stump can be assessed for size and echodensity; there are no published normal dimensions for size of the stump (Fig. 16.5). The umbilical vein runs cranially from the umbilical stump to the liver. It is located 1 to 2 cm deep to the skin and is a thin-walled ovoid structure that is 5 to 10 mm in maximal diameter (Fig. 16.6).[72] The paired umbilical arteries originate from the internal iliac arteries and run adjacent to the urinary bladder and urachus before emerging at the umbilical stump. The arteries atrophy postpartum and become the round ligaments of the bladder. They appear as thick-walled hyperechoic structures, which should measure less than 13 mm in diameter (Fig. 16.7).[72] Asymmetry in size is common, and there may be an echogenic core if filled with clot (Fig. 16.8). Pulsation may also be noted in very young foals. The urachus connects the apex of the bladder to the umbilical stump. It can be difficult to image unless it is fluid filled, as would occur during patency. At the level of the bladder apex the combined diameter of the urachus and arteries in transverse view should be less than 25 mm. The bladder wall should be examined for defects because a full appearance to the bladder does not preclude a leak (Fig. 16.9).

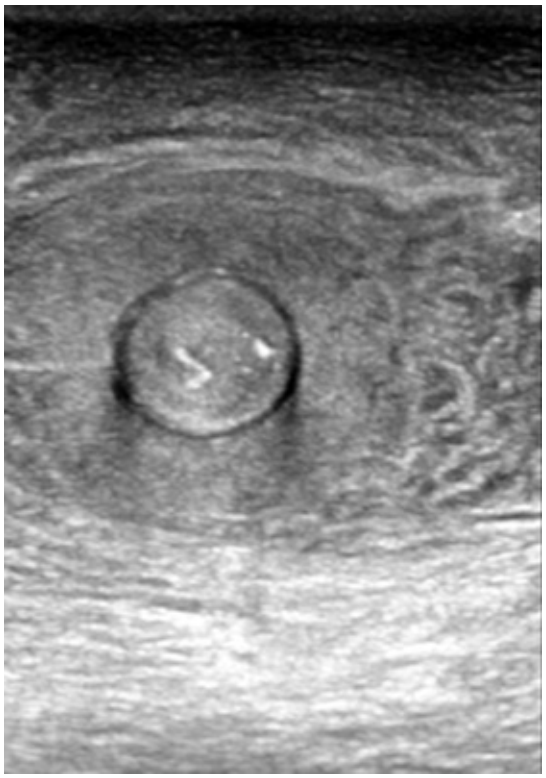


FIG. 16.5 An ultrasound image of an enlarged umbilical stump external to the body wall. The entire stump was 34 × 43 mm. Note the central core surrounded by thickened tissue.

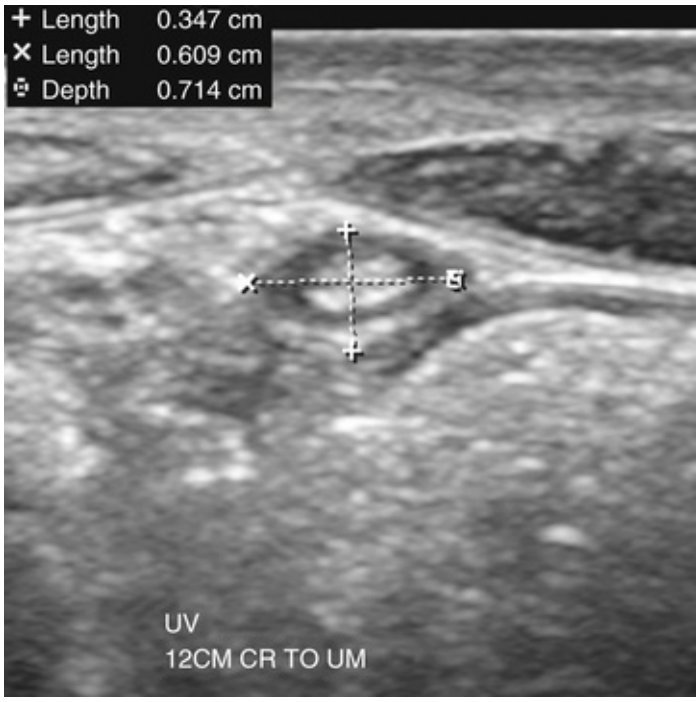


FIG. 16.6 A normal umbilical vein imaged transversely 12 cm cranial to the umbilicus.



FIG. 16.7 A transverse image taken 2 cm caudal to the umbilicus showing the normal paired umbilical arteries and the apex of the bladder. The

arteries measured 4.2 and 4.7 mm in diameter.



FIG. 16.8 A transverse image demonstrating asymmetry in size and echodensity between the two umbilical arteries. Both were considered normal, and the combined measurement was within normal limits.

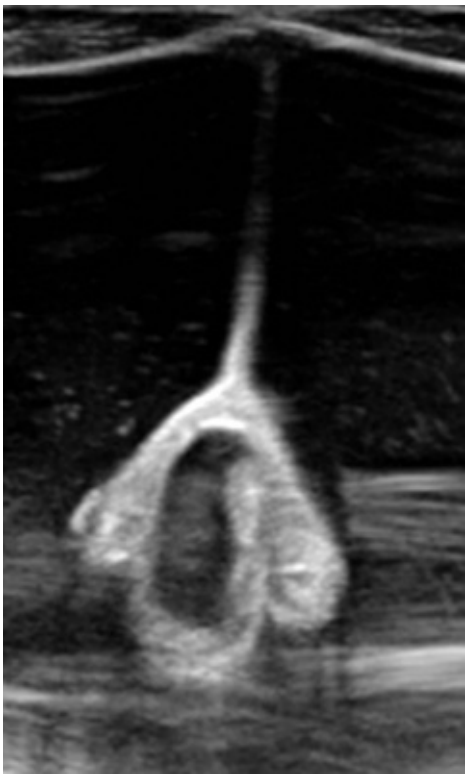


FIG. 16.9 A collapsed bladder attached to the body wall with a large-volume effusion consistent with uroperitoneum. The arteries give the collapsed bladder a classical shape.

Neurologic System

Differentiation of primary neurologic disease from systemic illness can be difficult as many critically ill foals are somnolent, recumbent, and unable to suck. Neurologic examination of the neonatal foal has several features that are unique to animals of that age.[73] While a domed skull could be consistent with hydrocephalus, it is also a physical feature of immaturity. Furthermore, hydrocephalus and other congenital brain abnormalities may occur with a normal skull shape and size. Examination of the head should be done with the foal standing or in sternal recumbency. The eyes have a normal slight ventromedial rotation in young foals. As described earlier, pupillary light responses are present but sluggish and the menace response is typically absent in the first week of life, although the foal should withdraw its head in response to a threatening gesture. Further assessment of vision can be through observations of behavior and navigation through obstacles.

The ability to suck and swallow milk should be evaluated. The suckle reflex

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should be evaluated using a clean and preferably gloved finger. Dysphagia can be recognized by nasal regurgitation of milk or milk coming out of the mouth. Although a cleft in the palate should be an important rule-out, it occurs less commonly than pharyngeal/laryngeal weakness and incoordination due to neonatal encephalopathy or systemic weakness. Dysphagia commonly resolves spontaneously but may take days to weeks.[74] Uncommon causes include persistent dorsal displacement of the soft palate, subepiglottic cyst, esophageal disease, or nutritional myodegeneration. Esophageal diseases are rare in the newborn foal. Reported conditions include congenital dilatation or ectasia, tubular or cystic esophageal duplication, megaesophagus, motor dysfunction, and stricture. Most descriptions are in foals outside of the neonatal period. Aspiration of milk into the airway may be difficult to identify due to immaturity of cough receptors; auscultation over the trachea after nursing may identify fluid sounds.

Limb reflexes can be evaluated with the foal loosely restrained in lateral recumbency. Spinal reflexes, such as the patellar, sciatic, and cranial tibial reflexes, are hyperactive in the newborn foal and therefore easily elicited. The neonatal foal can have strong thoracic and pelvic limb crossed extensor reflexes, where a stimulus to the distal limb causes flexion (withdrawal) of the affected limb and extension in the contralateral limb. This reflex is typically only seen in adults with severe or chronic upper motor neuron lesions.[75] The painful stimulus should also be recognized centrally.

The gait should be evaluated for evidence of paresis or ataxia. The normal gait is hypermetric and bouncy but should be precise and symmetric and be free of circumduction and toe-dragging.[73] Generalized hypotonia is seen with hypoxic-ischemic syndrome, sepsis, prematurity, botulism, white muscle disease, or heritable muscle disorders. A “bunny hopping” gait could be suggestive of a myelodysplasia, and examination of the anus, tail, and perineum is indicated. Peripheral nerve damage can occur with birthing trauma, particularly brachial plexus or radial nerve injury from forelimb traction. Affected limbs are weak, are hyporeflexic, and may have regions of anesthesia.

Seizures can vary from localized or partial to generalized. As described earlier, normal foals in REM sleep can be active, including galloping actions, neck extension, and vocalization. These can last for several minutes and be confused with seizures. Narcolepsy/cataplexy should be suspected in foals that collapse, remain laterally recumbent for several minutes in a sleep state, and then recover uneventfully. The condition has been reported in American Miniature

Horses, Morgans, Shetlands, and Suffolks.[73] It is possible to induce collapse and flaccidity by applying pressure to the thorax in normal newborn foals. The response is referred to as squeeze-induced somnolence.[76] There is a decrease in respiratory and heart rate and activation of the hypothalamic-pituitary-adrenal axis. The response was originally thought to be a form of narcolepsy or cataplexy, but electroencephalogram data in a small number of foals was not consistent with REM sleep, a feature of true narcolepsy.[76] An exaggerated head nod, a base wide stance with truncal sway, and dysmetric gait without weakness may indicate cerebellar dysfunction. The most common cause would be cerebellar abiotrophy, an inherited condition of Arabian horses and Gotland ponies.

Cerebrospinal Fluid Collection

Samples of cerebrospinal fluid (CSF) can be obtained from the atlanto-occipital (AO) or lumbosacral (LS) sites. The procedure is helpful in differentiating neonatal encephalopathy from bacterial meningitis. An AO CSF tap is a relatively straightforward procedure (Fig. 16.10). In comatose or profoundly somnolent foals, an AO tap can be performed using diazepam (0.05 to 0.2 mg/kg IV), local anesthesia, and adequate restraint. In more active foals general anesthesia should be used. In most neonatal foals the tap can be performed using a 3.8-cm, 18- to 20-ga hypodermic needle; in larger foals (>55 kg) a styletted spinal needle will be required. The needle is inserted at the intersection of a line drawn from the anterior wings of the atlas and midline. The poll is flexed tightly, and the needle is directed to the mandible. Alternatively, CSF can be collected from the lumbosacral (LS) site in the standing foal or in foals that are laterally recumbent without the need for general anesthesia. The landmarks for LS are the cranial borders of the tuber sacrale. A 3.5-inch styletted needle is inserted on midline approximately 5 mm cranial to a line intersecting the borders of the tuber sacrale after local anesthesia and a stab incision with a No. 15 blade. The sample should be analyzed within 30 minutes because of rapid cell degeneration. Normal CSF has 1 to 5 cells/μL with cells restricted to monocytes and lymphocytes. There should not be any neutrophils in normal foal CSF. Yellow discoloration (xanthochromia) and slight turbidity of the sample can be normal. Similarly, CSF protein concentration can be elevated in foals during the first 2 days of life.[77]



FIG. 16.10 Collection of cerebrospinal fluid at the atlanto-occipital site using a hypodermic needle.

Musculoskeletal System

The hoof wall of the newborn foal is covered by soft horn, or perionychium, a protective layer that is rapidly worn away when the foal begins to ambulate.[78] The coronary bands should be examined for hyperemia, an early indicator of systemic sepsis. Changes in hoof capsule temperature could also indicate regional or generalized perfusion problems. The limbs should be assessed for flexural laxity or contracture (Fig. 16.11). Mild to moderate limb contraction can make it difficult for the foal to stand and ambulate. In response to pain, foals with contracted tendons may have elevated heart and respiratory rates, as well as diffuse muscular tremor. In severe cases the foal may not be capable of standing. Treatment involves a combination of analgesia, splinting, and intravenous oxytetracycline. Repeated dosing of oxytetracycline is discouraged due to the risk of renal complications.[79] Extensor tendon rupture is a complication of flexural contraction and is recognized by discrete soft fluctuant swelling on the lateral aspect of the carpus.[80] The condition is often mistaken as septic synovitis. Foals usually respond well to conservative management. Fetlock laxity is common and can often be managed using heel extensions taped to the foot.



FIG. 16.11 Bilateral carpal and fetlock contracture in a newborn foal.

As part of the physical examination, all peripheral joints and physes should be palpated for swelling, heat, pain, and edema. Although trauma is often implicated as the source of any lameness, infection should always be considered as the most likely cause until proven otherwise. Other problems that may be identified in the neonate include rupture of the gastrocnemius muscle (Fig. 16.12) or associated muscle and patellar luxation. Foals are unable to bear weight when there is complete rupture of gastrocnemius muscle and cannot stand when bilateral rupture occurs.[81]



FIG. 16.12 Rupture of the gastrocnemius muscle has a guarded to poor prognosis in foals.

Premature or dysmature foals have joint laxity and delayed ossification. Joint laxity can predispose affected foals to angular limb deformities. These are managed through a combination of hoof trimming, exercise restriction, and splinting. Delayed ossification is assessed using radiography, centering on the cuboidal bones of the tarsus and carpus. The management of delayed ossification is difficult, and collapse or crush of cuboidal bones can sometimes be unavoidable. Preventative strategies include restricted exercise and splinting.

Supplementation of foals with selenium is recommended for those born in known selenium-deficient regions where mares have not been supplemented during pregnancy. Severe rhabdomyolysis has been reported in newborn foals, usually associated with selenium deficiency.[82] Glycogen branching enzymes deficiency is an inherited cause of mortality in Quarter Horse foals.[83] Clinical signs are variable and include seizure, persistent recumbency, respiratory failure, and cardiovascular collapse. The generalized nature of the clinical signs would likely lead to a false diagnosis of other more common neonatal diseases.

Dermis

A short, silky hair coat is consistent with immaturity. Skin abrasions occur in foals with prolonged recumbency or as a consequence to seizures, colic, or frequent unsuccessful attempts to rise. Lesions are commonly seen on the elbows, around the eyes, or on other skeletal prominences. They usually begin as focal regions of moisture. A syndrome of ulcerative dermatitis with widespread crusting and erythema has been seen in foals with alloimmune thrombocytopenia.[84] Edema can form on the ventrum, axilla, perineum, and periorbital region with fluid overload and renal dysfunction. Swelling under the axilla can also result from cellulitis, trauma, or fractured ribs. Ventral swelling over or around the umbilicus can occur with tearing of the urachus and urine leakage into tissues (Fig. 16.13).



FIG. 16.13 Swelling around the umbilicus caused by tearing of the urachus within the tissues of the body wall.

Immunoglobulin G and Colostrum

There is an association between low serum immunoglobulin G (IgG) and morbidity and mortality, most commonly due to sepsis. Measurement of serum IgG should be made between 12 and 18 hours of age. A normal foal that has consumed adequate amounts of colostrum will have a serum IgG measurement substantially greater than 8 g/L (800 mg/dL). Failure of passive transfer is generally defined as a serum IgG less than 4 g/L (400 mg/dL); partial failure of passive transfer is used when the serum IgG is between 4 and 8 g/L. Foals that

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have been exposed to chronic in utero infection can be born with IgG concentrations greater than 8 g/L. Furthermore, septic foals may catabolize immunoglobulins, resulting in lower concentrations than originally assessed. Tetanus prophylaxis, in the form of antitoxin (1500 IU), should be administered to foals with untreated failure of passive transfer.

Good-quality colostrum is typically yellow and highly viscous, but physical properties alone do not result in significant differences in foal IgG levels at 24 hours of age.[85] There is a strong linear correlation between colostral specific gravity and IgG concentration.[86,87] A modified hydrometer, the Equine Colostrometer (Jorgensen Laboratories, Colo.) is used to estimate the specific gravity of equine colostrum. It is important to accurately add the recommended volume of colostrum to the chamber. The temperature of the distilled water will also influence the final reading, and corrective tables are available. Handheld refractometers that measure sugar or alcohol content are also suitable for assessing colostral quality. The test can be performed rapidly by placing a single drop of mixed colostrum onto the glass prism of the refractometer. Values greater than or equal to 16 on the alcohol scale, or 23% on the BRIX sugar scale, correspond to a colostral IgG content greater than or equal to 60 gm/L.[85,88] The following guidelines have been recommended for evaluating BRIX readings: (1) 0% to 15% BRIX, 0 to 28 gm/L IgG, poor quality; (2) 15% to 20% BRIX, 28 to 50 gm/L IgG, borderline quality; (3) 20% to 30% BRIX, 50 to 80 gm/L IgG, adequate quality; and (4) greater than 30% BRIX, greater than 80 gm/L IgG, very good quality.[88]

A minimum dose of 60 to 90 gm/L of IgG has been recommended in the first 6 hours after birth.[89] This represents 1 to 1.5 L of good-quality colostrum, as defined by an IgG content of greater than 60 gm/L. Foals that received a minimum of 1.0 to 1.25 gm/L IgG/kg body weight within this time period should achieve a serum IgG above 8 gm/L.[90] The total IgG content in mammary secretions is highly variable but was reported to be 183 ± 58 gm/L (range 112 to 336 gm/L), equating to a mean volume of colostrum of 2.3 ± 0.5 L.[90] The specific gravity declines to below 1.040 by an average of 7 hours after parturition, reflecting a reduction in IgG concentration from a mean of 113 gm/L to 35 gm/L. Several factors influence colostral quality. Mares that are stressed or ill are less likely to produce good-quality colostrum, as are animals with adrenal hyperplasia secondary to pituitary dysfunction or those receiving exogenous glucocorticoids. Aged mares, particularly those older than 15 years of age, tend

to produce colostrum with a lower IgG concentration.[89]

Laboratory Data

Hematology and biochemistry can provide a critical insight in identifying foals at risk of developing clinical disease, in assessing the magnitude of clinical problems, and in monitoring response to treatment. Normal hematology, biochemical, and electrolyte data are reported in Tables 16.3 and 16.4. Foals that have been exposed to an abnormal in utero environment will frequently have abnormalities on routine blood work that can predict future clinical problems. Several important variations to adult values must be considered when interpreting laboratory data. In addition, there are some differences between horse foals and donkey foals and readers are directed to an appropriate reference.[91]

TABLE 16.3

Normal Hematology Reference Values for Neonatal Foals

	Gestational Age (Premature Foals)			Postnatal Age (Term Foals)	
Parameter	**300-309 Days Mean**	**310-319 Days Mean**	**320-334 Days Mean**	**1 Day Mean ± SD**	**2-7 Days Mean ± SD**
RBC (×10⁶/μL)	9.6	10.1	11.3	10.5 ± 1	9.26 ± 0.8
Hb (g/dL)	13.1	14.1	13.2	14.4 ± 1.1	13.2 ± 1.2
PCV (%)	41	42	43	42.0 ± 3.6	36.5 ± 3.1
MCV (fl)	42.7	42.2	38.6	40.2 ± 3.6	39.4 ± 2.3
MCH (pg)	14	14.4	11.8	13.6 ± 1.1	14.5 ± 1.1
MCHC (%)	32.4	33.8	30.5	33.8 ± 2	36.2 ± 1.1
Icterus index (u)				40.0 ± 15	30.3 ± 15
Total plasma protein (g/dL)				6.1 ± 0.8	6.4 ± 0.6
Fibrinogen (mg/dL)				243 ± 74	310 ± 90
Total WBC/μL	5000	6800	4900	8632 ± 2570	9075 ± 2200
Neutrophils/μL	1230	1540	1940	6381 ± 2225	6528 ± 2000
Bands/μL			2960	<50	>50
Lymphocytes/μL	3720	5090		2021 ± 2225	2203 ± 575
Monocytes/μL				222 ± 160	305 ± 145
Eosinophils/μL				0	22
Basophils/μL				8	17
Neutrophil-to-lymph ratio	0.33	0.3	0.66	3.16	2.96

Hb, Hemoglobin; *MCH,* mean corpuscular hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean corpuscular volume; *PCV,* packed cell volume; *RBC,* red blood cell; *SD,* standard deviation; *WBC,* white blood cell.

TABLE 16.4

Normal Serum Biochemical Reference Values for Normal-Term Postnursing Foals

	Age	
Parameter	**1 Day Mean ± SD**	**4-7 Days Mean ± SD**
Sodium (mEq/L)	139.7 ± 6	139.5 ± 4.2
Potassium (mEq/L)	4.4 ± 0.9	4.5 ± 0.4
Chloride (mEq/L)	103.5 ± 3	101.3 ± 4
Bicarbonate (mEq/L)	22.9 ± 3.4	34.3 ± 2.1
Calcium (mg/dL)	11.7 ± 1.1	11.4 ± 0.8
Inorganic phosphorus (mg/dL)	5 ± 0.85	6.4 ± 0.8
Magnesium (mg/dL)	2.2 ± 0.35	2.7 ± 0.15
Glucose (mg/dL)	136 ± 40	150 ± 30
BUN (mg/dL)	18.9 ± 4.3	13.6 ± 536
Creatinine (mg/dL)	2.3 ± 0.6	1.3 ± 0.3
Total bilirubin (mg/dL)	4.3 ± 2.2	4.4 ± 1.1
Direct bilirubin (mg/dL)	0.5 ± 0.2	0.8 ± 0.4
Indirect bilirubin (mf/dL)	3.8 ± 1.5	3.5 ± 1.1
Alkaline phosphatase (IU/L)	2282 ± 1100	1949 ± 1100
GGT (IU/L)	29.6 ± 15	18.3 ± 7.3
SDH (IU/L)	2 ± 0.9	2 ± 0.9
AST (SGOT) (IU/L)	154 ± 55	225 ± 60
LDH (IU/L)	487 ± 100	490 ±100

AST, Aspartate aminotransferase (SGOT); *BUN,* blood urea nitrogen; *GGT,* γ-glutamyltransferase; *LDH,* lactate dehydrogenase; *SD,* standard deviation; *SDH,* sorbitol dehydrogenase.

White Blood Cell Count and Differential

The total white blood cell (WBC) count at birth is similar to that in adult horses, but the proportion of neutrophils and lymphocytes is more variable. An elevated count at birth reflects a fetal response to placental infection with or without infection of the foal. Premature or dysmature foals with incomplete adrenal maturation will have low total white cell and neutrophil counts and a neutrophil-to-lymphocyte ratio that is characteristically less than 1 : 1.[92] It is important to determine if sepsis is present as neutropenia is also a common feature of this condition. Evidence of shifting toward immature cell types, and neutrophil toxicity should indicate primary sepsis or prematurity/dysmaturity complicated by sepsis. Premature foals that fail to improve their total white blood cell and neutrophil counts over the initial 24 to 48 hours of treatment have an even poorer prognosis for survival. Persistent decreases in lymphocyte counts (<1000/μL) in Arabian foals could be consistent with severe combined immunodeficiency.

Alloimmune neonatal neutropenia has been reported in foals and can persist for 2 to 4 weeks after ingestion of colostrum.[93] Affected foals are often outwardly normal but are considered to be at risk for sepsis and are therefore managed with prophylactic antibiotics.

Red Blood Cells and Platelets

The packed cell volume (PCV) at birth is 40% to 52% but decreases to 32% to 46% after colostrum and milk intake by 24 hours of age.[94] Increases in PCV can reflect dehydration, whereas decreases can be caused by blood loss, either internal or external, hemolysis, DIC, or prematurity. Platelet numbers are unaffected by age, but decreases are seen with alloimmune thrombocytopenia, DIC, and viral infection (equine herpesvirus−1, equine viral arteritis).

Plasma Protein and Acute Phase Proteins

Plasma or serum protein concentrations are low at birth but increase with globulin ingestion from colostrum. The albumin concentration should remain constant.[40] Plasma protein levels are 40 to 60 gm/L at birth and increase to 50 to 80 gm/L at 24 hours of age.[94] Levels increase with dehydration and chronic infectious processes and are decreased with whole blood loss, gastrointestinal disease, renal disease, or failure of passive transfer.

Fibrinogen concentrations are relatively low in newborn foals (2.16 ± 0.72 gm/L <12 hours of age; 3.10 ± 0.74 gm/L at 3 days of age), before increasing to a maximum at around 5 months of age (4.97 ± 0.91 gm/L), and then reducing to adult levels.[95] Hyperfibrinogenemia at birth is indicative of in utero sepsis and inflammation. Serum amyloid A (SAA) as determined by latex agglutination immunoturbidimetric assay in normal foals yielded median values of 0.9, 4.0, and 2.5 mg/L for days 1, 2, and 3, respectively.[96] These were contrasted against median values of 279.9, 195, 5.1, and 3.1 mg/L for systemic sepsis, localized sepsis, failure of passive transfer, and neonatal isoerythrolysis cases, respectively. The authors concluded that values greater than 100 mg/L were suggestive of local or systemic sepsis in young foals.

Glucose

Blood glucose concentrations are relatively low in newborn foals but increase

after nursing. Baseline values are typically 50% of maternal values at birth and reach a low approximately 2 hours after birth.[40] Many diseases of foals can directly or indirectly affect blood glucose concentrations, but the change in glucose can be difficult to predict. Hypoglycemia commonly occurs in foals with decreased milk intake. Conditions that may be associated with increased metabolic demands, such as systemic inflammatory response syndrome (SIRS) and sepsis or reduced gluconeogenesis, can contribute to hypoglycemic states. Gluconeogenesis is also impacted by SIRS and sepsis, as well as prematurity or in utero stress. Hyperglycemia is a consequence of overzealous glucose supplementation or can occur in conditions with slow or reduced insulin responses, insulin resistance, or with inappropriate sustained gluconeogenesis. This can occur in foals with hypoxic-ischemic syndrome (HIS), SIRS, sepsis, and prematurity.

Blood L-lactate Concentration

Lactate levels reflect peripheral perfusion and tissue oxygenation. Increased concentrations are expected after hemorrhage, in foals with systemic sepsis, neonatal isoerythrolysis, or HIS. Increases can also occur in hypermetabolic states where oxygen demand is increased; examples include seizures, increased muscle activity, and shivering. Lactate is cleared by the liver and kidney, and therefore decreased perfusion to those organs can contribute to increased systemic values. Reference ranges will vary slightly with different analyzers, but normal values should be less than 2.5 mmol/L in horse and donkey foals 24 to 48 hours of age or older.[50,97–99] Values during the first 24 hours after birth in normal foals are higher. The venous lactate concentration 20 to 140 minutes after birth (2.38 ± 1.03 mmol/L) was greater than at 24 hours (1.24 ± 0.27 mmol/L) in a small group of normal foals.[100] A second study reported mean values at birth, 12, 24, 36, and 48 hours of 3.8, 2.8, 2.1, 2.0, and 1.7 mmol/L, respectively.[98] There is a suggestion that lactate values in “healthy” premature or dysmature foals may be higher than in term foals.[101] Lactate concentrations at admission are correlated with outcome; foals with a value ≥5 mmol/L were 5.63 times more likely to die than foals with a value <5 mmol/L.[98] When the cutoff value was set at 7.94 mmol/L, the odds of nonsurvival increased to 15.98. Other studies have identified lactate concentration cutoff points of 4.4, 5.5, and 6.9 mmol/L to predict survival.[101–103] As important as the initial concentration is the change in

lactate concentration in response to treatment.[98,101] In nonsurviving foals elevated lactate levels typically persist beyond 24 hours of hospitalization. Samples should be analyzed within 10 minutes of collection, as erythrocytes can continue to produce lactate in lithium heparin tubes stored at room temperature.[104] If sampling is delayed, then samples should be collected into sodium fluoride-potassium oxalate and stored at 0° C to 4° C. In some point-of-care analyzers a high hematocrit can interfere with lactate measurement.[104] Anion gap can be used to approximate lactate, although direct measurement is preferred.

Creatinine and Blood Urea Nitrogen

Concentrations of both creatinine and blood urea nitrogen (BUN) can be elevated due to prerenal, renal, and postrenal causes. Marked elevation in creatinine concentration in newborn foals typically reflects problems with the fetoplacental unit; these foals are at risk of postnatal complications due to in utero compromise. Serum creatinine concentration is higher in foals with grossly abnormal placentas and in foals with a clinical diagnosis of perinatal asphyxia syndrome (PAS).[105] Assuming normal renal function, these elevated values should halve within 24 hours and approach normal levels by 72 hours. Failure to drop or a delay in decrease should suggest concurrent renal disease or other causes of azotemia. BUN is not typically elevated in cases of placental dysfunction. It can increase in conditions of increased catabolism.

Bilirubin, Hepatobiliary Enzymes, and Bile Acids

Relative to adult horses, newborn foals have increased total bilirubin concentrations that are attributable to the unconjugated component. The basis of the discrepancy is not known but could relate to accelerated breakdown of fetal and neonatal red blood cells or decreased uptake and conjugation of bilirubin. Concentrations peak shortly after birth before declining to adult levels by 2 weeks of age.[106] Increases in bilirubin above normal are seen with hemolytic conditions, such as neonatal isoerythrolysis, primary liver disease (including equine herpesvirus-1 infection, Tyzzer's disease, and cholangiohepatitis), sepsis, meconium impaction, and after internal hemorrhage or blood transfusion. Large increases in bilirubin can lead to the neurologic complication of kernicterus.

Gamma glutamyl transferase is normal at birth but increases between 5 and 14

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days of age before decreasing to adult levels by 4 weeks of age. The increase is thought to be due to hepatic enzyme induction associated with normal maturation. The hepatocellular enzyme, sorbitol dehydrogenase, is not affected by age. Glutamate dehydrogenase concentration has not been well described in healthy newborn foals. These enzymes are increased in a range of conditions, particularly sepsis.[107]

The concentration of aspartate aminotransferase increases slightly after 7 days of age; an increase attributed to enhanced muscle activity rather than hepatobiliary changes. Serum alkaline phosphatase (ALP) concentrations are substantially increased over adult levels in the first few days of life, remaining elevated through the first week. The initial increases are attributed to intestinal activity, including the pinocytosis of maternal immunoglobulin, and to the osteoblastic activity in growing and adapting bones. Premature or dysmature foals with incomplete ossification will have ALP concentrations that are higher and persist for longer than levels in term foals.[40]

Serum bile acid concentrations are also greater in foals during the first 6 weeks and are 6 to 7 times greater than adults during the first 2 days of life.[108] Increased concentrations of bilirubin or triglycerides or hemolysis may interfere with serum bile acid measurement under certain methodologies. Serum cholesterol is also elevated during the first 2 weeks of life.

Trigylcerides

Triglycerides increase from birth to the first day of life, peaking early in the first week, and then gradually declining to adult levels by 3 months of age.[106,109] Increases in lipids, reflected through serum hypertriglyceridemia, are commonly reported in sepsis in foals, presumably secondary to altered fat metabolism.[110,111] Serum triglyceride concentrations are higher in foals with positive blood cultures and higher in nonsurviving foals (survivors: 116 mg/dL median [41 to 379, range] versus nonsurvivors: 55 mg/dL, median [10 to 311, range]).[109]

Electrolytes

As with adult horses, serum electrolyte concentrations in foals are maintained within a relatively narrow range. Disruption of the urinary tract or primary renal disease classically produces a hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, and hyperkalemia. Many of these changes reflect the

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electrolyte intake associated with a milk diet and are less likely to occur when foals have received intravenous fluid therapy. Rhabdomyolysis due to selenium deficiency can cause a similar electrolyte profile to that of uroperitoneum in milk-fed foals.[82] Although both conditions may be associated with increases in creatinine and BUN, concurrent and substantial increases in creatine kinase and aspartate aminotransferase are expected with rhabdomyolysis.

Hyponatremia, hypochloremia, and hypokalemia are commonly seen with diarrheal disease in foals. Severe hyponatremia is more commonly seen in older foals with diarrhea that are allowed to replenish fluid losses by consumption of plain water. Hyponatremia is also a feature of renal disease, but hypernatremia can occur when affected foals are treated with relatively high volumes of sodium-rich intravenous fluids in the face of inadequate urine output.

Elevated total and ionized calcium concentration can be present in foals born to mares with marked placentitis.[40] Clinical hypocalcemia results in signs of tachycardia, sweating, tremor, muscular rigidity, and a stiff gait or recumbency. The syndrome is rare, but euthanasia is common due to failure to respond to calcium supplementation.[112] Parathyroid hormone concentrations may be elevated, decreased, or normal, suggesting differing syndromes.

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• CHAPTER 17

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Manifestations and Management of Disease in Neonatal Foals

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FOAL DISORDERS

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General Principles of Treatment and Care of the Abnormal Foal

Guy D. Lester • Jane E. Axon

Frequent monitoring of the ill newborn foal is essential, as early recognition of subtle clinical changes can have a significant impact on outcome. This includes observations of behavior and repeated structured physical examinations. Assessment of the foal is described in Chapter 16. It is important that the clinician develops a routine method of examination that is consistently followed, irrespective of the perceived level of illness. This ensures that the assessment is complete and no abnormalities are missed. Delivering detailed and potentially expensive therapy to a foal with a significant congenital defect is potentially avoided by adopting this approach.

By the time that many sick newborn foals are examined by veterinarians, they are critically ill and require emergency therapy to restore circulation, tissue perfusion, and oxygenation. This approach is conserved across many diseases. After fluid resuscitation there can be an investigation into underlying diseases, and directed therapy can be instituted.

Catheter Selection and Placement

If high-volume fluid resuscitation is anticipated, then a large-bore (14- or 16-gauge) catheter should be placed into the jugular vein. Identification of the vein can be facilitated by elevation of the hindquarters in lateral recumbency and by placing a rolled towel under the neck. Teflon catheters (Abbocath, Abbott Hospitals, North Chicago, Ill.) are more thrombogenic than Silastic or polyurethane catheters but are usually easier and quicker to place. Short catheters placed in peripheral veins can be difficult to maintain and are not suitable for large-volume, rapid fluid replacement. Most referral hospitals use polyurethane catheters as they reduce the incidence of thrombophlebitis and eliminate the need for frequent catheter replacement. Using strict aseptic technique, the catheter is typically inserted using the “over-the-wire” (Seldinger) technique. Once positioned, the catheters can often be left in place for up to 3 weeks. A combination of superglue and sutures are effective in keeping the catheters in place. Catheter sites are covered but monitored frequently for signs

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of infection. Insertion site swelling is not uncommon for 24 hours after placement of some catheters. Blood samples for culture, hematology, and biochemistry can be collected at the time of catheter placement if the condition of the foal is not highly critical.

Fluid Resuscitation

After placement of an intravenous catheter, warmed fluid can be delivered at a rate of 20 mL/kg over 15 to 20 minutes.[1,2] Typically the initial fluid of choice is a multielectrolyte replacement solution, such as lactated Ringer's solution (LRS) or Hartmann's solution. After the initial or subsequent fluid boluses, the patient is reassessed, specifically noting changes in mucous membrane color, capillary refill time, pulse quality and rate, mentation, warmth of peripheral tissues, intestinal sounds, and urine production.[3] If there is minimal or no improvement, then the bolus can be repeated a further three times, to a maximum of 80 mL/kg, or 4 L for a 50-kg foal. During this time, essential laboratory data can be collected, including the packed cell volume, total plasma protein (TPP), and blood glucose concentration. Ideally, an arterial or venous sample is obtained for blood gas, electrolyte, and lactate determination. Factors that influence the rate or total volume of fluid used during resuscitation include a low TPP concentration (<35 gm/L); preexisting limb, body, or head edema; or spontaneous hemorrhage.

Colloids are indicated in low-protein states. Plasma is the most commonly used colloid in foal practice but is expensive and requires thawing and the use of an in-line filter. However, the benefits of fresh or fresh frozen plasma are numerous, including improvement of osmotic pressure, provision of coagulation factors, to provide buffer base, and immunotherapy.[2] The administration of plasma has been associated with anaphylactic or anaphylactoid reactions, which can be fatal. It is for this reason that plasma is not routinely used for acute fluid resuscitation. Plasma should be administered at an average rate of 10 mL/kg/h. Give the first 100 mL slowly and monitor the foal's pulse, respiratory rate, and temperature. Synthetic colloids are less expensive and do not require special storage conditions or use of a special filter, but they do not have the range of benefits of plasma. The use of synthetic colloids in foals has been questioned.[1–3] Hydroxyethyl starch (hetastarch) has, however, been used successfully for rapid fluid resuscitation in foals with few adverse reactions (3 mL/kg at a rate of 10 mL/kg/h).[4]

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Correction of Dehydration

Once critical hypovolemia has been rectified, assessment can be made of residual dehydration.[3] Foals have a relatively greater proportion of extracellular fluid when compared with adults[5] and, in contrast to adults, can appear thin or emaciated when dehydrated. Traditional clinical parameters used to assess hydration in adult horses, such as moisture of oral mucous and skin tenting, are less reliable when used in foals. The volume of fluid is, however, calculated in a manner similar to that used in adults. A foal with moderately to severely sunken eyes is estimated to be 8% to 10% (of body weight) dehydrated. The estimated fluid deficit in a 40-kg animal that is 10% dehydrated would be approximately 4 L. The calculated deficit should be replaced over the following 12 hours, along with consideration of maintenance fluid requirements and any ongoing losses.

If an animal is mildly dehydrated and the gastrointestinal tract is not seriously compromised, fluid requirements can be provided by the enteral route, using milk or commercially available dextrose and electrolyte mixtures.

Maintenance Fluid Therapy

When using intravenous fluid therapy for maintenance of hydration, the Holliday-Segar formula has been advocated for calculation of fluid delivery rates in foals with impaired renal function, or in foals younger than 3 days of age where renal function is not known.[2,3] It employs a principle that slight fluid deprivation is less critical than overhydration, particularly when sodium-rich fluids are used. For the first 10 kg of body weight the foal receives 100 mL/kg/day; for 11 to 20 kg of body weight the foal receives 50 mL/kg/day; and for each kg over 20 kg the foal is assigned 25 mL/kg/day.[2] For a 50-kg foal this is calculated as 1000 mL/day for the first 10 kg, 500 mL/day for the second 10 kg, and 750 mL/day for the remaining 30 kg of body weight, for a total daily volume of 2250 mL or an hourly flow rate of 94 mL.[2] For older foals, or foals with normal renal function, higher flow rates can be used, typically in the range of 2 to 5 mL/kg/h.[3,6]

Use of Inopressor Drugs

If hypotension persists in the face of fluid resuscitation, inopressor therapy may be indicated. It has been recommended that the aim of therapy is to raise the mean arterial pressure (MAP) above 60 mm Hg, although this does not imply

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that tissue perfusion is adequate.[7] Agents that are commonly used include dobutamine, dopamine, norepinephrine, and vasopressin.[7] Dobutamine is a positive inotrope that improves cardiac output primarily by improving stroke volume. The drug is administered as a constant rate infusion (CRI) with a wide dose range of 3 to 20 µg/kg/min, but it is recommended to commence therapy at the low end of the range.[3] It is not common to administer a vasopressor with dobutamine to improve tissue perfusion. Norepinephrine acts at α_1- and α_2-receptors to mediate vasoconstriction, as well as acting at β_1-adrenergic receptors causing positive inotropic and cardiotropic effects.[7] The drug has a short half-life and is given by CRI at a highly variable dose range, from 0.05 to 5.0 µg/kg/min. Again, starting at the low end of the range is recommended.

Dopamine also has some combined α- and β-adrenergic effects, in addition to moderate to strong affinity for dopamine receptors (DA-1 and DA-2 receptors).[7] Activity at dopaminergic receptors primarily mediate vasodilation, particularly renal, cerebral, and splanchnic vascular beds. Lower infusion rates are used to improve renal and splanchnic perfusion (0.5 to 5 µg/kg/min), whereas higher infusion rates (10 to 25 µg/kg/min) will be required for patients in severe septic shock.

Vasopressin (0.25 to 1.0 mU/kg/min) acts at V1a receptors in the peripheral circulation causing vasoconstriction and at V2 receptors in the kidney to facilitate water reposition.[7] Low-dose vasopressin is commonly used in conjunction with norepinephrine infusion and is reported to be effective in the management of the hypotensive neonatal foal. Beneficial effects included an increase in MAP, a reduction in heart rate, and increased urine output.[8]

Glucose Supplementation

The fluid rate is in part dictated by the need to provide glucose supplementation. A rate of 5 mg/kg/min has been suggested as an initial CRI flow rate on the basis of the estimated placental supply in late gestation (6.8 mg/kg/min).[3,9] This equates to an hourly flow rate of 3 mL/kg (150 mL/h for a 50-kg foal) of a 10% glucose solution. Blood glucose concentrations should be monitored closely and the rate adjusted as required. Boluses of glucose solutions should be avoided as the resultant glucosuria will result in urinary losses of fluid, electrolytes, and glucose. It can produce a marked rebound hypoglycemia.

Electrolyte Management

In most foals, electrolyte concentrations will normalize over time, assuming adequate renal function and milk intake. However, there are several conditions where specific electrolyte supplementation or avoidance is important. Foals with uroperitoneum can develop life-threatening hyperkalemia. Specific management is discussed elsewhere in this chapter, but fluid therapy is typically based on 0.9% saline supplemented with glucose. Potassium supplementation may be required for critically sick neonates, anorexic foals, foals with diarrhea, or those receiving diuretic therapy. If serum concentrations fall below 2.5 mEq/L, intravenous supplementation is recommended. Potassium requirements are difficult to estimate from serum concentrations, but the following equation has been recommended:

$$\text{Replacement K (mEq)} = 0.4 \times \text{Body weight (kg)} \times \text{K deficit (mEq)}$$

Potassium can safely be added to fluids at a rate of 10 to 40 mEq/L, although when delivering fluids at a maintenance rate using the Holliday-Segar formula, concentrations up to 60 mEq/L may be used.[2] At higher concentrations it is important not to exceed recommended rates of administration. Potassium supplementation should not exceed 0.5 mEq/kg/h, or 25 mEq/h for a 50-kg foal.

Sodium overload is a problem associated with prolonged use of salt-rich replacement solutions.[2] The problem is avoided by using specially formulated low-sodium, high-potassium replacement solutions that are supplemented with glucose, or using 5% dextrose in water as the base solution for fluid therapy. The principles of hyponatremia or hypernatremia treatment are discussed in Chapter 32).

Sodium bicarbonate is commonly given to foals that are acidemic, assuming that that it is metabolic in origin. The initial approach to management should be rehydration and improvement in tissue perfusion. This is achieved using crystalloids, colloids, and inopressor agents. When bicarbonate is administered to foals where the acidosis has originated from poor tissue perfusion, the results are often disappointing. Bicarbonate supplementation is indicated in conditions where there has been loss of buffer, such as diarrhea or renal tubular acidosis. If bicarbonate deficits are greater than 10 mEq/L (serum $[HCO_3^-] < 15$ mEq/L)

after rehydration, then supplementation can be given using the following equation:

$$\text{Bicarbonate deficit (mEq)} = 0.6 \times \text{Body weight (kg)} \times \text{Base deficit (mEq)}$$

Isotonic bicarbonate can be made by adding 150 mL 8.4% bicarbonate solution to 850 mL sterile water, or 200 mL 5% bicarbonate solution to 800 mL of sterile water. Bicarbonate solutions should be given slowly. Bicarbonate solution should not be combined with any calcium-containing solution or precipitation will occur. The effect of the bicarbonate replacement therapy should be monitored closely and the dose adjusted accordingly. Neonates with severe diarrhea because of ongoing losses of bicarbonate through the feces may need considerably more than the calculated deficit to maintain an adequate blood pH until the diarrhea subsides.

Plasma Transfusion for Failure of Passive Transfer of Immunoglobulin

Plasma is administered through an aseptically placed catheter using a blood administration set with an in-line filter. The rule of thumb for plasma administration for FPT is 20 mL/kg or approximately 1 L for a 45-kg foal. In healthy foals, 1 L of plasma with [IgG] of 1200 mg/dL (12 g/L) raises the serum IgG 200 to 250 mg/dL (2 to 2.5 g/L). For foals with total failure of passive transfer, it may be necessary to provide 2 or 3 L of commercial plasma if the goal is to reach a serum IgG concentration of 800 mg/dL (8 g/L). The same amount of plasma has less effect in septic foals. Ill foals require relatively more plasma because the serum half-life of IgG is less, IgG may be sequestered in intravascular spaces or at sites of inflammation, and IgG may catabolize more readily.

Maintenance of Body Temperature

The thermoneutral zone describes an ambient temperature range in which heat production and heat loss are at a minimum.[10] The lower level of the range (Tlc) defines a temperature cutoff, below which the metabolic rate rises and the rate of evaporative heat loss increases. For 2-day-old pony foals the Tlc was estimated

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to be 25º C,[10] a value much higher than the typical ambient temperature that many foals experience. However, healthy foals are able to maintain their core body temperature down to an ambient temperature of 5º C, but premature or sick newborn foals are often unable to maintain their body temperature and frequently require external heat sources during treatment. Foals on phenobarbital therapy are also susceptible to a reduction in body temperature.

It is critical to dry the foal and remove it from drafts to reduce convective heat loss. If the rectal temperature is less than 100º F (37.7º C), efforts should be made to warm the foal by raising the environmental temperature. Rewarming the periphery only with high external heat without simultaneously warming the body core can produce peripheral vasodilation and accentuate cardiovascular collapse. Warming can be achieved using forced air warmers (Bair Hugger, 3M), radiant heat lamps, applying blankets, or careful use of heating pads. A heat pack can be made by placing a wet towel inside two rectal sleeves and microwaved to the desired temperature. It is important to address hypotension using warmed fluid therapy.

Bedding and General Environment

It is important that the environment for housing the sick foal is clean. A temporary barrier between the mare and recumbent foal facilitates treatment of the foal yet keeps the dam within sight, sound, touch, and smell of her foal, which facilitates bonding. Many of these foals are recumbent, making them further vulnerable to contagious or opportunistic pathogens. Recumbency increases the risk of pneumonia, predisposes to ileus and constipation, increases the risk of milk aspiration, and exacerbates musculoskeletal weakness. Recumbent foals are also at risk for the development of decubital ulcers and should be bedded on a soft and absorbent surface. They should be carefully turned and assisted to stand every 2 hours. Placement into custom-made V-pads (Dandy Products, Goshen, Ohio) can help the foal rest in sternal recumbency, improving oxygenation and reducing the risk of lung atelectasis and secondary pneumonia (Fig. 17.1).



FIG. 17.1 Sternal recumbency is facilitated by use of a V-pad.

Special Considerations of Drug Therapy

Differences between neonatal and adult animals in drug effects generally can be attributed to differences in drug distribution, metabolism, or excretion. Some general characteristics of the neonatal period include better absorption of drugs from the gastrointestinal tract, less drug binding to plasma proteins, increased apparent volume of distribution of drugs that are distributed in the extracellular fluid volume, increased permeability of the blood-brain barrier, and slower elimination (i.e., longer half-life) of many drugs.[11]

Some of these responses are attributed to differences in body water between neonates and adult horses. Total body water (TBW) in day-old foals was 744 ± 24 mL/kg, compared with 670 ± 60 mL/kg in adult horses.[5,12] During growth, the intracellular fluid compartment remains relatively consistent relative to size, while the extracellular fluid (ECF) compartment decreases as a percentage of body weight, with an increasing body fat percentage. The ECF volume was estimated at 381 ± 18 and 394 ± 29 mL/kg, in 1- and 2-day-old foals, respectively.[5,13] This compares with reported values in adult horses of 214 to 253 mL/kg. Plasma volume is around 96 mL/kg in neonates, again much greater

on a per-kg body weight basis than reported values in adults, 53 to 63 mL/kg.[5] Although the neonate has a higher percentage of TBW than the adult, it is more vulnerable to water loss because of increased basal metabolic rate and relatively greater surface area (both predisposing to increased heat and water losses), as well as reduced urine concentrating ability.

Nutritional Support

Provision of adequate nutritional support to the compromised neonate is an essential component of critical care. Common reasons for not providing adequate nutrition include failure to estimate the nutritional requirements of the sick neonate, the need to use alternate methods and routes of delivery, and a gastrointestinal tract that is often compromised and intolerant of nutrient intake. The nutritional requirements for optimum growth of the normal-term foal are poorly defined, let alone for the premature, growth-retarded, or debilitated animal whose caloric, protein, mineral, and vitamin requirements might be very different.

Measurements of milk production of mares combined with data concerning the free-choice milk intake of normal orphan foals and premature and sick foals recovering from various illnesses suggest that a figure of 125 to 150 kcal/kg/day, or even higher, is close to the normal caloric intake.[14] Healthy full-term foals nurse an average of 2 minutes, seven times an hour, and consume between 20% and 30% of their body weight in milk daily, resulting in weight gain of 1.3 to 1.7 kg/day.[15–17] On this diet, a 50-kg foal would therefore consume 10 to 12.5 L of milk daily to provide 120 to 150 kcal/kg/day, 50% of which is used for growth and 50% for basal metabolism and thermoregulation. Factors that influence weight gain include caloric intake, the level of exercise, and the resting energy expenditure (RER). Weight gain is reduced in hospitalized newborn foals. RER is, however, less in ill foals, approximately 44 to 49.5 kcal/kg/day, compared with 65 kcal/kg/day in healthy foals.[18] The general recommendation is to provide a minimum of 50 kcal/kg/day and aim for a positive growth rate of 0.6 to 1.0 kg/day.

If there is no medical contraindication for oral feeding and the gastrointestinal tract is functional, then enteral nutrition is the preferred and most effective route of nutritional supplementation. Enteral feeding stimulates normal gut maturation, growth of intestinal villi, production of crypt cells, hepatic and biliary secretions, and brush border disaccharidase enzyme activity. Therefore, even in foals that

must be fed parenterally, small volumes of enteral feeds are given to prevent gut atrophy.

Foals that are not nursing from the mare can be fed by bottle, bucket, or nasogastric tube. If an effective swallow reflex is present, bottle-feeding can be used. Bucket feeding allows the foal to drink with its head and neck in a flexed position and is helpful for foals with a weak swallow reflex or foals destined to be hand raised. Milk should be introduced in a shallow handheld bowl and the foal encouraged to suckle the finger or nipple as its head is lowered into the milk. Foals younger than 7 days of age should ideally be fed every 1 to 2 hours. Nasogastric intubation is required if ineffectual swallowing and sucking are present. A styletted small-bore flexible silicone tube (5 to 7 mm internal diameter) with a weighted tungsten end is preferred. Individual choice dictates whether the tube is passed for each feeding or left indwelling. Indwelling tubes can be sutured to the nares using a Chinese finger-trap suture technique[19] or taped to half a tongue depressor, which is then taped to the foal's muzzle and/or fleece halter. Tubes should be sealed between feedings to prevent aerophagia. Recumbent foals should be maintained in sternal recumbency using a V-pad immediately after tube feeding to reduce the risk of gastroesophageal reflux and aspiration. If the dam is available and milk production is adequate, free-choice nursing is optimal. A nurse mare is the next best substitute. Popular enteral formulas include mare's milk, goat's milk, and artificial milk replacers. Goat's milk is acceptable and is higher in fat, total solids, and gross energy than mare's milk. Foals raised on goat's milk occasionally become constipated and can develop a mild metabolic alkalosis. Cow's milk is not as digestible and can cause diarrhea, but it can be used if additional sugar is added and some of the fat is removed. This can be accomplished by using 2% skim milk and adding 20 g of dextrose per liter of milk. A variety of artificial milk replacers are available. The ideal replacer should have approximately 22% crude protein, 15% fat, and less than 0.5% fiber on a dry matter basis. Calf milk replacer can be used if it is mixed with mare's milk. Complications associated with enteral feeding include colic, abdominal distention, diarrhea, constipation, flatulence, misplacement of the nasogastric tube, aerophagia, nasal and pharyngeal irritation from the tube, and aspiration pneumonia.

Parenteral nutrition (PN) is used to supply at least a portion of the daily nutritional requirements to critically ill foals. PN is indicated whenever feeding via the gut is inadequate or contraindicated. Candidates for partial or total PN include those individuals with diarrhea, postsurgical patients, foals with

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botulism, premature and septic animals, and other individuals with gastrointestinal tracts poorly tolerant of enteral feedings. PN involves administration of hypertonic solutions containing dextrose, amino acids, lipids, vitamins, electrolytes, and trace minerals. These PN solutions must be administered continuously through a jugular catheter. Complications include metabolic disturbances such as hyperglycemia/hypoglycemia, glucosuria/osmotic diuresis, insulin resistance, hypertriglyceridemia, azotemia, and imbalances of trace minerals, vitamins, and electrolytes.[20,21] Catheter-related problems include thrombosis, phlebitis, and sepsis. Commonly used stock solution for PN includes 50% dextrose, 8.5% or 10% amino acids, and 10% or 20% lipid emulsion. Various PN worksheets are available, some of which are complicated.[22]

A simplified formula for 50 kg that is well tolerated in most foals is 2.5 L of 8.5% amino acids, 1 L of 20% lipid, and 1.5 L of 50% dextrose added to an empty 5-L bag. This mixture contains 750 g dextrose, 212.5 g amino acids, and 200 g lipids, and it provides 2550 kcal from dextrose (3.4 kcal/g), 850 kcal from amino acids (4.0 kcal/g), and 2000 kcal from lipids/glycerol (10.0 kcal/g). The PN solution has 47% of total calories from glucose, 16% from protein, and 37% from fat. It is recommended that foals should not receive more than 50% of nonprotein calories from lipid. The solution can be run at 104 mL/h over 48 hours, providing approximately 54 kcal/kg/day. It is common to supplement the solution with multivitamin concentrate, trace minerals, and KCl (to a final concentration of 20 to 40 mEq/L). The PN solution is hypertonic (1233 mOsm/L), so it is common to run concurrently with low-tonicity solutions or free water.

Foals receiving PN should have their blood and urine glucose monitored. Serum glucose concentration should remain greater than 80 mg/dL (4.4 mmol/L) and less than 180 mg/dL (10 mmol/L). Serum should be checked for gross lipemia. Heparin can be administered at 10 units/kg as an IV bolus to treat lipemia. Foals must be weaned onto and off of PN slowly. All IV lines must be checked and changed routinely. Most commonly, parenteral and enteral nutrition has been used in combination; parenteral nutrient delivery is used to supplement, not totally replace, oral intake. Details concerning the use of parenteral nutrition compounds can be found in Chapter 50.

Weakness and/or Somnolence

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Numerous conditions in the newborn foal can produce a primary complaint of weakness and/or somnolence. The gestational and postnatal age of the neonate should be established. If weakness has been present since birth, in utero acquired bacterial or viral infections, birth asphyxia and trauma, chronic placental problems, and congenital anomalies should be placed higher on the list of differential diagnoses. Lethargy and loss of suckle are often the first signs of neonatal illness. A full udder on the dam accompanies poor nursing behavior in the neonate. If the neonate is depressed and has injected mucous membranes and hyperemic coronary bands, then sepsis is the primary differential and the most life threatening. If the neonate is relatively bright but is becoming progressively weaker, consider peripartum hypoxia and early signs of neonatal encephalopathy. If the newborn shows signs of physical immaturity such as tendon laxity and silky hair coat, then weakness may be due to fatigue, hypothermia, hypoxia, and/or hypoglycemia. Unfortunately, many weak foals begin to fade as a result of multiple problems. Glycogen branching enzyme deficiency in certain Quarter Horse and Paint lineages is an example of a genetic mutation that is associated with a range of abnormal signs that could include persistent recumbency.[23]

If weakness is present without accompanying somnolence, then several other differentials should be considered, including trauma. If weakness is detected in one or more limbs immediately after birth, peripheral nerve and muscle damage associated with vigorous extraction from the birth canal should be ruled out. Affected limbs are weak and hyporeflexic, and there may be regions of cutaneous anesthesia.[24] The diagnosis is based on history and neurologic assessment and confirmed using electrodiagnostics after 10 to 14 days.[25] The prognosis for recovery is dependent on the severity of the neural lesion. Where axon continuity is preserved, the outlook is generally good with resolution within days to weeks; where there has been disruption to axons or whole nerves, the outlook is guarded. Regrowth and reinnervation of muscle is possible; axonal regrowth is estimated at 1 inch per month.[25] Foals with rupture of the gastrocnemius muscle will be unable to rise or stand unsupported.[26] The treatment includes limb stabilization and exercise restriction, with a guarded prognosis for an athletic career.

Neuromuscular diseases causing weakness without somnolence include botulism, nutritional myodegeneration (NMD, white muscle disease), and congenital myopathies. Botulism is an infection acquired via the gastrointestinal

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tract or through wounds or the umbilicus. Consequently, signs appear in neonates that are typically 10 days or older. Most cases of NMD associated with selenium and/or vitamin E deficiency occur during the first year of life among rapidly growing large animals, but an in utero form of NMD may occur, resulting in clinical signs in affected foals soon after birth. Clinical signs associated with NMD may include localized signs (dysphagia) or generalized paresis. Rhabdomyolysis in foals may be precipitated by stress such as sepsis or excessive periparturient hypoxia. Affected foals are reluctant to move, paretic, and occasionally dysphagic.[27] Pelvic limb muscles are often palpably firm. Elevated serum creatinine kinase and electrolyte disturbances of hyponatremia and hyperkalemia may be observed.

It should be determined whether drugs or anesthetics were administered to the dam before or at the time of delivery, as many agents cross the placenta and exert depressive and other adverse effects on the fetus. Phenylbutazone administered to normal pregnant mares crosses the placenta and results in substantial concentrations of phenylbutazone and its active metabolite oxyphenbutazone in the foal. Although clinical signs of phenylbutazone toxicity are not noted in the foals postnatally,[28] adverse effects are possible, particularly if other problems are present. Neonatal depression induced by drugs is particularly important following cesarean section deliveries. Maternally administered anesthetics and analgesics can suppress respiration and heart rate in the newborn. In horses, both xylazine and detomidine cause maternal and fetal bradycardia and reduced cardiac output.[29,30] These effects will cause a reduction in placental perfusion and fetal oxygenation. If the newborn shows depression associated with maternal administration of these drugs, an α_2-adrenergic antagonist, such as yohimbine, can be given. Adverse reactions to adrenergic antagonists in adult horses have been reported, some of which were fatal.[31]

Weakly basic drugs, when given to the mare, tend to concentrate in the fetus. Diazepam is an example of such a drug that crosses the placenta rapidly and accumulates in the fetal circulation resulting in lethargy, hypotonia, and hypothermia in the neonate following delivery. Flumazenil has been used to reverse the sedative effects of benzodiazepines. Maternal systemic illness of various types may also result in a weak newborn.

Many neonatal disorders are associated with severe electrolyte and metabolic derangements that may clinically manifest as weakness, including hypoglycemia, acidosis, hyponatremia, hypernatremia, or hyperkalemia. Such

abnormalities may occur before or at the time of birth, and laboratory assessment of the weak newborn is essential for accurate diagnosis. Young foals with hypocalcemia can present with stiff gait, muscular tremor, tachycardia, sweating, muscular tremor, and recumbency.[32] Profound weakness associated with metabolic acidosis is commonly observed in foals with diarrhea. Correction of the acidosis by rehydration or intravenous administration of bicarbonate usually produces rapid improvement.

A number of congenital bacterial, fungal, and viral infections that cause abortions and stillbirths may also result in the birth of a live, weak neonate. Clinical manifestations of fetal infections depend on the age of the fetus and virulence and trophism of the infecting agent.

Generally, weakness secondary to uroperitoneum, renal, and liver failure, postnatally acquired infections, and neonatal isoerythrolysis are not expected to appear during the first 24 hours of age. Rather, foals with neonatal isoerythrolysis are usually presented between 24 and 72 hours of age, foals with uroperitoneum at 2 to 5 days or older, and neonates with postnatally acquired infections most commonly at 2 to 5 days of age or older.

Paraplegia and tetraplegia are commonly associated with spinal cord compression. Compression of the spinal cord in neonates most commonly results from vertebral body malformations, osteomyelitis, or fractures. Occipitoatlantoaxial malformations (OAAMs) involve the occipital condyles of the skull and the first two cervical vertebrae.[33] Vertebral body malformations occur sporadically, with genetic, nutritional, and/or environmental factors being implicated.[34] Osteomyelitis and vertebral body abscess may be a sequel to bacteremia following neonatal sepsis or pneumonia. *Rhodococcus equi* vertebral osteomyelitis with or without associated pulmonary infection has been reported in foals.[35] Leukocytosis and hyperfibrinogenemia are commonly observed in neonates with vertebral body abscesses. In most instances, vertebral abscesses do not infiltrate the pachymeninges, so the cerebrospinal fluid (CSF) is normal or has a mild elevation of protein and or a mild pleocytosis.

A complete neurologic examination is an important component of the work-up of the weak neonate. In particular, it should be noted if the weakness is accompanied by signs of somnolence or diffuse cerebral disease. Limb reflexes should be tested to establish whether components of the spinal reflex pathways are involved in the disease process (sensory nerve, lower motor neuron, neuromuscular junction, muscle). For example, foals with severe spinal cord hemorrhage may have relatively normal mentation, but spinal reflexes may be

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greatly diminished and profound weakness may be present. Animals with other types of spinal cord disease (e.g., trauma, vertebral malformations) may also show weakness and ataxia yet appear clinically to have normal cerebral function.

Virtually any severe systemic disease such as generalized infection can cause both profound somnolence and weakness in a neonate without the presence of actual brain pathology. Primary neurologic disease in neonates is rare. Commonly, neurologic dysfunction is associated with multisystemic disease. A thorough comprehensive physical examination and work-up is required to define a problem list and formulate an appropriate management plan. A complete blood count, blood cultures, and assessment of immunoglobulin status provide an indication of the likelihood of sepsis. Hypoxia and metabolic acidosis are ruled out by assessing arterial blood gas status, and electrolyte disturbances and hypoglycemia are evaluated by measuring serum electrolytes and blood glucose concentration. Collection of cerebrospinal fluid to assess the central nervous system is usually performed when disease in other organ systems that may account for the altered mental state has been ruled out and no improvement in the patient's condition is observed following correction of electrolyte, blood gas, and metabolic derangements.

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Sepsis

David P. Byrne • Chris Sanchez

Introduction

Sepsis is the major cause of morbidity and mortality in the equine neonate.[36,37] The response to microbial invasion of the bloodstream involves the systemic inflammatory response syndrome (SIRS), and it is this nonspecific inflammatory response, rather than the infectious organism, that is responsible for the classical signs of sepsis. Deterioration can occur rapidly, even in the face of aggressive treatment.

A variety of terms have been used to describe the host response to infection and associated processes and syndromes. A set of definitions was published by the American College of Chest Physicians and Society of Critical Care Medicine in 1992.[38] Briefly, SIRS refers to a systemic response, regardless of the inciting cause, that results in at least two of the following four clinical features: fever; tachycardia; tachypnea or hyperventilation; or leukocytosis, leukopenia, or a relative increase of circulating immature neutrophils. When SIRS occurs in response to a suspected or confirmed infectious process, the process is termed *sepsis.* Specific definitions for SIRS in equine neonates of various ages have been published that modify the original definitions to include venous lactate and glucose concentrations.[39] More recently, in humans, it has been suggested that sepsis should be suspected when there is a combination of hypotension, tachypnea, and altered mental status.[40] Interestingly, hyperlactatemia did not improve the accuracy of the model in this set of definitions. This is not without controversy, with some arguing that SIRS remains more sensitive in detecting systemic sepsis in humans.[41,42]

Infection with gram-negative bacteria occurs commonly in neonatal foals.[37,43–45] The pathophysiology of septic shock in gram-negative sepsis involves bacterial endotoxin and the subsequent release of proinflammatory and antiinflammatory cytokines.[46,47] Septic foals can have decreased gene expression of tumor necrosis factor (TNF)-α and TNF-β and increased expression of IL-8 relative to healthy foals[48] or increased gene expression of IL-4 and TLR4[49] among other abnormalities.

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Predisposing Factors

Factors that may predispose to infection are numerous and include maternal illness, increases or decreases in gestational length, partial or complete failure of passive transfer, poor environmental conditions, and inadequate or improper umbilical care. Maternal factors have been reported to play a central role in 24% of bacteremic foals.[50] These include dystocia,[51] premature placental separation, placentitis, and various other forms of maternal illness such as colic and respiratory disease. Many of these factors coexist, but some occur primarily, such as placentitis, while others are secondary, such as premature placental separation. In utero infection of the fetus typically occurs due to an ascending infection of the fetal membranes and often results in premature delivery.[52] Because chronic placentitis often results in accelerated or precocious fetal maturation, a resultant premature foal born to such a mare likely has a greater chance of being septic but a higher probability of survival than a foal born at a similar gestational age to a mare without placentitis or other chronic stimulation.

Failure of transfer of passive immunity (FTPI) predisposes to an increased risk of postnatal infection. A number of studies have documented a close relationship between the foal serum IgG concentration, incidence of disease, and survival.[53–57] Colostrum administration via nasogastric tube was associated with disease in one report,[51] which supports the notion that route and timing of transfer are likely relevant, along with the potential for bacterial challenge. Farm management is important, including general hygiene, stocking density, exposure to disease, nutrition, and prepartum vaccination and deworming programs. Foals with partial failure of passive transfer were not at any greater risk of disease than those with adequate transfer on a well-managed Standardbred farm.[58]

Common postnatal routes of infection include umbilical remnants, gastrointestinal tract, and the respiratory tract. The umbilicus was traditionally regarded as the most important site for pathogen entry, but there has been heightened recognition of the role of the gastrointestinal tract as an important portal for bacteria.[59] The absorption of macromolecules in the proximal small intestine occurs through specialized cells via pinocytosis, with little discrimination between maternal immunoglobulin and other macromolecules. Absorption peaks shortly after birth and declines to less than 1% by 20 hours.[60] Unlike other species, the absorption of immunoglobulins does not appear to be Fc-receptor mediated in the foal. The foal will selectively absorb IgG and IgM

over IgA.[61] In neonatal pigs and lambs, deprivation of milk or colostrum can extend intestinal permeability to immunoglobulins by up to 5 days.[62] In contrast, intestinal permeability to immunoglobulins cannot be delayed through withholding of macromolecules to newborn foals.[63] It is not known if closure can be hastened by the feeding of macromolecules immediately after birth in foals. The other main postnatal factors beyond FTPI include gestational age and environmental conditions. Foals with exceptionally short or long gestational lengths may be at a heightened risk for development of sepsis.[64] Poor environmental conditions can result in an increased bacterial load to the gastrointestinal tract, especially during the initial periods of udder seeking.[59]

Causative Organisms

A summary of reported bacterial isolates is presented in Table 17.1. *Escherichia coli* is the predominant organism isolated from septic foals in recent studies, irrespective of location or methodology.[44,50,57,65–72] The next most common isolate varies with era and geographic location. In the late 1990s a group from the University of Pennsylvania reported an important role of gram-positive bacteria (*Enterococcus*, *Streptococcus*, *Staphylococcus* spp.), whereas the nonenteric gram-negative organism, *Actinobacillus* spp., accounted for approximately 30% of all isolates at Ohio State University in the late 1990s.[44,50] When evaluating trends over time (1982 to 1989, 1990 to 1999, 2000 to 2007) *E. coli* remained the predominant isolate in a Florida population of sick foals; *Actinobacillus* spp. were more common in the 1980s relative to the 1990s and 2000s, *Salmonella* spp. were isolated less frequently in the 2000s relative to other decades, and enteric gram-negative organisms were less frequently isolated in the 2000s relative to the 1980s.[45] In a similar study from California, gram-positive species became more important over time, mostly due to a decrease in *E. coli* and an increase in *Enterococcus* species.[72] Other groups have demonstrated the importance of gram-positive infections.[57,70,73,74]

TABLE 17.1

Summary of Selected Reported Frequency of Bacteria Isolated from Neonatal Foals—Data Expressed as Percentage of Total Isolates from Each Study

	Wilson and Madigan[69]	Koterba et al.[66]	Raisis et al.[67]	Gayle et al.[141]	Marsh and Palmer[44]	Stewart et al.[50]	Henson and Barton[65]			Corley et al.[43]	Russ et al
Location	CA, USA	FL, USA	NSW, Australia	TX, USA	PA, USA	OH, USA	GA, USA			CA, USA	NSW Aust
Number of foals	47	27	24	29	155	101	250			85	110
Blood cultures only?	No	Yes	No	Yes	Yes	Yes	No			Yes	Yes
Admission only?	No	No	No	NS	No	Yes	No			No	Yes
Years of study	1978-87	1982-83	1989-92	1988-95	1991-98	1993-2000	1986-90	1991-95	1996-2000	1995-2004	1999 200
Number of isolates	85	29	24	38	203	130	214	112	126	109	124
E. coli	30.6	58.6	50	36.8	18.7	30	59	29	26	40.3	31.4
Enterobacter spp.	3.5	3.4	12.5	18.4	12.3		18	8	9	1.8	8.1
Klebsiella spp.	12.9	6.9		10.5	3.9		16	15	7	4.6	0.8
Salmonella spp.		3.4	12.5	18.4	2.9		17	1	3		
Actinobacillus spp.	18.8	6.9	12.5	2.6	8.9	23.1	11	8	7	19.3	6.5
Pasteurella spp.		3.4			1.5						
Pseudomonas spp.	4.7	3.4		5.3	4.9						
Enterococcus spp./Group D *Streptococcus*					9.4		0	2	19	6.4	12
Streptococcus spp.	8.3		8	7.9	9.4		33	15	8	9.2	13
Staphylococcus spp.	3.5	3.4		5.3	9.8		7	8	15		9.7
Clostridium spp.	2.4	3.4									1.6
All gram-negative	75.3	93.1	91.7	78.9	62.6	72.3	77	69	58	74.3	57.3
All gram-positive	17.6	3.4	8.3	21.1	32.5	23.1	23	31	42	21.1	40.3
All anaerobe	2.4	3.4			3.4	4.6				4.6	2.4
All fungal/yeast					1.7						
Overall survival (%)	31.9	25.9	70.8	48.3	NS	55	44			67	74.5

[a]Survivors calculated from total septic foal population.

Admission only: Yes, samples restricted to those obtained within 24 hours of a foal's admission to the hospital; *Blood cultures only? Yes,* samples restricted to culture of blood only; *No,* samples included blood or infected tissue collected at necropsy; *Number of foals,* number of foals from which bacteria were cultured; *NS*, not stated.

Systemic fungal infections are uncommon in neonatal foals, with *Candida albicans*, a dimorphic fungus, the most frequently reported.[75,76] *Candida* infections have been associated with lengthy hospitalization and invasive monitoring techniques or immunodeficiency. Prolonged antimicrobial therapy and administration of parental nutrition have been suggested as risk factors for the development of candidiasis. Infection should be suspected when there is a fever that is unresponsive to antimicrobial therapy. Most foals with systemic infection will also develop thrush (white plaques on the lingual surface) either concurrently or before showing clinical signs of systemic infection.

Physical Examination Findings

Physical examination of the mare and placenta is an important adjunct to the foal's physical examination. Any indication of placental or maternal abnormality should raise suspicion for neonatal illness. Initial clinical signs of sepsis in foals can be vague and highly variable. Frequently reported signs include decreased or absent milk intake, diarrhea, and lethargy, which may progress to recumbency. Examination should always include assessment of the mare's udder for fill; depressed foals will often stand with their head underneath the mare but fail to suck, leading to dried milk on their foreheads (Fig. 17.2). Clinical signs of dehydration occur as time progresses due to lack of intake. Tachycardia and tachypnea are common but not always present. Oral, conjunctival, and vulvar mucous membranes can become hyperemic, injected, and/or petechiated. Petechiae may be noted along the internal pinnae of the ears, and hyperemia can be noted along the coronary bands. Capillary refill time may be rapid in hyperemic foals or substantially delayed in those that have become hypovolemic. Other signs of hypovolemia include decreased borborygmi, poor peripheral pulses, cool extremities, and decreased or absent urine output. It should be noted that the absence of signs of hypoperfusion does not rule out sepsis.[77] Rectal temperature may be normal or mildly increased, or low if there has been progression to shock. Sepsis should not be ruled out on the basis of a normal or low rectal temperature. If untreated, these early signs can progress to septic shock and, often, death.



FIG. 17.2 A septic somnolent foal standing under a mare that is spontaneously lactating.

Septic foals can also have localizing signs associated with specific foci of infection. Diarrhea is common, and can be the first clinical sign noted. Other localizing signs include uveitis, seizures, joint effusion, lameness, physeal swelling, respiratory disease or distress, subcutaneous abscesses, patent urachus, and omphalitis.

Clinicopathologic Findings

Consideration of clinical signs and historical information is often sufficient for a provisional diagnosis of sepsis, but laboratory data will increase the index of suspicion. The most common hematologic finding in acute sepsis is leukopenia, characterized by neutropenia with shifting toward immature forms and toxicity (Doehle bodies, toxic granulation, and vacuolization). Septic foals, younger than 1 week of age, have lower total white blood cell (WBC) counts, neutrophils, and lymphocytes, as well as a higher number of band neutrophils and monocytes than healthy age-matched controls.[78] Premature or dysmature foals will commonly have a decreased neutrophil count in the absence of sepsis, but without a degenerative left shift or evidence of toxicity, unless prematurity is

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complicated by sepsis. Age is an important factor in considering hematologic findings. In older foals (8 to 14 days) with confirmed sepsis, the total WBC count, neutrophil count, and number of band neutrophils were higher than in age-matched controls.[78] A high fibrinogen or serum amyloid A concentration at or shortly after birth should raise the suspicion of in utero infection.[66]

Blood glucose concentrations are commonly abnormal in septic foals. Hypoglycemia (<100 mg/dL; <5.6 mmol/L) is common initially, especially in foals younger than 24 hours of age.[66] Hypoglycemia is primarily related to decreased intake, but endotoxemia can also contribute to hypoglycemia. Hyperglycemia commonly occurs in response to dextrose infusion in septic foals. Other biochemical abnormalities common in septic foals include azotemia and hyperbilirubinemia.[37] Acidemia and hyperlactatemia are also common.[79] Arterial hypoxemia and hypercapnia can occur in sepsis independent of pulmonary disease but are not consistent findings and are influenced by recumbency. Triglyceride concentrations are higher in foals with positive bacterial cultures,[80] and albumin concentrations are higher in septic and hypoperfused foals,[77,81] likely related to circulatory volume status.

The coagulation and fibrinolytic systems of the septic newborn are often abnormal, with clinically relevant decreases in antithrombin III and elevations in prothrombin time, activated partial thromboplastin time, fibrin degradation products, and D-dimer concentrations.[78,82] Some patients may develop active hemorrhage and/or thrombosis. This can include thrombosis of the aorta, iliac, femoral, or brachial arteries. Nonsurviving foals often have postmortem evidence of fibrin deposits in the lungs and other organs.[83]

Endocrine adaptations to illness, including sepsis, occur in neonatal foals. Plasma AVP concentrations are higher in septic foals on admission than in healthy and sick nonseptic foals.[84] Increased concentrations of adrenocorticotropic hormone (ACTH) and cortisol have been documented in both septic and nonseptic hospitalized neonates.[85–91] Some septic foals are capable of a stress response, while critical illness−related corticosteroid insufficiency occurs in others. Consequently, nonsurvival has been associated with both higher and lower cortisol concentrations and a high ACTH-to-cortisol ratio.[86–90] Evaluation of basal total cortisol, ACTH, and the cortisol response to ACTH stimulation can provide information regarding HPA axis status in septic foals.[88] Other endogenous steroids, including aldosterone, dehydroepiandrosterone sulfate, allopregnenolone, and 17α-OH-progesterone,

have been shown to predict sepsis in neonatal foals, although commercial assays may not be widely available.[77] Similarly, sepsis is associated with alterations in the somatotropic axis, although considerable overlap between groups makes the interpretation of these alterations difficult in individual foals.[92] Septic foals often have dysregulation of calcium and phosphorous homeostasis, with lower concentrations of calcium and vitamin D and higher concentrations of phosphorous and parathyroid hormone.[93]

Establishing a Definitive Diagnosis

Blood culture is the gold standard for diagnosis of systemic bacterial infection. Identification of a causative organism allows for directed antimicrobial therapy, as well as monitoring for patterns of antimicrobial resistance. Samples for culture should be collected into a sterile syringe without anticoagulant from a large vein (usually jugular, cephalic, or saphenous) after surgical preparation. The sample should be placed into appropriate blood culture media using volumes consistent with manufacturer recommendations. For those foals receiving antimicrobial therapy before sample collection, an appropriate medium with resins may improve microbial recovery.[94] Collection from a venous catheter is acceptable, provided it is done directly from the catheter at the time of placement without compromise of aseptic technique. Healthy foals may have temporary bacteremia as detected by blood culture up to 12 hours of age.[95] However, false positives are unlikely in ill foals.

There are limitations to blood culture, including delayed results and reduced sensitivity. Many foals with histologic evidence of sepsis at necropsy have negative antemortem blood culture results. This can occur because of prior antimicrobial therapy or low circulating bacterial numbers. In one study, only 40% of *E. coli* infections were successfully identified by antemortem blood culture relative to recovery at necropsy.[69] These factors led to the development of scoring systems to predict sepsis.[96,97] The modified “sepsis score” is calculated using historical findings, physical findings, and laboratory data. The initial sensitivity and specificity of the score were reported at 92.8% and 85.9%, respectively,[96] but more recent data indicated regional variability with lower sensitivity and/or specificity.[50,65,74,98,99] Due to the heavy weighting of historical information and related problems, moderate to severely premature foals often have a positive sepsis score without positive blood culture. Many of the maternal

problems resulting in prematurity can also lead to systemic sepsis. Consequently, this crossover is predictable. When the original or modified equine neonatal SIRS criteria were added to the modified sepsis score, the diagnostic accuracy of the scores was low.[74] The problem with clinical application of these scoring systems is their relatively low specificity and negative predictive value. While a "positive" score is supportive of sepsis, a "negative" score should not be used as a basis of withholding antibiotic therapy from an at-risk animal.

Therapy

Antimicrobial Therapy

Antibiotics are the mainstay of therapy for septic foals. Initially a broad-spectrum bactericidal approach is recommended with selection influenced by costs, availability, and local knowledge of common isolates. Recommended dosages for commonly used antimicrobials are listed in Table 17.2. Reported antimicrobial susceptibility patterns of microorganisms isolated from equine neonates are presented in Table 17.3. Antimicrobial therapy should begin immediately when sepsis is suspected and should not be delayed pending blood culture results, as culture and sensitivity data typically require 3 to 4 days. Therapy can be altered if required when these data become available. A minimum therapeutic course of 2 weeks is recommended for bacteremic foals without localizing clinical signs. If localizing signs, such as pneumonia or septic arthritis, are present, a minimum course of 4 weeks is recommended.[64]

TABLE 17.2
Recommended Antimicrobial Dosages

Agent	Preparation	Route	Frequency (h)	Dosage (/kg)	References
Amikacin	Sulfate	IV, IM	24	21-25 mg	401,402
Gentamicin	Sulfate	IV, IM	36	12-15 mg	403
Ampicillin	Sodium	IV, IM	6	25 mg	
Ampicillin	Trihydrate	IM	12	25 mg	
Penicillin G	Potassium	IV	6	22,000-40,000 IU	
Penicillin G	Procaine	IM	12-24	22,000 IU	
Cefotaxime	Sodium	IV	6	40 mg	100,404
Ceftiofur	Sodium	IV, IM	12	5 mg	405
Ceftiofur	Crystalline free acid	SC	72	6.6 mg	406
Cefpodoxime	Proxetil	PO	6-12	10 mg	106
Cefquinome	Sulfate	IV, IM	12	1 mg	107

Trimethoprim/ sulfamethoxazole		PO	12	30 mg	
Oxytetracycline	Hydrochloride	IV	12-24	5-10 mg	

These represent recommendations only. Label indications and national or international rules regarding off-label usage of antimicrobials remain the responsibility of the provider.

TABLE 17.3

Reported Antimicrobial Susceptibility Patterns of Microorganisms Isolated from Equine Neonates

	Marsh and Palmer[44]	Henson and Barton[65]		Russell et al.[68]			Sanchez et al.[45]				Theelen et al.[72]			Toombs-Ruane et al		
Isolates	*E. coli*	GP	GN	GP	GN	ALL	GP	NEGN	EGN	ALL	GP	GN	ALL	GP	GN	A
Amikacin	90	55	90	0	100	42	45.8	77.8	97.9	84.3	45.9	96.8	87.0			
Gentamicin	80	50	75	34	74	56	62.0	79.2	92.1	83.6	42.9	77.4	71.0	73	73	73
Ampicillin	57	74	63	54	63	59	72.7	69.5	49.4	57.8	78.0	56.3	61.5	69	23	54
Penicillin		72	21	47	38	45	67.1	18.2	3.1	29.5	76.3			69		
Ceftiofur	80	73	73	37	75	60	50	76.0	85.5	76.6	91.3	90.6	90.7	76	52	68
Ceftazidime							52.9	85.7	98.9	90.5						
Chloramphenicol		90	75	73	83	78	92.2	94.4	84.6	87.5	87.5	72.7	76.4			
Tetracycline		77	73	61	74	69	70.9	90.1	76.4	77.7	64.5	63.5	63.8	65	47	59
Trimethoprim-sulfamethoxazole	57	37	79	62	71	67	79.7	90.0	80.4	81.9	87.3	69.4	72.8	72	43	65
Enrofloxacin		100	100	37	93	70	74.6	94.5	97.6	91.8	57.5	95.0	85.2	91	95	93
Imipenem							86.7	82.1	100	94.9	89.3	99.1	96.5			
Penicillin + gentamicin						72	84.1	78.9	92.1	88.0						
Penicillin + amikacin							79.5	77.8	96.3	89.3						
Ceftiofur + gentamicin						68										
Ampicillin + gentamicin							89.8	82.7	91.4	89.4						
Ampicillin + amikacin							87.5	81.3	97.1	92.1						
Amoxicillin + clavulanate														82	43	67

Antimicrobial susceptibility is expressed as a percentage of all isolates for which susceptibility to a given antimicrobial were reported.

EGN, Enteric gram-negative isolates; *GN,* gram-negative isolates; *GP,* gram-positive isolates; *NEGN,* nonenteric gram-negative isolates.

See Table 17.1 for key to study details.

A commonly recommended initial therapeutic approach involves combining an aminoglycoside, typically amikacin or gentamicin, with penicillin or

ampicillin. Alternatively, ceftiofur can be used alone, or in combination with an aminoglycoside. The use of amikacin or gentamicin should be tempered in light of the foal's cardiovascular and renal status. If a foal is severely hypovolemic and azotemic, a safer initial choice would likely involve a third-generation cephalosporin. If amikacin or gentamicin is used, therapeutic drug monitoring is recommended to ensure appropriate individual dosing. If not available, then an alternative recommendation includes serial creatinine monitoring every 2 to 3 days and/or serial urinalyses, including sediment examination. Cefotaxime is a good choice for foals with gram-negative meningitis[100] or those with poorly responsive pneumonia. Oxytetracycline has been recommended in foals with suspected or confirmed septic osteitis or osteomyelitis.[101]

Due to emerging resistance, trimethoprim/sulfa combinations should not be used in septic foals without documented sensitivity and then only as a long-term option following initial parenteral therapy. In contrast to older foals and adult horses, several aminobenzyl penicillins (amoxicillin and ampicillin) and first-generation cephalosporins (cefadroxyl and cephradine) have good bioavailability in young foals but a limited spectrum of activity.[102–105] Cefpodoxime proxetil, a third-generation cephalosporin available for oral administration, was effective against 90% of *Klebsiella* spp., *Pasteurella* spp., and β-hemolytic streptococci, and an increase in the frequency of administration would likely increase the effectiveness against *E. coli*.[106] Cefquinome is a fourth-generation cephalosporin licensed for neonatal sepsis in Europe, with good activity against *Streptococcus* spp., *Staphylococcus* spp., *Actinobacillus equi,* and the *Enterobacteriaceae*.[107,108] Fluoroquinolones, such as enrofloxacin, have an excellent spectrum of activity against gram-negative and some gram-positive bacteria but have been associated with arthropathy in foals.[109,110] Therefore use of these agents should be reserved for those cases where there is suspected resistance to other antimicrobial agents and informed owner consent.

Source control, where possible, should be instigated in any cases with identifiable local infection. This may include synovial structure lavage, abscess drainage, omphalitis resection, and removal of infected catheters.

Antifungal Therapy

Medical treatment options for systemic candidiasis include fluconazole, itraconazole, miconazole, and amphotericin B.[76,111] Fungal sensitivity profiles may help direct therapy if available. Pharmacokinetics of these drugs have not

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been established in foals. Amphotericin B (conventional form, not liposomal/lipid complex form) has been administered at a range of 0.1 to 0.5 mg/kg IV SID, starting therapy at the lower dose and increasing by 0.1 mg/kg increments per day.[76] Because this drug can cause potentially life-threatening nephrotoxicity, serum creatinine, urine production, and urinalysis should be monitored closely. Fluconazole has previously been administered at 4 to 10 mg/kg PO SID. This agent is cheaper and easier to administer and has far fewer side effects. Miconazole has also been used at a dose of 1 mg/kg IV q8h.[76] Voriconazole has also been used to treat pulmonary aspergillosis.[112]

Antiendotoxin Therapy

Many septic foals have detectable plasma endotoxin concentrations.[78] Concerns exist regarding the potential for antibiotics to exacerbate the release of endotoxin through death of circulating gram-negative bacteria. In vitro work has shown that β-lactam antimicrobials appear more likely than aminoglycosides (alone or in combination with ampicillin) to induce endotoxemia and TNF-α activity during treatment of *E. coli* sepsis. Agents commonly used for the treatment of endotoxemia include flunixin meglumine, pentoxifylline, and polymyxin B sulfate.[113,114] Recommendations are extrapolated with caution from work in vitro and in adult horses. Polymyxin B has been shown to improve certain clinical and clinicopathologic findings in experimental endotoxemia in foals,[115] but no survival benefit has been observed in septic humans using hemoperfusion with polymyxin B bound and immobilized to polystyrene fibers.[116] Flunixin and polymyxin B are potentially nephrotoxic, and flunixin has the potential for gastric ulceration. Pentoxifylline has also been shown to reduce mortality without adverse effects in septic neonates[117] but not adults.[118]

Cardiovascular Support

Cardiovascular support is critical in foals with hypovolemia, septic shock, or hypotension. When a foal presents in septic shock, initial fluid resuscitation choices commonly include a combination of crystalloid and colloid (such as hydroxyethyl starch) preparations. Meta-analyses in human medicine have shown that artificial colloid therapy is associated with coagulopathies and kidney injury in the critically ill.[119,120] Studies in healthy ponies and foals have not identified clinically significant effects, although this should be evaluated in

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critically ill foals.[121–123] Arterial or venous lactate concentration, systemic blood pressure, cardiac output, and central venous pressure can provide additional information regarding volume status and estimation of tissue perfusion.[124] Once normovolemia is restored, neonates typically require approximately 80 to 100 mL/kg/day (5 L/day for a 50-kg foal) in order to maintain adequate hydration. Clinicopathologic variables to monitor in septic foals include arterial or venous blood gases, electrolytes (especially sodium and potassium), and glucose. Physical parameters of importance include careful examination for the development of edema (conjunctiva, prepuce, ventrum, distal limbs, etc.), urine output and specific gravity, vital signs, and temperature of the distal limbs. Derangements in any of the monitored parameters should be addressed as they arise. One should be particularly mindful of sodium load in the neonate, as requirements and sodium tolerance can differ widely between foals, and specific care should always be taken to avoid fluid overload.[2] In human medicine, point-of-care ultrasound (US) has been used to evaluate “fluid tolerance” (i.e., whether additional IV fluid is likely to lead to fluid overload).[125,126] Respiratory variation in caudal vena cava collapsibility, as a component of fluid tolerance assessment, has been evaluated in healthy foals.[127]

If, with appropriate fluid resuscitation, hypotension and signs of poor perfusion persist, consideration should be given to the administration of vasopressors and inotropes, the use of which is covered earlier in this chapter. Previously recommended early–goal directed therapy protocols have been comprehensively shown to be no better than current usual care in the treatment of sepsis in humans.[128–130]

Antiacid Therapy

Although uncommon, sick foals can develop gastric ulcers in the glandular region of the stomach. The ulcers can preferentially occur in the cardiac gland region and may reflect reduced blood flow to the organ during hypovolemia. The use of prophylactic antiacid therapy is controversial and highly dependent on clinician preference. Gastric pH in critically ill foals can differ greatly from that seen in healthy foals.[131,132] Severely ill, predominantly recumbent patients frequently have alkaline pH profiles, and sick foals capable of acid production respond more variably to IV ranitidine administration than their normal cohorts.[132] Thus, glandular ulcer disease in sick neonates is likely not a strictly acid-related problem and factors such as alterations in mucosal blood flow may

contribute. In addition, gastric alkalinization can contribute to bacterial translocation.[133] The use of antiulcer medications (ranitidine, omeprazole) was associated with an increased risk of diarrhea in a large multicenter retrospective study.[134] In that report, antiulcer medications did not appear to protect against ulcer development in a small number of foals in which ulcers were detected. Should one choose to use them, options for acid suppression include ranitidine, omeprazole, and pantoprazole.[131,132,135–137] Sucralfate remains a possible alternative for ulcer prophylaxis, especially in foals receiving nonsteroidal antiinflammatory drugs, without altering intragastric pH.

Additional Therapy

In light of the critical illness−related corticosteroid insufficiency identified in some septic foals, low-dose corticosteroid therapy has been suggested for a subset of the septic foal population. But given the wide variability seen in the septic foal population, more data are needed before such therapy is recommended. The combination of hydrocortisone, vitamin C, and thiamine has recently been suggested to have dramatically improved survival in a small group of septic human patients, although the data are limited and not widely accepted.[138] Treatment of coagulopathies may include plasma transfusions as a source of procoagulant and anticoagulant factors, or low-molecular-weight heparin, although the effect of the latter on patient outcomes is currently unknown in neonates. Its use was not associated with adverse outcomes in a small number of septic foals, at a higher dose (100 IU/kg dalteparin SC) than that used in adults.[139]

Focal Infection and Potential Sequelae

The lungs are a common location of focal infection in the septic foal, with a reported incidence of pneumonia ranging from 28% to 50%.[50,140] Many bacterial pneumonias are acquired in utero through aspiration of contaminated amniotic fluid. Respiratory rate and effort, thoracic auscultation, and rectal temperature can often alert the clinician to the possibility of pneumonia in a given animal. Respiratory function is best assessed in septic foals via arterial blood gas analysis.[124] Thoracic radiography and ultrasonography can provide an estimation of disease severity and distribution. In addition to hematogenously acquired pneumonia, septic foals can be at risk for aspiration of either meconium or milk, depending on their presentation. Directed antimicrobial therapy and maintenance

of an acceptable arterial oxygen tension with intranasal oxygen insufflation are the most commonly administered forms of therapy. In those foals with severe hypercapnia in addition to hypoxemia, mechanical ventilation may be necessary.

Diarrhea and/or enteritis are common in septic foals, with reported incidence between 16% and 38%.[50,64,140,141] Conversely, approximately 50% of neonates with a primary complaint of diarrhea are bacteremic.[142,143] Therefore sepsis should be suspected in any diarrheic neonatal foal. Foals with *Actinobacillus* sp. bacteremia were six times more likely to have diarrhea than those with other isolates[50]; in another, gram-negative enteric bacteremia was positively associated with diarrhea.[45] With or without enteritis, septic foals can also display signs of ileus and/or colic. Most of these problems resolve with symptomatic treatment and systemic improvement. Ultrasound can be useful in differentiating enterocolitis from other forms of colic. Analgesic therapy in colicky foals is somewhat limited, and flunixin meglumine should be used cautiously due to the potential for gastric ulceration. Butorphanol can be used intramuscularly to control gut pain in foals with colitis without increasing the risk of ulceration and nephrotoxicity. Interestingly, diarrhea has been positively correlated with survival to discharge in one report of bacteremic foals.[45]

Omphalitis refers to infection of umbilical structures. Umbilical remnant infections are considered to be a common source of continued bacterial shedding. Ultrasonographic evaluation of these structures is critical, as external signs (pain, heat, and swelling) are frequently absent. Treatment options include long-term antibiotic therapy or surgical resection. The reported incidence in septic foals has ranged from 9% to 21%.[45,141] Many septic foals will develop a patent urachus without involvement of other structures. This problem will often resolve with continued antibiotic therapy, with or without topical therapy. Uroperitoneum in septic foals could result from ischemia and subsequent necrosis of the bladder and/or urachus. Most of these foals will not have classical serum electrolyte findings due to intravenous fluid therapy and limited milk intake. Routine ultrasonographic assessment of the umbilical structures is recommended in all hospitalized neonates in whom sepsis is either confirmed or suspected.

Meningitis is a rare but extremely serious complication. Major clinical signs include seizures and severe somnolence, although this is somewhat difficult to assess in a severely compromised foal. Other signs can include head tilt, strabismus, nystagmus, and extensor rigidity, depending on the areas of

involvement. CSF normally provides a definitive diagnosis, with a pleocytosis (normally neutrophilic) being the typical abnormality. Prognosis is poor to grave, but if therapy is attempted, third-generation cephalosporins (such as cefotaxime) have been recommended.[100] The major differential diagnosis for neurologic signs in a septic neonate is neonatal encephalopathy (NE). Typically foals with NE present within 24 to 48 hours following birth, whereas the age of foals with meningitis is more variable. One report noted that none of 11 bacteremic foals with meningitis survived to discharge from the hospital.[45]

The most common ocular complication in the septic foal is corneal ulceration, noted in up to 12% of bacteremic foals.[45] Ulceration can occur due to entropion in a dehydrated foal or, more commonly, trauma. Because foals do not always show clinical signs of corneal ulceration, a daily ophthalmic examination, including fluorescein staining, should be performed in all hospitalized foals. Uveitis can also occur as an ocular extension of systemic disease and is associated with positive bacterial blood cultures and survival.[144]

Disorders of coagulation can occur in septic foals, manifested clinically by either hemorrhage or thrombosis. Probably the most common abnormality is jugular venous thrombosis at the site of an indwelling venous catheter. Other areas of thrombosis include the brachial artery, digital artery, metatarsal and metacarpal arteries, diffuse vascular thromboses throughout the distal limb, the aortic termination, the lungs, and the colon.[78,145–148]

Prognosis/Outcomes

Survival rates have increased from the 25% reported in the early 1980s.[66] More recent retrospective studies have reported short-term survival rates ranging from 45% to 55%.[50,65,141,149] Others have reported survival rates as low as 32% and as high as 70% to 72%.[67,78,140,150] Given the overall advances in neonatal care, it is not surprising that year of admission was positively correlated with survival in a University of Florida report (with an overall survival of 60%) from 1982 to 2007.[45]

Several factors have been associated with survival in retrospective studies. Barton and colleagues[78] reported that foals infected with gram-negative organisms were more likely to die than those with gram-positive infections, although this is not universally true.[57] In another study, the duration of illness before admission was inversely related to survival, while the ability to stand on

admission was positively correlated with survival.[141] Foals were more likely to survive if they had a sepsis score <11, a negative blood culture at admission, blood glucose greater than or equal to 60 mg/dL (>3.3 mmol/L), body temperature greater than or equal to 100° F (37.8º C), TCO_2 greater than 15 mmol/L, or a low or normal fibrinogen in a study from the University of Georgia.[65] In a Florida study, age at admission, septic arthritis, band neutrophil count, and serum creatinine concentration were negatively associated with survival, whereas year of admission, diarrhea, rectal temperature, neutrophil count, and arterial blood pH were positively associated with survival to discharge in bacteremic foals.[45] In an Ohio study, foals with multiple blood isolates had longer periods of hospitalization but not decreased survival.[50] Arterial lactate concentration, either at admission or 18 to 36 hours after admission, was a good predictor of survival in a further study.[79] In a large, prospective, multicenter study, increased lactate concentrations were associated with increased odds of death in septic foals.[70] This relationship remained true when examining lactate concentrations over time during hospitalization, with septic foals having higher concentrations than sick, nonseptic foals.[151] Interestingly, lactate concentrations were slower to fall in septic foals, despite volume resuscitation, suggesting other sources of lactate production, or altered clearance. This is consistent with current understanding of lactate production in sepsis in humans.[152,153] While lactate concentrations in populations of nonsurvivors have been shown to be increased at all time points in comparison with survivors, considerable overlap between the groups makes prognostication difficult based on lactate concentrations alone.[154]

A foal survival score has been developed in a multicenter study using a seven-point scale and a combination of historical, physical examination, and clinicopathologic variables.[155] While this scoring system had a sensitivity and specificity for mortality of 96% and 71%, respectively, further external validation is required. Despite the multitude of scoring systems developed to predict survival, clinician gestalt has been shown to be more accurate in predicting survival than a multivariable model in a large population of ill foals.[156]

Few studies have addressed the long-term survival and performance of septic foals. In one report of bacteremic Thoroughbred foals, there was no significant difference in percentage of starters, percentage of winners, or number of race starts, relative to a control group of maternal siblings. But bacteremic foals had a

lower number of wins, total earnings, and Standard Starts Index rating, relative to control maternal siblings.[45] This is similar to that reported for overall neonatal intensive care unit (NICU) survivors, where the percentage of starters was lower than the control population, but performance over a 2-year period was not different in those animals able to make at least two starts.[150] Also, NICU treatment was found not to significantly affect sales performance.[157]

Preventative Strategies

Clearly, given the wide range of potentially devastating problems associated with sepsis, prevention will always outweigh treatment, but no one program will ever totally eliminate the risk of sepsis. Not surprisingly, methods of prevention coincide with the documented risk factors and routes of infection previously discussed. The following suggestions comprise a basic guide one can offer to clients. While many of the presented options make sense, none have been proven to reduce the incidence of sepsis. Thus the decision to implement some or all of these practices will depend on the individual farm scenario.

Maintain a Clean Environment

While this is one of the most basic concepts in all of medicine, its importance cannot be overemphasized. With specific reference to the foaling situation, foaling stalls should be thoroughly cleaned and disinfected between mares. For each inhabitant, the stall should be cleaned at least daily, if not twice daily, and plentiful clean, dry, fresh bedding provided for the mare and foal.

Reduce the Potential Bacterial Load Introduced During Udder Seeking

Ideally, the mare's hindquarters, perineum, and udder should be thoroughly cleaned with soap and water before the introduction of the foal.[59] The key feature to this step, which is often overlooked, is that the mare must also be dried. This should be done just outside the stall, rather than in the stall to prevent contamination of the environment. This step requires a great deal of commitment on the part of the farm, as it is labor intensive.

Ensure Gastrointestinal Intake of Colostrum

The volume, quality, and timing of colostrum administration are all likely

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important, rather than just the quality. The ideal scenario involves feeding 6 to 8 oz (180 to 240 mL) of good-quality colostrum as soon as the foal develops a good, strong suckle reflex. One of the main concerns with this recommendation is the risk of milk aspiration when untrained individuals are trying to bottle feed newborn, potentially weak foals.

Confirm Adequate Transfer of Passive Immunity

Traditionally, transfer of passive immunity to the foal has been considered to be the most important factor in disease prevention. While other factors clearly play a role, adequate immunoglobulin transfer should still be assessed and managed, if necessary. A complete discussion on treatment of FTPI is included elsewhere in this text. It should be noted that plasma transfusion in septic foals is not as effective at increasing serum IgG concentrations as in healthy or sick, nonseptic foals.[158]

Ensure Appropriate Umbilical Care

This recommendation is followed by most horse owners, from the backyard client to the large breeding operation. No published studies in foals have critically evaluated the different preparations used for routine umbilical care. In human neonates, surprisingly few randomized, double-blinded clinical trials have broached this issue. In a review of published studies, 4% chlorhexidine was a popular choice and consistently reduced the risk of umbilical and periumbilical infections.[159] This concentration of chlorhexidine is also commonly used for foals and thus appears to be a better alternative to previously used povidone-iodine solutions. Use of iodine solutions results in brown discoloration of the external umbilicus and surrounding hair, and therefore have an advantage of allowing managers and clinicians to confirm that a disinfectant is being applied.

Monitor Foals Closely and Treat Suspect Foals Quickly

When identified early, sepsis can often be treated effectively on the farm with few complications. Thus when prevention fails, early intervention is critical. Any foal with a fever, diarrhea, lethargy, or inappetence should be thoroughly evaluated and treated appropriately.

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Septic Arthritis and Osteomyelitis

Rachael L. Smith

Neonatal foals are particularly susceptible to septic arthritis, osteitis, and osteomyelitis.[160] The incidence of this form of sepsis was estimated at 1% of all foals in the 1970s[161] but has likely reduced in recent decades as a result of improved management practices. This manifestation of sepsis represents significant loss to the industry, with reported survival rates to discharge from veterinary facilities between 42% and 81%, but with only 30% of those with septic arthritis and 48% of those with septic osteomyelitis achieving long-term athletic soundness.[162–166] Prognosis is influenced by the number of joints affected, number of bones involved, age of the foal, and presence of other medical problems.[101,162,167]

A classification scheme for septic arthritis and osteomyelitis has been developed on the basis of radiologic and pathologic findings.[168] The “S-type” describes bacterial infection of the synovial membrane of one or more joints with no radiographic changes, but there is joint effusion and possible periarticular soft tissue swelling. This form is typically seen in the first 2 weeks of life, and the most commonly affected joints include the carpus, stifle, and hock. The “E-type,” or epiphyseal, classification describes infection of the joint and osteomyelitis of adjacent subchondral bone. It is usually seen at 3 to 4 weeks of age, and common sites are femoral condyles, distal radius, distal tibia, or patella. “P-type,” or physeal-type, classification is used for cases of osteomyelitis of the physis on the metaphyseal side of the growth plate. This form occurs in foals 1 to 12 weeks of age and occurs most commonly in the distal radius or tibia, as well as the distal metacarpi/tarsi. The “T-type,” or tarsal, classification describes osteomyelitis of the cuboidal bones of the tarsus or carpus.

Etiology and Pathophysiology

Joint and bone infections of neonates most commonly result from persistent or transient hematogenous dissemination of bacteria from distant sites of infection.[168,169] Gastrointestinal, respiratory and umbilical infection, and failure of passive transfer are common predisposing causes. Less commonly, infection

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can occur after direct trauma or penetrating wounds and extension of an infection from adjacent infected soft tissues. Common bacterial isolates include *Enterobacteriaceae (Escherichia coli), Salmonella, Actinobacillus equuli, Klebsiella* spp., *Streptococcus,* and *Rhodococcus equi*.[170] Bacterial colonization of joints resulting from bacteremia is facilitated by the vascular pattern of neonates. Rapidly growing bones and joints require increased blood flow, derived from a main arteriole providing blood supply to the synovial membrane and epiphysis, and the nutrient artery supplying the metaphysis. In neonatal foals, transphyseal vessels connect epiphyseal and metaphyseal blood supplies. Bacterial deposition in the synovium and subchondral bone occur as epiphyseal vessels branch toward the articular surface and form hairpin bends ending in wide venous sinusoids—regions of lower blood flow, oxygen tension, and pressure. The synovial membrane lacks a basement membrane; therefore bacteria that are deposited in the subsynovial capillaries are able to readily migrate into the joint. Physeal infection is more likely to occur after closure of the transphyseal vessels, around 7 to 10 days of age, because of localization of the infection in metaphyseal vessel loops.[168,171] Colonization of bacteria in the articular, metaphyseal, and synovial vessels can lead to thrombosis and subsequent ischemic necrosis.[172] This can initiate a severe inflammatory response in associated tissues, producing classical clinical signs of joint effusion, heat, lameness, and pain on palpation of the periarticular tissues. Normal synovial fluid production and drainage is also impaired, leading to compromised articular cartilage metabolism. An influx of degradatory inflammatory mediators, white blood cells, serum proteins, and proteolytic enzymes leads to further disruption of chondrocyte metabolism and degradation of the cartilage.

The magnitude of the inflammatory response is determined by the virulence of the causative organisms, the size of the inoculum, and host resistance. The described sequelae resulting from infection highlight the importance of early diagnosis and treatment to achieve successful resolution before permanent degradative changes occur in the joint and periarticular tissue.

Diagnosis

Any lameness, joint effusion, or periarticular swelling in a neonatal foal should be considered significant and investigated regardless of history. Often, reporting is delayed as owners commonly suspect mare-induced trauma to the foal, or they may describe the foal as moving “stiffly” or “slowly” rather than being overtly

lame. Large joints such as the stifle, hock, carpus, and fetlocks are more commonly affected.[163,166,172,173] Pain in the foot or swelling of the coronary band could also be due to septic arthritis or osteitis/osteomyelitis.[82,134] Other causes of lameness and swelling associated with joints include cellulitis, hemarthrosis, fracture, trauma, and subsolar/solar bruising of the foot (Box 17.1).

Box 17.1

Lameness in Foals

Septic arthritis/osteitis/osteomyelitis
- Fracture
- Common sites: PIII, physis of P1, proximal sesamoid bones, olecranon
- Hemarthrosis
- Cellulitis
- Flexural deformity
- Rupture of the common digital extensor tendons
- Rupture of the gastrocnemius muscle
- Subsolar/solar bruising of the foot
- Laminitis
- Peripheral nerve injury

The most consistent and early clinical sign of joint sepsis is effusion. Periarticular swelling, heat, pain on palpation of the bone or joint, and restricted passive movement of the joint are commonly reported. Less consistent clinical signs include lameness, an elevated rectal temperature, and hematologic changes consistent with infection. Lameness may escape identification if foals are systemically ill, weak, or recumbent. Lameness can take 8 to 24 hours to develop after bacteria have colonized the joints.[174] If there is swelling detected in one joint, thorough palpation of all other joints is recommended. Regardless of history and complete diagnostic findings, it is prudent to treat any joint swelling or lameness in a neonatal foal as septic until proven otherwise.

Hematologic changes can be inconsistent early in the disease course, but typically by 72 hours post inoculation there is leukocytosis and hyperfibrinogenemia. These findings lack both sensitivity and specificity.

Fibrinogen levels greater than 900 mg/dL (>9 g/L) can be a useful indicator for epiphyseal or physeal osteomyelitis, but again this is neither sensitive nor specific.[175] Ultrasonography can be useful in detecting bone irregularities; defining and classifying joint effusion; as well as detecting associated problems such as pneumonia, omphalitis, or omphalophlebitis.

In order to reach a definitive diagnosis of septic orthopedic disease, additional diagnostic tests are required. These include diagnostic imaging and synovial fluid analysis following arthrocentesis, including cytology, Gram stain, and bacterial culture. To facilitate these procedures, adequate restraint of the foal is required. For neonatal foals, diazepam (0.1 mg/kg body weight IV) provides around 10 to 15 minutes of sedation to perform minimally invasive procedures. Before synoviocentesis, the skin should be clipped and aseptically prepared at the site of needle placement. Chlorhexidine or povidone-iodine scrubs are commonly used with isopropyl alcohol. Practitioners should not be overly vigorous in preparation of the skin and should avoid use of abrasive swabs as the skin of foals is particularly susceptible to trauma. It is likely that repeated scrubbing will be needed during the course of treatment, so preservation of the epithelial integrity is important. Lavage of the prepared area following the procedure with saline, drying the skin, and application of a topical antibiotic or antiseptic emollient cream is recommended before covering the site. Intraarticular administration of antibiotic into the joint following synoviocentesis is recommended, even if sepsis is not yet confirmed on cytology.

Any region of fluid distention of the joint, identified by bulging or balloting of the joint capsule, is appropriate for sampling, provided there is awareness of local anatomy. Ultrasonography is recommended to identify pockets of synovial fluid. In joints such as the stifle, carpus, and hock where multiple joint compartments are in close proximity, the potential for communication should always be considered. For this reason, arthrocentesis from each compartment should be performed and the synovial fluid from each analyzed to determine the exact joint involvement. A 20- to 21-gauge needle can be used to aseptically collect synovial fluid. Fluid should be collected for cytologic examination into an EDTA tube and a sterile serum tube for culture. Alternatively, synovial fluid can be injected into a blood culture medium to increase the chance of a positive culture. Confirmation of synovial sepsis from synovial fluid evaluation and testing is not always straightforward.[176]

Normal synovial fluid is of a light yellow to straw color, is transparent (should be able to see newspaper print through the tube and fluid), and has good

viscosity. Signs consistent with sepsis include increased turbidity, darkening in color (dark yellow to orange), and reduced viscosity. In severe cases, flocculent debris may be identified. The total protein (TP) of normal joint fluid is typically less than 20 g/L. Septic fluid usually has a TP greater than 40 g/L, but values greater than 20 g/L should be regarded as suspicious if other findings are supportive of synovial sepsis. The total nucleated cell count (TNCC) and differential nucleated cell count are considered the most useful evaluation of synovial fluid when diagnosing sepsis. Typically cell counts that are considered diagnostic of septic arthritis are greater than 30×10^9 cells/L, but infection should be suspected with values between 10×10^9 cells/L and 30×10^9 cells/L, particularly if the percentage of neutrophils is high.[171,176] Sequestration of WBCs into fibrin clots within the joint can result in lower-than-expected cell counts. Normal synovial fluid has less than 10% neutrophils. A cytologic differential greater than 80% neutrophils is highly suggestive of sepsis.[177] Synovial fluid lactate, glucose, and pH have been evaluated to improve the accuracy of diagnosis, and it appears synovial lactate may be useful; however, reference ranges are yet to be established.[162]

Sympathetic synovitis results from increased blood flow to a region, most commonly due to adjacent infected bone. The TNCC and TP of synovial fluid in sympathetic effusions are often elevated, but the percentage of neutrophils remains less than 80%.[168] Despite a low sensitivity for identification of bacteria, a Gram stain of synovial fluid should be performed. If bacteria are present, the results can guide antimicrobial selection while culture results are pending. Given the difficulty in culturing bacteria from joint fluid, a Gram stain result can sometimes be the only available option.[172] Synovial fluid should be submitted for aerobic and anaerobic culture. Positive cultures are obtained in 55% to 85.7% of synovial fluid samples submitted.[162,165,178,179] This range likely reflects the different inclusion criteria and culture techniques used in the referenced studies.

A positive culture more accurately guides antimicrobial selection, but it is associated with a poorer prognosis.[179] Synovial biopsy for culture does not increase the chance of a positive culture compared with synovial fluid alone.[178] A blood culture should also be performed, especially in the neonatal foal. If septic physitis or osteomyelitis is present, culture of débrided and necrotic bone is indicated at the time of surgery.

Ultrasonography can aid in quantifying synovial distention, identifying the presence of intrasynovial masses, thickening of the joint capsule and synovial

membrane, and identifying irregularities of the subchondral bone and abnormalities of the physis. The contralateral limb is used for comparison when there are findings of questionable significance. Figs. 17.3 and 17.4 show both longitudinal and cross-sectional ultrasonographic images of the diverticulum of the lateral femorotibial joint, respectively, in a foal with septic arthritis. Radiographs of the affected and contralateral limb should be taken because concurrent infection of the physis and subchondral bone is common due to the vascular network of neonatal foal joints and extension of infection.[172,180] Bone infection has been reported in 38% to 80% of foals with septic arthritis.[67,101,163,166,168,172] In the initial stages of septic arthritis, radiographic changes may be absent or demonstrate mild soft tissue displacement as a result of joint distention. As progression occurs, joint space narrowing may occur, associated with articular cartilage destruction, periosteal reaction, and subchondral bone osteolysis. Radiographic changes of bone sepsis are not evident until 7 to 10 days after the onset of infection.[169] Baseline and serial radiographs over time can help to determine the progress of the disease and response to treatment.[172]

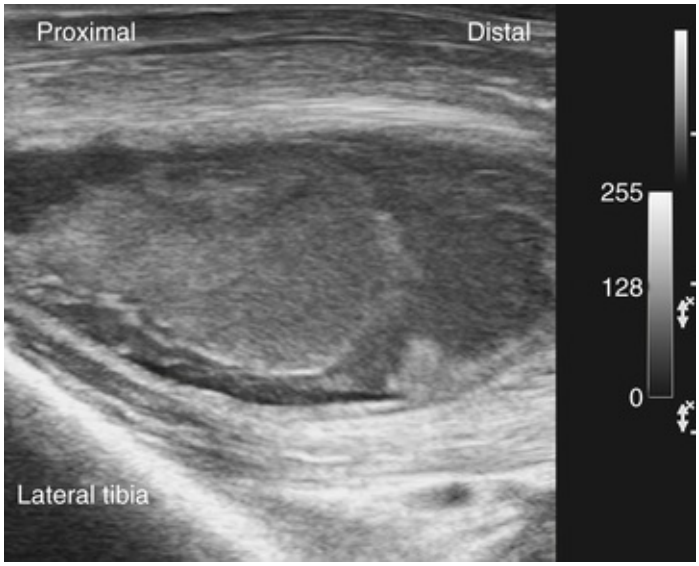


FIG. 17.3 A large mass of echogenic material consistent with fibrin. The distal aspect of the diverticulum of the lateral femorotibial joint is surrounded by hyperechoic synovial fluid.

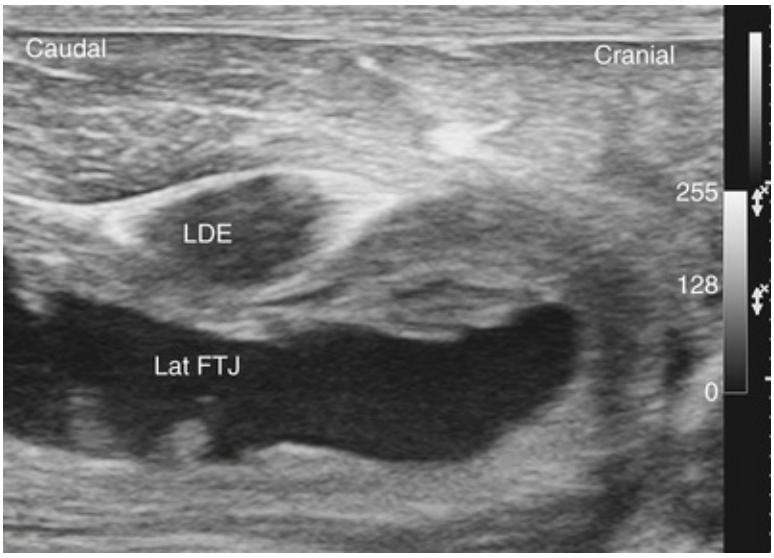


FIG. 17.4 The lateral femorotibial joint (Lat FTJ) compartment in cross-section positioned between the lateral tibia and tendon of the long digital extensor (LDE) tendon. The synovial fluid has increased echogenicity; the synovial lining and joint capsule is thickened with proliferative intrasynovial masses.

If radiographic examination is inconclusive or earlier identification of bone involvement is desired in cases where there is a high clinical suspicion of bone infection, advance imaging modalities should be recommended. Both computed tomography (CT) and magnetic resonance imaging (MRI) offer improved sensitivity for detection of bone and soft tissue pathology, respectively. These modalities are particularly valuable in the proximal limb or axial skeleton where overlying soft tissue and incomplete ossification of subchondral bone can limit radiographic evaluation of joint surfaces and physes.[170] CT provides increased sensitivity and detail with improved detection and characterization of periarticular lesions and osteomyelitis, but it is subject to availability and often requires general anesthesia. MRI offers superior imaging of periarticular soft tissue and cartilage, but the expense of the modality, limited availability, need for general anesthesia, and time for image acquisition limit the use of the modality for the diagnosis of septic orthopedic disease.[169]

It is imperative to clinically and diagnostically evaluate all other body systems in neonates with septic orthopedic disease to determine the presence of comorbidities, especially concurrent infections that have likely led to hematogenous dissemination to joints, bone, and physes. Failure to identify, diagnose, and treat comorbidities in neonatal foals will negatively influence prognosis when treating septic osteitis, physitis, or synovitis. In addition, serial

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body system and joint examinations are indicated on a daily basis to monitor response to therapy and identify development of additional sites of infection in joints or physes.[170]

Treatment

The early diagnosis of disease and initiation of aggressive therapy are paramount to successful outcomes. The cornerstones of therapy include resolution of distant underlying sources of infection, if present; systemic and local antimicrobial therapy; and drainage and lavage of the infected joint or joints. The choice of treatment regime will depend on facilities, economics, value of the foal, number and location of joints involved, any underlying disease process, presence of concurrent osteomyelitis, and identification of a causative organism.

Systemic Antibiotic Therapy

The selection of systemic antibiotics was discussed previously. Given the similarity between bacteria localized to joints of bone and those isolated from blood, the same initial protocols are warranted and should include broad-spectrum coverage, pending culture results. Despite a strong focus on local antibiotic delivery techniques for treatment of synovial or bone infection, the use of systemic antimicrobials is not negated and remains imperative for successful outcomes. This is likely due to primary and distant sources of infection and the development of multiple sites of joint infection due to hematogenous dissemination. Recently, a retrospective study of foals with septic arthritis reported that of the 85.7% of synovial fluid samples cultured that yielded growth, 62.4% were gram-negative organisms and 37.5% were gram-positive organisms.[162] Antimicrobial sensitivities for the isolates in this study suggest that aminoglycosides (gentamicin and amikacin) and cephalosporins (third generations or later) would be reasonable options for empirical treatment for septic arthritis in foals if gram-negative organisms are presumed to be the cause. Gram-positive organism susceptibilities were more varied with 81% tested susceptible to trimethoprim-sulfamethoxazole and 67% to ceftiofur. Most isolates were susceptible to fluoroquinolones, but the detrimental effects on developing cartilage and tendon cells preclude routine use in foals.[181,182]

Doxycycline (10 mg/kg PO bid) or oxytetracycline (5 to 10 mg/kg IV q12h) have been used successfully to treat septic arthritis and osteomyelitis.[164,183]

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Oxytetracycline has a relatively good spectrum of activity and good penetration into bone and synovial fluid. If osteomyelitis is present, continued treatment with systemic antimicrobials for up to 2 months is recommended. Serial monitoring of synovial fluid analysis is useful to determine the trend in response to therapy, but normalization should not determine when antimicrobials are discontinued due to the risk of recrudescence of infection if treatment is ceased too early.

Local Antibiotic Therapy

The local administration of antimicrobials allows delivery of higher concentrations to the tissues of interest. Intraarticular administration of antibiotics results in significantly higher synovial fluid levels than systemic routes. The technique is preferred when tourniquet application and regional perfusion are difficult, such as the proximal limb or axial skeleton. In addition, higher and more reliable antimicrobial concentrations are achieved in synovial fluid following intraarticular administration compared with regional perfusion techniques. Aminoglycosides, such as gentamicin (500 mg) and amikacin (125 to 250 mg), are commonly used (SID for 3 to 5 days) because of their effectiveness against many gram-negative pathogens. Ceftiofur sodium (125 to 500 mg) is also commonly used as an intraarticular therapy.

Regional limb perfusion techniques include intravenous (IVRP) and intraosseous (IORP) routes of antibiotic delivery, coupled with a tourniquet applied proximal to the affected joint or bone. IVRP or IORP can be performed concurrently with a joint lavage. A combination of sedation and local anesthesia or a short intravenous general anesthetic is usually required for these procedures, but these can be performed stall-side and should only take 30 to 40 minutes. The application of the tourniquet and injection of the infusate can be painful; therefore sedation and analgesia are required. Sedation can be achieved safely using diazepam (0.1 to 0.2 mg/kg IV) in combination with butorphanol (0.1 mg/kg IV). If general anesthesia is required, the regime just described serves as a good premedication, after which ketamine (2 to 2.2 mg/kg IV) can be used for induction. If additional time is required, the ketamine can be repeated. If the foal has minimal cardiovascular compromise, α_2 agonists, such as xylazine (0.5 to 1 mg/kg IV) or romifidine, in combination with butorphanol, also provide good sedation and analgesia; again, general anesthesia can be achieved through a follow-up bolus of ketamine.

The antibiotic is administered into a pressurized vascular environment, which

aids in diffusion of the antibiotic from the vascular system into the interstitial tissues distal to the tourniquet. This allows high concentrations of antibiotics to be achieved in the poorly perfused and infected or ischemic tissues and exudate. Regional perfusion techniques typically achieve 5 to 50 times the MIC required to inhibit common pathogens in synovial fluid.[172,184,185] The techniques are preferred over simple intrasynovial administration, if osteomyelitis is present.

Administration of local anesthetic via the intravenous catheter or intramedullary screw before infusion of the antibiotic-saline combination is helpful in improving tolerance of the procedure, if general anesthesia is not used. The total dose of lidocaine used in the regional perfusion technique should be in the range of 1.3 to 5 mg/kg. Therefore for a 50-kg foal, the amount used should be between 3.25 and 12.5 mL of 2% lidocaine, with the lower end of the range used in very young foals because of a lack of pharmacokinetic data.

Following sedation or induction of general anesthesia, an Esmarch bandage (or equivalent 5- to 12-cm-wide elastic or rubber bandage) or a pressurized tourniquet cuff can be applied proximal to the affected region. It should only be left on for 30 minutes following infusion of the antibiotic and a maximum of 60 minutes total tourniquet application time. For IVRP a 22-gauge butterfly needle, Teflon catheter, or polyurethane over-the-needle catheter is advanced into a superficial vein below the tourniquet. A small amount of cyanoacrylate glue can be used to fix the catheter to the skin to prevent removal, kinking, or movement. Commonly used veins include the saphenous, cephalic, or palmar/plantar vessels. The perfusate (local anesthetic followed by antibiotic and saline) can be injected over 1 to 5 minutes.[186] Following injection, the catheter is removed and gauze swabs are placed over the site with several wraps of tape to provide pressure. This can be removed following the removal of the tourniquet after the appropriate time. The procedure is typically repeated at 24- to 48-hour intervals for three to five treatments, depending on the response to therapy.

The intraosseous route requires a custom-made cannulated cortical screw with a welded Luer-Lok adapter or an intraosseous infusion needle (Cook Critical Care, Bloomington, Ind.). A hole is drilled through the cortex of the metacarpus or metatarsus for placement of the screw, after which time perfusate can be injected. Because of the small size of foals and the specific equipment required, intraosseous perfusion is used in limited situations or equine hospitals. In addition, increased complications are recognized with the intraosseous technique.[186]

The aminoglycosides amikacin and gentamicin are commonly used since most

joint infections are caused by gram-negative bacteria. Penicillin, cefazolin, and ceftiofur have also been used safely in local therapy, but only in response to culture and sensitivity testing. The size of foal and the area to be infused below the tourniquet should be considered when deciding on total volume, but volumes are typically between 30 and 60 mL, with 0.9% saline used to dilute the antibiotic. If local anesthetic is used, that volume is considered as part of the total perfusate. The daily systemic dose of aminoglycoside should be reduced by the amount used in the perfusion, and the total dose used in the perfusion should not exceed the total systemic dose. The procedure should be performed at the same time of day that the systemic dose is administered. Commonly recommended doses for foals are 250 to 500 mg of amikacin, 400 to 600 mg of gentamicin, and 500 mg of ceftiofur.[164,169]

Complications of IVRP or IORP include soft tissue swelling at the infusion site, thrombophlebitis, difficulty in injecting during IORP, and tissue sloughing. Most of these can be avoided with careful aseptic technique, by avoiding catheter repositioning and minimizing the number of procedures.[186]

Antimicrobial-containing substances, including collagen or beads made of bone cement such as polymethylmethacrylate (PMMA) or Plaster of Paris (POP), can also be implanted at the site of local bone infection. Their use within joints is not recommended due to the need for removal (PMMA) and rapid dissolution or inflammation incited (PMMA/collagen sponges). These beads are readily prepared aseptically for immediate use and, when using PMMA with a heat-stabile antibiotic such as aminoglycosides, can be gas or steam sterilized for later use. The beads provide an antibiotic depot when implanted adjacent to infected bone; however, the necessity for surgical removal following resolution of infection is one of the limitations of their use. The beads can be prepared by adding 10% to 20% antibiotic (2 to 4 g) to the bone cement powder (20 g), then mixing with the liquid (monomer) until the mixture can be molded into beads or cylinders. The larger surface area allows for increased antibiotic elution.[170]

Intrathecal catheters and constant rate infusion pumps can also be used for local delivery of antibiotics to infected synovial cavities in foals. High antimicrobial concentrations in synovial fluid lead to high concentrations in adjacent bone and physes.[187] Catheters can be passed into synovial cavities via arthroscopic guidance or placed directly. Included items are an intrasynovial catheter, flow control tubing, and an elastomeric pump (Mila International, Florence, KY.). The pump allows continuous rate delivery of the selected antibiotic solution. The flow of the pump and concentration of the solution is

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determined by the amount of antibiotic to be delivered over a timed period.[170] Maintenance of the catheter and the pump through frequent and careful monitoring is required prevent complications, such as dislodging, blockage, or restricted delivery rates.

Drainage and Lavage of the Septic Joint

Joint drainage, lavage, and débridement are important components in the management of synovial sepsis. The aim of lavage is to reduce the number of organisms in the synovial fluid, remove debris and inflammatory products, and reduce the level of pain associated with inflammation and joint distention. Techniques include needle lavage (ingress-egress, through and through), arthroscopic lavage and débridement, or arthrotomy. Needle lavage has the most beneficial effect if performed within 24 to 48 hours after the onset of infection, or, more importantly, before accumulation of fibrin. Ultrasound can aid in determining the location for needle placement and the amount of intrasynovial fibrin. A large amount of fibrin or intrasynovial masses will compromise lavage as a result of needle plugging. It is also unlikely that fibrin will be removed by needle lavage. Aggregates of microorganisms can be sequestered in fibrin and escape the effects of antibiotics, resulting in persistence of clinical signs or recrudescence of infection once therapy has been discontinued.

For needle lavage, the skin should be clipped and aseptically prepared, and the foal sedated or anesthetized as described previously. Synovial fluid should be collected for confirmation of sepsis or for serial cytologic monitoring to assess response to treatment. If general anesthesia is not used, the joint can be distended with local anesthetic after a single needle placement. The ingress-egress lavage technique involves repeated distention of the joint with sterile saline, followed by aspiration using a single portal. The technique is indicated in joints that have difficult access or where additional needles have become plugged or displaced from the joint. Through-and-through lavage is more commonly used. After distention of the joint with sterile saline or local anesthetic, additional superficial pouches of the joint become visible, aiding in placement of further needles. Needle size is based on clinician preference, but usually 18- to 14-gauge needles are used. Practitioners placing additional needles must try to keep the joint distended to avoid iatrogenic damage to the cartilage. Precise landmarks for needle placement are not necessary, but a sound knowledge of the local anatomy and visualization of the three-dimensional structure of the joint will help to maintain correct placement of the needles

during the lavage. Between 1 and 2 L of physiologic saline or lactated Ringer solution are typically used to complete the lavage. The bags can be pressurized and attached to the ingress needle, allowing the clinician to place additional needles and subtly adjust needle position to facilitate flow. The risk of using a pressure bag system is rapid delivery of saline outside the joint if the ingress needle position changes slightly. Joint lavage becomes futile once subcutaneous saline restricts the distention potential of the joint pouches. In joints with moderate periarticular soft tissue structures or swelling, the author prefers to use 20- to 30-mL syringes to lavage the joint. Any increase in resistance to injection is easily appreciated, and correction of needle placement can occur before fluid is delivered outside the joint (Fig. 17.5). The use of different ingress needles is recommended to increase turbulence and facilitate removal of joint debris, irrespective of whether syringes or pressurized bags are used. This also prevents the egress needles from plugging with fibrin. On completion of the lavage, as much fluid as possible should be expressed before removing all needles except one, which can then be used to administer intraarticular antibiotic.



FIG. 17.5 Lavage of a septic joint using a syringe and separate egress needle.

The number and frequency of needle lavages are determined by the response to treatment. If the clinical signs progress in the face of 3 to 5 days of systemic and local antibiotic therapy and needle lavage, then reevaluation of the foal including US and radiography is indicated. Signs of treatment failure include persistent lameness or pyrexia, periarticular swelling, persistence or worsening

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of joint effusion, additional joint involvement, or failure to decrease synovial cell counts or differential. It is important to identify if there has been subchondral bone lysis. Treatment failure may prompt an antibiotic change and/or more aggressive joint lavage via arthroscopy or arthrotomy, if arthroscopy is not available. Arthroscopy offers many advantages over needle lavage and arthrotomy and is the preferred choice for chronic or refractory cases of synovial infection, or those where there is evidence of fibrin or subchondral defects within the joint. The technique permits superior visualization of most aspects of the joint, including the articular cartilage, bone, joint capsule, and synovial membrane. Targeted lavage and débridement can be achieved for removal of fibrin and debris, synovial resection, and débridement of necrotic cartilage or subchondral bone. Arthroscopic and arthrotomy approaches and intraarticular anatomy of commonly affected joints are reviewed comprehensively elsewhere. Arthrotomy is generally reserved for chronic or refractory cases that have been poorly responsive to other forms of lavage and débridement. It is imperative that a sterile absorbent bandage is maintained for drainage of synovial fluid to reduce the risk of ascending infection.

Generally, the duration of local antimicrobial administration (intraarticular, regional perfusions or continuous delivery systems) is determined by clinical and synovial cytologic improvements, including resolution of joint swelling, lameness, and a neutrophil percentage below 80%. Systemic antimicrobial administration is usually continued for a minimum of 2 weeks beyond the resolution of clinical signs.[170]

Septic Osteomyelitis

Septic osteomyelitis occurs as a primary disease entity or concurrently with septic synovitis, with infections commonly occurring at the epiphysis of long bones, metaphyseal side of growth plates, costochondral junctions, and articular facets of vertebral bodies. Radiographic evidence of osteomyelitis includes regions of focal loss of bone density, osteolysis, or sequestrum formation. Necrotic bone can act as a nidus for continued bacterial growth. The treatment of osteomyelitis includes systemic and local antibiotics and possible débridement.[164,188] Necrotic subchondral bone can be débrided using arthroscopy, and infected physeal bone can be débrided under radiographic or fluoroscopic guidance. Débridement of necrotic bone is not indicated in extensive lesions where mechanical joint stability may be jeopardized or where

the surgical access and débridement would create significant surgical complications.[164,188] Evidence suggests that surgical curettage may not offer significant advantages over prolonged systemic and local antibiotic therapy alone.[164,183,189] In addition to the regional perfusion techniques described previously, there is occasional indication for implantation following débridement of antibiotic impregnated polymethylmethacrylate, calcium sulfate, or collagen sponges. These substances elute antibiotic at the site of bone infection.[171]

IV tetracycline (5 to 10 mg/kg IV q12h) or oral doxycycline (10 mg/kg bid PO), along with local treatment with amikacin (IVRP or IA 250 to 500 mg), is indicated if culture and sensitivity results suggest susceptibility, or if culture results are unavailable. Surgical débridement is indicated if there is radiographic evidence of sequestrum formation, chronicity of the disease in the face of medical therapy, or progression of the osseous infection.

In cases of osteomyelitis, serial monitoring of fibrinogen or SAA may aid in determining the response to therapy. A positive response results in decreasing SAA levels over 48 to 72 hours, and this commonly precedes improvement in lameness.

Management and Adjunctive Therapy

Nonsteroidal antiinflammatory drugs (NSAIDs) are indicated in the management of septic orthopedic disease resulting from antiinflammatory, analgesic, and antipyretic effects. Commonly used NSAIDs include flunixin meglumine, ketoprofen, phenylbutazone, and, less commonly, ibuprofen. Dosages cannot be directly extrapolated from adults because healthy foals have a greater volume of drug distribution and prolonged clearance.[190] For flunixin and ketoprofen, this results in a dose rate that is 1.5 times that of the adult dose and extension of the dosing interval to q24h. The drugs should be used judiciously in compromised or critically ill foals because of the potential adverse effects such as gastrointestinal (GI) ulceration, nephrotoxicity, and platelet dysfunction. Oral meloxicam at a dose rate of 0.6 mg/kg q12h achieves plasma concentrations that are likely therapeutic without evidence of drug accumulation in plasma. Foals appear to be more resistant to the adverse effects of meloxicam than adult horses, and drug clearance was more rapid in foals.[190] If additional analgesia is required, butorphanol (0.05 to 0.1 mg/kg IV or IM) or transdermal fentanyl patches (100 µg/h patch) can be used safely in foals. The clearance and systemic uptake of butorphanol are faster in foals, suggesting that higher doses may be required. A

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dose rate of 0.1 mg/kg of butorphanol-provided analgesia for 150 minutes in 4- and 8-week-old pony foals.[191]

The affected limb should be bandaged during treatment to cover needle/arthroscopy portals, provide compression and support to the limb, limit swelling and reduce pain, and absorb exudate if an arthrotomy has been performed. Application of bandages with adequate padding in the secondary layer is recommended in the distal limb because of the combination of thin skin, bony protuberances, and minimal subcutaneous soft tissues. Adhesive dressings can be used over joints where a bandage cannot be maintained.

Restoration of joint health and range of movement is important following infection. Gentle forced flexion and extension of the joint while non–weight bearing will help maintain joint function and movement. The foal should be stall confined and weight-bearing exercise avoided for 3 to 4 weeks following the resolution of infection and clinical signs. The stall should have a deep bedding of clean straw to reduce the risk of pressure necrosis during recumbency. The stall should be cleaned two to three times a day to reduce the risk of the foal lying in feces or urine-soaked bedding. Handlers and clinicians should use strict personal hygiene when treating foals. Controlled hand walking of the mare on a daily basis for 1 to 2 weeks should be initiated before free turnout.

The decision to discontinue antibiotic therapy is based on clinical judgment and resolution of clinical, hematologic, radiographic, and cytologic abnormalities. Generally, local antibiotic therapy and lavage are continued until normalization of the synovial fluid and cytology, and systemic antibiotic therapy is continued for 2 to 3 weeks beyond the resolution of clinical signs.

Prognosis

The prognosis of foals with septic arthritis/osteomyelitis is dependent on a number of factors, but short-term survival is considered good to excellent with studies reporting 71% to 81% survival to discharge.[101,163,166] The prognosis for future athletic performance is less favorable, with 30% to 48% of foals affected with septic arthritis/osteomyelitis going on to race.[101,166,167] Factors affecting prognosis include prolonged duration (>24 hours) of signs before the initiation of treatment, concurrent systemic disease or comorbidities, the number of joints infected, the location of infected joints, the presence of concurrent osteomyelitis, and the type and diversity of bacteria involved. The financial constraints for treatment, facilities, and technical skill available for treatment and the expected

long-term use of the foal can also affect outcomes.[164,166,167,171,172] These factors and the high cost and long duration of treatment should be considered when counseling owners. Foals that are treated expediently with appropriate systemic and local antibiotic therapy and without concurrent disease may have a more favorable prognosis for survival and athleticism than previously indicated.[162,170]

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Noninfectious Causes of Lameness

Rachael L. Smith

Fractures occur relatively commonly in young foals and are an important differential diagnosis for foals that are lame (see Box 17.1). They are most often due to traumatic insult or an isolated event. Fractures are differentiated from septic arthritis or osteomyelitis through history and physical findings; relevant laboratory data, including hematology and synovial fluid analysis; and, most importantly, diagnostic imaging. Several factors may predispose foals to fracture, including prolonged stall confinement leading to osteoporosis and weakened soft tissue support structures, trauma from the dam or other horses, or management systems that allow overexercise.[192] Common sites of fracture in the distal limb include the distal phalanx, physeal fractures of the first phalanx, and proximal sesamoid bones. Physeal fractures of other bones are also common due to the relative weakness of this structure and are described by the Salter-Harris classification system. Olecranon fractures are the most common fracture of the upper limb. Premature or dysmature foals are prone to crushing injuries of the cuboidal bones of the carpus or tarsus.

In foals, rupture of the common digital extensor tendon may be present at birth or develop within a few days of life. Rupture occurs within the carpal synovial sheath and produces swelling over the dorsolateral surface of the carpus at the level of the middle carpal and carpometacarpal joints. Palpation of the fibers reveals tearing of the tendon and can be confirmed with ultrasonography. Splinting of the limb is required in foals that continually buckle forward at the fetlock. Box confinement for the first 3 to 4 weeks usually results in healing. Surgery is not required, and the tendon ends usually reappose over 6 months with minimal swelling and a good long-term prognosis.

Rupture of the gastrocnemius muscle at the level of its fossa in the femur can also occur during parturition, especially if assisted, or if the stifle is forced into extension during delivery while the hock is flexed. Hyperflexion of the hock occurs, and diagnosis of this is confirmed with concurrent flexion of the hock and extension of the stifle (Fig. 17.6). Ultrasound evaluation usually shows hemorrhage within the muscle belly and edema at the fossa of the femur. Treatment is complete stall rest if the foal can bear weight, but if the hock is severely flexed, a full limb case should be applied. The prognosis for long-term

soundness is guarded.[26]



FIG. 17.6 Rupture of the gastrocnemius muscle.

Congenital contractural deformities of joints can be bilateral or unilateral and present at birth. They are usually the result of external environmental factors during gestation, bone or joint malformation, or other physiologic causes such as intrauterine malpositioning. They are described with reference to the affected joint and can occur in the carpus, fetlock, pastern, coffin joint, or tarsus. Diagnosis of contractural deformities is relatively straightforward based on the inability to straighten affected joints and difficulty in standing and movement at birth as a result.[172] This predisposes to failure of passive transfer of immunoglobulin by impeding the ability to adequately nurse. The degree of contracture varies from mild to severe and may be associated with scoliosis and/or torticollis.[193] Conservative therapy consisting of bandaging or splinting the limbs to induce tendon laxity may be helpful. Care must be taken to provide adequate padding under the splint and to reset the splint every day. Oxytetracycline (2 g slow IV) in combination with splinting induces relaxation of the musculotendinous unit, and although results can be remarkable, they are

not always reliable[172]; repeat treatments are often required.

Twins, premature foals, foals that are small for gestational age, and foals with in utero–acquired infection are likely to have incomplete ossification of cuboidal bones at birth. Foals with substantially reduced ossification may damage bone with limb loading. Limited exercise may be prudent until ossification begins to increase radiographically, which can be within 7 days. Hypothyroidism has been identified in foals with angular limb deformities, contracted tendons, and tarsal bone collapse.

Young foals can suffer physitis when there is excess load caused by overexercise or weight on the newly forming bone, or as a result of normal loading on abnormal conformation. The physis of the distal metacarpus/tarsus or proximal phalanx is most commonly affected. Clinical signs can vary and be subtle, such as a stiff gait, shortened cranial phase of stride, trembling when standing, or buckling forward at the carpus or fetlock. Pain in the physis can lead to contracture of fetlock tendons. Treatment is aimed at reducing pain with anti-inflammatory therapy and reducing exercise level or correcting underlying angular limb deformities.[172]

Other causes of lameness and swelling associated with joints include cellulitis, hemarthrosis, subsolar/solar bruising of the foot, and hoof wall cracks causing laminae pain.

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Seizures

Guy D. Lester

Recognition

Foals have a lower seizure threshold than adult horses.[194] Seizures are generated by abnormal electrical activity within the cerebral cortex. Depending on the location and extent of the abnormal activity, the seizures may be partial or generalized. Generalized seizure activity is characterized by recumbency, widespread involuntary muscle activity, paddling of the limbs, and extensor rigidity. Partial seizure activity may be more difficult to identify and could be limited to mild movements of the face and jaw, or stretching of the limbs.[25]

Rapid eye movement (REM) sleep can be easily confused with seizure activity. Normal activity is particularly prominent in premature or dysmature foals. Signs can include motor activity, including rhythmic paddling of the limbs, neck extension, chomping of the lips, rapid eye movements, and vocalization.[195] Episodes can last several minutes and be distinguished from seizure activity by attempting to arouse the animal. A foal in REM sleep should be easily aroused to full consciousness.

A foal that is simply resisting restraint in lateral recumbency may also appear to be seizuring, and violent paddling of the limbs and occasionally opisthotonos are noted. If confusion exists as to the cause of the activity, the animal should be encouraged to stand and its behavior reevaluated.

Once seizure activity is identified, a complete history should be obtained, including a detailed description of the delivery process, and complete physical and neurologic examinations should be performed. Any signs of trauma, infection, or congenital malformations should be noted. Evaluation of hematologic data and IgG status, combined with historic and physical examination parameters, result in an assessment of the likelihood of sepsis. Blood glucose and serum electrolyte concentrations should be determined promptly. A biochemistry panel, blood gas analysis, bacterial cultures of blood and other body fluids, and possibly CSF analysis complete the database in most cases.

CT or MRI scans are advanced diagnostic procedures for evaluating the

anatomic causes of seizures. Premortem diagnosis of agenesis of the corpus callosum and associated malformations was made using CT scanning in a foal that had an abnormally shaped head and seizures refractory to anticonvulsant therapy.[196] Identification of the specific abnormalities early in the clinical course allowed the owners to make more of an informed decision regarding the treatment of the foal and the clinicians to acquire valuable information regarding the prognosis of a specific malformation in the horse.

Seizures in foals have numerous causes (Box 17.2). The most common cause of seizure activity in foals is described by the syndrome known as *neonatal encephalopathy* (NE).

Box 17.2

Seizure Disorders in the Neonatal Foal

Neonatal encephalopathy
Bacterial meningitis
Viral encephalitis
Benign juvenile epilepsy
Lavender foal syndrome
Kernicterus
Hepatic failure
Congenital brain disease
Hydrocephalus, hydranencephaly
Head trauma
Hypoglycemia
Electrolyte disorders
Hypocalcemia, hyponatremia, hypernatremia
Tetanus
Toxicities
Ivermectin, moxidectin
Glycogen storage disease IV
Hyperammonemia of Morgan foals

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Neonatal Encephalopathy

David Wong

NE is one of the most common neurologic diseases affecting neonatal foals with a reported incidence of 1% to 2% of all equine births.[197] Other synonyms for NE reflect proposed etiologies of the disease, such as hypoxic-ischemic encephalopathy (HIE), perinatal asphyxia syndrome (PAS), and neonatal maladjustment syndrome; alternatively, more descriptive names reflecting the clinical manifestations of NE, such as barker, wanderer, or dummy foal, also have been used.[6] It is important to note that foals with NE may have a hypoxic-ischemic event contributing to the disease process, but it is not uncommon for foals with NE to have no evidence of hypoxia-ischemia and an apparently normal birth. Therefore other associated pathophysiologic mechanisms, such as excessive neurotransmitters, inflammation, and/or abnormal postpartum hormonal concentrations, also might contribute to the development of abnormal neurologic function.[198–201] In this text, the broader term of NE is used rather than HIE or PAS. Despite the frequency with which veterinarians encounter NE, there are no direct studies in regard to the pathophysiology of NE in foals, thus the reader must acknowledge this limitation as the knowledge of this condition has been extrapolated from infants and other animal models.

Pathophysiology

The exact biochemical and pathophysiologic mechanism(s) that result in NE are unknown, but at a rudimentary level, reduction in cerebral blood flow and oxygen to tissues during the antepartum (maternal hypotension, severe hypoxia, infection, placental insufficiency); peripartum (cord occlusion, premature placental separation, dystocia); or postnatal (neonatal shock, respiratory or cardiac arrest) period is believed to be a central theme in many affected patients.[201] After a reversible hypoxic-ischemic brain insult, neuronal injury and/or death occurs in two phases: an acute, primary neuronal cell death followed by a delayed phase of cell death. The primary or acute phase of injury results from reduced cerebral blood flow, which consequently decreases both oxygen and glucose delivery to the brain, thus resulting in a switch to anaerobic respiration and concomitant decrease in phosphocreatine and adenosine

triphosphate (ATP) and increased lactic acid production.[202,203] The decreased availability of ATP causes failure to maintain cellular integrity and homeostasis, in part due to decreased energy available to maintain both low intracellular calcium concentrations and the normal activity of cell membrane Na^+/K^+ pumps.[204] Not only does excessive influx of sodium into the cell cause concomitant movement of water into neurons, resulting in cell swelling and edema formation, but it also results in depolarization of neurons, which precipitates the release of the excitatory neurotransmitter, glutamate.[205] Glutamate also accumulates in the extracellular space because of failure of energy-dependent glutamate uptake back into neurons.[205,206] Glutamate then activates receptors within the central nervous system (CNS), resulting in sodium entry through ionotropic receptors, passive influx of chloride and water, additional influx of calcium, cell swelling, and potential cell lysis.[204,206] Depending on the severity of the initial insult to the brain, the acute phase of primary energy failure can result in impaired cellular integrity, disruption of the cytoskeleton and cell membrane, and ultimately cellular necrosis. Upon cell rupture, cellular contents are released, which results in additional inflammation. Microglia subsequently migrate into the area of necrosis and release further inflammatory mediators that can damage the CNS. If the insult is less severe, cells may recover or undergo apoptosis.[206] Once blood flow is restored, a brief recovery or latent period occurs in which normal cerebral metabolism is reestablished.[206]

Conceptually, neuronal cell death as a result of a hypoxic-ischemic event and energy failure is a plausible mechanism of CNS injury and certainly contributes to the pathophysiologic mechanisms of NE (Fig. 17.7). However, studies suggest that this mechanism alone is too simplistic and continued neuronal damage occurs after the initial hypoxic-ischemic insult.[205,207] The second phase of neuronal death, sometimes referred to as *delayed neuronal cell death* or *secondary energy failure*, occurs 6 to 48 hours after the initial injury and is believed to be associated with one or more of the following mechanisms: excitotoxicity, accumulation of intracellular calcium and resultant activation of numerous enzymes and pathways, reperfusion injury (oxidative stress), cytotoxic actions of activated microglia, inflammation, and apoptosis.[6,199,201,203,204]

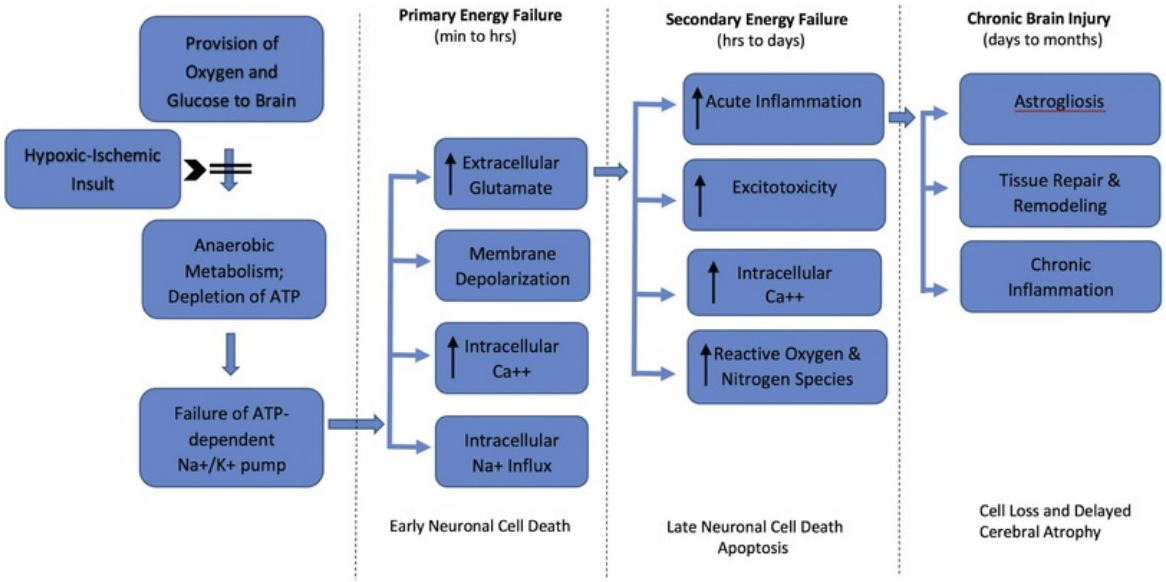


FIG. 17.7 Proposed pathophysiologic mechanisms associated with neonatal encephalopathy. Hypoxic-ischemic insult results in deprivation of oxygen and glucose to the central nervous system and cells shift to anaerobic metabolism. Reduction in adenosine triphosphate causes failure of energy-dependent cell membrane ion channels resulting in acute intracellular influx of calcium and sodium, along with cell membrane depolarization and accumulation of extracellular glutamate. This series of events can lead to cell swelling and cell death (primary energy failure). If initial insult is prolonged or severe, cascade of events can lead to excitotoxicity and increased production of inflammatory molecules and reactive oxygen species/reactive nitrogen species resulting in further cell death and apoptosis (secondary energy failure). Chronic brain injury, characterized by astrogliosis, chronic inflammation, and tissue repair and remodeling can occur over days to months and further contribute to loss of brain cells and cerebral atrophy. (Adapted from Li B, Concepcion K, Meng X, et al: Brain-immune interactions in perinatal hypoxic-ischemic brain injury. Prog Neurobiol 159:50−68, 2017.)

Linked with hypoxia-ischemia are other damaging processes, such as the accumulation of extracellular glutamate and production of reactive oxygen species (ROS) and inflammatory mediators. Glutamate is the predominant excitatory amino acid neurotransmitter in the brain and initiates biochemical changes through its interaction with specific receptors.[6,199,206] The ionotropic receptors, so named because they are linked to ion channels, include the N-methyl-D-aspartate (NMDA) receptor, which is linked to calcium channels, and the α–amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) and kainite (KA) receptors, which are linked to sodium channels.[6,199,206] In the healthy individual, glutamate is released from presynaptic nerve terminals when

signaled by neuronal depolarization.[208] Glutamate is rapidly removed from the synaptic cleft by glutamate transporters in astroglia and converted to glutamine, which is then transported back into nerve terminals for reuse.[208] Hypoxia or ischemia, as well as decreased glucose delivery to the brain, impairs normal function of astroglial glutamate transporters in the synaptic cleft, resulting in accumulation of extracellular glutamate and ensuing opening of ion channels operated by glutamate receptors.[199,208] In turn, increased glutamate concentrations result in excessive calcium influx into neurons, which consequently triggers activation of lipases, proteases, and endonucleases.[201] This excitotoxicity, in which excessive activation of glutamatergic neurotransmission occurs, can result in cell apoptosis and necrosis.[199,208]

The neonatal brain is particularly vulnerable to oxidative injury owing to its high concentrations of unsaturated fatty acids, high rate of oxygen consumption, and low concentration of antioxidants.[199,209] As a result of hypoxia-ischemia and/or increased intracellular calcium in neurons, a number of enzymatic pathways produce ROS through several enzyme systems including NADPH oxidase (NOX), glutathione peroxidase, cyclooxygenase, xanthine dehydrogenase, monoamine oxidase, myeloperoxidase, and nitric oxide synthase (NOS).[201,209,210] Some evidence suggests that NOS and NOX, along with an oxygen-deprived mitochondrial electron transport system, comprise the major sources of ROS in the brain during a hypoxic-ischemic event.[209] In addition, after a hypoxic-ischemic event, immune cells (infiltrating neutrophils, resident microglia) within the brain are stimulated and generate proinflammatory mediators and oxygen free radicals, such as superoxide anion ($\bullet O_2^-$), hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl), and hydroxyl radicals ($\bullet OH$).[6,209] Furthermore, NOS, specifically neuronal NOS (nNOS), which is localized with NMDA receptors and activated by calcium influx through the NMDA receptor, can produce nitric oxide ($\bullet NO$) and reactive nitrogen species (RNS); RNS can subsequently react with superoxide anion to form the powerful oxidant, peroxynitrite ($ONOO^-$).[208,211,212] Cumulatively, ROS and RNS can cause significant damage to biological proteins (membrane protein degradation), lipids (lipid oxidation), and nucleic acids (DNA degeneration).[209]

The inflammatory and immunologic response to a hypoxic-ischemic insult also contributes to the pathogenesis of cerebral injury.[201] In the neonatal brain, an immediate innate immune response occurs within minutes of hypoxic-

ischemic injury with stressed or dead neurons resulting in diffuse activation of neuroglial cells.[203] Activated astrocytes, microglia, and endothelial cells then release proinflammatory cytokines, such as tumor necrosis factor−α (TNF-α), interleukin (IL)-1, IL-6, and IL-8.[201,203] In addition, release of matrix metalloproteinases (MMPs) and proinflammatory chemokines and cytokines facilitates recruitment and activation of peripheral immune cells.[203] Subsequently, activated peripheral inflammatory cells release neurotoxic agents, such as proinflammatory cytokines, NO, ROS, and myeloperoxidase, which further contribute to neuronal death, cytotoxic edema, and brain injury.[203,213] Cytokines may injure white matter by inhibiting differentiation of developing oligodendrocytes, causing myelin degeneration and inducing oligodendroglial apoptosis, which further exacerbates neuronal injury.[210,213] Despite the detrimental effects of the inflammatory response, however, it also serves a beneficial role by facilitating functional recovery of the CNS by eliminating cellular debris and tissue recovery. Thus in response to hypoxic-ischemic injury, the inflammatory response attempts to remove cellular debris and promote healing of the tissues but paradoxically results in cellular injury.[6]

Evidence of hypoxic-ischemic injury is not always identified historically or microscopically in foals with NE, and long-term neurologic deficits commonly reported in people with NE, such as cerebral palsy, visual and auditory disorders, and epilepsy, are not typically observed in foals.[201] Thus alternative causes of NE have been explored. One such pathophysiologic mechanism that might play a role in a subset of foals with NE is the presence of altered concentrations of neurosteroids, which can cross the blood-brain barrier and have neuromodulatory effects resulting in clinical signs of NE in foals shortly after birth.[214] In utero, the fetus maintains a quiet, suppressed, and relatively inactive state under the influence of neurosteroids, as compared with the precocious newborn foal that must be active and ambulatory shortly after birth.[215] Some foals with NE have persistently increased concentrations of neurosteroids, such as plasma progestagens,[200,216] and in one study, several plasma progestagens (progesterone, epitestosterone, androstenedione) were significantly increased in foals with NE when compared with foals with other disorders.[214] Experimentally, intravenous infusion of allopregnenolone in a healthy newborn foal resulted in sedation and decreased responsiveness, with higher dosages of allopregnenolone resulting in dramatic neurobehavioral effects including recumbency, stupor, and unresponsiveness to the mare, environment, sound, and

tactile stimulation.[214] These clinical signs persisted during the CRI of allopregnenolone but waned over 15 minutes after cessation of the infusion followed by normal behavior 30 minutes post infusion.[214] Allopregnenolone is believed to mediate its effects in the CNS via the $GABA_A$ receptor, and although this study only involved one foal, consideration must be granted to the possibility that persistence of fetal progestagens by the newborn foal can affect the CNS and cause signs compatible with NE in a subset of foals.[77,217] Moreover, the rapid recovery from clinical signs of NE in some foals, especially in light of no obvious residual neurologic deficits, might be associated with a decline of pregnene-mediated sedative effects.[214]

Expanding on the theory that neurosteroids may impact the level of consciousness in newborn foals, one theory suggests that signaling of the transition from an in utero unconscious state to extrauterine consciousness may involve labor-induced physical compression (squeezing) and this compression might be associated with changes in neurosteroid concentrations.[218,219] Studies investigated the use of a rope restraint device (Fig. 17.8) in neonatal foals in efforts to demonstrate that application of physical pressure via rope restraints activates the HPA axis, affects neurosteroid concentrations, and causes quiescence that is essential to the transition from fetus to newborn by preventing malposition during parturition.[218,219] In one study involving eight healthy neonatal foals, a soft linen rope was secured around each foal's neck and under the shoulder and then looped around the thorax and abdomen using half-hitch knots positioned directly on the dorsal thoracolumbar area.[219] The handler gently pulled on the rope from behind the foal, which produced a generalized squeezing of the foal while a second individual assisted the foal to lay down; tension on the rope was maintained for 15 to 20 minutes.[218,219] During the restraint, foals assumed lateral recumbency with relaxed, somnolent behavior along with a significant decrease in heart and respiratory rate and rectal temperature. Furthermore, electroencephalography (EEG) recordings revealed patterns consistent with slow wave sleep and plasma ACTH, β-endorphin, dehydroepiandrosterone sulfate, and androstenedione concentrations significantly increased during restraint, compared with pre-restraint values.[219] A follow-up survey involved equine clinicians that collected observational data from foals with NE that were treated with standard medical therapy with or without the inclusion of the rope restraint/squeeze method.[218] The survey inquired about medical treatments and a response to medical treatment only

(nonsqueezed group) versus the squeeze procedure with or without medical therapy (squeezed group). There were 51 respondents to the survey providing information on 195 foals with NE (108 nonsqueezed; 87 squeezed). In this survey, foals that received the squeeze procedure with or without medical therapy had significantly faster recovery rates, were 3.7 times more likely to recover faster, and were 15 times more likely to recover in less than 1 hour than foals that were not squeezed.[218] The authors concluded that foals that were squeezed for 20 minutes had significantly faster and higher recovery rates than foals that did not receive the procedure. There were several limitations to this study, but the authors proposed that the pressure from the birth canal that the fetus is exposed to during stage 2 of labor might influence the balance of neurosteroids and play a role in the neonatal transition from neuroinhibition to neuroactivation.[218,220,221] Thus simulation of stage 2 labor with the rope restraint may reset the balance of these neurosteroids and expedite recovery from NE and facilitate normal behavior in the neonatal foal.



FIG. 17.8 Foal fitted with a soft linen rope restraint device. Squeeze effect generated by a person who stands behind the foal and gently pulls on the rope; an assistant helps the foal to lie down. Completion of the rope squeeze after 15 to 20 minutes.

Yet another alternate theory by which foals may develop NE outside the framework of a hypoxic-ischemic insult involves the inflammatory response in the neonatal brain associated with chorioamnionitis (placentitis), maternal and fetal inflammation, and resultant injury to the fetal/neonatal brain.[199,222,223] In health, the chorioallantois has properties of an immunologically privileged site in order to protect the allogenic fetus from rejection by the mother. When an infectious agent invades the placental membranes, both a maternal and fetal inflammatory response, characterized by release of proinflammatory and inhibitory cytokines and chemokines, can occur. The initial response to

intrauterine infection involves leukocytes derived from the maternal circulation (maternal inflammatory response).[223] Subsequently, intrauterine inflammation also involves leukocytes derived from the fetal vessels and systemic activation of the fetal innate immune system (fetal inflammatory response syndrome, FIRS).[223] Both maternal and fetal inflammatory responses are typified by production of inflammatory mediators (IL-1, IL-6, TNF-α) and activation of neutrophils and other components of the innate immune system.[222,223] Although not fully understood, the FIRS may induce cerebral white matter injury, intraventricular hemorrhage, and/or periventricular leukomalacia, manifesting clinically as neurologic deficits. Proposed mechanisms by which this occurs includes cerebral hypoperfusion and ischemia, activation of the coagulation cascade resulting in capillary thrombosis, and necrosis of white matter and/or increased permeability of the blood-brain barrier, which potentially allows direct passage of microbes and cytokines into the CNS.[222,223] Other body systems that may be impacted by FIRS include the hematopoietic system, thymus, adrenal glands, skin, kidneys, heart, and lung.[222] Equine studies directly linking placentitis, FIRS, and brain injury are lacking, but placentitis is a noted risk factor for the development of NE in foals and a study investigating placentitis in mares demonstrated significantly more expression of mRNA for IL-6 and IL-8 from the cervical star region in mares with experimentally induced *Streptococcus equi* ssp. *zooepidemicus* placentitis when compared with healthy pregnant mares.[6,224] Thus it is plausible, but unsubstantiated, that placentitis and FIRS may play some part in the pathophysiologic development of NE in foals.

Risk Factors and Clinical Signs

Recognized risk factors for NE in infants include maternal systemic hypotension, maternal cardiac arrest, clotting of placental arteries, placental abruption, uterine rupture, and inflammation.[203] In comparison, risk factors in horses associated with NE include dystocia, induced parturition, Cesarean section, placentitis, premature placental separation, severe illness, post-term pregnancy (fescue toxicity), and maternal hypotension (endotoxemia, hemorrhage, anemia, severe respiratory disease).[225–228] Other factors, such as meconium aspiration, twin foals, fetal infection, congenital malformations, and umbilical cord accidents, may also be risk factors for the development of NE.[225–228] In a retrospective study involving 79 neonatal foals with a primary

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diagnosis of NE, the presence of placental abnormalities (55% of foals), gestational problems (21%), premature placental separation (34%), and dystocia (30%) were reported.[197] Conversely, foals with NE may have no reported problems during gestation or parturition.

In regard to clinical signs, affected foals can be born demonstrating abnormal behavior or, alternatively, demonstrating clinical signs of NE 12 to 48 hours after birth. This temporal observation of delayed clinical signs may reflect the biphasic acute and delayed injury to the CNS discussed in the proposed pathophysiology. Clinical signs are quite variable and range in severity to include alterations of consciousness (stupor, somnolence, difficult to arouse, coma); weakness (hypotonia); inability to suckle; lack of affinity for the dam; inability to find the udder; inappropriate nursing behavior; localized or generalized seizures; tongue protrusion or weak tongue tone; star gazing; loss of recognition of the environment; abnormal vocalization; dysphagia; central blindness; irregular respiratory pattern (apnea, abnormally slow respiratory rate); and proprioceptive deficits.[6,25,229,230] In a retrospective study involving 94 foals, the most frequent reported clinical signs included abnormal udder seeking (59%), abnormal suckle (55%), inability to stand (42%), abnormal gastrointestinal motility (37%), abnormal consciousness (34%), and seizure activity (22%).[230] In another retrospective report, dysphagia was observed in 16 neonatal foals, and of these 16 foals, 6 foals (38%) had a clinical diagnosis of NE; 15/16 foals were discharged from the hospital (median 6.3 days; range 0 to 22 days), with 14/15 nursing from the mare with no evidence of dysphagia.[231] Clinical signs reflective of other body systems that can be impacted by hypoxic-ischemic injury, such as the renal, gastrointestinal, cardiac, and pulmonary system, also can be present. Moreover, clinical signs of other concurrent diseases that occur with NE, such as sepsis, pneumonia, prematurity/dysmaturity, patent urachus/omphalitis, limb deformity, colic, and uroperitoneum, may also be observed.[230]

Diagnosis

Currently, establishing a diagnosis of NE in foals remains at a rudimentary level and is confounded by concurrent diseases frequently encountered with NE, such as sepsis, hypoglycemia, prematurity, and congenital anomalies. In infants, diagnosis of NE is based on historical information, neurologic examination, and

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ancillary diagnostic tests such as brain imaging studies and EEG.[232,233] At present, MRI, including diffusion-weighted MRI, is the method of choice for imaging infants with HIE and has provided insight in regard to timing, location, and severity of brain injury.[232] The characteristic paradigm of brain injury in infants with HIE includes predominant injury to the gray matter structures, such as the basal ganglia and thalamus, related to acute profound asphyxia; watershed injury, which affects border zones of the brain between major arteries that lose blood flow and oxygen supply when blood perfusion is decreased, of the parasagittal white matter with possible extension to the cortex can also be observed and is related to partial prolonged asphyxia.[202,234–237] Other brain lesions include hemorrhage, focal to multifocal white matter injury, and global brain injury in more severe cases.[235]

Although MRI description of the healthy neonatal foal brain has been reported, there are minimal reports available in regard to MRI changes observed in foals with NE.[238] In one report involving a 10-hour-old foal with a putative diagnosis of NE based on presenting clinical signs of absent suckling behavior and disassociation from the mare, an MRI of the brain was performed because of worsening clinical signs of NE (i.e., seizures).[239] MRI revealed symmetric, poorly delineated areas of high signal intensity (compared with gray matter regions elsewhere) involving the basal nuclei (accumbens, putamen, claustrum); ventral thalamic nuclei; and rostral aspect of the ventral midbrain (in the region of the substantia nigra) on T1-weighted (T1-W) images (Fig. 17.9).[239] Hyperintensity associated with the margins of the lateral ventricles were noted on T2-weighted (T2-W) and T2-W fluid-attenuated inversion recovery (FLAIR) images.[239] The lesions noted in this foal were similar to those described in infants with HIE.[234,235] Whether or not MRI and its associated risks of general anesthesia and added client expense is a feasible diagnostic test in foals with NE remains to be determined, but imaging studies might help elucidate the pathophysiology of NE in foals and guide prognostication.

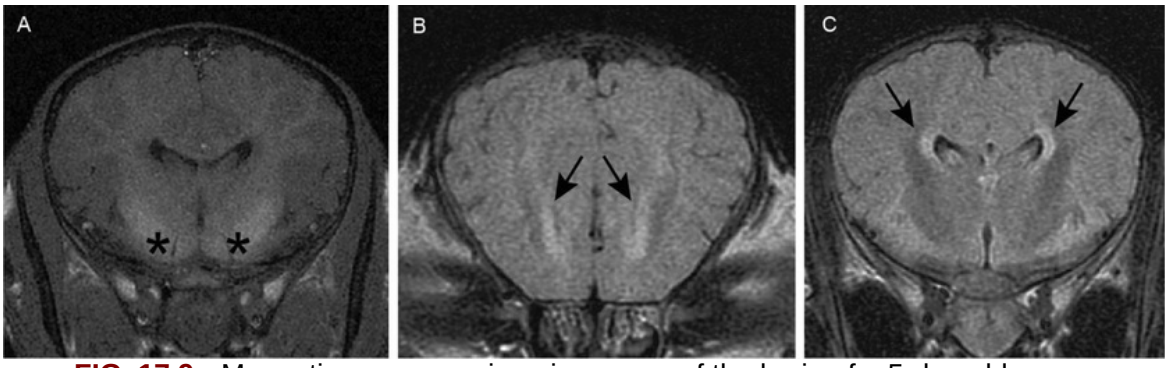


FIG. 17.9 Magnetic resonance imaging scans of the brain of a 5-day-old Thoroughbred filly with symmetric abnormalities in the cerebrum. **A,** T-1 transverse image through the cerebral hemispheres immediately rostral to the pituitary. *Asterisks* indicate regions of hyperintensity of basal nuclei. **B,** T2-weighted (T2W) fluid-attenuated inversion recovery (FLAIR) transverse image through rostral limit of lateral ventricles. *Arrows* indicate areas of hyperintensity associated with rostral poles of the ventricles. **C,** T2W FLAIR image through cerebral hemispheres immediately rostral to pituitary (same level as image A). *Arrows* indicate regions of hyperintensity adjacent to lateral ventricles. (From Wong DM, Jeffery N, Hepworth-Warren KL: Magnetic resonance imaging of presumptive neonatal encephalopathy in a foal. Equine Vet Educ 29:534-538, 2017).

The use of cranial US has also been used in infants to help identify neonates with HIE, as well as other disorders, such as cranial hemorrhage, congenital structural abnormalities of the cerebrum, and other causes of fetal brain injury.[232] Abnormalities associated with HIE in infants that were identified with cranial US included changes in ventricular size, periventricular echogenicity, increased echogenicity in the thalami, extra-axial fluid collection, and intracranial hemorrhage.[232] Although cranial US was able to identify all infants with a poor outcome, MRI was better at detecting changes associated with HIE.[240] One study in foals has examined and described ultrasonographic measurements of a variety of variables viewed from the atlanto-occipital (AO) space in healthy neonatal foals and foals with NE.[241] In that study, an 8-MHz microconvex transducer was used to image the AO space using a depth of 6 to 8 cm. Specifically, the transducer was placed immediately cranial to the wings of the atlas to obtain a transverse image and then rotated 90 degrees to obtain a longitudinal image.[241] Measurements of the height of the spinal cord, depth of dorsal subarachnoid space (mid-AO space), maximal depth of the dorsal subarachnoid space (cranial-AO space), and dorsoventral diameter of the ventral spinal artery were collected from longitudinal images (Fig. 17.10).[241] On

transverse images, measurements of the height, width, and cross-sectional area of the spinal cord and spinal canal were taken along with the depth of the dorsal subarachnoid space. In addition, ratios of the spinal canal to spinal cord height measurements, spinal canal to cord width measurements, and spinal canal to cord cross-sectional area measurements were calculated from transverse images. When comparing healthy foals with foals with NE, the dorsoventral diameter of the ventral spinal artery (longitudinal images) and absolute measurements of the spinal cord height, width, and cross-sectional area (transverse images) were all significantly smaller in foals with NE.[241] Moreover, ratios of spinal canal to spinal cord width and cross-sectional area were significantly larger in foals with NE when compared with healthy foals. One possible explanation for the reduced spinal cord dimensions in foals with NE is related to elevated intracranial pressure; however, the clinical application, utility, and reliability of ultrasonographic examination of the AO region in foals suspected to have NE is unknown and requires further study.[241]

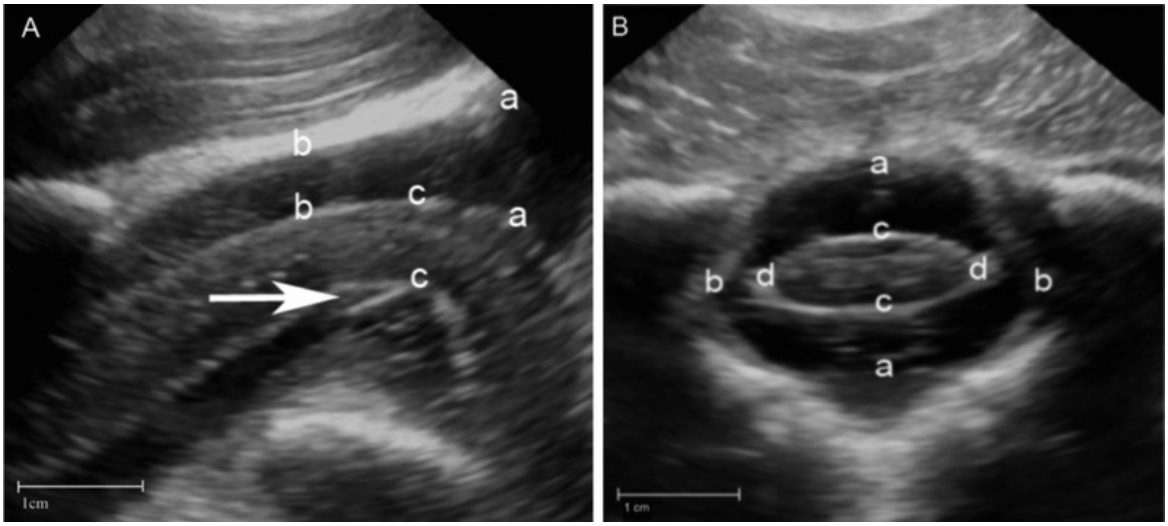


FIG. 17.10 Ultrasonographic images of the atlanto-occipital region in a 1-day-old Thoroughbred foal with neonatal encephalopathy. **A,** Longitudinal ultrasound image (cranial to right of image). Measurements of the maximal depth of the dorsal subarachnoid space (cranial atlanto-occipital space) (*a* to *a*), dorsal subarachnoid space (mid atlanto-occipital space) (*b* to *b*), height of the spinal cord (*c* to *c*), and dorsoventral diameter of the ventral spinal artery (*arrow*). **B,** Transverse ultrasound image (right side of foal to right of image). Measurements of the spinal canal height (*a* to *a*) and width (*b* to *b*), spinal cord height (*c* to *c*), and width (*d* to *d*), and dorsal subarachnoid space (dorsal *a* to dorsal *c*). (From Mackenzie CJ, Haggett EF, Pinchbeck GL, et al. Ultrasonographic assessment of the atlanto-

occipital space in healthy Thoroughbred foals and Thoroughbred foals with neonatal maladjustment syndrome. Vet J 223:55-59, 2017.).

EEG is the graphic recording of the rhythmic bioelectrical activity that arises predominantly from the cerebral cortex and has been used in people and, to a lesser extent, horses as a screening procedure in patients with intracranial neurologic disorders.[242] There is a lack of a single accepted classification system in regard to EEG interpretation in infants evaluated for NE, so a good degree of variation in terms of EEG definitions and grading schemes are published within the literature.[243,244] Commonly reported abnormal EEG findings in infants with NE include frequent spikes, positive temporal sharp waves, polyphasic sharp waves, mild voltage depression, persistent discontinuity, burst suppression, and modified burst suppression pattern.[243,244] In one study involving a 1-day-old filly, later confirmed to have histopathologic abnormalities compatible with NE, EEG recordings revealed diffuse high-voltage slow waves and focal discrete paroxysmal discharge activity, as well as multifocal paroxysmal activity. The practical application of EEG in equine medicine remains limited because of the restricted availability of equipment and trained personnel to perform and interpret the EEG.[242]

Finally, a variety of blood parameters also have been examined in foals with NE. In one study, 32% of foals with NE had increased serum creatinine concentration and 61% of affected foals had increased activity of serum creatine kinase.[197] Another retrospective study investigating spurious hypercreatinemia noted that of 28 foals with spurious hypercreatinemia (mean creatinine concentration 13.6 mg/dL), 20 foals (71%) had a clinical diagnosis of NE.[245] However, elevations in serum creatinine and creatine kinase can be associated with a number of other disease processes in neonatal foals. A more recent equine study measured plasma concentrations of ubiquitin C-terminal hydrolase 1, a biomarker for brain injury, and noted significantly higher values in foals with NE (mean 6.57 ng/mL; range 2.35 to 11.90 ng/mL) when compared with healthy foals (median 2.53 ng/mL; range 1.4 to 4.01 ng/mL). Currently, measurement of this biomarker is not readily available for clinical use.[246]

At present, practicality dictates that NE in foals be based primarily on clinical impression, founded on historical information, neurologic examination, compatible clinical signs, and exclusion of other disease processes. In foals, NE may occur as a primary problem or may be coupled with failure of passive transfer of maternal antibodies, sepsis, musculoskeletal abnormalities,

prematurity/dysmaturity, and other congenital disorders. Thus the clinician should perform diagnostics, such as a complete blood count, serum biochemistry profile, arterial blood gas analysis, blood culture, urinalysis, and assessment of passive transfer of maternal antibodies, to establish a complete assessment of the foal.[6]

Treatment

In equine medicine, the core component of treatment of NE is appropriate supportive and nursing care. This entails maintenance of adequate blood pressure and hydration, meeting caloric needs, facilitation of gas exchange, prevention of skin sloughing and ulceration by keeping the foal clean and dry, and prevention or treatment of infection. There are varied opinions on appropriate intravenous maintenance fluid rates for neonatal foals, but one approach is the Holliday-Segar method[2] (see previously and Chapter 44); the clinician must also consider renal function in calculating IV fluid rates as the kidneys can sustain injury from hypoxic-ischemic insult. Maintenance of adequate blood pressure and perfusion is also important for supporting cerebral (and other organ) perfusion and avoiding further ischemic injury.[247,248] Identifying any underlying cause(s) of hypotension, coupled with cautious use of IV fluid therapy and vasopressors or inotropes, might be necessary. Likewise, slow and judicious introduction of enteral milk feedings should be implemented as the gastrointestinal tract can be impaired from hypoxia-ischemia. Foals should be evaluated for gastric reflux before feeding. A conservative rate of 5% of the foal's body weight of mare's milk divided over a 24-hour period (i.e., 50 kg × 0.05 = 2.5 L mare's milk delivered every 2 hours over a 24-hour period = 100 mL every 2 hours) is a reasonable starting point, while monitoring for any clinical signs of indigestion (gastric reflux, colic). Milk supplementation should be increased gradually to a total of 20% to 25% of the foal's body weight per day over the next several days if the foal's gastrointestinal tract is functioning normally. Alternatively, or in addition to milk feedings, IV glucose supplementation can be used to provide another source of calories. A rate of 5 mg/kg/min of glucose has been suggested as an initial IV glucose CRI flow rate based on placental blood flow in late gestation (6.8 mg/kg/min).[9] This equates to an hourly flow rate of 3 mL/kg (150 mL/hr for a 50-kg foal) of a 10% glucose solution. Blood glucose concentration must be monitored and fluid rate adjusted routinely to avoid hyperglycemia or hypoglycemia. Moreover, as energy

depletion plays a role in the development of NE, coupled with the fact that neonates have minimal energy reserves, it is important to maintain the blood glucose concentration within the reference range.[247,248] If enteral feedings cannot be initiated in the first 24 to 48 hours, consideration of partial (PPN) or total parental nutrition (TPN) should be given. An arterial blood gas sample should be performed to gauge pulmonary function and supplemental intranasal oxygen provided if necessary. Furthermore, foals should be maintained in sternal recumbency where possible to facilitate adequate ventilation of both left and right lung lobes. If hypoventilation and hypercapnia are observed, doxapram (0.02 to 0.05 mg/kg/hr) can be administered as a CRI as a respiratory stimulant.[249] Although doxapram was found to be more effective at lowering $PaCO_2$ in foals with NE, caffeine can be administered per os (loading dose 7.5 to 12 mg/kg, followed by daily dose 2.5 to 5 mg/kg) if a CRI is not feasible. Provision of soft bedding with clean dry blankets will help prevent skin trauma and ulceration. Assessment of passive transfer of maternal antibodies should be evaluated as many NE foals fail to ingest enough colostrum and IV administration of equine plasma can be necessary. The rope restraint squeeze method can also be used in efforts to alter neurosteroid concentrations, and administration of broad-spectrum antimicrobials is indicated to treat or prevent sepsis.[219] Evaluation and treatment of other body systems, particularly the gastrointestinal and renal system, which are predisposed to hypoxic-ischemic insult, should be considered.

Many foals with NE will respond to the aforementioned treatment suggestions within 3 to 5 days and have a complete recovery. However, a few specific therapies should also be considered with more complicated cases of NE. Moreover, numerous medications have been suggested, mainly used in infants with NE, that target specific pathophysiologic mechanisms that may be involved with the development of NE. Importantly, seizures should be treated immediately if observed, as ongoing seizure activity increases cerebral oxygen consumption and can further contribute to neuronal damage. Intravenous diazepam (0.1 to 0.2 mg/kg) typically controls seizures in the neonatal foal and can be given intermittently if the incidence of seizures is infrequent. An alternative benzodiazepine that can be used for seizures is midazolam given as a single dose (0.04 to 0.1 mg/kg IV) or a CRI (0.02 to 0.06 mg/kg/h IV) to control intractable seizures.[250] If seizure activity persists, phenobarbital (2 to 10 mg/kg IV over 15 minutes, then 5 mg/kg PO q12h) may be necessary. Side effects of

phenobarbital, such as mild sedation, ataxia, and hypothermia, can be observed. Intravenous anesthesia with propofol can be required for several hours to manage intractable cases of status epilepticus.[25] Pharmacokinetics of levetiracetam, a novel antiepileptic drug used in people and dogs, has recently been investigated in healthy neonatal foals, but exact therapeutic ranges for this drug have not been established in horses.[251] On the basis of this study, levetiracetam administered at a dose of 32 mg/kg by mouth twice daily was predicted to maintain plasma concentrations above target concentrations for other species. Published use of levetiracetam in foals with NE is not available but might have potential for seizure control in future cases, although adjustment of dose and frequency of administration may be required in the clinical setting.[251] Hyperbaric oxygen therapy has been suggested as a potential therapy for NE with proposed benefits including reduced apoptosis, promotion of neuronal stem cell proliferation, enhancement of oxygen radical scavengers, increased oxygen delivery to the brain, and increased activity of superoxide dismutase.[6,210,252] Hyperbaric oxygen therapy has been used in a limited number of infants and foals with NE and has been purported to have beneficial effects.[253–255]

Medications that combat edema and oxidative damage have been used in foals with NE but have not undergone clinical trials or received scientific scrutiny; thus their effectiveness has been debated. Nonetheless, some clinicians have used mannitol (0.5 to 2.0 g/kg as a 20% solution over 20 minutes, IV q12-24h) or furosemide (1 mg/kg IV q12-24h) in efforts to reduce cerebral edema. Dimethyl sulfoxide (0.5 to 1 g/kg IV as a 10% solution given over 30 minutes, q12-24h) has also been used to treat cerebral edema and for its purported free radical scavenging abilities. Other putative therapeutics acting as free radical scavengers or antioxidants administered to foals with NE include thiamine (5 to 10 mg/kg IV or SC q24h), vitamin E (20/kg IU/kg, SC, or PO q24h), and vitamin C (100 mg/kg/day, IV). Allopurinol is a medication that inhibits xanthine oxidase, the enzyme responsible for production of superoxide radicals during reperfusion injury[201,209]; a dosage of 6 mg/kg PO once was used in a foal in conjunction with other treatments.[209a]

Accumulation of glutamate and excitotoxicity is another component of the pathophysiology of NE, and medications that help reduce the impact of excess glutamate have been investigated. Magnesium sulfate ($MgSO_4$) prevents calcium entry into the cell by noncompetitive voltage-dependent inhibition of NMDA

receptors.[201] This in turn blocks the release of glutamate and antagonizes the influx of calcium.[201,209] In addition, $MgSO_4$ reduces secondary inflammation-induced injury via cell membrane stabilization and inhibition of free radical formation.[201] Rodent models have demonstrated that $MgSO_4$ can be strongly protective against hypoxic-ischemic injury if given before or shortly after a hypoxic-ischemic insult.[208] A dose of 0.05 g/kg/h of $MgSO_4$ for the first hour, followed by 0.025 g/kg/h IV as a CRI has been suggested as a treatment for NE in foals.[256]

Therapeutic hypothermia is currently part of the standard treatment for neonatal infants with moderate to severe NE aiming for cooling to commence within 6 hours of hypoxic-ischemic insult to a temperature of 32°C to 34°C for 48 to 72 hours, followed by a gradual rewarming over 12 hours.[201] A number of studies have found improved neurodevelopmental scores in NE infants treated with hypothermia with proposed protective mechanisms of hypothermia including reduced cerebral metabolism, suppression of caspase-3 enzyme and microglial activation, prevention of activation of NMDA receptors, reduction of proinflammatory cytokines, and preservation of lipoprotein membranes.[201,203,229,257,258] Published reports of therapeutic hypothermia in neonatal foals with NE are not available. Other medications reported to be used in infants with NE or animal models, alone or in conjunction with hypothermia therapy, include melatonin (antiinflammatory, antiapoptotic, antioxidant properties); erythropoietin (antiinflammatory, antiapoptotic factors, angiogenesis, neurogenesis properties); N-acetylcysteine (clears free radicals, restores glutathione levels, antiinflammatory, reduces NO production); topiramate (glutamate receptor [AMPA and kainite] inhibition, blocks Na^+ channels and activates Ca^+ currents); desferrioxamine (reduction of free radical production by chelating iron); xenon (NMDA receptor antagonist, antiapoptotic factors); edaravone (free radical scavenger); and stem cells and IL-1 receptor antagonists.[201,203,208,209,229] These therapies and medications require further research in infants and have not been currently used for the treatment of NE in neonatal foals.

Prognosis and Pathologic Findings

In general, foals with a primary diagnosis of NE without complicating factors have a good prognosis for both survival and athletic function with reported

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survival rates ranging from 70% to 80%.[150,197,225–228,230] The prognosis is poorer in foals that demonstrate clinical signs at the time of birth, have evidence of brainstem or spinal cord involvement, have multiple organs affected by hypoxic-ischemic injury, have complicating factors (e.g., sepsis), remain comatose or are difficult to arouse, show no improvement in neurologic function in the first 5 days, or have severe recurrent seizures.[6,225,227] Recumbency was significantly associated with nonsurvival in one retrospective study,[230] and in a different retrospective study of 78 foals with NE, neurologic signs lasted 1 day in 29 foals (29/59 foals that survived; 49%), 2 days in 17 foals (17/59; 29%), 3 days in 8 foals (13.5%), 4 days in 4 foals (6.8%), and 5 days in 1 foal (1/59; 1.7%); 19/78 foals (24%) did not survive.[197] Rare long-term neurologic deficits include inability to suckle from the mare, prolonged visual impairment, residual spasticity, recurrent seizures, and docility as adults.[197,227]

Four major categories of neuropathology are noted in infants with NE: selective neuronal necrosis, parasagittal cerebral injury, periventricular leukomalacia, and focal ischemic brain necrosis.[229] Histopathologic findings reported in foals with NE are likely skewed toward more severe cases of NE as the majority of foals survive and accordingly do not undergo microscopic evaluation of the CNS. In one retrospective study involving 11 available microscopic descriptions of foals with NE, 10 of 11 foals had histologic evidence of neuronal necrosis and degeneration within the CNS consistent with ischemia.[230] In another study involving 18 foals with NE, necrosis of the cerebral cortex and local hemorrhage was noted in 9/18 foals,[259] whereas neuronal necrosis of the gray matter of the cerebral cortex, caudate nuclei, thalamus, hippocampus, cerebellar cortex, and medulla oblongata was reported in 3 foals with NE in another report.[246]

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Other Neurologic Conditions

Guy D. Lester

Bacterial meningitis should be suspected in a foal with neurologic disease and recent or current signs of generalized or localized sepsis. Agents causing meningitis are the same that cause systemic sepsis, most commonly bacteria such as *Escherichia coli*, *Enterobacter* spp., *Salmonella* spp., and Streptococcal spp.[66,100,194,260] Signs can include hyperesthesia, neck rigidity, varying degrees of obtundation, seizure activity, opisthotonus, limb ataxia and paresis, or specific cranial nerve abnormalities.[25] The definitive diagnosis is dependent on CSF analysis, which reveals a pronounced neutrophilic pleocytosis. Hematology and serum biochemistry reflect sepsis, and the serum IgG concentration often reflects failure of passive transfer.

Antibiotic treatment should be guided by culture and sensitivity data. Successful treatment has been reported using courses of broad-spectrum third-generation cephalosporins.[100] These include cefotaxime or ceftriaxone because of their excellent penetration into the central nervous system. Alternatives include ceftiofur, trimethoprim-sulfa combinations, chloramphenicol, or a combination of aminoglycoside with a β-lactam antibiotic. On the basis of data from human infants, one author has recommended the use of dexamethasone sodium phosphate (0.4 mg/kg IV q12h for 2 days).[25] In many cases, once the diagnosis is made, the infectious process is well advanced both in the brain and other tissues, resulting in a poor outcome. The prognosis is fair in foals where signs are limited to hyperesthesia and neck stiffness.[25]

Neonatal morbidity and mortality can be attributed to equine herpesvirus 1 (EHV-1), EHV-4, equine viral arteritis (EVA), and equine influenza (EI) viruses. The respiratory system is most commonly involved. Viral encephalitis is often quoted as an important differential for seizures in neonatal foals, but this appears to be a rare clinical entity in this age group.

Head trauma occurs commonly in neonates. Foals can receive direct blows to the head after kicks from the dam or other horses, as well as from head-on collisions with stationary objects. There is often external evidence of the trauma, such as hair loss, soft tissue swelling, asymmetry of the facial contour, fracture crepitus, or blood from the nares or ear canal. A range of neurologic signs may ensue that include varying degrees of obtundation; disorientation; head pressing;

compulsive walking, often in circles; and seizure. Trauma to the poll can result in vestibular and facial nerve dysfunction, ataxia, and paresis, as well as changes in mentation. The diagnosis is based on history and physical and neurologic findings but is supported by imaging. The management of CNS trauma is discussed elsewhere in this text (Chapter 35).

Benign juvenile epilepsy is a well-described neurologic entity of Arabian foals of Egyptian origin.[261] The age of onset of generalized seizures varies between 2 days and 6 months of age, and the reported duration of seizures is between several seconds and 5 minutes, with most lasting less than 60 seconds. Common postictal findings include obtundation and transient blindness. Physical and neurologic examination during the interictal period is normal, but there may be electroencephalographic changes.[261] As the name suggests, the condition does not persist into adulthood, with cessation seizures by 12 months of age in all foals. As described earlier, active seizures can be treated with diazepam or midazolam and prevented using oral phenobarbital (5 to 10 mg/kg PO as loading dose, followed by 2 to 5 mg/kg PO bid) or potassium bromide (100 mg/kg PO as loading dose, followed by 25 mg/kg PO q24h). Investigation of a small number of Egyptian Arabian foals with juvenile idiopathic epilepsy did not identify a link to the lavender foal syndrome (LFS) genetic mutation (see later).[262]

The role of glucose and electrolytes in seizure disorders should not be discounted. Hypoglycemia, hypocalcemia, hyponatremia, or hypernatremia can all produce signs of spontaneous, involuntary muscle activity with varying degrees of consciousness. Hypoglycemia is the most common metabolic derangement in newborn foals. The response of the nervous system to low glucose is categorized as neurogenic or neuroglycopenic.[263] Neurogenic signs are related to sympathetic discharge and include tremor, tachypnea, and irritability, whereas neuroglycopenic signs relate to impaired brain energy metabolism and include reduced level of consciousness, reduced or absent sucking, hypotonia, and seizure.[263] Specific electrolyte disturbances are discussed elsewhere in this text (Chapters 22, 32, and 44).

Hydrocephalus is the most common congenital brain disease in foals. Distention of the cerebral ventricular system produces a loss of normal cerebral structure. It can also occur secondary to inflammatory changes associated with meningitis.[25] Although pronounced doming of the skull is expected, it is relatively uncommon. Furthermore, a domed head is a physical feature of immaturity seen in premature or dysmature foals. Although signs are variable,

most foals are slow and somnolent and can have additional cerebral signs of head pressing, aimless and compulsive walking, blindness, and seizure activity. The diagnosis is usually based on persistence of neurologic signs and ruling out other causes of cerebral disease. The diagnosis is confirmed using CT or MRI. Dandy Walker−like syndrome has been reported as a cause of recurrent violent seizures in a newborn foal.[196] The condition involves agenesis of the corpus callosum with cerebellar vermian hypoplasia.

Tetanus is caused by the exotoxins produced by the anaerobe *Clostridium tetani*. Given the incubation period, clinical cases of tetanus are not likely before 7 days of age. Early signs include difficulty in locating and latching onto the teat and dysphagia. Signs then progress to include gait stiffness, elevation of the tail head, an anxious facial expression, prolapse of the third eyelid, tachycardia, and sweating. The foal will eventually become recumbent with recurrent bouts of tonic muscle contractions, which are severe enough to mimic seizure activity. Foals are at risk of disease if the mare has not been adequately protected through vaccination or the foal has untreated failure of passive transfer of immunity. It is recommended that mares receive a booster of tetanus toxoid 28 days before the estimated parturition date. Tetanus is discussed in great detail in Chapter 35.

Ivermectin and moxidectin toxicity have been described in neonatal and older foals after overdosage.[264–266] Reported signs of ivermectin toxicity can include obtundation, blindness, ataxia, head pressing, and seizure and are caused by opening of GABA-gated chloride channels with resultant membrane hyperpolarization and blockade of neuronal impulses. The related antiparasite drug, moxidectin, can also cause profound obtundation and coma when overdosed in juvenile animals.[267,268] Successful management of ivermectin toxicosis has included the use of intravenous lipid emulsions (20% soybean oil in water, 1.5 mL/kg IV bolus followed by 0.25 mL/kg/min for 30 minutes).[264] The benzodiazepine receptor antagonist, sarmazenil (0.04 mg/kg IV q2h), has been effective in managing moxidectin toxicosis.[268]

Kernicterus is a rare but serious neurologic complication of neonatal isoerythrolysis (NI).[269,270] The condition is also known as bilirubin encephalopathy or nuclear jaundice and results from deposition of bilirubin-IX α in the brain, primarily within the basal ganglia, *cornua ammonis* and *substantia nigra*, but also in the cortex, hypothalamus, cerebellum, and medulla.[271] Bilirubin-IX α is lipid soluble and readily crosses the blood-brain barrier. The mucous membranes of affected foals are deeply icteric, and neurologic signs

include altered mentation and seizures. The seizures are difficult to control, often necessitating euthanasia. In a retrospective study of 72 foals with NI, the heart rate at admission and maximum serum bilirubin concentration were significant factors in the development of kernicterus.[270] The authors determined that foals with serum bilirubin concentration greater than or equal to 27.0 mg/dL (≥466.1 µmol/L) were 17 times more likely to develop signs of kernicterus than foals with a peak bilirubin concentration less than 27.0 mg/dL. Tin-mesoporphyrin is an inhibitor of heme oxygenase and is a recommended therapy for severe hyperbilirubinemia in human infants.[272] The intramuscular therapy has been used in foals with NI at risk for kernicterus.[273] The antibiotic minocycline and the hypolipidemic drug clofibrate have had positive effects in certain experimental models and in human neonates with hyperbilirubinemia[271,274] but have not been evaluated for this purpose in foals.

LFS, also referred to as *coat color dilution lethal* (CCDL), is an autosomal recessive gene disorder of Arabian foals of Egyptian bloodlines.[275] The disorder is caused by a frameshift single base mutation in exon 30 of the myosin-Va gene *(MYO5A)*, resulting in premature termination of transcription. Disruption to the myosin-Va protein is thought to affect trafficking of melanosome to the cell periphery in melanocytes and transport of glutamate receptors and secretory granules in neurons.[275–278] Affected foals have a dilute coat color and are unable to achieve sternal recumbency.[278] Severe neurologic signs include frequent episodes of opisthotonus, limb paddling, and rapid eye movements. Spontaneous death or euthanasia typically occurs before 72 hours of age. The carrier frequency of LFS in the United States is 10.3% in Egyptian Arabians and 1.8% in non-Egyptian Arabians.[277] The disease occurs in homozygous foals, although neurologic dysfunction without coat color changes has been suspected in heterozygotes.

Glycogen storage disease IV is an autosomal recessive disease of Quarter Horses and Paint Horse breeds.[279] The defect has been identified as a mutation in the glycogen branching enzyme, encoded by the *GBE1* gene.[280] Clinical signs of foals not stillborn or aborted include profound muscular weakness and hypothermia. Foals may succumb to hypoglycemic seizures or cardiopulmonary failure. All affected foals have reportedly died or been euthanized by 18 weeks of age.[279]

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Anemia

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Anemia is a common finding in neonatal foals. The normal ranges of hematologic parameters must be considered when determining the significance of any anemia. The packed cell volume (PCV) at birth is 40% to 52% but decreases to 32% to 46% after colostrum and milk intake by 24 hours of age. PCV, red blood cell count (RBC), and the hemoglobin (Hb) concentration are similar to adult values at 24 hours of age, before decreasing over the first 2 weeks of postnatal life to values that are in the lower level of the normal adult ranges. These relatively low levels are sustained for several months.[281] The mean corpuscular volume (MCV) decreases over the first 4 months of life, leading to microcytosis and anisocytosis. The MCV increases after weaning.[281,282] Foals typically have reduced serum ferritin concentrations and increased total iron binding capacity when compared with adults. Serum ferritin increases significantly on day 1 and is attributed to ingestion of colostral iron, before reducing.[283] Data support relative iron deficiency as a cause of common foal anemia, but supplementation with iron does not improve red cell indices.[284] Supplementation of normal foals with a specific iron preparation, ferrous fumarate, resulted in acute hepatic failure and death.[285] There are reports of absolute iron deficiency anemia in foals,[286] including stabled Dutch Warmblood foals fed cut grass.[287] Findings include a low PCV, low serum iron and ferritin concentration, and normal to increased total iron binding capacity. Improvement is seen in those foals with oral iron supplementation.

Clinical signs of anemia are related to the magnitude and timing of the underlying disease process. Rapidly developing hemolytic anemias, such as NI, produce signs of weakness, lethargy and somnolence, mucous membrane pallor and icterus, tachycardia, and possible mild fever. Intravascular hemolysis will typically cause brown-red discoloration of urine. There is accentuation of cardiac murmur. Foals with hemoperitoneum or internal umbilical remnant hemorrhage are often colicky. Hemorrhage at the apex of the bladder can produce stranguria. Bleeding into the respiratory cavity can produce clinical signs of respiratory distress, and blood loss into the gastrointestinal tract will cause melena. Lameness will be seen in foals with spontaneous hemarthrosis.

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Causes

Hemolysis is most commonly seen after consumption of colostral antibodies that are directed against foal erythrocytes. The syndrome is known as neonatal isoerythrolysis (NI) and is discussed in detail in Chapter 53. Less common causes of hemolysis include non-NI immune-mediated hemolysis; intracellular RBC parasites; rapid administration of hypotonic or hypertonic solutions, such dimethyl sulfoxide; or equine infectious anemia. Red blood cell hemolysis can be caused by bacterial toxins, most commonly associated with clostridial infections.

Blood loss occurs commonly with separation of the umbilical cord. Hemorrhage most commonly occurs externally but can occur internally into the umbilical remnants, the urinary bladder, or the peritoneal cavity. Most external cord hemorrhage is a small volume and rarely impacts hematologic parameters.[288] Trauma can cause both internal or external blood loss. Rupture of the spleen often leads to uncontrolled internal blood loss, potentially requiring splenectomy.[289] Hemoperitoneum can also occur secondary to rupture of juvenile granulosa cell tumors in foals.[290,291] Rib shaft fractures can cause hemorrhage into the pleural cavity; on rare occasions fatal hemorrhage can occur if a major vessel or myocardium is lacerated.

Blood loss can occur secondary to problems in homeostasis. Affected foals may have spontaneous hemorrhage into joints, muscle or subcutaneous tissues, or the gastrointestinal tract. Disseminated intravascular coagulation (DIC) is an acquired homeostatic problem secondary to severe sepsis. Adult horses with DIC tend to present with signs associated with failure of fibrinolysis, such as widespread thrombosis. In contrast, septic foals often present with spontaneous or trauma-induced hemorrhage. Inherited disorders are discussed elsewhere in this text but include intrinsic platelet disorders, such as Glanzmann thrombasthenia, where the glycoprotein complex IIb-IIIa is reduced or absent on the surface of platelets, and extrinsic disorders including type 2 von Willebrand's disease.[292]

Decreased erythrocyte production is associated with absolute or relative iron deficiency and chronic inflammatory diseases. Anemia of chronic disease (ACD) is a complex disorder that involves altered iron metabolism, bone marrow depression, and reduced production or action of erythropoietin. Increased levels of hepcidin, released in response to inflammation, may be pivotal in the development of anemia by decreasing iron absorption and iron recycling.[293]

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Classically ACD is reflected by low serum iron, normal or decreased total iron binding capacity, and increased serum ferritin concentration.

A syndrome of bone marrow aplasia or hypoplasia was reported in three foals born to mares that were under therapy for equine protozoal myeloencephalitis. Therapy included sulfonamides, pyrimethamine, folic acid, and vitamin E.[294] There is a syndrome of anemia and B-cell lymphopenia in Fell pony foals.[295] Affected foals demonstrate initial bone marrow erythroid hyperplasia with concurrent erythroid and myeloid dysplasia, which progresses to severe erythroid hypoplasia by 5 weeks of age.

Determination of the nature of the anemia may allow specific treatment. The treatment of NI is discussed in Chapter 53. Drug-induced or autoimmune anemias may be treated with corticosteroids (0.05 to 0.1 mg/kg dexamethasone twice a day intramuscularly or intravenously). Blood transfusion following crossmatch may be indicated when anemia develops rapidly or PCV drops below 12%. Associated conditions, such as metabolic acidosis and hypoglycemia, should be corrected. Anemia of chronic disease requires correction of the primary disease condition.

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Maturity

Guy D. Lester

The terminology associated with birth maturity is difficult in horses due to the variability in normal gestational length. Retrospective studies report wide variability in gestational age but frequently do not report physical characteristics or foal survival. Gestational age ranges of 305 to 365 days, 315 to 387 days, and 286 to 370 days have been described in Thoroughbreds.[296–298] The term *premature* simply refers to the birth of an infant or animal after a gestational period shorter than normal. A premature human infant is defined as one that is delivered at least 21 days before the mean pregnancy duration of 266 days. The use of a gestational age to classify equine prematurity has been described with the most commonly reported definition being a foal born before 320 days of gestation.[299] This is loosely based on significantly lower birth weights and poor outcomes of foals born before 320 days.[300] It could be argued that foals born outside the lower 95% confidence interval of the normal gestational period would best fit the classification of premature; this would be less than 325 days in Thoroughbreds, using data extrapolated from Hintz and coworkers.[296]

Dysmaturity is a term commonly used to describe foals that have experienced some degree of intrauterine growth retardation. These foals typically demonstrate some signs of physical immaturity, such as a low birth weight. Dysmature foals can have shortened, normal, or prolonged gestation lengths. Other terms used to classify foals with incomplete maturation include *viable* and *nonviable*.[300] In a review on terminology, Koterba suggested the terms *viable* and *nonviable* were inappropriate because outcomes of premature foals are heavily influenced by access to facilities and the value of the animal.[300] The concept of *readiness for birth* was used to categorize foal outcomes based primarily on the degree of maturation of the fetal hypothalamus-pituitary-adrenal (HPA) axis. While this plays a critical role in determining postpartum survival, other factors including the degree of physical maturation and the consequences of an adverse intrauterine environment are also relevant in determining the ultimate outcome. Premature maturation of the HPA axis often will take place at an inappropriate developmental stage for some body systems causing asynchrony of organ maturation and postnatal problems.[301] Following on from the concept of *readiness for birth*, Rossdale introduced the term *twilight foals* to

describe those foals with accelerated but incomplete maturation of the HPA axis at the time of birth.[299,302]

The physical characteristics associated with prematurity include a low birth weight and small body size, a short and shiny hair coat, a prominent rounded head, periarticular laxity, and droopy ears (Fig. 17.11). Foals will typically have moderate flexor laxity with elevation of the toe, but some will have contracture of the lower limb. Muscle development is usually poor. Most will demonstrate generalized weakness and hypotonia and will have difficulty in standing. Severely premature foals may have lids naturally sutured closed and little hair covering of their body. Many will have difficulty in maintaining body temperature, blood pressure, and blood glucose.



FIG. 17.11 A premature foal demonstrating a low birth weight and small body size, a short and shiny hair coat, and a prominent rounded head.

Dysmature foals commonly experienced some degree of intrauterine growth retardation (IUGR). This is usually reflected by the birth of a foal that is small for its gestational age. The average relative weight of the term foal to its dam is around 10%. Postmature foals usually have an acceptable birth weight with a

large frame but poor muscle development. This gives the foal a lanky appearance. In contrast to premature animals, fetlock contracture is common, although laxity can be present. Consistent with their prolonged gestation, post-term or postmature foals will often have erupted incisors and a long hair coat. In term foals the central incisors typically erupt during the first 5 to 7 days of postnatal life.

Causes

The pregnant uterus is highly responsive to contractile agents such as oxytocin and prostaglandins throughout gestation. Consequently, one of the most important causes of premature birth and perinatal morbidity and mortality is the induction of labor with exogenous oxytocin or prostaglandins. The adverse consequences of premature induction of parturition were identified in a study where parturition was induced either before 300 days' gestation or between 300 and 320 days' gestation.[303] The overall survival rate was only 5%, with the youngest surviving animal delivered after 318 days' gestation. Other surviving foals were all delivered after 320 days' gestation. The decision to prematurely terminate a pregnancy may be done deliberately in the "normal" mare or may be forced due to significant maternal disease. The latter frequently involves delivery of a compromised and often premature foal by cesarean section. Chemical induction of parturition has occurred when late-pregnancy intestinal problems are misinterpreted as ineffective labor. Premature birth can occur as a sequel to placental problems, including placental infection, edema, and/or detachment (premature placental separation). Placental insufficiency due to twinning is another cause of intrauterine growth retardation.

The consumption by pregnant mares of tall fescue pasture infected with the *Neotyphodium coenophialum* leads to range of abnormal signs including prolongation of gestation, perinatal mortality, and agalactia.[304] The large skeletal frame of the postmature foal predisposes mares to dystocia. The delay in parturition may be due to toxin-induced interference with fetal corticotrophin-releasing horses (CRHs) and delay in maturation of the HPA axis. Foals born to mares grazing endophyte-infected fescue pasture have normal thyroxine and reverse T3 but reduced tri-iodothyronine levels compared with control foals.[305] This is also consistent with failure of cortisol-induced maturation of thyroid function. A syndrome of congenital hypothyroidism has been reported in foals in Western Canada.[306] Signs include prolonged gestation, dysmaturity, and a range

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of musculoskeletal abnormalities, including flexural deformities, delayed ossification, and mandibular prognathism. The specific cause has not been determined, although consumption of diets that contain nitrate or are deficient in iodine is suspected.[307]

Maturation of the Fetal Hypothalamic-Pituitary-Adrenal (HPA) Axis

The maturation of several organ systems coincides with changes in the fetal HPA axis.[301] Fetal cortisol is critical for organ maturation, but if the fetus is exposed too early in gestation or to too large a quantity, intrauterine growth restriction may occur. The fetus is protected from cortisol during much of gestation. The type 2 isoform of the enzyme 11β-hydroxysteroid dehydrogenase (11β-HSD) converts excess biologically active cortisol into the inactive cortisone in the placenta, thereby reducing the exposure of the fetus. The postnatal adrenal gland, under influence of ACTH from the pituitary, can readily synthesize cortisol from cholesterol and pregnenolone (P5). Several important enzymes are required for this conversion, including 3β-HSD, P450scc, and P450C17. These enzymes are either inhibited or deficient during most of pregnancy, again protecting the developing fetus from excessive cortisol. Consequently, during the majority of gestation the major products of steroidogenesis are progesterone and the 5α-reduced progestagens and not cortisol.[308] Foals, like other species studied, undergo enhanced adrenal activity prior to birth. This is reflected by high plasma cortisol and ACTH concentrations in term newborn foal plasma in the first hours after birth.[309] There is also a substantial change in the amount and localization within the adrenal gland of 3β-HSD, P450scc, and P450C17 around the time of birth.[310]

The trigger(s) for the process that results in fetal cortisol production, organ maturation, and birth is not known. Data from sheep indicate that upregulation of CRH mRNA in the fetal hypothalamus and proopiomelanocortin in the fetal pituitary is a key initiating event.[301,311] At the same time there is upregulation of ACTH receptors and key steroidogenic enzymes in the fetal adrenal glands. The consequence is a progressive increase in circulating ACTH and cortisol in the fetus. The rise in fetal cortisol has a direct effect on the placenta to increase prostaglandin H synthase 2, leading to secretion of prostaglandins such as PGE_2.[301,311,312] Prostaglandins further stimulate the fetal HPA axis, stimulate

placental 11β-HSD-1 (which favors the production of cortisol from cortisone), and also facilitate the conversion of estrogen from pregnenolone. It is not known if these events occur in the pregnant mare but do appear to be consistent across most species studied. An important difference between equids and other species is the timing of these events before parturition. In pregnant ewes maturation of the HPA axis occurs during the final 20 days of a 150-day gestation. In contrast, the production of significant fetal cortisol appears to occur during the final 48 to 72 hours of pregnancy in mares.[313] A number of important maturational events appear to be tightly associated with the prepartum increase in ACTH and cortisol.[308] These include changes in red and white blood cell parameters, most notably a large increase in the neutrophil to lymphocyte ratio.[313,314] Hepatic and renal glucose-6-phosphatase, a key enzyme of gluconeogenesis, also increases sharply around the time of birth coinciding with increases in hepatic and skeletal muscle glycogen stores.[315]

The prepartum rise in plasma cortisol likely induces deiodination of the outer ring of T4 to produce the biologically active tri-iodothyronine (T3).[316] Adequate levels of T3 are required for a number of biological functions including postnatal thermogenesis. Normal term foals have high levels of thyroid hormones, including T3 at the time of birth.[317,318] These levels decline over the initial weeks or months of postnatal life. A relationship between circulating T3 levels and cortisol was reported in premature, dysmature, and mature foals, and the increase in T3 appears to be dependent on maturation of the HPA axis.[302,319] Both cortisol and T3 are critical for lung maturation, particularly the normal postpartum reabsorption of lung liquid.[319]

Accelerated Maturation of the Fetal HPA Axis

Several factors can induce premature maturation of the fetal HPA axis. Hypoxemia is a potent stimulator of the axis in sheep with rises in fetal ACTH and cortisol.[320] The HPA axis can also be manipulated using exogenous glucocorticoids; betamethasone is commonly administered to women in danger of preterm birth in order to hasten HPA maturation and therefore improve the chances of postnatal survival. Poor nutrition before and after conception in sheep produces a shortened gestational period and hastened maturation of the fetal HPA axis.[311] Placental and/or fetal infection also can accelerate maturation of the HPA axis. The cytokines induced by infection increase prostaglandin synthesis

and decrease metabolism. Prostaglandins exert a range of actions in addition to promoting cortisol production. These include important actions on the cardiovascular, renal, and respiratory systems.[321] The healthy newborn foal has higher concentrations of 15-ketodihydro-$PGF_{2\alpha}$ (PGM) in the days after birth than values in adult animals.

The stimuli associated with precocious HPA axis maturation in foals are not well described. The exception is infection of fetal membranes where foals are often delivered preterm with laboratory findings consistent with axis maturation. Spatial and nutritional deprivation resulting from a Thoroughbred foal placed in a pony uterus using embryo transfer also leads to premature maturation of the fetal adrenal.[308,322,323] Many late-term maternal diseases do not appear to have a significant effect on foal maturity. Hypoxemia associated with anesthesia and colic surgery in pregnant mares during the final 60 days of pregnancy results in a high rate of preterm delivery of compromised foals that did not survive.[324] It is likely that the insult in these cases was so severe that the interval between surgery and delivery was inadequate for maturation of the axis to occur. Another important consideration in determining outcomes would be the effect of hypoxia and/or ischemia on other fetal organ systems.

Treatment of the at-Risk Late Pregnant Mare

The administration of corticosteroids to the pregnant mare appears to have little effect on maturation of the fetal HPA axis, at least when doses considered safe are used. Direct injection of $ACTH_{1\text{-}24}$ to the fetus results in increased fetal cortisol, but the effect is dependent on gestational age with maximal responses occurring at around day 313 with no measurable benefit when administered before day 295.[313] Direct administration of CRH, ACTH, or betamethasone to the fetus using US-guided IM injection results in increased maternal progestagen levels consistent with maturation of the fetal adrenal gland.[325,326] The procedure itself can lead to abortion in a small number of mares. Exogenous $ACTH_{1\text{-}24}$ administered to late-pregnant pony mares had an impact on both gestational length and fetal maturation.[327] Depot $ACTH_{1\text{-}24}$ given to mares at 300, 301, and 302 days of gestation produced a shortened gestational length and lower birth weight but evidence of HPA axis maturation. A confounding effect in this study was the time of conception, with the most significant findings observed in mares bred later in the breeding season.

It is preferable to maintain the fetus in utero to ensure not only adequate HPA axis maturation but also effective ossification and maturation of other body systems. Consequently, the primary focus of therapy for a mare with placental infection is to eliminate the pathogenic organisms, reduce inflammation, and maintain the pregnancy. The specific management of placentitis is not the focus of this chapter, but treatment may involve broad-spectrum antibiotics, nonsteroidal antiinflammatory drugs, pentoxifylline, β_2-adrenoreceptor agonists, and altrenogest. The efficacy of altrenogest use in mares with placentitis has been questioned.[328]

The termination of post-term pregnancies is a difficult decision for practitioners, particularly with the angst that is common in many owners. Given the wide variation in gestational range, it is almost always in the best interests of the foal to let the pregnancy continue. If facilities are available, then rectal and transabdominal US assessment of the fetus and chorioallantois should be made, looking carefully for thickening or detachment of the fetal membranes. Ideally, any induction of parturition should be based on appropriate changes in physical characteristics of the mare and in milk electrolytes. Mares grazing endophyte-infected tall fescue can be medicated with dopamine receptor antagonists, such as domperidone.[304]

Laboratory Assessment

The laboratory data will indirectly reflect the degree of HPA axis maturation. Premature or dysmature foals that fail to survive often have minimal cortisol secretion in the face of adequate endogenous ACTH. Furthermore, the change in plasma cortisol in response to exogenous ACTH (Cosyntropin, 0.125 mg IM) is inconsistent and usually inadequate. The foal with incomplete adrenal maturation will have a low total white cell and neutrophil counts, as well as a neutrophil-to-lymphocyte ratio that is characteristically less than 1 : 1.[314] It is important to determine if sepsis is present, as neutropenia is also a common feature of this condition. Evidence of shifting toward immature cell types and neutrophil toxicity should indicate primary sepsis or prematurity/dysmaturity complicated by sepsis. Premature foals that fail to improve their total white blood cell and neutrophil counts over the initial 24 to 48 hours of treatment have an even poorer prognosis for survival. Changes in red cell indices have also been reported in nonstressed preterm foals.[314] Most notably is an elevated MCV in preterm foals. An elevated plasma fibrinogen concentration is considered to be a

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good prognostic factor in premature foals as it often reflects prepartum exposure to bacterial infection. Induced or spontaneously delivered term foals have a significantly higher plasma glucose concentration than premature foals.[329] Plasma creatinine levels are often elevated in newly born preterm or dysmature foals due to placental dysfunction. This increase is independent of foal renal function. Measurement of low cortisol levels coupled with increased progestagens would provide further evidence that effective maturation of HPA axis has not occurred in the foal before birth.[216] Thyroxine (T4) is lower in premature foals than in normal foals and term, but sick, hospitalized foals.[317] This is consistent with failure of cortisol-induced maturation of thyroid function (see earlier). Premature foals respond to thyrotropin-releasing hormone (TRH; 0.5 mg IV), but the increase in T4 is less than that observed in both healthy and sick term foals.[317]

Establishing a Prognosis

The prognosis for survival of a prematurely delivered foal is dependent on a range of factors including the gestational age, reasons for delivery, complications associated with delivery, available resources (facilities and expertise), and financial limitations of the owner. Survival of very premature foals (280 to 300 days) would typically require a history of chronic in utero stress with resultant precocious maturation of the HPA axis and critical organ systems. The majority of these foals would still require a lengthy and costly period of hospitalization and experience a range of complications, some of which may be life threatening. Foals delivered prematurely as a consequence to chemical induction of parturition without evidence of chronic in utero stress or through cesarean section typically have a high mortality rate even when delivered close to calculated due dates. Foals delivered under these circumstances before 300 days will almost certainly die irrespective of available resources.

A complete blood count and fibrinogen estimation are key factors in determining short-term prognosis. A normal or elevated neutrophil count, neutrophil-to-lymphocyte ratio (N:L), or total white blood cell count are positive indicators of survival, as they typically reflect maturation of the HPA axis. In a survey of 135 neonates admitted to the University of Florida with a gestational age of fewer than or equal to 320 days' short-term survival was in part predicted by total white blood cell count, neutrophil count, lymphocyte count, and the N:L ratio at presentation.[330] The N:L ratio of surviving premature foals (12.5 : 1) was

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well above that reported for both normal term foals (2.5 : 1) and that of nonsurviving premature foals. Many of the surviving animals were exposed to confirmed or suspected placental infection. In utero stress, with hastened maturation of the HPA axis, is a good prognostic factor for survival in foals that are delivered preterm. In many foals, the greater the neutrophil count, the better the outlook, at least in terms of short-term survival. A high plasma fibrinogen concentration is also considered to be a positive factor. Reevaluation of the white cell indices on day 2 for appropriate increases also support a favorable prognosis.

A history of placental infection appears to be a positive factor when predicting survival in preterm foals. One obvious downside is that many of these foals are born with aspiration pneumonia (due to in utero aspiration of contaminated amniotic fluid) and/or systemic sepsis. This, coupled with the fact that many foals have an impaired immune system, warrants the use of broad-spectrum antimicrobial therapy.

Consideration should also be given to the long-term outcomes of preterm foals. These animals are at risk of significant and permanent musculoskeletal problems due to bone and ligamentous immaturity. Foals that survive the neonatal period are smaller than their peers, and this difference will often remain noticeable as weanlings and as yearlings. The differences may be less obvious at 2 years and older. Other common complications, such as pneumonia, will further reduce the growth rate in the first 6 months of life. There is nothing to indicate that premature fillies will experience fertility problems as adults.

Clinical Progression

The clinical progression will usually reflect the degree of endocrinologic maturity, additional perinatal stresses, and the extent of physical maturity. Typically foals born prematurely, but chronically exposed to an appropriate chronic in utero stress, such as placental infection, will appear weak and depressed in the immediate postpartum period. Some will require resuscitation. After a longer than normal period of postural adaptation, they will usually manage to stand but will often require assistance. Suckle reflex and appetite may be reduced or absent, and many will need to be fed initially via nasogastric tube. They will frequently have trouble maintaining their body temperature and blood glucose levels. After the initial 24-hour period, many of these foals demonstrate improvement both in physical strength and mentation. Their appetite for milk

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will often exceed that of a healthy term foal. Foals with inadequate maturation of the HPA axis will frequently require immediate resuscitation. They may mimic the clinical progression of in utero stressed premature foals up until 12 to 18 hours of age. This initial period after delivery can be deceptive, with many foals showing degrees of improvement, which often promote owner optimism. The rise of hormones accompanying delivery may lead to improvement in alertness and strength. However, after this period a range of progressive abnormalities develop. These include systemic weakness, depression, seizures, respiratory failure, and intolerance to feeding. Cardiovascular collapse may ensue, the first sign of which is a reduction in the intensity of peripheral pulses, followed by a reduction in urine flow, development of subcutaneous edema, and deteriorating neurologic function. Poor tissue perfusion leads to lactate accumulation and a mixed metabolic and respiratory acidosis. Death will certainly occur without aggressive support, and even with high-level intensive care, mortality rates are high.

Treatment of the Premature or Dysmature Foal

Successful outcomes are dependent not only on careful management of identified problems but also in predicting the problems that may arise in the hours, days, or weeks to come. Most premature and dysmature foals will experience some degree of pulmonary insufficiency. Factors that predispose these foals to respiratory problems, including structural and functional immaturity, a naïve and potentially immature immune system, altered pulmonary vascular reactivity, a highly compliant rib cage, and a propensity for prolonged or persistent recumbency. Final maturation of the respiratory system appears to be highly dependent on a functional HPA system. Arterial blood gas analysis is an important tool in the assessment of respiratory function, and the lower arterial oxygen concentration in term newborn foals is further decreased in dysmature or premature foals (Table 17.4). Extrapulmonary shunts account for more than 30% of the cardiac output, in contrast to less than 10% in normal full-term foals.[331] Ventilation/perfusion mismatching also occurs due to a poorly reactive pulmonary vasculature and dependent atelectasis. Deficiency of lung surfactant is not likely to play a primary role in the respiratory dysfunction in most premature or dysmature foals, as it is usually fully developed in most foals by 300 days but could be delayed until after 340 days in some foals.[332] The most severe form of respiratory failure is neonatal respiratory distress syndrome

(RDS), a disease characterized by progressive respiratory failure, severe hypoxemia and hypercapnia, and death. A diffuse, severe alveolar pattern is a classical radiographic finding. Intervention would ideally involve mechanical ventilation, bovine or synthetic surfactant, and glucocorticoids; however, outcomes are extremely poor irrespective of the level of care. Fortunately, RDS is relatively uncommon; most premature foals will demonstrate a less severe manifestation of lung dysfunction, characterized by reduced ventilation capacity, tachypnea, hypoxemia, and varying levels of hypercapnia. These foals are susceptible to dependent lung atelectasis from recumbency. Most foals will benefit from supplemental intranasal oxygen with initial flow rates of 5 L/min recommended. Adjustment in flow rate is dictated by positive changes in arterial blood gas analyses or improvement in ventilation rate and depth. It is important to avoid prolonged periods of lateral recumbency in order to minimize the impact of atelectasis. If the foal is unable to stand, then placement in sternal recumbency is recommended. This is made easier by use of a specially constructed V-pad.

TABLE 17.4

Normal Blood Gas Values for Foals[a]

Age Group	Arterial					Venous			
	O_2 (mm Hg)	CO_2 (mm Hg)	pH	Base Excess	HCO^-_3 (mEq/L)	O_2 (mm Hg)	CO_2 (mm Hg)	pH	HCO^-_3 (mEq/L)
Immediate post-foaling[b]	40-50	52-60	7.2-7.3	+2	24-26	—	—	—	—
2 hours[b]	68 ± 10	49 ± 2	7.37 ± 0.01	+4	26 ± 2	42 ± 2	56 ± 2	7.33 ± 0.01	28 ± 2
4-12 hours[c]	75 ± 5	47 ± 2	7.39 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 2
24 hours[c]	81 ± 6	48 ± 2	7.4 ± 0.01	+6	28 ± 2	42 ± 2	52 ± 2	7.38 ± 0.01	30 ± 3
1-3 days[c]	90 ± 6	148 ± 2	7.4 ± 0.01	+6	28 ± 2	43 ± 2	52 ± 2	7.38 ± 0.01	29 ± 2
4-14 days[c]	86 ± 5	45 ± 2	7.41 ± 0.01	+6	28 ± 1	38 ± 2	53 ± 2	7.38 ± 0.01	31 ± 2
Premature[b] birth	39 ± 5	55 ± 4	7.27	−3	24 ± 1	—	—	—	—
(320-330 days' gestation)—1 hour	52 ± 4	48 ± 3	7.33	−1.3	25 ± 1	—	—	—	—

[a]Lateral recumbency.

[b]Data from Rose RJ, Rossdale PD, Leadon DP: Blood gas and acid-base status in spontaneously delivered, term-induced and induced premature foals. *J Reprod Fertility* 32:521, 1982.

[c]Data from Stewart JH, Rose RJ, Barko AM: Response to oxygen administration in foals: effect of age, duration and method of administration on arterial blood gas values. *Equine Vet J* 16:329, 1984.

Failure of the cardiovascular system is common in foals with partial or incomplete maturation of the HPA axis. Management is challenging, in part due to inconsistent responses to standard inotrope and vasoreactive therapy (see earlier). Successful treatment is reliant on early detection of reduced perfusion. This is reflected clinically by cool extremities, the presence of limb and ventral edema, and darkening of the mucous membranes with prolongation of the capillary refill time. As failure ensues, peripheral pulses will become difficult to palpate, blood pH will fall, and there will be increases in plasma lactate and anion gap. Indirect (or direct) measurement of mean blood pressure along with determination of blood lactate will help guide therapy. An initial approach to the treatment of failing perfusion may involve intravenous plasma followed, if necessary, by dopamine and/or dobutamine infusion. Dopamine is widely available and relatively inexpensive, with effects that are dose dependent; (1) low doses (0.5 to 5 μg/kg/min) provide agonism of dopaminergic receptors and possible renotubular effects along with vasodilation of coronary and intestinal vasculature; (2) moderate doses (4 to 10 μg/kg/min) stimulate β_1-adrenergic receptors and result in chronotropy; and (3) high doses (≥10 μg/kg/min) cause agonism of α_1-adrenergic receptors, leading to widespread vasoconstriction. High-dose dopamine infusion is generally not recommended in human preterm infants due to the potential for right-to-left shunting.[333] Dobutamine (3 to 20 μg/kg/min) acts principally on β_1 adrenoreceptors, producing an improvement in myocardial contractility without vasoconstriction. Other potential pressor agents used in foal intensive care facilities include epinephrine, norepinephrine, and vasopressin. Milrinone infusion is used in human preterm infants and has been evaluated in anesthetized adult horses, but it has not been evaluated in premature foals.[333,334] The volume and type of fluids given should be carefully monitored, as fluid overload and hypernatremia are common. Urine output should be appropriate for the volume of fluids administered and anuria or oliguria treated aggressively. This may include low-dose dopamine or fenoldopam infusion, furosemide boluses or infusion, or mannitol infusion. Establishment of urine flow is critical in terms of survival.

Signs of gastrointestinal tract dysfunction are rarely evident on initial assessment of premature or dysmature foals; however, most will not tolerate aggressive force-feeding. These foals commonly develop intestinal stasis with

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reduced fecal passage, gas accumulation, and gastric distension. The combination of prolonged asphyxia and prematurity is also a risk factor for the development of necrotizing enterocolitis. Feeding should be restricted to small volumes (e.g., 10 to 20 mL hourly) until the foal appears to be systemically stable. Concurrent parenteral nutrition is indicated in order to prevent loss of body weight. Foals should be monitored closely for signs of gastrointestinal dysfunction irrespective of feeding volume or frequency. This includes assessment of fecal passage, changes in abdomen size (assessed using a measuring tape), testing for gastric reflux if a nasogastric tube is in place, and frequent assessment with transabdominal US.

Premature and dysmature foals are susceptible to hypothermia. Thermogenic mechanisms develop late in gestation and are related to circulating T3 levels. As discussed earlier, thyroid hormone generation is closely tied to maturation of the HPA axis. Consequently, problems with thermogenesis are exacerbated in preterm foals with incomplete adrenal function. Body temperature needs careful management as rapid warming may result in peripheral vasodilatation and possible cardiovascular collapse. Initially, the foal should be covered by blankets and removed from any drafts. Intravenous and oral fluids should be warmed before use. Once the foal begins to demonstrate vigor, heat lamps and circulating warm-water blankets can be used. The premature or dysmature foal often has inadequate gluconeogenic enzyme activity and limited glycogen stores at the time of birth. Consequently, most will have difficulty maintaining a normal blood glucose concentration. This is managed acutely by infusion of 10 mL/kg of a 10% dextrose solution over several minutes, followed by a constant infusion at about 6 mg/kg/min (≈200 mL/h of a 5% dextrose solution to a 30-kg foal). Blood glucose should be monitored regularly to avoid hyperglycemia. Some foals with persistent hyperglycemia will benefit from insulin supplementation.

Skeletal maturity is assessed by radiographing a carpus and tarsus for evidence of incomplete ossification. Accelerated ossification does not appear to be a feature of foals born prematurely after exposure to chronic in utero stress. Incomplete ossification coupled with periarticular laxity predisposes the premature or dysmature foal to long-term skeletal problems. Foals with incomplete ossification and more than 30% reduction of the central and/or third tarsal bones with pinching or fragmentation of the dorsal aspects of affected bones commonly develop degenerative joint disease and have a guarded prognosis for future athletic performance. Restriction of exercise is recommended in order to minimize collapse of developing carpal or tarsal bones,

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but forced recumbency may predispose the foal to or exacerbate pulmonary disease. Furthermore, normal load bearing encourages ossification. Periarticular laxity predisposes the premature foal to angular limb deformities that facilitates abnormal load bearing and increase the risk of cuboidal bone crush injury of the carpus or hock. Splinting and attention to hoof care is recommended if angular limb deviation develops. In most cases, flexural deformities and laxities will improve over time. Dorsal splints are recommended for flexural deformities involving the fetlock, and heel extensions are helpful to foals with flexural laxity.

Colostral transfer of maternal immunoglobulin may not occur in premature foals for several reasons. Mares may have lactated prematurely or not at all, and the foal may not be able to suck. It is crucial to ensure that the premature neonate receive ample amounts of high-quality colostrum (>20 mL/kg) in the first 6 hours after birth, although the intestinal tract may not be capable of efficient colostral uptake or may not tolerate large volumes of liquid. Consequently, plasma transfusion is often used even in foals younger than 18 to 24 hours of age. A serum IgG level should be measured to confirm successful transfer of immunity (>800 mg/dL; >8 g/L).

The use of glucocorticoid therapy in the management of prematurity is controversial. Dexamethasone has been used in human medicine due to its potency, but it is associated with adverse side effects including hypertension, hyperglycemia, and catabolism.[335] Hydrocortisone has a shorter half-life and lower biological activity and is as effective for improving lung function and reducing the risk of bronchopulmonary dysplasia. In addition, hydrocortisone is commonly given to preterm infants in the early postnatal life to treat hypotension.[336] There is a risk of adverse complications, including intestinal perforation, which can be minimized by using a lower dose (1 to 3 mg/kg/day divided).[336]

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Respiration

Guy D. Lester

The transition from the fluid-filled lung of the fetus to an organ that is responsible for efficient gas exchange is both rapid and complicated. The process can be complicated by a number of factors, including prematurity or dysmaturity; aspiration of meconium or milk; and bacterial, viral, or fungal infection. A highly compliant chest wall, an inefficient immune system, and failure to derive adequate antibody from colostrum (partial or total failure of passive transfer) are additive factors that predispose the neonate to respiratory problems.

The detection of respiratory disease in the newborn foal can be difficult. Thoracic auscultation can be highly misleading. Minute ventilation (frequency × tidal volume) is increased in the healthy neonate, resulting in easily heard bronchovesicular sounds. There is no need to accentuate breath sounds with rebreathing techniques. During the first few hours after birth, fluid can normally be auscultated throughout both lung fields and within the trachea. End-inspiratory crackles are commonly heard over the dependent lung during and shortly after rising from lateral recumbency. This is presumably due to simple atelectasis. Foals with respiratory disease will frequently have abnormal lung sounds, such as crackles and wheezes, but neonates with even severe pulmonary disease will occasionally have little detectable abnormality during auscultation. Clinical signs that are often associated with pulmonary tract disease in older foals and adult horses are frequently lacking in the sick neonatal foal. Fetal foals develop and mature in a relatively hypoxic environment within the uterus and therefore are more likely to tolerate postnatal hypoxemia than older foals or adults. Cough is also uncommon, likely due to a postnatal delay in maturation of irritant receptors within airways and delayed onset of the laryngopharyngeal cough reflex. This is clinically relevant in that aspiration of milk into the lower airway associated with force feeding can go undetected for several days. Of additional importance is that the respiratory rate and rhythm frequently do not accurately reflect arterial concentrations of oxygen or carbon dioxide. This is particularly relevant in foals that are showing signs suggestive of asphyxial injury, where rising arterial CO_2 concentrations occur in response to hypoventilation and fail to cause an increase in minute ventilation. In these foals

the primary drive for ventilation is arterial O_2 rather than CO_2.

In the absence of arterial blood gas data or radiographic information, the clinician must rely on vague signs, such as restlessness and agitation, increased respiratory rate, or respiratory distress. Historical information may also aid in diagnosis. This should include an estimation of gestational age, recognition of any maternal problems (e.g., fever, dystocia, placentitis, or prepartum vaginal discharge), the presence or absence of meconium staining of amniotic fluid, and an assessment of colostral quality and quantity. Failure to make an early identification of pulmonary disease often results in unfavorable outcome, with chronic pneumonia resulting. Malformations, inflammation, or other abnormalities of the upper respiratory tract can cause clinical signs of respiratory distress, stridor, and dysphagia and result in lower respiratory tract problems as well. A number of nonrespiratory conditions also cause clinical signs that mimic respiratory disease.

The ideal diagnostic tools for investigation of neonatal respiratory disease include arterial blood gas (ABG) analysis and thoracic radiography. ABG analysis is the most sensitive clinical tool used to assess lung function. The sample is usually collected from the dorsal metatarsal artery, easily palpated in most foals on the lateral aspect of the third metatarsal bone. Alternative sites include the brachial artery, located at the level of the medial collateral ligament of the elbow joint, or the carotid artery, but hematoma formation is a common sequel to aspiration from this latter site. The sample will remain useful for up to 90 minutes in a capped plastic syringe at room temperature.

Interpretation of the ABG sample involves consideration of the amount of struggling and position of the foal during sample collection. Normal arterial blood gas values for neonates of different postnatal and gestational ages are presented in Table 17.4. Lateral recumbency can reduce the PaO_2 by as much as 30 mm Hg. The sample needs to be handled appropriately, paying strict attention to avoidance of air contamination, which will artificially increase the PaO_2 and decrease $PaCO_2$. The inspired oxygen concentration must also be considered when analyzing ABG values. With supplemental oxygen, PaO_2 is increased variably, depending on the inspired oxygen concentration (FIO_2), the amount of pathology present (particularly the extent of right-to-left shunting), the respiratory rate and tidal volume of the foal, and if the oxygen is delivered by nasal insufflation. A flow rate of 10 L/min, delivered by nasal insufflation, increased the PaO_2 to 298 ± 69 mm Hg in the normal, term newborn foal,[331]

roughly equivalent to an FIO_2 of 1.0.[337] In the induced premature foal, the PaO_2 increased only to 111 ± 35 mm Hg.[331] If the respiratory rate of a foal is rapid and shallow, the supplemental oxygen will be diluted by room air because of the large quantity of room air entering the upper respiratory tract, and the concentration of alveolar oxygen will probably be much less than 100%. The two most common respiratory-derived ABG derangements include hypoxemia with normocapnia or hypocapnia or hypoxemia with hypercapnia. It is important to distinguish acute from chronic hypercapnia. Acute hypercapnia is associated with a more substantial drop in blood pH and may lead to circulatory collapse and coma, particularly if accompanied by acute hypoxemia. Chronic exposure to elevated CO_2 permits adaptation and more subtle clinical effects. The change in pH is less dramatic primarily because of enhanced bicarbonate reabsorption in the proximal tubules of the kidney. This effect begins within 6 to 12 hours of exposure to increased concentrations of CO_2 and is maximal by 3 to 4 days. Hypercapnia can be exacerbated by fever or the administration of carbohydrates or bicarbonate. The latter is often clinically relevant and highlights the danger of giving large amounts of sodium bicarbonate to foals with pulmonary disease.

Interpretation of blood gas values of venous blood (Table 17.4) can be deceptive and should be restricted to evaluation of metabolic conditions (e.g., metabolic acidosis) and not pulmonary gas exchange. To avoid problems associated with regional blood sampling, peripheral venous blood should be taken from a free-flowing jugular vein because the metabolic status of the head is usually stable. To obtain a sample representative of the whole body, mixed venous blood is drawn from the right atrium. Determination of mixed venous blood oxygen saturation is a good test for assessing the overall adequacy of oxygen delivery to tissues because it reflects the balance between oxygen delivery and oxygen use.

Several factors need to be considered when evaluating foal thoracic films. Thoracic radiographs are routinely taken only in the standing or recumbent lateral position in foals, with dorsoventral positioning reserved for the anesthetized or depressed foal. In healthy foals, radiographs taken before 4 hours of age will reveal increased opacity associated with retention of fetal fluids.[338] Thus interpretation can be limited because of positioning limitations. If the neonate has been in lateral recumbency for extended periods of time, atelectasis may result in diffuse or localized interstitial infiltrates that usually resolve once lung reexpansion occurs. It can be difficult to accurately distinguish bacterial

pneumonia from atelectasis and pulmonary edema on the basis of radiographic appearance alone. In these cases additional diagnostic aids (cultures, hematology, necropsy) should be used in conjunction with radiology to reach an accurate diagnosis. A false overinterpretation of disease is common due to motion artifact, caused by a combination of long exposure times, poor patient compliance, and high spontaneous ventilation rates. When the radiographic appearance of the lung fields is evaluated, the type of infiltrate (interstitial, nodular, alveolar, mixed); severity; and location (diffuse, perihilar, cranioventral, craniodorsal, caudodorsal, caudoventral) should be noted. Other soft tissue structures (including the heart, vessels, and diaphragm) and bones (ribs, vertebrae, long bones) should also be evaluated.

Serial thoracic radiographs are useful in monitoring the progress of a respiratory condition. Radiographic changes may either follow or precede changes in clinical condition, and major changes can occur surprisingly rapidly (Fig. 17.12). Clinical signs of pneumonia frequently resolve much earlier than chest radiographs, and hemograms return to normal. Unfortunately, both ABG analysis and radiography are difficult to perform in field situations.

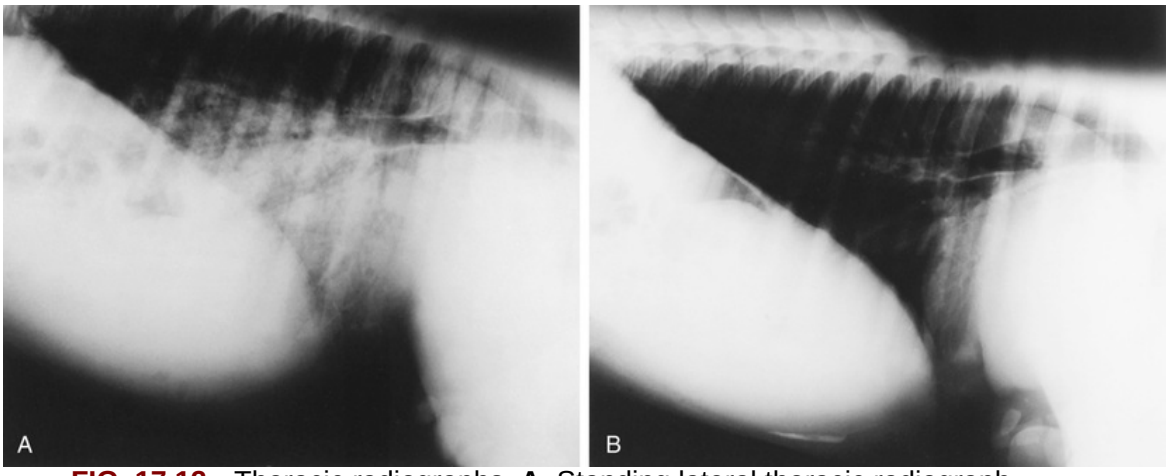


FIG. 17.12 Thoracic radiographs. **A,** Standing lateral thoracic radiograph of a 7-day-old Thoroughbred foal that experienced an acute onset of respiratory distress and cyanosis. Intubation and oxygen administration raised the PaO_2 to only 48 mm Hg. Severe pulmonary interstitial pattern is present in the caudoventral lung fields, and the tentative diagnosis was bacterial pneumonia. With no change in antimicrobial therapy, the foal improved clinically. **B,** Radiographs taken 3 days later revealed marked resolution of the pattern.

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A study of healthy, sedated neonatal foals compared plain radiography with computed tomography (CT) concluded that CT studies were less subjective and had superior interobserver agreement than plain radiography.[339]

Ultrasonographic evaluation of the foal's thorax can yield useful information in a variety of disease processes, including pleural effusion, such as hemothorax or pleuritis, bronchopneumonia, or abscessation. It is also the preferred method for diagnosing rib fracture or dislocation, congenital heart disease, and thus is often a useful technique to differentiate cardiac and pulmonary causes of hypoxemia.

Specific Respiratory Conditions

Upper Respiratory Tract Disorders

Upper respiratory tract disorders are relatively uncommon in neonates. Conditions affecting pharyngeal and laryngeal function are important, as they predispose to aspiration pneumonia. Dyspneic neonates also have difficulty nursing and are subsequently likely to become malnourished. Congenital defects of the upper respiratory tract include collapsed trachea, stenotic nares, choanal atresia, epiglottal cyst, and guttural pouch tympany. There have also been reports of pharyngeal dysfunction as a cause of acute dyspnea, stridor, and dysphagia in neonatal foals.[231,340,341] Endoscopic examination of the upper airways of these foals reveals a variety of abnormalities that include a flaccid, collapsed, and inflamed nasopharynx; intermittent or persistent dorsal displacement of the soft palate; or arytenoid paralysis (Fig. 17.13). Medical management with antiinflammatory drugs, enteral feeding via nasogastric tube, and broad-spectrum antibiotics (for any coexisting aspiration pneumonia) can result in permanent resolution of the problems within 1 to 14 days (mean of 5.5 days).[231] The underlying basis of the condition is not known but may be related to birth asphyxia.

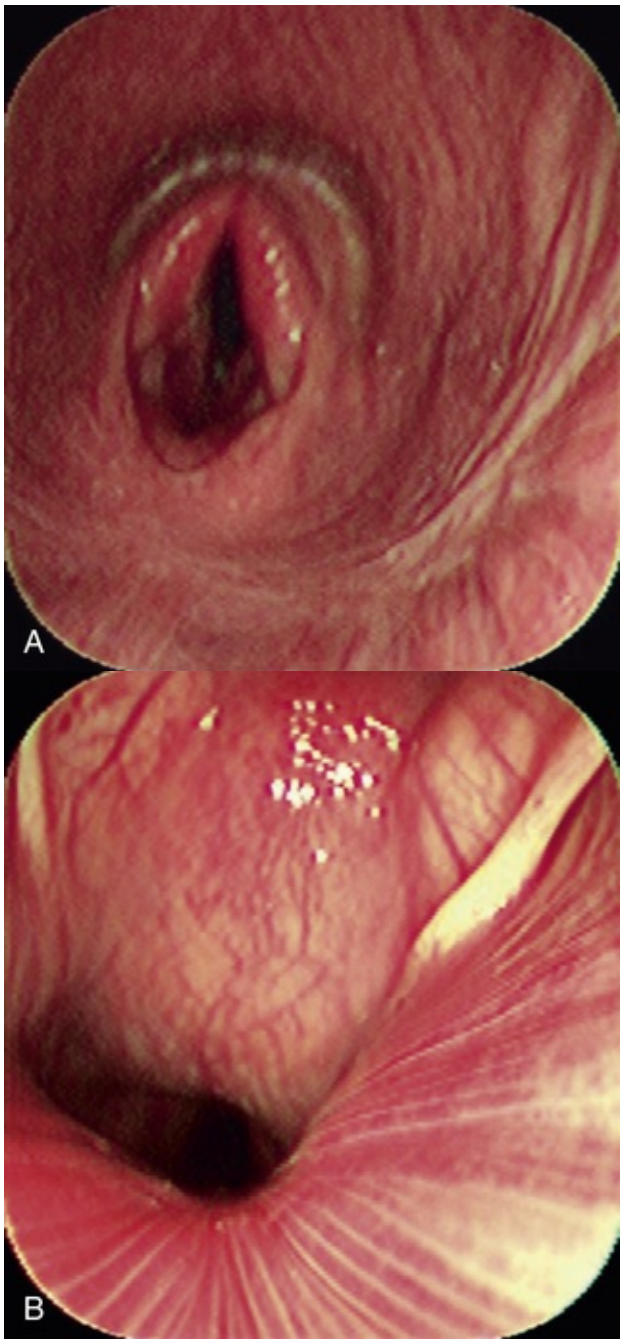


FIG. 17.13 Endoscopic images of a foal with dysphagia and stridor. **A,** Dorsal displacement of the soft palate. **B,** Collapse of nasopharynx associated with pharyngeal weakness.

Impaired pharyngeal and laryngeal function may result from physical deformation or neuromuscular disorders. Pharyngeal and laryngeal injuries are often associated with improper application or use of damaged feeding tubes and oral medication equipment. Compression of the larynx by a retropharyngeal abscess or mass tends to cause inspiratory dyspnea, and aspiration pneumonia is

a common sequela. Partial occlusion of the upper airway induces turbulent airflow and subsequently mucosal edema. Placement of a tracheostomy tube provides an alternate, sometimes life-saving, airway and rests the inflamed mucosa.

Nutritional myodegeneration, hyperkalemic periodic paralysis, and botulism may induce laryngeal paresis. Dysphagia and subsequent aspiration pneumonia is a common sequela of pharyngeal and laryngeal dysfunction associated with nutritional myodegeneration and botulism. Exercise- and excitement-induced respiratory stridor has been described in foals with hyperkalemic periodic paralysis.[342]

Collapsed trachea is a rare congenital or acquired condition. It is most commonly reported in American Miniature Horses, although those affected typically develop signs as adults.[343] Clinical signs include an intermittent honking cough, stridor, and dyspnea with mild exercise. There is no stenosis of the trachea but rather a dynamic dorsoventral collapse during inspiration. The caudal cervical and cranial thoracic sections of the trachea in the area of the thoracic inlet are most frequently affected. Acquired tracheal collapse is commonly associated with fractured ribs and compression of the trachea at the thoracic inlet by the subsequent bony callus.

Diagnosis of most upper airway disorders can usually be made with a combination of radiography and endoscopy. A 7-mm O.D. endoscope is usually small enough to pass through the ventral meatus of horse and pony foals weighing over 14 kg. An integral part of the diagnostic approach to the neonate with suspected upper airway obstruction is assessment of the lungs for aspiration pneumonia. If the primary upper respiratory problem is not corrected and normal nursing is allowed, the pneumonic process will likely persist and become chronic.

Respiratory Infection

Bacterial infection of the lower respiratory tract most commonly occurs during or shortly after birth, but it can also take place before parturition, through aspiration of contaminated amniotic fluid. This may take place in mares with bacterial placentitis. In the newborn foal pneumonia can result from direct aspiration or inhalation of bacteria or from the hematogenous spread of organisms in foals that are bacteremic. The most common bacterial organisms that have been associated with pulmonary disease in foals are identical to those

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that cause systemic sepsis. The most common isolates include *Escherichia coli, Klebsiella pneumoniae, Pasturella* spp., *Actinobacillus* spp., and *Streptococci* spp. Less common isolates include, but are not limited to, *Salmonella* spp., *Enterobacter* spp., *Pseudomonas* spp., *Serratia marcesans, Staphylococcus* spp., and *Yersinia pseudotuberculosis.*

The diagnosis of pneumonia involves identification of causative organism. Isolation of bacteria can be attempted from blood culture or culture of amniotic fluid or placental tissue if in utero infection is suspected. Lower airway culture can be difficult, as a tracheal aspiration can be dangerous in a compromised neonate. An alternative method involves passage of a guarded swab through a nasotracheal tube into the lower airway. A complete blood count and measurement of an acute-phase protein, such as fibrinogen or serum amyloid A, may support a diagnosis of infection but will not be helpful in localization of infection to the respiratory tract. The treatment of bacterial lung disease involves a combination of respiratory support techniques and antibiotic therapy. The neonatal foal readily develops dependent atelectasis in lateral recumbency. Consequently, positioning in sternal rather than lateral recumbency results in improved ventilatory capacity and higher arterial oxygen tension. Broad-spectrum antibiotic therapy should be commenced as soon as lung disease is suspected. The third-generation cephalosporins, such as ceftiofur, ceftazidime, ceftriaxone, or cefotaxime, have distinct advantages over aminoglycosides in the treatment of bacterial pneumonia. They have superior penetration into the lung and effective tissue concentrations are easily achieved by intravenous or intramuscular routes. Because premature discontinuation of antibiotic therapy has resulted in relapse in a number of cases, repeat radiographs, and hematology (complete blood cell count and plasma fibrinogen) are highly recommended before discontinuation of antibiotic therapy. A minimum course of therapy of 3 to 4 weeks' duration is not unusual in cases of severe pneumonia.

Several viruses can cause pneumonia in neonatal or young foals. These include equine herpesvirus type 1 (EHV-1) and type 4 (EHV-4), equine influenza, equine viral arteritis virus, and adenovirus.[344–347] Neonatal pneumonia due to EHV-1 infection is frequently fatal, even in the face of aggressive supportive therapies such as antiviral medication and mechanical ventilation. Several factors appear common to EHV-1 infected foals, but none should be considered pathognomonic. These include leukopenia with neutropenia and lymphopenia, depletion of the myeloid cell lines on cytologic examination of bone marrow aspirates, and the presence of dilated retinal vessels

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and a red discoloration to the optic disc on fundic examination. Fatal bronchointerstitial pneumonia occurred in neonatal foals (aged 2 to 12 days) infected with equine influenza virus during the 2007 influenza outbreak in Australia.[345,347] Infection with adenovirus can be a problem in any immunocompromised foal, especially Arabian foals with severe combined immunodeficiency (SCID) syndrome.

In utero infection with *Histoplasma capsulatum* can result in placentitis, abortion, or birth of an infected foal with multiple organ disease, including granulomatous pneumonia.[348] An antemortem diagnosis can be difficult to establish but is aided by airway cytology where characteristic yeastlike organisms (3 to 5 µm in diameter) are seen within macrophages. Infection with *Candida* species (especially *Candida albicans*) is an infrequent complication in foals with chronic bacterial infection. Lengthy antimicrobial use is an apparent risk factor for infection, and many cases begin with oral candidiasis. The diagnosis is based on a history that often includes persistent low-grade fever, worsening respiratory disease or the development of synovitis, and isolation of the organism through blood culture. Successful treatment of neonatal candidiasis has been achieved with ketoconazole, amphotericin B, or fluconazole.

Meconium Aspiration Syndrome

In utero asphyxia or umbilical cord occlusion can result in fetal passage of meconium into amniotic fluid. Hypoxia induces a redistribution of blood flow away from the GIT, resulting in mesenteric vasoconstriction and secondary intestinal ischemia. Transient hyperperistalsis and anal sphincter relaxation occur thereby allowing passage of meconium. Meconium aspiration may occur before, during, or immediately after delivery as a result of fetal breathing or gasping. Meconium can produce a variety of clinical signs including mechanical airway obstruction and regional air trapping, chemical pneumonitis and alveolitis, alveolar edema, and displacement of surfactant.[349] This reduces lung compliance and causes small airway obstruction and focal atelectasis. These events lead to increased pulmonary vascular and airway resistance and ventilation/perfusion mismatching. Meconium may also enhance the growth of bacterial species within the respiratory tract resulting in secondary bacterial pneumonia. It can be difficult to differentiate meconium aspiration from bacterial pneumonia, especially if the birth was unattended.

If meconium has been aspirated into the pharynx, then gentle suctioning of the

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nasal and oral cavities is recommended. The ideal time to suction the airways is while the animal is still in the birth canal, before it has taken its first breath. If the foal shows signs of meconium aspiration below the vocal cords, nasotracheal intubation and careful, aseptic suctioning are recommended. Intranasal oxygen should be administered during suctioning. ABG analysis dictates what long-term respiratory and metabolic support is necessary. Mild to moderate hypoxemia can be treated with humidified intranasal oxygen (2 to 10 L/min). Severe hypoxemia with accompanying hypercapnia requires positive pressure ventilation and is associated within increased mortality. If surfactant displacement and secondary atelectasis are contributing to hypoxemia, continuous positive airway pressure (CPAP) alone may improve oxygenation while avoiding any unnecessary increase in peak airway pressure. Exogenous surfactant administration has been advocated to treat the surfactant dysfunction, although efficacy data are lacking. Systemic antibiotic therapy is recommended to prevent secondary bacterial pneumonia. Good airway hygiene and coupage are crucial.

A diagnosis of meconium aspiration is based on a history of meconium-contaminated amniotic fluid and a meconium-stained newborn. Radiographs typically show a ventrocranial distribution of pulmonary infiltrate characteristic of aspiration. Clear, yellow to brown fluid may drip from the nose.

Milk Aspiration

Aspiration of milk into the lower airway may occur as a complication to a wide range of conditions. Most foals that aspirate milk will also demonstrate nasal regurgitation of milk. Unfortunately, the decreased sensitivity of the upper and lower airway to foreign material may make diagnosis of milk aspiration difficult. Aspiration can occur in foals with cleft palate, persistent dorsal displacement of the soft palate (DDSP), botulism, neonatal encephalopathy, or generalized weakness due to sepsis or prematurity. Iatrogenic contamination of the airway can occur when bottle-feeding is forced or if the foal is too weak or sleepy to receive feeding. Substantial and sometimes fatal pneumonia can result from inappropriate placement of nasogastric tube.

The diagnosis of milk aspiration is supported by historical data (nasal regurgitation of milk), physical examination findings (abnormal lung and tracheal sounds), and laboratory data (inflammatory leukogram, elevated fibrinogen and/or serum amyloid A, arterial hypoxemia). Radiographic examination commonly reveals a heavy, perihilar and/or ventrally located interstitial density, with or without air bronchograms.

The treatment of milk aspiration involves long-term, broad-spectrum antimicrobial therapy and prevention of further contamination of the airway. The underlying cause must be pursued diagnostically and treated. This may necessitate the use of further diagnostic tests, including endoscopy and plain and contrast radiography. Enteral feeding through a nasogastric or esophagostomy tube is indicated until the underlying problem has been resolved. Nasopharyngeal weakness will frequently resolve over time but may take weeks.

Pneumothorax, Hemothorax, or Uroperitoneum

Pneumothorax is usually an iatrogenic sequel of positive pressure ventilation of diseased lungs, but it may occur spontaneously as a result of birth trauma and rib fracture or from ruptured bullae within the lung parenchyma.[350,351] During mechanical ventilation, uneven alveolar ventilation leads to alveolar rupture and dissection of air into the interstitium. The air moves along bronchioles and other lung structures to pleural surfaces, forming blebs that can rupture into the pleural space. The condition should be strongly suspected if the respiratory condition suddenly worsens while an animal is being ventilated. Clinical signs may include respiratory distress, cyanosis, hypotension, or subcutaneous emphysema. Although auscultation may reveal decreased breath sounds, it may be misleading because of the wide referral of breath sounds in foals. Radiographs are indicated to confirm the diagnosis, but, if radiology is unavailable or the animal is very distressed, a direct needle aspirate is both diagnostic and therapeutic.

Pneumothorax may be treated conservatively if no distress is associated with the air leak and the condition appears stable. Thoracic tube insertion is indicated with continuing air leak, if underlying pulmonary disease is causing respiratory distress, and in those patients receiving mechanical ventilation. A trocar catheter is sterilely introduced into the chest cavity, and the catheter is secured using a Chinese Finger Trap suture technique.[352] Suction is applied at −15 cm H_2O until the tube has drained no air for 12 hours. The tube may then be placed under water seal for an additional 24 hours, and, if no air accumulates, the tube may be removed.

Hemothorax is occasionally noted in the large animal neonate. It has occurred secondary to unstable fractured ribs, with puncture of the lung parenchyma resulting in hemorrhage into the pleural space. Occasionally, a hemothorax may remain undiagnosed until clinical signs of anemia, hypovolemia, or shock appear in the young animal.

Accumulation of pleural fluid is a relatively common feature of moderate to severe uroperitoneum.[353] The fluid may result from increased hydrostatic pressure from uroperitoneum-induced compression of the caudal vena cava or urine migration from the peritoneal cavity to the pleural cavity through lymphatics.[353,354] In most foals the thoracic fluid is not recognized, but some foals develop tachypnea, tachycardia, hypercapnia, and hypoxemia. This signs can be exacerbated after removal of the abdominal fluid, potentially causing a "reexpansion pulmonary edema."[355]

Transient Tachypnea in the Neonate

A syndrome observed in Clydesdale, Thoroughbred, and Arabian neonatal foals has been the combination of fever and tachypnea. The condition appears to be more frequent during hot, humid weather conditions. The pathogenesis of the condition is unknown, but it is speculated that it results from a transient problem in central or peripheral control of thermoregulation and/or respiratory rate and pattern. There is a syndrome in human infants termed *transient tachypnea of the newborn* (TTN) that is self-limiting and, in contrast to the foal syndrome, is generally attributed to failure to adequately clear the lungs of perinatal fluid after birth.[356]

Affected foals are usually of normal gestation and experience a normal birth. Most display normal activity for a variable period after birth, with a sudden onset of clinical signs. There are usually no signs of pulmonary abnormalities as assessed by thoracic radiographs or ABG analysis. Body temperature is variable between foals, ranging from 102° F to 108° F (39° C to 42.2° C). A poor response to antipyretics has been noted. The respiratory rate and breathing pattern often resemble panting (respiratory rate >80 beats/min). The condition usually resolves spontaneously within a few days to weeks.

Before transient tachypnea is diagnosed, it is important to rule out a pneumonic process or other pulmonary abnormality, other sources of infection, metabolic acidosis, and other causes of an increased respiratory rate. Hematology, lung radiographs, and ABGs should be within normal limits, and bacterial cultures should be negative.

Treatment is directed at controlling the body temperature; body clipping, alcohol baths, and being in a cool environment are the most effective methods. If infection cannot be entirely ruled out, antibiotic therapy should be used.

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Treatment of Respiratory Distress

Oxygen therapy is an important component in the management of respiratory distress. The decision to institute oxygen therapy is ideally based on both clinical signs and blood gas analysis. Increased respiratory rate, labored respiration, increased intercostal and abdominal muscle activity, and restlessness are considered indications for a trial of oxygen therapy. A PaO_2 less than 55 to 60 mm Hg in lateral recumbency is considered an objective indication for oxygen therapy. If blood gas analysis is not available, clinical signs indicating a favorable response to oxygen therapy include a decrease in effort of breathing, decrease in respiratory rate, and a more comfortable appearing foal. An absence of response may indicate a nonrespiratory origin of the clinical signs, severe lung pathology, a cardiac malformation, or inadequate inspired oxygen concentration.

The inspired oxygen concentration is most easily increased by nasal insufflation using a bias flow of humidified oxygen. Depending on the severity of disease and size of the individual, oxygen is initially delivered at a flow rate of about 5 L/min and the response is noted. The oxygen catheter tip should be advanced into the nasopharynx, and the opposite end should be secured to the nostril using tape or sutures. The actual oxygen concentration delivered to the alveoli depends on several factors, including the position of the tube and the depth and rate of breathing. Oxygen therapy should be directed at maintaining a PaO_2 of 80 to 100 mm Hg, and the flow rate should be adjusted according to blood gas results. Oxygen therapy should be on a continuous basis, and weaning from support should be done gradually. Transtracheal oxygen delivery may be beneficial in larger foals; hypoxemic neonatal foals that have a rapid, shallow breathing pattern; or foals with severe pulmonary disease that are unresponsive to nasal insufflation.[357] A percutaneous catheter system is placed using local anesthetic and secured to the skin. The distal location of the catheter bypasses a substantial volume of dead space and results in a higher alveolar oxygen concentration.

Oxygen therapy is not effective in correcting hypoventilation, and, if hypercapnia is progressive and accompanied by signs of increasing respiratory distress, some type of mechanical ventilatory support is usually indicated. This decision to provide mechanical ventilation must take into account several considerations, including the worth of the individual, the commitment of the owners, the facility and availability of personnel, and the type of disease process

present. For additional information on mechanical ventilation the reader is directed to other reviews.[358]

Regardless of the level of respiratory support provided, the importance of meticulous respiratory supportive technique cannot be overemphasized. Maintenance in sternal position, frequent turning from side to side, regular coupage, and use of proper suction technique are all important components of respiratory support.

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Diarrhea in Neonatal Foals

Guy D. Lester

Diarrhea occurs frequently in foals of all ages and represents one of the most common medical conditions requiring veterinary intervention. The approach to diagnosis can be difficult, and establishment of a definitive diagnosis in a field setting is uncommon. The veterinarian must therefore consider a number of factors in order to construct a list of most likely causes. These factors include the ages of the affected animals, numbers of foals affected, volume and character of the feces, and duration of signs. There are some limited diagnostic tests that can be used to rule in or out many of the common causes of foal diarrhea.

In some foals, diarrheal diseases are associated with signs of colic. The abdominal pain can be severe and can mimic that seen in foals with strangulating intestinal lesions making case management difficult. Colicky signs frequently precede the onset of diarrhea. Passage of a nasogastric tube is equally important in colicky foals as it is in adults. Foals with intestinal ileus or inflammatory diseases of the small intestine will commonly produce large volumes of gastric fluid on reflux. The control of pain is required in order to reduce the chances of injury and to facilitate evaluation. Intramuscular butorphanol can be helpful in providing pain relief in foals with colitis. α_2-Adrenergic agonists should be used with caution in neonates due to their depressive effect on the cardiopulmonary system. If they are to be used, then start with lower doses or consider combining with butorphanol. Nonsteroidal antiinflammatory drugs should be avoided until a diagnosis is established. Neonatal foals generally tolerate flunixin well but require a slightly larger dose rate but reduced frequency when compared with older animals.

There are many causes of diarrhea in young foals including bacteria and bacterial toxins, viruses, nutrition, parasites, and antibiotic usage.[142] Normal physiologic adaptive processes can also produce diarrhea in most foals. The intestinal microbiota of newborn foals is described as “complex” as early as 24 hours of age.[359] The flora develops over the first weeks of life such that by 60 days of age it resembles that of an adult.

Bacteria

Escherichia coli is the most important mediator of systemic sepsis in newborn foals but is not a common primary cause of diarrhea in this age group. The organism is common in normal horse feces and is frequently isolated from animals with diarrhea,[360] but in the absence of typing the role of *E. coli* is highly questionable. There are rare reports implicating an association between *E. coli* and diarrhea in foals. Enterotoxigenic *E. coli* was isolated from a 3-day-old diarrheic foal.[361] The isolate was of the 0101 serotype, was LT-like toxin positive, but negative for STa. Earlier inoculation studies indicated that F4 (formerly K88)–positive *E. coli* was not likely to cause diarrhea in foals, although may have a synergistic role in foals infected with other potential pathogens, such as rotavirus.[362]

Intestinal disease mediated by Clostridial toxins occurs in foals worldwide. The toxins are most commonly derived from biotypes A and C of *Clostridium perfringens* or from *Clostridium difficile*. Classical intestinal clostridiosis of foals is caused by *C. perfringens* biotype C and is characterized by colic, rapid dehydration, cardiovascular collapse, and hemorrhagic diarrhea. The disease occurs most commonly in foals younger than 10 days of age; often younger than 36 hours of age. It is associated with a high mortality, and outcomes are rarely influenced by treatment.[363] Death may occur rapidly and occasionally before any diarrhea has been passed. Biotype C produces both α and β toxins along with variable amounts of enterotoxin. Cases can occur sporadically or as outbreaks and, on some farms, occur annually presumably associated with carriage in specific mares. Biotype A of *C. perfringens* has become well recognized as a specific cause of foal diarrhea over the past decade. Biotype A produces α toxin and enterotoxin and is associated with a slightly lower mortality rate than biotype C. Affected foals are more likely to respond to directed or supportive care. The development of clinical signs is rapid, and diarrhea may or may not contain blood; in the author's experience, passage of bloody diarrhea is common but usually transient. Reported risk factors for *C. perfringens* diarrhea in neonatal foals in Colorado include breed (stock horse type), birth on dirt, sand, or gravel, housing in stalls or on dry lots during the first 3 days of life, and maternal feeding practices. Feeding a low-grain diet prepartum was associated with a decreased risk of neonatal disease.[363] Hematologic findings are consistent with toxemia. This includes hemoconcentration; an initial leucopenia, characterized by a neutropenia with a left shift to immature forms and toxicity; and a lymphopenia. Chronic cases may develop a rebound leucocytosis and

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hyperfibrinogenemia. Altered coagulation may be evident clinically through prolonged bleeding or spontaneous hemorrhage, or through a propensity to develop thrombosis.

A definitive diagnosis of *C. perfringens* diarrhea is rarely established in practice. The diagnosis is usually based on signalment, clinical features, and outcome, rather than detection of specific clostridial toxins. Positive fecal culture is strongly supportive, noting that healthy foals may shed low numbers of *C. perfringens*. Identification of toxin is ideal but is limited due to availability of appropriate commercial assays. Fecal enterotoxin detection assays are available but lack sensitivity, particularly with biotype C isolates. Biotyping of *C. perfringens* isolates after culture can be achieved using polymerase chain reaction (PCR) analysis for toxin gene sequences. This may be helpful in increasing the accuracy of the diagnosis but again falls short in establishing a definitive cause. Fecal Gram stain is easy to perform and may support an early clinical suspicion of disease if there are abundant numbers of large gram-positive organisms or spores present.

C. difficile can produce an identical clinical syndrome to *C. perfringens,* although it appears to be more variable with respect to fecal blood. The two pathogens were isolated together in several foals with fatal hemorrhagic diarrhea.[364] *C. difficile* also occurs as sporadic cases or as clusters or outbreaks. Identical strains can be recovered in mare-foal pairs, indicating cross-infection.[365] It is important to recognize that clostridial infection can produce a severe inflammatory syndrome that is restricted to the small intestine and may not cause diarrhea. Affected foals can present with signs that mimic strangulating small bowel disease, including severe abdominal pain, gastric reflux, and sanguineous peritoneal fluid. Two principal toxins can be liberated from *C. difficile:* an enterotoxin (toxin A) and a cytotoxin (toxin B). Both nontoxigenic and toxigenic strains exist and can only be differentiated after culture using molecular techniques. Consequently, commercial toxin tests (available for both toxin A and B) are recommended in addition to fecal culture to establish a diagnosis. As with *C. perfringens* cases, a fecal Gram stain can also increase suspicion. Hematologic changes associated with *C. difficile* infection can mimic those associated with *C. perfringens* disease.

Most cases of clostridial enterocolitis require aggressive medical intervention, irrespective of clostridial type. Antimicrobial therapy should be both specific and broad spectrum. Targeted antimicrobial treatment typically includes both metronidazole and penicillin. The majority of affected foals will require, at a

minimum, intravenous crystalloid solutions. Some will also benefit from plasma or synthetic colloids and inotrope and vasopressor therapy. Additional therapies include *C. perfringens* biotype C and D antitoxin, di-tri-octahedral smectite clay, and lactase enzyme replacement.[366,367] The use of *C. perfringens* antitoxin and toxoid is off-label and not without some risk. Pretreatment with antihistamines has been suggested before antitoxin.[366] Prevention of clostridial enterocolitis centers on hygienic housing practices and avoidance of overfeeding of late-pregnant mares. Affected foals and their mares should be isolated, and strict protocols instituted to limit cross contamination. Administration of *C. perfringens* type C and D toxoid to pregnant mares has been used with anecdotal success on farms with recurrent problems with *C. perfringens* biotype C. The use of prophylactic metronidazole is highly controversial but understandable on properties with a high disease prevalence. Some isolates of *C. difficile* are reportedly resistant to metronidazole,[366] and although this appears to be dependent on geographic location the widespread prophylactic use could promote resistance. Prophylactic use of probiotic preparations are commonly recommended, but there are conflicting efficacy data.[368–371]

Bacteroides fragilis is a gram-negative anaerobic rod and occurs in both enterotoxigenic and nonenterotoxigenic forms. Enterotoxigenic strains of *B. fragilis* have been incriminated with diarrhea in several species, including lambs, calves, pigs, humans, and foals.[372] Enterotoxigenic *B. fragilis* was isolated from young foals (aged 2 to 60 days) with diarrhea.[373] Half of these foals had other potential pathogens detected, including *Salmonella* or rotavirus. In a study reviewing 20 isolates of *B. fragilis* from hospitalized foals with diarrhea, only 4 had the enterotoxin gene.[372] The most common isolate from foal feces was a nonenterotoxigenic strain casting doubt as to clinical relevance.

Enterococcus (Group D *Streptococcus*) *durans* has also been implicated as a cause of diarrhea in foals.[374] Similarly, *Aeromonas hydrophila* was isolated more commonly from foals with diarrhea than control animals, suggesting a potential role in foal diarrhea.[375] *Rhodococcus equi* is an important cause of pulmonary disease in foals. Although abdominal involvement appears common, the relevance of *R. equi* as a significant primary enteric pathogen, in terms of number of animals affected, is likely small. An intestinal syndrome has been directly attributed to *R. equi* that involves necrosis of the small intestinal Peyer's patches and multifocal thickening and necrosis of the cecum and large intestine.[376] The changes include multiple areas of intestinal ulceration with an

associated mesenteric lymphadenopathy. The diagnosis of *R. equi* ulcerative colitis is difficult for a variety of reasons. In contrast to *Salmonella* infection, where recovery of the organism from the feces has significance, the recovery of *R. equi* is common in asymptomatic animals. Up to 100% of foals older than 2 weeks of age may shed large numbers of the bacteria.[35]

Salmonella infection of neonatal foals is also associated with high mortality. As with clostridial infection, cases can occur sporadically or as part of an outbreak. Mares provide the most important source of *Salmonella* to newborn foals, but it is rare that both mare and foal will develop clinical disease. Clinical signs can become apparent by 24 hours of age but are more common in older foals. The severity of signs is related to virulence of the serotype involved, inoculation dose, and level of host immunity. In contrast to adult infections, detectable bacteremia occurs commonly in affected foals. Consequently, foals that may survive the initial intestinal or systemic disease remain at risk for secondary complications that include osteomyelitis, synovitis, meningitis, uveitis, hepatitis, or pyelonephritis. In some foals these complications may not become clinically apparent until days or weeks after resolution of enteric disease. Therefore appropriate and sustained broad-spectrum antibiotic therapy is important in known affected foals. The selection of antibiotic should be based on known sensitivity patterns understanding that in vitro sensitivity may not accurately translate into clinical efficacy due to the intracellular location of *Salmonella*. For example, the limited distribution of aminoglycosides can lead to therapeutic failure despite often promising in vitro sensitivity.

Viruses

Rotavirus is the most common cause of infectious diarrhea in foals. There are seven known groups of rotavirus (A through G) and many different serotypes within each group. Group A is the primary cause of rotaviral diarrhea in foals with G3 the most common serotype.[377] Rotaviruses have the ability to change their surface proteins over time, and this rearrangement of gene segments takes place during coinfections with other strains. This leaves the possibility for many variations of the virus.

Transmission may be direct from animal to animal or indirect through fomites. Disease occurs after a short incubation period. Experimentally, this period may be as brief as 48 hours.[378] Rotavirus replicates within the intestine and invades the lining of the proximal small intestine causing villous cell death and a

resultant loss of absorptive area. Diarrhea may result from several mechanisms: (1) a loss of absorptive capacity coupled with a decrease in lactase production can lead to an osmotic load of undigested lactose delivered to an immature hindgut; (2) a compensatory crypt cell proliferation may cause an increase in intestinal secretion; and (3) the virus produces an enterotoxin that causes or contributes to the development of diarrhea. The putative viral enterotoxin and cytotoxin, NSP4, is a nonstructural glycoprotein of rotavirus that is released from virus-infected enterocytes.[379] NSP4 is a noncompetitive inhibitor of the Na-glucose symporter and also enhances intestinal chloride secretion.

Disease can be seen between 2 and 160 days of age but is most common in foals younger than 60 days. Indeed, most clinical infections probably occur between 5 and 35 days of age. The presence and severity of diarrhea are highly dependent on the degree of hindgut maturation. Consequently, infection in foals younger than 2 weeks of age may result in life-threatening watery diarrhea, whereas infected older foals may have minimal or no diarrhea due to effective colonic compensation of osmotic and fluid loads. Diarrhea when present is often watery but nonfetid in odor.

There is serologic evidence that broodmares may have an important role in propagation of the virus within a herd. Infections can occur as isolated cases or as outbreaks following periods of overcrowding and stress. Shedding after infection is usually complete by 10 days after the cessation of clinical signs but may occur intermittently for up to 9 months.[380] The virus can persist in the environment for up to 9 months, and disinfection usually necessitates the use of substituted phenolic compounds.

The diagnosis of rotaviral diarrhea is based on an appropriate signalment, clinical signs, and detection of the virus in feces. Tests include electron microscopy, commercial immunoassays (enzyme-linked immunosorbent assay [ELISA] or latex agglutination), and PCR. Several diagnostic companies and university laboratories have developed comprehensive equine diarrhea PCR panels that include rotavirus. Virus is shed in large concentration early on during infection. Central to the management of affected foals is maintenance of hydration through enteral and/or intravenous fluid therapy.

Prevention involves good hygiene and reduction in crowding. Vaccination of mares during pregnancy has yielded variable results in terms of efficacy.[381,382] There is some evidence to suggest that vaccination may at a minimum delay the onset of disease, thereby reducing both the severity and duration of diarrhea.

Coronavirus can cause diarrhea in foals during the neonatal period. It was

originally thought to be an uncommon but severe cause of diarrhea.[383,384] Survey data using real-time PCR analysis indicated a high rate of carriage in both healthy and diarrheic foals.[385] Antemortem diagnosis can also be made using electron microscopy, serology, or commercial fecal-capture ELISA. As with rotaviral infection, shedding is greatest in the early stages of disease.

Parasites

Strongyloides westerii is a common parasite of foals, with early infection of the foal occurring through mare's milk. Experimental studies have indicated that higher numbers of infective larvae than are found in milk are needed to produce diarrhea.[386] Furthermore, foals with high egg counts are often asymptomatic.

Cryptosporidium parvum is not considered to be an important pathogen of foals in terms of numbers of animals diseased, although it can be a problem in specific locations.[387] On the basis of epidemiologic studies, the parasite appears to be concentrated in some breeding operations.[388] Foals diseased with *Cryptosporidium* shed enormous numbers of infective oocysts into the environment. The parasite is considered to be coccidian-like but differs from coccidia in terms of size (4 to 6 µm diameter compared with 23 to 34 µm for other coccidia), host specificity (not host specific), pathogenesis (only invades epithelium), and drug sensitivity (resistant to many drugs). Infection is by the fecal-oral route. The oocysts can survive in the soil or water for months. They do not require a period of sporulation outside of the host to become infective. In a study of asymptomatic foals, between 15% and 31% of foals were shedding *Cryptosporidium*, and that shedding began between 4 and 19 weeks of age and persisted no more than 14 weeks.[389] All shedding had ceased by weaning and was not identified in adult horses. The diagnosis is usually made through microscopic examination of the feces. Acid fast or Ziehl-Neelsen stains are required to detect oocysts. Immunofluorescence assays and flow cytometry techniques have also been described. *C. parvum* infection may be seen with concurrent enteric or systemic infections. The disease is generally self-limiting in immunocompetent animals. Historically, the pharmacologic control of *Cryptosporidium* has been difficult, but paromomycin, nitazoxanide, or azithromycin may be efficacious. The organism is potentially zoonotic, and transmission from foals to humans is reported.[390]

Giardia may be found in normal foals with infection rates reported from 17%

to 35%.[389] *Giardia* is present in all age groups, and it is believed foals acquire infection from nursing mares. Concurrent infection with *Cryptosporidium* and *Giardia* may be observed. Disease should be suspected if large numbers of parasites are seen on fecal analysis. Affected animals should respond within a few days to treatment with metronidazole; failure to respond should alert to other pathogens.

Nutritional Causes

Nutritional causes of diarrhea include overingestion of milk (as might occur when the mare and foal are separated and rejoined) or overfeeding orphaned or sick foals. Overwhelming the ability of the small intestine to digest and absorb results in presentation of milk to the colon, where it is fermented and produces osmotically active sugars and acids. In a controlled study of foals younger than 5 days of age, an elemental isotonic diet produced diarrhea in healthy foals when fed as the sole source of nutrition. Older foals fed a similar diet apparently did not develop diarrhea.[391] Orphan foals and foals fed commercial mare milk replacer may experience diarrhea associated with these diets. Foals that are fed raw cow's milk frequently experience diarrhea and failure to thrive. Cow milk replacer uncommonly causes diarrhea but remains a less than ideal replacement. In contrast, foals fed goat's milk grow well and rarely develop diarrhea, although they may develop a metabolic alkalosis of minimal to no clinical significance.

Transient lactase deficiency has been proposed in foals. An oral lactose tolerance test is conducted after a 4-hour fast. Foals are administered 1 g/kg of body weight of a 20% solution of lactose powder and observing an increase of plasma glucose of 35 mg/dL (1.9 mmol/L) by 90 minutes.[392] Agents such as rotavirus that damage epithelial cells may cause prolongation of the diarrhea because of temporary lactase deficiency.

Foal Heat Diarrhea

Diarrhea developing during days 5 to 14 of life has been termed “foal heat diarrhea” because of the time relationship to the occurrence of postfoaling estrous in the mare. Diarrhea has developed in foals in this age group that have been raised separated from the dam on a consistent diet and isolated from pathogens, so it does not appear to be causally related to estrous. The most likely cause of foal heat diarrhea is the establishment of normal flora in the hindgut.

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Foal heat diarrhea is typically preceded by coprophagy 2 to 3 days before the onset of diarrhea. Classical foal heat diarrheas are mild and require no specific therapy. Continued diarrhea, fever, or depression with signs of reduced sucking activity on the mare should raise concern of other etiologic agents with appropriate diagnostic testing and treatment.

Treatment and Prognosis

The three main components of therapy of diarrhea in the neonatal foal consist of (1) fluid therapy (either oral or intravenous), (2) intestinal protectants/adsorbents, and (3) antibiotics if indicated to treat suspected bacteremia or clostridiosis. Sodium-containing isotonic intravenous fluids are an important component of diarrhea therapy in the compromised neonate. Potassium is lost in severe diarrhea and, if hyperkalemia is not present, should be supplemented by adding 15 to 20 mEq/L of KCl to fluids. Foals that are not nursing normally may have hypoglycemia and may need glucose-containing fluids. Acid base correction by volume expansion and replacement of bicarbonate can be lifesaving and should be monitored frequently when significant intestinal fluid losses occur.

Ideally milk should not be withheld from foals with diarrhea. The clear exceptions are foals with colic and those with bloody diarrhea. The foal can be muzzled for 8 to 12 hours while the mare is milked out, and the foal provided oral fluids through stomach tube or a bottle if a suck reflex is present. Although labels of electrolyte replacers do not always specify for use in foals, many preparations used in calves have been used in foals. Most of these preparations provide insufficient energy and should be used for short intervals of no more than 24 to 36 hours unless parenteral nutrition of some type is provided to maintain blood glucose levels.

Intestinal protectants may be all that are required in uncomplicated cases or may be used in conjunction with other therapies. Bismuth subsalicylate, kaolin or pectin, and activated charcoal have been used for this purpose. Suggested advantages of bismuth subsalicylate are its neutralization of bacterial toxins and antisecretory effect through its local antiprostaglandin activity. DTO smectite clay is also commonly used in the management of diarrhea.

Systemic antibiotics should be used in the neonate with diarrhea that may have systemic sepsis or compromised immunity. Blood cultures should be obtained before initiation of antimicrobial therapy. Antibiotics with a spectrum

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against gram-negative and gram-positive organisms should be used. In general terms, renal toxicity associated with aminoglycoside use is uncommon in clinical practice. The clear exception is the foal that is dehydrated, most commonly due to ongoing losses through diarrhea. Consequently, the monitoring of renal function is indicated when using potentially nephrotoxic drugs.

Plasma therapy for hypoproteinemia associated with failure of passive transfer or protein-losing enteropathy is useful to maintain plasma oncotic pressure and expected protein binding of medications. Diarrheic foals with albumin levels below 20 g/L or total plasma protein levels less than 42 g/L may benefit from plasma therapy.

Prevention and Control

Prevention is best accomplished by minimizing density of populations of horses, separating of age groups, providing appropriate sanitation and hygiene, and obtaining adequate colostrum of good quality (see Chapter 53). The risk of neonates developing diarrhea in a hospital environment is increased with the use of histamine type 2 receptor antagonists or omeprazole.[134]

Distended and/or Painful Abdomen

Evaluation of the colicky newborn or older foal often presents a diagnostic challenge. As with adults, differentiation between surgical and nonsurgical abdominal diseases is often the primary focus in any evaluation of abdominal pain in foals. Rectal palpation, one of the most important diagnostic aids used in the assessment of adult animals with colic, is limited to digital palpation in foals for obvious reasons. This size limitation does, however, allow other diagnostic modalities to be used effectively, such as US and plain and contrast radiography.

The most commonly used analgesics in colicky neonatal foals include flunixin and butorphanol. Xylazine can be used, but care is needed in sick foals as the drug is associated with significant hypotension. Another important procedure is to pass a nasogastric tube and check for gastric fluid accumulation, a critical aspect of examination of the adult horse with colic but often overlooked in neonatal foals.

The decision to select certain diagnostic tests is based on a number of historical and physical examination findings. The duration and severity of signs, together with evaluation of response to chemical analgesia, will often dictate

surgical versus nonsurgical management. Severe, unrelenting pain that is poorly or unresponsive to analgesics is often unto itself a valid criterion for surgical exploration. The decision to explore the abdominal cavity in the newborn should not be taken lightly, as this age group appears more susceptible to the consequences of adhesion formation postoperatively.[393] A thorough physical examination is key as many gastrointestinal diseases in young foals can occur either as a secondary manifestation to other diseases (e.g., sepsis or prematurity) or in coexistence with other disorders that could impact adversely on either short- or long-term survival.

The evaluation of a colicky foal can often be guided initially by the presence or absence of gross abdominal distention. In young foals, this can be monitored by repeated use of a measuring tape around the abdomen. The position of the tape can be maintained in a constant site by clipping a small mark over the dorsum. The most frequent cause of an enlarged abdomen is gas accumulation within the intestinal lumen, most commonly the cecum and/or large colon. It may be important to determine if the gas is maintained within the intestinal tract or if it is free within the peritoneal cavity. This is particularly true in foals with clinical and/or hematologic evidence of sepsis or toxemia. Free peritoneal gas can be detected by US examination or, more easily, by plain radiography. This can occur secondarily to abdominal rupture or by inadvertent puncture or laceration of the bowel during attempted abdominal fluid collection.

Newborn foals with uroperitoneum can present with abdominal distention and low-grade pain. Differentiation between gas and fluid can generally be made by careful physical examination and confirmed by US examination. Typically, a large amount of free peritoneal fluid is noted and a free-floating empty bladder is clearly seen caudal to the umbilicus. If maintained on a milk diet, most neonates with uroperitoneum will develop the classical electrolyte derangements: hyponatremia, hypochloremia, and hyperkalemia. Foals that develop uroperitoneum during treatment of other diseases (e.g., necrotic urachus in a foal with systemic sepsis) may not develop the classical changes if maintained principally on replacement solutions intravenously.

An US examination of the foal abdomen is best done with the foal in a standing position. The ventral abdomen is clipped, and a coupling gel is applied in a liberal manner. A linear or sector probe with a frequency range between 5 and 7.5 MHz is the most common probe type used for routine scanning. In older foals and adults, a lower frequency probe is needed to provide deeper penetration into the abdomen. In newborn foals every abdominal US should

include examination of all umbilical structures, including both arteries, vein, urachus, and urinary bladder. The intestines should be evaluated for wall thickness (should be <4 mm), the presence of edema or gas within the wall, and echogenicity of contents. Fluid-filled loops of small intestine are often consistent with either primary or secondary ileus or enteritis. Gas echoes within the wall are a feature of necrotizing enterocolitis, a disease of neonates with a high mortality rate. Gas-filled intestine is seen on US as a bright line caused by reflection and refraction of sound waves when contact is made with the gas. A subjective assessment of intestinal motion can also be made during the examination. Typically, in foals with enteritis or enterocolitis intestines will be fluid and gas filled with frequent motion. In contrast, in foals with a mesenteric volvulus or ileus the intestine is relatively motionless. The diagnosis of small intestinal intussusception is commonly made on US examination alone. A series of concentric circles are seen within each other, the so-called target lesions.

Plain radiography is an important diagnostic tool in foals with abdominal pain. This technique is often useful in diagnosing intraluminal obstructions, caused by things such as meconium, bedding, or sand (Fig. 17.14). A knowledge of normal radiographic findings is important for comparison (Fig. 17.15). It is also helpful in differentiating small and large intestinal disease. Obstructive small intestinal disease, such as a mesenteric volvulus or an intussusception, when advanced, will produce characteristic hairpin or stacked loops. A prominent small intestinal gas pattern is commonly seen with ileus or enteritis. Ileus can occur in prematurity, after birth asphyxia, or as a consequence to systemic sepsis or toxemia, and often can be difficult to differentiate from mechanical obstruction. Meconium impactions usually occur in the most distal segments of the intestinal tract and therefore frequently lead to colonic distention with gas. The condition appears to be more common in colts than fillies, and foals with a prolonged gestational period (>340 days) are at greater risk. Large intestinal volvulus occurs infrequently in newborn and young foals and, as with catastrophic small intestinal lesions, should result in a period of violent abdominal pain. However, signs of severe pain may not be evident in some foals with other concurrent diseases, such as overwhelming sepsis or hypoxic-ischemic encephalomyelopathy. Contrast radiography using barium sulphate is helpful in defining problems related to gastric-emptying, small intestinal obstructive diseases and, when administered as an enema, can be helpful in identifying impactions or congenital abnormalities, such as atresia coli. When given as an enema, up to 20 mL/kg of a 30% wt/vol suspension may be administered

through a 24-French Foley catheter with an inflated cuff. Although not reported, rectal or colonic rupture could complicate the technique, particularly if the mucosa is inflamed and friable. For an upper gastrointestinal series, typically 5 mL/kg of barium sulfate is administered via a nasogastric tube and films are taken at times 0, 5, 15, 30, 150, and 270 minutes. An upper gastrointestinal contrast study should be avoided in foals with spontaneous gastric reflux or in foals with known small intestinal distention, as gastric rupture or aspiration of the contrast material could occur.

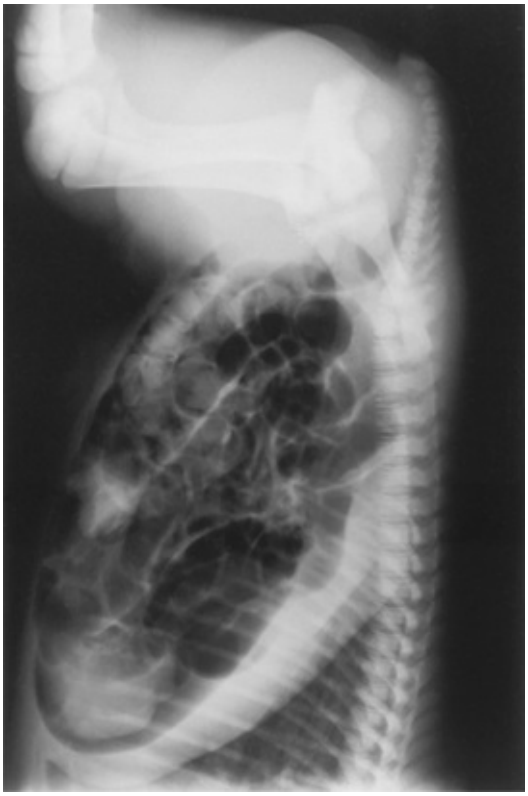


FIG. 17.14 Abdominal radiograph (lateral recumbency) of a 7-hour-old foal with atresia ani, showing meconium retention in a gas-filled large colon.

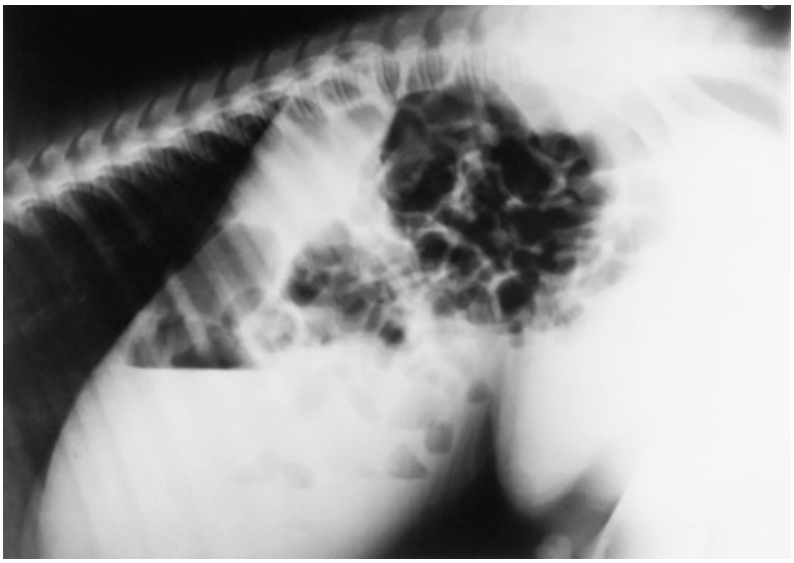


FIG. 17.15 Normal standing radiograph in a neonatal foal. Note the prominent fluid line in the stomach and presence of gas in various portions of the intestinal tract.

Congenital anomalies should be considered in all colicky newborn foals. Common abnormalities include atresia coli, atresia recti, and atresia ani. Plain radiography and digital examination of the anus and rectum will identify many of these foals. Contrast radiography may further identify others, hopefully avoiding the expense of exploratory celiotomy. White foals born to overo-overo or overo-tovero matings are at risk for intestinal agangliosis with or without atresia or stricture formation, so-called lethal white foals (Fig. 17.16). A careful digital examination in a young foal can provide key information including assessing patency of the anus and rectum. Fecal consistency can also be evaluated.



FIG. 17.16 A lethal white foal with colic at 18 hours of age.

Peritoneal fluid evaluation is a useful adjunct to the diagnostic work-up of some foals with abdominal pain. The incidence and severity of complications associated with this procedure in foals are greater than that in adults. Therefore, fluid collection should not be routine but reserved for cases where the distinction between surgical and medical diseases is not clear. Complications can be minimized by identifying pockets of fluid using US and by using a blunt instrument, such as a bovine teat cannula. Hypodermic needles can cause laceration if the foal moves suddenly during the procedure but are safe and efficient where a large amount of fluid is present. The technique should be avoided, if possible, in conditions with extensive accumulation of large intestinal gas.

Specific Conditions

Meconium Impaction

Meconium impaction is the most common cause of the colic in the newborn foal. This condition is more common in colts due to the narrow pelvic canal. Many foals show some degree of straining and discomfort while passing meconium, but in most instances it is passed uneventfully by 24 to 48 hours of age. The meconium most commonly becomes impacted in the rectum or small colon. The clinical signs associated with meconium impaction in the otherwise normal foal include repeated attempts to defecate, straining with the back arched, swishing of the tail, and restlessness. Nursing stimulates defecation through an oral-rectal reflex, so signs of discomfort may appear shortly after each milk meal. If left

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untreated, meconium impactions lead to varying degrees of abdominal distention. The foal's abdomen becomes gas distended with tympany detected over the paralumbar fossa. Digital examination often reveals a rectum packed with hard fecal balls. Occasionally, the impaction is located more proximally (large or small colon) and radiography or ultrasonography is required for diagnosis.

Low doses of analgesics such as flunixin meglumine (0.25 to 1.0 mg/kg IV) and butorphanol (0.01 to 0.1 mg/kg IV) may be required to prevent self-trauma during colicky episodes. Xylazine may exacerbate gut stasis and can cause respiratory depression and should be used with caution in newborn foals. A gravity enema with mild soap and warm water or a commercial enema usually results in prompt evacuation of the meconium. Refractory meconium impactions may respond to 4% acetylcysteine retention enemas. The supplies and procedure for a retention enema are as follows: Mix together 150 mL water, 6 g of acetylcysteine powder, and 20 g of sodium bicarbonate (baking soda). Alternatively, commercial acetylcysteine solution (acetylcysteine [Mucomyst] solution, 100 or 200 mg/mL) can be used. Insert a well-lubricated 12- or 14-French, cuffed Foley urinary catheter into the rectum and inflate the cuff. Slowly infuse 120 to 180 mL of the retention enema solution. Plug the end of the catheter. Tape the catheter loosely to the foal's tail. Leave in place a minimum of 15 minutes and then deflate the cuff and remove the catheter. This procedure can be repeated several times. Care must be taken to avoid traumatizing the rectal mucosa by stiff tubing or multiple enemas with harsh detergents. Clinical signs associated with meconium impaction in the compromised foal may be absent. In asphyxiated or premature individuals that are receiving little or no enteral feeding, meconium may remain in the large colon for days, gradually forming into hard concretions that are diagnosed by palpation or radiographs or at postmortem examination. In these cases the routine administration of an enema is often ineffective in mobilizing the impaction because it is high in the large colon. Additional therapy includes IV fluids, oral fluids, and laxatives (60 to 120 mL of mineral oil with 0.5 to 1 oz of psyllium, 60 to 120 mL of Milk of Magnesia). If the gas distention becomes severe, transcutaneous bowel trocarization can be pursued. The author avoids the use of DSS as an oral cathartic because it can cause excessive irritation resulting in diarrhea and colic. Analgesics may also be helpful in controlling the neonate's discomfort and to reduce the risk of self-trauma. Although most meconium impactions can be successfully treated with aggressive medical therapy, those few foals that are

refractory to treatment or display uncontrollable pain are candidates for surgical intervention.

Uroperitoneum

Uroperitoneum is a relatively common cause of abdominal distention and depression in the neonatal foal. The condition predominates in males but may occur in females as well. Uroperitoneum may be congenital or acquired. The congenital form occurs due to failure of the dorsal wall of the bladder to close during development. The most common cause of uroperitoneum is a ruptured urinary bladder, but other sites in the urinary tract may also leak, including the ureters, urachus, and urethra. Most cases of ruptured bladders are presumed to occur during parturition because of external pressure on a distended bladder. This form occurs most commonly in colts. Uroperitoneum can also occur secondary to ischemic necrosis or infection of the urinary bladder or urachus in the compromised foal. Critically ill, recumbent foals may rupture their bladders while being lifted and turned with a full bladder or from chronic overdistention associated with their generalized disease state. Foals with botulism may also rupture their bladder secondary to bladder atony and chronic overdistention. Older foals of either sex may experience bladder rupture secondary to focal infection of the umbilical arteries and/or urachus, or ischemic necrosis of the apex of the bladder.

Clinical signs of uroperitoneum are rarely noticed before 48 to 72 hours of age, particularly if the foal is not being watched closely. The first signs may be urinary incontinence or frequent attempts to urinate, with only small amounts voided. Sometimes, particularly in those animals that rupture sometime after birth, there is a history of a period of normal urination, which at some point stopped or became abnormal. Loss of suckle, mild colic, and increasing abdominal distention are usually accompanied by worsening depression and increasing heart and respiratory rate. If the condition is allowed to persist, foals become increasingly weak and dyspneic and may present in cardiovascular collapse. Fillies with ruptured ureters have been reported to have a characteristic protruding perineum, presumably as a result of retroperitoneal accumulation of fluid.[394]

Laboratory findings commonly associated with uroperitoneum are elevated serum creatinine and blood urea nitrogen, hyperkalemia, hyponatremia, hypochloremia, and metabolic acidosis. These changes are probably a result of the normal diet of the foal (milk being relatively high in potassium [25 mEq/L]

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and low in sodium [12 mEq/L]) and the third spacing of urine in the peritoneal cavity. With urine potassium concentration relatively higher than serum and urine sodium concentration lower than serum levels, the net effect of partial equilibration of serum with peritoneal fluid across a semipermeable membrane is hyponatremia and hyperkalemia, along with an inability to excrete the waste products of metabolism. Hyperkalemia may be severe enough to induce potentially fatal bradyarrhythmias. In hospitalized foals that developed uroperitoneum as a secondary complication, these typical electrolyte abnormalities are not consistently observed. Because most of those foals were receiving replacement intravenous fluids (high in sodium, low in potassium) and very little milk, it was theorized that intake has a great influence on the electrolyte abnormalities associated with uroperitoneum.[395] On the other hand, the electrolyte abnormalities typically associated with uroperitoneum are not pathognomonic for that disorder. Foals with renal failure, blocked urethra, white muscle disease, and enteritis have shown the same electrolyte changes.

A diagnosis of uroperitoneum often can be made quickly using transabdominal US and a 5- or 7.5-MHz transducer to visualize large volumes of free, nonechogenic fluid within the abdomen and a small, irregularly shaped, collapsed bladder. Abdominocentesis usually produces a free flow of peritoneal fluid that contains a low cell count, low specific gravity, and at least twice the creatinine concentration of peripheral blood. If the creatinine is the same in both serum and peritoneal fluid, other explanations for the clinical signs should be investigated. The WBC count, total protein, and cytology of the fluid should also be determined. Most uncomplicated cases of ruptured bladders have fairly normal values for peritoneal fluid. In some cases, however, an increased WBC count and total protein and the presence of bacteria may suggest peritonitis. This may be a result of the urine in the abdomen, but more commonly there is a primary ongoing infectious problem (necrotic urachus or bladder, enteritis) and the prognosis becomes worse. If laboratory facilities are not available, new methylene blue can be injected into the bladder using a urinary catheter, and a few minutes later a sample of peritoneal fluid should have a blue discoloration if a ruptured bladder is present. However, this technique may not detect other causes of uroperitoneum such as a ruptured ureter or distal urachus. Positive contrast cystography using a 10% solution of water soluble media may be helpful in detecting the location of the urinary tract leakage. The ability to obtain urine on catheterization of the urinary bladder does not rule out uroperitoneum. Hematology and blood cultures should be performed to detect primary or

secondary sepsis.

Treatment of uroperitoneum is surgical repair. However, the foal with uroperitoneum should not be rushed to surgery without first carefully stabilizing it. Serum electrolytes and blood gases should be run to determine the extent of hyperkalemia, hyponatremia, and acidosis present. Although the total amount of water in the body is usually grossly increased by the peritoneal accumulation of urine, effective circulating volume may be drastically reduced. If the eyeballs are sunken and pulse quality and capillary refill time are poor, aggressive fluid therapy is indicated to support the circulation. This is best performed by concurrently removing as much fluid as possible from the abdomen with a teat cannula, 14G catheter, or peritoneal dialysis catheter to avoid worsening fluid overload and respiratory distress. The fluids of choice to treat the typical electrolyte alterations associated with uroperitoneum are saline, dextrose, and possibly sodium bicarbonate solutions, depending on the degree of acidosis present. In most instances continuous dextrose infusion is effective in decreasing the serum potassium level to an acceptable level, but values should be rechecked before anesthesia is induced. Insulin and dextrose may also be used to treat hyperkalemia, but the patient must be monitored for hypoglycemia. One suggested regimen is regular insulin at 0.1 to 0.2 U/kg subcutaneously or intravenously accompanied by a continuous IV dextrose infusion (4 to 8 mg/kg/min). Some individuals also have pleural fluid accumulation and atelectasis secondary to the abdominal distention, so oxygenation and ventilation during and after surgery should be closely monitored. Broad-spectrum antibiotics should be started immediately after samples are taken for culture if infection is suspected.

The prognosis for uncomplicated ruptured urinary bladders is usually good (>80% survival), provided the animal is stabilized before anesthesia. The presence of concurrent septicemia carries with it a considerably poorer prognosis.[395] In one retrospective study among foals with uroperitoneum, 100% of those foals with a negative sepsis score lived and only 57% of foals with a positive septic score survived.[396]

Gas or Fluid Accumulation in the Gastrointestinai Tract: Ileus

Abdominal distention and colic secondary to excessive gas and/or fluid accumulation in all or a portion of the gastrointestinal tract are common

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complications in the compromised neonate undergoing intensive care. The exact mechanisms responsible for the presumably altered GI motility are not well defined. Ileus is associated with the absence of intestinal sounds, abdominal distention, and intolerance of oral feeds characterized by gastric reflux. Auscultation of reduced gastrointestinal borborygmi does not always correlate with the degree of intestinal compromise and decreased motility. Transabdominal ultrasonography helps identify absence of intestinal motility and the location and degree of intestinal distention. Ileus and the attending abdominal distention can cause severe colic and can induce respiratory distress in a weak or premature foal with preexisting pulmonary compromise.

Metabolic and infectious causes of ileus in the foal include hypokalemia, hypocalcemia, hypoxic-ischemic bowel injury, bowel obstruction, peritonitis, enterocolitis, and endotoxemia. Hypokalemia is associated with anorexia, diarrhea, and renal loss. Hypocalcemia is associated with prematurity, decreased dietary intake, excessive bicarbonate administration, diuretic therapy, and those conditions such as asphyxia, toxemia, and sepsis that stimulate release of cortisol and catecholamines. Peripartum hypoxia results in a preferential decrease in blood flow to the gut and kidneys. Poor perfusion of the intestines leads to varying degrees of mucosal damage and decreased motility. Severely damaged bowel requires a period of gut rest to allow healing to occur before restarting oral feeds. Premature resumption of enteral feeding is associated with colic, maldigestion, diarrhea (often bloody), and translocation of intraluminal bacteria across damaged bowel wall into the bloodstream. Some of the more common causes of bowel distention in the neonate include meconium retention, intussusception, ascarid impaction, and small intestinal volvulus. Peritonitis may be associated with intraabdominal abscessation, severe enteritis or gastroduodenal ulcer disease, and generalized septicemia. The most common causes of enteritis in foals include rotavirus, *Clostridia* sp., *Salmonella* sp., and dietary changes. Endotoxemia is usually part of generalized septicemia. Chronic bowel distention, regardless of the cause, further impedes return of normal gut motility. In the foal, aerophagia, particularly in the struggling or hypoxic neonate, often results in gas distention that is not easily removed through a nasogastric tube, since gas tends to move quickly through the GI tract. Abdominal distention is also commonly observed during mechanical ventilation in the foal and as a result of overfeeding in the calf. Foals with botulism are often intolerant of enteral feeding, probably because of altered gastrointestinal motility. Use of certain milk replacers can result in bloat, colic, and diarrhea,

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even in the apparently healthy orphan neonate. Discontinuation of or a decrease in the amount of enteral feeding and, if possible, increased activity of the patient usually results in resolution of the problem.

Abdominal radiographs reveal gas-distended loops of small or large intestine and may identify bowel obstruction. Sonographic examination permits evaluation of bowel wall thickness, peritoneal fluid volume and echogenicity, gut patency, intramural gas accumulation, location and degree of intestinal distention, and presence or absence of motility. An abdominal sonogram should be performed to rule out the presence of an intussusception or other obstructive lesion before initiating any prokinetic therapy.

Management of ileus includes nasogastric decompression, cessation or reduced volume and frequency of enteral feeds if gastric reflux is present, parenteral alimentation if enteral feeding cannot be maintained at a rate of at least 10% of BW/day, enema administration to relieve distal meconium or fecal retention, correction of any underlying electrolyte abnormalities, exercise for ambulatory foals, and judicious use of prokinetic agents. The gut atrophies without enteral feeding. Prokinetic drugs should not be used when bowel obstruction or compromised bowel integrity is suspected. Prokinetic agents that have been used include metoclopramide, bethanechol, and erythromycin. There have been anecdotal reports of small intestinal intussusception after prokinetic use in neonatal foals.

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a syndrome of acute intestinal necrosis that has been described in human infants and other species, including equine neonates.[397] The causes of NEC are not well defined, but predisposing factors include ischemic or hypoxic gut injury, the presence of intraluminal bacteria, and enteral feeding. Following gastrointestinal ischemia, mucosal cell metabolism diminishes and the protective mucous layer is lost. This allows enzymes to break down the mucosal barrier, and intraluminal bacteria can then invade and multiply within the bowel wall. Enteral feeding provides substrate for the bacteria. Abdominal signs include progressive abdominal distention, colic, ileus, and ascites. The condition may appear as a fulminant, rapidly progressive disease or progress at a much slower pace.[227]

Clinical signs associated with gut injury include ileus, gastric reflux, colic, lethargy, abdominal distention, and diarrhea. Reflux and feces may be positive

for blood. Generalized sepsis often accompanies NEC. NEC should be distinguished from intestinal ileus secondary to other neonatal diseases, other surgical GI lesions, bacterial or viral enterocolitis, and intolerance to a milk diet. Ultrasonography may reveal intramural gas accumulation (Fig. 17.17). If intestinal perforation has occurred, pneumoperitoneum and septic peritonitis may also be noted.[227,397] Intestinal perforation is associated with a hopeless prognosis.



FIG. 17.17 An ultrasound image demonstrating gas in the intestinal wall of a foal with necrotizing enterocolitis.

Hemoperitoneum

Hemoperitoneum is a relatively uncommon cause of abdominal distention in the large animal neonate. The most common structures responsible for the hemorrhage are the umbilical vessels and rupture of the liver or spleen secondary to trauma. Occasionally, other structures, such as a ruptured granulosa cell tumor, may bleed.[290] Depending on the cause and severity of the hemorrhage, clinical signs relating to hypovolemia and anemia may be mild or severe and appear shortly after birth or in the older foal. Diagnosis of hemoperitoneum is

based on the retrieval of free-flowing blood on peritoneal tap and the detection of free fluid in the abdomen. Ultrasound examination may be of benefit in detecting the source of the bleeding. Of critical importance, regardless of the source of the hemorrhage, is prevention of hypovolemic shock, and intensive patient monitoring and intervention is often indicated. Whole blood replacement may be necessary. If an internally bleeding animal with an unstable cardiovascular system is rushed to surgery without prior stabilization, profound shock may occur and a poor outcome usually results.

Umbilical Problems

The umbilicus contains a single umbilical vein, two umbilical arteries, the urachus, and vitelline vein remnant.[398] Guidelines for routine care of the umbilicus after birth are discussed in Chapter 16. The most common postnatal problem of the umbilicus is patency of the urachus. The urachus is the anatomic connection between the bladder and allantoic sac. During gestation the predominant flow of urine is through the urachus, but as gestation proceeds some urine will enter amniotic sac via the urethra. The urachus is closed at the time that the cord is broken. Excessive coiling of the umbilical cord during gestation may result in partial obstruction of the urachus with overdistention of the structure, thereby interfering with the normal process of involution when the cord is torn after birth. This is estimated to occur in around 6% of normal foals.[399] The structure may fail to close or reopen for a number of reasons, including cutting of the cord rather than tearing, infection, excessive handling, or weakness of the supporting abdominal musculature. The condition is a common complication in sick neonatal foals, particularly those that are mostly recumbent. Affected foals will typically dribble or stream urine from the umbilicus during urination. There may be excessive straining observed. Physical examination may reveal a moist umbilical stump. In a small number of foals a rent in the urachus occurs as it moves through the subcutaneous tissues, resulting in local swelling, that may be marked. If the tear in the urachus occurs intraabdominally, there will be uroperitoneum and in rare cases omentum may herniate externally through the urachal tear. Ultrasound is recommended, and a fluid-filled urachus is consistent with patency. The umbilical arteries and vein should be assessed for infection as an open urachus is a common finding in foals with umbilical remnant infections.[400]

Therapy for an uncomplicated patent urachus typically consists of

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conservative management, involving monitoring and frequent disinfection. Cauterization of the urachus using silver nitrate sticks or injection with procaine penicillin was once popular but appears to be used infrequently in recent times. Resection of the structure may be indicated if patency persists beyond 3 weeks of age.

When the umbilicus is enlarged and draining purulent material, infection is easily diagnosed. Many neonates may have a completely normal-appearing external umbilicus but have internal infection of the urachus, umbilical arteries, or vein. Ultrasound is the key tool to diagnose internal abnormalities of the umbilical structures. The umbilical area of neonates younger than 20 days of age with fever of unknown origin should be scanned, as well as any foal with suspected bone or joint infection. A description of normal US findings is described in Chapter 16.

The traditional approach was to surgically remove abnormal umbilical remnants if there were abnormalities detected on US or if the external umbilicus was enlarged and/or draining purulent material. The basis for this was to remove the potential for bacteremia with seeding of other structures, such as bone or joints. There is morbidity and cost associated with simple surgical removal, and there is little evidence that surgical excision is superior to long-term therapy with antimicrobial drugs. More recently, many clinicians favor long-term antimicrobial treatment with oral therapy, such as trimethoprim-sulfa combinations or minocycline. In this approach it is important to monitor responses to therapy using frequent US examinations. Surgical removal would be indicated if the internal appearance worsens in the face of medical treatment.

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• CHAPTER 18

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The Peripartum Ruminant

John K. House, Consulting Editor

Peripartum mortality is a common cause of loss across livestock industries.[1] The peripartum period is high risk for both fetus and dam. Approximately 5% to 10% of the annual calf crop and 15% to 20% of the annual lamb crop in the United States die before weaning.[2-4] Between 50% and 70% of neonatal mortality occurs in the first 3 days of life with dystocia, starvation, and hypothermia responsible for 50% to 60% of these losses.[3,5] The incidence of dystocia is particularly high in Holsteins with reports of 50% of heifers and 30% of cows requiring calving assistance.[6] The risk of neonatal morbidity and mortality is largely influenced by sire selection (calving ease), maternal management, and subsequently maternal health during the peripartum period.

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Late-Term Complications of Gestation

Uterine torsion, vaginal prolapse, hydrops allantois, hydrops amnii, and metabolic disorders are disorders of pregnancy and the peripartum period that negatively affect the health of the dam and fetus during late gestation. Over the past 15 years, there has also been increasing application of advanced reproductive technologies with the production of in vitro and cloned embryos. The initial application of these methods was associated with a higher incidence of complications during pregnancy and neonatal mortality. Improvements in embryo production techniques haves reduced the incidence of complications.

Uterine Torsion

Uterine torsion is more common in cattle than other domestic species. The exact etiology is unclear with most occurring during late first-stage or early second-stage labor.[7] Proposed risk factors include poor maternal muscle tone, strong fetal movement, and reduced rumen fill. Retrospective studies have reported no significant seasonal effect, a higher incidence in Brown Swiss cows, and a lower risk in Hereford, Angus, and Jersey cows compared with Holstein-Friesians.[8] Calf birth weight is typically above average, and a greater proportion of fetuses are male (63%).[8] The incidence is also significantly higher in cows as compared with heifers.[7]

Clinical signs associated with uterine torsions include fever, tachycardia, tachypnea, straining, anorexia, and vaginal discharge.[8] The diagnosis of uterine torsion is based on a history of advanced pregnancy and the presenting clinical signs. On transrectal palpation, the orientation of the broad ligaments is distinctly altered; depending on whether the torsion is to the left or the right, the respective broad ligament is pulled tightly across the uterus.[9] Approximately 60% of torsions involve the vagina, and spiral folds can be palpated per vagina.[9] Most torsions are to the left (counterclockwise); in general, the uterus rolls toward and over the nongravid horn (≈60% of all pregnancies in the cow are in the right horn).[9] Forty-five to 90-degree torsions are uncommon; 20% are 90 to 180 degrees, 57% are 180 to 270 degrees, and 22% are 270 to 360 degrees.[8] With severe torsion, circulation is compromised. Treatment involves correction of the torsion and delivery of the calf. In a retrospective study of 164 cases,

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vaginal delivery was possible after manual correction (20%) or rolling of the cow (18%). Cesarean section was performed immediately in 35% of the cases, after failed detorsion attempts in 7% and due to failure of the cervix to dilate following successful correction of the torsion in 20%. When manually manipulating the fetus per vagina, it sometimes helps to have a person assist by pushing on the calf externally. The prognosis for fetal survival rate influenced by duration of parturition before intervention with calf survival is around 35% when the duration is longer than 12 hours and 80% to 90% when parturition has progressed for less than 12 hours.[10] Often the duration of parturition is unknown. The presence of intact fetal membranes has also been associated with a better prognosis for calf survival, with 70% survival when membranes are intact versus 25% survival when fetal membranes are not intact.[11]

Vaginal Prolapse

The primary predisposition to cervicovaginal prolapse in cattle is elevated plasma estrogen concentrations during late gestation.[9] The higher prevalence in certain beef breeds implies a genetic predisposition, with Bos indicus, Herefords, Charolais, Limousin, and Shorthorns affected more frequently than other breeds.[12-14] Other factors that contribute to the risk of vaginal prolapse include increased intraabdominal pressure in late pregnancy, obesity, and poor vaginal conformation. The pathogenesis and development of vaginal prolapse is progressive; it starts with exposure of some of the vaginal mucous membrane. The prolapsed mass moves in and out as the cow gets up and lies down. Exposed mucosa dries out and becomes irritated, leading to straining and further prolapse. The prolapsed tissues become edematous, leading to circulatory impairment and swelling. Ultimately, the cervix and occasionally the bladder may become involved.[9] The objective of treatment in the case of pregnant animals is to replace and retain the vagina within the pelvic canal and to deliver a live calf. Numerous treatment options are described for vaginal and cervical eversions.[14] These methods include suturing the vulva (caslick, Bruhner's), vaginopexy (Minchef procedure), or cervicopexy (Winkler procedure). Close observation of the cow for signs of impending parturition is required after suture of the vulva. Failure to release the sutures before parturition can lead to severe laceration of the vulva and potentially the death of the calf. If the patient is close to parturition, induction is recommended to expedite the process and prevent

recurrence before parturition. As vaginal prolapse is likely to recur during the next pregnancy, it is recommended that the cow be culled when the calf is weaned.

Ring Womb

Ring womb, or incomplete dilation of the cervix, causes sporadic dystocia in sheep and goats. It is most commonly observed in sheep and may be heritable in some instances.[15] Ring womb has no predisposition associated with breed, age, or body condition score but is associated with a significantly higher lambing percentage.[15] Correction with gentle manual stretching can be attempted. The use of prostaglandin E_2, administered as an intracervical gel in the treatment of ring womb in ewes, is not effective at causing dilation of the cervix.[16] Due to the significant risk of tearing, a cesarean delivery is often required.[17] Ewes with diseases that cause abortion due to infectious agents may exhibit signs similar to ring womb, as can pregnancy toxemia, consumption of poisonous plants, consumption of estrogenic plants, and lasalocid toxicity.[17]

Early Dilation Syndrome

Early dilation syndrome is a condition of sheep that is similar to but considered separate from ring womb. In early dilation syndrome, incomplete dilation of the cervix occurs approximately 7 to 14 days before term. The ewe has little or no udder development or a sudden overnight blooming of the udder and placental membranes protruding when presented. The cervix usually can be dilated by hand, but the lambs, although born alive, are not viable. The syndrome occurs most frequently in ewe lambs and first-lambing 2-year-olds, but occasionally in older ewes. Affected flocks can have higher than 30% morbidity. The syndrome occurs in all breeds and flock management situations. No common link has been found from nutritional, physiologic, toxicologic, or infectious disease investigations.[17]

Hydropic Conditions

Fetal loss associated with abnormal placentation occurs sporadically and is reflected by alterations in volume and composition of allantoic and amniotic fluid. In a study of 60 cases of bovine hydrops, 88% were hydrallantois, 5%

hydramnios, and 7% a combination of both.[18] Hydrallantois is often associated with disease of the uterus and hydramnios with genetic or congenital defects of the fetus (Dexter cattle with bulldog calves, Angus calves with osteopetrosis, Guernsey calves with pituitary hypoplasia or pituitary aplasia).[19]

Hydrops Allantois (Hydrallantois)

Hydrops allantois is a sporadic condition of cattle in which there is progressive, excessive accumulation of allantoic fluid. Accumulation of allantoic fluid from midgestation is associated with placental dysfunction.[9] Placental dysfunction is characterized by a reduced number of placentomes (normal 75 to 100) and the development of more primitive villous placentation.[20] An increased incidence of hydrops allantois has been reported with pregnancies derived from in vitro–produced embryos. In a comparative study of in vitro fertilization (IVF) and artificial insemination (AI)–derived pregnancies, the percentage of cows with hydroallantois was 1.8% and 0.07%, respectively.[21] A herd outbreak of hydrops allantois has also been associated with severe nutritional deficiency.[9] Allantoic fluid volume may exceed 100 L (normal 8 to 15 L near term), leading to rapid abdominal enlargement. Rectal examination reveals tight distension of the uterus. The fetus and placentomes are not palpable due to the tightness of the uterine wall. Affected cows become anorectic, leading to dehydration, constipation, and eventually recumbency.

The concentration of sodium and chloride in allantoic fluid of cattle during the last 12 weeks of gestation is normally low (Na = 52 ± 20 mmol/L and Cl = 17 ± 11 mEq/L) and the concentration of creatinine is high (1224 µg/mL ± 458).[22] With hydrallantois, allantoic fluid sodium and chloride concentrations rise toward extracellular fluid concentrations (Na = 116 ± 13 and Cl 81 ± 12 mEq/L) and allantoic creatinine concentration decreases (193 ± 73 µg/mL).[22] Normal amniotic fluid has electrolyte concentrations similar to plasma (Na = 132 ± 7 and Cl 115 ± 8 mEq/L) and a lower creatinine concentration than allantoic fluid (70 ± 26 µg/mL).[22] Cows with hydrallantois are also often hyponatremic and hyperglycemic.[18,23]

Due to the poor prognosis, salvage slaughter is generally recommended. Parturition can be induced if the cow is reasonably close to term and is recommended for the salvage of the calf. Attempts at medical management of affected cows include slow decompression and supportive fluid therapy. The

grossly distended uterus is slow to involute and prone to severe metritis. The prognosis for future fertility is guarded.

Hydrops Amnii (Hydramnios)

Hydramnios is rare, accounting for 5% to 10% of uterine dropsy cases.[24] It has been associated with a genetic (autosomal recessive) or congenitally defective fetus in which swallowing is impaired and the amount of amniotic fluid gradually increases over several months.[24] It may affect only one of twin fetuses.[9] Normal amniotic fluid volume at parturition is about 4 to 8 L. Cattle with hydrops amnii may accumulate 20 to 100 L of amniotic fluid.[25] The slowly progressive accumulation of fluid during the latter half of gestation means that the abdominal muscles become stretched and the cow develops the typical "pear-shaped" abdomen. In contrast to the situation with hydrallantois, placentomes and often the fetus are palpable per rectum. The prognosis for the life and future fertility of cattle that have hydramnios is good.[25] The fetus itself is invariably defective and will not be viable. If the owner elects to keep the cow, the genetic implications should be considered. Clinical features that distinguish hydrops amnii and hydrops allantois are presented in Table 18.1.

TABLE 18.1

Differential Diagnosis Between Hydrallantois and Hydramnios in Cattle[9]

Characteristic	Hydrallantois	Hydramnios
Prevalence	85%-95%	5%-15%
Rate of development	Rapid (within 1 month)	Slow over several months
Shape of abdomen	Round and tense	Piriform, not tense
Transrectal detection of placentomes and fetus	Nonpalpable (tight uterus)	Palpable
Gross characteristics of fluid	Watery, clear, amber-colored transudate	Viscid, may contain meconium
Fetus	Small, normal	Malformed
Placenta	Adventitious	Normal
Refilling after trocharization	Rapid	Does not occur

Abnormal Offspring Syndrome

The transfer of bovine embryos produced and manipulated in vitro results in abnormalities in some conceptuses, foetuses, placentas, and offspring.[26,27] The

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term *abnormal offspring syndrome* is used to describe the range of abnormalities observed.[28] The exact etiology of the syndrome is uncertain, although developmental abnormalities of the fetus, placenta, and offspring have been predominantly attributed to the presence of serum in the culture medium.[29] In utero manifestations include prolonged gestation; abnormal placental development (placentomegaly, hydroallantois, and edematous placentomes in reduced numbers); and suboptimal embryonic and fetal survival.[20,30] Increased birth weight and incidence of dystocia, congenital deformities, and perinatal mortality are neonatal manifestations of this syndrome. The incidence of abnormal offspring syndrome has declined with refinement of IVF culture systems. There is increasing research focused on the epigenetic effects of assisted reproductive technologies, such as sex sorting and IVF on adult health and production phenotypic expression.[31]

Calves derived from somatic cell nuclear transfer, “cloned calves,” have a high incidence of respiratory disease during the neonatal period.[32,33] Possible causes of compromised respiratory function include hypoventilation, ventilation perfusion mismatch, right-to-left shunt resulting from persistent fetal circulation, and respiratory distress syndrome resulting from inadequate surfactant production. Nasal insufflation at birth is recommended to support the respiratory function of cloned calves.[32] In vitro–produced calves are also more frequently born with enlarged umbilical structures. Hemorrhage must be controlled at birth and navels monitored to prevent and manage navel infections.[33]

Maternal Nutrition

Maternal nutrition has epigenetic effects on the developing fetus, influencing postnatal growth, productivity, and reproductive performance.[34] Phenotypic effects are exhibited when stimuli occur during critical development periods, such as during ovarian meiosis, folliculogenesis, and hypothalamic-pituitary axis development.[35]

Reduced fetal viability often reflects mismanagement of maternal nutrition during the last trimester of pregnancy and/or during the prepartum and peripartum period. Maintenance of adequate nutrition throughout pregnancy is essential to provide for the growing fetus and to maintain a healthy dam capable of delivering and nursing the fetus. Pregnancy toxemia, hypocalcemia, protein energy malnutrition, micronutrient deficiencies, and obesity may all impair the

health of the fetus directly or indirectly by affecting the health or capacity of the dam to deliver the fetus.

Underfeeding of energy (40% to 70% of requirements)[36] or protein (65% of requirements)[37] during late gestation in beef cattle produces calves that are less able to generate heat to maintain body temperature after birth. This effect was observed despite no significant difference in birth weight.[36,37] The fetal response to growth-restrictive environmental conditions is to partition nutrients toward the development of organs essential to life, such as the brain, at the expense of less vital organs and tissues.[38,39] In humans the repartitioning of nutrients to support fetal development has been demonstrated to have long-term effects on postnatal growth and metabolism, apparent as an increased propensity to develop insulin resistance, high blood pressure, more rapid weight gain, and increased adiposity.[40] Similarly, nutrient restriction during gestation has been demonstrated to alter postnatal glucose metabolism in calves.[41] The consequences of overnutrition during gestation on the developing fetus are less clear. A number of overfeeding trials have resulted in increased birth weight, whereas others have not.[42,43] Maternal consequences include deposition of fat in the pelvis, which increases the risk of dystocia and subsequently fetal compromise.[44]

For high-producing dairy cows, good nutritional and cow management during the transition period is pivotal for maintaining cow health. Hypocalcemia and negative energy balance contribute to the risk of dystocia and subsequently the risk of neonatal morbidity and mortality.[45] Recently there has been a paradigm shift in the thinking regarding the nutrition of nonlactating cows before calving. Previously the focus has been on increasing the amount of energy in the ration fed to cows during the last 3 to 4 weeks before calving to meet the increasing energy needs associated with pregnancy in the face of the cows declining dry matter intake.[46] Paradoxically, overfeeding energy during the dry period has been found to contribute to negative energy balance postpartum and an increased incidence of disease in the peripartum period.[47] This phenomena appears to be associated with increased insulin resistance similar to type II diabetes. The current recommendation is to feed cows throughout the nonlactating period a ration that meets but does not exceed caloric needs. Straw is added to the ration to promote rumen health and prevent overeating.[45]

In regards to trace minerals, selenium and copper deficiency may contribute to neonatal morbidity and mortality. Copper deficiency has been associated with

impaired fertility, weak calves, and high calf mortality.[48] In a larger Canadian study, myopathy and cardiomyopathy were common findings in stillborn and neonatal mortality, suggesting the possible contribution of nutritional myopathy.[49]

Investigation of perinatal morbidity and mortality should begin with assessment of maternal management. Some of the more common causes of stillbirth and perinatal mortality are listed in Box 18.1.

Box 18.1

Common Causes of Stillbirth and Perinatal Death in Ruminants[2,3,162,163]

- Dystocia
- Cold stress
- Pneumonia (lambs)
- Nutrition
  - Energy deficiency
  - Protein deficiency
  - Pregnancy toxemia
  - Mineral
    - Copper excess/deficiency
    - Iron excess
    - Iodine excess/deficiency
    - Selenium deficiency
  - Vitamin A deficiency
- Infectious
  - Viruses
    - Infectious bovine rhinotracheitis virus
    - Bovine viral diarrhea
    - Border disease
    - Bluetongue
    - Akabane virus
    - Cache Valley virus
  - Bacteria

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- *Histophilus somni* (formerly *Hemophilus somnus*)
- *Brucella abortus*
- *Leptospirosis* spp.
- *Clostridium perfringens* types C and D
- *Streptococci* spp.
- *Campylobacter* spp.
- *Listeria monocytogenes*
- *Yersinia pseudotuberculosis*
- *Histophilus ovis*
- *Brucella ovis*
- *Campylobacter fetus var fetus*

Protozoa

- *Neospora*
- *Toxoplasma gondii*
- *Tritrichomonas foetus*

Fungus

- *Aspergillus* spp.

Rickettsia

- *Chlamydia* spp.
- *Coxiella burnetti*

Trauma

Obstetrical

Castration, tail docking

Toxins

Plant toxins

- Monterey pine *(Pinus radiata)*
- Perennial broomweed *(Gutierrezia microcephela)*
- Locoweed (*Astragalus lentiginosis*)
- Lupines (*Lupinus sericeus* and *Lupinus caudatus*)
- Poison hemlock *(Conium maculatum)*

Chemical toxins

Nitrate

Genetic

Epitheliogenesis imperfecta

Cardiac abnormalities (ventricular septal defects, tetralogy of Fallot)

Internal hydrocephalus

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	Cerebellar hypoplasia
	Arthrogryposis/cleft pallet
	β-Mannosidosis
	Spider lamb syndrome
	α-Mannosidosis
	Bovine citrullinemia
	Bovine maple syrup urine disease

Environmental Management

Environmental stress before or around the time of parturition may also compromise the fetus or neonate. Heat stress impacts fetal viability by impeding calf growth in the last trimester of pregnancy[50] and by depressing colostral quality[51] and immunoglobulin transfer.[52] Uterine blood flow and placental mass are reduced, and endocrine profiles are altered when cattle are heat stressed during the last trimester of pregnancy. Heat stress during the last 3 weeks of pregnancy lowers dry matter intake, contributing to a negative energy balance at this time, promoting mobilization of body fat and ketogenesis. Transfer of immunoglobulins to colostrum is impaired, and the concentration of protein, casein, lactalbumin, fat, and lactose in colostrum is reduced.[51] Cold, windy, and wet conditions also adversely affect calf survival. The magnitude of the effect of climate on neonatal survival depends on the age of the dam, sex and size of the calf, and on the incidence of dystocia in the herd.[53] Cold stress sufficient to cause hypothermia in calves leads to subcutaneous hemorrhages and delayed absorption of colostral immunoglobulins.[54]

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Assessment of Fetal Viability

Fetal viability is rarely evaluated during the prepartum period in production animals but is a serious consideration when the prepartum dam is diseased or debilitated. Assessment of fetal viability is diagnostically challenging, but a number of methods are available to evaluate the fetus and fetal environment. During the physical examination of cattle, uterine blood flow, uterine tone, and presence of a vaginal discharge may be evaluated via rectal palpation and a vaginal speculum examination. Reduced fremitus in the uterine arteries and increased uterine tone may be appreciated by rectal palpation following fetal death. Abdominal ultrasound is useful for examining the uterus, placenta, and fetuses of small ruminants.[55] When the gestational age of the fetus is known, it is possible to detect fetal growth retardation using ultrasound by measuring abdominal circumference and femur and tibial length.[56] Examination of the fetus may detect gross congenital abnormalities, and ultrasound of the fetal chest allows visualization of a beating heart and determination of fetal heart rate. The normal heart rate of full-term lambs is 108 to 126 beats per minute (bpm).[57] Following fetal death, some of the following may be observed: absence of fetal heartbeat, thickening of the uterine wall, increased echogenicity of chorioallantoic and amniotic fluid, altered fetal posture and definition, altered contour of the amnion, and reduced definition and ultimately reduced size of the caruncles.

The uterus and placenta of cattle can be examined by transrectal ultrasound; however, examination of the fetal calf via transrectal or transabdominal ultrasound is often compromised by limited access. Fortnightly ultrasound of the uterus and placenta of recipient cows carrying cloned calves is conducted to detect evidence of hydroallantois and placental edema in these high-risk pregnancies.[58] The absence of fetal heart beat is a specific sign of fetal death. The presence of large quantities of echoic particles in uterine fluids is also a sign of fetal distress or death. Fetal hyperactivity or inactivity over a 30-minute period of examination suggests fetal compromise.[59] Repeated examinations are required since hyperactivity or sleeping periods have been infrequently observed in other species, and the criteria for this classification is based on limited observations in cattle.[60] Measuring the heart rate of fetal calves is more difficult than small ruminants but can be achieved via transabdominal Doppler using a

1.5-Mhz probe. The normal heart rate of full-term calves is 90 to 125 bpm.[61] In human medicine, fetal heart rate is used as a measure of fetal viability. Fetal heart rate accelerations associated with fetal movement are considered a sign of fetal well-being, and persistent bradycardia or tachycardia is a sign of fetal stress.[62] Normal fetal heart rate patterns of ruminants need to be characterized in more detail before fetal heart rate measurements are used for prenatal clinical assessment of ruminant fetal well-being.[60,63]

Estrone sulfate is a marker of a viable fetoplacental unit and has been used to assess fetal viability in cattle.[64] Estrogen synthesized by embryonic tissue is converted to estrone sulfate by the endometrium, which contains the enzyme sulfotransferase. Estrone sulfate assays can be used to diagnose pregnancy in small ruminants after 50 days[65] and in cattle after 100 days.[66] Estrone sulfate may be measured in plasma or milk,[50,66] and baseline values are low after fetal loss, regardless of the stage of pregnancy. Compromise of the fetoplacental unit reduces estrone sulfate production. In a study of the effects of heat stress on pregnant cattle, plasma estrone sulfate concentrations were significantly lower throughout pregnancy in cows that gave birth to low-birth-weight calves.[50] Plasma concentrations of estrone sulfate rise slowly during the second trimester of pregnancy from 0.74 ng/mL to 3.66 ng/mL from day 90 to day 210 of pregnancy. The last trimester of pregnancy is associated with a rapid rise in the concentration of estrone sulphate to 13.36 ng/mL around 10 days before parturition.[67]

In human medicine, diagnosis of surfactant deficiency is based on the ratio of two phospholipids in amniotic fluid, lecithin (L) and sphingomyelin (S). If the L/S ratio is greater than 2.0, the surfactant system is mature and respiratory distress syndrome is rare.[68] The L/S ratio in amniotic fluid collected from cattle may also be used to assess surfactant system maturity,[69] providing a measure of readiness for birth, but is rarely employed in clinical veterinary medicine. Crude surfactant harvested from bovine lungs at a slaughterhouse has been used intratracheally with calves that appeared to be in respiratory distress shortly after birth.[70]

Induction of Parturition

Manipulation of parturition may be considered for maternal, fetal, or management reasons. Fetal viability following induced parturition is variable

between species. The viability of calves induced within 14 days of anticipated calving date is good.[71] Viability of lambs and kids induced greater than 5 days before anticipated parturition date is poor.[19] Absorption of colostral immunoglobulins by premature calves is reduced, so colostral transfer should be monitored closely in induced neonates.[72] Induction of parturition or cesarean section is often necessary to prevent mortality of small ruminants with pregnancy toxemia.[73] Fetal viability is often improved by induction of parturition with dexamethasone, yet delivery of the fetuses via cesarean section is often necessary due to the debilitated state of the dam. Secretion of glucocorticoid hormones from the adrenal cortex increases markedly during the final days of gestation. The prenatal increase in fetal glucocorticoid secretion plays an important role in the cascade of endocrine events leading to parturition and stimulates maturational events in the lungs, liver, kidney, and gastrointestinal tract in preparation for postnatal life.[74]

Steroids stimulate production of surfactant phospholipids by alveolar type II cells, enhance the expression of surfactant-associated proteins, reduce microvascular permeability, and accelerate overall structural maturation of the lungs.[75] Administration of flumethasone (10 mg) or dinoprost (25 mg) to pregnant cows 30 hours before elective cesarean section increases the lecithin–to–sphingomyelin ratio, improving lung function and reducing complications associated with respiratory acidosis in the calf.[76] Induction of parturition has been used to reduce the incidence of dystocia in herds or breeds experiencing a high incidence of dystocia associated with fetomaternal disproportion.[77] Large birth weights are strongly correlated with fetomaternal disproportion.[78,79] Induction of parturition within 14 days of anticipated calving date is associated with good calf viability and a 3.2-kg reduction in birth weight of beef calves.[71]

Exogenous glucocorticoids, prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), or a combination may be used to induce parturition in cattle (dexamethasone 20 to 30 mg alone or in combination with 25 mg of $PGF_{2\alpha}$), sheep, and goats (10 to 20 mg dexamethasone and or 15 mg $PGF_{2\alpha}$).[19] Glucocorticoids are more effective than prostaglandins for inducing parturition in sheep.[80] A lower incidence of dystocia and higher viability of calves has been reported in cattle induced with glucocorticoids compared with cows induced with prostaglandins.[81] Cows treated with dexamethasone or prostaglandin within 14 days of anticipated calving date usually calve within 72 hours of treatment.[71] Combination of

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dexamethasone with prostaglandin increases the efficacy and reduces the interval to parturition (36 hours).[82,83] Retention of fetal membranes is a common complication of induced parturition in cattle.[84] Induction of parturition with dexamethasone causes a failure of immune-assisted detachment of fetal membranes and the accompanying release of chemotactic factors.[85] Retention of fetal membranes may be associated with reduced first service conception and subsequent pregnancy rates.[86] Treatment of cows with prostaglandin at calving was reported to reduce the incidence of retained fetal membranes,[87] but subsequent studies have failed to support this.[82,88] Induction of cattle by administration of 25 mg/cow of triamcinolone (Opticortinol, Scharwoude, The Netherlands) at day 270 followed by treatment with dexamethasone and prostaglandin 6 days later appears to reduce the incidence of retained fetal membranes associated with induction.[84,89] Where calving induction is used to align calving patterns to pasture availability, cows are induced to calve at around 7 months' gestation. Induced cows have increased rates of mastitis, metabolic disease, and retained placenta[90,91] and have reduced milk production in the lactation of treatment.[92,93] Calves born to cows induced at 7 months' gestation are often stillborn, die, or are subject to euthanasia shortly after birth because they are too weak or suffer from other neonatal diseases.[94,95] This management practice was historically used in seasonal pasture−based New Zealand and Australian dairy production systems. It is now banned in New Zealand and is being phased out in Australia.

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Perinatal Adaptation

At birth the fetus must successfully make a series of structural and physiologic changes to survive. Perinatal mortality is often attributable to cardiovascular, pulmonary, thermoregulatory, or metabolic physiologic abnormalities. Dystocia and severe birth asphyxia compromises physiologic transitions, increasing the risk of neonatal mortality. Compromised neonates that survive the birth process are less likely to consume adequate colostrum and are subsequently more likely to die of hypothermia and infectious diseases.

The placenta functions as the respiratory organ of the developing fetus, and efficiency of oxygen transfer to the fetus is increased by the high oxygen affinity of fetal versus adult hemoglobin.[96] In utero the potential spaces of alveoli and the tracheobronchial tree are distended with fluid secreted by pulmonary tissue.[97] Oxygenated blood is delivered to the fetus via the umbilical vein, which anastomoses with the portal vein near the liver, and approximately two thirds of the blood flow is shunted via the ductus venosus directly into the caudal vena cava.[98] The caudal vena cava drains into the right atrium, where over 50% of the volume shunts directly into the left atrium via the foramen ovale.[98] The relatively hypoxic in utero environment causes constriction of pulmonary vessels and dilation of the ductus arteriosus.[98] Because pulmonary arterial resistance is higher than systemic arterial resistance, nearly 70% of pulmonary artery flow is shunted via the ductus arteriosus into the aorta, with the remainder perfusing the lung.[99] Left ventricular output is distributed to the systemic circulation via the aorta. Two umbilical arteries arise from the aorta in the region of the last lumbar vertebra to carry predominantly venous blood back to the placenta via the umbilicus.

At birth some of the lung fluid is evacuated through the trachea during spontaneous delivery.[100] When the umbilicus ruptures, asphyxia triggers reflex gasping, respiratory movements, and increased peripheral vascular resistance.[99] The majority of lung fluid is absorbed through alveolar walls in the initial stages of ventilation.[100] This mechanism is prompted by activation of adrenaline-mediated α-adrenergic receptors in the pulmonary epithelium.[101] The rapidity of lung fluid absorption by the body is optimized at thoracic pressures between 35 and 40 cm H_2O.[100] Pulmonary ventilation reduces pulmonary vascular

resistance, promoting perfusion of the ventilated alveolar tissue.[98] The increased O_2 saturation of blood stimulates closure of the ductus arteriosus within 4 to 5 minutes of birth.[99] The foramen ovale functionally closes within 5 to 20 minutes of birth when increased pulmonary venous return raises blood pressure in the left atrium, reversing the right to left shunt.[99] The septum secundum, a thin fold of tissue that lies in close apposition to the foramen, acts as a valve closing the opening. Healthy calves have mean pulmonary arterial pressures ranging from 40 to 82 mm Hg immediately after birth, declining to 22 to 25 mm Hg by 2 weeks of age.[102] Systemic arterial pressure is approximately 100 mm Hg, and arterial saturation is greater than 90%.[98] Transient mild metabolic and respiratory acidosis are observed following rupture of the umbilical cord due to anaerobic glycolysis in poorly perfused tissues during the transition between placental oxygen delivery and establishment of respiratory function. The mild acidosis is normally corrected within 1 to 4 hours of birth.[103] Anatomic closure of the foramen ovale and ductus arteriosus may take several weeks.[99] Normal blood gas values for the calf during the immediate postpartum period are presented in Table 18.2.

TABLE 18.2
Arterial and Venous Blood Gas Values for Newborn Calves

	Parameters					
	Calf Age	**pH**	**pO_2**	**pCO_2**	**HCO_3**	**Base Excess**
Venous[a]	1 hour	7.219 (0.05)	N/A	41.0 (5.9)	24.2 (2.7)	−2.9 (3.2)
Arterial[b]	1 hour	7.3 (0.05)	58.43 (11.61)	50.40 (5.27)	23.52 (2.78)	N/A

[a]Blood was taken from the brachial artery while the calf was in lateral recumbency (*N* = 30).[164]

[b]Blood taken from the jugular vein immediately postpartum.[103] Values represent mean with standard deviation parenthesis.

N/A, Not available.

Dystocia is commonly associated with prolonged hypoxia and acidosis. Hypoxia and acidosis maintains constriction of pulmonary arterioles, and the subsequent maintenance of high pulmonary vascular resistance favors continuation of in utero right to left vascular shunts, which contributes to systemic hypoxia. Following dystocia, neonates are less active, slow to stand, slow to nurse, and prone to hypothermia and hypogammaglobulinemia. The

normal duration of stage 2 labor (from appearance of fetal membranes at the vulva to delivery of the fetus) in ruminants is generally shorter in multiparous animals (≈30 minutes) than primiparous animals (≈60 minutes).[104] Fetal viability is improved with early intervention; multiparous animals should be assisted after 30 to 60 minutes of stage 2 labor and primiparous animals after 60 to 90 minutes.[79]

The range in ambient temperatures over which newborn animals are able to maintain homeothermy is much narrower than growing or adult animals. Neonates are more susceptible to fluctuations in environmental temperature due to their large surface area to mass, evaporation of amniotic fluid, and limited caloric reserves. Starvation and hypothermia is the second leading cause of death of neonatal lambs.[3] Neonatal mortality increases with decreasing ambient temperature and with increasing precipitation on the day of birth.[53] Thermoneutrality is maintained by shivering and metabolism of brown adipose tissue. Normally at birth, blood glucose concentration in calves ranges between 50 and 60 g/dL, rising to 100 mg/dL within the first 24 hours of life.[98] Lambs born in warm weather can survive for up to 4 days without supplemental nutrition. Severe weather stress may increase energy requirements by 500% and deplete the energy reserves of newborn lambs in 6 to 16 hours.[105] Starvation exacerbates the effects of environmental stress by reducing the available substrates for heat production, and energy depletion leads to hypoglycemia. Administration of glucose to hypothermic neonates before and during warming is important to avoid deaths from cerebral hypoglycemia induced by increased utilization of glucose by peripheral tissues.[106] Warming hypothermic lambs by immersion in 38° C water is more efficient than infrared lamps or wrapping the lamb in a cotton cloth.[107]

No intrauterine transfer of immunoglobulin occurs in ruminants; hence, at birth, neonatal ruminants are agammaglobulinemic and immunologically naive. Infectious disease is the leading cause of morbidity and mortality in calves greater than 3 days of age.[108] Failure of passive transfer increases the risk of neonatal mortality.[109] Colostrum provides a concentrate source of energy and immunoglobulins. Immunoglobulins are concentrated in colostrum by an active, receptor-mediated transfer of IgG_1 from the blood of the dam across the mammary gland secretory epithelium beginning several weeks before parturition.[110] Colostral IgG_1 concentrations may be 5 to 10 times the maternal

serum concentrations. IgM, IgA, and IgG_2 concentrations in colostrum are much lower.[111] The large numbers of leukocytes also contribute to providing passive immunity to the newborn.[112] Methods of assessing passive transfer and management of failure of passive transfer are discussed in detail in Chapter 19.

Dystocia

Forty to sixty percent of stillbirths are associated with dystocia. Calves that survive dystocia are more likely to have edema of the head and tongue, making suckling difficult. They are also weak and exhausted and likely to be recumbent for a longer period of time and expose themselves to more fecal pathogens.[113] Dystocia affects the uptake of immunoglobulins by the calf, and calves that survive dystocia are more likely to become sick in the first 45 days of life.[114] Maternal variables correlated with dystocia and consequently calf mortality at birth include parity and conformation. Dystocia and stillbirths in heifers is most commonly secondary to fetopelvic incompatibility. Fetopelvic incompatibility accounts for a lower proportion of dystocias in multiparous cows, but weak labor secondary to hypocalcemia, uterine torsion, and incomplete cervical dilation are more common in older cows.[44] The prevalence of stillbirths in dairy herds globally is reported to be increasing.[1] In the U.S. dairy industry the incidence is currently 8% (11.3% in primiparae and 5.3% in pluriparae).[115] Dam pelvic diameter is an important determinant of dystocia for heifers.[116] Pelvic measurements can be used to identify abnormally small or abnormally shaped pelvises. Large frame size of the dam correlates with a reduced risk of dystocia; however, continued selection for large frame size tends to select for larger birth weight and dimensions of calves.[117] Age at first calving for heifers is not correlated with risk of dystocia as long as heifers are fed and managed to achieve appropriate growth and stature before calving.[118-120] The risk of dystocia in heifers is increased by poor nutrition in the last trimester.[121] Appropriate nutrition and management of replacement heifers to achieve appropriate size and stature at parturition reduce maternal and neonatal losses by reducing the incidence of dystocias. Maternal consequences associated with calving difficulty and delivery of a stillborn calf include decreased milk production and reduced reproductive efficiency. Reductions in milk production ranging from 100 to 400 kg have been reported to be associated with the birth of a stillborn calf. If the stillborn calf is delivered by cesarean section, the reduction in milk yield is on

the order of 300 to 500 kg.[122] Delivery of a stillborn calf is also associated with depressed conception rates, increased services per conception, and delayed conception.

Use of calving ease bulls over primiparous cows helps to reduce the incidence of dystocia and subsequently mortality during parturition. The heritability of calving ease is relatively low; estimates of maternal calving ease range from 0.03 to 0.24,[44,123,124] and paternal heritability is around 0.147. Despite the relatively low heritability of calving ease, selection for calving ease should not adversely affect other production parameters in dairy cattle as the genetic correlation between calving ease and other dairy production traits is generally close to 0.[44] Calving ease evaluations are intended to increase the use of AI for heifers. To facilitate sire selection, most breed associations provide guidelines regarding calving ease or expected progeny difference for calf birth weights. An example of such a scheme is the calving ease and reliability values assigned to AI Holstein bulls. In this system the calving ease score is the expected percentage of difficult births predicted for calves delivered by primiparous cows.[125] The reliability score provides an indication as to the number of births that were considered in deriving the calving ease score. The higher the reliability score, the larger the number of observations the calving ease score is based on and the more likely it is that the calving ease prediction will accurately reflect the outcome.

Management variables that influence the risk of dystocia and perinatal mortality include stocking density of preparturient cows, timing of calving, and cow grouping. In a study of 123 beef herds, the dystocia rate was highest for cows housed in a barn and decreased progressively through barn/yard, barn/pasture, and pasture-only calving location categories.[126] The most common cause of dystocia in penned heifers was vulvar constriction, while dystocias in paddocked heifers were most commonly associated with malpresentations.[127] Calving beef heifers 6 weeks before cows has been recommended to allow the heifers longer to recover and conceive after calving than cows.[128] In a herd-level comparative study, this practice was associated with a higher incidence of dystocia and stillborn calves.[126] Heifer dystocia rate is reduced the longer heifers are maintained as a separate group from cows before calving.[126]

Fetal variables that influence the risk of mortality include sex, size, and number. Calves born to primiparous cows, twins, and bull calves are more likely to die at birth than calves born from multiparous cows, single calves, and heifer

calves.[53,129] Low- and high-birth-weight calves are at greater risk of mortality than average-birth-weight calves.[53] Small calves experience greatest mortality at parities greater than one.[118] Large-birth-weight calves have greatest risk of mortality when delivered by heifers. Statistical modeling suggests that for every 1 kg increase in body weight, there is a 13% increased probability of dystocia.[130] Compared with other dairy breeds, Holsteins have the highest ratio of calf birth weight to dam body weight, averaging 7.1%.[131] Holstein cows subsequently have the highest incidence of dystocia.[130,131] Fetal viability may be compromised in utero by a number of infectious agents. Common infectious agents associated with abortion and or birth of weak calves are listed in Box 18.1. Manifestations of disease in the newborn are dependent on the time of exposure to the infectious agent.

Peripartum Assessment of Fetal Vitality

During parturition fetal reflexes can be assessed to ascertain appreciable signs of life. The interdigital, bulbar, and swallowing reflexes can be assessed in calves presenting in an anterior presentation. The interdigital and anal reflex and pulse in the umbilical cord can be evaluated in calves presenting in a posterior presentation.[132] Depressed responsiveness is a feature of impaired acid-base status. An increasing proportion of calves fail to respond as the severity of the acidosis increases. Failure to elicit reflexes is not confirmatory of fetal death as an absence of reflexes has been observed in severely acidotic live calves.[133] Six percent of fetuses with no reflexes intrapartum are normal at the time of delivery.[134]

Criteria commonly used to assess the vitality of the newborn calf are presented in Table 18.3. Timely assessment of the newborn calf is indicated as two thirds of perinatal mortality occur within an hour of birth and 95% of this loss occurs within 5 minutes of birth.[135] Abnormal neonatal behavior in the immediate postnatal period is commonly secondary to perinatal hypoxia and a combination of metabolic and respiratory acidosis. Traditional Apgar parameters, heart rate, respiratory rate, and mucous membrane color, are not predictive of acidemia in newborn calves.[136] Depressed tongue withdrawal and weak suck reflex are correlated with perinatal acidemia in calves.[136]

TABLE 18.3

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Assessing the Newborn Calf

Criterion	Good Vitality	Poor Vitality
Respiration	50-75 bpm and thoracic breathing	Gasping; primary apnea; irregular, abdominal breathing; bellowing and secondary apnea
Hair coat appearance	Placental fluid covered	Meconium stained
Peripheral edema	None	Capital, lingual, or limb edema
Mucous membranes	Pink and normal capillary refill time	Cyanotic, pale, and slow capillary refill time
Response to reflex stimulation	Vigorous head shake; strong corneal, suck, or pedal reflex	Weak or no response
Muscle tone	Active with head-righting within minutes	Inactivity and flaccid musculature
Heart rate	100-150 bpm and regular	>150 bpm followed by bradycardia (<80 bpm) and an irregular, decreasing rate
Rectal temperature	102°-103° F (39°-39.5° C) after calving declining to 101°-102° F (38.5°-39° C) by 1 hour and stable	103°-104° F (39.5°-40° C) after calving declining to 101° F (<38.5° C) by 1 hour and decreasing
Sternal recumbence	Achieved within 5 minutes	Prolonged lateral recumbence
Attempts to rise	Attempting to stand within 15 minutes Standing within 1 hour	Delayed or no attempts to rise
Suckling	Commences within 2 hours	Delayed or no attempts to suckle

From Mee JF: Managing the calf at calving time. In Proceedings of the 41st Annual Conference American Association of Bovine Practitioners, Charlotte, NC, 2008, p 46.

Calves and lambs normally have a head righting reflex almost immediately after birth. Sternal recumbency is usually attained within 2 to 4 minutes followed rapidly by attempts to stand, at 10 to 20 minutes for lambs and 15 to 30 minutes for calves.[137-139] Failure for calves to achieve sternal recumbency within 15 minutes of birth is highly predictive (84%) of compromised vitality and risk of mortality.[139] Hypoxic neonates may struggle and appear bright initially but have difficulty maintaining sternal recumbency, have depressed or absent suck reflex, are slow to stand or remain recumbent, and develop a depressed mentation within hours. Hypoxic calves can also have an impaired response to environmental stressors such as cold temperature.[140] Reduced muscle tonicity prevents shivering,[141] and the metabolic activity of brown adipose tissue may be reduced, compromising nonshivering thermogenesis.[142] Furthermore, calves with low vitality have a limited ability to generate heat through natural physical behavior, and delayed colostrum ingestion may limit the energy available to generate heat.[131]

The normal heart rate of calves is between 100 and 150 bpm immediately after birth. Heart rate normally stabilizes within minutes of calving, but in at-risk

calves peripartal tachycardia (>150 bpm) is followed by a declining bradycardia.[132] Following experimentally induced hypoxia, nonviable hypoxic calves had similar heart rates (118 ± 36 bpm) and body temperatures (39.6 ± 0.2° C) as viable calves but lower respiratory rates (14 and 18 vs. normal 49 ± 12).[137] The rectal temperature of a normal newborn calf is higher than normal at calving 102° F to 104° F (39° C to 40° C) and gradually drops to normal within 3 to 5 hours. Calves that experience a protracted, difficult calving may experience hyperthermia (>103° F, >39.5° C) at birth, which drops in the hours following birth and is slow to return to normal.[132]

The normal time taken to stand and nurse varies between species and breeds. The average time from birth to standing and nursing for beef calves is 35 and 81 minutes, respectively. Dairy calves are more variable and take approximately twice as long.[143] A high prevalence of delayed first sucklings has been reported among dairy calves. Failure of the newborn to nurse may result from reduced neonatal vigor, poor mothering, poor maternal conformation, or adverse conditions such as slippery flooring.[144] Calves have difficulty locating teats on low slung udders (<45 cm from the ground)[145] and difficulty nursing teats greater than 35 mm in diameter.[146] Small ruminants are generally quicker to stand and nurse than calves, with most lambs standing within 30 minutes[138] and nursing within 90 minutes of birth.

Observation of interaction between the newborn and dam in the immediate postnatal period allows early recognition of the compromised neonate and facilitates timely intervention if maternal conformation or behavior threatens to impede the neonates' efforts to nurse. Failure of maternal bonding is more common with primiparous dams, multiple offspring, and following delivery via caesarean section. Maternal bonding in sheep is mediated by an olfactory mechanism.[147] Parturition alters the release of monoamines, amino acids, and oxytocin within the olfactory bulb, stimulating an attraction to amniotic fluid and acceptance of the lamb.[148] Artificial vaginocervical stimulation with a gloved hand induces similar alterations in the release of monoamines, amino acids, and oxytocin within the olfactory bulb and is useful for triggering formation of maternal bonds to foster lambs for at least 27 hours postpartum.[148]

In utero infections and congenital neurologic abnormalities should also be considered as possible causes of abnormal neonatal behavior. Collection of sera before feeding colostrum is useful for diagnosing in utero infections. Precolostral serum immunoglobulin concentrations in calves are low (IgM 0.126

± 0.015 mg/mL, IgG 0.044 ± 0.003 mg/mL).[149] Elevated serum concentrations of immunoglobulins before ingestion of colostrum may be observed with in utero infections.[149] Specific serologic tests are available for Cache Valley virus, Akabane virus, bovine viral diarrhea virus, *Neospora* spp., toxoplasma, and Bluetongue virus.[150] Teratogens and inherited diseases that may cause the birth of weak neonates are listed in Box 18.1**.**

Resuscitation of the Neonate

Two thirds of perinatal calf mortality occur within an hour of birth, and some 95% of this loss occurs within 5 minutes of birth, underpinning the need for rapid assessment.[135] Survival of the compromised fetus is facilitated by prompt initiation of supportive care. Immediately after birth, almost all calves have mild metabolic and respiratory acidosis.[151] In the first 30 to 60 minutes after birth, there is a decrease in both pH and base excess. After this time, the values normalize in healthy calves but not in calves with respiratory distress.[152] Suction is useful for clearing the pharynx and nasal passages and has been shown to improve pulmonary function in newborn calves.[153] Squeezing the trachea gently may also illicit a cough reflex, which assists airway clearance.[154] Suspending the newborn by the hind legs for less than 90 seconds after delivery is an alternative method for clearing the airways.[155] If the newborn breathes spontaneously, it is placed in sternal recumbency to facilitate efficient pulmonary gas exchange and correction of the mixed acidosis.[155] If the calf does not breathe or move spontaneously within a few seconds after birth, tactile stimulations (inserting a finger or a length of straw in the nasal cavity, pinching the nasal septum, rubbing the calf's body with straw or towel,[156] pouring cold water in the ear or over the head or body of the calf[153]) are necessary to initiate a gasping reflex. In dyspneic neonatal calves, the respiratory center can be stimulated with respiratory stimulants such as doxapram (1 to 2 mg/kg intravenously).[157] Doxapram should be used judiciously as the stimulatory action of the drug is nonselective. Convulsions may be observed with repeated dosing, increasing the demand for O_2 in an already hypoxic neonate.[158]

Weak fetuses are often born with strongly beating hearts but have difficulty initiating adequate inspiratory efforts to expand their lungs. Positive pressure ventilation is required to overcome surface tension in alveoli and the elastic

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recoil of lung tissue. Fluid within alveolar spaces and the lumen of the tracheobronchial tree is absorbed into the pulmonary interstitium most efficiently at thoracic pressures between 35 and 40 cm H_2O.[100] Less pressure is usually needed for succeeding breaths. Observation of chest wall movement is a reliable sign of sufficient inflation pressure. Ventilation with a pulmonary resuscitation bag (Ambu bag, Copenhagen, Denmark) with a pressure relief valve set at 42 cm H_20 avoids inadvertent overinflation.[159] Applying external pressure across the esophagus helps to prevent inadvertent inflation of the abomasum. Direct mouth-to-mouth resuscitation is generally ineffective at delivering air into the abomasum and poses a risk for contracting zoonotic diseases such as Leptospirosis, Brucellosis, or Q fever. While correction of respiratory acidosis is dependent on achieving adequate pulmonary ventilation, correction of metabolic acidosis requires neutralization of hyperlactatemia. This can be achieved by bolus administration of hyperosmotic sodium bicarbonate (50 to 100 mL of 8.4% solution, IV) once effective pulmonary ventilation has been established.[135]

Thermoregulation is important as recovery from acidosis is delayed by hypothermia.[160] Cold stress leads to increased metabolic needs and produces hypoxia, hypercarbia, metabolic acidosis, and potentially hypoglycemia—metabolic sequelae that resuscitation is aimed at correcting.[161]

Resuscitation procedures for more critical neonatal calves and small ruminants is similar to the approach taken with foals as discussed in Chapter 17.

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• CHAPTER 19

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Initial Management and Clinical Investigation of Neonatal Ruminants

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Environmental Management

Maternal shedding of enteric pathogens increases around the time of parturition. In intensive dairy production systems, calf pathogen exposure and subsequently the risk of morbidity and mortality can be reduced by removing the calf from the dam after birth and placing the calf in a clean, dry, sheltered environment. Conversely, under extensive livestock husbandry systems where pathogen load is sparse and dispersed, the emphasis is on minimal interference to avoid mismothering. Neonatal calves are cold tolerant when dry and sheltered from drafts. Due to their lower body mass, lambs and kids are more susceptible to cold. Wet, drafty conditions lead to depletion of energy reserves and hypothermia. Hypothermia compromises colostral transfer and increases vulnerability of newborns to contagious and opportunistic pathogens. In cold conditions neonates generate heat by shivering and metabolism of brown adipose tissue. Neonates are born with short-lived, stored energy in the form of muscular glycogen.[1] Colostrum is a critical source of concentrated energy to meet the metabolic demands of thermogenesis.

Colostrogenesis and Colostral Components

Colostrogenesis begins 5 weeks before calving under the influence of prolactin and other lactogenic hormones, with peak production occurring 1 to 3 days prior to parturition.[2] Colostrum is nutrient dense and has a higher level of energy and protein than is found in milk. Bovine colostrum contains approximately 45 mg/mL[3] of immunoglobulin and 1×10^6 leukocytes/mL.[4] Immunoglobulin G1 (IgG1) is transported from blood in endosomes through the polarized mammary epithelial cell by a process known as *transcytosis*.[5] IgG1 is bound by the neonatal Fc receptor (FcRn) at the basal side and transferred to the apical side under the control of intracellular proteins termed *small GTPases*.[6] The FcRn consists of two subunits: an integral membrane α-chain (Fc fragment of IgG, receptor, transporter, alpha; FcGRT) and a β light chain (β2 microglobulin; β2M). In vitro the expression of FcGRT and several of the small GTPases controlling the transfer of IgG are upregulated by estrogen and progesterone, and it is thought that this mechanism results in the marked increase in transport of IgG1 observed in the 4 weeks prior to calving.[6,7] Immunoglobulins account for more than 95% of the whey protein at calving, and IgG1 accounts for approximately 80% of this amount.[8] IgG2, IgA, and IgM account for 10%, 7%, and 5%, respectively. The amount of IgA remains constant throughout all lactations, whereas the colostrum of cows in their first lactation contains less IgG1, IgG2, and IgM. Immunoglobulin levels in mature milk are much lower, comprising only 7% of the total whey protein, with an increase in the relative contribution of IgA. Older cows tend to have a higher ratio of IgG1 to IgG2.[9] This is consistent with a lower level of IgG1 in the serum of heifers. The transport of IgG into bovine colostrum has been associated with a transient decrease in serum total protein, globulin, and IgG concentrations during the pre-parturient period, particularly in dairy cows. Up to 500 g of IgG1 a week are removed from blood during the most active period of colostrum formation.[10]

Colostrum also contains hormones (growth hormone, relaxin, prolactin, insulin, glucagon), essential fatty and amino acids, minerals, trace elements and vitamins (especially betacarotene; vitamins A, B, D, and E) (Table 19.1), as well as cytokines, growth factors (members of the insulin-like growth factor [IGF]

system, including IGF binding proteins [IGFBPs]), and nonspecific antimicrobial factors such as lactoferrin. Colostrum is a significant source of copper to the newborn calf but not a source of selenium or zinc.[11]

Table 19.1

Composition of Colostrum of Holstein Cows[69]

Item	Mean	SE
Fat (%)	6.70	4.16
Protein (%)	14.92	3.32
Lactose (%)	2.49	0.65
Total solids (%)	27.64	5.84
Ash (%)	0.05	0.01
IgG1 (mg/mL)	34.96	12.23
IgG2 (mg/mL)	6.00	2.82
IgA (mg/mL)	1.66	0.99
IgM (mg/mL)	4.32	2.84
Lactoferrin (mg/mL)	0.82	0.54
Retinol (µg/g)	4.90	1.82
Tocopherol (µg/g)	2.92	3.65
Betacarotene (µg/g)	0.68	0.63
Vitamin E (µg/g of fat)	77.17	33.51
Thiamin (µg/mL)	0.90	0.28
Riboflavin (µg/mL)	4.55	0.31
Niacin (µg/mL)	0.34	1.57
Vitamin B_{12} (µg/mL)	0.60	0.35
Pyridoxal (µg/mL)	0.15	0.07
Pyridoxamine (µg/mL)	0.21	0.07
Pyridoxine (µg/mL)	0.04	0.07
Calcium (mg/kg)	4716.10	1898.00
Phosphorus (mg/kg)	4452.10	1706.29
Magnesium (mg/kg)	733.24	286.07
Sodium (mg/kg)	1058.93	526.02
Potassium (mg/kg)	2845.89	1159.89
Zinc (mg/kg)	38.10	15.90
Iron (mg/kg)	5.33	3.09
Copper (mg/kg)	0.34	0.14
Sulfur (mg/kg)	2595.67	904.97
Manganese (mg/kg)	0.10	0.11

Ig, Immunoglobulin; *SE,* standard error.

The Immunological Benefits of Colostrum

Cows, sheep, and goats have an epitheliochorial type of placenta that does not allow passage of immunoglobulin, hence neonates are born virtually

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agammaglobulinemic, rendering them susceptible to infection. Ingestion of colostrum provides maternal immunoglobulins that enterocytes selectively absorb by pinocytosis during the first 24 hours after birth. The ability of the enterocytes to absorb immunoglobulins decreases rapidly soon after birth, resulting in "closure" of the intestines by 24 to 36 hours postpartum. "Closure" of the intestines is thought to be mediated through growth factors, including IGF-1, transforming growth factor–beta 2 (TGF-β2), and growth hormone (GH), all of which are present in colostrum.[12] Ingestion of these growth factors through colostrum causes hyperplasia of intestinal epithelium and a decrease in crypt-to-villus ratio, indicating a shift toward differentiated mature enterocytes.[12] Passively derived immunoglobulins enhance neonatal immunity by functioning as neutralizers and opsonins.

The immune system of the neonate starts to develop from birth, with endogenous IgG reaching functional levels at 3 to 6 weeks of age.[13] The uptake of maternal leukocytes by the calf also plays a significant role in the development of the neonatal immune system, by enhancing the antigen-presenting capacity of the calf and regulating the immune response.[14-16] Comparison of the immune response of calves fed leukocyte-replete or leukocyte-depleted colostrum indicates that colostral leukocytes enhance humoral immunity and phagocyte function.[17-21] Following experimental *Eschericia coli* infection, calves fed leukocyte-replete colostrum recovered more quickly and shed fewer bacteria than calves fed leukocyte-depleted colostrum.[4] Transfer of cellular immunity via colostral leukocytes has also been demonstrated in sheep.[22] Colostral leukocytes are destroyed when colostrum is frozen, pasteurized, or fermented.

Ingestion and absorption of colostral immunoglobulins is essential for neonatal ruminants to thrive, and inadequate colostrum consumption increases the risk of disease. The association between failure of passive transfer of immunoglobulins and neonatal infection has been well established in the calf.[23,24] Passive transfer achieving serum IgG concentrations of 10 mg/mL or greater at 24 to 48 hours is associated with reduced risk for morbidity and mortality.[25-27]

The Nonimmunological Benefits of Colostrum

Provision of adequate good-quality colostrum results in improved daily weight

gain and feed conversion efficiency both pre and post weaning, although the effect of this on joining dates and age at first calving varies between studies.[27-31] Calves receiving larger volumes of colostrum at birth have been shown to require less veterinary input in the preweaning period.[28] An increased volume of colostrum fed followed by a higher plane of milk nutrition can significantly increase the average daily weight gain during the first 80 days of life compared to calves fed a lower volume of colostrum followed by the same plane of milk nutrition. In addition, postweaning feed intake was increased in calves fed the higher volume of colostrum. This suggests that there are nonnutritive factors present in colostrum that may contribute to appetite regulation and feed conversion efficiency and that extend into the postweaning period.[32]

Both serum IgG at 24 to 48 hours and the provision of adequate good-quality colostrum have been associated with increased milk production in the first and second lactations.[28,33] There may not be a direct cause-and-effect relationship between serum IgG and future milk production but rather an indirect relationship in that calves with adequate IgG can develop more efficient metabolic systems, which in turn could contribute to future milk production.

Growth factors and hormones in colostrum and milk have been shown to enhance the development of tissues in the gastrointestinal tract of other species.[34] The effect of such bioactive factors in colostrum and milk on the development of specific tissues and/or physiologic functions in the neonate is called the “lactocrine hypothesis.”[35] This maternal programming is an example of epigenetics in that the dam continues to influence the development of the neonate even after parturition has occurred. This influence is derived from bioactive factors present in colostrum that can direct the development of specific tissues.[36,37]

The factors present in colostrum that are likely to influence long-term outcomes include IGF-1, IGF-2, insulin, GH, epidermal growth factor, leptin, and prolactin.[38] It is unknown whether all of these factors are absorbed by the gastrointestinal tract of the newborn calf, but studies have shown that serum IGF-1 levels are higher in calves fed colostrum compared to those deprived of colostrum.[39] This may be due to increased endogenous production of IGF-1 as a result of increased intake of energy and protein in colostrum, as opposed to direct absorption of IGF-1 itself.

Lactose intake is insufficient to maintain plasma glucose concentrations, and colostrum feeding increases plasma glucose, most likely due to stimulation of

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gluconeogenesis. Newborn calves are deficient in vitamin A and have a low lactoferrin status. Both are found in elevated quantities in colostrum compared with milk. Lactoferrin is an iron-binding glycoprotein that is a potent antimicrobial factor in the milk cistern and in the alimentary tract of newborn animals. Digestive functions develop during fetal life and undergo the largest morphological and functional changes during the first 48 hours of extrauterine life under the influence of IGF-1, lactoferrin, and other bioactive substances, many of which are present in significantly higher concentration in colostrum than milk. These factors are key regulators in the development of the gastrointestinal tracts of bovine neonates, including stimulation of mucosal and submucosal growth, brush border enzymes, intestinal DNA synthesis, increased duodenal villus size, and apoptosis; protein synthesis and degradation; and digestion and absorption. They also exert systemic effects outside the gastrointestinal tract on metabolism and endocrine systems, vascular tone and hemostasis, activity and behavior, and systemic growth.[40-42]

Provision of Adequate Colostrum

Optimal transfer of immunoglobulin will occur when calves are administered first milking colostrum at 7.5% to 10% of body weight within 2 hours after birth. The initial feed should provide the calf with a minimum of 150 g of IgG within 2 hours after birth. This is required to ensure that 90% of calves have optimal passive transfer.[43] Dairy calves should be administered colostrum by nipple bottle or esophageal tube, as there is increased failure of passive transfer in dairy calves that are left on their dam.[3,44,45] This is due to the reduced volume of colostrum, and therefore mass of IgG, consumed by the calf if left to suckle naturally during the first 24 hours.[27] Conversely, separation of beef calves from the dam is not practical and may result in mismothering. Generally, failure of passive transfer is less of a problem in beef cattle, as the lower volume of colostrum produced results in elevated concentration of IgG, and supplementation is recommended only following dystocia.

Failure of Passive Transfer of Immunity

Failure of passive transfer (FPT) occurs when calves do not absorb sufficient immunoglobulins. Only small amounts of IgG and IgM to unknown antigens are made by the fetus, and they offer no protection against disease. It has been

estimated that approximately 31% of preweaning mortality events occurring in the first 3 weeks of life can be attributed to FPT.[46] The problem in mixed-source calf-rearing properties is significantly worse.[25] A high percentage (19.2% to 38%) of dairy calves are still found with significant FPT.[44,45,47] There is some debate as to the serum IgG concentration that signifies FPT. Calves are generally defined as having FPT if the calf serum IgG concentration is less than 10 mg/mL when sampled between 24 and 48 hours of age.[48] More recently it has been suggested that serum IgG concentration below 13.4 mg/mL constitutes FPT.[43,49] Ensuring that every calf has adequate passive transfer is challenging, and rates of 10% probably indicate good management practices.[43]

In on-farm monitoring programs for effectiveness of passive transfer, IgG levels are often inferred by measuring serum total protein. A serum protein below 5 g/dL (≈9 mg/mL IgG) will result in a 2.4 to 6 times greater risk of mortality up to 6 months of age.[25,26,50,51] There is still an increase in relative risk of mortality when serum protein is between 5 and 5.5 g/dL as compared to greater than 5.5 g/dL (13.4 mg/mL IgG), but it is not as marked, and the cost benefit of ensuring that all calves achieve a serum protein greater than 5.5 g/dL to prevent mortality is questionable. However, the growing body of evidence suggesting that other colostral factors are positively associated with feed conversion efficiency and lactation performance emphasizes the long-term benefits of actively feeding colostrum and not just the short-term immunological provision of IgG.

On any farm the baseline mortality will reflect management, nutrition, and the pathogens present. The risk of mortality associated with varying levels of passive transfer is independent of baseline mortality rate. Hence where the baseline mortality is high, adequate passive transfer will not prevent calves dying, but as serum immunoglobulin levels decrease below 13.4 g/L, the risk of mortality will increase relative to that herd's specific baseline mortality. It is important to recognize that most calves with total FPT will survive, especially where baseline mortality is low.[25,52] The role of the passive transfer of immunity in preventing morbidity per se is well documented, but the effect of immunoglobulin levels on prevalence of specific disease syndromes varies. Epidemiological studies reflect the variation in management, environment and disease pathogens between properties, and the greater impact of other risk factors on disease incidence. Consequently, there are inconsistent results on the impact of adequate passive transfer on both main calfhood diseases—diarrhea

and pneumonia—also reflecting study design and varying serum IgG levels used to define FPT.[24,26,27,53-56] Studies on the risk of pneumonia generally demonstrate FPT as a risk factor, but the impact of FPT as a risk factor of diarrhea is less consistent. Often where a significant effect of IgG levels on the incidence of a specific disease has not been demonstrated, increasing the sample size to examine correlation with all calves treated with antibiotics, or all morbid calves within the study, has demonstrated a significant benefit of adequate passive transfer. The benefits of adequate passive transfer on disease incidence are likely to be long lasting, with evidence of ongoing prevention of postweaning disease, particularly feedlot pneumonia, although, again, not all studies demonstrate this effect.[26,29,57]

A better indication of the effect of passive transfer on disease appears to be consistent positive correlation demonstrated between adequate passive transfer and average daily weight gain both pre and post weaning.[27-29,55,56,58] It is likely that much of the variation in weight gain is secondary to changes in the incidence of disease.[26,57,58]

Risk Factors for Inadequate Colostrum Uptake

The major factors influencing the effectiveness of passive transfer of immunoglobulins in calves are (1) the concentration of immunoglobulins in colostrum fed, (2) the volume of colostrum ingested, (3) the age of the calf at first colostral feeding, and (4) the bacterial load of the colostrum ingested.

There is large variation in colostrum immunoglobulin concentrations between individual cows and a variety of influences (genetic, environmental, physical) on the uptake of colostral antibodies by the calf. Although calves born to beef cows with lower colostrum immunoglobulin concentration had an increased risk of mortality,[59] numerous other studies in beef and dairy calves have failed to demonstrate an association between the colostral immunoglobulin levels and the serum immunoglobulin of the calves at 48 hours of age.[60-64] Administration of a known volume and concentration of colostrum to dairy calves via oroesophageal feeder at a specific time after birth has been shown to have more linear correlation with calf serum IgG,[43,65] but administration of sufficient colostrum to provide 150 g IgG within 4 hours of birth can still result in FPT.

Factors Affecting the Immunoglobulin

Concentration of Colostrum

The immunoglobulin concentration of colostrum is known as *colostrum quality*. At the herd level colostrum quality is affected by breed, parity, and climate. For individual cows the biggest determinants are colostral volume and time from calving until milking.[66,67] Colostrum concentrations of Holstein Friesian cows varied from 20 g/L of immunoglobulin to more than 110 g/L of IgG1 in cows from a single herd.[66] First milking colostrum samples collected within 4 hours of milking from cows at 11 dairies in Pennsylvania varied from 9 to 166 g/L IgG1.[68] The mean concentration of IgG1 in first milking colostrum in three large studies of dairy cows varied between 37.5 ± 30.2 and 48.2 ± 28.9 g/L.[66,68,69] Colostrum IgG concentration declines with time after calving, even if the cow is not milked.[66,67,70,71] One study showed that colostral IgG concentration decreased by 3.7% in each subsequent hour after calving.[67] However, several studies have demonstrated that this decline is minimal until the cow has been calved 8 to 9 hours.[66,70] There is no increase in colostral volume if postpartum milking is delayed, so it appears that the declining IgG is not due to dilution.[67,71,72] During the colostrum phase mammary cells have leaky tight junctions,[73,74] so it is likely that once parturition occurs, the active transcytosis of IgG1 ceases and it is passively reabsorbed.

Studies of colostrum and calf immunoglobulin levels in specific beef breeds have failed to demonstrate consistent differences between specific breeds, and many studies showed evidence of variations within breed lines. In dairy breeds colostrum from Holstein cows was statistically lower in total IgG than colostrum from Jersey, Ayrshire, and Guernsey cows.[75,76] In other studies, high-producing Holstein Friesians have a tendency to have lower IgG concentrations in their colostrum than lower producing Jersey cows.[66,75,77] Prepartum dairy cows have a significantly greater decline in serum IgG compared with beef cows,[7] but the colostrum of dairy cows has lower concentrations of IgG due to the much larger volume. Some studies have shown very low volumes of colostrum (<2 L) in beef cows.[78,79] The volume of colostrum produced and the concentration of immunoglobulin in the colostrum are markedly affected by differences in the onset of lactogenesis and the resulting dilution of colostral immunoglobulins; hence it is likely that much of the variation observed between breeds, lines, and cows is an effect of colostrum volume.

The weight of first colostrum produced has a direct influence on the colostrum

quality, with cows producing large volumes of first colostrum having a significantly lower concentration of IgG.[66,80] The strong negative association between colostral IgG concentration and volume of colostrum produced is likely to result from the dilution of total IgG with other mammary gland secretions.[7] It has been suggested that using colostrum from cows that have produced less than 8.5 kg will increase the percentage of high IgG concentrations from 64% to 77% in second lactation cows.[66] However, other studies reported a very low sensitivity for weight of first milking colostrum in identifying poor-quality colostrum (<50 g/L).[81]

Parity has been shown to significantly affect the immunoglobulin concentration in colostrum.[80] First and second calving beef and dairy cows often have a lower immunoglobulin concentration than cows of third or greater parity.[9,62,66,76,82,83] Similarly, calves born to beef heifers and second parity cows have a significantly lower mean concentration of serum IgG compared with that of calves born to mature cows.[82,84,85] Other studies contradict this, suggesting that there is no difference in IgG concentration in colostrum from first, second, or fourth parity cows.[86-88] Because good-quality colostrum is such a valuable commodity, the practice of discarding first lactation colostrum is discouraged by some authors.[89]

Genetic variance has been found in the genes encoding the FcRn involved in trancytosis of IgG1 into the mammary gland. In Holstein Friesian cows haplotype 5 of the FcGRT subunit has been shown to be significantly associated with a high colostrum IgG, and FcGRT haplotype 2 shows a similar trend.[90] FPT in beef calves from 16 breeds has been associated with FcGRT haplotype 3, and conversely calves with FcGRT haplotype 2 were less likely to have high levels of serum IgG.[91] FPT in these calves is also associated with one of eight haplotypes of the β2M subunit of the FcRn.[92] It is likely that variation in this receptor affects the concentration of IgG1 in colostrum rather than the uptake of IgG1 by the calf, as neonatal uptake does not involve the FcRn. An estimated 10% of Holstein cows are capable of high mass transfer of IgG1, resulting in an IgG mass more than 1 standard deviation above the mean.[68] Variation in the FcRn probably contributes to this variation, along with other genetic or hormonal regulation of transport. Potentially there is opportunity to enhance the concentrations of immunoglobulins in colostrum by genetic manipulation of IgG transport in the mammary gland. However, it should be remembered that serum

IgG concentrations in the periparturient cow are already decreased because of IgG transport into colostrum,[7] and further decrease in immunoglobulins may exacerbate the immunosuppression that occurs during the peripartum period.

Numerous studies have failed to demonstrate an effect of often severe protein and/or energy restriction for up to 3 months before calving on colostrum immunoglobulin levels.[93-96] Protein restriction may result in an increase in IgG levels and a concurrent decrease in colostral volume, making the colostrum more viscous and difficult to suckle, especially in heifers, resulting in decreased IgG levels in the calves.[84,97] This is likely to be a direct volume response, as shown in other studies of colostral IgG concentration.[7,66] There was no significant effect of dietary restriction on colostral IgM in any of the studies. Selenium supplementation has been shown to increase IgG levels in the colostrum of selenium-deficient cows[98] but not lambs. IgG uptake by the calf may also be affected by serum copper levels.[99]

Twins have not been demonstrated to affect colostrum IgG concentration in beef cows[59,82]; however, a study of sheep, goats, and dairy cows demonstrated an increase in total protein, whey protein, and IgG concentration.[100]

Short dry periods of 28 to 35 days do not affect colostrum IgG levels, but when the dry period was eliminated completely there was a decrease.[101-103] Elimination of the dry period did not affect colostogenesis in terms of cellular and fluid composition, and it is likely that the reduced quality is due to the lack of a period of secretion and accumulation. The mean colostral IgG of these cows remained close to 50 g/L so that 3 L of colostrum would provide the calf with adequate IgG. Treatment of cows with internal teat sealant at drying off has no effect on transfer of colostral antibodies following calving but will help prevent leaking of colostrum prior to calving and the consequential reduction of the quality of the colostrum harvested.[87,88,104]

Few studies look at the effects of periparturient disease on IgG levels in colostrum. A decrease in colostral IgG has been observed in cows with periparturient infections and clinical mastitis[59]; where colostral IgG was not measured, calves of cows with periparturient mastitis had a lower serum IgG.[82] The reported effect of subclinical mastitis is also inconsistent. At the quarter level, a persistent infection at the time of calving, detected by serial cultures, results in a decrease in total volume of colostrum produced but no variation in IgG1 concentration, compared with a matched quarter on the same cow.[105] At

the cow level an increased risk of colostrum with an IgG content of less than 30 g/L is found in cows with a somatic cell count greater than 50,000 cells/mL, measured at the herd recording after calving.[83] At the herd level, cows from farms with an average count less than 200,000 cells/mL in the month prior to sampling produced colostrum with higher levels of IgG2, tocopherol, vitamin A, potassium, and total solid levels, but no significant variation was noted in IgG1.[69]

Environmental temperatures affect colostral IgG concentrations, with several large studies in dairy cattle demonstrating an increase in colostral IgG concentration in the summer[83,106,107]; however, heifers exposed to heat stress had decreased colostral IgG concentration.[108] Photoperiod has no effect on colostral IgG concentration or volume.[67]

Factors Affecting the Mass of Immunoglobulin Absorbed

The key influences on immunoglobulin absorption by the neonatal calf are the concentration of immunoglobulins in the colostrum, volume fed, and time between birth and colostrum feeding. When small volumes are fed, the method of feeding can also affect the final serum IgG level.

Volume of First Feed.

The volume of colostrum fed shortly after birth has a direct, linear relationship with the concentration of serum immunoglobulin in the calf up to 40 hours of age.[109] As the mass of IgG consumed increases, there is a significant difference in serum IgG concentrations in calves fed 3 L of colostrum at birth compared to those fed 1.5 L.[48] The exact volume of colostrum, and therefore mass of IgG, required to avoid FPT has been shown to be variable.[3,81,110] There is no difference in the IgG concentration at 48 hours when 40-kg calves are administered either 3 L or 4 L of colostrum with equivalent immunoglobulin levels regardless of IgG concentration.[43,65] Similarly, with lower quality colostrum, higher serum IgG levels will be achieved when two feeds of 2 L are given at 2 and 6 hours postpartum than when 4 L is given in one feed.[110] The pathophysiology underlying these observations is not fully understood, but 22% of the variation in the effective absorption of colostrum is attributed to abomasal

emptying rate, and it is likely that the excessive mechanical distention of the abomasum with 4 L of colostrum delays outflow.[65,110,111]

Calves should be fed a minimum of 150 g of IgG within 4 to 6 hours of birth and earlier whenever practical. The exact volume at each feed should be determined after measuring, usually by indirect estimation of colostrum IgG levels, and is more important to optimize where lower quality colostrum is the only source (Table 19.2). Calf serum IgG levels will be significantly boosted by a further feed of 5% of body weight of colostrum within 12 hours of birth[110]; if less than 150 g of colostrum was fed at the initial feeding due to limitations of quality or volume, a further 7.5% should be fed.[49] Emphasis should be placed on feeding colostrum with the highest concentration of immunoglobulin at the initial feed, when the effectiveness of absorption is higher. Many farmers are currently feeding 10% to 12% of body weight as a single initial feed. Although this will provide good levels of IgG where colostrum quality is adequate, it may result in moderate depression and discomfort in the calf.[112]

Table 19.2

Liters of Colostrum Required to Achieve Adequate Passive Transfer (Blood IgG Level ≥13.4 mg/mL) for Different Birth Weights, Absorption Rates, and Colostrum Qualities

Calf Weight	Hours After Birth	Brix (%)				
		14-16	18-20	22-24	26-28	30-32
		Antibody Concentration (g/L)				
		20-30	40-50	60-70	80-90	100-110
30	0-3	5.6[c]	2.8[b]	1.9[a]	1.5[a]	1.5[a]
	3-6	6.4[c]	3.2[b]	2.1[a]	1.6[a]	1.5[a]
	6-9	7.1[c]	3.6[b]	2.4[a]	1.8[a]	1.5[a]
	9-12	8.3[c]	4.1[b]	2.8[b]	2.1[a]	1.7[a]
	12-18	9.4[c]	4.7[b]	3.1[b]	2.3[a]	1.9[a]
	18-24	10.5[c]	5.3[c]	3.5[c]	2.6[c]	2.1[a]
40	0-3	7.5[c]	3.8[b]	2.5[a]	2.0[a]	2.0[a]
	3-6	8.5[c]	4.3[b]	2.8[a]	2.1[a]	2.0[a]
	6-9	9.5[c]	4.8[b]	3.2[b]	2.4[a]	2.0[a]
	9-12	11.0[c]	5.5[b]	3.7[b]	2.8[a]	2.2[a]
	12-18	12.5[c]	6.3[c]	4.2[b]	3.1[b]	2.5[a]
	18-24	14.0[c]	7.0[c]	4.7[c]	3.5[c]	2.8[a]
50	0-3	9.4[c]	4.7[b]	3.1[a]	2.5[a]	2.5[a]
	3-6	10.6[c]	5.3[b]	3.5[a]	2.7[a]	2.5[a]

	6-9	11.9[c]	5.9[b]	4.0[b]	3.0[a]	2.5[a]
	9-12	13.8[c]	6.9[c]	4.6[b]	3.4[a]	2.8[a]
	12-18	15.6[c]	7.8[c]	5.2[c]	3.9[b]	3.1[a]
	18-24	17.5[c]	8.8[c]	5.8[c]	4.4[c]	3.5[a]

[a]Calves should be fed 7.5% of body weight or, at a minimum, the volume shown. IgG levels would be enhanced by 5% of body weight 6 to 12 hours later.

[b]Calves should be fed 7.5% of body weight and an equivalent volume 6 to 12 hours later.

[c]It is unlikely that adequate passive transfer will be achieved.

Calculations of total IgG required and apparent efficiency of absorption are based on Chigerwe et al. (2008)[43,198] using blood volume calculations from Quigley et al. (1998).[325] The correlation between the Brix refractometer reading and serum IgG levels was calculated using Quigley et al. (2013).[72] This table was compiled with the assistance of Zoe Vogels from The Vet Group, Timboon, Australia.

It is assumed that the minimum volume fed would be 5% of body weight even where good-quality colostrum is available. It should be noted that below a Brix reading of 22%, it is not possible to achieve adequate passive transfer with a single feed of colostrum.

IgG, Immunoglobulin G.

Time of First Feed.

Early ingestion of colostrum is crucial; IgG is absorbed by the intestinal epithelial cells of the newborn ruminant, and the ability of enterocytes to transport immunoglobulin declines linearly from 2 to 20 hours after birth and completely ceases (intestinal closure) between 24 and 36 hours.[113] Serum IgG concentrations peak around 32 hours and then decline until the production of antibodies by the neonate exceeds the decay of passively acquired antibodies. Any delay in first feeding of colostrum results in decreased absorption of immunoglobulin and a lower serum IgG.[43,114] Absorption of immunoglobulins occurs along the whole length of the small intestine in calves, with the amount transported increasing from the duodenum to the ileum,[115] whereas in lambs and kids there is virtually no absorption from the duodenum and most absorption occurs in the jejunum.[116,117] IgG and other macromolecules are mainly absorbed by micropinocytosis, although some receptor-mediated endocytosis has been demonstrated, but this does not involve the FcRn.[115,116,118] Preferential absorption of homologous IgG has been observed in pigs; however, recent studies in kids and lambs have shown that similar IgG transfer can be achieved by feeding bovine colostrum, although in lambs the apparent efficiency of absorption is lower.[119-121]

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The age of the calf when it receives its first feeding and the amount of immunoglobulins received will influence the time of closure of the intestinal permeability to colostral immunoglobulins and the final serum immunoglobulin levels of the calf.[122-126] Cessation of absorption occurs by 24 hours in calves that receive a full feed of colostrum within the first 4 hours after birth. When the colostrum volume is less than 2 L, the gut will remain permeable for a longer time and the rate of absorption will increase in response to a subsequent feed. If the calf is older than 12 hours when it receives its first feed, there is a significant increase in the possibility of the calf being agammaglobulinemic. It is likely that the time of closure is related to the immunoglobulin concentration of the colostrum as well as the volume fed. Delay in colostrum feeding will also result in lower plasma insulin and IGF-1 for up to 48 hours after first colostrum intake and reduce plasma concentrations of betacarotene, retinol, and α-tocopherol for nearly a month after birth.[127,128]

Method of First Feed.

Method of feeding also has a significant effect on colostrum intake. A high proportion of calves left to suckle their dams show evidence of FPT, compared to those artificially fed by teat or esophageal feeder.[3,129,130] This is due to the reduced volume of colostrum, and therefore mass of IgG, consumed by the calf if left to suckle naturally during the first 24 hours; hence it is strongly recommended that dairy calves be administered colostrum containing 150 g IgG within 2 hours of birth.[27] Teat-feeding stimulates a reflex closure of the esophageal groove allowing colostrum to pass directly to the abomasum, where it clots before moving to the small intestine for absorption. When an esophageal feeder is used, this reflex does not occur, and the colostrum passes to the reticulorumen.[131,132] Promotion of the advantages of closure of the esophageal groove has resulted in the use of a nipple bottle as the more common method of administering colostrum. Calves fed a small volume of colostrum (1.5 L) via an esophageal feeder have a lower efficiency of absorption than calves fed colostrum via a teat feeder.[133] However, several studies[134] have demonstrated that there is no difference in immunoglobulin concentrations at 48 hours between calves that sucked larger volumes of colostrum from a nipple bottle and those that were administered a similar quantity via an esophageal feeder, although there may be a delay of approximately 3 hours before the serum IgG increases in the tube-fed calves.[112,135,136] This delay is not due to the deposition of colostrum

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in the reticulorumen, as all except 400 mL will immediately pass into the abomasum due to the pressure gradient resulting from the placement of the reticulorumen dorsal to the abomasum in the neonatal calf.[137] Instead the delay is likely to be due to delayed abomasal emptying resulting from distention and changes in physiologic and neuronal control mechanisms.[111,138]

Calves fed by a nipple bottle will commonly not ingest sufficient colostrum to minimize the risk of FPT and should be encouraged to ingest the maximum volume they will voluntarily ingest within 1 to 4 hours of age.[49] Calves should be fed as soon as they are standing; delaying up to 6 hours after birth or providing a heat lamp will not increase the amount of colostrum suckled.[49,139] Calves that have a high degree of vigor during the first hour of life and during colostrum suckling will consume more colostrum from the bottle, as will larger calves.[139] Bottle-fed calves that do not ingest their full allocation of colostrum at either the first or the second colostrum feed should be targeted for immediate esophageal feeding, and the total remaining should be fed.

To minimize trauma when an esophageal feeder is used, the calf should be standing with its rump against a solid wall or corner. The feeder used should have a total volume of at least 3 L so that intubation has to occur only once. The calf should be encouraged to swallow prior to insertion by sucking a finger to produce saliva or by being fed a few mouthfuls of colostrum. The tube should be introduced without physical exertion, and the head should be positioned slightly downward to allow swallowing as the tube is inserted into the esophagus. Before feeding, the knob at the end of the tube should be palpated on the left-hand side dorsal to the trachea to ensure that positioning is correct. At this point the calf head may be tilted slightly upward as the bottle is elevated to administer the colostrum. It is important that the tube remains fully inserted during colostrum delivery. It is common for calves to chew during administration, causing retrograde movement of the tube that may lead to the bulb of the tube migrating to the level of the pharynx, resulting in aspiration.

On beef properties, routine administration of colostrum to the newborn calf is disruptive and delays the time until first sucking[140] but will decrease the incidence of FPT.[60,141] Feeding colostrum to high-risk calves is likely beneficial, most commonly after dystocia. Beef cows often produce smaller colostrum volumes; where volumes less than 1.5 L are fed, use of a nipple bottle is recommended, as serum IgG at 24 hours of age is higher compared to that of calves administered colostrum with an esophageal feeder.[142] This most likely

occurs because a greater percentage of the total colostrum is deposited into reticulorumen. Where dairy colostrum was fed, this was also shown to be a biosecurity risk.

Other Factors Influencing Immunoglobulin Absorption.

Calves that have experienced dystocia are more likely to have failure of passive transfer.[27,84,85,143] Decreased vitality of the neonate, potential hypoxia in the small intestine secondary to respiratory acidosis, and in many cases edema of the head and tongue result in a slower time to stand and inadequate colostrum intake as a consequence. Calves born to primiparous cows have been shown to have a higher risk of FPT compared to those born to multiparous cows.[27,75,144] This may be related to primiparous dams having lower IgG concentrations in their colostrum[145] as a result of reduced exposure to antigens[144] or an indirect effect of increased risk of dystocia in primiparous dams.[146] Another study showed that there was no effect of dam parity or dystocia on calf serum IgG concentration.[81,147] Respiratory acidosis did not result in decreased levels of IgG at 37 to 48 hours in studies where blood gases were measured promptly using arterial blood, although delayed absorption was observed in one study.[148,149] The effects of twinning are equivocal, with two large studies, both in beef herds, demonstrating opposite effects of twinning on calf serum IgG. This is likely to be related to management, as the study that showed an increase in IgG with twinning moved all cows with twins to a barn for care and observation.[82,143]

It has been shown that the conformation of the dam's udder and ventral abdomen has a significant effect on the average teat-seeking time prior to first suckling. There was nearly a 30-minute delay in the time to suckle.[150] Overall effect on the calf IgG was not measured, but a separate study demonstrated a significantly lower serum IgG in cows with pendulous udders.[151]

Protein restriction in the last third of gestation may affect uptake of IgG by the calf,[152] although IgM concentration was unaffected. This finding was attributed to the selective absorption of IgM in newborn calves, which is highly efficient when colostrum intake is low. IgM is the primary immunoglobulin that provides protection to the neonatal calf during the first few days of life, and it has been suggested that the efficient absorption of IgM is a compensatory measure that provides immunity to calves even when they are hypogammaglobulinemic.[153,154]

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There is a seasonal variation in the IgG levels of calves and efficiency of absorption after colostrum feeding, being lower in the winter in cold climates and lower in the summer in hot climates.[61,144,155-157] Colostral immunoglobulin concentration is reduced in hot and cold weather,[106-108] and this is exacerbated by calves also being less willing to suckle in extreme temperatures. Heat stress results in smaller calves that may be less vigorous,[156,158] with one study demonstrating that calves subjected to a cold and wet environment had a slower rate of colostral absorption,[159] although the serum immunoglobulin at 24 hours was not significantly different from that in the control calves. In that study the calves exposed to cold temperatures were fed colostrum via an esophageal feeder. The effect would be exacerbated in cold-stressed calves, as they are less likely to suckle voluntarily.

There is some evidence that IgG levels in calves at 24 and 36 hours have low to moderate heritability. The breed of the sire and dam has some effect, but there is variation within lines of the same breed.[62,64,85,160] Haplotypes of both the FcGRT and β2M genes coding for the FcRn are associated with FPT in neonatal beef calves, as discussed previously.[91,92] Since this receptor is not involved in the uptake of IgG by the calf, it is likely that the risk factor for FPT is the colostrum quality of the dam.

Calves that are allowed to remain with the dam for longer periods after birth have been shown to have a higher risk of FPT. Calves removed from the dam within 3 hours of birth are less likely to have FPT compared to those allowed to stay with the dam for more than 3 hours.[45,47] The gender of the primary calf carer has also been shown to influence the odds of FPT,[47] with female calf carers having a positive effect on serum protein levels compared to male calf carers.

Management to Ensure Adequate Passive Transfer

The effectiveness of passive transfer achieved at a farm level reflects farm management. Best practice colostrum management strategies for dairy and beef calves are presented in Box 19.1 and 19.2.

Box 19.1

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Best Practice Colostrum Management for Dairy Calves

- Milk cows as soon as possible after calving. Immunoglobulin G (IgG) concentration declines by 3.7% for each hour after calving.
- Remove calves from the calving area at least twice daily.
- Measure quality of colostrum (Brix refractometer). This will determine the quantity of colostrum to be fed. For the first feed, administer colostrum containing 150 g IgG within 4 hours of calving. Feed a maximum of 7.5% of body weight. If calf does not suckle the full amount, top with esophageal feeder.
- Feed an additional 5% to 7.5% of body weight by 12 hours of age. If the calf did not receive 150 g of colostrum in the first feed, it is preferable to supplement 7.5% of body weight at the second feed.
- On farms with a history of Johne's disease, salmonella, mycoplasma, or leukosis, pasteurize colostrum.
- Avoid pooling colostrum where possible. If pooling of colostrum is unavoidable, mix colostrums of similar quality.
- Implement a monitoring program for failure of passive transfer.

Box 19.2

Best Practice Colostrum Management for Beef Calves

- Avoid severe restriction of dietary intake prior to calving; this will reduce volume and make colostrum more difficult to suckle.
- Minimize disruption of calving cows.
- Ensure that calves receive colostrum within 6 hours of calving (active suckling); intervene when there is dystocia or dumb calf.
- Intervention may involve restraining the dam and encouraging suckling or administering colostrum by a nipple bottle. An esophageal feeder should be

used only when volumes greater than 1.5 L are available or if the calf will not suck.

Ensuring Optimal Immunoglobulin Concentration

Colostrum Collection, Handling, and Storage.

Colostrum collection should occur as close to parturition as possible. Fresh cows should be removed from the calving area and milked out at least twice daily to help ensure optimal colostrum quality. Colostrum collected from cows that have leaked milk prior to calving, have signs of ill health, or have evidence of mastitis should not be fed to neonatal calves.

Colostrum quality is compromised in cows that have leaked milk prior to calving.[87,88] The colostrum from cows exhibiting signs of ill health or mastitis will have increased potential for the presence of infectious pathogens, such as *Mycobacterium avium* subsp. *paratuberculosis, Salmonella* spp., *Mycoplasma bovis, Staphylococcus aureus,* bovine diarrhea virus, and bovine leukemia virus.[161-163] Neonatal enteric pathogens such as cryptosporidium may also be present.[164,165] Consequently, unpasteurized colostrum is a potential risk factor for calf diarrhea and neonatal septicemia.[166,167] Unpasteurized colostrum is also a biosecurity risk, and the use of colostrum from cows from a different property is not recommended. Pooling of colostrum significantly increases the biosecurity risk, as organisms are disseminated, subsequently infecting a larger number of calves.[167-169] This is exacerbated further if storage is poor, resulting in pathogen proliferation.[166,170] Colostrum with high bacterial levels not only present a significant disease risk, but also affect absorption of IgG by direct blocking of uptake and transport of immunoglobulin molecules across intestinal epithelial cells or by binding free immunoglobulin in the gut lumen.[48,171] Pooling of colostrum will also result in reduced IgG concentrations due to the overrepresentation of high-volume, low-immunoglobulin colostrum and consequently is associated with an increased level of FPT.[44,89] When pooling is necessary for pasteurization, the colostral IgG should be estimated using a Brix refractometer and low-quality colostrum of less than 22% Brix excluded. However, heat treatment of colostrum increases IgG absorption efficiency even in low-quality colostrum.[172]

Microbial contamination of colostrum compromises colostral quality and

subsequently calf health. Bacterial contamination may occur during harvest, storage, or administration.[161,166,170,173] Possible sources of contamination include cow skin, milking cup liners, hoses, milking buckets, and storage and feeding utensils. Contamination of colostrum with pathogens during harvest can be avoided by careful and hygienic teat preparation in fresh cows prior to applying cups.[161] This may involve washing and drying teats and applying a pre-milking teat disinfectant.[174,175] Thorough and effective cleaning and disinfection of collection, storage, and feeding equipment is essential. It is important that separate, clearly marked esophageal feeders are used for feeding colostrum and are not used with sick calves, as this may also be a significant disease risk. Milk feeding equipment should not have cracks or scratches that allow for buildup of bacteria. Equipment should be rinsed in lukewarm water and then actively scrubbed in water hotter than 50° C (122° F) containing either detergent and bleach (6% sodium hypochlorite) or dry chlorinated detergent to remove any residue. Bottle brushes should be used to clean esophageal feeders, nipples, and feeding bottles. Finally, they should be rinsed in water containing acid or an acid rinse and allowed to dry completely before stacking them upside down for storage.

When there is concern about hygiene practices, plating 10 µL of colostrum onto a blood plate and incubating at 37° C overnight provides a simple crude assessment of microbial contamination of colostrum being fed to calves and allows identification of the origin of any process failure. Fresh colostrum fed to calves should have a total bacteria count of less than 100,000 colony-forming units/mL and less than 10,000 coliforms/mL.[161,167]

Short-term storage of colostrum is necessary in order to deliver known good-quality colostrum to neonatal calves within hours of birth to reduce the risk of failure of passive transfer. When colostrum is stored at ambient temperatures, bacterial proliferation leads to fermentation, thus reducing total solids, protein, fat, and lactose content. Refrigeration of colostrum delays bacterial growth. The rate of colostrum cooling in a refrigerator is influenced by the volume and surface area of the container in which it is stored. Colostrum should be dispensed into 2-L containers prior to refrigeration. Producers should aim to feed refrigerated colostrum within 2 days of collection.[170] Storage of colostrum in the refrigerator for more than 24 hours will result in a decreased amount of IgG absorbed, and this may lead to FPT if stored for more than 48 hours.[176] Adding 10 mL of 50% potassium sorbate solution per liter of colostrum at the time of

collection (0.5% wt/vol), in combination with refrigeration, inhibits bacterial growth for 4 days.[166]

Heat treatment of colostrum is an effective way to control colostrum bacterial load, reducing the risk of infectious disease transmission from cow to calf.[177] Degradation of immunoglobulins may be a problem with large-batch colostrum pasteurizers. Calves fed large-batch pasteurized colostrum have significantly lower serum IgG levels than those fed unpasteurized colostrum.[48] However, pasteurization of small batches of colostrum (57 L) at 67º C (152.6º F) or lower for 30 minutes caused a minimal decrease in the immunoglobulin concentration of colostrum compared to pasteurization of large batches (95 L) or batches at higher temperatures (76º C [168.8º F] for 15 seconds) and had little effect on the subsequent serum immunoglobulin in calves at 24 hours of age.[178,179] At this temperature *M. avium* subsp. *paratuberculosis* may survive.[180,181] Heat treatment of colostrum (at 60º C [140º F] for 60 minutes) at a commercial level has been shown to effectively reduce colostrum microbial counts while maintaining IgG concentration.[182] Calves fed such colostrum were also found have reduced morbidity.[183] This critical temperature and time period appears to significantly reduce the bacterial load while not denaturing the IgG or changing the viscosity of colostrum.[184] Calves fed heat-treated colostrum (in either single aliquots or batch treatment) had significantly improved apparent efficiency of absorption and serum IgG compared to calves fed fresh frozen or fresh refrigerated colostrum (Kryzer, 2015).[172,184a]

The use of ultraviolet (UV) light to reduce the pathogen load of colostrum has been described. UV light inactivates microorganisms by disrupting their RNA and DNA structure.[185,186] However, this process depends on exposure of the microorganisms to UV light, which can be problematic in opaque mediums such as colostrum and milk. Although some microbial reduction has been observed using this process, the significant negative effect on colostral immunoglobulin level is deemed unacceptable, with a final mean IgG reduction of 40% to 50%.[187,188]

Longer term preservation of colostrum can be achieved by freezing or lyophilization without change in the immunoglobulin and nutritional content.[189-191] However, the cellular content of colostrum is destroyed by freezing, which may have longer term effects on the development of the immune system.[192] In kids the feeding of lyophilized colostrum resulted in higher IgG levels than the

feeding of frozen colostrum.[193] The freeze-thaw cycle is associated with an 8% to 30% loss in IgG1, with the magnitude of the loss dependent on the method of thawing. Thawing at 40º, 50º, 60º, and 70º C is associated with losses of 8%, 14%, 15%, and 26%, respectively. Thawing in a microwave at 200 and 350 watts causes losses of 20% and 31%, respectively.[194] Thawing larger volumes in a microwave may result in uneven heating and clots and is generally not recommended.[134] The speed of thawing colostrum can be facilitated by freezing 1- to 4-L aliquots in flat plastic bags or purpose-designed equivalents. Thawing in a rocking heated water bath at 40º C (104º F) is recommended; alternatively colostrum may be thawed at room temperature or in a fridge.

Monitoring Colostrum Immunoglobulin Quality.

The quality of colostrum has traditionally been measured by visual inspection or by using a colostrometer (a hydrometer). The level of IgG in colostrum cannot be accurately predicted based on its appearance,[88,195] hence the need for more objective instruments. The colostrometer (hydrometer) measures the specific gravity of a liquid, which in the case of colostrum is associated with the protein content. Globulins contribute greatly to this protein, so the colostrometer has been used to determine the immunoglobulin content of colostrum.[196] Although they are relatively quick to use on-farm, the sensitivity and specificity of colostrometers are variable depending on the cut-point selected and the instrument used. The sensitivity of colostrometers to detect high-quality colostrums ranges from 0.32 to 0.84, and specificity for detecting low-quality colostrums ranges from 0.77 to 0.97.[197-199] Colostrometer readings are also significantly affected by temperature,[200] and for a known quality of colostrum, the colostrometer can differ by 0.8 g/L for every degree Celsius change in temperature. The specific gravity of colostrum also can differ between breeds and can be influenced by lactation number, month of calving, year of calving, and protein yield in the previous lactation.[107] Field experience has shown that colostrometers are most accurate in diagnosing samples of moderate or inferior quality but may indicate erroneously high readings for samples in the superior range.[63] It should be noted that the markings on a colostrometer are calibrated for Holstein cows. From a practical perspective, colostrometers are very fragile and prone to breakage in the farm environment.

Cow-side immunoassay kits for measuring colostral IgG are available and

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have been shown to have an acceptable sensitivity and specificity for this purpose.[201] However, their lack of availability on a global scale, along with financial constraints, limit their use.

Optical and digital Brix refractometers can be used to measure the quality of colostrum using fresh and frozen samples.[202] For colostrum from Holstein cows, the optical Brix refractometer demonstrated a specificity of 85% and a sensitivity of 90.5% using a cutoff of 22% Brix. A cutoff of 22% Brix was deemed to equate to 50 g/L of immunoglobulin using radial immunodiffusion (RID), thus samples greater than 22% Brix were considered to be of adequate quality.[202] In another study the results showed that a cut-point of 21% was estimated in samples greater than 50 g/L, as measured by RID.[72] Breed influences colostrum Brix readings. The cut point for 50 g/L for Jersey colostrum is lower with a Brix of 18% providing a sensitivity of 92.3% and a specificity of 94.7%.[203]

The benefits of the Brix refractometer are that they are not affected by ambient temperature and they are robust, easy, and economical to use at an on-farm level.[198] It has been found that high-quality colostrum samples can yield a "fuzziness" through the viewfinder of a Brix refractometer. Generally this happens in samples greater than 22%. A smaller sample size on the prism can help with clarity in these high-quality samples. The poorer the quality of colostrum, the clearer the value is to read.

Brix refractometers are inexpensive, easily available, and robust, and as such should be standard dairy farm equipment. Farmers are advised to purchase a refractometer that only measure degrees Brix with a scale from 0% to 32%, so that they are easy to read. To get an accurate reading it is necessary to press the cover plate firmly over the prism while looking through the viewfinder, as some thick samples will cause the cover plate to lift off the prism. It is also important that each sample is placed on a clean, dry prism.

The Role of Vaccines in Colostrogenesis.

A potential approach to achieving an increased level of protective immunity in neonatal calves is by vaccination of the dam during the period of colostrogenesis. This practice has frequently been adopted to aid in the control of diarrhea-causing pathogens such as *E. coli*, rotavirus, coronavirus, and *Salmonella*.[204-209] Calves fed colostrum from vaccinated cows have shown increased serum IgG and reduced morbidity and mortality compared to calves

fed colostrum from unvaccinated dams.[206] Herd-level vaccination has led to an increase in the colostrum quality observed as determined by Brix refractometry.[210] The timing of vaccine administration during the dry period is critical, as an increase in dam serum IgG in response to vaccination must coincide with colostrum production in the udder tissue.[211] If a vaccine is administered too close to parturition, there is an inadequate period for a peak IgG response and subsequent transfer of IgG into colostrum. If a vaccine is administered too far away from expected parturition, peak IgG response will not coincide with colostrogenesis. No one generic vaccination protocol fits all vaccines, so the manufacturer's directions should be followed. Producers should be reminded that the usefulness of vaccines depends on active colostrum feeding and delivery of an adequate mass of IgG to the calf in a timely manner after birth.

Enhancing IgG Uptake.

Numerous attempts have been made to artificially augment passive transfer by adding substances to colostrum that aim to increase efficiency of absorption or provide an increased concentration of immunoglobulins. Addition of dried colostrum powder,[110,212] casein, or concentrated whey protein[213,214] had either no benefit or a detrimental effect on colostrum absorption. Feeding colostrum containing 1000 IU vitamin E to calves does not influence uptake of IgG by the calves but did result in higher levels of vitamin E in the calf plasma.[215] Similarly, the addition of 30 g sodium bicarbonate to colostrum had no effect on uptake.[216] However some studies have demonstrated positive benefit. The addition of spray-dried bovine serum to lower quality colostrum to provide the equivalent level of IgG as found in a high-quality colostrum resulted in a higher level of IgG at 12 and 24 hours of age.[217]

The addition of 5 g/L of a mineral adsorbent zeolite (clinoptilolite) up to a total of 0.5 g/kg/day has been shown to increase rate of absorption of colostrum in the first 16 hours and in some cases to increase serum IgG at 24 and 48 hours, especially where lower colostrum volumes were fed.[218-220] The exact reason for this has not been explained, but it is thought that clinoptilolite may bind some degradation products of colostral proteins, such as ammonia, in the gut, thus preventing their negative effects on mucosal epithelial cells designated for immunoglobulin absorption. It may also slow the passage rate of digesta through the intestine, allowing increased time for absorption. The addition of 1 and 2

g/kg/day of clinoptilolite has a negative effect on serum IgG concentration at 24 and 48 hours, but when colostrum from cows vaccinated against K99 and F41 antigens of *E. coli* was fed, calves fed 1 and 2 g/kg/day had increased blood serum levels of specific antibodies against *E. coli* at 12, 24, and 48 hours.[221,222] In all of these studies very high-quality colostrum (80 to 100 g/L) was fed, and no more than 2 L was fed at any one feeding and often 0.75 L was fed to a 35-kg calf. The benefits of clinoptilolite when larger volumes of lower quality colostrum are fed have not been evaluated. When clinoptilolite is added to milk replacer as well as colostrum, an added benefit of increased hematopoiesis is seen, presumably as this mineral is high in iron.[222,223]

The addition of gut-active carbohydrate (mannan-oligosaccharide) to colostrum has been shown to affect IgG uptake with variable results.[224-226] Again, the mechanisms responsible for this effect have yet to be elucidated. Bacteria in colostrum may directly block uptake and transport of immunoglobulin molecules across intestinal epithelial cells or bind free immunoglobulin in the gut lumen.[48,171] Gut-active carbohydrates have been shown to adsorb pathogens expressing type 1 fimbriae, reducing their ability to colonize the gastrointestinal tract.[227] Thus there is a potential role for gut-active carbohydrates to play in the uptake of IgG from the gastrointestinal tract. However, it is still unclear as to whether the addition of gut-active carbohydrates to colostrum enhances or reduces IgG absorption.[224]

These studies demonstrate that it is possible to influence uptake of IgG with specific additives and that further research is required to investigate their potential while accommodating the variation in colostrum IgG concentration and standard management practices within herds.

Monitoring for Successful Passive Transfer

Calves.

Monitoring programs for FPT are an integral step in neonatal calf disease outbreaks and proactive calf health programs. A range of tests have been used to assess passive transfer.[228-230] The RID assay is considered the reference method and is a direct measure of serum IgG. However, its usefulness is compromised by the processing time and expense. There is some variation in the published research as to the level of serum IgG that indicates adequate passive transfer, but most researchers use 10 mg/mL (1000 mg/dL).[149,228,231,232]

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Precipitation Tests.

The sodium sulfite and zinc sulfate turbidity tests use salts to precipitate serum proteins, in particular the larger molecular weight immunoglobulins. A measured amount of calf serum is added to a standard volume of solution and incubated at room temperature for up to 30 minutes. The test results are quantified according to the degree of cloudiness of the mixture caused by protein precipitation. The sodium sulfite turbidity test has traditionally been described as a three-step semiquantitative test using 14%, 16%, and 18% solutions. The sensitivity, specificity, and degree of association with IgG are similar to measuring serum protein with a refractometer, but the test is more complicated to perform.[228] The sensitivity has been estimated as 85% to 100% and the specificity as 53% to 87% using an 18% solution (1+ end point).[228,232] The zinc sulfate turbidity test can be influenced by hemolysis, making it difficult for routine use.[89] The standard test is carried out by adding 0.1 mL of calf serum to 6 mL of 208 mg/L zinc sulfate and incubating the mixture for 1 hour at 23º C (73.4º F). The test has a sensitivity of 100% and a specificity of 55%, which is lower than serum protein or sodium sulfite turbidity.[228] The specificity of the test can be improved by increasing the strength of the solution to 300 or 350 mg/L.[233] These solutions resulted in an increase of the specificity to 65% and 76%, respectively, with little decrease in sensitivity.

Recently, ammonium sulfate (immunocrit), previously developed for piglets,[234] was evaluated in dairy calves.[235] The reported advantage of the use of ammonium sulfate is that it only precipitates immunoglobulins and is non–species specific. The test is performed by mixing an equal volume of 55% ammonium sulfate and serum to be tested, followed by collecting the mixture in a microhematocrit capillary tube, and then centrifuging. The capillary tubes are then removed from the centrifuge, and immunocrit values are read with a microhematocrit reader card from the top of the capillary tube sealant to the intersection between the precipitated IgG and the remaining serum. Immunocrit values of 11% or greater indicate adequate transfer of immunity.[235]

Enzymatic Activity.

Measurement of serum gamma-glutamyltransferase (GGT) in calves aged 24 hours can indicate positive ingestion of colostrum but has poor correlation with actual serum IgG levels.[236] A limitation of this test is that serum GGT declines rapidly during the first week of life.[237] Thus accurate records reflecting the age

of the calf are vital for this test to be interpreted accurately. Both colostrum and milk contain GGT, but activities in milk are considerably lower than in colostrum.[238] GGT rises quickly after the ingestion of colostrum and then falls rapidly over the subsequent 24 hours, followed by a slow decline for the next 2 months. Calves that do not ingest colostrum have serum GGT activities similar to adult cattle. GGT is a useful test when assessing the passive transfer status of clinically ill calves younger than 21 days of age where disease confounds interpretation of serum proteins; a GGT cutoff of 50 IU/L classifies 93% of calves correctly (sensitivity 93%, specificity 92%).[239]

Immunoassay.

The on-farm lateral flow immunoassay is one method for identifying calves with less than 10 mg/mL serum IgG. It takes approximately 20 minutes to perform and is relatively inexpensive, but it is not commercially available worldwide. The test yields only a positive or negative result as opposed to the actual level of serum IgG. This is considered a limitation of the test.[48] Published results show that sensitivity ranges from 93% to 99% and specificity from 88% to 89%.[232,240]

Refractometry.

An optical handheld clinical refractometer may be used to measure serum protein of calves between 24 hours and 7 days of age. Although it is not a direct measurement of IgG concentration, it is considered an accurate indicator of the immunoglobulin status of the animal (Table 19.3).[241] Studies have compared refractometry to turbidity testing and GGT activity and have shown that it is equivalent or superior to these assays in the proportion of calves classified correctly.[25,228,236,237] This method is easier to standardize between laboratories and operators than many other indirect methods and is cheaper, quicker, and easier than most direct tests for IgG.[25] A minimum of 12 calves need to be sampled; when interpreted on a group level, this method provides a good correlation between serum protein and serum IgG, as measured by RID.[48] Sick (scouring) calves should not be included in the sample set, as dehydration will falsely elevate the serum protein. It has been suggested that the accuracy of serum protein could be improved if packed cell volume (PCV) is also measured as a proxy for hydration status.[239] The benefits of this method are that it is quick and inexpensive and samples do not need centrifugation.[242] This has an added advantage, as this method can be implemented at the farm level on large calf-

rearing units to monitor for FPT in groups of calves. A serum protein concentration less than 5.0 g/dL reflects FPT, between 5.0 and 5.5 g/dL reflects marginal passive transfer, and greater than 5.5 g/dL reflects adequate passive transfer. At a herd level the target should be for 80% of calves to have serum protein concentrations greater than 5.5 g/dL.[161] More recently it has been suggested that a serum total protein of 5.8 to 6.3 g/dL should be used to indicate adequate transfer of immunity in dairy calves.[147] Assessment of serum protein using a refractometer is not a reliable estimate of IgG levels in calves that have received colostrum substitutes or replacers.[243] Using the same methodology, a Brix refractometer can also be used to indirectly assess passive transfer using serum protein. A cut-point of 8.3% Brix can be used to estimate FPT (serum IgG <1000 mg/dL) with reasonable sensitivity (85.5%) and specificity (82.85%).[244]

Table 19.3

Relationship Between Serum Protein and Serum IgG[a] (R^2 = 0.76)[175]

Serum Protein (g/dL)	Serum IgG (mg/mL)
6.5	22.4
6	17.9
5.5	13.4
5.2	10.7
5	8.9
4.5	4.4
4	0

[a]It should be recognized that there is variation among refractometers.[326]

IgG, Immunoglobulin G.

Lambs.

Determination of serum GGT activity,[245-247] serum total protein using the biuret method, and γ-globulin concentrations[247] has been recommended for assessing passive immunity in lambs. However, serum total protein determination by refractometry is considered beneficial in making clinical decisions because of the immediate availability of test results.[247] Previous studies that used zinc sulfate turbidity tests to assess passive transfer in lambs indicated that zinc sulfate readings of less than 10[248,249] and less than 12[249] were associated with increased morbidity and mortality. The zinc sulfate readings of less than 10 and less than 12 were equivalent to serum total protein concentrations of 5.2 and 5.4

g/dL, respectively.[247] Serum total proteins of 5.2 and 5.4 g/dL were also determined to be equivalent to serum IgG concentrations of 1332 and 1521 mg/dL.[247] Serum γ-globulin concentrations of 0.5 g/dL or less were associated with higher mortality rates compared to lambs with higher γ-globulin concentrations.[250] γ-Globulin concentrations of 0.5 g/dL were equivalent to serum IgG concentrations of 681 mg/dL. Based on these observational studies, serum IgG concentrations that provide optimal health below which FPT occurs in 1- to 2-day-old lambs were estimated to be between 600 and 1600 mg/dL.[247] However, the risk for morbidity and mortality for various strata in this serum IgG range has not been fully described and will depend on other components of the epidemiologic triad (agent and environmental factors). Algorithms for predicting passive transfer status of various ages using GGT have been developed in lambs.[245,246] In summary, serum GGT activity and serum protein determination by biuret method are currently the most widely used tests for assessing immunity in lambs. Although determination of serum protein concentration by refractometry is cheaper and practical and test results are readily available, it is likely to misclassify FPT status compared to the other methods.[247]

Goat Kids.

FPT in goat kids is defined as serum IgG concentrations less than 1200 mg/dL.[251] Practical tests reported as useful in assessing passive transfer status include the 18% sodium sulfite test and serum total protein by refractometry.[251] Serum total protein concentrations of 5.4 g/dL or higher were considered indicative of adequate passive transfer of immunity.[251]

Management of FPT.

Calves may be managed for FPT by the administration of bovine plasma at a dosage of 20 to 40 mL/kg. The initial rate of administration should be 5 mL/kg/h with close observation for adverse effects, which most commonly include trembling, hives, edema, piloerection, stertorous breathing, and increases in heart rate and respiratory rate. If no adverse effects are noted in the first 30 minutes, the rate can be increased to 10 to 20 mL/kg/h with continued monitoring.[252] Whole blood also can be used, but the dosage should be increased to account for the presence of red blood cells.[89] Calves should be monitored as for plasma

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transfusions; adverse reactions are very uncommon with first-time transfusions, as there are a large number of blood types in cattle. Plasma or whole blood may also be administered via the intraperitoneal route. An area in the center of the left paralumbar fossa is clipped and surgically prepared. A 14- to 16-gauge, 1.5-inch needle is used to penetrate the skin, abdominal musculature, and peritoneum, and the serum is administered through a giving set.[89] The benefits of plasma administration in healthy or sick calves with FPT has been questioned. Plasma administrations to healthy calves attained serum IgG concentrations greater than 1000 mg/dL, but the decay of transfused plasma was significant such that by 12 hours post transfusion, the serum IgG concentrations were less than 1000 mg/dL.[253] The half-life of transfused IgG was 4.4 days compared to 17.1 days for colostral-derived IgG.[253] In addition, calves with FPT transfused with plasma were five times more likely to experience mortality compared to calves with adequate passive transfer of immunity.[253] This increased rate of decay of plasma-derived IgG may necessitate repeat plasma transfusions, which might predispose calves to transfusion reactions. In another study plasma transfusion had no effect on oxidative and phagocytic activity of neutrophils of calves with FPT.[254] Due to high costs associated with plasma transfusions, the procedure should be considered on a case-by-case basis.

Precautions should also be taken to minimize risk factors for infection in calves with FPT, including minimizing potential exposure to pathogens. Colostrum may be fed beyond the period of closure to provide protection at the level of the gut lumen. Where the environment is less than desirable, the prophylactic administration of broad-spectrum parenteral antimicrobials in calves with FPT should be considered.

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Navel Treatment

Omphalitis occurs in 1% to 14% of newborn calves.[255,256] It can lead to reduced growth, joint ill, and other adverse sequelae associated with bacteremia.[257] Prevention of navel ill is based on maintenance of maternity pen hygiene, reducing the residency time of calves in unhygienic maternity pens, ensuring adequate early intake of good-quality colostrum, and navel antisepsis.[258] Literature on the efficacy of navel treatment in reducing calf mortality is divided. In a study of 104 dairy farms, a farm policy of navel treating newborn calves had no significant effect on calf mortality rates. Similarly, spraying the navels of lambs with iodine spray or applying clamps to the navels failed to change the incidence of joint ill in lambs compared to no treatment.[259]

A significant beneficial effect was observed when the navels of calves that had assisted deliveries were dipped with chlorhexidine; other navel treatments such as iodine tended to be associated with increased odds of dying.[260] Chlorhexidine has a wide antimicrobial spectrum, long duration of activity, and high efficacy in the presence of organic matter.[261] In a controlled clinical trial investigating the efficacy of navel dips, a reduction in the incidence of omphalophlebitis was observed in calves when navels were dipped with tincture of iodine (7% iodine), dilute iodine (0.5% or 0.2%), or a commercial product (Navel Guard [NG], Sirius Chemical Group, McDonough, Ga.) as compared to calves with nondipped navels.[255] Conversely, navel treatment with iodine was associated with significantly higher mortality in another study of 48 farms; however, the association of navel treatment with mortality on these farms may have reflected the response of producers to high neonatal mortality rather than indicated that iodine navel treatment is a risk factor for high calf mortality.[262]

It is interesting to note that navel treatment has been associated with both a reduced[263] and an increased[264] risk of respiratory disease. The bases of these associations are unclear.

Nutrition

Although the neonatal calf stomach has four parts, the rumen is not functional at birth. At birth the abomasum is the only truly functional part and has a capacity twice that of the other compartments. Liquid is shunted past the reticulorumen

into the abomasum via the esophageal groove. The groove is closed by a reflex that is stimulated by the intake of liquids (milk is best, electrolyte and glucose water is usually effective, but straight water becomes ineffective in closing the groove fairly early in life). The first enzyme to start the process of milk digestion is salivary lipase. When whole milk enters the abomasum, casein is denatured by the acidic (pH 2.0) conditions. Rennin cleaves a specific peptide bond in κ-casein, which in the presence of calcium ions causes coagulation of the casein proteins. Fat is entrapped within the coagulum, but the whey proteins, lactose, and soluble minerals and vitamins are excluded into the liquid portion (whey) as the coagulum contracts. The soluble components enter the small intestine within 2 to 3 hours after a meal, whereas the casein coagulum is digested more slowly.[265] Casein is partially digested by the abomasal protease pepsin. Polypeptides released from caseins enter the small intestine for further digestion. Milk fat trapped in the abomasum undergoes some digestion by the enzyme pregastric lipase, which is secreted in the mouth. The products of its action are diacylglycerols and free fatty acids, which enter the small intestine for further digestion and absorption. Lactose is hydrolyzed to its component sugars, glucose and galactose, by the intestinal brush border enzyme lactase, and the monosaccharides are absorbed into the epithelial cells by specific active transport proteins.[265] The age at which ruminal digestion begins depends on the diet of the calf. Transition to ruminal digestion begins at 3 to 4 weeks of age; the earlier dry feed is provided, the earlier ruminal development starts.

The energy requirements of the calf may be divided into maintenance and growth requirements, with the magnitude of maintenance requirements influenced by environmental conditions. The basal maintenance requirement for neonatal calves is between 44.7 and 52.4 kcal/kg/day.[266,267] Energy requirements for growth are between 268 and 307 kcal/100 g of body weight gain.[267,268] Since whole milk contains about 70 kcal/100 mL, a 40-kg neonatal calf needs about 3 L of whole milk for maintenance and an additional 4 to 5 L to gain 1 kg of body weight. Cold stress significantly increases energy requirements. A 40-kg calf at –20° C requires 3.31 Mcal/day to meet maintenance requirements and maintain body temperature compared to only 1.59 Mcal/day at 20° C.[265] Similarly heat stress increases maintenance energy requirements by 20% to 30%.[265] The energy requirements of calves managed at different temperatures are presented in Table 19.4. The requirements for a sick, stressed calf are not well established.

Table 19.4

Maintenance Requirements for Metabolizable Energy as Affected by Body Weight and Environmental Temperature in Calves Less Than 21 Days Old

BW (kg)	Environmental Temperature (° C)				
	20	10	0	−10	−20
	(Maintenance ME, Mcal/day)				
30	1.28	1.63	1.97	2.38	2.67
40	1.59	2.02	2.45	2.96	3.31
50	1.88	2.39	2.90	3.50	3.91
60	2.16	2.74	3.32	4.01	4.48

BW, Body weight; *ME,* metabolizable energy.

Data from National Research Council: *Nutrient Requirements of Dairy Cattle,* ed 7, Washington, DC, 2001, National Academy Press.

Conventional milk replacers contain 20% to 22% crude protein (CP),[269] but calves benefit most from the increased feeding when milk replacers contain higher protein and lower fat (up to 30% CP with 15% to 20% fat).[269] Digestible protein requirement for maintenance is 0.5 g/kg, and the amount required for growth is about 22 g/100 g gain in body weight. Digestibility of the protein is an important concern in evaluating milk replacers. Some milk replacers substitute legume proteins for milk-derived proteins. Legume-derived proteins contain antinutritional factors that include antigenic proteins, lectins, and trypsin inhibitors.[270] Trypsin provides a protective mechanism against clostridial disease by cleaving the clostridial beta toxin.[271] Soybean flour has been used experimentally to induce *Clostridium perfringens* type C enterotoxemia in lambs.[272]

Many calves are raised according to the “calf starter method,” which became popular in the early twentieth century.[273] According to this method, calves are fed limited amounts of milk (approximately 10% body weight). Milk intake is limited to encourage intake of calf starter, facilitating weaning at about 7 to 8 weeks of age. Forage feeding is discouraged during the milk feeding phase, as it lowers starter intake. Rumen papillae growth is stimulated by production of volatile fatty acids (VFAs), in particular butyrate, which is highest in calves that are consuming larger volumes of starter.[274] During the last decade several studies have challenged the “calf starter method.” Limiting how much calves are fed has been shown to lead to poor weight gains[275] and a higher risk of disease

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and abnormal behaviors, indicating reduced calf welfare.[276] Providing greater quantities of milk or milk replacer improves growth and feed efficiency.[276] To achieve biologically appropriate growth, milk feeding rates are approximately twice those of the calf starter method. This calf feeding approach is often referred to as the "accelerated feeding" method. A rule of thumb is to provide 1.5% of body weight as milk solids during the first week of life, then 2% of body weight from the second week of life until the week before weaning, when one feeding is dropped.[277] Intake of starter lags behind that of calves fed on conventional systems, but increases at approximately the same rate once the amount of liquid is cut back.[277] To avoid or minimize growth slumps around weaning, calves should not be weaned until they are consistently eating 1 kg of starter daily.[265] With accelerated feeding programs it is not uncommon to see a postweaning growth slump. This may reflect poor rumen development due to delayed starter intake. Subclinical acidosis may also be a problem when well-grown calves with poor rumen development eat larger volumes of starter. Variable manure quality in a pen of calves is commonly observed in this scenario. Calves may also have a preoccupation with chewing on inanimate objects in the pen and an increased incidence of respiratory disease. The link between subclinical ruminal acidosis and risk of pneumonia is recognized in beef feedlots, but the mechanism is not yet known.[278] Starter intake, nutrient composition, physical form, and palatability along with the age of the calf affect the risk of rumen acidosis. Experimental trials that feed forage to preweaned dairy calves have produced inconsistent results. The fermentation rate of a starter formulation influences the risk of rumen acidosis and the need to include forage in the diet. Grain type, particle size, and processing affect the fermentation rate of starch in the rumen. Trials in which provision of forage increased starter intake tended to be those feeding a pelleted starter. Conversely, trials in which forage had a negative or no effect on starter intake have often involved the feeding of a textured starter where starch fermentation is slow.[279]

A rule of thumb for preweaning growth is for calves to double their birth weight by time of weaning at 7 to 8 weeks of age. Higher rates of growth observed early in life are associated with reduced breeding age[280] and higher milk yield when the calf matures.[281] One study reported that approximately 25% of the variation in first-lactation milk production could be explained by preweaning average daily body weight gain.[281] Subsequent studies have reported variable milk production responses to preweaning growth. A more recent meta-

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analysis reported a positive yet less dramatic relationship between first lactation performance and preweaning average daily weight gain; however, the magnitude of the relationship was less than the relationship between the postweaning and puberty periods.[282,283]

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Clinical Investigation of Neonatal Disease

The principles of clinical investigation of neonatal disease are similar to those for adults; however, the neonate signalment carries with it a higher risk for sepsis, congenital malformations, and a number of specific neonatal diseases, resulting in a shift in the emphasis of history, physical examination, and diagnostic work-up. When a single individual is involved, observation from a distance, recording of vital signs, and a physical examination guide the clinician to the selection of appropriate diagnostic tests to establish a cause, make a diagnosis, and evaluate the prognosis. For conditions that affect a flock or herd of animals, the examination of affected individuals remains an essential component of the diagnostic work-up, but evaluation of records, the environment (housing and other animals), nutrition, colostrum, treatment, and vaccination protocols is also needed.

History

The investigation of neonatal disease problems is facilitated by the defined period of risk and temporal distribution of the more common disease syndromes. For health problems involving individuals or the flock or herd, it is best to start at birth and work forward. For the individual a history of dystocia indicates the likelihood of neonatal compromise and the possibility of failure of passive transfer. The risk of specific diseases may be influenced by pathogen-specific immunity, which may be manipulated through either maternal or neonatal vaccination. Details of the farms vaccination protocol should be collected. The specifics regarding the timing of vaccination are important, as timing influences the likelihood of achieving effective immune specific passive transfer. At a herd level the likelihood of FPT and the efficacy of maternal vaccination are determined by colostrum management. From a herd perspective it is important to determine the farm's protocol for harvesting, storing, and administering colostrum, as these protocols determine immunoglobulin and microbial quality and the likelihood of achieving adequate passive transfer.

Risk of neonatal infectious disease is determined by the balance among host immunity, environment, and pathogen dose and virulence. Management should

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strive to maximize host immunity through good colostral management and provision of adequate nutrition and by minimizing environmental stress. The risk of pathogen exposure is influenced by environmental conditions at birth, amount of time spent with the dam, facility hygiene, colostrum and milk hygiene, personnel hygiene, and neonate age grouping. Defining the onset and progression of disease is useful, as certain diseases are more likely to occur at different times. Response to treatment or lack thereof may provide clues regarding pathogen involvement, and details of treatment protocols may identity inappropriate, ineffective treatment. Occasionally disease is iatrogenic, so it is important to collect details of all products administered, specifically time, volume, frequency, and route.

Examination From a Distance

The physical examination begins with examination from a distance, with assessment of behavior, body condition, and stance. Drooping of the head and ears is an early sign of illness. Sick calves spend increasing amounts of time recumbent and are less inclined to drink. In beef calves, lambs, and kids this may be reflected by udder distention in the dam. With dairy calves the calf feeder reports that the calf requires stimulation to stand and fails to drink. Abdominal contour should be noted, with consideration of the neonate's reported appetite; an abdominal contour that appears normal may actually be abnormal if the calf has not eaten for a couple of days. Observing the neonate navigate its environment provides a simple assessment of vision. From a distance, mentation, posture, vision, abdominal contour, stance, lameness, respiratory rate, breathing effort, characters of nasal and ocular discharge, and spontaneous coughing can be evaluated. Abnormal postures exhibited by patients with respiratory conditions may be recumbency, open-mouth breathing, abnormal extension of the head and neck, head tilt, or reluctance to lie down. Abnormal breathing characteristics include prolongation of the inspiratory or expiratory phase of respiration, an expiratory abdominal press or snap, marked tachypnea, frequent spontaneous coughing, stridor, or inspiratory or expiratory noises. Abnormal mentation of neonatal ruminants may be the result of meningoencephalitis, hypoglycemia, hypoxic ischemic encephalopathy, calving injury, or severe metabolic acidosis. Abnormal posture of the head and neck are exhibited by neonates with respiratory difficulty, but meningoencephalitis, otitis media, hypernatremia, polioencephalomalacia, congenital defects of the central nervous system, and

lasalocid toxicity should be considered.

Examination from a distance on-farm also provides an opportunity to assess the neonate's environment. Environmental and/or management-induced compromise in the form of inappropriate stocking density; mixed age-groups; inadequate ventilation or shade; wet, muddy conditions; moldy bedding; inadequate protection from adverse weather; evidence of poor hygiene; inappropriate feed on offer; and excessive fly challenge may all contribute to the risk of disease.

With the increasing use of robotic calf feeders, a plethora of data is available on farms that use this technology to monitor calf behavior. Reductions in drinking speed, unrewarded visits, and milk consumed may be observed 3 to 4 days prior to overt clinical signs of disease.[284] The onset of change in these parameters relative to detection of clinical signs is dependent on disease type, with changes observed earlier in association with diarrhea than pneumonia.[284]

Hands-on Examination

Physical Appearance, Body Weight, and Body Condition.

It has been increasingly recognized that genetics influences the risk of perinatal mortality, with the heritability for perinatal mortality ranging from 0.03 to 0.13.[285] Congenital disorders may present with subtle changes in physical appearance and behavior. For example, Salers calves with beta-mannosidosis have moderately domed heads, mild superior brachygnathism, and a slight head tremor.[286] Similarly, in utero infections that lead to growth retardation may be reflected by low birth weight and poor body condition. Low birth weight, contracted tendons, and/or abnormal mentation should prompt consideration of testing for persistent infection with bovine viral diarrhea (BVD).

Head.

Observation of facial expression provides an opportunity to assess cranial nerve function. Normal eyeball position and movement is consistent with normal function of cranial nerves III, IV, VI, and VIII. Normal facial expression and ear and eyelid position suggest normal functioning of cranial nerve VII. Vision (cranial nerve II) is assessed by watching the neonate navigate its environment. Because the menace response is learned, it is not particularly useful in very young animals. Normal sucking behavior is consistent with normal functioning

of cranial nerves V, VII, IX, and XII. Absence of atrophy of the neck is consistent with normal functioning of cranial nerve XI. Functioning of cranial nerves V, VI, and VII are further assessed by the palpebral and corneal reflexes, and cranial nerves II and III are assessed by the pupillary light response. Eyeball position and skin tent duration are used to assess dehydration and estimate base deficit in calves with diarrhea (Table 19.5).

Table 19.5

Assessment of Hydration and Acid-Base Status of Neonatal Calves With Diarrhea

Clinical Signs	Demeanor	Skin Tent Duration (Seconds)	Eyeball Recession (mm)	Dehydration (%)	Approximate Base Deficit (mmol/L)
Minimal clinical signs, suck reflex present	Normal	<1	None	5	5
	Slightly depressed	1-2	2-4	6-8 (mild)	10
Suckling decreased, cool extremities	Depressed	2-5	4-6	8-10 (moderate)	15
Very weak or absent suck reflex, cold mouth and extremities	Comatose	5-10	6-8	10-12 (severe)	20
Absent suck reflex, hypothermia	Comatose/dead	>10	8-12	>12	>20

Adapted from Ravary-Plumioen B: Resuscitation procedures and life support of the newborn calf. *Rev Med Vet* 160:410, 2009; Constable PD, Walker PG, Morin DE, Foreman JH: Clinical and laboratory assessment of hydration status of neonatal calves with diarrhea. *J Am Vet Med Assoc* 212:991, 1998; Smith GW: Treatment of calf diarrhea: oral fluid therapy. *Vet Clin North Am Food Anim Pract* 25:55, 2009.

Depressed mentation is a feature of a number of neonatal diseases. Sepsis and diarrhea are both commonly associated with depressed mentation secondary to toxemia and/or metabolic derangements. Bacterial meningitis is common in neonates following bacteremia; diarrhea, septic arthritis, omphalophlebitis, and uveitis are frequent concurrent clinical problems. The clinical signs of meningitis in neonates (lethargy, anorexia, recumbency) are nonspecific. Concurrent metabolic derangements may appear to provide an adequate explanation for the observed depressed mentation. In a retrospective study of 32 cases of bacterial meningitis in calves, concurrent metabolic derangements included hyperkalemia (15 of 25, 60%), respiratory acidosis (11 of 24, 46%), hypernatremia (3 of 20, 15%), and hypoglycemia (3 of 7, 43%).[287] The more classical clinical signs described for bacterial meningitis in older animals (fever, opisthotonus, extension of the head, convulsions, hyperesthesia, signs of neck

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pain) may not be evident or perceived in neonates. Seizures in calves are often subtle, manifesting as facial twitches or jaw champing. Common causes of cerebral disease in lambs and kids include polioencephalomalacia and focal symmetric encephalomalacia. Affected animals are typically depressed and blind but have normal pupillary light reflexes.

Mouth.

Examination of the mouth includes assessment of the mucous membranes, moisture, color, and capillary refill time. Mucous membranes should be moist and pale pink with a capillary refill time of less than 2 seconds. Gray or cyanotic mucous membranes are associated with severe hypoxia, circulatory collapse, hypovolemic shock, cardiovascular anomalies causing a right-to-left shunt, and/or severe pulmonary disease. Absence of cyanosis is not a reliable indicator of adequate oxygenation in the neonate since the partial pressure of oxygen may reach very low levels (<35 to 40 mm Hg) before cyanosis is observed. Cardiac and pulmonary causes of cyanosis must be distinguished. Petechiae on the oral or nasal mucous membranes are consistent with sepsis-induced vasculitis or thrombocytopenia induced by type II BVD (Fig. 19.1). Proliferative lesions may be observed with bovine popular stomatitis in calves or Orf in lambs. Oral erosions are often observed with BVD infections in calves. Common congenital defects include cleft palate and brachygnathism (inferior and superior). The hard and soft palates should be evaluated; animals with cleft palate may have milk run from the nose and are prone to developing aspiration pneumonia. Examination of the mouth should include assessment of breath odor. A malodorous breath may be present with necrotic pharyngeal injuries, necrotic laryngitis, cleft palate, or aspiration pneumonia. Application of slight pressure on the larynx exacerbates inspiratory stridor associated with necrotic laryngitis. Airflow from each nostril should also be assessed. Conditions causing occlusion of the upper airway—such as choanal atresia, necrotic laryngitis, and pharyngeal swelling or edema—often induce pronounced inspiratory dyspnea, stridor, and/or open-mouth breathing.

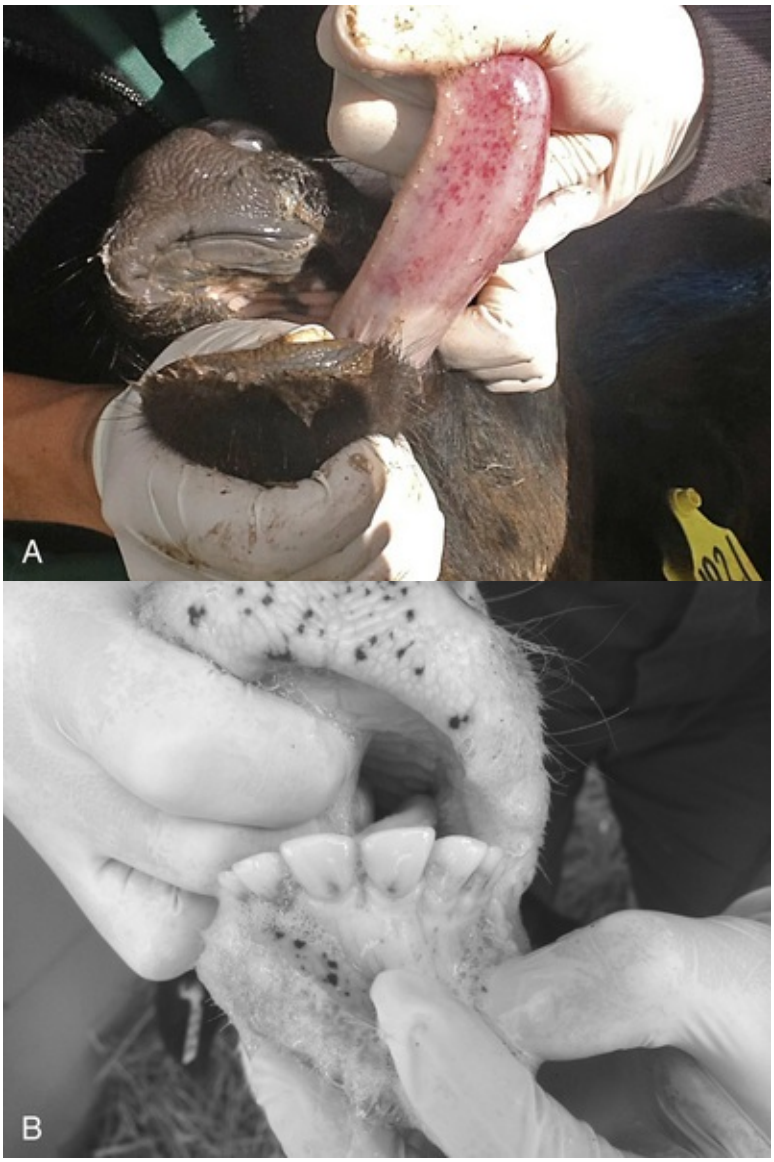


FIG. 19.1 **A,** Petechial hemorrhages on the underside of the tongue of a calf with thrombocytopenia. **B,** Petechial hemorrhage on gums.

Eyes.

Eyes should be examined for the presence of entropion, ectropion, corneal abrasions or ulcers, uveitis and hyphema, congenital cataracts, microphthalmia, corneal dermoids, scleral injection, and scleral hemorrhage. Entropion is a relatively common cause of corneal edema and ulceration, conjunctivitis, and lacrimation in lambs. It should be corrected promptly before serious corneal ulceration and keratitis develop. Mild cases may respond to subcutaneous injections of procaine penicillin G into the lower eyelid. Alternatively, entropion

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may be corrected by placing vertical or horizontal mattress sutures in the affected eyelid. Treatment following correction of entropion includes topical administration of 1% atropine to dilate the pupil and relieve ciliary body spasm and topical antibiotics to prevent bacterial infection.

Examination of the sclera is useful to detect icterus, scleral injection, and scleral hemorrhage. Icterus may be observed secondary to liver or hemolytic diseases; both tend to be uncommon in neonatal milk-fed ruminants. Conversely, scleral injection is a common finding and suggests sepsis. Observation of fibrin in the anterior chamber of the eye of a neonate is highly indicative of sepsis. Ecchymotic hemorrhages may be observed on the sclera with type II BVD infections, bovine neonatal pancytopenia, or disseminated intravascular coagulopathies, or following birth trauma.

Ears.

Bilateral drooped ear carriage is a common observation in sick calves and should prompt a closer examination. Unilateral ear droop may be observed with otitis and facial nerve paralysis. *Mycoplasma* spp., *Pasteurella* spp., and *Haemophilus* spp. are reported to cause otitis in calves. Clinical signs may include facial and vestibular nerve deficits and a purulent discharge from the ear. Calves infected with *Mycoplasma* spp. may also present with tenosynovitis and respiratory disease. Poor perfusion is reflected by cold extremities. A high incidence of pinna abscesses usually reflects contamination of equipment used to place ear tags. Ears should be warm and mobile.

Neck and Back.

There are a number of congenital anomalies that affect the alignment of the vertebral column. These include atlantoaxial malformations, scoliosis, kyphosis, lordosis, and combined anomalies, such as kyphoscoliosis. Atlantoaxial malformations may occur with or without cervical scoliosis or signs of spinal cord compression. Holstein calves affected by the hereditary condition complex vertebral malformation may present with a range of abnormalities that include retarded growth, malformation of the head (dysplasia or palatoschisis), bilateral symmetric flexion of the carpal and metacarpophalangeal joints, posterior arthrogryposis, and interventricular septal defects. Of these, growth retardation, vertebral malformation, and symmetric arthrogryposis are the most consistent findings.[288]

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The neck and brisket should be examined to evaluate jugular fill and to detect brisket edema. Distention of the jugular veins and brisket edema are consistent with right-sided heart failure but may be absent with left-sided heart failure. Examination of the skin on the side of the neck is a good place to detect lice and fleas, and a skin fold test is performed to assess hydration. Parotid and prescapular lymph nodes should also be palpated to assess size and symmetry. Enlargement of all peripheral lymph nodes may be observed with juvenile lymphoma. Enlargement of specific nodes suggests a localized inflammatory response.

Thorax.

Heart rate and respiratory rate vary with activity, excitement, and feeding. Tachypnea can be attributed to elevated temperature humidity index, fever, thermoregulation dysfunction, excitement, pain, stress, respiratory disease, hypoxia (cardiac disease, pulmonary disease, shock), dehydration, shock, toxemia, or metabolic acidosis. Periodic apnea and abnormally slow respirations are often the result of metabolic disturbances (hypoglycemia, hypocalcemia), hypothermia, prematurity, or hypoxia-induced suppression of the respiratory center. Tachycardia may be present with excitement, pain, injury, inflammation, toxemia, dehydration, shock, infectious disease, metabolic acidosis, hypokalemia, hypocalcemia, or heart disease. Bradycardia of neonatal ruminants may be associated with hyperkalemia, central nervous system dysfunction, hypothermia, or starvation.

Cardiovascular disease in neonates may be primary or secondary to other disease processes.

Congenital cardiac anomalies may be asymptomatic. Dyspnea and coughing are often the predominant clinical signs of congestive heart failure in calves. Cardiac auscultation should be carried out systematically with the aim of evaluating cardiac rhythm and detecting normal heart sounds and cardiac murmurs. In most calves the first and second heart sounds are easily audible. The third heart sound is not normally heard in calves, and the fourth heart sound is heard infrequently.[289] Cardiac murmurs are not uncommon during the newborn period. Various congenital anomalies of the heart occur in cattle as the result of defective septa and formation of the cardiac chambers.[290] The prevalence of congenital heart disease in cattle has been reported to be approximately 0.7%,[291] with ventricular septal defects representing the most

common type.[292] Other frequent defects include noncyanotic anomalies (atrial septal defect, patent ductus arteriosus without pulmonary hypertension) and cyanotic anomalies (tetralogy or pentalogy of Fallot, Eisenmenger's complex associated with reversion of a previously left-to-right shunt secondary to pulmonary hypertension).[290] The prevalence of the different congenital heart diseases in calves is shown in Table 19.6. Serious heart anomalies may not be accompanied by any murmur, whereas a closing ductus arteriosus may cause a murmur that is very loud. This normal ductal murmur is best ausculted on the left side of the chest at the third intercostal space at the level of the shoulder. In some instances, however, it is described as a continuous machinery-type murmur, but far more commonly a grade II to V/VI holosystolic murmur is ausculted. Cardiac auscultation will determine heart rate, rhythm, and the presence of murmurs. Abnormal radiation of heart sounds caudal to the fifth intercostal space or dorsal to the level of the scapulohumeral joint on either side of the thorax should be noted. Thoracic percussion may be used to identify the presence of thoracic fluid, cranioventral consolidation, or atelectasis in neonatal ruminants.

Table 19.6

Prevalence of the Most Common Congenital Heart Diseases in Calves, According to Ohwada and Murakami (2000)[a,290,327]

Congenital Heart Diseases	No. of Cases
Ventricular septal defects	198
Atrial septal defects	148
Double outlet right ventricle	66
Aortic stenosis	53
Double cranial vena cava	50
Patent ductus arteriosus	45
Anomaly of the caudal vena cava	42
Tetralogy of Fallot	32
Hypoplastic left ventricle	25
Transposition of the great arteries	24
Abnormal pulmonary vein connection	21
Total	704

[a]A total of 469 cases of congenital heart diseases were studied.

Cardiac arrhythmias are observed sporadically in neonates, often associated with diarrhea. Metabolic acidosis secondary to losses of electrolytes and water causes a transcellular shift of potassium ions into the extracellular fluid in exchange for hydrogen ions.[293] Hyperkalemia decreases the membrane potential

and slows down impulse conduction by inactivating sodium (Na) channels.[294] As serum potassium increases (>5.5 mEq/L), aberrations in cardiac excitability occur and are manifested as progressive atrial standstill, progressing to ventricular fibrillation and asystole.[295] The response of the myocardial cells to catecholamines decreases with the reduction of blood pH.[294] Influxed H^+ ions repress ventricle contraction by competing with Ca^{2+} ions in binding to myocardial troponins.[294] Tachyarrhythmias may be observed in calves with cardiomyopathies, ionophore toxicosis,[296] or hypomagnesemia.

Cardiomyopathy secondary to selenium deficiency, gossypol, monensin, or lasalocid toxicity may present as a syndrome of sudden death during periods of excitement precipitated by feeding or moving calves out of hutches into group pens.[297]

Inspiratory stridor is often a feature of extrathoracic airway obstruction, and increased abdominal effort on expiration is often an indication of pulmonary disease causing reduced lung compliance. Lung disease in the newborn is usually diffuse and is the result of infection acquired in utero or postpartum and/or lung atelectasis associated with immaturity, recumbency, or surfactant dysfunction. Signs of lung disease include increased work of breathing characterized by nostril flare, rib retractions, and increased abdominal effort. It is useful to palpate the ribs carefully to check for rib fractures, as these may also lead to tachypnea and dyspnea. A cough and nasal discharge, salient features of respiratory disease in older neonates, are infrequent findings in newborns with lung disease. Animals with few or no audible thoracic abnormalities may have severe respiratory disease.

Auscultation of the trachea, thorax, and occasionally the nasal passage are essential elements of the respiratory examination. Tracheal compression should not induce multiple coughs. Lung sounds of neonates are typically easier to hear than those of adults, but lung sounds do not always correlate well with the severity of respiratory condition that is present. Interpretation of the intensity of thoracic breath sounds can be validated by comparison to tracheal breath sounds. The intensity of tracheal breath sounds is gradually attenuated as the stethoscope is moved from trachea to the lung hilus, again to the anteroventral thorax, and finally to the caudal thorax in normal animals. Loud tracheal breath sounds that are not attenuated over the thoracic area may be indicative of atelectasis, lung consolidation, or cardiac enlargement. Added breath sounds such as crackles or wheezes should be noted but may not be heard without augmenting the depth

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and frequency of the breathing effort with the use of a rebreathing bag.

The advent of portable ultrasound machines commonly used on-farm for reproductive work provides a useful tool for assessing the thorax of calves. The pleural cavity and lungs can be examined through the intercostal spaces. The 5.0 to 7.5 MHz rectal linear transducers used for reproductive work are suitable for this task. Thoracic ultrasound has similar sensitivity (76.5%, 60.2% to 88.8%) for diagnosis of bronchopneumonia as auscultation but a higher specificity (92.9%; 86.5% to 97.1%).[298] In young calves, the lung fields extend cranioventrally from the tenth to the first and second intercostal spaces on the right and left sides, respectively.[299] When standing, it is easiest to scan reaching over the dorsum to the opposite side (Fig. 19.2). The transducing agent of choice is 70% isopropyl alcohol, and the hair is not clipped. Bronchopneumonia most commonly localizes to the cranial aspect of the right cranial lung lobe, followed by the right middle lung lobe and the caudal aspect of the left cranial lung lobe. The cranial aspect of the right cranial lung lobe is imaged from the right first and second intercostal spaces. The right middle lung lobe is imaged from the right fifth intercostal space, whereas the caudal aspect of the left cranial lung lobe can be imaged between the left fourth and fifth intercostal spaces.[299] It is important to scan both sides of the thorax because consolidation may occur unilaterally in up to 1 in 3 dairy calves. When imaging normal lungs the sound waves are reflected at the pleural surface, precluding visualization of the lung. Normal scans reveal a thin, white echogenic, moving pleural line. An increase in pleural fluid is reflected by separation of the visceral and parietal pleura; fibrin may be observed moving in the pleural fluid with the respiratory cycle (Fig. 19.3). Ultrasound is useful for identifying the optimal site for thoracentesis. The inundation of fluid in a consolidated lung provides an opportunity to visualize pulmonary architecture. Similarly, thoracic and/or pulmonary abscesses located adjacent to the thoracic wall may be imaged.



FIG. 19.2 Scanning calf lungs.



FIG. 19.3 Pleural effusion containing fibrin in cranial ventral thorax.

Abdomen.

Much can be learned about gastrointestinal function by observing abdominal contour, appetite, and fecal consistency and volume. A normal abdominal contour and vigorous appetite associated with the passage of an appropriate volume of pasty stool suggests normal gastrointestinal function. Examination of the neonatal ruminant should include assessment of abdominal size and contour.

Gradual abdominal distention may be observed with congenital atresia of the gastrointestinal tract (Fig. 19.4, *A*). Atresia may be observed in the colon (coli) (Fig. 19.4, *B*), rectum (recti), or anus (ani); the spiral loop of the ascending colon (spiral colon) is the most commonly affected segment of intestine in calves.[300] Neonates presenting with atresia often have a distended abdomen and a history of declining appetite. Astute owners may notice the lack or reduced volume of feces (Fig. 19.4, *C*).


A
B



FIG. 19.4 **A,** Atresia coli progressive abdominal distention. **B,** Atresia coli dilated proximal section of spiral colon and nondistended distal colon. **C,** Atresia coli—mucus with the absence of feces.

External palpation of the abdomen can be rewarding, depending on the cooperation of the animal and the tenseness of the abdominal musculature. In calves it is usually possible to palpate enlargement of the umbilical vein and arteries. The inguinal rings and umbilical area should also be palpated for hernias. Abdominal auscultation, while important, is not used for the forestomach and intestinal motility parameters typically evaluated in the adult ruminant; along with simultaneous auscultation and succession; however, ballottement, or percussion may show evidence of gas, fluid, or disordered motility. Abnormal forestomach function in neonatal ruminants is often reflected by altered abdominal contour. Left and right abomasal displacement and abomasal torsion are observed sporadically in calves. Succussion (simultaneous auscultation and percussion) is useful for delimiting the boundaries of distended visci. Passage of a stomach tube helps distinguish rumen and abomasal distention and facilitates collection of a rumen fluid sample. A putrid odor to neonatal rumen fluid is common with putrefactive indigestion when milk is delivered to the rumen in greater quantities than normal by escaping the esophageal groove or via excessive backflow from the abomasum. Reflux of abomasal contents into the reticulum and rumen, independent of feeding, occurs in connection with abomasal inflammation and obstructions.[301] Evaluation of rumen fluid pH and renin activity are useful for distinguishing abomasal reflux from esophageal groove overflow. Rumen fluid pH is usually 7 or higher with

rumen putrefaction and low to normal with abomasal reflux.[301] Chymosin (renin) is normally present in abomasal juice, and renin activity in rumen fluid suggests abomasal reflux.[302] Renin activity is measured by adding 2 mL rumen juice to 2 mL whole milk on a California mastitis test (CMT) plate. Presence of renin in the ruminal fluid causes coagulation of the casein in the milk. Chloride ion concentration in rumen fluid from calves is higher than in adults (55 to 102 mmol/L calves[303] vs 25 mmol/L adults[301]), possibly reflecting the high chloride content of milk (45 mmol/L); as such, the chloride concentration of rumen fluid is not useful for identifying abomasal reflux in calves.

Abomasal ulceration may lead to localized or generalized peritonitis. Normal peritoneal fluid from calves has a higher nucleated cell count than that of adult cattle (3350 cells/µL vs 1371 cells/µL). Total protein concentration in the peritoneal fluid of calves is similar to that in adults (2.5 g/dL vs 3.1 g/dL).[304]

Umbilicus.

After rupture of the umbilical cord, the two umbilical arteries retract actively, and the urachus is pulled back passively by these vessels into the abdomen. Smooth muscle contraction brings about luminal closure. The umbilical arteries ultimately become the lateral ligaments of the urinary bladder.

The umbilical vein does not retract but rather collapses in association with some minor smooth muscle contraction. The umbilical sheath shrinks and dries within 3 days postpartum. The body wall closes completely around the umbilical structures within days to a few weeks after birth.[305]

During the physical examination the navel is assessed for diameter, discharge, and pain while the neonatal ruminant is standing and again while it is in lateral recumbency. Abdominal palpation, using both hands pressing together, is useful for evaluating the umbilicus of standing calves. Enlargement of the umbilical arteries can be palpated coursing caudally toward the bladder and enlargement of the umbilical vein coursing cranially to the liver. Application of pressure caudal to the xiphoid often elicits a soft grunt from calves with a septic umbilicus and associated peritonitis. Extensive adhesion of bowel to inflamed umbilical structures produces a large, easily palpable intraabdominal mass. The uterine vein and artery may also be traced within the abdomen with the calf in recumbency. Common abnormalities of the calf umbilicus include umbilical hernias, omphalophlebitis, external umbilical abscess, urachal abscess, and omphaloarteritis. Patent urachus is uncommon in calves. Disorders of the

urachus or the umbilical arteries are often associated with pollakiuria and a prolonged stance of urination. Umbilical hernias in cattle do not tend to close spontaneously and are believed to be hereditary.[306]

Ultrasound examination of the calf is performed with the calf standing; occasionally the umbilical vein is easier to identify with the patient in left lateral recumbency.[307] The umbilical vein courses from the umbilicus to the liver, which in the calf is located on the right side. The lumen is generally larger near the body wall, with a diameter ranging from 10 to 25 mm. It appears as a round-to-oval anechoic to hypoechogenic structure. Within 3 weeks after birth, ultrasonographic identification of the intraabdominal umbilical vein becomes impossible in up to 50% of healthy calves. If still visible, the vein appears hypoechogenic to the surrounding tissue and indistinctly marginated.[305] In cattle the umbilical arteries and urachus retract into the abdominal cavity when the cord ruptures and thus cannot be identified in the external umbilical stalk in normal calves.[307] The umbilical vein of calves is scanned from the umbilical stalk to the liver along the right abdominal wall. The umbilical vein enters the liver caudoventral to the gallbladder. The umbilical arteries are most easily located adjacent to the urinary bladder and cannot normally be identified much beyond the apex of the urinary bladder, unless enlarged and abnormal. Identification of a urachal remnant in calves is abnormal.[307] Umbilical ultrasound is useful for evaluating the need for umbilical surgery and identifying other organs involved that may influence the complexity of the procedure (Fig. 19.5).

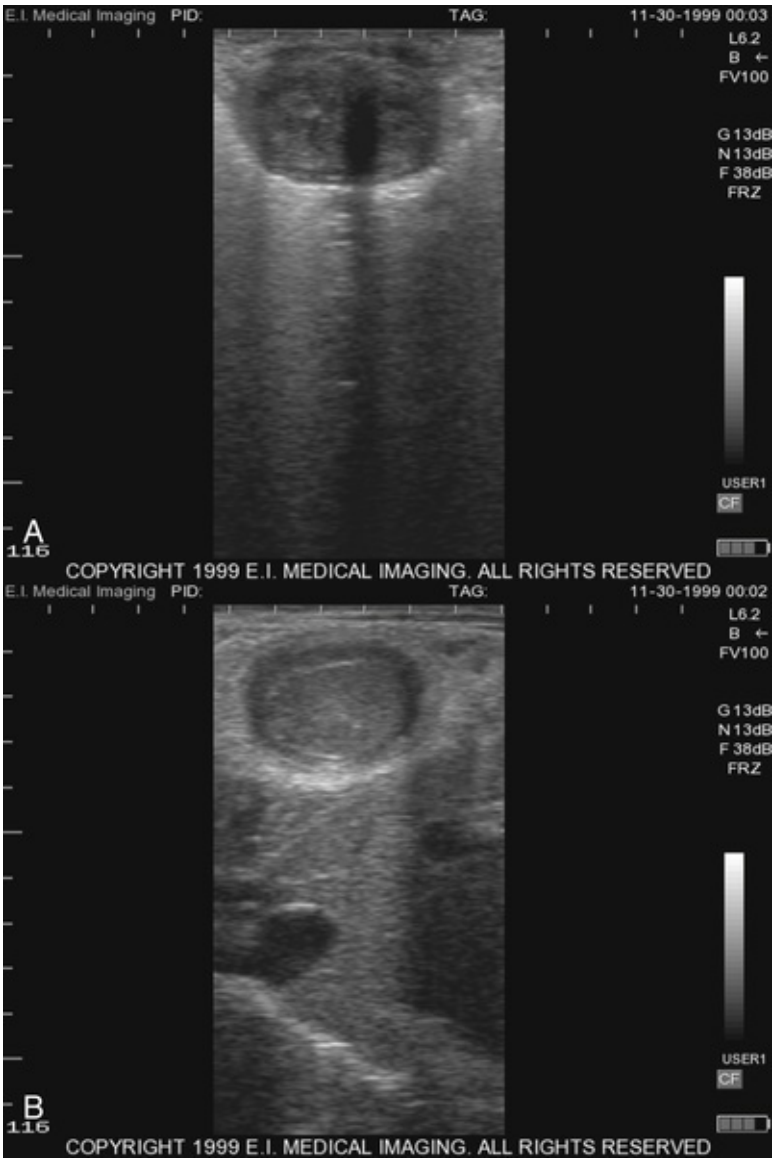


FIG. 19.5 **A,** Enlarged umbilical vein cranial to external umbilical stump. **B,** Enlarged umbilical vein just before entering the liver.

Musculoskeletal System.

The musculoskeletal system should be examined for evidence of birth trauma, including fractured ribs, long bones, and mandibles; brachial plexus injuries; and soft tissue trauma, which includes an edematous head and tongue from excessive traction or compression in the pelvic canal. The vertebral column, ribs, and limbs should be palpated carefully to elucidate swelling, heat, or painful areas. Strenuous manipulation during dystocia can result in Salter Harris type 1 fractures characterized by disruption of the distal physis in one or more limbs.

Femoral nerve paralysis occurs as a sporadic complication of dystocia associated with “hip lock” in calves.[308]

Dwarfism is a relatively common inherited problem in most cattle breeds. Osteopetrosis has been reported in Angus, Hereford, and Simmental breeds of cattle. Syndactyly is considered an inherited disorder in Holstein Friesan cattle, and affected animals are also predisposed to hyperthermia. Growth retardation, vertebral malformation, and bilateral symmetric arthrogryposis affecting the carpal and metacarpophalangeal joints are features of complex vertebral malformation in Holsteins, a genetic condition associated with a mutation in the gene *SLC35A3* coding a uridine diphosphate *N*-acetylglucosamine transporter.[288]

Peripheral pulses in the middle coccygeal, brachial, and auricular arteries should be strong and regular, and the peripheral extremities should be warm. Assessment of pulse quality includes consideration of pulse strength and frequency. Concurrent cardiac auscultation is useful to verify that heart rate and rhythm matches the pulse. With cardiovascular disease the pulse may be weak and/or uneven and may not correlate with the heart rate and rhythm.

The limbs should be examined for laxity, flexural, and angular limb deformities. Flexor tendon laxity occurs more commonly in calves born prematurely and in calves that are small for their gestational age. Unilateral or bilateral hyperextension of the tarsus can be encountered in newborn calves following forced extraction. A rupture of the peroneus tertius causes the hyperextension of the tarsus (Fig. 19.6). The gait is abnormal but does not appear to be painful.[309] Congenital contracted flexor tendon is a common defect in cattle; etiologic origins include inherited factors, in utero malpositioning, and overcrowding caused by the size of the fetus relative to the dam. Contracted tendons may occur with other congenital abnormalities, such as cleft palate, dwarfism, and arthrogryposis.[309] Arthrogryposis, abnormal fixation of joints because of damage to or contracture of soft tissues, may be hereditary, secondary to infection in fetal life with teratogenic viruses, or may result from ingestion of teratogenic plants. Following teratogenic viral infections, the clinical presentation is secondary to mild to extensive loss of ventral horn motor neurons in the spinal cord gray matter and Wallerian degeneration of ventral spinal motor nerves.[310] Hereditary congenital deformity in Hereford cattle is characterized by arthrogryposis, kyphosis, torticollis, scoliosis, and cleft palate.[311] Ingestion of lupines by pregnant cows between 40 and 70 days’ gestation has also caused various degrees of arthrogryposis with other associated congenital defects.[312]



FIG. 19.6 Peroneus tertius rupture. **A,** Standing. **B,** Extended, showing hyperextension of the tarsus with concurrent flexion of the stifle.

Skeletal muscle myopathy is an important differential for lame neonatal ruminants. Affected neonates may present with a history of falling behind the mob when mustered and dropping into sternal recumbency. Close examination reveals firmness of the triceps and quadriceps. Deep palpation of affected muscles elicits a pain response. Lambs and kids with selenium and/or vitamin E deficiency are often mentally bright, reluctant to stand, walk with a stiff gait, and cry when forced to move. Evaluation of serum creatinine phosphokinase, blood selenium, and plasma vitamin E concentrations is useful to confirm the diagnosis.

Any heat or cold, swelling, edema, pain around the joints or physes, or lameness should be noted (Fig. 19.7). Due to the propensity of neonates to succumb to sepsis, a swollen joint should be considered infected until proven otherwise. When sepsis is present it is not uncommon to observe enlargement of the corresponding prescapular or prefemoral lymph node in the affected limb. When multiple animals on the same property are affected, this may reflect an infectious etiology such as salmonellosis or mycoplasma; alternatively, poor colostral management may contribute to a high incidence of opportunistic infections of immunologically compromised neonates leading to joint ill. An inflammatory leukogram provides supportive evidence of a septic process, and aseptic collection of joint fluid for cytology and culture provides confirmatory evidence. When interpreting neonatal hematology and biochemistry results, it is important to be aware of age-associated normal values (Table 19.7).



FIG. 19.7 Calf with cold, swollen hind limbs and serum exuding through the skin on the left hock. The calf was developing gangrenous necrosis secondary to Salmonella *enterica* serotype Dublin infection.

Table 19.7

Normal Hematology Reference Values for Neonatal Calves[154,155]

Parameter	Age			
	Birth	24 Hours	48 Hours	3 Weeks
RBCs (1×10^6/μL)	9.35 ± 1.02	8.17 ± 1.34	7.72 ± 1.09	8.86 ± 0.68
Hgb (g/dL)	12.86 ± 1.85	10.93 ± 2.05	10.49 ± 1.8	11.32 ± 1.02
PCV (%)	41 ± 6	34 ± 6	32 ± 6	35 ± 3
MCV (fL)	43.2 ± 2.4	41 ± 2.8	41.1 ± 2.3	39.1 ± 1.9
MCHC (g/dL)	31.3 ± 1.1	32.1 ± 0.8	32.6 ± 1.0	32.8 ± 1.6
Total WBCs/μL	13.99 ± 5.73	9.81 ± 2.8	7.76 ± 1.95	8.65 ± 1.69
Neutrophils/μL	10,940 ± 5700	6480 ± 2660	4110 ± 2040	2920 ± 1140
Bands/μL	100 ± 150	310 ± 460	210 ± 450	10 ± 30
Lymphocytes/μL	2980 ± 2730	2730 ± 820	2850 ± 880	5050 ± 800
Monocytes/μL	590 ± 660	230 ± 210	350 ± 280	620 ± 330
Eosinophils/μL	0	20 ± 40	20 ± 30	20 ± 40
Basophils/μL	0	0.02 ± 0.05	0.02 ± 0.05	0.02 ± 0.04
TP (g/dL)	4.8 ± 0.3	6.4 ± 0.7	6.4 ± 0.7	6.4 ± 0.3
Fibrinogen (mg/dL)	258 ± 138	288 ± 105	335 ± 116	283 ± 147
Urea nitrogen (mg/dL)	6.36 ± 2.36	7.52 ± 2.13	7.52 ± 2.13	
Creatine (mg/dL)	4.14 ± 1.27	1.69 ± 0.35	1.27 ± 0.24	
Total bilirubin	0.34 ± 0.66	1.28 ± 0.5	0.89 ± 0.41	
Sodium (mEq/L)	141 ± 3.77	135 ± 2.86	135 ± 3.68	
Potassium (mEq/L)	6.1 ± 1.86	5.46 ± 0.56	5.63 ± 0.96	
Chloride (mEq/L)	97.39	95.76	95.28	
Calcium (mg/dL)	12.24 ± 1.64	10.22 ± 1.2	10.65 ± 0.56	
Phosphorus (mg/dL)	8.16 ± 1.39	7.22 ± 0.87	7.46 ± 0.87	
Creatine phosphokinase (U/L)	83 ± 42	531 ± 532	256 ± 364	
Aspartate aminotransferase (U/L)	18 ± 19	99 ± 18	72 ± 25	
γ-Glutamyl transferase (U/L)	8 ± 3	1761 ± 1058	846 ± 517	

Hgb, Hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean cell volume; *PCV,* packed cell volume; *RBCs,* red blood cells; *TP,* total protein; *WBCs,* white blood cells.

In older neonates metabolic bone disease should be considered as a differential diagnosis for lameness associated with flaring of the physis. Diets high in energy and protein that have low calcium and high phosphorus promote rapid weight gain, increasing the physical load on metabolically compromised growing bones. Damage to the growing physis may result in the subsequent development of angular limb deformities. Calcium deficiency in calves leads to reduced mineralization of bone. The transverse processes of the lumbar vertebrae become soft and bend when palpated. Copper deficiency causes metabolic bone disease that is manifested by physitis and brittle bones, reflected by a propensity to spontaneous fractures.

Posterior paresis is common in neonates; causes include border disease, enzootic ataxia, vertebral body abscesses, caprine arthritis encephalomyelitis virus, and vertebral body fractures associated with dietary copper deficiency (or secondary copper deficiency due to molybdenosis) or calcium phosphorous imbalance. These neurologic problems are discussed in Chapter 33.

Perineal Region

The examination from the rear includes assessment of body condition, measurement of rectal temperature, palpation of the coccygeal artery to assess pulse, examination of mucous membranes (female), and collection of urine and feces. Examination of the tail may also reveal evidence of diarrhea. Chronic diarrhea may be reflected by poor body condition and hair loss from the caudal surface of the rear hind limbs.

Body Temperature.

Rectal temperature in calves ranges between 37.2° and 38.9° C (99° and 102° F) during the first 4 days after birth. Abnormalities of vital signs in neonatal ruminants may be difficult to interpret, as a fever can be transient and patients with septicemia, infection, dehydration, or circulatory shock can be hypothermic or normothermic. Premature calves are prone to hypothermia.[313] Hyperthermia during the first week of life has been reported to be common in cloned calves.[314]

Feces.

In contrast to the adult, rectal palpation of the abdominal structures of the large animal neonate is of limited value. Small amounts of blood may be observed in the feces of healthy calves. Passage of blood and fibrin is associated with inflammatory bowel disease induced by pathogens such as *Salmonella* and coronavirus that damage the gastrointestinal mucosa. Passage of melena may be associated with infectious enteritis (e.g., clostridiosis, salmonellosis) and necrotizing enterocolitis due to hypoxic-ischemic bowel injury. Infectious diarrhea is the leading cause of mortality in calves between 3 and 21 days of age. Typically more than one pathogen is involved, and the physical examination provides no indication of the etiologic agent. Fecal pH may be used as an indicator to distinguish secretory diarrhea (enterotoxigenic *E. coli*) from diarrhea associated with malabsorption and maldigestion. Secretory diarrhea produces an

alkaline pH, whereas malabsorption and maldigestion are associated with an acidic fecal pH.[315] Infectious agents causing diarrhea and ancillary tests available to establish an etiologic diagnosis are discussed in Chapter 20.

Urine.

Normal urine osmolarity in the 2- to 3-day-old calf has been reported to be 286 to 391 mOsm/L, and urine volume voided is 34 mL/kg/day.[316] Congenital abnormalities of the urinary system include ruptured urinary bladder, ruptured ureter, ectopic ureter, blocked urethra, renal agenesis, fused kidney, and polycystic kidneys. Rupture of the urinary bladder at parturition is uncommon in ruminants. Hemodynamically mediated renal disease is observed sporadically in calves after chronic enteritis.[317] Prolonged reduced renal perfusion secondary to hypovolemia may lead to ischemia and acute tubular necrosis. Failure to thrive following apparent recovery from diarrhea may reflect compromised renal function.

External Genitalia.

The external genitalia of both sexes should be examined for congenital malformations. In the calf congenital defects described include ovarian aplasia, duplication of the cervix in Hereford cattle, persistence of the hymen (white heifer disease), and rectovaginal constriction in Jersey cattle. Congenital urolithiasis has been described in calves and lambs. Calcium oxalate is the most commonly reported congenital form of urolithiasis and may be associated with other congenital abnormalities.[318] A report of renal oxalosis in a number of Beefmaster calves suggests a possible recessively inherited metabolic defect resulting in primary hyperoxaluria in this breed.[319] Freemartins (XX/XY chimeras) occur in more than 90% of bovine[320] and 1% of ovine[321] female heterosexual twins. Typically freemartins are sterile and have hypoplastic ovaries and internal tubal genitalia; the external genitalia normally are not affected. Males should be examined for cryptorchidism and male pseudohermaphroditism, and both sexes should be assessed for evidence of hermaphroditism (gonads of both sexes).

Problem Solving

The process of diagnostic investigation for neonates is similar to that for adults.

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A problem list is developed at the conclusion of the physical examination. Differential diagnoses for each problem are considered, and the likelihood of differentials is ranked according to the history, signalment, and physical findings. This process progresses to a tentative diagnosis and development of diagnostic and treatment plans. Details regarding the presentation, diagnosis, and treatment of common neonatal diseases are presented in Chapter 20.

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• CHAPTER 20

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Manifestations and Management of Disease in Neonatal Ruminants

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Weakness and/or Depressed Mentation

Geoffrey W. Smith

If weakness has been present since birth, in utero–acquired bacterial or viral infections, birth asphyxia and trauma, chronic placental problems, and congenital anomalies should be considered on the list of differential diagnoses. A number of congenital, bacterial, fungal, and viral infections that cause abortions and stillbirths may result in the birth of a live but weak calf. In cattle, brucellosis, salmonellosis, leptospirosis, listeriosis, *Escherichia coli*, *Corynebacterium* spp., and *Aspergillus* spp. may cause placentitis and disease in the newborn. In sheep, in utero infection with chlamydia, *Campylobacter*, *Coxiella*, bluetongue virus, and border disease may cause disease in the newborn. Congenital viral infections of neonates are listed in Box 20.1. Clinical manifestations of fetal infections depend on the age of the fetus and the virulence and tropism of the infecting agent (see individual diseases).

Box 20.1

Differential Diagnoses for the Weak or Depressed Large-Animal Neonate

Bacterial Infection: In Utero or Postnatally Acquired

Septicemia
Joint and bone
Enteritis
Pneumonia
Meningitis
Peritonitis (primary or secondary)

Congenital Viral Infection

Bovine viral diarrhea virus (B)
Bluetongue virus (B, O)

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Infectious bovine rhinotracheitis virus (B)
Akabane virus (B)
Parainfluenza (B)
Caprine herpes (C)
Border disease virus (O)
Equine herpesvirus (E)
Equine viral arteritis (E)

Prematurity/Postmaturity

Weak calf syndrome
Bacterial or fungal placentitis
Insufficient fetoplacental matching (twin)

Birth Asphyxia

Placentitis
Dystocia
Cesarean section
Premature placental separation
Induced parturition
Birth trauma
Brachial plexus injuries
Fractured rib, pneumothorax, hemothorax
Ruptured bladder

Congenital Malformations

Cardiac malformations
Central nervous system malformations (e.g., hydrocephalus, hydranencephaly)
Angular limb deformities
Arthrogryposis

Metabolic Derangements

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Hypoglycemia
Hyponatremia
Hypokalemia or hyperkalemia
Hypocalcemia
Acidosis (respiratory or metabolic)
Uroperitoneum (with electrolyte abnormalities)
Renal failure

Severe Anemia

Blood loss
Neonatal isoerythrolysis

Brain Disease

Hemorrhage
Ischemia, edema, necrosis
Traumatic injury
Meningitis
Malformations
Narcolepsy-cataplexy syndrome (intermittent weakness)

Spinal Cord Disease

Spinal cord hemorrhage
Vertebral malformation (e.g., atlanto-occipital)
Vertebral abscessation or osteomyelitis
Vertebral fracture or other trauma to spinal cord

Peripheral Nerve and Muscle Disease

White muscle disease
Tetanus
Congenital myopathy, polymyositis
Neuropathy of spinal roots or peripheral nerves

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Botulism
Collagen disorder
Aminoglycoside-induced neuromuscular blockade

Liver Disease

Hepatitis
Severe hypoxic insult
Toxin (iron fumarate given to foals)

Storage Disorders

Maple syrup urine disease
Citrullinemia
Shaker calf syndrome (neurofilament accumulation)
GM1 gangliosidosis

Ingestion of Drugs or Toxins

Transplacental transfer of anesthetics and sedatives
Inadvertent oversedation of neonate

Gastrointestinal Disease

Gastrointestinal ulceration
Necrotizing enterocolitis

B, Bovine; *C*, caprine; *O*, ovine.

Neonatal calves with storage diseases primarily affecting the nervous system may appear reasonably normal for a short period after birth and then show progressive signs of neurologic dysfunction, including tremors, spasms, depression, recumbency, and coma. Differential diagnoses for weakness and depressed mentation after a period of apparently normal strength and mentation include sepsis, electrolyte and acid-base disturbances, hypoglycemia, and

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hypothermia. A complete history is obtained, including a detailed description of the delivery process, and complete physical and neurologic examinations are performed. Any signs of trauma, infection, or congenital malformations should be noted. Evaluation of hematologic data and immunoglobulin G (IgG) status, combined with historical and physical examination parameters, results in a high suspicion of sepsis. Blood glucose, blood gas, serum electrolyte concentrations, and passive transfer status should be determined promptly. Blood cultures and cerebrospinal fluid (CSF) analysis are useful for verifying central nervous system (CNS) involvement and targeting antimicrobial therapy.

Septicemia

Neonatal septicemia is the third most common cause of calf mortality in the United States (behind diarrhea and respiratory disease) and occurs most commonly in calves associated with failure of passive transfer (FPT). The phagocytic and bacterial killing function of polymorphonuclear neutrophils (PMNs) is a crucial component of the primary immune response against invading pathogens. Despite a larger number of neutrophils in the circulation of normal calves at birth, neutrophils from neonatal calves are functionally less effective than adult cells. Reduced Fc-receptor expression in neonatal PMNs may contribute to impaired phagocytosis and antibody-dependent cellular cytotoxicity.[1-3] Depressed PMN bacterial killing[4] may be related to reduced superoxide anion[5] and myeloperoxidase-hydrogen peroxide-halide antibacterial activity.[3] Adult-level superoxide activity in fetal PMNs suggests that some of the deficits in neonatal PMN function may be a manifestation of perinatal PMN suppression.[6] Calves have elevated cortisol levels for the first 10 days of life, which may contribute to depression of neutrophil function.[7] Dexamethasone depresses neutrophil phagocytosis, antibody-dependent cellular cytotoxicity, and bacterial killing.[8,9] Undefined serum factors also appear to be important for PMN function, as phagocytosis and bacterial killing by neonatal PMNs is similar to that of adult PMNs when bacteria are opsonized with adult serum but is reduced when bacteria are opsonized with neonatal serum.[4] T-helper cells (CD4+) play a central role in humoral and cell-mediated immunologic memory. Lymphokines produced by CD4+ cells, interleukin-2 (IL-2), IL-4, and interferon-γ (IFN-γ) are essential components of antigen-specific immunity. Virtually all IL-4 and most IFN-γ produced by polyclonally activated adult

human CD4+ cells is mediated by a subset of "functional memory cells."[10] Leukocyte production of IL-4 and IFN-γ is reduced in human neonates[10] and of IFN-γ is reduced in bovine neonates,[11] possibly reflecting their antigenically naive status. Depressed lymphocyte proliferation and IL-2 activity in the perinatal period correlates with elevated cortisol levels.[7]

Acquisition of humoral immune competence is age and antigen dependent.[12] Neonates are capable of producing humoral immune responses to good immunogens (protein antigens) but may fail to respond to lesser immunogens (sugars and lipids). Calves younger than 3 months of age that are vaccinated with modified live or killed salmonella vaccines produce an adult-type humoral immune response to salmonella protein antigens but do not respond to salmonella lipopolysaccharide.[13] Ingestion of colostrum suppresses the humoral response to some antigens but not others.[12]

Adverse management and environmental conditions further compromise neonatal immunity. Cold stress depresses neutrophil chemotaxis, and vasoconstriction reduces delivery of leukocytes to peripheral tissues.[14] Protein energy malnutrition in calves is associated with depressed lymphocyte IL-2 activity, lymphocyte proliferation, and humoral immune responses.[7] Micronutrient deficiencies also depress immunity. Selenium, zinc, copper, and vitamin E deficiencies depress lymphocyte and phagocyte function.[15,16]

Inherited defects in immune function are sporadically observed in neonates and should be considered when recurrent or atypical infections are observed, such as bovine leukocyte adhesion deficiency in Holsteins.

If invading bacteria are not quickly controlled by the immune system, they can establish focal infections in areas such as the joints, meninges, heart valves, or growth plates. Septicemia refers to a bacterial infection of the blood associated with adverse systemic signs. If not successfully treated, this can lead to multiple organ dysfunction, septic shock, and death. Meningitis is particularly difficult to treat successfully, and therefore prevention of septicemia through good colostrum management is essential.

Blood culture studies of debilitated calves indicate that gram-negative bacteria account for approximately 80% of bacterial isolates; *E. coli* is the most common bacterium isolated.[17-19] In a study of 190 recumbent calves on a large calf-raising facility, 31% were determined to be bacteremic; *E. coli* accounted for 51% of the isolates, other gram-negatives for 25%, gram-negative anaerobes for 5.9%, gram-positive cocci for 11.8%, and gram-positive rods for 5.9%.[17] Other

common bacterial isolates include *Salmonella*, *Campylobacter*, *Klebsiella*, and different *Staphylococcus* species. A summary of bacterial pathogens found to be responsible for septicemia is provided in Table 20.1. Polymicrobial infections are common in septicemic calves (28%).[19]

TABLE 20.1
Bacterial Species Found to Be Associated With Neonatal Septicemia in Calves

	Fecteau et al.[23]	Hariharan et al.[18]	Lofstedt et al.[24]
E. coli	26 (50%)	17 (65%)	29 (55%)
Klebsiella species	7 (14%)	0	0
Salmonella species	4 (8%)	0	0
Campylobacter species	2 (4%)	2 (8%)	8 (16%)
Staphylococcus species	4 (8%)	0	5 (10%)
Streptococcus species	2 (4%)	3 (12%)	1 (2%)
Other gram positives[a]	3 (6%)	2 (8%)	1 (2%)
Other gram negatives[b]	0	1 (4%)	4 (8%)
Anaerobic bacteria[c]	4 (8%)	0	1 (2%)
Total cases reported	51	26	50

[a]*Trueperella pyogenes, Bacillus* species, *Listeria monocytogenes*

[b]*Pseudomonas aeruginosa, Mannheimia haemolytica*

[c]*Clostridia* species, *Bacteroides* species, *Prevotella* species

Calves lack a normal adult intestinal flora, and when born in a heavily contaminated environment, colonization of the gastrointestinal (GI) tract with virulent bacteria may occur prior to the establishment of normal flora. Septicemia may also result from bacterial colonization of another site such as the umbilicus. Bacterial infection and the host inflammatory response should be differentiated. The immune response, in combination with the reticuloendothelial system, prevents the development of sepsis from an opportunistic or pathogenic invasion. However, this initiates an inflammatory cascade involving highly toxic mediators, which, if uncontrolled, will eventually lead to the systemic inflammatory response syndrome (SIRS) and subsequent multiple organ dysfunction syndrome (MODS). There is a balance between an appropriate yet effective immune response and an overzealous response to the bacteria or their toxins.[20,21]

The interaction between endotoxin (lipopolysaccharide) and the immune system triggers a complex inflammatory cascade involving cytokines and other

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inflammatory mediators. Initiation of the cascade results in the production of arachidonic acid metabolites, release of myocardial depressant factors, activation of the complement system, and production and release of many other mediators of sepsis.[20] The results include dehydration, tachycardia, pyrexia, leukopenia, hypotension, a decrease in systemic oxygen delivery and cardiac output, and generalized weakness. There is a severe and complex pulmonary vasculature response to endotoxin, leading to hypoxemia. Cattle are very sensitive to endotoxin, and even small doses can produce severe lung injury. Severe endotoxemia is frequently associated with death from respiratory failure in both calves and adult cattle. Therefore nonsteroidal antiinflammatory drugs (NSAIDs) are critical in blocking the formation of reactive metabolites (e.g., thromboxanes) and restoring lung function.

Neonatal septicemia should be seriously considered whenever there is multiple organ dysfunction or when severe cardiac and/or respiratory signs are encountered. Classic septicemia is described as a condition affecting newborn calves between 2 and 8 days of age. The progression is rapid and most often fatal. Very early in the disease, the clinical signs are vague, nonspecific, and likely attributed to other disease. An alteration in mental status ranging from a mild depression to coma is commonly observed. Lack of suckling ability or enthusiasm toward nursing are early nonspecific clinical signs.[20] Abnormal rectal temperature (fever or hypothermia) is not consistent; however, sustained tachycardia and eventually tachypnea develop. Hyperemia of the mucous membranes and scleral injection is frequently observed. Capillary fragility may initiate petechiation of the mucous membranes. Eventually, hypotension and clinical signs that are associated with poor cardiac output (slow capillary refill, diminished peripheral pulse, cold extremities, and decreased urine output) become prominent. Dehydration usually develops. Diarrhea is not present in all cases but is common in the terminal stages of septicemia. In a recent study investigating the clinical and laboratory findings of 1400 calves with diarrhea, clinical signs consistent with septicemia, including hypoglycemia, umbilical infection, or predicted sepsis using a scoring model, carried a higher risk for mortality than either clinical findings (poor suckle reflex, comatose) or other blood work abnormalities (severe metabolic acidosis).[22]

Early clinical signs of septicemia can be subtle and nonspecific. Sepsis scoring models have been developed for calves but lack good sensitivity and specificity.[23,24] The most useful parameters for predicting septicemia in calves as determined by these studies include toxic changes in neutrophils, FPT, presence

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of a focal infection, or elevated serum creatinine concentrations. Ultimately, the presence of clinical signs including lethargy, pyrexia, diarrhea, tachypnea, polyarthritis, uveitis, omphalitis, and meningitis, along with documented presence of FPT, should make the clinician highly suspicious of septicemia. If multiple clinical signs are present, the likelihood of disease is increased. However, the definitive diagnosis of septicemia can be based only on a blood culture. The jugular vein should be clipped and scrubbed prior to sampling. An amount of 10 mL of whole blood is drawn using a sterile syringe and needle, and the blood is placed into a blood culture bottle using a new sterile needle. Taking two samples (from blood collected 1 hour apart) is sometimes recommended to increase the chances of isolating the bacteria and to facilitate the interpretation of results if opportunistic or contaminating bacteria are found in one sample.[20] The bottle is then submitted to the laboratory for culture and susceptibility testing. If the bottle is not submitted immediately, it should be stored at room temperature or at 37° C. A negative blood culture must be interpreted with caution, since many factors may interfere with bacterial isolation from a blood culture. Cultures of other body fluids such as joint, cerebrospinal, peritoneal, or pleural fluids may be helpful for bacteriologic diagnosis whenever the blood culture is negative.

Some laboratory findings may increase the suspicion of septicemia. Hematologic abnormalities of septicemia vary with the severity of the disease. Abnormal neutrophil count (neutrophilia and neutropenia) and increased immature forms (bands) are frequently seen. Fibrinogen concentration is often elevated. Thrombocytopenia may be present in severe cases. One study of suspected septic shock in calves found that 8 of 12 calves had at least three abnormal coagulation parameters, most commonly activated partial thromboplastin time (aPTT) and prothrombin time (PT).[25] Hypoglycemia, or less often hyperglycemia, may be observed. A metabolic acidosis is also frequently present in septic calves. Lactic acidosis occurs as the disease progresses. Some calves will develop respiratory disease (respiratory distress syndrome) or pneumonia and will suffer from hypoxemia and/or hypoventilation.

Neonatal septicemia is a severe disease with high mortality. The primary goals of treatment are to (1) control the infection, (2) modulate the inflammatory response, and (3) support the animal during the disease. Treatment is based on selecting an appropriate antimicrobial drug and dosage, antiinflammatory therapy, and supportive therapy (including fluids). Differences between neonatal and adult animals in drug effects generally can be attributed to differences in

drug distribution, metabolism, or excretion. Some general characteristics of the neonatal period include better absorption of drugs from the GI tract, less drug binding to plasma proteins, increased apparent volume of distribution of drugs that are distributed in the extracellular fluid volume, increased permeability of the blood-brain barrier, and slower elimination (i.e., longer half-life) of many drugs. In general terms, antimicrobials have longer elimination times in neonates (<2 weeks of age) than adults, and as such larger doses are administered with a longer dosage interval to achieve similar peak and trough antimicrobial concentrations. Antimicrobial therapy should begin as soon as possible in order to minimize the bacteremia. The choice and the dosage of antibiotic depend on several factors, and personal preference, along with past experience, is often important. It is generally accepted that the intravenous route is preferable whenever possible and that broad-spectrum drugs are preferred. Appropriate antimicrobial choices include third- or fourth-generation cephalosporins (ceftiofur 5 to 10 mg/kg/day IM or IV have been used, although doses higher than the labeled dose of 2.2 mg/kg are now illegal in the United States), sodium ampicillin (10 to 20 mg/kg tid IV), and florfenicol, although even when given intravenously at the extralabel dosage of 20 mg/kg bid, it only exceeds the MIC_{90} value in plasma for 1 hour.[26] Combinations of drugs can be used to broaden the spectrum of activity (such as ampicillin-ceftiofur or ampicillin-trimethoprim-sulfonamide). Fluoroquinolones can also be effective in countries where their use is permitted. Once the pathogen has been identified and the susceptibility pattern determined (on the individual or on the farm), the most appropriate antibiotic can be chosen.

As just described, the inflammatory response if uncontrolled often causes severe clinical signs. Therefore NSAID therapy should be considered for ancillary treatment. Possible side effects of aggressive NSAID treatment include abomasal ulcers and renal toxicity, particularly in dehydrated animals. The duration of NSAID treatment is often limited to 2 to 3 days because of their potential toxicity. NSAIDs should not be continued for any longer than they are considered essential for survival.

Supportive treatments for septicemic calves include correction of secondary problems, administration of fluids, plasma transfusion, oral or parenteral nutrition, and oxygen administration. Problems that must be addressed include hypovolemia, hypoglobulinemia, hypoglycemia, metabolic acidosis, electrolyte abnormalities, and hypoxia. IV fluids (or oral as a compromise on the farm) should be administered. Dextrose (5%) combined with normal saline (0.9%)

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should be administered at a rate of at least 50 mL/kg/day. Nutrition is important, and septic calves either nurse reluctantly or are inappetant; as a result, they do not ingest an adequate amount of milk. If the animal refuses to nurse, tube feeding should be used to ensure that the calf ingests at least 10% to 15% of its body weight of milk per 24 hours. The feeding schedule may involve several (three to five) feedings per day and should be gradually increased in amount to prevent abdominal distention. If the GI system does not tolerate the tube feeding regimen, parenteral nutrition should be considered. There is usually no need for total parenteral nutrition, since most animals will continue to nurse or tolerate tube feeding up to 5% of their body weight.

Multiple cases of septicemia occurring on the same farm calls for careful inspection of the environment and management practices. Clusters of septicemia could be related to specific risk factors. As an example, feeding heavily contaminated colostrum could be the origin of the septicemia on some farms.[20,27] Prevention through excellent cleanliness and management practices is the most effective means of controlling and preventing neonatal sepsis.

Meningitis

Meningitis refers to an inflammation of the meninges and potentially brain. It represents an important complication associated with neonatal septicemia in calves. Exactly how bacteria get into the meninges is poorly understood. Multiple mechanisms have been proposed, including the development of a sustained and high-grade bacteremia in the highly perfused dural venous system and choroid plexuses, adherence of fimbriae from some strains of *E. coli*, or the phagocytosis of the pathogens by circulating monocytes and endocytosis through the microvascular endothelial cells.[20] What is apparent is that once they cross into the CNS, bacteria are able to survive and proliferate well in the poorly defended CSF. Complement is essentially nonexistent in CSF, and there are low numbers of antibodies, leading to inadequate clearance of pathogens from the CNS. Gram-negative bacteria also release endotoxin, leading to inflammatory infiltrates that cause thromboses of the arachnoidal or subependymal veins. Congestion or hemorrhagic infarction may follow, with subsequent necrosis of nerve cells. Inflammatory changes in the subarachnoid space may affect the choroid plexus, decreasing the absorption of fluid and potentially creating hypertensive hydrocephalus.[28]

Although bacterial meningitis may occur as a primary entity, it more

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commonly is a result of generalized septicemia in neonates with FPT. Agents that cause meningitis are the same agents that cause septicemia, most commonly the gram-negative enteric bacteria such as *E. coli*, *Enterobacter* spp., and *Salmonella* spp. In a review of 32 cases of meningitis in calves, the clinical signs of CNS disturbance observed were lethargy, recumbency, anorexia, loss of suckle reflex, coma, opisthotonos, convulsions, tremor, and hyperesthesia.[29] Leukocytosis and a left shift were evident in 11 of 15 calves (73%). Concurrent metabolic problems were common and included hyperkalemia, respiratory acidosis, hypernatremia, hyponatremia, hypomagnesemia, and hypoglycemia. Analysis of CSF revealed pleocytosis, xanthochromia, turbidity, and high total protein concentration. Cytologically, neutrophils predominated in the CSF in calves with acute disease. Mononuclear cells dominated in calves with chronic disease. Microscopically, bacteria were evident in 10 of 22 (45%) of the antemortem CSF samples, and bacteria were isolated from slightly more than half (11 of 19). All of the calves in this review died.[29]

Calves with meningitis are often presented because they have lost their suckle reflex and appear lethargic (Fig. 20.1, *A* and *B*). Previous treatment for diarrhea is common. Fever is often present unless NSAIDs have been given or if the animal is in an extremely cold environment. The calves may have an extended head and neck, and attempts to flex or reposition the neck can result in a tonic extension and thrashing of the limbs. Calves with meningitis almost always have abnormal mentation. As the disease progresses, profound depression develops and eventually the animal becomes comatose and nonresponsive or may develop seizures (Fig. 20.1, *C* and *D*). Presumptive diagnosis of bacterial meningitis is based on demonstration of FPT, presence of a septic focus such as omphalophlebitis or septic arthritis, and the presence of abnormal neurologic signs. However, the definitive diagnosis is based on an abnormal CSF analysis. Collection of CSF from the lumbosacral space is easy and safe in calves. For collection of fluid from the lumbosacral space, a 20-gauge, 1- to 2-inch needle with a clear hub may be used. A change in resistance is felt when the needle penetrates the dural membranes, and CSF appears in the plastic hub as soon as the subarachnoid space is entered. Approximately 5 to 10 mL of fluid may be removed safely.



FIG. 20.1 Calves exhibiting clinical signs of meningitis secondary to septicemia. **A,** The calf is depressed and maintains an extended neck when manipulated. **B,** The presence of fibrin and white blood cells in the anterior chamber of the eye (hypopyon) is suspected. **C and D,** Calves with more advanced meningitis exhibiting profound opisthotonus. Images reprinted with permission from Dore V, Smith G. Cerebral disorders of calves. veterinary clinics of north america-food. *Animal Practice* 2017;33:27.)

Urinary reagent strips can be used to rapidly obtain general information about the fluid. If blood is detected, the sample should be spun down after the cytologic examination. Red blood cells contaminating the sample will settle, and the supernatant should be colorless. If hemorrhage occurred before the procedure, the sample remains xanthochromic (yellow). Glucose should be present in “trace” or “positive” (+) amounts in the normal sample. Negative values in the adult suggest severe meningitis, but in the neonate they may also be caused by profound hypoglycemia. CSF analysis is most useful in determining the presence of septic meningitis. A summary of CSF findings from calves with meningitis is presented in Table 20.2. Generally an elevation in total protein and white blood cell concentration are strongly suggestive of meningitis, combined with a high percentage of the cells being neutrophils. The ratio of CSF to plasma glucose concentration is less than 1 in animals with bacterial meningitis because

of bacterial metabolism of glucose in the CSF. Xanthochromia (yellow color) is inconsistent. Free or intracellular bacteria may be observed in some cases. An elevated albumin quotient suggests increased blood-brain permeability and can be seen in both hypoxic-ischemic brain injury and meningitis, but an elevated IgG index indicates increased intrathecal IgG production and is more compatible with a diagnosis of meningitis.

TABLE 20.2
Cerebrospinal Fluid (CSF) Findings in Calves With Meningitis

	Normal	Green et al.[29]	Scott et al.[29a]
Specific gravity	<1.007	NR	1.011
Total protein	<0.4 g/L	3.07 g/L	3.2 g/L
White blood cell concentration	<10 cells/µl	4004 cells/µl	2400 cells/µl
Percent lymphocytes	>80%-90%	NR	Range of 1%-17%
Percent neutrophils	<10%-15%	73%	Range of 78%-100%
Culture positive		6 of 9 cases	11 of 19 cases

NR, Not reported.

When treating calves with meningitis in a hospital environment, the mortality rate is high; however, aggressive early treatment can be successful. The economics and welfare implications of treating commercial calves in a field setting are questionable. Empiric antimicrobial therapy for meningitis in neonatal calves should include a gram-negative and gram-positive spectrum. Antibiotics enter the CSF predominantly via passive diffusion down a concentration gradient. The major determinant of CSF penetration is lipid solubility. Lipophilic agents diffuse via transcellular pathways; peak concentrations in CSF occur relatively rapidly, and entry into CSF is affected minimally by the presence of inflammation. In contrast, hydrophilic agents enter the CSF through paracellular pathways; their transport depends on the opening of tight junctions, and peak concentrations are relatively delayed.[30]

The ratio of a drug in the CSF to blood generally gives a good indication of the potential for that antimicrobial to penetrate the CNS. Since very few of these studies have been conducted in animals, for the most part we extrapolate data from human medicine. Table 20.3 lists CSF-to-blood concentration ratios (penetration) derived from multiple species for a handful of antimicrobial drugs available for use in cattle.

TABLE 20.3

CSF-to-Blood Concentration Ratios (Penetration) of Antibiotics Available for Treatment of Meningitis in Calves[2,3]

	Concentration CSF/Concentration Serum (%)	
Antimicrobial[a]	**Human**	**Animals**
Ampicillin	13-14	8-12
Florfenicol		46 (calves)
Gentamicin	0-30	21-25
Penicillin	5-10	5-6
Trimethoprim-sulfamethoxazole	<41	35-39

[a]The list is not conclusive, reflecting the paucity of available data.

CSF, Cerebrospinal fluid.

It is also important to consider the safety margin of drugs. For example, the β-lactams don't diffuse very efficiently into the CSF, but they have a high safety margin and therapeutic concentrations can be achieved in the brain, since increased doses can be used without toxicity. In contrast, aminoglycosides diffuse relatively easily across the blood-brain barrier but likely represent a poor choice for meningitis, since standard doses are not high enough to achieve therapeutic concentrations in the CSF and higher-than-standard doses carry a high risk for nephrotoxicity.[28] Although broad-spectrum antimicrobials are indicated, *E. coli* is the most common isolate from meningitis cases and so should be the primary target of initial therapy. The choice of antimicrobial for treating meningitis will depend largely on the veterinary drug laws in the country where the calf is being treated. For example, common recommendations for meningitis treatment in calves have included ceftiofur (5 to 10 mg/kg q8h IM or IV) or enrofloxacin (5 mg/kg q12h IV).[20] Either of these would likely represent a reasonable option, but both are prohibited in the United States. Labeled doses of ceftiofur (2.2 mg/kg IM) could be used, or possibly sodium ampicillin (10-20 mg/kg q8h IV) could be tried. Another potential option would be potentiated sulfonamides such as trimethoprim-sulfamethoxazole dosed at 5 mg/kg (trimethoprim component) q8-12h IV. Potentiated sulfonamides could also be given concurrently with sodium ampicillin or ceftiofur to try to broaden the spectrum of activity. Intrathecal therapy (administering antibiotics directly into the CSF) has not been shown to improve outcome in human medicine and is likely too complicated for use in farm animals.[31]

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In a CSF pharmacokinetic study of florfenicol in calves, the maximum concentration of florfenicol attained in CSF was 4.67 ± 1.51 µg/mL following a single intravenous dose of 20 mg/kg.[26] The levels remained above the minimum inhibitory concentration (MIC) for *Histophilus somni* over a 20-hour period. This concentration is below the MIC_{90} for *E. coli.* Bactericidal antibiotics are proposed to be more effective for treatment of meningitis in humans, and it is recommended that the concentration of antibiotic in the CSF should be maintained at 10 times the MIC of the target pathogen.[30] Unfortunately, owing to the lack of CSF pharmacokinetic data in cattle, antimicrobial treatment of meningitis is an inexact science. Antiinflammatory therapy and nursing care should be instituted as described previously for neonatal septicemia. Convulsions in calves can be treated with diazepam (0.1 to 0.2 mg/kg IV). This can be repeated every 30 minutes until convulsions are controlled.

Metabolic Acidosis

Profound weakness associated with metabolic acidosis or “strong ion” acidosis is commonly observed in calves with diarrhea and sporadically in kids (“floppy kid syndrome”) and calves without other clinical signs of disease.[32,33] This acidosis is often associated with an increased concentration of D-lactate (the anion of D-lactic acid) resulting from bacterial fermentation of carbohydrates in the GI tract of milk-fed calves. Clinical signs of impaired CNS function, including ataxia and coma, in sick calves have been attributed at least partially to the increased D-lactate concentrations.[34,35]Assessment of weak neonatal ruminants for the presence of metabolic acidosis is a critical part of the physical examination. Correction of the acidosis by intravenous administration of bicarbonate produces a rapid recovery. An improvement in mentation and strength should be observed within 12 hours; persistent depression is likely to reflect incomplete correction of acidosis, sepsis, hypoglycemia, hypernatremia, or hyponatremia.

Hypoglycemia

Hypoglycemia is a common sequela to withdrawal of milk for more than 48 hours, especially in cold weather. Affected calves are weak or recumbent but appear to be normally hydrated or minimally dehydrated.[36] They are often emaciated and can occasionally have neurologic signs, including facial twitches, convulsions, opisthotonos, and coma. They will respond to a bolus of 50%

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dextrose or an infusion of 5% glucose, but often this response is temporary, especially in calves with severe malabsorptive disease. It is important to rapidly restore adequate energy intake to ensure resolution of these cases. Starvation and hypothermia resulting from mismothering are common causes of weakness in neonatal lambs. Similarly, weakness, poor body condition, and increased susceptibility to infectious diseases are observed with protein-calorie malnutrition induced by feeding poor-quality or incorrectly mixed milk replacers.[37] Hypoglycemia is also frequently seen in calves with neonatal septicemia, as discussed previously. In a recent study that reported serum glucose concentrations in more than 10,000 calves 3 weeks of age and younger, the presence of severe hypoglycemia (glucose ≤36 mg/dL or 2 mmol/L) was associated with a poor survival rate, as only 20.6% of these calves survived compared to 74.0% of calves with normal glucose levels.[38]

Hyponatremia

Hyponatremia occurs when loss of isotonic fluid through the GI tract is replaced by free water or hypotonic solutions. The latter often occurs when too much water is added when making up an oral electrolyte solution. Hyponatremia may also occur when isotonic oral electrolyte solutions are administered to calves with compromised sodium absorption capacity. This may be a result of severe pathologic changes or an inadequate level of agents that facilitate sodium cotransport within the oral electrolyte solution. Hyponatremia results in a fluid shift from the extracellular space to the intracellular compartment along the osmotic gradient, and the resultant swelling of the cells can result in neurologic disturbances, depression, disorientation, and even convulsions.[39] Hyponatremia should be considered in calves with serum sodium less than 132 mmol/L; calves with serum sodium less than 120 mmol/L have severe hyponatremia.

The goal of therapy is to restore serum sodium levels to greater than 125 mmol/L over the first 6 hours and then to restore to normal levels over 24 hours.[39] In hypovolemic calves the initial treatment should be achieved using normal saline, and in normovolemic calves hypertonic saline should be used for the initial treatment, since the administration of large fluid volumes will exacerbate cerebral edema. If the calves are also suspected to be acidotic, this should be corrected with sodium bicarbonate solutions of appropriate tonicity.

The amount of sodium required in the first 6 hours to raise the sodium level to 125 mmol/L can be calculated as follows.[39]

$$\text{mEq Sodium} = (125 - \text{Measured mEq serum sodium}) \times (0.6 \times \text{Body weight in kg})$$

Calves should then be maintained on a sodium-containing isotonic fluid, such as normal saline or lactated Ringer, and treated with oral electrolyte solution as appropriate. The sodium level should be monitored frequently in the first 24 hours because of unknown losses through the GI tract as well as unknown kidney function in a severely dehydrated patient.

Hypernatremia

Hypernatremia (also known as sodium or salt toxicity) is a relatively common problem encountered in young calves. These cases are generally a result of the calf ingesting excessive concentrations of salt without an adequate balance of water to balance the sodium load. The most common clinical scenarios involve calves ingesting milk replacers high in sodium without access to fresh water[40,41] or calves that are being treated for diarrhea and receive oral electrolyte solutions with high sodium concentrations.[42,43] Recently, cases of hypernatremia in calves have been observed associated with the use of high-sodium water on farms. Affected calves are typically younger than 3 weeks of age and often (but not always) exhibit neurologic signs.

The volume of the extracellular fluid (ECF) is determined by the total body sodium content, whereas the osmolality and sodium concentration of the ECF are determined by sodium and water balance. Multiple control mechanisms work in the body to detect and respond to changes in the osmolality and volume of the ECF. These homeostatic mechanisms primarily control retention and excretion of sodium. Examples of regulatory control include the thirst response (water ingestion) and excretion or retention of sodium by the kidneys. Although it sounds simple, these are under complex control by multiple hormonal pathways, including antidiuretic hormone (ADH), atrial natriuretic peptide (ANP), the renin-angiotensin-aldosterone system (RAAS), and the autonomic nervous system. A complete discussion of the physiology of sodium and water homeostasis is beyond the scope of this chapter, but readers are referred to other recent review articles for more detailed information.[44,45] When calves take in too much sodium, this results in expansion of the ECF at the expense of intracellular fluid (ICF) in order to return the osmolality of the blood to normal (relative dehydration). In cases where there is no water intake, fluid loss is associated with reduction in total body water content (absolute dehydration). In cases of

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hypernatremia, the brain has to adapt to the hyperosmolar state, which typically involves shrinkage of neurons as water follows concentration gradients and moves into the hyperosmolar CSF and plasma. This results in dehydration of neurons and brain shrinkage. As the brain moves away from the calvaria, disruption of the normal blood supply can occur.[44] Neurologic signs often worsen during treatment of calves with hypernatremia, since rapidly lowering the sodium concentration with free water will allow water to flow into neurons, causing the already shrunken cells to swell, resulting in cerebral edema. This edema can lead to seizures and in many cases death.[28] Hypernatremia is defined as a serum or plasma sodium concentration of 160 mEq/L or greater, and neurologic signs of salt toxicity can be seen. Serum sodium concentrations greater than 180 mEq/L generally indicate a guarded to poor prognosis. Sodium concentrations in the CSF of cattle normally range from 130 to 142 mEq/L but are typically above 160 mEq/L in animals with hypernatremia.[46] Ocular fluid represents a good sample to submit to the diagnostic laboratory in dead calves, since it does not change appreciably with advancing postmortem autolysis and provides a stable representation of sodium levels at the time of death. Ocular fluid sodium concentration is reported to be about 95% of the serum sodium value, and levels are significantly elevated in cattle with hypernatremia.[46] In cattle that are dead, the entire brain or cerebral cortex should be submitted to a diagnostic laboratory for sodium analysis and histopathology. Typically no gross lesions of the brain are apparent at necropsy in cases of hypernatremia, and histopathology is nonspecific with cerebral edema present. Therefore submitting fresh brain and/or ocular fluid for sodium analysis in addition to requesting histopathology is critical. Sodium concentrations in brain tissue are generally greater than 2000 µg/g (ppm) in calves with hypernatremia.

Early clinical signs of hypernatremia include lethargy and depression, which, without blood work, cannot be differentiated from many other possible diseases such as acidemia, dehydration, hypoglycemia, or hypothermia. More advanced clinical signs of hypernatremia include twitching of facial muscles, muscle rigidity, tremors, and myoclonus.[28,44,47] Calves will demonstrate seizure and/or coma activity near death. Prognosis in these calves is often guarded to poor even with aggressive treatment.

Treatment of calves with chronic hypernatremia is often very difficult and should be reserved primarily for valuable animals. Classic recommendations call for sodium concentrations to be lowered very slowly, since replacing free water

too rapidly could cause neurons to swell, cerebral edema, and a worsening of neurologic signs. The total body free water deficit can be calculated using the following formula:

$$0.6 \times \text{Body weight (kg)} \times ([\text{Current serum sodium concentrations}/\text{Normal serum sodium concentration}] - 1)$$

However, if this fluid is given rapidly, neurologic complications will often arise. In general the recommendation is to formulate fluids that have a sodium concentration approximately equal to that of the calf.[28,44,47] This can be done by adding small volumes of hypertonic saline (1.2 mEq/mL) or 23.4% sodium chloride (4 mEq/mL) to whatever fluid type you have chosen to give the calf. For example, if the calf has an acidemia, additional sodium can be added to isotonic sodium bicarbonate (sodium concentration of 156 mEq/L). However, if the calf has a relatively normal pH, additional sodium could be added to 0.9% saline (sodium concentration of 154 mEq/L). The idea is to decrease the sodium level of the calf very slowly over several days to avoid cerebral edema. A case example below will illustrate the calculation.

A 45-kg Hereford calf had clinical signs of hypernatremia. The calf had a serum sodium concentration of 187 mEq/L. To calculate the free water deficit in this calf we would multiple 0.6 × 45 × ([187 – 145) – 1)] to get a free water deficit of 7.82 L. In this example we used 145 to represent the “normal” serum sodium concentration for a calf. If we wanted to give 0.9% saline to this calf (154 mEq of sodium per liter), we would need to add 33 mEq of additional sodium to reach the calf's level of 187. The simplest way to do this would be to add a small volume of hypertonic saline (33 mEq/1.2 mEq/mL = 27 mL of hypertonic saline added per liter of fluids). You could also add hypertonic saline to isotonic sodium bicarbonate if the calf had an acidemia. Since isotonic sodium bicarbonate has a sodium concentration of 156 mEq/L, you would need to add 31 mEq of sodium. Be careful about adding large volumes of dextrose to these solutions, as that will lower the sodium concentration.

Although not always successful, a report of treating several hypernatremic calves with 5% dextrose either alone or in combination with sodium bicarbonate has been published.[42] In this study calves were given 2 to 4 L of 5% dextrose at a slow drip (about 500 mL/h) and had their serum sodium concentrations decreased much faster than is usually recommended. However, the four calves in

the case report were treated successfully. Although this approach may not always work and could easily result in cerebral edema, it may be practical for times when the clinician does not have the ability to formulate fluids or monitor serum sodium concentrations frequently. In calves with chronic hypernatremia where “idiogenic osmoles” have formed, it is likely critical to lower sodium levels slowly, whereas the clinician may be able to lower sodium more rapidly in cases of acute hypernatremia.

If the calf's neurologic signs get significantly worse after fluid therapy has started, cerebral edema should be suspected. Treating cerebral edema is difficult but imperative to prevent further brain damage and/or death. Corticosteroids are the easiest choice normally; however, they are only marginally effective in treating moderate to severe cases of cerebral edema. Mannitol (25%) at 1 g/kg given IV over 30 minutes or an oral solution of glycerin diluted 1 : 1 with water has also been recommended for severe cases of cerebral edema but can be more difficult to obtain.[28]

Hypernatremia is largely avoidable by proper management. Since hypernatremia occurs largely under one of two conditions—(1) calf ingests too much sodium without an adequate volume of water in a short period of time, or (2) sustained water deprivation—the key becomes preventing both of these conditions from occurring. Whole milk is typically fairly low in sodium concentration, so typically calves fed whole milk have little problem with sodium toxicity unless given a large amount of oral electrolytes. Some milk replacer products can have significantly higher sodium concentrations as compared to whole milk (up to 85 to 100 mmol/L). Water quality is another factor that can have a profound effect on the amount of sodium calves ingest. Water that has been through a softening process to remove minerals such as calcium and magnesium can often have very high sodium concentrations and therefore should not be used to dilute commercial milk replacers unless a water analysis has been performed and sodium levels are less than 100 ppm. In one case report of salt poisoning in calves, milk replacer samples diluted with farm water had sodium concentrations ranging from 171 to 185 mmol/L.[40] When cases of hypernatremia are diagnosed on a farm, veterinarians should not forget to consider the drinking water source as a possible source of excess sodium.

In addition to watching how much sodium we feed calves in their normal milk diet, attention must also be given to the feeding of oral electrolyte solutions in calves with diarrhea. When homemade oral electrolyte products are used or when labeled mixing directions are not followed correctly, sometimes the

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sodium concentration fed to calves can be extremely high. In some cases oral electrolyte products are purchased in bulk containers, and more powder is added to 2 L of water than indicated in the directions. Multiple case reports describing hypernatremia in calves have involved the feeding of unknown amounts of oral electrolyte solution to calves multiple times per day.[42,43] This situation is exacerbated when calves do not have access to fresh water or when the fresh water also contains high sodium concentrations. In one case report, hypernatremia was diagnosed associated with neurologic signs and deaths in a group of 6- to 10-month-old Holstein calves that had access to a salt block without free-choice water available.[48] So ultimately, paying attention to the calf feeding program and the diarrhea treatment (oral electrolyte) feeding protocol for the farm is critical, along with ensuring that calves always have a supply of fresh, good-quality water.

Neuromuscular and Musculoskeletal Disease

Primary neuromuscular or musculoskeletal disease should be considered when weakness is not associated with depressed mentation. Weakness associated with micronutrient deficiencies results from myodegeneration (white muscle disease, selenium, and vitamin E) or demyelination (copper, enzootic ataxia). If weakness is detected in one or more limbs immediately after birth, peripheral nerve and muscle damage associated with birth trauma should be ruled out (see Box 20.1). Femoral nerve paralysis may be observed in calves following a “hip lock” dystocia.[49] A condition resembling congenital myasthenia gravis has also been described in Brahman calves.[50]

Nutritional myodegeneration associated with selenium or vitamin E deficiencies may produce localized (dysphagia) or generalized paresis. Neonatal small ruminants appear to be particularly susceptible. Affected lambs may be unable to rise; others can stand but may be unable to nurse because they are unable to raise their heads. Diagnosis is based on clinical signs, increased serum creatine kinase concentration, and reduced whole blood glutathione peroxidase and/or selenium concentrations (see Chapter 42). Vitamin E deficiency is observed when pregnant ewes are fed stored forage low in vitamin E; the clinical signs in affected lambs are identical to selenium deficiency, but selenium status is adequate. Since vitamin E is labile, serum should be harvested quickly after blood collection, frozen, wrapped in aluminum foil, and sent via express mail on ice.

Paraplegia and tetraplegia are commonly associated with spinal cord compression. Compression of the spinal cord in neonates most commonly results from vertebral body malformations, osteomyelitis, or fractures. Generally vertebral body malformations occur sporadically; genetic, nutritional, and environmental factors have been implicated.[51,52] In older calves, underlying metabolic bone disease (copper, vitamin D, or phosphorous deficiency) may increase the propensity for fractures to occur. Osteomyelitis and vertebral body abscess may be sequelae to bacteremia following neonatal septicemia or pneumonia.[53] The frequent isolation of *Trueperella pyogenes* from vertebral body abscesses in ruminants suggests that chronic respiratory infection is more frequently the source in these species.[54,55] Vertebral body abscesses in lambs are occasionally a sequela to infected docking wounds. Leukocytosis and hyperfibrinogenemia are commonly observed in neonates with vertebral body abscesses. In most instances vertebral abscesses do not infiltrate the pachymeninges, so the CSF either is normal or has a mild elevation of protein and/or a mild pleocytosis.[53,54]

Differential diagnoses for paresis in goat kids include caprine arthritis encephalitis virus (CAEV) and enzootic ataxia. Enzootic ataxia is also common in lambs. Progressive ataxia and paresis or paralysis is a feature of both diseases. There are two forms of enzootic ataxia (swayback): the neonatal and the delayed types. In the neonatal condition, animals are affected at birth; in the delayed type, signs of incoordination appear at 14 to 30 days of age.[56] Most affected kids are afebrile, bright, and alert, and they will continue to eat if it is physically possible. Enzootic ataxia is associated with low liver copper content and occasionally low serum copper concentration. It has been proposed that reduction in the activity of the copper-dependent enzyme cytochrome oxidase impairs phospholipid synthesis and subsequently myelin production. Microcytic anemia and increased fragility of bones may be observed in more chronic cases.[57] The copper, molybdenum, and sulfur content of the maternal diet should be evaluated and adjustments made for copper deficiency or molybdenum or sulfur excess.

Goat kids with the neurologic form of CAEV will have mild to moderate fevers and evidence of cerebral involvement. Cerebral signs commonly identified include depression, head tilt, torticollis, and circling. Evidence for CAEV includes CSF pleocytosis and increased CSF protein and a positive CAEV (agar gel immunodiffusion, or AGID) or enzyme-linked immunosorbent

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assay (ELISA) test.[58] Both the neurologic form of CAEV and enzootic ataxia carry a poor prognosis.

A complete neurologic examination is an important component of the work-up of the weak neonate. In particular, it should be noted if the weakness is accompanied by signs of depression and diffuse cerebral disease. Strength is preserved if ataxia is caused by cerebellar disease. Limb reflexes should be tested to establish whether components of the spinal reflex pathways are involved in the disease process (sensory nerve, lower motor neuron, neuromuscular junction, muscle). Animals with other types of spinal cord disease (e.g., trauma, vertebral malformations, enzootic ataxia) may also show weakness and ataxia yet appear clinically to have normal cerebral function. Virtually any severe systemic disease such as generalized infection can cause both profound depression and weakness in a neonate without the presence of actual brain pathology. Intermittent signs of severe weakness and depression may be caused by the narcolepsy-cataplexy syndrome.

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Respiratory Difficulty

Sheila M. McGuirk

Respiratory conditions of the neonatal ruminant can be attributed to upper airway problems, pulmonary pathology, CNS dysfunction, cardiac disease, metabolic derangements, or other nonpulmonary disorders (Box 20.2).

Box 20.2

Causes of Respiratory Distress

Upper Airway Conditions

Pharyngeal trauma
Necrotic laryngitis
Choanal atresia (nasopharyngeal atresia)
Laryngeal edema
Tracheal malformation: stenosis, collapse

Developmental Disorders

Pulmonary hypoplasia
Diaphragmatic hernia

Lung Parenchymal Diseases

Pneumonia (bacterial or viral)
Atelectasis
Hyaline membrane disease
Pulmonary edema, congestion
Aspiration syndromes
Air leaks (e.g., pneumothorax)
Pulmonary hemorrhage

Transient tachypnea syndromes

Nonpulmonary Causes

Congestive heart failure
Central nervous system lesions
Metabolic derangements (e.g., acidosis, hypoglycemia)
Severe anemia
Hypovolemia
Fractured ribs
Nutritional myodeneration of thoracic muscles or diaphragm
Persistent pulmonary hypertension
Birth asphyxia
Pain, abdominal crisis
Fever, high environmental temperatures
Excitement
Pleural effusion (e.g., pleuritis)
Endotoxemia and gram-negative sepsis

Examination

A complete examination of the neonate is essential when clinical signs are indicative of a respiratory condition. When a single individual is involved, observation from a distance, recording of vital signs, and a physical examination guide the clinician to select appropriate diagnostic tests to establish a cause, make a diagnosis, and evaluate the prognosis. For respiratory conditions that affect a flock or herd of animals, the examination of affected individuals remains an essential component of the diagnostic work-up, but evaluation of records, the environment (housing and other animals), nutrition, colostrum, treatment, and vaccination protocols is also needed.

From a distance, mentation, posture, respiratory rate, breathing effort, characters of nasal and ocular discharge, and spontaneous coughing can be evaluated. Abnormal postures exhibited by patients with respiratory conditions may be recumbency, open-mouth breathing, abnormal extension of the head and neck, head tilt, or reluctance to lie down. Abnormal breathing characteristics include prolongation of the inspiratory or expiratory phase of respiration, an expiratory abdominal press or snap, marked tachypnea, frequent spontaneous

coughing, stridor, and inspiratory or expiratory noises.

When in contact with the patient, assess airflow from each nostril and evaluate ocular, oral, pharyngeal, and vaginal mucous membrane characteristics, including temperature, color, moisture, and capillary refill time. The hard and soft palates should be evaluated. Animals with cleft palate may have milk run from the nose and are prone to developing aspiration pneumonia. Gray or cyanotic mucous membranes are associated with severe hypoxia (i.e., Pa_{O_2} <35 to 40 mm Hg) and/or circulatory collapse as seen with hypotensive, endotoxic, or hypovolemic shock. Cardiac and pulmonary causes of cyanosis must be distinguished. Cyanosis from congenital cardiac disease of the neonatal ruminant frequently reflects right-to-left shunting of blood that may be from a tetralogy of Fallot, transposition of the aorta, great vessel anomalies, or Eisenmenger's complex. Absence of cyanosis is not a reliable indicator of adequacy of oxygenation in the neonate, since the partial pressure of oxygen may reach very low levels (<35 to 40 mm Hg) before cyanosis is observed.

Auscultation of the trachea, thorax, and occasionally the nasal passage are essential elements of the respiratory examination. Tracheal compression should not induce multiple coughs. Lung sounds of neonates are typically easier to hear than those of adults, but lung sounds do not always correlate well with the severity of respiratory condition that is present. Interpretation of the intensity of thoracic breath sounds can be validated by comparison to tracheal breath sounds. The intensity of tracheal breath sounds is gradually attenuated as the stethoscope is moved from the trachea to the lung hilus and again to the anteroventral thorax and finally to the caudal thorax in normal animals. Loud tracheal breath sounds that are not attenuated over the thoracic area may be indicative of atelectasis, lung consolidation, or cardiac enlargement. Added breath sounds such as crackles or wheezes should be noted but may not be heard without augmenting the depth and frequency of the breathing effort with the use of a rebreathing bag. Cardiac auscultation will determine heart rate, rhythm, and the presence of murmurs. Abnormal radiation of heart sounds caudal to the fifth intercostal space or dorsal to the level of the scapulohumeral joint on either side of the thorax should be noted. Thoracic percussion may be used to identify the presence of thoracic fluid, cranioventral consolidation, or atelectasis in neonatal ruminants. During the examination the ribs should be palpated to detect fractures.

Heart and respiratory rates vary with activity, excitement, and feeding. Tachypnea can be attributed to elevated temperature humidity index, fever,

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thermoregulation dysfunction, excitement, pain, stress, respiratory disease, hypoxia (cardiac disease, pulmonary disease, shock), dehydration, shock, toxemia, or metabolic acidosis. Periodic apnea and abnormally slow respirations are often the result of metabolic disturbances (hypoglycemia, hypocalcemia), hypothermia, prematurity, or hypoxia-induced suppression of the respiratory center.

Abnormal posture of the head and neck are exhibited by neonates with respiratory difficulty, particularly upper airway obstruction, but meningoencephalitis, otitis media, hypernatremia, polioencephalomalacia, congenital defects of the CNS, and lasalocid toxicity should be considered.

Conditions causing occlusion of the upper airway, such as choanal atresia, necrotic laryngitis, and pharyngeal swelling or edema, often induce pronounced inspiratory dyspnea, stridor, and/or open-mouth breathing. Expiratory stridor and increased and prolonged expiratory effort are usually associated with lower airway disease. A malodorous breath may be present with necrotic pharyngeal injuries, necrotic laryngitis, cleft palate, or aspiration pneumonia. Inspiratory stridor is often a feature of extrathoracic airway obstruction, and increased abdominal effort on expiration is often an indication of pulmonary disease causing reduced lung compliance.

Lung disease in the newborn is usually diffuse and is the result of infection acquired in utero or postpartum and/or lung atelectasis associated with immaturity, recumbency, or surfactant dysfunction. Signs of lung disease include increased work of breathing characterized by nostril flare, rib retractions, and increased abdominal effort. A cough and nasal discharge, salient features of respiratory disease in older neonates, are infrequent findings in newborns with lung disease. Animals with few or no audible thoracic abnormalities may have severe respiratory disease.

Respiratory Condition Diagnostic Testing

A complete blood cell count, a serum chemistry profile, electrolyte concentrations, arterial or venous blood gas concentrations, and a test of immune transfer status provide useful information to the clinician concerned about a respiratory condition in a neonatal ruminant. Normal values for neonatal calves are presented in Table 20.4.

TABLE 20.4

Normal Hematology and Biochemical Reference Values for Neonatal Calves [59,60]

	Age			
Parameter	**Birth**	**24 hours**	**48 hours**	**3 weeks**
RBC (×10⁶/μL)	9.35 ± 1.02	8.17 ± 1.34	7.72 ± 1.09	8.86 ± 0.68
Hb (g/dL)	12.86 ± 1.85	10.93 ± 2.05	10.49 ± 1.8	11.32 ± 1.02
PCV (%)	41 ± 6	34 ± 6	32 ± 6	35 ± 3
MCV(fL)	43.2 ± 2.4	41 ± 2.8	41.1 ± 2.3	39.1 ± 1.9
MCHC (g/dL)	31.3 ± 1.1	32.1 ± 0.8	32.6 ± 1.0	32.8 ± 1.6
Total WBC/μL	13.99 ± 5.73	9.81 ± 2.8	7.76 ± 1.95	8.65 ± 1.69
Neutrophils/μL	10,940 ± 5700	6480 ± 2660	4110 ± 2040	2920 ± 1140
Bands/μL	100 ± 150	310 ± 460	210 ± 450	10 ± 30
Lymphocytes/μL	2980 ± 2730	2730 ± 820	2850 ± 880	5050 ± 800
Monocytes/μL	590 ± 660	230 ± 210	350 ± 280	620 ± 330
Eosinophils/μL	0	20 ± 40	20 ± 30	20 ± 40
Basophils/μL	0	0.02 ± 0.05	0.02 ± 0.05	0.02 ± 0.04
TP (g/dL)	4.8 ± 0.3	6.4 ± 0.7	6.4 ± 0.7	6.4 ± 0.3
Fibrinogen (mg/dL)	258 ± 138	288 ± 105	335 ± 116	283 ± 147
Urea nitrogen (mg/dL)	6.36 ± 2.36	7.52 ± 2.13	6.93 ± 3.13	
Creatinine (mg/dL)	4.14 ± 1.27	1.69 ± 0.35	1.27 ± 0.24	
Total bilirubin	0.34 ± 0.66	1.28 ± 0.5	0.89 ± 0.41	
Sodium (mEq/L)	141 ± 3.77	135 ± 2.86	135 ± 3.68	
Potassium (mEq/L)	6.1 ± 1.86	5.46 ± 0.56	5.63 ± 0.96	
Chloride (mEq/L)	97.39	95.76	95.28	
Calcium (mg/dL)	12.24 ± 1.64	10.22 ± 1.2	10.65 ± 0.56	
Phosphorus (mg/dL)	8.16 ± 1.39	7.22 ± 0.87	7.46 ± 0.87	
Creatinine phosphokinase (U/L)	83 ± 42	531 ± 532	256 ± 364	
Aspartate aminotransferase (U/L)	18 ± 19	99 ± 18	72 ± 25	
Gamma-glutamyl transferase (U/L)	8 ± 3	1761 ± 1058	846 ± 517	

Hb, Hemoglobin; *MCHC,* mean corpuscular hemoglobin concentration; *MCV,* mean corpuscular volume; *PCV,* packed cell volume; *RBC,* red blood cells; *TP,* total protein; *WBC,* white blood cells.

Knowing whether there is anemia, evidence of infection, endotoxemia, organ dysfunction, metabolic abnormalities, hypercarbia, hypoxemia, or FPT of immunity may distinguish upper airway problems from lower airway disease or pulmonary disease from a nonpulmonary cause of respiratory difficulty.

Arterial blood gas concentrations provide a useful measure of respiratory function. Optimal sites for collection of arterial blood samples from neonatal calves are the brachial artery proximomedial to the elbow[61] or the caudal auricular artery.[62] Normal arterial blood gas values for neonates of different postnatal and gestational ages are presented in Table 20.5.

TABLE 20.5

Normal Arterial Blood Gas Values for Calves

Age-Group	O_2 (mm Hg)	CO_2 (mm Hg)	pH	HCO^-_3 (mEq/L)
1 hour	58.43 ± 11.61	50.40 ± 5.27	7.30 ± 0.05	23.52 ± 2.78
4 hours	62.30 ± 9.27	47.92 ± 3.97	7.34 ± 0.03	24.49 ± 2.35
12 hours	67.23 ± 9.32	45.36 ± 3.97	7.38 ± 0.03	25.74 ± 2.37
24 hours	70.53 ± 11.47	44.04 ± 3.45	7.40 ± 0.03	26.44 ± 1.87
48 hours	63.85 ± 10.82	45.25 ± 3.69	7.42 ± 0.01	27.98 ± 1.91

Several factors can interfere with accurate interpretation of blood gases in the neonate. First, significant inaccuracies can occur if the blood sample is collected, handled, or measured improperly. The most common artifact is the introduction of room air into the sample, resulting in an artificially increased Pa_{O_2}, decreased Pa_{CO_2}, and more alkaline pH. The position of the patient and amount of struggling during sample collection may also potentially cause transient changes in all blood gas values. The inspired oxygen concentration should always be considered when analyzing arterial blood gas values. With supplemental oxygen, Pa_{O_2} is increased variably, depending on the inspired oxygen concentration (Fi_{O_2}), the amount of pathology present (particularly the extent of right-to-left shunting), and the respiratory rate and tidal volume. Hypoxemia due to hypoventilation is usually addressed by increasing inspired PO_2 via a face mask or intranasal oxygen.

Common patterns of arterial blood gas derangement in the neonatal ruminant include hypoxemia (Pa_{O_2} <70 mm Hg) with low or normal Pa_{CO_2} and hypoxemia with hypercapnia (Pa_{CO_2} >50 mm Hg). If hypercapnia and resulting respiratory acidosis exist, ventilation is inadequate or there is ventilation-perfusion inequality. Hypoventilation in neonatal ruminants may reflect depression of the respiratory center, medullary trauma, ischemia, hemorrhage or encephalitis, lack of surfactant in the premature neonate, compromised muscle function (white muscle disease), or fractured ribs.

Interpretation of venous blood gas can be deceptive and should be limited to evaluation of metabolic conditions such as metabolic acidosis but not considered adequate for assessment of pulmonary gas exchange. To avoid problems associated with regional blood sampling, peripheral venous blood should be taken from a free-flowing jugular vein, since the metabolic status of the head is usually stable.

Plasma lactate measurement may provide prognostic value for calves with acute bronchopneumonia.[63] Acute phase proteins such as haptoglobin,

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fibrinogen, serum amyloid A, and lipopolysaccharide-binding protein have also been evaluated for diagnostic and prognostic value in bovine respiratory disease (BRD), but they are not specific for BRD, vary with etiology and stage of infection, and do not offer a clear distinction between normal and abnormal animals.

Thoracic radiographs are helpful in diagnosing the presence, type, and extent of respiratory disease in neonatal ruminants. Shortly after birth the smaller vessels posterior to the heart and in the caudodorsal lung fields should be clear. The heart, posterior vena cava, and aorta should be clearly defined. When the radiographic appearance of the lung fields is evaluated, the type of infiltrate (interstitial, nodular, alveolar, mixed), severity, and location (diffuse, cranioventral, caudodorsal) should be noted. Other soft tissue structures (including the heart, vessels, and diaphragm) and bones (ribs, vertebrae, long bones of the forelimb) should also be evaluated. Thoracic radiographs are routinely taken in the standing or lateral recumbent position in calves. Cranioventral consolidation is a common radiographic finding of infectious bronchopneumonia in calves. Radiographic changes may either follow or precede changes in clinical condition, and sometimes major changes can occur surprisingly rapidly. Clinical signs of pneumonia frequently resolve earlier than the thoracic radiographs return to normal.

Ultrasonographic evaluation of the neonatal ruminant thorax is useful for identification of aspiration of amniotic fluid, atelectasis, pleural effusion, nonventilated lung, pleuritis, and chest wall abscesses, and for detecting congenital heart defects. It appears most suitable for detecting pathologic processes close to the pleura.[64]

Respiratory endoscopy can be used for evaluation of the nasal cavity and septum, oropharynx and nasopharynx, epiglottis, larynx, and trachea. It is particularly useful for diagnostic evaluation of neonatal ruminants with respiratory stridor, stertorous breathing, malodorous breath or nasal discharge, inspiratory dyspnea, or related clinical signs indicative of upper airway problems.

Airway sampling is useful to determine presence, type, and etiology of respiratory inflammation and infection of neonatal ruminants. Deep pharyngeal swabs with a guarded catheter, transtracheal fluid aspirate, tracheobronchial lavage fluid, or bronchoalveolar lavage fluid analyses and cultures have been described. Techniques, sample handling, and interpretation are described in Chapter 31. For a neonate in respiratory distress, airway sampling may not be

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indicated until the patient is stabilized. Selection of the appropriate airway sampling method will depend on the patient condition and demeanor, supplies and equipment, test cost, technical assistance, clinician preference, anticipated etiology, sample handling, processing, and interpretation expertise. Specific airway sample, culture, polymerase chain reaction (PCR), ELISA, and other available tests for respiratory bacterial, *Mycoplasma*, *Chlamydia*, and viral pathogens are discussed in Chapter 31. Test positive and negative predictive values may be improved when used for herd-level testing rather than for individual animal test interpretation.

Postmortem examination is a useful diagnostic tool for evaluation of respiratory conditions of neonatal ruminants. In addition to the examination of the upper and lower respiratory tract, brain, heart, GI tract, immunologic sites, navel, other mucosal surfaces, and cavity fluids can provide information pertinent to a diagnosis. Lung culture, pathology, and immunohistochemistry (IHC) results can be particularly useful.

Upper Respiratory Tract Disorders

Conditions of the upper airway of neonatal ruminants are not common, but choanal atresia, stenotic nares, congenital cysts, cleft palate, pharyngeal trauma, pharyngeal and laryngeal edema, pharyngeal dysfunction, necrotic laryngitis, and tracheal collapse have been described. With the exception of necrotic laryngitis, most upper respiratory conditions of neonatal ruminants are present within the first week of life but may become progressive with age. Upper airway conditions, particularly those affecting pharyngeal and laryngeal function, predispose to aspiration pneumonia.

Diagnosis of most upper airway disorders can usually be made with a careful physical examination in combination with arterial blood gas concentrations, radiography, and/or endoscopy. Clinical signs of upper airway conditions include inspiratory effort, dyspnea, upper respiratory noise, stridor, malodorous nasal discharge, and cough. Dysphagia, poor appetite, milk reflux from the nostril, and aspiration pneumonia may be noted. Dyspnea is likely to result in failure to thrive and malnourishment.

Impaired pharyngeal and laryngeal function may result from physical deformation or neuromuscular disorders. Sporadic outbreaks of pharyngeal and laryngeal injuries are often associated with improper application or use of damaged feeding tubes and oral medication equipment. Compression of the

larynx by a retropharyngeal abscess or mass tends to cause inspiratory dyspnea. Edema and necrosis of the larynx may be observed with infectious bovine rhinotracheitis virus infections in neonatal calves.[65,66] *Fusobacterium necrophorum* typically causes necrotic laryngitis in weaned calves but sporadically infects neonates following pharyngeal trauma.[67] Necrotic laryngitis is frequently detected only when clinical signs of dyspnea with stridor are evident. By this stage the disease tends to be chronic, and the response to systemic antimicrobial and antiinflammatory treatment is generally poor.[68] Partial occlusion of the upper airway induces turbulent airflow and subsequent mucosal edema. Placement of a tracheostomy tube provides an alternate, sometimes life-saving airway and rests the inflamed mucosa. Surgical intervention may be required; tracheotomy, tracheostomy, laryngotomy, laryngostomy, and tracheolaryngostomy have been described, with variable outcomes.[67-69]

Nutritional myodegeneration and botulism may induce laryngeal paresis. Dysphagia and subsequent aspiration pneumonia are common sequelae. Collapsed trachea is a rare congenital or acquired condition. In this condition, there is a dynamic dorsoventral collapse of the trachea during inspiration, but no stenosis is present. The caudal cervical and cranial thoracic sections of the trachea in the area of the thoracic inlet are most frequently affected. Acquired tracheal collapse is commonly associated with fractured ribs and compression of the trachea at the thoracic inlet by the bony callus that develops with healing. Clinical signs include an intermittent honking cough, stridor, and dyspnea with mild exercise. Treatment of collapsed trachea in the calf by surgical reconstruction has been attempted, but the prognosis is poor.[70-73]

Respiratory Infection

A number of respiratory disease syndromes may be observed in neonatal calves. Pneumonia in calves younger than 5 days of age is most likely hematogenous in origin, a consequence of neonatal septicemia or aspiration pneumonia from inhalation of fetal fluid, meconium, colostrum, or milk as a complication of recumbency, obtunded mentation, large volume forced feeding, large holes in teat nipples, poor esophageal tubing technique, or pharyngeal dysfunction (white muscle disease). Fever, cough, and nasal discharge are not consistently present in the early stages of pneumonia in the neonate. With hematogenous pneumonia, evidence of infection in other organs, including omphalophlebitis, meningitis,

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enteritis, and polyarthritis, is frequently present. Without early and aggressive treatment, sepsis can progress to shock, multiple organ dysfunction, and death relatively rapidly. *E. coli* or other gram-negative bacterial organisms are the most common culprits. With aspiration pneumonia, a mixture of gram-positive, gram-negative, and anaerobic bacteria can be cultured from the lungs, inciting a severe inflammatory response, toxemia, and occasionally sepsis. For hematogenous and aspiration pneumonia, broad-spectrum antimicrobial coverage must be instituted early and accompanied by antiinflammatory drug therapy, fluid therapy, nutritional supplementation, and supportive care. Long-term treatment is frequently necessary, and prognosis for survival is guarded.

Bacterial pneumonia of dairy calves, frequently described as affecting calves 2 to 6 months of age, may occur as early as 2 weeks of age and frequently peaks in incidence at 5 to 6 weeks of age. In bacterial pneumonia of calves, inhaled pathogens first colonize the bronchoalveolar junction, overcome host defenses, incite inflammation at that site, and go on to spread through the contiguous airways or through adjacent lung tissue. Pneumonia occurs as an endemic problem on many farms but can also occur as an outbreak. Frequently the problem is multifactorial, including bacterial organisms, individual and farm, or environmental risk factors.

Clinical signs of bacterial pneumonia in young calves usually include a combination of the following: fever, nasal discharge, lacrimation or ocular discharge, cough (spontaneous or inducible by tracheal compression), depression, reduced appetite, rough hair coat, expiratory effort, and abdominal breathing effort. Concurrent signs of otitis may be noted. Subjective parameters like attitude, appetite, appearance, activity level, or respiratory character that are used to detect pneumonia on farms can be insensitive and delay the pneumonia diagnosis and treatment. Remote recording devices that monitor objective parameters such as core body temperature, activity levels and behavior, and frequency and volume of milk consumption are becoming more common and will improve farm pneumonia detection. Automatic or computerized calf feeding is gaining popularity, providing opportunities to monitor calf feeding behavior. Parameters commonly measured include milk volume consumed, drinking speed, rewarded visits to the feeder (calf is fed), and unrewarded visits to the feeder (calf is not fed, as the interval from the last feed is too short). Calves with respiratory disease have been observed to have reduced milk intake and a reduced number of unrewarded visits. The changes in calf behavior were detectable 3 days prior to clinical recognition of disease and persisted for 7 days

following identification of respiratory disease.[74] Similar changes have been reported by others, including reductions in drinking speed, milk volume consumed, and rewarded and unrewarded visits. However, these behavioral changes were found to be less sensitive at detecting calves with respiratory disease compared to calves with diarrhea.[75]

Bacterial agents are frequently the primary pathogens in calf pneumonia. Alone or in combination, *Mannheimia haemolytica*, *Pasteurella multocida*, *Mycoplasma bovis*, or *Mycoplasma dispar* are the most common bacterial isolates cultured from airway samples early in the infection. *Histophilus somni* or *T. pyogenes* is found in more advanced pneumonia cases. While any *Salmonella* species can cause pneumonia, *Salmonella dublin* can be the cause of fulminating pneumonia in 1- to 8-month-old calves. Outbreaks of respiratory disease in this age-group may be associated with mixed bacterial infections, including *M. bovis*, or with primary or concurrent viral infection with bovine respiratory syncytial virus (BRSV), bovine coronavirus (BCV), or bovine viral diarrhea virus (BVDV) infection. Viral infections increase the risk of opportunistic bacterial infections by their immunosuppressive effects and damage to the respiratory epithelium and pulmonary clearance mechanisms. Pleuritis is an uncommon feature of most neonatal respiratory infections but may be a manifestation of a generalized polyserositis with specific pathogens such as *Mycoplasma* infections of ruminant neonates[76] and occasionally *Pasteurella* infections in lambs.[77]

FPT of immunity is one of the most important risk factors for the development of calf pneumonia in individual animals and in herds. Calves with FPT had 1.6 times greater odds of being treated for respiratory disease.[78] In this study the prevalence of FPT was 32%, and the attributable fraction of BRD associated with FPT was 21%, suggesting that 1 in 5 cases of respiratory disease could have been avoided among calves with FPT if they had had adequate passive transfer.[78]

Poor nutrition is another risk factor for pneumonia in dairy calves that are limit-fed milk or milk replacer. A number of pathogens capable of causing respiratory disease are shed in milk. These include *Mycoplasma* spp.,[76,79,80] CAEV,[81,82] and *S. dublin*. The practice of feeding unpasteurized mastitic milk or nonsaleable milk to neonates increases the risk of disease transmission, including *S. dublin*, an invasive host-adapted *Salmonella* serotype, to cattle, *Mycoplasma* spp. infections to goat kids and calves, and CAEV to goat kids. CAEV produces a number of disease syndromes in goats, including mastitis,

arthritis, encephalitis, and pneumonia. Encephalitis and subclinical respiratory disease typically occurs in kids 2 to 4 months of age and occasionally in kids as young as 1 month of age.[81,83] Goat kids infected with *Mycoplasma mycoides* subsp. *mycoides* (large colony type) are often in a lot of pain, febrile, and reluctant to stand, and have multiple hot, swollen joints from acute polyserositis. Approximately 50% of kids develop pneumonia or pleuropneumonia manifested by an increase in respiratory rate and auscultable lung sounds.[76] Outbreaks of *Mycoplasma* pneumonia in calves are usually caused by feeding waste milk contaminated with *M. bovis*.[84,85] Clinical signs include an increased rate and effort of breathing associated with pneumonia, joint and tendon sheath distention reflecting arthritis, polyserositis, tenosynovitis, auricular discharge, and a head tilt reflecting otitis media or interna[79,85]; decubital abscesses are a less common manifestation.[86] Clinical signs associated with *Mycoplasma* otitis include cranial nerve 7 and 8 deficits, unilateral or bilateral ear droop, ptosis, epiphora, head tilt, and recumbency in severely affected calves. Pasteurization of milk fed to goat kids and calves is recommended.

Additional environmental risk factors for pneumonia include extremes of temperature, poor ventilation, dust, ammonia, and overcrowding. Overcrowding, especially with commingled age-groups of calves, creates a high risk for pneumonia. Housing factors associated with reduced respiratory disease prevalence in naturally ventilated dairy calf barns are solid panels between calves that prevent contact, deep bedding, and low airborne bacterial counts.[87] A minimum space requirement of 2.2 to 3 m^2 per calf is associated with low airborne bacterial counts and less respiratory disease for calves in individual and group pens. Increased time between successive occupants of individual or group calf pens reduces the environmental exposure to disease organisms. An all in–all out housing system on farms reduces the chance for endemic pneumonia problems. Other risk factors for pneumonia include poor-quality feed, limited availability of water, stress, inappropriate medications, overvaccinating, parasitism, and concurrent infection.

Herd-based pneumonia problem solving is needed where respiratory disease in calves is endemic. Routine calf care, herd vaccinations, navel care, colostrum feeding, feed types, amounts, times, and additives are important. Learn the pneumonia definition, screening method, and treatment protocols. Review records to find seasonal trends, relationship to passive transfer of immunity, age at first diagnosis, and related management factors. Survival curves and incidence

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calculations can be useful. Observe people and procedures, and examine animals. Determine how many current cases have been detected and treated. Successful management of endemic pneumonia problems requires early detection, effective treatment, and resolution of the most important risk factors.

For treatment consideration, many antibiotics are labeled for BRD. Treatment plans for individual animals or farm protocols should be based on valid diagnostic information, recent examinations, and responsible use of antibiotics. Compliance with prescribed dose, route, and frequency of administration is factored into antibiotic selection. For one-dose respiratory treatment protocols, enrofloxacin, tulathromycin, ceftiofur, florfenicol, gamithromycin, or tildipirosin may be considered. For antibiotics like spectinomycin, enrofloxacin, ceftiofur, and florfenicol, multiple-dose treatment protocols are also effective for BRD.

Mycoplasma spp. are susceptible to antimicrobial agents that affect DNA, RNA, protein synthesis, or the integrity of the cell membrane. *Mycoplasma* spp. are not susceptible to agents that interfere with synthesis of folic acid or that act on the cell wall. Tylosin, tetracyclines, erythromycin, tilmicosin, tulathromycin, gamithromycin, florfenicol, aminoglycosides, and fluoroquinolones have been shown to have activity against one or more *Mycoplasma* spp.[88] However, the efficacy of antimicrobial therapy to eliminate the organism is limited, and while animals may recover, chronic infections may persist.[89]

Prevention of neonatal ruminant respiratory conditions includes appropriate vaccination programs, frequent observation of adults and neonates, uncomplicated births, adequate colostrum, navel care, optimal nutrition, and housing that is clean, dry, and draft free.

Neonatal Apnea and Irregular Breathing Patterns

Periods of apnea in the neonate are commonly associated with nonrespiratory factors, including infection, CNS disorders, hypothermia, and metabolic causes such as hypoglycemia. Seizure activity may be expressed by changes in breathing rate and pattern, and neonatal asphyxia may induce respiratory depression, whether or not cerebral lesions are present.[90] Neonatal respiratory distress may also cause apnea resulting from respiratory center depression or diaphragmatic fatigue. There are two mechanisms of apnea: central apnea, resulting from cessation of diaphragmatic activity; and obstructive apnea, resulting from obstruction of the airway, usually at the pharyngeal level.

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Abdominal Distention

Geoffrey W. Smith

Ruminal Bloat

Ruminal bloat is uncommon in calves younger than 5 weeks of age because of the relatively undeveloped state of the neonatal rumen. Causes of ruminal bloat in calves include ruminal putrefaction, obstruction of the cardia or esophagus, and vagal indigestion (Box 20.3).

Box 20.3

Causes of Abdominal Distention

Obstruction

Foreign body (hairballs in calf)
Malformation (atresia coli, recti, ani)
Intussusception
Volvulus, torsion, or strangulation

Uroperitoneum

Ruptured bladder (uncommon)
Torn or necrotic urachus, ureter

Peritonitis

Generalized infection
Devitalized bowel
Perforated gastric or intestinal ulcer
Severe umbilical infection

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Gas and Fluid Accumulation in Abomasum, Intestinal Tract

Intolerance to diet
Ileus
Gastric, abomasal, duodenal ulceration
Necrotizing enterocolitis
Ruminal bloat

Miscellaneous

Hemoperitoneum
Ruptured umbilical vessels
Ruptured spleen or liver
Congenital tumor

Ascites

Severe liver or renal failure
Severe hypoproteinemia

Ruminal bloat must be differentiated from abomasal bloat, which is much more common in young calves. However ruminal bloat can occur as a consequence of inadequate esophageal groove closure in young calves. The esophageal groove is a continuation of the lower esophagus, passing the medial wall of the reticulum and terminating in the reticulo-omasal orifice. The closure reflex is maintained by the suckling activity of the calf, and the groove is not properly closed if the calves drink out of buckets. It may also not close if milk temperatures are variable, the calves are under stress, the calves are fed too low to the ground, or milk flow rates are too high.[91] Failure of esophageal groove closure leads to rumen drinking, where greater than normal amounts of milk enter the ruminoreticulum instead of the abomasum. Prolonged retention of milk in the rumen results in anaerobic bacterial fermentation and production of lactic acid,[92] leading to both a ruminal and a systemic (metabolic) acidosis.[93] Clinical findings in ruminal drinker calves include refusal of milk, poor suckle reflex, recurrent ruminal bloat, and splashing sounds on the left side of the distended

abdomen in young calves (Fig. 20.2). Calves are frequently depressed and dehydrated and may die due to the severity of the metabolic acidosis. Treatment primarily involves rumen lavage with a stomach tube to siphon off the fermented milk remaining in the rumen, along with fluid therapy to correct the acidosis. Although ruminal drinker syndrome has been described in calves representing multiple breeds, it appears to be most common in Simmental calves from Germany and Switzerland.[94] Reducing the volume of milk fed per feeding, feeding from nipples rather than buckets, and introducing calf starter to promote ruminal development help prevent the condition. Antimicrobial therapy may also help affected calves by killing the putrefactive gut flora.



FIG. 20.2 Classic appearance of a rumen drinker calf. The calf is extremely depressed from systemic acidosis with abdominal distention. Note the front legs extended caudally, which can often be seen in these cases.

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Bloat is occasionally observed as a complication of severe bronchopneumonia in calves as a consequence of swollen mediastinal lymph nodes compressing the esophagus or compression or inflammation of the vagus.[95] Relief of rumen distention is important for return of rumen function. Chronic ruminal bloat may be relieved by placement of a rumen fistula. Correct placement of the trocar, as described by Dirksen and Garry,[95] reduces the risk of inducing peritonitis. The rumen must be bloated so that it lies firmly against the body wall as the trocar is screwed into place. The site for the trocar is shaved and scrubbed, a small skin incision is made, and the trocar is quickly and forcefully screwed into the belly wall and rumen. After removal of the stylet, the outer rim of the trocar is kept under constant outward tension so that the ruminal wall is held tightly against the parietal peritoneum by the last ridge of the screw. To fix the trocar in this position, gauze soaked in antibiotic should be wrapped around the stem of the trocar between the outer rim and the body wall.[95]

Abomasal Ulcers

Abomasal ulcers are usually asymptomatic in young calves, but if perforation occurs, peritonitis and shock rapidly develop. It is often difficult to determine the underlying cause of abomasal ulcers; however, several possibilities have been identified, including trauma to the mucosa from the addition of coarse roughage feeds, pica resulting from enteritis, abomasal bezoars, environmental and physical stress, hyperacidity, vitamin E deficiency, lactic acidosis, mycotic infection, and low immune status associated with copper deficiency.[96-98] Inconsistency of milk fed to calves (varying osmolality or total solid levels) and/or inconsistency of feeding schedules also appear to be significant risk factors. Several bacteria, including *E. coli* and *Sarcina* and *Clostridium* species, have also been isolated from various calves with ulcers.[99] Although no definitive infectious component has been identified in cattle, some authors have hypothesized that a bacterial component is likely in some cases.[100] This could be similar to humans, in which *Helicobacter pylori* and gastric ulcers routinely occur together.

Four categories of ulcers are described in calves[97,98]:

Type 1: Nonperforating ulcer—The ulcer does not perforate the abomasal wall, and intraluminal hemorrhage is minimal.(Fig. 20.3, *A*)



FIG. 20.3 Abomasal ulcers in calves can range from small reddish erosions **(A)** to perforated lesions that lead to diffuse peritonitis **(B)**.

Type 2: Nonperforating ulcer with severe blood loss—The ulcer does not perforate the abomasal wall but erodes a major vessel in the submucosa, resulting in severe intraluminal hemorrhage.

Type 3: Perforating ulcer (Fig. 20.3, *B*) with local peritonitis—The ulcer perforates the abomasal wall, and abomasal contents leak into the peritoneal cavity or omental bursa. Peritonitis is localized by fibrin deposition, and the abomasum becomes adhered to the peritoneum, omentum, or surrounding viscera.

Type 4: Perforating ulcers with diffuse peritonitis—The ulcer perforates the abomasal wall, and abomasal contents quickly leak into and spread throughout the peritoneal cavity, resulting in diffuse peritonitis.

Abomasal ulcers can be very difficult to diagnose antemortem in calves. Clinical signs are vague and include sudden death, abdominal distention, pain on abdominal palpation, expiratory grunt, drooling saliva, bruxism, and melena. Less commonly, a syndrome of chronic abdominal pain is observed after abomasal perforation.[101] Absence of inflammatory changes suggests that the gut is unlikely to be perforated or necrotic. Severe hypoproteinemia is common with diffuse peritonitis, presumably because of the combination of poor colostral uptake and loss of protein into the abdominal exudate. Obtaining peritoneal fluid from normal calves is difficult; if peritonitis is suspected, collection of

abdominal fluid is facilitated by locating pockets of peritoneal fluid via abdominal ultrasound.

In general, treatment is limited to calves with bleeding or deep, nonperforated ulcers. Therapy can include blood transfusions, antibiotic administration, changes to the diet, oral administration of antacids, and administration of histamine H_2-receptor antagonists. Aluminum hydroxide/magnesium hydroxide —$Al(OH)_3$/$Mg(OH)_2$—antacids neutralize acid in the abomasum and require three doses per day. Antacids are an inexpensive option for treatment of cattle with ulcers and have a potential therapeutic advantage. $Al(OH)_3$ directly absorbs pepsin, thus decreasing the proteolytic action of pepsin in the stomach.[102] Also, $Al(OH)_3$ and $Mg(OH)_2$ bind bile acids, thus protecting against ulceration caused by bile reflux.[102] Ahmed and colleagues found that healthy calves given 25 to 50 mL of oral antacid had a transient increase in abomasal luminal pH.[103] This effect appeared to be dose related, and the extent of the acid neutralization was increased when not given with milk replacer.

Histamine H_2-receptor antagonists reduce acid secretion of parietal cells by selective and competitive antagonism of histamine at H_2 receptors on the parietal cells. Cimetidine and ranitidine are synthetic H_2-receptor antagonists that inhibit basal as well as pentagastrin- and cholinergic-stimulated gastric acid secretion. Daily oral administration of cimetidine at 10 mg/kg for 30 days in veal calves was found to aid healing of abomasal ulcers.[104] Oral administration of cimetidine (50 to 100 mg/kg q8h) and ranitidine (10 to 50 mg/kg q8h) caused a dose-dependent increase in abomasal luminal pH, and ranitidine had greater potency than cimetidine.[105] Omeprazole, a proton pump inhibitor, has also been studied in calves. Once-daily oral administration of omeprazole (4 mg/kg) to calves increased the mean 24-hour luminal pH by 1.3 pH units; however, this increase in pH was less pronounced with subsequent daily treatments.[106]

Surgical repair of ulcers can be performed on selected cases. Calves need to be in an operable condition and have isolated ulcers. Surgery needs to be performed early in the disease process. Typically ulcers are diagnosed during a laparotomy and either they can be resected or the serosa can be inverted with a mattress suture. One study reported a survival rate of 74% following surgical repair, with survival being defined as calves living at least 3 months past surgery date or dying because of another disease.[107]

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Abomasal Displacement

Abomasal displacement is rare in neonatal ruminants. Clinical signs include reduced appetite, poor weight gain, recurrent tympany (left side), and diarrhea. An association of left-sided abomasal displacement with pneumonia in calves suggests that altered vagal function may be involved in the pathogenesis of the condition.[108,109] Typically, left-sided abomasal displacement in calves occurs between 6 and 14 weeks of age, but younger calves may be affected. Displacement of the abomasum is diagnosed by auscultation and percussion; affected animals may have a hypochloremic metabolic alkalosis. Correction can be attempted by rolling the calf on its back or by surgery.

Abomasal Bloat

A number of reports on a complex syndrome known as abomasal tympany, abomasal bloat, braxylike disease, and abomasitis have been published.[98,110,111] This syndrome in young calves is characterized by anorexia, abdominal distention (often bilateral), bloat, and often sudden death within 48 hours. In mild cases clinical signs are described as diarrhea, watery fluid in the abomasum, and depression. Hyperglycemia (10.5 to 28 mmol/L) accompanied by glucosuria (3 to 6 mmol/L) was also reported in those calves. Severely affected calves show perceptible dehydration, colic, prominent abdominal distention, diarrhea, and recumbency. Systemic acidosis, as evidenced by low blood pH, low serum bicarbonate concentration, and base deficit, was also reported for calves with abomasal bloat.[112] Calves typically exhibit abdominal distention on the right side of the abdomen or potentially on both sides as the abomasum fills up with gas and occupies the majority of the abdominal cavity. At necropsy most of these calves present with abomasal tympany, forestomach and abomasal edema, hemorrhage, mucosal inflammation, erosion and necrosis, and occasionally mural emphysema. Emphysematous bullae are present in the stomach walls of these calves.[111]

Abomasal bloat most commonly occurs in dairy calves and seems to have a sporadic occurrence, with some farms having multiple outbreaks at times.[98] Abomasal bloat has been identified on farms using conventional milk replacers, “accelerated growth” milk replacers, and both pasteurized and unpasteurized whole milk. No single diet type or feeding method emerged as a conspicuous risk factor for abomasal bloat in this survey. Other risk factors that have been

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reported for abomasal bloat include high-osmolality milk replacers or oral electrolyte solutions, improper mixing of milk replacers, feeding a large volume of milk in a single daily feeding, cold milk (or milk replacer), not offering water to calves, erratic feeding schedules, and FPT.[98]

A bacterial etiology is often mentioned in association with abomasal bloat. The most frequently incriminated bacterial pathogens are *Clostridium perfringens* along with *Campylobacter* and *Sarcina* species.[111,113] These pathogens have also been associated with abomasal bloat in small ruminants.[114,115] Additional bacterial pathogens isolated from calves affected with abomasal bloat include alpha streptococci, other *Streptococcus* species, and *E. coli*. *C. perfringens* is most frequently seen as type A, E, or C, producing beta toxin.[112] Beta toxin damages the intestinal microvilli, mitochondria, and terminal capillaries in the mucosa. Progressive necrosis of the mucosa follows, and a large number of gram-positive bacilli invade those areas. *C. perfringens* type A was identified as the causative agent in a case report of 24 dairy calves dying from severe acute abomasal disease.[116] In another report, *Sarcina*-like bacteria were reported to contribute to the development of abomasal bloat in goat kids.[114] Histologic evidence of *Sarcina ventriculi* and *Sarcina maxima* was detected in the superficial mucosa, but no bacteria could be cultured from the lesions.[117] Vatn and colleagues reported that evidence of *Sarcina* could be identified in the abomasal wall of all lambs with bloat; however, the bacteria could be isolated in only one case.[115] Intraruminal inoculations of *C. perfringens* type A into healthy dairy calves resulted in anorexia, depression, bloat, diarrhea, and death.[118] The authors assumed that esophageal groove dysfunction allows abnormal amounts of milk to enter the abomasum, where bacteria like *C. perfringens* find a suitable environment for proliferation and invasion of the abomasal mucosa, resulting in abomasitis.

Experimental induction of abomasal bloat in calves was achieved by drenching Holstein calves younger than 10 days of age with a carbohydrate mixture containing milk replacer, corn starch, and glucose mixed in water to provide a meal with excessive fermentable carbohydrate.[119] The authors suggested that the syndrome of abomasal bloat in calves is multifactorial and proposed that the pathophysiology primarily involves excess fermentation of high-energy GI contents in the abomasum (from milk, milk replacer, or high-energy oral electrolyte solutions), along with the presence of fermentative enzymes (produced by bacteria), leading to gas production and bloat. This

process would be accelerated by anything that slowed abomasal emptying or caused GI ileus. Ultimately the exact etiology of abomasal bloat is unknown, but it likely involves both bacteria that produce gas and something that slows down abomasal emptying.

Treatment generally involves placing the calf in dorsal recumbency and inserting a needle or catheter into the abomasum to relieve the gas.[120] Attempting to deflate the bloat in a standing calf is often unrewarding, since this approach generally fails to completely drain the abomasum and carries a high risk of inducing peritonitis.[120,121] The best results occur when the calf is turned upside down and the abomasum is deflated with a 14-gauge, 50-mm needle inserted into the highest point of the abdominal wall between the umbilicus and xiphoid.[120] With this technique, 20 of 21 calves with abomasal tympany were successfully managed without complications. Repeated paracentesis carries a high risk of inducing peritonitis; if after paracentesis the calf's condition deteriorates or tympany recurs, a right flank laparotomy is performed to correct a possibly torsed abomasum.[122] Intravenous fluids are administered to correct dehydration and electrolyte and metabolic derangements. Antibiotic therapy may also be indicated in these calves (most likely parenteral procaine penicillin or oral β-lactam antibiotics to target *Clostridium* bacteria).

Control of abomasal bloat problems on a dairy farm generally begin with a thorough evaluation of the nutrition program to see if any changes need to be made. This evaluation would include what type of milk or milk replacer is being fed, volume fed at each feeding, feeding schedule, temperature of milk fed to calves, how the milk replacer is mixed, how feeding equipment is sanitized, and possibly even a water analysis in some cases. Recording the total solids of the milk replacer and potentially even measuring osmolality will provide additional information about the density and mixing consistency of the milk replacer being fed. Anecdotally, focusing on controlling abomasal bloat through nutritional approaches and minimizing feeding practices that slow abomasal emptying is often much more successful than trying to control the problem by instituting *C. perfringens* vaccination.[123] However, specific data on the efficacy of clostridial vaccines to control bloat have not been published.

Abomasal bloat is a significant problem in artificially raised lambs. Feeding systems that allow lambs to drink large quantities of milk replacer at infrequent intervals and housing lambs on litter are predisposing factors.[124,125] Proliferation of *Lactobacilli, E. coli,* and *C. perfringens* has been implicated in the disease

process.[125,126] Fermentation of sugars contained in milk replacer produces carbon dioxide, distending the abomasum.[127] Lambs may die within hours because of acute abdominal tympany compromising vascular return and respiration. Early treatment of bloated lambs with oral doses of antibiotics is sometimes an effective treatment. Addition of 0.1% formalin (37% formaldehyde) to milk replacer reduces the incidence of the condition.[126]

Intestinal Atresia

Intestinal atresia is the most common cause of abdominal distention of calves in the first week of life. Typically calves are born normally but develop progressive abdominal distention shortly after birth. Signs of mild colic are occasionally observed. The spiral loop of the ascending colon is usually the site of atresia.[128] Other congenital abnormalities may also be present (18% of cases).[128,129] Historically there was some thought that pregnancy diagnosis by palpating the amniotic sac before 40 days of gestation may cause colonic atresia in cattle[130]; however, recent studies have not supported that theory.[131,132] An autosomal recessive inheritance in Holstein cattle has also been proposed.[133] Surgical repair of atresia ani that can be treated with a perineal incision and rectal pull-through carries a good prognosis. However, surgical repair by resection of the distended proximal blind end and anastomosis of the proximal segment of intestine to the descending colon or use of a colostomy has a guarded to poor prognosis.[128,129,134]

Intussusception

Intussusception occurs most commonly in the jejunum, but the frequency of ileocecal and colon intussusceptions appears to be higher in calves than adults.[135] Commonly there is a history of diarrhea. Clinical signs may include intermittent colic, absence of feces, and melena; however, these are inconsistent. The inconsistency of clinical signs and inability to perform a rectal examination make the diagnosis more difficult in calves than adults.[135] Abdominal ultrasound may be useful. The prognosis following surgical correction is strongly influenced by the duration of the condition prior to correction.

Twisting of the intestinal mass around the cranial root of the mesentery is a rare event but occurs more frequently in calves than adults.[135] Clinically the

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condition is characterized by a sudden onset of severe colic (kicking at the abdomen, dropping to the ground) that rapidly progresses (abdominal enlargement, tachycardia, tachypnea, reduced or absent fecal passage) to signs of shock and recumbency. Early diagnosis and rapid surgical correction, using either a right paralumbar or a ventral midline, together with a supportive fluids approach allow for a good prognosis.

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Diarrhea

Alison A. Gunn • Mathew Izzo • John K. House

Herd management variables that affect the risk of neonatal death losses in housed calves include efficiency of passive transfer, calf nutrition and environmental management (pathogen exposure), calving area sanitation, and cow vaccination status and health. Successful calf rearing is based on good management. A goal of less than 3% death loss from diarrhea is achievable. With neonatal death losses in pasture or range animals, it is important to evaluate the dystocia rate, physical management and nutritional status of the calving and nursing herds, cleanliness of the calving and nursing areas, provision of shelter from wind, and any biosecurity risks.

Rotavirus, cryptosporidia, coronavirus, enterotoxigenic *E. coli*, and *Salmonella* are recognized as the major pathogens associated with diarrhea in calves (Table 20.6). Rotavirus, cryptosporidia, coronavirus, and enterotoxigenic *E. coli* are common pathogens in beef calves.[136-139] Salmonella is more frequently implicated in intensive calf-rearing systems.[138-140] Enteropathogenic strains of *E. coli* are occasionally implicated in calf diarrhea, but the true prevalence of disease associated with these strains is unknown due to the lack of routine definitive diagnostic tests. Torovirus has been associated with neonatal calf diarrhea (NCD) in Canada, the United States, and Europe.[141-144] Bovine virus diarrhea is infrequently associated with diarrhea in young calves.[145,146] More recently, norovirus and nebovirus have been implicated as causes of neonatal diarrhea, but their prevalence and importance in the field situation is unclear. Infectious agents implicated as causes of neonatal diarrhea are presented in Table 20.7. The incidence of the various etiologic agents varies with the age of the calf, and this is useful in establishing the likelihood that a particular agent is involved (Fig. 20.4). It is usually impossible to make a definitive etiologic diagnosis on clinical grounds. It is possible to detect signs of straining or passage of frank blood and mucus that suggest the presence of colitis, implicating possible salmonella, coronavirus, bovine viral diarrhea, enteropathogenic *E. coli*, or coccidial infections.

TABLE 20.6

Common Enteropathogens in Dairy Calves (Comparative

Frequency of Isolation From Diarrheic and Normal Calves Is Shown)

Pathogens	Overall % Positive	% Positive Among Diarrheic Calves	% Positive Among Healthy Calves	*p*-Value	Odds Ratio
Bovine norovirus	29.1	44.7 (89/199)[a]	16.3 (40/245)[a]	0.042	2.0 (1.002-3.9)[b]
Cryptosporidium parvum[c]	15.1	33.7 (67/199)	0.0 (0/245)	0.0007	173.0 (8.9-3365.1)
Bovine coronavirus	20.9	31.7 (63/199)	12.2 (30/245)	0.0034	2.7 (1.4-5.1)
Bovine rotavirus group A	12.2	27.1 (54/199)	0.0 (0/245)	0.0025	79.9 (4.7-1369.5)
Nebovirus	0.9	21.6 (43/199)	1.6 (4/245)	0.0001	16.7 (4.0-68.8)
Salmonella spp.	4.1	9.0 (18/199)	0.0 (0/245)	0.0056	80.6 (3.6-1803.7)
Bovine enterovirus	20.3	5.0 (10/199)	32.7 (80/245)	<0.0001	0.113 (0.04-0.3)
***Escherichia coli* K99+**	1.8	4.0 (8/199)	0.0 (0/245)	0.0143	98.4 (2.5-3859.9)
Bovine torovirus	1.1	2.5 (5/199)	0.0 (0/245)	0.2404	10.4 (0.2-520.3)
Bovine viral diarrhea virus	0.5	0.5 (1/199)	0.4 (1/245)	–	–
Clostridium perfringens beta toxin	0.0	0.0 (0/199)	0.0 (0/245)	–	–

[a]Numbers in parentheses show number of positive feces/number of samples tested.

[b]Numbers in parentheses are the 95% confidence interval of the estimated odds ratio.

[c]Boldface type indicates microorganisms detected only in feces from diarrheic calves.

From Cho Y-I et al.: Case-control study of microbiological etiology associated with calf diarrhea. *Veterinary Microbiology, 166*(3–4):375–385, 2013.

TABLE 20.7

Evaluation of the Pathogenicity of Various Infectious Agents as Gauged by Their Ability to Experimentally Produce Diarrhea in Calves, Field Surveys of the Incidence of Infection in Diarrheic and Healthy Calves, and Similarity in the Distribution of Intestinal Pathology and the Infectious Agent

Agent Name	Experimental Production of Diarrhea		Isolated With Higher Frequency From Diarrheic Calves	Organism Associated With Intestinal Pathology
	Gnotobiotic Calves	Conventional Calves		
Bacterial				
Enterotoxigenic *Escherichia coli*		+	++/–	+
Enterohemorrhagic *E. coli*	+	+/–		++++
Salmonella species	++	+	+	
Campylobacter faecalis		+		
Campylobacter coli		++	—	
Campylobacter jejuni		++	+/–	
Clostridium perfringens				
Type A	+	–	+	+
Type C	+			++
Clostridium sordellii	+			
Viral				
Rotavirus	++	++	+++	+++
Coronavirus	+++	+	+	+++
Bovine virus diarrhea	+	+++		+
Bovine torovirus (Breda virus)	+++		+	+
Bovine norovirus	+	+	+	+
Nebovirus	+		+	+
Parvovirus		+/–		+
Astrovirus		–		
Parasitic				
Cryptosporidium species		++++	++	+
Eimeria species		++		+

–, Negative finding; +, positive finding.

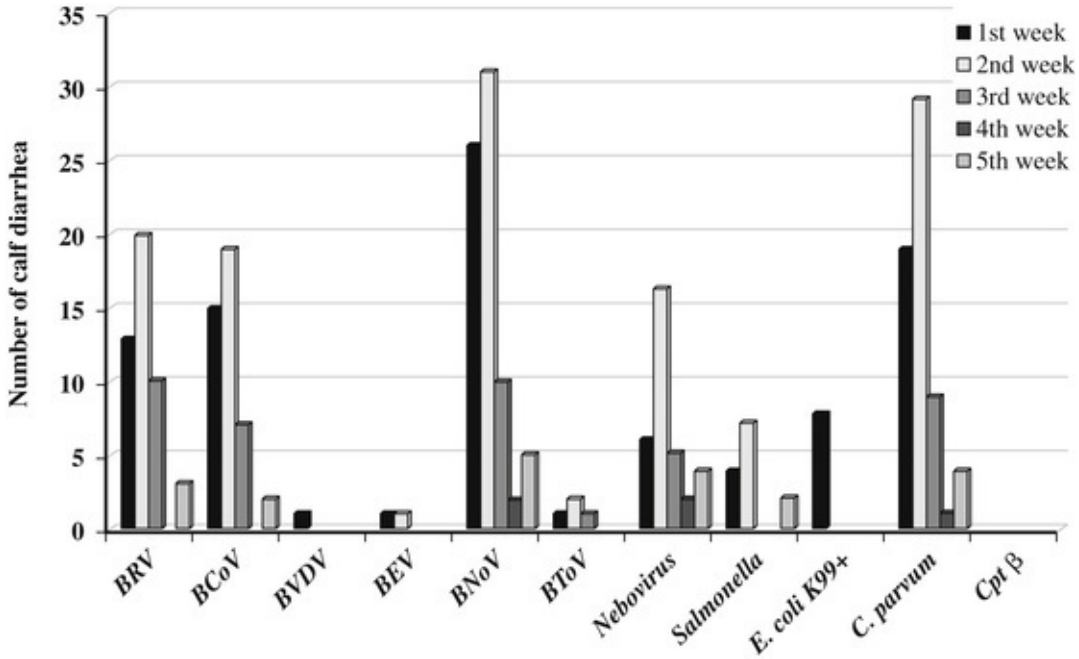


FIG. 20.4 Age distribution of diarrheic calves whose feces were positive for one or more enteric pathogens. Animals of 0 to 4 weeks of age are classified on a weekly basis after birth based on the information provided by submitting veterinarians. These data were compiled from submissions to the Iowa State University Veterinary Diagnostic Laboratory and represent approximately even numbers of beef and dairy calves. *BCoV,* Bovine coronavirus; *BEV,* bovine enterovirus; *BNoV,* bovine norovirus; *BRV,* bovine rotavirus; *BVDV,* bovine viral diarrhea virus; *C. parvum, Cryptosporidium parvum; Cpt β, Clostridium perfringens* beta toxin; *E. coli* K99+, *Escherichia coli* K99+. (From Cho Y-I et al.: Case-control study of microbiological etiology associated with calf diarrhea. *Veterinary Microbiology*, 166(3–4):375–385, 2013.)

Pathogenesis

Diarrhea can be the result of either increased secretion or decreased absorption. Bacteria such as enterotoxigenic *E. coli* and to some extent *Salmonella* cause neonatal diarrhea by secreting enterotoxins that stimulate increased intestinal secretions.[147,148] These changes are thought to be mediated by cyclic adenosine monophosphate (AMP) or cyclic guanosine monophosphate (GMP), calmodulin, and changes in tyrosine kinase activity.[149-151] The cell's structure is not affected, but the activity of the membrane pumps is altered, and there is increased secretion of chloride, bicarbonate, and potassium.[151-153] Heat-stable enterotoxin also induces bicarbonate secretion through the tyrosin kinase pathway and

inhibits the sodium hydrogen exchanger, reducing absorption of sodium from the GI tract.[153] Sodium absorption linked to glucose and amino acid transport across the mucosal epithelium is not affected.[154,155]

Protozoa and enteric viruses cause neonatal diarrhea as a result of the destruction of the absorptive villous epithelial cells.[156-159] Diarrhea results because intestinal digestive secretions continue while absorption is impaired.[160,161] In rotavirus and coronavirus infections this is further exacerbated by compensatory hyperplasia of the crypt cells. The crypt cells have secretory functions, and their multiplication adds to the secretory load.[160] Rotavirus can also stimulate intestinal secretion both at a cellular level and by stimulation of the enteric nervous system. This is associated with a viral nonstructural protein, NSP4.[162,163] NSP4 causes increases in intracellular calcium and inhibits the sodium glucose cotransporter. Increased intracellular calcium inhibits the translocation of disaccharidases from the intracellular vesicles to the luminal surface, decreasing the ability to digest carbohydrates and contributing to maldigestion.[151]

Continued feeding may result in more nutrients presented to the small intestine than the damaged villi can absorb[164,165]; excess nutrients are fermented in the large intestine, promoting bacterial overgrowth[149,166] and generation of organic acids and other deleterious compounds. The osmotic effect of the unabsorbed nutrients drags water into the gut and contributes to the diarrhea.[160] Marked inflammation is a feature of salmonellosis and clostridiosis. This contributes to diarrhea by increasing mucosal pore size and hydraulic pressures within the intestinal wall, by destroying absorptive cells, and by increasing prostaglandin production, which in turn stimulates secretory mechanisms within the enterocytes.[149,160]

On an individual animal basis, diarrhea is significant because of fluid and electrolyte losses. As long as the neonate can compensate for these losses, it will remain fairly bright and continue to suck. If the losses exceed intake, systemic effects of dehydration (salt and water loss) or acidosis are seen. Fluid is lost preferentially from the vascular compartment,[167,168] and cardiovascular collapse results. Acidosis has several causes, including fecal loss of bicarbonate, endogenous synthesis of L-lactic acid in response to dehydration and poor tissue perfusion, and D-lactic acid production through bacterial fermentation of undigested or malabsorbed milk within the GI tract.[169-174] Acidosis contributes

to the calf's malaise by increasing vascular resistance, impairing cardiac function by direct effects, and inhibiting the action of catecholamines. Esophageal groove function may be compromised in acidotic calves, promoting ruminal drinking with the consequences of further production of D-lactic acid in the rumen and subsequent ruminal acidosis.[174,175]

The neonate becomes depressed, loses its suck reflex, and becomes weak; if the disease progresses, recumbency and coma may develop. One cause of death is believed to be heart failure as a result of myocardial potassium imbalance due to the combined effects of potassium losses into the GI tract and the redistribution of potassium from the cells to extracellular fluid as a result of acidosis.[176-178] Hypothermia will also contribute to cardiac failure. In cases of enterotoxigenic *E. coli*, cryptosporidia, rotavirus and coronavirus infections, correcting the fluid, electrolyte, and acid-base imbalances restores the neonate's ability to walk and suck. A residual degree of malaise may persist, which can be attributed to inflammation within the gut wall and damage to the integrity of the mucosal barriers allowing invasion of enteric microbes or their toxins. If malabsorption persists, cachexia can develop—particularly if milk continues to be withheld as part of therapy—and death from malnutrition or hypoglycemia may occur.

Salmonella are invasive and release endotoxins in the systemic circulation. Clostridia produce exotoxins. Both endotoxins and exotoxins have profound systemic effects, which are often directly responsible for malaise, microcirculatory failure, and cardiovascular collapse. Correcting fluid and electrolyte disturbances in these infections will aid the neonate but will not overcome the effects of toxemia or bacteremia.

Etiology

Bacteria

Escherichia coli.

E. coli are part of the normal flora of the bovine GI tract. Pathogenic strains of *E. coli* possess virulence attributes that are involved in the pathogenesis of disease. Virulence attributes include adhesins, enterotoxins, and cytotoxins. Pathogenic strains of *E. coli* may be shed by adult cattle with transmission to neonates by the fecal-oral route. Sick neonates amplify environmental

contamination via prolific fecal shedding.

Enterotoxigenic *E. coli*.

Enterotoxigenic *E. coli* (ETEC) possess two virulence factors: fimbriae (pili) and enterotoxins. F5 (K99) and/or F41 fimbriae mediate adherence, and thermolabile (LT) and thermostable (STa and STb) enterotoxins stimulate a secretory response by intestinal crypt cells. Expression of fimbriae is influenced by the pH, with expression occurring at a pH of 6.5 or greater.[179] The distal small intestine is the initial site of colonization because the pH of intestinal fluid increases as it moves caudally, reaching this threshold at the ileum.[151] Bicarbonate-containing oral replacement fluids may favor the proliferation of ETEC, expression of the K99 antigen, and secretion of STa.[151] Oral electrolyte solutions containing acetate are recommended for treatment of ETEC diarrhea.[151]

Although some bovine-origin ETEC produce LT, most strains that cause diarrhea in neonatal calves produce STa heat-stable enterotoxin.[180] The STa enterotoxin and F5 antigen are plasmid-mediated virulence factors. Susceptibility to ETEC is age dependent according to the binding specificity of pili antigens to immature enterocytes.[181] Disease is typically observed in calves younger than 3 days of age, but concurrent infection with rotavirus may extend this window to 7 to 14 days of age.[182,183] Intestinal cells of calves older than 2 days of age acquire natural resistance to F5 adhesion.[181] Despite this, F5-positive *E. coli* have been isolated from healthy 4- to 12-week-old calves, and F5-positive ETEC are shed in feces for several weeks following experimental infection of newborn calves.[184] A recent worldwide study has shown that the prevalence of F5-positive ETEC appears to be decreasing.[185]

Attaching and Effacing *E. coli* and Shiga Toxin–Producing *E. coli*.

Attaching and effacing *E. coli* (AEEC) and Shiga toxin–producing *E. coli* (STEC) have also been identified as causes of diarrhea and dysentery in calves.[186,187] Disease is mediated by cytotoxic damage to the intestinal mucosa. Lesions may be observed in the ileum, cecum, and descending colon.[188] AEEC (verotoxin- or HeLa toxin–producing) induce a mucohemorrhagic colitis, with petechial or ecchymotic hemorrhages in the wall of the colon and rectum.[189-191] *E. coli* that carry this toxin often belong to O serogroups 5, 26, 111, 118, and

145.[190,192] Naturally occurring outbreaks have been reported in 2-day-old to 4-week-old calves.[193] Diarrhea and enteritis has been associated with naturally occurring *E. coli* 0157:H7 in 1- to 3-week-old calves in Argentina, the United Kingdom, and Korea.[194-196] The most common clinical sign is diarrhea, but dysentery, dullness, reluctance to move, weight loss, anorexia, abdominal pain manifested by bruxism, and dehydration are seen in some cases. The feces of affected calves can appear normal, but more commonly feces are watery yellow with blood.

STEC serotypes associated with dysentery in calves include O5:H-, O26:H11, O111:H-, and O113:H21[197]; these serotypes may produce Shiga toxins, those that are immunologically similar to the Shiga toxin produced by *Shigella dysenteriae* (STx1) and those that are immunologically distinct from *S. dysenteriae* Shiga toxin (STx2).[198] Bovine STEC produce either STx1 or STx2, or both.[199] AEEC that cause disease and do not produce enterotoxins or Shiga toxin is referred to as enteropathogenic *E. coli* (EPEC).

The prevalence of AEEC and STEC in calves and the incidence of disease caused by these strains are not clearly defined, as most diagnostic laboratories do not routinely screen for AEEC and STEC. A recent meta-analysis investigated the prevalence of STEC in 8053 isolates from calves in 19 countries included in 61 publications. The average prevalence of STEC isolated from healthy animals was 19.4% and from diseased animals was 18.2%. Moreover there was a significant decrease of STEC from pre-1990 to the present.[185] Similarly, in a study aimed at determining the clinical significance and prevalence of AEEC in Swiss cattle, fecal swabs of 93 cattle from two farms with calf diarrhea and of 54 cattle from two similar farms without clinical problems were screened for AEEC by PCR and colony-blot hybridization. On average, 21% of all cows were positive for AEEC by PCR, with no differences between farms with and without diarrhea problems. By contrast, AEEC were detected by PCR in 60% of animals younger than 2 years from farms with diarrhea problems, whereas only 32% of comparable control animals from farms without clinical problems had AEEC.

The relevance of AEEC and STEC has increased in recent years due to the zoonotic potential of the organisms. Cattle are a major reservoir of STEC and enterohemorrhagic *E. coli* (EHEC), including *E. coli* 0157:H7, which is the EHEC serotype most often associated with hemorrhagic colitis and hemolytic uremic syndrome in humans.[196,200]

Salmonella.

There are more than 2600 reported serotypes of *Salmonella*, yet fewer than 2% of these account for approximately 80% of the disease reported in livestock.[201] In cattle, more than 95% of salmonella associated with disease is in serogroups B, C, D, and E. *Salmonella* induces a wide spectrum of disease in cattle of all ages, ranging from inapparent subclinical infections to acute fulminant bacteremia, endotoxemia, and death. The variable manifestations of disease reflect the tissue trophisms of different *Salmonella* serotypes and the influence of challenge dose and host immunity. Common clinical signs associated with "salmonellosis" include fever, diarrhea, anorexia, depressed mentation, and dehydration. Many of the clinical signs are associated with endotoxemia. Systemic signs of endotoxemia include fever, tachypnea, tachycardia, scleral injection, leukopenia or leukocytosis, and weakness. Some serotypes, particularly *Salmonella typhimurium*, have a tendency to induce severe inflammation of the bowel mucosa, resulting in dysentery and passage of fibrin and mucosal casts. Fluid, electrolyte, and protein loss may progress rapidly and become life threatening if not corrected. With severe disease, animals rapidly become emaciated due to the catabolic state induced by release of tumor necrosis factor (TNF)–α. Sequelae occasionally observed following invasive *Salmonella* infections in neonates include septic osteoarthritis and meningitis.

Immunity to *Salmonella* changes rapidly during the first 3 months of life. At 2 weeks of age the LD_{50} for some virulent strains is 10^5,[202] at 6 to 7 weeks is 10^7, and at 12 to 14 weeks is 10^{10}.[203] In contrast, administration of 10^{10} *Salmonella* to 24- to 28-week-old calves failed to induce clinical signs of disease.[203] The numbers cited reflect the influence of age on immunity but should not be interpreted as absolute. Different age predilections, manifestations of disease, and virulence are observed between *Salmonella* serotypes and between different strains of the same serotype.[204,205] Although adults may serve as carriers and a source of infection of *S. dublin* infection for neonates, disease in adults is less common in mature cattle compared to calves. In contrast, *S. typhimurium* tends to manifest disease in an epidemic manner, causing illness in all age-groups. Environmental stressors such as heat, cold, and inadequate nutrition often play a role in herd disease outbreaks via compromising host immunity. Environmental conditions also influence the dynamics of *Salmonella* in the environment and subsequently the challenge dose encountered. *Salmonella* may proliferate in manure packs when they become wet; warmth promotes this process.

Calves on endemically infected farms may be infected in utero.[206] *Salmonella* challenge frequently occurs during the first 24 hours of life.[207] Exposure may occur via contaminated colostrum or milk, surface contamination of teats and udder, personnel, equipment, or the environment. Chronically infected carriers may shed 2.5×10^8 *Salmonella* in milk per day (25 kg of milk containing 10^5 *Salmonella*/mL).[208] Feeding utensils and personnel often play a significant role in transmitting *Salmonella* between calves.[209] *Salmonella* infects the salivary glands and is shed in saliva and nasal secretions.[210,211] Adequate cleaning and disinfection of feeding and medicating utensils is necessary to remove *Salmonella* contamination. *Salmonella* is sensitive to most disinfectants, but removal of contaminating organic debris is imperative, as the activity of disinfectants is reduced by the presence of organic matter.[212]

Flys, birds, and rodents may also play a role in disseminating *Salmonella* in feed, the environment, and between calves.[213,214]

Clostridia.

Although Clostridia are not commonly considered a major pathogen causing NCD, they are recognized as a cause of enteritis and abomasitis. In contrast to the other enteric pathogens, the disease tends to be more sporadic. Prerequisites for disease include the presence of the organism in the GI tract, sufficient carbohydrate or protein nutrients to support bacterial growth, and reduced GI motility that allows segmental overgrowth of bacteria within the GI tract.[215]

Clinical disease is associated with rapid bacterial overgrowth within the GI tract and subsequent exotoxin release. Passage of soluble carbohydrates or protein into the small intestine may induce rapid replication of Clostridia and elaboration of toxins from the vegetative state. Neonates are more susceptible due to the presence of trypsin inhibitors, which attenuate the digestion of clostridial exotoxins, in colostrum and milk for up to the first 10 to 21 days after parturition. Disease can occur in older ruminants if bacterial or plant-derived trypsin inhibitors are present in the feed.[215]

Management practices that increase the risk of clostridial-associated enteritis and abomasitis in beef calves include calf separation or environmental conditions that delay or interrupt normal nursing patterns.[215] Poor milk hygiene, intermittent feeding of large volumes of milk, and milk replacers with higher carbohydrate or protein concentrations contribute to increased risk in dairy

calves. Variables associated with delayed abomasal emptying include feeding large volumes in single feedings, feeding with an esophageal tube, high caloric content, and high osmolality milk.[123,215]

C. perfringens (see also Chapter 32) is the most important cause of clostridial enteric disease in calves. Although limited tissue invasion by *C. perfringens* does occur, most local and systemic lesions result from the effects of potent exotoxins. Some types of *C. perfringens* (mainly type A) are consistently recovered from the intestinal tracts of animals and from the environment, whereas others (types B, C, D, and E) are less common in the intestinal tracts of animals and can occasionally be found in the environment in areas where disease produced by these organisms is enzootic.[216] All five genotypes produce alpha toxin; type B also produces beta and epsilon toxin, type C produces beta toxin, type D produces epsilon toxin, and type E produces iota toxin. Multiplex PCR is used to identify *C. perfringens* genotypes from anaerobic culture of samples.

C. perfringens type A has been associated with acute hemorrhagic abomasitis in neonatal calves. Clinical signs include acute abdominal distention, colic, depression, and sudden death. Onset of clinical signs is rapid; affected animals become anorexic, depressed, or restless. Signs of abdominal discomfort are observed in approximately half of the cases and include treading on the spot and kicking at the abdomen. On physical examination, splashing and metallic sounds are heard on succussion of the distended abdomen; passage of a stomach tube fails to relieve the distention. Fecal output is reduced, and melena may be observed. Gross pathology may include abomasal ulcers, abomasitis, and abomasal tympany.[112,118] Trace mineral deficiencies of copper and/or selenium may also be involved in the pathogenesis of the condition.[217] A decreased prevalence of abomasal tympany and ulceration was reported in neonatal calves from herds having a history of these problems following implementation of a *C. perfringens* vaccination program.[217,218] Enterotoxemia caused by *C. perfringens* type A has been described in 2- to 4-month-old calves, with the condition observed more often in beef than dairy calves.[219] The disease is characterized by a high case fatality rate, sudden deaths, lesions of necrotic and hemorrhagic enteritis of the small intestine, and, most often, an absence of other clinical signs.[220]

C. perfringens type B is not commonly associated with neonatal diarrhea in calves. *C. perfringens* type C infections are most frequently observed in neonates younger than 10 days of age, reflecting the trypsin inhibitors

attenuating the digestion of beta toxin.[215,221] Vigorous, healthy calves develop hemorrhagic, necrotic enteritis and enterotoxemia, often accompanied by evidence of abdominal pain and neurologic signs that may include frenzied bellowing, aimless running, tetany, and opisthotonus. Death may be peracute, occasionally without other clinical signs, but may also follow a clinical course of several days.

Clostridium difficile has recently emerged as a pathogen in both human and veterinary medicine. Toxins released cause epithelial cell death and activation of the enteric nervous system, resulting in a malabsorptive and secretory diarrhea.[222] The role of *C. difficile* as a primary pathogen has not been established, as it has been detected in both healthy and diarrheic calves[223] and experimental infection has not induced disease.[224]

Campylobacter Species.

The clinical significance of *Campylobacter* spp. in calf scours is inconclusive. *Campylobacter* spp. are part of the normal intestinal flora. Experimental challenge studies have demonstrated the capacity of *Campylobacter jejuni* to cause enteritis in calves.[176,225-227] However, there is a paucity of convincing reports that demonstrate a causal association in naturally occurring cases.[228]

Viruses

Intestinal viruses multiply within enterocytes. As the epithelial cells are destroyed, villous atrophy develops. The various agents cannot be readily separated on clinical grounds. Diarrhea can vary in severity from soft to watery feces.

Rotavirus.

Rotaviruses are the most common cause of neonatal diarrhea in calves.[229,230] Affected calves are generally 5 days to 2 weeks of age, although disease can occur at 24 hours, particularly in colostrum-deprived calves (see Fig. 20.4).[231,232] This age predilection is thought to exist because many cows secrete antirotavirus antibody in their colostrum, which confers local protection against rotavirus attack until antibody levels in milk decline 48 to 72 hours postpartum.[233,234] Resistance to infection is not age dependent, but age-dependent resistance to clinical disease has been demonstrated.[235] Age

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restriction may be related to acquired immunity, as neutralizing antibodies increase with age and virus exposure. In addition, the expression of intestinal mucins and the rate of epithelial cell replacement and fluid absorption are also age dependent and have been shown to affect rotavirus infection and disease expression.[236]

Mature villous enterocytes of the small intestine are the main target for rotavirus.[159] Infected enterocytes are rapidly shed and replaced with immature squamous and cuboidal cells from the crypts, resulting in villous blunting.[159,237] Intestinal secretions are increased due to the compensatory hyperplasia of crypt cells and enterotoxigenic activity of the viral nonstructural protein NSP4.[162,163] Both increased secretory load and impaired absorption due to villus hypoplasia contribute to the diarrhea. It is thought that virulent strains replicate more quickly and infect a larger area of epithelium. Difference in rotavirus replication rates in the gut and age-dependent differences in the rate of enterocyte loss and natural replacement rate may explain the differences in clinical outcome. Concurrent infection with ETEC has also been shown to cause clinical signs at a later age than a single infection of either agent alone.[238]

Rotavirus of calves, lambs, kids, pigs, foals, mice, and children are morphologically identical. They are classified by the antigenic properties and/or sequence of the genes encoding the viral capsid proteins. Viral protein (VP) 6 is used to separate them into nine antigenically distinct serogroups, A to FI. Rotaviruses from serogroups A, B, and C have been isolated from cattle, and serogroup A is the most common cause of diarrhea in calves. Group B rotaviruses have been isolated from calves and adult cattle, but there is less information regarding their significance and prevalence in cattle.[239-243] Group B rotaviruses are more common in lambs than calves.[244] Group C rotaviruses have been isolated only from adult cattle.[242] Each serogroup may be classified further by G-types (glycoprotein) and P-types (protease-sensitive protein), which correlate to the serotype and/or genotype of capsid proteins VP7 and VP4, respectively.[245] A range of both serotypic and genotypic diversity and virulence has been reported within serogroup A.[235,246-248] Rotavirus is shed in the feces of infected animals, and transmission is primarily through the fecal-oral route. Clinical signs occur 1 to 3 days after infection and last for 5 to 9 days. Virus excretion commences with the onset of clinical signs and continues for 3 to 7 days.[235,249] Adult cows can be subclinically infected and intermittently shed the virus during pregnancy and especially at parturition.[250-252] It is likely that this is

the most common source of infection, with carrier cows infecting their calves and then these calves infecting other calves.[253] Calves from carrier cows have a significantly higher risk of clinical disease, and the birth of calves from known carrier cows have been associated with the beginning of an outbreak. Recovered calves can become reinfected and shed virus.[254]

The environment may be an important source of infection. Rotaviruses can survive in fresh water for more than 2 weeks at 23º C and for months in water or soil at less than 5º C.[255] They are also stable in feces and effluent for up to 9 months and therefore are likely to remain in calving areas from year to year.[256]

Coronavirus.

BCV commonly causes diarrhea in calves 5 days to 1 month of age.[138,143,257,258] Disease can occur within 24 hours in colostrum-deprived calves and has also been recorded in calves up to 5 months of age.[259] Respiratory infections are common in older calves and may be important in the epizootiology of enteritis.[259]

Calves may be infected with coronavirus by the oral or respiratory route.[249] Fecal shedding commences 3 days after infection and persists for up to a week; nasal shedding can be detected 2 days after infection and persists for 2 weeks. Once infected, calves initially excrete high levels of virus and are potent sources of contamination. Infection persists for weeks in apparently recovered calves, and they excrete low levels of virus for weeks.[260] Subclinical infection is common. Disease is more common in the winter months, and coronavirus survives in the environment from year to year.

Calves may be infected by virus shed by persistently infected cows.[261] Coronavirus has been detected in the feces of more than 70% of clinically normal cows.[252] The rate of virus excretion increases at parturition and in the winter months.[250,262] Calves born to carrier animals are at a significantly increased risk of developing diarrhea.[250]

The pathology of coronavirus is often more severe than rotavirus, resulting in a mucohemorrhagic enterocolitis. The virus infects both the small and the large intestine. In the spiral colon there is widespread destruction of the cells of the colonic ridges.[156,158] Virus replication occurs in the surface epithelium, especially in the distal half of the villi, resulting in stunting and fusion of the villi. Immature cells replace epithelial cells, and in severe infection there can be

areas of complete desquamation. Intestinal secretions continue, and absorption is impaired by reduced surface area. Undigested lactose accumulates in the intestinal lumen, often resulting in a secondary bacterial overgrowth, fermentation, lactate production, and an osmotic imbalance that draws fluid into the intestinal lumen. Most infections are self-limiting because the virus rarely attacks crypt epithelial cells.[261] In response to infection, the mitotic rate of crypt cells increases, producing immature cells that are more resistant to virus infection and that migrate up the villi to replace the damaged cells.

In experimental challenge studies, diarrhea develops 48 hours after infection. Calves are initially depressed and anorexic for the acute phase and may become dehydrated and pyrexic in a severe infection.[261] Severe infections can result in death due to dehydration, acidosis, shock, and cardiac failure. Respiratory signs are generally mild. Rhinitis, sneezing, and coughing may occur. Lesions may be found in the lungs but clinical signs of pneumonia are rare, except when secondary infection occurs.

Bovine Viral Diarrhea Virus.

BVDV occasionally causes diarrhea and thrombocytopenia in young calves outside the confines of the persistently infected disease model.[145,146] Colostral antibodies generally protect young calves from BVDV infection, but disease may occur due to FPT or the introduction of novel BVDV strains with new cattle or viral mutation in persistently infected homegrown cattle. BVDV is also thought to exacerbate infections due to other pathogens.[263] It has also been implicated in necrotic enteritis, an acute enteritis of 7- to 12-week-old beef calves reported in the UK.[264] Affected calves usually show oral ulcerations, particularly on the hard and soft palate. The buccal papillae are often blunted, and the tips may be ulcerated.[265] Some variants of the virus produce intestinal bleeding, petechiation, ecchymosis, or prolonged bleeding from venipuncture sites secondary to thrombocytopenia.[145,266-268] Hematologic findings often include leucopenia and thrombocytopenia. The disease must be differentiated from other causes of enteritis that are complicated by bovine papular stomatitis infection. Bovine papular stomatitis (see Chapter 32) is common in neonatal calves. It produces oral lesions that are hyperemic and red, with a central white area of necrosis and often a raised rim of proliferating epithelial cells. These lesions often involve the mucosa around the molars. They are usually of little consequence and their importance lies in the fact that they may be confused with

BVDV. One feature that helps identify BVDV ulcers is that they lack the zones of epithelial proliferation seen in bovine papular stomatitis.

Bovine Torovirus (Breda Virus).

Bovine torovirus has been detected worldwide[269-272] and has recently been implicated as an important cause of calf diarrhea.[141,142] Initially known as Breda virus, it is part of the *Coronaviridae* family. It has been relatively infrequently reported because it is difficult to recognize by electron microscopy (EM) and it cannot as yet be grown in cell culture, which has precluded the development of routine immunospecific diagnostic tests.[141] Laboratory studies using PCR have implicated it as the sole pathogen isolated in 25% to 30% of fecal samples from calves with diarrhea younger than 6 weeks of age.[141,142] It is also found in the feces and nasal secretions of asymptomatic animals,[141,143] implicating that the epizootiology is likely to be similar to that of rotavirus and coronavirus, with asymptomatic carriers acting as a reservoir of infection within a herd.[250] It is mainly a disease of calves younger than 3 weeks of age, with diarrhea commencing as early as 1 to 3 days after birth,[271,272] but clinical signs have been observed up to 10 months of age.[142,273] Clinically it produces mild to moderate diarrhea in calves under both experimental and field conditions.[272,274] The virus infects the distal half of the ileum, jejunum, and colon, resulting in necrosis of the crypts and villous enterocytes.[275,276] Clinical signs develop 24 to 72 hours after experimental infection.[272] It has also been isolated from the respiratory tract of cattle and associated with respiratory signs in calves at 1 month and 4 to 6 months of age.[277]

Other Viruses.

Norovirus, nebovirus, torovirus, astrovirus, enterovirus, kobuvirus, adenovirus, parvovirus, and picobirnavirus have all been associated with neonatal calf diarrhea.[278-283] The pathogenicity and contribution of these viruses to field outbreaks is uncertain. In a larger case control study, nebovirus and norovirus were isolated in higher frequency from diarrheic calves, suggesting they may play a role in neonatal scours in the United States.[284] The lack of readily available diagnostic assays for detection of these viruses in veterinary diagnostic laboratories limits their routine detection. As with rotavirus and coronavirus, the different viruses have been isolated from both healthy and diseased calves. Some

of the viruses such as norovirus and nebovirus do induce lesions in experimental infections of gnotobiotic calves. Others such as kobuvirus, astrovirus, enterovirus, and torovirus have not been demonstrated to or inconsistently induce pathology in gnotobiotic calves.[283]

Protozoa

Cryptosporidium.

Four species of *Cryptosporidium* have been identified in cattle: *Cryptosporidium parvum, Cryptosporidium andersoni, Cryptosporidium bovis,* and *Cryptosporidium ryanae.*[285] Conventional understanding has been that *C. parvum* is mostly found in preweaned calves, and numerous studies have shown a significant correlation between its occurrence and diarrhea.[286-289] *C. andersoni* is seen in low prevalence in asymptomatic adult cattle, and the two other common species, *C. bovis* and *C. ryanae,* usually infect weaned calves and yearlings and are generally nonsymptomatic.[287,288,290]

However, similar to the situation in humans, it is becoming apparent that the distribution of *Cryptosporidium* spp. varies between geographic regions.[291] In China, where preweaned calves are mostly infected with nonpathogenic *Cryptosporidium* spp., *C. parvum* is starting to appear in dairy calves associated with concentrated animal feeding operations.[292] However, in Sweden, studies have shown *C. bovis* to be the dominant species in dairy calves, even in this age-group,[293,294] and in suckler beef herds all four species were detected in calves younger than 3 months of age.[295]

C. parvum was initially thought to be a single species that affected both humans and a broad range of animals. Later, it was recognized that two distinct genotypes were present: type 1, which was found in human sources; and type 2, which was considered to be zoonotic and could be isolated from bovines and other farm animals such as sheep and goats.[296,297] The most recent molecular work recognizes that *C. parvum* genotype 1 isolates are *Cryptosporidium hominis,* a human-specific pathogen that is responsible for the majority of cases of cryptosporidiosis in humans in the United States.[298] Calves generally become infected between 1 and 4 weeks of age and display clinical signs for 4 to 14 days. Animals of all ages can be infected, but diarrhea is mainly associated with calves before weaning.[299] Cryptosporidial infections are asymptomatic in cattle

older than 4 months of age. *C. parvum* mainly infects the distal small intestine, but lesions are also found in the cecum and colon and occasionally the duodenum.[300] The parasite invades the superficial cells of the mucosa in the intestine but is surrounded by an invagination of the host cell membrane and remains extracytoplasmic. Parasitic invasion of the mucosa leads to epithelial destruction and mild to moderate villus atrophy, with microvillus shortening and destruction. This leads to impaired nutrient digestion and malabsorption diarrhea. Increased mucosal prostaglandin secretion promotes crypt secretion of chloride and bicarbonate and inhibits villus sodium chloride absorption.[301]

Affected calves often show no sign other than diarrhea but can show depression, dehydration, and anorexia.[302] Pyrexia and tenesmus have been noted.[303,304] Variable levels of morbidity have been reported, and mortality is generally low.[302,303,305] Other pathogens can be involved and are likely to contribute to the severity of the disease. Affected calves can take 4 to 6 weeks to recover. Cryptosporidiosis occurs less frequently in suckler calves at pasture, but when these calves are affected, outbreaks were reported to be more severe than those found in dairy calves, with mortality rates of up to 30%.[306] High mortality rates have been attributed to lack of herd immunity in seasonal calving herds where the transmission cycle is broken. Neutralizing antibodies in colostrum and milk reduce infectivity by immobilizing the parasite, blocking invasion, and inhibiting adhesion to host cells or direct cytotoxicity to *Cryptosporidium* sporozoites.[307] High mortality rates have also been associated with concurrent low levels of selenium, inadequate nutrition, presence of concurrent enteric infections, and specific management practices.[306]

Transmission is fecal-oral by ingestion of an encysted, sporulated oocyst. Transmission can be direct from host to host, by ingestion of contaminated food or water, and probably mechanically via flies.[308] A study of oocyst shedding in experimentally infected neonatal calves demonstrated a prepatent and a patent period ranging from 3 ± 6 and 4 ± 13 days, respectively.[286] The parasite is capable of autoinfection, sporulating within the intestine and immediately infecting adjacent cells, which can result in protracted clinical illness and relapses. The ability to autoinfect results in huge parasite burdens following very small infective doses. Calves 1 week to 4 months of age are most likely to be actively shedding significant numbers of oocysts, with peak shedding occurring between 1 and 3 weeks of age.[286,299,309,310] Infected calves can shed in excess of 10^6 oocysts/g of feces.[286,311] *C. parvum* oocysts have also been isolated from

adult cows, with herd prevalence ranging from 7% to 100%.[299,312-314] Mean shedding intensity reported for adult cows has ranged from 3 to 900 oocysts/g of feces.[314-316] It is likely that carrier cows are a source of infection for young calves.

The most critical factor affecting environmental oocyst survival is the temperature. Drying of oocysts has been shown to dramatically reduce their viability and infectivity in mice.[317,318] Oocysts can enter watercourses and groundwater by direct contact with cows or from runoff of rain or irrigation water from pastures and manure storage areas.[306,319] *Cryptosporidium* oocysts have been shown to survive in water for at least 12 weeks at 4º C.[320] Oocysts are resistant to chlorination of water and most disinfectants.[306] They have also been shown to survive in silage.[321] Wildlife may be a significant reservoir for *C. parvum* and act as a method of amplification and infection in the environment.[312,322,323]

Cryptosporidium spp. cause diarrhea and sometimes death in 3- to 30-day-old lambs. Protracted infections and mortality are most common in lambs infected in the first few days of life, as age resistance is seen after about 3 weeks of age.[169,324-326] Cryptosporidiosis has also been described in goats, where it affected 5- to 20-day-old kids, signs lasted from 3 to 7 days, relapses were not uncommon, and there was a moderate mortality rate.[327]

People working with diarrheic neonates should be warned of the risk of zoonotic disease. An outbreak of cryptosporidiosis has been described in caregivers in a veterinary hospital treating diarrheic calves. Affected people suffered from watery diarrhea, cramping, flatulence, and headache.[328] One person became infected as a result of handling soiled clothing.

Giardia.

Giardia is often found in diarrheic calves in association with other pathogens, but its relevance as a pathogen in its own right is unclear. Several authors have documented cases of diarrhea where *Giardia* infection has been implicated as the causative agent either by itself or in conjunction with *C. parvum* and *rotavirus.*[329-331] Affected calves are at least 2 weeks old, and often older than 1 month of age, with infection often becoming chronic and lasting for several months.[309,329,332-334] *Giardia* has a prepatent period of 7 to 8 days, and the delayed interval between birth and infection likely relates to high levels of

colostral protection against *Giardia* but low protective levels in milk.[335] Many calves were shown to have a poor specific immune response to the infection, accounting for the chronicity of the infection.

The significance of *Giardia* as a primary pathogen has been questioned by the observation of similar or lower rates of infection in calves with diarrhea compared to asymptomatic calves.[309,336] Treatment of affected calves with fenbendazole reduces the duration but not the number of diarrhea episodes.[331]

Coccidiosis.

Thirteen species of *Eimeria* have been reported in cattle.[337] *Eimeria bovis* and *Eimeria zuernii* have historically been the most common pathogenic species, but there are increasing reports of *Eimeria alabamensis* causing disease.[338-340] Transmission is fecal-oral. Infected animals pass unsporulated oocysts in their feces that sporulate and become infective. The sporulated oocysts are protected from the environment by a double cyst wall.[341] Moist, temperate, cool conditions favor sporulation, and oocysts can survive for several years. Sporulated oocysts can resist freezing to –8^{o} C for several months but are destroyed by high temperatures and dry conditions within a few weeks.[342] Under optimal conditions, sporulation can occur within a few days. The prepatent period of the two main pathogenic species is 15 to 20 days, and the patent period is around 11 days. *E. alabamensis* has a prepatent period of only 8 days and a patent period of 5 days.

Calves start shedding at about 1 month of age and shed for 3 to 4 months. *E. bovis* and *E. zuernii* schizonts first reproduce in the lower small intestine and then produce second-generation schizonts and gamonts in the cecum and colon, where they attack crypt cells.[337] These latter stages induce both local and more extensive lesions.

Outbreaks of disease in calves and lambs are often related to overcrowded and confined conditions. Up to 95% of infections are subclinical, causing decreased growth rates that are often unnoticed.[343] Clinical disease can be chronic or acute and is generally found in calves ages 3 weeks to 6 months, although animals of 2 years of age or older may be affected. In beef cattle the most common reports of clinical disease are associated with weaning stress.[344] Clinical signs may include diarrhea, ill thrift, increased susceptibility to pneumonia, tenesmus, increased mucus in feces, and hematochezia. Pyrexia, dehydration, and anemia may also

be observed. The disease is usually self-limiting without reinfection. Chronic disease is often underdiagnosed.[343] Calves appear weak and listless with pasty feces, drooping eyes, and a staring coat. Fecal oocyst count is low or negligible. Disease results from continual reinfection due to a heavily contaminated environment.

Nutritional Diarrhea

Producers often express the opinion that scours is caused by calves consuming too much milk. However, there is no documented research in healthy calves to support this. Calves fed 16% to 20% of body weight per day or allowed ad libitum access to milk have not developed problems with diarrhea.[345,346] However, in studies where calves are also infected with enteric pathogens, the diarrhea and depression were exacerbated by feeding normal amounts of whole cows milk in the early stages. Villous atrophy as a result of attack by an enteropathogen reduces the ability of the calf to digest nutrients,[161,165] and this predisposes to GI overload with fermentation of milk in the large intestine. Deliberate underfeeding of healthy calves also predisposes to diarrhea.

Studies in Scotland have shown that poor clotting ability of milk is associated with diarrhea and abdominal distention in calves 1 to 3 weeks of age in beef suckler herds.[347-349] Milk should clot within 7 minutes when incubated with rennet; the milk from the affected cows took at least 1 hour to clot and in some cases took more than 24 hours. Diarrhea may be caused by the rapid passage of undigested milk through the bowel or be secondary to infection by enteric pathogens facilitated by the conditions created in the bowel. Milks with poor clotting ability were shown to have low ultrafilterable calcium levels and low total magnesium levels.[349] Calves responded to treatment with 30 mL of 1 molar solution of calcium chloride (CaCl) administered three times daily orally (PO) and relapsed when this treatment was stopped. The majority of the milk samples clotted when 100 µL of 1 mol/L CaCl solution was added prior to the addition of rennet. The exact cause of the impaired clotting ability was not determined. The diet of one group of affected cows was shown to be low in calcium.[347,348] After a mineral mixture containing additional calcium was added to the diet of these cows, the clotting time was reduced to less than 12 minutes, treatment of the calves was stopped, and there was no recurrence of clinical symptoms.[347]

Calves seem to experience more problems with diarrhea when fed certain milk replacers. One study showed that calves performed well on milk replacers

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containing soy protein when healthy, but that during an outbreak of salmonellosis there was better weight gain and less mortality in calves fed whole milk.[350]

Establishing an Etiologic Diagnosis

An etiologic diagnosis is useful in selecting specific diagnostic and preventative regimes for bacterial infections. Establishing an etiologic diagnosis for viral infections will allow establishment of specific control methods and development of an appropriate vaccination strategy. Diagnosis of salmonellosis, cryptosporidiosis, and giardiasis can have public health implications. Once an agent has been identified, one of the major problems is in interpreting whether or not that agent is responsible for diarrhea in the individual or herd, since most agents can also be found in a percentage of normal calves (see Table 20.6).

Sample Collection

Appropriate selection of diagnostic specimens is required to achieve a meaningful diagnosis. Best results are obtained when fresh samples and specimens are collected from calves early in the course of disease. To establish causality, a fresh necropsy is informative, as it provides an opportunity to relate the presence of pathogens to a disease process. The quality of the information gathered is to a large extent determined by the quality of the samples submitted to the diagnostic laboratory. Autolysis and bacterial invasion of gut mucosa begin within 5 minutes of death. Autolysis is a common cause of poor tissue sections for histopathology; this may reflect prolonged postmortem interval or poor tissue preparation, handling, or transport. To avoid autolysis, formalin needs to distribute into the lumen of intestinal sections, hence intestinal specimens should be no longer than an inch long and the tissue to formalin ratio should be no greater than 1 to 10.

Diagnostic Tests

Bacterial Pathogens

Escherichia coli.

E. coli is a normal inhabitant of the GI tract. Isolation of *E. coli* from fecal

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samples or gut contents is therefore of no significance unless the isolates are demonstrated to possess virulent attributes that are consistent with the clinical and or pathologic presentation. Virulence attributes include adhesins, enterotoxins, and cytotoxins. Enterotoxigenic *E. coli* adhere to enterocytes in the jejunum and ileum.[351] On gross pathology, enterotoxigenic *E. coli* is associated with fluid-distended loops of bowel without enteritis.[352] Calves infected with enterotoxigenic *E. coli* have a mild inflammatory reaction in the small intestinal wall and some villous atrophy. In fresh specimens, sheets of gram-negative bacilli can be seen adhering to the small intestinal wall.[351] Definitive diagnosis of enterotoxigenicity rests on demonstration of the ability of the *E. coli* to dilate intestinal loops.[353] Enterotoxigenic *E. coli* can also be identified by the presence of F5 (K99) using antigen-specific immunoassays, including latex agglutination,[354] ELISA,[355] fluorescent antibody,[356] slide agglutination,[356] multiplex PCR,[199] real-time PCR (RT-PCR),[357] and rapid dipstick tests. A potential limitation of immunoassays is the specificity of the antibodies used, as strains of enterotoxigenic *E. coli* using non-F5 fimbriae will not be detected by these tests.[187,358]

Attaching and effacing *E. coli* (AEEC) and Shiga toxin–producing *E. coli* (STEC) mediate disease by cytotoxic damage to the intestinal mucosa. The confirmatory diagnosis of AEEC is made by microscopic examination of the small intestine and colon. A distinct histologic appearance occurs at the attachment sites, where clusters of gram-negative rods attach and form a scalloped appearance to the epethelial cells.[193,359] Diagnosis of *E. coli* infection may be achieved using phenotypic differentiation of pathogenic strains from nonpathogenic normal flora *E. coli* via bioassays or immunoassays for toxins and fimbriae. Immunoassays have been developed to identify the presence of STx1 and STx2 in feces as a presumptive test for the detection of STEC in cattle feces.[360-362] An alternative approach to identifying and differentiating ETEC, AEEC, and STEC is to use PCR to identify virulence-associated genes commonly found in these *E. coli* strains (F5, F41, enterotoxin, intimin, STx1, and STx2).[199] The significance of STEC, EPEC, and AEEC in bovine enteritis is unknown due to a lack of appropriate assays for routine detection and because of the widespread presence of verotoxin producing *E. coli* strains in healthy cattle that complicate the interpretation of detecting fecal shedding in sick animals.[363-365] Demonstration of verotoxin in cultures from bovine enteritis is not sufficient to imply a causative association.

Clostridium Species.

Clostridium perfringens has been associated with enterotoxemia and hemorrhagic abomasitis in calves.[216,220] *C. perfringens* are normal flora of the GI tract, hence isolation of *C. perfringens* from feces is not in itself diagnostic. Pathogenic strains of *C. perfringens* produce exotoxins, five of which (α, β, ε, ι, and enterotoxin) are involved in the pathogenesis of disease.[216] Production of specific toxins can only be demonstrated in a proportion of cases.[366] Isolation of toxin-positive *C. perfringens* from intestinal contents does not confirm a clinical diagnosis of bovine enterotoxemia, as almost as many *C. perfringens* isolates from normal calves produce toxin and toxin production cannot be demonstrated in as many as 40% of affected calves.[367]

A fresh necropsy is required to definitively diagnose clostridial enteritis. Observing many gram-positive bacilli in the mucosa associated with hemorrhagic enteritis is suggestive of clostridial enterotoxemia. Quantitative bacterial counts of intestinal contents at the site of the lesion have proven to be one of the most reliable methods for diagnosing enterotoxemia.[220] A *C. perfringens* count greater than 10^6/mL of intestinal contents is consistent with a diagnosis of enterotoxemia.[220] Demonstrating the presence of *C. perfringens* toxins or the capacity to produce toxins provides support for the diagnosis. Tests for detecting toxins or the bacteria's capacity to produce toxins include bioassays, immunoassays, western blot, and PCR.[368] The basis of the bioassay is to demonstrate protection of mice using antitoxin. *C. perfringens* enterotoxin is produced during sporulation. In vitro detection of enterotoxin production capacity by a *C. perfringens* isolate using western blot or immunoassays requires sporulation to occur. In vitro techniques to induce sporulation are not 100% efficient, so detection of enterotoxin using these methods are less sensitive than PCR is at detecting the genes required to produce enterotoxin.[369]

Salmonella Species.

Salmonellae are capable of causing disease in cattle of all ages. Neonatal infections are common. The classic pathologic lesion is fibrinous or fibrinonecrotic to ulcerative enteritis.[370] The severity of lesions is usually greatest in the distal small intestine and proximal large bowel. Hypertrophy of the mesenteric lymph nodes is a common finding.[371] Serosal hemorrhages may

be observed in the small and large intestine. Septic infarcts in the kidneys and inflammation of the gallbladder are less common findings. Pneumonia is a common finding with *S. dublin* infections, and gangrenous necrosis of distal extremities may also be observed.[372] Bacteremia is a feature of neonatal salmonellosis and may manifest as osteomyelitis and/or meningitis.

Isolation of salmonella from feces of calves with diarrhea is consistent with a diagnosis of salmonellosis but in itself does not necessarily establish causality, as salmonella may be isolated from the feces of apparently healthy calves.[373] Isolation of salmonella from tissues at necropsy is indicative of invasive salmonellosis. A definitive diagnosis of salmonellosis is based on the clinical presentation, pathologic lesions, and isolation of salmonella from tissues at necropsy.

There are numerous methods for isolating and detecting the presence of salmonella. These include direct culture, enrichment cultures, PCR (both conventional and real-time), immunoseparation, and immunoassays.

The process of directly inoculating tissues or other samples onto selective plating media, except in the case of acute infections, is usually nonproductive. Typically, with subclinical infection the number of salmonellae shed in feces is low relative to the high number of other bacteria. Fecal samples should be inoculated into selective enrichment media for optimal recovery of *Salmonella*. Selective-enrichment broths are formulated to selectively inhibit other bacteria while allowing *Salmonella* to multiply to levels that may be detected after plating. Internal organs that are normally sterile do not need to be inoculated on selective media; rather, they should be inoculated onto nonselective (blood agar) or weakly selective (MacConkey agar) media.

A number of rapid detection methods have been developed to expedite the detection of salmonella. These methods include electrical conductance and impedance, immunologic techniques, nucleic acid–based assays, and PCR. These methods generally take 24 to 52 hours to screen for or detect and identify salmonella. The majority of these tests, particularly the enzyme-linked immunologic techniques, require 10^5 cells/mL for reliable results. Accordingly, all of these tests involve a pre-enrichment stage, and some also involve a selective enrichment culture.[374] When salmonella is causing disease, clinically affected calves may shed 10^9 salmonella/gram of feces.[375] Detection of salmonella in clinical samples when it is the inciting cause of the disease process is not normally difficult when multiple samples are collected from a

representative sample of the affected population.

Viral Enteropathogens

Viruses are usually identified by direct examination of the feces, immunoassays, or fluorescent antibody examination of intestinal mucosa. Molecular techniques involving PCR and RT-PCR have been described for most pathogens but are not routinely available in all diagnostic laboratories. Electron microscopic examination of feces is not a sensitive means of detecting virus particles, but it has the advantage that many different types of viruses can be detected, including those such as parvovirus that are not recognized as common causes of diarrhea. The recent development of relatively inexpensive immunoassay diagnostic test kits makes these an attractive option; limited test-specific data regarding test sensitivity and specificity limit the application of some of these tests.

Coronavirus.

Coronavirus replication occurs in the epithelial cells of the distal half of the villi of the lower small intestine and colon. Infected cells die, slough, and are replaced by immature cells. In the small intestine these changes result in stunting and fusion of adjacent villi, and in the large intestine they lead to atrophy of the colonic ridges. On histopathology the tall columnar epithelial cells are replaced by cuboidal and squamous epithelial cells, and in severe infections there may be areas of complete desquamation.[376] Virus is shed in respiratory secretions and feces. There are several methods for detecting bovine coronavirus in feces. These include isolation of the virus in cell culture,[377] EM,[378] immunoelectron microscopy,[259] immunoassays[252,355,379-382] and molecular techniques including dot blot hybridization assays,[383] and conventional and real-time PCR.[384-387] Isolation of bovine coronavirus using cell culture techniques is not often performed in diagnostic laboratories, as the technique is difficult and requires viable virus (fresh samples or samples shipped on dry ice).[388] EM has been used as a standard diagnostic method for bovine coronavirus. Although the intact virion of bovine coronavirus is fairly characteristic in appearance, it is not uncommon for the identifying surface projections of the virus to be lost during sample preparation or storage, making it difficult to properly identify virus particles by EM.

Numerous ELISAs have been described for the detection of BCV antigen in feces. A number of companies have developed commercial kits using this

technology. The use of monoclonal antibodies rather than polyclonal antibodies is reported to increase the sensitivity and specificity of bovine coronavirus ELISAs.[382] The limit of detection for ELISAs range from 10^4 to 10^5 virions/mL of feces.

A one-step RT-PCR assay, targeting a 730-bp fragment of the nucleocapsid gene of bovine coronavirus, and a nested PCR assay, targeting a 407-bp fragment of the nucleocapsid gene, have been developed to detect bovine coronavirus. Compared to an antigen capture ELISA, the limit of detection for the RT-PCR and nested PCR was 10^3 and 10 virions/mL, respectively, compared to 10^5 virions/mL for the ELISA.[389,390]

Two quantitative RT-PCR methods have been used for detection of coronavirus in feces: TaqMan and SYBR Green.[386,387] Detection levels achieved using the TaqMan assay for coronavirus have been in the order of 10^1 to 10^9 RNA copies and were shown to be 1 log more sensitive than gel-based RT-PCR. The SYBR Green chemistry assay had similar detection levels but was unable to differentiate between different coronaviruses like the TaqMan assay.

Rotavirus.

Bovine rotavirus infects enterocytes of the intestinal villus; infected cells are predominantly in the distal third to half of the villus. The age at time of infection influences the distribution of the virus in the GI tract and the number of virions shed in feces. In experimental challenge studies, infection of 1-day-old calves resulted in a uniform distribution of virus throughout the small intestine.[391] Challenge of 10-day-old calves led to a patchy distribution of the virus, with maximal viral load observed in the mid small intestine.[391] Villus stunting is more pronounced in young calves.

Methods for detection of rotavirus include cell culture, fluorescent antibody staining, EM, immunoelectron microscopy, immunoassays, electrophoretic procedures, and conventional and real-time PCR.[239-243,354,355,380,392-395] Bovine rotavirus is difficult to isolate in cell cultures because of the cytotoxic nature of feces and fecal filtrates and because the virus is inconsistent in production of cytopathic effects.[393] The fluorescent antibody technique is simple, rapid, and specific, but rotaviral antigen is usually difficult to detect within 24 to 72 hours after the onset of diarrhea because rotavirus-infected epithelial cells are rapidly shed from the tips of the villi.[396] Comparative studies evaluating methods of

detecting rotavirus in feces give good agreement between antigen capture assays (ELISA, latex agglutination) and EM.[354,380,393,397] Direct immunoflorescence testing of fecal samples gives good agreement (90%) with electron microscopic examination for rotaviruses when samples are collected during the 24 hours following the onset of diarrhea[398] but poor agreement (33%) for field specimens submitted to a diagnostic laboratory.[393]

RT-PCR detection for rotavirus has been shown to be both highly sensitive and specific when the correct primers and probes are identified.[395] RT-PCR assays have the ability to increase the sensitivity of detection by up to 100-fold when compared to one-step RT-PCR.[399]

Bovine Virus Diarrhea.

Bovine viral diarrhea virus rarely causes diarrhea in neonatal calves.[146] Sporadic disease may be observed in persistently infected calves. Pathologic lesions include ulceration of the oral cavity, particularly on the hard and soft palate, and blunting of the buccal papillae.[265] Erosions may be observed in the esophagus, and necrosis of Peyer's patches may be observed in the ileum. Thrombocytopenia has been observed with BVD type II infections. Outbreaks of neonatal disease have been observed with this strain. Petechial and ecchymotic hemorrhages are a feature of this condition.[145,267,268] Hematologic findings often include leucopenia and thrombocytopenia.

Several options are available for the detection of BVD, including virus isolation,[400,401] RT-PCR,[402] immunohistochemistry,[403] and antigen capture ELISA.[404] Immunohistochemistry and antigen capture ELISA are used in most commercial laboratories (see Chapter 32 for more on this). Maternal antibodies reduce the sensitivity of the ELISA in young calves.[402]

Bovine Torovirus (Breda Virus).

Bovine torovirus produces cytolytic infections of villi and crypt enterocytes in the small and large intestine.[405] Bovine torovirus does not grow in tissue culture, cell culture, or embryonated eggs.[406] Therefore the large-scale preparation of reference antisera and antigens for the development of diagnostic tests has been precluded. Torovirus is capable of causing diarrhea in cattle, with disease observed most frequently in calves younger than 3 weeks of age.[143,272,274,276,407,408] Like other enteric viruses, bovine torovirus has been

detected in feces of normal calves; therefore detection of the virus in feces from diarrheic cattle cannot be interpreted as causal. The lack of diagnostic reagents has limited the study of bovine torovius, leaving questions about its epidemiology and relative importance in calf diarrhea.[142] Diagnostic methods that have been used to detect bovine torovirus include EM, immunofluorescence, antigen capture ELISA, and RT-PCR[142,272]

Protozoa

Eimeria Species.

Eimeria spp. are host specific. *E. bovis* affects primarily the mucosa of the cecum and the proximal part of the large intestine, whereas *E. zuernii* affects the mucosa of the cecum as well as the entire large intestine, including sometimes the rectum.[409] The clinical signs of bovine coccidiosis are associated with the final stages of the eimerian life cycle and commence shortly prior to oocyst shedding. Gross lesions in the cecum and large intestine range from semiliquid contents with little or no blood and few areas of epithelial sloughing to extensive hemorrhage and large areas of epithelial sloughing and necrosis of the mucosa.[409] The serosal surface is often reddened opposite the affected mucosal area and the submucosa and external muscular layers thickened by edema.

Oocysts usually can be recovered 2 to 4 days after the onset of diarrhea.[410] Oocysts can be identified microscopically either by direct smear or preferably following flotation or centrifugation methods. The sensitivity of coproscopical methods is reduced in diarrheic feces due to dilution[411] and particularly in severe *E. bovis* or *E. zuernii* infections when large amounts of blood, tissue, or mucus are shed. Oocysts become trapped within tissue and fibrin and are thus obscured in conventional coproscopy.[411,412] Oocyst counts of 5000 per gram of feces or greater are considered significant in cattle.[341] Identification of oocysts in feces is not diagnostic for clinical coccidiosis, as the parasite is frequently detected in small numbers in the feces of healthy cattle.[413] When investigating scour problems, multiple samples should be collected for oocyst counts to provide an indication as to the level of infection within the group. The potential for discord between clinical signs and fecal shedding limits the diagnostic utility of a single sample from an individual animal.

Giardia.

Giardia infection is not associated with changes in intestinal villus height or crypt depth. However, transmission EM has been used to demonstrate a reduction in microvillus surface area.[414] Diagnostic methods for detection of *Giardia* include direct microscopy, immunomagnetic separation, fluorescent antibody staining,[330,415] ELISA,[416] and PCR.[417,418] When using direct microscopy, fecal samples should be examined within 24 hours of collection. Trophozoites and cysts are concentrated via density gradient centrifugation or filtration.[309,419,420]

Cryptosporidia.

Cattle are commonly infected with four *Cryptosporidium* spp.: *C. parvum*, *C. bovis*, *C. ryanae*, and *C. andersoni*. *C. parvum* is of most concern due to the potential of some subtypes to infect humans.[291] No matter which PCR tool is used in genotyping or subtyping *Cryptosporidium*, all broadly specific tools have the problem of detecting only the dominant genotype in the specimen because of the inherent nature of exponential amplification by PCR, and consequently mixed infections are difficult to detect.[291] *Cryptosporidium* infections are mainly concentrated in the distal small intestine, but lesions may also be found in the cecum and colon, and occasionally in the duodenum.[421] The pathologic findings associated with *Cryptosporidium* are a mild to moderate villous atrophy, villous fusion, and changes in the surface epithelium with infiltration of mononuclear cells and neutrophils in the lamina propria.[421]

Calves infected with *C. parvum* usually develop diarrhea in 72 to 96 hours; diarrhea is observed for 4 to 23 days,[422] during which time oocysts are excreted in feces. *C. parvum* and *C. andersoni* have morphologically distinct oocysts and differ genetically.[423] *C. bovis* and *C. ryanae*, which are morphologically identical to *C. parvum*, are mainly responsible for diarrhea in weaned calves,[289,424-426] but they have also been found in all age-groups of cattle.[295,427] Oocysts are stable in feces for many days at room temperature.[428] Laboratory methods for the diagnosis of cryptosporidial infections include microscopic examination of fecal smears or fecal preparations, immunoassays, and PCR. Cryptosporidia oocysts are small (4 to 6 µm in diameter) and easily missed on a fecal smear. Because fecal smears do not concentrate the oocysts, this technique is less sensitive than fecal flotation. Concentration of the protozoa is achieved by

salt[429] or sugar flotation. Special stains may be used to facilitate detection of cryptosporidia during microscopic examination. Differential staining techniques are useful to distinguish cryptosporidium oocysts from other fecal components (especially some yeasts) of similar size and shape.[430-433]

A number of immunoassays have been developed for the detection of cryptosporidia. The detection threshold of the different methods have been reported to be 3×10^5 oocysts/g for a monoclonal antibody–based antigen capture ELISA, compared with 1×10^6 oocysts/g detected by examination of acid-fast stained fecal smears and 1×10^3 oocysts/g detected by indirect immunofluorescence.[434] The detection threshold may be further enhanced by using a combination of immunomagnetic separation coupled with immunofluorescent microscopy. With this combination it is possible to detect as few as 10 oocysts/g.[435] A number of dipstick immunoassays have also been developed. The detection threshold for this technology is reported to be 1×10^3 oocysts/g.[436] This technology offers the potential for rapid, cost-effective detection of cryptosporidia in fecal specimens.

Molecular techniques have been described for detection and typing of cryptosporidia.[296,425] The capacity to differentiate the different genotypes makes this approach useful for epidemiologic studies of cryptosporidia.[425]

Multiplex RT-PCR

Several multiplex RT-PCR assays have been developed for the simultaneous detection of the major enteric pathogens.[437] The multiplex quantitative RT-PCR offers significant advantages over individual pathogen testing in that 96 fecal samples can be tested at the same time within 4 hours. This offers increased efficiency through decreased cost, labour, and turnaround time. Another major advantage of RT-PCR is the ability to detect and measure the accumulation of amplicon during the reaction, thus allowing precise quantification, which can be important in determining causation.

Risk Factors for Neonatal Calf Diarrhea

It is important to identify risk factors, both to set up effective preventive programs and to initiate control in the face of a disease outbreak. The etiology of calf diarrhea is multifactorial, so it is common for several factors to contribute to

the outbreak and perpetuation of disease in a herd.

Dystocia

Dystocia is associated with neonatal calf diarrhea in more intensive beef and dairy systems[137,438] and is a risk for preweaning mortality, with more than 40% of preweaning deaths occurring in calves born to cows suffering dystocia.[439-441] Dystocia affects the ability of the calf to suckle colostrum, resulting in decreased serum IgG levels; consequently calves that survive dystocia are two to four times more likely to become sick in the first 45 days of life.[442-444] Calves that experience dystocia are likely to have edema of the head and tongue, making suckling difficult. They are weak, exhausted, and likely to be recumbent for longer, increasing exposure to fecal pathogens.[257]

Stocking density and cow grouping of preparturient cows, timing of calving, breed, cow pelvic area, multiple calvings, calf sex, gestation length, and dam nutrition all influence the risk of dystocia.[445,446] Low- and high-birth-weight calves are at greater risk of mortality.[440] Small calves experience greatest mortality at parities greater than one, and large calves experience greatest mortality at first parity.[447] Increased feed intake before calving will increase calf birth weight but does not increase the risk of dystocia unless cattle become obese.[448-450] Weight loss is associated with prolonged labor, increased dystocia, and increased perinatal mortality.[450,451]

Dam Parity

Calves born to first- and second-parity cows have an increased mortality compared with those born to older cows, and the risk of diarrhea in calves born to heifers is 3.9 times greater than those born to cows.[440,452,453] Heifers have an increased risk of dystocia, lower colostrum quality, and inferior mothering ability.[442,443,453-455] The difference in the rate of dystocia between the first and second parity is usually much greater than between the second and subsequent parities.[456] The stocking density of heifers is often increased prior to calving to facilitate observation, with the consequence of exposing their calves to a greater environmental pathogen load. These factors are all likely to contribute to increased morbidity, and consequently the percentage of heifers in the herd will affect the risk of diarrhea. Calves from carrier heifers shedding rotavirus and bovine coronavirus are more likely to develop clinical disease than calves born

to carrier cows.[250] Studies in dairy herds have shown that there is a positive correlation between the number of young stock in the herd, the overall herd size, and herd production with the risk of neonatal calf diarrhea.[457-459]

Colostrum Management

Many studies have shown that FPT results in increased risk of neonatal calf diarrhea in beef and dairy herds.[460-467] Calves are able to absorb immunoglobulins only for a limited time after birth, and the subsequent serum Ig concentration is determined by the perinatal state of the calf, the timing of colostrum ingestion, and the mass of Ig consumed.[468] Colostrum also provides local (enteric) immunity, with the major benefits lasting for about 3 to 4 days after birth.[469-471] After this period, milk contains little Ig, and most colostral antibody has been cleared from the intestine. Colostral antibodies protect against rotaviral infections in the first 4 days of life[233,234]; in contrast, anti-F5 (K99) *E. coli* antibody is present in low amounts in unvaccinated cows,[472] and enteric *E. coli* infections are usually seen in very young calves. After 4 days the protective effects of colostrum are primarily due to systemic antibodies, and there is evidence that these can leak back into the gut and probably give limited long-term protection against diarrhea.[473] Colostral quality is affected by colostral volume, genetics, nutrition, parity, timing of collection, climate, and periparturient vaccination.

Beef Cow Herd Management

In beef herds, high stocking rates in the calving area and the use of one calving area are major risks for neonatal calf diarrhea.[474,475] The practice of leaving nursing dams and calves with calving cows further increases stocking rates and promotes disease transmission.[462] The weather at calving affects both pathogen survival and calf comfort, and shelter in the nursing area is associated with decreased mortality due to neonatal calf diarrhea.[452] Major calf scour pathogens can survive in the environment for months or years in cool, wet conditions, and consequently both the incidence and mortality from diarrhea increase with prolonged use of the same paddock or a longer calving season, and the incidence of diarrhea increases as the calving season progresses.[441,452,453] Adverse weather conditions cause cows to move to shelter and shade, concentrating cows and calves in small contaminated areas. Calves born into a contaminated

environment potentially become infected during or shortly after birth and shed enteropathogens even when they remain clinically normal. This further increases the environmental load of infectious agents, infecting adult cattle as well as calves. The outcome of host-pathogen interactions is largely influenced by the pathogen challenge dose and the age of the animal, with clinical disease becoming more frequent both in younger animals and as pathogen exposure increases (Fig. 20.5).



FIG. 20.5 Areas where cows and calves camp can act as a significant reservoir of calf diarrhea pathogens in a pasture-based suckler beef system.

Farms that purchase replacement calves younger than 4 weeks old have an increased mortality due to neonatal calf diarrhea.[452] Purchased calves may introduce new pathogens that challenge a susceptible population. Stress from transport and arrival at a new location may increase shedding and predispose to clinical disease, increasing the environmental pathogen load. The risk of pathogen introduction increases when introduced calves are commingled from multiple properties prior to introduction.

Intensive Calf-Rearing Systems

Intensively reared calves have an increased risk of diarrhea associated with housing, nutrition, and weaning. Variables that have been observed to increase

the risk of scours include feeding milk once versus twice a day within 14 days of birth,[476] placing preweaned heifers in groups of seven or more, damp versus dry bedding,[476] a male having primary responsibility for the care and feeding of preweaned heifers, calves not receiving hay or other roughages until more than 20 days old, and feeding mastitic or antibiotic milk versus whole milk.[477] Use of individual calf hutches has been reported to increase the risk of scours but also to reduce mortality.[476]

Factors associated with a decreased risk of cryptosporidia infection include ventilation in calf-rearing areas, daily addition of bedding, daily disposal and cleaning of bedding, and use of antibiotics.[478] The effect of feeding milk replacer versus whole milk on shedding of *Cryptosporidium* has varied between studies.[478-480] Postweaning practices that reduce risk of infection include moving animals after weaning, cleaning soiled bedding, and use of antibiotics and ionophores as preventive measures.[478] Maternity management factors that reduce risk of infection include vaccination of the dam against *E. coli*, rotavirus, and coronavirus; removal of the calf from the dam within 1 hour of birth; use of fresh colostrum to feed calves; and having a concrete floor in the calving area.[478-480] The reduced *Cryptosporidium* shedding in calves from vaccinated cows is unlikely to be a direct effect but more likely reflects a better standard of management. General management factors that influence risk include the total number of dairy cattle, the total number of other species of livestock on the farm, and the distance of the barn water source from the septic system.[478]

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Herd Strategies to Prevent Neonatal Diarrhea

Management practices that reduce the risk of calf scours also promote good health, improve growth rates, and reduce the risk of transmitting other enteric pathogens such as *Mycobacterium paratuberculosis*.

The principles of prevention are to:

1. Minimize pathogen exposure
2. Ensure adequate colostral intake
3. Boost specific and nonspecific immunity
4. Promote farm biosecurity

It is good practice to conduct a risk assessment for calf scours as part of any herd health program in beef or dairy cattle, as well as when investigating an outbreak. The risk assessment should (1) thoroughly evaluate all potential risks that may affect the four principles above, (2) determine what actions are needed and at what relative cost to mitigate those hazards, (3) share the action plan with all members of the team, as well as keep records to show what was done and whether the actions were successful.[481]

Minimizing Pathogen Exposure

Enteric pathogens may be shed in large numbers by calving cows, scouring calves, and asymptomatic cohorts, especially those up to 4 months of age. All enteric pathogens can survive in the environment for months or years in moist, damp conditions. Other sources of infection include people that have treated or handled infected calves, contaminated water, contaminated colostrum, milk, or solid feed and equipment that has been used to feed or medicate infected calves.[210,250,252,306,315,482-484]

Minimizing Pathogen Exposure in Dairy Herds.

Strategies to prevent disease in dairy calves focus on calving cows in a clean environment; removing calves from cows at birth; feeding adequate good-quality colostrum; placing calves in a clean, dry environment separate from other stock; feeding good-quality milk or milk replacer; providing adequate shelter; and providing access to water and high-quality calf pellets. Microbial contamination

is an important determinant in the quality of colostrum and milk. Good sanitary practices are required for the harvest, storage, and feeding of both products. Microbial contamination of colostrum compromises passive transfer and in the case of pathogens like salmonella may lead to a direct pathogen challenge. Similarly, feeding milk with a high bacteria count increases the risk of diarrhea. On-farm heat treatment of colostrum (60° C for 1 hour) significantly decreases bacterial numbers without affecting IgG levels.[485] Calves that are fed heat-treated colostrum have significantly higher IgG levels and lower incidence of neonatal calf diarrhea when compared to calves fed untreated colostrum.[486]

In dairy systems, where calves are reared by hand, the number of young stock on the farm and the incidence of respiratory disease are positive predictors for calf diarrhea.[457] Cleanliness of the calving area is important; bedding should be changed between each calving, and large numbers of cows should not be cycled through a few stalls.[457] Prior to calving the udder and the perineum of the cow should be cleaned. The calf should receive adequate colostrum.[475] In recent years the use of calf hutches has gained widespread acceptance for managing calves after they have been separated from their dam. This system provides individual isolated housing for each calf. Cleaning is facilitated because the hutches can be moved to new sites between calves. Keeping preweaned calves in groups larger than six puts them at increased risk of diarrhea.[459]

Cleaning and disinfection after each calf batch plays an important role in reducing contamination in housed calves. The key to decontamination is the physical cleaning. Physical removal of organic contamination through scrubbing is preferred to application of high-pressure sprays, which can aerosolize organisms and allow dissemination. On smooth, ideal surfaces, physical removal of visible contamination by thorough washing with soap and water removes 99% of the microbial load (2 logs). However, on typical housing surfaces, washing removes only 90% (1 log). Application of disinfectant after washing is important to eliminate remaining pathogens and to prevent bacterial pathogens from proliferating. Physical cleaning cannot be replaced by applying disinfectants in larger quantities, as organic material neutralizes most disinfectants. In regard to disinfectants, pathogen elimination is time dependent.[487] Other important variables that influence the effectiveness of disinfectants and rate of pathogen reduction include concentration, temperature, pH, and water hardness.

In addition to cleaning between batches, it is important to clean nipple buckets and other feeding utensils between each feed. Separate equipment should be

used to administer oral electrolytes and colostrum. *Salmonella* and coronavirus are shed in saliva and can contaminate equipment used for oral medication. Washing with warm, soapy water is required to remove the fat residue left by milk- and colostrum-handling equipment

Several microbial characteristics should be considered when disinfecting equipment that contacts calves. Rotavirus is susceptible to sodium hypochlorite but is relatively resistant to many common disinfectants, such as chlorhexidine. As a nonenveloped virus, rotavirus is not affected by soaps; washing with soap alone actually may spread the virus around on the washed surface.[488] Coronavirus is an enveloped single-stranded RNA virus and is not as stable in the environment as rotavirus. Because of their envelope, these viruses retain infectiousness better at lower rather than higher relative humidity[489] and are considerably more sensitive to soaps and common disinfectants than are nonenveloped viruses. Because *Cryptosporidium* can autoinfect the original host, the infectious dose can be small. In the environment, cryptosporidia are extremely resistant to most veterinary disinfectants except 5% ammonia, 6% hydrogen peroxide, 10% formalin, or 2% cresolic disinfectants.[317,490-492] They survive very well in water, requiring 4 to 11 weeks to decline by one log.[493] On the other hand, cryptosporidia are susceptible to drying, with oocyst infectivity declining in 1 to 4 days.[318]

The most readily cleaned surfaces are made of smooth, impervious materials such as plastic and varnished wood (Table 20.8). Usually buildings are cleaned and then either disinfected or fumigated.[494] Many disinfectants are inactivated by organic matter; viruses, coccidia, and particularly cryptosporidia may be resistant to their action (Table 20.9). Disinfectants may also be toxic and are best applied by personnel wearing rubber gloves and respirators (if indoors). In general, potent phenolics such as cresol (cresylic acid) are very useful for disinfecting dirty surfaces because they are not inactivated by organic matter and are effective against gram-negative bacteria and viruses. The phenolics are highly toxic and leave lingering odors. Hypochlorite solutions (5 g available chlorine/L) have a broad spectrum of action but are rapidly inactivated by organic matter. They would be useful as a final disinfectant on previously cleaned surfaces. Because hypochlorite is unstable, it is unlikely to leave toxic residues. Iodophors are not very effective against rotavirus, particularly if organic matter is present. Virkon S™, a disinfectant/cleaner containing potassium monopersulfate as the active ingredient, is effective for all pathogens

except cryptosporidia. Normally a 1% solution is used and is prepared by mixing 10 g of powder in 1 L of water. Contact time should be a minimum of 10 minutes. Virkon S™ has the advantage of having a detergent action that facilitates cleaning.

TABLE 20.8

Ability of Bacteria to Persist on Various Types of Surfaces Found in Farm Buildings

	Total Bacterial Count per 100 cm^2	
Material	**Uncleaned**	**Cleaned**
Brick	76,000	
Painted wood	34,000	
Block board	116,000	
Ply board	77,000	23,000
Fiber board	57,000	
Chip board	35,000	
Formica	29,000	
Polystyrene	29,000	
Metal		14,000
Concrete		13,000
Plastic	16,000	100
Varnished wood	5000	

Modified from Morgan-Jones SC: In Collins E et al: *Disinfectants: their use and evaluation of effectiveness,* London: Academic; 1981, p. 199.

TABLE 20.9

Efficacy of Disinfectants Against Enteropathogens[408, 446–451]

		Efficacy		
Group	**Compound**	**Gram-Negative Bacteria**	**Rotavirus**	**Cryptosporidia**
Phenolics	Hexachlorophene	+	++	
	Triclosan	+	++	
	Cresol (coal tar derivation)	++	++	–
	Phenol	±	–	–
Halogens	Povidone-iodine	+	–	–
	Hypochlorite	+	+	
Biguanides	Chlorhexidine	++	–	
Aldehydes	Formaldehyde[a]	+	+	+
	Glutaraldehyde	+		
Quaternary ammonium	Benzalkonium chloride	+	+	–
	Cetrimide	+		
Ammonia	Ammonia			+

Oxidizing agent	Potassium monopersulfate	+	+	–

[a]Requires long contact time—18 hours to kill cryptosporidia.

[++], Highly effective, not inactivated by organic matter; +, moderately effective, inactivated by organic matter; ±, some effect; –, little effect.

Formaldehyde is one of the few agents that is effective against cryptosporidia. It requires a long contact time and is highly toxic. It is usually used for terminal fumigation in buildings that can be tightly sealed. Formaldehyde gas is best generated by heating paraformaldehyde (5 g/m^3 of building) in an electrically heated pan at 204° C. Some manufacturers of paraformaldehyde provide pans specially designed for this purpose. The pans should be placed no more than 30 m apart and arranged so that electricity to the pan can be controlled from outside the building. There must be a safety mechanism to ensure that the pan does not overheat and cause a fire. The building must be sealed for at least 24 hours and cannot be entered until it has been thoroughly ventilated. Formaldehyde gas can also be generated by boiling formalin or by adding potassium permanganate to formalin. The latter method generates a violent chemical reaction and carries risks of explosion. Formalin aerosol generators are ineffective.[495] After cleaning and disinfection one should allow a rest period for the building to ventilate before reintroducing calves. It is very important that cleaning and disinfection be thorough. Attention should also be given to rodent control, since rodents can be a reservoir for *Salmonella*.[496]

Minimizing Pathogen Exposure in Beef Herds.

In beef herds, calving areas should be located to take advantage of natural shelter and drainage and rotated from year to year to avoid pathogen buildup.[453,474,497,498] Pregnant cattle are moved into a clean paddock no more than 2 weeks prior to the start of calving. It is best that cows and heifers are managed separately until after calving. This gives the opportunity to provide better feed to the heifers and to minimize infection between the groups. Confined, wet, or muddy areas should be avoided for calving cows, and where they need to be used, the stocking rate should be decreased. Feed-out areas should be rotated to encourage cow disposal and separated from watering points. When pasture for calved cows is limited, supplementary feed should be fed to dry cows to ensure enough fresh pasture for calving and nursing cows. Clean water should be available in a trough that is accessible to cows and calves. Chronically sick animals, weak calves, and cows with no milk should be

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removed from the calving paddock and kept isolated from the herd.

Grazing and reproductive management have a significant impact on pathogen load. Where appropriate to grazing management, calving paddocks should be left vacant during the summer. In colder spring calving systems that hold cattle on a small protected site during the winter, use of this same area as spring calving pastures can significantly affect the incidence and severity of calf scours. The buildup of pathogens and organic matter is problematic where there is a heavy stocking density. These areas should be avoided for calving or should be adequately cleaned and rested to minimize the disease load. For producers that manage periparturient cows in smaller calving paddocks to facilitate supervision, the emphasis should be on minimizing the stocking density in the calving paddock by removing cows and calves shortly after parturition.[474,497] Alternatively, cows can be moved away from cows with calves every 1 to 2 weeks or more frequently in large herds. Young calves in the calving paddock will markedly increase the rate of pathogen buildup and the subsequent challenge to newborn calves. Moreover the increased stocking rate will amplify stress, affecting both transfer of passive immunity and the ability of young calves to rest. During its first 6 weeks of life, a healthy calf will spend 75% of its time each day lying.[499] Often calving areas are small due to the perceived need to assist cows for dystocia.[498] Well-grown and appropriately fed heifers mated to suitable sires can minimize the need for assistance. Beef cows with calves at foot moved from the calving paddock should be moved into nursing groups that have a maximum age range of 4 weeks and a low stocking rate. Groups should not be mixed until all calves are at least 4 weeks old.[474,497,498] Reproductive management influences pathogen load by determining the age spread of the calves. Sick calves amplify environmental contamination. A prolonged calving period leads to a buildup of contamination so that calves born later in the calving period experience an increased pathogen challenge. It is desirable to maintain a calving period that is less than 60 days.

One system that meets these requirements is the Sandhills calving system.[481] This management system minimizes contact among beef calves by (1) segregating calves by age to prevent direct and indirect transmission of pathogens from older to younger calves, and (2) scheduled movement of pregnant cows to clean calving pastures to minimize pathogen dose-load in the environment and contact time between calves and the larger portion of the cow herd. The objective of the system is to recreate the more ideal conditions that

exist at the start of the calving season during each subsequent week of the season.[500] Rather than using a single large calving pasture, the Sandhills calving system divides large pastures into a series of smaller ones based on length of the calving season and the predicted calving pattern of the cows. Pregnant cows are placed in the first of the smaller pastures. After cows have been calving for a week, cows that have calved remain in the pasture with their calves, and cows that have not yet calved are moved to an adjacent small pasture. After another week of calving in the second pasture, those that have calved are left in the pasture with their calves, and those that have not calved are moved to the next pasture. This is repeated throughout the calving season. The result is cow-calf pairs distributed over multiple pastures, each pasture containing calves within 1 week of age of each other. Cow-calf pairs from different pastures may be commingled after the youngest calf is 4 weeks old and all calves are considered low risk for neonatal diarrhea.[481,500] This system can be adapted depending on the size of the herd; in some herds, moving cows every 10 to 14 days may be appropriate. Early pregnancy testing combined with good record keeping will also allow later-calving cows to be added to the system after 3 to 4 weeks. To implement this system, a plan is required well in advance of the calving system that identifies pastures of appropriate size with suitable pasture, water, and shelter, and the feed available in them managed in accordance with the calving pattern.

Boosting Specific and Nonspecific Immunity

Ensuring adequate passive transfer is necessary to achieve enhanced pathogen-specific immunity through maternal vaccination. Colostrum management is discussed in detail in Chapter 19.

Enterotoxigenic *E. coli.*

The protective efficacy of enterotoxigenic *E. coli* bacterins is well documented[501-504] (also see Chapter 48). Because ETEC scours occurs during the first 3 days of life, the neonate does not have time to mount a protective immune response to vaccination. Protection is afforded by vaccinating cows in late gestation so as to ensure high concentrations of anti-K99 colostral antibodies. Good maternal management is required to ensure that the calf receives the maternal antibodies. Anti-pilus antibodies block the adhesion of the pathogen to enterocytes and subsequently prevent disease. In general, it is

recommended that the vaccines are given 6 and 3 weeks prior to calving. Studies with some vaccines have shown that the vaccine is still effective if the priming dose is given 18 months before calving and boosting is carried out in the second half of gestation.[505] Clinical experience in beef farms suffering severe outbreaks of *E. coli* F5 (K99) diarrhea indicates that vaccinating cows that are more than 10 days from parturition can give considerable protection against death from enterotoxigenic *E. coli* infection.

Products containing monoclonal antibodies against F5 (K99) antigen have been shown to reduce the severity of diarrhea when calves are experimentally challenged a few hours after receiving the product.[506] In field situations, however, monoclonal products can have a low efficacy, presumably because a single dose only provides a short period of enteric protection. Antibody supplements are expensive, and vaccination of the dam to boost colostral immunity usually will be more cost-effective. On farms experiencing an outbreak of neonatal diarrhea caused by F5 (K99) *E. coli*, there may be a place for the use of these products until vaccinated cows begin to calve. However, short-term administration (once a day for the first 3 days of life) of an antibiotic to which the *E. coli* is susceptible is also highly effective in preventing diarrhea in herds experiencing outbreaks of enterotoxigenic *E. coli*.

Salmonella.

The successful reduction of *Salmonella* prevalence in livestock on a national level via implementation of a *Salmonella* control program emphasizing immunoprophylaxis with modified live and killed *Salmonella* vaccines indicates the potential benefits that can be derived from the application of effective *Salmonella* vaccines.[507] *Salmonella* vaccine studies in cattle have focused on killed whole cell (bacterins), bacterial fractions (subunit), and attenuated modified live *Salmonella*.

There are conflicting reports regarding the efficacy of *Salmonella* bacterins. The reported efficacy of *Salmonella* bacterins ranges from good to ineffective.[508-516] The overall consensus of these reports is that vaccination of cattle with *Salmonella* bacterins provides partial protection against *Salmonella* challenge. In the only reported controlled field trial, an autogenous *Salmonella* bacterin was not found to have any effect.[516] Adverse reactions in the form of anaphylactic reactions are occasionally reported in cattle vaccinated with *Salmonella* bacterins. The cause of these reactions is unknown but has been

suggested to be associated with the lipopolysaccharide content of these products. Similar allergic-type reactions in humans caused by *Salmonella* bacterin vaccination during typhoid outbreaks are well documented.[517]

A commercial subunit vaccine, which is based on purified extracts of siderophore receptors and porins (SRP) of *Salmonella newport*, has become available in the United States.[518] The SRP proteins are critical for iron acquisition and are highly conserved between most gram-negative organisms.[519] Vaccination of dry cows has been demonstrated to increase the titer of anti-*Salmonella* antibodies in colostrum, but this has not been demonstrated to reduce the risk of disease in calves.[520] There are no peer-reviewed studies examining the efficacy of the vaccine for the prevention of neonatal salmonellosis.

Several naturally occurring and genetically manipulated attenuated *Salmonella* strains have been used to immunize cattle against salmonellosis. The most widely tested genetically altered *Salmonella* mutant vaccines in cattle are the auxotrophic strains. Aromatic amino acid (aro) and purine (pur) auxotrophs of *Salmonella* are attenuated and have decreased virulence.[521-527] Comparative vaccine trials indicate that modified live attenuated *Salmonella* vaccines provide greater protection against virulent *Salmonella* challenge than *Salmonella* bacterins.[514,527,528] Vaccination with modified live *Salmonella* vaccines attenuates the severity of clinical signs and pathologic lesions and reduces *Salmonella* shedding and mortality.[507,523,529]

Calves immunized with modified live *Salmonella* vaccines are protected from homologous and heterologous *Salmonella* serotypes when challenged within 3 weeks of vaccination.[530-532] Live *Salmonella* vaccines induce transitory T-cell independent nonspecific protection, which disappears about 1 month after immunization following clearance of the organisms from the reticuloendothelial system. Thereafter protection to oral challenge is species and serotype specific, with recall of immunity presumably involving specific antigen recognition.[533,534]

The level of passive protection of calves achieved via feeding colostrum from vaccinated cows is questionable. A number of reports suggest immune colostrum provides passive protection, and others report no protective effect. In trials where protection was achieved, calves were challenged at 1 week of age; trials where no protection was observed involved challenging calves at 3 weeks of age, suggesting that the duration of passive immunity associated with colostral transfer is relatively short. Considering that many calves are exposed to

Salmonella in the first week of life, colostral protection may be useful.

Rotavirus and Coronavirus.

Bovine coronavirus is associated with a number of diseases in cattle; all BCV isolates are believed to belong to a single serotype.[535] Differences in hemagglutination-inhibition characteristics have been used to classify strains as types 1 through 3.[536] There are seven serogroups of rotavirus, with group A accounting for the majority of pathogenic isolates. Members of the group A rotaviruses are further classified according to antigenic and genetic differences in their outer capsid proteins, G and P. Both of these proteins are involved in neutralization of infectivity in vitro and in vivo.[537] In the United States, eight G serotypes/genotypes and four P serotypes/genotypes have been identified in cattle isolates.[246] The genome of rotavirus is composed of 11 gene segments that can be exchanged among isolates when animals are infected by more than one virus at the same time.[538] Genetic reassortment can generate new progeny viruses that can evade what was once a protective immune response, thus allowing persistence of rotavirus in susceptible populations.[537]

Two approaches have been taken with immunoprophylaxis against rotavirus and coronavirus infections in calves. The first approach involves oral vaccination of neonatal calves with a modified live vaccine. Calves begin producing detectable levels of local secretory IgM within 4 to 6 days of vaccination.[539] Calves are resistant to challenge from the initial appearance of local IgM antibodies.[539] To consistently elicit an effective immune response, the vaccine must be administered orally, immediately after birth, and before the calf has nursed because the colostrum of most cows contains virus-neutralizing antibodies that interfere with the vaccine.[540] There are conflicting reports of efficacy with these type of vaccines. In double-blind field studies that include vaccinated and nonvaccinated calves, the vaccine was not shown to be effective.[541] Conversely, when all calves were either vaccinated or not vaccinated in sequential comparisons, morbidity and mortality were significantly reduced.[541]

The second approach involves intramuscular vaccination of pregnant cows with either modified live vaccine or inactivated viral vaccines to stimulate high levels of specific virus-neutralizing antibodies in colostrum and milk during the first several days of the calf's life. Infectious viral particles are neutralized within

the gut lumen, preventing infection of intestinal villus enterocytes. One advantage of passive immunization is the fact that cross-protection between serotypes is less of a problem. This is due to the fact that vaccination of a mature cow that has had natural rotavirus exposure leads to cross-serotype stimulation of heterotypic antibodies.[542] Single-serotype vaccination therefore stimulates antibody production to a wide range of rotavirus serotypes, negating the need for multivalent rotavirus vaccines. Passively absorbed anti–bovine rotavirus IgG1 antibodies are transferred to the small intestinal lumen, where they protect against experimental challenge.[543] Antigen-sensitized maternal lymphocytes also confer partial protection against challenge with virulent bovine rotavirus.[544] Colostrum and milk with a high virus-neutralizing antibody titer are highly protective while they are being consumed by the calf. For example, administering 400 mL of immune colostrum daily to calves from day 2 to day 12 reduced the incidence of diarrhea from 41% to 3% in one study.[545] The concentration of rotavirus- and coronavirus-neutralizing antibodies in milk of vaccinated cows falls below protective levels by 3 to 7 days after parturition.[546-548] In lieu of complete protection, the manifestations of passive immunity to bovine rotavirus often noted are (1) a delay of a few days in the onset of clinical signs, and/or (2) a reduced severity of clinical signs, and/or (3) a reduction in the length of the period of viral shedding associated with infection.[549] Although there are reports of successful field trials involving bovine rotavirus/bovine rotavirus-coronavirus–vaccinated cows,[503,550,551] negative results have also been reported.[552] A common problem with commercial vaccines on the market in the United States and Europe is a lack of vaccine-specific data supporting efficacy claims. Protection correlates with serum titers; independent studies have sometimes failed to demonstrate effective seroconversion with some products.[553]

Nonspecific Immunity

Diet.

The two most important dietary variables affecting the risk of calf scours are nutrient delivery and microbial quality. When calves are limit-fed milk or milk replacer to drive starter intake, the availability of nutrients from milk or milk replacer is typically adequate for maintenance at birth but inadequate to support significant growth and then drops below maintenance requirements by about 1

week of age.[554] With limit feeding, growth is derived from calf starter intake. Good-quality starter with an effective delivery system is required to promote starter intake. If starter quality or delivery is inadequate, calves become nutritionally stressed. Poor body condition is a feature of this scenario and should trigger an investigation of calf nutrition. High morbidity and mortality are common in nutritionally stressed calves.

The microbial quality of the diet is an important factor in preventing diarrhea. Calves that are fed milk from mastitic quarters or antibiotic-containing milk are at increased risk of diarrhea.[459] Following fresh colostrum feeding, young calves have less diarrhea if placed on whole milk rather than other diets. Pasteurizing surplus colostrum and waste milk reduces the incidence of diarrhea on these diets.[555] It is also important to offer good-quality calf starter from about 2 to 3 days of age; initially intakes will be low, so a small amount is offered daily to keep it fresh. Spoiled starter should be disposed of rather than adding fresh starter to spoiled feed.

Recent studies in dairy calves have shown that administration or stimulation of glucagon-like peptide 2 (GLP-2) can be used prophylactically to reduce intestinal damage, improve barrier function, and increase nutrient absorption in calves subsequently infected with cryptosporidia.[556] It is proposed that GLP-2 treatment reduces the ability of *C. parvum* to attach to the microvilli and penetrate the host epithelium. GLP-2 can be stimulated by supplementing milk with Sucram (Pancosma, Geneva, Switzerland) at 400 mg/kg dry matter (DM) of milk replacer.[557]

Some producers routinely administer vitamin A to neonatal calves. Many but not all studies in children indicate that supplementation can reduce the incidence of diarrhea in areas where clinical and subclinical vitamin A deficiency is endemic.[558] Neonates normally derive fat-soluble vitamins (A, D, and E) from colostrum; deficiency is most likely when colostrum is heat treated and a diet of unsupplemented straw and grain is fed. Calves born to cows fed good-quality, green forage or cattle receiving a vitamin A supplement should not require supplementation, particularly if they received adequate fresh colostrum. Enteric absorption of vitamin A is diminished in calves with cryptosporidiosis, so the systemic route should be used in calves with this type of infection.[559]

Fermentation products derived from *Saccharomyces cerevisiae* are reported to improve enteric health and increase leukocyte function.[560,561,562] SmartCare (SC) and XPC (both Diamond V, Cedar Rapids, Iowa) are *S. cerevisiae*

fermentation products that can be supplemented to calf diets via milk (or milk replacer) and starter grains, respectively. In a *Salmonella* challenge trial, the combination of SC and XPC *S. cerevisiae* fermentation products were associated with significant reductions in pyrexia, diarrhea, and intestinal colonization following experimental *S. typhimurium challenge*.[561] These results were consistent with improvements in GI health observed in supplemented preweaned dairy calves naturally exposed to *Salmonella*.[560] In a more recent study, supplementing preweaned Holstein calves with both SC in milk replacer and XPC in calf starter improved starter intake and fecal consistency following a mild *Salmonella enterica* challenge, but there was no reduction in *Salmonella* shedding.[563]

Probiotics.

Calves are born with a sterile GI tract that is rapidly colonized by microbes from the dam and the environment. The developing microbial community of commensals and their metabolites influences the health of the gut mucosa and associated immune cells.[564,565] The composition of the microbiota is unstable in the first month of life, influenced by colostrum intake, nutrition, stress, antibiotic use, and environment, and hence varies at an individual and farm level.[566,567-570] Stresses such as abrupt diet changes and weaning can result in dysbiosis, the loss of commensal bacteria providing opportunity for pathogenic microorganisms to proliferate.[569,571]

Probiotics are viable, nonpathogenic microorganisms that, when ingested, are expected to confer beneficial physiologic effects to the host animal. The addition of both prebiotics and probiotics to milk in the first weeks of life is thought to prevent the establishment of opportunistic pathogenic bacterial populations and result in both an increase in the ratio of lactic acid bacteria (LAB) to coliforms and a reduction in the prevalence of diarrhea.[572,573] Probiotic additives generally contain LAB, primarily *Lactobacilli* but also *Streptococcus* and *Enterococcus* species. LAB commonly used include *Enterococcus faecium*, *Lactobacillus acidophilus*, *Lactobacillus lactis*, *Lactobacillus paracasei* subsp. *paracasei*, *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Lactobacillus salivarius, and Streptococcus salivarius* subspecies thermophiles. *Bifidobacterium bifidum, Aspergillus oryzae*, *Candida pintolepesii,* and more recently *Faecalibacterium prausnitzii* may also be included in some combinations.

General mechanisms of action ascribed to probiotics include immune system

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stimulation, such as production of anti-inflammatory cytokines, excretion of antimicrobial substances such as bacteriocins (nisin and pediocin), and competition with pathogens for intraluminal nutrients and receptor sites on the intestinal surface.[574,575] *Lactobacilli*, one of the most common probiotics used in calves, bind or chelate iron, a nutrient essential for most bacteria, hence limiting the availability to pathogenic microorganisms.[575]

Several studies demonstrate improved fecal consistency and reduced incidence of undifferentiated diarrhea. A meta-analysis of trials involving calves that were supplemented with LAB from younger than 10 days of age demonstrated a significant reduction in the incidence of diarrhea, particularly in calves fed whole milk supplemented with a multistrain inocula.[572] LAB were also administered to calves that were subsequently infected with *S. dublin*, leading to a reduction in the severity of histopathologic lesions.[571] Another study showed a significant reduction in the incidence of diarrhea when the nonpathogenic *E. coli* strain Nissle 1917 was administered to calves from birth for the first 10 to 12 days of life.[576]

More recently, additional species of bacteria have been tested as next-generation probiotics. This includes an obligate anaerobe belonging to the phylum Firmicutes, *F. prausnitzii*. Oral administration of viable *F. prausnitzii* from less than a week of age to calves fed ad libitum acidified nonsaleable milk reduced the incidence of diarrhea and mortality and improved weight gain.[577]

It can be concluded that feeding probiotics containing multispecies LAB, *E. coli* strain Nissle 1917, or *F. prausnitzii* to calves from less than a week of age that are fed whole milk has the potential to positively influence the microbiome of the neonatal calf and provide a protective effect, reducing the incidence of diarrhea. However, the benefits in healthy calves are likely to be small, and the protective effect will not overcome an overwhelming challenge. Due to the potential range of bacterial species that can be included in a probiotic mix, experimental data should be examined for any commercial product. This is particularly important in light of a study in foals where administration of a lactobacilli probiotic resulted in an increase in morbidity and diarrhea.[578]

Prebiotics.

Prebiotics are carbohydrates or other organic compounds that are not hydrolyzed or absorbed in the upper part of the GI tract and affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in

the colon that can improve host health.[579] The most well-studied prebiotics are nondigestible oligosaccharides. These compounds stimulate the growth and activity of LAB, promoting production of short-chain fatty acids that lower intraluminal pH, preventing adhesion of Enterobacteriaceae to the intestinal epithelium, most notably *E. coli* and *Salmonella*.[573,580,581]

Prebiotics studies in calves have examined mannan-oligosaccharides, which are complex mannose sugars and components of yeast cell walls, galacto-oligosaccharides produced from lactose or lactulose, and fructo-oligosaccharides that naturally present in some edible plants such as Jerusalem artichoke tubers and chicory roots.[573,580] These studies have not conclusively demonstrated a reduction in the incidence of diarrhea, and hence currently these prebiotics cannot be recommended as a preventive measure.[580,582-586]

Lactoferrin.

Lactoferrin is an iron-binding milk glycoprotein naturally found in colostrum that has antimicrobial, antiviral, antiinflammatory, and immunomodulatory effects. It has been extensively investigated as a prophylactic to prevent sepsis in high-risk infants and as an intervention strategy to reduce *E. coli* O157:H7 carriage in ruminants.[587,588]

There are several studies investigating its use in calves both as prevention and treatment for diarrhea and as a growth promoter. Two studies using lactoferrin prophylactically have demonstrated a significantly reduced incidence of diarrhea as assessed by fecal consistency scores.[589,590] In one of these studies lactoferrin was combined with another bioactive protein lactoperoxidase system.[590] That study also demonstrated that significantly reduced numbers of *E. coli* in the colonic digesta and feces of the treated calves. On postmortem the villi in the distal jejunum of calves from the treatment group were significantly longer.

Biosecurity.

Infectious diseases are often purchased with brought-in stock. Operations that buy in calves for rearing purposes should be encouraged to buy from as few sources as possible. Direct purchase from one farm is best; assembling collections of calves through auction markets should be avoided if possible.

Treatment of Individual Calves

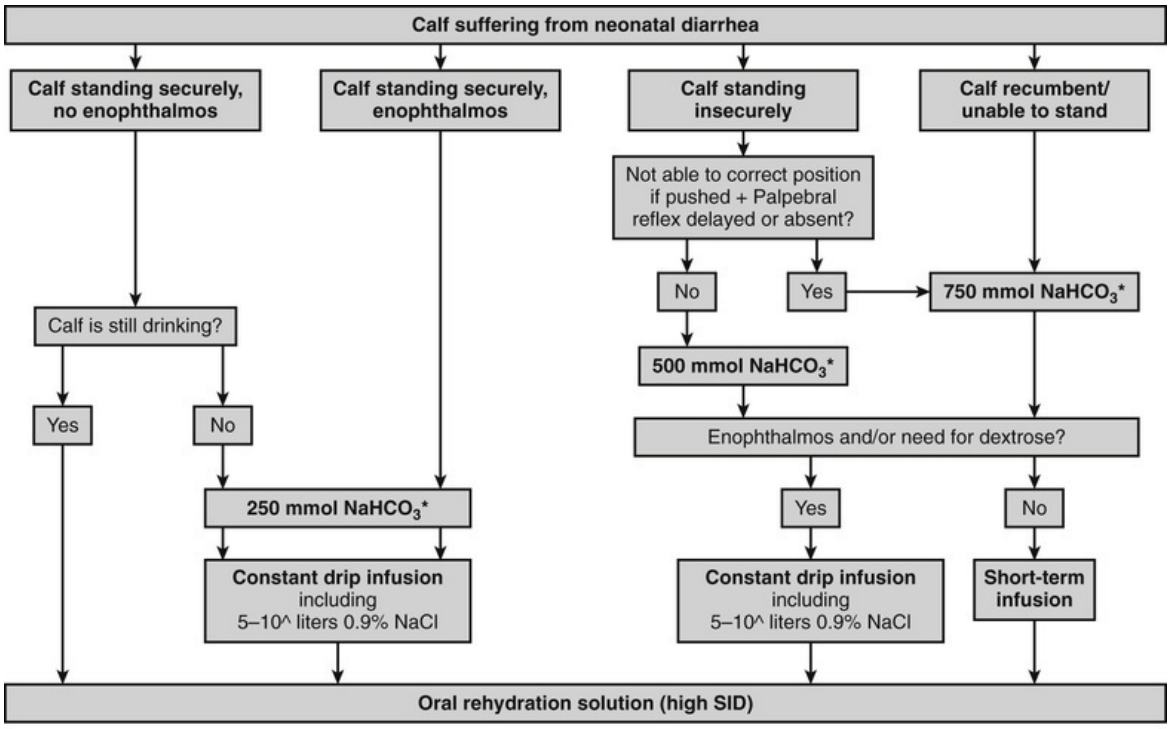
Examination

Physical examination of the diarrheic calf is the first step in establishing therapeutic needs. It is important to determine the presence of any intercurrent disease, as concurrent CNS disease, ileus/abdominal emergency, or orthopedic problems result in an increased likelihood of mortality.[591] Treatment of uncomplicated cases of diarrhea depends on the estimation of dehydration, severity of acidosis, likelihood of intercurrent infection, presence or absence of hypothermia, and hypoglycemia. The severity of dehydration is gauged from the eyeball position and skin tent (Table 20.10). In acute diarrhea the degree of enopthalmos is the most reliable indicator of dehydration, but because the position of the eye within the orbit is also dependent on body fat stores, the skin tent in the cervical region may be the most reliable indicator in calves with chronic diarrhea or cachexia.[592] Skin tent can be measured over the eyelids and neck. Best results are obtained when the neck is held straight and the skin of the mid-neck is tented in the direction of the long axis of the neck to avoid the natural skin folds that run across the neck. Estimation of severity of acidosis from either laboratory or physical findings is very important to the successful therapy of severely depressed calves. The degree of acidosis should be assessed separately to the degree of dehydration, as there is little relationship between them.[593] Strong ion (metabolic) acidosis in calves with diarrhea is due to fecal loss of sodium as well as dehydration and reduced tissue perfusion. The calves will also have a variable degree of hyper-D-lactatemia, and studies have shown that clinical signs originally attributed to the base excess values are primarily due to hyper-D-lactatemia.[172,175,594,595] Hyper-D-lactatemia may not affect the sucking reflex but will result in an impaired palpebral reflex and significant neurologic defects such as depressed mentation, staggering, drunken gait and tottering, standing with a lowered head and drooping ears, and eventual recumbency.[595,596] A significant correlation exists between D-lactate concentrations and base excess values, allowing clinical signs to still be used to estimate the degree of metabolic acidosis in calves with naturally acquired diarrhea (Fig. 20.6).[35,175,591,597,598]

TABLE 20.10
Guidelines for Assessing Dehydration in Neonatal Calves

Eyeball Sunkenness	Neck Skin Tent (Seconds)	Mucous Membranes

% Dehydration			
0	None	<1	Moist
1–5	None to slight	1–4	Moist
6–8	Slight separation of eyeball and globe	5–10	Tacky
9–10	Gap, <0.5 cm, between eyeball and orbit	11–15	Tacky to dry
11–12	Gap, 0.5–1 cm, between eyeball and orbit	16–45	Dry



* represents the intended amount of sodium bicarbonate
^ An infusion volume of 10 liters is recommended for calves with estimated enophthalmos ≥7mm

i) Short term infusion may be 4.2% or 8.4% sodium bicarbonate solution.
ii) Where calves require dextrose 1L of isotonic saline may be replaced by 1 liter of 20% dextrose solution

FIG. 20.6 A treatment decision tree for calves with diarrhea. Ability to stand, eye position, and reflexes may be used to predict the severity of metabolic and/or D-lactate acidosis and determine the treatment required. (From Trefz, FM et al.: Construction and validation of a decision tree for treating metabolic acidosis in calves with neonatal diarrhea. *BMC Veterinary Research*, 8:238; 2012.)

Rectal temperature measurement will determine whether or not the calf is hyperthermic or hypothermic. Heart rate is variable in diarrheic calves. Bradycardia (<90 beats/minute) is clinically important and may indicate the presence of hypothermia, hypoglycemia, or hyperkalemia. Cardiac arrhythmias[599] are usually caused by severe hyperkalemia (K^+ above 8 mEq/L; Fig. 20.7). Severe hyperkalemia in diarrheic calves may be characterized by a

general weakness similar to D-lactic metabolic acidosis. The impairment or promptness of the palpebral reflex was found to be a good clinical indicator that allows a distinction to be made between these two disorders. Potassium and D-lactate concentrations are negatively correlated in diarrheic calves, which makes the simultaneous occurrence of D-lactic acidosis and hyperkalemia unlikely.[597,600] Hyperkalemic arrhythmia usually can be differentiated from arrhythmia due to cardiomyopathy (selenium deficiency) because the heart rate is not elevated. The presence of bradycardia or arrhythmia indicates the need for immediate fluid therapy with bicarbonate-containing solutions to prevent death.

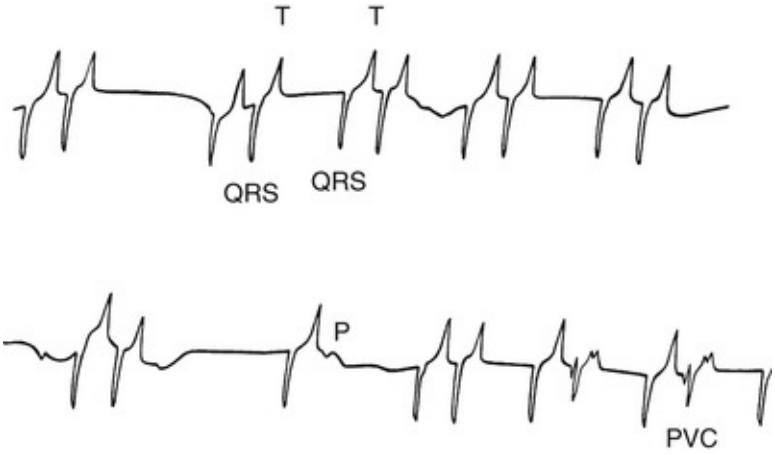


FIG. 20.7 Bradycardia and atrial standstill in a severely hyperkalemic diarrheic calf. Heart rate is 84 beats/minute. There is bigeminy, and the T waves are abnormally large. There is only one P wave, and it is not conducted. Serum potassium was 8.9 mmol/L, and sodium was 116 mmol/L.

Body condition is usually good at the onset of diarrhea. Poor condition often indicates chronic infection, mismothering, or poor feeding programs, which may be exacerbated by milk withdrawal. Advanced cachexia in diarrheic calves is a reliable indicator of mortality.[591]

It is important to check for intercurrent infections; these are easily missed even with careful examination. The lungs should be examined for signs of pneumonia; the navel palpated for pain, swelling, and wetness; and the joints checked for signs of distention and lameness. The boundary between calves in which the primary insult is septicemia with a secondary diarrhea and those in which primary diarrhea is complicated by septicemia is blurred. Calves that are recumbent, under 1 week of age, have lost their suck reflex, or have evidence of

intercurrent infection are more likely to be septicemic and require concurrent antibiotic therapy.[21] Calves in which septicemia has progressed to produce signs of meningitis (e.g., extended neck with reluctance to flex the neck), joint involvement, or ophthalmic signs (congested scleral vessels with hypopyon or iridospasm) carry a poor to very poor prognosis. It is best to identify these cases prior to instigating therapy so that the owner can decide whether treatment is economically feasible.

The laboratory is useful in quantifying metabolic disturbances in diarrheic calves. Blood gas analysis will accurately determine the degree of metabolic acidosis. The development of point-of-care devices (such as i-STAT [Abbott Laboratories, Abbott Park, Ill.]) that are relatively affordable have enabled practitioners to evaluate acid-base abnormalities in the field. The portable analyzers are capable of quantifying concentrations of Na^+, K^+, iCa^{2+}, and tCO_2 as well as determining pH, $paCO_2$, paO_2, base excess, and hematocrit. Correlations between the i-STAT and a reference analyzer in cattle and sheep were good or excellent for most variables.[601] Alternatively, blood can be collected into a heparinized syringe, capped, placed in a styrofoam cup surrounded by ice, and transported 4 hours or more to a laboratory. The practice laboratory may also have a total CO_2 (Harleco) analyzer or access to serum bicarbonate estimation as part of serum chemistry profile. Total CO_2 or bicarbonate is a useful index of the severity of metabolic acidosis. Blood glucose and D-lactate can be readily determined using test-specific point-of-care handheld meters.

Treatment Goals

The primary goals of treating calf diarrhea are as follows[602]:

1. Correct free water and electrolyte abnormalities
2. Correct acid-base deficits (acidemia)
3. Provide nutritional support
4. Treat or prevent bacterial infections if indicated

The first of these goals can be met with fluid therapy.

Fluid Therapy

The most common causes of death in diarrheic calves are dehydration and acidosis.[603] The immediate objective in treating depressed diarrheic calves is to restore them to a normal systemic state. In some calves it may also be necessary to correct hypoglycemia or hypothermia, restrict milk intake, or give antibiotics.

The estimated severity of dehydration can be combined with estimates of losses through diarrhea and for the maintenance of essential functions to give the total daily fluid requirement (see Table 20.10). The hydration status of the calf can be estimated from the degree of enopthalmus and the degree of skin tent on the neck and by evaluating the mucous membranes (see Table 20.10). The volume (L) required to replace the deficit is Percent dehydration × Calf body weight (kg). The ongoing losses through diarrhea should be estimated from the nature and volume of the diarrhea. Fecal losses can range from 1 to 6 L in diarrheic calves.[604] Maintenance requirements have been estimated at 50 to 100 mL/kg/day.[36,604] The degree of hydration and the volume of feces passed should be reassessed daily and the treatment adjusted accordingly. Only 60% to 80% of oral fluids are absorbed, and this needs to be accounted for in the calculation.[605]

Bicarbonate requirements can be calculated from base deficit values (based on blood gas measurements or estimated from physical findings) as follows:

$$\text{mmol Bicarbonate} = \text{Body weight (kg)} \times \text{Base deficit (mmol/L)} \times \text{Volume of distribution (0.6 in calves)}$$

A chart of bicarbonate requirements for various body weights and base deficit values is available (Table 20.11).

TABLE 20.11

Calculation of Bicarbonate Requirement From Calf Body Weight and Severity of Acidosis

Calf Weight (kg [lb])	Base Deficit (mmol/L)	Bicarbonate Requirements (mmol)	Volume 1.3% $NaHCO^-_3$ (L)[a]
30 (66)	5	75	0.5
	10	150	1.0
	15	225	1.5
	20	300	1.9
35 (77)	5	88	0.5

	10	175	1.1
	15	263	1.6
	20	350	2.3
40 (88)	5	100	0.6
	10	200	1.3
	15	300	1.9
	20	400	2.6
45 (99)	5	113	0.7
	10	225	1.4
	15	338	2.1
	20	450	2.9
50 (110)	5	125	0.8
	10	250	1.6
	15	375	2.4
	20	500	3.2
55 (121)	5	138	0.9
	10	275	1.8
	15	413	2.7
	20	550	3.6
60 (132)	5	150	1.0
	10	300	1.9
	15	450	2.9
	20	600	3.8

[a]Isotonic 1.3% sodium bicarbonate solution is prepared by adding 13 g of sodium bicarbonate to 1 L distilled water (155 mmol of bicarbonate per liter).

Measurements of serum total carbon dioxide content or bicarbonate are also reliable estimates of bicarbonate requirements.[606] Bicarbonate requirements are:

$$\text{mmol Bicarbonate} = \text{Body weight (kg)} \times (30 - \text{tCO}_2) \times 0.6$$

For example, a 40-kg calf has a serum bicarbonate or tCO_2 of 10 mmol/L. The calf has a bicarbonate deficit of 30 mmol/L – 10 mmol/L = 20 mmol/L, so 40 kg × 20 mmol/L × 0.6 = 480 mmol bicarbonate is required to replace existing deficits. Ongoing diarrhea may require additional bicarbonate.

Calves that are unwilling to suck and severely depressed are best treated with intravenous fluids. Calves that are only moderately depressed may also be treated with intravenous fluids if the condition is worsening rapidly. Catheterization is easier if a no. 15 scalpel blade is used to nick the skin. If it proves very difficult to catheterize the calf, the calf can be suspended upside down so that blood will pool and distend the jugular veins. The calf's neck should be clipped and prepared prior to inversion, and the calf laid flat as soon as the catheter is placed. It should be possible to place a catheter in less than a

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minute even in severely dehydrated calves using this technique. Alternatively, the auricular vein can be easily catheterized using a 20-gauge catheter, or fluids may be administered by intraosseous infusion in the critically ill neonate when intravenous access is not possible. In calves, intraosseous fluids may be administered via placement of a 16- or 14-gauge needle in the head of the femur or humerus. A 16- or 14-gauge needle is inserted in a longitudinal plane. Neonatal bones are soft, so the needle can be drilled into the bone using finger pressure. Commonly a core of bone will plug the needle, requiring the drilling needle to be discarded and replaced with a new needle placed in the same hole. After placement of the needle, attach a 60-cc syringe and inject sterile saline under slight pressure to start the flow. As the fluid is administered, check for subcutaneous leakage to ensure that the needle is correctly placed within the bone marrow. One to two liters of saline or isotonic bicarbonate administered to the severely dehydrated calf is often sufficient to restore blood pressure enough that an intravenous catheter can be placed.

Once the catheter is placed, fluids can be administered. If the calf is hypothermic, these should be warmed prior to administration because cold fluids can decrease cardiac output and may kill a critically ill calf. Fluids can be warmed using a number of methods; one convenient technique is to run the fluids through a coil of tubing immersed in a bucket of hot water (check the temperature regularly) on the way to the calf.

Saline-based fluids are suitable for rehydration (Table 20.12), but most severely depressed calves are acidotic, and more consistent recovery is obtained if an alkalizing agent is also used. A wide variety of alkalizing agents are available (lactate, acetate, gluconate), but clinical trials show that only bicarbonate is consistently effective in severely acidotic calves (Fig. 20.8).[170,607] Many diarrheic calves require large amounts of bicarbonate to correct their acidosis (see Table 20.11).[168] An isotonic solution (156 mmol/L) of bicarbonate can be readily made by dissolving 13 g of sodium bicarbonate (baking soda) in 1 L of water.[608] Sodium bicarbonate solutions can be mixed with saline; there is a possibility that precipitates may form if bicarbonate is mixed with calcium containing solutions such as Ringer's solution.

TABLE 20.12

Fluids Commonly Used in Intravenous Therapy

Item	Concentration (mmol/L)									
	Na^+	K^+	Ca^{++}	Mg^{++}	Cl^-	HCO^-_3	$Lactate^-$	$Acetate^-$	$Gluconate^-$	Glucose
0.9% saline	155				155					
1.3% sodium bicarbonate[a]	156					156				
Ringer's	147	4	5		156					
Lactated Ringer's[b]	130	4	2.7		109		30			
Ionalyte (diluted)[b]	139	10		3	101			55		167
Normosol R[b]	140	5		3	98			27	23	
Plasmalyte 148[b]	140	5		3	98			27	23	
5% dextrose (D_5W)[c]										278

[a]Do not mix sodium bicarbonate with calcium-containing solutions; precipitates may form. Mixtures of 1.3% sodium bicarbonate and saline are usually used for treating recumbent diarrheic calves.

[b]Multiple electrolyte solutions are equivalent, with the exception that one should be careful of using Ionalyte in severely hyperkalemic neonates. All are suitable for rehydrating neonates that can stand.

[c]Intravenous fluids are often spiked with 50% dextrose to give a final concentration of 5% dextrose in the drip when hypoglycemia is suspected.

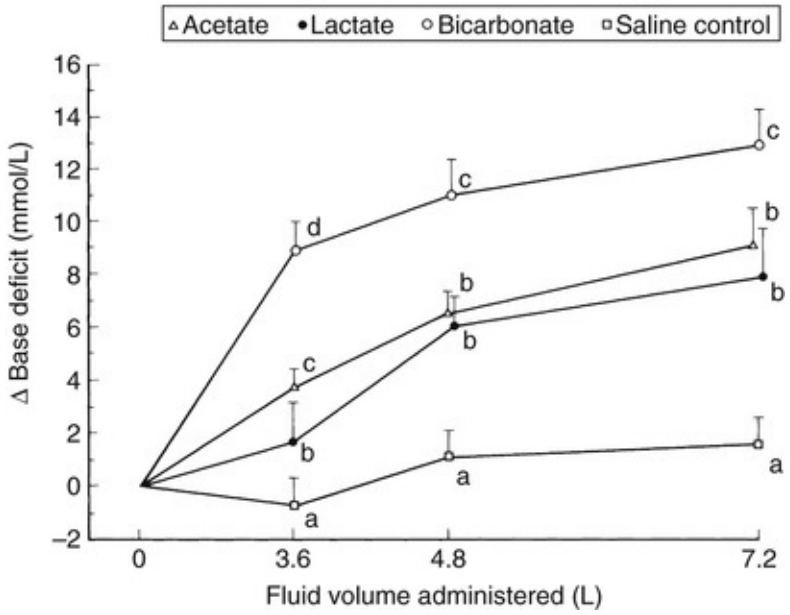


FIG. 20.8 Comparison of the alkalizing effect of various bases in diarrheic calves with severe dehydration and acidosis. At the start of the trial, all calves were at least 8% dehydrated and had a mean blood pH of 7.032 and a base deficit of 18 mmol/L. All calves received a total of 7.2 L of fluid containing 102 mmol/L of saline plus 50 mmol/L of the sodium salt of the respective alkalizing agent. Letters *(a, b, c, d)* are statistically different ($P < 0.5$) from one another at that point. (From Kasari TR, Naylor JM: Clinical

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evaluation of sodium bicarbonate, sodium L-lactate, and sodium acetate for the treatment of acidosis in diarrheic calves, *J Am Vet Med Assoc* 187:392; 1985.)

It is not always necessary to completely correct acidosis; a blood pH from 7.25 to 7.45 has little adverse affect (normal calves have a venous blood pH of 7.34, bicarbonate of 30 mmol/L, and base excess of 5 mmol/L). Ideally, dehydration and acidosis should be corrected over a 24-hour period. However, it is unusual to see problems when the fluid and acid-base deficits are corrected over 4 hours, although the calf may continue to improve after this period. Rapid resuscitation techniques include the administration of either hypertonic saline (± dextran) or hypertonic sodium bicarbonate. Hypertonic saline (7.2% NaCl) or hypertonic saline dextran (7.2% NaCl containing 6% dextran 70) administered at 4 mL/kg body weight during a 4-minute period concurrently with an isotonic alkalizing oral electrolyte solution is effective in resuscitating dehydrated calves with diarrhea.[609,610] Hyperosmotic sodium bicarbonate solutions may also be used to rapidly resuscitate acidotic dehydrated calves.[611] The base deficit can be corrected by administering 8.4% sodium bicarbonate intravenously at a rate of 1 mL/min/kg over 15 minutes.[612,613] Hypertonic bicarbonate has also been shown to have clinical advantages for the rapid resuscitation of hyperkalemic diarrheic calves, compared to hypertonic NaCl or glucose solutions.[591] Although calves with diarrhea lose potassium through the intestines, hyperkalaemia is often found due to acidosis. Hypertonic fluids should always be given concurrently with an isotonic oral electrolyte solution. After 24 hours of appropriate therapy one would expect the calf to be standing and show a good suck reflex. Persistent depression is usually a sign of uncorrected acidosis or toxemia.

Most diarrheic calves are not markedly hypoglycemic, but glucose supplementation is needed to treat severe hypoglycemia (glucose concentrations <2 mmol/L or <36 mg/dL). Glucose concentrations less than 2 mmol/L are associated with a significantly reduced chance of survival.[38] These animals often have clinical and/or necropsy evidence of septicemia, and generally this is a result of a peritonitis. Severe hypoglycemia is treated by adding glucose to the intravenous fluids to a final concentration of 2.5% to 5%. Severe hyperkalemia is seen in some dehydrated diarrheic calves, but this responds to rehydration (restores renal perfusion and dilutes out potassium) and correction of acidosis (redistributes potassium into the cells). Nutritional support is not needed if the calf is in good body condition but should be given if the calf is emaciated or if

the calf has been deprived of milk for more than 3 days.

There are increased losses of potassium in diarrhea, and potassium depletion can result in weakness. When necessary, potassium supplementation can be estimated using the following equation:

$$\text{Replacement K (mEq)} = 0.4 \times \text{Body weight (kg)} \times \text{K deficit (mEq)}$$

Potassium can safely be added to fluids at a rate of 20 to 30 mEq/L. The rate of potassium administration should not exceed 0.5 mEq/kg/h. If acidosis is present, hydrogen ions are exchanged for intracellular potassium ions, resulting in a relative increase in serum [K]. As the acidosis is corrected, there will be an influx of K ions back into cells, resulting in potential hypokalemia, which must be anticipated during fluid therapy.

Oral Electrolyte Therapy

Once the calf is able to nurse or drink, therapy is usually switched to oral electrolytes, which should continue for as long as the calf has diarrhea. This is also the route of choice for treatment of mildly affected calves on the farm. Calves with weak suck reflexes and calves that are unused to hand feeding can be tubed.

Oral electrolyte solutions need to supply sufficient sodium to facilitate normalization of extracellular fluid deficits, nutrients (glucose, citrate, acetate, propionate, or glycine) to facilitate absorption of sodium from the intestine, alkalizing agent to treat metabolic acidosis, and supplemental energy because most calves that have diarrhea are in a state of negative energy balance.[614,615] The first two requirements depend on the coupled active transport of glucose and sodium ions across the brush border membranes of enterocytes, which results in passive absorption of water and other electrolytes.[616] This function remains largely intact in calves with enterotoxigenic *E. coli* diarrhea, but where there is endothelial damage it may be impaired. Much of the research into oral electrolyte solutions has been conducted in healthy calves. Although the current understanding of the advantages and disadvantages of the different electrolytes is presented here, it is important to recognize that milk clotting, abomasal luminal pH, and abomasal emptying rates could differ between diarrheic and nondiarrheic calves.

The ideal sodium concentration for oral rehydration therapy in calves is thought to be between 90 and 130 mmol/L.[615] Lower concentrations of sodium will not adequately correct dehydration. Products with a sodium concentration greater than 130 mmol/L should be avoided, as they may predispose to hypernatremia and can also delay abomasal emptying rates because of increased osmolality.[617] The osmolality of the electrolyte solution is primarily determined by the concentrations of sodium and glucose. Commercially available oral electrolyte products in North America can range from approximately isotonic (280 to 300 mOsm/L) to extremely hypertonic (700 to 800 mOsm/L), with the greatest variation being in the amount of glucose added. The osmolality at the tip of the villi is approximately 600 mOsm/L, and use of solutions up to this osmolality will provide additional nutritional support.[602] However, extremely hyperosmotic electrolyte solutions (700 to 717 mOsm/L) have the potential to increase dehydration and have been shown to have a slower abomasal emptying rate than calves fed iso-osmotic solutions (300 to 360 mOsm/L), increasing the risk of bloat or abomasitis and resulting in a slower rate of plasma expansion.[602,617-619] Calves that are deprived of milk will lose more weight when fed isotonic low-glucose solutions.[620]

Oral electrolyte solutions should contain between 40 and 80 mEq/L chloride and 10 and 30 mmol/L potassium. Potassium is lost in the feces of calves with diarrhea, and with dehydration there can also be increased potassium losses from the kidney. Consequently calves with chronic diarrhea may have profound hypokalemia resulting in severe muscular weakness.[602]

Severely acidemic calves are unable to correct their metabolic acidosis when rehydrated with nonalkalinizing solutions, and consequently fluid therapy must be designed to address the strong ion (metabolic) acidosis and hyper-D-lactatemia.[602,607,615] The ability to counteract acidosis varies greatly between oral electrolyte products. These differences are therapeutically important and are responsible for differences in survival rates between products. It is important that an oral electrolyte solution contains greater than 50 mmol/L of an alkalizing agent and has a strong ion difference ($[Na^+]+[K^+]–[Cl^–]$) of at least 60 to 80.[602] Commercial oral electrolyte solutions use acetate, propionate, bicarbonate, and citrate as alkalizing agents.

Understanding of the attributes of the alkalizing agents has evolved over the past few years, but there is little consensus on which is most suitable. Bicarbonate combines with hydrogen ions directly, whereas the other agents

remove hydrogen ions during their metabolism within cells.[604] Several studies have shown that oral electrolyte solutions containing bicarbonate (≤62 mmol/L) and citrate (≤12 mmol/L) do not interfere with milk clotting in vivo.[619,621,622] Many authors still prefer bicarbonate precursors such as acetate or propionate for their energy value once metabolized, their water absorption capabilities, and the fact that they do not alkalinize the abomasum.[602] It is important that solutions containing acetate and propionate also have a high strong ion difference to ensure a rapid restoration of base excess. Solutions containing bicarbonate alkalize the GI tract of milk-fed calves, and several authors have expressed concern that this may result in bacterial overgrowth in the small intestine as well as ETEC attachment and toxin production.[602,623] In reality, concerns about the effects on milk clotting have been alleviated for most electrolyte solutions; it is likely that feeding a sufficient volume of an oral electrolyte solution with a recommended strong ion difference has the most significant impact on the rapid correction of dehydration and acidosis.[594,621]

There are a wide variety of oral electrolyte preparations on the market (Table 20.13), and many do not meet the requirements stated above, so care should be taken to select an appropriate solution. Beware of products that are designed for medicating hundreds of liters of water, as the final solution is often very dilute (<10 g electrolytes/L) and will not rehydrate sick calves. These products are often marketed as “boosters” and “stress relievers.”

TABLE 20.13

As-Fed Composition of Some Available Oral Electrolyte Solutions for Calves

Product	Company	Na (mmol/L)	K (mmol/L)	Cl (mmol/L)	HCO_3^- (mmol/L)	Acetate (mmol/L)	Citra (mmo
Advance Arrest	Manna Pro	46	7	30	12	0	0
Advance Pro-Lyte Plus	Manna Pro	117	23	a	a	0	a
ASGOLD	Volac	84	10	74	19	0	0
Blue Ribbon	Merrick's Inc.	144	20	75	0	0	a
BlueLite C	TechMix, Inc.	48	34	57	0	0	a
BlueliteReplenish[M]	TechMix, Inc.	123	28	71	0	59	0
Bounce Back	Manna Pro	150	9	122	37	0	0
Bovi-Mate[ORS]	Drenchmate	130	20	60	0	66	0

Calf-Lyte II	Vetoquinol	112	15	43	0	80	0
Calf-Lyte II HE	Vetoquinol	112	15	43	0	80	0
Calf GoldLyte	Bio-Vet	154	27	92	a	0	a
Calf Quencher	Vedco	142	24	80	86	0	0
Calf Restart One-4	TechMix, Inc.	261	153	a	0	0	a
Calf-Gel 95	Van Beek Scientific	42	9	a	a	0	a
C.H.E.E.R.S.	Nouriche Nutrition	115	35	58	0	63	6
Comeback	AgriPharm	112	24	a	0	0	a
Diaque	BoehringerIngelheim	87	12	54	a	a	a
Electrolytes Plus Supplement	Sav-A-Caf (Milk Products)	137	7	a	18	0	0
Entrolyte HE	Zoetis	100	23	45	78	0	0
EPIC Calf Electrolyte	Tomlyn	92	20	86	0	52	0
Formula 911	Advantech	132	19	a	a	0	0
Hydrafeed	A&L Laboratories	115	11	62	86	0	14
Hydra-Lyte	AgriLabs	85	30	45	0	60	10
Hy-sorb	Bimeda	113	9	64	38	0	9
Land O'Lakes Electrolyte System Base	Land O'Lakes	67	20	a	0	0	10
Land O'Lakes Electrolyte System Base+ Add Pack	Land O'Lakes	119	20	a	0	51	10
Land O'Lakes Complete	Land O'Lakes	121	20	a	38	0	a
LifeaidXtra	Norbrook	90	25	60	0	20	7
Multi-Electrolyte	Aspen	130	27	a	a	0	a
“O” Calf GoldLyte	Bio-Vet Inc.	143	27	93	a	0	0
“O” PectiLyte	Bio-Vet Inc.	111	19	a	a	0	0
One Day Response	Farnam	65	10	39	a	0	a
PectiLyte	Bio-Vet Inc.	110	18	a	a	0	0
Re-sorb	Zoetis	80	26	80	0	0	2
Revitilyte	Vets Plus Inc.	110	18	50	80	0	0

Revitilyte-Gelling	Vets Plus Inc.	110	18	50	80	0	0
SX Oral Electrolyte	EcoPlanet	[a]	[a]	[a]	0	0	0
Theracaf® Plus Calf Solutions®	Sav-A-Caf (Milk Products)	128	27	70	45	0	4
VitaLyte Plus	Vita Plus Corp	150	31	45	80	0	[a]

[a]Nutrient is provided by the product, but label contains insufficient information to calculate concentration.

[F,M,L,S,A]In addition to glucose, product contains another carbohydrate source: F = fructose, M = maltodextrin, L = lactose, S = sucrose, A = amylose.

[1]Instead of glucose, product contains 96 mmol/L of lactose (glucose and galactose).

[2]Contains maltodextrins instead of or as well as glucose; value listed for glucose is glucose equivalents.

[3]Energy source is organic sugar; label does not specify the form.

[4]Energy source is not specified; contains reed-sedge peat and organic dried kelp.

[5]Instead of glucose, contains sucrose.

[6]Energy source is not specified; contains roughage products, reed-sedge peat, and dried kelp.

Note: Concentrations of calcium, magnesium, phosphate, and sulfate are not included. Molarities assume that all compounds dissociate completely in solution. Where a maximum and minimum value for a compound was provided, the mean value has been used.

?, Published information insufficient to provide reasonable estimate; *SID,* strong ion difference.

This table does not include every available product. Information updated based on Table 20-12 in *Large Animal Internal Medicine,* Fifth edition. Calculated from information listed in the *Compendium of Veterinary Products,* U.S. edition, 2018, available online at https://pbs.cvpservice.com, and on product labels. Additional information obtained from Smith GW, Berchtold JF: Fluid therapy in calves, *Veterinary Clinics of North America Food Animal Practice, 30*(2):409–427, 2014; Jones C, Heinrichs J: *Comparison of commercial electrolyte products,* Pennsylvania State University, PennState Extension, College of Agricultural Sciences, 2017, available at https://extension.psu.edu/table-comparison-of-commercial-electrolyte-products; and Smith G: *Analysis of oral calf electrolytes,* 2017, available at https://www.techmixglobal.com/sites/default/files/doc/reference/Oral%20Electrolyte%20Analysis_D

Neutral amino acids such as glycine, alanine, or glutamine are usually added to oral electrolyte solutions to facilitate sodium absorption in the small intestine by a mechanism similar to that of glucose. Research in humans has shown that adding glycine to solutions containing 110 mmol/L of glucose aids rehydration. It is probable, however, that there is little additional benefit to supplementing solutions that contain more than 200 mmol/L of glucose with glycine. Glutamine is also an important fuel for the GI tract and can promote mucosal repair. A recent review concluded that addition of glutamine to a high-calorie oral

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electrolyte solution results in improved clinical recovery from diarrhea in preweaned calves.[624] Volatile fatty acids such as acetate or propionate also facilitate sodium absorption in the gut.[625,626] These appear to use a different mechanism to facilitate sodium absorption to that of glucose or amino acids, and consequently significant increases in intestinal sodium absorption can be expected in electrolyte products containing volatile fatty acids, even when they already contain high concentrations of glucose and/or amino acids.[624]

Solutions that contain large amounts of glucose are hyperosmolar and are absorbed more slowly than isotonic solutions, but the differences are too small to be clinically important.[627] The ionic composition also affects absorption; mixtures of sodium chloride and citrate, bicarbonate, or acetate have improved absorption over chloride salts alone. Oral electrolyte solutions are almost completely absorbed in healthy calves, but absorption can be as low as 60% in severe *E. coli* diarrhea.[628]

Psyllium has been added to some oral electrolyte solutions for a number of perceived benefits, but controlled studies show no clinical advantages, although there may be some moderation of bacterial fermentation within the GI tract.[629,630]

The other problem to be considered in the chronically scouring calf is the need for nutritional support (Fig. 20.9). Maintenance metabolizable energy requirements for a 50-kg calf are about 2000 kcal, and 3500 kcal are required to support a weight gain of 0.5 kg/day. These requirements can be met by 3.3 and 5.7 L of whole cow's milk, respectively. Comparative studies indicate that weight loss in calves fed oral electrolytes are inversely proportional to the energy content of the solutions.[620] Assuming a 4-L daily intake and 100% digestibility of oral electrolyte nutrients, regular electrolyte solutions supply between approximately 15% and 25% of energy needs. As a result, diarrheic calves that are held off milk for prolonged periods lose weight[631] and can become emaciated. When maintaining body condition is a concern and little milk or solid food is being ingested, a high-energy oral electrolyte should be fed. Products such as Biolyte, Lifeguard/Enterolyte HE and RESTART H.E. provide about 50% of energy requirements if fed twice a day (total intake 4 L) and about 75% if fed three times a day (total intake approximately 6 L).

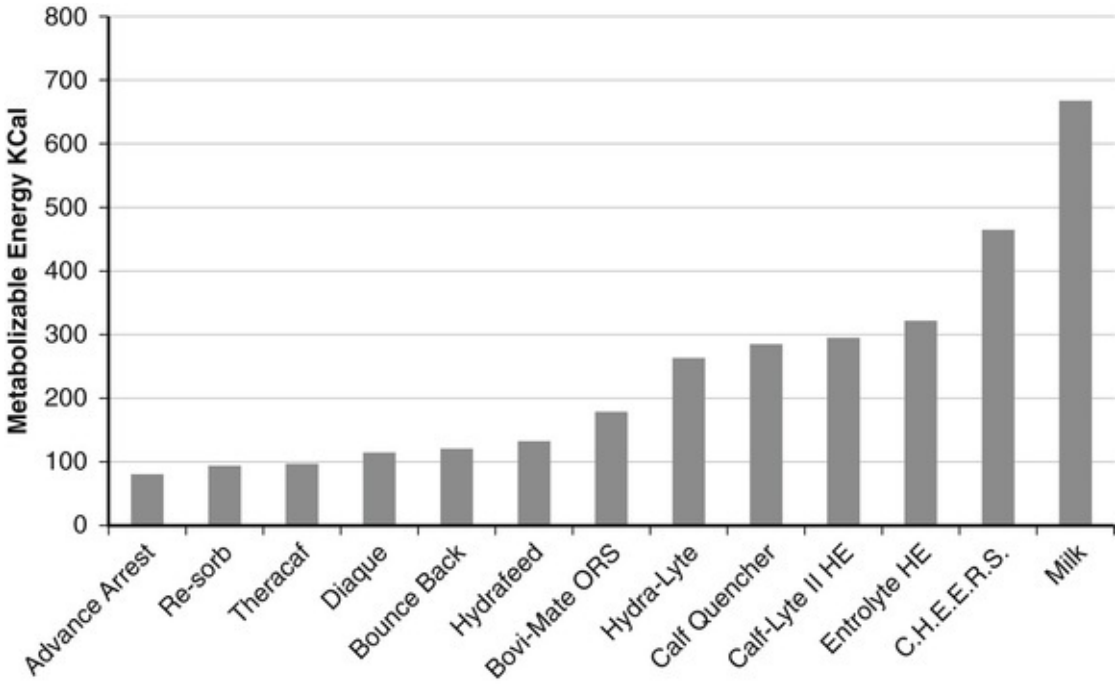


FIG. 20.9 Comparison of the energy content of various electrolyte solutions. Milk is shown for comparative purposes. Metabolizable energy content for products other than milk is estimated from glucose and other water-soluble carbohydrates of the as-fed electrolyge solution. Calculations are made with the assumption that 1 g of carbohydrate equals approximately 4 Kcal of metabolizable energy. This figure applies to electrolyte solutions fed to neonatal calves prior to rumen development. See text for manufacturers.

Milk withdrawal can reduce the severity of diarrhea and depression in severe scours. This is because malabsorption exacerbates diarrhea through the osmotic effect of unabsorbed milk nutrients and also promotes bacterial overgrowth and D-lactic acidosis. Milk also has a trophic effect on epithelial cells and maintains higher GI tract enzyme activities as well as providing protein for repair of damaged intestinal epithelium.[632] In experimental trials, continued feeding of milk maintained weight gain; however, when calves were fed enough milk to fully meet their requirements and the undrunk milk was tube fed, calves initially had greater inappetence.[633,634] Withdrawal of milk without a high-energy alternative can rapidly result in cachexia and malnourishment.[633] In many calves, particularly the less severely affected, there is often a considerable degree of residual absorptive capacity, enough to support body weight gain if limited amounts of milk are fed. Milk withdrawal for up to 12 hours is recommended if the calf is depressed and not interested in sucking. In most cases electrolyte therapy will restore a calf's vigor and sucking drive within 1 to 2 days. Milk can

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then be reintroduced in small amounts (e.g., 1 L given two to four times daily). However, forced feeding (by tubing or drenching), dysfunction of the reticular groove reflex, or reflux of abomasal contents may result in ongoing acidosis due to the production of D-lactate from fermentation of carbohydrates entering the reticulorumen.[600] If the calf is not interested in drinking or becomes depressed when reintroduced to milk, a high-energy oral electrolyte preparation can be tried instead. Studies indicate that diarrheic calves have a generalized malabsorption rather than specific lactose intolerance.[165] Thus it may be more important to manage calves with milk intolerance by giving smaller amounts of milk in each feed rather than by changing carbohydrate source. There is little point in withdrawing milk from calves that remain alert and interested in nursing, as it is unlikely to result in clinical improvement. This is particularly likely to be the case when the calf receives whole cow's milk in frequent small quantities (i.e., by natural sucking of the dam).

Role of Antimicrobials

The majority of calves with diarrhea do not require treatment with antimicrobials, and since use of antimicrobials in neonatal calves is a driver of antimicrobial resistance (AMR) on farms, they should be used judiciously.[635] Antimicrobial use in calves with diarrhea should be based on a protocol that (1) details the clinical signs indicating the use of antimicrobials; (2) specifies an antimicrobial product, dose, and duration of treatment that is appropriate for the likely pathogen and is likely to maintain a therapeutic concentration at the site of infection (small intestine and blood); (3) avoids the use of “medically important” antibiotics, unless indicated by culture results or when treatment with other antimicrobials has not been effective; (4) advocates antimicrobials registered for treating diarrhea in calves and as directed on the label or by a veterinarian whenever possible; and (5) avoids adverse local or systemic effects and violative residues. The use of antibiotics should always be accompanied by an infection control plan. The practice of continually feeding antibiotics to calves has been prohibited in many countries, but prophylactic antibiotics are still commonly used in some countries to prevent calf diarrhea.[636,637] Although older studies generally demonstrated a reduction in the duration and severity of the diarrhea, there was little or no effect on diarrhea incidence or mortality rates.[638] More recent studies have demonstrated benefits from stopping prophylactic and routine treatment with antimicrobials. A large study in the United States found a

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decrease in the prevalence of diarrhea in calves given targeted treatment for diarrhea with specific symptoms, compared with calves given both prophylactic antibiotics in the milk and routine antibiotics for all clinical cases.[639] Another study demonstrated that there was no increase in mortality when a protocol for selective treatment of systemically ill calves was introduced on two large farms that had previously been using antibiotics in more than 75% of their calves with diarrhea.[640] Moreover, a change in the fecal microbiota was observed in calves on both farms 12 months after the introduction of the new protocols. Although the relative proportions of the different bacteria were not always consistent across the two farms, both farms had a significant reduction in the percentage of Enterobacteriaceae isolated in healthy calves 12 months after the protocols were introduced.

Therapeutic Targeting.

The bacterial pathogens commonly associated with neonatal calf diarrhea are *Salmonella* and *E. coli*. Coliforms are normal inhabitants of the GI tract and one of the most common representatives of the aerobic gram-negative microbiota. Calves with diarrhea often have significantly increased coliform bacterial numbers in the small intestine, regardless of etiology,[641-643] and this colonization is associated with altered small intestinal function, morphologic damage, and increased susceptibility to bacteremia.[643] Bacterial overgrowth and subsequent fermentation in the GI tract results in the production of D-lactic acid. D-lactic acid is a major component of acidemia in diarrheic calves and is accompanied by systemic signs of weakness and ataxia. Calves with diarrhea are more likely to have failure or partial failure of passive transfer, and this group of calves, in turn, is more likely to be bacteremic.[24,644] Blood cultures indicate that gram-negative bacteria account for approximately 80% of bacterial isolates, and *E. coli* is the most common bacteria isolated.[18,19,644] In a study of 190 recumbent calves on a large calf-raising facility, 31% were determined to be bacteremic; *E. coli* accounted for 51% of the isolates, other gram-negatives for 25%, gram-negative anaerobes for 5.9%, gram-positive cocci for 11.8%, and gram-positive rods for 5.9%.[644]

Antimicrobial therapy must be targeted at a specific bacterial enteric pathogen isolated from sick calves or used in severely ill calves (as manifested by reduced suckle reflex, >6% dehydration, weakness, inability to stand, or clinical depression) to manage the risk of bacteremia. The antibiotic selected should be

directed toward gram-negative organisms, particularly *E. coli*.

Antimicrobial Susceptibility.

Antimicrobial susceptibility testing of fecal isolates should be specifically directed at enterotoxigenic *E. coli* and *Salmonella* spp. During a suspected outbreak of salmonellosis, fecal samples from 10 calves in the affected age-group should be cultured using an enrichment media, and antimicrobial susceptibility should be determined from the isolates obtained.[645] Multiple isolates of ETEC should also be tested to determine antimicrobial susceptibility, where this is shown to be a primary etiology.

When antibiotics are used to prevent coliform septicemia, fecal samples cannot be used to determine the correct antimicrobial. The predominant strain of *E. coli* in the feces of a scouring calf can change several times during an episode of diarrhea, and one study has shown that 9 of 20 calves with diarrhea had different strains of *E. coli* isolated from upper and lower small intestines.[646,647] Hence fecal *E. coli* strains may not be representative small intestinal *E. coli* strains, and multiple studies have shown that determining the appropriate antibiotic from fecal isolates is not a good predictor of clinical outcome.[648-650]

Antimicrobial susceptibility testing has more clinical relevance for predicting the clinical response to antimicrobial treatment when applied to bacteria isolated from blood or tissues of bacteremic calves, because the minimal inhibitory concentration break points are based on achievable antimicrobial concentrations in human plasma and MIC_{90} values for human *E. coli* isolates, which provide a reasonable approximation to achievable MIC values in calf plasma and MIC_{90} values for bovine *E. coli* isolates.[647] Within a given herd there will be a diversity of bacteria isolated from bacteremic calves, so the collection of blood cultures and assessment of antimicrobial susceptibility does not necessarily provide information applicable to the next case.

When determining the correct antibiotic for prevention of septicemia in the absence of postmortem or blood cultures, antimicrobial efficacy is best evaluated by the clinical response of a number of calves to treatment, with calves randomly assigned to treatment groups, rather than the results of in vitro antimicrobial susceptibility testing performed on fecal *E. coli* isolates.[647]

Minimizing Antibiotic Resistance.

The young, preweaned calf rapidly acquires multiple-resistant commensal *E. coli*

enteric flora within days of birth.[651-654] Although colonization with *E. coli*–carrying AMR genes occurs regardless of antimicrobial exposure, the proportion of antimicrobial-resistant *E. coli* on a farm is driven by the antibiotic use on that farm.[655-659] Although these coliforms are generally not pathogenic, they serve as a reservoir of AMR genes that can be shared between bacteria, including *Salmonella* spp., in both humans and animals.[660,661]

Several dietary and environmental factors influence the proportion of AMR coliforms shed. However, administration of antibiotics both fed in milk and given parenterally is a key driver, with preferential growth of antimicrobial-resistant *E. coli* strains starting within 3 hours of antimicrobial administration.[655,659,662-666] Administration of antibiotics also converts the opportunistic pathogenic bacteria in the respiratory tract into reservoirs of AMR.[659,666] As the calf gets older, changes in the commensal enteric microflora occur that result in an intestinal microbiota that is more effective at excluding these bacteria, and the proportion of resistant *E. coli* reduces.[651,652,659,667] The prevalence of these bacteria also decreases when antibiotics are withdrawn, but a high number of resistant *E. coli* are sustained in the bedding for more than 1 month.[668-670] Use of florfenicol and ceftiofur in one pen also results in an increase in the proportion of resistant bacteria shed by calves in adjacent pens.[670] Consequently, administration of antibiotics to neonatal calves, more so than other age-groups, has been shown to be one of the key drivers of the development of AMR on a farm.[635]

Particularly concerning is the relationship between use of third- and fourth-generation cephalosporins on farms and the emergence and spread of broad-spectrum β-lactamase–producing *E. coli*.[656,670-672] Broad-spectrum β-lactamases are a significant resistance mechanism that is a serious threat to the currently available antibiotic armoury, conferring resistance to some of the most commonly used antibiotics in humans, including penicillins, cephalosporins, clavulanic acid, and monobactams. In addition, these organisms are commonly multidrug resistant.[673-675] It is now evident that the use of antimicrobials in calves is a major risk factor for broad-spectrum β-lactamase–producing *E. coli*, which is consistent with the rapid increase in antimicrobial-resistant coliforms observed following antimicrobial use in this age-group.[635,667] Also of concern is the strong relationship demonstrated between the use of fluoroquinolones and the development of multidrug antimicrobial resistance, as is the co-selection of broad-spectrum β-lactamase resistance when cattle are treated with

florfenicol.[665,670,676]

Third- and fourth-generation cephalosporins and fluoroquinolones have been identified as “highest priority critically important antimicrobials” for human medicine by national and international bodies, including the World Health Organization (WHO), Food and Agriculture Organization of the United Nations (FAO), and World Organisation for Animal Health (OIE). Hence it is imperative that veterinarians consider the impact that their selection of antimicrobial, where indicated, will have on the development of resistance. Critically important antimicrobials must not be used as the initial treatment in a disease outbreak; instead their use should be limited to those cases where culture and sensitivity has ruled out the use of other antimicrobials with likely efficacy or cases where lower priority antimicrobials result in a poor response. In some countries, the use of some of these antibiotics in food-producing animals is already banned. Logically, the range of antimicrobials used in calves on any farm should be limited, and when resistance becomes apparent, the antimicrobial type should then be changed. This strategy is likely to result in a slow decrease in resistance to that antimicrobial. However, the epidemiology of antimicrobial resistance is extremely complex, and experience in cattle and other species has shown that a reduction in resistance at a farm level can be slow.[677-679] The development of AMR in *Salmonella* is also of concern, with cattle acting as an important reservoir of multidrug resistance.[680] Administration of antibiotics or feeding of medicated milk to young calves may result in the transfer of resistance to *Salmonella*,[664] but feeding medicated milk to young calves tends to reduce fecal *Salmonella* shedding and counterintuitively was not associated with increased shedding of antimicrobial-resistant *Salmonella* in epidemiologic studies.[652] The presence of β-lactamase–secreting *E. coli* can protect other Enterobacteriaceae, such as *S. enterica*, without evidence of gene transfer.[681] Asymptomatic *Salmonella* shedding is common. Because *Salmonella* spp. can be recovered from dairy cattle for up to 3.5 years after clinical infection, the prevalence of AMR in *Salmonella* creates a risk for people in direct contact with the animal, its feces, or milk.[682-685] Although several studies in the United States have failed to show a significant increase in the prevalence of AMR in *Salmonella* in the last 10 to 15 years, this has been attributed to variation in strain prevalence, with common cattle strains showing an increase in multidrug resistance.[677,686]

Antimicrobial Safety.

A number of antimicrobials have been demonstrated to produce deleterious effects when administered orally to healthy milk-fed dairy calves. Administration of neomycin sulfate (300 mg PO q24h for the first 4 days of life) tended (P = .060) to increase the proportion of calves developing diarrhea (99 of 233 = 43%) compared with the proportion in an untreated control group (58 of 174 = 33%).[687] Administration of neomycin sulfate (25 mg/kg PO q6h, n = 10), ampicillin trihydrate (12 mg/kg PO q8h, n = 6), or tetracycline hydrochloride (11 mg/kg PO q12h, n = 6) for 5 days increased the occurrence of diarrhea and decreased glucose absorption through unknown mechanisms compared with untreated controls (n = 6).[688] Two other studies did not observe adverse side effects in calves administered tetracycline hydrochloride (40 mg PO q12h; 11 mg/kg PO q12h).[689,690] Parenteral administration of aminoglycosides is prohibited in many countries due to prolonged slaughter withdrawal times (18 months), but there is also a potential for nephrotoxicity in dehydrated calves.

Efficacy of Oral Antimicrobial Therapy.

The response to oral antimicrobial therapy is variable, with many formulations failing to demonstrate a beneficial effect.[647] Oral antimicrobials may be used to treat *E. coli* overgrowth of the small intestine in mildly sick calves. Calves with diarrhea and moderate to severe systemic illness should be treated with parenteral antimicrobials. Efficacy of oral antimicrobials will vary depending on whether they are a liquid that will bypass the rumen or a capsule that will be deposited into the rumen. Due to reduced transit times in diarrheic calves, the antimicrobial concentration in the small intestinal lumen is lower than in healthy calves, and the rate of antimicrobial elimination is faster.[662]

Efficacy in either reducing mortality or reducing the duration of naturally acquired diarrhea has been demonstrated using either apramycin administered orally at either 20 or 40 mg/kg for 5 days or marbofloxacin (a fluoroquinolone) at 1 mg/kg/day for 3 days.[691,692] The calves treated in the marbofloxacin study were younger than 5 days of age, and ETEC was isolated from more than 50% of the cases. Similarly, aminoglycosides and aminocyclitols are very poorly absorbed from the GI tract and are therefore only useful for the treatment of a confirmed enterotoxigenic *E. coli* infection and not for treatment of septicemia. Cephamycin C (0.75 to 20 mg/kg bid for 3 to 6 days), a broad-spectrum β-lactam antimicrobial, and enrofloxacin (5 mg/kg PO q24h for 3 days) have been shown to significantly reduce mortality in experimentally induced enterotoxigenic *E.*

coli infections.[693,694] However, it is illegal to use both fluoroquinolones and third-generation cephalosporins in some countries, as they are critically important antimicrobials for human medicine; therefore other antimicrobials should be used when indicated.

Trials with orally administered neomycin reduced the duration of diarrhea but did not reduce mortality.[695,696] Similarly, trials with orally administered ampicillin failed to demonstrate a significant reduction in mortality, although the lack of success in this study was later attributed to a delay in commencement of antibiotic treatment.[697] Conversely, orally administered amoxicillin trihydrate has been demonstrated to reduce mortality and the duration of diarrhea when administered at a dose of 10 mg/kg PO q12h.[154,698] Amoxicillin is absorbed from the GI tract more effectively than ampicillin and can be used in combination with clavulanate potassium, providing potent irreversible inhibition of β-lactamase and increasing the antimicrobial spectrum of activity.

The results of trials with orally administered trimethoprim have been variable, with no significant improvement in outcome observed in a large field trial[699] and a significant reduction in mortality observed in an experimental *Salmonella* challenge study where calves were administered 5 mg/kg of trimethoprim and 25 mg/kg of sulfadiazine PO daily for 5 days.[700]

Efficacy of Parenteral Antimicrobial Therapy.

The frequency of bacteremia is sufficiently high in calves with diarrhea that are severely ill (as manifested by reduced suckle reflex, >6% dehydration, weakness, inability to stand, or clinical depression) that routine treatment should include antimicrobials, with an emphasis on treating potential *E. coli* bacteremia.[647]

Antimicrobial drugs with an appropriate gram-negative spectrum of activity include potentiated penicillins (amoxicillin), trimethoprim-sulfonamide (TMS) combinations, aminoglycosides, sulfonamides, florphenicol, fluoroquinolones, third-generation cephalosporins (ceftiofur), and tetracyclines. There is a paucity of efficacy data to support the use of aminoglycosides, tetracycline, and nonpotentiated sulfonamides.

Potentiated sulfonamides have been evaluated in enterotoxigenic *E. coli* and *Salmonella* challenge experiments. Mortality was reduced in 2- to 3-week-old calves medicated with trimethoprim/sulfadiazine (in a 1 : 5 ratio) for 5 days 24 hours after an *S. dublin* oral challenge.[700] Administration of either sulfadiazine

or trimethoprim alone did not reduce mortality.[700] TMS may be used to treat sepsis in neonatal calves, but its half-life rapidly declines as rumen function develops. In ruminating (6- to 8-week-old) calves, subcutaneous or oral administration of TMS leads to high serum levels of sulfadiazine but little or no serum trimethoprim.[701]

Intramuscular administration of amoxicillin reduced mortality in *S. dublin*–challenged calves.[702] In a comparative trial of amoxicillin and trimethoprim/sulfadiazine, both drugs were found to have equal efficacy in reducing adverse clinical signs of disease when dosage regimens were based on the MIC of the pathogen.[703] A large study of calves with naturally acquired diarrhea demonstrated a decrease in mortality after treatment with ampicillin, and the efficacy was increased further with β-lactamase inhibition.[704] Parenteral apramycin (20 mg/kg q24h, unstated route, for 5 days) significantly decreased the mortality rate of calves in a similar study.[691] Fluoroquinolones are efficacious against both experimental challenge and natural ETEC infections.[705,706] Florfenicol (20 mg/kg) given IM every 48 hours for two doses has been shown to be efficacious in treating salmonella.[707] There are concerns about its use in treating a coliform septicemia because the MIC_{90} for *E. coli* is very high and can be achieved for only a short period when administered at 20 mg/kg IV.[647,708] In most countries florfenicol is only labeled for intramuscular or subcutaneous use.

Ceftiofur has an appropriate antimicrobial spectrum, and therapeutic drug concentrations can be maintained with once-daily dosing. In a *S. typhimurium* challenge experiment, intramuscular administration of ceftiofur hydrochloride (5 mg/kg q24h for 5 days) reduced the severity of clinical signs and reduced fecal shedding of *Salmonella*. The MIC of the challenge strain in this experiment was 1 µg/mL, and the therapeutic protocol maintained plasma concentrations above this concentration for the duration of therapy.[375] Ceftiofur is a third-generation cephalosporin and is listed by the WHO in the highest priority of critically important antibiotic. Its use should be limited to appropriate cases.

A national survey in the United States found bacterial isolates to frequently be resistant to tetracycline, streptomycin, ampicillin, and ceftiofur. Less AMR was observed with aminoglycosides, fluoroquinolones, and trimethoprim-sulfas.[709] The therapeutic options are subsequently limited, as the U.S. Animal Medicinal Drug Use Clarification Act prohibits extralabel use of fluoroquinolones, ceftiofur, and certain sulfonamides. In addition, there is a voluntary ban on the

use of aminoglycosides, such as gentamicin and amikacin, in food-producing animals because of long-term tissue residues.[710]

In summary, parenteral administration of a broad-spectrum β-lactam antimicrobial—amoxicillin or ampicillin (10 mg/kg IM q12h) or trimethoprim/sulfadiazine (20 mg/kg sulfadiazine with 5 mg/kg trimethoprim IV or IM q24h for 5 days)—is recommended for treating calves with diarrhea and systemic illness (note that these are off-label doses and require an extended meat withholding period). Antimicrobial therapy is not recommended for calves with diarrhea and no systemic illness (i.e., normal appetite for milk or milk replacer, no fever).[647]

Alternatives to Antibiotics.

Prebiotics and probiotics have been investigated as alternatives to antibiotics, but to date there is no evidence of clinical efficacy. The use of prebiotics and probiotics to prevent diarrhea is discussed in the Nonspecific Immunity section earlier. Lactoferrin is an iron-binding milk glycoprotein naturally found in colostrum that has antimicrobial, antiviral, antiinflammatory, and immunomodulatory effects. It has some efficacy as a preventive but has also been used in a large trial to treat calves with diarrhea on an organic farm. There was no difference in clinical scores compared with controls post treatment, but there was a significantly reduced risk of mortality and culling by 60 days in the subset of calves with severe diarrhea at enrollment.[711]

Antiprotozoal Drugs

Drugs reported to have some efficacy against cryptosporidia in calves include halofuginone,[712-719] paromomycin,[720,721] azithromycin,[722] decoquinate,[723,724] and β-cyclodextrin.[725] Halofuginone appears to be the most efficacious, but it is not licensed in all countries. A meta-analysis of 15 cohort and clinical studies showed that prophylactic use of halofuginone delayed the shedding of *Cryptosporidium,* with a lower prevalence of shedding at days 4 and 7 but a higher prevalence at day 21 when treated calves were compared to controls.[726] Prevalence of diarrhea was also lower on days 4 and 7 in treated calves. Because calves frequently become infected with cryptosporidia during the first 24 hours of life, prophylactic use of halfuginone administered to calves daily for the first week of life is effective at reducing disease when husbandry procedures are implemented to minimize cross-infection between calves.[727] The efficacy of

decoquinate is questionable, with the only controlled clinical study failing to demonstrate a beneficial therapeutic effect with treatment at 2 mg/kg/day.[724] Lasalocid has been trialed for treatment of cryptosporidia. Using a toxic dose of 8 mg/kg, it was found to reduce the shedding of cryptosporidia, but the calves suffered adverse side effects. At a dose of 0.8 mg/kg, lasalocid was not effective.[728] The registered dose for preventing coccidiosis in calves is 1 mg/kg per head per day.

Coccidiosis is uncommon in calves younger than 6 weeks of age. In hand-reared calves, coccidiostats (lasalocid, amprolium, or decoquinate) may be added to milk replacer. Prophylactic options for beef calves are restricted to coccidiostat-medicated pellets (monensin, lasalocid, amprolium, or decoquinate) or water (amprolium or sulfonamides). Therapeutic options include amprolium or sulfonamides such as sulfadimidine.

Both fenbendazole (5 mg/kg PO once daily for 3 days) and albendazole (20 mg/kg PO once daily for 3 days) have been shown as effective treatments for *Giardia*.[331,414,729] Due to the high level of subclinically affected animals, all cows and their dams need to be treated, and reinfection is likely to occur unless calves are removed from environmental sources of infection.

Antiinflammatory Drugs

The routine administration of an NSAID is recommended for a calf with diarrhea that is systemically ill. It is important that administration of NSAIDs occurs after fluid therapy has commenced due to the risk of reduced renal perfusion. To avoid damaging the abomasal mucosa, no more than three doses should be given, particularly in intensive calf-rearing facilities with a history of calf deaths due to perforated abomasal ulcers.[730] Although the benefits of NSAIDs have been demonstrated clinically, the underlying pathophysiology has yet to be determined and could be due to their analgesic, antiinflammatory, antisecretory, or antipyretic properties. Clinical trials have been performed with meloxicam and flunixin. Meloxicam 0.5 mg/kg SC given at the onset of diarrhea increased feed intake, hydration score, and fecal consistency and decreased signs of visceral pain compared to administering a placebo.[731,732] A nonstatistical trend toward decreased morbidity has been reported in a study evaluating the benefits of a single or double injection of flunixin meglumine in scouring calves, but only when fecal blood was present.[733] The routine administration of a corticosteroid to calves with diarrhea is not recommended, as corticosteroids suppress the

immune system and diarrheic calves have been shown to have high levels of plasma cortisol when compared to healthy calves.[734]

Intestinal Protectants

A number of products that include intestinal protectants are marketed for treatment of calves with scours. Intestinal protectants include bismuth subsalicylate, kaolin or pectin, and activated charcoal. No efficacy data are available regarding the use of kaolin in scouring calves. Suggested advantages of bismuth subsalicylate are its neutralization of bacterial toxins and antisecretory effect through its local antiprostaglandin activity.[735,736] The results of one prospective study indicated that the aforementioned nonantibiotic treatments for calf diarrhea resulted in a longer duration of treatment and increased morbidity and mortality when compared to medicated milk replacer and parental antibiotic treatment.[737]

Recent studies demonstrated that a commercially available standardized crofelemer extract, a natural product with antisecretory properties, increased fecal dry matter and reduced the severity of dehydration in both an experimental and a natural outbreak of calf scours.[738,739]

Prognosis

The prognosis for recovery decreases with the severity of depression. Severe hypothermia and the presence of intercurrent disease are grounds for a guarded prognosis.[740-742] An initial examination should be performed. Calves with a primary problem of septicemia are not usually worth treating because of the poor prognosis. The severity of dehydration, hypothermia, and acidosis should be estimated. Recumbent calves are usually treated intravenously with a saline-based rehydrating fluid (0.9% saline, Ringer's, lactated Ringer's, etc.) and isotonic sodium bicarbonate (especially for older and comatose calves). Calves that can suck are treated with oral electrolytes that contain 50 to 80 mmol/L of alkalizing agent. Products that use mainly acetate as the alkalizing agent are best for calves that are still drinking cow's milk (small quantities, frequently). Any alkalizing agent is likely effective in calves held off milk.

Summary

Calf scours is caused by a variety of infectious agents. At the present time, the

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need to make a definitive diagnosis of enterotoxigenic *E. coli* and *Salmonella* infections has been established; these diseases can be controlled by antibiotics and prevented by vaccination.[743] There are public health implications to the diagnosis of cryptosporidiosis and salmonellosis. New vaccines may facilitate controlling rotavirus and coronavirus infections. Treatment of neonate diarrhea is primarily based on correcting dehydration and acidosis through the use of oral and intravenous electrolytes. Only in the case of bacterial infections can direct action be taken against the invading organism, but antibiotics may still be useful in preventing secondary bacteremias. Colostrum feeding will help reduce diarrhea in the first days of life. Management is very important in the control of diarrhea, and since infectious agents are almost always present at some exposure level, the underlying theme is to minimize the level of pathogen exposure and stress on the calf. In approaching a problem of neonatal death losses, the areas to examine should include calf immunoglobulin status, calf feeding, calf housing, cleanliness of environment, calving area, cow vaccinations, diagnosis of specific infectious agents, and treatment protocols.

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Lameness and Reluctance to Walk

John K. House

Septic Arthritis

Septic arthritis may result from direct trauma or contamination of the joint, from extension of periarticular infection, or via hematogenous spread from another site. Systemic sites of infection include enteritis, pneumonia, and inflamed umbilical structures. FPT increases the risk of sepsis. Destruction of the epiphysis and extension of infection into the joint may be primary in some cases, rather than starting as a primary synovial membrane infection that spreads to the epiphysis or physis. The most common pathogens isolated from septic joints of neonatal calves are enteric organisms, including *E. coli* and *Salmonella* spp. *Streptococcus* spp., *Staphylococcus* spp., and *T. pyogenes* are less common isolates. *T. pyogenes* is the most frequently isolated organism from joints of older calves.[744-746] Vertebral body osteomyelitis is another manifestation of hematogenous bacterial spread, with localization of bacteria in the vertebral veins. The presumed origin of the bacteremia most frequently is pulmonary or umbilical infections in calves and tail docking wounds in lambs.[747] The etiologic agent usually is *T. pyogenes* or *F. necrophorum*, alone or as part of a mixed infection.[748] The clinical signs vary depending on location of the compressive abscess. Affected animals often have clinical signs pertaining to other body systems (e.g., coughing, diarrhea, decreased weight gain compared with herdmates) before the onset of neurologic signs. The diagnosis of vertebral osteomyelitis is made by history, clinical signs, laboratory findings suggestive of chronic infection (elevated fibrinogen, globulin, and neutrophil count), and radiographs that demonstrate the affected vertebrae. Spinal fluid analysis is variable, but in most cases it is normal or has a pleocytosis (macrophages and some neutrophils) caused by chronic inflammation of the dura mater.[747]

Bacteria commonly isolated from septic joints in lambs include *Streptococcus* spp., coliforms, *Arcanobacterium pyogenes, Erysipelothrix rhusiopathiae,* and *F. necrophorum*.[455] Predisposing factors include poor docking hygiene and contaminated sheep dip. Sporadic outbreaks of polyarthritis in lambs, kids,[76,749,750] and calves[751] are associated with *Chlamydia* and *Mycoplasma* spp.

infections. *Chlamydia* infections may occur in utero or postnatally, whereas *Mycoplasma* infections often result from ingestion of *Mycoplasma*-contaminated milk.

Diagnosis of septic arthritis is based on the combination of clinical signs, radiographic examination, bacterial culture, and cytologic analysis of synovial fluid. A bacterium is isolated in only 60% of cases of septic arthritis in bovine medicine.[752] Synovial fluid cytologic analysis is useful for the differentiation between infectious and noninfectious arthritis. Trauma is the chief differential. Lambs and kids with septic arthritis often fail to nurse and may present with significant weight loss. Typically polyarthritis caused by *Mycoplasma* spp. and *Chlamydia* is associated with high fevers and respiratory and occasionally neurologic disease. High morbidity and mortality are common. Conjunctivitis is commonly observed with chlamydial infections.[749] Cytologic findings consistent with septic arthritis include a synovial fluid total protein concentration greater than 4.5 g/dL, a nucleated cell count greater than 25,000 cells/mL, a polymorphonuclear cell count greater than 20,000 cells/mL, and a percentage of polymorphonuclear cells greater than 80%.[753] Chlamydial inclusions may be found in Giemsa-stained smears of synovial cells and the organism isolated from joint fluid or plasma in early cases.[749] Isolation of *Mycoplasma* spp. requires specific media (Hayflick media) and microaerophilic conditions. Normal synovial fluid does not rule out septic physitis or osteomyelitis because the infection may be in the physis or small tarsal bones.

Careful examination of high-quality radiographs is important for the detection of bone lysis indicating infection. Initial radiographs may be normal because the degree of damage is often not detectable for 10 to 14 days after initial infection occurs. Radiographic features of septic arthritis include soft tissue swelling, widening or collapse of the joint space, osteoporosis, and osteosclerosis. Ultrasound may be used to confirm involvement of the joint and rule out periarticular or tenosynovial infection to avoid iatrogenic contamination of the joint during arthrocentesis. Joint distention and hyperechogenic fragments in the synovial fluid are suggestive of septic arthritis. Normal synovial fluid is anechoic.

Acute septic arthritis in neonatal ruminants may be treated effectively via joint lavage combined with systemic and local antimicrobial treatment. Typically, however, neonatal ruminants are presented with a chronic disease process. Treatment options include joint lavage or arthrotomy to remove destructive inflammatory products and long-term antimicrobial therapy. Joint lavage is

rarely efficacious in the treatment of chronic septic arthritis in calves, as accumulation of fibrin and pocketing of purulent material often make adequate joint drainage impossible.[754] Joint lavage may be facilitated via use of a rigid arthroscope or, in the case of simple joints (elbow and stifle), arthrotomy.[755] Empirical antimicrobial therapy should include a gram-negative and gram-positive spectrum. Culture of synovial fluid facilitates antimicrobial selection.

Therapeutic synovial concentrations of penicillin, oxytetracycline, ampicillin, and cephapirin can be attained in inflamed and normal joints of calves following systemic administration.[756-759] The distribution of trimethoprim/sulfadiazine, penicillin, oxytetracycline, and cefapirin in joints is not enhanced or reduced by inflammation.[756-758] Penicillin, trimethoprim, and sulfadiazine equilibrate in 0.5 to 1 hour, and oxytetracycline equilibrates in 4.5 to 6 hours.[757] The subsequent decline in antibacterial drug concentration in synovial fluid parallels that in serum.[756] Synovial inflammation accelerates distribution of antimicrobial drugs into joints[757] but has little effect on the peak drug concentration achieved in synovial fluid.[756,757] The peak concentration of ampicillin in synovial fluid following a single intramuscular injection of ampicillin trihydrate at a dosage of 10 mg/kg is higher in normal and inflamed synovial fluid than in sera.[759] There is a paucity of bovine-derived data regarding the distribution of the newer-generation antimicrobials into synovial fluid following systemic administration. Studies in other species suggest that most classes of antibacterial drugs are capable of crossing the synovial membrane. Synovial tissue is very vascular and does not have a basement membrane. In humans synovial fluid concentrations of most antibacterials generally average at least 60% to 70% of serum drug concentrations at the time of peak serum concentrations and frequently exceed those in serum immediately before the subsequent systemic dose in patients with septic arthritis.[760] Antimicrobial dosing is targeted to achieve a peak antibacterial concentration that exceeds the MIC of the infecting organism by fivefold to tenfold.[760] The duration of therapy depends on the antimicrobial sensitivity of the pathogen and the immune status of the patient; prolonged (4 to 8 weeks) antimicrobial therapy is commonly required. In a review of 81 cases of septic arthritis in cattle, a 72% recovery was achieved with a combination of surgical treatment (opening of the joint capsule; débridement; and excision of the synovium, infected cartilage, and bone), joint immobilization, and systemic antibiotic therapy. Of cattle treated conservatively with systemic and intraarticular antimicrobials, 43% recovered.[761]

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Noninfectious Lameness

Neonatal ruminants with nutritional myodegeneration often have a stiff, stilted gait. Lambs and kids may have difficulty nursing if they are unable to lift their head and may cry with pain when assisted to stand (see Chapter 42).

Contracture of joints or tendons of the limbs produces difficulty in movement and predisposes to FPT by impeding the ability to adequately nurse. Degree of contracture varies from mild to severe and may be associated with scoliosis and/or torticollis. Conservative therapy consisting of splinting the front limbs to induce tendon laxity may be helpful. Calves with severe digital flexor tendon contractures often require surgical resection of one or both digital flexor tendons, followed by bandaging or casting and stall rest for 3 to 4 weeks.

Peripheral nerve injuries may occur secondary to dystocia, trauma, or injection site reactions, causing damage to peripheral nerves in the proximity of the injection site. The femoral nerve and brachial plexus are more commonly affected in calves. Femoral nerve damage is usually secondary to stretching the nerve during a “hip lock”dystocia. Clinical signs of femoral nerve paralysis include inability to extend the stifle and advance the limb and analgesia of the medial aspect of the limb down to the tarsus. Atrophy (“dished-out appearance”) of the quadriceps is noticeable in 7 to 10 days if there is complete tearing of the femoral nerve.[747] Atrophy of the quadriceps predisposes to patella luxation. Complete or partial avulsion of the brachial plexus has also been observed in calves following dystocia.[762] The clinical presentation will depend on the severity of the injury. Clinical signs include abnormal positioning of the limb, abnormal locomotion, paresis, muscle atrophy, hyporeflexia, and sensory loss.[747]

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Umbilical Enlargement

The umbilicus consists of three types of structures and undergoes functional and anatomic changes at birth. Two umbilical arteries connect internal iliac arteries to the placenta. These later regress and become the round ligaments of the bladder. One umbilical vein connecting the placenta to the liver and porta cava regresses to become the round ligament of the liver within the falciform ligament. The urachus connects the fetal bladder to the allantoic cavity.

Patent Urachus

Patent urachus is a persistence after birth of the tubular connection between the bladder and umbilicus. The urachus drains the bladder into the allantoic sac during gestation. Urine flow should gradually change, with some urine entering the amniotic sac through the urethra in later gestation. At birth, with umbilical cord rupture the urachus should be closed, and urine should be voided through the urethra. Neonates with a patent urachus may dribble urine from the urachus during or after urination or may simply present with a constantly wet umbilical stump.

Differentials include concurrent infection of the navel (omphalophlebitis). Ultrasound may assist the diagnosis and determine the involvement of umbilical arteries or vein. Moist hairs around the umbilicus and visualization of fluid coming from the navel are diagnostic. A complete physical examination should be performed. If abnormalities are noted, serum IgG, complete blood cell count, and urinalysis are helpful for detecting susceptibility to infection and presence of systemic or urinary tract infection. Surgical resection of the urachus to the tip of the bladder is the treatment of choice. Associated arteries and veins should be ligated and removed if they are infected or necrotic. Merely ligating the exterior stump can trap organisms and cause infection.

Omphalitis

Omphalitis is inflammation of umbilical structures that may include the umbilical arteries (omphaloarteritis), umbilical vein (omphalophlebitis), urachus, or tissues immediately surrounding the umbilicus. Umbilical infection is one of the most common diseases in newborn calves, occurring in 1.3%[763] to 29.9% of

newborn calves.[764]

Umbilical abscess or infection of any of the three components of the umbilicus may produce local infection or be a source of septicemia. The source of infection is most commonly the external environment, coupled with FPT. Bacteria isolated from calf umbilical cord remnant infection include *T. pyogenes*, *E. coli*, and *Proteus* and *Enterococcus* spp. Herd management variables that influence the risk of umbilical infection include maternity pen hygiene, cleanliness of the newborn calf environment, effectiveness of passive transfer, and umbilical cord management.[765]

The urachus is the most commonly affected structure in calves, and the umbilical arteries are the least affected.[766] Omphalophlebitis may extend the length of the umbilical vein into the liver and result in liver abscessation. When the umbilicus is enlarged and draining purulent material, infection is easily noted. When the urachus is fixed to the abdominal wall, calves are prone to cystitis and may show signs of pollakiuria and dysuria. In other cases the umbilicus may be dry and larger in diameter than expected. In addition, neonates may have a completely normal-appearing, dry external navel and be severely ill from infection of the urachus, umbilical arteries, or umbilical vein. In a septic neonate without external signs of infection, involvement of the umbilicus can be difficult to determine. Abdominal palpation of the umbilical vein and arteries is a useful, simple, and effective means of assessing their size and detecting pain associated with these structures. Inflamed structures may be identified by standing behind the neonate and pressing the hands together above the umbilicus. Ultrasound is also a useful ancillary diagnostic aid.[767] Persistent dilation of the umbilical vein or arteries with a hypoechoic-to-echogenic fluid, intraluminal gas, and wall thickening are findings consistent with infection. In calves, the urachus normally retracts up into the abdomen at birth, and ultrasonographic identification of a urachal remnant is abnormal.[768]

Overt signs of infection are heat, swelling, purulent discharge, or pain. Concurrent signs of systemic infection such as joint infection, pneumonia, diarrhea, meningitis, or uveitis may be noted. Calves with urachal abscesses may show signs of dysuria or pollakiuria.[769,770] Infection in more than one umbilical vessel in the neonate is common, and urachal involvement is frequent. Umbilical abscessation that is walled off and does not involve deeper structures is a less severe problem and may be treated with drainage without surgical removal of the entire umbilicus.

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Early treatment with antibiotics and supportive care may allow resolution before development of abscessation and distention of the urachus or the umbilical arteries and vein. Established infection usually requires surgical removal of involved structures in addition to medical therapy.[766] When omphalophlebitis extends into the liver, the umbilical vein may be marsupialized to facilitate drainage and flushing.[771] Prognosis is improved when adequate passive transfer of colostral immunoglobulins has occurred and when joints or other structures are not involved. Sequelae such as renal abscessation, joint or bone infection, peritonitis, and other complications described for septicemia may develop if therapy is started too late or discontinued prematurely.

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Anemia

Anemia in the neonate should be interpreted in the context of the realization that normal hematologic values of the neonate may vary from the adult. In calves, the incidence of anemia (hemoglobin <10 g/dL) is quite high, ranging from 15% to 30% in many herds,[772,773] and is normocytic, normochromic, and poikilocytic. Anemia is reported to be secondary to iron deficiency.[772,773] Potential causes are reduced amounts of iron in milk, poor placental transfer of iron, or decreased intestinal absorption. Anemic calves with poikilocytosis have similar levels of serum iron, total iron binding capacity, and marrow iron and plasma copper levels compared with normal calves.[774] Anemic calves do not appear to have an increased incidence of disease or decreased growth rates.[775] An overall higher plane of nutrition versus iron supplementation alone produces higher packed cell volumes (PCVs) and hemoglobin levels.[774] Calves younger than 6 weeks of age have three types of hemoglobin in various amounts (adult 28%, fetal 40%, and neonatal 25%). The poikilocytosis may be a function of erythrocyte membrane defects or maturation transitions.[774]

In addition to frank blood loss from an injury, diseases causing anemia in the neonate include neonatal isoerythrolysis (NI), non-NI immune-mediated hemolytic anemia,[776] blood loss caused by gastric ulcer, anemia secondary to bone marrow necrosis, and anemia of chronic disease associated with localized infections. Hemolytic disease of newborn calves is uncommon but has occurred after vaccination of pregnant cows against anaplasmosis or babesiosis. The presence of red cell antigens in the vaccine causes the production of antierythrocyte antibody, primarily against the A and F systems.[777] Cows mated to bulls carrying these red cell antigens may have hemolytic disease develop in their A- and F-positive calves after ingestion of colostrum-containing alloantibodies.

Hemolytic disease processes produce signs of weakness, pale or jaundiced mucous membranes, fever, and depression. Blood loss produces weakness and pale mucous membranes. Intestinal parasitism does not normally lead to anemia during the neonatal period. Intravascular hemolysis may produce hemoglobinuria and hemoglobinemia. Icterus develops when the ability of the liver to conjugate bilirubin is exceeded. Mainly, indirect bilirubin is elevated. Anisocytosis is observed in responsive anemias. Nonspecific stimulation of bone

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marrow may produce a leukocytosis.

Anemia has also been reported in calves infected with bovine viral diarrhea virus, secondary to bone marrow necrosis.[778]

Determination of the nature of the anemia may allow specific treatment. Blood transfusion may be indicated when anemia develops rapidly or PCV drops below 14%. Associated conditions such as metabolic acidosis and hypoglycemia should be corrected. Anemia of chronic disease requires correction of the primary disease condition.

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Fever

Differentials for fever in neonates include bacterial or viral infections, excitement, seizures with subsequent generation of heat by muscular overactivity, and environmentally induced hyperthermia. Fever is an unreliable indicator of sepsis in neonatal calves.[23] Septic neonates often have a normal or subnormal temperature. Older ruminants with localized infection such as in joints or bone are more likely to have fever. Fever may be beneficial. The need to administer antipyretics to the febrile neonate is controversial. Body temperatures lower than 40.8° C (105.4° F) are not considered detrimental unless they are associated with heat stroke or seizures,[779] in which case cooling and antipyretics are indicated. Because many antipyretics are antiprostaglandins that can cause deleterious GI and renal effects, these agents should be used judiciously. Correction of the initiating cause and maintaining fluid balance are also important.

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Cyanosis

Cyanosis is the purple-blue coloration observed on mucous membranes or skin caused by reduced or poorly oxygenated hemoglobin in blood.[780] Cyanosis may be caused by congenital heart disease, respiratory impairment, or any circulatory condition that produces a right-to-left shunt (Box 20.4). The degree of cyanosis depends on the arterial oxygen saturation, hemoglobin concentration, pH, peripheral circulation, and temperature of the neonate.[780] Shock and hypothermia are important causes of peripheral cyanosis. The affinity of hemoglobin for oxygen is reflected in the standard oxyhemoglobin dissociation curve. This curve is similar for neonates but is affected by the amount of 2,3-diphosphoglycerate (DPG) in the erythrocyte. Calves' erythrocytes have higher levels of 2,3-DPG, but the higher levels do not affect the affinity of hemoglobin for oxygen. A separate fetal hemoglobin exists in calves to increase affinity for oxygen.[781] Severe hypothermia and acidosis cause the oxygen dissociation curve to shift to the right and therefore contribute to tissue hypoxia. Cyanosis can be either central or peripheral.[780] Peripheral cyanosis results from increased peripheral extraction of oxygen from normally saturated blood or a significant decrease in the perfusion to an extremity.[780] In the neonate, causes include septic shock and severe hypothermia. Central cyanosis is more common in neonates and is related to congenital heart disease that causes right-to-left shunting or severe respiratory conditions that result in hypoxia. Examination and clinical pathologic evaluation for metabolic causes of cyanosis, hypothermia, and cardiac abnormalities should be conducted. History, medication use, auscultation, thoracic radiographs, and arterial blood gases are useful in determining the degree of respiratory component to cyanosis. Echocardiography may be required for identification of cardiac anomalies.

Box 20.4

Causes of Cyanosis

Cardiovascular Origin

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Tetralogy of Fallot
Tricuspid atresia
Truncus arteriosus
Pentalogy of Fallot
Double outlet right ventricle
Single ventricle
Eisenmenger complex
Ventricular septal defect
Patent ductus arteriosus

Respiratory Causes

Alveolar hypoventilation
Drug-induced central nervous system (CNS) depression
CNS trauma or hemorrhage
Hypoglycemia or hypocalcemia
Altered neurologic function of spinal nerves (of respiratory muscles)
Thoracic cage abnormalities: pneumothorax, fractured ribs
Diaphragmatic hernia
Upper airway obstruction
Restrictive pleural space disorders: hemothorax, pleuritis
Hypoplastic lung

Impaired Diffusion

Pulmonary: pneumonia, edema, atelectasis
Shunting
Anatomic (congenital heart defects)
Pathologic: pulmonary hypertension
Ventilation-perfusion mismatch

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Heart Murmur

Heart murmurs in the neonate may be heard normally before physiologic closing of the ductus arteriosus during the first 1 to 5 days of life. Other causes of murmurs include congenital anomalies, severe anemia, or infectious valvular disease. Physical examination for other signs of heart disease helps determine the severity of the murmur. Jugular pulse, weak or irregular arterial pulse, and palpable thrill indicate a serious condition. Dyspnea, cyanosis, tachypnea, and failure to gain weight are common signs of congenital heart disease in calves. Timing and location of the heart murmur should be determined. Thoracic radiography may aid in determining heart size and in detecting pulmonary edema or distended pulmonary vessels. Echocardiography may reveal atrial or ventricular enlargement, thickened ventricular walls, anomalous orientations of outflow tracts, or ventricular septal defects.

Patent ductus arteriosus (PDA) produces a continuous murmur localized over the left heart base. The diastolic component may not be heard with auscultation over other parts of the heart. As pulmonary hypertension develops, the murmur is shortened to a holosystolic type with normal arterial pulse. Large shunting of blood produces a bounding arterial pulse caused by wide fluctuations of systolic and diastolic pressures. Radiographs may reveal an enlarged heart with increased vascularity due to left-to-right shunting of blood. Echocardiography may reveal an increased left atrial and left ventricular diastolic dimension or volume and hyperdynamic septal and left ventricular wall systolic motion (depending on the degree of right-to-left shunt).

Ventricular septal defect (VSD) produces a large, harsh, holosystolic murmur that is heard loudest on the right cranial region of the thorax and is softer over the left heart base. Radiography may reveal heart size increase, left atrial enlargement, and dilated pulmonary vasculature. Two-dimensional echocardiography may show aortic and septal discontinuity. Injection of saline bubbles into the left ventricle and observation of bubbles in the right atrium or ventricle document a left-to-right shunting of blood. Tetralogy of Fallot or other types of complex malformations often produce loud murmurs and are associated with cyanosis, weakness, fatigue, and stunted growth. Tetralogy of Fallot produces a systolic ejection murmur heard at the left heart base. Echocardiography may reveal a thickened right ventricular wall, septal echo dropout in the area of the VSD, rightward displacement of the aortic root, and an

abnormal pulmonary outflow region. Saline injection into the jugular vein demonstrates right-to-left flow from the right ventricle to the left ventricle or the aorta.

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Icterus

Icterus is a relatively uncommon finding in neonates. It may be observed with sepsis, anorexia, liver disease, and hemolytic anemia. Liver disease in the neonate may be caused by exposure to hepatotoxins or sepsis-producing bacterial hepatitis, or it may be secondary to hypoxia. *C. perfringens* type A has been implicated in an enterotoxemic condition in nursing lambs, kids, and calves characterized by icterus, hemoglobinuria, anemia, and intravascular hemolysis.[112]

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Bleeding Disorders

Bleeding disorders are relatively uncommon in calves. In 2007 a bleeding disorder characterized by trilineage hypoplasia of bone marrow was recognized in Europe. Affected calves were 1 to 4 weeks of age. A strong association between the condition and vaccination of the dam with the bovine viral diarrhea virus vaccine Pregsure was established.[782] It is believed that vaccination induced colostral alloantibody-mediated destruction of hematopoietic progenitor cells in bone marrow, causing cytopenias, including thrombocytopenia, and hence bleeding. The condition was subsequently recognized in the UK in 2009.[782] Differential diagnoses include thrombocytopenia secondary to septicemia and disseminated intravascular coagulation (DIC), Type II BVD infection, acute braken toxicity, and trichothecene mycotoxicosis.

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Failure to Thrive: Cachexia and Weak Calf Syndrome

John Maas

In calves, the weak calf syndrome has been reproduced by feeding low-protein diets to prepartum cows that subsequently calved in environments in which the temperature was well below the thermoneutral zone for calves.[783] The dietary recommendation for crude protein intake for third-trimester pregnant cows and heifers is 0.9 kg (2 lb) of total crude protein per day. This is particularly important for heifers and cows calving early in the spring calving season, when temperatures well below freezing can occur. Cold rains, however, also can produce the hypothermic conditions that aid in precipitating this syndrome.

Cows weighing 450 kg (1000 lb) therefore need to consume 9.9 kg (20 lb) dry matter of good- to excellent-quality hay that is 10% or more crude protein. A quadratic equation has been developed to predict crude protein (CP) intake of the dams if their serum total proteins, urea nitrogen, and creatinine are known.[784] This equation predicts the daily crude protein intake on a continuing basis.

$$\begin{aligned}\text{Daily CP consumption (kg)} = {} & 0.1806 + 0.04327\,(\text{BUN}) \\ & - 0.33497\,(\text{creat}) + 0.06963\,(\text{TP}) - 0.00025\,(\text{BUN})^2 \\ & + 0.06049\,(\text{creat})^2 - 0.00666\,(\text{BUN} \times \text{creat})\end{aligned}$$

where *BUN* is blood urea nitrogen (mg/dL), *creat* is serum creatinine (mg/dL), and *TP* is serum total protein (g/dL).

Also, the use of this formula could predict CP intake for pregnant heifers and pregnant cows. This relationship may prove to have important clinical applications when weak calf syndrome or protein-calorie malnutrition is suspected and the gestation diet of the dams is not available for analysis (as under some range conditions). Supplements such as molasses licks that contain urea may tend to overestimate CP intake.[785]

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• CHAPTER 21

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Colostrum and Milk Replacers

Sandra Godden, Robert E. James, Consulting Editors

MAJOR CLINICAL SIGNS OR PROBLEMS ENCOUNTERED

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The goals of colostrum and milk feeding programs for preweaned calves and small ruminants are to achieve optimal rates of gain, support and develop a strong immune system, maximize health, and stimulate ruminal development, all in a cost-effective manner. Although feeding high-quality, clean maternal colostrum and whole milk may be considered by many to be gold standards, the use of high-quality colostrum replacement products and milk replacers may be attractive to producers for a variety of reasons, including consistency, convenience, as a means of breaking the transmission cycle of some infectious diseases, or simply to capture economic efficiencies. This chapter reviews important considerations in the manufacture, selection, and use of high-quality colostrum replacement and milk replacer products.

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Colostrum Supplements and Replacements

The principles of colostrum management are reviewed in Chapter 19. Although feeding 3 to 4 L of clean, high-quality maternal colostrum shortly after birth remains the gold standard, farms can experience periods when an adequate supply of high-quality fresh or stored maternal colostrum is not available. Also, it may not always be practical or convenient to harvest first milking colostrum from fresh cows within a timely manner after calving (<1 to 2 hours). Contributing to this shortage, some producers may discard colostrum from cows that test positive to such pathogens as *Mycobacterium avium* subsp. *paratuberculosis* or *Mycoplasma bovis*.[1-3] Under such circumstances, feeding commercially available colostrum replacement (CR) products may offer a simple, consistent, and convenient means of delivering the necessary immunoglobulins (Ig) to newborn calves while reducing the risk of pathogen exposure. In addition, if cowside testing indicates lower-than-desirable colostrum quality (e.g., colostrum IgG <50 g/L, as indicated by Brix refractometer reading <22%),[4] then supplementing maternal colostrum feeding with a colostrum supplement (CS) may be beneficial; however, the optimal protocols and efficacy of this strategy require further study. This chapter section discusses types of CS and CR products, manufacture and licensing, evaluating product efficacy, impact of Ig source on antibody profiles, monitoring passive transfer, and use of CR or CS products in minor species. Although some studies have demonstrated that supplementation of the milk diet with Ig from either maternal colostrum or CS may reduce the severity of rotavirus or coronavirus scours occurring during the first 14 days,[5-7] the current discussion is limited to use of CS and CR products in the first 24 hours after birth.

Colostrum Supplements Versus Colostrum Replacements

Colostrum supplements, which typically cost between $13 and $19 USD per package, are designed to provide exogenous IgG to calves to supplement low-volume or poor-quality maternal colostrum (colostral IgG <50 g/L).[8] Most CS

products provide between 25 and 60 g of IgG per package. Feeding one package (packet) of a CS will not provide a sufficient mass of IgG to prevent failure of passive transfer (FPT) in young calves, nor will it provide sufficient levels of nutrients necessary for calf survival or optimum growth.[8,9] By comparison, CR products, which typically cost between $26 and $40 USD per package, are designed to be fed instead of maternal colostrum. They should provide a minimum of 100 g of IgG per package and should also provide sufficient levels of nutrients to the calf to support metabolic needs in the first day of life. It should be noted that feeding multiple packages of some CS products can achieve the same result. For example, HeadStart®/Calf's Choice Total® Gold CS in a 60-g IgG package is licensed as a CR product for prevention of FPT when fed at 180-g IgG (3 packs) in the United States or at 2 packs in Canada. However, it can also be used as a supplement if producers elect to feed fewer packages. Some CR products are also labeled with directions for feeding lesser amounts to supplement rather than replace maternal colostrum. It is recommended that CS or CR products be mixed in water, according to the manufacturer's directions, and fed in conjunction with any available high-quality colostrum.[10]

Manufacturing

Immunoglobulins in commercial CR and CS products are most often derived from spray-dried bovine colostrum or spray-dried bovine serum or plasma. For colostrum-derived CR products, sometimes referred to as lacteal derived, fresh frozen bovine colostrum is collected from Grade A dairies and assembled at a manufacturing plant where it undergoes pooling, heat treatment or irradiation, spray drying, testing for IgG concentration, and packaging. Immunoglobulins may also be sourced from milk or whey for some products not licensed by the Center for Veterinary Biologics (CVB). For colostrum-derived products, the concentrations of most non-Ig colostral components (e.g., nutrients, hormones, growth factors), with the exception of cellular fractions (i.e., leukocytes, bacteria), should be similar to maternal colostrum unless the colostrum has been fully or partially defatted and/or casein and other whey proteins have been removed to enhance the proportion of IgG in the final product.

For serum-derived CR or CS products, blood is collected from abattoirs under U.S. Department of Agriculture (USDA) inspection, centrifuged to separate plasma and/or serum from red blood cells, ultrafiltered, spray dried to produce a concentrated powder containing approximately 20% Ig, and then mixed with

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other ingredients (e.g., lactose, dry fat blend consisting of animal and/or vegetable fats, dextrose, vitamin and mineral premix). Because fat is entirely supplemented, crude fat concentrations will vary among CS products, with low levels (<10%) in some products. Serum-derived products will contain some of the same bioactive compounds as colostrum, since many are derived originally from serum (e.g., insulin-like growth factor 1 [IGF-1], trypsin inhibitor), but may have reduced or nondetectable concentrations of other bioactive compounds found in maternal colostrum (e.g., lactoferrin). The final product may be irradiated. Exact manufacturing methods vary among manufacturers and products.

Is the Colostrum Replacer or Colostrum Supplement Licensed?

Licensed CR products are allowed the following label claim: “to aid in the treatment of failure of passive transfer (FPT).” In Canada it is required that all CR and CS products be licensed through the Canadian Food Inspection Agency (CFIA), Canadian Center for Veterinary Biologics (CCVB, Ottawa, Ont.).[11] Serum- and plasma-derived CR or CS products are not permitted in Canada. In the United States only some manufacturers have acquired a license for certain CR products through the USDA CVB (Ames, Iowa). The IgG in licensed CR products must come from bovine colostrum collected from Grade A dairies and be processed by heat treatment or ionizing radiation using accepted protocols, and every serial release (batch) made for sale and distribution must be tested for purity and potency at a minimum.[12,13] Data on product (efficacy, safety, purity, and potency) must be submitted to and reviewed by the CFIA or USDA before licensing. Purity requirements allow a specified total bacteria and fungi count. However, coliforms and *Salmonella* spp. must not be present. Potency tests require a minimum IgG content for products with an FPT claim. In the United States efficacy testing for licensed FPT products requires that, in 90% of animals, the increase in IgG concentration (pretreatment vs 24 hours posttreatment) must be at least equal to concentration of the IgG Species Standard approved by the USDA's Animal and Plant Health Inspection Service (APHIS) (e.g., approximately ≥10 to 11 g/L serum IgG for neonatal calves) (USDA: 9 CFR 113.450; 9 CFR 113.499).[12] Also, the overseeing regulatory body completes an approximately annual site inspection to review processes and

records. As such, licensed products can guarantee safety, potency, purity, efficacy, and traceability. Products licensed by regulatory agencies as bovine IgG for treatment of FPT may not claim nutrient profiles on the label, so this information must be obtained from manufacturers' promotional materials. Table 21.1 lists licensed products currently available in Canada and the United States.

TABLE 21.1

Licensed Colostrum Replacements and Supplements in the United States (US) and Canada (CA)[a]

Product Name	Manufacturer/Distributor	Country	IgG Provided (g)
Colostrum Replacement Products			
Replacer 115	Manufacturer: SCCL (Sask., CA) Distributor: MWI Animal Health (Idaho, US)	US	115 g in 640-g pack
CALF'S CHOICE TOTAL	Manufacturer: SCCL (Sask., CA). Distributors: SCCL (Sask., CA), Rafter 8 (Alta., CA), Grober (Ont., CA)	CA	100 g in 470-g pack
Colostrum 150	Manufacturer: SCCL (Sask., CA) Distributor: Alta Genetics (Alta., CA)	CA	150 g in 830-g pack
GroStart	Manufacturer: SCCL (Sask., CA) Distributor: Grober Nutrition (Ont., CA)	CA	100 g in 470-g pack
CALF'S CHOICE TOTAL HiCal	Manufacturer: SCCL (Sask., CA) Distributor: Alta Genetics (Wis., US)	US CA	100 g in 700-g pack
Land O' Lakes COLOSTRUM REPLACEMENT	Manufacturer: SCCL (Sask., CA) Distributor: Land O' Lakes (Minn., US)	US	100 g in 470-g pack
COLOSTRUM PLUS 100 with *Escherichia coli* Antibody	Manufacturer & Distributor: La Belle Associates (Wash., US)	CA US	100 g in 500-g pack
COLOSTRX CR Colostrum Replacer	Manufacturer: La Belle Associates (Wash., US) Distributor: AgriLabs (Mont., US)	US	100 g in 500-g pack
PREMOLAC PLUS Colostrum Replacement	Manufacturer: Zinpro Corp. (Minn., US) Distributor: Milk Products (Wis., US)	US	152 g in 375-g pack
Land O' Lakes COLOSTRUM REPLACEMENT for Kid Goats & Lambs	Manufacturer: SCCL (Sask., CA) Distributor: Land O' Lakes (Minn., US)	US	50 g in 235-g pack
HeadStart Hi-Cal for Lamb & Goat Kids	Manufacturer and Distributor: SCCL (Sask., CA)	CA	100 g in 700-g pack
LambGRO/KidGRO Colostrum	Manufacturer: SCCL (Sask., CA) Distributor: Grober Nutrition (Ont., CA)	CA	100 g in 700-g

			pack
PureStart Colostrum for organic use	Manufacturer: SCCL (Sask., CA) Distributor: Alta Genetics (Wis., US)	US	100 g in 700-g pack
Colostrum Supplement Products			
Supplement 57	Manufacturer: SCCL (Sask., CA) Distributor: MWI Animal Health (Idaho, US)	US	57.5 g in 320-g pack
CALF'S CHOICE TOTAL Gold	Manufacturer: SCCL (Sask., CA) Distributor: Alta Genetics (Wis., US)	US	60 g in 225-g pack
HeadStart	Manufacturer & Distributor: SCCL (Sask., CA)	CA	60 g in 225-g pack
COLOSTRX CR Colostrum Supplement	Manufacturer: La Belle Associates (Wash., US) Distributor: AgriLabs (Mont., US)	US	50 g in 300-g pack
Colostro	Manufacturer: SCCL (Sask., CA) Distributor: Federated Coop (Sask., CA)	CA	50 g in 235-g pack
Bovine Dried Colostrum	Manufacturer & Distributor: SCCL (Sask., CA)	CA	50 g in 350-g pack
FIRST COLOSTRUM 50 Colostrum Supplement	Manufacturer: La Belle Associates (Wash., US)	CA US	50 g in 350-g pack
Immu-Start 50 with *Escherichia coli* Antibody	Manufacturer: Imu-Tek Animal Health (Colo., US)	CA US	50 g in 400-g pack
Just Like Mom	Manufacturer: SCCL (Sask., CA) Distributor: Aspen Veterinary Resources (Mont., US)	US	50 g in 300-g pack

[a]Product list may change in future. Specifications may change in future; read the label. Licensing bodies: Canadian Center for Veterinary Biologics, Canadian Food Inspection Agency[11]; Center for Veterinary Biologics, U.S. Department of Agriculture.[62] IgG source for all licensed products is bovine colostrum.

IgG, Immunoglobulin G.

Although products that do not have a USDA CVB license are not legally able to claim to supply IgG or to purport to be used for the prevention of FPT, their use for this purpose is widespread in the United States. Bovine colostrum and dried bovine colostrum are official feed ingredients under the Association of American Feed Control Officials (AAFCO) guidelines (www.aafco.org). As such, claims for nonlicensed CR or CS products must adhere to nutrition-based claims but can make no immunity claims. Under AAFCO guidelines, every state (i.e., state Department of Agriculture) adopts and regulates its own animal feed per its applicable laws and regulations relating to label specifications or guaranteed analysis. Although all U.S. manufacturers of non–CVB-licensed CR

and CS products will conduct some kind of internal quality control testing, the design of these programs are at the manufacturer's discretion. External product testing or plant inspections by regulatory authorities (e.g., state Department of Agriculture) are not typically completed for non–CVB-licensed products unless a problem or complaint is brought to their attention.

Evaluating the Efficacy of Colostrum Replacement Products

Producers are strongly encouraged to consult their veterinarian and to select CR or CS products that have undergone independent evaluation of efficacy in controlled field studies. Evaluation of efficacy should ideally consider passive transfer of adequate IgG, nutritional support, and calf health and performance. In addition to the age of the calf at time of feeding, passive transfer of IgG will be determined primarily by the mass of IgG (g) administered as well as the apparent efficiency of absorption (AEA %) of the IgG; AEA % is a calculated estimate of the percentage of IgG administered that is absorbed systemically.[14] Each product must be independently evaluated, since differences in manufacturing processes can have a significant impact on both AEA % and final mass of IgG in a package.[14,15] Head-to-head studies are necessary to make valid comparisons between products. Table 21.2 presents the results of field efficacy studies for commercially available CR and CS products that were mixed and fed according to label directions.

TABLE 21.2

Selected Efficacy Studies of Colostrum Supplement (CS) and Colostrum Replacement (CR) Products (Limited to Studies of Commercially Available Products Mixed and Fed According to Label Directions)

Citation	CS or CR Product Fed	N	Total IgG Fed (g)	Age Fed (hours)	AEA IgG (%)	Serum IgG (mg/mL)	APT (%)
CS Studies							
Smith & Foster, 2007[20]	First Day Formula CS (CD)	21	100 (2 packs)	<3	NR	7.5[b]	5[b]
	First Day Formula CS (CD)	21	150 (3 packs)	<3		9.1[b]	24[b]

	Maternal Colostrum	21	NR (3.8 L)	<3		17.6[c]	95[c]
Arthington et al, 2000[21]	First Milk Formula CS (CD)	10	50 (2 packs)	<2 & 12	≈16[b]	2.2[b]	NR
	Colostrx CS (SD)	10	60 (2 packs)	<2 & 12	≈24[c,d]	3.5[c]	
	Lifeline CS (SD)	10	90 (2 packs)	<2 & 12	≈28[c]	6.8[d]	
	Maternal Colostrum	10	200 (3.8 L)	<2 & 12	≈22[b,d]	12.1[e]	
CR Studies							
Godden et al, 2009a[19]	Land O' Lakes CR (CD)[a]	24	100 (1 pack)	<1	36[b]	9.6[b]	54[b]
	Land O' Lakes CR (CD)[a]	23	200 (2 packs)	<1	37[b]	19.0[c]	100[c]
	Maternal Colostrum	22	271 (3.8 L)	<1	32[b]	20.7[c]	91[c]
Godden et al, 2009b[23]	Land O' Lakes CR (CD)[a]	24	100 (1 pack) - Bottle	<1	51[b]	12.5[b]	100[b]
	Land O' Lakes CR (CD)[a]	24	100 (1 pack) - Tube	<1	41[c]	9.9[c]	42[c]
	Land O' Lakes CR (CD)[a]	24	200 (2 packs) - Bottle	<1	41[c]	19.7[d]	100[b]
	Land O' Lakes CR (CD)[a]	25	200 (2 packs) - Tube	<1	39[c]	18.7[d]	100[b]
Shea et al, 2009[24]	Land O' Lakes CR (CD)[a]	8	105 (1 pack)	<2	41[b]	10.7[b]	80[b]
	Land O' Lakes CR (CD)[a]	8	210 (2 packs)	<2 & 12	31[c]	14.5[c]	90[c]
Brakefield et al, 2010[25]	Calf's Choice Total Bronze CR (CD)[a]	27	200 (2 packs)	<2	30[b]	20.0[b]	100[b]
	Calf's Choice Total Bronze CR(CD)[a]	28	200 (2 packs) + Probiotic	<2	29[b]	20.1[b]	100[b]
Morrill et al, 2010[26]	Calf's Choice Total Gold CR (CD)[a] + dam not fed anionic salts prepartum	10	198 (3 packs)	<1 & 6	27[b]	13[b]	80[b]
	Calf's Choice Total Gold CR (CD)[a] + dam fed anionic salts prepartum	10	198 (3 packs)	<1 & 6	26[b]	13[b]	90[b]
Place et al, 2010[27]	Land O' Lakes CR (CD)[a]	36	150 (1.5 packs)	<2	38[b]	14.7[b]	94[b]
	Colostrx 130 CR (SD)	38	130 (1 pack)	<2	28[c]	9.6[c]	37[c]
Fidler et al, 2011[28]	Colostrx 130 CR (SD)	22	130 (1 pack)	<2	≈20[b]	7.4[b]	14[b]
	Colostrx 130 CR (SD)	22	260 (2 packs)	<2	≈14[c]	10.6[c]	86[c]
	Maternal Colostrum	22	211 (3 L)	<2	≈36[d]	21.4[d]	95[c]
Cabral et al, 2012[29]	Calf's Choice Total Gold CR (CD)[a]	13	191 (3 packs/1 feeding)	<1	32[b]	15.8[b]	92
	Calf's Choice Total Gold CR (CD)[a]	13	191 (3 packs/2 feedings)	<1 & 6	33[b]	16.8[b]	100
Pithua et al, 2013[30]	Land O' Lakes CR (CD)[a]	295	200 (2 packs)	<6	27[b]	15.2[b]	89[b]
	Maternal Colostrum	273	80 (3.8 L)	<6	29[b]	7.5[c]	30[c]
Priestley et al, 2013[31]	Calf's Choice Total Silver CR(CD)[a]	49	100 (1 pack)	<2	39%[b]	11.4[a]	49%[a]
	Lifeline Rescue CR (SD)	49	150 (1 pack)	<2	22%[b]	9.3[a]	29%[b]
	Maternal Colostrum	49	≈190 (3.8 L)	<2	NR	21.0[b]	92%[c]

Ellis et al, 2018[32]	HeadStart/Calf's Choice Total Gold (CD)[a]	9	150 (1 pack)	<6	NR	13.8[a]	NR
	Lifeline Rescue (SD)	9	150 (1 pack)	<6		9.3[c]	
Foster et al, 2006[34]	Immu Start 50 CS (CD)[a]	21	100 (2 packs)	<3	NR	7.0[b]	10[b]
	Land O' Lakes CR (CD)[a]	21	100 (1 pack)	<3		11.6[c]	81[c]
	Land O' Lakes CR (CD)[a]	21	200 (2 packs)	<3		16.9[d]	95[c]
	Maternal Colostrum	21	448 (3.8 L)	<3		27.2[e]	90[c]
Lago et al, 2018[38]	First Day Formula CR (CD)	609	150 (1 pack)	<1	34.4	19.6[b]	NR
	Maternal Colostrum	606	178 (2.8 L)	<1	35.9	23.4[c]	
Swan et al, 2007[39]	Acquire CR ± Lifeline CS (SD)	218	125 (CR) ± 45 (CS)	<4 ± 12	NR	5.8[b]	7[b]
	Maternal Colostrum	239	291 (3.8 L)	<4 ± 12		14.8[c]	72[c]

[a]Product licensed through Center for Veterinary Biologics (Canadian Food Inspection Agency and/or U.S. Department of Agriculture).

[b,c,d,e]Means within column within study with different superscripts differ (P <0.05).

AEA, Apparent efficiency of absorption; *APT,* acceptable passive transfer (serum IgG ≥10 g/L); *CD,* colostrum-derived IgG source; *IgG,* Immunoglobulin G; *N,* number of calves per treatment group; *NR,* not reported; *SD,* Serum/plasma-derived Ig source.

Mass of IgG Provided in Colostrum Replacements.

Although experts originally estimated that producers should feed a minimum mass of 100 g of IgG in the first colostrum feeding, and this has been demonstrated to be sufficient under ideal conditions, most recent studies, especially if conducted under field conditions, have shown that at least 150 g, and preferably 200 g, of colostral IgG must be fed to consistently achieve acceptable passive transfer (APT; serum IgG ≥10 g/L) in the majority (≥90%) of calves.[16-19] This dose effect was demonstrated in one study wherein three groups of calves fed either 100 g or 200 g of IgG in a colostrum-derived CR product or 3.8 L of fresh maternal colostrum achieved a mean serum IgG concentration at 24 hours of 9.6 g/L (46% with FPT), 19.0 g/L (0% with FPT), and 20.7 g/L (9% with FPT), respectively (see Table 21.2).[19] Although many CR products are packaged to provide 100 to 130 g IgG per pack, some CR products now provide a larger mass of IgG per pack (e.g., 150 g) and/or provide label directions that suggest feeding increased masses of IgG, at the discretion of the producer.

Apparent Efficiency of Absorption (AEA %) of IgG.

When considering how APT can be achieved in calves, grams of IgG should be

considered more important than absorption percentages. Under most circumstances, the *total mass* (g) of IgG fed and the *age of the calf* at feeding are the most important predictors of APT in calves fed CR products. That said, simply examining the mass of IgG provided by the CR is not an adequate predictor of product efficacy.[20] There can be significant differences in AEA % among products due, but not limited, to such factors as manufacturing methods and IgG concentration after reconstitution, as well as inclusion of other nutrients or additives in the product. Controlled field studies using commercially available CR or CS products, mixed and fed according to label directions, have reported widely varying AEA % values (see Table 21.2). The AEA % reported for CS products has ranged between 16% and 28%.[21,22] The AEA % reported for CR products has ranged between 14% and 51%.[19,23-30] In comparison, the AEA % of IgG reported for calves fed 3 to 4 L of fresh maternal colostrum within 6 hours of birth has ranged between 21% and 36%.[19,21,22,28,30]

Studies to date have generally reported the AEA % to be significantly higher for colostrum-derived CR products compared to serum- or plasma-derived CR products. In one early CS study in which calves were fed two packs of a colostrum-derived CS (50 g IgG), two packs of one of two different serum-derived CS products (60 g or 90 g Ig, respectively), or 3.8 L of maternal colostrum, the AEA % reported for the colostrum-derived CS (16%) was inferior to that of the two serum-derived CS products (24% and 28%) and the maternal colostrum (22%) (see Table 21.2).[21] However, because all three CS products delivered an insufficient mass of IgG compared to maternal colostrum, all three CS products failed to provide APT to calves.

To date, three head-to-head controlled field studies have compared the AEA % of commercially available serum-derived and colostrum-derived CR products. In one study calves fed 150 g of a colostrum-derived CR had significantly improved AEA % and serum IgG concentrations (AEA % 38.2%, serum IgG 14.7 g/L) compared to calves fed 130 g of a serum-derived CR (AEA % 28.4%, serum IgG 9.6 g/L) (see Table 21.2).[27] In this study the improved final serum IgG values for the colostrum-derived CR group were attributed to both increased mass fed (g) and improved AEA %. In another study calves fed 150 g of a serum-derived CR had inferior AEA % (21.6%) compared to calves fed 100 g of a colostrum-derived CR (38.8%).[31] In a third recent, randomized controlled study, newborn calves fed 150 g of Ig from a serum-derived CR product had significantly lower serum IgG at 24 hours (median 9.3 g/L, range 6.8 to 12.3

g/L) compared to calves that received 150 g of IgG from a colostrum-based CR product (median 13.8 g/L, range 12.4 to 19.4 g/L).[32] Based on the present body of research, it appears that a higher total mass of Ig needs to be fed if using serum-derived CR products to achieve the same final serum IgG concentration that is achieved by feeding colostrum-derived CR products.

Passive Transfer Levels, Health, and Performance of Calves Fed Commercial CS or CR Products.

If given alone as a single package, CS products (given the lower mass of IgG delivered) will result in significantly lower serum IgG concentrations and a high risk of FPT in calves as compared to feeding 3 to 4 L of maternal colostrum (see Table 21.2).[20-22,33,34] Furthermore, there is no added benefit to feeding a CS if calves are fed 3 to 4 L of high-quality maternal colostrum.[35,36] Although an opportunity may exist for producers doing on-farm testing of colostrum using such instruments as the Brix refractometer for the purpose of supplementing poor-quality colostrum with a CS, the effectiveness of this strategy requires further study.[4,37] Several commercially available CR products, when administered at a high enough IgG mass (150 to 200 g IgG) within a few hours after birth, can provide acceptable to very good serum IgG concentrations and APT rates in calves (goal: ≥90% of calves with serum IgG ≥10 g/L) (see Table 21.2).[19,24-27,29,30,34,38] However, unless fed under ideal management conditions,[23] low APT rates are achieved if an insufficient mass of Ig (<150 g) is fed in either maternal colostrum or a CR product.[19,23,27,28]

Studies comparing the health of calves fed CR or maternal colostrum have reported equivocal results, with between-study differences likely attributable in large part to significant differences in the mass of Ig provided in the CR versus maternal colostrum treatment groups. In one early study of 457 calves on 12 Upper Midwest dairy farms, there was no significant difference in morbidity or mortality in 218 calves assigned one package of a serum-derived CR product providing 125 g of Ig, compared to 239 calves fed 3.8 L of fresh maternal colostrum, despite the fact that the CR group had lower serum IgG concentrations and higher FPT rates than the calves fed maternal colostrum (see Table 21.2).[39] In a study conducted by Pithua and colleagues, calves fed the CR product at birth were at reduced risk to test positive for infection with *M. avium* subsp. *paratuberculosis* as adults (7.6% test positive; odds ratio 0.52 [0.27 to 1.003]), compared to control calves fed maternal colostrum (11.9% test positive),

demonstrating that CR products may be a useful management tool for dairy herds attempting to reduce the prevalence of Johne's disease.[40] In addition, Pithua and colleagues determined that the colostrum treatment group had no significant effect on longevity, milk production, or reproductive performance during the first three lactations.[41] In a different study of 147 calves at a Florida dairy, the percentage of calves with FPT, preweaning morbidity rates, and preweaning mortality rates for 49 calves fed 150 g of a plasma-derived CR were as follows: FPT 71%, morbidity 71.4%, and mortality 16.3%. For 49 calves fed 100 g of a colostrum-derived CR, these rates were FPT 51%, morbidity 67.3%, and mortality 24.5%. For the remaining 49 calves fed 3.8 L of maternal colostrum, with average IgG intake estimated to be 190 g, these rates were FPT 8%, morbidity 46.9%, and mortality 8.2%.[31] The authors concluded that, under the conditions of the study, maternal colostrum was superior to CR, primarily due to an insufficient mass of Ig fed in the CR groups.

Conversely, two more recent studies that fed higher levels of colostrum-derived CR products reported similar or improved health in CR-fed calves compared to calves fed maternal colostrum. In a study of 1220 Jersey and Jersey-Holstein calves born at one California dairy, calves fed 150 g of IgG from a colostrum-derived CR product had lower, but still acceptable, mean blood IgG and serum total protein (STP) concentrations (IgG 19.6 g/L, STP 5.16 g/dL) compared to calves fed 2.8 L of maternal colostrum (IgG 23.4 g/L, STP 5.84 g/dL).[38] Evaluating STP to classify calves as APT or FPT is discussed in detail later in this chapter. In that study, the preweaning risk for treatment for scours (CR 85.8%, maternal colostrum 89.0%), risk for treatment for pneumonia (CR 55.2%, maternal colostrum 58.6%), and risk for death (CR 9.4%, maternal colostrum 7.1%) were not different between treatments, although CR-fed calves were 1.5 kg lighter at weaning (CR 47.1 kg, maternal colostrum 48.6 kg).[38]

A second randomized controlled study of 568 calves at another California dairy reported higher serum IgG concentrations and improved health and growth in calves fed 200 g of IgG in a colostrum-derived CR at birth (serum IgG 15.2 g/L, scours 15.9%, weaning weight 58.9 kg) compared to calves fed 3.8 L of maternal colostrum (serum IgG 7.5 g/L, scours 24.5%, weaning weight 57 kg) ($P < 0.05$).[42] In this second study CR was superior to maternal colostrum, but this was most likely attributable to the fact that the calves fed maternal colostrum were fed very poor-quality maternal colostrum, averaging only 21 g/L of IgG (average dose: 78 g IgG) (see Table 21.2).[30,42] Clearly, if producers hope for CR-

fed calves to match or exceed the health and performance of calves fed 3 to 4 L of high-quality maternal colostrum, they will need to feed a sufficiently high mass of Ig from the CR—at least 150 g and preferably 200 g.

Does Ig Source Affect the Antibody Profile in CR or CS Products?

Veterinarians frequently ask if the antigen-specific antibody profile in CR products will complement the antigen profile on their clients' dairy farms. Because the colostrum used to manufacture CVB-licensed colostrum-derived CR or CS products is collected from cows living on commercial North American Grade A dairy farms, these authors consider it a safe assumption that the cows will have been exposed to, and therefore produce colostral antibodies against, most of the common pathogens endemic on most commercial dairies (e.g., *Escherichia coli*, rotavirus, coronavirus, *Cryptosporidium* spp.), whether achieved through natural exposure and/or through vaccination programs. However, published studies to verify this hypothesis are extremely limited for colostrum-derived CR products and lacking entirely for serum-derived CR products. One recent Alabama field study reported that calves fed 200 g IgG of a colostrum-derived CR had greater levels of bovine viral diarrhea virus (BVDV)–neutralizing antibodies in serum, and similar levels of antibodies to bovine herpesvirus 1 (BHV-1), bovine respiratory syncytial virus (BRSV), and parainfluenza type 3 virus (PI3V) in serum, as compared to calves fed 3.8 L of maternal colostrum.[43] Additional studies are needed to describe antigen-specific antibody concentrations, particularly to enteric pathogens, found in calves fed CR or CS products.

Another frequent question relates to whether the antibody profile in colostrum-derived CR products is superior to that in serum-derived products. Although the concentrations of the subclasses IgG1 and IgG2 are approximately equal in serum (50 : 50 ratio, or 50% IgG1), IgG1 naturally occurs in much higher concentrations than IgG2 in colostrum (7 : 1 ratio, or approximately 90% IgG1) due to the selective transfer of IgG1 into the mammary secretions of cows.[44-46] Immunoglobulin G is the main class of Ig secreted into the bovine intestinal tract.[47-49] Furthermore, IgG1 is the predominant Ig subclass secreted into the bovine intestinal tract, lungs, nasal secretions, vaginal secretions, and saliva.[50-52] Secretion of serum IgG1 rotavirus immunoglobulin into the intestinal

lumen, if in sufficient quantity, provides protection against rotavirus infection.[47,49,50,53-55] In a review of this topic, Thornsberry and Wood (2011) stressed the importance of newborn calves consuming a sufficient mass of IgG1 prior to closure of intestinal absorption of Ig molecules.[14] All else being equal, one could theorize that the increased proportion of IgG1 found in colostrum-derived CR products (90% IgG1) should result in improved calf health, as compared to serum-derived CR products (50% IgG1). Ellis and colleagues reported higher levels of IgG1 BRSV-specific antibodies in the nasal secretions of calves fed equal IgG mass (150 g IgG) of a colostrum-based CR compared to calves fed a serum-based CR product.[32] It has been argued that the relative content of IgG1 in a CR may be immaterial for consideration (provided that a sufficient total mass of IgG is provided) because studies have demonstrated that both colostrum- and serum-derived CR can achieve desired goals of calf production.[14] Further research on the health implications of calves fed serum-based CR versus colostrum is needed.

Monitoring Passive Transfer Rates When Feeding CR or CS Products

Measurement of STP by handheld refractometer offers a simple, rapid, and inexpensive method by which producers can monitor the colostrum program when feeding maternal colostrum. However, producers must be cautious if trying to use STP measures to monitor passive transfer rates in groups of calves fed CR or CS products, since the proportions of IgG and non-IgG proteins can be different than in maternal colostrum. For calves fed maternal colostrum, it is well established that STP test end points of 5.0 or 5.2 g/dL most accurately predict APT (serum IgG ≥10.0 g/L, sensitivity >0.80, specificity >0.80, proportion classified correctly >0.85).[56,57] However, these same STP cut-points are not necessarily accurate predictors of APT when feeding a CR or CS. Three studies of calves fed colostrum-derived CR products have reported that, similar to maternal colostrum, an STP cut-point of 5.0 or 5.2 g/dL most accurately predicts APT.[27,30,31] However, a significant association was not found between STP and serum IgG in one study wherein calves were fed a colostrum-derived CS product.[34] For serum-derived CS or CR products, the relationship between STP and serum IgG in calves may vary dramatically among products, depending on the source, level of inclusion, and/or degree of absorption of non-Ig proteins.

Studies of different serum-derived CS or CR formulations have reported widely varying STP cut-points ranging between 4.2 and 5.6 g/dL.[15,27,31,39,58] Given the large variation in predicted STP cut-points, and particularly for the serum-derived CR products, veterinarians are encouraged to use refractometry to monitor the effectiveness of a CR feeding program only if independent studies are available describing the relationship between STP and serum IgG for the specific commercial CR product in use on the farm. If such studies are not available, veterinarians are advised to periodically submit frozen serum samples for serum IgG analysis using direct methods such as radial immunodiffusion or turbidimetric immunoassay.[56,59,60]

Use of Colostrum Supplements or Replacements for Organic Producers or Minor Species

While most CS and CR products target calves, products also exist for minor species, including goat kids, lambs, foals, llama or alpaca cria, pigs, fawns, and elk calves (see Table 21.1). Although many products available for minor species are not licensed, CVB-licensed products do exist for goat kids and lambs, meeting CFIA and USDA standards guaranteeing purity, potency, safety, efficacy, and traceability (see Table 21.1).[61] Because the dose of IgG required for multispecies CR or CS products will vary by species, producers should follow individual product label directions for feeding. Currently one CVB-approved CR product, PureStart™ Colostrum (Manufacturer: SCCL; Distributor: Alta Genetics), is approved for use on organic dairy farms in the United States (see Table 21.1).

Summary

High-quality CR products can offer a consistent and convenient source of Ig and nutrients for newborn calves when clean, high-quality maternal colostrum is not available, plus they may be a useful management tool to help break the transmission cycle of some infectious diseases (e.g., Johne's disease). Additional controlled field studies are needed to further describe and compare efficacy among various CR products and particularly to describe the effects of feeding CR on short- and long-term health and performance outcomes. However, studies conducted to date demonstrate that when fed a large enough dose (150 to 200 g IgG) of a high-quality CR product within a short period of time after birth,

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calves can achieve passive transfer levels and health outcomes at least equal to those of calves fed fresh maternal colostrum. Given the significant differences in quality and efficacy among various commercially available products, producers may want to consider whether a product is CVB licensed and are strongly encouraged to select CR or CS products that have demonstrated efficacy in independently conducted controlled field studies.

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Milk Replacers

The digestive anatomy of the newborn calf consists of a four-compartment stomach like the adult stomach, but the abomasum predominates with 60% of the total stomach capacity. During the first weeks of life the calf is essentially monogastric as milk is shunted directly to the abomasum by closure of the esophageal groove. Closure is stimulated as a behavioral response associated with milk feeding by bottle or bucket. During this time the calf depends on the consumption of highly digestible nutrients provided by food-grade feedstuffs, as it depends on enzymatic digestion of proteins, fat, and simple sugars in the form of lactose. The consumption of limited quantities of dry feed along with free-choice water stimulates rapid colonization of the stomach with ruminal microorganisms and rapid differential growth of the stomach tissue, which enables it to digest more complex carbohydrates and vegetable proteins. The impact of diet on rumen development is depicted by Heinrichs.[63]

There are multiple goals in feeding the preweaned calf, which requires a degree of compromise. Ultimately the goal should be to provide the environment and nutrient supply that enable the calf to achieve its genetic growth potential with minimal health problems at a reasonable cost. There are different philosophies as to what constitutes a successful calf-rearing program. A goal favored in more traditional programs has been limit feeding of the liquid diet to encourage dry feed intake and encourage early weaning. This practice reduces daily feed costs during the preweaning period, and there has been the perception that digestive disturbances could be substantially reduced by transitioning the calf to a dry diet as soon as possible. This feeding program frequently provides only enough energy from the liquid diet to meet maintenance requirements under thermoneutral conditions, with enough remaining to support only very modest growth. This is especially true during the first weeks of life when calves consume negligible amounts of calf starter grain. More recent research supports calf feeding programs that provide nutrients to encourage more biologically normal growth rates of 700 to 1000 g/day during the preweaning period. These programs cost more per day but frequently result in lower costs per unit of gain. Higher protein and energy intake results in lower morbidity and mortality in dairy calves, particularly during the winter months.[64] Ultimately the goal for the milk feeding program should be to foster the growth of the animal, which results

in the most economical lifetime performance rather than the lowest daily rearing cost during the preweaning period. Recently, Soberon and Van Amburgh demonstrated that enhanced feeding programs providing 28% crude protein and 0.3 Mcal of metabolizable energy/kg of body weight (4.2 to 8.4 Mcal/day) compared to those providing only 2.8 Mcal/day resulted in greater mammary secretory tissue in young heifer calves.[65]

Liquid Diets for the Dairy Calf

Calves can grow well on whole milk, waste milk, or milk replacers. Although the most recent National Animal Health Monitory System (NAHMS)[66] survey indicates that more than 50% of calves are fed milk replacer, there is increased interest in the use of waste milk for calves, particularly on larger farms that pasteurize it prior to feeding to reduce risk of disease. Pasteurized waste milk has been viewed as a means of increasing nutrient intake and reducing feed cost. However, the manager must be aware of the challenges involved in these feeding systems, which include monitoring efficacy of the pasteurizer and milk solids level and accounting for variation in supply.[67,68]

Milk replacers were first developed in the early 1950s with the goal of reducing costs and increasing the convenience of feeding dairy calves. These milk replacers resembled gruels and frequently resulted in poor calf performance. The challenge in using milk replacers is to provide sufficient nutrients to encourage acceptable growth at less cost than feeding whole milk. Table 21.3 compares the nutrient content of 4 L of average-quality whole milk and 4 L of a typical 20% protein–to–20% fat milk replacer diluted to approximately 12.5% solids. These milk replacers fed in the limited amounts shown here allow for lower daily feed costs and encourage early starter intake but at reduced rates of gain and possibly impaired health. More recent research has been directed toward achieving gains closer to those of whole milk feeding programs. The quality of milk replacers and expected performance is influenced by the ingredients used and manufacturing practices and quality control.

TABLE 21.3

Comparison of Four Liters of Whole Milk to Four Liters of a 20 : 20 Milk Replacer Diluted to 12.5% Solids

Parameter	Whole Milk	20 : 20 Milk Replacer

Total solids (%)	12.5	12.5
Fat % (liquid/DM)	3.6/28.8	2.5/20
Protein % (liquid/DM)	3.0/24	2.5/20
Fat g/4 L	144	100
Protein g/4 L	120	100

20:20, 20% protein–to–20% fat; *DM,* dry matter.

Ingredients Used in Milk Replacers

Ingredients used in milk replacers providing the protein, fat, carbohydrate, and minerals should be of high digestibility and low bacteria count for the young calf. Traditionally these ingredients originate as products from the processing of milk, as shown in Fig. 21.1. The skim milk and cream portions, although highly desirable, are generally too expensive to be considered in milk replacer manufacture.

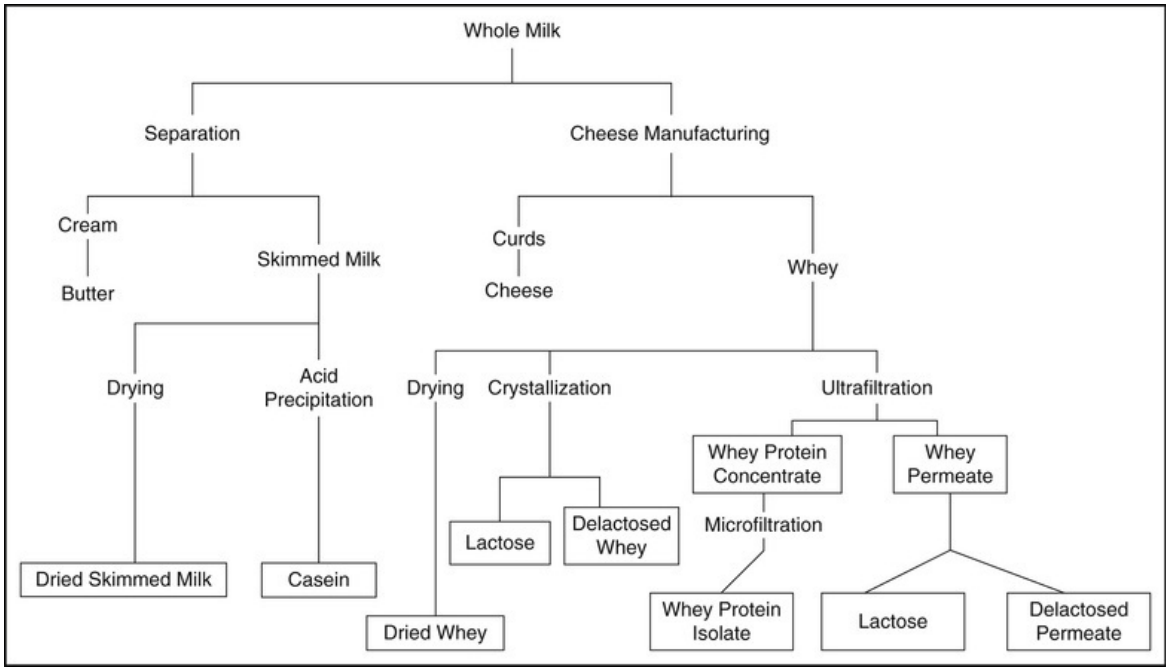


FIG. 21.1 Steps in milk processing and by-products potentially used in the manufacture of milk replacers. (Courtesy T.J. Earleywine.)

Protein Sources.

Common proteins used in the manufacture of milk replacers can be classified as

either milk or alternative proteins. Most milk-derived proteins used in milk replacers have originated from the whey fraction. Whey can be processed through evaporation or filtration to separate the lactose and minerals from whey proteins to yield ingredients commonly used in milk replacers. The nutrient value of these different fractions is shown in Table 21.4.

TABLE 21.4
Chemical Composition of Ingredients Commonly Used in Milk Replacers[69-71]

Ingredient	Dry Matter (%)	Crude Protein (%)	Crude Fat (%)	Crude Fiber (%)	Lactose (%)	Ash (%)	Salt (%)
Whole milk solids	100	25.6	29.6		29.2	5.6	
Dried skim milk	98	34	0.1		52-54	8.5	3.5
Whey protein concentrate	98	33.5	2.5-3.5		50-52	7.0	2.5
Delactosed whey	98	21	1.0-1.5		55	16-18	–
Dried whey	98	11.5	1.0-2.0		70-72	6-7	1.8-2.3
Soy protein isolate	94	85-89	<1.0	0.2	<1.0	4.0-6.0	
Soy protein concentrate	95	66-70	1.0-2.0	3.6-4.5	–	4.0-7.0	
Soy flour	95	50-53	1.0-1.5	2.5-3.3	–	6.3	
Modified wheat protein	94	79-81	5.0-7.0	<0.5	–	1.0-3.0	
Animal plasma	97	68-82	0.5-2.0	<0.5	–	8.0-10.0	
Spray-dried whole egg	95	41-47	39-41.5			3.5-3.65	

Many feeding trials have evaluated the nutritional value of different protein sources on calf growth, health, and feed efficiency. Variation in nutrient content and digestibility of whey proteins is due to the type of cheese being manufactured and the efficacy of the different processes used. Special care must be taken during the drying process to prevent denaturation of the protein. Digestibility of whey-based ingredients generally exceeds 85% and more commonly exceeds 90%. One concern with the use of whey-based proteins is that, unlike casein in skim milk protein, these proteins do not form a clot in the abomasum shortly after being consumed. It seems that the failure to clot would impair protein digestion and use by the calf. However, Terosky and colleagues[72] formulated milk replacer diets containing 0%, 33%, 67%, and 100% replacement of skim milk protein with whey protein concentrate. During the 8-week

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experiment, daily gains were similar, although calves in which 100% of the protein was from whey protein concentrate experienced a slightly lower incidence of scouring.

The value of whey protein concentrate has fluctuated considerably from approximately $0.34/lb in 1985 to as much as $1.50/lb in 2012 followed by a drop to $0.72/lb in early 2018. Although whey prices have fluctuated over the years, it is apparent that whey proteins will continue to find favor in the human health food market. As a result, the use of alternative proteins in calf milk replacers continues to be an active field of research. The nutritional content of milk-derived and alternative ingredients found in milk replacers is shown in Table 21.4. There are two major concerns with the use of alternative proteins. One is the digestibility by the calf, particularly for the calf less than 2 weeks of age. Research on the alternative proteins has shown a wide range in digestibility of these proteins from as low as 54% to more than 90%. Variation is due to the processing and the age of the calf receiving the liquid diet. Soy proteins probably offer the greatest promise. Untreated soybean protein is strongly antigenic, causing infiltration of the lamina propria of the small intestine with T and B lymphocytes, hypersensitivity reactions, villous atrophy, and decreased intestinal absorptive ability.[73] Soybeans are treated to remove the fat and all or part of the carbohydrate and reduce these antigenic properties. Soy flour represents the least processing, whereas isolated soy protein results from extensive processing with an alkali wash, acid precipitation, alkali resolubilization, and drying. Tomkins and colleagues[71] noted that feed conversion by calves 1 to 14 days of age fed soy protein concentrate containing milk replacers was reduced by as much as 30%. However, more recent research has shown improved responses. Unfortunately, due to extensive processing, the cost of isolated soy protein is not always economically feasible.

Wheat gluten is protein derived from wet milling of wheat after separation of the starch. The protein is rather insoluble and has antigenic properties that cause reactions by intestinal tissue. However, acid treatment to partially hydrolyze the wheat protein increases its solubility and reduces antigenicity. Although the digestibility of wheat gluten is comparable to that of whey proteins, it is deficient in lysine. Wheat gluten proteins have found wide use in veal-type diets, but research has shown that growth in replacement heifers less than 14 days of age may be depressed. At higher rates of feeding in younger calves, the depression in average daily gain becomes ever more evident.[73]

Animal plasma proteins from porcine or bovine blood have been used in milk

replacers. The protein has an excellent amino acid profile that compares well with skim milk protein.[74,75] Calves fed milk replacers in which 25% of the whey proteins had been replaced with plasma proteins were found to grow at a slightly lower rate during the first 28 days; however, growth rates were similar over a 56-day feeding period.[74,75]

Spray-dried whole egg is an undesirable alternative protein in milk replacers, as incorporation at levels above 5% of the total dry matter result in reduced rates of calf growth.[76]

Other proteins—including pea, lupine, potato, fish, red blood cells, meat solubles, yeast, and bacterial proteins—have shown be unacceptable sources of protein for milk replacers due to poor solubility, low digestibility, or inadequate amino acid content.[77]

Supplementation of plasma protein with isoleucine and threonine[78] and vegetable protein-based milk replacers with lysine and methionine may have merit.[79,80] At present, there are no data to support supplementation of milk protein–based milk replacers with amino acids.

Carbohydrates.

During the first weeks of life, the intestine of the young calf has limited carbohydrase activity except for lactase. The only carbohydrates usable in large amounts are lactose, glucose, and galactose. Lactose from whey is the main carbohydrate source in milk replacers. Whole milk contains approximately 29% lactose, 29% fat, 20% casein, 5% whey protein, and 5% ash on a dry matter basis. The most popular milk replacers containing 20% protein and 20% fat have substantial space for the addition of more lactose than is present in whole milk, given that high levels of ash are undesirable. Consumption of higher amounts of lactose from milk replacer than might be present in whole milk does not appear to be a concern.[70] The inclusion of starch and other carbohydrates in milk replacers is not advised for calves younger than 2 to 3 weeks of age due to limited amylase and maltase activity. Toullec and colleagues[81] suggest a limit of 2% to 3% starch in dry matter intake for younger calves.

Lipids.

Milk fat is highly digestible; however, it is too expensive to be included in milk replacers. Tallow, lard, choice white grease, and coconut and palm oil are the

primary sources of fat used in milk replacers. A comparison of the fatty acid composition of a tallow-based milk replacer with that of one based on coconut oil to whole milk is shown in Table 21.5. Although digestibility of tallow and lard is somewhat lower than milk fat, performance is adequate. In general, highly unsaturated vegetable oils are poorly tolerated by the young calf.

TABLE 21.5
Fatty Acid Composition of Milk Replacers Based on Animal Fat, Coconut Oil, and Palm Oil Compared to Whole Milk[82]

Fatty Acid	Animal Fat Source (% of Total Fat)	Coconut Oil (% of Total Fat)	Palm Oil[a] (% of Total Fat)	Whole Milk (% of Total Fat)
C4:0 butyric	0.40	0.41		3.30
C6:0 caproic	0.20	0.92		3.00
C8:0 caprylic	0.36	9.18		2.00
C10.0: capric	0.40	5.06		3.00
C12:0 lauric	0.99	23.63	0.20	3.50
C14:0 myristic	2.12	9.91	1.10	10.20
C16:0 palmitic	23.31	14.51	44.00	26.30
C16:1 palmitoleic	2.29	0.90		2.30
C18:0 stearic	12.75	6.73	4.50	12.00
C18:1 oleic	38.35	19.15	39.20	25.10
C18:2 linoleic	14.07	7.30	10.20	2.40
C18:30 linolenic	0.63	0.36	0.40	0.80
Other	4.05	1.94	0.40	6.10

[a]www.chempro.in/fattyacid.htm.

Two fat sources that have been used are palm and coconut oil. These fats are higher in medium chain fatty acids found in milk fat. Mills and colleagues[82] studied the effect of adding medium chain fatty acids at a rate of 32% of the fat as coconut oil or oil high in caprylate. No differences were found in body composition, intake, or fecal score between the animal fat–based milk replacer or coconut oil treatments. Empty body fat was about 5% higher, and livers in heifers fed coconut oil contained 15% more fat than those in heifers fed animal fat. Hill and colleagues[83,84] replaced part of the animal fat in a milk replacer

with low levels of coconut oil or blends of coconut and canola oil and found higher average daily gains and less scouring than calves fed diets with only animal fat. The formulation of milk replacers with special attention to fatty acid composition is an active field of research.

Vitamins and Minerals.

Vitamins and minerals are generally added to milk replacers to provide levels similar to those found in whole milk. The most recent (seventh) edition of *Nutrient Requirements of Dairy* Cattle (NRC)[85] recommended a substantial increase in vitamin A from 4000 to 9000 IU/kg of dry matter. Vitamin E recommendation was increased from 40 to 50 IU/kg of milk replacer dry matter. These levels are sufficient to prevent deficiencies under stressful conditions of digestive or respiratory disease and to avoid a toxic response with higher levels of milk replacer observed with more intensive feeding programs. Recommended vitamin D is 600 IU/kg of dry matter. Water-soluble vitamin and trace mineral recommendations are described in the seventh edition of the NRC.[85] Osorio and colleagues[86] evaluated the impact of supplementing organic trace minerals to calves fed diets formulated for a low or high plane of nutrition (568 g vs >1000 g milk replacer solids). Calves fed at a high plane, but not those fed at a low plane, of nutrition responded with increased growth. This suggests that growth of calves at a lower feeding rate was limited by factors other than trace mineral nutrition.

Recommended Protein and Fat Levels in Milk Replacers

The most important factors influencing the price of a milk replacer are the protein and fat content and the source of each. Replacers labeled as “all milk usually contain blends of dried whey, delactosed whey, and “whey protein concentrate.” Milk replacers with alternate proteins will have some of the whey proteins (up to 50%) replaced by soy, wheat, or animal plasma proteins. Table 21.6 represents industry classification of the suitability of protein sources for milk replacers.

TABLE 21.6

Classification of Protein Sources Used in Milk Replacers Suitable for Young Calves[77]

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Classification of Protein Sources Used in Milk Replacers Suitable for Young Calves

Acceptable Milk Ingredients	Acceptable Nonmilk Ingredients	Not Acceptable
Dried whey protein concentrate	Soy protein isolate	Meat solubles
Dried skim milk	Protein-modified soy flour	Fish protein concentrate
Casein	Soy protein concentrate	Wheat flour
Dried whey	Animal plasma	Soy flour
Dried whey product	Wheat gluten or isolate	Egg products

It should be noted that dried skim milk and casein are rarely present in milk replacers in sufficient amounts to affect nutrient content or quality due to their high cost. For calves younger than 3 weeks of age, digestibility and amino acid content of milk-derived proteins tend to be more suitable.

Commercially available milk replacers contain between 18% and 28% protein. The level of protein and fat depends on the desired performance and conditions of the calf's environment. The seventh edition of the NRC[85] continued to recommend limited feeding of milk and milk replacer solids to calves (454 g/day) to encourage the early intake of calf starter and early weaning. At this level of intake, 18% to 20% protein is adequate with minimal rates of daily gain. However, more recent work focused on the nutritional requirements of calves growing to their genetic potential has resulted in the manufacture of milk replacers with higher protein content fed in amounts as high as 1.1 kg of milk or milk replacer solids.[87-90] Work by Blome and colleagues[87] suggests that lean tissue growth is optimal between 26% and 28% crude protein at higher feeding rates.

Calf milk replacers usually contain between 10% and 25% fat. This is lower than the level found in cow's milk, which would be in excess of 28%, with milk containing 3.6% fat on a liquid basis. The impact of the fat content of the milk replacer on body composition and calf growth depends on the feeding rate and environmental conditions. At lower feeding rates (454 g solids/day), body fat deposition increases as the level of fat increases in the milk replacer. The optimal level of body fat for the preweaned calf has not been determined. Body fat at birth is heavily dependent on the body condition of the dam. During the end of the first week of life, it is not uncommon for calves to have less than 2% body fat.[90] This is probably an inadequate reserve should the calf become ill, decrease dietary energy intake, and have increased energy requirements due to environmental temperature or the response to disease. Therefore, there is probably some benefit to the calf experiencing accretion of body fat, especially during the first weeks of life. Jersey calves fed a moderate amount of milk solids (700 g/day) were found to have approximately 9% body fat at 5 weeks of age.[90]

As fat percentage and daily fat intake from milk replacer increases, calf starter grain intake is delayed or occurs at a lower rate. Most milk replacers contain approximately 10% to 20% fat, which is adequate over a wide range of intake levels and protein percentages. Bascom and colleagues[90] suggested that smaller calves would benefit from higher levels of fat in the diet during periods when the environment is below the thermoneutral zone. However, during warmer months there appears to be little benefit to milk replacers with more than 15% fat. Milk replacers specially formulated to contain desired fatty acid composition with 10% fat provide sufficient energy for desired growth during summer months.

It is important to note that the grams of nutrient intake and megacolories (Mcal) of energy intake are more important in meeting the calf's nutrient requirements than percentages. Therefore, greater attention should be paid to the amount of solids intake rather than percentages of protein or fat.

Manufacturing Milk Replacers

Production of milk replacers begins with procurement of quality ingredients and enactment of a strict quality assurance program at the manufacturing facility.[91] Whey products are monitored for protein, fat, ash, pH, sodium, moisture, color, solubility, dispersibility, bacterial growth, lactic acid production, and evidence of overheating. With fats and oils, color, melting point, odor, peroxide, free fatty acid content, and fatty acid profile are considered. Most manufacturers rely on supplier histories as each incoming load of ingredient is tested. The main variables influencing the nutritional value of whey proteins are the type of cheese produced, heating history, length of storage, and sanitation. Sanitation factors are critical since they influence microbial and peroxide loads of the final product. Standard plate count must be less than 30,000 cfu/g, less than 10 cfu coliforms/g, less than 10 mold or yeast colonies/g, and no detectable *Salmonella*. Excessive heating can lead to denaturation of the protein, whereas underheating can contribute to excessive microbial growth. Reputable manufacturers use only ingredients that are edible by humans rather than feed grade.

The next process in producing a milk replacer is to combine the ingredients into a product that has good wettability and mixability characteristics and does not separate. *Wettability* is a measure of how fast the powder breaks water tension and drops below the surface of the water. A test used is the amount of powder that drops below the surface of the liquid within 60 seconds. Wettability is related to ingredients used and the amount of surfactant added. *Mixability* is

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how completely the powder goes into solution and stays in suspension. Although wettability appears to make the product more convenient, mixability is more important to the calf. *Separation* is how much the ingredients separate from the rest of the solution, including those that float to the surface and those that sink to the bottom. Ingredients low in fiber (milk proteins, plasma, wheat gluten, and soy isolate) have better mixing characteristics than soy protein concentrate or flour. A powder that has all of the nutritional characteristics of a desirable milk replacer must also have physical characteristics that enable the calf to consume a uniform, digestible, and palatable product.

Several methods are used in manufacturing milk replacer powders: dry blending, chilling towers, and agglomeration. Each method can provide a finished product of desirable nutrient content. However, differences in the three characteristics mentioned previously may affect the nutrients consumed by the calf. Dry blending is the simplest method because the dry protein and fat sources are mixed together, and additional liquid fat is sprayed on later. The issue with dry blended products is getting fat into suspension, since it is very hydrophobic. The nature of the fat product greatly determines how this is accomplished. Some fats used in milk replacers have protein sprayed on their surface, which improves mixing, whereas others use higher amounts of emulsifiers. Milk replacers may also be agglomerated to enhance wettability and mixability. These processes result in encapsulation of difficult ingredients such as fat with more hygroscopic ingredients and an increase in particle size, resulting in a powder that goes into solution quicker and stays in suspension. The process of agglomeration generally provides a finished product that is easiest to mix on the farm. Ideal mixing temperature for a milk replacer is heavily dependent on the ingredients and processing method used. Excessive temperature can result in disruption of the agglomerated product and separation of the fat and protein. Low temperatures will result in inadequate mixing. One must closely follow the recommendations for mixing temperature provided by the manufacturer. Typically, dry blended milk replacers require higher mixing temperatures.

Another small but important detail is how milk replacer powder is mixed. Ideally about 50% to 70% of the total water needed for a batch is added to a receiving container followed by addition of the prescribed amount of powder. After initial mixing the remaining water is then added for the final mixing. During cold weather the temperature at the end of mixing should be warmer (46.1^{o} C/115^{o} F), as the liquid will cool prior to feeding, especially in slower feeding systems. A thermometer should always be used to check mixing

temperatures (see manufacturer recommendations) and feeding temperature (37.8º to 40.6º C/100º to 105º F).

Ideally both the water and the powder should be weighed for each batch of milk replacer liquid. Most milk replacer powders are approximately 96% to 97% dry matter. When powder is diluted, the final solution should be fed at a solids concentration of 12% to 15%. The influence of solids level on calf performance is relatively small within this range. However, formulation of liquid diets with higher dry matter percentages permits delivery of more nutrient solids within a given volume. Delivery of adequate nutrients to support desired growth can be challenging with feeding systems using 2-L bottles and twice-daily feeding. Under such systems it is difficult to deliver more than 500 g of milk solids per day to calves. Feeding milk replacer at solids levels above 15% has been associated with increased scouring in calves, especially if free-choice water is not available. For this reason, many calf operations have switched to the use of 3- to 4-L bottles or have fed calves in buckets allowing larger meal sizes.

A degree of confusion exists on many operations about how to calculate the level of milk solids in a liquid feeding system. Adding 150 g of powder to 1 L of water does not result in a 15% solids solution, as 150 g of powder plus 1000 g of water equals 1150 g of final weight (150/1150 = 13.04% solids).

The quality of water used to mix milk replacers has received increased emphasis, as it can influence how the final liquid is digested and metabolized by the calf. Suggested guidelines for water quality are shown in Table 21.7.

TABLE 21.7

Calf Water Quality Guidelines[92]

Analyte	Expected	Borderlines[a]	Concern Levels
pH	6.8-7.5	<6; >8.4	<5.5; >8.5
TDS (total dissolved solids)	≤500 ppm	>500 ppm	>1000 ppm
Hardness	0-180 ppm	>200 ppm	>300 ppm
Calcium	0-43 ppm	>100 ppm	>200 ppm
Chloride	0-100 ppm	>100 ppm	>300 ppm
Copper	0-0.2 ppm	>0.2 ppm	>0.5 ppm
Iron	0-0.2 ppm	>0.2 ppm	>0.3 ppm
Magnesium	0-29 ppm	>50 ppm	>100 ppm
Manganese	0-0.05 ppm	>–0.05 ppm	>0.05 ppm
Nitrate	0-44 ppm	>50 ppm	>100 ppm
Nitrate-nitrogen	0-10 ppm	>11.4 ppm	>22.7 ppm
Phosphorus	0-0.7 ppm	>0.7 ppm	>0.7 ppm
Potassium	0-20 ppm	>20 ppm	>20 ppm

Sodium	0-3 ppm	>50 ppm	>200 ppm
Sulfate	0-50 ppm	>50 ppm	>300 ppm
Zinc	0-5 ppm	>5 ppm	>25 ppm
Total bacteria/mL[b]	<2	>10	>10,000
Total coliform/100 mL[c]	<0.5	>0.5	>1
Total fecal coliform/100 mL[c]	<0.1	>0.1	>1
Fecal strep/100 mL[c]	<0.1	>0.1	>3

[a]May be concern level if complicated by other factors such as management, stress level, and variation in feeds fed.

[b]Also called aerobic, total, or standard plate count.

[c]May also be listed as just – or + (none or detected).

Acidification of Milk Replacers

Workers in Canada[93] have described a system of free-choice feeding either cold milk or milk replacer treated with formic acid, which lowers the pH of the liquid to approximately 4.5. This system results in higher levels of liquid diet intake and lower initial calf starter intake but noticeable improvements in gains and labor efficiency. However, currently, formic acid is not permitted as a feed ingredient in the U.S. dairy industry. Nocek and Braund[94] observed more gain in calves fed *ad libitum* to 35 days as compared to limit-fed calves offered a nonacidified milk replacer. However, there were no significant differences in scouring, and calves of both treatments reached 136 kg of body weight in the same number of days, likely due to weaning challenges and postweaning diets that were not adjusted for body weight differences. Jaster and colleagues[95] compared calves fed twice daily at 10% of body weight either “sweet” or acidified milk replacers containing 12.5% solids. Citric acid was used to decrease the pH to 5.3. No differences were found in gains, and there was a slight reduction of scours in calves fed the acidified replacer. Acidified milk replacers using combinations of organic acids other than formic acid are commercially available. Cold liquid feeding systems will reduce feed efficiency due to the impact of liquid temperature on the energetic requirements of the calf. Additional challenges of free-choice systems using acidified milk include low palatability of the milk for calves during the first week of life. However, they tend to adjust to the taste and frequently consume more than 10 L/day. Higher levels of milk intake present challenges in weaning calves to dry feeds.

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Additives to Milk Replacers

Before 2010, neomycin and oxytetracycline were added to milk replacers to aid in the control of bacterial enteritis. However, the Veterinary Feed Directive enacted in January 2017[96] restricts the use of oxytetracycline, chlortetracycline, and neomycin by or on the order of a licensed veterinarian. Commonly used milk replacer medications are shown in Table 21.8.

TABLE 21.8
Commonly Used Milk Replacer Medications[77]

Medication	Use Level	Statement	Withdrawal
Diflubenzuron	9.1-22.6 g/ton	Larvicide prevents house flies, stable flies, face flies, and horse flies from maturing into breeding adults.	None
Decoquinate	12.9-90 g/ton to provide 22.7 mg decoquinate/100 lb body weight	For prevention of coccidiosis in calves and cattle caused by *Eimeria bovis* and *Eimeria zuernii.*	None
Lasalocid	1 mg lasalocid/2.2 lb body weight	For control of coccidiosis caused by *E. bovis* and *E. zuernii*.	None

Other additives used in milk replacers include yeast products, probiotics, and fermentable fibers. Heinrichs and colleagues[97] found similar performance of calves fed a milk replacer diet with no additives or supplementation with the pre-2010 level of oxytetracycline/neomycin or with 4 g/day of mannan oligosaccharide (MOS). Addition of either the antibiotic or MOS reduced scours. Calf starter intake increased at a faster rate for those calves fed MOS. Inclusion of fermentable fibers from psyllium to a milk replacer powder at 1.1% of the dry matter intake increased populations of bifidobacteria and lactobacilli in the rumen and reticulum of preweaned dairy calves. It also increased the mass of the gastrointestinal tract.[98] Daily addition of probiotics in the form of *Lactobacillus acidophilus* had no effect on body weight over a 6-week trial, but calf health and growth were improved during the first 2 weeks of life.[99] Harris and colleagues[100] found that supplementing milk replacer with yeast fermentation products improved calf starter intake and improved fecal consistency after a mild *Salmonella enterica* challenge. The study of the efficacy of additives will continue as those in the milk replacer industry seek to find replacements for antibiotics in milk replacers.

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Feeding Recommendations for Dairy Calves

Traditional calf feeding programs consisted of daily consumption of 454 g of milk or milk replacer solids in 4 L of liquid divided into two daily feedings. These recommendations existed solely to encourage calves to begin consumption of dry feed and promote early weaning. There is little evidence to support this from a biological perspective, as such limited intake during the first 2 to 3 weeks of life barely provides sufficient energy and protein to meet maintenance requirements in calves under thermoneutral conditions between 10° and 25° C. During periods of cold stress, intake of milk or milk replacer should increase by 30% to 50%. More recently, research has shown the benefits of "accelerated" or "intensive" calf feeding programs where liquid diet intake of milk or milk replacers with up to 28% protein is fed at rates up to 1 to 1.2 kg of solids per day. These terms are probably a misnomer, as the intake of milk or milk replacer are more similar to liquid feeding programs for sheep, pigs, and beef cattle. Ollivett and colleagues[101] showed that calves challenged with *Cryptosporidium parvum* recovered faster and gained weight shortly after challenge if fed this more appropriate plane of nutrition, whereas controls fed the traditional diet continued to lose weight. The seventh edition of the NRC[85] uses the factorial approach to estimate requirements for growth and maintenance with consideration of environmental temperature. More progressive calf feeding programs encourage enhanced growth, higher feed efficiency, and more economical gains, especially during the first 3 weeks of life, when calf starter intake is minimal. One concern expressed is that calf starter intake is delayed. However, calves quickly adjust, and weaning by 6 weeks of age is achievable.

The seventh edition of the NRC[85] was published in 2001. An eighth edition was in preparation as this chapter was being written. The reader is encouraged to consult this updated version for nutrient requirement recommendations for preweaned calves.

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PART 4
Collection of Samples and Interpretation of Laboratory Tests

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• Chapter 23 Collection and Submission of Samples for Hematologic and Cytologic Evaluation
• Chapter 24 Alterations in the Erythron
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• CHAPTER 22

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Clinical Chemistry Tests*

Henry Stämpfli, Consulting Editor, Olimpo Oliver-Espinosa

MAJOR BIOCHEMICAL ABNORMALITIES OR PROBLEMS ENCOUNTERED

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Laboratory data are discussed in relation to case management. The focus is on interpretation of an abnormal finding in the typical clinical situation. An in-depth pathophysiologic explanation of these alterations is beyond the scope of this section. Should additional information be required, a textbook on veterinary clinical pathology should be consulted.[1,2]

All samples should be submitted with specific objectives in mind, following laboratory submission guidelines. In general, these objectives fall into one of the following categories:

- Evaluating organ system involvement or functional impairment

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- Confirming a diagnosis or ruling out a disease condition
- Directing therapy formulation
- Assessing response to therapy
- Determining a more accurate prognosis

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Submission of Laboratory Samples

Veterinary Diagnostic Services

The clinician must be aware of inherent limitations of laboratory testing in certain clinical settings. In general, veterinary diagnostic laboratories are preferred to human medical laboratories because these latter laboratories will be unfamiliar with animal diseases, normal physiology, and the responses of animals to disease. There may also be significant differences in test methodology and normal reference ranges. These species differences can cause confusion when results are evaluated on the basis of human reference intervals, which are not applicable to animals.

Various desktop or portable handheld point-of-care devices (POCD) are available to veterinarians for determination of serum chemistry, electrolytes, and acid-base balance. Point of care (POC) refers to any laboratory testing done outside the conventional laboratory and in close proximity to the patient. Many of these devices use self-contained strips, cartridges, or rotors and thus reduce errors associated with the maintenance, measurement, and mixing of reagents. Some of these devices can use heparinized whole blood or plasma. Some POCDs require refrigerated storage of reagent cartridges, which must then be warmed to room temperature before use. There are relatively few independently published data comparing the results obtained with these POCDs with standard laboratory procedures. Many of these POCDs need species-specific controls and reference intervals, as well as validation.[3] Given these requirements, the American Society for Veterinary Clinical Pathology (ASVCP) has recommended the following guidelines when using them: taking a formal approach to POC testing including development of written policies regarding use, operator training, assessment of instrument analytical performance, use of validated reference intervals, and checks on accuracy of patient results reporting.[4] A widely used handheld device (iSTAT) has been shown to yield comparable results to standard laboratory techniques when blood electrolyte concentrations and acid-base balance are determined in dogs and horses.[5] However, it was noted that the correlation between results from this device and from standard laboratory techniques was poor for sodium in the dog and for hematocrit in the horse. A study using the same handheld device in cattle, horse, and sheep showed that, except for sodium concentration and hematocrit in horses and

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sheep, correlation was good or excellent for most variables reported.[5] Portable POCDs can provide rapid, accurate, and relatively inexpensive results. As technology continues to improve, wider and more general application of these devices is taking place in many large animal practice settings.

Selection of Procedures

Selection of specific laboratory tests fosters logically integrated thinking and concentrates on evaluation of the primary medical problems. However, the sophisticated autoanalyzers used by large commercial laboratories can perform a battery of tests quickly and efficiently with little additional cost. These panels may be broadly defined (e.g., a general large animal health panel) or may offer a more focused evaluation of a specific organ system (e.g., liver, kidney, or muscle). The clinician must ensure that the panel selected contains all the appropriate tests for a thorough evaluation of the individual patient's medical problems identified.

The following recommendations for diagnostic panels are intended to provide a clear indication of organ damage and/or dysfunction. The most directly applicable diagnostic procedures are listed under “Recommended,” and additional procedures that may be of benefit in certain circumstances are listed under “Optional.”

General Panel.

The broad-based general chemistry panel should provide a balanced evaluation of the most likely medical problems, and reports should include reference intervals for each analyte and for each species from which the sample was obtained.

Recommended

Glucose
Serum/plasma urea
Creatinine
Creatine kinase (CK)
Aspartate aminotransferase (AST)
Sorbitol dehydrogenase (SDH)

γ-Glutamyltransferase (GGT)
Glutamate dehydrogenase (GLDH)
Alkaline phosphatase (ALP)
Bilirubin (direct, indirect, and total)
Total protein
Albumin
(Globulin) (calculated: total protein concentration–albumin concentration)
Albumin/globulin ratio (A/G ratio)
Haptoglobin (mostly food animals)
Serum amyloid A (equine)
Bicarbonate or total carbon dioxide (TCO_2) (often routinely reported)
Sodium
Potassium
Chloride
Calcium
Phosphate
Magnesium (total Mg)

Optional

Fibrinogen
Venous or arterial blood gases
Ionized calcium
Ionized magnesium

Muscle Panel.

The muscle panel should detect active skeletal and cardiac muscle injury (rhabdomyolysis) and the degree of secondary renal damage. The possible causative factors are evaluated as optional procedures, depending on the history, clinical findings, or special circumstances. Muscle biopsy with special staining may be critical to the diagnosis of specific muscle diseases such as polysaccharide storage myopathies, immune-mediated myopathy, and mitochondrial myopathy. Special tests for muscle function and the genetic basis for some myopathies are discussed in the chapters on muscle and genetic tests (see Chapters 42 and Chapter 52).

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Recommended

CK
AST
Muscle biopsy
Urinalysis
Blood urea nitrogen and creatinine

Optional

Alanine aminotransferase (ALT)
Myoglobin
Blood selenium/Vitamin E
Venous blood gases including L-lactate
Deoxyribonucleic acid analysis (hyperkalemic periodic paralysis [HYPP], polysaccharide storage myopathy type 1; type 2 offered but not currently recommended)
Calcium (ionized and total)
Magnesium (ionized and total)
Fractional excretion of:
- Sodium
- Potassium
- Chloride
- Myoglobin
- Calcium

Cardiac troponin I (evaluation of cardiac muscle)

Liver Disease Panel.

The liver panel should detect active damage to the hepatic parenchyma, involvement of the biliary system, and alteration in hepatic function.

Recommended

SDH
GDH

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AST
GGT
ALP
Blood urea nitrogen (BUN)
Serum bile acids (good diagnostic utility in Equidae; insensitive in ruminants)
Blood glucose
Fibrinogen
Total protein
Albumin
Globulin
Bilirubin (direct also called *conjugated*, indirect also called *free* or *unconjugated*, and total bilirubin)
Complete urinalysis

Optional

Liver ultrasound
Liver biopsy/culture
Blood ammonia (arterial preferable to venous samples and always run with a control animal sample)
Coagulation panel
Bromsulphalein clearance halftime test (BSP $t/_{1/2}$)

Renal Disease Panel.

The kidney panel and urinalysis provide an estimation of renal function and should indicate the location and nature of the damage to the urinary tract.

Recommended

BUN (or serum/plasma urea)
Creatinine
Na
K
Cl
Calcium

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Phosphate
Total protein
Albumin
Globulin
Complete urinalysis

Optional

Renal ultrasound
Renal biopsy
Urine culture
Urine/plasma osmolality ratio
Fractional excretion of:
- Sodium
- Potassium
- Chloride
- Calcium (ruminants)
- Endogenous creatinine clearance
- Sodium sulfanilate clearance

Gastrointestinal Disease Panel.

The gastrointestinal disease panel should include evaluation of acid-base status, fluid and electrolyte balance, and renal function, which are common complicating features of gastrointestinal diseases. Additional optional or special diagnostic procedures may be necessary in calves or foals with neonatal diarrhea, in horses with colic, and in ruminants with gastrointestinal stasis or displacements.

Recommended

Packed cell volume (PCV)
Total protein (TP)
Sodium
Potassium
Chloride
Calcium (ionized and total)

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Venous blood gases, pH, bicarbonate
Strong ion difference (SID) calculation
Anion gap
Strong ion gap calculation
BUN (serum/plasma urea)
Creatinine
Glucose
Peritoneal fluid cytology
Peritoneal fluid protein
Fecal occult blood
Fecal parasites
Ruminal fluid pH and analysis
Rumen fluid chloride concentration

Optional

Peritoneal fluid (glucose, L-lactate, Serum Amyloid A (SAA), and pH)
Serum immunoglobulin
Plasma lactate (D and L forms)
Fecal protozoa
Fecal culture
Fecal *Clostridium difficile* toxin testing
Fecal *Clostridium perfringens* Enterotoxin A
Fecal cytology
Rectal biopsy (histology, culture)
Absorption tests:
- Glucose
- D-Xylose
- Oral lactose tolerance test

Metabolic Profiling

The health status and productivity of dairy cattle, swine, and other food animals maintained in large confined groups involve a delicate balance among metabolic events, nutrition, agents of disease, management, and environmental factors. In these production units, the health status of the herd as a whole is of paramount importance. Subclinical disease and physiologic or nutritional imbalances may

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contribute to suboptimal productivity. Most productivity problems in these settings are multifactorial.[6] Defining and finding solutions to these problems can be a difficult and complicated task. Sequential assessment of weight gains, body condition scores, milk quality (fat and protein concentrations), and milk production are useful measures of the presence of subclinical production disorders but do not identify the cause. Metabolic profiling is a tool that has been used with mixed results. Blood samples are drawn from a number of randomized individuals as representative of the group as a whole. Some have recommended the submission of pooled serum samples from representative individuals, much like the use of bulk tank tests as a reflection of the general level of mastitis in a herd; however, sampling may also be done routinely and sequentially (longitudinally). In dairy cattle this may be done during gestation or lactation but frequently focuses on the periparturient period when a combination of nutritional and metabolic events often contributes to costly production disorders. Metabolic profiles might include most of the parameters listed under the recommended general panel with the addition of magnesium, total cholesterol, nonesterified fatty acids (NEFA), and β-hydroxybutyrate (BHB). BHB, NEFA, and cholesterol may provide an indication of energy balance, whereas serum/plasma urea, creatinine, total protein, albumin, globulin, and CK may be helpful in assessing protein status along with urea levels in milk. In certain settings, trace minerals or fat-soluble vitamin concentrations may be important indicators of underlying nutritional problems. Milk citrate measurement is a promising biomarker of physiologic imbalance in postpartum cows on farm.[7] To monitor specific subclinical entities such as subacute ruminal acidosis (SARA), subclinical hypocalcemia and subclinical ketosis, measurements of rumen pH, urine pH, and β-hydroxybutyrate in blood for each disease, respectively, have been used.[8] It has been suggested that the interpretation of the herd test results should depend on the biology of the specific metabolic disease. When assessing a metabolite that is associated with disease depending if it is above or below a cut point, this test should be interpreted as a proportional outcome above the cutoff point.[9] Metabolic profiling is not a substitute for careful clinical examination, analysis of husbandry practices, and ration analysis, but it may play a useful role in some modern large-scale operations in which a variety of subclinical, mostly management-related problems may quickly translate into financial disaster.

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Sources of Variation in Normal Values

Laboratory

One of the most commonly overlooked sources of variation in clinicopathologic data is the difference in results obtained by different laboratories in comparison with one another and especially to POCD. This can result in a 5- to 10-fold difference in the normal range of certain enzyme activities among laboratories using similar but not identical methodologies. The standard method of representing serum enzyme activity is in international units per liter (IU/L), which is used in this text. Correction factors for converting the commonly used but older units of measure to international units are given in Table 22.1. The normal values given in Tables 22.2 and 22.3 are those currently used at the Ontario Veterinary College (Animal Health Laboratory: American Association of Veterinary Laboratory Diagnosticians full accreditation) or are from the literature.[2] It is always best and crucial to use validated reference intervals established for the species, age, and production type by the diagnostic laboratory to which samples are submitted.

TABLE 22.1

Conversion of Conventional Units to International Units[2]

Component	Conventional Unit	Multiply by	International Unit (IU)
Chemistry			
Ammonia	µg/dL	0.5872	µmol/L
Bilirubin	mg/dL	17.1	µmol/L
Cholesterol	mg/dL	0.02586	mmol/L
Creatinine	mg/dL	88.4	µmol/L
Glucose	mg/dL	0.05551	mmol/L
Lactate	mg/dL	0.111	mmol/L
Urea nitrogen	mg/dL	0.357	mmol/L
Electrolytes			
Sodium	mEq/L	1	mmol/L
Potassium	mEq/L	1	mmol/L
Chloride	mEq/L	1	mmol/L
Calcium	mg/dL	0.2495	mmol/L
Magnesium	mg/dL	0.4114	mmol/L
Phosphorus	mg/dL	0.3229	mmol/L
Blood Gas			
P_{O_2}	mm Hg	0.1333	kPa
P_{CO_2}	mm Hg	0.1333	kPa

Bicarbonate	mEq/L	1	mmol/L
T_{CO_2}	mEq/L	1	mmol/L
Protein and Hematology			
Protein	g/dL	10	g/L
Albumin	g/dL	10	g/L
Fibrinogen	mg/dL	0.01	g/L
Hemoglobin	g/dL	10	g/L
Iron	µg/dL	0.1791	µmol/L
Transferrin	mg/dL	0.01	g/L
Haptoglobin	mg/dL	0.01	g/L
Hormone			
Cortisol	µ/dL	27.59	nmol/L
Triiodothyronine (T_3)	ng/dL	0.01536	nmol/L
Thyroxine (T_4)	µg/dL	12.87	nmol/L

kPa, Kilopascal; *PO_2,* partial pressure of oxygen; *PCO_2,* partial pressure of carbon dioxide; *TCO_2,* total carbon dioxide.

TABLE 22.2

Clinical Chemistry: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
Chemistry					
Total bilirubin	mg/dL	1.0-2.0	0.01-0.5	0.1-0.5	0-0.1
Direct	mg/dL	0-0.4	0.04-0.44	0-0.27	0-0.1
Indirect	mg/dL	0.2-2.0	0-0.3	0-0.12	0-0.1
Cholesterol	mg/dL	75-150	80-120	52-76	80-130
Creatinine	mg/dL	1.2-1.9	1.0-2.0	1.2-1.9	1.0-1.8
Glucose	mg/dL	75-115	45-75	50-80	50-75
Fibrinogen	mg/dL	100-400	300-700	100-500	100-400
Haptoglobin	mg/dL	0.01-0.17	0.0-0.05	NA	NA
Serum amyloid A	mg/dL	0-2.0	NA	NA	NA
Protein (total serum)	g/dL	5.2-7.9	6.7-7.46	6.0-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
Urea nitrogen	mg/dL	10-24	20-30	8-20	10-20
Enzyme					
ALP	IU/L	143-395	0-488	68-387	93-387
AST	IU/L	226-366	78-132	60-280	167-513
CK	IU/L	108-430	44-211	64-158	104-219
GGT	IU/L	7-54	15-39	40-79	20-56
LDH	IU/L	162-412	697-1445	238-440	123-392
LDH-1	%	6.3-18.5	39.8-63.5	45.7-63.6	29.3-51.8
LDH-2	%	8.4-20.5	19.7-34.8	0-3.0	0-5.4
LDH-3	%	41-65.9	11.7-18.1	16.4-29.9	24.2-39.9
LDH-4	%	9.5-20.9	0-8.8	4.3-7.3	0-5.5
LDH-5	%	1.7-16.5	0-12.4	10.5-29.1	14.1-36.8
SDH	IU/L	1.9-5.8	4.3-15.3	5.8-27.9	14-23.6
Electrolyte					

Sodium	mEq/L	132-146	132-152	139-152	142-155
Potassium	mEq/L	2.4-4.7	3.9-5.8	3.9-5.4	3.5-6.7
Chloride	mEq/L	99-109	97-111	95-103	99-110
Calcium	mg/dL	11.2-13.6	9.7-12.4	11.5-12.8	8.9-11.7
Phosphorus	mg/dL	3.1-5.6	5.6-6.5	5.0-7.3	6.5
Magnesium	mg/dL	2.2-2.8	1.8-2.3	2.2-2.8	2.8-3.6
Osmolality	mOsm/kg	270-300	270-300	NA	NA
Anion gap	mEq/L	6-15	14-20	NA	NA
Acid-Base (Venous Blood)					
pH		7.32-7.44	7.31-7.53	7.32-7.54	NA
P_{CO_2}	mm Hg	38-46	35-44	37-46	NA
Bicarbonate	mEq/L	20-28	17-29	20-25	NA
T_{CO_2}	mEq/L	24-32	21-32	21-28	26-30
Special					
Red blood cell acetylcholinesterase	IU/L	450-790	1270-2430	640	270
Ammonia	µg/dL	13-108	NA	NA	NA
BSP ($t_{1/2}$)	Min	2.0-3.7	2.5-4.0	1.6-2.7	2.1
Serum iron	µg/dL	73-140	57-162	166-222	NA
TIBC	µg/dL	200-262	63-186	NA	NA
Lactic acid	mmol/L	1.11-1.78	0.56-2.22	1.00-1.33	NA
Ketones					
Acetone	mg/dL	NA	0-10	0-10	NA
Acetoacetate	mg/dL	NA	0-1.1	NA	NA
BHB	mg/dL	NA	0-10	NA	NA

ALP, Alkaline phosphatase; *AST,* aspartate aminotransferase; *BHB,* β-hydroxybutyrate; *BSP ($t_{1/2}$),* bromsulphalein clearance halftime; *GGT,* γ-glutamyltransferase; *CK,* creatine kinase; *LDH,* lactate dehydrogenase; *NA,* not applicable; *PCO_2,* partial pressure of carbon dioxide; *SDH,* sorbitol dehydrogenase; *TCO_2,* total carbon dioxide; *TIBC,* total iron-binding capacity.

Data from Kaneko JJ, Harvey JW, Bruss ML, editors. *Clinical biochemistry of domestic animals,* ed 6, Burlington, MA, 2008, Academic Press, and the Normal Values Clinical Pathology Ontario Veterinary College and Animal Health Lab-Guelph, 2012.

TABLE 22.3

Serum Protein Electrophoresis: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
Total protein	g/dL	5.2-7.9	6.74-7.46	6.0-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
α1	g/dL	0.06-0.7	NA	NA	NA
α2	g/dL	0.31-1.31	NA	NA	NA
A	g/dL	NA	0.75-0.88	0.3-0.6	0.5-0.7
β1	g/dL	0.4-1.58	NA	0.7-1.2	0.7-1.2
β2	g/dL	0.29-0.89	NA	0.4-1.4	0.3-0.6
B	g/dL	NA	0.8-1.12	NA	NA

γ_1	g/dL	NA	NA	0.7-2.2	NA
γ_2	g/dL	NA	NA	0.2-1.1	NA
Γ	g/dL	0.55-1.9	1.69-2.25	NA	0.9-3
Albumin/globulin (A/G) ratio		0.62-1.46	0.84-0.94	0.42-0.76	0.63-1.26

NA, Not applicable.

Data from Kaneko JJ, Harvey JW, Bruss ML, editors: *Clinical biochemistry of domestic animals,* ed 6, Burlington, MA, 1997, Academic Press.

Species

There is relatively modest variation among species for most clinicopathologic parameters. Notable exceptions are plasma electrolyte concentration; erythrocyte potassium concentration in some breeds of horse, pigs, llamas, cattle, and sheep; and serum bilirubin concentration, which is higher in horses than in other species. Urea nitrogen (UN) is a less reliable indicator of renal function in ruminants and horses than creatinine because UN can be metabolized by the intestinal microflora. Donkeys and burros have a much higher γ-glutamyltransferase (GGT) level than horses and cattle. Young calves of up to 1 month have high GGT levels compared with other species because of increased concentrations of this enzyme in bovine colostrum.

Breed

Significant differences in hematologic parameters exist between hot- and cold-blooded horses. Hot-blooded horses include most of the athletic breeds of horses (Thoroughbred, Quarter Horse, Standardbred, and Arabian breeds). Cold-blooded horses include the pony and draft breeds. Cold-blooded horses have lower red blood cell (RBC) values both at rest and after exercise and maintain a slightly lower leukocyte count; they also have lower resting and fasting indirect bilirubin concentrations.

Age

Several important differences in hematologic and clinical chemistry findings exist between neonatal and adult animals within species. The effects of age have been studied most carefully in horses and cattle. In comparison to adult animals, suckling neonatal animals tend to have lower BUN, slightly lower total protein and globulin, moderately higher GGT and phosphate, and markedly greater

alkaline phosphatase. Creatinine in foals can be a bit higher in well-muscled foals (up to 2.5 mg/dL; 221 μmol/L) and occasionally very high (up to 8 mg/dL; 707 μmol/L) shortly after birth and returning to normal values within 24 to 72 hours with maintenance fluid support, and it is thought to be due to defective placental transfer (spurious hypercreatinemia).[10]

Sex

With the obvious exception of sex hormone concentrations, there are few recognized differences in clinical chemistry values between sexes. In most domestic animals the intact male tends to have a slightly higher erythrocyte count, hemoglobin concentration, and PCV than the female or neutered male.[11] This sex-related difference has been demonstrated most clearly in the horse.

Factors Influencing Results or Their Interpretation

Many factors influence the reliability and interpretation of results obtained by laboratory analysis. The main factors are quality of the sample (preanalytic phase), quality of the laboratory analysis (analytic phase), and quality of results dissemination and record keeping (postanalytic phase).[12] Sample collection and handling are important. The sample collection site (e.g., jugular vein, mammary vein, tail vein, cephalic vein, lateral thoracic vein, ear vein or carotid artery, transverse fascial artery, metatarsal artery) can have an important effect on the results of tests such as blood gas evaluation, glucose, or ketones. The choice of anticoagulants depends on whether the samples are to be submitted for serum, plasma, or whole blood analyses. The specific sample requirements for the most commonly ordered clinical chemistry determinations are listed in Table 22.4. Serum is required for most chemistry analytes, and serum separator tubes work well in most settings. There have been some indications that results of some serum hormone assays may be influenced by collection of blood in serum separator tubes. Lithium heparin is the anticoagulant of choice for most chemical determinations requiring plasma. Historically fluoride-oxalate was the anticoagulant of choice for blood glucose determination because it did slow down glycolysis by the RBCs. However, fluoride may interfere with certain chemical procedures (specifically the glucose oxidase method for blood glucose determination) and should be used only for blood lactate determination or in

selected circumstances in which glucose determinations are required and samples must be held for some period of time without refrigeration. Citrate is the required anticoagulant for clotting tests and blood typing. Ethylenediaminetetraacetic acid (EDTA) is the anticoagulant most often used for hematologic evaluation. Both citrate and EDTA are chelating agents, which will interfere with calcium determination and, in the case of EDTA, spuriously increase potassium.

TABLE 22.4

Recommended Anticoagulants for Hematologic or Clinical Chemistry Evaluation

Anticoagulant	Specimen	Test or Procedure
Ethylenediaminetetra-acetic acid (EDTA)	Whole blood	Complete blood count, cross-match, platelet count (hematologic testing preferred anticoagulant)
	Whole blood	Blood selenium
	Plasma	Refractometric protein and fibrinogen
	Peritoneal fluid	Fluid analysis
	Bone marrow	Hematologic evaluation
	Synovial fluid	Fluid analysis
Heparin	Whole blood	Blood pH, blood gases, electrolytes, lactate, ionized calcium, glucose (automated BG machines)
	Plasma	Electrolytes, osmolality
	Synovial fluid	Mucin clot test
Fluoride and oxalate	Plasma	Lactate
Citrate	Whole blood	Blood typing
	Plasma	Coagulation tests (PT, PTT, factor analyses)
None, serum separator tubes	Serum	Most chemistries, electrolytes, osmolality, trace elements (Se, Cu, etc.)
		Protein electrophoresis
		Hormones (cortisol, T_3, T_4)
		Immunoglobulins (IgG, IgM, IgA)

PT, Prothrombin time; *PTT,* partial thromboplastin time; T_3, triiodothyronine; T_4, thyroxine.

Tube selection guide at: http://www.eclinpath.com/chemistry/sample-collection-chem/ and https://ahdc.vet.cornell.edu/docs/Blood_Tubes_and_Labeling_Guidelines.pdf.

Modified from Brobst DF, Parry BW. Normal clinical pathology data. In Robinson NE, editor: *Current therapy in equine medicine,* ed 2, Philadelphia, 1987, Saunders.

Samples should be submitted as soon after collection as possible, but

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circumstances may require storage of some samples for 12 to 24 hours. For collection of serum, whole blood should be allowed to clot before refrigeration. Serum should be separated from the RBCs immediately after clot formation and then kept refrigerated. Serum samples should be stored in clean containers (e.g., plain tubes) free from exposure to sunlight, medications, or chemicals. If whole blood is left at room temperature for longer than 60 minutes, blood glucose will be falsely decreased as a result of RBC glycolysis. Storage of whole blood may result in in vitro hemolysis, with the potential for misleading increases in the serum or plasma enzymes AST and lactate dehydrogenase (LDH) and potassium and phosphorus concentrations as a result of hemolysis. In addition, failure to separate serum or plasma from the RBCs within an hour of collection may lead to leakage of erythrocyte potassium and a falsely elevated serum or heparinized-plasma potassium concentrations.

Stress, transportation, excitement, and handling produce physiologic responses in animals that affect a variety of hematologic and biochemical parameters. This is most evident in the horse, which shows marked increases in RBC mass and to a lesser extent plasma protein concentration in response to excitement, exercise, or catecholamine administration. The RBC count, hematocrit, and hemoglobin concentration can increase by as much as 50%, whereas plasma protein concentration may increase by 1 to 2 g/dL (10 to 20 g/L). Leukocytosis, mainly seen as neutrophilia, is induced as the marginating leukocyte pool is mobilized into general circulation. Prolonged stress results in the release of endogenous corticosteroids, which produce the typical “stress response” leukogram. A similar leukogram is found in racehorses some 4 to 6 hours after racing. The combination of catecholamine and glucocorticoid release associated with stress, transport, and excitement, as well as with many gastrointestinal catastrophes, may result in markedly elevated blood glucose concentrations (up to 400 mg/dL; 22 mmol/L). Modest elevations (twofold to fourfold increase) in muscle-derived enzymes occur in association with prolonged transport or endurance exercise.

Large losses or compartmentalization of sodium-containing fluid accompanies many systemic disorders, particularly digestive problems such as diarrhea, colic, displacement of viscera, excessive sweat losses, and some urinary tract diseases. These forms of dehydration lead to decreases in plasma volume, which are indicated by moderate-to-marked increases in the PCV and TP concentration. The concentration of other compounds dissolved in the plasma may also increase as a result of decreases in the plasma volume. The concentrations of compounds

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that are largely protein bound, such as calcium, are generally closely related to albumin concentration. Up to 50% of serum calcium is bound to proteins, predominantly to albumin. Increases or decreases in plasma protein concentration normally result in proportional changes in total serum calcium concentration, whereas the physiologically active ionized calcium may remain unchanged.

Diseases that cause a reduction in effective circulating fluid volume often also cause alterations in renal function. This so-called prerenal azotemia results in moderate to marked elevation in BUN and creatinine. Although this is generally considered primarily a prerenal azotemia, real pathologic changes in the kidneys often are associated with the systemic processes initiated by these disorders. Longitudinal reevaluation of renal function (urinalysis, serum BUN, and creatinine) in these patients during the course of disease is important because it assists with prognosis, assesses response to fluid administration, and therefore the potential for nephrotoxicity and systemic toxicity of a variety of chemotherapeutic agents used in such patients.

Fasting laboratory data are important for evaluation of many disease conditions in human and small animal patients. Truly fasting conditions are rather difficult, given the large and complex gastrointestinal tract of most herbivores, and are thus seldom used. The feeding of animals in relation to sample collection, however, can have an impact on the data obtained. Hay feeding in horses is reported to affect sodium, potassium, and protein concentrations within the first few hours after feeding. Animals feeding on lush green pasture or large amounts of silage may have slightly different parameters from those fed high-concentrate rations. The anion-cation balance of the ration has an impact on relative serum electrolyte concentration, acid-base balance, and urine pH and urinary electrolyte excretion. Lactescent (cloudy from chylomicrons) plasma may be observed in samples from nursing foals or calves. The fluid intake of the normal nursing neonate may range from 100 mL/kg/day to more than 250 mL/kg/day. This high fluid intake is reflected by a commensurately high output of urine with a low specific gravity and low osmolarity.

The administration of certain medications may have an impact on some laboratory parameters. Tranquilization may be necessary for restraint and safe sample collection. The practitioner should be aware that tranquilizers often decrease RBC mass and plasma protein concentration. This is particularly true of the phenothiazine-derivative tranquilizers when used in the horse. Xylazine

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administered to large animals produces a modest catecholamine release, which may be evidenced by the slight sweating response seen in many horses sedated with this drug. Glucose concentration will increase modestly in response to the xylazine-induced catecholamine release. Repeated intramuscular injections with certain antibiotics (especially erythromycin and tetracycline) or other preparations that are locally irritating may produce slight-to-moderate elevations in muscle-derived serum enzyme activities. Intravenous administration of certain drugs and compounds such as dimethyl sulfoxide (DMSO) can produce intravascular hemolysis and hematuria. The amount of hemolysis in these circumstances is relatively small and of little consequence, except that it can cause confusion as to why hemoglobinuria occurred.

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Fluid and Electrolyte Balance

Packed Cell Volume and Total Plasma Protein

PCV and total plasma protein (TPP) concentration are simple and convenient indicators of acute fluid alterations. Changes in the plasma volume generally are reflected by changes in the PCV and the TPP concentration. In dehydrated humans, changes in the PCV are believed to be the more reliable guide to changes in plasma volume because substantial protein fluxes into and out of the circulation have been shown to occur. However, in most animal species the range of normal for the PCV is much wider than for the TPP concentration. This is particularly true of horses, in which excitement, pain, or catecholamine release can produce variable mobilization of splenic erythrocytes, making it difficult to obtain a truly resting PCV. For these reasons, precise quantitative estimation of a change in plasma volume using these parameters is more complex and less reliable in large animal species. As plasma volume increases or decreases, the change in the PCV is always less than the change in the TPP concentration. However, a large disparity in the changes in the PCV and the TPP concentration in a patient with a history of loss of sodium-containing fluid and clinical evidence of reduced effective circulating fluid volume suggests blood or protein loss. Marked increases in the PCV with a normal-to-low TPP concentration frequently are encountered in animals with acute protein-losing enteropathies such as salmonellosis or equine toxic enteritis, or enterocolitis. In horses undergoing treatment for diarrhea, the excessive administration and retention of sodium-containing fluids is a key factor in the development of edema and hypoproteinemia. Blood loss generally results in a decrease in both PCV and TPP concentration with a lag time of up to 24 to 48 hours.

Serum Sodium

The serum sodium concentration is a function of the exchangeable cation content (i.e., the exchangeable sodium [Na] in the extracellular fluid [ECF] volume plus the exchangeable potassium [K] in the intracellular fluid [ICF] volume relative to total body water). The ECF *sodium* content determines the ECF volume, whereas the ICF volume is a function of ICF *potassium* content.

Changes in the sodium concentration reflect the net changes in this

relationship and often do not represent accurately the changes in sodium balance. Changes in water balance are thus primarily responsible for changes in the serum sodium concentration, and one should always consider the hydration status of the patient for sodium concentration interpretation. Hyponatremia is an indication of a relative water *excess*, whereas hypernatremia is an indication of a relative water *deficit*.

Dehydration is defined as a loss of body water (fluid volume contraction). It occurs in a variety of clinical circumstances. The serum sodium concentration provides a means of categorizing dehydration in a physiologically meaningful way. Hypertonic dehydration, which occurs when water losses exceed the losses of sodium and potassium, is indicated by hypernatremia (free water loss or hypotonic fluid losses). The response of horses to feed and water deprivation is an example of this form of dehydration. Isotonic dehydration occurs with a balanced loss of water and electrolytes—that is, approximately 140 to 150 mEq of sodium plus potassium (Na + K) for each liter of water lost. Because the relative water balance has not changed, the serum sodium concentration remains unchanged despite the accumulation of what may have been a substantial body sodium deficit. The early stages of acute diarrhea and the dehydration of heavily sweating endurance horses are examples of isotonic dehydration. Hypotonic dehydration occurs when the losses of exchangeable cations (Na + K) exceed the net change in water balance; this condition is indicated by hyponatremia. Hypotonic dehydration often is seen in animals with subacute or chronic diarrhea that develop substantial water and electrolyte deficits but then replace part of the water deficit through water consumption. Fig. 22.1 shows the compartmental distribution of fluid between the ECF volume and ICF volume in four situations.

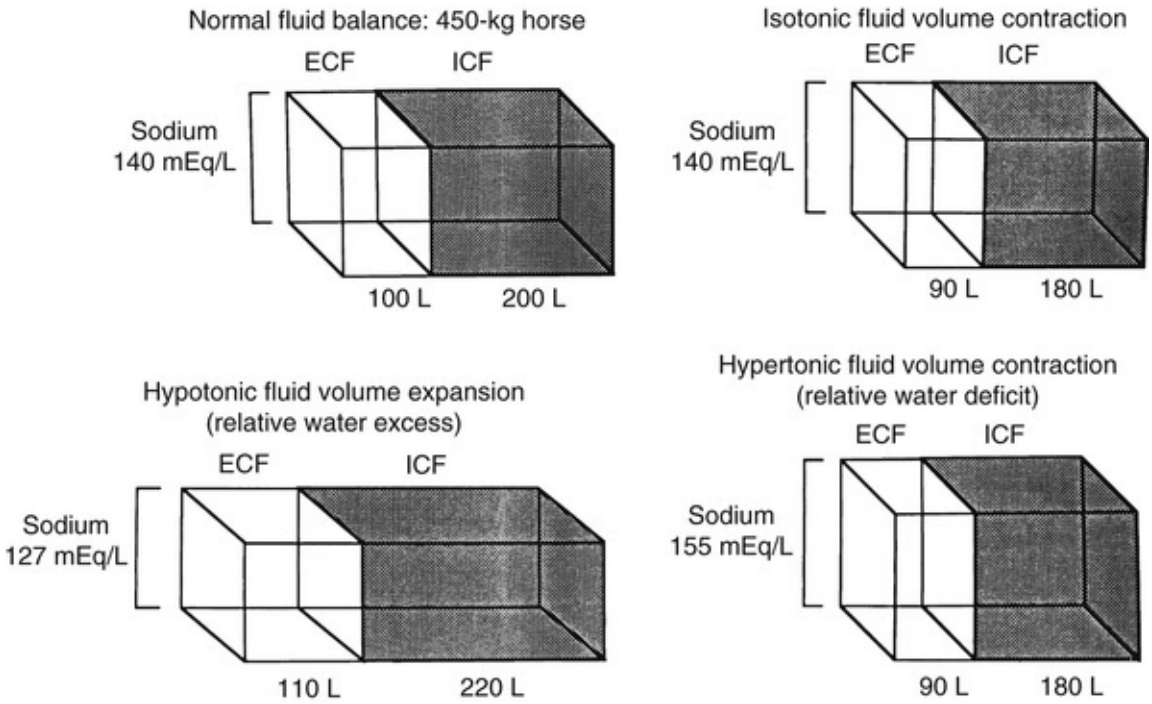


FIG. 22.1 Compartmental distribution of fluid between the extracellular fluid (ECF) volume and the intracellular fluid (ICF) volume in a 450-kg horse with normal fluid balance, isotonic fluid volume contraction, hypotonic fluid volume expansion, and hypertonic fluid volume contraction. (Modified from Kaneko JJ, Harvey JW, Bruss ML, editors: *Clinical biochemistry of domestic animals*, ed 6, New York, 2008, Elsevier Academic Press.)

Hyponatremia.

Hyponatremia results from retention of free water or excess loss of sodium. It is often but not invariably associated with conditions that cause sodium depletion such as vomiting, diarrhea, excessive sweat losses, and adrenal insufficiency. The fluid losses in these conditions are most often hypotonic or isotonic, and initial fluid and electrolyte deficits do not result in hyponatremia until water intake, renal water retention, or both disturb the balance between the remaining exchangeable cations and the total body water.

The accumulation of sodium-containing fluid in body cavities or the gut lumen caused by ascites, peritonitis, or rupture of the bladder or by displacement, torsion, or volvulus of the gut is referred to as a *third-space problem.* When such accumulations develop rapidly, the plasma volume is reduced and the serum sodium concentration subsequently may decrease as compensating renal responses cause water retention. Rupture of the bladder in neonatal foals is associated with marked hyponatremia and hypochloremia. As

fluid intake continues and dilute urine accumulates in the abdomen, sodium, chloride, and other ions are drawn from the rest of the ECF into this accumulating fluid. No sodium or chloride has been lost from the body, and the observed decreases in the electrolyte concentration are caused by changes in the relative water balance ("water follows solute"). The neurologic signs seen in these foals are largely caused by the effects on the central nervous system of the rapidly developing and marked hypotonic hyponatremia. Progressively severe neurologic disturbances may be seen as the serum sodium concentration falls below 115 mEq/L and then below 100 mEq/L. The severity of the neurologic abnormalities is a function of both the rate at which hyponatremia develops and the absolute degree of hyponatremia. Neurologic disturbances can occur iatrogenically if excessive amounts of free water (usually given as 5% dextrose) are administered to patients with altered renal function.

Mastitis results in an increased loss of sodium in the milk, and a low-grade mastitis problem in a dairy herd on a marginal dietary salt intake may result in sodium depletion and medullary washout. Decreased milk production, polyuria, hyposthenuria, and a low urine sodium level may be noted, although the serum sodium concentration may remain within the lower range of normal.

The most common causes of hyponatremia are listed in Box 22.1. Marked hyperlipidemia or hyperproteinemia produces a falsely low sodium concentration value because lipid or protein occupies a significant volume in the serum or plasma sample and because sodium is present only in the aqueous phase. This potential cause of hyponatremia is indicated by an increase in the osmolar gap between measured and calculated osmolality. The use of direct ion-selective electrodes (direct potentiometry; all modern blood gas machines; and modern multianalyzers of big laboratories) for electrolyte determinations avoids this potential cause of a falsely low sodium concentration value.

Box 22.1

Causes of Hyponatremia

Common Causes

Relative water excess

Loss of sodium-containing fluid (decreased effective circulating

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volume)
- Diarrhea
- Excessive sweating
- Blood loss
- Fluid drainage
- High-volume gastric reflux
- High-volume pleural drainage

- Adrenal insufficiency
- Sequestration of fluid (third-space problems)
  - Peritonitis
  - Ascites
  - Pleuritis
  - Ruptured bladder
  - Torsion or volvulus of the gut
  - Excessive administration of 5% dextrose to patient with renal disease
- False hyponatremia
  - Hyperlipidemia
  - Hyperproteinemia
  - Hyperglycemia

Uncommon Causes

- Water retention with normal effective circulating volume
  - Psychogenic polydipsia
  - Renal disease
  - Inappropriate antidiuretic hormone secretion
  - Use of diuretics

Marked hyperglycemia causes a reduction in the measured serum sodium concentration of approximately 1.6 mEq/L for every 100 mg/dL increase in the glucose concentration. Increases in the plasma glucose concentration generate osmotic forces that result in the movement of cellular water into the ECF, diluting the plasma sodium concentration.

Hypernatremia.

Hypernatremia can develop if water is lost in excess of sodium or if sodium is ingested in excess of water. Hypernatremia can occur in the initial stages of diarrhea, vomiting, or renal disease if water loss exceeds electrolyte loss (Box 22.2). When water losses are replaced by increased water consumption, enhanced renal water retention, or both, the serum sodium concentration decreases. Food and water deprivation in normal horses and cattle is associated with substantial reduction of renal and fecal output, but continued cutaneous and respiratory insensible water loss may result in hypernatremia (primary water loss). Hypernatremia may occur transiently as a result of sodium excess after administration of hypertonic saline or hyperosmolar sodium bicarbonate if water intake is restricted or impaired. Hypernatremia has been reported in calves fed an inappropriately mixed oral electrolyte replacement solution as their only fluid intake.[13] The hypernatremia observed with salt poisoning in cattle and swine is the result of water restriction in animals that have been maintained on a high-salt intake.

Box 22.2

Causes of Hypernatremia

Common Causes

- Pure water losses
  - Panting
  - Water deprivation
- Sodium excess (water restriction)
  - Salt poisoning
  - Feeding only electrolytes, no free water

Uncommon Causes

- Water loss exceeds electrolyte loss
  - Vomiting
  - Diarrhea
  - Burns

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Intrinsic renal disease
Diuretics
Diabetes insipidus
Central
Nephrogenic
Hypertonic saline or sodium bicarbonate administration
Mineralocorticoid excess

Serum Potassium

Potassium is the major intracellular cation. Between 60% and 75% of total body potassium is found within muscle cells and in bones. Only 5% is in the ECF and is not always a reflection of total body potassium. The serum potassium concentration is influenced by factors that alter internal balance (the distribution of potassium between the ECF and the ICF) and those that change external balance (potassium intake and output). Potassium is higher in foals compared with adult horses. Generally, herbivores have a net positive intake in potassium, which is usually carefully regulated by the renal system. Serum potassium concentrations correlate relatively well with total body potassium content in cattle but not in horses. Changes in the serum potassium concentration occur in a wide variety of clinical circumstances and have profound neuromuscular effects that are largely the result of changes in cell membrane potential. The responses to dehydration and acid-base imbalance often complicate the evaluation of the potassium concentration. For example, calves with acute diarrhea often develop body potassium depletion because of excessive losses and inadequate intake, but the serum potassium concentration of these animals is usually normal to increased as the result of renal shutdown and the metabolic acidosis induced by dehydration, sodium depletion, and hypovolemia. Hypokalemia may become evident only as other fluid and electrolyte losses are replaced.

Measuring the erythrocyte potassium concentration is relatively easy and has been suggested as an aid in assessing the need for potassium supplementation in racehorses with recurrent muscle disease or in alert downer cows early postpartum. However, experimental studies in horses indicate that the erythrocyte potassium concentration does not always accurately reflect potassium deficits.

Hypokalemia.

Hypokalemia increases resting membrane potential, resulting in muscle weakness, impaired urine concentration ability, and arrhythmias. Hypokalemia may result from depletion of the body's potassium stores or from a redistribution of potassium from the ECF into the ICF space (Box 22.3). Hypokalemia is most commonly seen with altered intake and absorption and with excessive potassium losses from the gastrointestinal tract caused by vagal indigestion, torsion of the abomasum, ileus, or diarrhea. Excessive renal loss may result from mineralocorticoid excess, certain diuretics, or altered renal function, as reported in horses with renal tubular acidosis. Marked hypokalemia develops when reduced dietary intake caused by anorexia is associated with excessive potassium losses (e.g., causing muscle paresis in dairy cows early postpartum). A hypokalemia syndrome has been observed in cattle,[14] mainly in postpartum lactating cows, but also in younger animals. The exact causes have not been completely elucidated except for isoflupredone administration. The syndrome is characterized by muscle weakness, severe depression, recumbency, tachycardia, cardiac arrhythmia, and abnormal neck posture. The lowest reported serum potassium concentration levels are between 2.2 and 2.5 mmol/L.

Box 22.3

Causes of Hypokalemia

Common Causes

Altered External Balance[a]

Vomiting
Vagal indigestion with internal vomiting
Diarrhea
Third-space problems (gut or abomasal torsion or volvulus; peritonitis)
Excessive sweat losses
Dietary deficiency
Prolonged anorexia

Altered Internal Balance

Metabolic alkalosis

Uncommon Causes

Altered External Balance

Mineralocorticoid excess
Use of corticosteroids with mineralocorticoid activity
Diuretics
Renal tubular acidosis
Postobstruction diuresis

Altered Internal Balance

Excessively rapid sodium bicarbonate administration
Insulin and/or glucose administration
Catecholamine administration or endogenous release

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[a]External balance refers to the relative changes in potassium intake and output; internal balance refers to the distribution of potassium between the extracellular and intracellular fluid compartments.

Hypokalemia without potassium depletion results from the movement of extracellular potassium to the intracellular space. This form of hypokalemia occurs in response to an acute alkalosis and the administration of insulin or glucose. Overzealous and rapid administration of sodium bicarbonate can produce an alkalosis with a profound and rapidly developing hypokalemia. Animals with moderate potassium deficits that are vigorously treated with sodium bicarbonate to correct a coexisting mild metabolic acidosis may be particularly prone to this problem. The initial response to catecholamine administration is a modest, transient increase in potassium caused by α-adrenergic stimulation, which is often followed by hypokalemia caused by β-adrenergic receptor responses.

Pseudohypokalemia is seen in severe lipemia with potassium measured with indirect potentiometry (e.g., older automated profile chemistry analyzers).

Hyperkalemia.

Hyperkalemia may develop in vitro as a result of hemolysis or leakage of erythrocyte potassium after storage of whole blood (Box 22.4). The release of potassium from leukocytes or platelets into the serum after clot formation is a potential cause of hyperkalemia if marked leukocytosis or thrombocytosis is present. Hyperkalemia also results from renal potassium retention in Addison disease, acute renal failure (ARF), and renal shutdown. A number of factors contribute to the movement of intracellular potassium into the ECF, resulting in hyperkalemia. Hyperkalemia is often associated with metabolic acidosis, particularly when the acidosis results from volume depletion and is complicated by renal shutdown. Hyperkalemia has been reported in animals with massive muscle necrosis, but neither hyperkalemia nor metabolic acidosis is a common feature in horses with exertional rhabdomyolysis. Vigorous short-term exercise of horses at high intensity results in a marked but transient hyperkalemia (9 to 10 mEq/L) that may be associated with the profound lactic acidosis seen with anaerobic workloads.[15] Potassium returns to normal within minutes, and often a modest hypokalemia occurs later in the recovery period. Episodic hyperkalemia and muscular weakness are associated with the condition of HYPP.[16] HYPP is inherited as an autosomal-dominant trait in horses, with a specific Quarter Horse lineage having a sodium channel defect[17] (see Chapter 42 for a more complete discussion of this disorder). The disease is the result of a single DNA base pair substitution that leads to the production of an abnormal voltage-regulated sodium channel at the cell membrane.[18] Sudden marked increases in the serum potassium concentration, up to 8 to 9 mEq/L, are the result of transcellular movement of potassium and are associated with profound electrocardiographic abnormalities and fluid shifts.

Box 22.4

Causes of Hyperkalemia

Common Causes

False hyperkalemia
- In vitro hemolysis

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- Prolonged storage of blood (over 6 hours) without separation of serum or plasma
- Altered external balance
  - Hypovolemia with renal shutdown
- Altered internal balance
  - Metabolic acidosis
  - Vigorous exercise
- Uroperitoneum

Uncommon Causes

- False hyperkalemia
  - Markedly elevated leukocyte or platelet count
- Altered internal balance
  - Hyperkalemic periodic paralysis in Quarter Horses
  - Diabetes mellitus
  - Tissue necrosis
  - Renal disease
  - Addison disease

In drug-induced hyperkalemia, trimethoprim has been associated with hyperkalemia by inhibiting normal sodium reabsorption in the cortical renal collecting duct.

Serum Chloride

Chloride is a major ECF anion and important with sodium for osmolality and acid-base balance. Together with sodium it is the main component of the strong ion difference (SID). Alterations in the chloride concentration are usually associated with nearly proportional changes in the sodium concentration as the result of changes in relative water balance. In addition, the chloride concentration tends to vary inversely with the bicarbonate concentration; therefore when disproportionate changes in the chloride concentration relative to sodium occur, significant acid-base imbalances should be anticipated. Disproportionate increases in chloride are associated with a normal-to-low anion gap hyperchloremic metabolic acidosis, but they also are seen as a result of the

compensating responses for a primary respiratory alkalosis (Box 22.5). A striking hyperchloremic metabolic acidosis has been reported in horses with renal tubular acidosis.[19,20] Iatrogenic hyperchloremic acidosis can be induced by overzealous NaCl fluid treatment.[21]

Box 22.5

Causes of Hyperchloremia

With Proportional Increase in Sodium

Common Causes

- Relative water deficit
  - Panting
  - Water deprivation
  - Salt poisoning

Uncommon Causes

- Vomiting
- Diarrhea
- Burns
- Intrinsic renal disease
- Diuretics
- Diabetes insipidus
  - Central
  - Nephrogenic
- Hypertonic saline administration
- Mineralocorticoid excess

Without Proportional Increase in Sodium

Common Causes

- Hyperchloremic metabolic acidosis

Renal tubular acidosis

Uncommon Cause

Compensation for respiratory alkalosis

Disproportionate decreases in chloride relative to sodium are characteristically seen in metabolic alkalosis but also may be seen as part of the compensating response for chronic primary respiratory acidosis (Box 22.6). Hypochloremic metabolic alkalosis is a common feature in many digestive disorders of ruminants and is caused by loss of chloride-rich fluids or sequestration of such fluids in the abomasum and forestomachs. It is also seen in horses with diarrhea as chloride is absorbed in the ileum and colon. Horses treated with diuretics (e.g., furosemide-induced metabolic alkalosis) may show hypochloremia.[22] Heavy sweating in horses is associated with hypochloremic metabolic alkalosis.

Box 22.6

Causes of Hypochloremia

With Proportional Decrease in Sodium

Common Causes

Relative water excess
- Diarrhea
- Excessive sweating
- Blood loss
- Fluid drainage
- High-volume gastric reflux
- High-volume pleural drainage
- Sequestration of fluid (third-space problems)
- Peritonitis
- Ascites
- Ruptured bladder
- Renal disease

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False hypochloremia
- Hyperlipidemia
- Hyperproteinemia
- Hyperglycemia

Uncommon Causes

Psychogenic polydipsia
Inappropriate antidiuretic hormone secretion
Adrenal insufficiency

Without Proportional Decrease in Sodium

Common Causes

Metabolic alkalosis
- Exhaustive disease syndrome
- Abomasal torsion
- Vagal indigestion with internal vomiting
- Response to furosemide in horses

Uncommon Cause

Compensation for respiratory acidosis

Osmolality

ECF osmolality is maintained around 300 mOsm (isotone). Measurement of the serum osmolality provides an indication of relative water balance in much the same way the serum sodium concentration does. In most circumstances these parameters are closely correlated. Comparing the measured osmolality with the calculated osmolality, as determined from the measured concentrations of the major solutes in serum (sodium, chloride, glucose, and urea), provides a means of determining if the serum water content deviates widely from normal or if foreign, low-molecular-weight substances are present in the blood. The difference between the measured osmolality and the calculated osmolality is called the *osmolar gap*. Decreases or increases in the osmolar gap could indicate

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laboratory error, but increases of >10 mOsm/kg generally are the result of either a decrease in serum water content (caused by hyperlipidemia or hyperproteinemia) or the presence of abnormally high concentrations of low-molecular-weight substances in the serum. These substances can include a variety of exogenous and potentially toxic compounds such as mannitol, ethanol, methanol, propylene glycol, ethylene glycol, isopropanol, ethyl ether, acetone, trichloroethane, and paraldehyde. All hypernatremic animals are hyperosmolal. Hypo-osmolality is always associated with hyponatremia, but not all cases with hyponatremia are hypo-osmolal (e.g., concurrent hyperglycemia).

Serum Calcium

Calcium plays a vital role in many of life's processes including maintenance of neuromuscular excitability, permeability of cell membranes, conduction of nerve impulses, muscle contraction, and blood clotting. For these reasons the serum calcium concentration or, more correctly, the ionized calcium concentration is normally maintained within a relatively narrow range, despite wide variation in intake and output. Calcium metabolism is regulated by dietary factors, vitamin D and its active metabolites, and the hormones parathormone and calcitonin. Compared with ruminants in horses, a relatively larger percentage of calcium is excreted in the urine. The serum calcium concentration is maintained by adjusting intestinal absorption, renal excretion, and mobilization of available calcium from the large stores in bone. Calcium exists in the serum in three forms: ionized calcium, complexed calcium, and protein-bound calcium. Ionized calcium, which normally constitutes 50% to 60% of the total calcium, is the physiologically active form of calcium. Protein binding can cause confusion (protein-bound calcium normally constitutes 40% to 50% of the total calcium, and most of it is bound to albumin). Hyperalbuminemia may result in a modest hypercalcemia, whereas hypoproteinemia, especially hypoalbuminemia, regularly results in a moderate hypocalcemia. The ionized calcium concentration, usually measured with ion selective electrodes, generally remains within normal limits, despite increases or decreases in total calcium associated with the change in protein concentration. The acid-base balance has additional influence on the amount of ionized and protein-bound calcium. Alkalosis reduces ionized calcium and increases protein binding, whereas acidosis produces the opposite effect. Ion-specific electrodes are available for determining the ionized calcium level, which can be useful if blood samples are

handled appropriately. Most diagnostic laboratories provide the total serum calcium value, which is composed of ionized, complexed, and protein-bound calcium.

Hypocalcemia.

Large increases or decreases in the serum calcium concentration generally are the result of a failure in the normal mechanisms of calcium homeostasis rather than a reflection of absolute calcium deficits or calcium-phosphorus imbalances. Hypocalcemia occurs with some frequency in domestic animals, particularly in high-producing dairy cattle at the onset of lactation. In cattle the serum calcium concentration normally decreases to <8 mg/dL (<2 mmol/L) with the stress of parturition and onset of lactation (Box 22.7). Failure to mobilize sufficient calcium to maintain serum calcium results in the clinical syndrome of parturient paresis (see Chapter 41 for a more detailed discussion of this syndrome). Most animals are recumbent with a calcium level of 6 mg/dL (≤1.5 mmol/L) or less, and fatalities may occur if the level drops below 4 mg/dL(<1 mmol/L). Parturient paresis is associated with hypocalcemia, hypophosphatemia, and a normal to increased serum magnesium level. Change in the cation-anion balance in the diet (increased proportion of strong anions) of dairy cattle during the periparturient period has modest effects on the acid-base balance and enhances calcium mobilization from storage sites, thus reducing the incidence of milk fever in cows at high risk. Grass tetany is associated with marked hypomagnesemia and modest hypocalcemia, whereas the inorganic phosphorus level remains within the normal range.

Box 22.7

Causes of Hypocalcemia

Common Causes

Parturient paresis (milk fever)
Grass tetany
Hypoalbuminemia (decreased total calcium; ionized calcium may remain unchanged)

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Fat necrosis
Lactation tetany
Transport tetany
Synchronous diaphragmatic flutter
Blister beetle toxicosis (cantharidin)
Acute renal failure
Anorexia in lactating cows
Colic in horses

Uncommon Causes

Acute toxemia and associated anorexia in lactating dairy cows
Hypoparathyroidism
Exertional rhabdomyolysis
Malignant hyperthermia
Pancreatic disease
Oxalate toxicity
Tetracycline administration
Furosemide administration
Alkalosis induced by excessive bicarbonate administration

Systemic diseases resulting in anorexia (e.g., traumatic reticuloperitonitis, ketosis, and displaced abomasum) or acute toxemic conditions (e.g., coliform mastitis, septicemia, or aspiration pneumonia) that produce anorexia in lactating cattle frequently result in hypocalcemia. Hypocalcemia is also seen in sheep on marginal rations if stressed by inclement weather or when being moved and during late pregnancy as well. Hypocalcemia is seen in cattle with fat necrosis, presumably as the result of incorporation of calcium with the fat as a form of soap. Horses sweating or with exhaustive disease syndrome or transit tetany often develop decreases in ionized calcium with resultant muscle cramps and synchronous diaphragmatic flutter, which generally respond to intravenous calcium and electrolyte fluid administration. Horses, cattle, and sheep usually respond initially to acute renal tubular damage with mild hypocalcemia and hyperphosphatemia. Idiopathic hypocalcemia, which may exist in foals 4 to 5 days old, has poor prognosis, and a cause is not established.[23] Transport tetany and lactation tetany of horses are associated with hypocalcemia. In lactation

tetany of mares, this is correlated with high milk production.

Hypercalcemia.

Marked hypercalcemia, with a serum calcium level ranging from 14 to 20 mg/dL (3.5 to 5 mmol/L), and modest hypophosphatemia are frequently observed in horses with chronic renal failure (CRF) that are fed a high-calcium diet such as alfalfa hay (Box 22.8). In these horses, blood samples collected in standard EDTA tubes may actually clot. This occurs because the serum calcium concentration is so high that there is insufficient EDTA to bind all the calcium, and some free calcium is available to complete the clotting process. Vitamin D intoxication can develop as a result of excessive dietary supplementation or the ingestion of certain plants such as *Cestrum diurnum* (day blooming jasmine), *Solanum malacoxylon*, Solanum *sodomaeum*, and *Trisetum flavescens*, which contain toxic quantities of vitamin D analogs. Primary hyperparathyroidism is exceedingly rare in large animals, but pseudohyperparathyroidism with hypercalcemia occasionally can develop in animals with tumors that produce protein substances with parathormone-like biologic activity. This has been reported in a few horses with lymphosarcoma, squamous cell carcinoma, adrenocortical carcinoma, multiple myeloma, and ameloblastoma. Hypercalcemia has also been reported in idiopathic systemic granulomatous disease and some foals with neonatal asphyxia.[24]

Box 22.8

Causes of Hypercalcemia

Common Causes

- Chronic renal failure in horses
- Hypervitaminosis D
  - Excessive dietary supplements
  - Plant intoxication
    - *Cestrum diurnum* (day blooming jasmine)
    - *Solanum malacoxylon*
  - Excessive or too rapid intravenous administration of calcium

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Uncommon Causes

- Neoplasia (pseudohyperparathyroidism)
  - Lymphosarcoma
  - Gastric squamous cell carcinoma
- Hyperparathyroidism

Serum Phosphorus

Phosphorus is found primarily in the skeleton and teeth in close association with calcium in the intricate and dynamic crystalline structure of bone. Intracellularly, phosphate plays an essential role in the degradation and synthesis of many compounds. Also, in the forms of adenosine triphosphate (ATP), adenosine diphosphate (ADP), and adenosine monophosphate (AMP), it is the primary form of energy storage and transfer required for almost all of life's processes. Phosphorus in the ECF exists primarily in the organic and inorganic form, specifically as the “buffer” pair H_2PO^{-3} and HPO^{-4}, and plays a role in acid-base balance. Like calcium, phosphorus is regulated by dietary factors, the active metabolites of vitamin D, and the hormones parathormone and calcitonin. Imbalances of calcium and phosphorus or the presence of compounds that bind these substances in the gut can produce serious imbalances that are not always evident on analysis of serum samples. Measurement of urinary output or creatinine clearance ratios for calcium and phosphate are simple and helpful procedures. They provide an indication of an imbalance while more definitive procedures such as ration analysis are contemplated.

Hypophosphatemia.

Serum phosphorus concentrations are not always an accurate guide to phosphate balance, but dietary deficiencies of phosphorus are frequently manifested by hypophosphatemia. Hypophosphatemia is a common feature in cattle with parturient paresis (see also Chapter 41) and horses with CRF (Box 22.9). It has been reported in animals with experimental oxalate toxicity, in chronic wasting states, or with starvation. Postparturient hemoglobinuria is a disorder of cattle, primarily lactating dairy cattle, that often is associated with diets low in phosphorus. Although marked hypophosphatemia is often reported, it is not an invariable feature of this disorder. Hypophosphatemia has also been seen in

cattle on acidogenic diets as a consequence of increased excretion and can also be observed due to compartmental phosphorus shifts as in hypertonic dextrose administration.[25] Hypophosphatemia in horses has also been observed in renal failure, sepsis, malignancies, hyperinsulinism, metabolic alkalosis, and parenteral nutrition.[24]

Box 22.9

Causes of Hypophosphatemia

Common Causes

Chronic renal failure in horses
Parturient paresis in cattle
Postparturient hemoglobinuria

Uncommon Causes

Brassica toxicity
Inadequate dietary intake
Starvation or chronic wasting diseases
Hyperparathyroidism, pseudohyperparathyroidism

Hyperphosphatemia.

Age-related differences exist in the normal range of serum phosphorus concentration. Young animals have much higher values than adults, with values for neonates commonly up to 7 to 9 mg/dL (2.3 to 3.0 mmol/L). The serum phosphate concentration declines progressively with age. Hyperphosphatemia is seen in animals with vitamin D toxicity, transiently in horses after long-distance endurance rides, and initially in horses with ARF (Box 22.10). It has also been observed in hypothyroidism, marked tissue necrosis (e.g., rhabdomyolysis, intestinal infarction, tumor lysis syndrome, hemolysis), hypoparathyroidism, and in foals treated with phosphate-containing enemas. In ruminants, hyperphosphatemia is more commonly seen in dehydration and ensuing

hemoconcentration as in abomasal displacement and volvulus, where it has been shown to be closely associated with dehydration.[26]

Box 22.10

Causes of Hyperphosphatemia

Common Causes

Acute renal failure
Nutritional secondary hyperparathyroidism (excess phosphate intake)
Endurance exercise in horses
Higher normal range in neonates

Uncommon Causes

Acute rhabdomyolysis
Vitamin D toxicity

Serum Magnesium

Between 20% and 30% of magnesium is bound to mostly albumin, 10% is bound to weak acids, and 60% is free (ionized).[27] Free magnesium can be measured with ion-selective electrodes. Disturbances of magnesium metabolism occur principally in cattle and sheep. Complex nutritional and environmental interactions contribute to a variety of clinical syndromes attributed to magnesium deficiency and the onset of tetany in grazing animals.

Hypomagnesemia.

Hypomagnesemia is reported in cattle with grass tetany, transport tetany, winter tetany, and in sheep with grass staggers (Box 22.11) (see also Chapter 41). A serum magnesium level below 1.8 mg/dL (0.75 mmol/L) is considered low; values <1 mg/dL (0.4 mmol/L) are considered severe and are likely to be associated with clinical signs. However, there is better association with magnesium levels in the CSF.[28] Hypomagnesemia caused by dietary magnesium

deficiency has been reported in calves reared in confinement and fed a milk diet exclusively (milk tetany). In chemistry panels of normal horses, hypomagnesemia (total serum magnesium) is often reported to be close to or below 1 mg/dL (0.4 mmol/L) without clinical signs and is mostly rightly or wrongly considered irrelevant by the clinician. However, a study found that 48.7% of hospitalized horses had hypomagnesemia and that horses with colic and hypomagnesemia were less likely to die.[29]

Box 22.11

Causes of Hypomagnesemia

Common Causes

- Grass tetany
- Winter tetany
- Grass staggers
- Calves on a milk-only, magnesium-deficient diet
- Endurance exercise
- Fatty liver syndrome

Uncommon Cause

- Undernutrition

Hypermagnesemia.

Hypermagnesemia occurs infrequently but may be seen with overzealous administration of Epsom salts ($MgSO_4$), either orally as a drench by means of nasogastric intubation or as an enema for the treatment of digestive disorders (Box 22.12). Intravenous administration of magnesium produces muscle relaxation but does not alter consciousness, and hypertonic $MgSO_4$ solutions are not considered a humane means of euthanasia.

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Box 22.12

Causes of Hypermagnesemia[a]

Epsom salt ($MgSO_4$) overdose given orally or as an enema
Intravenous administration of magnesium in excessive amounts
Use of $MgSO_4$ IV

[a]Hypermagnesemia is an uncommon condition in large animals.

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Acid-Base Imbalance (Traditional Approach or Hydrogen Ions–Centered Approach)

Using the traditional approach to acid-base balance, the four primary acid-base imbalances and their compensating responses are presented in Table 22.5. Acidosis is associated with an increase in the hydrogen ion concentration (decreasing pH), whereas alkalosis is caused by a decrease in the hydrogen ion concentration (increasing pH). When the primary imbalance is associated with a change in the bicarbonate concentration, the acid-base imbalance is called a *metabolic disorder.* The compensating response for a metabolic acid-base imbalance is mediated by the respiratory tract, which alters the partial pressure of carbon dioxide (P_{CO_2}) to counterbalance the primary imbalance and to partly restore the pH toward normal, but this mechanism has a limited capacity quantitatively to correct bicarbonate concentrations back to normal values (maximum only about 2 mEq/L) (Fig. 22.2). Primary respiratory imbalances are related to changes in alveolar ventilation, which result in an increased P_{CO_2} in respiratory acidosis and a decreased P_{CO_2} in respiratory alkalosis. The compensating response for these primary respiratory acid-base imbalances is mediated by the kidneys through presumed alterations in the excretion or retention of hydrogen ions and bicarbonate. Heparinized blood samples for acid-base evaluation must be drawn anaerobically and sealed immediately. Arterial blood samples should be submitted for evaluation of primary respiratory disorders and for evaluation of ventilation in patients under general anesthesia. Venous blood samples are easier to obtain and provide reliable data for most primary metabolic acid-base abnormalities.

TABLE 22.5

Acid-Base Imbalances and Compensatory Responses

Disorder	pH	$[H^+]$	Primary Imbalance	Compensatory Response
Metabolic acidosis	↓	↑	↓ $[HCO_3^-]$	↓ P_{CO_2}
Metabolic alkalosis	↑	↓	↑ $[HCO_3^-]$	↑ P_{CO_2}
Respiratory acidosis	↓	↑	↑ P_{CO_2}	↑ $[HCO_3^-]$

Respiratory alkalosis	↑	↓	↓ P_{CO_2}	↓ [HCO_3^-]

[HCO_3^-], Bicarbonate concentration; *PCO_2,* partial pressure of carbon dioxide.

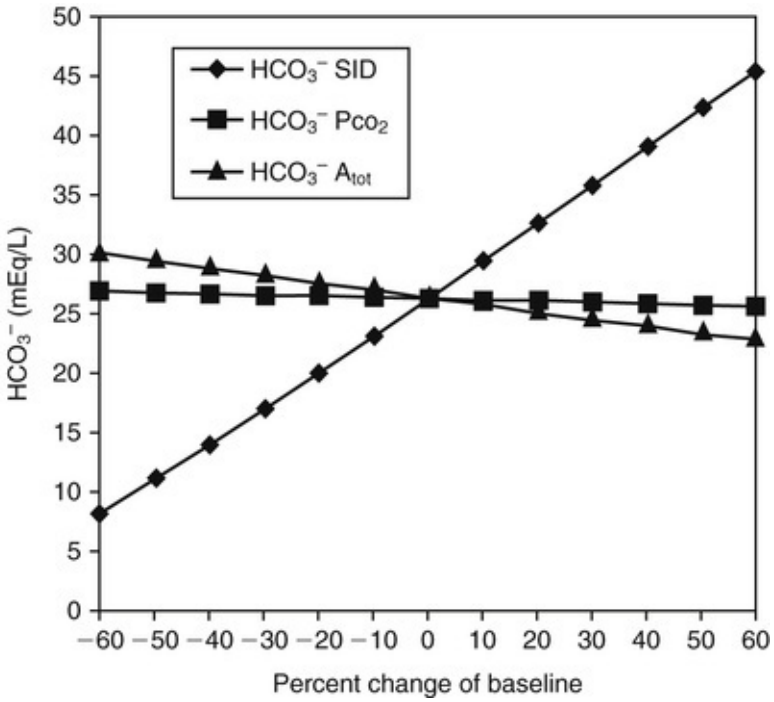


FIG. 22.2 Spider plot graphically showing the dependence of plasma bicarbonate (HCO_3^-) concentration on changes in the three independent variables (SID, PCO_2, and A_{tot}). The spider plot was obtained by systematically varying one independent variable while holding the other two independent variables at their reference values (y axis values at 0 on the x axis) for plasma. Please note how little changes in PCO_2 affect concentrations of HCO_3^-.

Blood gas analysis should be performed as soon after collection as possible. However, appropriately collected blood samples yield reliable results for as long as 4 hours if held in ice water. The patient's rectal temperature should be provided to the laboratory so that corrections can be made for variation in body temperature. Changes in body temperature have a major impact on the partial pressure of oxygen (P_{O_2}) as well as the P_{CO_2}, but relatively little effect on estimations of bicarbonate or base balance. During brief exercise at maximal intensity, the temperature of the central venous blood may exceed the rectal temperature by as much as 3° C. In these circumstances, the central blood temperature is more appropriate than the rectal temperature for correcting blood

gas determinations. The blood sampling site (arterial, venous, or capillary blood) has a significant impact on the blood gas values obtained.[30] Arterial blood samples yield higher values for pH and lower values for P_{CO_2} than venous blood, but the bicarbonate is higher in venous blood. The use of blood gas data for evaluation of acid-base imbalances in animals has been reviewed.[31,32] In addition, a review of the traditional and nontraditional approaches to evaluation of acid-base balance as related to fluid therapy in small animals has application to many large animal situations and is well worth reading.[33]

Metabolic Acidosis

Metabolic acidosis is characterized by a decrease in pH and bicarbonate concentration. Metabolic acidosis is traditionally thought to be produced by the addition of hydrogen ions or the loss of bicarbonate ions. The most common causes include the lactic acidosis of ruminal overload, D-Lactic acidosis in neonates ruminants, hypovolemia associated with loss or compartmentalization of sodium-containing fluid, ketoacidosis in ketosis (rare in large animals) and pregnancy toxemia, loss of sodium bicarbonate–rich saliva with oral diseases or esophagostomy in cattle, gastrointestinal loss of sodium bicarbonate as a result of diarrhea, and renal failure, which may result in decreased ability to excrete hydrogen and thus to retain bicarbonate (Box 22.13). Other causes include ingestion of certain drugs or toxic compounds such as salicylate, methanol, ethylene glycol, or paraldehyde (rare in large animals). Increased ventilation provides a respiratory response for metabolic acidosis, and a decline in the P_{CO_2} generally begins within minutes. This temporarily minimizes the fall in blood pH, but long-term correction of metabolic acidosis requires classically explained renal bicarbonate retention and enhanced acid excretion. Complete correction of metabolic acidosis may be difficult in patients with intrinsic renal disease or those with diseases such as renal tubular acidosis that impair the ability of the kidneys to excrete acid or retain bicarbonate, or both.

Box 22.13

Causes of Metabolic Acidosis

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Common Causes

Rumen overload (lactic acidosis)
Ketosis
Pregnancy toxemia
Hypovolemic shock
Acute diarrhea
Colic with strangulated bowel
Strangulating abomasal torsion
Peritonitis
Uroperitoneum (ruptured bladder)
Exercise above anaerobic threshold (normal response in horses)

Uncommon Causes

Renal failure
Renal tubular acidosis
Urea toxicity
Salicylate toxicity
Methanol toxicity
Paraldehyde toxicity
Ethylene glycol toxicity

Metabolic Alkalosis

Metabolic alkalosis is characterized by an increase in pH and bicarbonate. It occurs fairly commonly in domestic animals, particularly in association with digestive disturbances in ruminants. An initiating process capable of generating alkalosis is necessary and must be coupled with additional factors to maintain metabolic alkalosis. Generation of metabolic alkalosis is traditionally thought to be caused by excessive hydrogen loss, bicarbonate retention, or contraction alkalosis (Box 22.14). Contraction alkalosis occurs when the ECF volume is reduced because of loss or sequestration of fluids high in sodium and chloride but without proportionate loss of bicarbonate, which really contradicts electroneutrality of watery solutions. This is thought to be traditionally a contributing mechanism for the generation of the metabolic alkalosis reported in

heavily sweating endurance horses and in response to the diuretic furosemide in the horse. The most common causes of increased hydrogen ion loss are the gastrointestinal losses caused by salivary secretions in ponies after surgical esophagostomy[34]; massive gastric reflux associated with anterior enteritis, ileus, or small bowel obstruction in horses; and sequestration of fluid in the abomasum and forestomach associated with a variety of gastrointestinal displacements or functional disturbances (vagal indigestion, functional pyloric stenosis) of ruminants. Continuous salivary losses in horses after surgical esophagostomy result in transient metabolic acidosis followed by progressive metabolic alkalosis. Most of these disorders cause significant dehydration and sodium, chloride, and potassium deficits.

Box 22.14

Causes of Metabolic Alkalosis

Common Causes

- Sequestration of fluid in the abomasum and forestomach in ruminants (internal vomiting for abomasal reflux)
- Gastric reflux in horses with ileus
- Massive sweat loss in horses (endurance horses)
- Chloride depletion
- Potassium depletion
- Contraction alkalosis (extracellular fluid volume contraction without bicarbonate loss)
- Salivary loss of chloride in horses with esophagostomy
- Use of diuretics (especially furosemide)
- Functional pyloric stenosis

Uncommon Causes

- Excessive bicarbonate supplementation or therapy
- Mineralocorticoid excess

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The factors responsible for maintaining metabolic alkalosis involve classically explained impaired renal bicarbonate excretion. These factors are associated with the renal response to decreases in the effective circulating fluid volume, chloride depletion, or potassium depletion. Renal tubular sodium resorption is enhanced in response to hypovolemia. Maintenance of electroneutrality requires that sodium resorption in the proximal tubule be accompanied by a resorbable anion, whereas in the distal tubule sodium resorption is associated with the secretion of another cation, usually hydrogen or, to a lesser extent, potassium. Chloride is the only resorbable anion normally present in appreciable quantities in the proximal tubular fluid. In metabolic alkalosis, plasma bicarbonate is increased and the chloride concentration is generally decreased as a result of disproportionate chloride losses. The relative lack of the resorbable anion chloride in the proximal tubule thus allows a larger amount of sodium to reach the distal tubule, where aldosterone and other factors enhance hydrogen or potassium loss into the tubular lumen in exchange for sodium. Potassium depletion reduces or eliminates potassium exchange as a means of sodium retention, thus classically explained placing greater emphasis on hydrogen ion exchange, which stoichiometrically and quantitatively is difficult to explain. Because renal hydrogen excretion is linked with bicarbonate resorption, the excess bicarbonate cannot be eliminated and metabolic alkalosis is maintained. Thus the traditional explanation is the reason for the paradoxic aciduria seen in some patients with metabolic alkalosis, and it is the reason these patients respond when given intravenous fluids containing sodium, chloride, and potassium. The compensating respiratory response to metabolic alkalosis is hypoventilation, resulting in an increase in the P_{CO_2}. Excessive sodium bicarbonate administration is an additional potential cause of metabolic alkalosis. Most normal animals can tolerate large doses of sodium bicarbonate, and excesses are rapidly eliminated by renal excretion.[35] However, patients with decreases in effective circulating fluid volume, particularly when coupled with potassium or chloride deficits, may not tolerate a bicarbonate load because renal clearance of excess bicarbonate is likely to be impaired. Attempts to alter the acid-base balance, and thereby affect the athletic performance of racing horses, by prerace administration of high doses of sodium bicarbonate–containing “milkshakes” have become a major concern around the world. This has stimulated substantial research on the acid-base balance of horses before and after racing. In many racing jurisdictions, stringent prerace or postrace standards for blood pH or bicarbonate or T_{CO_2} levels (or both) have been enacted to

control this practice. The prerace administration of the diuretic furosemide is allowed in several racing jurisdictions of North America. This drug results in a mild metabolic alkalosis with increased bicarbonate, and allowances for this may be included in some regulations. Racing supplements (which may contain sodium bicarbonate), bicarbonate precursors, and diets that supply a high positive cation-anion balance also have the potential to produce a significant metabolic alkalosis.

Respiratory Acidosis

Respiratory acidosis is characterized by a decrease in pH and an increase in P_{CO_2}, which develop because of decreased effective alveolar ventilation. CO_2 diffuses through the lungs much more readily than oxygen; thus diseases that compromise ventilation normally result in decreases in PO_2 before significant increases in P_{CO_2} develop. The most common causes are acute upper respiratory obstruction and primary pulmonary diseases including pneumonia, pneumothorax, pulmonary edema, and severe equine asthma (Box 22.15). Diseases or drugs that affect the respiratory center of the central nervous system may also produce respiratory acidosis, as can general anesthesia. The compensating response for respiratory acidosis is classically thought to be renal retention of bicarbonate. This response requires days to develop and is seen only in chronic respiratory acidosis. Exogenous sodium bicarbonate does not correct respiratory acidosis and should not be administered to affected patients. It should be treated by improving ventilation and alveolar gas exchange.

Box 22.15

Causes of Respiratory Acidosis

Common Causes

Primary pulmonary disease
Obstruction of the upper airway
Laryngeal edema
Aspiration pneumonia
Pneumonia

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- Pneumonia and pleuritis complex
- Pneumothorax
- Severe equine asthma
- Depression of the respiratory center of the central nervous system
- General anesthesia with inappropriately assisted ventilation
- Drugs
    - Opiates
    - Anesthetics
    - Tranquilizers
- Central nervous system diseases

Uncommon Causes

- Cardiac arrest
- Muscle weakness or dysfunction
- Tetanus
- Botulism
- Myasthenia
- Severe hypokalemia
- Neonatal respiratory distress syndrome

Respiratory Alkalosis

Respiratory alkalosis is caused by hyperventilation, which may be stimulated by hypoxemia associated with pulmonary disease, congestive heart failure, severe anemia, or neurologic disorders (Box 22.16) or residence or extended stay at high altitudes. The initial compensating response to acute respiratory alkalosis is a modest decline in the ECF bicarbonate concentration—the result of cellular buffering. Subsequent renal responses result in a decrease in the ECF bicarbonate concentration through reduced renal bicarbonate resorption. The decline in bicarbonate may be offset by chloride retention; thus hyperchloremia and decreased P_{CO_2} may be associated with compensated respiratory alkalosis, as well as with compensated metabolic acidosis. Compensating renal responses for chronic respiratory alkalosis that lasts several weeks actually may be sufficient to return pH to normal.[36]

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Box 22.16

Causes of Respiratory Alkalosis

Common Causes

Hypoxemia
Pulmonary diseases
Congestive heart failure
Severe anemia
Stimulation of the respiratory center of the central nervous system
Psychogenic hyperventilation
Excitement, fear, transport, pain
Gram-negative septicemia
Neurologic disorders

Uncommon Causes

After correction of metabolic acidosis
Inappropriate mechanical ventilation
Salicylate toxicity

Mixed Acid-Base Imbalances

Mixed acid-base disorders occur when several primary acid-base imbalances coexist. Metabolic acidosis and alkalosis can coexist, and either or sometimes both may occur with either respiratory acidosis or respiratory alkalosis. The following factors should be considered when evaluating possible mixed acid-base disorders:

- Compensating responses to primary acid-base disturbances do not result in overcompensation.
- Compensating responses, except for long-term renal compensation, rarely correct pH to normal. A normal

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pH in a patient with an acid-base imbalance is an indicator of a mixed acid-base disturbance.

- A change in pH in the opposite direction to that predicted for a known primary disorder indicates a mixed disturbance.
- Bicarbonate and P_{CO_2} always deviate in the same direction with primary acid-base disturbances. If these parameters deviate in opposite directions, a mixed abnormality exists.
- If the change in the anion gap does not approximate the change in bicarbonate, a mixed acid-base imbalance should be suspected.

Mixed acid-base abnormalities occur with some frequency in domestic animals and often are overlooked. The practitioner must be aware of the potential for mixed acid-base imbalances to correctly interpret blood gas data in complex clinical situations.

Anion Gap

The anion gap can be an extremely helpful tool for categorizing causal factors in acid-base imbalances and may prove a useful prognostic guide in animals with serious digestive disorders. The anion gap can be calculated as the difference between the major cations (sodium plus potassium) and measured anions (chloride plus bicarbonate). The anion gap normally is 12 to 17 mmol/L and provides an approximation of the so-called unmeasured anions. These are anions that are not measured routinely in the clinical laboratory; they include “physically” the anionic equivalents of plasma proteins (debatably albumin in particular) which comprises about 95% of total anion gap in normal adult animals, and sulfate, phosphate, lactate, and ketones, with a variety of inorganic anions. Significant differences exist in the normal range of the anion gap among species, and there may also be age-related differences. Foals are reported to have

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a larger anion gap than do adult horses.

Hypoproteinemia and hyperchloremic metabolic acidosis are the most common causes of a decrease in the anion gap. The cause of normal to low anion gap hyperchloremic metabolic acidosis often can be differentiated on the basis of the serum potassium concentration. Animals with hyperchloremic metabolic acidosis associated with gastrointestinal fluid losses or renal tubular acidosis most often manifest hypokalemia, whereas hyperkalemia generally is seen in patients with decreased mineralocorticoid secretion (Addison disease) or renal failure with renal shutdown. Decreases in the anion gap also result from overhydration caused by decreases in the protein concentration and changes in the relative concentration of plasma sodium and chloride.

Most commonly, high anion gap acidosis is associated with accumulation of a metabolizable acid, most commonly L and D lactic acid associated with anaerobic exercise, grain overload, acute gastrointestinal accidents, or hypovolemic shock (e.g., diarrhea in young calves). The commonly used laboratory procedures (mostly automated blood gas machines; point of care equipment) for the determination of lactate only measure the L form of lactate. Microbial fermentation in the gastrointestinal tract may result in the production of both the D and L forms of lactate. Recent studies have shown in milk-fed calves and kids that accumulation of D-lactate is a major factor in the profound acidosis associated with certain digestive disorders.[37,38] Unfortunately, at present, determination of D-lactate requires special procedures, which are now available only in special diagnostic commercial kits. Ketoacidosis, uremic acidosis, and poisoning with a variety of anionic poisons result in increases in nonmetabolizable acids that are also causes of an increased anion gap (rare in large animals). When a high anion gap metabolic acidosis is found, a thorough search for the potential causes of the accumulated unmeasured anions is indicated. The anion gap is also useful for identifying mixed acid-base imbalances. A mixed metabolic acid-base imbalance should be suspected when the change in the anion gap does not approximate the change in bicarbonate. Increases in the anion gap can also be associated with dehydration and contraction alkalosis caused by changes in the protein concentration and the relative concentration of plasma sodium and chloride.

Bicarbonate and Total Carbon Dioxide

Bicarbonate accounts for approximately 95% of the measured CO_2; thus T_{CO_2} or

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"CO_2 content" of serum or plasma provides a measure of metabolic changes in the acid-base balance. Most automated chemistry profiles now provide the TCO_2 level. Bicarbonate or TCO_2 is decreased in metabolic acidosis and increased in metabolic alkalosis. However, the bicarbonate or TCO_2 values provide only a crude indication of acid-base status. When acid-base abnormalities are suspected, appropriate samples should be submitted for blood gas and electrolyte determination run on the same analyzer. It should be pointed out that bicarbonate levels are always calculated on automated measuring systems.

Buffer Base, Standard Bicarbonate, and Base Excess or Base Deficit

The terms *buffer base*, *standard bicarbonate*, and *base excess* (or *base deficit*) represent derived calculated estimates of the metabolic component of acid-base balance and do not really physically exist. The buffer base indicates the sum of all the buffer anions in blood under standardized conditions. The standard bicarbonate is the plasma bicarbonate concentration that would be found under specific conditions that eliminate respiratory influences on the values obtained. The base excess or base deficit is often supplied in routine assessment of acid-base balance; it indicates the deviation of bicarbonate from normal, usually the stored "normal" for humans in blood gas machines, and thus not directly applicable to large animal blood gas interpretations. The calculated base deficit provides a means of estimating the amount of bicarbonate required to correct metabolic acidosis. The conundrum is that bicarbonate cannot be given without a cation (mostly Na). The bicarbonate estimate is calculated by multiplying the base deficit by the probable sodium bicarbonate space (about 30% [adults] to 50% [neonates and young animals] of body weight), as in the following equation:

$$\text{mEq } NaHCO_3^- \text{ needed} = \text{mEq base deficit} \times \text{kg body weight} \times 0.3 \text{ or } 0.5$$

It should be pointed out that normal ranges of plasma bicarbonate concentrations are different in humans and large animals, with normal large animals being an average of 4 to 5 mEq/L higher compared with normal humans.

Modern blood gas machines providing base excess calculations most commonly will use human equations with normal bicarbonate concentrations of 24 mEq/L. When given clinical interpretations of values of base excess, this should be taken into consideration when applying the above equation to calculate $NaHCO_3^-$ deficits. The factor of 0.3 to 0.5 actually represents the sodium space in adult and young animals encompassing the ECF compartment.

Strong Ion-Centered Approach to Acid-Base Balance.

In the strong ion-centered approach (also known as the Stewart approach or physicochemical approach), acid-base balance is determined by three independent variables: strong ion difference (SID), the partial pressure of CO_2, and the total concentration (mass) of nonvolatile weak acids (A_{tot}), the principal components of which are plasma proteins and, to a lesser extent, inorganic phosphate.[33,39] Bicarbonate and pH are dependent variables determined by these three independent variables. Briefly, this approach is a quantitative approach applying physical laws of chemistry of watery solutions to calculate parameters involved in determining acid-base equilibria and disequilibria. These laws include electroneutrality (Σ cations = Σ of anions), dissociation equilibria (proteins, bicarbonate system, water), and mass conservation. If one of the independent variables (strong electrolytes, proteins, or P_{CO_2}) changes the other dependent variables, pH, bicarbonate, and weak electrolytes adjust. Several studies have adapted the physicochemical approach for practical application in human and veterinary medicine.[32,39-44] Experimentally determined species-specific A_{tot} and Ka data are now available for horses, cattle, dogs, and humans.[45-48]

Strong Ion Difference

Strong electrolytes are completely dissociated in aqueous solution and chemically nonreactive. The SID is simply the difference between the total concentration of strong cations (sodium, potassium, calcium, and magnesium) and total concentration of strong anions (chloride, sulfate, lactate, acetoacetate, and β-hydroxybutyrate) with sodium, potassium, and chloride normally being quantitatively the principal determinants of SID. In fluids with little or no protein, such as cerebrospinal fluid (CSF), bicarbonate concentration is the same as the SID, but it should be noted that the chloride concentration is higher (≈10

to 11 mEq/L) and SID is lower compared with blood; thus normal acid-base equilibria in such fluids are different from acid-base equilibria of blood. Abnormalities in P_{CO_2} are viewed in essentially the same manner in both the traditional and nontraditional approaches to acid-base balance. Plasma albumin debatably makes up the majority of A_{tot}. The A_{tot} (total mass of proteins) exists physically in blood in both dissociated (A^-) and undissociated forms (HA). A decrease in A_{tot} (A^-) resulting from hypoalbuminemia/hypoproteinemia causes an alkalosis with an increase in bicarbonate, whereas hyperalbuminemia has the opposite effect. Increases in A^- can cause an increase in anion gap, whereas decreases in A^- result in a decrease in anion gap. A change in protein concentration has effects on acid-base balance. The literature describes hyperproteinemic acidosis or hypoproteinemic alkalosis.[40] Details are outlined in Figs. 22.2 and 22.3.

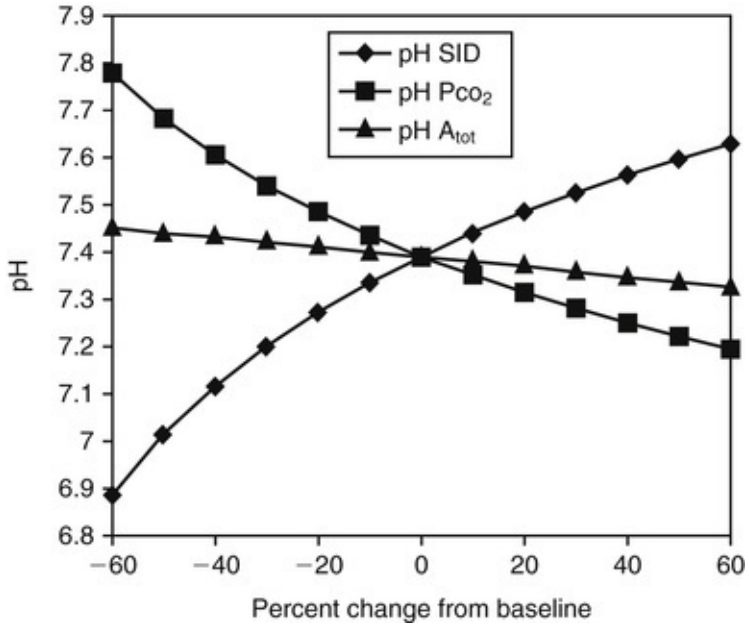


FIG. 22.3 Spider plot graphically showing quantitatively the dependence of plasma pH concentration on changes in the three independent variables (SID, PCO_2, and A_{tot}). The spider plot was generated by systematically varying one independent variable while holding the other two independent variables at their reference values (y axis values at 0 on x axis) for plasma.

When protein and inorganic phosphate remain within the normal range, acid-base balance is controlled by changes in P_{CO_2} mediated by the respiratory

system and changes in SID, which are largely under the control of the kidneys. Heavy sweat loss in an endurance horse, displaced abomasum in a cow (trapping of chloride in abomasum), or the prerace administration of the diuretic furosemide (chloruresis) in a racehorse produces metabolic alkalosis (mainly observed abnormalities are decreases in serum chloride concentrations). In each case the alkalosis is the result of a disproportionate loss of chloride relative to sodium, yielding hypochloremia and an increase in SID. The dissociation equilibrium of serum bicarbonate concentrations will adjust to fulfill electroneutrality requirements of watery biologic solutions. Correction of the alkalosis is brought about by the provision of relatively more chloride relative to sodium, generally as sodium chloride or potassium chloride. This results in changing SID to more normal concentrations and thus a return of bicarbonate and pH toward normal. Metabolic acidosis with a large base deficit is generally treated with sodium bicarbonate, with sodium being the strong cation added to the ECF and bicarbonate adjusting according to its dissociation equilibrium and sodium added without a strong anion. Other metabolizable anions (short-chain fatty acids such as lactate, acetate, gluconate, and propionate, added with Na as the cation) could be substituted for bicarbonate and achieve similar effects. Short-chain fatty acids are quickly metabolized to glucose and ATP as sources of energy for the body; in physicochemistry, this will result in a relative increase of the SID.

Calculation of SID is simple and provides useful insight in patients with metabolic acid-base disturbances. Factors that influence SID range from changes in free water, to sodium-chloride imbalances that result from excessive losses or disproportionate retention of sodium or chloride, to the accumulation of strong organic anions (most commonly L and D lactate). Organic acidosis can be produced by the accumulation of exogenous and endogenous anions. The anion gap does not always accurately predict the presence of unmeasured strong anions. Mathematic methods have been developed as a means for the detection of unmeasured anions[49,50] and for the calculation of the simplified strong ion gap.[51]

Both the traditional and nontraditional or strong ion approaches to acid-base balance have proven useful to address practical problems in both research and medical settings. The traditional approach to acid-base balance is more widely accepted and user-friendly. The strong ion approach may provide a better understanding as to why the bicarbonate concentration is changing as it integrates acid-base and electrolyte disorders. The strong ion approach has

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recently gained wider acceptance from members of the human critical care community, who have found it useful for the analysis of the complex fluid, electrolyte, and acid-base problems of patients in intensive care units. Several easy-to-use computer or calculator programs have been developed for the mathematically challenged that facilitate implementation of the strong ion approach to acid-base balance.

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Serum Enzymes

Serum enzyme levels are proportional to their cell or tissue concentrations and activity. A number of variables affect the appearance in serum or plasma. The amount of any single enzyme in serum depends on concentration in the cell, total tissue mass, magnitude of cell/organ damage, normal death of the cell, apoptosis, degradation rate of the enzyme in serum or its half-life, and whether the injury is single or continuous.[2] Some of the common and less common causes of elevated serum enzyme activity are listed in Box 22.17.

Box 22.17

Causes of Elevated Serum Enzymes

Elevation of Sorbitol Dehydrogenase (SDH)

Common Causes

- Severe anoxia
- Acute liver failure
- Liver abscess
- Secondary to damaged bowel
  - Strangulating intestinal lesion
  - Acute toxic enteritis
- Chronic liver failure

Less Common Causes

- Acute and severe anemia
- General anesthesia
- Anoxia

Elevation of γ-Glutamyltransferase (GGT)

Common Causes

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Acute liver failure
Chronic liver failure
Pyrrolizidine alkaloid toxicity
Aflatoxicosis
Cholangiohepatitis
Cholelithiasis
Liver flukes

Uncommon Causes

Higher normal range in young animals
Fatty liver

Elevation of Alkaline Phosphatase (ALP)

Common Causes

Acute liver failure
Chronic liver failure
Pyrrolizidine alkaloid toxicity
Cholangiohepatitis
Cholelithiasis
Liver flukes

Uncommon Causes

Higher normal range in young animals
Fatty liver

Elevation of Creatine Kinase (CK)

Common Causes

Exertional rhabdomyolysis (azoturia, myositis, tying-up)
Polysaccharide storage myopathy
Streptococcus equi–associated myopathy
Nutritional myodegeneration (selenium, vitamin E deficiency)

Post–endurance ride multisystemic disorder
Alert downer cow syndrome (muscle crush syndrome)
Malignant hyperthermia
Malignant edema
Prolonged recumbency with inability to rise

Uncommon Causes

Normal postexercise modest increase
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections

Elevation of Lactate Dehydrogenase (LDH)

Common Causes

Muscle disease
    Exertional rhabdomyolysis (azoturia, myositis, tying-up)
    Polysaccharide storage myopathy
Streptococcus Equi–Associated Myopathy
Nutritional myodegeneration (selenium, vitamin E deficiency)
Post–endurance ride multisystemic disorder
Alert downer cow syndrome (muscle crush syndrome)
Malignant hyperthermia
Malignant edema
Liver disease
    Acute liver failure
    Chronic liver failure
    Cholangiohepatitis
    Cholelithiasis
In vitro hemolysis

Uncommon Causes

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Hemolytic anemia
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections
Fatty liver

Elevation of Aspartate Aminotransferase (AST)

Common Causes

Muscle disease
    Exertional rhabdomyolysis (azoturia, myositis, tying-up)
    Polysaccharide storage myopathy
Streptococcus equi–associated myopathy
Nutritional myodegeneration (selenium, vitamin E deficiency)
Post–endurance ride multisystemic disorder
Alert downer cow syndrome (muscle crush syndrome)
Malignant hyperthermia
Malignant edema
Liver disease
    Acute liver failure
    Chronic liver failure
    Cholangiohepatitis
    Cholelithiasis
    Liver flukes
    In vitro hemolysis

Uncommon Causes

Hemolytic anemia
Acute cardiomyopathy
Purpura hemorrhagica
Equine influenza
Sarcosporidiosis
Local irritation from intramuscular injections

Sorbitol Dehydrogenase

Sorbitol dehydrogenase (SDH) is a cytoplasmic enzyme that reversibly oxidizes D-sorbitol to D-fructose with the cofactor NAD. It is a liver-specific enzyme in all large animal species. Increases in this enzyme indicate hepatocellular damage and leakage of enzymes. Increases in SDH are also seen with obstructive or strangulating gastrointestinal lesions and with acute toxic enteritis as a result of liver damage associated with absorption of bacteria or their toxins (or both) from the damaged bowel into the portal circulation. This enzyme is a sensitive indicator of liver damage, and modest increases may be seen with anoxia, acute anemia, or general anesthesia. The half-life of SDH in the circulation is short (a matter of hours), and elevations indicate active and ongoing liver damage. This enzyme is not stable when stored at room temperature (only for 5 hours), but refrigerated samples may yield useful results up to 24 to 72 hours if frozen. SDH activity has also been observed increased in horses and cattle with intestinal diseases and in foals with sepsis indicating hepatic involvement in these circumstances.[52,53]

Creatine Kinase

Creatine kinase (CK) is present in high concentrations in the cytoplasm of myocytes; it catalyzes the reversible phosphorylation of creatinine to form creatinine phosphate, which is a major storage of high-energy phosphate in the muscle. It is a “leakage” enzyme and a highly sensitive and specific indicator of muscle damage in domestic animals. Normal values of CK activity vary according to physical activity, restraint, age, and sex. There are four important CK isoenzymes. CK-1 is a BB isoenzyme found mostly in brain. CK-2 MB isoenzyme is found mainly in cardiac muscle and small proportions in skeletal muscle. CK-3 MM isoenzyme is found mainly in skeletal muscle and lesser levels in heart muscle and is responsible for the serum CK levels in large animals. CK-Mt is found mainly in mitochondria and is 15% of cardiac activity.[54] Although CK is found in both cardiac and skeletal muscle, elevations of this enzyme most commonly are associated with exertional myopathies (rhabdomyolysis) and are seen as musculoskeletal manifestations of systemic disease. Intramuscular injections, vigorous exercise, or prolonged shipping may

result in modest releases (up to a fourfold increase over resting values) of CK into the circulation without producing histologic evidence of muscle damage. Endurance exercise may lead to moderate elevation of CK (2000 to 15,000 IU/L) in some horses that show no recognizable sign of exertional myopathy. Experimentally it has been shown in horses that when administered IV, the half-life of this enzyme in the circulation is short, 2 hours, but if given IM the half-life is 12 hours.[55] In cattle the half-life is 8 to 9 hours[56]; its activity peaks at 6 to 12 hours, and even marked elevations in CK may return to normal within 24 hours after a single muscle insult. Although marked elevation of CK can be a guide to the extent of muscle damage, the short half-life and the potential for continuing myonecrosis have a marked influence on the enzyme activity observed at any point in time. A persistent elevation of CK suggests a process resulting in active and continuing muscle damage and provides grounds for resting athletic horses; it can also be used as a prognosticator in downer cows (>3500 IU/L carries a guarded prognosis). Elevated CK provides no information on the factors responsible for the rhabdomyolysis; more precise information regarding the etiology can be obtained by muscle biopsy and its histologic and histochemical examination. Hemolysis or delayed separation of serum from clot may produce falsely high values for CK as a result of inadvertent muscle penetration during venipuncture.

Aspartate Aminotransferase

Aspartate aminotransferase (AST) is found in high concentrations in a variety of tissues, including skeletal and cardiac muscles, the erythrocytes and kidneys, and the liver. AST enzyme catalyzes the transfer of the α-amino group of aspartic acid to α-ketoglutaric acid, resulting in formation of oxaloacetic acid and glutamic acid. This enzyme is a nonspecific indicator of tissue damage and tends to be less sensitive to mild insults than the tissue-specific enzymes SDH and CK. The half-life of AST in the circulation is relatively long (it has been reported in horses to be between 7 and 8 days by some and 3 to 4 days by others[57] and around 1 day in cattle[58]), and elevations may persist for as long as 10 days after an episode of myonecrosis or liver damage. As a general rule, extensive muscle necrosis tends to produce much higher elevations of AST than severe liver necrosis. This enzyme is most useful when compared with the tissue-specific enzymes as determined sequentially over the time course of a disease process. Elevations of CK and AST indicate muscle damage, whereas elevations of SDH

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and AST indicate liver damage. Marked but transient elevations of CK and SDH are associated with a single insult to the muscles and liver, respectively, whereas AST increases gradually and remains elevated for a much longer time. Thus a moderate to marked increase in AST in an animal with progressively declining SDH or CK indicates that some tissue damage occurred within the past 7 to 10 days, but also that the process may no longer be active. This is often a favorable prognostic indicator. Persistent elevation of or a progressive increase in CK or SDH and AST over time indicates an active, continuing process of tissue damage, and the prognosis is more guarded. AST is relatively stable at room temperature, but hemolysis, icterus, or lipemia may interfere with the assay.

γ-Glutamyltransferase

γ-Glutamyltransferase (GGT) is a membrane-bound enzyme that functions in the γ-glutamyl cycle, where it catalyzes the transfer of γ-glutamyl groups from γ-glutamyl peptides. It is important in glutathione metabolism, amino acid absorption, and protection against oxidant injury. This enzyme is found in the biliary tract from where it derives the serum activity in health and disease, therefore making it an important marker of hepatobiliary disorders and cholestasis in large animals. GGT is also found in the pancreas, gastrointestinal tract, urinary tract, mammary gland, and reproductive tract; it does not increase in serum in disorders involving these organs. GGT is quite stable, and reliable results can be obtained from samples submitted several days after blood samples have been drawn, provided the serum is refrigerated. The half-life of GGT activity in blood is not known, but it has been suggested to have a half-life of 3 days in horses. The activity of this enzyme is highest in the cells of the periportal region of the liver, in the pancreas, and in the renal tubular cells. Pancreatic diseases resulting in inflammation and necrosis are relatively rare in large animal species. Damage to the renal tubular cells leads to a release of GGT into the tubular lumen and urine. Because this enzyme is a relatively large molecule, it is not resorbed into the systemic circulation and renal tubular damage does not result in elevated serum GGT activity. Increases in GGT relative to creatinine in the urine have been used as an index of acute renal tubular damage. However, the validity of the normal range for this ratio in horses has been questioned.

In large animal species, an elevation in serum GGT is one of the more reliable indicators of damage to the liver and biliary obstruction. Disease processes such as pyrrolizidine alkaloid intoxication (in subclinical liver diseases showed a 75%

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sensitivity and 90% specificity); chronic active hepatitis, cholangiohepatitis, and cholelithiasis produce liver damage, primarily in the periportal region, leading to marked and persistent elevation of GGT activity in the serum.[59] In these instances, elevations in serum ALP activity are generally associated with the increase in GGT. Two syndromes—fatty liver syndrome in dairy cows and hyperlipemia syndrome of periparturient mares of pony and miniature horse breeds—are associated with liver damage, which is often reflected by elevation of GGT.

Most suckling neonatal large animals, except horses, have high levels of GGT activity in their serum. This is the result of absorption of maternal GGT, which is present in relatively high levels in the colostrum, making its serum levels a sensitive indicator of passive transfer. Elevation of GGT in neonates should be regarded as a normal finding unless it is associated with other evidence of liver disease. Serum GGT concentrations are relatively higher in foals than in adults.[60] The normal range of serum GGT activity for burros, donkeys, and asses may be substantially higher (two to three times) than the normal range of serum GGT activity for horses. Caution should therefore be used when evaluating this enzyme in these species. Elevation in serum GGT activity has been reported in Thoroughbred racehorses that are performing below expectations. The reasons for the increase in GGT are not known, but horses often respond to a period of rest or reduction in workload. These horses show little histologic evidence of liver damage, and other indices of liver damage and dysfunction usually are within normal limits. The stress of training may be associated with an elevated GGT. Certain trainers, often highly successful ones, appear to have a disproportionately large number of horses with elevations of this enzyme. The normal range for GGT of Thoroughbreds in race training may be slightly higher than that of normal sedentary horses.

Alkaline Phosphatase

Alkaline phosphatase (ALP) is used in most species as a marker for intrahepatic or extrahepatic obstruction of the biliary system. The enzyme is also released by osteoblasts from metabolically active bone. This may be the reason that young, rapidly growing animals normally have high levels of serum ALP, which accounts for the 100-fold higher levels in foals than in adults. Serum ALP in adult horses is 80% liver ALP and 20% bone ALP. Elevations in ALP are also reported in cases of rickets and healing fractures. The intestinal isoenzyme of

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ALP is similar to the ALP isoenzyme found in neutrophils. Elevations in the ALP activity of abdominal fluid in horses with intraabdominal disease may reflect the release of this enzyme from the neutrophils rather than being a specific marker of damage to the bowel.

ALP has been useful for evaluating liver disease in large animals, particularly in horses with pyrrolizidine alkaloid intoxication, chronic active hepatitis, and cholangiohepatitis, and in some patients with cholelithiasis. A profound elevation in ALP activity is thought to reflect periportal liver damage and biliary obstruction in these patients. A moderate to marked elevation in ALP may be observed in a wide range of disorders resulting in hepatic necrosis and intrahepatic cholestasis. Because this enzyme is not organ specific in large animals, elevations in ALP activity must be interpreted in relation to more organ-specific enzymes such as SDH and GGT.

Other Enzymes

LDH is a metalloenzyme that hydrolyzes many types of phosphate esters at an alkaline pH in the presence of zinc and magnesium ions. It is found in relatively high concentrations in a variety of organs and tissues of the body from the heart, liver, muscle, and kidney to the erythrocytes and leukocytes. An elevation in serum LDH enzyme activity must be evaluated in relation to other, more organ-specific enzymes. LDH isoenzyme analysis can be helpful in differentiating organ system damage, but the analysis is time consuming and not always available. An elevation in LDH activity is expected in hepatic necrosis and serves as an indicator of an active disease process. Extensive muscle damage and rhabdomyolysis tend to result in a more massive release of enzyme and much higher serum enzyme activity. A modest elevation in LDH may be seen in some hemolytic disorders and some cases of leukemia. Blood samples must be handled with care because hemolysis results in falsely elevated serum LDH activity.

Glutamic dehydrogenase (GLDH) and ornithine carbamoyltransferase (OTC) are two enzymes that are reported to be sensitive indicators of hepatic necrosis in ruminants. GLDH is a mitochondrial enzyme that catalyzes the conversion of glutamate to 2-oxoglutarate. Injury to the hepatocyte has to be severe enough to damage the mitochondria. It is suggestive of either hepatocyte death or sublethal hepatocyte injury. In large animals, it is more liver specific than AST and has better storage stability than SDH. OTC is a hepatic-sensitive enzyme that

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catalyzes the reaction between ornithine and carbamoylphosphate-forming citrulline and inorganic phosphate. OTC has been used mostly to evaluate fatty liver in cattle and as a prognostic indicator in abomasal displacement and fatty liver.[61] ALT is an important liver-specific enzyme that has wide application in small animals and is often included in automated chemistry profiles. This enzyme has not been useful for evaluation of liver disease in large animal species, and occasionally horses with marked rhabdomyolysis and no other evidence of liver disease show an elevation in serum ALT activity.

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Bilirubin

Bilirubin is a breakdown product of the heme component of the hemoglobin molecule and to a lesser extent of the breakdown of other porphyrin-containing compounds (e.g., myoglobulin, cytochrome P_{450}, peroxidase, catalase). Bilirubin exists in the serum in three forms (unconjugated bilirubin, conjugated bilirubin α, and bilirubin δ) and is responsible for the yellow color known as *icterus*, or *jaundice*, of the mucous membranes. Unconjugated, prehepatic, albumin-bound bilirubin is also known as *indirect-reacting bilirubin*, which used to be determined by the van den Bergh reaction; currently total bilirubin is measured by the 2,5-dichlorophenyldiazonium (DPD) method, and direct bilirubin is determined by the method of Jendrassik and Grof.[62] Indirect-reacting bilirubin must be taken up by the liver cells, where it is conjugated and then excreted in the bile. Conjugated bilirubin is known as *direct-reacting bilirubin*, as determined by the van den Bergh reaction. Horses normally have a much higher serum bilirubin level than ruminants, and hot-blooded horses have a higher bilirubin level than cold-blooded horses of the pony and draft breeds. The horse also differs from ruminants in that horses often develop moderate icterus in response to fasting or anorexia associated with many systemic diseases. The increase in the bilirubin concentration in these horses is caused almost entirely by an increase in unconjugated (indirect-reacting) bilirubin, and within a few days the bilirubin can increase from the normal range up to 6 to 8 mg/dL (103 to 137 μmol/L). Therefore the total serum bilirubin concentration is of little diagnostic value in the ill horse unless both the direct- and indirect-reacting bilirubin values are determined. However, in general terms unconjugated hyperbilirubinemia occurs when there is increased production of bilirubin or when either hepatic uptake or conjugation of bilirubin is diminished. Conjugated hyperbilirubinemia is caused by either intrahepatic cholestasis or extrahepatic bile duct obstruction.

Total serum bilirubin is elevated in animals with hemolytic anemia, and this increase is caused largely by an increase in indirect-reacting bilirubin (Box 22.18). The degree to which bilirubin is elevated in hemolytic anemia is a function of the rate of RBC destruction and the capacity of the liver to excrete the newly formed bilirubin. The total bilirubin rarely exceeds 10 mg/dL (170 μmol/L) in hemolytic anemia. An exception is the hemolytic anemia of neonatal

isoerythrolysis in newborn foals, which is often associated with marked clinical icterus. In these foals the serum bilirubin may exceed 25 mg/dL (428 μmol/L), a variable but substantial proportion of which (40% to 60%) is likely to be direct-reacting bilirubin causing kernicterus in some cases.

Box 22.18

Causes of Elevated Serum Bilirubin

Elevation of Total Serum Bilirubin

Common Causes

Hemolytic anemia
Liver failure
Secondary to systemic disease or anorexia in horses

Uncommon Cause

Chronic liver failure in cattle

Elevation of Indirect-Reacting Bilirubin

Common Causes

Secondary to systemic disease or anorexia in horses
Liver failure
Hemolytic anemia

Uncommon Cause

Chronic liver failure in cattle

Elevation of Direct-Reacting Bilirubin

Common Causes

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Liver failure
Cholelithiasis
Cholangiohepatitis
Neonatal isoerythrolysis

Uncommon Cause

Hemolytic anemia

The second major cause of clinical icterus and increased serum bilirubin is liver failure. Liver failure results in impaired uptake and excretion of bilirubin. Acute liver failure caused by hepatic necrosis results in marked to moderate increases in both direct- and indirect-reacting bilirubin. In horses with acute liver failure, bilirubin often exceeds 10 mg/dL (170 µmol/L), and this increase is caused primarily by increases in indirect-reacting bilirubin. Direct-reacting bilirubin rarely exceeds 25% of the total bilirubin in the horse, and increases of this magnitude suggest an intrahepatic or extrahepatic biliary obstruction. With chronic liver failure, icterus is more variable and total bilirubin rarely exceeds 10 mg/dL (170 µmol/L). Liver failure in ruminants, particularly chronic liver failure, is associated with a much less striking elevation in serum bilirubin than occurs in horses. In the absence of hemolytic anemia, a bilirubin value above 2 mg/dL (34 µmol/L) indicates impaired hepatic function in ruminants. Hyperbilirubinemia without clinical icterus may be observed in cattle and in sheep with fatty liver associated with ketosis/acetonemia; in such cases, the predominant pigment is unconjugated bilirubin. In horses, unconjugated hyperbilirubinemia can occur a few days after prolonged halothane anesthesia.[63]

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Glucose

Blood glucose concentration represents an equilibrium among dietary intake, hormonal interactions (insulin, glucagon, glucocorticoids, catecholamines, and growth hormone), and biochemical pathways (glycogenolysis, gluconeogenesis, and glycolysis). Glucose is an essential substrate for brain cells and erythrocytes. Major storage sites for glucose in the body are skeletal muscles and liver in the form of glycogen.

Hypoglycemia

Hypoglycemia is either the result of poor sample handling, pathologic states, or fasting. Delayed separation of serum from the blood cells may allow time for these cells to consume glucose, thus causing false low glucose levels. Fasting usually does not result in hypoglycemia except in neonatal animals (Box 22.19). Newborns have limited energy reserves, and any disease (mainly septicemia and diarrhea), injury, congenital defect, maternal rejection, agalactia, or management error that limits energy intake can result in marked hypoglycemia associated with profound depression, even coma. In calves with acute severe diarrhea, blood glucose may fall below 40 mg/dL (2.2 mmol/L) in 30% to 50% of cases.[64] One study has shown that 34% of critically ill foals are hypoglycemic.[65] Hypoglycemia may also be seen in animals with acute toxic enteritis, coliform mastitis, septicemia, and colic associated with strangulated bowel, as well as in the later stages of endotoxemia and in some horses with exhaustion after prolonged exercise, hepatic insufficiency, islet B cell neoplasia, hepatocellular carcinoma, and surreptitious injections of insulin. Hypoglycemia is a reasonably consistent feature with primary ketosis and fat cow syndrome in cattle, with pregnancy toxemia in sheep and goats, and in hyperlipemia syndrome, which is seen primarily in pregnant or lactating ponies. Rapid, semiquantitative field tests for blood glucose (Dextrostix, Boehringer Mannheim Diagnostics, Inc., Indianapolis, Ind.) or handheld human glucometers provide a practical means of early recognition of this problem. It should be pointed out that this method reads glucose concentrations slightly low compared with standard laboratory procedures by 10% to 15%.[66]

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Box 22.19

Causes of Hypoglycemia

Common Causes

Inappetence in newborns
Sepsis
Pregnancy toxemia
Endotoxic shock (late stages)
Hepatic failure

Uncommon Causes

In vitro glycolysis by red blood cells
In vitro glycolysis by eperythrozoonosis

Hyperglycemia

Hyperglycemia may be seen with excitement, transportation, or stress and probably is mediated by increases in catecholamine and glucocorticoid hormones (Box 22.20). The stress and pain of acute severe colic in horses frequently results in hyperglycemia occurring in approximately 50% of the colic cases, and elevations of blood glucose above 250 mg/dL(14 mmol/L) are associated with a poor prognosis in such cases. In one study all the animals with colic that did not survive had a mean glucose level of 234 mg/dL (13 mmol/L).[67] Endotoxemia initially results in a transient hyperglycemia that may be followed by marked hypoglycemia in the terminal stages of toxemia. The later stages of Cushing syndrome in horses are generally associated with a non–insulin-responsive hyperglycemia and glycosuria. Similar changes can be induced transiently when exogenous glucocorticoid hormones are administered at a high dose rate. Insulin-responsive diabetes mellitus rarely occurs in large animals but has been reported in association with destructive pancreatic lesions. Hyperglycemia in large animals has also been associated with iatrogenic hyperadrenocorticism, pheochromocytomas, after strenuous exercise, after

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prolonged halothane anesthesia, administration of xylazine or detomidine, during administration of glucose, endotoxemia, proximal duodenal obstruction in cattle, and pituitary pars intermedia dysfunction in horses. Hyperglycemia is rarely encountered in equine metabolic syndrome (EMS).

Box 22.20

Causes of Hyperglycemia

Common Causes

- Acute severe colic in horses
- Stress and excitement
- Cushing syndrome
- Glucocorticoid administration
- Xylazine administration

Uncommon Causes

- Overly rapid administration of dextrose
- Diabetes mellitus

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Creatinine

Creatinine is generated by muscle metabolism and derived from the cyclic use of phosphocreatine—the muscle energy store—resulting in the production of inorganic phosphate and creatine that degrades into creatinine. In the resting animal, this process occurs at a relatively constant rate. The absolute muscle mass and level of physical activity may influence the rate of creatinine production and thus the serum concentration. Starvation, with loss of muscle mass, may result in a slightly reduced serum creatinine level, whereas serum creatinine may be slightly higher in muscular, athletic individuals compared with sedentary animals. Creatinine is distributed throughout the body water and is not reused. Creatinine is normally excreted by the kidneys, primarily by glomerular filtration, and is not normally reabsorbed in the tubules. In azotemic patients a substantial part of creatinine is metabolized and excreted by nonrenal routes. Serum or urine creatinine concentrations determined by the standard alkaline picrate reaction may be falsely elevated by the presence of noncreatinine chromogenic compounds in the serum. These chromogens include glucose, fructose, ascorbic acid, hippuric acid, urea, ketones, cephalosporins, amino acids, and several other compounds. The contribution of these compounds can be reduced or eliminated, and most automated chemical laboratories use such methodology. However, if inappropriately high creatinine is reported in patients without other evidence of renal failure, the method of creatinine measurement should be ascertained.

The serum creatinine concentration provides a crude measure of the glomerular filtration rate. However, serum creatinine, like BUN, is not a sensitive or early indicator of changes in renal function. Alterations in renal blood flow caused by decreases in effective circulating fluid volume (hypovolemia) produce an elevation in serum creatinine and BUN; this can be considered a prerenal azotemia (Box 22.21). It occurs with some frequency in animals with acute enteritis, peritonitis, acute heart failure, massive blood loss, and some forms of colic and in horses with exhaustive disease syndrome. An important point is that many of these disorders initiate the release of inflammatory mediators, which may cause renal damage and impaired renal function above and beyond that associated with impaired renal blood flow and hypovolemia. Prerenal azotemia is usually seen in animals that are dehydrated and volume depleted and that have a history of loss or compartmentalization of

sodium-containing fluid. Prerenal azotemia often can be marked (creatinine level above 6 mg/dL; 530 μmol/L), but if uncomplicated, it generally responds rapidly to fluid replacement therapy. Urine production, the urine sodium concentration, and the fractional excretion of sodium are usually low, and the urine specific gravity is usually elevated. The ratio of urine to plasma urea or creatinine, as well as the urine-to-plasma ratio of osmolality, is reported to be higher in horses with prerenal azotemia compared with renal azotemia.[31] In ruminants, creatinine is a more reliable indicator of renal failure than is BUN. Urea nitrogen can be secreted in saliva and metabolized by the ruminal microflora; this frequently results in a disparity between BUN and creatinine levels in ruminants with renal failure.

Box 22.21

Causes of Elevated Creatinine

Common Causes

- Prerenal azotemia
  - Reduced renal perfusion
  - Hypovolemia
  - Congestive heart failure
  - Dehydration after endurance exercise
- Renal azotemia
  - Acute renal failure
  - Chronic renal failure
- Postrenal azotemia
  - Urolithiasis
  - Renal calculi
  - Ureteral calculi
  - Urethral calculi
- Ruptured bladder

Uncommon Causes

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- False azotemia
  - Noncreatinine chromogens in serum or plasma
- Perirenal abscess
- Renal carcinoma
- Renal dysgenesis
- Carcinoma of the bladder
- Postexhaustion multisystemic syndrome in horses
- Severe exertional rhabdomyolysis with myoglobinuria
- Severe intravascular hemolysis with hemoglobinuria
- Intoxication or poisoning
  - Heavy metal poisoning
  - Nonsteroidal antiinflammatory drug intoxication
  - Aminoglycoside intoxication

Although small increases in creatinine may be seen with progressively compromised renal function, nearly two thirds to three fourths of the nephrons must be nonfunctional before the serum creatinine level clearly exceeds the normal range. Both ARF and CRF are usually associated with elevated creatinine. ARF, especially in animals with anuria or oliguria, is usually associated with progressive daily changes in blood parameters. In contrast, blood parameters of animals with CRF tend to remain relatively constant. A transient but markedly elevated serum creatinine has been observed in some newborn foals that have no other evidence of compromised renal function. Many of these foals are born to mares that had medical problems before parturition. Alterations in placental function may allow the accumulation of creatinine in the foal's circulation. This is called *spurious hypercreatinemia* in foals, and the exact mechanism for this to date is not elucidated. In most of these otherwise normal foals, this marked elevation in serum creatinine resolves within the first few days of life; but usually fluid therapy has been used to help resolve it. There is no clinical significance to decreased serum creatinine levels.

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Blood Urea Nitrogen

The term *blood urea nitrogen* (BUN) is ingrained in the veterinary literature, despite the fact that urea nitrogen determinations usually are performed on serum (SUN) or plasma samples. This is of little consequence because the actual difference in urea concentrations of whole blood and serum or plasma is relatively small; instead of urea nitrogen, in some parts of the world, urea is measured as the whole molecule. Urea concentration in serum is approximately twice that of the BUN. Urea provides a nontoxic means of excreting ammonia generated by amino acid catabolism and the intestinal microflora. It is distributed throughout the body water. In the intestine, urea is broken down by urease, which is produced by the intestinal microflora, and the nitrogen, as ammonium ion, is recycled to the liver. Urea is excreted by the kidneys, primarily by glomerular filtration, intestine (in high concentration in horses), saliva, and sweat. Ruminants excrete urea into the gastrointestinal tract, where it is converted to ammonia and amino acids that result in protein production.

Urea production occurs almost exclusively in the liver and is synthesized by hepatocytes from ammonia derived from amino acid catabolism. Blood or serum urea is dependent on hepatic urea production and renal tubular flow rate. Urea excretion is not solely determined by GFR because once in the tubules, at rapid flow rates, 40% of the urea is reabsorbed. However, at slow flow rates, as occurs in hypovolemia, 60% is reabsorbed, thus increasing urea levels in serum or blood. Liver failure is frequently associated with a decrease in BUN (Box 22.22). Urea nitrogen tends to be low in nursing animals because of their high fluid intake and urine output and their anabolic state of rapid growth. Urea nitrogen may be reduced slightly in animals given anabolic steroids or fed diets low in protein but of adequate calorie content.

Box 22.22

Causes of Decreased Blood Urea Nitrogen

Common Causes

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Liver failure
Neonatal animals (blood urea nitrogen is normally lower than in adults)

Uncommon Causes

Low-protein diet
Anabolic steroid administration

Starvation or other processes that result in rapid tissue catabolism such as fever, burns, exercise, and increased protein digestion (e.g., hemorrhage in the gastrointestinal tract) decrease GFR, or corticosteroid administration may result in modest increases in BUN (Box 22.23). BUN, along with creatinine, provides a crude index of altered renal function in most animal species. BUN is influenced more directly by dietary factors than is creatinine, and creatinine is generally a better guide to renal failure. This is particularly true in ruminants, in which BUN may remain within normal limits in animals with marked impairment of renal function.

Box 22.23

Causes of Increased Blood Urea Nitrogen

Common Causes

Prerenal azotemia
Reduced renal perfusion
    Hypovolemia
    Congestive heart failure
    Dehydration after endurance exercise
Renal azotemia
    Acute renal failure
    Chronic renal failure
Postrenal azotemia
    Urolithiasis
    Renal calculi

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- Ureteral calculi
- Urethral calculi
- Ruptured bladder

Uncommon Causes

- Gastrointestinal bleeding
- Perirenal abscess
- Renal carcinoma
- Renal dysgenesis
- Carcinoma of the bladder
- Postexhaustion multisystemic syndrome in horses
- Severe exertional rhabdomyolysis with myoglobinuria
- Severe intravascular hemolysis with hemoglobinuria
- Intoxication or poisoning
  - Heavy metal poisoning
  - Nonsteroidal antiinflammatory drug intoxication
- Aminoglycoside intoxication

The BUN-to-creatinine ratio has been used to try to aid in differentiating prerenal azotemia and intrinsic renal azotemia based on the proportion of increases of each substance in the ratio. However, given the wide variation in BUN and creatinine concentration along with the differences of species, it is not a reliable indicator. In the horse a BUN-to-creatinine ratio of less than 10 : 1 is expected with ARF; when it exceeds 15 : 1, CRF is more likely. With these considerations in mind, the discussion of prerenal, renal, and obstructive causes of azotemia in the creatinine section apply to BUN.

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Serum Protein

The serum or plasma proteins consist of albumin and globulin fractions. These are discussed in detail in Chapter 26.

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Urinalysis

Urinalysis can be an extremely useful diagnostic tool, providing information on many systemic disorders. Ideally urine is collected at the same time as blood for clinical chemistry and before any treatment is administered. The interpretation of certain abnormalities in urine (e.g., glucosuria, ketonuria) is facilitated by concurrent knowledge of chemistry results. Urinalysis is essential in the evaluation of primary renal disease. Urine normally is collected as a voided sample or after catheterization. Voided urine samples are safe and easy to collect but are easily contaminated. Catheterization is preferred for bacteriologic evaluation, but the resultant mild trauma may result in a slight increase in urine RBCs and protein. Because of the urethral diverticulum at the level of the pelvis, it is difficult to successfully catheterize male ruminants. Urethral obstruction is common in male small ruminants, and percutaneous aspiration may be the only way to obtain a urine sample in affected animals. Urinalysis should be performed as soon after collection as possible (within 30 minutes) to avoid degeneration of cellular elements, changes in pH, or bacterial overgrowth (cytolysis, crystallization). If this is not possible, samples should be refrigerated but brought back to room temperature before tests. Urine volume and composition are influenced by feed and water intake, salt supplementation, environmental factors, exercise, stress, systemic disease, and drug administration. Urine samples collected after administration of a diuretic are dilute and unsuitable for routine urinalysis. The tranquilizer xylazine, which is often used to assist in the catheterization of male horses, may alter the results of the urinalysis because it produces diuresis as a result of glycosuria and specifically also kaliuresis.

When urinalysis is performed, the color should be noted along with the organoleptic characteristics of the urine such as the fact that an adult horse's urine has a lot of mucus and becomes cloudier at the end of urination.

Specific Gravity

Specific gravity is defined as the weight of urine relative to the weight of distilled water (=1 at 4° C [60° F]). The normal specific gravity of serum is approximately 1.008 to 1.012. The urine specific gravity is an indicator of renal function because it reflects the action of the renal tubules and collecting ducts on the glomerular filtrate by providing an estimation of the number of particles

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dissolved in the urine (e.g., whether the urine is concentrated or diluted via serum). It is usually measured by refractometry on urine supernatant. Urine dipsticks with reagent pads for estimating the urine-specific gravity in humans should not be used for this purpose in domestic animals because a poor correlation has been reported compared with refractometry in large animals.[68] Normal animals have the capacity to dilute their urine specific gravity to less than 1.010 and to concentrate greater than 1.050. The normal range reported for most adult large animals is 1.020 to 1.050. Suckling neonatal animals normally produce very dilute urine with a specific gravity below 1.010. Although this could represent immature renal function, it more likely reflects their high-volume fluid intake, because normal neonates can concentrate their urine if fluids are withheld.

Failure to produce concentrated urine, as reflected by a specific gravity below 1.020, in the face of dehydration is an indication of altered renal function, which may be caused by primary renal disease, diabetes insipidus, medullary washout, or nephrogenic diabetes insipidus. With severe and chronic sodium depletion, tubular sodium may be insufficient to sustain normal countercurrent mechanisms for water resorption. This process is called *medullary washout* and has been reported as a cause of polyuria in lactating dairy cattle on a salt-deficient diet. At least 50% of renal function must remain for highly concentrated urine to be produced. Isosthenuria, a urine-specific gravity that remains around 1.010 despite variation in hydration, occurs when renal disease progresses to the point at which renal function is reduced to less than a third of normal. Altered renal function in these animals is usually reflected by a moderate to marked elevation in BUN and creatinine levels and by other changes in the urinalysis. Hyposthenuria occurs when the specific gravity remains below 1.010; this indicates altered release of or response to antidiuretic hormone, which occurs with diabetes insipidus, medullary washout with chronic sodium depletion, nephrogenic diabetes insipidus, psychogenic polydipsia, and chronic liver failure in some horses. Hypersthenuric urine occurs when SG is greater than 1.030 to 1.035, and it occurs commonly in states of dehydration. It is also common in horses fed a high percentage diet of hay and in those living in hot environments.

pH

The normal range of urine pH for adult herbivores is alkaline, with values ranging from 7 to 9. Neonatal foals tend to have slightly acidic urine with a pH

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below 7. Aciduria in adults may be seen in postrace samples collected from racehorses, after prolonged fasting, with ketosis in ruminants, or in response to metabolic acidosis. A paradoxic aciduria is seen in ruminants with hypochloremic, hypokalemic metabolic alkalosis and has been recently attributed to K concentration changes in the urine.[69] Urine pH is also influenced by the cation-anion balance of the diet. The SID of urine, specifically the potassium concentration, has the strongest influence on urinary pH in dairy cattle and most likely in horses as well.[69]

Protein

Protein is not normally detected in urine, although a false-positive protein reaction may be noted on urine dipsticks as the sample of herbivores is normally strongly alkaline. Urine with a positive reaction for protein on dipsticks should be checked for protein by a chemical method (urine protein sulfosalicylic acid precipitation test). Proteinuria should be evaluated in relation to the other findings in the urinalysis. Persistent and strongly positive reactions for protein in the absence of leukocytes, RBCs, bacteria, or casts suggest glomerular protein loss, as in glomerulonephritis or amyloidosis. The presence of bacteria and leukocytes with proteinuria suggests sepsis in the urinary tract, whereas hemorrhage or inflammation in the urogenital tract is often associated with proteinuria. A transient postexercise proteinuria is observed in performance horses at submaximal or maximal levels of exertion.

Mild proteinuria is associated with tubular diseases, whereas severe proteinuria is more commonly related to glomerular damage. Urine urea to protein ratio has been used in horses to evaluate more accurately the protein concentration in urine. In horses this ratio is < 1.0 in normal animals.[70]

Glucose

Glucose is not found in the urine of normal large domestic animals unless the blood glucose level increases above the renal threshold, which is thought to be approximately 100 to 140 mg/dL (5.5 to 7.7 mmol/L) in ruminants and approximately 160 to 180 mg/dL (8.8 to 10 mmol/L) in horses. The causes of hyperglycemia and glycosuria were described in a previous section; they include Cushing syndrome, stress, and catecholamine or glucocorticoid hormone release. Hyperglycemia and glycosuria can be created iatrogenically when glucose-

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containing fluids are administered at an excessive rate. Glycosuria is a fairly consistent finding in sheep with enterotoxemia type D (pulpy kidney). The presence of glycosuria without hyperglycemia strongly suggests renal tubular damage resulting from a toxic or ischemic insult.

Ketone Bodies.

The presence of ketone bodies in urine is abnormal in large animals. In horses, ketonuria is uncommon because they are poorly ketogenic; however, it is common in ruminants that are in negative energy balance, early-lactation cows, and pregnant ewes (pregnancy toxemia). Measurement of these ketone bodies in blood, milk, and urine has been used to diagnose and monitor clinical and subclinical ketosis in cattle.

Occult Blood

Both myoglobin and hemoglobin give a positive reaction on urine occult blood dipsticks. In most instances proteinuria shows a positive result as well. A tentative clinical impression sometimes can be formed to differentiate myoglobin from hemoglobin in dark urine if the sample is shaken vigorously in a closed, transparent container. Myoglobin tends to produce a brown foam, whereas hemoglobin produces a reddish foam. Hemoglobinuria caused by intravascular hemolysis is generally associated with clinical and hematologic evidence of hemolytic anemia. Hematuria may result in a positive occult blood reaction if lysis of some of the intact RBCs has occurred. This is likely to happen if the urine is very dilute or if it is held at room temperature for an extended period before analysis. False-positive reactions can occur if microbial peroxidase or oxidizing contaminants are present. Hematuria should be confirmed by cytologic examination of the urine sediment.

Myoglobin

Myoglobinuria should be associated with clear clinical and clinicopathologic evidence of extensive muscle damage. The ammonium sulfate precipitation method of differentiating hemoglobin from myoglobin is imprecise and frequently fails to detect myoglobin in the dark, coffee-colored urine of horses with severe rhabdomyolysis. Accurate differentiation of these compounds in urine requires more sophisticated procedures.

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Cells

Cytologic evaluation of urine is deemed essential in cases of unexplained fever, hyperfibrinogenemia, weight loss, and complicated neurologic disease. The normal range for cells is generally considered to be up to five RBCs or leukocytes per high-power field. An increased number of erythrocytes indicates hematuria, which may be caused by neoplasia, trauma, inflammation, or coagulopathy. Pyuria, an increase in urine leukocytes, indicates an inflammatory process; when associated with bacteriuria, it indicates a septic process in the urinary tract. The presence of sheets or rafts of transitional cells suggests neoplasia. Foals' urine has relatively more epithelial cells compared with urine of adult animals.

Casts

Casts are accumulations of protein (Tamm-Horsfall glycoprotein) and cellular material that form in the renal tubules, and when present in the urine, they indicate renal damage or tubular disease. Casts can consist of erythrocytes, leukocytes, or renal tubular cells. As cellular degeneration proceeds, the cell type is more difficult to determine and the casts become granular and then waxy. Hyaline casts are noncellular and are formed from mucoprotein. They may be seen with glomerulonephritis, fever with passive congestion, or severe dehydration with altered renal blood flow. However, casts are soluble in alkaline pH, which is the usual urine pH of large animals, thus making their documentation in urine sediment difficult. If present, they indicate tubular involvement.

Crystals

The crystalline structures in the urine of large animals are those usually associated with an alkaline urine. Calcium carbonate crystals normally are found in abundance in horse urine, particularly if the horse has been fed alfalfa hay. Triple phosphate and calcium oxalate crystals are frequently observed in relatively small numbers. In foals calcium oxalate crystals are more prevalent. The major crystals involved in urolithiasis of feedlot cattle is struvite ($MgNH_4PO_4 \cdot 6H_2O$). In the western United States, silicate stones are most common in livestock under range conditions. Carbonate and oxalate stones are common causes of urolithiasis in small flocks of backyard sheep and goats fed

alfalfa hay.

Bacteria

Bacteria are sometimes seen in small numbers in voided urine samples and may represent surface contaminants. Bacterial infections of the urinary tract are usually associated with significant pyuria. When this is noted, a catheterized sample (horse) or clean midstream catch (ruminant) should be obtained for Gram stain, culture, and sensitivity testing. Results from ruminant samples must be carefully interpreted because male ruminants routinely urinate within the prepuce, thus heavily contaminating samples. Fortunately, urinary tract infections in male ruminants and horses are rare.

Urine Creatinine Clearance Ratio[71]

Urinary electrolyte excretion is affected by a variety of factors, including dietary intake, alterations in renal function, and specific hormones that regulate renal electrolyte excretion. Determination of electrolyte concentrations from randomly collected urine samples is easily done and can be clinically useful when these concentrations are compared with serum concentrations. The presence of substantial amounts of sodium in the urine of an animal with hyponatremia suggests excessive renal sodium loss caused by altered renal function or hormonal control. However, marked variation in the rate of urine production can lead to serious problems in the interpretation of urine electrolyte concentrations. The standard physiologic methods of determining renal electrolyte clearance are complicated by the need for quantitative urine collection and are not well suited to most practical clinical situations. One means of overcoming these difficulties is expression of the renal electrolyte clearance relative to the endogenous creatinine clearance. Expression of the renal clearance as a ratio eliminates the need for quantitative urine collection. This derived value is known as the *creatinine clearance ratio* or the *fractional excretion* (FE), and it is calculated by the following formula:

$$\mathrm{FE} = \mathrm{Urine/(X)Serum/(X)} \times \mathrm{Serum/(C)Urine/(C)} \times 100$$

where *X* represents the electrolyte concentration and *C* represents the creatinine

concentration.

The FE fluctuates somewhat during the day in relation to physical activity and feed and water intake. However, under standardized conditions, there is close agreement between the FE determined from single random samples of blood and urine and that based on samples quantitatively collected during a 12- to 24-hour period.[31] The FE of electrolytes has a wide range of normal values. The principal sources of this variation are differences in dietary intake and environmental or experimental conditions. The FE of electrolytes has been useful for detecting specific dietary deficiencies or imbalances. Dietary salt deficiency is associated with an extremely low FE of sodium and chloride, whereas the plasma concentration of these ions generally remains within normal limits. In a similar fashion, dietary calcium and phosphorus imbalances seldom are reflected by the serum concentrations of these ions. Calcium deficiency and phosphorus excess are relatively common dietary problems in large animals and result in a low FE for calcium and a high FE for phosphorus. There are technical problems with the determination of the urine calcium concentration in horses because of their normally alkaline urine and the resultant precipitation of calcium carbonate in the urine. Mixed urine samples from horses must be acidified (hydrochloric acid can be used) to solubilize the calcium. It has favored the use of fractional excretion of phosphorus to diagnose nutritional secondary hyperparathyroidism in horses.

Increases in the FE of sodium are noted with renal tubular damage and impaired sodium resorption. The sodium FE increase has been a useful indicator for the differential diagnosis of prerenal azotemia, which almost invariably results in a low sodium FE, from the azotemia caused by primary renal disease, in which the FE for sodium often is markedly increased. Specific criteria of interpretation in horses have been suggested. In the case of the FE_{Na+}, the reference range varies between 0.01% and 1.0%. A level lower than 0.02% indicates Na^+ conservation by the kidney; an increase may result from excess of dietary intake, Addison disease, and more commonly tubular insufficiency. FE_{K+} normal values are considered between 15% and 80%; values below 15% have been associated with potentially recurrent myositis and chronic laminitis. FE_{Cl}^- has not been reported with a diagnostic value. FE_{Ca++} normal values are between 0% and 33% when used in association with FE_P. The reference values for FE_P have been reported up to 0.5% and as a sensitive diagnostic indicator of calcium and phosphorus balance in horses. An increase above 0.5% is mainly considered

an indicator of possible nutritional secondary hyperparathyroidism, renal tubular disease, or pseudohyperparathyroidism.

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Useful Websites for Clinical Chemistry

Acid-base program, Stämpfli. [WWW page] http://www.uoguelph.ca/~pjf/1.4.html.

Online clinical pathology textbook. Cornell University College of Veterinary Medicine, Animal Health Diagnostic Center. http://www.eclinpath.com.

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*Contributions to previous editions by Gary P. Carlson are acknowledged.

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• CHAPTER 23

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Collection and Submission of Samples for Hematologic and Cytologic Evaluation*

Catherine J. Benson, Consulting Editor

Proper test choice and sample acquisition, preparation, and submission of specimens to a reference laboratory are crucial to making diagnostic decisions to aid in patient care and treatment. Numerous preanalytic factors such as incorrect labeling of samples, presence of interfering substances, use of incorrect collection tubes for a certain test, sampling the wrong tissue for cytologic evaluation, and samples with low cellularity can all impact data results and interpretation. Hematologic and cytologic sample quality can also be affected by the ambient storage temperature and the time interval between collection and evaluation. Care should be taken to eliminate or minimize sources of preanalytic errors to ensure high-quality laboratory results. Hematologic data and cytologic results should always be interpreted in light of the clinical history, physical examination findings, and other diagnostic testing such as imaging or histopathology results. If there are questions regarding sample collection, submission, or handling, contact the reference laboratory.

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Venipuncture Site and Technique

Venipuncture site should be based on where it is safe to access a vein that will not collapse when blood is withdrawn.[1] In horses and goats, the jugular vein is most commonly used for blood collection. Alternative but often less recommended sites for venipuncture in horses resulting from safety concerns include the facial sinus, cephalic vein dorsal to carpus, and saphenous veins. In cattle, the jugular and coccygeal (tail) vein can be accessed. Less often, the mammary vein is used due to the risk of personal injury and of hematoma formation at the blood draw site. Depending on the venipuncture site, species, and size of the animal, an 18- to 22-gauge needle and syringe or a double-ended needle and sheath or Vacutainer system (Becton Dickinson and Co., Franklin Lakes, N.J.) with a collection tube can be used to collect blood after the site of the venipuncture is cleaned with an absorbent and 70% isopropyl alcohol and the vein is digitally occluded. After venipuncture, digital pressure should be applied over the site where the needle is removed to prevent hematoma formation.[2] Good technique is important because traumatic venipuncture can result in platelet activation and clumping of platelets. This can falsely decrease the measured platelet count generated by hematology analyzers. Clotted samples will necessitate a recollection.

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Handling and Transportation of Samples

Samples for complete blood cell counts (CBCs) should be submitted in ethylenediaminetetraacetic acid (EDTA) tubes, filled to the proper amount indicated on the container, and inverted several times to ensure proper mixing of the blood with the anticoagulant. Too little blood may result in a falsely decreased packed cell volume (PCV) caused by shrinkage of red blood cells (RBCs). When collecting for both a CBC and serum biochemical profile, blood should first be put in an EDTA tube and then in a serum tube that does not contain anticoagulant. Care must be taken to avoid contaminating the blood remaining in the syringe with retrograde flow of EDTA blood because this can alter calcium and potassium values on the serum biochemistry.[1] Samples for coagulation testing (prothrombin time and activated partial thromboplastin time) should be placed in a sodium citrate tube at a proportion of 1 : 9 with blood. Concurrently sending blood from a clinically healthy animal can serve as a control to help assess artifacts if there is a delay in sample transit. Samples for plasma fibrinogen concentration can be submitted as whole blood in either EDTA tubes or in sodium citrate tubes.[3] Consultation with the reference laboratory is advised because the technique used by a specific laboratory will dictate how the sample should be submitted.

Blood smears for microscopic evaluation should be made immediately to minimize artifacts from deterioration of cells. Blood smears should also routinely be made for manual differential counting, to check for platelet clumps that may be artificially decreasing the platelet count and to evaluate for hemoparasites and atypical cells that would otherwise not be detected. Hematologic results are affected by the ambient storage temperature and the time interval between collection and evaluation. If samples cannot be run immediately on a hematology analyzer, they should be refrigerated. In cattle and goats, if blood samples are handled appropriately, hemoglobin concentration, RBC count, and total white blood cell (WBC) count are stable for the first 24 hours after collection. PCV is stable for up to 12 hours with mild increases at 24 hours.[4] Blood should not be frozen because this will rupture the cells.[1] Shipping and packaging of samples for hematologic and cytologic evaluation should follow guidelines from the reference laboratory.

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General Principles for Submitting Cytology Samples

Proper labeling of slides with patient name and sample site will help ensure accurate record keeping and minimize error. Slides that have one edge that is frosted should be labeled with a pencil with the patient identification and sample site before the sample is put on the slides. This is preferred to “permanent” ink marking pens because the preparation stains and fixatives used in the staining process will often wash off the ink.[5] When submitting samples to a diagnostic laboratory, it is important to fill out a complete history including the patient signalment; tissue sampled; location; duration of the mass or illness; a description of the mass or lesion (color, three-dimensional size for masses, shape, texture, consistency, etc.); other important clinical findings (bloodwork, surgical, imaging results); and differential diagnoses. Minimizing the amount of blood present on slides is also important, especially in cases in which inflammation is suspected. In these cases, cytologic findings may need to be interpreted in conjunction with CBC data to aid in determining if inflammation is present or if leukocytes are blood associated. Samples can be obtained by fine-needle aspirate, impression smears, scrapings, and swabs of lesions. Depending on the sample, blood smear, squash, or roll preparations can be made to spread cells on the slide. Once air-dried samples are made, they can be stained with Romanowsky type stains (Wright-Giemsa, Diff-Quik, etc.). Although stained slides may be submitted, it is also important to include some unstained slides when submitting samples to a diagnostic laboratory. Keep unstained cytology slides/samples away from formalin during surgery and when biopsy samples are also being prepared and submitted because the formalin fumes can render cytology samples nondiagnostic.[5]

Bone Marrow Aspirates and Core Biopsy Samples

Please refer to Chapter 28.

Lymph Node Aspirates

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Lymph nodes should be manually stabilized, and aspiration or nonaspiration techniques as have been described elsewhere can be used to collect cells.[6] In both techniques, the needle should be maintained within the lymph node and it can be redirected to obtain cells from multiple areas. Peripheral lymph node samples tend to be highly cellular because the lymphocytes tend to exfoliate well and blood contamination is often mild. As a result, it is important to spread the cells out well, which can be done by the squash preparation or blood smear technique. Evaluation of poorly stained thick areas should be avoided. Lymphocytes are often fragile and are prone to lysis; it is therefore important to be gentle when making the preparations. Evaluate only intact lymphocytes because ruptured lymphocytes can appear larger than normal, leading to the misdiagnosis of lymphoma.

The main differential diagnoses for lymph node aspirates include normal lymph node, reactive lymph node, various inflammations (lymphadenitis), lymphoma, and metastatic neoplasia.[6] Normal lymph nodes are composed of mostly small lymphocytes with fewer medium and large lymphocytes. Low numbers of plasma cells, macrophages, eosinophils, nondegenerate neutrophils, and rare mast cells can also be seen. In reactive lymph nodes, small lymphocytes still predominate, but there are increased numbers of medium and large lymphocytes and plasma cells. Reactive lymph nodes are a relatively nonspecific finding in animals with antigenic stimulation, inflammation, or neoplasia. Increased numbers of degenerate or nondegenerate neutrophils, macrophages, or a combination of these 2 cell populations should prompt evaluation for an underlying infectious organism (bacteria or fungus) and for metastatic neoplasia. Eosinophilic inflammation can be seen with parasitic disease, some fungal diseases, and allergic conditions.[6]

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General Principles for Various Body Fluids

Fluid should be collected in both EDTA tubes and tubes without anticoagulant. EDTA tubes are best for cell counts, cytologic examination, and total protein measurement, whereas tubes lacking anticoagulant are used for biochemical and microbiological analysis. At least 1 mL of fluid should be collected in each tube if possible.[7] It is recommended to consult with a reference laboratory for the most current guidelines regarding sample collection, storage, and transport for culturing abdominal, pericardial, thoracic, cerebrospinal, and synovial fluids. Direct preparations of highly cellular turbid fluid or concentrated preparations of low cellularity clear fluid should be made as soon as possible, especially when a delay in transportation cannot be avoided. Cytologic findings that may be seen with delayed processing of fluid samples include erythrophagocytosis, vacuolization of large mononuclear cells, and pyknosis. Bacterial overgrowth can also impair interpretation.[8]

Body Fluid Analysis

Abdominocentesis, thoracocentesis, and pericardiocentesis techniques have been previously described in horses[2,7,9,10] and cattle.[2,11] Gross impressions such as the amount of fluid, color, and consistency/turbidity should be evaluated. Normal fluid should be light straw-colored and clear.[11] Samples from thoracic, abdominal, and pericardial fluid should be evaluated on the basis of total nucleated cell counts (TNCC) and total protein concentration (TP). The TNCC and TP together aid the clinician in classification of the fluids into the broad categories of transudate, modified transudate, and exudate. However, microscopic analysis should always be performed to evaluate the cellular differential and to assess for neoplastic cells, organisms, or evidence of chronic hemorrhage. In adult horses, samples from the thoracic cavity are generally transudates if they have fewer than 5000 cells/µL and a total protein of less than 2.5 g/dL, are modified transudates with 5000 to 15,000 cells/µL and a total protein of 2.0 to 5.0 g/dL, and are exudates if the TNCC is greater than 10,000 to 15,000 cells/µL and the TP is greater than 3.0 to 3.5 g/dL.[12] Samples from the peritoneal cavity are similar except that modified transudates can have a TNCC

of 1500 to 10,000 cells/µL and a TP of 2.5 to 3.5 g/dL.[8] TNCC and TP interpretations vary widely in cattle, and appropriate references should be consulted.[11] Further information can be obtained in Chapters 30–32.

Synovial Fluid Analysis

Collection of synovial fluid should be aseptic, and a full description of techniques is found in other sources.[13,14] Synovial fluid should be placed in an EDTA tube for cytologic analysis, as well as in a serum tube if a mucin clot test or cultures are desired.[13] The gross and microscopic appearance of the synovial fluid, total nucleated cell count, protein concentration, viscosity, and mucin quality (assessed via the mucin clot test) are all important features to analyze when making interpretations of joint fluid.[14] Normal joint fluid is clear to pale yellow, does not clot, and is highly viscous. Although there is some variability in the TNCC obtained from normal joints from various locations, generally synovial fluid samples are of low cellularity (often < 1000 cells/µL). Hemarthrosis should be distinguished from blood contamination, and the overall differential cell count should be interpreted in light of the degree of blood contamination. Overall, the percentage of neutrophils in normal joint fluid should not be greater than 10% in the absence of significant blood contamination. Large mononuclear cells and small lymphocytes predominate in normal joint fluid. Neutrophilic inflammation can be due to septic inflammation, immune-mediated disease, or acute trauma. Bacterial cultures and sensitivities are recommended to rule out infectious organisms. Immune-mediated diseases affecting joints are relatively uncommon in the horse.[13]

Bronchoalveolar Lavage/Tracheal Washes

Please refer to Chapter 31.

Cerebrospinal Fluid Analysis

Please refer to Chapter 35.

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• CHAPTER 24

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Alterations in the Erythron

Leslie C. Sharkey, Erin N. Burton, Consulting Editors

MAJOR ALTERATIONS

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The *erythron* is defined as the total mass of circulating erythrocytes and their precursors within the bone marrow. Alterations in the erythron are common in clinical practice, and developing an approach to interpreting these abnormalities

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is important. Initial assessment of the erythron is generally accomplished through evaluation of a complete blood cell count (CBC). Major alterations include anemia and erythrocytosis. On the basis of CBC results, clinical history, and physical examination, additional diagnostic tests can then be selected to further characterize these abnormalities in an attempt to identify a specific underlying pathophysiologic process.

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Erythropoiesis

Erythrocytes are produced in the bone marrow, largely under the influence of erythropoietin (EPO), with increased erythropoiesis occurring in response to blood loss or hemolysis. Horses are unique in that equine erythrocytes generally remain in the bone marrow until fully mature before they are released into circulation. As a result, peripheral indicators of regeneration used in other species such as polychromasia and reticulocytosis are typically absent or unreliable in the horse. Detection of relatively low numbers of reticulocytes in the peripheral blood of anemic horses, however, has been described using an automated hematology analyzer, which may be a more sensitive means of detecting these cells than the manual methods used previously.[1-5]

Laboratory Evaluation of Erythrocytes

General reference intervals are presented for common erythrocyte parameters in large animals (Table 24.1); however, laboratory- or instrument-specific reference intervals should be used whenever possible. A complete discussion of age- and breed-related influences on erythrocyte parameters is found elsewhere.[6-8] What follows is a brief review of common laboratory evaluators of the erythron.

TABLE 24.1

Reference Intervals for Ruminants and Horses

	Cattle[a]	Sheep[b]	Goats[b]	Horses (Hot-Blooded Breeds)[b]	Horses (Cold-Blooded Breeds)[b]
PCV/HCT (%)	22-33	27-45	22-38	32-53	24-44
Erythrocytes ($\times 10^6$/µL)	5.1-7.6	9-15	8-18	6.8-12.9	5.5-9.5
Hemoglobin (g/dL)	8.5-12.2	9-15	8-12	11-19	8-14
MCV (fL)	38-50	28-40	16-25	37-58.5	—
MCHC (g/dL)	36-39	31-34	30-36	31-38.6	—
Reticulocytes	—	0	0	—	—

[a]From George JW, Snipes J, Lane M: Comparison of bovine hematology reference intervals from 1957-2006. *Vet Clin Pathol* 39:138, 2010.

[b]From Jain NC: *Schalm's veterinary hematology,* ed 4, Philadelphia, 1986, Lea & Febiger.

PCV, Packed cell volume; *HCT,* hematocrit; *MCV,* mean cell volume; *MCHC,* mean cell hemoglobin concentration.

Hematocrit, Packed Cell Volume, Hemoglobin Concentration, and RBC Count

Hematocrit (HCT), packed cell volume (PCV), hemoglobin (Hgb) concentration, and red blood cell (RBC) count are all ways of quantifying the erythrocytes in peripheral blood, and these measures tend to increase (erythrocytosis) or decrease (anemia) together. HCT and PCV are similar in that they describe the percentage volume of whole blood occupied by erythrocytes. The HCT is a calculated value and is a function of the mean cell volume and RBC count, whereas the PCV is determined by centrifugation of whole blood in a

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microhematocrit tube. The Hgb concentration and RBC count are measured values generated by hematology analyzers.

Mean Cell Volume

The mean cell volume (MCV) is directly measured by most hematology analyzers and represents the average erythrocyte volume. An increased MCV can be the result of a regenerative anemia in the ruminant and occasionally in the horse. Decreased MCV is seen with iron-deficiency anemia (also copper) and can also be seen in healthy calves and foals.[3,4,7,8]

Mean Cell Hemoglobin Concentration and Mean Cell Hemoglobin

The mean cell hemoglobin concentration (MCHC) is the cellular Hgb concentration per average erythrocyte and is calculated from the Hgb concentration and HCT. A decreased MCHC can be seen in ruminants with regenerative anemias, but this would not be expected in the horse. Both horses and ruminants can have decreased MCHC as the result of iron-deficiency anemia. A low MCHC has also been reported in calves (<5 weeks) as an age-related change.[5,9] Increased MCHC values are almost always false increases and can be seen with hemolyzed, severely icteric, or lipemic samples or those with large numbers of Heinz bodies present.

Mean cell hemoglobin (MCH) is the amount of hemoglobin per average erythrocyte (in picograms). This is a calculated value based on the Hgb concentration and the RBC count. In general, MCH is affected in a similar manner to MCHC. MCHC, however, is considered more useful since it takes into account cell volume and is thus preferred over MCH when evaluating the erythron.

Erythrocyte Morphology

Anisocytosis.

Anisocytosis is variation in erythrocyte size. A mild to moderate degree of anisocytosis can be seen in healthy ruminants, whereas mild anisocytosis can be seen in healthy horses. Increased anisocytosis can be the result of a regenerative

anemia in ruminants and occasionally in horses. The RBC distribution width (RDW) provides an index of the variation in erythrocyte size.

Polychromasia.

Polychromatophilic erythrocytes are slightly immature, macrocytic cells that appear blue-gray on a Wright-stained blood smear because of their retained cytoplasmic ribonucleic acid. An increase in these cells in the peripheral blood is indicative of a regenerative response in ruminants. Increased polychromasia is not expected in horses because in this species erythrocytes complete maturation in the bone marrow before release into circulation. Polychromatophilic erythrocytes are relatively analogous to reticulocytes; however, not all reticulocytes will be viewed as polychromatophilic erythrocytes on a peripheral blood smear. Thus a reticulocyte count is considered a more objective and sensitive means of detecting a regenerative response, particularly if performed by an automated hematology analyzer. If a reticulocyte count is not available, a moderate to large degree of polychromasia observed on a peripheral blood smear is a good indicator of a regenerative response in ruminants.

Howell-Jolly Bodies.

Howell-Jolly bodies are small, dark, circular structures consisting of nuclear material within erythrocytes. These can be present in small numbers in healthy horses. Increased numbers can be associated with regenerative anemias and splenic dysfunction. Note that in cattle Howell-Jolly bodies can appear similar to *Anaplasma marginale* and can be difficult to differentiate from these organisms in some cases.

Nucleated Erythrocytes.

Nucleated erythrocytes (nRBCs) are not normally seen in the peripheral blood of healthy horses or ruminants. In ruminants, small numbers associated with regenerative anemias can sometimes be present but should be accompanied by a significant degree of polychromasia. Bone marrow damage (e.g., toxic damage, hypoxia, neoplasia) can also result in circulating nRBCs. The presence of nRBCs and basophilic stippling in the absence of significant anemia should prompt consideration of lead toxicity (more common in ruminants).

Basophilic Stippling.

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Basophilic stippling is seen as multiple small basophilic inclusions within erythrocytes and is the result of staining of ribosomal aggregates. Basophilic stippling is often seen in association with regenerative anemias in ruminants. As described previously, it can also be seen in cases of lead toxicity.

Heinz Bodies.

Heinz bodies form in erythrocytes as a result of oxidative damage that leads to precipitation of Hgb. They are recognized on Wright-stained blood smears as rounded, pale pink staining structures that protrude from the edge of erythrocytes. Heinz bodies can be confirmed by visualizing them with use of a new methylene blue stain that stains Heinz bodies as dark, rounded structures associated with the erythrocyte membrane. Ingestion of oxidants such as wilted red maple leaves, onions, and garlic; phenothiazine; *Brassica* spp.; and copper toxicity can result in Heinz body formation in large animals. Heinz body formation causes affected erythrocytes to be more susceptible to both intravascular and extravascular hemolysis.

Eccentrocytes.

Eccentrocytes also form as a result of oxidative damage. In the case of eccentrocytes, oxidative damage results in partial fusion of the erythrocyte membrane causing displacement of Hgb contents to one side of the erythrocyte. Oxidants listed as causes of Heinz bodies can also result in eccentrocyte formation. Eccentrocytes have also been reported in horses with glucose-6-phosphate dehydrogenase deficiency and flavin adenine dinucleotide deficiency. Both are rare erythrocyte enzyme deficiencies that result in the affected animal's erythrocytes being more susceptible to oxidative damage by endogenous or exogenous sources.[10]

Rouleaux.

Rouleaux formation is seen as linear stacking of erythrocytes on a peripheral blood smear. Rouleaux formation is common in healthy horses. A consequence of rouleaux formation is that equine blood samples tend to have a relatively high erythrocyte sedimentation rate, and as a result whole blood samples should be thoroughly mixed before evaluation. Rouleaux formation is uncommon in healthy ruminants but can be seen with increased plasma proteins such as fibrinogen and immunoglobulins. Increases in these plasma proteins can also

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enhance rouleaux formation in horses. In any species, care should be taken to differentiate rouleaux from erythrocyte agglutination.

Agglutination.

Agglutination is the result of surface-associated antibody on erythrocytes causing clumping. When viewed microscopically on a peripheral blood smear, aggregation produces clumps of erythrocytes that are described as having the appearance of “clusters of grapes.” Agglutination is significant in that it is indicative of immune-mediated hemolytic anemia (IMHA). In some cases, it may be difficult to differentiate prominent rouleaux from agglutination. A saline dilution test can be done to confirm true agglutination. This test is accomplished by diluting whole blood with saline and evaluating a wet preparation. Rouleaux will disperse with dilution, whereas true agglutination will persist. Generally a 1 : 2 to 1 : 4 dilution will disperse rouleaux; however, occasionally higher dilutions are needed. Agglutination confirmed by a saline dilution test is generally considered to preclude the need for Coombs testing. Agglutination in the horse has also been described as a result of treatment with unfractionated heparin.[11]

Erythrocyte Parasites

A variety of erythrocyte parasites can be detected by review of peripheral blood smears. Examples include *Mycoplasma* spp., *Anaplasma* spp., *Theileria* spp., and *Babesia* spp.[12]

Coombs Test

The Coombs test or direct antiglobulin test is used to detect erythrocyte surface-associated antibody. Positive Coombs test results support a diagnosis of IMHA (including neonatal isoerythrolysis). A negative Coombs test result, however, does not rule out IMHA because this test is known to have a relatively low sensitivity (i.e., many false negatives).

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Evaluation of the Anemic Patient

Anemia develops from one or more of three main pathophysiologic mechanisms: blood loss, hemolysis, and Decreased erythrocyte production. More specific causes are often categorized in terms of these three main mechanisms (Boxes 24.1 and 24.2). Specific causes of anemia are also sometimes grouped in terms of whether they cause regenerative or nonregenerative anemia. Anemias that are the result of blood loss or hemolysis are typically regenerative, whereas those that are the result of decreased erythrocyte production will be nonregenerative.

Box 24.1

Causes of Anemia in the Horse

Common Causes

Blood Loss

Trauma
Surgery
Ectoparasites (lice, ticks)
Endoparasites (strongyles)
Gastrointestinal bleeding (ulcers, neoplasia)
Immune-mediated thrombocytopenia
Equine purpura hemorrhagica

Hemolysis

Neonatal isoerythrolysis
Red maple leaf toxicosis
Equine infectious anemia

Decreased Erythrocyte Production

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- Anemia of inflammatory disease (chronic inflammation, neoplasia)
    - Chronic abscessation
    - Chronic pneumonia or pleuritis
    - Lymphoma

Less Common Causes

Blood Loss

- Bleeding diathesis associated with disseminated intravascular coagulation (DIC)
- Guttural pouch mycosis
- Hematuria
- Hemoabdomen
- Moldy sweet clover toxicosis
- Rodenticide toxicity (brodifacoum)
- Congenital coagulation factor deficiencies (hemophilia A)
- Platelet function disorders (von Willebrand disease, Glanzmann thrombasthenia)

Hemolysis

- Fragmentation (DIC, vasculitis)
- Immune-mediated hemolytic anemia (idiopathic)
- Immune-mediated hemolytic anemia (secondary)
    - Clostridial infections
    - Penicillin therapy
    - Lymphoma
- Theileriosis/Babesiosis
- Onion toxicosis
- Phenothiazine toxicosis
- Glucose-6-phosphate dehydrogenase deficiency

Decreased Erythrocyte Production

- Anemia of chronic renal failure
- Bone marrow neoplasia (leukemia, metastatic neoplasia)

Myelofibrosis
Aplastic anemia (idiopathic, drugs including phenylbutazone)

Box 24.2

Causes of Anemia in Ruminants

Common Causes

Blood Loss

Trauma
Endoparasites (*Haemonchus* sp. and liver flukes[14])
Ectoparasites (lice, ticks)
Abomasal ulcers, bleeding
Acute severe Salmonella hemorrhagic diarrhea
Oak toxicosis with hemorrhagic diarrhea
Hemorrhagic bowel syndrome (jejunal hemorrhage syndrome)

Hemolysis

Bovine viral diarrhea virus vaccine
Anaplasmosis
Brassica spp. toxicosis
Leptospirosis
Onion toxicosis
Clostridial infections
Chronic copper toxicosis
Water deprivation or salt poisoning followed by ingestion of fresh water

Decreased Erythrocyte Production

Anemia of inflammatory disease (chronic inflammation, neoplasia)
Chronic pneumonia
Chronic abscessation
Johne's disease

Chronic bovine virus diarrhea infection
Lymphoma

Less Common Causes

Blood Loss

Hemorrhagic enteritis
Hemoabdomen
Bleeding diathesis associated with disseminated intravascular coagulation
Moldy sweet clover toxicosis
Caudal vena cava syndrome
Severe acute pyelonephritis
Bovine viral diarrhea and mucosal disease complex[22]

Hemolysis

Babesiosis/theileriosis
Mycoplasma spp. infection
Postparturient hemoglobinuria
Immune-mediated hemolytic anemia

Decreased Erythrocyte Production

Anemia of chronic renal failure
Bracken fern toxicosis (also hemorrhage in enzootic hematuria)
Radiation toxicosis
Myelofibrosis (pygmy goats)
Myelophthisis

A regenerative response in the ruminant is best identified by a moderate to marked degree of polychromasia or a reticulocytosis. Note that following an acute episode of hemorrhage or hemolysis in ruminants, it takes 2 to 4 days for the bone marrow to respond by beginning to release increased numbers of polychromatophilic cells/reticulocytes into circulation. Peak bone marrow response generally occurs within 7 days. This time frame must be kept in mind

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when assessing peripheral blood for indicators of regeneration. Other findings that can support the regenerative nature of an anemia would be an increased MCV, a decreased MCHC, basophilic stippling, nRBCs, increased numbers of Howell-Jolly bodies, and increased anisocytosis. It may take 2 to 4 weeks or more in ruminants for the HCT to return to normal after an episode of hemorrhage or hemolysis.

As noted previously, classifying an anemia as regenerative or nonregenerative is more difficult in the horse because of the relative absence of peripheral indicators of regeneration (e.g., polychromasia, reticulocytosis). In these patients, serial CBCs can be performed to detect increasing HCT over time. Similar to ruminants, it takes about 4 days for the bone marrow to begin to respond to an episode of hemorrhage or hemolysis. Mild increases in the MCV can be seen in some horses with regenerative anemias. The bone marrow response to anemia in horses is relatively sluggish compared with other species, and it may take up to 1 to 2 months following severe hemolysis or 2 to 3 months following severe hemorrhage for HCT values to return to normal.[13] In both horses and ruminants, the regenerative response to hemolysis is generally considered to be somewhat more vigorous than the response to hemorrhage. It is suggested that this may be in part due to the fact that in hemolysis, iron (from Hgb) is not lost from that body and is then made available for production of new erythrocytes. Evaluation of bone marrow can also be performed in horses to evaluate for a regenerative response. Enumeration of polychromatophilic cells and reticulocytes in the bone marrow, assessment of overall cellularity, and calculation of the myeloid-to-erythroid ratio (M:E) are used to determine if a regenerative response is present. Excessive hemodilution of the bone marrow sample and the variable M:E ratios present in normal animals, however, can complicate interpretation in some cases.

Blood Loss

Immediately following an episode of acute blood loss, the HCT and plasma protein concentration are generally within the reference interval. The HCT in horses can actually increase mildly above baseline in some cases as a result of splenic contraction. It is only after fluid shifts have occurred from the interstitial space into the vasculature that the HCT and plasma protein concentration begin to decrease. Increased thirst and renal conservation of free water contribute to the fluid shifts that will continue to occur over a 24- to 48-hour period as

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vascular volume is restored. Hypoproteinemia concurrent with anemia is supportive of hemorrhage as the cause, assuming there are no other significant sources of protein loss (e.g., gastrointestinal [GI] or renal). Evidence of regeneration should also be present if sufficient time has passed since the episode of blood loss. In some cases, the source of blood loss is obvious (e.g., trauma, surgery, severe epistaxis), whereas in other cases more abstruse sources of blood loss must be investigated. Evaluation of the patient for endoparasites, ectoparasites, hematuria, GI blood loss (e.g., ulcers, neoplasia), and hemoabdomen is warranted in these instances. Chronic blood loss, commonly from parasitic causes,[14] GI ulcers, or GI neoplasia, can result in an iron deficiency anemia. Supportive findings for iron deficiency anemia are decreased MCV, decreased MCHC, hypochromic erythrocytes, and a mild degree of erythrocyte fragmentation (i.e., schistocytes and keratocytes). Iron-deficiency anemia is initially regenerative but, if ongoing, can become poorly regenerative to nonregenerative. Hypoproteinemia may be present; however, protein concentration is within the reference interval in some animals because protein loss is compensated by increased production by the liver. Iron deficiency anemia can also occur in young foals and calves as a result of low dietary intake.[15] An iron panel can be performed to confirm iron deficiency.

Hemolysis

Hemolysis results in a regenerative anemia often with a normal to increased plasma protein concentration. Erythrocyte morphology should be assessed for evidence of Heinz bodies, eccentrocytes, schistocytes, erythrocyte parasites, and agglutination. Hemolyzed plasma and hemoglobinuria are supportive of an intravascular hemolytic process, whereas icterus and hyperbilirubinemia support extravascular hemolysis. Hemoglobinuria, however, should be differentiated from hematuria and myoglobinuria, and liver disease and anorexia (in the horse) should be ruled out as causes of the icterus and hyperbilirubinemia. Feed and/or pasture should be evaluated if ingestion of an oxidant is suspected. Additional diagnostics to consider in cases of hemolytic anemia are Coombs testing (IMHA) and Coggin's testing (equine infectious anemia).

Decreased Erythrocyte Production

Anemia of inflammatory disease, often the result of infection, inflammation, or

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neoplasia, is the most common cause of a mild to moderate nonregenerative anemia. An inflammatory leukogram and hyperfibrinogenemia would be supportive of the presence of a systemic inflammatory response. Chronic renal failure can also result in a nonregenerative anemia of variable severity (moderate to severe) and can initially be assessed by a serum biochemical profile and urinalysis. Feed and/or pasture conditions and drug history should be determined to prioritize other causes of anemia resulting from decreased erythrocyte production. Bone marrow evaluation is indicated to investigate unexplained nonregenerative anemias, especially when other cytopenias are present.

Erythrocytosis

Erythrocytosis (polycythemia) refers to an increased RBC count, Hgb concentration, and HCT. Erythrocytosis can be either relative or absolute in nature (Box 24.3). In general, relative erythrocytosis is far more common than absolute and these causes should be considered or ruled out first. With relative erythrocytosis, there is no actual increase in total body erythrocyte mass; however, hemoconcentration or splenic contraction causes apparent increases in these measures in the peripheral blood. Hemoconcentration is most often due to dehydration and loss of plasma volume (e.g., diarrhea, excessive sweating, water deprivation, diuresis). Endotoxic shock can also result in hemoconcentration because of increased vascular permeability and subsequent fluid shifts from the intravascular to extravascular space. In both cases, plasma volume is decreased, effectively concentrating the erythrocytes in circulation. With dehydration, increased plasma protein concentration and clinical evidence of dehydration (e.g., skin tent, tacky mucous membranes, sunken eyes) would be supportive. Epinephrine-mediated splenic contraction as the result of excitement, pain, fright, or vigorous exercise can also cause a relative erythrocytosis as a result of redistribution of relatively high HCT splenic blood into the peripheral circulation. This is most often seen in the horse. Plasma protein concentration is not expected to increase with splenic contraction as compared with dehydration. Erythrocytosis caused by splenic contraction is a transient change and typically normalizes within a few hours if the inciting stimulus has been removed.

Box 24.3

Causes of Erythrocytosis in Large Animals

Relative Erythrocytosis

Dehydration
Endotoxic shock
Splenic contraction

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Absolute Erythrocytosis

Primary

Primary erythrocytosis

Secondary Appropriate

Chronic pulmonary disease
Right-to-left cardiovascular shunting
Residence at high altitude

Secondary Inappropriate

Erythropoietin-secreting neoplasms
Renal pathology causing local hypoxia

Absolute erythrocytosis occurs when there is a true increase in total erythrocyte mass as a result of increased erythropoiesis and can be primary or secondary in nature. Absolute erythrocytosis is considered secondary when it is in response to increased erythropoietin (EPO) levels or activity. This can be an appropriate physiologic response to chronic hypoxemia (e.g., chronic pulmonary disease, right-to-left cardiovascular shunting, or animals living at high altitude); however, tumor production of EPO or EPO-like substances or renal pathology causing local tissue hypoxia can result in a secondary erythrocytosis in the absence of systemic hypoxemia. Primary absolute erythrocytosis is considered a chronic myeloproliferative disease (primary erythrocytosis or polycythemia vera) where erythropoiesis occurs independent of EPO. There are rare reports of primary erythrocytosis in the horse.[16] Absolute erythrocytosis of unknown cause has also been described in a herd of Jersey calves and in a Japanese black heifer.[17]

Clinical evaluation of animals with an erythrocytosis should first begin by considering causes of relative erythrocytosis because these are much more common. If dehydration, shock, and splenic contraction are ruled out and if the increased HCT persists over time without response to fluid therapy, then the erythrocytosis may be considered absolute. Arterial blood gas, thoracic

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radiographs, and echocardiography can help to identify decreased cardiorespiratory function and systemic hypoxia as the cause. Neoplasia (e.g., lymphoma, hepatoblastoma, hepatocellular carcinoma) and renal disease should also be ruled out before considering the erythrocytosis primary in nature.[18-21] Bone marrow aspiration and biopsy are generally not helpful in differentiating causes of absolute erythrocytosis (i.e., primary vs. secondary) because erythroid hyperplasia would be expected in both cases. Serum EPO concentrations would be expected to be normal to low in primary absolute erythrocytosis and increased in secondary absolute erythrocytosis. This assay, however, is not widely available, and there is likely some overlap in EPO levels among patients with primary and secondary absolute erythrocytosis, making interpretation difficult in some cases.

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• CHAPTER 25

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Alterations in the Leukogram*

Leslie C. Sharkey, Daniel A. Heinrich, Consulting Editors

MAJOR ALTERATIONS

Neutrophilia, 431
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Interpretation of the leukogram in the context of the clinical history, the physical examination, and the rest of the minimum laboratory database (complete blood cell count, serum biochemical data, and urinalysis) can provide valuable insights into the diagnostic process in large animal species. Often leukogram data are used to evaluate patients for the presence of inflammation or hematopoietic neoplasia. Careful attention to sample collection and handling (see Chapter 23) will help to ensure high-quality results. Key components of the leukogram include the total white blood cell (WBC) count, differential cell counts including the absolute numbers of each leukocyte type, and a microscopic evaluation of the blood film. Blood film evaluation is necessary to visually verify the WBC count, to generate the differential, and to evaluate the leukocytes for important morphologic abnormalities that contribute to the diagnostic interpretation of the

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quantitative data. Although the newer automated hematology analyzers will generate leukocyte differentials for numerous species, the Clinical and Laboratory Standards Institute still considers the manual differential cell count to be the reference standard.[1] Microscopic examination of the blood film for the presence of toxic change, band neutrophils, reactive changes in lymphocytes, neoplastic and atypical cells, and organisms as well as for validation of the total leukocyte count is required for a full characterization of the leukogram. For instance, in cases of equine acute lymphoid and myeloid leukemia, only small numbers of circulating atypical cells may be present, highlighting the importance of peripheral blood film review.[2]

The concurrent measurement of acute phase proteins such as fibrinogen can augment the diagnostic interpretation of leukogram data.

When evaluating the leukogram, clinicians should remember that each data set is a snapshot in time of a dynamic system in which the numbers of cells in the circulation reflect a balance between the release of cells from the bone marrow and egress of cells into the tissues. Serial monitoring of patients often provides more information than a single time point. It is also important to keep in mind that the numbers of cells trafficking in the circulation may not be reflective of the tissue content of cells; therefore cytology or biopsy of tissues may be necessary to confirm the presence of inflammation or hematopoietic neoplasia.

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Leukocytes

Leukocytes are partitioned into granulocytes (neutrophils, eosinophils, basophils) and mononuclear cells (lymphocytes, monocytes). In postnatal life the main source of hematopoiesis is the bone marrow, except for lymphocytes, which migrate from the bone marrow to tissues such as the lymph nodes, spleen, and mucosal-associated lymphoid tissue after birth. The following sections briefly describe the biology of each type of leukocyte as well as the interpretation of high and low values and common morphologic abnormalities. Note that the reference intervals for some leukocyte subtypes encompass zero, making the detection of low values difficult and therefore the interpretation of questionable clinical significance (Table 25.1). Although reference intervals are provided here for guidance, clinicians should use laboratory-specific reference intervals because of the potential effect of instrumentation and geographic variation on leukocyte parameters. Other factors that influence reference intervals in large animal species include age, reproductive and lactation status, and husbandry issues that are explored in further detail elsewhere.[3-5]

TABLE 25.1

Normal Values for Leukogram Data (Adult Animals)

	Cattle	Sheep	Goats	Horses
White blood cells (1 ×10³/μL)	4.9-12	4-12	4-13	5.4-14.3
Neutrophils (1 ×10³/μL)	1.8-6.3	0.7-6	1.2-7.2	2.3-8.6
Bands (1 ×10³/μL)	Rare	Rare	Rare	0-1
Lymphocytes (1 ×10³/μL)	1.6-5.6	2-9	2-9	1.5-7.7
Monocytes (1 ×10³/μL)	0-0.8	0-0.75	0-0.55	0-1
Eosinophils (1 ×10³/μL)	0-0.9	0-1	0.05-0.65	0-1
Basophils (1 ×10³/μL)	0-0.3	0-0.3	0-0.12	0-0.29
Neutrophil/lymphocyte (N/L) ratio	0.4-2.34	0.3-0.7	0.6-3.6	0.8-2.8

Neutrophils

Neutrophils develop from hematopoietic stem cells in a process that usually takes about 6 days under the influence of an array of cytokines. Some species can accelerate the process in situations of increased demand, but that capacity

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appears to be limited in cattle.[6] There is a storage pool of neutrophils in the marrow; however, once that is depleted, earlier precursors, including band neutrophils and sometimes metamyelocytes or even myelocytes, may be observed in the peripheral circulation in a phenomenon known as a “left shift.” Neutrophils circulate for only a few hours after release, existing either in the circulating pool where they can be measured or in the marginal pool along the endothelial surface where they are not recovered during blood sample collection. Shifts between the circulating and marginal pools in response to hormonal mediators can result in rapid changes in neutrophil numbers measured in the leukogram.

Neutrophils migrate into tissues, especially the gastrointestinal and respiratory tracts and the skin, through selectin-mediated rolling followed by integrin-mediated adhesion of neutrophils to the endothelium. Transmigration between or through endothelial cells allows neutrophils to enter the tissues, where they will bind to chemokines that direct them toward targets in the tissue. Receptor-mediated phagocytosis of bacteria and other particulate matter is followed by proteolytic digestion and/or the respiratory burst using granule contents. Neutrophils also amplify local inflammation and interact with cells of the adaptive immune response.[7] These mechanisms can result in damage to normal tissues in addition to the killing of infectious agents, contributing to acute respiratory distress syndrome and multiple organ failure. Senescent neutrophils undergo apoptosis in tissues and are cleared by tissue macrophages.

Some of the morphologic abnormalities that can be relevant to the interpretation of the leukogram in large animals include toxic change, Pelger-Huët and pseudo–Pelger-Huët anomalies, and the presence of intracellular organisms, including *Anaplasma phagocytophilum*. The common components of toxic change include cytoplasmic basophilia and vacuolization and the presence of Döhle bodies in the cytoplasm of neutrophils; rarer manifestations include nuclear abnormalities, toxic granulation, and increased cell size (both larger neutrophils and giant neutrophils). Larger and giant neutrophils can be induced by endotoxin infusion and can be misclassified as monocytes by automated hematology analyzers and potentially by inexperienced microscopists, indicating the benefit of slide review by an experienced hematologist.[8] It is important to be aware that normal foals can have intracytoplasmic purple granules (staining primary granules) for as long as 30 days after birth and that these should not be confused with toxic granules.[9] Toxic change is subjectively evaluated during the blood film evaluation and graded as 1+ to 4+. These changes occur in the

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neutrophil cytoplasm during the development in the marrow and signal the likelihood of inflammation; toxic change may be accompanied by a left shift. To further support the importance of blood film review when evaluating the overall leukogram, the presence of band neutrophils and more severe toxic change is associated with the presence of systemic inflammatory response syndrome (SIRS) and poorer outcome in horses admitted for emergency care,[10] and higher band neutrophil counts are associated with nonsurvival in equine neorickettsiosis.[11] Pelger-Huët anomaly is an incidental asymptomatic congenital condition in which a defect occurs in the segmentation of leukocyte nuclei, giving the impression of a severe left shift in the absence of toxic change or other signs of inflammation.[12,13] In contrast, pseudo–Pelger-Huët is pathologic hyposegmentation that occurs as a result of severe inflammation and is accompanied by toxic change and inflammatory disease. *A. phagocytophilum* is a tick-borne bacterium common to humans as well as small and large animal species that survives in neutrophils by avoiding the bactericidal mechanisms.[14] Organisms are most likely to be identified microscopically in acute infection, when serologic methods for detection may still be negative.

Eosinophils

Eosinophil development in the marrow is very similar to that of neutrophils, although it occurs under the influence of distinctive cytokines. Normally eosinophils spend a short time in the circulation before entering the tissues using similar mechanisms to neutrophils, although the numbers in the peripheral blood are usually quite small. The tissue survival time of eosinophils is usually short; however, eosinophils may persist in tissues for longer periods if appropriate survival factors are present. Recirculation is even possible under some conditions. Although eosinophils have the capacity for phagocytosis, more prominent functions include defense against parasites by externalization of granule contents and modulation of inflammation, particularly allergic and hypersensitivity disorders. Eosinophils are primarily tissue dwelling cells, so numbers of cells in the circulation may not accurately reflect tissue eosinophilia.

Basophils

Basophil development largely parallels that of eosinophils, although it is associated with a specific growth factor repertoire. Basophils are the least

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numerous leukocyte in the peripheral blood under most conditions, where, like other granulocytes, they circulate briefly before entering tissues through similar mechanisms. With even less phagocytic and bactericidal potential than eosinophils, basophils are important in hypersensitivity responses and allergic conditions, which they mediate through release of their granule contents into the local environment. The accuracy of basophil counts by automated analyzers has been questioned.

Lymphocytes

Lymphocytes encompass a heterogeneous group of mononuclear leukocytes fundamental to the adaptive immune response, although some, like natural killer cells, are aligned with innate immunity. Circulating lymphoid cells are generally divided into natural killer cells, B cells, and T cells, with an expanding number of T-cell varieties being characterized, each with a specific function. Advanced diagnostic techniques such as flow cytometry are required to identify cells from different lymphocyte subsets, which are not routinely distinguished during blood film evaluation. All originally derive from bone marrow stem cells; however, T cells complete maturation in the thymus and participate in cell-mediated immunity, whereas B cells develop in the marrow and other peripheral tissues to eventually disperse throughout the body to effect humoral immunity. Unlike most leukocytes in the peripheral blood, lymphocytes have significant potential for proliferation. Lymphocytes continually recirculate among tissues in a process called “trafficking,” which is most relevant for T cells because B cells release antibodies that are carried by the circulation to relevant sites. At any given time, only a tiny fraction of an animal's lymphocytes is present in the circulation, so the peripheral blood lymphocyte count is not reflective of total body lymphoid activity. Likewise, advanced diagnostic techniques are required to characterize the lymphocyte subsets in circulation, which may change with different pathologic processes. In many large animal species, it is not uncommon to see circulating lymphocytes with small, eosinophilic cytoplasmic granules.

Monocytes

Monocytes develop in the bone marrow and enter the circulation, where they persist longer than other leukocytes. Like other leukocytes, monocytes migrate into tissues; however, they have the potential to differentiate into a variety of

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macrophage subtypes (e.g., Kupffer cells, alveolar macrophages, microglial cells) depending on the local microenvironment. Monocytes can reenter the circulation from the tissues. Unlike mature granulocytes that are postmitotic, monocytes have a limited capacity for replication in tissues. The major functions of macrophages once in the tissues include inhibiting the growth of intracellular pathogens, antigen processing, removal of dead cells and debris, control of iron metabolism, and complex regulation of the inflammatory response. Depending on the stimuli, macrophages can develop into proinflammatory M1 macrophages or antiinflammatory M2 cells.[15]

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Principles of Leukogram Interpretation

As noted previously, the absolute numbers of leukocyte subtypes are interpreted in the context of appropriate reference intervals. If there are questions about the validity of available reference intervals, clinicians should consider the option of submission of samples for comparison from one or more age- and sex-matched unaffected individuals sharing the husbandry conditions and genetics of the patient of interest. Although individual abnormalities are discussed in the following sections, integration of all leukogram data to identify diagnostic patterns is often the best approach.

Neutrophilia

Although bacterial infection is the most common cause of neutrophilia in large animal species, nonbacterial infectious agents such as *Blastomyces dermatitidis* infection in alpaca,[16] noninfectious inflammatory processes such as traumatic tissue damage, surgery, foaling in horses,[17] and immune-mediated hemolytic anemia can also cause increased neutrophil concentrations (Boxes 25.1 and 25.2).[18] A left shift and toxic change provide additional evidence of an inflammatory cause for neutrophilia, but they may not always be present, especially with mild or chronic compensated inflammation. In fact, normal neutrophil numbers do not exclude infectious or inflammatory diseases because the numbers of circulating cells do not reflect tissue activity in all conditions. Neutrophilia can signal the presence of otherwise difficult-to-detect processes such as extrapulmonary *Rhodococcus equi* infection in foals,[19] musculoskeletal *Corynebacterium pseudotuberculosis* infection,[20] meningitis or meningoencephalomyelitis in horses,[21] liver abscesses and cholangiohepatitis in dairy cattle,[22,23] leukoencephalomalacia and eosinophilic myocarditis in horses,[24,25] and endocarditis in rams.[26] Stress resulting from causes such as transport and changes in housing can be another important cause of neutrophilia in cattle.[27] Marked neutrophilia occasionally follows a period of neutropenia induced by inflammation (overshoot effect), and very rare genetic causes such as bovine leukocyte adhesion deficiency have been documented. Some authors advocate the use of a neutrophil/lymphocyte ratio to augment the interpretation of absolute neutrophil and lymphocyte numbers on the basis that ruminants have

been described to have greater numbers of lymphocytes than neutrophils in the circulation under normal circumstances. Recent information on bovine leukocyte reference intervals suggests that clinicians should exercise caution with that approach and consider laboratory- and herd-specific information when interpreting the ratio.[28]

Box 25.1

Causes of Neutrophilia in Horses

Common Causes

Excitement, exercise
Stress, exogenous corticosteroid administration
Chronic pneumonia, pleuritis
Strangles (*Streptococcus equi* infection)
Chronic peritonitis, abdominal abscess
Other internal abscessation
Chronic salmonellosis or colitis
Thrombophlebitis
Purpura hemorrhagica (vasculitis)

Less Common Causes

Bacterial endocarditis
Cellulitis
Pyelonephritis
Chronic hepatitis, cholangiohepatitis
Cholelithiasis
Lymphosarcoma
Meningitis, meningoencephalitis
Other internal neoplasia
Pituitary adenoma (equine Cushing's syndrome)
Autoimmune hemolytic anemia
Granulocytic leukemia

Systemic fungal infections

Box 25.2

Causes of Neutrophilia in Ruminants

Common Causes

Stress, exogenous corticosteroid administration
Chronic pneumonia
Chronic traumatic reticuloperitonitis
Peritonitis
Internal abscessation
Caseous lymphadenitis (O, C)
Mycoplasmal or chlamydial polyarthritis (O, C)
Chronic pyelonephritis
Chronic metritis
Liver abscesses
Enteritis
Umbilical abscessation
Chronic salmonellosis
Septic arthritis

Uncommon Causes

Autoimmune hemolytic anemia
Toxins
Pregnancy toxemia (O, C)
Bovine granulocytopathy syndrome

C, Caprine; *O*, ovine.

Neutropenia

Endotoxemia results in rapid redistribution of neutrophils from the circulating

pool to marginal pool and tissues, resulting in neutropenia followed by fast-onset neutrophilia.[8] Neutropenia resulting from bone marrow depletion is often observed in large animal species during the first 24 to 48 hours of an acute inflammatory episode, especially in cattle (Boxes 25.3 and 25.4).[29] Persistent neutropenia is a poor prognostic sign or may indicate bone marrow pathology if other peripheral cytopenias are present. Neutropenia at a single time point may also have prognostic significance; for example, neutropenia in foals 2 weeks of age or younger when admitted to an intensive care unit (ICU) was associated with nonsurvival.[30] Transient viral infections in cattle, such as bovine viral diarrhea virus and bluetongue virus, can cause neutropenia, as can some tick-borne diseases. As for any species, toxic damage to the marrow or bone marrow necrosis, fibrosis, or neoplasia can result in generalized peripheral cytopenias, including neutropenia. Recent work identified neutropenia without toxic change in 10 of 12 horses with acute leukemia in conjunction with at least one other cytopenia and circulating blasts.[2] Alloimmune neonatal neutropenia has been reported in horses.[31]

Box 25.3

Causes of Neutropenia in Horses

Common Causes

Acute salmonellosis
Acute toxic colitis
Acute peritonitis (ruptured viscus)
Gram-negative septicemia, endotoxemia
Neonatal septicemia
Acute pleuritis
Acute metritis
Proximal enteritis (duodenitis, proximal jejunitis)
Equine influenza
Equine herpesvirus type 1 infection

Less Common Causes

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Equine ehrlichial colitis (Potomac fever, *Ehrlichia risticii* infection)
Equine ehrlichiosis (*Anaplasma phagocytophilum* infection)
Idiopathic aplastic anemia
Equine viral arteritis
Radiation toxicosis
Myelophthisic disease (e.g., leukemia)
Alloimmune neonatal neutropenia

Box 25.4

Causes of Neutropenia in Ruminants

Common Causes

Gram-negative septicemia, endotoxemia
Septic metritis
Septic (coliform) mastitis
Diffuse peritonitis
Ruptured uterus with peritonitis
Ruptured abomasal ulcer
Acute salmonellosis
Acute pneumonia
Toxemia- or toxin-induced bone marrow suppression
Fat cow syndrome (fatty liver)
Clostridial infection

Uncommon Causes

Bovine virus diarrhea
Bracken fern toxicosis
Trichloroethylene toxicosis
Radiation toxicosis
Idiopathic aplastic anemia

Eosinophilia

Eosinophilia is not common in large animal species, even when parasitism can be demonstrated (Boxes 25.5 and 25.6). This may be related to the tissue predilection of eosinophils and the relatively short transit time from marrow to target tissue. However, marked eosinophilia has been reported, such as secondary to *Sarcocystis fayeri* infection in horses[32] and demodicosis in cattle.[33] Rare hypereosinophilic syndromes that are accompanied by peripheral eosinophilia have been described; an example is idiopathic chronic eosinophilic pneumonia in horses.[34] Paraneoplastic eosinophilia resulting from lymphoma has been reported in multiple species. Although eosinopenia may characterize the corticosteroid response in most species, it is difficult to recognize because the lower limit of the reference interval is often zero.

Box 25.5

Causes of Eosinophilia in Horses

Uncommon Causes

Internal parasitism
Cutaneous habronemiasis
Systemic hypersensitivity reaction
Lymphosarcoma
Eosinophilic leukemia

Box 25.6

Causes of Eosinophilia in Ruminants

Uncommon Causes

Milk allergy
Atypical interstitial pneumonia
Acute bovine pulmonary emphysema
Sarcocystosis

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Toxoplasmosis
Migrating parasite larvae, such as:
- Lungworms
- Ascarids
- Flukes
- *Trichostrongylus* spp.
- *Hypoderma* spp.
- *Parelaphostrongylus* spp.

Basophilia

Basophilia is rare in large animal species and is often attributed to hypersensitivity responses. It has been reported in association with certain snake envenomation in horses,[35] and acute basophilic leukemia was recently reported in a calf; however, circulating cells in peripheral blood were blasts and not terminally differentiated basophils.[36] Basopenia is not recognized as clinically significant.

Lymphocytosis

Lymphocytosis characterizes an epinephrine response (especially in young horses) as well as antigenic exposure (Boxes 25.7 and 25.8). The lymphocytosis caused by antigenic stimulation may be accompanied by morphologic changes in lymphocytes, including reactive lymphocytes that have increased amounts of cytoplasm, cytoplasmic basophilia, increased azurophilic granules, or larger cell size. Spontaneous lymphoid leukemias, both acute and chronic in nature, are described sporadically in horses, with chronic forms potentially lacking cytopenias[37] and bovine leukemia virus causing persistent lymphocytosis in a third of infected cattle and leukemia in approximately 4%.[29]

Box 25.7

Causes of Lymphocytosis in Horses

Common Cause

Excitement, exercise

Uncommon Causes

Lymphocytic leukemia
Equine infectious anemia

Box 25.8

Causes of Lymphocytosis in Ruminants

Persistent lymphocytosis (bovine leukemia virus infection)
Lymphocytic leukemia
Chronic infections (pneumonia, peritonitis, pericarditis, liver abscess)

Lymphopenia

The most common cause of lymphopenia in large animal species is corticosteroid effects, although the acute phase of systemic infectious diseases may also be associated with a transient period of lymphopenia (Boxes 25.9 and 25.10). Rarely, congenital combined immunodeficiency syndromes, especially in Arabian and Arabian-cross foals, cause severe lymphopenia and global depletion of lymphoid tissues.

Box 25.9

Causes of Lymphopenia in Horses

Common Causes

Stress, exogenous corticosteroid administration
Equine influenza
Equine herpesvirus type 1 infection
Endotoxemia, septicemia

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Acute peritonitis (gastrointestinal rupture)

Less Common Causes

Malnutrition, starvation
Equine viral arteritis
Combined immunodeficiency disease

Box 25.10

Causes of Lymphopenia in Ruminants

Common Causes

Stress, exogenous corticosteroid administration
Gram-negative septicemia, endotoxemia
Septic mastitis
Diffuse peritonitis
Ruptured abomasal ulcer
Acute pneumonia
Infectious bovine rhinotracheitis

Uncommon Causes

Bovine virus diarrhea
Immunodeficiency

Monocytosis

Monocytosis can be seen with inflammation or tissue necrosis, or occasionally as part of a stress leukogram. Because the reference intervals for monocytes approach or include zero, monocytopenia is not a diagnostically useful observation (Box 25.11).

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Box 25.11

Causes of Monocytosis in Large Animals

Uncommon Causes

Granulomatous disease
Chronic bacterial infections

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Approach to Interpretation of the Leukogram in Horses

Reference intervals for equine patients are often wide due to the inclusion of a range of ages and breeds; the benefits of using breed- or age-specific reference intervals must be balanced against the preference for reference intervals generated by the laboratory performing the testing.[38] As an approximation, 20,000 leukocytes/µL indicates moderate leukocytosis, 30,000/µL indicates marked leukocytosis, and greater than 30,000/µL is considered extreme. Marked rebound neutrophilia can be observed after an episode of neutropenia resulting from neutrophil depletion caused by acute inflammation or endotoxemia. Foals often have greater absolute numbers of neutrophils and lower numbers of lymphocytes than adult horses for the first several months of life. Variable effects of training on leukocyte counts have been reported.

Epinephrine-mediated (physiologic) leukocytosis is observed more frequently in horses than in many other species, particularly in young warm and hot bloods and horses that are not habituated to transport or handling. This type of leukocytosis is typically characterized by a mild mature neutrophilia and a moderate lymphocytosis that persists for about 20 to 30 minutes. In contrast, the corticosteroid leukogram is less age or breed specific and includes a moderate mature neutrophilia with no left shift or toxic change, lymphopenia, eosinopenia, and inconsistent monocytosis. Corticosteroid leukograms are more persistent than physiologic leukocytosis and frequently can be superimposed on inflammatory leukograms because of the stress of illness.

Leukemias are rare but have been reported in horses. Lymphocytic leukemia is the most common, frequently associated with high lymphocyte counts and/or immature lymphocytes. Other forms of myeloid leukemia may present with large numbers of atypical cells originating from any myeloid lineage or relatively small numbers of circulating atypical cells. The presence of multiple cytopenias may indicate further assessment of bone marrow in patients with small numbers of circulating atypical cells.[2] Disruption of the hematopoietic microenvironment by proliferating neoplastic cells often suppresses the production of other cell lines.

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Approach to Interpretation of the Leukogram in Ruminants

Most sources report that neutrophils predominate in neonatal calves and lambs, with a reversal of this ratio about a week after birth.[29] One study examining reference interval data in Holstein cows longitudinally from 1957 through 2010 suggests that, over time, mean neutrophil counts have increased while other leukocyte counts have dropped.[28] A survey of other laboratories suggested that this observation had been made elsewhere but was not universal. Potential causes hypothesized include genetic selection, changes in management practices, and decreased prevalence of viral pathogens such as bovine viral diarrhea and bovine leukosis virus. Because a predominance of neutrophils compared with lymphocytes regardless of whether absolute cell counts deviate from the reference intervals has been used as an indicator of inflammatory disease in cattle, these findings may be significant to ruminant leukogram interpretation. In light of these findings, clinicians should be especially attentive to the source of reference intervals provided by laboratories.

Corticosteroid leukograms are relatively common in ruminants, as opposed to the changes associated with excitement, which are rare. Stress leukograms are commonly observed in cattle, sheep, and goats in the periparturient period. Stress leukogram changes are often superimposed on inflammation. As described previously, cattle have a sluggish marrow response to increased demand for neutrophils, resulting in the frequent observation of neutropenia in the first 24 to 48 hours after an acute inflammatory stimulus. Persistent neutropenia of more than 3 to 4 days indicates marrow suppression or inability of the marrow to respond to excessive tissue demands. As in the horse, rebound neutrophilia may ensue, often accompanied by a significant left shift that may include myelocytes and metamyelocytes in addition to band neutrophils. The left shift will resolve as neutrophil numbers increase with marrow compensation for increased demand. In chronic or low-grade inflammation, there may be no abnormalities in the leukogram, in which case evaluation of acute phase proteins may be helpful. The leukogram responses of sheep to inflammation generally mirror those of the bovine, whereas goats tend to respond more like small animal species with less frequent periods of leukopenia in response to inflammation.

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• CHAPTER 26

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Alterations in Blood Proteins

Jennifer L. Johns, Consulting Editor, Meera Heller

MAJOR ALTERATIONS

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Serum or plasma protein measurements constitute a vital component of laboratory diagnostic evaluations. Globulin and total protein measurements will be higher in plasma than serum due to the presence of coagulation proteins, particularly fibrinogen. It is vital to use appropriate reference intervals for the sample type. The following measurement techniques are widely used (units for the following serum or protein measurements are g/dL or the SI unit: g/L):

Refractometry: The total protein concentration of serum, plasma, or body fluids can be determined via refractometry. The principle of measurement is that the degree of light refraction by a solution is proportionate to the concentration of solids. Refractometers are calibrated under the assumption that the solids are largely proteins and that other substances are present in constant concentrations.[1] Increases in other substances can

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increase the refractive index of a solution and falsely increase the total protein reading; for example, marked hyperglycemia with glucose concentration of 700 mg/dL or azotemia with blood urea nitrogen (BUN) concentration of 300 mg/dL can falsely increase the protein reading by 0.6 g/dL.[2] Hemolysis does not alter refractometer protein readings. The effect of marked icterus is unclear.[3] Use of the urine specific gravity scale for direct measurement of serum, plasma, or body fluid protein concentration is inappropriate, as calibration differs for these different fluid types.[1] Conversion tables are available for translation of specific gravity values into protein concentration values.[4]

Biuret reaction: Serum total protein is commonly measured via modified biuret testing on automated analyzers. The principle involves basic spectrophotometry measuring color change following copper binding to peptide bonds. Depending on the specific assay, hemolysis can cause a positive interference (e.g., hemoglobin of 400 mg/dL can cause a 12% positive bias).[5] This method is not sensitive to very low protein concentrations (e.g., in cerebrospinal fluid).

Bromcresol green (BCG) albumin binding: Albumin concentration in serum or plasma is usually measured via the BCG reaction. The principle involves basic spectrophotometry measuring color change when BCG binds to albumin. Nonspecific BCG binding to globulins can artifactually inflate the albumin value, particularly with a very low albumin concentration.[6] Plasma albumin values can be increased over serum values because of nonspecific plasma globulin binding. Also, heparin interference can increase or decrease an albumin reading depending on the assay.[7] Globulins are typically calculated by subtracting the albumin value from the total protein value.

Protein electrophoresis (PE): Serum or plasma proteins can be separated into albumin and globulin fractions electrophoretically. The principle of measurement is that an electrical charge is applied to a cellulose acetate or agarose gel matrix, allowing serum and plasma proteins to migrate through the matrix and separate into bands based on their charge and size. The acetate or gel is stained to detect the protein bands and read via densitometry to generate a tracing. Albumin has a low molecular weight (roughly 66 kDa), is highly anionic, and migrates the furthest to form a band near the anode. The identical nature of all albumin molecules and

therefore their migration to a single band generates a single sharp, narrow-based peak on the tracing. Globulins are divided into α-, β-, and γ-globulin regions in ruminants. In horses, globulins are further divided into α_1, α_2, β_1, β_2, and γ-globulin regions (Fig. 26.1). The heterogeneity of globulin fractions results in broad-based peaks for each, as the diverse proteins in each region migrate slightly differently. Rarely, a narrow-based peak will be seen in the γ-globulin region (see the Hyperglobulinemia section later). The presence of coagulation proteins will cause higher globulin peaks on plasma protein electrophoresis (PPE) than serum protein electrophoresis (SPE). In particular, fibrinogen will migrate into either the "late-beta" peak or the β-γ junction and in rare cases might obscure the presence of a monoclonal peak.[8,9] α- and β-globulins include many acute phase proteins (see the Acute Phase Response section later), whereas immunoglobulins (antibodies), primarily immunoglobulin G (IgG), comprise the γ-globulins. IgA and IgM are immunoglobulins that migrate in the β_2 or β-γ junction regions but are not detected in health via PE testing.

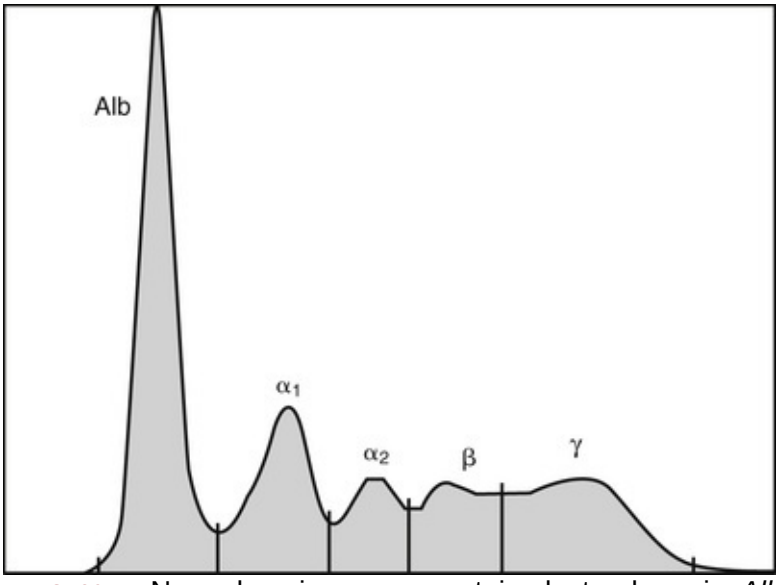


FIG. 26.1 Normal equine serum protein electrophoresis. *Alb,* Albumin.

Immunoelectrophoresis: Immunoelectrophoresis is a specialized technique for quantifying each immunoglobulin subtype (e.g., IgG, IgM) via electrophoresis followed by immunoprecipitation using subtype-specific

antibodies. Units are usually mg/dL. Other immunoglobulin measurements are designed specifically for detection of IgG in neonatal samples and are discussed under failure of passive transfer (Chapter 53).

Reference values for proteins vary by species (Table 26.1): When evaluating protein concentrations in a patient, some clinicians use the ratio of albumin to globulins (A/G ratio). However, it is often simpler to evaluate albumin and globulins separately, as the A/G ratio can change with alterations in one or both parameters.

TABLE 26.1

Normal Serum Protein Values for Horses, Cows, Sheep, and Goats

	Value	Horse	Cow	Sheep	Goat
Total	g/dL	5.2-7.9	6.74-7.46	6-7.9	6.4-7
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3	2.7-3.9
Globulin	g/dL	2.62-4.04	3-3.48	3.5-5.7	2.7-4.1
Fibrinogen	mg/dL	200-400	200-700	200-500	200-300

From Kaneko JJ, Harvey JW, Bruss ML, eds: *Clinical biochemistry of domestic animals,* ed 5, San Diego, 1997, Academic Press (Appendix VIII, Blood analyte reference values in large animals).

Biological variation with life stage: Transfer of immunoglobulins from the dam to the neonate via colostral ingestion is a key process that determines the neonate's subsequent immunocompetence and is often reflected in serum globulin levels in the first few weeks of life. In addition, neonates generally have lower serum albumin levels; for example, calves had decreased albumin values in the first 8 days of life.[10] Total protein levels in calves are decreased at birth, rise immediately following colostrum intake, then fall below the reference interval again at about 2 weeks of age and remain subnormal for some time.[10] IgG measurement also reflects the combined presence of maternal and neonatal proteins (Fig. 26.2). Studies in cows found gradually increasing plasma globulin levels during pregnancy until 4 weeks preparturition, then a steady drop until parturition.[11] IgG1 production is greatly increased at parturition, and the half-life is decreased, corresponding with transfer to colostrum.[12] Serum total protein steadily increased during lactation in Danish Landrace goats.[13] In pregnant and lactating mares, no significant differences in albumin, globulins, and total protein were found

at any stage.[14] Aging can be associated with alterations in some laboratory parameters. However, no significant differences in biochemical parameters or specific concentrations of IgG, IgA, or IgM were found in aged horses, despite alterations in lymphocyte populations.[15,16]

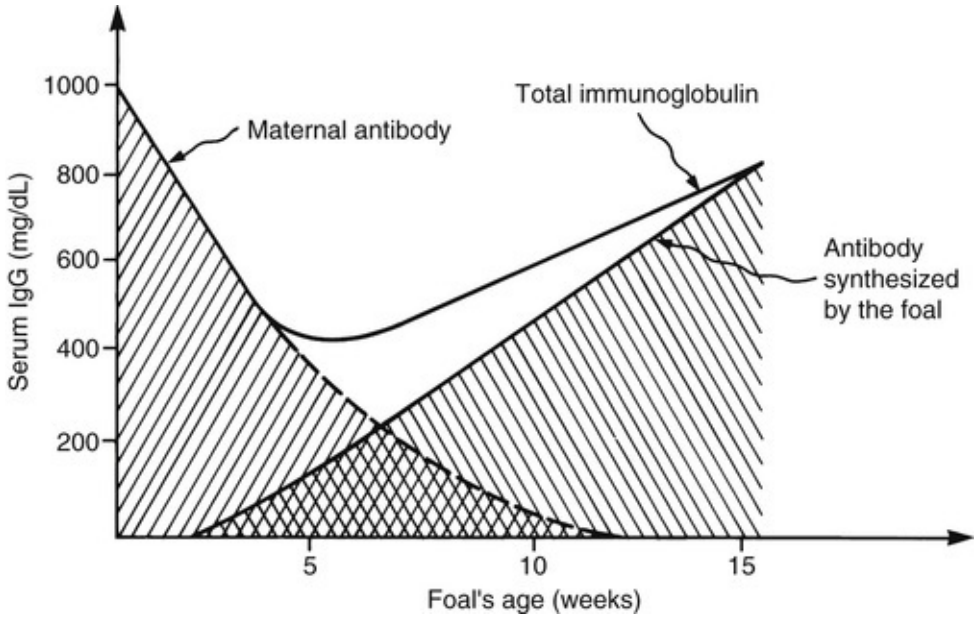


FIG. 26.2 Immunoglobulin in foal serum during the first 15 weeks of life. *IgG,* Immunoglobulin G. (From Tizard I: Veterinary immunology, ed 3, Philadelphia, 1987, Saunders.)

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Hyperproteinemia

Hyperproteinemia can result from an increase in both albumin and globulins (panhyperproteinemia) or an increase in only globulins (hyperglobulinemia) (Boxes 26.1 and 26.2).

Box 26.1

Causes of Hyperproteinemia in Horses

Panhyperproteinemia-Dehydration

Common Causes

- Acute toxic colitis of unknown cause
- Acute salmonellosis
- Potomac horse fever
- Intestinal clostridiosis
- Intestinal strangulating obstruction
- Proximal enteritis
- Gram-negative sepsis, endotoxemia
- Botulism
- Choking (esophageal obstruction)

Less Common Causes

- Chronic renal failure
- Chronic hepatic disease
- Guttural pouch mycosis with dysphagia
- Equine protozoal myelitis
- Salt toxicity
- Toxins, poisonous plants
- Lead toxicity
- Yellow star thistle poisoning (dysphagia)
- Dysphagia of unknown cause

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Hyperglobulinemia

Common Causes

Abdominal (mesenteric) abscess (including “bastard” strangles)
Pulmonary abscess
Chronic pleuritis
Purpura haemorrhagica
Equine infectious anemia

Less Common Causes

Chronic hepatic disease
Strongylosis
Lymphoma (lymphosarcoma)
Immune-mediated cytopenia

Box 26.2

Causes of Hyperproteinemia in Ruminants

Panhyperproteinemia-Dehydration

Common Causes

Ruminal acidosis (grain overload)
Abomasal torsion
Acute salmonellosis
Peritonitis
Sepsis, toxemia (mastitis, metritis)
Intussusception
Vagal indigestion
Oral or pharyngeal foreign body with dysphagia
Coccidiosis
Diarrhea, undifferentiated
Salt toxicity
Toxins, poisonous plants

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Less Common Causes

- Renal amyloidosis
- Lymphoma
- Pregnancy toxemia
- Rabies

Hyperglobulinemia

Common Causes

- Abdominal abscess (traumatic reticuloperitonitis, uterine tear, other)
- Chronic pneumonia
- Umbilical abscess
- Lymphoma
- Caseous lymphadenitis (sheep and goats)
- Other abscess

Less Common Causes

- Parasitism
- Pregnancy

Panhyperproteinemia

An increase in the concentration of all blood proteins results from hemoconcentration. Dehydration (due to decreased fluid intake, excessive fluid loss, or both) causes panhyperproteinemia with an associated increase in packed cell volume (PCV). This is due to a relative increase in protein and red blood cell (RBC) concentrations in blood. True hyperalbuminemia (i.e., increased albumin synthesis) does not occur. Hyperalbuminemia is an insensitive indicator of dehydration. If the true albumin level is decreased, a dehydrated patient may have a normal albumin result that masks both hemoconcentration and hypoalbuminemia. Similarly a dehydrated, anemic animal may have hyperproteinemia with a normal or decreased PCV. In an animal with a plasma protein concentration of 7.0 g/dL in health, a 10% decrease in plasma volume (severe dehydration) will result in a plasma protein concentration of 7.8 g/dL.[3]

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As with albumin measurement, the total plasma protein measurement will underestimate degree of dehydration if the patient is losing protein along with fluid. This is relatively common in renal disease, in protein-losing enteropathy with diarrhea, and in third-space loss when fluid and protein accumulate in the thoracic and/or abdominal cavity. Dehydration alone can result from gastrointestinal (GI) fluid sequestration, including intestinal obstruction, vagal indigestion with internal vomiting, and grain engorgement. Less common causes of dehydration include polyuria with renal failure, exudation from extensive skin wounds, and excessive sweating. Physiologic responses to dehydration include increased urine concentration and decreased urine output, increased fluid absorption from the GI tract, and increased thirst.

Hyperglobulinemia

The most common cause of hyperglobulinemia with normal hydration status (i.e., without hemoconcentration) is inflammation resulting in increased production of numerous globulins, including many acute phase proteins (see the Acute Phase Response section later). Chronic inflammation frequently results in a nonspecific increase in γ-globulins *(polyclonal gammopathy)* due to production of different immunoglobulins by plasma cells in response to chronic antigenic stimulation. A broad-based peak will be seen on SPE in the γ region and can extend into the β region due to production of IgM and/or acute phase β-globulins. An increase in both β- and γ-globulin fractions (β-bridging) can occur with intense antigenic stimulation, chronic active hepatitis, or lymphoma. Increased IgG in the γ-globulin fraction is termed *hypergammaglobulinemia* and can be seen in a range of chronic inflammatory diseases, including internal abscessation, chronic hepatitis, immune-mediated diseases (e.g., immune-mediated hemolytic anemia or thrombocytopenia), and lymphoma. Infection with the agent of epizootic bovine abortion triggered significant increases in IgG in clinically affected heifers.[17]

Increased production of a single immunoglobulin by a clonal population of B lymphocytes/plasma cells is known as a *monoclonal gammopathy.* On SPE, the monoclonal peak is as narrow-based and sharp as the albumin peak due to the identical migration of the monoclonal immunoglobulins (also known as *paraproteins*). Monoclonal gammopathies are usually secondary to neoplasia of B lymphocytes or plasma cells, including B-cell lymphoma, multiple myeloma, and B-cell lymphocytic leukemia. Increased susceptibility to hemorrhage can

occur with monoclonal gammopathy due to impaired platelet function caused by immunoglobulin coating and can be exacerbated by hyperviscosity syndrome.

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The Acute Phase Response

Acute inflammatory processes can trigger an acute phase response. Infectious causes are common, but many noninfectious causes (e.g., trauma, strenuous exercise) are documented. The body's response to the inflammatory insult is altered liver production of many proteins, termed *acute phase proteins* (APPs). A few proteins are negative APPs, and their production decreases with acute inflammation. Albumin is the most prominent negative APP, and levels will decrease in circulation proportionate to its half-life in each species. For example, the albumin half-life is 19.4 days in horses and 16.5 days in cattle, so hypoalbuminemia due to inflammation will take several weeks to develop in these species.[6,18] Transferrin and transthyretin (prealbumin) are other negative APPs, as is apolipoprotein A1 (see the Apolipoprotein A1 section later). The presumed role of decreased production of certain proteins is to shift available amino acids to the synthesis of proteins that are useful in host defense.[19]

Most acute phase reactants are positive APPs, meaning production increases with inflammation. These proteins will migrate into the α and β regions on SPE or PPE. The positive APPs are a diverse group, including proteins involved in coagulation, opsonization, iron regulation, and limiting tissue injury. Protein electrophoresis can reveal increased globulin fractions that are composed largely of APPs. Some diseases cause fairly specific alterations; for example, internal parasitism in diarrheic horses caused increased β_1 globulin levels that were significantly higher than those in diarrheic horses with other disorders.[20] Nonprotein assays are also used to diagnose an acute phase response; for example, serum iron outperformed plasma fibrinogen as an indicator of acute inflammation in horses.[21]

Measurement of individual APPs can be useful diagnostically and is not limited to blood; assays for APPs in milk and saliva have also proven useful.[22-24] The following is a list of major APPs in large animals.

Fibrinogen

Fibrinogen is a useful marker of inflammatory disease in large animals. Increased plasma fibrinogen, termed *hyperfibrinogenemia*, can occur in a myriad of conditions. Fibrinogen is semiquantitatively measured via the heat

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precipitation method, along with total plasma protein, as part of the routine complete blood cell count (CBC). Serum samples cannot be used to measure fibrinogen. The heat precipitation method cannot be used to detect hypofibrinogenemia (see Chapter 27).

As for other proteins, fibrinogen concentration can be increased due to dehydration. Calculating the plasma protein/fibrinogen (PP/F) ratio is useful when fibrinogen is increased. If the PP/F ratio is greater than 15, hyperfibrinogenemia is likely due to dehydration. If the PP/F ratio is less than 10, the patient has true hyperfibrinogenemia (due to inflammation).[25] Severe inflammatory disease in horses and ruminants consistently causes hyperfibrinogenemia, although the increase in fibrinogen may not be proportionate to the degree of inflammation. Increased fibrinogen often precedes development of an inflammatory leukogram in ruminants, particularly in cattle.[25] Hyperfibrinogenemia can persist for a period of time postoperatively. In one study more than half of horses undergoing subchondral bone cyst removal still had hyperfibrinogenemia 15 days post operation; in another study fibrinogen remained increased through day 11 following laparotomy and other procedures.[26,27]

In adult horses a number of conditions, including colic, sterile inflammation, surgical intervention, and chronic internal abscessation, are associated with hyperfibrinogenemia (Box 26.3).[26,28-30] Vaccination of horses induces an acute phase response including increases in both fibrinogen and serum amyloid A.[31] Fibrinogen response in foals is more variable. In healthy neonatal foals fibrinogen levels are initially lower than adult values and then equilibrate within a few weeks of age.[32,33] Hyperfibrinogenemia lags behind leukocytosis as an indicator of inflammation in foals.[32,34] Fibrinogen was an unreliable marker of foal sepsis in one study,[35] although marked hyperfibrinogenemia of 900 to 1500 mg/dL had utility as a diagnostic marker of foal osteomyelitis.[36] Fibrinogen may be useful as an indicator of foal pneumonia due to *Rhodococcus equi*: One study found that hyperfibrinogenemia had greater specificity than leukocytosis, but another reported better diagnostic performance (encompassing both sensitivity and specificity) of leukocytosis over hyperfibrinogenemia.[37,38] Late pregnancy correlates with increased fibrinogen concentration in mares. In one study fibrinogen concentration progressively increased roughly 1 week prior to foaling, peaked at the time of foaling, then gradually decreased but remained increased over control values for several weeks post foaling.[39]

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Box 26.3

Causes of Hyperfibrinogenemia in Horses

Abscess (abdominal or other)
Chronic peritonitis
Pleuritis
Pneumonia
Osteomyelitis
Septic arthritis
Cholelithiasis
Neoplasia with inflammatory response
Vasculitis (equine purpura haemorrhagica)
Cellulitis
Gastrointestinal inflammation
Salmonellosis

Fibrinogen is a particularly useful indicator of inflammation in cattle and other ruminants, as they develop substantial hyperfibrinogenemia in response to inflammation (Box 26.4).[40] A number of inflammatory diseases in cattle are associated with hyperfibrinogenemia, including peritonitis, mastitis, and pneumonia. Lymphoma and uncomplicated displaced abomasum (without peritonitis) did not present with hyperfibrinogenemia.[40] Progressive increase in fibrinogen concentration occurs with pregnancy in cattle, with a significant increase just prior to parturition compared to the 2 days prior to calving.[41] Fibrinogen is reportedly low to undetectable in neonatal calves.[42] One study of healthy calves reported a peak in fibrinogen at postnatal day 6 (mean value 400 mg/dL), then a gradual decline until reaching a mean nadir of 250 mg/dL at day 50 followed by a slight rise; values always remained within the reference interval for adult cattle.[8] Fibrinogen was significantly increased in calves with suspected septic shock.[43]

Box 26.4

Causes of Hyperfibrinogenemia in Ruminants

Acute mastitis, especially coliform
Abscess
Traumatic reticuloperitonitis, pericarditis
Salmonellosis
Gastrointestinal inflammation
Pyelonephritis
Endocarditis
Pleuritis
Pneumonia
Chronic peritonitis
Necrotic rumenitis
Lymphoma (lymphosarcoma)
Septic arthritis
Cellulitis
Omphalophlebitis
Osteomyelitis

Other APPs

The usefulness of individual APP measurement in diagnosis of inflammatory disease varies by species (Table 26.2). The following APPs have proven utility in one or more large animal species.

TABLE 26.2

Useful Acute Phase Proteins (APPs) in Large Animal Species

APP	References for Use in Each Species
Haptoglobin	Cattle[22,23,51,87,88]; Goats[54,89-91]; Pigs[70,92]; Sheep[52,53,93-96]
C-reactive protein (CRP)	Cattle[57]; Horses[58]; Pigs[70,92]
Serum amyloid A (SAA)	Cattle[22,23,50,51,87,97]; Goats[89]; Horses[46-49,60-64,79,98-100]; Pigs[69,70,92,101]; Sheep[94]
Apolipoprotein A1 (Apo A1)	Pigs[69,70]
Ceruloplasmin (CP)	Horses[67]; Sheep[93]
α2-Antiplasmin (α2-AP)	Horses[30]
Pig major acute phase protein (pig-MAP/ITIH4)	Cattle[71]; Pigs[69,70,102]
Ferritin	

	Horses[103]
α1-Acid glycoprotein (α1-AG)	Cattle[75]; Goats[89]; Sheep[94]

Haptoglobin.

When haptoglobin enters the circulation, it immediately binds hemoglobin to form a complex that is then internalized by hepatic Kupffer cells.[44] Increased haptoglobin during the acute phase response occurs due to transcriptional activation. Haptoglobin may regulate and modulate the immune response during inflammation.[45] Serum haptoglobin concentration increased in experimentally induced bacterial placentitis in mares and experimentally induced strongyle infections of young horses.[46,47] Both acute and chronic heaves correlated with increased serum haptoglobin following allergen challenge.[48] Interestingly, in one study haptoglobin concentration decreased in serum but increased in peritoneal fluid in horses with colic.[49] Serum haptoglobin concentration increases in the first week postpartum in dairy cows.[50] Measurement of haptoglobin in milk is superior to measurement in serum for diagnosis of mastitis, although serum measurement is also useful.[22,51] Haptoglobin performs well as an acute phase marker in sheep, with increases found during inflammatory diseases including bacterial metritis and pneumonia.[52,53] Serum haptoglobin concentration varies with reproductive status in goats: Pregnant does in the second trimester have decreased values, and lactating does have increased values when compared to open, nonlactating does.[54]

C-Reactive Protein (CRP).

In health, CRP is present in trace amounts in circulation. Inflammation and tissue necrosis can markedly upregulate CRP levels.[55] The role of CRP in the acute phase response may be clearance of endogenous or exogenous substances (e.g., microorganisms, cellular debris), but CRP may also worsen inflammatory tissue damage via complement activation.[56] Dairy cattle had increased serum CRP levels during lactation that were highest at peak lactation and declined thereafter; mastitis and other inflammatory diseases caused further increases (e.g., a threefold increase in CRP levels in mastitic cows compared to healthy lactating cows).[57] Increased CRP has been associated with pneumonitis, enteritis, and arthritis in horses.[58]

Serum Amyloid A (SAA).

The SAA protein family of apolipoproteins includes both constitutively expressed proteins and acute phase reactants that are markedly upregulated during inflammation.[59] The induced proteins chemotactically recruit leukocytes and are implicated in the pathogenesis of chronic inflammation, as they are precursors of the amyloid A protein in amyloidosis. SAA testing via point-of-care handheld devices has become standard practice in some equine facilities. Studies support the use of SAA measurement as an indicator of acute inflammation (including septic inflammation and heaves) and a useful monitoring tool for clinically ill horses, with diagnostic accuracy often superior to that of total white blood cell (WBC) count, fibrinogen, and/or A/G ratio.[46,48,60-62] In one study systemic inflammation in horses caused substantial increases in SAA compared to local inflammation, and a cutoff value of greater than 10 mg/L yielded sensitivity of 82% and specificity of 71% in differentiating inflammatory from noninflammatory disease in horses.[62] SAA concentration in both serum and peritoneal fluid increased in horses with colic.[49] In contrast, experimental strongyle infection failed to elicit an increase in serum SAA concentration.[47] SAA has demonstrated prognostic value in horses with colic but was not useful as a prognostic marker in general inflammatory disease when used as a single measurement.[63,64] As with haptoglobin, SAA increases in the first postpartum week in dairy cows, and measurement of milk SAA levels is superior to serum levels to diagnose mastitis, although both are useful.[22,50,51]

Apolipoprotein A1 (Apo A1).

Apo A1 is a negative acute phase reactant in humans and domestic animals. Apo A1 is associated with high-density lipoproteins. A role as a constitutive antiinflammatory factor has been posited for Apo A1.[65]

Ceruloplasmin (CP).

CP plays a key role in iron metabolism, and CP-bound copper accounts for 95% of plasma copper concentration. CP interacts with several proteins, including ferritin, neutrophil myeloperoxidase, and lactoferrin.[66] Equine serum CP concentration increases with sterile inflammation and surgical manipulation. Transient changes in serum CP concentration occur in mares immediately before and after foaling.[67]

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α2-Antiplasmin (α2-AP).

α2-AP is a fibrinolytic inhibitor via its specific inactivation of plasmin. Measurement of increased plasmin α2-AP complexes is one indicator of fibrinolysis. α2-AP increases in horses with colic, as does plasminogen, and therefore may have utility as an acute phase biomarker.[30,68]

Pig Major Acute Phase Protein (pig-MAP, also ITIH4).

Pig-MAP is the porcine homolog of a human kallikrein-sensitive protein and is a useful indicator of inflammatory diseases.[69,70] The related proteins in humans, pigs, and rats have been designated collectively as ITIH4, a new member of the inter-alpha-trypsin inhibitor (ITI) protein family with unknown biological function. The utility of ITIH4 as an acute phase reactant in cattle is also described.[71]

Ferritin.

Ferritin is an iron storage and transport protein. Ferritin levels can markedly increase during infectious and other inflammatory disorders, presumably to sequester iron and limit availability to microbes.[72] Species-specific assays are generally needed to measure ferritin. An equine-specific assay is available and has some cross-reactivity with other species.[73] Ferritin has shown usefulness as a biomarker in horses. Strenuous exercise also causes an increase in ferritin that persists for up to 2 days.[74]

α1-Acid Glycoprotein (α1-AG).

Also known as orosomucoid, α1-AG is a carrier of basic substances, including therapeutic drugs and steroids. Increased α1-AG values have been found in cattle with various inflammatory disorders, including mastitis and traumatic pericarditis.[75]

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Hypoproteinemia

Hypoalbuminemia

Albumin is the most abundant of the plasma proteins. It accounts for approximately 75% of plasma colloidal oncotic pressure (COP), and its synthesis is primarily regulated by COP. Albumin is a nonspecific transport protein for a number of substances, including calcium, lipids, and hormones, and serves as an amino acid source for body tissues. Hypoalbuminemia is caused by a decrease in albumin production and/or an increase in albumin loss, most commonly renal or GI loss (Boxes 26.5 and 26.6). As described above, decreased albumin synthesis is a common component of the acute phase inflammatory response. Overall hypoproteinemia generally does not occur, partly because the decrease in albumin is usually mild and partly because of the corresponding increase in globulins.

Box 26.5

Causes of Hypoproteinemia in Horses

Hypoalbuminemia

Common Causes

Parasitism
Glomerulonephritis
Pyelonephritis
Idiopathic granulomatous enteritis
Intestinal lymphoma (lymphosarcoma)
Parasitism
Salmonellosis
Equine ehrlichial enterocolitis (Potomac horse fever)
Colitis
Clostridiosis
Nonsteroidal antiinflammatory drug toxicosis

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Less Common Causes

Chronic hepatic fibrosis (pyrrolizidine alkaloid toxicity and other causes)
Hepatic neoplasia
Chronic hepatitis
Amyloidosis
Tuberculosis
Histoplasmosis
Chronic eosinophilic gastroenteritis
Starvation, malnutrition

Panhypoproteinemia

Common Causes

Excessive fluid therapy or water intake
Acute blood loss
Gastrointestinal ulceration
Strangulating gastrointestinal obstruction, infarction
Protein-losing enteropathy (chronic granulomatous bowel disease)
Acute severe peritonitis
Nonsteroidal antiinflammatory drug toxicity
Glomerulonephritis

Less Common Causes

Blood-sucking gastrointestinal or external parasites
Intestinal lymphoma (lymphosarcoma)
Urinary tract blood loss
Congenital vascular disorders: renal trauma
Renal calculi
Pyelonephritis
Neoplasia
Cystic calculi
Disseminated intravascular coagulation
Immune-mediated thrombocytopenia
Congestive heart failure

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Box 26.6

Causes of Hypoproteinemia in Ruminants

Hypoalbuminemia

Common Causes

Protein malnutrition, starvation
Amyloidosis
Pyelonephritis
Glomerulonephritis
Salmonellosis
Johne's disease
Trichostrongylus infection

Less Common Causes

Chronic liver failure
Intestinal lymphangiectasia
Intestinal lymphoma

Panhypoproteinemia

Common Causes

Excessive intravenous fluid therapy or water intake
Acute blood loss
Abomasal ulceration
Blood-sucking gastrointestinal or external parasites
Gastrointestinal ulceration

Less Common Causes

Ingestion of caustic chemicals
Strangulation, infarction of intestine

Congestive heart failure
Pyelonephritis
Urinary tract blood loss

Albumin production can decrease with chronic insufficient intake of amino acids. In particular, protein-energy malnutrition can lead to hypoalbuminemia more quickly than total starvation.[76] Hypoalbuminemia is an indicator of chronic malnutrition given albumin's relatively long half-life, and clinical signs relating to hypoalbuminemia develop over a prolonged period. GI disorders that disrupt normal protein digestion and absorption can lead to decreased protein synthesis and are discussed below under protein-losing enteropathy (PLE).

Although albumin is produced by the liver, synthesis generally does not decrease in acute liver disease. Chronic, diffuse liver diseases such as chronic hepatitis, fibrosis, and hepatic neoplasia may cause hypoalbuminemia. Because the half-life of albumin is longer in horses and cattle than in dogs and humans, hypoalbuminemia is uncommon in large animal hepatic disease but can occur in conditions such as chronic hepatic lipidosis or chronic pyrrolizidine alkaloid toxicosis. In one study 6% of horses with acute liver disease and 18% of those with chronic liver disease were hypoalbuminemic; increased globulins were found in 64% of all horses with liver disease.[77] Decreased albumin and increased globulins can indicate a poorer prognosis in horses with liver disease.[78] A potentially more useful indicator of liver disease in horses than hypoalbuminemia is a postalbumin shoulder (a small hump on the right [cathodal] side of the albumin peak) on SPE; this shoulder can also appear with acute inflammatory disease or severe hypoalbuminemia.[25,79]

Excessive albumin loss usually occurs through the urinary and/or GI tracts. Less common causes include chronic blood loss (acute substantial blood loss is associated with panhypoproteinemia) and burns or other exudative skin disease. Normal urine contains little or no protein due to resorption of filtered small proteins in the proximal tubule. Transient physiologic proteinuria, sometimes referred to as *functional proteinuria*, can occur with exercise, stress, seizures, and excessive protein intake, and following colostrum ingestion in neonates. These are (mostly) prerenal sources of proteinuria and do not cause hypoproteinemia.[80]

Renal proteinuria arises due to diseases of the glomeruli and/or proximal tubules; hemorrhage or inflammation within the kidney is another cause but is

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often categorized under “postrenal” proteinuria. Albumin is readily filtered through defects in the glomerular basement membrane due to its low molecular weight. Proteinuria due to glomerular lesions consists largely of albumin and can result in hypoalbuminemia and overall hypoproteinemia, whereas tubular proteinurias do not produce hypoalbuminemia.[80] Glomerulonephritis, amyloidosis, and less commonly pyelonephritis are top differentials for glomerular disease leading to proteinuria and hypoalbuminemia.[81]

PLE is a GI condition resulting in net loss of protein from the body, due to abnormal loss of protein from the GI tract and/or inability of the GI tract to absorb proteins. PLE is not a disease itself; it is a manifestation of numerous GI disorders. The diagnosis of PLE includes ruling out urinary protein loss, body cavity effusion, increased protein catabolism, and decreased synthesis due to liver disease. The clinically important mechanisms of PLE are defective lymphatic transport, increased mucosal permeability, GI parasitism, exudative inflammation, and/or ulcerative blood loss. Hypoalbuminemia can be useful both diagnostically and prognostically in PLE. In a study of horses with diarrhea, albumin was lower in horses that died than in those that survived, likely reflecting albumin leakage across inflamed intestinal mucosa.[20]

In horses the most common cause of PLE is idiopathic granulomatous enteritis, one of the chronic inflammatory bowel diseases of the horse.[14] Other causes of equine PLE are acute enterocolitis, including bacteria-associated disease; GI lymphoma and other GI neoplasia; nonsteroidal antiinflammatory drug (NSAID) toxicity, including phenylbutazone toxicity; GI parasitism; and other conditions in the chronic inflammatory bowel disease group, including intestinal tuberculosis, histoplasmosis, and eosinophilic gastroenteritis. Proliferative enteritis of foals or yearlings due to *Lawsonia intracellularis* infection often presents with hypoalbuminemia or panhypoproteinemia.[82,83]

The most common cause of chronic PLE in ruminants is infection with *Mycobacterium avium* subsp. *paratuberculosis*, also known as *Johne’s disease*. Intestinal protein loss in Johne's disease arises from both mucosal lesions and secondary intestinal lymphangiectasia.[84] Other differentials include parasitism such as *Trichostrongylus* infection, intestinal lymphangiectasia, and GI lymphoma.

In addition to the above causes of decreased albumin production and increased albumin loss from the body, hypoalbuminemia can arise from dilution within the body. Redistribution of albumin into subcutaneous tissues and higher-protein

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body cavity effusions can result in hypoalbumemia. Edema and peritoneal effusions may contribute to the severe acute hypoalbuminemia described in fescue toxicity in horses.[85] Some edematous and effusive disorders such as congestive heart failure (see the Panhypoproteinemia section later) can cause either hypoalbuminemia or panhypoproteinemia.

The clinical sequelae of hypoalbuminemia relate to the decrease in COP and subsequent fluid shift. Severe hypoalbuminemia (e.g., from protein-losing nephropathy or chronic liver disease) can cause a very low-protein effusion called a pure transudate. Other clinical signs of hypoalbuminemia include edema of the limbs, head, and ventrum. The albumin level generally must be below 1.5 g/dL in horses and below 1 g/dL in ruminants before clinical signs occur. A correlate of the longer albumin half-life in large animals is that albumin replacement by synthesis is also slower, resulting in more clinically significant edema due to hypoalbuminemia.[79]

Panhypoproteinemia

Vigorous fluid therapy or excess water intake can cause dilution of plasma proteins and subsequent relative panhypoproteinemia. Panhypoproteinemia due to both dilution and increased GI protein loss occurs frequently in patients with acute GI disease receiving intravenous fluid therapy.

Acute blood loss with subsequent interstitial fluid shift into the vasculature, and volume expansion during pregnancy, can also cause relative panhypoproteinemia. Acute blood loss results in loss of all plasma proteins, and then interstitial fluid rapidly shifts into the intravascular space to help maintain volume. This dilution effect is intensified by increased water intake that commonly occurs after acute blood loss. Acute hemorrhage resulting from trauma, severe epistaxis, or internal vascular rupture should be ruled out in a hypoproteinemic, anemic animal.

GI disorders can lead to panhypoproteinemia via loss of either blood or protein alone. Differentials for GI blood loss include abomasal or gastric ulcers, blood-sucking parasites (e.g., *Haemonchus contortus* in ruminants), viral or bacterial infection, azotemia, neoplastic invasion, or exposure to caustic chemicals. NSAID toxicosis and strangulating GI obstructions or infarctions can result in mucosal necrosis and leakage of plasma proteins into the gut lumen. Although protein-losing enteropathy usually initially causes hypoalbuminemia, panhypoproteinemia often develops over time. Proliferative enteropathy of

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young horses (described above) often results in panhypoproteinemia. Acute severe peritonitis with massive protein exudation due to GI rupture can also quickly lead to hypoproteinemia.

Other conditions resulting in clinically significant blood loss include urinary tract disorders due to congenital vascular disorders, renal trauma, renal or cystic calculi, pyelonephritis, and renal neoplasia. Coagulopathies, including disseminated intravascular coagulation (DIC) or immune-mediated thrombocytopenia, may cause either external blood loss via the GI or urinary tract or internal bleeding into body cavities.

Congestive heart failure may cause either hypoalbuminemia or panhypoproteinemia via several mechanisms, including dilutional effects from plasma volume expansion, protein loss into ascitic fluid and the interstitium, and decreased albumin synthesis due to hepatic congestion and/or concurrent inflammation.[86]

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• CHAPTER 27

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Alterations in Hemostasis

Jennifer L. Johns, Consulting Editor, Meera Heller

MAJOR ALTERATIONS

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The diagnostic test panel to evaluate coagulation in large animals can include platelet count, plasma semiquantitative fibrinogen to assess for increased fibrinogen concentration, prothrombin time (PT), partial thromboplastin time (PTT), and serum fibrin and fibrinogen degradation products (FDPs). Alternatively, thromboelastography (TEG) may be substituted for (or performed in addition to) the combination of PT, PTT, and FDPs. Proper collection and preparation of blood samples are paramount in obtaining accurate results (see Chapter 23). Platelet counts are routinely performed as part of the complete blood cell count (CBC). Citrated blood is required for coagulation testing

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including PT, PTT, FDPs, and TEG, and can also be used for platelet analysis including platelet count. It is critical to have a 1 : 9 ratio of citrate to whole blood. The patient's hematocrit can affect coagulation results when whole blood is used. When the hematocrit is more than 55%, correction to a lower citrate volume is recommended to prevent overcitration and prolonged coagulation times.[1] If the laboratory does not have reference intervals for a particular species, plasma from two or more healthy animals should be collected and assayed in a similar manner for comparison. Table 27.1 shows reference values for platelets and fibrinogen, but laboratory-specific values are preferable for these analytes and are necessary for other coagulation parameters.

TABLE 27.1

Normal Values for Hemostatic Data in Ruminants and Horses

	Horses	Cattle	Sheep	Goats	Llamas	Pigs
Platelet count (1×10^{-3}/L)	100-600	100-800	250-750	300-600	[a]	200-500
Fibrinogen (mg/dL)	200-400	200-700	200-500	200-300	100-400	200-400

[a]Insufficient data available.

Modified from Duncan JR, Prasse KW, Mahaffey EA, eds: *Veterinary laboratory medicine,* ed 3, Ames, IA, 1994, Iowa State University Press; and Kaneko JJ, Harvey JW, Bruss ML, eds: *Clinical biochemistry of domestic animals,* ed 5, San Diego, 1997, Academic Press.

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Platelet Parameters

The platelet count is technically the platelet concentration in whole blood. Units = [platelets] × 10^3/µL; SI units = [platelets] × 10^9/L. Automated analyzers are routinely used to generate a platelet count. A rough estimate can be made via manual smear review: at 100× oil objective, the total number of platelets in 10 fields is counted. This count is then divided by 10 to yield an average number. This average is multiplied by a 15,000 to 20,000 conversion factor to yield [platelets]/µL.[2] Both this estimate and the automated platelet count will be artifactually decreased if platelet clumps are present. Cattle normally average around 8 to 10 platelets per 100× oil field, and horses normally have 5 or more platelets per field.[2]

Mean Platelet Volume (MPV)

The mean platelet volume (MPV) is the mean or average platelet volume and is measured in femtoliters (fL). This value is an average and does not represent the range of platelet volumes. Increased MPV is consistent with increased release of large or giant platelets and usually indicates a platelet regenerative response. The measurement of reticulated platelets (analogous to reticulocytes for red blood cells) is used diagnostically in human medicine and is likely to become an accepted index of platelet regeneration in veterinary medicine as well.

Platelet Distribution Width (PDW)

The platelet distribution width (PDW) is a calculated range of platelet volumes (representing anisocytosis), analogous to the red cell distribution width. The PDW is expressed as a percentage. A higher percentage indicates a greater variation in platelet volume. The PDW in combination with the MPV value can indicate whether there are increased numbers of smaller and/or larger platelets.

Thrombocrit

Also called the *plateletcrit*, the thrombocrit value is a function of the platelet count and the MPV. It is a better indicator of the total platelet functional potential than the platelet count, due to the greater functional capacity of larger

platelets.[3]

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Thrombocytopenia

A decrease in the circulating platelet count is termed *thrombocytopenia*. Thrombocytopenia is caused by one of three basic mechanisms: platelet sequestration, decreased platelet production, and decreased platelet life span due to consumption or destruction (Boxes 27.1 and 27.2). Spurious thrombocytopenia occurs occasionally in horses when blood is collected into ethylenediaminetetraacetic acid (EDTA) anticoagulant, causing in vitro platelet clumping.[4] Platelet clumps are visible in the stained blood smear and may be indicated by error messages on an analyzer. Collection of a second sample into sodium citrate can yield an accurate platelet count and confirm a suspicion of spurious thrombocytopenia. Heparinized samples are not recommended for platelet counts, as heparin-induced clumping can occur in any species. If citrated samples are used for platelet counts, the count must be corrected for citrate dilution (i.e., multiplied by 1.1).

Box 27.1

Causes of Thrombocytopenia in Horses

Common Causes

Disseminated intravascular coagulation (DIC)
Immune-mediated thrombocytopenia (IMT) (drugs: penicillin, trimethoprim-sulfadoxine)
Endotoxemia, septicemia (e.g., acute toxic colitis, intestinal strangulating obstruction, neonatal septicemia)
Equine infectious anemia
Equine anaplasmosis *(Anaplasma phagocytophilum)*
Lymphoma

Less Common Causes

Salmonellosis

Equine viral arteritis
Equine influenza
Myeloproliferative disease (myelogenous leukemia)
Plasma cell myeloma
Aplastic anemia
Stachybotryotoxicosis
Neonatal alloimmune thrombocytopenia

Box 27.2

Causes of Thrombocytopenia in Ruminants

Common Causes

Disseminated intravascular coagulation (DIC)
Bracken fern *(Pteridium aquilinum)* toxicosis
Septic mastitis or metritis (endotoxemia)

Less Common Causes

Salmonellosis
Gram-negative sepsis
Trichloroethylene-extracted soybean meal
Lymphoma
Plasma cell myeloma
Immune-mediated thrombocytopenia (IMT)
Stachybotryotoxicosis
Myelofibrosis (pygmy goats)

Splenic platelet sequestration can occur as a result of splenomegaly. Splenomegaly occurs due to various disorders, including infiltrative diseases such as lymphoma, leukemia, and multiple myeloma; infectious and other inflammatory diseases such as immune-mediated hemolytic anemia that result in splenitis; lymphoid hyperplasia; and/or splenic extramedullary hematopoiesis. In addition, congestive splenomegaly occurs when venous outflow is occluded by

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torsion, intestinal displacements, or congestive heart failure. Platelet sequestration is a relative thrombocytopenia due to redistribution (versus an absolute thrombocytopenia), is reversible, and does not result in increased bleeding tendency.

Decreased platelet production can occur with various bone marrow disorders, including myelophthisis (replacement of normal marrow). Myelophthisis is often due to marrow infiltration with neoplastic cells (e.g., plasma cells in multiple myeloma) and can result in pancytopenia. Familial myelofibrosis was reported in pygmy goats and resulted in marked pancytopenia, including thrombocytopenia with myelophthisis.[5] Toxic damage to the marrow (e.g., from bracken fern toxicosis or nonsteroidal antiinflammatory drug administration) can result in myelosuppression and potentially aplastic anemia. Immune-mediated destruction of megakaryocytes, a variant of immune-mediated thrombocytopenia (IMT), causes decreased platelet production and release. Infectious agents can cause decreased platelet production via either indirect effects on megakaryocytes (e.g., equine infectious anemia virus) or direct infection of megakaryocytes (e.g., acute bovine viral diarrhea infection).[6,7] Evaluation of a bone marrow aspirate and core biopsy is indicated to evaluate megakaryocyte numbers and assess for dysplasia in a patient that is either pancytopenic or persistently thrombocytopenic without evidence of peripheral consumption or destruction.

Blood loss is a rare cause of thrombocytopenia; it is more likely that any concurrent bleeding is the result rather than the cause of severe thrombocytopenia. Studies in dogs found that acute severe blood loss induces a mild to moderate thrombocytopenia, with up to 50% reduction in platelet count.[2] Rapid dilution of the blood volume with aggressive fluid therapy can decrease the platelet count as well as other hemostatic elements. This decrease is generally mild to moderate.

Platelet life span can be reduced by destruction of platelets or by platelet consumption in widespread coagulation. Immune-mediated platelet destruction is a common cause of thrombocytopenia in horses. IMT can be either idiopathic or secondary to various etiologies, including viral and bacterial infections, drug administration, and hemic neoplasia.[7-10] Thrombocytopenia due to idiopathic IMT is often marked, in contrast to thrombocytopenia due to other causes. The thrombocytopenia of equine anaplasmosis due to infection with *Anaplasma phagocytophilum* is apparently multifactorial; an element of IMT is possible but not supported by experimental studies, and splenic sequestration is also a

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potential contributor.[11,12] Neonatal alloimmune thrombocytopenia has been reported in horses, mule foals, and pigs and is caused by colostral antibodies against foreign (paternal) epitopes on the neonate's platelets.[2]

Excessive consumption of platelets occurs with disseminated intravascular coagulation (DIC). DIC is a clinical condition of disordered hemostasis that arises secondary to severe trauma, infectious diseases, or other inflammatory diseases, including septicemia and disseminated neoplasia.[13] Examples include DIC in horses with colic, calves with septic shock, and pigs with spontaneous heatstroke.[14-17] The diagnosis of DIC in most species relies on finding evidence of both platelet and coagulation factor consumption (thrombocytopenia with one or more coagulation test abnormalities, described later) along with evidence of increased fibrinolysis (see the Increased Fibrin and Fibrinogen Degradation Products section later). Snake envenomation directly causes platelet destruction in the absence of typical DIC, as some snake venoms contain platelet-activating factors. Endothelial damage or necrosis (e.g., due to equine viral arteritis infection) can also result in platelet destruction with or without concurrent DIC.[18]

Clinical Signs of Thrombocytopenia

Thrombocytopenia is characterized by petechial or ecchymotic hemorrhages on the oral, nasal, and/or vaginal mucous membranes and the nictitans, sclerae, pinnae, and ventral abdomen. Epistaxis, melena, hyphema, and/or hematuria may occur, although spontaneous hemorrhage is rare unless the platelet count drops below 10,000 to 20,000/µL. Concurrent inflammation can increase a thrombocytopenic patient's propensity for spontaneous hemorrhage.[19] Prolonged bleeding from injections or wounds and a propensity to form hematomas with minor trauma are relatively common with a platelet count below 40,000/µL.

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Thrombocytosis

Thrombocytosis is an increase in platelet count over the reference interval. A physiologic increase in platelet count can occur at high altitude.[2] Relative thrombocytosis due to redistribution from splenic and other tissues stores can occur with exercise or epinephrine release. Splenectomy can result in thrombocytosis for several weeks due to both increased production and decreased platelet sequestration and destruction in the absence of the spleen.

Absolute thrombocytosis can occur as a secondary reactive change in a number of conditions. Thrombocytosis due to any cause other than myeloproliferative disease does not generally result in increased risk of thrombosis or other clinical abnormalities; it is a reflection of the underlying disease(s). Many infectious and other inflammatory disorders, including immune-mediated diseases, can cause “reactive thrombocytosis,” as can surgery, neoplasia, and other inflammatory disorders. A less common cause of thrombocytosis is iron deficiency, and this may be true in large animal species as well. Chronic blood loss can be associated with thrombocytosis, and iron deficiency may be one factor. Administration of vincristine or vinblastine can result in thrombocytosis. Thrombocytosis can also occur as a rebound effect following prior thrombocytopenia with an appropriate bone marrow response. A very rare cause of persistent severe thrombocytosis is primary thrombocythemia or other chronic myeloproliferative disease; bone marrow evaluation is indicated in this situation.

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Platelet Function Defects and Von Willebrand Disease

Defects in platelet function have been described in large animals, but diagnosis can be challenging. The template bleeding test is routinely performed in small animals to assess primary hemostasis (e.g., platelet number/function and von Willebrand factor [vWF] function) but is criticized for poor reproducibility in both humans and animals, including horses.[20] Template bleeding tests have been useful for monitoring effects of aspirin therapy on hemostasis in horses and may be suitable for serial monitoring of a patient if other factors such as platelet count remain constant. Aggregometry is considered a gold standard assay for platelet function but can be cumbersome; automated platelet function analysis with the PFA-100 device has become a standard platelet function assay in human medicine and is emerging as a valuable assay in veterinary medicine. More specific assessment of platelet function can require specialized assays.

Glanzmann's thrombasthenia is a disorder resulting in poor platelet aggregation and clot retraction in humans and animals and is caused by one or more defects in quantity or quality of platelet surface glycoprotein IIb/IIIa. Hereditary Glanzmann's thrombasthenia has been diagnosed in a few adult horses of various breeds.[21-24] Other hereditary thrombopathias are infrequently described in animals, including a novel disorder that is termed *atypical equine thrombasthenia*.[25] Chédiak-Higashi syndrome is reported in Hereford, Japanese Black, and Brangus cattle. The bleeding diathesis associated with this syndrome is defined by substantial impairment of platelet aggregation in response to collagen.[26] A hereditary thrombopathy in Simmental cattle is characterized by impaired platelet aggregation, with clinical signs including periodic epistaxis and severe hemorrhage following surgical procedures.[27] Inheritance of this thrombopathy appears to be multigenetic, and aggregometry was not useful in differentiating carrier versus clear animals. A variant form of von Willebrand disease has also been described in a Simmental calf.[28] Von Willebrand disease has been reported in Quarter Horses and consisted of a deficiency in high molecular weight multimers of vWF, consistent with type 2 von Willebrand disease in other species.[29]

Acquired defects in platelet function are common secondary to drug

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administration. Drugs that impair platelet function include aspirin, phenylbutazone, sulfonamides, estrogens, and phenothiazines.[14] Several underlying medical conditions can also negatively affect platelet function, including uremia and liver disease. Production of high levels of immunoglobulins, particularly immunoglobulin M (IgM), in monoclonal gammopathies hinders platelet function via protein coating of platelet surfaces.

Prolonged Prothrombin Time

The PT, or one-stage prothrombin time, is a measure of the extrinsic (tissue factor) and common pathways of coagulation (Fig. 27.1). The assay tests the time after the calcium-thromboplastin reagent is added to the plasma sample until formation of a fibrin clot. The PT is prolonged when the fibrinogen level drops below 100 mg/dL or with a marked deficiency of one or more coagulation factors in the common pathway (factors II [prothrombin], V, and/or X) or the tissue factor pathway (factor VII). The sensitivity of PT testing is variable and generally insensitive to mild coagulation factor deficiencies; a study in horses found that standard PT testing is reasonably sensitive to an overall decrease greater than 20% in coagulation factor activity.[30] As with other basic coagulation time assays, a common approach is to interpret the coagulation time as prolonged if it is more than 25% above the upper end of the reference interval.

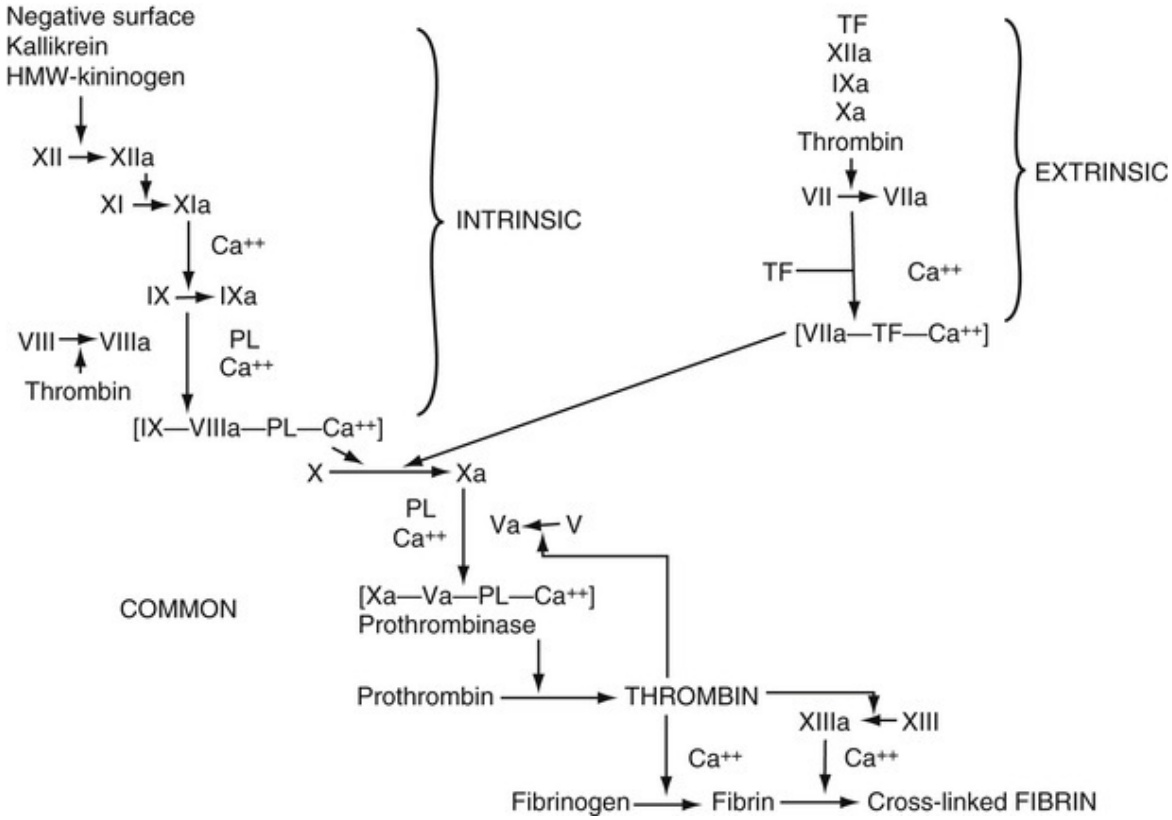


FIG. 27.1 Coagulation pathways. *HMW,* High molecular weight; *PL,* membrane phospholipids; *TF,* tissue factor.

Acquired defects in coagulation factors are much more common than inherited defects and generally involve deficiencies in multiple rather than single coagulation factors. Causes of acquired defects include hepatic disease, vitamin K antagonism (e.g., moldy sweet clover poisoning), and increased consumption via DIC (Boxes 27.3 and 27.4). The PT is usually the first abnormal coagulation test with decreased coagulation factor production in chronic liver disease.[14] Widespread coagulation and consumption in DIC also causes a prolonged PTT and thrombocytopenia, along with increased fibrinolysis. In addition to quantitative deficiencies, coagulation factors may be functionally impaired by increased FDPs or circulating anti-factor antibodies.

Box 27.3

Causes of Prolonged Prothrombin Time in Horses

Common Causes

Disseminated intravascular coagulation (DIC)
Anticoagulant or rodenticide toxicosis
Acute hepatic necrosis
Pyrrolizidine alkaloid toxicosis
Aflatoxicosis
Chronic hepatic fibrosis

Less Common Cause

Moldy sweet clover

Box 27.4

Causes of Prolonged Prothrombin Time in

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Ruminants

Common Causes

Moldy sweet clover (*Melilotus* species) toxicosis
Disseminated intravascular coagulation (DIC)

Less Common Causes

Anticoagulant or rodenticide toxicosis
Pyrrolizidine alkaloid toxicosis
Rubratoxicosis
Aflatoxicosis
Bitterweed *(Hymenoxys odorata)* toxicosis
Chronic hepatic fibrosis
Hereditary fibrinogen deficiency

Vitamin K is necessary for hepatic production of functional coagulation factors II, VII, IX, and X as well as anticoagulant proteins C and S. The action of vitamin K is inhibited by coumarin compounds acquired via moldy sweet clover hay or anticoagulant rodenticide ingestion or by therapeutic adminstration (e.g., warfarin in horses). Vitamin K inhibition results in deficient carboxylation of coagulation factors and a resulting inability to bind endothelium stably. These incompletely carboxylated factors are termed *PIVKAs* (*p*roteins *i*nduced by *v*itamin *K a*ntagonism/absence). A modified PT assay called the Thrombotest PT is specific for defects in factors II, VII, and/or X and can be used in cases of suspected coumarin toxicosis; specific tests for PIVKAs are not available for domestic animals.

Clinical signs of coagulation factor deficiencies include spontaneous hemorrhage (e.g., epistaxis, melena, hematuria) or prolonged bleeding after trauma, diagnostic procedures, or surgery. Hematomas or hemarthroses are common after minor trauma or normal exercise, and bleeding into body cavities can occur. Coagulation times are designed primarily for screening purposes and are very insensitive to minor defects of one or more factors (e.g., the PT was prolonged with factor VII levels ranging from 16% to 39% of normal in one study).[1] Less severe coagulation defects may require specific factor assays for

diagnosis.

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Prolonged Activated Partial Thromboplastin Time

The PTT is a measure of the intrinsic (contact activation) and common coagulation pathways (see Fig. 27.1). The activated PTT is now the only test used, and it measures time from the addition of calcium to plasma with partial thromboplastin reagent and a surface activator until clot formation. The PTT is prolonged with deficiencies or defects in factors XII, XI, IX, and VIII coagulant (VIII:C) as well as prekallikrein (PK). Most PTT assays detect PK deficiency, and the assay can be corrected to prove that a PK abnormality is the cause of prolonged PTT. The activated coagulation time (ACT) is a simplified variation of the PTT that can be tested by mixing whole blood with activator and calcium. It is less sensitive to factor defects, as prolonged ACT may not occur until a single factor is at 5% to 10% of normal function, and can be prolonged also with severe thrombocytopenia.[1] As with all tests, reference values vary by species; for example, alpacas have substantially shorter PTTs normally than horses or cattle.[31] Age may also play a role, as healthy newborn foals have PTTs and PTs that are longer than adult reference values.

The most common cause of a prolonged PTT is increased consumption of clotting factors induced by DIC (Boxes 27.5 and 27.6). Liver failure and vitamin K antagonism prolong both PTT and PT. Single factor defects will prolong the PTT and not affect the PT. Inherited deficiencies of factors VIIIa (the precursor form of VIII:C) and XI and PK have been described in horses.[32-36] Congenital factor VIIIa deficiency (hemophilia A) is sex-linked, and males are clinically affected; carriers cannot be detected via PTT, as factor levels are insufficiently decreased. The level of factor VIIIa must drop below 5% of normal before spontaneous bleeding occurs. Clinical signs of coagulation factor deficiencies are those of hemorrhagic diathesis, as described in the previous section. Inherited factor XI deficiency is transmitted in Holstein cattle by an autosomal recessive trait.[37] Cattle deficient in factor XI rarely demonstrate bleeding tendencies.

Box 27.5

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Causes of Prolonged Activated Partial Thromboplastin Time in Horses

Common Causes

Disseminated intravascular coagulation (DIC)
Anticoagulant or rodenticide toxicosis
Acute hepatic necrosis

Less Common Causes

Moldy sweet clover toxicosis
Hemophilia A (deficient factor VIII coagulant [VIII:C])
Congenital deficiencies of factor IX, factor XI, prekallikrein, or high molecular weight kininogen
Hepatotoxins (pyrrolizidine alkaloids, rubratoxins, aflatoxins, bitterweed)

Box 27.6

Causes of Prolonged Activated Partial Thromboplastin Time in Ruminants

Common Causes

Moldy sweet clover toxicosis
Disseminated intravascular coagulation (DIC)

Less Common Causes

Congenital deficiency of factor XI
Anticoagulant or rodenticide toxicosis
Hepatotoxins (pyrrolizidine alkaloids, rubratoxins, aflatoxins, bitterweed)
Hereditary fibrinogen deficiency

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Although both PT and PTT can be prolonged during DIC, it is not uncommon for only one test to be abnormal initially. Serial analyses should reveal a trend toward prolongation of both tests along with decreasing platelet count. When a persistently prolonged PTT is the only laboratory abnormality, hereditary factor deficiency should be suspected. As with PT, the PTT is a relatively insensitive screening test. The assays generally have prolonged times when at least one factor is decreased to 30% or less of normal function or when combined factor activity is at least mildly decreased. Both PT and PTT can be shortened (times will be below reference interval) with increased fibrinogen, factor V, and/or factor VIII (PTT only). Shortened coagulation times are not traditionally used as indicators of clinical hypercoagulability, as other causes of shortened coagulation times include traumatic venipuncture and insufficient anticoagulation. However, there is evidence in other species that shortened PT and/or PTT can correlate with evidence of hypercoagulability via thromboelastography and/or clinical thromboembolic disease.[38-40] Hypercoagulability should therefore be considered a differential for shortened PT and/or PTT in a large animal patient.

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Increased Fibrin and Fibrinogen Degradation Products

FDPs can be composed of fragments of fibrin and/or fibrinogen. Assays are either serum or plasma specific, as fibrinogen present in plasma can react to the polyclonal antibody of the serum assays, and are relatively species specific. A study in horses found that two FDP assays, one serum-based and one plasma-based, had low sensitivity for FDPs in horses with colic.[41] At the same time, a plasma D-dimer assay was a useful adjunct test. Commercial D-dimer assays have also been used in cattle; in one study peritoneal fluid D-dimer was a useful indicator of peritonitis.[42] D-dimer (one form of FDP) is a cross-linked fibrin fragment and is therefore specific for fibrinolysis, whereas FDPs as a group are less specific. When measurable, increased levels of FDPs and/or D-dimer generally indicate increased fibrinolysis in response to excessive coagulation (Box 27.7). In addition to DIC, localized intravascular fibrin deposition following surgery, internal hemorrhage, sepsis, and other severe inflammatory processes may cause increased FDP levels. Plasmin perturbations may occur with snake envenomation, heatstroke, surgery, or administration of plasminogen activators and can lead to fibrinogenolysis and increased FDPs.[1] Decreased FDP clearance due to hepatic or renal disease can also lead to increased FDP levels.

Box 27.7

Causes of Elevated Fibrin and Fibrinogen Degradation Products in Large Animals

Common Causes

Disseminated intravascular coagulation (DIC)
Thrombophlebitis
Postoperative state
Severe inflammation
Immune-mediated thrombocytopenia (IMT)

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Uncommon Causes

- Massive internal hemorrhage
- Primary hyperfibrinolysis

Increased serum FDPs can contribute in turn to hemorrhagic clinical manifestations of DIC by interfering with thrombin activity, fibrin polymerization, and platelet aggregation. Interpretation of FDP or D-dimer tests depends on evaluation of the other components of the hemostasis profile (platelet count, PT, PTT) in concert with the patient's history and clinical signs. Serum FDP levels greater than 40 µg/mL or plasma levels greater than 20 µg/mL most often occur with DIC; lower values do not exclude DIC. Horses have measurable D-dimer concentrations in health, so an upper cutoff value must be used to report abnormal values.[41] In one study horses with clinical evidence of DIC secondary to colic had decreased D-dimer levels consistent with hypofibrinolysis during hypercoagulation.[17]

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Decreased Plasma Antithrombin III

The physiologically most important inhibitor of coagulation is antithrombin or antithrombin III (ATIII). This low molecular weight glycoprotein primarily neutralizes activated factors IX, X, and II (thrombin) along with other coagulation proteins. Heparin is a necessary cofactor to potentiate ATIII and enable its rapid inhibitor activity. ATIII is measured via chromogenic assays to evaluate functional activity; activity is expressed as the percent relative to a species-specific plasma pool from healthy animals. Plasma ATIII levels may be reduced by decreased liver production, excessive use, loss from the intravascular compartment, or increased catabolism. Inherited ATIII deficiency is not reported in animals. Newborn foals have lower ATIII levels than adult horses normally.[43]

Chronic liver disease may result in failure to produce ATIII and a number of other important plasma proteins. However, horses with chronic liver disease were shown to have increased plasma ATIII levels.[44] These findings suggest that ATIII may behave as an acute phase protein in horses, as some horses also had increased fibrinogen levels. A second group of horses in the study with acute diarrhea or colitis had decreased ATIII levels. ATIII is variably reported as a positive or negative acute phase protein in animals.[1,44] Estrogens may contribute to ATIII deficiency due to negative effects on synthesis.[1]

In conditions such as DIC, ATIII is consumed and can be decreased as a result of binding to activated coagulation factors and subsequent hepatic clearance of the ATIII-factor complexes. Any pathologic activator of coagulation, including trauma, neoplasia, or sepsis, may cause reduction of plasma ATIII (Boxes 27.8 and 27.9). ATIII can be reduced as a component of coagulopathy secondary to endotoxemia in foals.[45] Administration of unfractionated or low molecular weight heparin leads to decreased ATIII levels via increased activity and subsequent clearance of ATIII.[46]

Box 27.8

Causes of Reduced Antithrombin III in Horses

Common Causes

Disseminated intravascular coagulation (DIC)
Protein-losing enteropathy (e.g., granulomatous enteritis, intestinal lymphosarcoma, nonsteroidal antiinflammatory drug toxicosis)
Chronic glomerulonephritis

Less Common Causes

Acute toxic enteritis
Acute hepatic necrosis
Venous thrombosis

Box 27.9

Causes of Reduced Antithrombin III in Ruminants

Common Causes

Disseminated intravascular coagulation (DIC)
Renal amyloidosis
Johne's disease

Less Common Causes

Venous thrombosis
Hepatic failure

Diseases that cause massive proteinuria or protein-losing enteropathy result in loss of ATIII in addition to other plasma proteins. Because of the small size of ATIII, it is lost in approximately the same proportion as albumin. Nephrotic syndrome in humans and animals may lead to secondary hypercoagulability and thrombotic disease due to urinary ATIII loss and other complicating factors; hypoalbuminemia can be a useful predictor of thrombotic risk given concurrent loss of ATIII and albumin and may also play a contributory role.[47,48]

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The major clinical sequela of ATIII deficiency is a tendency to develop venous thrombosis. Thrombosis in nephrotic syndrome was discussed earlier. Venous thrombosis is commonly recognized in horses with severe toxic colitis or endotoxemia, but the potential role of ATIII deficiency is unknown. Decreased ATIII has been documented in nonsurviving horses with colic and in horses with strangulating obstructions.[49] The contribution of ATIII consumption in DIC to the clinical manifestations is complex and difficult to evaluate; however, use of ATIII concentrates in human patients with acute DIC has improved survival in some instances.[44] As with all components of the hemostatic system, plasma ATIII must be evaluated in combination with other hemostasis values.

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Hypofibrinogenemia

Decreased fibrinogen concentration, termed *hypofibrinogenemia*, can be detected via a modified thrombin time test, the Clauss TT, or via immunoassay using anti-fibrinogen antibodies. Heat precipitation is useful to detect increased fibrinogen but is too insensitive to detect hypofibrinogenemia. Plasma fibrinogen levels represent the balance between fibrinogen production and degradation, an important concept in large animals since fibrinogen production is often increased due to inflammation (see Chapter 26) and increased consumption may potentially be masked. Pregnancy also can cause increased fibrinogen.[50]

Hypofibrinogenemia may result from impaired hepatic synthesis, increased consumption with DIC, or uncompensated loss during massive hemorrhage (Boxes 27.10 and 27.11). Decreased plasma fibrinogen is uncommon in liver disease of large animals; increased production due to concurrent inflammation appears to be more common. With DIC and fibrinolysis, decreased fibrinogen concentration due to consumption is expected in most species. However, hypofibrinogenemia is not common in horses with DIC. Horses with colic in one study had evidence of increased coagulation postoperatively, including decreased ATIII and increased D-dimer, with concurrent hyperfibrinogenemia.[51] Hypofibrinolysis has also been shown in horses with DIC.[17]

Box 27.10

Causes of Hypofibrinogenemia in Horses

Uncommon Causes

Acute hepatic necrosis
Acute severe disseminated intravascular coagulation (DIC)
Severe hepatic fibrosis

Box 27.11

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Causes of Hypofibrinogenemia in Ruminants

Uncommon Causes

Hereditary afibrinogenemia (goats)
Acute severe disseminated intravascular coagulation (DIC)

Hereditary afibrinogenemia has been described in a family of Saanen dairy goats with a hemorrhagic diathesis in newborn kids that included umbilical bleeding and recurrent hemarthroses.[14] Fibrinogen was undetectable in the affected animals, while heterozygotes had hypofibrinogenemia.

Thromboelastography

Thromboelastography (TEG) analysis is a viscoelastic measurement technique used to assess global clot formation and lysis in whole blood. It is sometimes termed *rotational TEG;* a similar measurement technique is ROTEM (rotational thromboelastometry). The advantage of TEG analysis over traditional minimum coagulation panels consisting of platelet count, PT, and activated PTT testing is that TEG can detect hypercoagulable states and increased fibrinolysis (Fig. 27.2). TEG is therefore the only readily available test of hypercoagulability in veterinary medicine. Fibrinolysis can be assessed by D-dimer in horses or by FDPs in other large animal species, but with the specificity issues inherent to FDP testing as described earlier. Disadvantages of TEG or ROTEM testing include the need for analysis within 2 hours of blood collection and the impact of marked anemia on testing.[52,53] Substantial thrombocytopenia can alter TEG results, but the results may be useful as a potential index of bleeding tendency in the patient and may be superior to platelet count alone for this use because TEG also accounts for platelet function.[54,55] A concurrent CBC is vital for interpretation of TEG results.

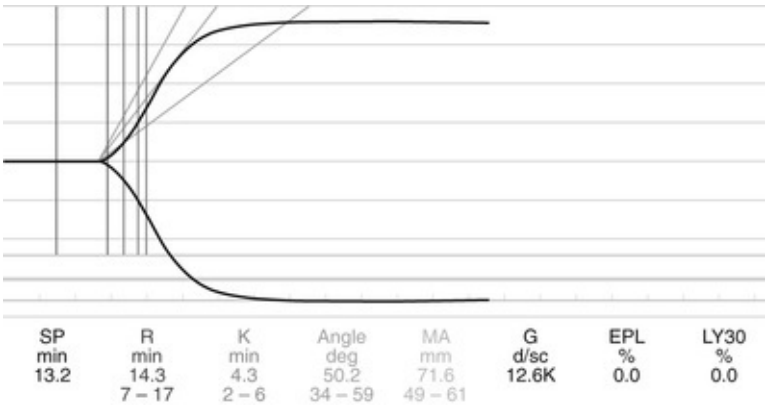


FIG. 27.2 Thromboelastograph (TEG) tracing from a horse demonstrating increased maximum amplitude *(MA),* suggestive of platelet hyperresponsiveness and/or other potential causes of hypercoagulable tendency. Other values including the R (reaction) time and K (kinetics) time are within reference intervals.

Studies have shown some diagnostic and prognostic utility of TEG in

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evaluating coagulation in horses with gastrointestinal disease.[56-58] Using TEG and other viscoelastic testing, studies in neonatal foals have determined both that coagulation parameters in normal neonatal foals can differ from those in adult horses and that septic foals can have evidence of coagulation abnormalities, including hypercoagulability.[59,60] Other common uses of TEG or ROTEM in large animal research studies include evaluation of the effects of plasma or artificial colloid transfusion on coagulation and assessment of the effects of dexamethasone treatment in healthy adult horses (no differences seen) and in veal calves (treated calves had evidence of hypercoagulability).[61-65]

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Other Tests of Hemostatic Function

Other tests of hemostasis may be indicated in specific disease situations; they include the following.

Thrombin Time

The standard thrombin time test measures the rate of fibrinogen to fibrin conversion and can be a useful assay for the effects of FDPs, heparin, and paraproteins; for example, a prolonged thrombin time can indicate the presence of FDPs that interfere with fibrin polymerization. This test also evaluates for the presence of hypofibrinogenemia, but the Clauss TT (described earlier) is a better assay for that purpose, as any interference effect from FDPs, heparin, and other factors is largely eliminated.

Specific Factor Assays

Specific factor analyses are generally indicated for the diagnosis of hereditary factor deficiencies. Prolonged PTT values along with the signalment, history, and clinical picture may indicate that specific factor assays are needed. In DIC, specific factor analysis is unlikely to be useful.

α_2-Antiplasmin

α_2-Antiplasmin (α_2-AP) binds plasmin to cleave and inactivate it, and then the complexes are cleared from circulation. In humans, α_2-AP is decreased by severe liver disease (reduced production) and with DIC (consumption). Experimental studies in ponies suggest that α_2-AP may be reduced with chronic or subclinical DIC.[66] Conversely, increased α_2-AP is reported in horses with colic as part of the acute phase response (see Chapter 26).

Protein C

The protein C pathway provides the second major anticoagulant mechanism that regulates hemostasis. Protein C is activated by thrombin complexed to

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thrombomodulin and subsequently inactivates factors Va and VIIIa via proteolysis and using the cofactor protein S. In humans, decreased protein C can occur in liver failure or DIC, increasing the risk of thrombotic disease, and decreased protein C is reported in horses with severe colic.[49]

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• CHAPTER 28

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Collection and Analysis of Bone Marrow

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Bone marrow is composed of hematopoietic cells as well as structural components, including trabecular bone, adipose tissue, a sinusoidal system, supporting reticular cells, and an extracellular matrix. The hematopoietic system is composed of erythrocytes, leukocytes, and platelets; their precursor cells; and the tissues that support the continuous cycles of cell differentiation required for maintenance of oxygen delivery, protection from infectious agents, and hemostasis. A single multipotent stem cell is the precursor for all hematopoietic cells. From this cell arise progenitor cells directed toward various cell lineages. Postnatally, hematopoiesis to replenish circulating erythrocytes, granulocytes, monocytes, and platelets predominantly occurs in the bone marrow. Although lymphocytic precursor cells continue to travel from the bone marrow to the thymic cortex and enteric mucosa for differentiation postnatally, most circulating lymphocytes are associated with the extramedullary lymphoid organs.

Constantly replenishing blood cells, the bone marrow is one of the most active tissues in the body. Blood cell turnover is rapid; for example, neutrophils have a circulatory half-life of approximately 10 hours. The life span of platelets, on average, is approximately 7 to 10 days, and the life span of large animal erythrocytes is approximately 5 months, with slightly shorter half-lives reported in some breeds.[1-3] Readers are referred to a veterinary hematology textbook for more in-depth information on the hematopoietic system.[4]

Multipotent mesenchymal stromal cells are progenitor cells that give rise to the structural components of bone marrow and show great promise in regenerative medicine. Bone marrow–derived mesenchymal stem cells (BMSCs) have shown higher osteogenic capacity compared to mesenchymal stem cells (MSCs) from adipose tissue, umbilical cord tissue, and cord blood,[5] although they seem to proliferate at a slower rate than MSCs originating from other tissue

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types.[6] Bone marrow aspirates are routinely performed in equine practice to obtain bone marrow concentrates and BMSCs. Bone marrow aspirates without processing, concentrates, and BMSCs are frequently used to treat tendon, ligament, and meniscal injuries. Intra-articular administration is also used to enhance healing of cartilage defects and treat subchondral bone cystic lesions in horses.[7,8]

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Diagnostic Indications for Bone Marrow Aspiration or Biopsy

Bone marrow evaluation provides important diagnostic information on the hematopoietic status of an animal; it is typically performed to evaluate hematopoiesis and to detect evidence of neoplastic or infectious disease (Box 28.1). The complete blood cell count (CBC) is the most common method used to evaluate the hematopoietic system, but a more comprehensive evaluation includes bone marrow aspiration and/or biopsy. Bone marrow aspiration is commonly used to evaluate the cause of cytopenia. Unexplained nonregenerative anemia, neutropenia, thrombocytopenia, and pancytopenia are indications for bone marrow aspiration. In these cases, bone marrow evaluation is used to determine if the cytopenia is more likely a result of lack of production or of consumption or destruction of the cell in question. If an animal's clinical presentation and other laboratory data provide a reasonable explanation for cytopenia, a decision to perform the procedure may not be justified. For example, if another disease process is present that could explain nonregenerative anemia, such as a chronic inflammatory disease or chronic renal failure, bone marrow aspiration is not indicated in most cases.

Box 28.1

Indications for Bone Marrow Evaluation

- To assess regeneration in anemic horses
- To investigate cause of cytopenia
  - Unexplained nonregenerative anemia
  - Unexplained neutropenia
  - Unexplained thrombocytopenia
  - Pancytopenia
- To investigate for neoplasia
  - Atypical cells in peripheral blood
  - Lytic or proliferative bone lesions

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Hypercalcemia
Monoclonal gammopathy
To investigate for infectious disease
Fever of unknown origin
Lytic or proliferative bone lesions

Another common reason for bone marrow aspiration is the observation of atypical cells, unexplained immature cells, or abnormal blood cell morphology on a peripheral blood film. In these cases bone marrow is evaluated for the diagnosis of leukemia, myelodysplastic syndromes, and infiltrative disease. Potential infiltrative disease is sometimes detected radiographically, and the presence of lytic or proliferative bone lesions can also be an indication for bone marrow aspiration. Because abnormalities within the bone marrow are not always reflected in the peripheral blood, it may be prudent to perform bone marrow aspiration if a neoplastic or infectious process is clinically suspected but cannot be found elsewhere. This suspicion may arise from finding cytopenias or detecting an unexplained hypercalcemia or monoclonal gammopathy, conditions that are often associated with neoplasia; identifying a fever of unknown origin; or recognizing the probability of an infectious agent that may have bone marrow involvement.

Even though complication rates are low, bone marrow aspiration should not be performed indiscriminately, and, as for all testing, the clinician should consider what question is being asked and if bone marrow evaluation is the appropriate diagnostic test for answering that question. Examination of a peripheral blood film often provides clues as to the necessity of bone marrow evaluation. In general, cytopenia should be persistent and confirmed before bone marrow evaluation is performed. Rechecking a low cell count by drawing a new blood sample, especially if initial results do not fit with the clinical presentation of the animal, is recommended. An ethylenediaminetetraacetic acid (EDTA)–associated pseudothrombocytopenia has been reported in horses,[9] which can be ruled out by drawing blood into a heparin or sodium citrate tube for platelet counts. A low platelet count can also be artefactual if platelet aggregation occurs during blood collection. The presence of clumped platelets on a peripheral blood film is an indication that platelet aggregation has occurred and that a low platelet count should be viewed with skepticism. Repeated CBCs can also be used to assess persistence of an abnormality. It can take up to 5 days for the bone marrow to respond to acute anemia and for regeneration to be evident in the

peripheral blood. Bone marrow aspiration is typically not indicated when there is evidence of regeneration in the peripheral blood. Evidence of erythroid regeneration in the peripheral blood includes an increase in the number of reticulocytes or polychromatophilic cells, basophilic stippling, and macrocytosis. Because the changes typically associated with regenerative anemia are rarely seen in horses, bone marrow aspiration is often the only way to assess erythropoiesis in this species. [See Color Plates 28.1 to 28.4 for an example of erythroid hyperplasia in a horse.] Evidence of regeneration in granulocytes includes the presence of a left shift and toxic changes.

Cytologic evaluation of bone marrow aspirate is more commonly performed than core biopsy because results can be attained more quickly and the morphology of the cells is superior, allowing a more accurate assessment of cell types. The disadvantage of aspiration versus biopsy is that architecture cannot be assessed with an aspirate, and it can be impossible to confirm whether a poor cellular sample is a result of a pathologic process or an unsatisfactory sampling. The core biopsy provides a better assessment of bone marrow cellularity and is necessary for the confirmation of myelofibrosis, generalized bone marrow suppression, or necrosis. [See Color Plates 28.5 to 28.8 for core biopsy samples of generalized bone marrow hypoplasia from a bovine.] The core biopsy also provides a more accurate assessment of metastatic neoplasia because architecture can be assessed. It is generally recommended to submit both aspirates and biopsy for evaluation or, at least, collect a core biopsy to be stored in formalin for later evaluation, if needed.

If a bone marrow sample is being submitted for evaluation, a CBC should be submitted concurrently because interpretation of the bone marrow is dependent on CBC results and changes can occur quickly in the blood.

Bone Marrow Collection

Sites

Hematopoietically active bone marrow is most consistently found in the flat bones (sternum, ribs, pelvis, vertebrae) and proximal ends of long bones (humerus, femur). The most commonly described sites for bone marrow aspiration in large animals are the sternum, ribs, and iliac crest (Figs. 28.1 and 28.2). Which location is chosen may depend on species, age, and temperament of the animal as well as on available facilities.

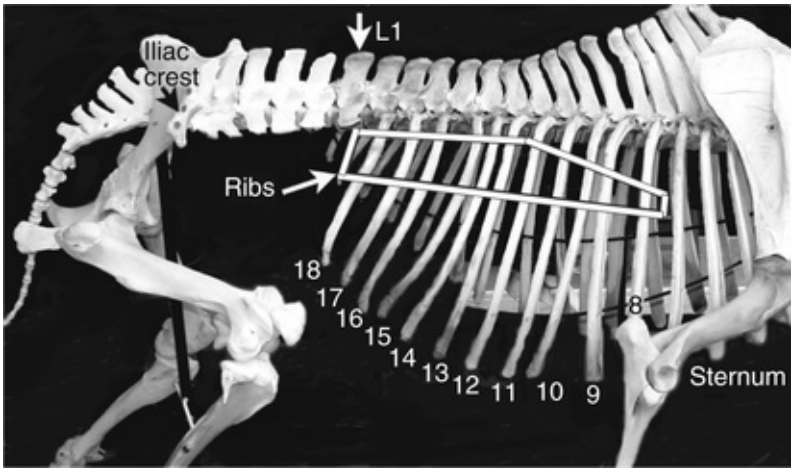


FIG. 28.1 Equine skeleton depicting sites for bone marrow aspiration: the sternum, iliac crest, vertebral ends of ribs *8* to *18*, and first lumbar vertebra *(L1)*.

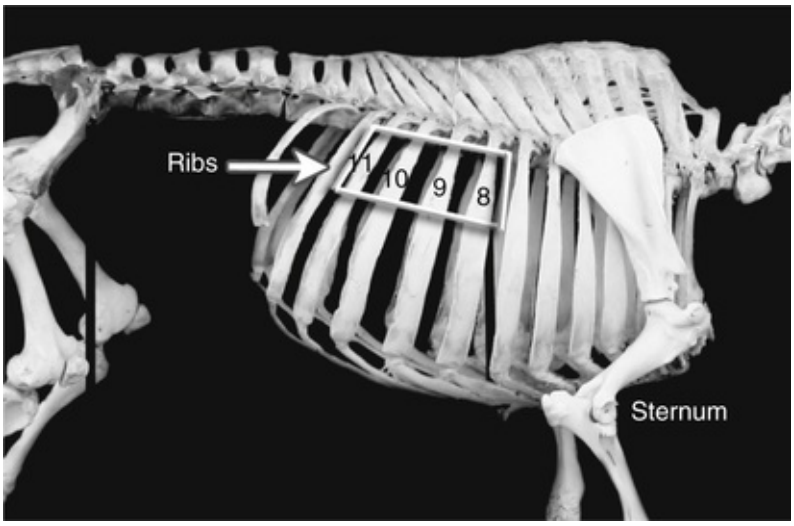


FIG. 28.2 Bovine skeleton depicting sites for bone marrow aspiration: the sternum and vertebral ends of ribs *8* to *11*.

The ventral sternum is the preferred site in adult horses, small ruminants, and camelids (Figs. 28.3 to 28.6). It is one of the preferred sites in cattle. The advantages of the sternum are that it is covered by only a thin layer of bone, it has areas not covered by thick muscles, and samples can be reliably obtained from the site. The disadvantages of the sternum are that it is near vital organs and that the operator is in an awkward position when working on a standing animal. A procedure for sampling the cranial aspect of the sternum has also been described in horses[10] (see Fig. 28.3). There is more muscle to go through with this approach.

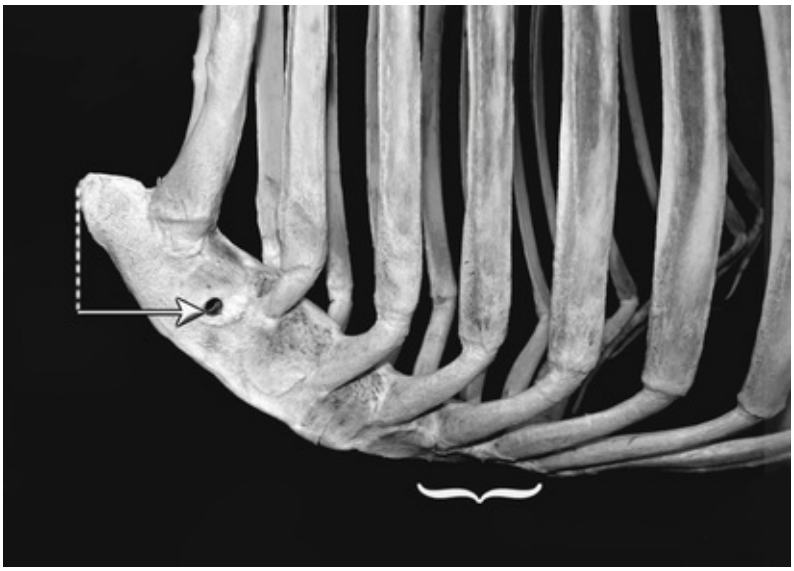


FIG. 28.3 Lateral view of equine sternum. The ventral sternum is the most popular site for sampling bone marrow in the adult horse *(bracket),* but the cranial sternum can also be used. The aspirate site of the cranial sternum is reached by going one hand width below *(dotted line)* and one hand width lateral to its cranial tip. From there, the needle is advanced in a horizontal plane at a 45-degree angle to the longitudinal axis of the horse *(arrow).*

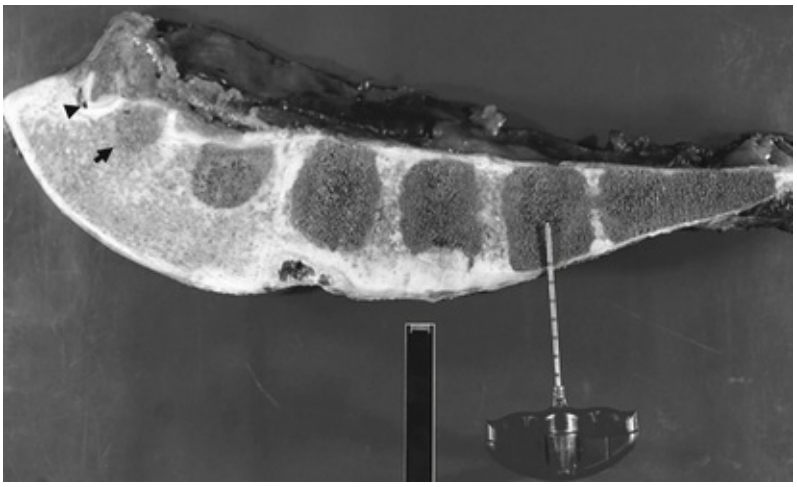


FIG. 28.4 Equine sternum sectioned on midline. The bone marrow aspiration needle is anchored in the center of the fifth sternebra. The arrowhead indicates the first sternocostal joint; left and right joints are usually fused together in horses. The black arrow indicates the first sternebra.



FIG. 28.5 Cross-section of sheep sternum. The needle is entering the second sternebra. The second through fourth sternebrae are recommended as optimal sites for bone marrow collection.



FIG. 28.6 Llama sternum. The llama sternum can be sampled at ventral midline, inserting the needle vertically through the callosity, or from a lateral approach, inserting the needle dorsal to the callosity.

The ribs are one of the preferred sites for bone marrow aspirates in cattle. The dorsal ends of ribs 8 to 11 can be accessed for sequential aspirations[11] (see Fig.

28.2). Ribs can also be used in the horse, but the needle slips off the bone more easily. In calves, sheep, and goats the marrow cavity of the rib is small and more difficult to hit,[12] and in camelids the rib marrow is less consistent in location than the sternum.[13] Successful collection from ribs has been described in camels, with the fifth to eighth ribs as the best sites.[14]

The iliac crest is the site often used for bone marrow sampling in foals, and it can also be used in young adult horses up to a couple of years in age[15] (Fig. 28.7). Samples can also be obtained from older horses at this site, but the needle must be inserted more deeply, needle placement is more critical, and it becomes difficult to obtain a successful sample in horses more than 9 years old.[16] The wing of the ilium is generally considered too thin for bone marrow aspiration in camelids,[13] although successful bone marrow aspiration from the iliac crest of a 2-year-old alpaca has been reported[17] (Fig. 28.8). The iliac crest can also be used in sheep (Fig. 28.9).

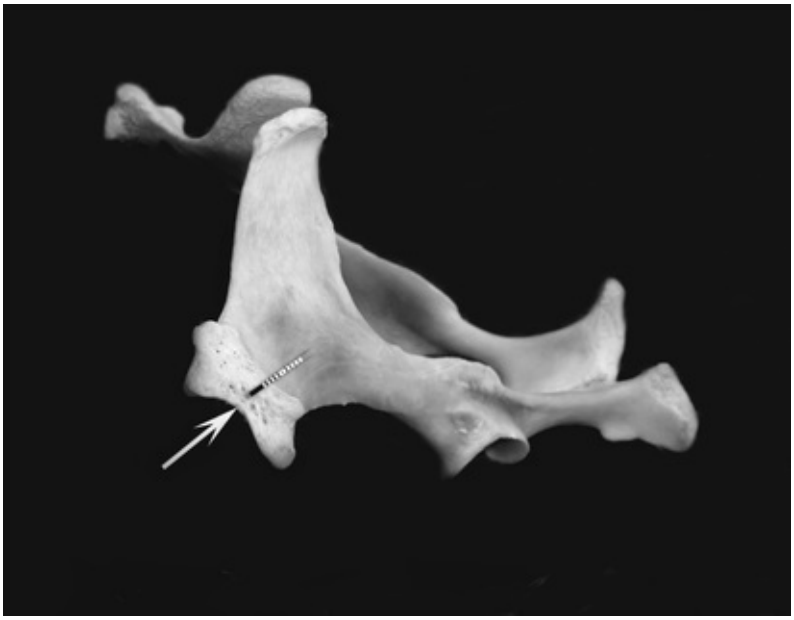


FIG. 28.7 Equine pelvis. To obtain bone marrow, the needle should be placed near the center of the tuber coxae *(arrow)* and advanced toward the opposite coxofemoral joint *(dotted line).*



FIG. 28.8 Llama pelvis. The wing of the ilium *(arrows)* is generally considered too thin for easy bone marrow collection in camelids.



FIG. 28.9 Bone marrow aspirate from the ileum of a sheep. This sheep was undergoing necropsy, and the wing of the ileum has been dissected out.

Another site informally described for horses is the spinal process of the first lumbar vertebra (Fig. 28.10). It is usually vertical, whereas the adjacent processes tend to be more angled. The tip of the process is wider than the shaft and has a thin layer of bone. The needle is advanced straight down into the marrow cavity, which is narrow, but if the needle is close to correct placement the walls of the process help guide the needle into the marrow cavity. The advantage of this site is that the operator is not working under the horse. The spinal process is reported to be a poor site to sample in the cow.[18]

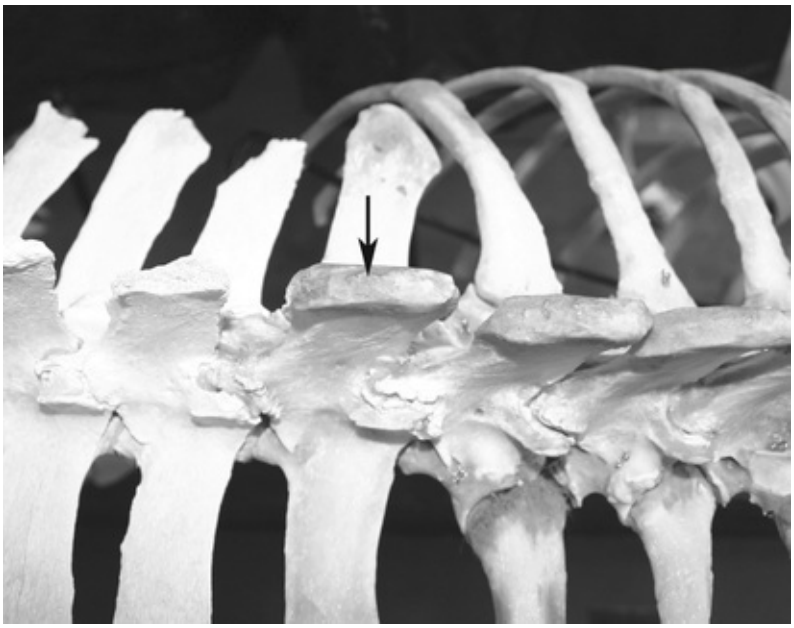


FIG. 28.10 First lumbar vertebra of a horse. Although not widely used, the spinal process of L1 *(arrow)* is another site from which bone marrow can be obtained in the horse.

Preferred collection sites to obtain equine bone marrow for regenerative therapeutic purposes include the sternum and tuber coxae. For young horses either site can be elected. However, in older animals aspirates from the tuber coxae yield significantly lower numbers of BMSCs.[19] Complication rates associated with the procedure are generally low for both sites[20]; nevertheless, severe complications have been reported following sternal aspirates.[21] In vitro, BMSCs from ileal aspirates showed higher chondrogenesis properties (glycosaminoglycan accumulation) than cells isolated from the sternum[22]; however, in vivo studies to validate this potential advantage are lacking.

Approach to the Sternum.

In the horse, bone marrow aspiration is typically performed in the standing animal. Sedation or a twitch may be used if necessary. The preferred site is on the ventral midline. A recent study performed in horses revealed that the fifth sternebra is the most consistent and safe site for aspiration of bone marrow.[23] Ultrasound can be used to select the desired sternebra and provide guidance for the optimal puncture site (Fig. 28.11). If ultrasound is not available, the optimal insertion site is exactly on the ventral midline in the cleavage between the deep pectoral muscles where a line connecting the points of the elbows would cross[24]

(Fig. 28.12).

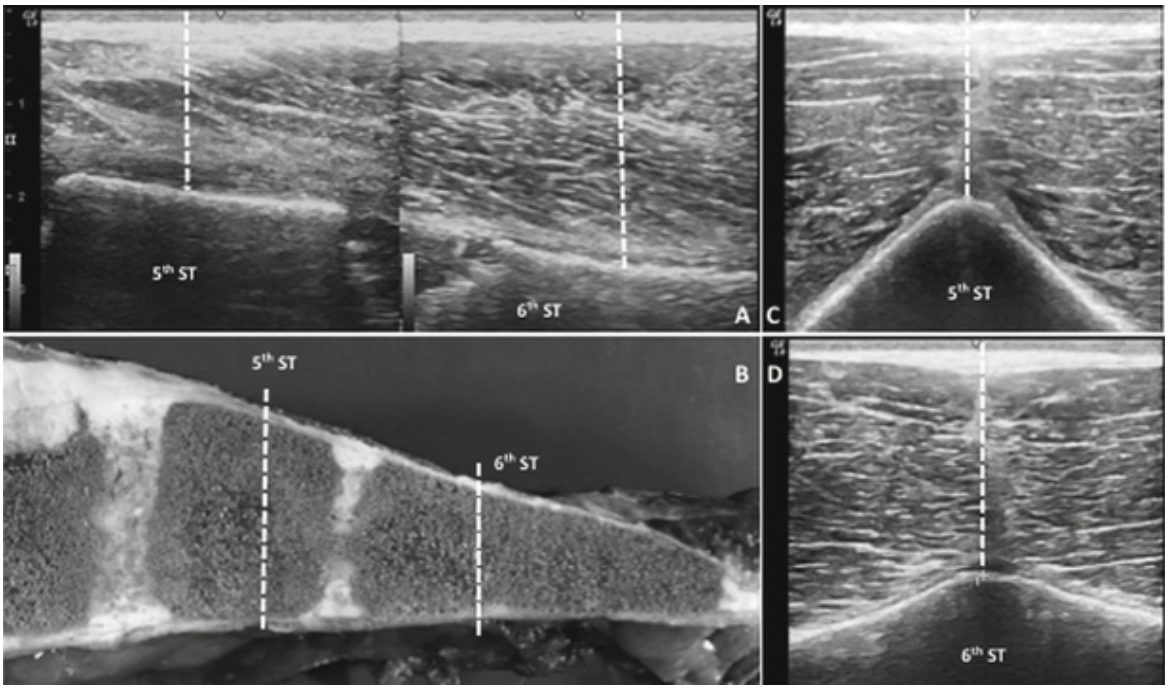


FIG. 28.11 Equine sternum. **A,** Longitudinal ultrasound of the fifth and sixth sternebrae. Cranial is to the left and ventral to the top of the image. The fifth sternebra is more superficial *(dotted line,* 1.88 cm) than the sixth sternebra *(dotted line,* 2.71 cm). **B,** Longitudinal section of equine sternum with the same orientation as in A. The fifth sternebra is more cuboidal and shorter longitudinally than the sixth sternebra. White dotted lines correspond to the position of the measuring lines in image A. Transverse ultrasound of the fifth **(C)** and sixth **(D)** sternebrae: the more conical shape of the fifth sternebra compared to the flat shape of the sixth sternebra might make it more difficult to anchor the aspiration needle in the center.



FIG. 28.12 Bone marrow aspiration in a standing, sedated horse. **A,** The ventral sternum between the horse's elbows is clipped and surgically scrubbed. **B,** After local anesthetic and stab incision, a spinal needle is inserted at the intersection of the ventral midline with a parallel line between the points of both elbows. A heparin-primed 60-mL syringe is used for therapeutic bone marrow collection.

The manubrium of the sternum can also be sampled in horses by finding the cranial end of the sternum and going one hand width below and one hand width laterally from the end (see Fig. 28.3). From this spot the needle is advanced through the muscle in a horizontal plane at a 45-degree angle to the longitudinal axis of the horse.[10]

Sternal bone marrow can be sampled from adult cattle standing in stocks or a squeeze chute. It may be necessary to use techniques to prevent kicking, such as jacking the tail, or sedation. Unruly adult cattle and large calves can be cast and held in lateral recumbency. The upper front leg of the cast animal is held extended along the neck, exposing the sternum, after the other legs are secured with a rope.[25] Calves that weigh less than 300 lb can be placed in dorsal recumbency and secured by assistants or with ropes.[12] The needle should be placed on the midline and inserted perpendicular to the third or fourth sternebra. The appropriate sternebra is located by palpating the third or fourth rib and following it to the sternum.

For the sternum of a small ruminant to be sampled, the animal is placed in dorsal recumbency with legs secured, or it can be restrained in a sitting position with an assistant standing behind, supporting the animal and holding a foreleg in each hand.[12] The location of the appropriate site is midline, between the front legs. The second through fourth sternebrae can be used in sheep (see Fig. 28.5). A prominence may be felt between the first and second sternebrae. The appropriate sternebrae can also be located by palpating ribs and following them to their articulations.[26] In sheep, the needle will advance approximately 0.5 cm into the bone (2.5 to 3.8 cm from the skin) before entering the marrow cavity.[26]

The sternum of llamas can be sampled with the animal either standing in a chute or in left lateral recumbency, usually sedated[27] (see Fig. 28.6). The sample can be taken by inserting the needle vertically through the callosity on the ventrum of the sternum or with a lateral approach, approximately 3 to 4 cm dorsal to the callosity with the needle directed medially and slightly dorsally to engage bone.[13] Marrow will be approximately 2.5 cm deep in an adult. The sample is normally more dilute with blood than in other species.[13]

When the ventral sternum is sampled, unless a lateral approach is used, the needle should be placed on the midline, as near to the center of the bone as possible, and advanced perpendicular to the bone. A sudden reduction of resistance may be felt when the marrow cavity is entered; because the sternal cortex is so thin, especially in horses; however, there may be no obvious change. Care needs to be taken to not enter the thoracic cavity. Because a change in resistance may not be felt, once the tip of the needle is firmly seated in the bone an aspiration attempt should be made.

Approach to the Rib.

The vertebral end of the rib more consistently contains marrow than does the sternal end of the bone[28,29] (Fig. 28.13). Palpation can be used to find the rib that has the least amount of fascia covering it. In the horse, the eighth to eighteenth ribs can be used, going as high as possible but below the latissimus dorsi and serratus posticus muscles[28] (see Fig. 28.1). In cattle, place the needle approximately 3 inches ventral to the ninth or tenth costovertebral junction[18] (Figs. 28.2 and 28.14). The needle should be inserted perpendicularly at the middle of the rib, midway between the anterior and posterior borders (see Fig. 28.14, A). To help keep the needle from sliding off the bone, a scalpel can be first inserted until it touches the bone to be used as a guide.[15]

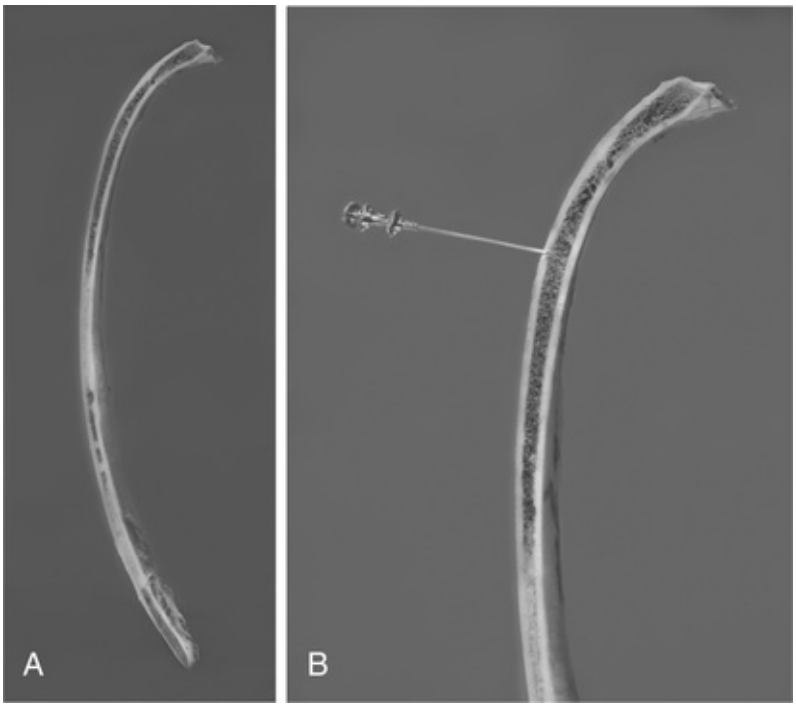
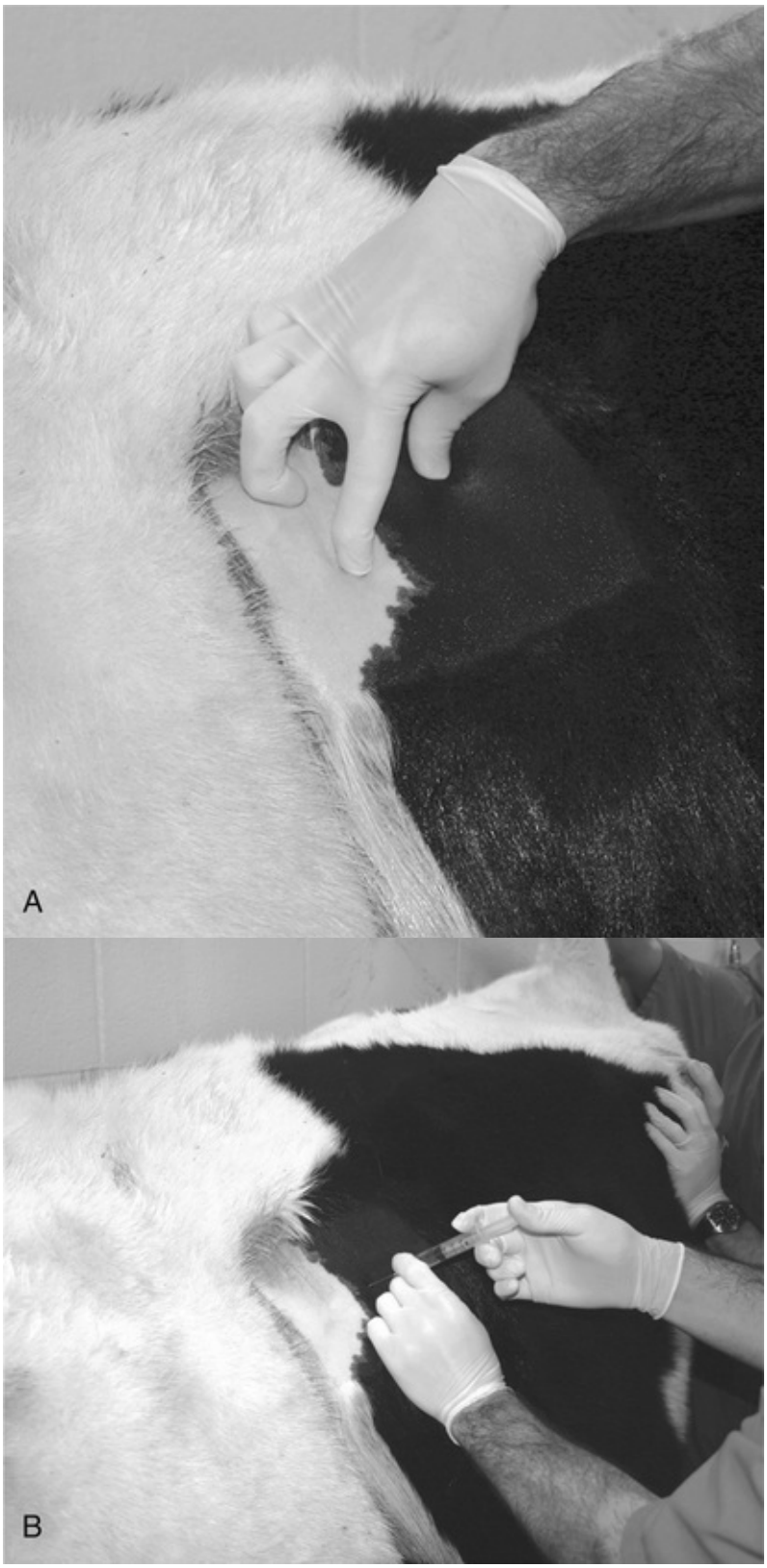


FIG. 28.13 Cross-section of bovine rib 10. **A,** Bone marrow is more consistently present in the vertebral end. **B,** Rosenthal bone marrow needle is inserted into the rib approximately 3 inches below the costovertebral junction.


A
B


C
D



FIG. 28.14 Bone marrow aspirate of a cow. The animal was placed in a head gate and sedated, and a tail jack was applied. **A,** The area over the vertebral end of rib 11 has been clipped and surgically scrubbed. The cranial and caudal edges of the rib are palpated approximately 3 inches down from the costovertebral junction, and the midpoint of the rib is identified for aspiration location. **B,** At the chosen aspiration site, lidocaine is injected from skin to periosteum. **C,** After a stab incision has been made and the Jamshidi-type bone marrow needle has been inserted through the skin, the needle is forcibly pushed forward through cortical bone as it is rotated in a clockwise-counterclockwise motion. **D,** After a decrease in resistance is felt, the stylet is removed. **E,** A syringe is attached to the needle, and a few sharp pulls on the plunger are needed before sample is noted in the hub of the syringe.

Approach to the Iliac Crest.

The iliac crest is often used in foals (see Fig. 28.7). The needle should be placed midway between the two tuberosities of the tuber coxae and somewhat toward its posterior border. With regard to angle, the needle should be pointing at the coxofemoral joint of the opposite side.

Bone marrow will be hit when the needle is inserted approximately $\frac{1}{8}$ inch for foals, whereas in adult horses bone marrow may be more than 2 inches deep. The main benefit of using this method is that there is no risk of inadvertently entering the thoracic cavity.[16]

Preparation for Bone Marrow Aspiration or

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Biopsy

Bone marrow aspiration should be performed as a sterile procedure. After the animal has been restrained and the site of approach has been identified, hair should be clipped and the area surgically scrubbed (see Fig. 28.12, A). Local anesthetic is injected at the site where the needle will be inserted, from the skin to the periosteum (Figs. 28.14, B and 28.15, A). A small stab incision is typically made with a scalpel to aid the needle's approach to the bone. If the rib is to be sampled, the scalpel blade can be held in place to act as a guide for the needle. It is important to be organized and have all supplies ready so that the procedure will flow smoothly and the sample will not clot before it can be processed (Box 28.2; Fig. 28.16).



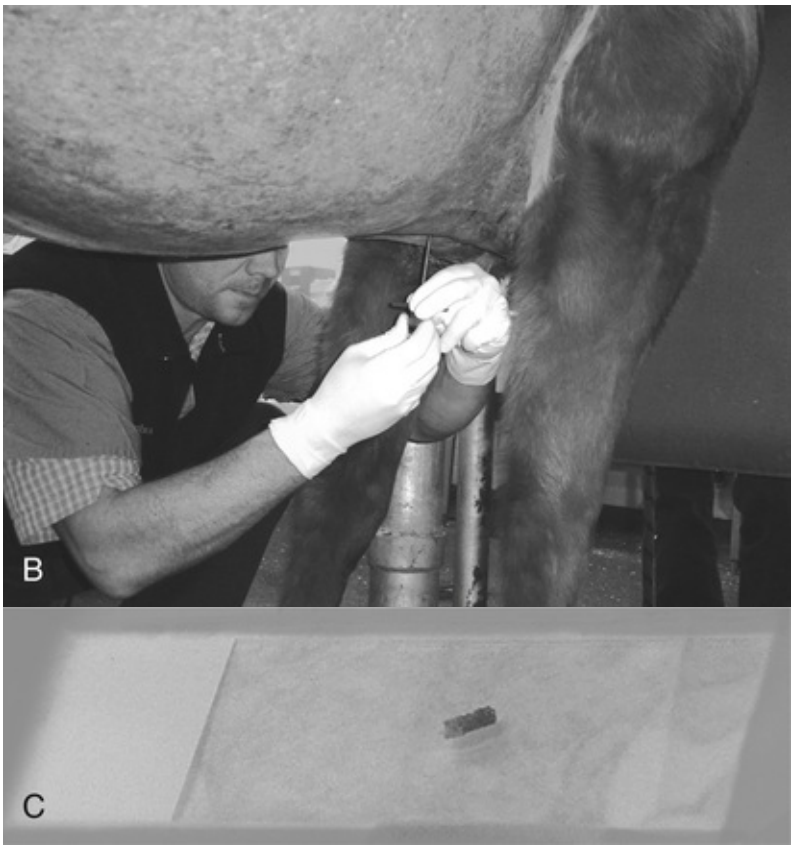


FIG. 28.15 Core bone marrow biopsy of a horse. The animal was placed in a stock and sedated; the ventral sternum between the elbows was clipped and surgically scrubbed. **A,** Lidocaine is injected from the skin to the periosteum. **B,** After a stab incision, the Jamshidi bone marrow biopsy needle is advanced into cortical bone. Here, the stylet is about to be removed before the needle is advanced further. **C,** Core biopsy sample.

Box 28.2

Supply Checklist for Bone Marrow Collection

General

Clippers
Surgical scrub
Lidocaine
Syringe and needle
Sterile gloves

Scalpel blade (No. 15 adequate)
Bone marrow needle

Therapeutic

13-gauge bone marrow needle
Heparin
60-mL sterile syringes

Diagnostic

Bone marrow needle: ≥16 gauge, 1½ inches
10- to 20-mL sterile syringe
Glass slides
Jar of formalin for core biopsy
Optional:
- Anticoagulant
- EDTA blood tubes
- Petri dish or watch glass

EDTA, Ethylenediaminetetraacetic acid.

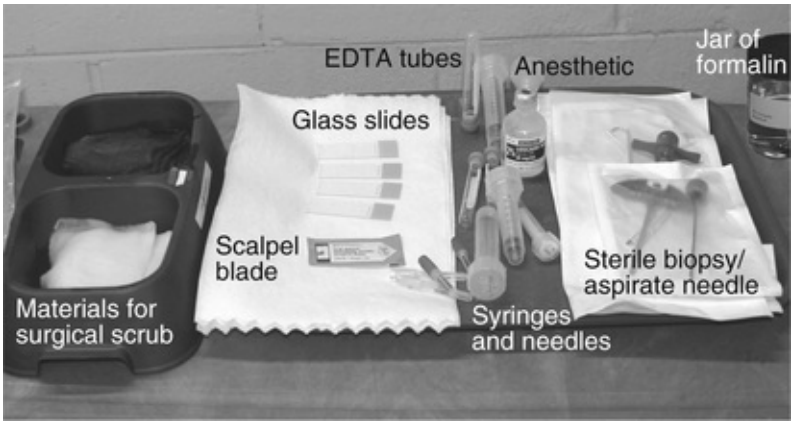


FIG. 28.16 Supply table is set up and ready for bone marrow aspiration. Sterile gloves were opened on an adjacent table. *EDTA,* Ethylenediaminetetraacetic acid

How the sample ultimately will be handled will dictate some of the available supplies needed: syringes, glass slides, Petri dish, EDTA blood tubes, and/or anticoagulant. One option is to prime the syringe that will be used for aspirating the sample with anticoagulant. Syringes are primed with heparin for therapeutic bone marrow harvesting. To prevent clotting in diagnostic samples, 1 to 2 mg of EDTA is recommended per milliliter of blood. One to two drops of a 3% to 15% EDTA solution should be adequate. The EDTA solution can be aspirated from a purple-topped blood tube. Priming the syringe with anticoagulant, although it adds a preparatory step, decreases the worry that the sample will coagulate and allows more time for processing the sample. If the syringe is not primed, as soon as the sample is seen in the syringe hub, the syringe needs to immediately be disconnected from the needle and the sample quickly processed before it has a chance to clot. If a reticulocyte count is to be performed to assess erythroid regeneration, supravital stains, such as new methylene blue and brilliant cresyl blue, require mixing with a portion of anticoagulated, liquid sample before slides are made; therefore placing at least some of the bone marrow sample in an EDTA tube is recommended.

The diagnostic sample in the syringe may be processed by expressing it directly onto several clean glass slides, into an EDTA blood tube, or into a Petri dish or watch glass. The Petri dish or watch glass must contain anticoagulant if no anticoagulant was used in the syringe. The anticoagulant commonly used is EDTA, which can be used in solution or as a salt, but other anticoagulants such as sodium citrate are also effective. Samples placed in an anticoagulant should be gently mixed immediately.

Collecting the Sample

The goal of bone marrow aspiration is to obtain a good sample of hematopoietic cells with minimal blood contamination. Anatomically, within the bone marrow, hematopoietic cells are extravascular and found in spaces dissected by venous sinuses and a central vein.[30] To collect the sample, a bone marrow or spinal needle with stylet should be used. Commonly used needles include Rosenthal, Illinois sternal-iliac, and Jamshidi bone marrow needles (Fig. 28.17). Some needles come with a guard that can be adjusted to prevent deeper penetration than desired. The needle used should be 16 gauge or larger and at least $1\frac{1}{2}$ inches long. Larger needles may be needed, depending on the site of aspiration and the age and size of the animal. For therapeutic collection, a 13-gauge bone

marrow aspiration needle is recommended.



FIG. 28.17 Bone marrow needles with stylets separated. On the *left* is a 14-gauge, $2\frac{1}{4}$-inch Rosenthal needle. On the *right* is an 11-gauge, 4-inch Jamshidi needle.

After an animal has been properly prepared, the bone marrow needle is inserted through the skin, perpendicular to the bone. Once the needle contacts bone, it can be advanced using manual pressure and a clockwise-counterclockwise twisting motion (see Fig. 28.14, C). One hand can be used to stabilize the needle angle and placement while the other hand is on the needle hub pushing and turning the needle.[24] If the needle is going through dense bone, a wood mallet can also be used to advance it.

For a diagnostic sample, once it is suspected that the needle has entered the marrow cavity, either because of detection of a sudden reduction in resistance or because of needle depth, the stylet should be removed and an aspiration attempted (see Fig. 28.14, D). In dense bone, pliers may be helpful in removing the stylet.[12] After the stylet is removed, a 10- to 20-mL sterile syringe is securely attached to the needle, and the plunger of the syringe is pulled back quickly and sharply, creating negative pressure in order to dislodge bone marrow particles

(see Fig. 28.14, E). Suction can be repeated two or three times. As soon as blood is seen in the hub of the syringe, suction should be discontinued, the needle and syringe removed from the animal, and the sample processed promptly. Additional suction will likely result in only dilution of the sample with peripheral blood. The first drop of blood is the most cellular, and further aspiration results in lower cellularity of the sample.[31]

For collection of equine therapeutic bone marrow, the needle is seated firmly into the center of the medullary cavity of the fifth sternebra (see Fig. 28.4). Once the needle is inserted approximately 3 to 5 mm into the bone, the stylet is removed and aspiration can begin (see Fig. 28.12, *B*). One or two 60-mL syringes with 10 mL each of heparin (1000 IU/mL) are used for aspiration. The syringe is then capped, and the sample is mixed thoroughly by rocking the syringe gently back and forth. Studies have shown that the first 5 mL of an aspirate contain the highest proportion of BMSCs.[22,23] Furthermore, for sequential aspirates (two aspirates of 50 mL each), the second aspirate yields few to no BMSCs.[22]

If the initial aspiration does not obtain any material, remove the syringe, replace the stylet, and carefully advance the needle a little further. If still no sample is obtained after additional advancement of the needle and repeated suction, slowly withdraw the needle while applying suction to the syringe. Ultimately, repositioning the needle to a different site, such as moving a couple of centimeters cranially or caudally, may result in a successful aspiration.[13] It has been reported that the use of a multidirectional bone marrow aspiration needle improves the colony-forming unit fibroblast counts in a bone marrow aspirate.[32]

Processing the Sample for Diagnostic Purposes

Whether the bone marrow sample is directly applied to glass slides or expressed into a Petri dish or watch glass, processing needs to proceed rapidly to prevent clotting or drying out of the sample. When on the slide, if the sample contains a lot of excess blood, the slide can be briefly tilted so that the fluid portion can run off into an absorbent surface, leaving behind adherent particles for spreading (Fig. 28.18, C and Fig. 28.19, A). If the sample is placed into an EDTA tube or Petri dish with anticoagulant, spicules (small grayish particles) can be transferred out of the bloody sample using a pipette and placed on a glass slide[20] (see Fig. 28.18).

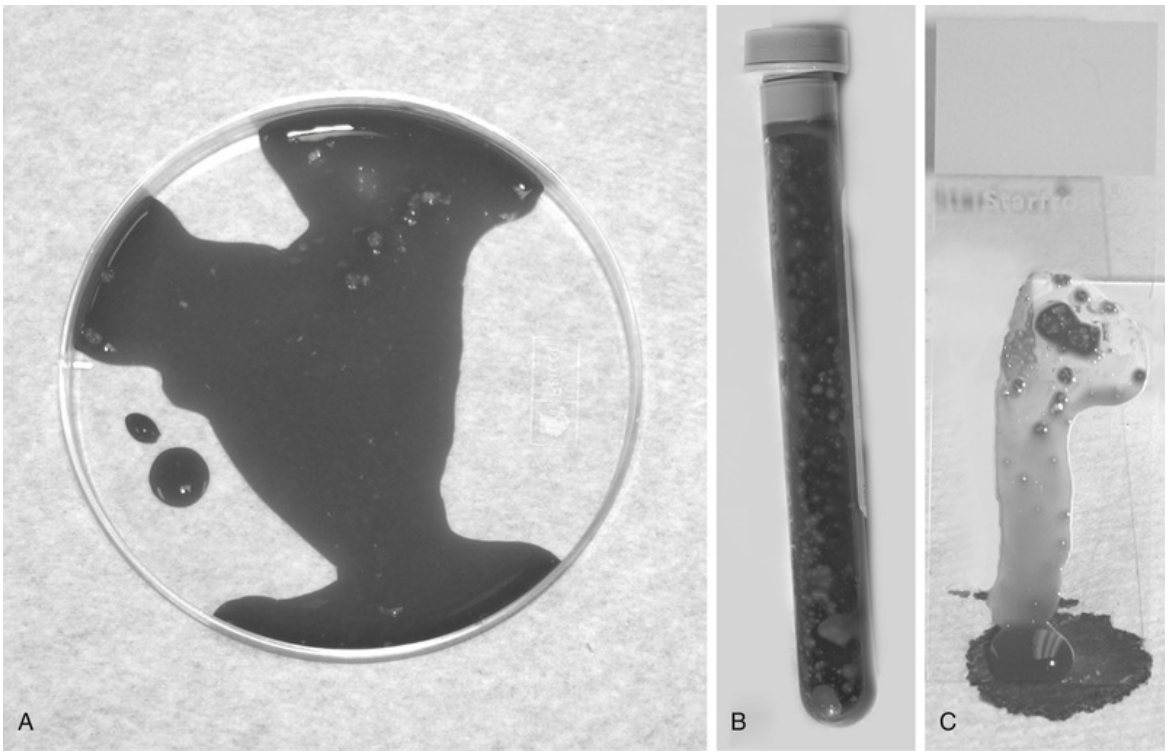
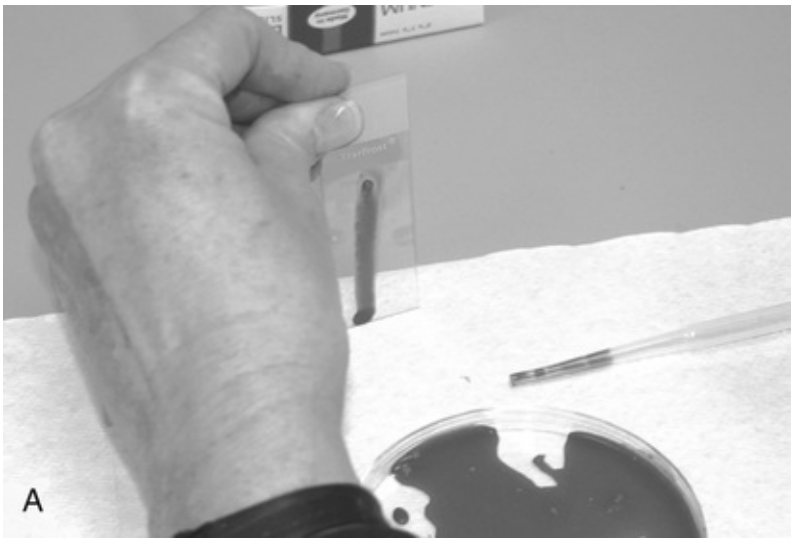


FIG. 28.18 Bone marrow spicules (small grayish particles) should be seen in the aspirated sample. **A,** Particles can be picked out of background blood from a Petri dish. **B,** Particles can be seen adhering to the sides of an ethylenediaminetetraacetic acid (EDTA) blood tube. **C,** Particles will adhere to a glass slide while excess blood runs off.



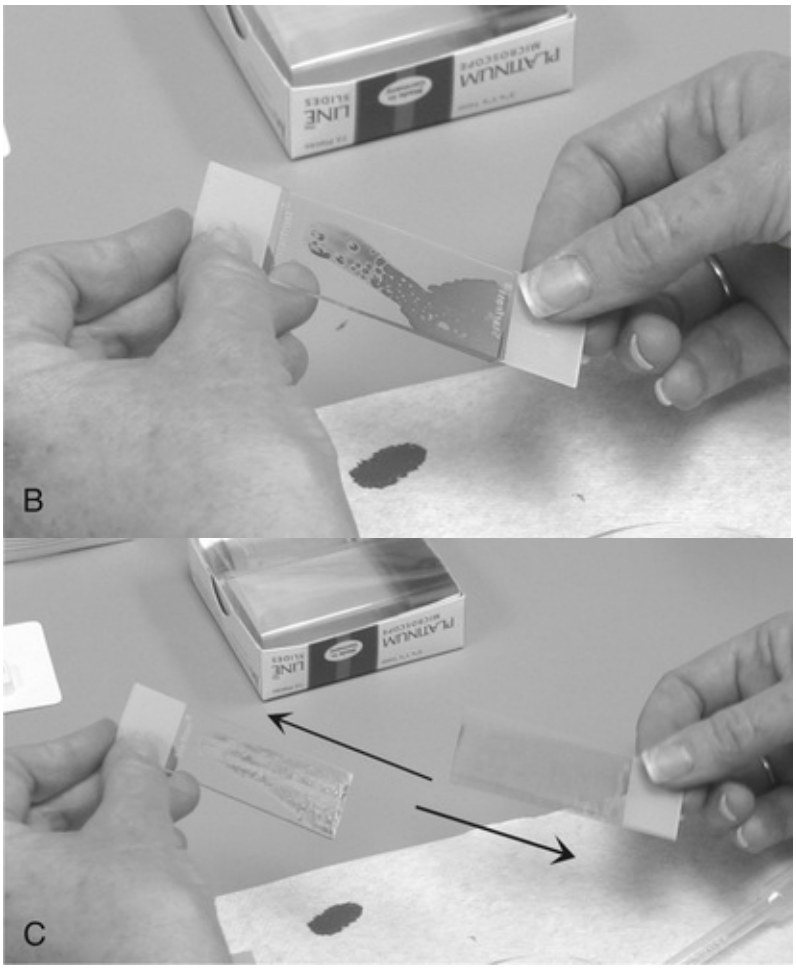


FIG. 28.19 Making slides of a bone marrow sample. **A,** Excess blood is allowed to run off the slide onto an absorbent surface while the spicule remains adhered to the slide. **B,** A second slide is laid on top of the sample, causing the sample to spread out between the slides. **C,** The slides are horizontally pulled apart, then allowed to air dry.

To spread the sample on a slide, place a second glass slide flat on top of the sample, allowing the sample to form a thin layer between the slides (Fig. 28.19, B). Without additional pressure other than the weight of the slide, gently pull the slides apart from each other horizontally and without vertical separation, which can create suction and rupture cells (Fig. 28.19, C). This typically results in a nicely spread sample with intact particles and nice monocellular layers for evaluation. Several slides should be made. After slides are made, they should be allowed to air dry, kept away from formalin fumes, and stored at room temperature until staining.

Some bone marrow slides are stained with a Romanowsky-type stain (Wright, Giemsa, Diff-Quik) for cytologic examination, and some should be left

unstained in the event that special staining procedures are wanted. It is highly recommended that at least one slide be stained right away for microscopic examination in order to determine sample quality and to ensure that bone marrow elements are present while the animal is still available and prepped, in the event that the first aspiration is nondiagnostic and additional attempts will be needed (Fig. 28.20). If a sample containing mostly peripheral blood without spicules is obtained, it may be possible to acquire diagnostic information by centrifuging the sample in Wintrobe hematocrit tubes and making smears from the buffy coat. Staining for reticulocytes requires that an anticoagulated, liquid bone marrow sample be mixed and incubated with a supravital stain before slides are made.

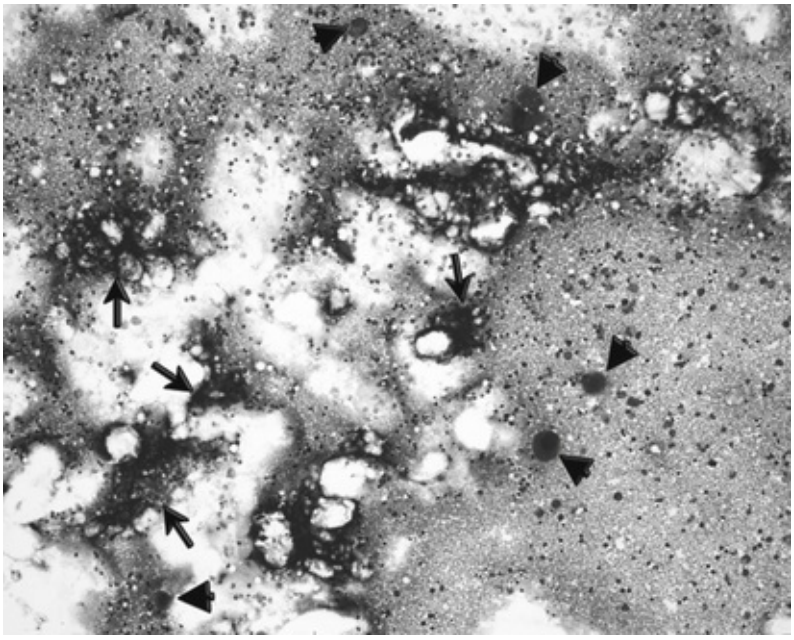


FIG. 28.20 Stained slide of adequate bone marrow aspirate sample. Megakaryocytes *(arrowheads)* and particles *(arrows)* are present. There is also increased cellularity compared with peripheral blood. (Wright-Giemsa stain, 10× objective.)

If a core biopsy sample is obtained, the tissue can be gently rolled on a slide to make an impression smear for cytologic evaluation. The biopsy tissue should then be placed in 10% neutral buffered formalin for preservation. A larger gauge needle (10 to 13 gauge) is generally recommended for core biopsy. The Jamshidi needle, designed so that the distal tip tapers to help retain the sample, is the most popular needle for biopsy. The needle and stylet are initially inserted as for

aspiration (see Fig. 28.15, B). Once the needle enters the bone marrow, the stylet is removed and the needle is advanced further with the same twisting motion. Ideally, the needle is inserted at least an additional 1 to 2 cm, but this may be limited by location. After the needle is advanced to obtain the core, it is rotated and rocked forcibly to help break the core at its base for successful removal. Once the needle is removed from the animal, a probe is inserted into its lumen at the distal tip, pushing the sample out the hub end (see Fig. 28.15, C).

Often bone marrow aspirates are placed into an EDTA blood tube for submission to an outside laboratory. In this case it is still recommended to make slides of the sample to submit along with the fluid sample. If the sample is left in the fluid phase, cells can deteriorate during transit, and it is always helpful for the cytologist to have a freshly prepared sample to examine (of both bone marrow and peripheral blood). In addition, a slide can be stained and evaluated for diagnostic quality before the sample is shipped.

If repeated aspirates all result in samples of low cellularity, a core biopsy is typically indicated. Cytologically, it can be impossible to differentiate low cellularity caused by a pathologic process from that resulting from poor sampling; therefore a biopsy is used to evaluate cellularity.

Processing the Sample for Therapeutic Purposes

Bone marrow aspirates and concentrates have the advantage of being immediately available for injection after collection with minimal processing. However, multipotent stromal cells represent a minor fraction of the total population of nucleated cells in these samples. The other cells that comprise the aspirate include hematopoietic cells, monocytes and macrophages, and low numbers of lymphoid cells and endothelial progenitors. Studies suggest that after density centrifugation, which removes granulocytes and immature myeloid precursors, BMSCs are only 0.001% to 0.01% of the mononuclear cells remaining.[33,34] Concentrated bone marrow is made by centrifuging the heparinized bone marrow aspirate sample at 1500 revolutions per minute (rpm) for 10 minutes and removing the supernatant. In concentrated bone marrow, platelet and leukocyte concentrations increase (~8 times), but erythrocyte concentration decreases.[35]

Because BMSCs comprise such a small proportion of bone marrow, techniques have been developed for their selection and isolation. Commercial

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closed systems are available to separate MSCs. These kits can optimize cell viability after collection and reduce the risk of contamination[36] (PrepaCyte-CB, U.S. Patents 6,933,148 and 7,160,723). Studies in humans have shown that these closed systems provide a fast and reliable separation of human cord blood, with higher recovery rates of nucleated cells compared to other methods. Although this method removes most red blood cells, the addition of ammonium chloride solution to lyse the remaining red blood cells is recommended. The remaining nucleated cells are washed with a buffered isotonic media (Dulbecco's phosphate-buffered saline [DPBS]) and spun at 2100 rpm for 5 minutes. After the supernatant is discarded, the cells are resuspended in growth media. Another commonly performed open isolation method for enriching nucleated cells is to place the bone marrow aspirate in a density gradient solution for separation of the mononuclear fraction by centrifugation, prior to culture in growth media. Two density gradient solutions, Percoll and Ficoll, are commonly used for this method. A study performed with equine bone marrow showed that Percoll solution may have a higher yield of BMSCs and earlier self-renewal (14 days) than Ficoll solution.[37] This same study also compared both density gradient solutions to a classic isolation method based on MSCs from bone marrow concentrates adhering to plastic culture dishes, and no significant difference in cell viability or in osteogenic or chondrogenic differentiation was identified between the protocols.[37]

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Bone Marrow Evaluation

Bone marrow evaluation requires expertise (advanced training and experience), and in most cases it is anticipated that samples will be sent to a trained cytologist for evaluation. To obtain the most information from a bone marrow aspirate, it is important to have a good-quality sample. Even if not reading the sample oneself, it is recommended that one stain a slide to confirm that a diagnostic sample was obtained (stain the worst slide; if it is acceptable, one can expect the others to be acceptable, too). Recent CBC results and freshly made blood films are also essential for full interpretation of a bone marrow sample. Relative changes among different cell lines are assessed in the evaluation of hematopoiesis because absolute cell counts are unreliable in bone marrow aspirates.[31] Knowledge of the peripheral blood picture is necessary to assess whether changes (or lack of changes) in the bone marrow are consistent with normal hematopoiesis. Freshly made blood films are important to have when comparing the morphology of cells in the bone marrow with the morphology of those in the peripheral blood. Results from cytologic evaluation of bone marrow should ultimately be correlated with history, clinical presentation, and other laboratory data.

Cytologic Examination

In general, the evaluation of bone marrow includes assessment of the following parameters. On low magnification the cellularity and quality of the sample as a whole are assessed, as well as the cellular density of bone marrow particles. Iron stores are evaluated within the particles. Megakaryocyte numbers are also best assessed at low magnification. On high magnification the sample is evaluated for the presence of myeloid and erythroid cell lines. The cell lines are evaluated for orderly maturation, and cell morphology is assessed for evidence of dysplastic changes. The relative proportion of myeloid to erythroid cells is determined by subjective assessment or by counting cells to derive a myeloid/erythroid (M/E) ratio. The sample is also evaluated for the presence of other cell types or infectious organisms. Results from the bone marrow evaluation are then interpreted in accordance with peripheral blood abnormalities.

Cellularity of bone marrow spicules is subjectively determined by assessing how much area of a particle is composed of cells versus fat. Cellularity of

normal marrow can vary according to the age of an animal, with higher cellularity in younger animals and lower cellularity in older animals. Examples of differing cellularities are depicted in Fig. 28.21. Iron stores are assessed within spicules and typically described as *present*, *decreased*, or *increased* (Fig. 28.22).

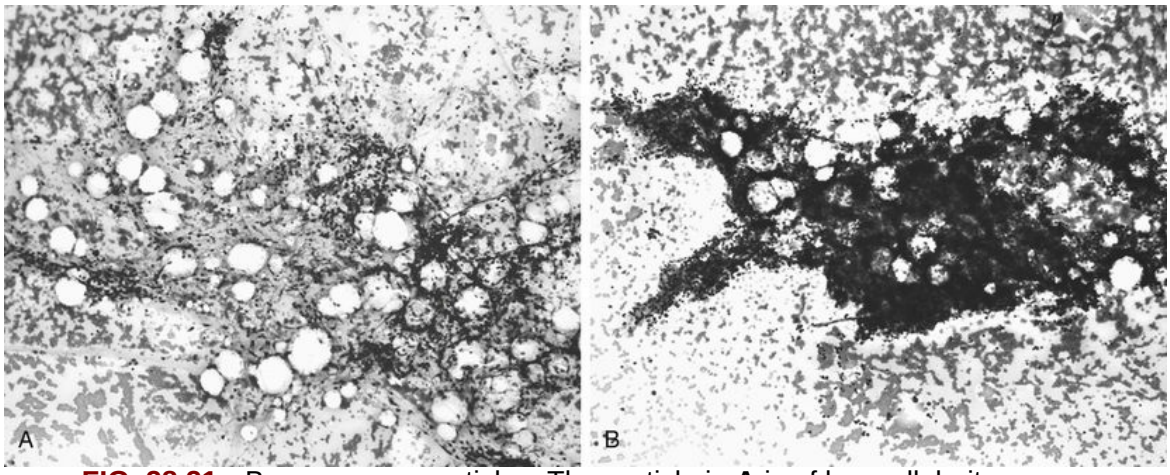


FIG. 28.21 Bone marrow particles. The particle in **A** is of low cellularity. Only a small proportion of the particle is composed of nucleated cells. The particle in **B** is of high cellularity. At least 75% of the particle is composed of nucleated cells. (Wright-Giemsa stain, 10× objective.)

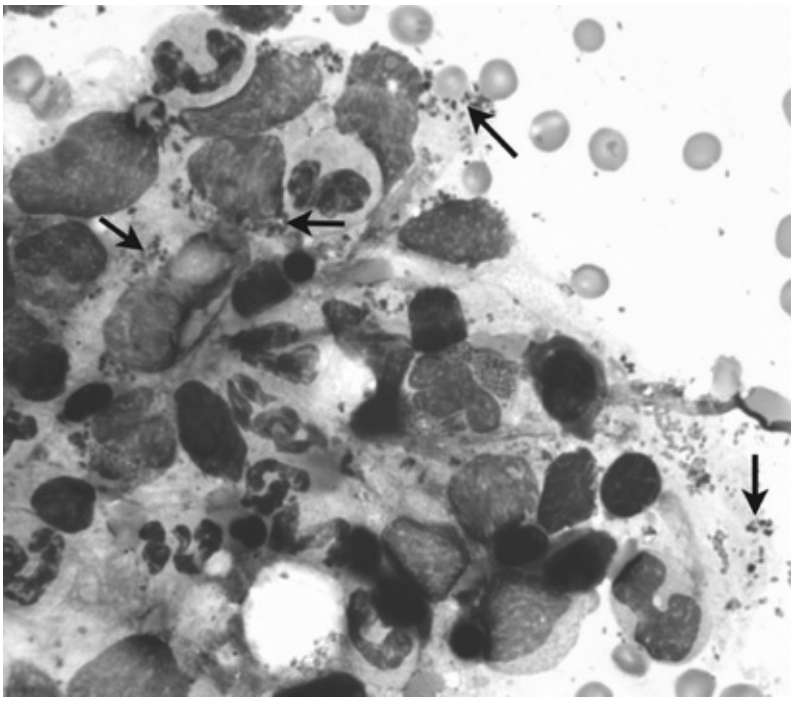


FIG. 28.22 Bone marrow aspirate. The blue-black granules visible extracellularly and within macrophages represent iron stores *(arrows).* Iron stores can also be seen as brown crystalline material within particles. (Wright-Giemsa stain, 100× objective.)

Maturation of bone marrow cell lines follows somewhat of a pyramidal pattern, with cells dividing as they mature, resulting in higher numbers of cells in the more mature cell stages (Color Plates 28.9 and 28.10). In bone marrow of healthy animals, rubriblasts and myeloblasts typically comprise at most a small percentage of the total cell population. Twice as many prorubricytes and promyelocytes may be seen. Numbers of cells in each stage increase up to polychromatophilic rubricytes and metamyelocytes, after which there are relatively stable numbers between the subsequent maturational phases. In general, for each blast there are 16 mature granulocytes or erythrocytes. Mitotic figures are normally present in low numbers.

The M/E ratio is most accurately determined by counting a minimum of 500 cells. Nucleated cells of all maturational stages are included in the count and categorized as myeloid or erythroid. The ratio is calculated by simply dividing the total number of myeloid cells by the total number of erythroid cells. It is important to include several different areas of the sample to make it as representative of the whole sample as possible. Blood contamination can also affect the M/E ratio, especially if leukocytosis is present. Reported M/E ratio ranges for healthy animals of different species have varied. In some sources the

M/E ratio in cattle is listed as less than 1, although ranges from 0.27 to 2.59 have been reported.[11,29,38-40] The range of M/E ratios in ten 3- to 6-year-old pregnant sheep was reported as 0.77 to 1.68.[26] The reported range for the M/E ratio in a low number of llamas is 0.9 to 2.9.[27] Llama, alpaca, and vicuna have a lower M/E ratio at high elevation (4200 m) versus low elevation.[2] M/E ratios in horses generally range from 0.5 to slightly greater than 1, with 1.5 sometimes reported as the upper value.[10,41-43]

Evidence of dysplastic changes in hematopoietic cells includes asynchronous maturation between the cytoplasm and nucleus, large cell forms, and abnormal nuclei, such as ring-shaped nuclei. Cell types other than hematopoietic cells should be evaluated as to their presence and proportion of the total cell population. Low numbers of macrophages (<1%), plasma cells (<2%), and small lymphocytes (<10%) are commonly seen in bone marrow samples.

Interpretation

It is easy to make a conclusion about bone marrow cellularity if the sample is highly cellular, but a poorly cellular sample is more difficult to interpret if adequate particles are not present. A core biopsy may be needed to differentiate between a poorly cellular marrow and a nonrepresentative sample. In general the bone marrow will become more cellular in a hyperplastic or regenerative response.

In many cases it is adequate to describe iron stores as being present without quantification. When assessing the cause of anemia, an abnormality in iron stores may provide useful diagnostic information. Lack of iron stores would suggest iron deficiency, whereas abundant iron stores are associated with anemia of chronic inflammation. Perls' iron stain (Prussian blue reaction) can be used on bone marrow slides to confirm low iron stores. Llama bone marrows normally contain abundant iron.[27]

No definitive criteria for megakaryocyte numbers have been determined. If thrombocytopenia is not present, any number of megakaryocytes is acceptable. Many megakaryocytes are expected to be seen within individual particles when there is regeneration associated with thrombocytopenia. Higher numbers of immature megakaryocytes may also be seen; these will be smaller cells (still larger than other bone marrow cells) with a higher nuclear/cytoplasmic ratio, deeper basophilic cytoplasm, and fewer lobes to the nucleus. If megakaryocytes

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are not frequently seen in the bone marrow from an animal with thrombocytopenia, this suggests hypoplasia or destruction of megakaryocytes.

When assessing bone marrow for normal, progressive maturation of cell lines, it is expected that all developmental stages will be present, with greater numbers of the more mature cells. Variation from normal can be seen for many reasons, often reflected by a shift to the left or what appears to be a maturation arrest. A shift to the left is the situation in which all maturation stages are represented but there is a higher proportion of the less mature cells (the proliferating pool) than normal. *Apparent maturation arrest* is a term used when maturation appears to terminate at a particular stage; the earlier maturation stages are present, but later stages are poorly represented. Suppression of hematopoiesis can result in abnormalities in maturation progression but often is reflected by a decrease in all stages of maturation. If the number of cells within a cell line is too low, progression of maturation can be difficult to evaluate. Destruction of cells, such as with immune-mediated disease, at a particular maturation stage will result in decreased numbers of cells of the affected type as well as cells at all later stages, which can appear as a maturational arrest. If a disease process results in large demand or rapid mobilization of cells out of the bone marrow, depletion of the more mature cell stages can appear as a maturational arrest. In such cases a left shift also is often associated with the increased demand. Acute leukemia is typically reflected as an apparent maturational arrest or left shift. Therefore it can be difficult to differentiate between hyperplastic marrow in which there has been rapid mobilization of mature cells out of the marrow and a myeloproliferative disorder on cytologic examination alone. In some instances sequential bone marrow aspirations can be useful in helping to determine disease pathogenesis. Abnormalities in maturational progression may also be reflected by the presence of dysplastic changes.

The M/E ratio is used to help determine if the erythrocyte or myeloid cell lines are hypoplastic or hyperplastic. An equal number of nucleated erythroid and myeloid cells will result in an M/E ratio of 1. An M/E ratio greater than 1 (or greater than the reference interval) often indicates that granulocytic production exceeds erythroid production, but it could also indicate a decrease in erythropoiesis. Likewise, an M/E ratio less than 1 (or less than the reference interval) often indicates that erythropoiesis exceeds granulopoiesis, but it could also indicate suppression of the latter. Determining which interpretation is appropriate requires knowledge of concurrent CBC results. An increase in the M/E ratio would be appropriate in an animal with neutrophilia, but if the

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neutrophil count is normal and anemia is present, it would indicate erythroid hypoplasia. In the face of anemia, a decrease in the M/E ratio would indicate erythroid hyperplasia and regeneration, but a decrease in a neutropenic animal that is not anemic would indicate myeloid hypoplasia. In some disease states both the myeloid and the erythroid series may be affected, which could potentially exacerbate or mask alterations.

Whereas most species readily reflect an erythroid regenerative response in the peripheral blood, horses do not. Reticulocytes are rarely seen in equine peripheral blood, and in one investigation it took several days of severe anemia (packed cell volume [PCV] of 13% to 14%) in horses before a reticulocytosis of 1% to 2% was seen.[44] An increase in mean corpuscular volume (MCV) may be detected in the peripheral blood of horses with chronic anemia or acute, massive hemolytic or hemorrhagic anemias,[43-46] but the best way to assess erythropoiesis in horses is to examine the bone marrow. The number of reticulocytes significantly increases in the bone marrow of horses with regenerative anemia. In the study of acute blood loss in which only 1% to 2% of reticulocytes were seen in peripheral blood, bone marrow reticulocytes went from 4.1% (pre–blood loss) to as high as 66.5%.[44] Reticulocytes typically comprise less than 2% of erythrocytes in normal bone marrow, and a regenerative response is considered present if reticulocytes comprise greater than 5%.[15] Determining the number of reticulocytes per 1000 erythrocytes after staining with a supravital stain such as new methylene blue is the most reliable method, but an estimate can be made by counting the number of polychromatophils per 100× oil objective field in a Wright-stained smear (assuming the field of view includes approximately 100 cells; this can vary with the microscope). In the face of anemia, greater than 5 polychromatophils/oil field is considered a good regenerative response, and less than 2 polychromatophils/oil field is indicative of erythropoietic suppression.[47] Care should be taken not to dilute the sample with peripheral blood, as this will dilute the number of reticulocytes from the bone marrow.

Other bone marrow parameters that indicate erythrocyte regeneration in horses include a decreased M/E ratio (<0.5) and a left shift of erythroid precursors.[43,47] Depending on the type of blood loss, it could take several weeks to reduce the M/E ratio below the reference interval.[48] With regeneration, a doubling of the proliferating pool of erythrocyte precursors can occur within 3 days of an acute severe hemorrhage, with maximal response at 9 days.[49] The proportion of basophilic and polychromic rubricytes can reach 39% to 55% of all

cells in the regenerative equine bone marrow.[43]

Atypical cell populations in the bone marrow can represent a myeloproliferative disorder, an infiltrative neoplastic process, inflammation, or antigenic stimulation. Atypical cell populations can be a result of significant increases in cell numbers of types normally seen in the marrow. Blast cells normally constitute only a small percentage of total cells in the bone marrow. A diagnosis of acute leukemia is typically associated with blast cells that constitute more than 20% to 30% of cells within the bone marrow. Cytologic results need to be correlated with other clinical data because granulopoiesis characterized by a marked left shift in bone marrow precursor cells with rapid mobilization of more mature cells from the bone marrow can resemble a myeloproliferative disorder.

Another cause of increased numbers of cells normally residing in the bone marrow is inflammation. Suppurative inflammation can be seen, typically associated with septicemia. Histiocytic or granulomatous inflammation is characterized by increased numbers of macrophages. Both suppurative and histiocytic inflammation can be associated with infectious or noninfectious disease processes. If inflammation is present, the sample should be thoroughly inspected for organisms, and culture may be indicated.

Increased numbers of lymphocytes and plasma cells can be seen with antigenic stimulation or with neoplasia. In general, it is rare to see the proportion of lymphocytes or plasma cells exceed 20% with antigenic stimulation. The morphology of lymphocytes and plasma cells should be well differentiated if they are associated with nonneoplastic processes. Cells associated with neoplasia can also appear well differentiated; therefore cell morphology alone may not be useful in establishing a diagnosis. Clinical presentation and ancillary testing (e.g., serum protein electrophoresis, flow cytometry) can be helpful in interpreting lymphocytoses and plasmacytoses.

The presence of cells not typically seen in the bone marrow or cells exhibiting a high degree of pleomorphism or other criteria of malignancy should raise suspicion of a neoplastic process. Neoplasia can arise from within the bone marrow or can metastasize to the bone marrow from other sites.

Degenerative cells or amorphous proteinaceous debris suggests bone marrow necrosis. This can occur secondary to infarction, neoplasia, or inflammation. Degenerative cells are often unidentifiable.

After cytologic evaluation of bone marrow and correlation with CBC results, a determination can be made as to whether any of the cell lines are hypoplastic or

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hyperplastic and whether there is evidence of maturational arrest, dysplasia, neoplasia, or inflammation. This information can then be correlated with the clinical information to determine appropriate differential diagnoses and likely disease pathogenesis.

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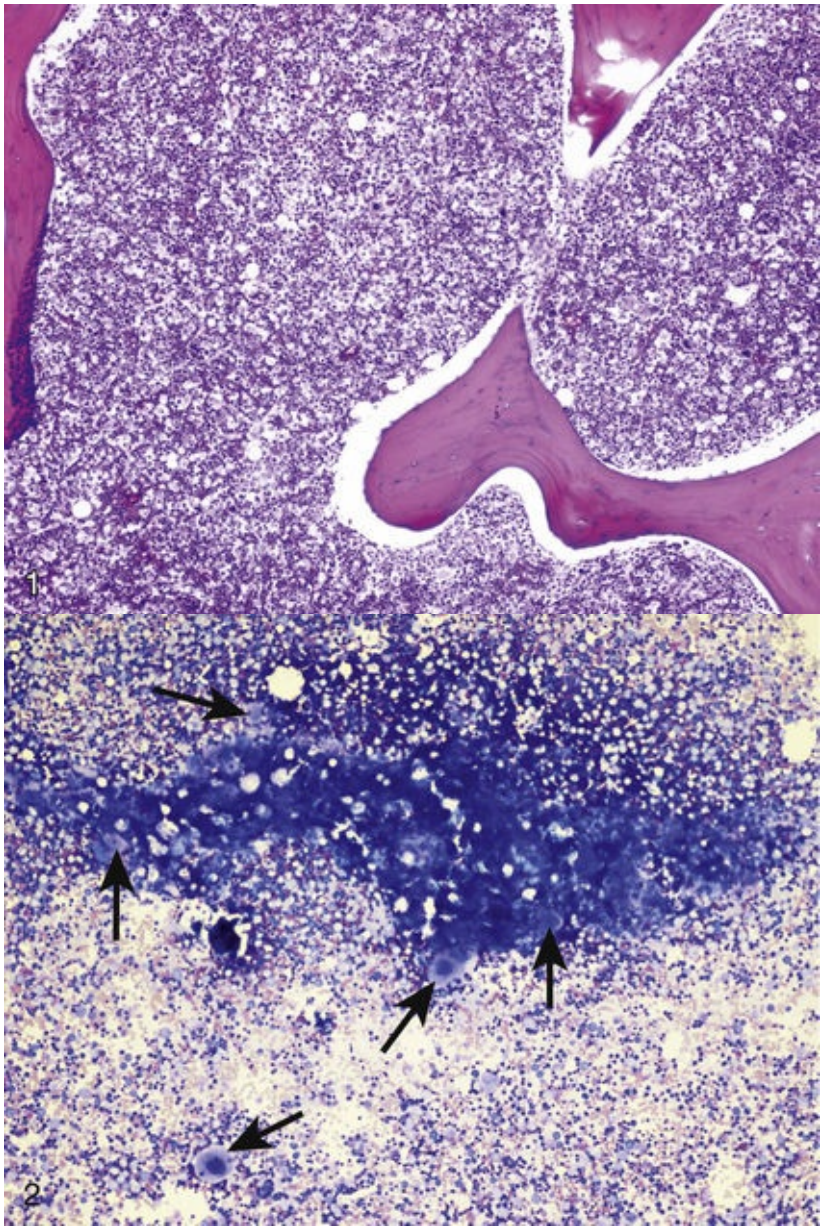
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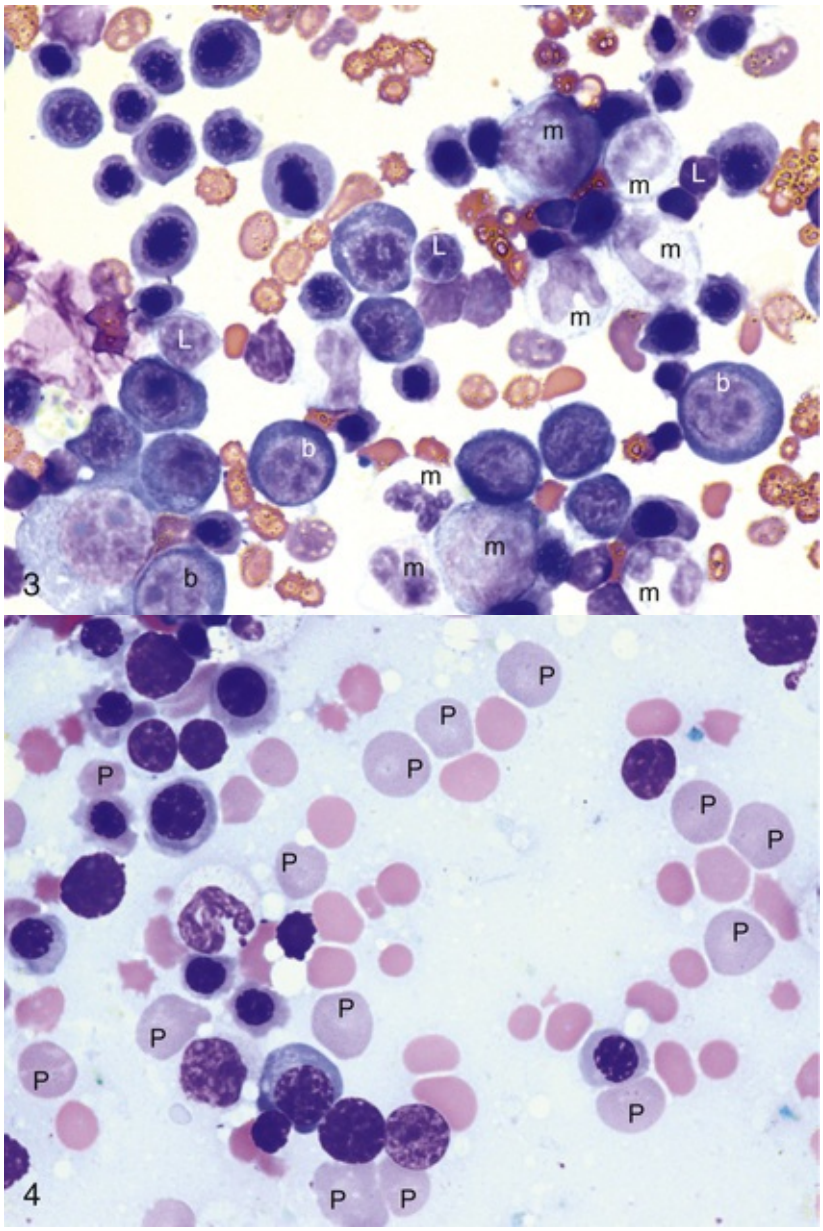
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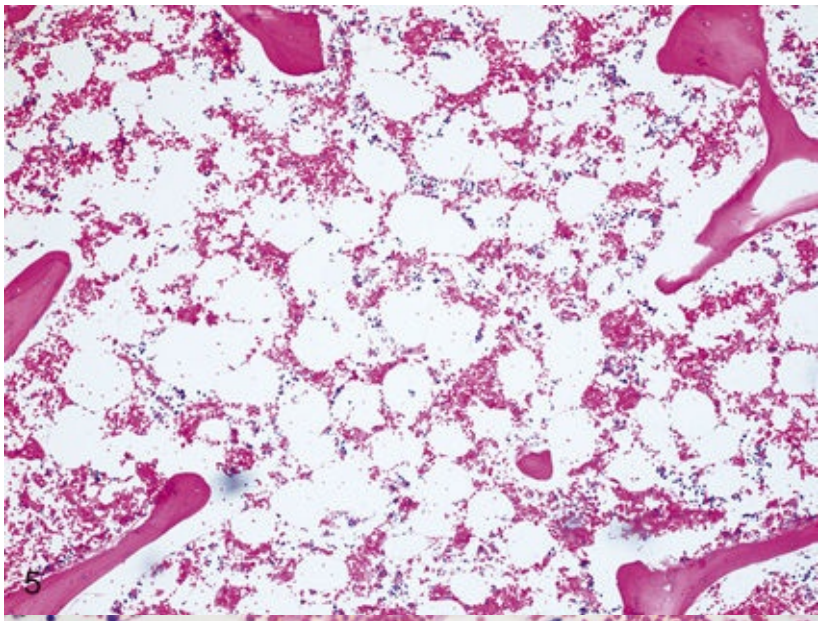
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Color Plates

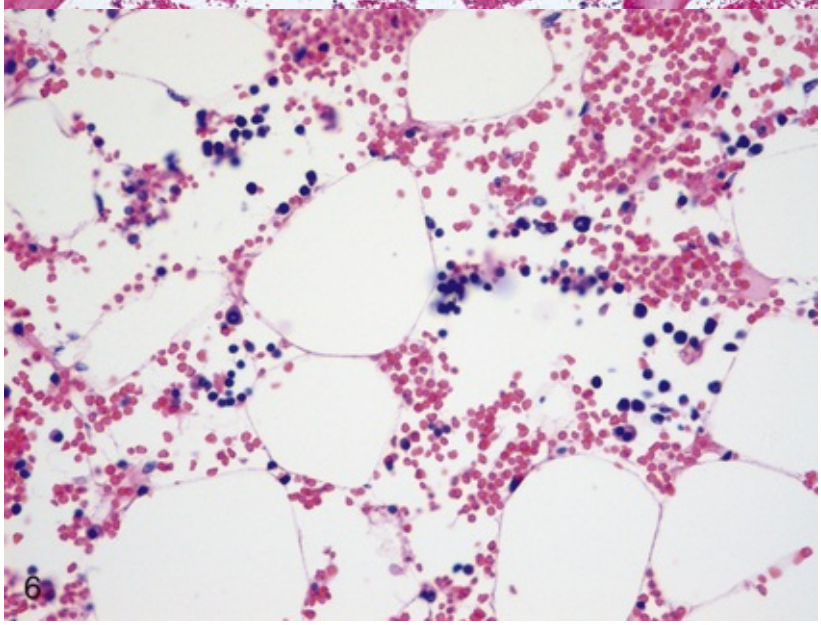




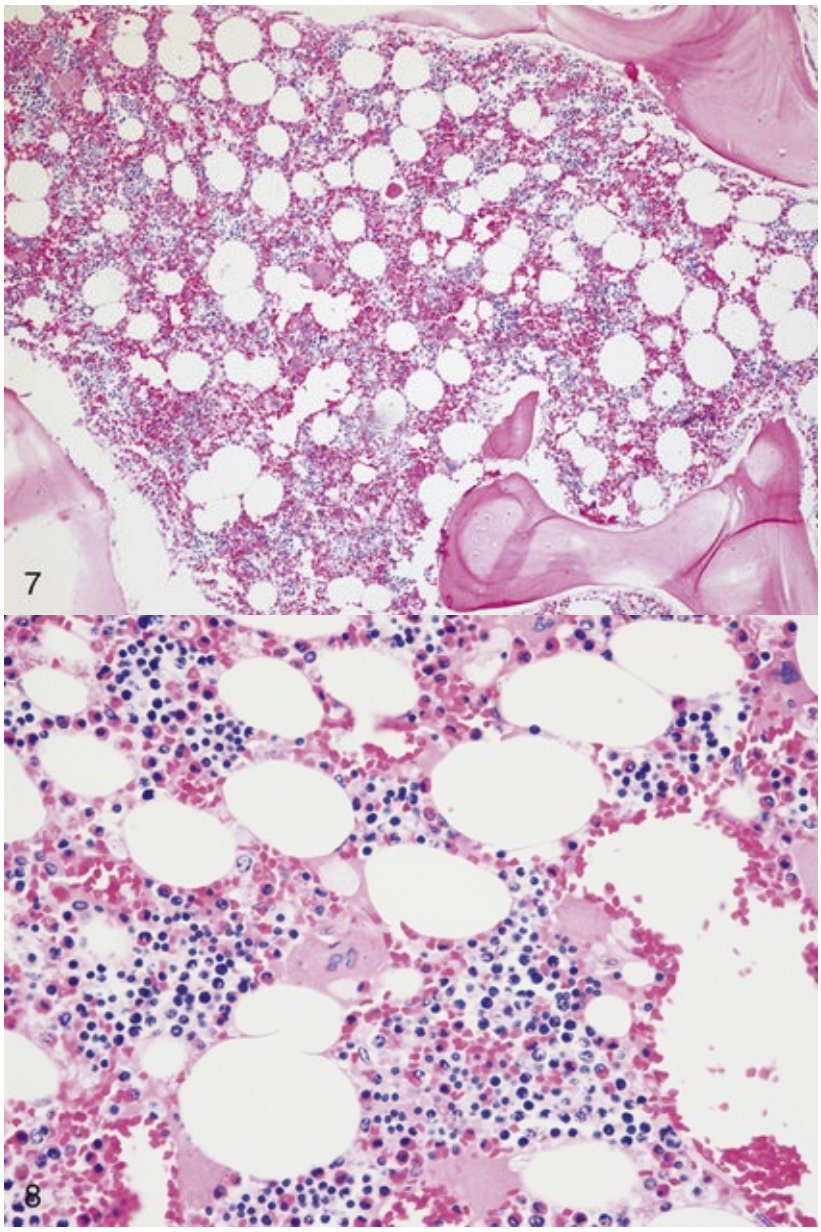
COLOR PLATES 28.1 TO 28.4 Bone marrow biopsy and aspirate from a 5-year-old female Quarter Horse with marked anemia (packed cell volume [PCV] = 9%; 31%-47%) and thrombocytopenia (42,000 platelets/µL; 125,000-300,000/µL). The bone marrow is highly cellular as seen in Color Plates 28.1 (H&E) and 28.2 (Wright-Geimsa); arrows point to megakaryocytes, 10× objectives. The myeloid/erythroid (M/E) ratio is decreased at 0.3, and polychromatophils comprise 30% of red blood cells (RBCs). Color Plate 28.3 shows a large erythroid population (unmarked cells and b = erythroblast) with fewer myeloid cells *(m)* and lymphocytes *(L)*; many polychromatophils *(P)* can be seen in Color Plate 28.4 (Wright-Geimsa, 100× objective). This is representative of regeneration and consistent with either chronic blood loss or immune-mediated destruction of erythrocytes, which could both be occurring in this horse. The horse was diagnosed with intramuscular hemangiosarcoma.



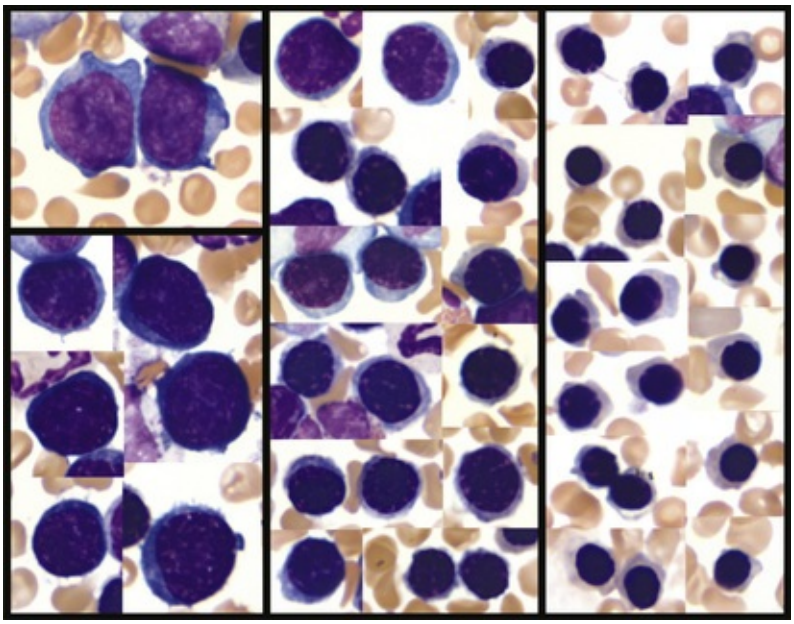
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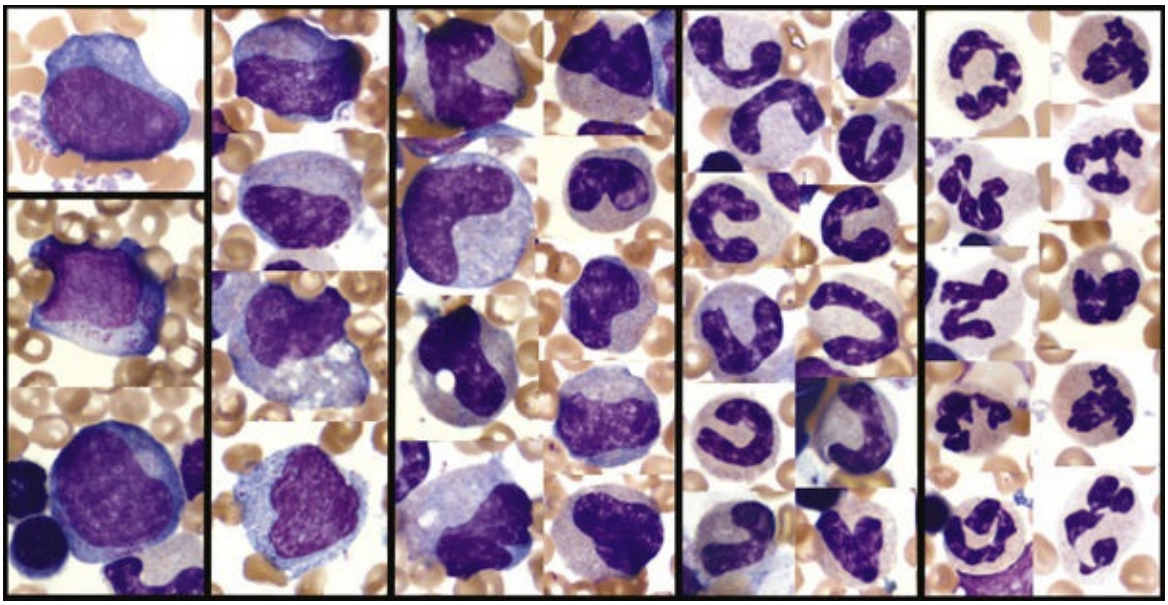
6



COLOR PLATES 28.5 TO 28.8 Bone marrow biopsy from a 2-year-old mixed-breed steer with mild anemia (packed cell volume [PCV] = 23%; 24%-46%), severe neutropenia (0/µL; 600-4000/µL), and thrombocytopenia (3000 platelets/µL; 100,000-800,000/µL) (Color Plates 28.5 and 28.6), compared to a normal age-matched control (Color Plates 28.7 and 28.8). Severe generalized bone marrow hypoplasia is apparent. The marked bone marrow suppression in this case is due to bracken fern toxicity. H&E; 10× (Color Plates 28.5 and 28.7) and 40× (Color Plates 28.6 and 28.8) objectives.



COLOR PLATE 28.9 Maturational stages of erythrocytes within the bone marrow. The *left panel* contains rubriblasts in the upper square with prorubricytes below. Rubriblasts are large cells with large nuclei containing coarse-grained chromatin and nucleoli; a perinuclear halo is present within scant, deeply basophilic cytoplasm. Prorubricytes have a more mature nucleus; chromatin condensation begins, and no nucleoli are present. The *middle panel* contains basophilic and polychromatophilic rubricytes; chromatin condensation is distinct, and the cytoplasm is paler, grayer, or polychromatic. The *right panel* contains metarubricytes with dark, intense chromatin condensation and pink cytoplasm. (Wright-Giemsa stain, 100× objective.)



COLOR PLATE 28.10 Maturational stages of granulocytes within the bone marrow. The *left panel* contains a myeloblast in the upper square with promyelocytes below. Myeloblasts are large cells with large nuclei containing fine reticular chromatin and nucleoli; the cytoplasm is basophilic and agranular. Promyelocytes contain coarse cytoplasmic granulation; nuclear chromatin is beginning to condense, and nucleoli are present. *Subsequent panels, moving to the right,* contain myelocytes, metamyelocytes, band neutrophils, and segmented neutrophils. Myelocytes have a lower nuclear/cytoplasmic ratio and contain fewer and finer cytoplasmic granules; the nucleus is round to kidney-shaped and contains no nucleoli. As maturation progresses, the cells become smaller, the cytoplasm becomes more eosinophilic, the chromatin becomes more condensed, and the nucleus indents and segments.

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• CHAPTER 29

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Molecular Diagnostics

Nicola Pusterla, Christian M. Leutenegger, Consulting Editors, Beate M. Crossley, Sharon Hietela

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Molecular Diagnostics in Large Animals

Christian M. Leutenegger • Nicola Pusterla

Of the four classes of organic molecules that compose the basic physical structure of all living beings, nucleic acids are the only molecules that carry replicable instructive information. Nucleic acids differentiate themselves from lipids, carbohydrates, and even proteins in their ability to organize the basic unit of life, the cell. Even minor alterations in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) molecules can disrupt the fine balance between health and disease. The field of molecular diagnostics seeks to elucidate the variations and mutations in genetic material that can cause disorder in the otherwise intricately organized body.

The amplified era of molecular diagnostics for infectious diseases began in 1983 when Dr. Kary Mullis of Cetus Corporation first conceptualized the polymerase chain reaction (PCR). He went on to win the Nobel Prize in Chemistry for this revolutionizing technology 10 years later.[1,2] Since the inception of PCR technology, infectious disease diagnostics have been at the forefront of molecular medicine, with the promise of detecting contagious pathogens in a safer and more sensitive way to aid in controlling their spread. Infectious disease testing is expected to continue to dominate the molecular diagnostic market for large animals in the foreseeable future. The use of amplified and nonamplified tests to assay the molecular makeup of the host rather than the pathogen is growing. Whereas cancer diagnostics is in its infancy for large animal testing, parentage and forensic testing together with single-nucleotide polymorphism (SNP) detection using in situ hybridization (ISH), fluorescent in situ hybridization (FISH), and sequencing technologies is gaining importance in assessing the presence and prognosis of genetic diseases.

The ability of molecular diagnostic assays to sensitively and specifically detect the primary cause of a disease, with short turnaround time, is giving significant advantages to disease diagnostics. Molecular tests are able to detect a specific unknown. Such tests are binary by nature; they provide a yes-or-no answer. However, certain tests when used quantitatively provide more insight into the medical manifestation induced by *Clostridium perfringens* toxins, for example. The clinically valuable information rests in determining the presence or absence of a specific pathogen in a biological sample derived from an animal. Because detection of viral, bacterial, rickettsial, fungal, or parasitic nuclear

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material in a biological sample gives clinically important information, molecular tests have direct clinical utility. However, the clinical context is always important to consider when making an interpretation on a molecular test. Determining the presence of a gene sequence per se without the clinical context does not necessarily correlate with a given clinical action, since diseases are generally multifactorial. In contrast, establishing the presence of the neuropathogenic form of equine herpesvirus (EHV)-1 in an equine patient's blood sample has direct association with EHV-1 infection, whether this translates into a symptomatic stage or not. The binary nature of molecular tests, which establishes the presence or absence of genetic material in a sample with a high degree of accuracy, has an accepted clinical value for infectious disease diagnostics because of its correlation with clinical signs.

Rapid results have tremendous clinical value in curtailing infection. Molecular methods can provide results in hours compared with days for culture-based or alternative technologies. The high sensitivity and specificity of molecular testing are particularly valuable in early determination of infection and make it advantageous compared with antibody and antigen testing without amplification techniques. In most cases pathogens enter the host and replicate exponentially; early detection provided by the higher sensitivity allows for earlier clinical intervention and a better prognostic outlook. Molecular tests have been shown to produce fewer false-positive and false-negative results compared with other test platforms. Therefore molecular tests are becoming the gold standard in the laboratory in terms of sensitivity and specificity. Key features for the adoption of molecular diagnostics for infectious agents are as follows:

- Superior sensitivity and specificity compared with most immunoassays
- Automated platforms that significantly increase throughput
- Quantitative assessment of viral load, which is clinically useful
- Fast turnaround time that speeds detection and reduces overall costs

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- Simultaneous analysis of multiple analytes
- Standardized environment with the potential for full comparability across laboratory systems
- Ability to tightly quality control and monitor all aspects of the test workflow, including sample quality, DNA and RNA quantity, contamination situation during extraction and in the laboratory in general, presence of inhibition, and performance of the PCR test and reagents

Technologic Superiority of Molecular Tests

The relative technologic superiority of molecular methods makes them likely to partially replace other types of more conventional methods, such as culture-based tests or certain direct antigen and antibody tests to determine the presence of an infectious pathogen in a sick animal. Whereas antibody testing is more of a broad screening tool, molecular diagnostics allow accurate detection of the genome of a pathogen in a clinically sick animal. Culture-based tests have a turnaround time of days and are labor intensive. In addition, certain infectious agents are difficult to culture or are biohazardous for laboratory personnel (e.g., *Mycobacteria* species, fungi, *Mycoplasma* species, *Lawsonia intracellularis*). In such instances, molecular detection of selected pathogens has already supplanted conventional culture.

Rapid and High-Throughput Applications Promote Molecular Tests

Rapid and specific detection of infectious disease agents is crucial for the prevention or containment of outbreaks. In the case of avian flu, the rapid detection of H5N1 strains of that virus is critical for containment. The avian flu pandemic concerns necessitate rapid and high-throughput molecular tests to maintain the well-being of animal and human community health. Similarly, West Nile virus (WNV) screening of mosquito pools and birds, as well as screening for exotic Newcastle disease, are additional examples of high-throughput applications with predominance for molecular tests.

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Increasing Adoption of Molecular Tests by University and Commercial Laboratories

Since the advent of molecular platforms in the diagnostic laboratory, most molecular tests in veterinary medicine are performed by several commercial and public laboratories. Unlike the market in human molecular diagnostics, which is dominated by four large players (Roche, Bayer, Gen-Probe, and Abbott), veterinary molecular diagnostics show significant fragmentation in particular with many university diagnostic laboratories. However, the transition to the more advanced real-time PCR platform within the past 5 to 7 years and the abandonment of conventional PCR tests by many laboratories has led somewhat to a concentration process in the veterinary diagnostic landscape for a good reason: real-time PCR is the more advanced method and is considered a fully matured technologic platform with great incentives for automation, operational efficiency, and affordability.

Simultaneous Testing of Multiple Pathogens

Parallel testing of multiple infectious agents in highly standardized platforms is a central advantage of molecular assays; it essentially allows several tests for both DNA and RNA pathogen targets to be performed simultaneously on a single sample, therefore condensing the medical message obtained on a given diagnostic sample. This development is a noteworthy driver for molecular diagnostics because it allows acquisition of more meaningful data from a single sample. This so-called panel strategy allows an efficient workup of complex clinical syndromes with general symptomatology that do not allow an etiologic diagnosis based on clinical signs. These clinical cases are complex for the decision-making process for the veterinarian dealing with patients unable to communicate the pain matrix. In complex organ-related problems with general or unspecific symptomatology, multiple infectious agents can be responsible for a clinical picture or aggravate other primary events in the differential workup. Even though veterinarians tend to make a single-pathogen diagnosis, it has become more evident in recent years that many syndromes are caused by multiple infections present at a given time. Panel testing on a large scale will uncover unknown co-infections in animals, which can diffuse the clinical picture. It has long been speculated, for example, that seemingly clinically irrelevant EHV-2 infections in horses may be a predisposing factor for *Rhodococcus equi* pneumonia in foals. More characteristic examples include

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respiratory infections in companion animals, often initiated by subclinical viral or bacterial infections that lead the way to secondary infections. In addition, many vectorborne pathogens have a high tendency to persist in infected animals and therefore may facilitate viral infections or aggravate preexisting conditions such as feline immunodeficiency virus or feline leukemia virus infection. Sepsis caused by infectious agents is expected to become an important segment for equine molecular diagnostics, especially in neonatal medicine. Molecular diagnostics enable fast turnaround time with rapid initiation of treatment. In the future, panel testing for the most important sepsis-inducing agents could be complemented by the addition of assays targeting antimicrobial resistance genes. This would allow the modification of treatment regimens in case antimicrobial resistance is detected.

Indications for Use of Polymerase Chain Reaction Assays for Infectious Diseases

Diagnostic tests such as PCR assays offer the potential for fast and accurate determination of the presence of an infectious agent, which can lead to an improved clinical outcome because of the faster initiation of more etiologic-based treatment and the possibility for quantitative treatment monitoring. Even if molecular-based tests are more expensive than more traditional diagnostic assays, their overall impact will lead to reduction in treatment costs.

Key indications for use of a molecular test are the speed and accuracy of molecular assays. In comparison with traditional culture for bacteria, rickettsial organisms, fungi, and viruses, molecular testing offers direct detection of the target pathogen within a fraction of the time. Owing to its speed, PCR assays have the potential to replace traditional culture methods for infectious agents that are difficult to culture or are not cultivable at all.

Compared with serology testing, molecular tests offer the advantage of detecting an infectious agent before an immune response occurs and a detectable antibody titer is developed. Immunoglobulin M (IgM) analysis in certain applications (such as WNV) can alleviate this problem; however, molecular testing methods are more reliable in picking up early virus replication and allow a faster epidemiologic assessment and earlier patient treatment.

In certain instances, for the discrimination of a clinically relevant EHV-4 infection from a latent infection, the detection of viral DNA is not informative. In such cases the quantitative assessment of viral loads is necessary.[3] Similarly,

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the choice of RNA or DNA affects the ability to distinguish disease (active virus replication and production of viral transcribed RNA) from nondisease (viral DNA of latently infected cells) status.

Molecular Biology Technologies

The main methodologies used for molecular diagnostics include the following:

- Nucleic acid capture, probe hybridization
- ISH, FISH
- Isothermal amplification of nucleic acids[4]
- Transcription-based amplification methods
- Signal amplification by branched-chain DNA
- Qualitative pathogen identification using nucleic acid amplification
- Quantitative assays
- Genotyping assays
- Genotype sequencing assays
- Multianalyte testing panels

Genotyping assays are typically used to test for known mutations associated with inherited genetic conditions such as hyperkalemic periodic paralysis (HYPP) in horses, an autosomal dominant condition that causes potassium-induced attacks of skeletal muscle paralysis. Many of these assays depend on sequence-specific probes designed to hybridize with known genetic variations. For infectious agents, genotyping or speciation is achieved by using highly specific PCR- or hybridization-based assays or by restriction enzyme fragment length polymorphism (RFLP) assays. In these assays, amplified material is digested with a certain restriction enzyme that characterizes the difference between two target sequences.

Polymerase Chain Reaction in Veterinary Molecular Diagnostics

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Because of its predominance in research and diagnostic applications, PCR assays will be discussed in more detail in later chapters. To give practitioners guidance about what to look for when PCR-based molecular diagnostic assays are offered, we will discuss some aspects such as design guidelines, differences between traditional and real-time PCR assays, sampling, controls, and interpretation of results in greater depth.

PCR testing in its pure form is a three-cycle event: denaturation of double-stranded target (or, in later cycles, PCR products), annealing of target and primers, and extension of the DNA strand from the primer.

Comparing Real-Time Polymerase Chain Reaction With Traditional Polymerase Chain Reaction Testing for Diagnostic Applications.

Real-time PCR testing was introduced into the marketplace in 1996 and replaced the tedious gel electrophoresis step to detect PCR products after amplification. In one survey, 98% of equine veterinarians knew about PCR testing, and 79% of equine veterinarians at universities knew the difference between conventional and real-time PCR testing.[5] During gel electrophoresis, the PCR products are separated by size and visualized using a dye (ethidium bromide) that intercalates with the double-stranded DNA. Real-time PCR detects the PCR products by using an internal probe that is labeled with two fluorescent dyes: a reporter dye and a quencher dye. The fluorescent activity of the reporter dye is absorbed (quenched) by the quencher dye. The probe binds to the PCR products between the two PCR primers. If the primers are extended by the DNA polymerase, the 5′ nuclease activity of the DNA polymerase digests the internal probe (hence hydrolysis probe) and releases the quenched fluorescence. Alternatively, hybridization probes that are not digested during amplification and that allow melting curve analysis can be used. This single change in the protocol regarding how to detect the PCR products revolutionized the use of PCR testing for both research and diagnostic applications. Most of the advantages resulting from this principle originate from the fact that the PCR tube does not have to be opened after a PCR assay for analysis. This principle is called *closed-tube detection.* The advantages are as follows:

1. Because of the closed-tube detection format, PCR products cannot escape from the PCR reaction containers. If escape occurs, it leads to the

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contamination of the PCR laboratory and subsequently the next PCR reactions. The consequence is false-positive PCR results. Real-time PCR efficiently eliminates this risk of PCR product carryover. There is also a second safety system called AmpErase UNG (Invitrogen, Grand Island, N.Y.),[6] which eliminates contaminating PCR products.

2. Real-time PCR is a kinetic PCR principle, underlining the fact that PCR product accumulation is measured during every single PCR cycle in real time. Because of this fact, real-time PCR is a quantitative method.
3. The real-time PCR platform introduced in 1996 consisted of a laser-based thermocycler, software to design real-time PCR assays, reagents, disposables, and protocols. Because of its integrated design, PCR assays generated with the new system were highly standardized.
4. Data analysis is run on an attached computer that collects fluorescent data points. This principle eliminates all laboratory steps after the real-time PCR cycling is finished. Because of the computer-formatted end analysis, results can be fed directly into the information and management systems of diagnostic laboratories. Real-time PCR has also enabled rapid cycling to finish the PCR process in less than 1 hour. Real-time PCR results therefore can be turned around significantly faster than with traditional PCR testing (normally within a 24-hour period).
5. Because of the probe used to detect the PCR products, real-time PCR is also a more specific assay than single-round traditional PCR. Only specific PCR products are detected by the probe. Real-time PCR testing, essentially a liquid-based hybridization method, is considered as specific as Southern blotting, which is a solid-based hybridization method.
6. Because real-time PCR incorporates hot-start enzymes, the specificity is even greater than with regular non–hot-start DNA polymerases. Hot-start enzymes are inactive at ambient temperatures and have to be heated to 95° C for 20 seconds to 10 minutes in order for the DNA polymerase activity to begin. Because of the hot-start nature, nonspecific binding of primers does not lead to unspecific PCR products and results in an overall increased specificity of the assay.
7. In combination, real-time PCR is described to be as sensitive as or more sensitive than double-round (nested) traditional PCR. Analytic sensitivity and limit of detection using real-time PCR testing is normally in the single molecule range, whereas the limit of quantitation with traditional PCR testing is in the range of 10 to 20 molecules.

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Preanalytic Variables

In general, molecular diagnostic laboratories provide strict recommendations for sample collection, including shipping instructions. These instructions include specimen type, volume, and anticoagulant and specimen transport, storage, and handling. The sample type is largely influenced by the pathogenesis of the disease and plays a key role in the performance and interpretation of the test results. Veterinarians are advised to adhere to these recommendations, because the quality of the result is directly correlated to the quality of the sample and preservation of the nucleic acid content. Molecular assays often offer the convenience of using a small specimen acquired with a minimally invasive procedure. The diagnosis of herpesviruses is a classic example in which culture and neutralization assays have been largely replaced by PCR testing on a small volume of aspirate or swabs from mucosal surfaces. Molecular tests can detect the presence of small numbers of organisms, and the probability of detection increases when a larger volume of specimen is added to the amplification reaction. Because molecular assays do not need viable organisms for testing, more flexibility in specimen transport is possible than with culture methods.

Appropriate specimen collection and transport conditions are important to ensure successful extraction of intact nucleic acid and to prevent cross-contamination. Specimen transport and storage conditions are likely to vary among specimen types and between RNA and DNA tests. RNA is more susceptible to degradation, but in general molecular diagnostic samples should be cooled in order to slow the nucleic acid degradation within the sample. Because of the difficulty of maintaining a freeze chain, molecular diagnostic samples should only be cooled throughout the collection, storage, and transportation process in order to minimize sample deterioration. Detailed storage and shipping instructions are crucial for a successful molecular diagnostic workup. Practitioners should be aware of these recommendations and consider using appropriate cooling containers when samples are collected in the field. Such samples maintain stability if stored appropriately in a cooled environment. Freezing and in particular the thawing process often adversely affect the quality and should be avoided if not otherwise instructed by the laboratory.

Sampling errors are among the many preanalytic variables that can affect the outcome of the results. It is therefore recommended that the laboratory have the appropriate labeling material available for blood containers or other sample types. Blood or body liquid contamination on the outside of the containers is an

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obvious cause of sample cross-contamination before the samples are manipulated in the laboratory. Proper collection procedures are essential to prevent these kinds of artifacts.

Nucleic Acid Extraction.

Many commercially available manual and automated methods have been successfully applied to infectious disease testing using a variety of clinical materials. Especially in veterinary molecular diagnostics, the variety of sample types can be challenging for processing through a single platform but can be achieved by validating sample type−specific pretreatment procedures in order to create a lysate of similar viscosity and nucleic acid concentration, which maximizes the extraction efficiency. Automated or semiautomated platforms are rapid and usually require only a small volume of specimen. In general, these systems are total nucleic acid extraction systems and support the parallel analysis of DNA and RNA pathogens from the same sample in a panel configuration. In addition, commercially available automated systems can reduce hands-on labor requirements and speed up the process significantly, leading to even shorter turnaround times. Most systems can accommodate sample volumes ranging from 100 to 500 µL and even 1 mL of specimen lysate. Nucleic acid binding capacity varies and can be as high as 200 µg per individual extraction position, which allows the maintenance of a good limit of detection even when many infectious agent targets are analyzed in parallel for a given panel.

Interpretation of Results.

Interpretation of results obtained with molecular assays for infectious diseases requires understanding of the pathogenesis and biology of the target organisms. Some challenges are unique to molecular tests and are different from considerations in interpreting other microbiological tests. Such differences are related to the distinction of viable from nonviable organisms and the correlation of nucleic acid detection with presence of disease or disease association.

Interpretation of a negative result includes information about the sensitivity and nucleic acid extraction efficiency. A false-negative result may be caused by a degraded or unstable sample. Insufficient volume or inappropriate sample type, inadequate sampling procedures, and transport problems are additional sources for potentially false-negative results. Sample-specific internal positive controls targeting endogenous genes such as the universal 18S rRNA (ssrRNA) or

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glyceraldehyde-3-phosphate dehydrogenase *(GAPDH)* gene help to identify these problems. These so-called internal positive controls allow quantification of the sample-specific nucleic acid (both DNA and RNA) and allow validation of a diagnostic sample for its use in PCR; samples below a certain quantity of DNA are at risk of being called false negative; therefore repeat collection can be recommended. In addition, inhibition phenomena originating from difficult sample matrixes such as feces, urine, or environmental samples contaminated with trace amounts of soil (humic acid) have to be controlled with internal positive controls to assess the inhibitory effects.

The factors requiring consideration for the interpretation of positive results include assay specificity and contamination issues. PCR testing or any other target amplification method is subject to these considerations. Real-time PCR testing using closed-tube detection procedures reduces the risk of PCR product carryover as a source of false-positive results and the availability of systems, which mark the PCR products when produced with certain types of nucleotides (uracil instead of thymidine), allows the specific degradation of contaminating PCR products before the next PCR amplification occurs (AmpErase UNG system). Combined with air movement control in the molecular diagnostics laboratory (overpressurized clean laboratory and negative-pressurized sample preparation laboratory) and limited access to trained laboratory technicians, great safety can be achieved, leading to valid results.

In general, molecular assays do not provide information about the viability of an infectious agent. Exceptions to this are DNA viruses, bacteria, and parasites analyzed for transcribed genes instead of their genomic DNA. This approach allows the assessment of the replication competence of a target and therefore is highly correlated with viability. Examples are toxin quantification, differentiation of vaccination versus infection, and herpesvirus quantification in order to differentiate between lytic (acute) and chronic (latent) infection, which has immediate implications to the ability of the virus to cause or contribute to clinical signs. In addition, spliced RNA occurs only if viral genes are actively transcribed and provides a means for obtaining information about the replication activity of a virus and the stage of infection. In other cases, targeting the ribosomal RNA of parasites such as *Toxoplasma* and *Cryptosporidium* is a means for obtaining viability information and also may increase the analytic sensitivity.[7]

Detection of the nucleic acid of a pathogen does not necessarily ensure that the organism is the cause of the disease. A primary example is herpesvirus

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infections (EHV-1 and EHV-4), in which the detection of DNA may indicate the presence of lytic, nonreplicating, or latent virus. Studies indicated that high viral loads of EHV-4 DNA allow the formulation of a cutoff value to differentiate between lytic and latent infection.[8] In this particular case, high viral loads were associated with the presence of clinical signs and viral RNA transcripts. Therefore quantitative real-time PCR testing can provide a means to obtain much improved disease association and invalidates the notion that PCR "just detects dead DNA."

Reporting of Molecular Results.

Reporting results for qualitative assays in infectious disease monitoring is simple: a sample either does or does not contain the nucleic acid of a target organism. Further relevant information includes the nucleic acid extraction efficiency, nucleic acid stability, and sample integrity determined with the various quality controls.

Reporting results for quantitative molecular infections is more complex. For veterinary medicine, some quantitative applications have been established and are progressively phased into diagnostic routine analysis. Such quantitative PCR (qPCR) tests combined with fully standardized protocols will continue to expand within the veterinary diagnostic market as our understanding of the biology and pathology of infectious agents grows.

Regulatory Considerations of Molecular Laboratories

Veterinary molecular diagnostics is an emerging market with a growing level of regulation. Standards such as those defined by the American Association of Veterinary Laboratory Diagnosticians (http://www.aavld.org), Molecular Methods (CLSI; http://clsi.org/), or MIQE (minimum standard guidelines for fluorescence-based quantitative real-time PCR experiments) are adopted by commercial laboratories aiming to provide a comprehensive diagnostic service. Other sources for guidelines are U.S. Food and Drug Administration guidelines (www.fda.gov) for the detection of nucleic acids; ASTM guidelines (*Standard Guide for Detection of Nucleic Acid Sequences by the Polymerase Chain Reaction Technique;* www.astm.org); and the Association for Molecular Pathology (*Recommendations for In-House Development and Operation of Molecular Diagnostic Tests;* www.ampweb.org).

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Guidelines for Clinicians to Select Molecular Diagnostic Laboratories

Veterinarians can use a variety of guidelines to select laboratories for molecular diagnostics. However, there are some major factors worth considering before samples are submitted. First, it is worthwhile to obtain information about the nature of the PCR test (traditional vs. real-time). Second, questions addressing the quality control and quality assurance system within a particular laboratory should be asked. Third, turnaround time, pricing, and the level of guidance with result interpretation and availability of consulting resources are additional factors worth investigating before samples are submitted.

Summary

As with any methodologies, qPCR is a work in continuous progress, development, and improvement. Although all of the methods described in this review use the Nobel Prize–awarded PCR process, the advantages and disadvantages of subtle differences in assay format, accuracy, and reliability of quantitation have to be rigorously compared. The next generation of quantitative real-time PCR processes will be increasingly automated, standardized, and miniaturized. The time for nucleic acid preparation and PCR amplification will be further reduced by using small microtiter-formatted microfluidic cards or silicon-based chip technology.[9-11] Amplification time has been brought down to several minutes by using an advanced nucleic acid analyzer (ANAA) consisting of a battery-powered array of silicon-based PCR microchips with thin-filmed resistive heaters, thus enabling ultrafast amplification, further pushing the technologic possibilities in order to improve the diagnostic results output.[10]

How will these new systems be incorporated in routine veterinary diagnostics? Veterinary medicine will experience a broad adoption of many quantitative assays for infectious agents and genetic abnormalities in the near future. The ability to standardize assays will allow high-throughput applications that have not been possible with traditional molecular methods. For this reason, applications for veterinary medicine may experience not only quantitative but also qualitative growth. These assays will help improve patient management and client satisfaction.

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Molecular Testing for Infectious Diseases in Horses

Nicola Pusterla • Christian M. Leutenegger

The ready availability of a correct etiologic diagnosis, particularly in contagious infections, enables the veterinarian to make early decisions regarding the patient's care and management, address appropriate treatment, and allow timely notification and discussion of management issues pertaining to the prevention of disease spread. The past 2 decades have seen a revolution in the understanding, management, diagnosis, control, and prevention of infectious diseases.[1,2] This period has encompassed the discovery of emerging equine agents, antimicrobials, and vaccines, as well as a wealth of improved diagnostic tests for equine practitioners. Despite these advances, infectious diseases remain a leading cause of equine morbidity and mortality, with resurgence of certain infections (e.g., West Nile virus); an increasing population of elderly, more susceptible horses; and an increasing international equine commerce, expanding the geographic distribution of pathogens.[3,4] The focus of rapid diagnosis of infectious diseases has also shifted during this time. The most obvious change has been the appearance and increasing importance of nucleic acid (NA) amplification-based techniques, primarily the polymerase chain reaction (PCR), at the expense of traditional methods of clinical microbiology.[5] PCR has become an increasingly important tool in microbial diagnosis in recent years, mainly because of its rapidity, high sensitivity, and high specificity. These superior characteristics have propelled the field of PCR-based molecular diagnostics into the arena of applied diagnostics for infectious agents. Because the number of published and offered PCR assays is steadily rising, there is a need for critical evaluation, comparison of performance, and eventually standardization of methods to enable equine practitioners to select the optimal methodology.

Sample Submission

NA techniques to detect the presence of infectious agents in biological specimens require stringent quality guidelines. These guidelines aim to ensure the stability of NAs (both genomic DNA and total RNA), which are the target for molecular-based diagnostic methods. Whole blood samples are collected

aseptically into evacuated blood tubes containing ethylenediaminetetraacetic acid; body fluids (e.g., thoracic, abdominal, joint, cerebrospinal, tracheal wash, bronchoalveolar lavage, guttural pouch lavage fluid) and tissues should be collected into serum tubes without additives; nasal or nasopharyngeal secretions should be collected with rayon- or batting (Dacron, Invista, Wichita, Kan.)-tipped swabs and are best kept in a sterile serum or conical tube (virus transport medium is recommended for the detection of viruses); and fecal material should be collected into small fecal cups or serum tubes (Fig. 29.1; Table 29.1). All samples must be sent cooled on blue ice by express mail overnight to the laboratory. Freezing of samples should be avoided. Short-term storage for a period of 2 to 3 days before shipment (over a weekend) should be done in a refrigerated compartment. Each sample should be properly labeled and accompanied by a submission form containing information pertaining to the patient, owner, veterinarian, sample, and pathogen(s) to be tested (most submission forms can be downloaded from the respective laboratory website). The laboratory should be notified in advance, and inquiry should be made about the availability of the offered tests, as well as turnaround time and associated costs. Incoming samples normally are processed the same day, and PCR results usually are available within 24 to 48 hours if the NA passes quality control.

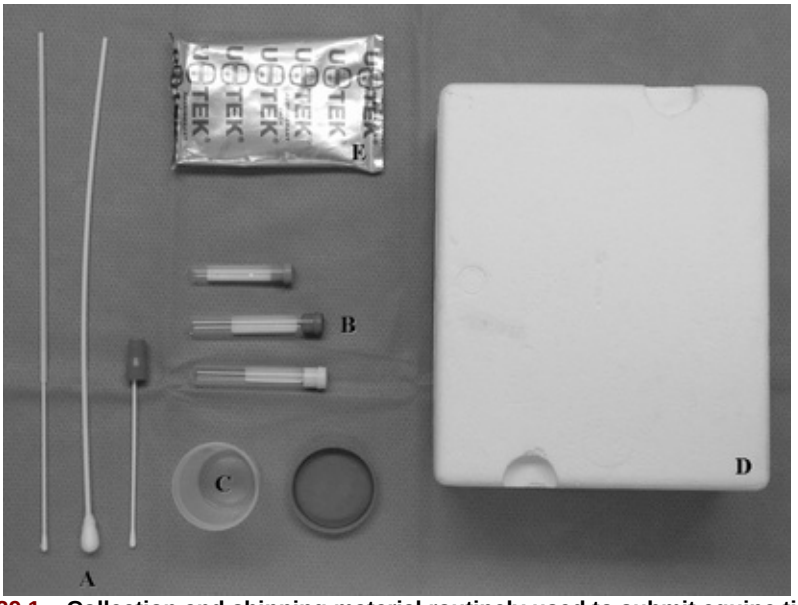


FIG. 29.1 **Collection and shipping material routinely used to submit equine tissue samples for molecular detection. A, Three sterile swabs of different lengths. B, Three sterile, evacuated tubes with and without additives. C, Sterile cup with lid. D, Styrofoam shipping container. E, Cooling element to keep the samples cooled.**

TABLE 29.1

Tissue Samples Commonly Used for Molecular Detection of Common Equine Pathogens

Pathogen	Tissue Submission
Anaplasma phagocytophilum	Whole blood
Babesia caballi	Whole blood
Borrelia burgdorferi	CSF, CNS
Clostridium botulinum	Feces, gastrointestinal content, feed, wounds, and carrions
Clostridium difficile (antigen and toxin A and B)	Feces
Clostridium perfringens	Feces
Corynebacterium pseudotuberculosis	Aspirate from abscess, body fluid
Cryptosporidium spp.	Feces
Equine arteritis virus	NPS, uterine swab, placenta, aborted fetus, semen
Equine coronavirus	Feces
Equine herpesvirus 1	NPS, whole blood, TW, BAL, CSF, CNS, uterine swab, placenta, aborted fetus
Equine herpesvirus 2	NPS, whole blood, TW, BAL
Equine herpesvirus 4	NPS, TW, BAL
Equine herpesvirus 5	NPS, whole blood, TW, BAL
Equine influenza virus	NPS, TW, BAL
Equine rhinitis A virus	NPS, urine
Equine rhinitis B virus	NPS
Equine rotavirus	Feces
Lawsonia intracellularis	Feces, intestinal biopsy
Leptospira spp.	Urine, blood, uterine swab, placenta, aborted fetus
Neorickettsia risticii	Whole blood, feces
Neospora hughesi	CSF, CNS
Rhodococcus equi	TW, BAL, feces
Salmonella spp.	Feces
Sarcocystis neurona	CSF, CNS
Streptococcus equi subsp. *equi*	NPS, NPL, GPL, lymph node aspirate
Streptococcus equi subsp. *zooepidemicus*	NPS, NPL, GPL, lymph node aspirate
Theileria equi	Whole blood
West Nile virus	Whole blood, CSF, CNS

BAL, Bronchoalveolar lavage fluid; *CNS,* central nervous system tissue; *CSF,* cerebrospinal fluid; *GPL,* guttural pouch lavage; *NPL,* nasopharyngeal lavage; *NPS,* nasal/nasopharyngeal swab; *TW,* tracheal wash fluid.

Clinical Applications

An array of NA amplification techniques may be offered by laboratories in order to establish an etiologic diagnosis of equine infectious diseases. Several published studies have shown the benefit of NA amplification techniques in comparison with conventional microbiological techniques. Current efforts are

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aimed at improvement of the diagnostic efficiency of molecular techniques, for both common and less common pathogens. To facilitate a decision on which pathogens should be evaluated for a specific case, some laboratories offer panels covering specific organ systems (e.g., respiratory, gastrointestinal, neurology, bloodborne). Such panels test several common pathogens for each organ system. Some of the diagnostic PCR applications most relevant for equine practice are presented as follows, along with their advantages and potential pitfalls.

Respiratory Pathogens.

Respiratory pathogens are often contagious, and infections must be diagnosed rapidly in order to prevent a disease outbreak and institute the appropriate management plan. The short turnaround time and reliability of PCR make this molecular technology an ideal tool for the diagnosis of respiratory pathogens.

Equine influenza is commonly diagnosed by virus isolation or detection from nasal or nasopharyngeal swabs collected from horses during the early febrile stage of the disease. Virus can be grown from nasal and nasopharyngeal swabs by inoculation and incubation of embryonated chicken eggs or passage through Madin-Darby canine kidney cells. Although isolation of the virus is essential to allow antigenic and genetic characterization of the strain, this technology is time consuming and successful isolation is, at best, to be expected in 50% of the cases. Further, since mutations have been reported to occur during the process of viral culture, recovered isolates must be viewed critically. In recent years new methods for virus detection, such as antigen-detection enzyme-linked immunosorbent assays (ELISAs) and PCR, have been described. Collectively these detection methods have shown higher sensitivity than virus isolation and antigen-capture ELISAs.[6-9] Amplification of the single-stranded RNA of equine influenza viruses is performed by reverse transcription-PCR (RT-PCR) technology, using a one-step, nested, or real-time approach. The hemagglutinin, nucleoprotein, and matrix gene are the commonly targeted genes for these molecular assays. Unfortunately, comparison of the different PCR assays is precluded by the use of different technologies, the lack of standardization among the assays, and variation in targeted genes. Nucleotide and deduced amino acid sequences of portions of the hemagglutinin gene are now routinely used for phylogenetic characterization of outbreak strains. Further, novel real-time PCR assays can be used as a viable replacement for the more traditional methods of quantifying equine influenza virus in vaccine efficacy studies. Another advantage of assays such as antigen-detection ELISAs and PCR is their ability to

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detect a nonviable virus, a situation that may occur when nasal or nasopharyngeal samples are frozen or not adequately stored and/or shipped to a diagnostic laboratory, allowing a rapid diagnosis in the acute phase of infection. Routine diagnostic testing for equine influenza virus does yet not allow differentiation between clade I and clade II viruses of the Florida sublineage.

EHV-1 and *EHV-4* are important and widespread equine viral pathogens that cause important economic losses in the equine industry. Both are double-stranded DNA alphaherpesviruses that affect the equine respiratory tract and can establish lifelong latent infection after primary exposure. Traditionally, virus isolation has been the gold standard for diagnosing EHV-1 and EHV-4 infections. The sample of choice is a nasal or nasopharyngeal swab, which should be taken early in the febrile phase of the disease. The swabs should be kept in viral transport medium and shipped on ice to a veterinary diagnostic laboratory. Because of the lymphotropism of EHV-1, virus isolation can also be attempted from citrated or heparinized whole blood. Virus isolation requires the maintenance of specific cell culture lines, making this process relatively expensive and time consuming. EHV-1 can be propagated in a broad range of cell lines; however, EHV-4 grows only in cell lines of equine origin. Virus isolation is often hampered by the fragility of the virus, intermittent viral shedding, and interference with local antibodies. PCR offers an alternative to virus isolation and has proven to be a sensitive method of detecting EHV-1 and EHV-4 in respiratory secretions, peripheral blood lymphocytes, and other tissues.[10-12] Many PCR assays have been established to study the pathophysiology and improve the diagnosis of these viruses. Conventional one-step or nested PCR assays do have inherent risks of carry-over contamination as a result of postamplification steps required to detect the PCR products. Novel molecular platforms such as real-time qPCR have strongly reduced the risk of contamination. PCR assays used in routine diagnostics are based on the detection of viral genomic DNA and are therefore unable to distinguish among lytic, nonreplicating, or latent viruses. Alternative molecular approaches have recently been established using real-time PCR to allow discrimination among the different viral states in horses naturally infected with EHVs.[13,14] Discrimination among the different viral states is now possible by 1) targeting several genes (e.g., glycoprotein, latency-associated transcripts), 2) detecting viral genomic DNA and transcriptional activity of the target genes at the messenger RNA (mRNA) level, and 3) using absolute quantification. Viral threshold loads are used in selected human infectious diseases (i.e., HIV, HCV) to determine disease

stage and response to antiviral therapy. A similar concept is used diagnostically for EHV-1– or EHV-4–infected horses in order to discriminate between lytic and nonreplicating virus, to determine their infectious risk based on viral load in respiratory secretions, and to monitor their response to treatment.[13,14]

Streptococcus equi subsp. *equi* infection is rarely associated with detection difficulties when using conventional cultures in clinically affected horses. Culture, however, may be unsuccessful during the incubation, and early clinical phases of infection and the presence of other β-hemolytic streptococci, especially *S. equi* subsp. *zooepidemicus,* may complicate interpretation of cultures. Available PCR assays are designed to detect the DNA sequence of various virulence genes of *S. equi.* PCR assays can be completed in a few hours, and results may be available on the same day that samples have been submitted to the laboratory. One of the pitfalls of PCR has been its inability to distinguish between live and nonviable organisms; therefore positive results have in the past been considered presumptive until confirmed by culture. Nowadays, the viability issue can be addressed by quantitation of *S. equi* virulence genes or the detection of transcriptional activity for virulence genes at the RNA level.[15] In several studies, PCR proved to be up to three times more sensitive than culture.[16-17] PCR accompanying culture on a nasal swab or guttural pouch lavage may be used in a control program to select possible carrier animals, because PCR is capable of detecting *S. equi* DNA in guttural pouch lavages for weeks after disappearance of live organisms. Such is not the case for the nasopharynx, in which the efficient mucociliary apparatus removes organisms and DNA at the same time. PCR should be considered in order to detect asymptomatic carriers, establish the *S. equi* infection status of asymptomatic horses, and determine the success of elimination of *S. equi* from the guttural pouch. A particular problem in the management of strangles outbreaks is the lack of a suitable assay to differentiate between wild-type and vaccine *S. equi* strains. However, recent studies have shown gene variations in the N-terminal region of the SeM gene of various field isolates, allowing epidemiologic analysis of disease transmission.[18] Further, a deletion in the *aroA* gene of a live-attenuated strangles vaccine marketed in Europe (Equilis StrepE, Merck Animal Health, Walton Manor, Walton, Milton Keynes, UK) has allowed the development of a PCR assay able to differentiate between wild-type and vaccine strains.[18] Such assay has, however, not yet been developed to differentiate between the intranasally applied attenuated live vaccine marketed in North America (Pinnacle I.N., Zoetis,

Overland Park, Kan.) and field isolates. However, when needed for forensic reasons, differentiation can be done via the morphology of colonies, biochemical analysis, genotyping, and restriction digest.[19] Together, these assays allow differentiating between wild-type and vaccine/ancestor strains.

Streptococcus equi subsp. *zooepidemicus (S. zooepidemicus)* is a commensal, opportunistic equine pathogen that is generally present in the upper respiratory tract and responsible for secondary bacterial bronchopneumonia in young and adult horses. The literature reports on a few outbreaks of upper respiratory disease associated with *S. zooepidemicus*.[20,21] The clinical signs are indistinguishable from *S. equi* infection and include lethargy, anorexia, elevated rectal temperature, serous to purulent nasal discharge, coughing, and lymphadenopathy with abscessation. Single clones of *S. zooepidemicus*, as determined by sequencing of the szP gene and multilocus sequence typing, have been associated with increased pathogenicity.[20] From a diagnostic standpoint, one should not test for *S. zooepidemicus* in nasal secretions from horses with upper airway disease due to the ubiquitous nature of this bacterial organism. However, *S. zooepidemicus* should be considered as the etiologic agent in respiratory cases when detected by culture or qPCR from a draining lymph node or guttural pouch empyema and other respiratory pathogens have been ruled out.

Rhodococcus equi is an important cause of chronic suppurative bronchopneumonia with extensive abscessation in foals 3 weeks to 6 months of age. Culture of the organism from tracheal wash (TW) fluid currently is considered the gold standard for diagnosis.[22] However, it can be difficult to reliably grow *R. equi* from a single TW sample, possibly because of prior antimicrobial administration or overgrowth by multiple pathogenic bacterial species.[23,24] Hillidge[25] reported that only 62% of foals with positive *R. equi* cultures at necropsy and 64% of those with radiographic evidence of lung abscessation yielded *R. equi* on culture of TW fluid. PCR has been evaluated in order to increase the diagnostic sensitivity of TW fluid samples. Strains of *R. equi* isolated from sick foals uniformly contain an 85- to 90-kb plasmid that carries the gene responsible for expression of a 15- to 17-kDa antigen (vapA) of undetermined function.[26,27] Environmental strains of *R. equi* not associated with disease do not contain this plasmid. Therefore detection of the vapA gene of *R. equi* in a TW fluid sample from a foal with pneumonia can be considered diagnostic. Both culture and PCR, however, may detect environmental contaminants of *R. equi* in TW fluid, but PCR has the ability to distinguish

between virulent and avirulent strains. Foals, however, may have virulent or avirulent strains of *R. equi* present as contaminants in their airways that are not responsible for clinical signs of pneumonia. This situation may be more likely on farms in which *R. equi* problems are endemic. In a study evaluating the sensitivity of conventional culture, PCR, and serology from 53 foals with pneumonia, PCR of TW fluid was found more sensitive and specific for the diagnosis of *R. equi* pneumonia than the other two available diagnostic tests.[28] PCR should be used in conjunction with standard culture because of the probability of the presence of multiple bacterial pathogens and the inability of PCR to determine antimicrobial sensitivity of *R. equi*. PCR with its higher sensitivity and specificity may be useful to rule out *R. equi* pneumonia in culture-negative foals that have failed to improve with standard antimicrobial therapy and have clinical signs consistent with *R. equi* pneumonia. It may also be useful in monitoring response to therapy and deciding when to discontinue therapy in foals that are confirmed to have *R. equi* pneumonia. In clinical situations in which the severity of the respiratory signs of the patient prevents the collection of TW fluid, feces have been shown to be a sensitive surrogate specimen for the molecular detection of *R. equi*.[29,30] However, serial *R. equi* qPCR testing on feces should not be used as a screening test for clinical *R. equi* foal pneumonia.[31]

Equine rhinitis A and B virus and equine arteritis virus, although less commonly associated with infectious upper respiratory disease, should also be considered as target pathogens during respiratory outbreaks.[32-34]

EHV-2 and EHV-5 are widespread in horse populations; therefore the detection of any of these viruses can occur in healthy but also sick animals. These two viruses are optimally adapted to their host, which means that significant clinical expression of infection is rarely encountered. Recent work has shown that different genetic variants of these viruses circulate among healthy horses, hypothesizing that viral reinfections or reactivations may be the origin of clinical disease and also explaining the sporadic occurrence of such cases.[35] Another characteristic of the gammaherpesviruses is their ability to immunomodulate the immune system, potentially increasing the susceptibility of horses to various infectious pathogens.[36] A recently described atypical interstitial pneumonia named equine multinodular pulmonary fibrosis (EMPF) has been linked to the presence of EHV-5 in affected pulmonary tissue.[37] The diagnosis of this disorder is based on clinical signs, radiographic abnormalities of the lungs,

lower airway fluid cytology, histopathology of pulmonary tissue, and EHV-5 detection by qPCR in bronchoalveolar fluid and/or pulmonary tissue.[37,38] Due to their high prevalence in the horse population, and in order to avoid dilemmas with the interpretation of PCR results, testing of EHV-2 and EHV-5 in horses with upper respiratory tract disease is not recommended at this time.

Neurologic Pathogens.

Although highly sensitive and specific PCR assays have been developed for detection of viral and protozoal genomes in the cerebrospinal fluid (CSF) of neurologic patients, these methods are often of limited value in the routine diagnosis of these diseases because viremia is often short-lived or the pathogen has no affinity to the cells of the CSF. Consequently, pathogens are usually no longer detectable at the onset of systemic or central nervous system signs.

Equine protozoal myeloencephalitis (EPM), caused by the protozoal Apicomplexa parasites *Sarcocystis neurona* and *Neospora hughesi*, represents one of the greatest diagnostic challenges for equine practitioners. Detection of the parasite at necropsy is considered the gold standard. Therefore clinical diagnosis is based on clinical findings, exclusion of other neurologic diseases, and the use of serologic assays (e.g., Western immunoblot, indirect immunofluorescent assay, ELISA) on serum and CSF.[39-41] Molecular diagnostics have also been investigated, but their sensitivity was found to be low.[42]

Apparently, intact merozoites rarely enter CSF, and free parasite DNA is destroyed rapidly by enzymatic action.[43] On the basis of low sensitivity, PCR testing of CSF should not be recommended for routine diagnosis of EPM. In contrast, PCR testing of neural tissue has been shown to be useful as a postmortem test.[44] Sequence analysis is routinely used to identify *S. neurona* and *N. hughesi* isolates and to determine the heterogeneity and evolutionary relatedness within these and related species.[45,46] Detection and isolation of *S. neurona* from peripheral blood have been reported only in experimental studies.[47,48] Therefore molecular detection of *S. neurona* in blood is insensitive and should not be used in order to document or rule out EPM in a neurologic horse.

Diagnosis of WNV encephalitis in horses currently is based on observation of compatible clinical signs (e.g., ataxia, paresis, paralysis, hyperesthesia, muscle fasciculation, seizures, fever) and one or more of the following: isolation of WNV from blood, CSF, or tissue; a fourfold increase in plaque reduction

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neutralization test antibody titers on paired serum samples taken 2 weeks apart; or the detection of IgM antibody to WNV by IgM-capture ELISA.[49,50] Given the nonspecificity of the IgM ELISA (i.e., does not differentiate between disease and exposure) and the time required to serologically confirm WNV infection, alternative tests able to rapidly detect WNV in clinical specimens are important. RT-PCR using a one-step, nested, or real-time approach has been evaluated to investigate antemortem cases of suspected WNV encephalitis in horses and humans using blood. The diagnostic sensitivity of WNV RT-PCR using either serum or whole blood was low.[51-53] However, 57% to 70% of CSF samples from human beings with serologically confirmed WNV infection tested positive by real-time RT-PCR.[51,52] The reduced ability to detect WNV in CSF or serum from patients with serologically confirmed WNV infection is likely due to the short-lived viremia in dead-end hosts, and it emphasizes the fact that, in order to detect WNV in blood or CSF, the sample should be collected early during the disease process. Investigation of the sensitivity of RT-PCR on CSF from horses with WNV encephalitis has not yet been reported. RT-PCR has also been shown to accurately identify WNV in field-collected mosquito pools, avian tissues, and human and equine brain tissue samples with a degree of sensitivity approaching that of virus isolation in Vero cells.[52-54]

Myeloencephalopathy is an uncommon presentation of EHV-1 infection and should always be considered as a differential diagnosis when a horse develops sudden neurologic signs (e.g., ataxia, paresis, urinary incontinence), especially if multiple horses on the premises are involved or when a recent history of fever, abortion, or viral respiratory disease in the affected horse or herdmates is reported.[55] Diagnosis is often based on history, clinical signs, and xanthochromia and elevated total protein concentration in CSF resulting from vasculopathy. Attempts to isolate virus from the blood or CSF of patients are often unsuccessful because the peak of viral shedding has usually passed by the time neurologic signs appear.[56] However, affected horses can shed the virus in nasal secretions and thus represent a risk of infection for unaffected in-contact horses. This outcome has been reported in a hospital setting in which horses developed neurologic disease after having been exposed to horses with EHV-1 myeloencephalopathy.[57] Therefore it is imperative to determine the risk of shedding in a suspected horse in order to initiate appropriate infectious disease control protocols. PCR, as previously shown for viral respiratory diseases, is a fast and sensitive molecular diagnostic tool and should be performed on blood

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and nasal or nasopharyngeal swabs to document viremia and nasal shedding, respectively.[58,59] The dilemma as to whether the virus is in a lytic, nonreplicating, or latent state can be addressed by using absolute quantitation or transcriptional activity of the target gene similar to the approach used for EHV-4.[13] A recently identified single nucleotide polymorphism (SNP) at position 2254 in the DNA polymerase gene *(ORF 30)* correlates with neurologic disease.[60] This SNP is responsible for a single amino acid residue at position 752 of the DNA polymerase with EHV-1 strains associated with neurologic outbreaks involving a D_{752} genotype (also referred to as G_{2254}), whereas most nonneurologic outbreaks involve a N_{752} genotype (also referred to as A_{2254}). Rapid qPCR assays have been established to allow differentiation between neuropathogenic and nonneuropathogenic strains.[61-63] However, the genotyping of field isolates needs to be interpreted carefully as 14% to 24% of EHV-1 isolates from horses with EHM do not have this neuropathogenic marker.[64] Strain characterization may be important given that the potential of EHM development is greater in horses infected with a neuropathogenic genotype (D_{752}). Furthermore, detection of a neurotropic EHV-1 strain may influence therapy, especially in the use of antiviral drugs such as valacyclovir, used to decrease viremia and prevent the development of neurologic sequelae.

Borrelia burgdorferi, the causative agent of Lyme disease, is a helical-shaped, gram-negative, unicellular spirochete transmitted by infected *Ixodes* ticks. In general, the diagnosis of Lyme disease in horses is made on the basis of the geographic origin of the horse, ruling out other causes of clinical signs and a high antibody titer to *B. burgdorferi*.[65] qPCR for *B. burgdorferi* in CSF has been shown to be specific, but the results are often negative due to the rare occurrence of the spirochetes in the CSF.[66] However, PCR can be used to help document the presence of *B. burgdorferi* at postmortem on neurologic tissue or infected ticks.[67]

Gastrointestinal Pathogens.

The detection of equine gastrointestinal pathogens using conventional or molecular tests is often challenging because these pathogens are difficult to grow in cell culture systems or can be present in pathogenic or nonpathogenic forms, making interpretation of positive results difficult. Furthermore, the use of fecal material for molecular diagnostics has been associated with false-negative

results because of the presence of inhibitory substances in the feces that can interfere with NA extraction or amplification.[68] However, development and use of specific extraction kits (DNA Stool Mini Kit, QIAGEN, Valencia, CA) have improved the yield of NA from feces.[69]

Neorickettsia risticii is the rickettsial agent responsible for equine neorickettsiosis (EN) (formerly Potomac horse fever), a serious enterocolitis of horses. Because of the nonspecific nature of the clinical signs, a provisional diagnosis of EN is often based on the presence of typical clinical signs and the seasonal and geographic occurrence of the disease. A definitive diagnosis of EN, however, should be based on isolation or detection of *N. risticii* from blood or feces of infected horses.[70] Isolation of the agent in cell culture, although possible, is time consuming and not routinely available in many diagnostic laboratories. The recent development of *N. risticii*–specific PCR assays has greatly facilitated the diagnosis of PHF.[71-72] These molecular assays have contributed to the investigation of the epidemiology of PHF, allowing the discovery of helminthic vectors and intermediate and definitive helminthic hosts, as well as determining the natural route of infection.[73-75] Nucleic acid of *N. risticii* can be detected in the blood and feces of naturally or experimentally infected horses, but the detection period does not necessarily coincide between the two sample types (Fig. 29.2). On the basis of these results, we recommend analyzing both blood and feces from suspected horses in order to enhance the chance of molecular detection of *N. risticii*.

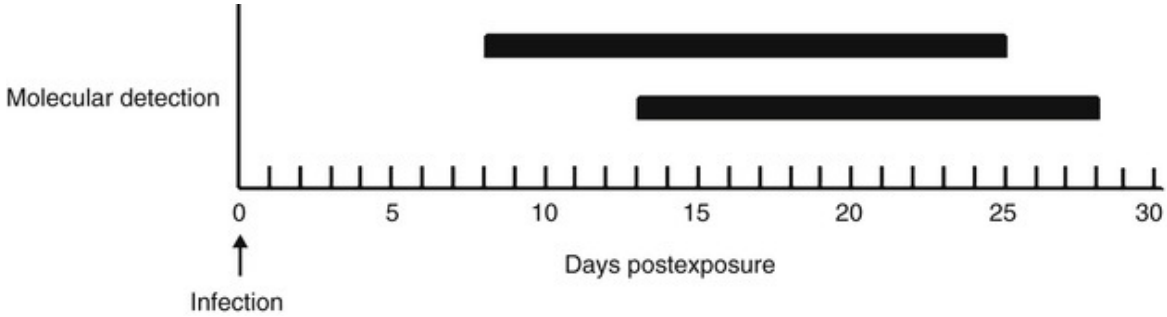


FIG. 29.2 Molecular detection period of *Neorickettsia risticii* in blood and feces of experimentally infected horses. (From Pusterla N, Madigan JE, Leutenegger CM: Real-time polymerase chain reaction: a novel molecular diagnostic tool for equine infectious diseases. J Vet Intern Med 20:3, 2006. Reprinted with permission of the American College of Veterinary Internal Medicine.)

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Lawsonia intracellularis, an obligate intracellular bacterium, is the causative agent of proliferative enteropathy in a variety of domestic and wild animal species.[76] In horses, Equine proliferative enteropathy (EPE) often affects young horses. Antemortem diagnosis can be challenging and is based on interpreting clinical signs (e.g., lethargy, anorexia, fever, weight loss, subcutaneous edema, diarrhea, colic), clinicopathologic results (e.g., hypoproteinemia resulting from hypoalbuminemia), and ultrasonographic findings (e.g., thickened small intestinal walls) and excluding other causes of similar gastrointestinal findings.[77] Currently, culture of the organism is difficult and is not routinely offered by laboratories. Antemortem diagnosis relies on serology and PCR.[78] The combination of both tests and repeated fecal sampling for PCR from target animals will increase the chance of diagnosing the disease. PCR has the advantage of being fast and can yield positive results in the early stage of disease, when antibodies are not yet measurable. Prior use of antimicrobials can negatively affect the molecular detection of *L. intracellularis* in feces. Therefore in a suspected case, fecal collection for PCR testing should be performed before the institution of any antimicrobial treatment.

In recent years, PCR assays for the detection of *Salmonella* spp. in fecal samples from horses admitted to veterinary hospitals have been evaluated.[79-82] Collectively, these studies have shown an unquestioned higher analytic sensitivity for the detection of *Salmonella* spp. PCR assays when compared with conventional microbiological culture. The higher detection rate of *Salmonella* by PCR has been attributed to the detection of nonviable organisms and of previously undescribed *Salmonella*-like bacterial organisms. The use of novel virulence target genes for the molecular detection of *Salmonella* spp. has considerably improved the performance and accuracy of such assays. More and more veterinary hospitals across North America are switching from conventional microbiological culture to qPCR for the testing of *Salmonella* as part of their infectious disease control program. In such instances, qPCR is performed on fecal and environmental samples following a 24-hour selective enrichment step. The use of qPCR is cost effective and has the potential to reduce contamination risks and turnaround time, with results being available within 22 to 28 hours from sample collection (18 to 24 hours enrichment time, 4 hours for DNA purification and amplification). Further, the use of absolute quantitation allows assessment of the infectious nature of hospitalized animals and may be an excellent alternative to conventional culture methods for surveillance and

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research studies.[83] Although qPCR for *Salmonella* spp. is an accurate and fast screening test, one must still consider microbiological culture to confirm positive molecular results and to determine the serovar and antibiogram of the isolated *Salmonella* spp.

The detection of equine coronavirus (ECoV) by qPCR in the feces of foals with fever and diarrhea is difficult to interpret because ECoV has also been detected in the feces of healthy foals.[84] Healthy foals have been found to be infected mostly by ECoV in a single infection without any other co-infecting agents, whereas ECoV was found exclusively in association with other co-infecting agents in sick foals. This is in agreement with coronaviruses in other species, where the virus may not have enough pathogenic potential to cause disease but causes local immune suppression, allowing secondary infections to take place more efficiently. In adult horses, ECoV causes a self-limiting disease characterized by lethargy, anorexia, fever, and less frequently changes in fecal character and colic.[85,86] The diagnosis of ECoV infection in adult horses should be supported by the qPCR detection of ECoV in the feces.

Equine rotavirus poses a challenge each foaling season to farm managers and veterinarians in intensive horse-breeding areas throughout the world. A quick and reliable diagnosis is essential in order to separate affected foal with diarrhea and reduce the spread of this virus. The diagnosis of rotavirus infection has in the past relied on direct virus detection using a rapid antigen-capture ELISA. Commercially available qPCR assays have shown high analytical sensitivity, specificity, and accuracy in the diagnosis of equine rotavirus infection and will likely replace the less sensitive ELISA test in the near future.[87]

Clostridium difficile is a fastidious anaerobe considered an important cause of colitis, although it can also be found in the intestinal tract of healthy horses.[88] Although the dynamics of colonization are unknown, it is likely that horses can carry *C. difficile* for long periods without ever developing disease. Carrier status is generally higher in foals and adult horses treated with antimicrobials. The diagnosis of *C. difficile* infection is generally based on the detection of toxin A or B or both in feces, gastric reflux, or colonic content, ideally using a test that has been validated in horses.[88] A variety of immunoassays are available, but only one assay has been validated in horses (*Clostridium difficile* TOX A/B II ELISA, Techlab, Blacksburg, Va.).[89] This test, which detects toxin A and B, has a reported sensitivity of 84% and specificity of 96% compared with the gold standard (cell cytotoxicity assay). qPCR targeting the toxin A and B genes of *C.*

difficile has been shown to be highly sensitive with the advantage of a short turnaround time.[90] However, the clinical specificity will depend on the overall background prevalence of *C. difficile* colonization in the population of horses tested. qPCR is considered an acceptable screening tool to rule in or rule out *C. difficile* infection, allowing proper management and isolation of qPCR-positive patients.

Clostridium perfringens type A and C are important causes of enteric disease in young foals. Disease induced by *C. perfringens*, especially type C, is associated with hemorrhagic diarrhea, abdominal distention, and circulatory shock.[91] The diagnosis of *C. perfringens* infection is challenging because the microbe can be cultured from the feces of healthy foals. Therefore identification of toxins and ruling out other etiologies of diarrhea are key.[91] For toxin assays, fresh feces should be submitted to a laboratory with immunoassays for *C. perfringens* toxins including alpha, beta, and epsilon toxins. Fecal assays for *C. perfringens* enterotoxin (CPE) are readily available but lack sensitivity because only minorities of equine isolates produce CPE.[92] The alternative diagnostic avenue is to submit isolates cultured from feces for qPCR analysis. The novel pore-forming necrotizing toxin (netF) of *C. perfringens* type A is an important advance in understanding the virulence of this pathogen and potentially improves the diagnostic field.[93]

Miscellaneous Pathogens.

Equine granulocytic anaplasmosis (EGA) is caused by *Anaplasma phagocytophilum*, a rickettsial pathogen transmitted by *Ixodes* spp. ticks. Diagnosis is often based on awareness of the geographic area for infection, typical clinical signs, abnormal laboratory findings, and identification of characteristic pathogen inclusions in the cytoplasm of neutrophils and eosinophils in a peripheral blood smear.[94] qPCR has been used for many years to study several aspects of the epidemiology and pathophysiology of EGA.[95] For clinical purposes, the material of choice is whole blood. PCR has been shown to be a sensitive and specific tool, supporting the diagnosis especially during the early and late stages of the disease, at times when the number of organisms is too small to be detected via microscopy (Fig. 29.3).

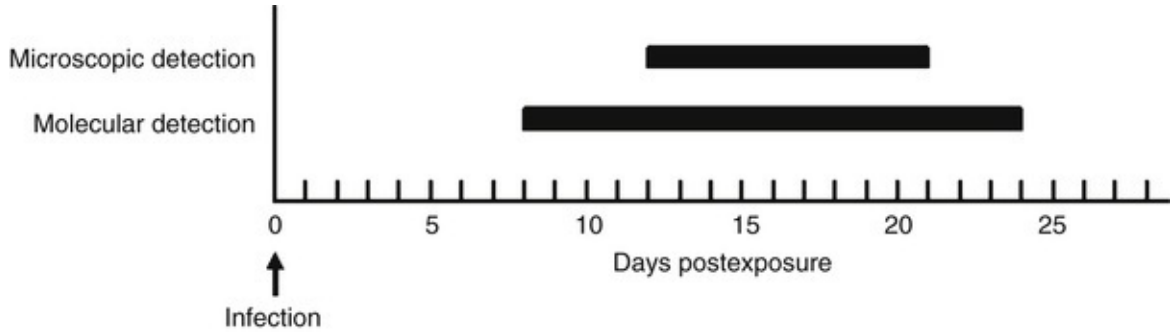


FIG. 29.3 Microscopic and molecular detection period of *Anaplasma phagocytophilum* in the blood of horses experimentally infected with *Ixodes scapularis.* (From Pusterla N, Madigan JE, Leutenegger CM: Real-time polymerase chain reaction: a novel molecular diagnostic tool for equine infectious diseases. J Vet Intern Med 20:3, 2006. Reprinted with permission of the American College of Veterinary Internal Medicine.)

Corynebacterium pseudotuberculosis is a common cause of external and internal abscesses in horses from arid regions of North America.[96] The epidemiology has been investigated with the help of qPCR, and flies have been identified as potential vectors.[97] *C. pseudotuberculosis* is easy to grow on culture, and use of qPCR on clinical samples is restricted to specific situations (e.g., culture-negative aspirates or body fluids).

Additional PCR assays for *Leptospira* spp., *Clostridium botulinum* neurotoxins, *Mycobacterium* spp., *Mycoplasma* spp., *Babesia caballi, Theileria equi, Cryptosporidium* spp., and methicillin-resistant *Staphylococcus aureus* have been developed and are being used in the research setting.[98-102] These assays will likely be offered in the near future for diagnostic purposes when additional epidemiologic information has been evaluated and accuracy of the tests has been validated using clinical samples from infected horses.

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Molecular Testing for Infectious Diseases in Cattle, Sheep, and Goats

Beate M. Crossley • Sharon K. Hietala

The availability of molecular-based diagnostic technologies designed to identify infection or genetic conditions by detecting specific genome targets in the host or agent DNA or RNA has expanded logarithmically in the past decades. Diseases and genetic conditions affecting cattle, sheep, and goats are commonly studied and diagnosed using a variety of molecular techniques and, in particular, PCR assays and increasingly using genome sequence analysis.

Whole genome sequencing, the ability to rapidly generate the genetic sequence of an entire pathogen, is increasingly available as a diagnostic tool and provides a high level of both diagnostic sensitivity and specificity, although at the expense of rapid turn-around and high technical costs that are most often passed on to the user. PCR-based technologies and assays that target a single gene or part of a gene remain the most common of the molecular-based diagnostic assays currently available for routine diagnostic services. These services are provided by state and federal diagnostic laboratories, university laboratories, and commercial laboratories; due to the technical complexity of molecular-based diagnostics, paired with the wide range of assays available to diagnose genetic and infectious diseases of food animals; however, no single laboratory can feasibly provide comprehensive testing for all species and all diseases. Instead, laboratories tend to focus on the diseases or genetic conditions of primary significance to their allied industries and use the technologies that provide the most rapid, reproducible, and economic results for their particular group of clients. Largely based on this specialization within laboratories, molecular-based assays may be developed and put into use without significant effort toward assay standardization and validation. The list of PCR-based assays available for detection of infectious agents, in particular, has grown significantly in the past decades and continues to expand, although with no guarantee that the assays have been suitably designed, tested in the field, or clearly advertised as to their “fitness for purpose.” For PCR-based assays, the selection of the genetic sequence (DNA or RNA) used as the target of the diagnostic assay is heavily dependent on the proposed use of the test and on the availability of known genomic sequence(s) for development of the assay. All genomes accumulate

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mutations over time, with some genes being highly mutable to allow evolutionary advantage, such as those genes that encode antimicrobic resistance or protein conformations for evading the host immune system. Other genes such as those encoding specific functions (e.g., replication) tend to remain highly conserved and stable to protect the survival of the organism. Assays used to detect a specific agent, such as bovine viral diarrhea (BVD) virus, can be designed to target a conserved region of the genome that is shared by all members of the species. Alternatively, assays used to characterize or subtype particular strains or isolates, such as BVD virus type 1b, can be designed to target regions with significantly more mutability or sequence variation. Assays designed as “fit” for surveillance testing must often sacrifice the ability to discriminate closely related pathogens, for instance, separating BVD viruses from the genetically related Border disease viruses in order to have the needed surveillance sensitivity to detect the broad range of potential BVD virus isolates. Similarly, assays designed for test and cull, or related disease control programs, must have a high diagnostic specificity for detecting only the agent or trait of interest. These assays tend to sacrifice diagnostic sensitivity or detection level in order to minimize the risk of false-positive results. Although molecular diagnostics provide a powerful and rapidly advancing tool, the clinician is advised to use molecular-based assays with appropriate awareness of their individual strengths and weaknesses, including the designated use or “fitness for purpose.” Unquestionably, molecular technologies will continue to be developed and implemented in veterinary medicine. Although it can be expected that newer technologies will replace existing procedures, it should be expected that many of the molecular tools will be no more than a supplement to traditional diagnostic approaches.

Sample Submission

As with any diagnostic technology, the specimen used must be appropriate for the disease or genetic condition and take into consideration the timing and pathogenesis of the disease process and availability of the intact genetic material being targeted by the diagnostic assay. Among the important criteria in the selection and use of molecular-based assays are onset and duration of agent replication in the host, specific tissue(s) affected, and the relative abundance of target DNA or RNA over the course of the infection. In addition to tissues obtained from postmortem investigation or surgical sampling, antemortem diagnostic testing can target genetic material recovered from swabs of mucous

membranes; blood, urine, milk, or skin scrapings; or fecal material as appropriate to the disease process.

Because all molecular-based diagnostics detect genomic material in one form or another, the isolation and purification of nucleic acids (DNA or RNA) from the diagnostic specimen are critical to the success of the assays. Dependent on the tissue or specimen used for diagnostic testing, recovery of sufficient quantities and quality of nucleic acid can be problematic. Common sources of assay failure include substances in the sample that can interfere with the chemistries used in detection or PCR-based amplification steps. Examples include, but are not limited to, heparin, iron, peroxidases, hemoglobin, and myoglobin, as well as the relative abundance of total DNA or RNA associated with the different specimen types. This type of assay error is controlled in an increasing number of PCR assays by the inclusion of internal controls before initiating the assay in order to monitor for specimen-based interference or related-assay failure. Another common source of assay failure is destruction of target nucleic acids in the specimen before testing, commonly as a result of enzymes associated with postmortem autolysis or those chemistries used in preserving the sample, such as formalin fixation.[1] Because of the complexities of nucleic acid recovery and target nucleic acid detection, assays developed for use with one matrix, such as whole blood, may not be suitable for use with other matrices, such as milk or feces. Appropriate sample collection buffers, storage temperatures, and shipping requirements are available from the laboratories performing the specific testing.

Molecular-Based Diagnostic Technologies

Nucleic acid fragments, either DNA or RNA, can be detected by binding to a complementary fragment of nucleic acid that has been marked with a reporter dye or enzyme. The short strands of DNA or RNA, generally chemically synthesized and referred to as *oligonucleotides*, are identified as *hybridization probes* when marked with a reporter dye or enzyme. Radioactively labeled probes, although once the standard, have almost uniformly been replaced by enzymatic tags, such as avidin-biotin, peroxidase, or chemiluminescent tags. Target nucleic acids can be detected directly in the diagnostic specimen when sufficiently abundant, or they may be detected following PCR-based amplification of the nucleic acid target.

Southern Blots, Northern Blots, and Dot-Blots.

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Various techniques are used to immobilize genetic material before detection steps, with or without prior PCR amplification. As a group, the techniques are referred to as “blots.” Dot-blots and Southern blots refer to DNA bound to nitrocellulose membranes, whereas Northern blotting is the terminology used when RNA is immobilized onto membranes. In Southern and Northern blots, nucleic acid fragments are first separated by size using an electric current running through a semisolid gel, a technique referred to as *gel electrophoresis.* The nucleic acid detection step for DNA and RNA blots may include a specific hybridization probe or may simply use the molecular weight of the DNA or RNA fragment. Related terminology includes Western blot, which describes protein immobilized on a membrane, and immunoblot, referring to detection of the immobilized protein using specific antibody as an immunologic marker. Variations of this approach, using proteins or capture antibodies immobilized on specialized paper strips, form the basis for lateral flow (“dip-stick”) pen-side tests including those developed for the rapid field detection of foot-and-mouth disease virus.

The laboratory technique referred to as in situ hybridization allows for localization and observation of a DNA or RNA target within a histologic tissue section.[2-5] The hybridization probes are typically end-labeled with a reporter molecule. Examples of hybridization assays used in veterinary diagnostics include FISH to identify genetic abnormalities and RNA probes (riboprobes) used as assay controls or for selected infectious disease detection in tissue samples. In situ hybridization technology can be applied to frozen or formalin-fixed tissues, with best results provided when the tissue is fixed as soon as possible postmortem to avoid loss of target nucleic acids during tissue autolysis. Nucleic acids from veterinary pathogens have been shown to be stable in formalin-fixed, paraffin-embedded tissues for up to 15 years.[2,6] Because of technical complexity, in situ hybridization is not widely applied to routine diagnostics but appears to be advancing in that direction.

Polymerase Chain Reaction.

PCR is the most commonly applied of the molecular technologies and can be grouped roughly into standard PCR and the more rapid real-time and quantitative PCR. Both techniques amplify minute quantities of target DNA to levels that are detectable using laboratory instrumentation or special staining procedures. The principal difference in the two approaches is that standard PCR

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is divided into two major processes in the laboratory: 1) amplification of the DNA target, followed by 2) detection of the amplified target DNA. Real-time PCR combines the two steps so that target detection occurs during the DNA amplification process. The advantages of PCR over standard isolation and identification techniques is the significantly reduced time required to obtain a result, with PCR results generally provided in hours instead of days. Real-time PCR results can be reported as dichotomous results (positive, negative) or on a continuous numeric scale, generally as a cycle threshold (Ct) with the lower numeric values correlating with higher concentrations of the target pathogen or genetic marker. Diagnostic caution is generally needed in interpreting “weak-positive” real-time PCR results caused by technical limitations and the nature of how real-time PCR results are captured in the laboratory. Advantages for standard PCR assays are the generally longer products (amplicons) that are more reliable for genetic sequence analysis and confirmation as compared with shorter real-time PCR amplicons. PCR-based technologies are a particularly powerful tool when designed to detect the presence of organisms that are extremely slow growing or difficult to culture, such as the *Mycobacterium avium* subsp. *paratuberculosis* (Johne's disease) bacterium, *Leptospira* spp., and bluetongue virus, among others. Because PCR-based assays detect nucleic acids, they do not require that the organism is viable in the sample. This is considered an advantage for those agents that may be easily destroyed during sample transport to the laboratory but a disadvantage where fragments of a pathogen's genome may persist for weeks or months after the animal has become noninfectious. An excellent example of this is the bluetongue virus, in which PCR can detect nonreplicating viral genome adherent to red blood cells for several weeks after live virus can be recovered from the blood. With the proliferation of PCR assays being developed in research laboratories, state diagnostic laboratories, and commercial laboratories, it is often difficult for the practitioner to know which genetic marker or gene fragment was used in the design of a particular assay. This is of particular diagnostic importance because different gene segments in an individual pathogen's genome may favor screening assays (high detection sensitivity, greater risk of cross-reactivity with lower diagnostic specificity) versus confirmatory assays (high specificity for the target but lower detection sensitivity). The number of different assays, often identified by just the name of the agent, creates confusion and frustration for those faced with selecting the appropriate assay to use. It is important when selecting and interpreting results of PCR assays to remember that not all assays targeting a specific pathogen will

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have the same genomic target or are even designed to have equivalent sensitivity in detecting an infection, making direct comparison of results between laboratories difficult. Quality diagnostic laboratories will be able and willing to discuss the assays performed in their laboratory including the designated diagnostic purpose of the specific assay, as well as the benefits and pitfalls identified during the assay validation process.[7,8]

Standard PCR.

Standard PCR is used for detection of DNA or RNA and can be applied to mammalian, microbial, or viral genomes. The PCR technique is based on the natural cross-linking of complementary (matching) nucleic acids to form double-stranded DNA. When DNA is sufficiently heated, double-stranded DNA separates into single strands, each of which can then be used as a template for chemically (or biologically) generating an exact copy. Specific heat-stabile polymerase enzymes are used in the laboratory for the process of DNA replication. The PCR reaction amplifies DNA using multiple cycles of heating double-stranded DNA to generate a single-strand template and cooling sufficiently to allow the polymerase enzyme to generate a new double-stranded DNA made up of the original strand and its test-tube synthesized copy. For diagnostic assay purposes, it is necessary to copy only a small but diagnostically characteristic fragment of any particular genome. This fragment is generally referred to as the PCR target or target sequence. PCR primers are short chemically synthesized fragments typically 10 to 30 nucleic acids in length that are used to mark the beginning and end of the selected target sequence and, as their name implies, are used to prime or start the initial PCR amplification process. The choice of target sequence and appropriate primer design are critical to the accuracy and efficiency of PCR-based diagnostic assays. For detecting target RNA, as is needed for the PCR diagnosis of an RNA virus, the technique of reverse transcriptase PCR (RT-PCR) is used. The reverse transcriptase enzyme converts target RNA into DNA, identified as cDNA or copy DNA for use in the PCR steps. The PCR amplification process typically takes 2 to 6 hours to complete and is followed by detection steps that require additional hours to days to complete. Detection of the amplified DNA fragment, often referred to as an *amplicon,* uses techniques that identify the DNA fragment by molecular weight, by marking a specific target sequence in the amplified DNA with hybridization probes, or by a combination of both (PCR/probe). PCR amplification followed by hybridization probe detection offers increased

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specificity, thus less chance of a false-positive finding, and often provides a 10-fold or greater increase in detection sensitivity. Dependent on the stringency designed into the assay by balancing such measures as temperature, length of replication cycles, and enzyme concentrations, false-negative results will occur when the sequence of the primers or probe does not precisely match the sequence of the target. In some cases, PCR assays are very precise and designed to recognize a single nucleic acid polymorphism (SNP analysis) in the target sequence, and in other cases they are intentionally designed with lower stringency to allow some degree of variability among isolates or strains being detected by the assay. Because RNA viruses in general lack the proofreading enzymes found in DNA viruses, bacteria, and protozoa, they are at greater risk for appearance of random mutations at primer or probe sites. PCR false-negative results associated with primer or probe mismatches resulting from random genomic mutations at the primer or probe binding sites are of particular concern for RNA viruses, and they provide ample justification for a laboratory to investigate with alternative or additional technologies when negative PCR-assay results clearly do not match a clinical or epidemiologic pattern of disease.

Nested PCR.

Nested PCR is a PCR technique modification generally used to increase the detection sensitivity of an assay.[9] During nested PCR, an initial PCR reaction amplifies a selected fragment of DNA, which is then used as a template in a second round of PCR. The second or nested PCR reaction targets one or more unique fragments of DNA within the initially amplified region. The two-step process has the advantages of increasing detection sensitivity and detection specificity and of diluting the impact of interference from potential PCR inhibitors found in some tissues and clinical materials. Nested PCR assays have been described for WNV, malignant catarrhal fever virus, and *Chlamydia* spp., among others. The significant disadvantage of the two-step process comes from handling the first round of amplified DNA in the laboratory. With the high concentrations of target DNA available following PCR amplification, laboratories must take rigorous precautions to mediate the risk of contaminating laboratory workspaces, equipment, and reagents with the amplified DNA. The significant risk and associated costs of laboratory contamination and resulting false-positive results are used in many diagnostic laboratories as justification for charging additional fees or not offering nested PCR techniques.

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Real-time PCR.

Diagnostic assays originally developed using standard PCR approaches have over the years been converted to real-time PCR and real-time qPCR technology, to take advantage of the speed, technical efficiency, and cost reduction often associated with this approach.[10] Because real-time PCR technology completes both amplification and detection in the same reaction tube or well, there is no need for the laboratory to handle amplified DNA and risk workspace contamination. Importantly, the combination of amplification and detection in a single-reaction vessel not only decreases the time required to complete the test, but importantly has allowed expansion of PCR-based assays into high-throughput, portable, and on-site formats as described for foot-and-mouth disease virus, anthrax detection, and others. Because real-time PCR targets shorter genetic sequences, the methodology is more effective than standard PCR for testing formalin fixed tissue.[1] The preservation method tends to destroy longer strands of genetic material. Real-time PCR offers an additional advantage of supporting quantitative approaches for measuring and reporting the amount of the original target in the sample tested. qPCR answers a frequent criticism of standard PCR, specifically that detection limits, potentially as low as a single cell or viral particle, may produce a positive finding that is biologically irrelevant to clinical disease. qPCR allows the relative amount of target nucleic acid to be correlated with the associated clinical presentation. Despite the significant benefits, real-time PCR is, however, less efficient than standard PCR in producing amplified genetic material that can be used for subsequent nucleic acid (genome) sequence analysis, as is often employed to confirm positive PCR findings, or further characterize a pathogen on the basis of genetic material obtained from the diagnostic case materials.

Multiplex PCR.

Multiplex PCR expands the use of PCR and real-time PCR-based detection from a single target to multiple targets simultaneously from a single specimen.[11-13] The ability to include multiple genome targets for a single virus or bacteria in a PCR assay minimizes the risk of a PCR false-negative as a result of genetic diversity within the agent of interest. Technically, the inclusion of an internal control, which is rapidly becoming a standard quality practice in veterinary diagnostic laboratories, is a simple form of multiplexing. Inclusion of targets for multiple closely related viruses has been used to differentially detect related

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pathogens, such as the closely related sheep and wildebeest-associated forms of malignant catarrhal fever; to subtype BVD viruses; and to differentially detect virulent *Escherichia coli*. Multiplex PCR also has broad application in syndrome-based testing where several pathogens may produce similar to identical clinical pictures. A single diagnostic specimen can be used in a multiplex format to detect one or more agents associated with a particular clinical presentation, such as the multiple viral and bacterial agents in shipping fever complex. Prototypes of this approach have been developed but are not yet widely deployed, and there are technologic limits to the number of PCR assays that can be combined without significant loss of assay performance. In real-time PCR formats, three to five unique assays have been the practical limit, based on the technical limitations of commonly available equipment and detection dyes.

Isothermal Amplification.

Isothermal techniques use alternate chemistries to PCR that allow amplification of nucleic acids to be carried out at a single temperature. Among the isothermal amplification technologies that have been used for the detection of veterinary pathogens are nucleic acid–based amplification, loop-mediated isothermal amplification (LAMP), rolling circle amplification, and direct signal amplification systems.[14,15] Although there are increasing efforts, especially for the development of LAMP-type diagnostic assays, none of these technologies has seen widespread diagnostic application, largely based on the complexity in initial assay design. However, LAMP-type assays may offer future PCR alternatives that can be developed into automated portable diagnostic tools, or possibly be developed as fully integrated self-contained testing units for use in the field rather than limited to a laboratory environment.

Microarrays.

Arrays of DNA or RNA fragments, variously referred to as gene chips and microarrays, consist of thousands of oligonucleotides attached in a specific pattern to a solid surface, typically a glass slide or silica chip.[16-22] The sample nucleic acids compete with fluorescently labeled competitor oligonucleotides for binding to the chip. A fluorescent detector and computer software are then used to analyze the patterns of fluorescence,

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indicating where nucleic acids have (or have not) been bound to the chip. Microarrays have been used primarily as research tools focused on detecting and understanding gene expression. The practical application to veterinary medicine includes studies such as the evaluation of genetic resistance to naturally occurring nematode infections, including Hemonchus, Trichostrongylus, and Ostertagia in sheep. Microarray technology has not seen wide use in veterinary diagnostic laboratories, largely because of the large initial investment required for equipment. However, examples of diagnostic microarrays have shown promise, and it is expected that, once established, the technology will be cost effective on an individual animal basis. In human diagnostic medicine, microarrays designed with genetically conserved sequences for all major groups of microorganisms have been used to identify or "mine" for unknown pathogens. This approach was used to detect and identify the SARS virus, before it was initially recovered and characterized by virus isolation techniques. Alternately, genotyping arrays have been designed to target specific virulence-associated genes, allowing differentiation of disease-associated subtypes of organisms from other members of the same or closely related species, such as enterotoxigenic E. coli and multidrug-resistant Salmonella strains.

An alternative to gene chip technology is liquid array technology, in which the nucleic acids are captured by oligonucleotide probes bound to a microbead, rather than to a flat surface. Bead sets are internally labeled with different-colored dyes used to distinguish the specific agents being measured. Liquid array systems use flow cytometry, laser technology, and signal processing to recognize the internal color of the beads and measure associated surface-binding of a target-specific fluorescent hybridization probe. The bead-based modification to microarray technology allows a laboratory to create a flexible diagnostic-test panel in a single assay by adding or removing target beads on the basis of the unique clinical presentation, diseases suspected, or species' specificity of interest. In theory, 100 different targets are detectable in a single assay.

Restriction Fragment Length Polymorphism.

Molecular techniques provide a valuable tool for genotypic characterization or subtyping of viral, bacterial, and parasitic agents. Subtype characterization[23-26] is essential for, among other things, taxonomic classification, differential

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detection of virulent strains, identification of genetic sources of antimicrobic resistance or virulence factors, recognition of vaccine escape mutants, epidemiologic investigation of disease outbreaks, and identification of interspecies transmission of specific pathogens. Restriction fragment length polymorphism (RFLP) is a technique useful for subtyping of pathogens based on genetic sequence variation within specific genes.[27] Target DNA, which may or may not previously have been PCR amplified, is digested using one or more well-characterized restriction enzymes. Characteristic profiles or patterns produced by the different-sized DNA fragments remaining after enzyme digestion are detected by gel electrophoresis. RFLP has been used to investigate interspecies transmission of enterotoxigenic *Staphylococcus aureus* associated with intramammary infections in cattle, sheep, and goats.[28] Random amplified polymorphic DNA (RAPD) analysis is a technique that has proved useful in detecting genetic variation and for strain typing.[29] Rather than amplifying a specific region of a genome, RAPD relies on random amplification of genomic DNA using short arbitrary sequences as PCR primers. RAPD does not require prior knowledge of an organism's DNA sequence for specific primer design and can be applied to small amounts of template DNA. The RAPD technique has been applied, for example, to rapid differentiation of pathogenic from nonpathogenic coccidia of sheep including *Toxoplasma gondii* and *Sarcocystis* spp. Identification of nonculturable, slow-growing, and atypical bacterial species using sequence analysis of the *16s ribosomal RNA (rRNA)* gene has become recognized as a valuable diagnostic tool in recent years. The basis of the *16s rRNA* typing technique is the highly conserved nature of the *16s rRNA* gene within bacterial species, as well as among species of the same genus.[13,30,31] Automation developed to support *16s rRNA* amplification, sequencing, and data analysis is available to and currently in place in selected veterinary diagnostic laboratories. Although the technique is not currently cost effective for routine identification of all microbial isolates in a clinical setting, the technology is used for identification of atypical, slow-growing, and rarely encountered species.[32] Because *16s rRNA* databases continue to be updated to include pathogens of veterinary and zoonotic interest, it is likely that the technology is seeing broader application.

Sequence Analysis.

Nucleic acid sequence analysis is used to identify and compare the exact nucleic

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acid sequence of a gene fragment, gene, or possibly entire genome for forensic purposes; to investigate disease outbreaks; to track evolutionary changes in rapidly mutable microorganisms; or for precise phenotype or genotype analysis of animals or organisms. The technology used for sequence analysis is progressing exponentially since initially introduced in the 1970s and most recently includes “next-generation sequencing,” high-throughput sequencing procedures, and metagenomics used for routine diagnostic applications, food safety, and detection and characterization of new and emerging pathogens. Equipment and computational strength used for sequence analysis were once limited to specialized research laboratories and reference centers, but they are increasingly available in well-equipped diagnostic laboratories. Next-generation, also called second-generation, sequence analysis approaches use bench-top commercialized equipment based on DNA synthesis, ligation, or ion semiconductor technology for the rapid and highly accurate genome sequencing of pathogens. The complete genomic sequence of individual pathogens can be completed within a matter of hours to days using next-generation sequencing technologies.

For diagnostic purposes genetic sequencing may be paired with PCR amplification of specific genetic markers or regions of known pathogens, or it may be used in de novo applications that determine the genetic sequence and identity of an unknown or previously uncharacterized pathogen.[20,21] Sequence analysis, using an approach known as *Sanger sequencing*, is most commonly used in diagnostic medicine to confirm the identity of a pathogen testing positive in a PCR assay, to detect genetic variants or diagnostically important mutations in a pathogen's genetic makeup, and for forensic investigation into the source of an agent or disease outbreak based on specific genetic markers in the recovered pathogens. The target for Sanger sequencing is the amplified DNA (or cDNA) generated from routine standard PCR or real-time PCR testing of diagnostic samples. Sanger sequencing is currently used by the majority of veterinary diagnostic laboratories as a supplementary diagnostic tool. Next-generation sequencing is a rapidly developing tool that, unlike Sanger sequencing, which targets small pieces of DNA such as a specific part of a single gene, targets entire genes or genomes, making it an ideal tool for discovery of novel pathogens; identification of genetic disorders, which is often done by looking for the same genetic markers in animals previously linked to human genetic diseases[1]; and genomic and phylogenetic research of both pathogens and host animals.[33,34] Next-generation sequencing is not yet a routine diagnostic tool, as the sensitivity

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of next-generation sequence analysis is highly dependent on the quality of the sample, the precision needed in sample processing, and the relatively complex data analysis. However, the field of study is rapidly evolving. A number of platforms including devices for field applications[35] are currently available, each of them operating with slightly different methods resulting in both advantages and limitations.[36] Sampling bias, enzymatic reaction with associated error rate and bias, and computing database bias all must be addressed before reliable results can be communicated to the client, the public, and those making animal health policy decisions.[37] Multiple guidelines addressing the importance of a rigorous data analysis have been published for human medicine and are equally applicable to veterinary medicine for ensuring the reliability of results.[38] Relevant examples of new and emerging viruses identified using next-generation sequencing approaches include the Schmallenberg virus that spread rapidly in European cattle, resulting in reproductive inefficiency and fetal abnormalities,[39] a new Bluetongue serotypes,[40] as well as a tickborne “looping-ill”−related virus in goats and novel astroviruses in both cattle and sheep associated with encephalitis and gastrointestinal diseases.[39] Importantly, next-generation sequencing continues to expand the clinically important molecular characterization of uncultured bacteria.[41] In the future, metagenomics and next-generation sequencing data are expected to allow monitoring of treatment interactions with the host's microbiome, as has already been demonstrated with poultry data.[42]

Genetic Diseases

Diseases that are linked to genetic mutations in specific breeds—such as bovine leukocyte deficiency and complex vertebral malformation in Holstein cattle, β-mannosidosis in cattle or goats, and spider-lamb syndrome in sheep—can be controlled by selective breeding using PCR-based testing to identify carriers of the defective gene. Similarly, susceptibility to certain diseases has been linked to specific genetic haplotypes that can be detected by molecular analysis.[43] Although at times controversial, rapid PCR-based genotyping of sheep[44] has been used for selective breeding programs targeting the genetic alleles associated with “scrapie resistance.” DNA testing for genetic selection, parentage confirmation, coat color, and related management purposes is also available for cattle, sheep, and goats. For genetic testing, the appropriate sample is typically

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whole blood, from which genomic DNA is extracted; the gene of interest is amplified by PCR; and then mutations are detected by sequence analysis, microsatellite target testing, and restriction enzyme analysis to identify the mutations in the gene of interest.[45,46]

Summary

For molecular diagnostics, as with any new technologic advance, there was initial hesitation or mistrust of the techniques, followed by a rush to take advantage of new diagnostic tools. With routine implementation of PCR, sequence analysis, and associated molecular diagnostic techniques have come significant advantages in diagnostic sensitivity and specificity, in the speed that a laboratory diagnosis can be reached, and in the potential for in-depth genome-level investigation of disease occurrences. At the same time, molecular techniques have introduced a new level of complexity to diagnostic medicine. The use and interpretation of molecular-based diagnostic results require sufficient understanding of the techniques used in order to judge the reliability and the relevance of the findings. Molecular techniques have become, and will continue to grow as, extremely valuable diagnostic tools, but like any tools in diagnostic medicine, they must be used with caution and with a clear understanding of their strengths, limitations, and appropriate applications to specific clinical investigations.

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Molecular Testing for Infectious Diseases in Cattle, Sheep, and Goats

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PART 5
Disorders of the Organ Systems

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• CHAPTER 30

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Diseases of the Cardiovascular System*

Virginia B. Reef, Consulting Editor

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Performing the Electrocardiogram

No single electrocardiographic lead system has been universally accepted for use in large animals. Bipolar leads (I, II, III, base-apex, X, Y, and Z of the orthogonal lead system) and unipolar leads (aV_F, aV_R, aV_L, thoracic) have been described, but the amplitude, duration, and configuration of the different waveforms vary widely depending on an animal's breed, size, body type, and sex. In addition, there is lability of certain waveforms within each animal depending on its level of exercise, excitement, or organic heart disease. Large animals have a deeply penetrating Purkinje system, and depolarization from the ventricular endocardium to the epicardium occurs explosively and in many directions at once. This period of ventricular activation is responsible for the electrocardiographic criteria that indicate ventricular enlargement in small animals but contributes little to generating the QRS complex of large animals. Establishing specific diagnostic criteria for chamber enlargement in large animal species has been difficult, because changes in the QRS complex are not sensitive or specific for ventricular enlargement.

The electrocardiogram (ECG) is used primarily to detect cardiac arrhythmias. For this purpose, a single-channel machine can be used, and the lead system chosen can be any that generates distinctive P, QRS, and T complexes. If an arrhythmia is detected, other leads should be obtained to further characterize the QRS and T complexes and confirm their origin. The lead system should be easy to apply, and the tracing free of artifacts created by muscle tremors, skin movement, shifting of weight, and changes in limb position. Two such leads commonly used to obtain a rhythm strip for the diagnosis of cardiac arrhythmias are the base-apex lead[1] and the Y lead of the orthogonal lead system.[2] The base-apex lead is attached by placing the positive electrode from one of three standard bipolar leads (lead I, II, or III) on the left thorax in the fifth intercostal space at the level of the elbow or at the location where the apex beat is most readily palpable. The negative electrode is attached to the skin of the right jugular furrow two thirds of the way from the ramus of the mandible to the thoracic inlet or at the top of the right scapular spine. The ground electrode can be attached to any site remote from the heart. Electrical contact is improved by clipping hair or wetting the skin with alcohol. The base-apex lead ECG is recorded by switching the machine to the bipolar lead that has been attached to the horse and recording

the ECG (Table 30.1). Lead Y is attached by placing the positive electrode over the xiphoid and the negative electrode cranially to the front of the chest. Smartphone-enabled ECGs are useful to obtain a rhythm strip by placing the microphone end of the recording device at a 30-degree angle craniodorsally over the heart in the left fifth intercostal space.[3]

TABLE 30.1

Standard Bipolar Electrocardiographic Leads

Lead	Positive Electrode	Negative Electrode
I	Left arm	Right arm
II	Left leg	Right arm
III	Left leg	Left arm

Continuous electrocardiographic recording over a 24-hour or longer period (Holter monitoring) or with telemetry is also useful for evaluating horses with arrhythmias. Continuous ECG recording can be performed with high-quality sticky electrodes applied to the skin underneath the surcingle, electrode patches that are held against the skin with a surcingle, or electrode patches attached to shaved skin with a cyanoacrylate adhesive and protected underneath a surcingle.[4,5] In the latter two situations, a dry sponge may help absorb motion, yielding a cleaner tracing. With sticky electrode patches, the electrodes may be applied directly to the skin or are taped to a small square of cardboard to provide them with some support and embedded in foam to minimize motion artifacts. The best recording with a three-lead system is usually obtained with the left arm electrode placed on the sternum, the right leg electrode on the right side in the fifth intercostal space at the level of the point of the shoulder, and the right arm electrode placed on the left side in the fifth intercostal space at the level of the point of the shoulder. These electrodes are then held in position with a tight surcingle. The electrodes are connected to a digital recorder that records the animal's heart rhythm for the entire monitoring period (Holter monitor) or a telemetry device that sends the ECG signal back to the receiver to be displayed on a monitor. To obtain an exercising ECG, high-quality sticky electrodes are applied to clean, dry hair. Several ECG placements enable a more motion-free tracing. The positive electrode (left arm) is placed near the left cardiac apex, and the negative electrode (right arm) is near the left shoulder area. The right leg electrode is placed near the positive electrode (left arm), and the ground electrode (right leg) is placed near the left shoulder electrode. Positioning the

electrodes so that the negative (right arm) is under the surcingle or girth on the right shoulder region enables lead three to have a larger amplitude on the three-lead telemetry system. With this configuration, the ground electrode is under the surcingle on the left dorsal thoracic region, the positive electrode is over the cardiac silhouette, and the right leg is ventral to this; both electrodes are underneath the surcingle or girth. Electrode placement will vary somewhat with the tack that is applied and whether the horse is being ridden or driven. The entire recording or monitoring period can be stored on a smart card for subsequent analysis. The continuous 24-hour Holter ECG is useful for diagnosing arrhythmias that occur intermittently or monitoring cardiac rhythm during exercise for later analysis. Telemetry electrocardiography is useful for real-time cardiac rhythm monitoring during treatment or exercise.

In the base-apex lead, the P wave is positive in most horses and ruminants. The P wave is most frequently bifid in horses. In many horses a T_a wave, indicative of atrial repolarization, occurs as a negative deflection after the P wave (Fig. 30.1). The QRS complex begins with a small positive deflection (rS) and is followed by a large negative deflection that terminates in the ST segment. The T wave is variable and can be positive, negative, or biphasic in horses and ruminants. Frequently the appearance of the T wave is variable within one recording. Fig. 30.2 illustrates a typical base-apex ECG recorded from both a cow and a horse at a 25-mm/s paper speed with the gain set at 10 mm/mV.

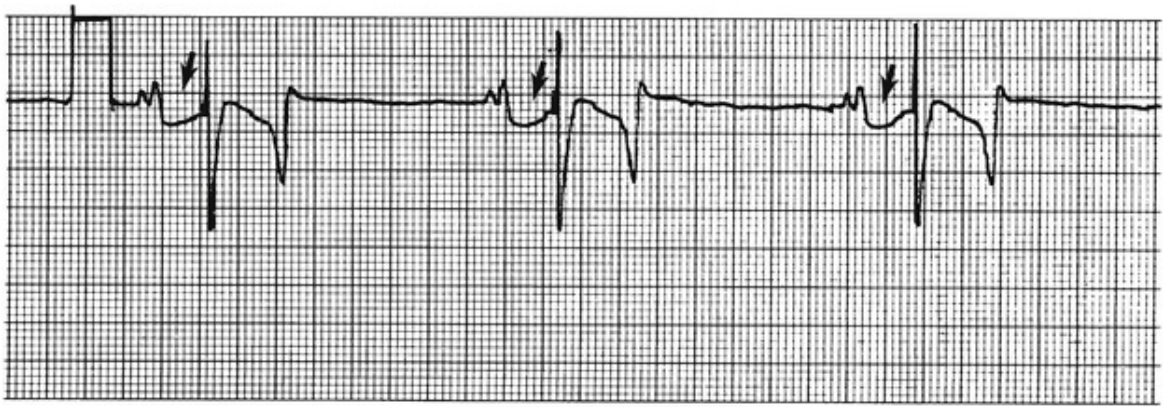


FIG. 30.1 Base-apex lead electrocardiogram recorded from a horse. *Arrows* point to the atrial repolarization wave (Ta) frequently seen in normal horses. It follows the notched P wave and precedes the QRS complex. Paper speed 25 mm/s, calibration 1 cm/mV.

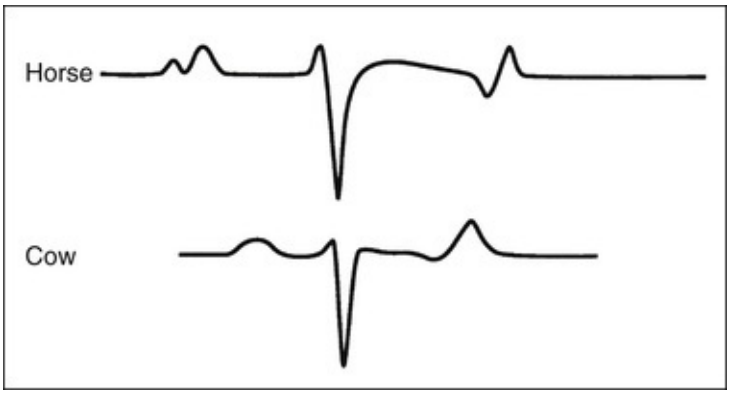


FIG. 30.2 Schematic representation of a typical base-apex lead electrocardiogram recorded from a cow and horse. In horses the P and T waves may be variable in appearance.

A systematic approach is used to analyze the ECG. The following step-by-step approach is recommended:

1. Identify all the QRS complexes. Each QRS complex should be followed by a T wave, and the QT interval should be similar for all QRS configurations unless there is a marked change in heart rate. Identify the remaining complexes. Are P waves, “F” (flutter) waves, or “f” (fibrillation) waves present? Are there any artifacts?
2. Determine the atrial and ventricular rates. Are they identical? Is one too fast or too slow? This determines whether there is a tachycardia or bradycardia.
3. Are the P-P and R-R intervals regular? Determine whether an irregular rhythm has underlying regularity that is interrupted by irregular intervals or whether the rhythm is consistently irregular. Second-degree atrioventricular block (AVB) and atrial and ventricular premature beats are arrhythmias with underlying regularity, whereas atrial fibrillation (AF), sinus arrhythmia, and sinus arrest are truly irregular rhythms.
4. Are P waves present? If so, is there a P wave preceding every QRS complex? If not, there are premature depolarizations, ventricular tachycardia (VT), escape beats, or AF. Are all P waves followed by QRS complexes? If not, second-degree AVB may be present. Is the resultant P-R interval constant? If not, there may be a wandering pacemaker or first-degree AVB.
5. Are all P waves and QRS complexes identical or normal in contour? If not, this signifies more than one pacemaker, premature depolarizations,

or escape beats.

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Use of Echocardiography in Large Animals

Echocardiography is a noninvasive diagnostic tool that uses sound waves in the range of 1.0 to 18.0 MHz to visualize the heart in motion, using either a single icepick (M-mode) or a two-dimensional (2D; B-mode) image. Noninvasive evaluation of blood flow in the heart and great vessels is performed with pulsed-wave, color-flow, and continuous-wave Doppler echocardiography. Precise localization of abnormal flow within the heart and great vessels is performed with pulsed-wave and color-flow Doppler echocardiography, whereas continuous-wave Doppler echocardiography is used to determine the peak velocity of blood flow and to noninvasively estimate pressure gradients. In contrast to M-mode and 2D echocardiography, for which the best image is obtained with the ultrasound beam perpendicular to the structures being imaged, optimal Doppler signals are obtained with the ultrasound beam parallel to the blood flow being evaluated. For accurate peak blood flow velocities to be recorded with continuous-wave Doppler echocardiography, the ultrasound beam should be as close to parallel as possible (<20-degree angle) to the direction of blood flow being measured. This alignment is difficult or impossible to achieve in most large animals with valvular heart disease, so accurate peak blood flow velocities often cannot be obtained; the peak velocity is thus underestimated. Noninvasive estimations of pressure gradients are inaccurate in these instances. Alignment of the ultrasound beam parallel to shunt flow is possible with most ventricular septal defects (VSDs) because of the typical location of the VSD is in the membranous or perimembranous portion of the interventricular septum. A review of the theory and application of basic echocardiography in horses and cattle has been published.[6–12] There is currently a large body of literature concerning routine M-mode and 2D echocardiography in normal large animals and in those with a wide variety of cardiac diseases. Tissue Doppler imaging (TDI) and speckle tacking are now being used in horses to evaluate atrial and ventricular myocardial function.[13–20] Most recently, 4D echo (3D over time) has been used in horses to evaluate cardiac structure and function.[21]

Echocardiography is particularly useful in evaluating large animals with cardiovascular disease because the examination is noninvasive and can be performed in a timely fashion in most standing, unsedated animals.

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Acepromazine is the sedative of choice if sedation is needed for the examination and should be administered ahead of time if it appears that sedation will be necessary.[22,23] Diagnostic criteria for valvular, myocardial, pericardial, and congenital lesions of the heart are well established, and the information obtained assists the practitioner in confirming a diagnosis, assessing the extent of the disease, determining the severity of cardiac dysfunction, monitoring the response to treatment, and providing an accurate prognosis. Large animal echocardiographic equipment should provide satisfactory resolution of images at depths of ≥28 cm; a 30-cm depth of field is ideal for most until there is marked cardiomegaly. Portable ultrasound machines that can display depths of up to 40 cm for equine and bovine cardiology are available. These machines are available with pulsed-wave, continuous-wave, and color-flow Doppler. However, Doppler echocardiography is used primarily by specialists experienced in large animal cardiology, because performing and interpreting the echocardiogram, including Doppler, requires a significant amount of training and expertise. In addition, state-of-the-art color-flow and tissue Doppler equipment remains fairly expensive, although it has decreased in price.

Echocardiographic examination is performed in a systematic way, using standardized images to obtain information about chamber size, wall thickness, myocardial function, valve appearance, valve function, great vessels, blood flow, and presence of abnormal structures or echodensities. The standard adult equine or bovine echocardiogram is performed from the right parasternal window (right fourth intercostal space in horses and third intercostal space in ruminants) with a 2.5-MHz or lower-frequency transducer. Higher-frequency transducers should be used to examine younger or smaller animals, South American camelids, and small ruminants. Both long- and short-axis views of all cardiac structures should be evaluated. The cardiac valves should be carefully examined for any abnormalities of structure or function (dysplasia, thickening, prolapse, ruptured chordae tendineae [RCT], fenestrations, flail valve leaflet, vegetative lesion, or high-frequency vibrations). The relative size, shape, and relationship of the cardiac chambers and great vessels should be assessed, and an evaluation of myocardial function and blood flow performed. Measurements of left atrial diameter and left atrial area can be obtained from the 2D echocardiogram at end systole.[24] Standard measurements of left ventricular internal diameter, left ventricular free wall thickness, interventricular septal thickness, and right ventricular internal diameter should all be obtained at end diastole and peak systole from the M-mode echocardiogram. The diameter of the aortic root and

left atrial appendage, the distance between the interventricular septum and the peak opening of the septal leaflet of the mitral valve (septal to E point separation), and the left ventricular ejection time (ET) should also be determined. End-diastolic measurements are obtained at the Q wave of the ECG, whereas peak systolic measurements are made from the peak downward deflection of the interventricular septum. Calculations of fractional shortening (FS) and ejection fraction (EF) can then be performed to assess left ventricular function using the following formulas:

$$\mathrm{FS} = \frac{\mathrm{LVID}_d - \mathrm{LVID}_s}{\mathrm{LVID}_d} \times 100$$

$$\mathrm{EF} = \frac{\mathrm{LVID}_d - \mathrm{LVID}_s}{\mathrm{LVID}_d} \times \mathrm{ET} \times 100$$

in which $LVID_d$ is the left ventricular internal diameter at end diastole (cm), $LVID_s$ is the left ventricular internal diameter in systole (cm), and *ET* is the left ventricular ejection time (seconds).

Echocardiograms should also be performed from the left cardiac window when the entire heart cannot be successfully imaged from the right side; AF is present; abnormalities of the mitral valve, aortic valve, pulmonic valve, aorta, pulmonary artery, left atrium, left ventricle, or outflow portion of the interventricular septum are suspected or detected; or murmurs originating from the mitral, aortic, or pulmonic valves are detected or a pericardiocentesis is planned. The maximal diameter of the left atrium should be obtained at peak systole from the left cardiac window at the level of the left coronary artery, parallel to the mitral valve (Fig. 30.3), and the left atrial area can also be measured from this view.[24] The diameters of the aorta and pulmonary artery should be measured from similar locations in the vessel on the 2D echocardiogram and compared. Echocardiography should be considered a useful diagnostic test to evaluate patients with the following complaints, physical examination findings, or tentative diagnoses:

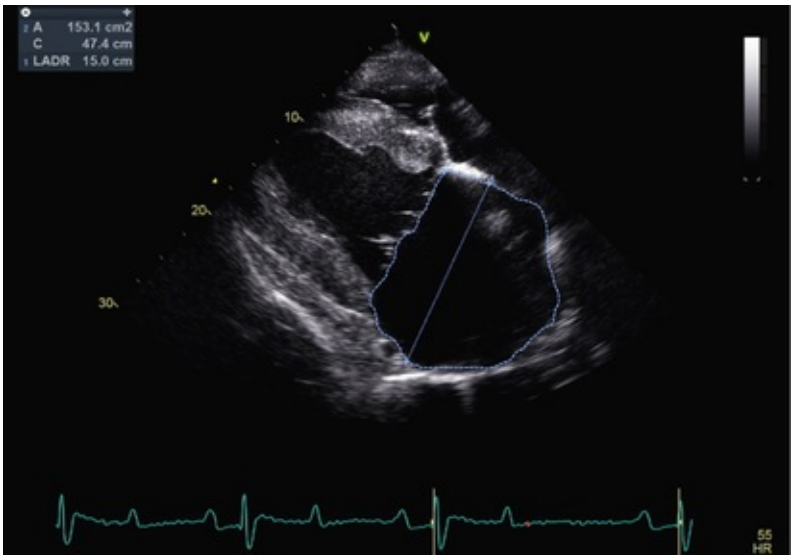


FIG. 30.3 Two-dimensional echocardiographic image of the left atrial diameter and left atrial area obtained from the right parasternal long-axis window in a horse with mild left atrial enlargement secondary to cardiomyopathy and mitral regurgitation.

1. Cardiac murmur, to determine the etiology of the murmur
    a. Any grade 3/6 or louder holosystolic or pansystolic murmur on the left side of the thorax
    b. Any grade 4/6 (3/6 in prepurchase setting) or louder holosystolic or pansystolic murmur on the right side of the thorax
    c. Any holodiastolic decrescendo murmur
    d. Any continuous machinery murmur
2. Congenital heart defects, especially VSDs and atrial septal defects (ASDs)
3. Acquired valvular heart disease
4. Cardiac enlargement
5. Cardiac arrhythmias not associated with high resting vagal tone
6. Unexplained exercise intolerance or collapse or exercise intolerance attributed to cardiac causes
7. Muffled heart sounds, pericardial friction rubs, or pericardial effusion
8. Myocarditis or myocardial dysfunction
9. Congestive heart failure (CHF)
10. Pulmonary hypertension
11. Cardiovascular neoplasia

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12. Aortic rupture or other abnormalities of the great vessels
13. Ionophore toxicity or exposure to other myocardial toxins
14. Any unexplained fever of unknown origin, with or without a cardiac murmur

Color-flow Doppler echocardiography should be used to map the size and location of a turbulent jet associated with an intracardiac or extracardiac shunt, valvular regurgitation, or stenosis (rare) and to semiquantitate its severity.[25,26] Continuous-wave Doppler echocardiography can then be used to measure the peak velocity of blood flow in the jet, estimating (noninvasively) the pressure difference between cardiac chambers using the Bernoulli equation. This can be accurately performed in most patients with a VSD, yielding information about the hemodynamic significance of the defect, but is difficult to impossible to accurately perform in many patients with valvular insufficiencies because of the limited windows available for interrogating blood flow in large animals and the inability to align the ultrasound beam to within 20 degrees of the turbulent blood flow. This poor alignment of the ultrasound beam with the regurgitant jet results in an underestimation of the peak regurgitant jet velocity. Contrast echocardiography, a technique involving microbubble-laden injections of saline, carbon dioxide, or indocyanine green, can also be used to demonstrate valve dysfunction and the direction of intracardiac and extracardiac shunts (VSDs, ASDs) but has largely been replaced by color Doppler echocardiography. TDI should be performed to look for left atrial systolic dysfunction (left atrial stunning) post conversion of AF.[27] TDI and speckle tracking are also useful in identifying ventricular myocardial dysfunction.[28–32]

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Cardiac Catheterization in Large Animals

Cardiac and great vessel catheterization can be performed in standing unsedated large animals to determine the following data:

- Pressure and waveforms (shape of the pressure curve)
- Oxygen tension, oxygen saturation, oxygen content
- Cardiac output and other indicators of ventricular size and function

Cardiac catheterization is also used for special diagnostic studies such as angiocardiography, nuclear angiocardiography, and indicator dilution studies. These data are used to determine the direction and size of intracardiac and extracardiac shunts, chamber size and contractility, and valvular and myocardial function. Most of this information is now obtained noninvasively with echocardiography, minimizing the need for more invasive techniques.

Cardiac catheterization is usually reserved for specialty practices and referral institutions, owing to the equipment needed and skills required for acquiring and interpreting accurate data. Results are not always specific, but catheterization can add quantitative measurements that increase diagnostic and prognostic accuracy for certain cardiac conditions and may provide a direction for therapy.

Blood Pressure Measurements

Normal blood pressures for cattle and horses are listed in Table 30.2.[33–36] The values for horses represent a summary of data from numerous authors as cited in the references given. Accuracy of pressure recordings is greatly influenced by the choice of catheter and recording equipment used. While an oscillometric blood pressure device placed over the coccygeal artery corrected to the height of the heart is good for estimating blood pressure noninvasively and assessing marked trends, its accuracy and precision is low when compared with invasive blood pressure monitoring in standing horses.[37] Pulmonary artery wedge

pressure (PAWP) is an indicator of left atrial mean pressure so long as balloon inflation of the catheter occludes flow in the segment of the pulmonary artery that is catheterized. PAWP is superior to central venous pressure (CVP) as a monitor of left ventricular function and fluid therapy. However, CVP is a good indication of intravascular volume in horses with dehydration.[38]

TABLE 30.2

Cardiac Pressure Measurements in Normal Horses and Cattle[a]

	Horses[33]	Cattle[34]
RA	12–28/22–5 (4–10)	(5)
RV	30–59/24–14 (9–25)	42–56/0–1 (19–28)
PA	34–48/14–22 (16–30)	33–46/19–21 (24–31)
PAW	13/3 (8)	(5–21)[35]
LV	140–148/15–17	(120–144)[36]
AO	131–144/86–100 (110–115)	
CA	142–157/98–119 (113–124)	160–208/110–147 (135–175)

[a]Pressure ranges are reported as systolic/diastolic (mean) in mm Hg unless otherwise designated.

AO, Aorta; *CA,* carotid artery; *LV,* left ventricle; *PA,* pulmonary artery; *PAW,* pulmonary arterial wedge; *RA,* right atrium; *RV,* right ventricle.

The shape of the pressure curve in the ventricles, aorta, or pulmonary artery may have diagnostic significance in conditions like constrictive pericardial disease (Fig. 30.4); pulmonic stenosis (giant A wave), rare as an isolated defect in large animals; or tricuspid or mitral valve regurgitation (large V wave). These conditions are more commonly assessed by echocardiography. An abnormal rise in pressure going from one chamber to the next indicates a stenotic lesion (uncommon in large animals) at the level of the pressure gradient. The size of the pressure gradient can be used to determine the severity of the lesion.

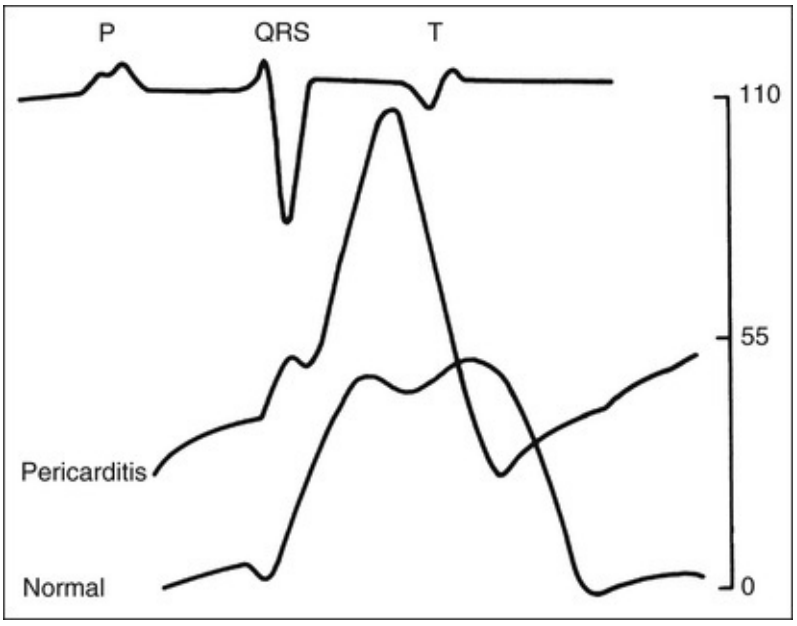


FIG. 30.4 Schematic representation of ventricular pressure curves recorded from a normal horse and a horse with pericarditis, showing the relationship between pressure changes and the electrocardiogram. With pericarditis, the ventricular end-diastolic and systolic pressures are elevated and pressure declines sharply in early diastole.

Blood Oxygen Measurements

Blood oxygen measurements are taken from the chambers on the right side of the heart to detect abnormal elevations indicative of a left-to-right shunt (ASD, VSD, patent ductus arteriosus [PDA]). Criteria for oxygen step-ups have not been established for large animals, but human guidelines have been accepted for qualitative assessment of shunts.[39,40] In humans, oxygen content step-ups of the following magnitude are considered abnormal and indicative of a left-to-right shunt.[41]

- ≥1.9 volume percent from the superior vena cava to the right atrium
- ≥0.9 volume percent from the right atrium to the right ventricle
- ≥0.5 volume percent from the right ventricle to the

pulmonary artery

Because oxygen content depends on hemoglobin concentration, oxygen saturation, which is independent of hemoglobin concentration, may be a more accurate indicator of shunts in anemic or polycythemic patients. Changes in the animal's physiologic status during sampling (cardiac output, ventilation, oxygen consumption); incomplete mixing of shunted blood; and variable time intervals between sampling can be potential sources of error. Several samples within a single chamber improve reliability of results. Small shunts and shunts in animals with low systemic arterial oxygen tension may not be detected by this technique.

Shunt calculations can be made once oxygen saturation or content has been measured in each of the right heart chambers, the pulmonary artery, and a systemic artery. For a left-to-right shunt, the pulmonary flow/systemic flow ratio (QP/QS) is determined as follows:

in which SAO_2 is the arterial blood oxygen content, MVO_2 is the mixed venous blood oxygen content, and PAO_2 is the pulmonary artery oxygen content. A 2 : 1 QP/QS represents a 50% left-to-right shunt, indicating that 50% of the pulmonary flow is from the left side of the heart.

For a right-to-left shunt, the QP/QS is determined as follows:

in which PVO_2 is the pulmonary venous oxygen content (assumed to be 98% of oxygen capacity plus 0.3 mL of dissolved oxygen).[42]

Cardiac Output and Ventricular Function Assessment

Cardiac output is determined by indicator dilution methods (usually by dye dilution or thermodilution or, more recently, by lithium dilution), by the Fick method, or by using 2D or Doppler echocardiography. The Fick method requires use of a face mask and simultaneous determination of mixed venous and arterial blood samples. Dye dilution and thermodilution results are comparable when 30 to 40 mL of 5% dextrose are injected rapidly at 32° F (0° C).[40] Lithium dilution compares favorably with thermodilution in anesthetized horses and foals.[43,44] Volumetric echocardiography using the Bullet method achieves results similar to those obtained with the lithium dilution method in anesthetized foals.[45] Transthoracic Doppler echocardiography was closely correlated with

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thermodilution in standing horses.[46]

Cardiac output values in the resting horse range from 32 to 40 L/min.[47] Cardiac index is the cardiac output divided by a measure of body size (body weight in kilograms) and is expressed in mL/kg/min.[47] The normal cardiac index for the adult horse ranges from 72 to 88 mL/kg/min.[47,48] Cardiac output values of 20.9 to 23.6 L/min have been reported in normal anesthetized horses.[43] In cattle a cardiac index of approximately 110 mL/kg/min has been reported.[36] Cardiac output measurements in clinical patients vary with heart rate, excitement, hydration, and many other factors and are best determined in the pulmonary artery. Electronic integration and computation of area under the curve by means of battery-powered units that can display results instantly provide the most reliable results.[49]

Cardiac output results or indicator dilution curves can provide quantitative and qualitative assessment of cardiac shunts. Characteristic changes in the temperature-time curve (thermodilution methods) or dye concentration–time curve indicate the presence of a left-to-right, right-to-left, or bidirectional shunt. Calculation of the cardiac output in the chamber just proximal to the shunt and distal to it can give a quantitative estimate of the size of the shunt.[40]

Angiocardiography

Angiocardiography is used in neonates or animals small enough to have the entire cardiac silhouette visualized on a single radiograph cassette. The contrast medium must be injected rapidly, and in most cases this is done with a pressure injector. Specialized radiographic requirements include rapid film change capabilities, rapid image sequence acquisition, or cineradiography. Angiocardiography is used to confirm the presence of an intracardiac shunt (ASD, VSD) or extracardiac shunt (PDA, truncus arteriosus) or valve dysfunction, to visualize chamber size, or to estimate contractility. Angiocardiography is performed in anesthetized animals.

Nuclear Angiocardiography

In nuclear angiocardiography, specialized equipment captures sequential digitized images of the right side of the heart, lung, and left side of the heart after rapid injection of radiographic tracer into peripheral circulation. A more

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extensive review of this subject has been published.[50] Nuclear angiocardiography can be used to confirm valvular dysfunction, which is manifested by chamber enlargement or prolonged washout of affected vessels or cardiac chambers and is quantitated by the regurgitant fraction. It also can reveal enlargement of chambers and prolonged washout resulting from cardiac failure. The presence of intracardiac or extracardiac shunts is demonstrated by the simultaneous visualization of left- and right-side cardiac chambers or slow washout downstream of the shunt. In addition, nuclear angiocardiography is used to calculate cardiac output and ejection fraction (EF) and other indices of cardiac function.

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Congenital Cardiovascular Disease

The cause of congenital cardiac defects has not been established, although hereditary factors may be responsible for some defects. In humans, additional factors such as maternal infection, age, and nutritional status have been identified; fetal anoxia from placental insufficiency, fetal infection or metabolic dysfunction, or other causes may contribute to the development of congenital cardiac defects. The same factors may apply in animals. Congenital cardiac defects in large animals can occur alone or in combination. The most commonly reported is VSD.[25,39,51–54] Multiple cardiac anomalies including PDA,[55,56] tetralogy of Fallot,[57,58] truncus arteriosus,[59,60] total anomalous pulmonary venous connection,[61] and Eisenmenger complex in calves[62] have been reported. Congenital anomalies of the tricuspid,[59,63–65] mitral,[66] and pulmonic valves[59,67,68] are uncommon. Congenital abnormalities of the aorta are reported in calves and foals but are also uncommon.[54,69,70] ASD occurs more commonly in calves than in foals and is frequently accompanied by other defects.[54,60,71,72] Hypoplasia of the left and right ventricles has been infrequently reported in calves and foals.[54,73,74]

Congenital cardiovascular disease should be suspected in a young patient if examination reveals a holosystolic (pansystolic), holodiastolic, or continuous murmur or a murmur with a palpable thrill or wide radiation over the thorax. Cyanosis at rest or with exercise in a patient with a cardiac murmur warrants consideration of a right-to-left cardiac shunt, obstructive pulmonary disease, or severe stenosis of the structures of the right side of the heart. The presence of any of these findings in a young animal with a history of lethargy, weakness, or failure to thrive constitutes grounds to suspect congenital cardiovascular disease.

Ventricular Septal Defect

Definition and Etiology.

A VSD is an opening in the interventricular septum that creates communication between the left and right ventricles. In large animals most defects occur in the perimembranous septum and are imaged ventral to the right and/or noncoronary cusp of the aortic valve and cranioventral to the septal leaflet of the tricuspid

valve, including or adjacent to the fibrous part of the interventricular septum.[25,39,52,54] VSD can occur as a single defect or as part of a complex anomaly. Many cardiac malformations such as tetralogy and pentalogy of Fallot, truncus or pseudotruncus arteriosus, common atrioventricular canal defect, tricuspid atresia, and double outlet right ventricle include a VSD. The cause of VSD is unknown, although it has been documented to be a heritable defect in Limousine[54] and possibly Hereford[75] cattle. VDSs are more common in Welsh Mountain ponies (Section A) and in the Arabian, Standardbred, and Quarter Horse breeds, suggesting a possible hereditary predisposition.[76,77] The defect is thought to result either from failure of fusion of a part of the endocardial cushion and the muscular ventricular septum or failure of fusion of the truncal and conal septa.[78]

Clinical Signs and Differential Diagnosis

The clinical signs of an isolated VSD vary and depend on the size of the defect, direction of the shunted blood, and presence of concurrent valvular or myocardial disease. In isolated VSD the blood flow is shunted from the left ventricle to the right ventricle through the defect in the interventricular septum. The size of the shunt depends on the size of the defect and the pressures in the left ventricle, right ventricle, and pulmonary artery.

VSD is suspected when there is a loud, grade ≥4 to 6/6 harsh, plateau-shaped pansystolic murmur with its point of maximal intensity (PMI) in the tricuspid valve area and a slightly softer (usually one grade softer), more crescendo-decrescendo holosystolic murmur that is loudest in the pulmonic valve area. The murmur on the left side has its PMI in the pulmonic valve area, associated with a relative pulmonic stenosis (increased blood flow across a normal pulmonic valve). Occasionally there is splitting of the second heart sound. The murmur may be the only clinical sign identified if the defect is small or moderate size. On the other hand, poor growth, lethargy, dyspnea, exercise intolerance, and signs of CHF can be exhibited by animals with a large VSD. This usually develops by the time the animal is 5 years old. CHF may develop later in horses with a moderate-sized VSD and cardiomyopathy or in those with a moderate to large VSD with aortic prolapse who then develop aortic regurgitation (AR). Occasionally there is a diastolic murmur of aortic insufficiency associated with a large VSD, the location of which compromises the support of one of the aortic valve cusps.[10,25,53] Cardiac arrhythmias, particularly AF, may be associated with

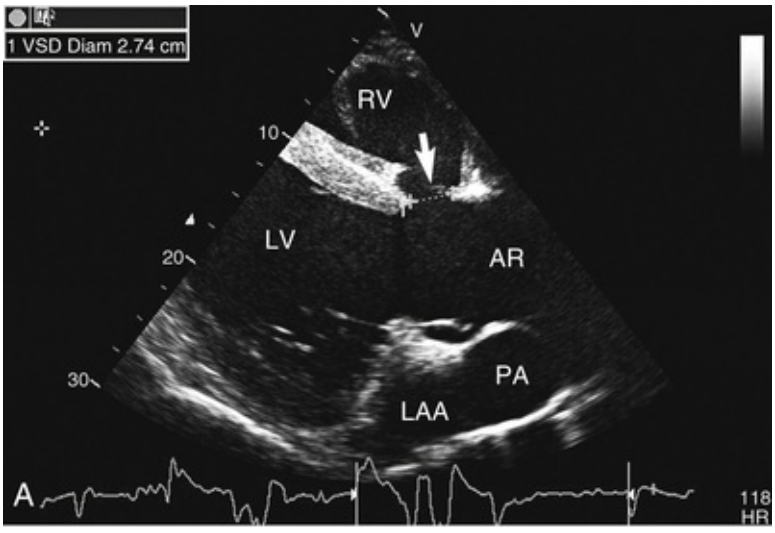
VSD when there is cardiac enlargement or failure. The development of AF may be the “tipping point” for the development of congestive heart failure.

If the systolic murmur is loudest on the left side of the thorax, a subpulmonic VSD or a complex anomaly with pulmonic stenosis (or some form of right ventricular outflow tract [RVOT] obstruction) should be suspected.[10,25,53,79] The pulmonic murmur is usually louder than the tricuspid murmur in large animals with tetralogy of Fallot. Large animals with tetralogy of Fallot may have cyanosis at rest (uncommon in horses) or with exercise or exertion. Cyanosis is also a distinguishing feature of Eisenmenger complex, a defect in which right-sided heart resistance to blood flow causes the shunt associated with VSD to become right to left (which is rare). Congenital abnormalities of the mitral and tricuspid valves (dysplasia) cause a loud systolic murmur audible on both sides of the thorax but are rare. The PMI of the left-sided systolic murmur is more caudally located (in the mitral to aortic valve area) than the relative pulmonic stenosis murmur. Usually the murmur of mitral regurgitation (MR) is louder than the murmur of tricuspid regurgitation (TR). An innocent flow murmur of neonates can usually be distinguished from VSD by its crescendo-decrescendo shape, PMI at the left heart base, lack of radiation, and low to moderate intensity.

Clinical Pathology

Echocardiography is the diagnostic technique of choice for identifying a VSD. With 2D echocardiography the VSD can be imaged directly (Fig. 30.5, *A*) and the shunt size, location, and direction demonstrated with color-flow Doppler echocardiography (Video 30.1) or the injection of microbubbles. Maximal shunt velocity is obtained with continuous-wave Doppler echocardiography (Fig. 30.5, *B*). Careful scanning of the interventricular septum should be performed with 2D echocardiography to directly image the VSD and measure its maximal diameter in two mutually perpendicular planes.[10,25,53] The typical perimembranous VSD (≤2.5 cm in both planes) is missed if the long-axis view of the left ventricular outflow tract (LVOT) is not examined. The membranous VSD is located underneath the right and/or noncoronary leaflet of the aortic valve and ventral to the septal leaflet of the tricuspid valve. If a perimembranous defect is not found, the entire septum should be carefully scanned in all imaging planes to detect the VSD. The subpulmonic location, more common in calves, is easy to miss. This defect is usually best imaged in the short-axis view, scanning the interventricular septum between the LVOT and RVOT. With a left-to-right shunt a high-velocity

turbulent jet is depicted from the right parasternal window, originating in the left ventricle, traversing through the defect in the interventricular septum into the right ventricle with color-flow Doppler echocardiography (Video 30.1), whereas a negative contrast jet is imaged in the right ventricle with a right-sided injection of microbubbles.[10,25,53] Moderate to large VSDs show left atrial and left ventricular enlargement, right ventricular enlargement, and pulmonary artery dilation. The left atrial–to–aortic root ratio is increased. Aortic valve prolapse and AR may also be detected because of loss of support of the aortic root from the VSD, more likely with larger VSDs and VSDs with malalignment of the ascending aorta with the upper portion of the interventricular septum. Myocardial dysfunction and subsequent CHF may occur with a large VSD. Most horses with VSDs that are compatible with a normal life expectancy ultimately develop MR secondary to the chronic left atrial and ventricular volume overload. Continuous-wave Doppler echocardiography should be used to noninvasively assess the hemodynamic significance of the shunt (see Fig. 30.5, *B*). A peak shunt flow velocity of 4.5 m/s or greater indicates a restrictive VSD with normal or near-normal right ventricular pressures.[77] The radiographic presence of cardiomegaly and increased vascularization of the lungs provide only nonspecific evidence of VSD. If polycythemia is found, a complicated VSD should be suspected.



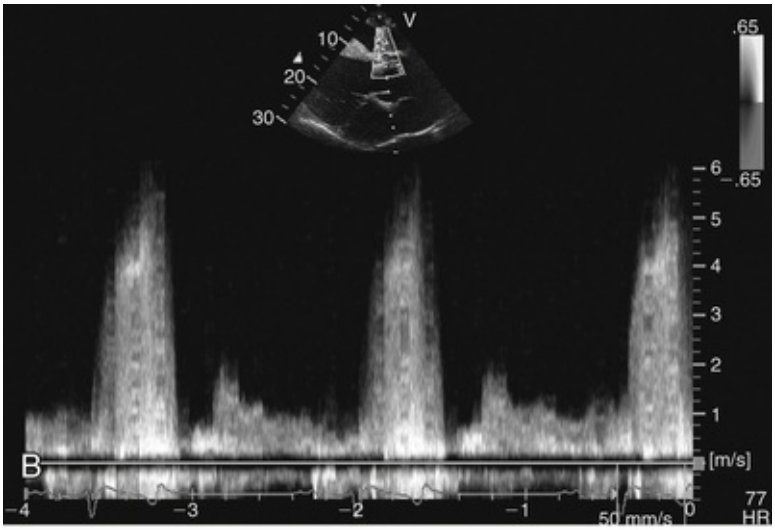


FIG. 30.5 Two-dimensional echocardiographic image **(A)** and continuous-wave Doppler spectral tracing **(B)** of a ventricular septal defect (VSD) *(arrow)* in a Thoroughbred gelding who presented for poor racing performance. The VSD is located just underneath and cranial to the septal leaflet of the tricuspid valve and just ventral to the noncoronary and right coronary cusp of the aortic valve and measured 2.74 cm in this view. There is significant left ventricular enlargement in this gelding. The right ventricle *(RV),* left ventricle *(LV),* left atrial appendage *(LAA),* aortic root *(AR),* and pulmonary artery *(PA)* are all visible in this view. The spectral tracing shows a peak shunt velocity of over 5 m/s in systole. Some turbulent flow (spectral broadening) is also detected in diastole, with a peak flow velocity of approximately 1.75 m/s.

Cardiac catheterization can be used for qualitative and quantitative assessment of the VSD but has been supplanted by echocardiographic diagnosis. Elevated cardiac pressures provide qualitative evidence of a VSD. Right ventricular systolic pressure elevation is most common and may equal left ventricular pressure with a large VSD. Pulmonary artery pressure (PAP) can be increased as a result of increased blood flow from the left-to-right shunt or increased pulmonary vascular resistance and decreased flow (restrictive pulmonary hypertension). Elevation of left or right ventricular diastolic pressure provides evidence of cardiac failure in the patient with VSD. Oximetric data (oxygen content or oxygen saturation) can be used to locate the shunt and provide some evidence of the size of the defect. A step-up in oxygen content or saturation between the right atrium and the pulmonary artery suggests a moderate or large VSD. Because most VSDs are located high in the RVOT, there may be inadequate mixing of shunted blood in the right ventricle to detect the shunt in this chamber, unless the catheter is directed to the outflow tract for sampling. When the oxygen step-up is detected first in the pulmonary artery, a PDA cannot

be ruled out. A small shunt may be missed by oximetry as described earlier under oxygen sampling.

By using the indicator dilution methods described previously, the shape of the concentration-time or temperature-time curve can be used to demonstrate the left-to-right shunt of a VSD. A comparison of the cardiac output measured in the right ventricle with the cardiac output measured in the pulmonary artery can give an estimation of the percent of pulmonary blood flow coming from shunted blood and therefore an estimation of the size of the defect.[40]

Angiocardiography in the anesthetized neonate can definitively demonstrate VSD if there is simultaneous opacification of the left and right ventricles when dye is injected into the left ventricle but has been supplanted by color Doppler echocardiography.

Pathophysiology

A small VSD may provide enough resistance to flow that the left-to-right shunt is minimal and the patient remains asymptomatic. Horses can race successfully with small VSDs (≤2.5 cm in diameter with peak shunt velocities ≥4.5 m/s), although they are not usually successful as elite racehorses.[10,25,77] In smaller horses and ponies or very large horses, a VSD-to–aortic root ratio less than 0.3 is unlikely to be hemodynamically significant.[76,77] Most horses in this study that presented with CHF or exercise intolerance had a VSD-to–aortic root diameter of 0.64.[76] VSDs produce a left-to-right shunt because the pressure in the left ventricle exceeds that in the right ventricle. A peak shunt velocity of 3.5 to 4.5 m/s indicates an increased right ventricular pressure and a less restrictive VSD, but the defect is usually compatible with a normal life expectancy. A peak shunt velocity less than 3.5 m/s is indicative of a large shunt that is hemodynamically significant. These animals usually develop CHF by 5 years of age. Occasionally the VSD is so large that the pressure between the two chambers is equalized. The right ventricle, pulmonary circulation, left atrium, and left ventricle must compensate for this volume overload, which generally results in dilation of cardiac chambers and development of pulmonary hypertension.

Simultaneous pulmonary disease or left-sided heart failure due to chronic volume overload can increase pulmonary vascular resistance. In addition to volume overload, the right ventricle is subjected to a chronic pressure overload that may be sufficient to reverse the direction of the shunt (Eisenmenger complex, more common in cattle). Because of the pressure and volume overload

with moderate to large VSDs, patients with this condition run a greater risk of developing CHF.

Considerable turbulence associated with left-to-right shunts and endocardial damage increase the risk of endocarditis in patients with VSD.[80] Because the VSD is usually located high in the LVOT, structural support of the aortic valve cusps may be lost, especially with large VSDs and/or malalignment VSDs, and AR may develop.[10,25,77] Significant AR adds to the left ventricular volume overload caused by the VSD.

Epidemiology

The true incidence of VSD in large animals is unknown, although it is recognized as the most common congenital cardiac defect. In one study, 36 calves had 78 congenital cardiac defects, of which 11 were VSDs.[54]

Necropsy Findings

VSD is usually located high in the interventricular septum just ventral to the right or noncoronary cusp of the aortic valve in the left ventricle and underneath the septal leaflet of the tricuspid valve or caudal or ventral to the crista terminalis in the right ventricle.[77] It can be an isolated defect or accompanied by other cardiac or organ anomalies. If the defect is moderate or large, there is right ventricular, left atrial, and left ventricular enlargement and pulmonary artery dilation. Increased pulmonary blood flow can lead to lung congestion and secondary pneumonia is not uncommon. If pulmonary vascular resistance is increased, right ventricular hypertrophy may be present. There may be secondary endocarditis (infrequent in large animals)[80] or endocardial lesions as a result of turbulent blood flow across the defect.

Treatment and Prognosis

There is no practical treatment for VSD in large animals. A complete echocardiographic examination is indicated to identify the presence and significance of a VSD. The size of the VSD, peak shunt velocity through the VSD, degree of left atrial and left ventricular volume overload, presence of aortic valve prolapse, detection of AR or MR, and myocardial function all have to be assessed to determine the VSD's significance. It is important to identify

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those animals with moderate to large defects, because the prognosis for normal production or function is poor. Horses with large defects (>3.5 cm or VSD/aortic root ratio of 0.64) and peak shunt velocities through the defect of less than 3.5 m/s are likely to develop CHF early in life and have a shortened life expectancy.[25,76] These horses are not suitable for use by a child or in a lesson program. Animals with small defects may remain asymptomatic throughout life. Rarely, spontaneous closure of the VSD may occur.[81] It is important to recognize that small defects, which provide a large resistance to flow, can produce loud murmurs, so murmur intensity is not a good predictor of defect size.

VSDs may be heritable in some breeds, and because of the increased risk of heart failure and other cardiac complications, breeding animals with this defect is not advised. As a general rule, bull studs do not accept animals with this defect into a breeding program.

Patent Ductus Arteriosus

Definition and Etiology.

A PDA is persistent patency of the vessel (normally present in the fetus) that connects the pulmonary arterial system to the aorta. The ductus arteriosus fails to close at birth when breathing begins and placental circulation is removed. Closure of the ductus arteriosus occurs in response to decreasing pulmonary vascular resistance and increased systemic vascular resistance.

A PDA can occur as a single defect (rare in large animals) or with other cardiac anomalies. In large animals the most common other defects reported with PDA are tetralogy of Fallot and pseudotruncus arteriosus.

Clinical Signs and Differential Diagnosis

The clinical signs of PDA depend on the length and diameter of the ductus arteriosus, direction of the shunted blood, and presence of other cardiac defects. A PDA should be suspected when a continuous “machinery murmur” is auscultated. The murmur may be heard on the left and right sides of the thorax but is usually loudest in the left third or fourth intercostal space at the level of the point of the shoulder. The intensity of the murmur increases with increased heart rate, exercise, or excitement. The arterial pulses are usually bounding because of the runoff of blood from the systemic to the pulmonary circulation. Occasionally the PDA is manifested by a holosystolic murmur[82] because the

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diastolic component is barely audible, except at the left heart base. Large PDAs can exist without producing a murmur. In the animal with increased pulmonary vascular resistance and reversal of the shunt, there may be cyanosis of the caudal parts of the body if the PDA enters the aorta caudal to the brachiocephalic trunk (rare). Stunting of growth may also occur.

Other causes of a continuous murmur in neonatal large animals are extremely rare, but detecting a continuous machinery murmur should lead the veterinary clinician to suspect a complex congenital cardiac defect that includes a PDA, rather than an isolated defect. In older horses an aorticocardiac fistula should be suspected, particularly if the machinery murmur is of recent onset and is loudest on the right side of the chest. If the horse is a Friesian, an aortopulmonary fistula should be suspected. A systolic and diastolic murmur can be present in young animals with a large VSD causing AR. A similar murmur is possible with vegetative endocarditis of one of the atrioventricular or semilunar valves, producing insufficiency and stenosis of the affected valve. These latter conditions should not have the machinery murmur characteristic of the PDA. A loud systolic ejection murmur, which is confused with a PDA, frequently can be heard at the left heart base of foals shortly after closure of the PDA. This murmur may persist for 2 to 3 months.[55]

Clinical Pathology

No characteristic clinicopathologic changes are associated with a PDA. Radiography may show enlargement of the cardiac silhouette and pulmonary overcirculation in an uncomplicated PDA. Pulmonary venous congestion, interstitial pulmonary edema, and alveolar edema are evidence of a large PDA with left-sided heart failure. These signs are not specific for PDA and can be present with any congenital heart defect that results in a left-to-right shunt. No consistent electrocardiographic pattern has been identified with PDA. Echocardiographic detection of an enlarged left atrium and left ventricle, with a pattern of left ventricular volume overload and increased values for the ratio of the left atrial to aortic root dimension, are consistent with a PDA.[10,53,82,83] Direct visualization of the ductus arteriosus echocardiographically is difficult but is most successful from the left cardiac window looking dorsally between the aorta and main pulmonary artery. A PDA arising from the pulmonary artery has been imaged echocardiographically in an 11-month-old Friesian-Holstein heifer.[56] A PDA has also been imaged by the author in a 9-year-old Quarter Horse mare.

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High-velocity turbulent flow in the pulmonary artery and ductus arteriosus is detected throughout the cardiac cycle with pulsed-wave, continuous-wave, or color-flow Doppler echocardiography.[10]

Cardiac angiocardiography and nuclear angiocardiography using a selective aortic angiogram provide definitive evidence of a PDA. Oximetric data show a step-up in oxygen content or saturation in the pulmonary artery proportional to shunt size. Indicator dilution methods also provide evidence of a left-to-right shunt occurring in the pulmonary artery in cases of an uncomplicated PDA. Pulmonary arterial and right ventricular pressures may be increased with a large PDA.

Pathophysiology

Normally the ductus arteriosus narrows near term and constricts rapidly after birth in response to lowered pulmonary vascular resistance, increased systemic vascular resistance, increased blood volume, and increased left ventricular pressure when breathing begins and the placental circulation is removed. If the ductus arteriosus is large or the resistance to flow across the ductus is minimal, there is a significant left-to-right shunt that produces a large left ventricular volume overload. The left ventricular response may be failure or, with time, dilation (primarily) and hypertrophy. Pulmonary hypertension and congestion result. The right ventricle can be affected by the pulmonary pressure load, and right ventricular hypertrophy can also develop. If the pulmonary resistance equals or exceeds the systemic vascular resistance, a right-to-left shunt occurs.

Epidemiology

Normal foals may have a PDA for a few days after birth, but functional closure of the ductus arteriosus is expected by 96 hours of age.[82] Normal ruminants rarely have a PDA after birth, and if one is present it is considered abnormal. Functional closure may precede anatomic closure of the PDA. This defect is uncommon in older animals. No evidence suggests that this is an inherited defect in horses or cattle.

Necropsy Findings

The ductus arteriosus can be of variable length and diameter but is patent

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between the aorta and pulmonary artery. The PDA often enters the aorta caudal to the origin of the brachiocephalic trunk. Changes in the left and right ventricles and lung and pulmonary vasculature are variable and depend on the size of the shunt. When the PDA is large, there may be cardiomegaly with left atrial and left ventricular dilation, right ventricular hypertrophy, dilation of the pulmonary artery, pulmonary congestion, and edema.

Treatment and Prognosis

There is insufficient evidence on which to base a prognosis for animals with PDA. The condition can be corrected surgically in neonates, but future performance has not been documented. Animals with small defects may remain asymptomatic throughout life. However, a marked dilatation of the pulmonary artery around the shunt is a safety concern in a horse that is to be ridden or driven, as pulmonary artery rupture is possible. The prognosis is poor if the defect is large, because the risk for left (primarily) and right ventricular failure is increased. Pharmacologic closure of the PDA using inhibitors of prostaglandin synthesis has been successful in humans but is not without risk of complications and recurrence. The efficacy of prostaglandin inhibitors has not been evaluated in large animals.

Tetralogy and Pentalogy of Fallot

Definition and Etiology.

Tetralogy and pentalogy of Fallot are characterized by biventricular origin (overriding) of the aorta, VSD, obstruction of pulmonary arterial flow, and secondary right ventricular hypertrophy. When there is an associated ASD or PDA, the anomaly is referred to as *pentalogy of Fallot.* The defect is caused by abnormal development of the conal septum in the embryonic heart, which leads to narrowing of the right ventricular infundibulum (pulmonic stenosis), an inability of the conal septum to participate in closure of the interventricular foramen (VSD), and overriding of the aorta. Right ventricular hypertrophy due to pulmonary outflow obstruction develops.

Clinical Signs and Differential Diagnosis

Tetralogy of Fallot is one of the more common congenital cardiac defects that

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cause cyanosis in large animals. Resting cyanosis is rare in horses, although it may be detectable after exercise. Cyanosis of the oral and nasal mucosa, tongue, vaginal mucous membranes, and occasionally the nose and skin of light-colored animals is noticed when >5 g/dL of hemoglobin are reduced (unoxygenated). Exercise intolerance is often marked and is usually characterized by dyspnea or collapse. Frequently the owner complains of slow growth or small size. A loud pansystolic murmur associated with a palpable thrill is loudest in the left third to fourth intercostal spaces. The murmur may be a crescendo-decrescendo murmur of pulmonic stenosis or the harsh, plateau-shaped murmur of a VSD; one of these usually predominates. A harsh band-shaped pansystolic murmur is also auscultated in the tricuspid valve area but is usually one or two grades softer than the pulmonic stenosis murmur. Excitement of the animal may result in auscultation of a gallop rhythm or an early systolic ejection click. A continuous machinery murmur associated with continuous shunting through the PDA can be auscultated in some patients with pentalogy of Fallot.

Tetralogy and pentalogy of Fallot must be distinguished from other causes of cyanosis in young animals. Respiratory distress syndrome of neonates can be distinguished by the presence of tachypnea, dyspnea, and abnormal lung sounds in the absence of a cardiac murmur. Cyanosis caused by central nervous system disease has other neurologic manifestations. Cyanosis from congenital cardiac disease may be caused by a right-to-left shunt or heart failure with pulmonary edema. Cyanosis resulting from heart failure or respiratory disease improves with oxygen administration, whereas the patient with a right-to-left cardiac shunt fails to improve. Right-to-left cardiac shunting does or can occur with tetralogy and pentalogy of Fallot, reverse PDA or VSD (rare), tricuspid valve or right ventricular atresia, left ventricular hypoplasia, persistent truncus arteriosus, pseudotruncus arteriosus, and other complex congenital cardiac disease, all of which may occur with cyanosis and a cardiac murmur. A complete echocardiographic examination (Video 30.2) using a segmental approach to cardiac anatomy is necessary to accurately diagnose the correct congenital cardiac malformation and has widely supplanted other methods of diagnosing complex congenital cardiac disease in large animals. Radiography and cardiac catheterization provide supplemental information that may be helpful in distinguishing among the causes of right-to-left cardiac shunting.

Clinical Pathology

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Increased packed cell volume (PCV), red blood cell count, and hemoglobin concentration (polycythemia) may be present in some animals with tetralogy and pentalogy of Fallot.[58] However, polycythemia is uncommon in foals with cyanotic congenital cardiac disease and the PCV is usually <45% in most calves. The degree of arterial hypoxemia is variable, depending on the amount of right-to-left or bidirectional shunting. Electrocardiographic changes are usually nonspecific, but a right-axis deviation may be detected.[58] Radiographs of the lungs may show decreased vascularity. Echocardiography easily visualizes the four components of tetralogy of Fallot. The VSD and overriding aorta are usually clearly visible with 2D echocardiography (see Video 30.2). The malalignment VSD is usually large and located just below the right cusp of the aortic valve, separated from the pulmonic valve by the crista supraventricularis. The aortic root is usually large and dextroposed, and it overrides the VSD. Echocardiography shows increased thickness of the right ventricular wall, ventricular septal hypertrophy, paradoxical septal motion, and similar left and right ventricular internal dimensions. Narrowing of the RVOT, pulmonic stenosis, or a hypoplastic pulmonary artery (most common) may be imaged as the cause of the RVOT obstruction. Pulsed-wave, continuous-wave, and color-flow Doppler echocardiography can be used to further characterize the abnormalities of blood flow associated with tetralogy of Fallot, in particular the severity of the RVOT obstruction. Contrast echocardiography also nicely demonstrates the path of blood flow with a peripheral venous injection. Contrast echoes are imaged entering the right ventricle from the right atrium, and then simultaneous opacification of the pulmonary artery, left ventricle, and aorta occurs.

Cardiac catheterization can be used to demonstrate equalization of ventricular pressures and a pressure gradient between the right ventricle and pulmonary artery. Oximetry should demonstrate decreased oxygen content in the left ventricle compared with the pulmonary vein. Angiocardiography demonstrates simultaneous filling of the right ventricle, left ventricle, and overriding aorta, with decreased pulmonary artery filling and increased right ventricular trabeculation (hypertrophy).

Pathophysiology

The VSD is usually large, resulting in equalization of pressures in the two ventricles and aorta. The degree of shunting is controlled by the resistance across

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the stenotic RVOT compared with the resistance across the aortic valve. If the RVOT is severely obstructed, the clinical signs of cyanosis are more marked. Excitement, drugs, or increased myocardial contractility from any cause decreases right ventricular volume and worsens clinical signs. Right ventricular failure is usually not a consequence of the pressure overload because of equalization of the ventricular pressures.

Epidemiology

The prevalence of tetralogy and pentalogy of Fallot in large animals has not been documented, but these defects seem to be more common in calves than foals. There is no evidence that these disorders are inherited.

Necropsy Findings

Examination of the heart reveals a rounded apex caused by right ventricular enlargement. A high, usually large VSD; a dextroposed overriding aorta that straddles the VSD and the left and right ventricle; right ventricular hypertrophy; and septal hypertrophy are present. There is usually right ventricular infundibular narrowing and a hypoplastic pulmonary artery, although there may be valvular pulmonic stenosis with a poststenotic dilation. The right and left atria may be enlarged.

Treatment and Prognosis

There is no practical treatment for tetralogy and pentalogy of Fallot in large animals. When cyanosis or exercise intolerance is present or growth is stunted (the latter two are common findings in affected animals), the prognosis for long-term survival, production, or performance is poor. Affected foals should not be used for performance or broken to ride if they live long enough. As with many congenital cardiac diseases, the intensity of the murmur is not a good predictor of the severity of the condition, and further diagnostic tests are indicated.

Other Congenital Cardiac Defects

Atrial Septal Defect.

ASD is a connection between the left and right atria at the septal level. The most

common type of defect is the ostium secundum defect, of which patent foramen ovale (PFO) is seen most frequently. PFO is relatively common in calves and is due to failure of the septum primum, the valve of the foramen ovale, to become adherent to the crista dividens after birth, when changes in left and right atrial pressures produce functional closure of the foramen ovale. PFO is frequently associated with PDA in calves.[54]

Animals with an ASD are frequently asymptomatic, but a holosystolic crescendo-decrescendo murmur may be heard at the left heart base. The shunt is usually left to right, and the murmur is the result of increased volume being ejected across the pulmonic valve. If the defect is large, right atrial, right ventricular, and left atrial dilation may be present. Differential diagnostic considerations are a functional murmur, pulmonic stenosis, VSD, or PDA. A definitive diagnosis can be made by 2D echocardiography, in which an enlarged right atrium, right ventricle, and left atrium are imaged. Pulsed-wave Doppler, color-flow, or contrast echocardiography can be used to demonstrate the shunt through the ASD.

Pulmonic Valve Stenosis.

Pulmonic valve stenosis is rare as a single defect but has been reported in a foal with VSD and as one of multiple defects in calves and foals.[10,54,68] Clinical signs of cardiac murmur, cyanosis, and polycythemia are variable and depend largely on the other cardiac defects present. Characterization of the severity of the pulmonic stenosis and other associated cardiac defects can be performed with a complete echocardiographic examination.

Tricuspid Valve Atresia.

Tricuspid valve atresia has been reported in foals[59,63–65] in conjunction with other cardiac defects. The abnormalities associated with tricuspid atresia include PFO, VSD, small right ventricle, large left ventricle, and large mitral valve orifice. The foals showed cyanosis and a crescendo-decrescendo or band-shaped holosystolic or pansystolic murmur audible over the left and right heart base. Tachycardia, tachypnea, and weak peripheral pulses also were present. Polycythemia was commonly reported. Echocardiographic diagnosis of tricuspid atresia in foals has been reported.[59,64] A thick echo in the region of the tricuspid valve that does not separate in diastole (absent tricuspid valve), an ASD (usually PFO), a VSD, a small right ventricle, a large left ventricle, and a large mitral

valve orifice are the echocardiographic findings in tricuspid atresia. Blood flow (right to left) through the PFO into the left atrium and left ventricle, followed by simultaneous opacification of the aorta and right ventricle, is detected with contrast echocardiography. Affected foals rarely live past weanling age. Necropsy showed tricuspid atresia, along with ASD, VSD, small right ventricle, and large left ventricle. Pulmonic valve stenosis and dextropositioning of the aorta have also been reported.

Mitral Valve Dysplasia.

Mitral valve dysplasia is a rarely reported early developmental anomaly in the horse.[10,66,84] Affected foals have a grade 3/6 to 5/6 holosystolic decrescendo or coarse-type murmur loudest in the mitral to aortic valve area. Echocardiographically in the foal with mitral valve dysplasia, the mitral valve leaflets appeared thickened, bright, and irregularly nodular with a cleft in the free wall leaflet and abnormal papillary muscle and chordae tendineae.[66] In the other foal, the parachute configuration of the mitral valve was readily imaged echocardiographically.[84] The foals died or were humanely euthanized due to their poor prognosis. Other congenital variations in the configuration of mitral valve leaflets, usually the free wall and accessory leaflets, occur more frequently in horses, usually compatible with a normal life expectancy. These horses usually a have mild MR with little or no progression over many years.

Ventricular Hypoplasia.

Ventricular hypoplasia has been reported in foals and calves.[54,73] The defect may be present with other cardiac defects and is usually associated with early death. The defect was present in three closely related Holstein calves, suggesting possible genetic factors.[54]

Truncus or Pseudotruncus Arteriosus.

Persistent truncus arteriosus refers to the condition in which one arterial vessel leaves the heart above a VSD. The coronary and pulmonary arteries and aorta arise from this vessel. Persistent truncus arteriosus has been diagnosed in foals and calves.[60] Subclassifications of this condition have been applied to humans, depending on the origin of the pulmonary trunk or arteries. Pseudotruncus arteriosus has also been described in foals and a calf and is characterized by the

presence of a remnant of an atretic pulmonary trunk.[59,85] With pseudotruncus arteriosus, the pulmonary blood supply comes from bronchial arteries or a PDA. Clinical manifestations of these conditions include tachycardia, exercise intolerance, and a cardiac murmur. The murmur may be a continuous machinery murmur if a PDA is also present; holosystolic and crescendo-decrescendo, loudest at the left heart base; or the coarse murmur of the VSD may be auscultated, although the relative pulmonic stenosis component is absent. Cyanosis, dyspnea, or syncope may be seen with exercise or excitement. CHF and stunted growth may be present. Polycythemia was detected in a calf with a pseudotruncus arteriosus.[85] The presence of cyanosis with the cardiac murmur helps differentiate this condition from a simple VSD or PDA. Definitive diagnosis may be made by echocardiography, angiocardiography, or nuclear angiocardiography. These foals and calves have a guarded to grave prognosis. Their life expectancy depends on the magnitude of their pulmonary blood flow.

Aortic Anomalies.

Dextropositioning or transposition of the aorta are the most common aortic anomalies of foals and calves and are seen most frequently with other defects. Other aortic anomalies of foals and calves are persistence of the right aortic arch and double aortic arch, which may cause esophageal compression. The clinical presentation is one of esophageal obstruction. Interruption of the aortic arch in two foals with VSD, ASD, and PDA has been reported.[70] The foals showed weakness, lethargy, cyanosis, and tachycardia. The murmur was pansystolic and plateau shaped, with the PMI on the right side of the thorax. Radiology showed cardiomegaly and increased vascularization of the lungs. Cardiac catheterization showed left ventricular failure.

Bicuspid and quadricuspid cusps of the aortic and pulmonic valves occur in large animals and usually result in both stenosis and valvular insufficiency. An aneurysm of the sinus of Valsalva was detected in a 3-year-old Thoroughbred gelding as an incidental finding.[86] Occasionally a diastolic murmur may be associated with AR in horses with sinus of Valsalva aneurysms.[87] These sinus of Valsalva aneurysms usually rupture later in life, and the horse develops acute distress, colic, and uniform VT. A continuous machinery murmur associated with the presence of an aorticocardiac fistula (ACF) is usually present on the right side of the thorax (see Vascular Disease).

Eisenmenger Complex.

Eisenmenger complex has been described in a stunted 24-month-old Holstein heifer that had a loud, crescendo-decrescendo, pansystolic murmur heard best over the pulmonic valve.[62] The heifer had a prominent gallop rhythm from a loud fourth heart sound, exercise intolerance without cyanosis, and polycythemia. Cardiac catheterization showed increased pressures in the right atria, right ventricle, and pulmonary artery, with normal left-sided pressures. The echocardiogram was characterized by a VSD, overriding aorta, and dilation of the pulmonary trunk, a feature that distinguished this from tetralogy of Fallot. Left ventricular function was decreased, and at necropsy the heart was enlarged and rounded with a dilated pulmonary trunk and small aorta. The right ventricle was dilated and hypertrophied, whereas the left atria and ventricle were only mildly dilated.

Ectopia Cordis Cervicalis.

Ectopia cordis cervicalis is a relatively common defect of cattle.[54,69] Although this defect usually results in the heart being in the cervical region, a few animals may have the heart in the pectoral region (14%) or abdomen (3%).[69] Various defects are associated with ectopia cordis cervicalis, including defects of the heart, great vessels, neck (torticollis), ribs, and sternebrae. The heart is usually contained within the pericardium under the muscles of the skin in the ventral cervical area, with the double apex of the heart pointing craniodorsally. The ligaments of the pericardium are most frequently attached to the mandibles and the parotid fascia cranially, the cervical fascia laterally, and the first rib or manubrium caudally. The lung may lack the cardiac notch and often protrudes to the base of the heart. Although the prognosis for a productive life is poor, some calves lived until about 1 year of age.

Miscellaneous Cardiac Defects.

Other cardiac defects occur, but the defect has been recorded infrequently. Complete atrioventricular canal defect has been reported in several foals.[71,72,88] Anomalous coronary artery development has been reported at postmortem examination in both calves and horses and has been thought to be the cause of death in most cases.[89–91] Congenital hematomas of the atrioventricular valves also have been noted, but the significance is unknown.[54] Endocardial

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fibroelastosis, an anomalous development of the endocardium associated with left ventricular hypertrophy, is usually a severe defect resulting in death of the animal. The frequency of this defect in large animals is not established.

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Valvular Heart Disease

Definition and Etiology

In adult animals, disorders of the tricuspid, pulmonic, mitral, or aortic valves are usually acquired, resulting in insufficiency of the affected valve. These disorders may be the result of degenerative changes, infection (bacterial or viral endocarditis or myocarditis), inflammation (valvulitis), trauma, myocardial disease (cardiomyopathy), or unknown causes. They are usually manifested by a cardiac murmur, most frequently of valvular regurgitation, with the PMI at the location of the affected valve or in the direction of the regurgitant blood flow. The mitral and aortic valves are the most common location of degenerative valve disease in horses.[92] Chronic active infection such as foot abscesses, rumenitis, reticular abscess, or other septic process may lead to sustained or recurrent bacteremia, predisposing the animal to the development of bacterial endocarditis, particularly in cattle, or a nonvegetative valvulitis, probably more common in horses. Experimentally, valvular vegetative endocarditis can be induced by intravenous (IV) administration of bacteria without preliminary damage to a valve.[93] Rupture of a valve leaflet or chordae tendineae can cause valvular heart disease, as can dilation of a cardiac chamber from any cause or rupture of the aortic root or of a sinus of Valsalva aneurysm.[87,94–96] In rare cases neoplasia, primarily lymphosarcoma of cattle, can cause valvular heart disease. Congenital valvular heart disease in adult animals is rare. The most common bacterial isolates from equine and bovine endocarditis cases are streptococci and *Pasturella* or *Actinobacillus* spp. and *Trueperella pyogenes* (formerly *Arcanobacterium [Actinomyces] pyogenes*) in horses and cattle, respectively, although a wide variety of organisms has been isolated from large animals with endocarditis.[97–105]

Clinical Signs and Differential Diagnosis

Most animals with valvular heart disease have no clinical signs, but a cardiac murmur is usually detected during a routine examination. Clinical signs vary depending on lesion severity and its rate of development. Murmurs of valvular heart disease are frequently holosystolic (Fig. 30.6), pansystolic, or holodiastolic (Fig. 30.7). They radiate from the PMI in the direction of the abnormal blood

flow; are coarse and band-shaped, crescendo or musical or honking (if systolic), or decrescendo and blowing or musical or sound like a “dive bomber” (if diastolic); and are usually moderate to loud in intensity (≥grade 3/6) but may be softer if holodiastolic. All these characteristics help distinguish these murmurs from functional or innocent murmurs, which generally occur early or late in systole or diastole but can be holosystolic; are soft and blowing or crescendo-decrescendo in quality; are localized to a small area; do not radiate; and are soft to moderate in intensity (≤3/6). Murmur intensity is not a reliable indicator of lesion severity except in horses with tricuspid regurgitation (TR), in which the longer, louder murmurs are associated with a larger jet of TR.[106] In cattle in particular, severely involved valves (usually in cattle with endocarditis) commonly have faint or no audible murmurs.

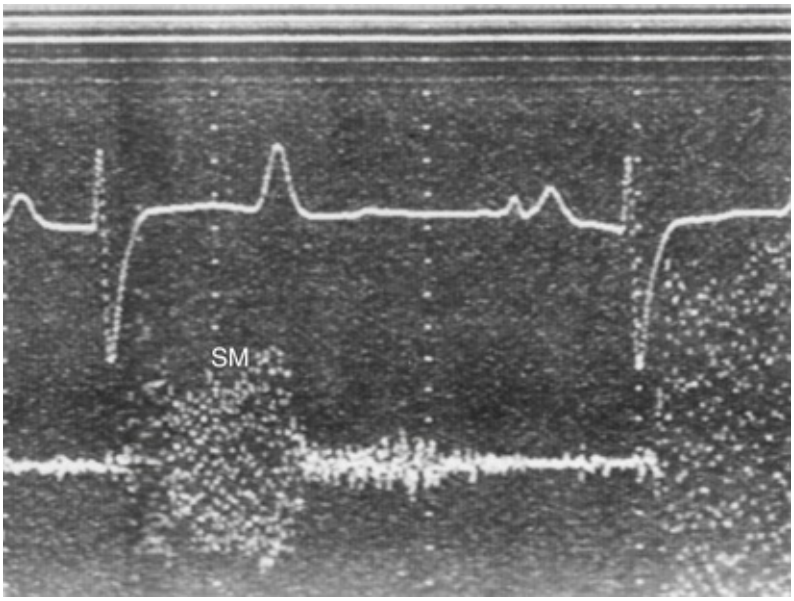


FIG. 30.6 Phonocardiogram obtained from a horse with a ruptured mitral valve chorda tendineae. A loud plateau-shaped holosystolic murmur *(SM),* which is variable in intensity, occurs when the free wall leaflet of the mitral valve is prolapsing into the left atrium.

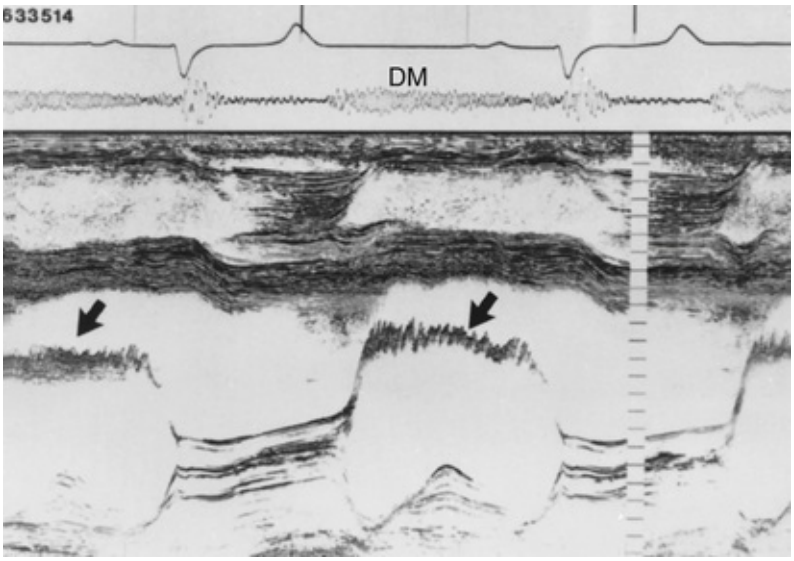


FIG. 30.7 Phonocardiogram and M-mode echocardiogram obtained from a horse with a holodiastolic murmur *(DM)* caused by aortic valve regurgitation. The M-mode echocardiogram shows diastolic flutter *(arrows)* of the septal mitral valve leaflet, characteristic of aortic valve insufficiency.

The location of the PMI of the murmur is helpful in distinguishing which valve is involved, although more than one valve can be affected in the same animal. The PMI for lesions of the mitral valve is often in the mitral valve area, although murmurs of MR usually radiate dorsally toward the left heart base and aortic valve area. Therefore loud systolic murmurs with the PMI in the aortic or mitral valve area in horses are usually MR murmurs. Disorders of the tricuspid valve commonly have the PMI on the right side of the thorax (third to fourth intercostal spaces [horses] or second to third intercostal spaces [cattle]). Rarely the murmur may also be heard on the left side of the thorax cranial to the pulmonic valve location in the second intercostal space. Aortic and pulmonic valve lesions produce murmurs with the PMI at the left heart base in the fourth or third intercostal space, respectively. Acquired valvular lesions of the mitral and tricuspid valves produce primarily systolic murmurs.[26,97,98,100,106–111] Diastolic tricuspid flow murmurs have been reported, however, and may be associated with right-sided mural or valvular masses in horses[80] or may be physiologic, associated with normal blood flow across the atrioventricular valves.[112,113] Lesions of the aortic and pulmonic valves may produce diastolic murmurs, systolic murmurs (rare), or both,[97,114–116] but diastolic murmurs of regurgitation are most common in large animals. AR associated with degenerative valve disease is most common in horses, whereas pulmonic

regurgitation (PR) associated with bacterial endocarditis is more common in cattle. Aortic valve lesions in horses have primarily holodiastolic, decrescendo, musical murmurs (see Fig. 30.7) but can also be decrescendo, soft, and blowing. AR murmurs are accompanied by a water-hammer or bounding arterial pulse if the AR is associated with a significant left ventricular volume overload.[26,97,117,118] The musical quality of the murmur (harmonic) indicates that some part of the aortic valve is vibrating during diastole. The arterial pulse quality becomes more bounding as the AR becomes more severe and is a good clinical indicator of the degree of left ventricular volume overload. Ventricular premature beats and AF may also be detected in horses with significant AR.[118]

Besides the cardiac murmur, animals with valvular heart disease may have exercise intolerance, arrhythmias, weight loss, or signs of CHF evidenced by tachycardia, coughing, respiratory distress, jugular venous distention, subcutaneous edema, and ascites (uncommon in large animals, especially horses). In adult cattle, mammary vein distention is another sign of CHF.[98] Cardiac enlargement may be noted as an increased area of auscultation and/or percussion or caudal dislocation of the apical impulse of the heart. AF may be present. This development is usually an indicator of atrial enlargement in animals with valvular heart disease. If TR is present, there may be abnormal systolic jugular venous pulsations. If MR is present there may be tachycardia, tachypnea, poor recovery to resting respiratory rate after exercise, coughing, and frothy pulmonary edema (uncommon). Lung sounds may be harsh at rest and on deep inspiration may include crackles or moist bubbly sounds (both of the later auscultatory findings are rare). Most horses with pulmonary edema have only harsh breath sounds that are detected at rest and on deep inspiration.

One of the clinical signs of bacterial endocarditis is a cardiac murmur, the PMI and timing of which depend on the valve or valves affected. Other signs may include tachycardia, arrhythmias, auscultation of prominent heart sounds, tachypnea, coughing, recurring fever, anorexia, weight loss, or signs of CHF. Evidence of disseminated sepsis such as pneumonia, hematuria, or pyuria is usually present in cattle but not in horses. Shifting leg lameness and swollen joints or tendon sheaths are common but usually have an immune-mediated cause, although a horse with bacterial endocarditis and septic tenosynovitis has been reported.[101] Mastitis and decreased milk production are common in cattle. The presence of weight loss, fever, and signs of recurring sepsis help distinguish bacterial endocarditis from other forms of acquired valvular disease.

The clinical signs of a major mitral valve ruptured chordae tendineae (RCT)

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or its characteristic murmur distinguish this disease from other mitral valve diseases. The murmur is usually a widely radiating musical murmur of MR (see Fig. 30.6) with a distinctive honking quality (the honking quality is consistent with vibration of the mitral valve chorda tendineae or leaflet with blood flow in systole).[118] However, the honking quality may be absent and replaced by a band-shaped pansystolic murmur. There may be evidence of acute hemodynamic collapse. Acute onset of respiratory distress with coughing and expectorating foamy pulmonary edema fluid (this fluid is also detected at the external nares) is a relatively consistent feature with a major RCT. Signs of right-sided heart failure (jugular venous distention, subcutaneous edema, and ascites) may develop rapidly. Atrial arrhythmias, most frequently AF, often develop secondary to atrial enlargement. Supraventricular arrhythmias have also been reported in foals with a mitral RCT.[109] Acute onset of respiratory distress, along with a honking systolic murmur, distinguishes mitral RCT from other causes of MR. The honking systolic murmur of a mitral RCT can also be heard in the absence of any clinical signs in horses with a minor chordal rupture. The murmur of mitral valve prolapse (MVP) is also a distinctive murmur and should be suspected in horses whenever a crescendo midsystolic to late-systolic or holosystolic murmur is auscultated with the PMI over the mitral valve area.[26,118,119] A similar murmur is frequently auscultated in horses with tricuspid valve prolapse (TVP). Murmurs of MVP or TVP can be detected in horses with all degrees of valvular insufficiency. Most frequently, however, only small amounts of valvular regurgitation are associated with valvular prolapse. An increased prevalence of MR and TR has been reported in young horses in training.[120–123]

Clinical Pathology

Diagnosis of valvular disease is best performed with a complete echocardiographic examination including M-mode, 2D, and Doppler echocardiography. Two-dimensional echocardiography is superior to M-mode for detection of valvular abnormalities (Figs. 30.8 and 30.9), measurement of valvular masses (see Fig. 30.9, *B*) (Video 30.3), and global assessment of ventricular function, but chamber enlargement, high-frequency vibrations of the valve leaflets (Video 30.4), and shortening fraction (an indication of ventricular systolic function) can be determined by both. Pulsed-wave, continuous-wave, and color-flow Doppler echocardiography can be used to semiquantitate the

severity of valvular regurgitation and should be performed from both sides of the thorax, interrogating the left atrium in multiple imaging planes.[10,119,124,125] The size of the regurgitant jet at its origin and the extent of the jet within the left atrium detected with pulsed-wave and/or color-flow echocardiography are two indicators of the severity of the valvular insufficiency.[26] Detection of proximal flow convergence indicates hemodynamically significant MR. The duration of the MR jet is also important in assessing severity. Clinically insignificant jets of regurgitation are detected only just behind the valve when it is closed. Valvular insufficiency is mild when the jet occupies one third or less of the receiving chamber, moderate when the jet occupies greater than one third but less than two thirds of the receiving chamber, and severe when the jet occupies greater than two thirds of the receiving chamber. The intensity and shape of the spectral Doppler tracing of the MR jet also provide information about its severity. Severe MR is associated with an intense triangular rather than parabolic signal that increases rapidly at the onset of systole.

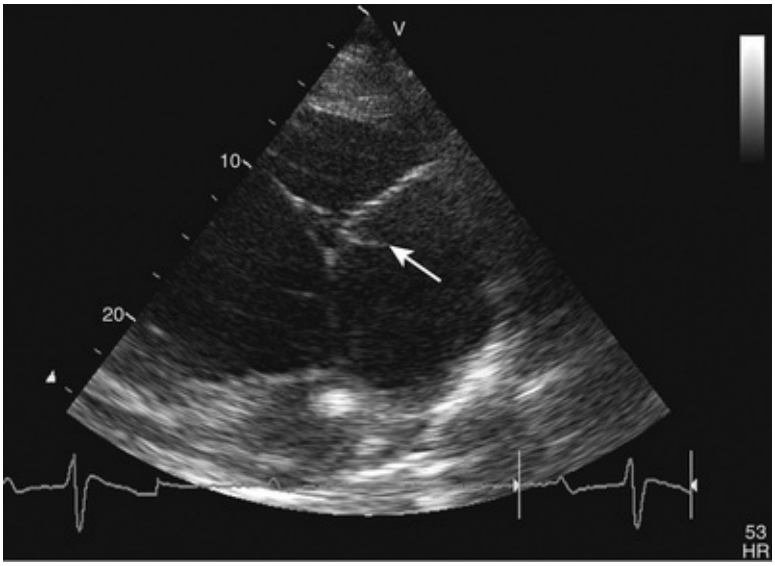


FIG. 30.8 Two-dimensional echocardiographic image obtained from the left parasternal window of a ruptured mitral chorda tendineae *(arrow)* in the left atrium of a gelding with mitral regurgitation and a honking pansystolic murmur.

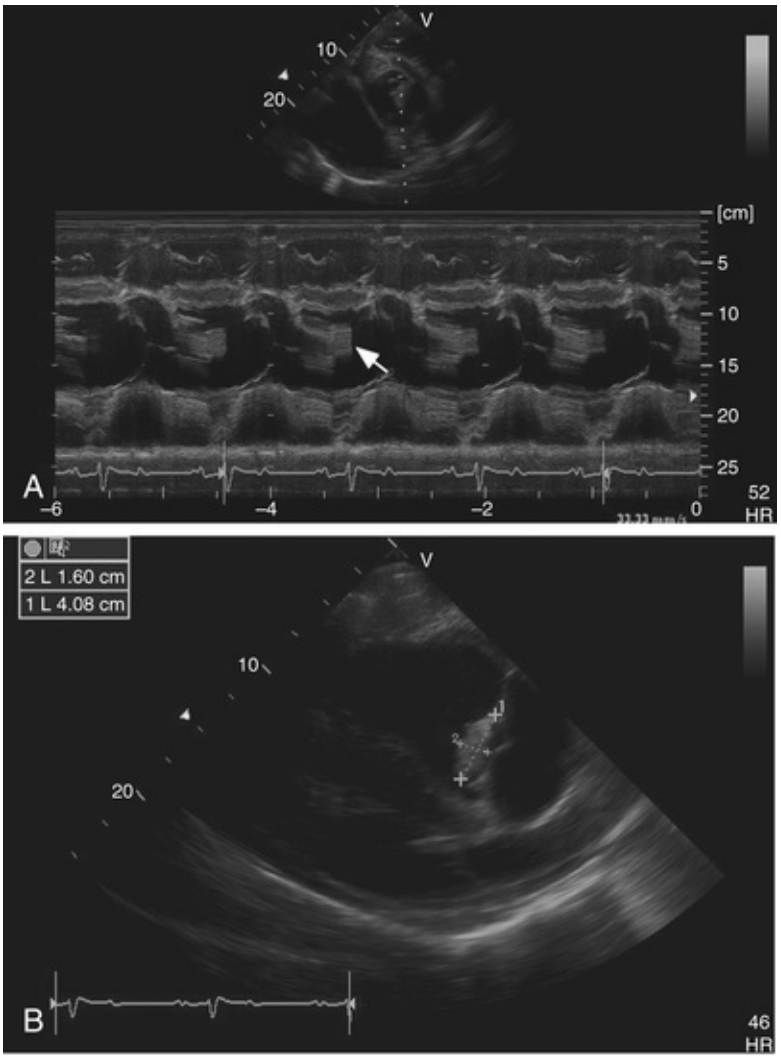


FIG. 30.9 Echocardiograms of a bacterial endocarditis lesion on the aortic valve of a horse. The lesion can be seen on the aortic valve M-mode **(A)** as a thick echoic band *(arrow)* and is measured in the two-dimensional echocardiographic image of the left parasternal long-axis view **(B).**

Echocardiographic signs of MR are increased left atrial (Fig. 30.10; also see Fig. 30.3) and left ventricular dimensions, rounding of the left ventricular apex, and a pattern of left-sided volume overload. Left ventricular function may be normal (if MR is mild) or the FS may be increased (if there is a significant left ventricular volume overload associated with acute moderate to severe MR), unless there is concomitant myocardial disease. Normal or decreased contractility is present with chronic, severe MR. A round, turgid left atrium with bulging of the interatrial septum toward the right is another indication of hemodynamically severe MR. A larger-than-normal pulmonary artery (larger than the aortic root) is compatible with severe pulmonary hypertension and left-

sided heart failure. A smaller-than-normal aortic root is detected echocardiographically in horses in low-output left-sided heart failure (Video 30.5).[10,26,109,110,119]

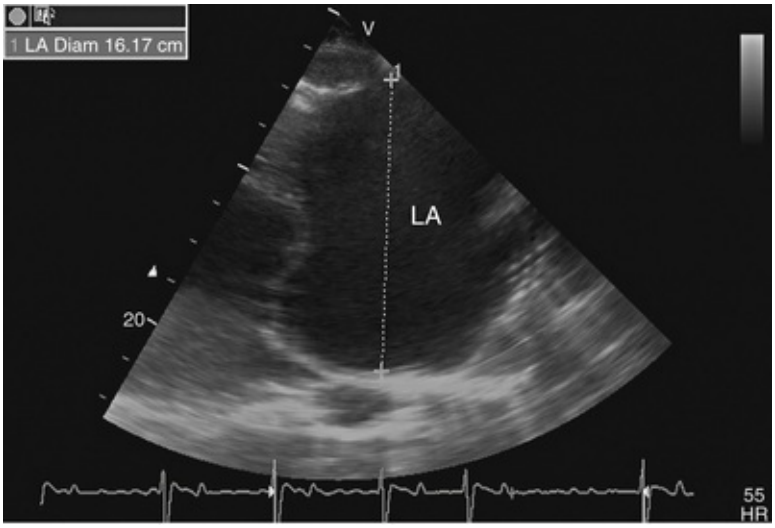


FIG. 30.10 Left parasternal echocardiographic image of the left atrium *(LA)* and mitral valve from a horse with left atrial enlargement (16.17 cm).

The cause of the valvular regurgitation can often be determined. Endocarditis, mitral RCT (see Fig. 30.8), a flail valve leaflet, valvular prolapse, or thickening of the valve leaflet are readily imaged echocardiographically.[110] The regurgitant jet detected with pulsed-wave or color-flow Doppler echocardiography usually originates from the site of the valvular abnormalities detected with 2D echocardiography. In some animals, the lesion responsible for the valvular insufficiency is not visualized with 2D echocardiography, but the regurgitant orifice is detected with pulsed-wave or color-flow Doppler echocardiography.[6,10,125] A mitral RCT is diagnosed by finding a mobile linear echo everting into the left atrium (see Fig. 30.8) or a flail leaflet that may prolapse into the left atrium during systole, systolic and chaotic diastolic mitral valve flutter, rapid mitral valve opening with increased excursion of the affected leaflet, and lack of coaptation of the mitral valve in systole. The asynchronous movement of any portion of the valve leaflet during any phase of the cardiac cycle indicates the presence of a flail valve leaflet.[10,26,107,110]

TR may produce echocardiographic evidence of right atrial and right ventricular enlargement with paradoxical septal motion. Frequently the cause of

tricuspid valve regurgitation in cattle is bacterial endocarditis, and the incompetent valve can be visualized. In cattle, neoplasia of the right atrium, tricuspid valve, or right ventricle can usually be visualized when present.[126] TR is common in horses with no obvious valvular lesion.[113,121,127] However, tricuspid valve bacterial endocarditis is detected in some horses with septic jugular vein thrombophlebitis.[128]

AR is diagnosed echocardiographically by observing left ventricular dilation, increased aortic root diameter (Fig. 30.11), increased left ventricular FS (if the AR is moderate to severe and left ventricular function is normal), diastolic fluttering of the septal mitral valve leaflet (see Fig. 30.7), or less frequently by observing high-frequency vibrations of the interventricular septum (Fig. 30.12) or aortic valve in diastole.[10,26,115,117,129] Rarely, premature closure of the mitral valve is detected. Thickening of the left cusp of the aortic valve is frequently detected echocardiographically, but prolapse, fenestration, healed endocarditis lesions, and tears of the aortic cusps also occur. A decrease in the aortic root diameter during diastole is an echocardiographic indicator of increased severity of the AR.

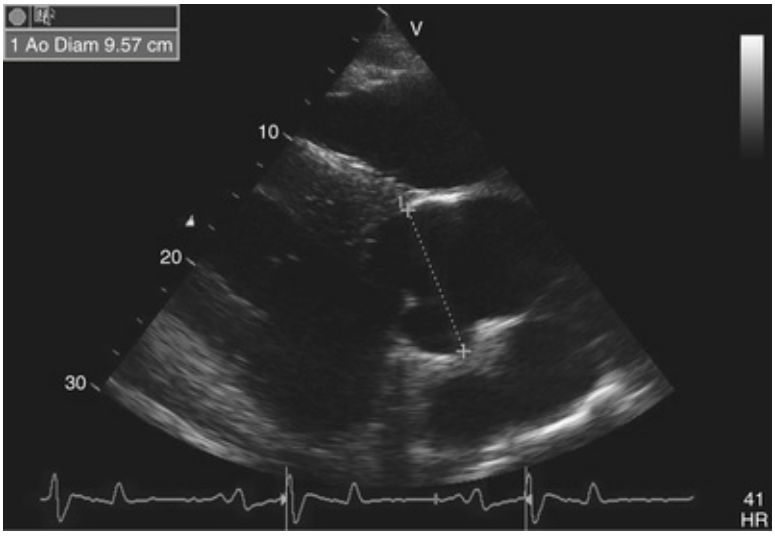


FIG. 30.11 Two-dimensional echocardiographic image of an enlarged aortic root (9.57 cm) obtained from an aged gelding with moderate aortic regurgitation that has been present for several years.

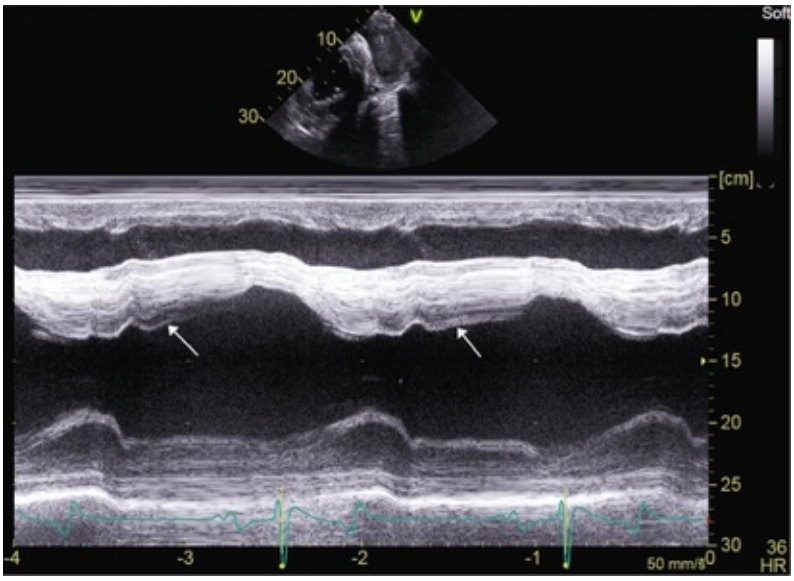


FIG. 30.12 M-mode echocardiogram obtained from a gelding with moderate chronic aortic regurgitation. Notice the high-frequency vibrations *(arrows)* on the interventricular septum.

Acquired pulmonic valve lesions are uncommon in large animals and when present are usually associated with bacterial endocarditis.[116,130] Diagnosis is established by finding the mass associated with the pulmonic valve. Severe PR associated with pulmonic valve rupture has been reported in one horse.[131] PR is most common in horses with pulmonary hypertension and CHF but is rarely detected clinically.

Lesions of bacterial endocarditis (see Fig. 30.9 and see Video 30.3) may have a shaggy, ragged, or cystic appearance on 2D echocardiography. These lesions are even better visualized with 4D echocardiography. Occasionally the only abnormality noticed is valve thickening, with ventricular hyperkinesis and enlargement of the chambers on the side of the affected valve. Acoustic reverberation and production of microbubbles have also been associated with valvular bacterial endocarditis.[109,112] Other laboratory evidence of bacterial endocarditis includes anemia, neutrophilia (a left shift may be present), an increased serum globulin concentration, increased serum amyloid A (SAA), and hyperfibrinogenemia. Liver enzymes are frequently mildly elevated, and a urinalysis sometimes shows hematuria or pyuria. Positive blood cultures taken during febrile episodes confirm the diagnosis when associated with these findings, but many times culture results are negative in large animals with bacterial endocarditis. Other laboratory evidence of disseminated sepsis includes neutrophilic response in peritoneal, tracheal wash, or joint fluid. Ventricular

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arrhythmias (VA) are frequently detected electrocardiographically in individuals with mitral or, more commonly, aortic valve endocarditis. Radiographic or sonographic evidence of disseminated pneumonia may also be found with bacterial endocarditis, usually in large animals with a right-sided lesion.

Other laboratory evidence of valvular heart disease is nonspecific. The ECG is valuable for documenting cardiac arrhythmias occurring secondary to chamber enlargement or the underlying myocardial disease. Radiographic findings of cardiac enlargement, increased pulmonary vascular pattern, or pulmonary edema are also nonspecific. Cardiac catheterization and pressure measurements help determine the degree of cardiac dysfunction. Nuclear angiocardiography shows cardiac enlargement or prolonged washout of contrast material. Time-activity curves can be helpful in accurately documenting ventricular dysfunction and the valvular regurgitant fraction.[50]

Pathophysiology

Acquired valvular heart disease that is slow in onset or gradually progressive may be asymptomatic at first, but cardiac changes occur that eventually may lead to CHF in some large animals. Valvular incompetence from endocarditis, degenerative changes, RCT, or other causes results in volume overload of the recipient chamber. Initially the output of the chamber is increased to maintain forward output, but the increased volume of the recipient chamber leads to compensatory dilation and a mild elevation in pressure. Compensatory hypertrophy may also result. In the later stages of valvular regurgitation, contractile function of the volume-overloaded chamber may diminish, leading to further elevation of pressure and decreased compliance. In the case of severe AR and MR, this causes elevation of left atrial pressure and eventually pulmonary venous hypertension. PAWP is higher at rest and during exercise in horses with moderate MR.[132] With severe TR, right atrial pressure or CVP increases. Increased myocardial oxygen consumption is a natural sequela, and biventricular failure can ensue.

If valvular heart disease is acute in onset, as with major RCT of the mitral valve, the regurgitation and volume overload are imposed on the left atrium, which cannot dilate and adapt acutely to the increased diastolic filling. The sudden hemodynamic change leads to pulmonary venous hypertension and acute pulmonary edema. However, most horses with MR do not have acute fulminant pulmonary edema. Instead, chronic pulmonary hypertension leading to subtle

respiratory signs associated with interstitial pulmonary edema and the subsequent development of right-sided CHF are common in horses with severe MR.[110] In one study, 12 of 14 horses with CHF had jugular distentions or pulsations, 10 had abnormal lung sounds (crackles), and 9 had a cough.[133]

Bacterial endocarditis of the mitral or tricuspid valve may lead to RCT. Mitral RCT has been reported in adult horses and foals with bacterial endocarditis, leading to acute left-sided CHF.[109] In addition to the hemodynamic load placed on the heart from an incompetent valve, bacterial endocarditis also results in disseminated sepsis. The vegetations are made up of layers of fibrin, blood cells, necrotic tissue, and bacteria and are relatively resistant to short-term antimicrobial therapy. Disseminated sepsis may be the cause of death or the reason for culling of the animal. Myocardial necrosis of a papillary muscle was associated with mitral chordal rupture in one foal.[109]

Epidemiology

Acquired valvular heart disease is common in large animals, involving 356 of 1557 horses (22.9%) in one abattoir survey.[92] Endocarditis, one form of valvular heart disease, was reported in 4% of cattle in another study.[134] Bacterial endocarditis most commonly affects the tricuspid valve in cattle but has been reported on the pulmonic, mitral, and aortic valves as well.[98,111,115,116] Most cases of tricuspid valve bacterial endocarditis have been reported in horses with septic jugular vein thrombophlebitis.[97,100,135] Tricuspid valve endocarditis has also been reported in a horse with a VSD.[80] Aortic and mitral valve endocarditis are most common in horses, occurring with nearly equal frequency.[99,100] In the largest survey of acquired valvular heart disease in horses, the aortic valve was affected most commonly with degenerative valve changes, followed by the mitral valve, tricuspid valve, and (uncommonly) pulmonic valve.[92] Not all valvular lesions are associated with incompetency of the valve. Degenerative valvular changes, particularly changes involving the aortic valve, are seen more commonly in older horses.

Necropsy Findings

Acquired valvular disease is associated with finding nodular thickening, fibrous bands, valve fenestrations, rupture of mitral valve chordae tendineae, fibrinous

masses typical of endocarditis, or combinations of these lesions on postmortem examination. There may be associated or secondary changes varying from enlargement of a chamber or vessel to degeneration, inflammation, and fibrosis. Enlargement (primarily dilation) of the chamber receiving the regurgitant flow, in addition to enlargement (primarily dilation) of the chamber or vessel from which the regurgitant flow arises, is commonly detected. Jet lesions, usually found in the receiving chamber, are associated with the high-velocity turbulent regurgitant blood flow.

Subcutaneous edema, congestion and mottling of the liver, and increased pericardial, pleural, or peritoneal fluid may be present and indicate CHF. Ascites associated with CHF is uncommon in large animals, particularly in horses. A primary source of chronic or active infection, along with evidence of bacterial embolization, may be seen in cattle with endocarditis but is rare in horses.

Treatment and Prognosis

Treatment and prognosis of acquired valvular heart disease depend on the cause, onset, duration, and severity of the lesion. In general, the prognosis is guarded to poor when evidence of valvular incompetence includes tachycardia, exercise intolerance, signs of CHF, or echocardiographic evidence of severe chamber enlargement. Degenerative valve disease may be asymptomatic except for a cardiac murmur, or it may be mild, but it generally is slowly progressive and therefore historically has been given a guarded prognosis. A more accurate prognosis for horses with murmurs can now be obtained from a complete echocardiographic examination, including Doppler echocardiography.[10,26,118] The valve affected, the lesions detected on the valve leaflets, the degree of chamber enlargement and volume overload detected, the echocardiographic assessment of myocardial function, and the severity of the regurgitation determined with Doppler echocardiography, coupled with the animal's age and intended use, can be used to formulate a prognosis.[10,26,118] Valvular regurgitation associated with no detectable abnormalities, valvular prolapse, and mild valvular thickening usually has a fair to good prognosis if the amount of valvular regurgitation is small.[10,26,118,136,137] Individuals with RCT, flail valve leaflets, and marked valvular thickening usually have moderate to severe regurgitation, which is likely to progress more rapidly and usually warrants a guarded to poor prognosis.[10,26,110,118,138] MR is the most likely valvular insufficiency to be associated with clinical signs of cardiovascular disease, whereas primary AR and

TR infrequently result in the development of CHF or death of the animal, except in horses with severe AR. Bacterial endocarditis has a guarded to grave prognosis, even with long-term antibiotic therapy, and frequently results in sudden death of the animal, although bacteriologic cures are possible. When a bacteriologic cure occurs, severe scarring of the affected valve ensues. The severity of the valve damage depends on the size of the original endocarditis lesion. This scarring can lead to rapid progression of the regurgitation and, ultimately, result in the animal's demise.

Despite the guarded long-term prognosis, palliative therapy can be applied for most forms of acquired valvular heart disease. Bacterial endocarditis is treated with long-term administration (ideally intravenously) of bactericidal antimicrobials, the choice of which is based on blood culture and sensitivity results. Continuous IV infusion of antimicrobials is the ideal initial treatment when feasible. In cattle, initial therapy is directed at the likelihood of a gram-positive infection. Combination antibiotic therapy consisting of penicillin and an aminoglycoside is recommended for broad-spectrum coverage in a horse until the results of culture and sensitivity testing are available. Using rifampin at an oral (PO) dose of 5 mg/kg twice daily in combination with another antibiotic with appropriate spectrum has improved the short-term outlook for large animals with bacterial endocarditis. Clopidogrel (2 mg/kg/day PO) has largely replaced aspirin and subcutaneous SC low-dose heparin in the horse in patients with valvular endocarditis in an attempt to prevent platelet adhesion and increased size of the valvular mass. In ruminants however, aspirin (100 mg/kg/day PO) and subcutaneous (SC) low-dose sodium heparin (30 to 40 units/kg twice daily) continue to be used. Early diagnosis and aggressive treatment with the appropriate antimicrobials for a prolonged period are important for successful treatment of bacterial endocarditis. The long-term outcome for successfully treated cases is still poor because the scarring that results as the endocarditis lesion heals may lead to severe valvular regurgitation and death of the animal, particularly with left-sided bacterial endocarditis lesions.[26,100–102,139] Compliance and economics are also major drawbacks in treating endocarditis.

The hemodynamic consequences of valvular heart disease (volume overload or CHF) may be improved by using diuretics. Furosemide has been used most commonly at a dose of 1 mg/kg as needed. With the low bioavailability of PO furosemide, IV administration is preferred to obtain the maximal diuretic effect.[140] Digoxin can be used to improve contractility when CHF has occurred. Conditions such as AR or MR may show little or no long-term improvement,

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although many individuals improve for 2 to 6 months or more, before the CHF becomes refractory to treatment. Administration of a maintenance dose of digoxin at 2.2 µg/kg IV twice daily or 11 µg/kg PO twice daily has resulted in therapeutic plasma digoxin concentrations and clinical improvement in horses with CHF, with no significant adverse effects (Box 30.1).[141] Loading doses are rarely used because of problems with digoxin toxicity.[142] An IV loading dose of 12 to 14 µg/kg can be used in horses but must be divided into three administrations, followed by a maintenance dose of 6 to 7 µg/kg daily.[143] Digoxin is administered IV to cattle at a loading dose of 22 µg/kg followed by a maintenance dosage of 11 µg/kg three times daily or, preferably, at an infusion rate of 0.86 µg/kg/h.[144] Although the 11 µg/kg IV tid dosing may slightly increase the risk of digoxin toxicity, it is more practical than the q4h administration of 3.4 µg/kg IV.

Box 30.1

Guidelines for Digoxin Therapy in Horses and Cattle

Horses

Priming dose IV: 4.4−7.5 µg/kg q12h for 2 doses (rarely used)
Maintenance dosage IV: 2.2 µg/kg q12h (most commonly used)–3.75 µg/kg q12h
Maintenance dosage PO: 11 µg/kg q12h (most commonly used)–17.5 µg/kg q12h

Cattle

Priming dose IV: 22 µg/kg
Maintenance dosage IV: infusion of 0.86 µg/kg/h, or give 11 µg/kg tid

IV, Intravenous; *PO,* by mouth; *tid,* three times daily.

Horses benefit from the use of vasodilators, as do other species. Clinical and echocardiographic improvement has been seen in horses with moderate MR or AR treated with the angiotensin-converting enzyme (ACE) inhibitor, benazepril at 1 mg/kg PO twice daily.[145] Benazepril at 0.5 mg/kg PO once daily was shown to be effective at inhibiting serum ACE activity in healthy horses compared with other ACE inhibitors.[146] Quinapril at 120 mg/horse/day increases stroke volume and cardiac output after 8 weeks of treatment in horses with MR.[147] Clinical and echocardiographic improvement has been seen in horses with CHF. Although enalapril appeared effective in horses with moderate to severe MR or AR and in horses with CHF, at a dose of 0.5 mg/kg PO twice daily, oral enalapril (single-dose or once-daily administration) did not significantly reduce ACE activity in normal horses and ponies.[148,149] Ramipril at 50 µg/kg daily PO was beneficial in treating one horse with CHF.[150] Clinical improvement has also been seen with hydralazine at 0.05 to 1.5 mg/kg PO twice daily. Although the short-term outlook may be improved with the use of these cardiovascular drugs, the prognosis is guarded for long-term survival or production.

Prevention and Control

Many causes of acquired valvular heart disease cannot be controlled. Appropriate therapy for chronic active infections and careful attention to asepsis with IV medication and other invasive procedures may help prevent endocarditis and possibly nonvegetative valvulitis. Effective parasite control measures may eliminate some predisposing causes of valvular heart disease, such as trauma to heart valves, microembolism, or infarction in horses.

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Brisket Disease, Cor Pulmonale, and Pulmonary Hypertension

Definition and Etiology

Cor pulmonale is a term used to refer to the effect of lung dysfunction on the heart and is therefore a secondary form of heart disease. Regardless of the cause, the underlying feature is pulmonary hypertension that leads to right ventricular hypertrophy, dilation, or failure. The primary cause of cor pulmonale in cattle is high-mountain disease (HMD), also called *high-altitude disease* or *brisket disease*, which leads to hypoxic vasoconstriction from high-altitude dwelling. Some cattle are resistant to developing cor pulmonale when grazed at high altitudes, but others are genetically much more susceptible.[151,152] Pneumonia, lungworm, and prolonged exposure to cold temperatures contribute to the development of HMD. The disease is worsened by ingestion of locoweed (*Oxytropis* and *Astragalus* spp.).[153,154] Chronic pulmonary disease such as bronchopneumonia or lungworm infection in cattle can also result in cor pulmonale.[155] In the horse, right-sided heart dysfunction (e.g., decreased cardiac output, increased right ventricular end-diastolic pressure, increased right atrial pressure or CVP, jugular venous distention, or subcutaneous edema) associated with chronic pulmonary disease is rare but may be more common than previously recognized. However, right-sided heart dysfunction associated with pulmonary hypertension and left-sided heart dysfunction is a common cause of CHF.

Clinical Signs and Differential Diagnosis

Frequently the primary presenting clinical sign of brisket disease is subcutaneous edema of the brisket, ventral thorax, submandibular area, and occasionally the limbs. Lethargy, weakness, bulging eyes, diarrhea, collapse, and death occur.[151] Jugular venous distention or pulsations may be present. Dyspnea and tachypnea are frequent. Tachycardia is present, and a gallop rhythm may be auscultated. Splitting of the second heart sound (S_2) is a variable finding. Pulmonary hypertension may accentuate the separation of the aortic and pulmonic valve closures, producing audible splitting of S_2 that is most noticeable during

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inspiration. In some horses with moderate or severe equine asthma (also known as recurrent airway obstruction [RAO]) and increased vascular impedance, pulmonic valve closure occurs early and only a single S_2 is audible.[156]

A cardiac murmur may be auscultated, caused either by TR or a pulmonic valve ejection murmur. The murmur of TR, which is secondary to right ventricular dilation, is regurgitant or plateau shaped, with the PMI over the right thorax or, less frequently, the left second intercostal space. The pulmonic valve ejection murmur, found less commonly, is audible as a crescendo-decrescendo murmur at the left heart base.[6] Pleural or pericardial effusion is not common with cor pulmonale.[157] In horses with RAO leading to cor pulmonale, tachypnea, labored breathing, coughing, and exercise intolerance are common complaints. Wheezes are usually auscultated bilaterally in the thorax of affected horses.

These clinical signs are not specific for brisket disease (cor pulmonale) and largely reflect right-sided heart failure. Other considerations when signs of right-sided heart failure are present should be bacterial endocarditis or TR from any cause, cardiomyopathy, cardiac lymphosarcoma or other thoracic neoplasms, traumatic reticulopericarditis or other causes of pericarditis, left-sided heart failure, pleuritis or pleural effusion, and congenital pulmonic valve stenosis (rare). With pericarditis, heart sounds may be muffled, or the characteristic “washing machine murmur/rub” may be audible. Left-sided heart failure is frequently accompanied by pleural effusion, pulmonary edema, and weak peripheral pulses. In horses, however, expectoration of pulmonary edema fluid occurs only with sudden onset of severe left-sided heart failure. In horses with chronic left-sided heart failure, tachypnea, coughing, poor recovery after exercise, and harsh lung sounds may be all that is detected.

Clinical Pathology

A complete blood cell count (CBC) may reveal a neutrophilia in cases of cor pulmonale caused by primary lung disease. Radiography of the thorax reveals primary pulmonary disease such as bronchopneumonia, bronchiectasis, or chronic bronchitis in cattle that have developed this disease at low altitudes. Radiographic findings in horses with RAO usually reveal an interstitial pattern. Arterial blood gases demonstrate the presence of hypoxia and may also show hypercapnia. Transtracheal wash fluid cytology and bacterial culture may provide evidence of the cause of the primary lung disease. Fecal sedimentation helps rule out parasitic bronchitis or pneumonia. Electrocardiographic findings

are not specific. An echocardiogram may provide further evidence of pulmonary hypertension and right-sided heart dysfunction by showing right ventricular hypertrophy and dilation, increased septal thickness, and abnormal septal motion (Fig. 30.13).[158,159] Dilation of the pulmonary artery is also detected with 2D echocardiography and is a sensitive indicator of pulmonary hypertension or increased flow through the pulmonary artery. A dilated pulmonary artery has been reported in horses with cor pulmonale and in horses with acute pulmonary obstruction from RAO.[159,160] Cardiac catheterization reveals elevated pressure in the pulmonary artery, right ventricle, and right atrium. Elevation of right ventricular end-diastolic pressure is a sign of right ventricular failure.

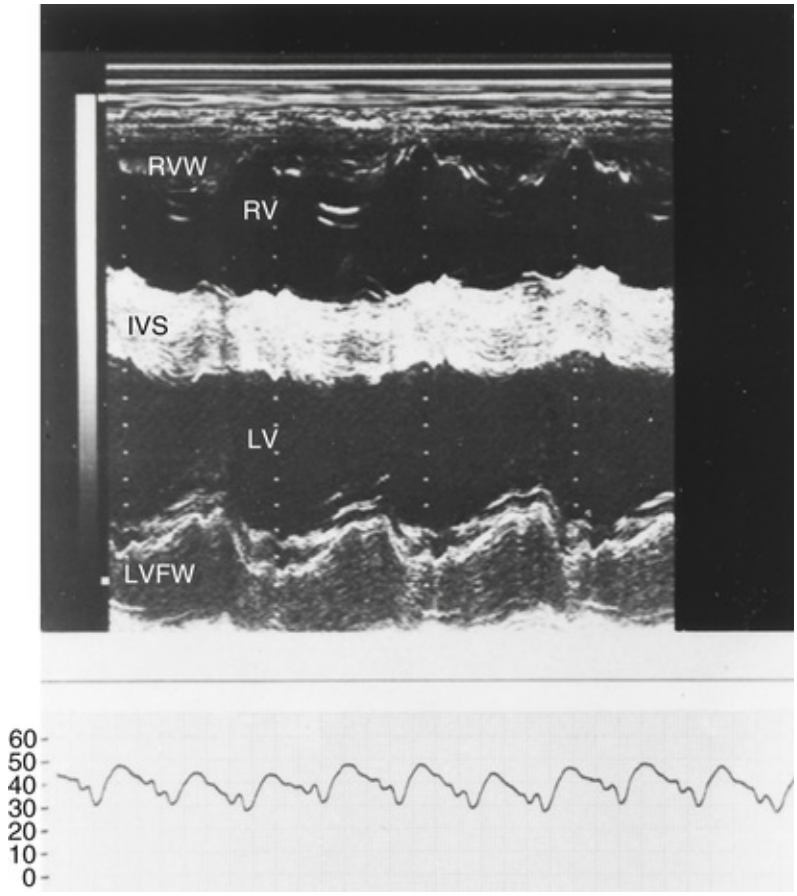


FIG. 30.13 M-mode echocardiogram and pulmonary artery pressure (PAP) curve obtained from a cow with pulmonary hypertension and cor pulmonale. The echocardiogram shows mild thickening of the right ventricular wall *(RVW)* and interventricular septum *(IVS),* dilation of the right ventricle *(RV),* and abnormal septal motion. *LV,* Left ventricle; *LVFW,* left ventricular free wall. The PAP curve demonstrates elevated systolic and diastolic pressures. (PAP curve in millimeters of mercury [mm Hg].)

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Pathophysiology

Pulmonary arteriolar constriction is the response to hypoxia from high-altitude dwelling or pulmonary disease. The response to hypoxia varies depending on the amount of smooth muscle in the pulmonary arteries. In cattle, increased pulmonary vascular resistance and pulmonary hypertension frequently develop. Chronic pulmonary artery hypertension causes a pressure overload on the right ventricle, which responds to the increased workload with hypertrophy, dilation, or failure, depending on the speed with which the condition develops. The disease is progressive, and at some stage the right ventricular myocardium is unable to compensate, dilates, and fails. With failure come the typical signs of jugular venous distention and development of subcutaneous edema. Chronic right-sided heart failure may result in diastolic dysfunction of the left ventricle.

Epidemiology

The disease is more common in cattle than in other animal species, especially when cattle are kept at altitudes over 6000 feet, where the incidence has been estimated at 0.5% to 5% in cattle native to high altitude.[151,152] In cattle adapted to low altitude and moved to higher altitude for grazing, however, the incidence is much higher.[151,152,161] Mainly calves and yearlings are affected. A genetic predisposition to develop pulmonary arterial constriction when subjected to hypoxia at high altitude is present in many breeds. Some breeds and pedigrees within breeds are more resistant than others to the effects of high altitude, and the inheritance appears to be complex.[151,152] More cases of HMD are detected in the fall and winter and are due to cold weather exacerbating pulmonary hypertension.[152] Ingestion of swainsonine contained in locoweed (*Oxytropis* and *Astragalus* spp.) also predisposes cattle to right-sided heart failure at high altitudes by causing toxic myocardial damage.[153] Pulmonary hypertension has also been detected in cattle fed ionophores at high altitude.[151]

Necropsy Findings

There is evidence of right-sided heart failure (e.g., subcutaneous edema) in the submandibular area, brisket, and ventral abdomen. Findings include dilation and

hypertrophy of the right ventricle, congestion of the liver, and ascites. Perirenal edema, mesenteric edema, and pleural effusion are often present. The lung may have evidence of concurrent pneumonia, bronchitis, bronchiectasis, or emphysema. Lesions of locoweed toxicity may be found in other organs in cattle.[153] Lesions of chronic interstitial pulmonary disease are found in horses with equine asthma.

Treatment and Prognosis

Removing the animal from high altitude, treating the primary lung disease, and administering oxygen may help eliminate the hypoxia and thus the pulmonary hypertension. Cor pulmonale from high altitude is potentially reversible when the animal is returned to a lower altitude. However, cattle with other lung disease and a mean PAP of 50 to 55 mm Hg rarely have their mean PAP return to an acceptable level for high-altitude living.[151] The heart failure can be treated with digoxin and diuretics. Beneficial effects of vasodilator therapy have not been documented. Once heart failure signs have developed, the prognosis is guarded even with appropriate treatment. Removing the horse from the environment inducing equine asthma is critical to treating the cor pulmonale. A more detailed discussion of the treatment and management of horses with equine asthma can be found in Chapter 31.

Prevention and Control

Selection of breeding stock with low or normal PAPs at altitudes above 5000 feet (mean PAP <35 mm Hg) helps eliminate the predisposing genetic susceptibility to the effects of hypoxia of high altitude.[151,152,161] Recently, more specific guidelines have been formulated for the selection of cattle to be kept at high altitudes.[151] Cattle older than 12 months of age with a mean PAP of less than 41 mm Hg at over 5000 feet elevation are good to select for breeding stock for high altitudes and should have a low risk of HMD. Cattle with a mean PAP of 49 or higher at any elevation are at high risk for developing HMD and should not be selected as high-altitude breeding stock.[151] Cattle with a mean PAP in between these two guidelines are at risk and should be used with caution at high altitudes.[151] The disease can also be controlled by removing susceptible animals from high altitude and preventing locoweed ingestion. Herd health practices such as avoiding crowding and poor ventilation and using appropriate

vaccinations to reduce the incidence of pulmonary disease help reduce the incidence of other causes of cor pulmonale.

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Myocardial Disease: Myocarditis and Cardiomyopathy

Definition and Etiology

Myocarditis is inflammation of the myocardium caused by bacterial, viral, or parasitic organisms or thromboembolic disease caused by these organisms. In large animals, recognized bacterial causes include *Staphylococcus aureus, Streptococcus equi, Clostridium chauvoei,* and *Mycobacterium* spp. Myocarditis can also occur after bacteremia, septicemia, pericarditis, or endocarditis, regardless of the causative agent. Known viral causes of myocarditis include foot-and-mouth disease, equine infectious anemia, equine viral arteritis, equine influenza, and African horse sickness. Parasitic causes of myocarditis may include strongylosis[162] or onchocerciasis in horses and toxoplasmosis, cysticercosis, or sarcocystic infection in ruminants.[163,164] Currently it is thought that infection with the spirochete *Borrelia burgdorferi* may be a cause of myocarditis in domestic animals, as it is in human beings.[165] Cardiomyopathy is a subacute or chronic disease of the ventricular myocardium that occurs without anatomic valvular disease, congenital malformations of the heart or vessels, or pulmonary disease. In large animals, dilated cardiomyopathy is the most common cardiomyopathy. However, hypertensive cardiomyopathy occurs in horses associated with chronic renal disease, pain associated with chronic laminitis, and to some extent in ponies with equine metabolic syndrome (EMS) where left ventricular hypertrophy has been detected.[166] Dilated cardiomyopathy is associated with ventricular dilation, increased ventricular mass, and decreased systolic function. Although the cause is frequently undetermined,[126,167,168] several conditions have been related to or identified with cardiomyopathy. An inherited cardiomyopathy thought to be linked to the red Holstein gene has been found in Holstein-Friesian cattle in Canada, Australia, the Netherlands, and Switzerland.[169–171] There is also a cardiomyopathy associated with a curly hair coat in polled Herefords and in Japanesse black calves.[172–173] Cardiomyopathy has been associated with ingestion of monensin, lasalocid, salinomycin, gossypol, *Cassia occidentalis,* and *Phalaris* spp. Vitamin E and selenium deficiency, copper deficiency, excessive molybdenum, or high sulfates

(secondary copper deficiency) may cause cardiomyopathy.[174–184] Consumption of plants in the Acer family and several other plants cause myocardial injury, myocarditis and cardiomyopathy.[185,186] Myocardial infiltration by neoplasia, such as lymphosarcoma or fibrosarcoma, also may cause cardiomyopathy. A fibrofatty infiltration of the right ventricle and interventricular septum similar to arrhythmogenic right ventricular dysplasia occurs in horses.[187–189] Envenomation associated with rattlesnake bite can result in myocardial necrosis and secondary cardiomyopathy.[190–192] The most common cause of cardiomyopathy in horses is probably myocarditis, although the inciting insult is usually difficult to identify.

Clinical Signs and Differential Diagnosis

The manifestations of myocarditis are highly variable depending on the extent of the disease, location of the inflammation within the myocardium, and associated systemic illness. Myocarditis can easily be missed because of the lack of specific cardiac signs or the predominance of signs related to the organ system with primary involvement (e.g., strangles in horses or mastitis in cattle). Animals suspected of having myocarditis are often febrile or have a recent history of fever and may have tachycardia. The elevated heart rate may be sinus tachycardia or other paroxysmal or sustained supraventricular or VA because cardiac arrhythmias are common. Premature beats are also often detected in large animals with suspected myocarditis and may be present in animals with a normal or increased heart rate. Occasionally, acute myocarditis is associated with auscultation of a pronounced gallop rhythm or a cardiac murmur of TR or MR. Jugular venous distention, other signs of CHF such as peripheral edema, and signs of circulatory collapse may be present. Horses may show evidence of myalgia, reluctance to move, or exercise intolerance. With these signs it may be difficult to distinguish myocarditis from colic, respiratory disease, lameness, or septicemia. If signs are more clearly cardiac (e.g., murmur, arrhythmia, jugular venous pulsations), the practitioner should rule out endocarditis, cardiomyopathy, cardiac neoplasia, and CHF from another cause.

The clinical signs associated with dilated cardiomyopathy can also be variable but are usually more clearly associated with heart disease. Most animals have signs of cardiac failure, such as peripheral edema and jugular venous distention or pulsations (Fig. 30.14). Auscultation frequently reveals tachycardia, gallop rhythm, muffled heart sounds, or a cardiac arrhythmia. Cardiac murmurs of TR

or MR are usually present secondary to the ventricular dilation. Breath sounds are increased, tachypnea is present, and percussion of the thorax frequently reveals signs of pleural or pericardial fluid. Occasionally, respiratory distress is evident with hyperpnea, dyspnea, coughing, and presence of a bloody froth at the nostril. Nonspecific signs of cardiomyopathy, such as exercise intolerance, syncope, diarrhea, or anorexia, may also be present. In cattle, decreased milk production and abomasal displacement have been associated with dilated cardiomyopathy.[169] Palpable liver enlargement has also been reported in cattle with cardiomyopathy.[170] Most affected cows develop clinical signs within 3 months of calving.[170]



FIG. 30.14 Holstein cow with cardiomyopathy showing signs of congestive heart failure (submandibular and brisket edema, jugular venous distention, and pulsations).

The clinical signs of hypertrophic cardiomyopathy in horses are usually

primarily referable to the underlying disease. Tachycardia is common but is also expected in many horses with chronic laminitis and renal failure. Both of these diseases in their chronic stages coupled with tachycardia should prompt obtaining a blood pressure measurement to determine if echocardiographic evaluation is indicated.

Sudden death can be a feature of myocarditis and dilated or hypertensive cardiomyopathy, and it frequently follows stress or exercise. Recumbency, collapse, and sudden death are common presenting signs in animals with ionophore toxicosis, envenomation, and consumption of large amounts of the seeds containing hypoglycin A from predominately trees of the *Acer* species.[174–180,182,184,185,190,191] In many animals with inherited cardiomyopathy, death occurs within 6 months of age.[171–173] In Holstein-Friesian cattle with suspected inherited cardiomyopathy, heart failure and death may not occur until cattle are 2 to 4 years old.[169,170] Other acquired causes of cardiomyopathy can occur at any age.

When animals show clinical signs of dilated cardiomyopathy, many differential diagnoses should be considered. If the animal is young, other congenital heart defects, cor pulmonale, and nutritional myodegeneration should be considered. In adults, bacterial endocarditis, cardiac neoplasia, thoracic abscess, pericarditis, pleuritis, and diaphragmatic hernia may also have similar clinical manifestations. Although the cause of dilated cardiomyopathy may be difficult to determine, nutritional (vitamin E, selenium, or copper deficiency); toxic (monensin, gossypol, salinomycin, lasalocid, hypoglycin A, *Cassia* spp., or *Phalaris*); infectious (viral, bacterial, or parasitic); or drug-induced causes should be investigated.

Clinical Pathology

Depending on the cause of the myocardial disease, the clinicopathologic findings may vary. Routine CBC may be normal, or a neutrophilic leukocytosis may be present. No consistent changes are expected in the serum chemistry profile, but serum albumin concentration may be slightly decreased, and serum urea nitrogen, creatinine, γ-glutamyltranspeptidase (GGT), sorbitol dehydrogenase (SDH), and bilirubin concentrations may be increased because of congestive liver disease when signs of CHF are present. Serum concentrations of creatine kinase (CK) and lactic dehydrogenase (LDH) may be elevated, but hepatic and skeletal muscle contribution to these elevations cannot be ruled out. Large

elevations of the myocardial isoenzymes of CK (myocardial bound [MB]) and LDH (LDH_1) were detected in one outbreak of monensin toxicosis[177] and have been detected in other horses with myocardial necrosis of unknown etiology. A better indication of myocardial disease may be the elevation of cardiac troponin I (cTnI), which has been detected in horses with acute gastrointestinal (GI) disease, as well as in many types of myocardial diseases.[185,193,194] Marked elevations of cTnI have been reported in a horse with multiform VT and myocardial necrosis of unknown cause,[195] as well as in a horse with VT and aortic septal rupture.[196] Elevations of cTnI were detected in horses following exposure to lethal and sublethal concentrations of monensin and lasalosid.[183,184,197] Analysis of pericardial or pleural fluid reveals a transudate with low protein concentration (<2.5 g/dL) and cellularity (white blood cell [WBC] count < 2500/μL), with the predominant cell type being mononuclear cells unless the myocarditis is an extension of pericarditis. Serum should be tested for serologic evidence of bovine leukosis (BLV) infection in adult cattle, α-tocopherol, glutathione peroxidase, and copper concentrations. Whole blood selenium levels should be determined. In infectious myocarditis or inherited cardiomyopathy, results of these tests will most likely be normal. A negative BLV test result essentially eliminates lymphosarcoma as a cause of the myocardial disease; a positive test result does not confirm a causal relationship. In horses, serum should be tested for serologic evidence of a variety of equine viruses, particularly influenza, equine viral arteritis, and herpesvirus. Hemoglobinuria, if present, suggests consideration of monensin, gossypol, or nutritional myodegeneration as the cause of myocardial disease. Arterial blood oxygen tension may be reduced below 80 mm Hg in animals with myocardial disease.

An ECG may demonstrate sinus tachycardia or other cardiac arrhythmias; the frequency and severity of these arrhythmias are best demonstrated with continuous ECG monitoring. There may be some evidence of conduction abnormalities in the base-apex lead, but these findings are not specific for myocardial disease. Echocardiography may be normal in animals with myocarditis, or the abnormalities detected may be caused by the arrhythmias present. A small left ventricular internal diameter, thickened left ventricular free wall and interventricular septum, small aortic root diameter, and decreased FS may be detected in animals with sustained VT and decreased cardiac output (Fig. 30.15). A small left ventricular internal diameter, thickened left ventricular free

wall, interventricular septum, and right ventricular free wall with an increased relative and mean wall thickness and left ventricular mass is present echocardiographically in horses with hypertensive cardiomyopathy.[166] More frequently, however, there is increased ventricular chamber size, decreased thickness of the interventricular septum and left ventricular free wall, and decreased myocardial function (decreased FS, decreased EF, and myocardial dyskinesis), especially in more severe cases of myocarditis and in animals with dilated cardiomyopathy (Fig. 30.16 and Video 30.6). In humans with myocarditis there may be evidence of abnormal left ventricular wall motion, paradoxical motion of the interventricular septum, or an echo-free pericardial space.[174] Additional echocardiographic features of dilated cardiomyopathy are increased end-systolic and end-diastolic dimensions of the left and right ventricles (see Fig. 30.16), increased left atrial size, and an increased left atrial–to–aortic root dimension ratio. There may be abnormal mitral valve closure (increased EF slope) and increased separation of the septal mitral valve leaflet and interventricular septum. A decreased aortic root diameter may be detected along with a shortened ET in animals with low-output, left-sided heart failure. An enlarged pulmonary artery indicative of pulmonary hypertension (Fig. 30.17) may also be present.

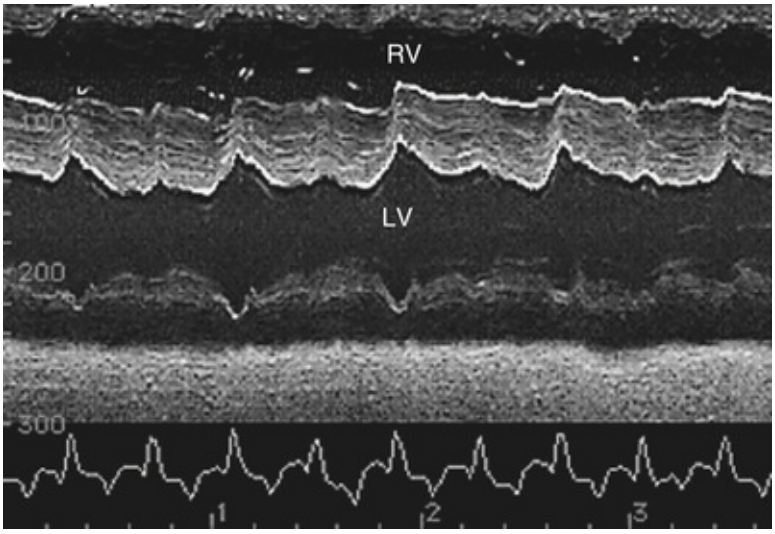


FIG. 30.15 M-mode echocardiogram of the left ventricle *(LV)* obtained from a mare with sustained uniform ventricular tachycardia. Note the small end-diastolic and end-systolic dimensions of the left ventricle and the little variation between systole and diastole in this dimension. *RV,* Right ventricle.

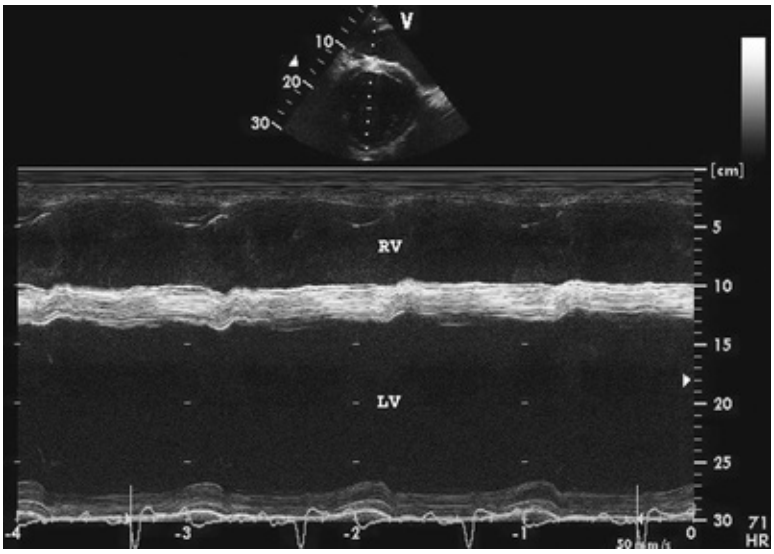


FIG. 30.16 M-mode echocardiogram of the left ventricle obtained from a mare with cardiomyopathy and severe left ventricular dysfunction. Note the large end-diastolic dimension of her left ventricle *(LV),* the thin interventricular septum and left ventricular free wall, and the poor left ventricular contractility. The fractional shortening in this mare varied from 2% to 8%. *RV,* Right ventricle.

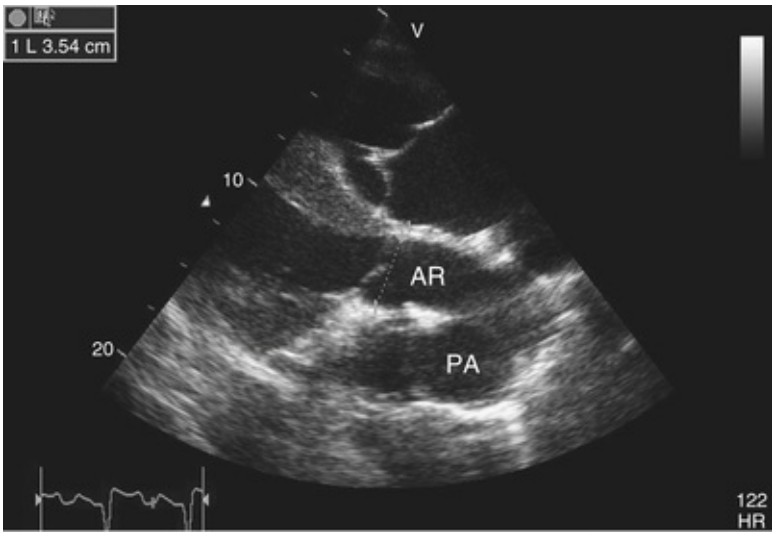


FIG. 30.17 Two-dimensional echocardiogram of the aorta *(AR)* and main pulmonary artery *(PA)* obtained from a foal with cardiomyopathy and severe mitral and TR. The pulmonary artery is larger than the aorta, indicative of pulmonary hypertension and impending left-sided CHF. The

aorta measured 3.54 cm at its origin.

Cardiac catheterization may reveal elevated intracardiac pressures (right atrial, right ventricular, pulmonary artery, pulmonary capillary wedge, and left ventricular end-diastolic) in animals with dilated cardiomyopathy. Horses with acute infectious myocarditis may show hypotension and a narrow pulse pressure. Nuclear angiocardiography may be used to show decreased EF[50] in animals with myocardial disease.

Pathophysiology

The pathophysiologic changes associated with myocardial disease depend on the specific nature and extent of the disease. Acute myocarditis or angiopathic myocardial lesions[162] may go on to develop into idiopathic dilated cardiomyopathy. It is speculated that changes in cellular metabolism occur with either acute myocarditis or dilated cardiomyopathy, resulting in ECG abnormalities and reduced myocardial performance (reduced cardiac output). In an attempt to compensate for reduced cardiac output, circulating fluid volume is increased by activation of the renin-angiotensin-aldosterone system and arterial resistance is increased. These compensatory mechanisms frequently lead to only minor improvement in the cardiac output of the failing heart, and the increase in ventricular preload (venous return) and afterload (arterial resistance) may cause pulmonary edema and a further reduction in cardiac contractility. Ventricular dilation, further reduction in cardiac output, and signs of heart failure occur.

Epidemiology

The prevalence of acute myocarditis is difficult to estimate because frequently the disease goes undiagnosed, is mild or masked by disease in another organ system, or the animal recovers spontaneously. Similarly, it is difficult to assess the clinical significance of postmortem findings of myocardial inflammation and fibrosis. The morbidity of myocarditis in large animals is probably underestimated because it is rarely the cause of mortality and is associated with viral, bacterial, and parasitic infections that manifest without specific signs of cardiovascular disease.

Inherited cardiomyopathy has been reported in cattle in Japan, Australia, the Netherlands, Canada, and Switzerland, with the incidence in inbred populations

reaching 3% to 5%.[170,171] A familial form of dilated cardiomyopathy has also been reported in cattle in Sweden, Denmark, Australia, and the United Kingdom.[170] These cattle may be genetically linked by the presence of the red gene in Holstein-Friesian cattle.[169] Although in some cattle, inherited cardiomyopathy resulted in death by 6 months of age,[171,173] other cattle failed to show clinical signs until 2 to 6 years of age.[126,168,170,172] No sex predilection is recognized in inherited cardiomyopathy of cattle.

The morbidity and mortality from cardiomyopathy stemming from other causes in cattle and horses is not known. From the number of clinical reports, inherited cardiomyopathy seems to be more prevalent in cattle than in horses. Idiopathic dilated cardiomyopathy or cardiomyopathy secondary to viral or bacterial infections may be more common in horses and is a cause for the acute onset of CHF in horses of racing age.

Necropsy Findings

There may be no gross lesions associated with myocarditis. Depending on the relationship between death and the occurrence of myocarditis, microscopic examination of the myocardium may show increased fibrous tissue in the interstitium in the absence of inflammation, or there may be foci of inflammatory cells (typically mononuclear cells), variation in the cross-sectional area of the cardiac myocytes, degeneration of adjacent myocardial fibers, myocardial necrosis, and fibrosis. Replacement of the myocardium by fibroadipose tissue has been reported in horses that experienced unexpected sudden death and were thought to have arrhythmogenic right ventricular cardiomyopathy at postmortem examination.[187–189] Focal interstitial nephritis and fibrosis were reported in eight of nine Holstein-Friesian cattle with dilated cardiomyopathy in Scotland.[170] Often the inciting cause of myocardial necrosis in horses is unknown.[195] Samples of gastric or ruminal contents should be obtained and submitted for analysis of ionophores if ionophore toxicosis is suspected. Feed samples should also be obtained and submitted for ionophore analysis in these cases. Submitting the heart muscle itself for ionophore analysis is the best tissue for identifying toxicosis and is superior to gastric contents.[198]

On gross examination, the lesions of cardiomyopathy are recognized more easily as enlargement of the heart, which may be rounded to globose. Biatrial, biventricular, and pulmonary artery dilation are usually present. Patchy or

uniform streaks of myocardial pallor may be detected. In rare cases, one of the chambers or major vessels (usually pulmonary artery) may rupture. Generalized edema is frequently found as ascites (uncommon in horses), pericardial or pleural effusion, and edema of the mesentery and subcutaneous tissues. There may be evidence of vascular congestion of the liver, lungs, and spleen. The kidneys may be pale and swollen and have an irregular, granular, pitted surface.

Microscopically the lesions of cardiomyopathy are characterized as myocardial vacuolation and degeneration with necrosis and fibrosis. Calcification may be associated with these lesions. Occasionally there is increased vascularization with proliferative regeneration of myofibers. Loss of cardiac myocytes and replacement by fibro-fatty tissue occurs in horses with arrhythmogenic right ventricular cardiomyopathy.[187–189] In some cases of cardiomyopathy, no histopathologic abnormalities are found.

Treatment and Prognosis

Treatment of myocarditis includes treating the underlying causative agent if it is recognized and controlling complications such as arrhythmias, CHF, or shock. Thromboembolism is rarely a complication recognized in animals. Prompt administration of vitamin E may be beneficial to the survivors in cases of ionophore toxicosis. Performance animals should be rested. Corticosteroids may be beneficial in animals with severe toxemia, complicated arrhythmias, or intractable heart failure, but their use in early cases of myocarditis or in infections suspected of having a viral cause is controversial because viral recrudescence may occur. However, in many cases corticosteroids appear to have a beneficial effect. Prognosis is good if there are no signs of heart failure and if cardiac arrhythmias are managed successfully. Prognosis is guarded to poor if signs of CHF are present.

Therapeutic strategies currently used for treatment of dilated cardiomyopathy include positive inotropic agents (digoxin), diuretics, vasodilators, rest, and in some cases removal of pleural or abdominal fluid. The advantages of vasodilators (venodilators to relieve pulmonary edema and arterial dilators to reduce preload and afterload and improve contractility) in the treatment of cardiomyopathy are recognized in humans and small animals.[199]

Digoxin is the positive inotropic agent used almost exclusively in large animals but is contraindicated in animals with acute monensin toxicosis. A priming or loading dose can be used in horses with acute severe CHF, followed

by a maintenance dose, or more frequently, the horse is started on a maintenance dose from the onset of therapy. In horses, the drug can be administered PO or parenterally. In cattle, low bioavailability limits its use to the IV route of administration.[177] Guidelines for the use of digoxin are given in Box 30.1.[141,200,201] In general, maintenance dosages are used because of the lowered risk of adverse reactions. A peak and trough serum digoxin concentration should be obtained 3 to 5 days after digoxin therapy is begun, and the dosage should then be adjusted accordingly. Ideally, the trough and peak digoxin concentration should be between 1 and 2 ng/mL.

Dehydration, acid-base imbalance, and electrolyte abnormalities should be corrected before digoxin therapy. The dose of digoxin should be decreased in animals with elevated creatinine or blood urea nitrogen (BUN) until these values return to normal. In horses, the IV loading dose of digoxin should be administered slowly or divided and given at a rate of one third of the loading dose hourly until completion.[200] Alternatively, therapy can be initiated with the maintenance dose. Close monitoring of body weight, appetite, electrolyte concentrations, creatinine or BUN concentration, and cardiac rhythm is essential during therapy. Therapeutic drug monitoring with digoxin plasma concentrations can be helpful during initial therapy, when the volume of distribution of the drug and the patient's body weight may be in a state of flux. Samples for determination of peak serum digoxin concentrations should be obtained 1 to 2 hours after digoxin administration and should not exceed 2.5 ng/mL.[141,202]

The diuretic used most commonly in large animals is furosemide. It is administered parenterally at the rate of 1 mg/kg twice daily or as needed to control edema. Oral absorption of furosemide is poor or variable in horses.[140] A continuous-rate infusion of furosemide is recommended in horses when rapid profound diuresis is needed.[203] The half-life and diuretic effect of bumetanide, a sulfonamide diuretic, are shorter than those of furosemide in horses.[204] The PK/PD information about torsemide, a new loop diuretic that is much more potent than furosemide, indicates it may be a better diuretic for long-term diuresis in horses.[205] The recommended dosage is 0.5 to 1 mg/kg orally twice daily, which should be adjusted accordingly thereafter. Electrolyte concentrations and water consumption should be monitored closely in patients receiving diuretics.

The vasodilator used most frequently in horses in the United States is the ACE inhibitor benazepril. However, the cost of the ACE inhibitors varies wildly in

different countries, so other ACE inhibitors or hydralazine are often used because of cost and availability issues. Other ACE inhibitors that have been used but are less effective include quinapril, ramipril, and enalapril. These vasodilators have resulted in clinical improvement in animals treated for CHF. Benazepril at 1 mg/kg PO twice daily has recently been shown to be most effective at suppressing ACE activity.[145,150] Quinapril at a dose of 0.25 mg/kg PO once daily has also been shown to increase stroke volume and cardiac output in horses with MR after 8 weeks of therapy.[146] Ramipril resulted in clinical and echocardiographic improvement of a horse with CHF at a dosage of 50 µg/kg daily PO.[149] Enalapril has been used at a dose of 0.5 mg/kg PO twice daily in the management of horses with moderate to severe MR or AR and in the treatment of horses with CHF. However, after a single 0.5-mg/kg oral dose of enalapril, neither enalapril nor enalaprilat was detectable in the serum, and ACE activity was not significantly reduced.[147] Hydralazine is administered PO at a dose of 0.5 to 1.5 mg/kg twice daily.

Control of cardiac arrhythmias should be attempted in animals that are hemodynamically unstable or threatened with development of worsening arrhythmias. Quinidine is usually the drug of choice for control of atrial and VA in cattle and is one of the drugs of choice in horses. Procainamide, lidocaine, propafenone, phenytoin, and sotalol have also been successful in treating VA in horses (Table 30.3). Although flecainide has been used successfully in horses, its use is not recommended due to the risk of sudden cardiac arrest. Although administration is limited to the IV route in cattle, oral or IV administration in horses results in adequate plasma concentrations to control arrhythmias. Quinidine is administered IV by infusion or divided bolus injections as shown in Box 30.2.

TABLE 30.3

Drug Therapy for Ventricular Tachycardia

Drug	Usual Dose
Bretylium tosylate	0.5-5 mg/kg IV for life-threatening ventricular tachycardia or ventricular fibrillation
Dexamethasone	0.05-0.22 mg/kg, IV or IM
Furosemide	1-2 mg/kg IV as needed for pulmonary edema
Lidocaine	*Equine:* 0.25-0.5 mg/kg slowly IV every 10-15 min; repeat up to a total of 1.5 mg/kg
	Bovine: 0.5 mg/kg, slowly IV; can repeat in 15 min
Magnesium SO_4	IV infusion at 1 g/min to effect, up to a maximum of 25 g
Procainamide	1 mg/kg/min IV to a maximum of 20 mg/kg

Propafenone	*Equine:* 2 mg/kg PO tid
	0.5-1 mg/kg in 5% dextrose slowly IV over 5-8 min for refractory sustained ventricular tachycardia (not available in United States)
Propranolol	0.03 mg/kg IV
Quinidine gluconate (IV)	1.5-2 mg/kg boluses every 10 min, not to exceed a total dose of 12 mg/kg
Sotalol	*Equine:* 1-4 mg/kg PO bid; 1 mg/kg IV results in high plasma concentrations (dose to treat ventricular arrhythmias needs to be determined)

bid, Twice daily; *IM,* intramuscular; *IV,* intravenous; *PO,* by mouth; *tid,* three times daily.

Box 30.2

Quinidine Administration in Horses and Cattle

Horses

IV: 1.5–2 mg/kg every 10 min until conversion or desired effect, not to exceed a total dose of 12 mg/kg

PO: 22 mg/kg (1 g/100 lb of body weight) q2h until conversion or desired effect, not to exceed a total dose of 132 mg/kg q2h. If quinidine plasma concentrations cannot be obtained promptly, a total dose of 88 mg/kg q2h should not be exceeded.

Cattle

IV: 48 mg/kg infused IV over a 4-hr period

IV, Intravenous; *PO,* by mouth.

When quinidine is used IV, concurrent IV administration of a balanced electrolyte solution at the rate of 3 to 4 mL/kg/h may be desirable to maintain blood pressure in animals with severely compromised cardiovascular status.

Prognosis for animals with dilated cardiomyopathy is poor. Echocardiography is useful in determining the severity of the myocardial dysfunction and in formulating a prognosis. The results of the initial echocardiographic examination

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were the best prognostic indicator of survival in a recent outbreak of monensin toxicosis.[177] Recovery of animals with cardiomyopathy is unusual, constant therapy is required for maintenance of animals with CHF, and sudden death can occur at any time. Some animals may have significant myocardial dysfunction without CHF and are “cardiac cripples,” comfortable at pasture but not safe to use for performance. These animals may later develop CHF.

Prevention and Control

Maintenance of a good vaccination program may limit the bacterial and viral causes of myocarditis. Parasite control may also reduce myocardial injury that predisposes to myocarditis or cardiomyopathy in horses. Toxic myocardial diseases are prevented by making horse feed in mills where feeds containing ionophores are not made, by proper mixing of feeds containing monensin, salinomycin, or lasalocid in feed mills in which horse feed is made, by not shipping bulk horse feed in trucks in which medicated ionophore-containing feed has been transported, and by preventing horses from ingesting these medicated feeds. Gossypol toxicity can be prevented by feeding no cottonseed meal or cottonseed meal with low gossypol content, especially when feeding preruminants.[206] Feeding of cottonseed meal can be limited by providing more forage or additional protein sources in the diet of ruminants so that ingestion of gossypol is limited to concentrations of 1 to 2 g/kg or less of feed for adult cattle and 0.5 to 1 g/kg or less of feed for immature cattle.[207] Nutritional myocardial disease can be prevented by adequate feeding of vitamin E, selenium, and copper with supplementation as required. Inherited cardiomyopathy is controlled by avoiding breeding of known or suspected carriers of the polled Hereford and Holstein-Friesian breeds. Not grazing horses on pastures containing *Acer* spp. will eliminate myocardial injury associated with consumption of the hypoglycin A toxin that causes atypical myopathy.[208]

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Pericarditis

Definition and Etiology

Pericarditis is inflammation of the pericardium that results in accumulation of fluid or exudate between the visceral and parietal pericardium. Pericarditis in large animals occurs with trauma from penetration of ingested foreign objects or external wounds, hematogenous spread (septicemia) of infection, extension of infection from the lung or pleura, viral infections such as equine viral arteritis or equine influenza, and neoplasia. Pericarditis has also been associated with the mare reproductive loss syndrome (MRLS), with *Actinobacillus* species isolated in the majority of these horses.[209] Idiopathic pericarditis, characterized by an aseptic inflammatory exudate, is not uncommon in horses and has recently been reported in cattle.[210–217] Autoimmune, hereditary, and metabolic causes of pericarditis have not been documented in large animals.

Clinical Signs and Differential Diagnosis

The clinical presentation of pericarditis can vary depending on the volume and rate of development of the pericardial effusion and the cause. Nonspecific clinical signs—fever, anorexia, depression, or weight loss—may be the chief complaints, but more frequently, peripheral edema, jugular venous distention and pulsations, tachypnea, or dyspnea is the presenting clinical sign. Cattle may exhibit pain by an abnormal stance characterized by abducted elbows, a spontaneous or induced expiratory grunt, reluctance to move, or preference to stand with the forequarters elevated. Horses may show signs of colic or syncopal episodes.

The most consistent findings on auscultation are tachycardia, muffling of heart sounds, and absence of lung sounds in the ventral thorax. Dorsally the lung sounds are louder than normal. These findings are in contrast to pleuritis, an important diagnostic rule-out for pericarditis, in which lung sounds are muffled ventrally but heart sounds are not, and radiation of the heart sounds occurs over a wider area than normal.[218] In cattle, splashing sounds are frequently audible in the cardiac auscultation area, a sound some refer to as a “washing machine murmur or rub.” This is attributed to accumulation of gas and fluid in the pericardium and is indicative of the presence of gas-forming (anaerobic)

organisms and a grave prognosis. In cattle this murmur distinguishes pericarditis from cardiac neoplasia or other causes of CHF. The splashing sounds are absent in horses and muffled heart sounds are the rule, but pericardial friction rubs may be auscultated, especially after pericardial fluid accumulation has been relieved.[213] A gallop rhythm may be auscultated in either horses or cattle.

Mucous membranes may be congested and have a prolonged capillary refill time. Jugular venous distention and pulsations are usually present. Arterial pulses are weak. The latter findings may help distinguish pericarditis from primary pleuritis. Percussion of the thorax reveals ventral dullness, and pleural effusion is frequently present in horses with pericarditis. A concurrent pleuropneumonia or septic pleuritis is present in some horses.[215,219–222] Ascites is infrequently detected in horses with pericarditis, but concurrent peritonitis has been reported.[223]

Clinical Pathology

CBC changes are nonspecific and depend on the cause of the pericarditis. There may be hemoconcentration if the animal is dehydrated or toxemic, or there may be a mild anemia associated with chronic infectious pericarditis. WBC count may be normal or increased. There may be an absolute neutrophilia or a lymphopenia. Frequently the fibrinogen concentration or SAA is elevated. Serum chemistries are usually normal except for albumin concentration, which may be low[212,213] and accompanied by an elevation in globulin concentration. Liver enzyme, bilirubin, serum urea nitrogen, and creatinine concentrations are frequently mildly elevated, consistent with the development of CHF. Laboratory evidence of dehydration (increased PCV, total protein, serum urea nitrogen, and creatinine concentrations) may be exaggerated when diuretics have been administered previously. Although total serum LDH concentration may be elevated, more specific information may come from finding an increase in the cTnI or the myocardial isoenzymes CK and LDH. An elevated cTnI was reported in one cow with hemorrhagic pericarditis.[216] Electrolyte concentrations are frequently normal, but serum calcium and potassium concentrations may be low because of anorexia. Decreased sodium and chloride concentrations have been reported in horses with pericarditis.[213] No consistent abnormalities in arterial or venous blood gas concentrations have been reported in large animals with pericarditis.

Radiography is not a sensitive diagnostic test for pericarditis in horses, although an enlarged rounded cardiac silhouette is detected with large pericardial effusions. In cattle, traumatic pericarditis frequently results in fluid and gas accumulation in the pericardium that is detectable radiographically and relatively specific for this disease. A metallic foreign body is usually detected radiographically in the cranial reticulum or caudal thorax in cattle with traumatic pericarditis (Fig. 30.18). Radiographic changes may not be detected in early or uncomplicated pericarditis. If fluid accumulation is large and there is concurrent pleural effusion, changes are indistinguishable from those associated with pleuritis. An enlarged, rounded cardiac silhouette is not specific for pericarditis and is seen with other causes of generalized cardiomegaly. An obscured cardiac silhouette, vena cava, and diaphragm, with dorsal displacement of the trachea, may be seen with pericarditis or pleuritis. The lungs, which may be aerated only dorsally, frequently have interstitial infiltrates.

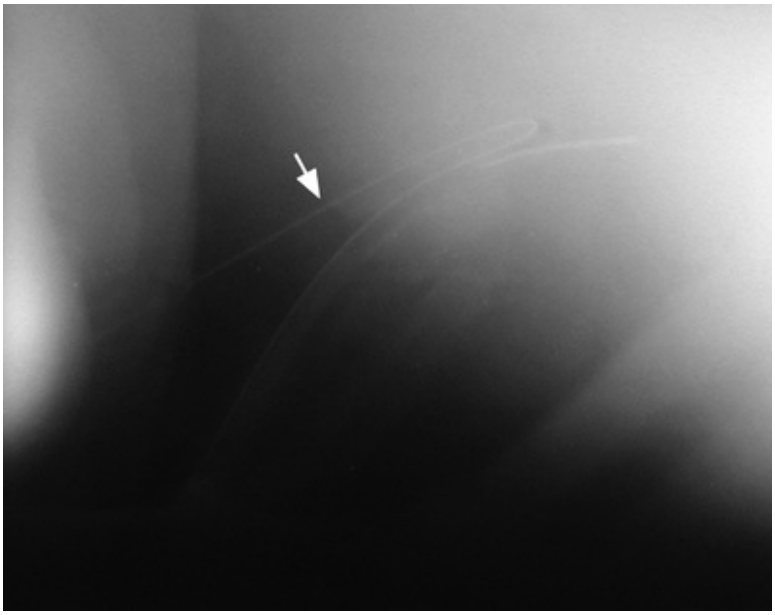


FIG. 30.18 Lateral radiograph of the caudal thorax and cranial reticulum showing a wire *(arrow)* in a cow with traumatic reticuloperitonitis.

The ECG changes most commonly associated with pericarditis in large animals are decreased amplitude of the QRS complexes (<1.5 mV in the base-apex lead)[213,214,223] (Fig. 30.19), electrical alternans (altered configuration of the P, QRS, or T complexes on a regular basis), and ST-segment elevation or slurring.[212,213,219,223,224] A right-axis deviation in the standard limb leads may be

apparent.[212,224] Cardiac arrhythmias (usually atrial or ventricular premature beats) may be detected in affected animals, suggesting a concurrent myocarditis (Fig. 30.20). In some animals, no ECG changes are evident.[225]

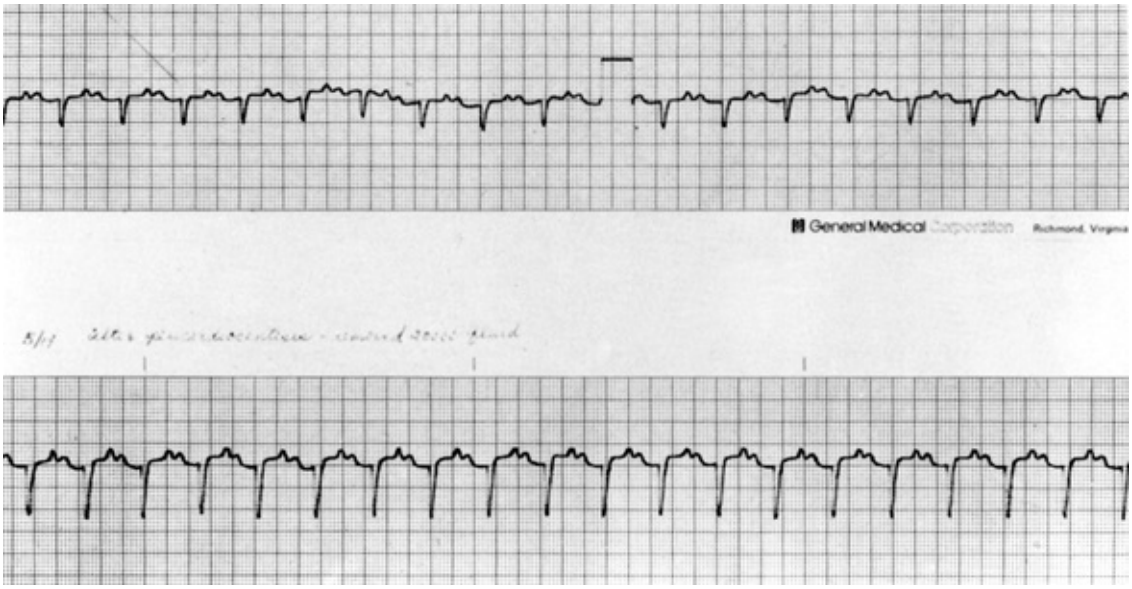


FIG. 30.19 Base-apex lead electrocardiogram taken from a cow before *(upper strip)* and after *(lower strip)* removal of 2 L of pericardial fluid. The markedly decreased amplitude (0.6 mV) of the QRS complexes is improved (1.2 mV) after pericardiocentesis.

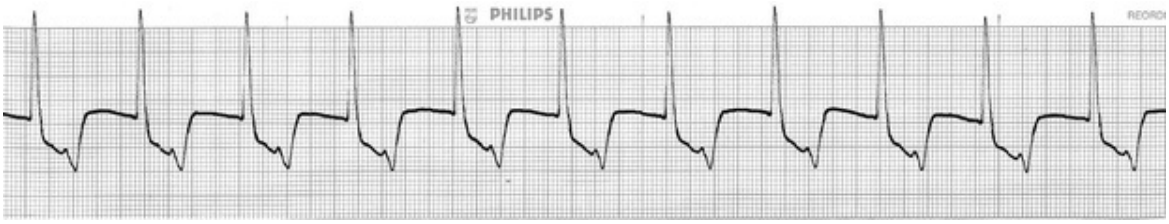


FIG. 30.20 Electrocardiogram (rhythm strip) obtained from a horse with pericarditis and junctional tachycardia. Note the P wave at the same place in the QT interval.

Echocardiography reveals findings specific for pericarditis and is used to confirm the diagnosis noninvasively. An echo-free space between the visceral and parietal pericardium is evident (Fig. 30.21) and apparent even with a minimum amount of fluid accumulation.[218,219] Frequently, hypoechoic to echoic

strands that correspond to fibrin are imaged in the pericardial space, with a hypoechoic to echoic layer covering the epicardial surface of the heart in large animals with pericarditis (Fig. 30.22). The pericardial effusion is often anechoic to hypoechoic, but more echoic pericardial fluid is occasionally seen, consistent with a more exudative fluid. Bright hyperechoic pinpoint echoes representing free gas are often imaged in cattle with pericarditis (Fig. 30.23). Gas in the pericardial sac of cattle with splashy heart sounds may limit the ability to obtain an echocardiographic evaluation of all cardiac structures. The visualization of intrapericardial gas is a sensitive indicator of anaerobic pericarditis. Pericardial effusion is differentiated from pleural effusion by finding the fluid- or fluid and gas–filled space surrounding the right ventricle and left ventricular free wall within the pericardial sac. Pericardial effusion is rarely imaged behind the left atrium, whereas pleural fluid is frequently imaged there. Right ventricular diastolic collapse (see Fig. 30.22) and right atrial collapse are common findings with large pericardial effusions and are an indication of the development of cardiac tamponade and hemodynamically significant pericardial effusion (Video 30.7).[214] Other echocardiographic findings consistent with pericarditis are decreased left ventricular chamber dimension, decreased left ventricular free wall motion, and decreased parietal pericardial motion.[214,215,219,226] Increased (see Fig. 30.21) or paradoxical motion (cranial motion beginning before the QRS complex) of the interventricular septum may be apparent.[226]

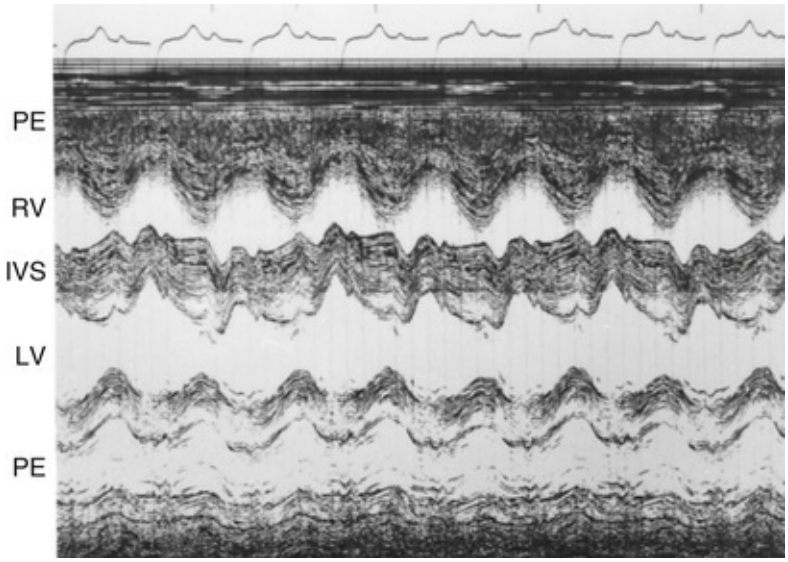


FIG. 30.21 M-mode echocardiogram obtained from a cow with traumatic pericarditis. There is a separation between the visceral and parietal

pericardium cranial to the right ventricle *(RV)* and caudal to the left ventricle. The cranial pericardial effusion *(PE)* is echogenic, suggesting that fibrin or debris is present. The left ventricular *(LV)* dimension is reduced, and there is marked cranial motion of the interventricular septum *(IVS)* just before the QRS complex.

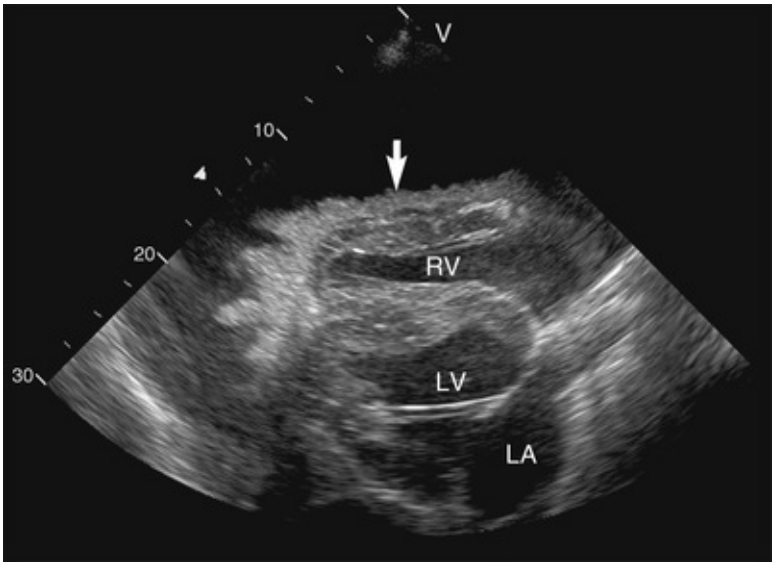


FIG. 30.22 Two-dimensional echocardiogram obtained from a horse with fibrinous pericarditis. Note the thick layer of echoic fibrin *(arrow)* covering the epicardial surface of the heart. There is a large anechoic pericardial effusion causing right ventricular *(RV)* collapse. The left atrial *(LA)* and left ventricular *(LV)* dimensions are reduced.

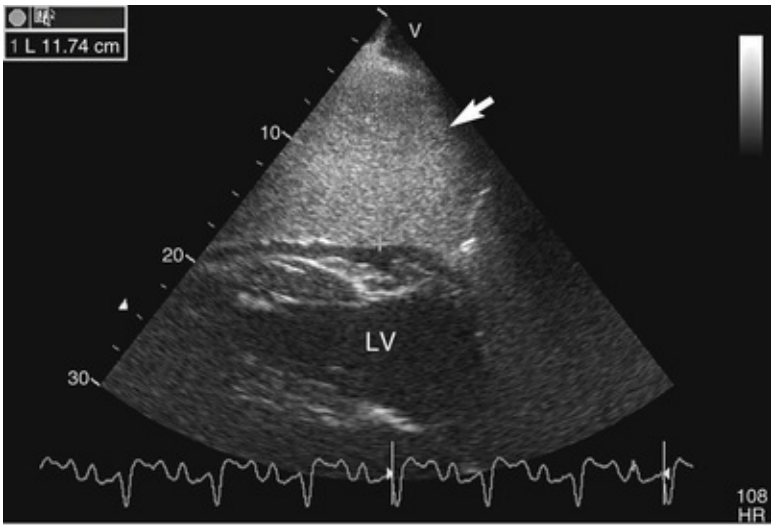


FIG. 30.23 Two-dimensional echocardiogram obtained from a cow with anaerobic pericarditis. Note the large amount (11.74 cm) of hyperechoic fluid *(arrow)* between the pericardium and left ventricle *(LV)* consistent with gaseous fluid.

The site for pericardiocentesis should be selected echocardiographically. Pericardial fluid is obtained most commonly from the left fifth (fourth in cattle) intercostal space 2.5 to 10 cm dorsal to the olecranon, above the level of the lateral thoracic vein, the safest site for pericardiocentesis. When there is a large volume of pericardial effusion, pericardiocentesis can be productive from the right side at about the same location. If at all possible, a pericardial catheter (large-bore Argyle tube) should be inserted into the pericardial space at the time of the initial pericardiocentesis to enable repeated drainage and lavage of the pericardial sac (Fig. 30.24). Fluid analysis and bacterial and viral culture results depend on the cause. In cattle with traumatic pericarditis, fluid analysis usually reveals elevated protein concentration (>3.5 g/dL) and an elevated WBC count (>2500/µL) composed primarily of neutrophils. The fluid is urine colored to slightly blood tinged and foamy, and it has a foul odor. A mixed population of gram-positive and gram-negative aerobic and anaerobic bacteria (GI flora) are usually present. Protozoa may be found in unusual circumstances. Hemorrhagic effusion has been reported in several cows with idiopathic pericarditis that responded favorably to pericardial drainage (usually with lavage) along with systemic antimicrobial therapy.[216] In horses, protein concentration of the pericardial fluid is elevated (≥2.5 g/dL) and the WBC count is normal or elevated with a population predominantly of neutrophils, although red blood cells, lymphocytes, eosinophils, mesothelial cells, and histiocytes have been

observed.[212–214,219,223] Bacterial (aerobic and anaerobic) cultures and viral cultures may be negative. *Actinobacillus* organisms were frequently isolated from mares with pericarditis in association with the MRLS.[209] Paired serum may support a viral cause. Analysis of pleural and peritoneal fluid (when present) usually reveals fluid characterized as a modified transudate or as mildly inflammatory.



FIG. 30.24 Insertion of a pericardial chest tube into the left fifth intercostal space for drainage and lavage of the pericardial space. Note that the left foreleg is being pulled forward, the clinician is inserting the large-bore Argyle chest tube into the left fifth intercostal space above the lateral thoracic vein, and the cow is wearing a radiotelemetry electrocardiogram system underneath the surcingle.

Cardiac catheterization demonstrates an elevation in central venous or right atrial pressure, and the atrial and ventricular pressure curve may be abnormal in appearance. Right atrial, right ventricular, and pulmonary artery end-diastolic pressures may equilibrate.[224] In combination, these findings are relatively specific for pericarditis.

Pathophysiology

Accumulation of fluid in the pericardium occurs as a result of inflammation. The rate of fluid accumulation and the degree to which the pericardial pressure increases determine the pathophysiologic consequences. Generally pericarditis

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results in decreased distensibility (increased ventricular end-diastolic pressure) of the heart, which impairs the ability of the heart to fill during diastole. The elevation in end-diastolic pressure and impairment of ventricular filling elevate atrial pressure and reduce venous flow or venous return to the heart and diastolic perfusion of the myocardium. The result is a depression of ventricular contractility, stroke volume, and consequently cardiac output. In addition, arterial pressure and renal blood flow are decreased. Initially, compensatory mechanisms consisting of vasoconstriction, increased heart rate, and sodium retention (increased vascular volume) may maintain cardiac output. Failure to maintain cardiac output results in circulatory collapse.

Pericarditis can be classified as primarily effusive, constrictive, or a combination of both.[224] The hemodynamic consequences of effusive pericarditis are primarily caused by the physical presence of pericardial fluid, whereas constrictive pericarditis is classified as such, because the reduction in ventricular compliance is due to fibrinous or fibrotic involvement of the pericardium and epicardium. Removal of pericardial fluid results in improved cardiac performance in effusive pericarditis but is of limited usefulness in constrictive pericarditis.

Epidemiology

Pericarditis is uncommon in horses; when it does occur, it is most frequently idiopathic and can occur in a horse of any age. History of a recent respiratory tract infection is not uncommon. Exposure of horses to Eastern tent caterpillars was the greatest risk factor for the development of fibrinous pericarditis during the MRLS epidemic.[227] Traumatic pericarditis has been reported in horses but is rare.[228] Traumatic pericarditis is not uncommon in cattle, but it occurs in less than 10% of cattle with traumatic reticuloperitonitis.[75] Most cattle are affected in late gestation or at parturition. Idiopathic pericarditis is rare in cattle. Cattle with idiopathic hemorrhagic pericarditis may eventually develop cardiac lymphosarcoma.[210]

Necropsy Findings

Gross postmortem examination shows distention of the pericardial sac with serosanguineous or urine-colored fluid that is foamy and may be malodorous (cattle). There may be organization of fibrinous exudate and fibrosis that is also

evident on the epicardium (Fig. 30.25) and may infiltrate the myocardium. Pleural effusion may be present. Other signs of CHF such as pulmonary congestion, pulmonary edema, and chronic passive congestion of the liver may be present. If the cause is traumatic, the offending object may be well contained in a fibrous tract located between the reticulum and the pericardium.

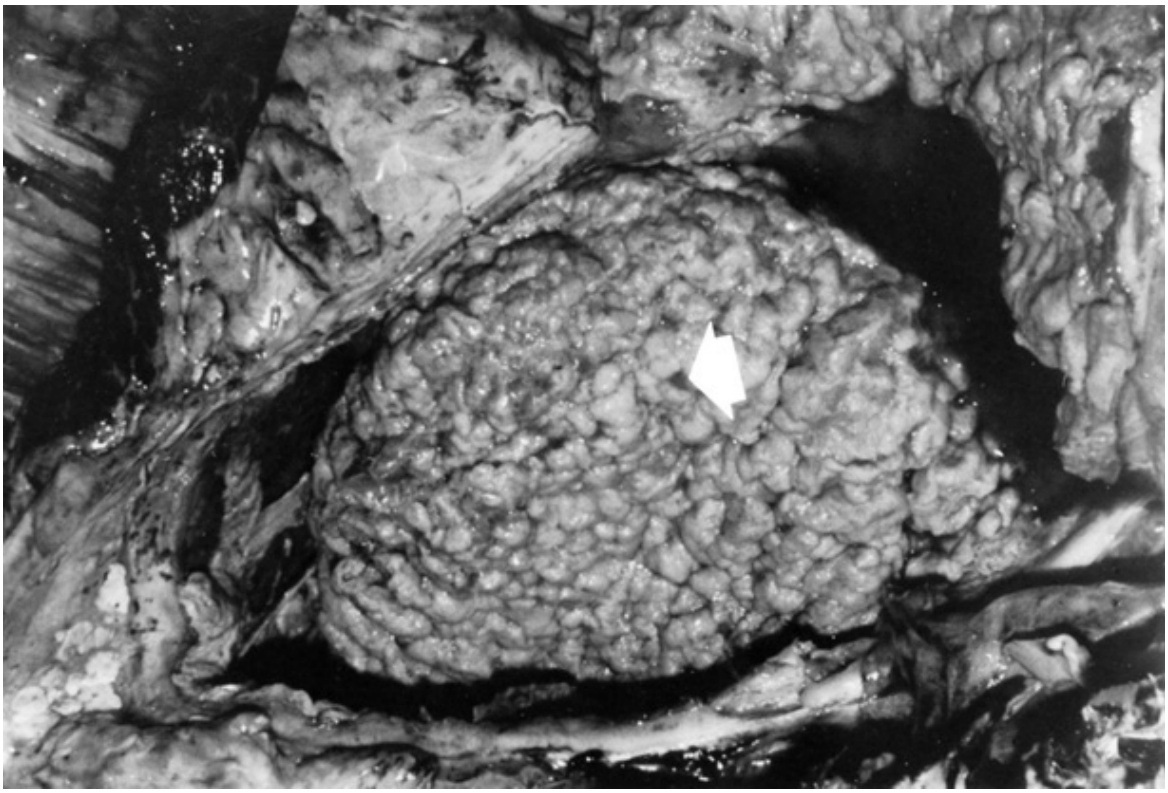


FIG. 30.25 Postmortem photograph of a cow with constrictive pericarditis. The pericardium is opened and reflected, revealing the epicardium *(arrow)* covered in fibrinopurulent exudate.

Histopathologic examination reveals pericardial, epicardial, and occasionally myocardial fibrosis and inflammation with neutrophilic, lymphocytic, eosinophilic, or plasma cell infiltrates. Bacteria may be visible. The liver may show diffuse centrilobular necrosis, fatty change, dilation and congestion of sinusoids, and perivenous fibrosis.

Treatment and Prognosis

Treatment of traumatic pericarditis in cattle is generally unrewarding and is

usually addressed toward salvage or short-term survival to calving. Repeated pericardial drainage by means of pericardiocentesis or a fifth rib resection, lavage, or pericardiectomy may be useful for short-term survival, but the prognosis for return to normal function is poor because CHF results from involvement of not only the pericardium but also the epicardium and myocardium (see Fig. 30.25). Thoracotomy by a split-rib technique followed by pericardiectomy has been effective in treating some cattle with traumatic, restrictive pericarditis.[229]

Treatment of pericarditis not caused by trauma has been successful in horses, but the initial prognosis should be guarded. Aggressive treatment of horses with moderate to large pericardial effusions should include the placement of a large-bore indwelling chest tube into the pericardial sac under echocardiographic guidance and drainage and lavage of the pericardial sac, with local infusion of antibiotics in addition to the initial broad-spectrum antimicrobial therapy. Obtaining a sample for cytologic examination and culture and sensitivity testing via a pericardiocentesis should be postponed until an indwelling catheter can be safely inserted, if pericardial drainage and lavage is considered as a probable treatment, because it is difficult to insert the catheter once the pericardiocentesis has been performed. The pericardial drainage and lavage, performed once or twice daily as needed, has been effective in treating idiopathic or septic pericarditis in horses.[10,214,215,219,223] The indwelling tube should remain in situ until the fluid recovered at the time of drainage is consistently less than or equal to the volume instilled in the pericardial sac with antimicrobials 12 to 24 hours earlier. The ECG should be monitored because occasionally cardiac arrhythmias occur during the therapeutic procedure or during a routine pericardiocentesis. All horses with pericarditis should initially be treated for septic pericarditis with systemic broad-spectrum bactericidal antimicrobial drugs. The antimicrobial choice should be based on the most likely causative agents and modified as needed by the results of culture and sensitivity testing. Fibrinous pericarditis has been successfully treated in horses with broad-spectrum bactericidal antimicrobials when the amount of pericardial fluid detected echocardiographically was too small to safely obtain a sample for cytologic evaluation and culture and sensitivity testing. Treatment of idiopathic pericarditis with corticosteroids should be initiated only after the results of these diagnostic studies demonstrate no evidence of sepsis. Pericardiotomy or (preferably) pericardiectomy are the treatments of choice if signs of constrictive pericarditis are present. However, the long-term prognosis for large animals after this

surgery is guarded. A partial pericardiectomy was performed in one horse with constrictive pericarditis but was only transiently successful.[220]

In traumatic pericarditis the antibiotic selected must be capable of covering gram-positive and gram-negative aerobic and anaerobic bacteria. Nonsteroidal antiinflammatory drugs (NSAIDs) have been deemed useful as adjunctive therapy, as have corticosteroids if bacterial culture of the fluid is negative and no evidence of sepsis is detected cytologically.

Although diuretics are effective in eliminating the severity of peripheral edema, they further reduce venous return and preload in animals with pericarditis. The result is further compromise of cardiac output and worsening of heart failure.

Prevention and Control

Traumatic pericarditis in cattle can be prevented by routine administration of magnets to heifers at the time of pregnancy diagnosis. At each subsequent pregnancy diagnosis, the cow should be checked for the presence of the magnet in the reticulum. It is not beneficial to have more than one magnet present at one time.

Horses should not be grazed on pastures containing trees infected with Eastern tent caterpillars. Removal of black cherry trees from equine pastures removes the preferred host tree for the Eastern tent caterpillar. Some types of infectious pericarditis in horses may be controlled by routine vaccination against the common respiratory pathogens.

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Cardiac Tumors

Definition and Etiology

The heart may be the primary site of neoplastic disease or be involved secondarily by tumors from adjacent structures, such as the lungs, pleura, lymph nodes, or diaphragm. Cardiac neoplasia is uncommon in large animals. The most common primary cardiac tumor is lymphosarcoma. Mesotheliomas, melanomas, lipomas, fibrosarcoma, adenocarcinomas, and other carcinomas, especially squamous cell carcinomas in horses, may involve structures adjacent to the heart and may extend to the heart or heart base, producing signs of heart disease.[230,231] An infiltrative cardiac lipoma has been reported in a horse, but no signs of cardiac disease were attributed to it.[232] A metastatic anaplastic pulmonary carcinoma caused signs of CHF in one horse,[231] and disseminated hemangiosarcoma with myocardial involvement was thought to be responsible for VA in another horse.[233] Primary pericardial hemangiosarcomas have also been reported in a horse.[234]

Clinical Signs and Differential Diagnosis

The clinical signs of cardiac neoplasia are nonspecific and depend on the cardiac site involved and other sites of tumor manifestation. Nonspecific signs of neoplasia are common and include anorexia, depression, weight loss, and fever. These signs can be produced by any site of chronic disease, and in large animals, pneumonia, peritonitis, enteritis, and liver and kidney disease are considered differential diagnoses, among others. If the tumor involves the pericardium, signs of pericarditis or pericardial effusion such as tachycardia, pain, jugular venous distention, peripheral edema, and weak arterial pulses may be seen. Myocardial involvement, as is most common with lymphosarcoma, may result in cardiac signs that include tachycardia, cardiac arrhythmias, and cardiac murmur (atrioventricular valve insufficiency) or signs of CHF such as peripheral edema, ascites, and diarrhea. Clinical signs attributable to tumor involvement of the endocardium (e.g., obliteration of a cardiac chamber, valvular obstruction or damage, embolic showering) are rare in large animals.

Tumor involvement of other organ systems and tissues can be manifested by

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lymphadenopathy, peripheral edema, diarrhea, melena, dysphagia, tachypnea, pleural effusion, or rectal palpation of abdominal masses.

Clinical Pathology

Cardiac tumors present no consistent clinicopathologic feature. The CBC from horses or cattle with lymphosarcoma may reveal neoplastic lymphocytes. The absence of leukemic changes does not rule out lymphosarcoma. Cattle with lymphosarcoma may test positive for fecal occult blood. A serum chemistry profile may reveal nonspecific changes, such as hypoalbuminemia, hyperglobulinemia, or elevated liver enzyme concentrations, depending on the other organ systems affected by the tumor or the animal's debilitation. Diagnosis of the cardiac tumor is based on histopathology of tumor tissue. Tumor cells may be found in pericardial or pleural fluid or adjacent lymph nodes. Serologic evidence (agar gel immunodiffusion or radioimmunoassay) of BLV infection does not confirm a diagnosis of lymphosarcoma, but a negative test result virtually rules out the adult or enzootic form of lymphosarcoma in cattle. No evidence of BLV infection is found in cattle with the thymic form of lymphosarcoma.

If electrocardiographic evidence of cardiac tumors is present, it is nonspecific. Cardiac tumors may produce cardiac arrhythmias, reduce amplitude of the QRS complexes, or alter the normal appearance of the P, QRS, and T complexes. Two-dimensional echocardiography or an ultrasound examination of the lungs or pleura may show evidence of the cardiac tumor by providing direct evidence of echogenic masses involving the heart or surrounding tissue, abnormal fluid accumulation, or myocardial functional changes. Ultrasound findings can determine whether any masses can be safely biopsied to confirm the diagnosis.

Radiographs may provide evidence of cardiac tumors by showing abnormal soft tissue densities in the thorax that obscure the cardiac silhouette or ventral lung borders.

Pathophysiology

Lymphosarcoma, the most common cause of cardiac tumors in cattle, has a predilection for the right atrial myocardium. Right ventricular myocardial involvement is not uncommon; left atrial or left ventricular involvement is rarer. Involvement of the right side of the heart may result in little or no evidence of

heart disease. More commonly, the myocardial involvement results in dilation of the chamber involved. As a consequence, the tricuspid valve ring may be dilated, and TR occurs. Chamber enlargement or infiltration of the myocardial conduction system may cause cardiac arrhythmias. Myocardial function may be impaired so that signs of right-sided heart failure become apparent, including tachycardia, peripheral edema, jugular venous distention or pulsations, pericardial or pleural effusion, hepatic congestion, and ascites.

Epidemiology

Cardiac tumors are rare in large animals. The most common cause in cattle is lymphosarcoma. Although more than 50% of cattle in some parts of the United States are infected with BLV, only 1% to 5% develop lymphosarcoma.[235–237] In herds with more than 50% of cattle infected with BLV, the incidence of lymphosarcoma may be higher. Cardiac involvement is common in cattle with the adult or enzootic form of BLV, a disease that occurs most commonly in cattle older than 4 years old.[238] Thymic lymphosarcoma, which is not associated with BLV infection, also involves the heart but is much less common, occurring in cattle younger than 30 months of age.

Lymphosarcoma, mesothelioma, and squamous cell carcinoma are probably the most common causes of neoplastic involvement of the equine heart, but the prevalence is not documented.

Necropsy Findings

Necropsy findings depend on the type of cardiac tumor. Direct involvement of the myocardium with lymphosarcoma is associated with finding diffuse infiltration by a pale, tan, homogeneous tissue that frequently causes enlargement of the cardiac chamber. Involvement of the right atrium (Fig. 30.26) is the most common manifestation of adult enzootic BLV, but any area of the myocardium and pericardium may be involved. Intracavitary extension of the tumor may be evident (see Fig. 30.26). Histologic evaluation of the tumor shows diffuse infiltrates of lymphoblastic cells that obliterate the normal architecture of the myocardium.



FIG. 30.26 Postmortem photograph of a cow with lymphosarcoma demonstrating right atrial myocardial infiltration by a tumor and extension of the tumor into the atrial lumen.

Other tumors, such as fibrosarcoma, squamous cell carcinoma, pulmonary carcinoma, thymic lymphosarcoma, mesothelioma, and melanoma, may involve the heart by extension or metastasis from other sites in the thorax.

Treatment and Prognosis

No definitive treatment exists for cardiac neoplasias, and the prognosis for survival is poor. Death is expected within 6 months with most cardiac tumors. Lymphosarcoma of the heart in cattle has a grave prognosis and is usually associated with death within a few months. Short-term improvement has been achieved in cattle with lymphosarcoma treated with a combination of corticosteroids, L-asparaginase, and cytotoxin. Thoracoscopic pericardiotomy has been used as a palliative treatment in a cow with pericardial lymphoma.[239]

Prevention and Control

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Prevention and control of BLV can be accomplished by isolation of BLV-positive and BLV-negative animals; use of individual or sterilized supplies, such as needles, rectal examination sleeves, tattooing, dehorning, and ear-tagging equipment on each animal; rigorous attention to a vector control program; and feeding colostrum from serologically negative cows only.[236,240] Frequent testing (at least every 6 months) and isolation of serologically positive animals over 6 months of age should be performed. Prevention and control of other cardiac tumors are not possible.

Vascular Disease: Aneurysms, Thrombosis, and Embolism

Definition and Etiology

Aneurysms, which are vascular dilations, develop from weakening of the medial elastic coat of blood vessels. The medial weakness may be primary or caused by progression of an intimal atherosclerotic lesion that has enlarged from hemorrhage, calcification, ulceration, and thrombus formation. The specific causes of aneurysms in large animals are unknown, but trauma (internal or external), sepsis, parasite migration, degenerative vascular disease, atherosclerosis, or aging changes (dilation, elongation, and loss of elasticity of blood vessels) may play a role.[241–243] Histopathologic study of the Friesian with aortopulmonary fistulation and thoracic aortic rupture suggest an underlying connective tissue disorder of the aortic media collagen or elastin as the root cause.[244] Congenital aneurysms of the sinus of Valsalva have been reported in horses.[87,94–96] Hypertension can accelerate degeneration of the wall.

Thrombosis is the formation of a clot that obstructs blood flow in the circulatory system. The causes of thrombosis are numerous and include trauma, venous stasis, and catheterization for administering medication or fluids. Needle penetration, indwelling catheters, thrombogenic solutions, or bacterial contamination can cause thrombosis associated with catheterization. Secondary thrombosis can result from perivascular inflammation caused by cellulitis, lymphangitis, or other sources of bacterial invasion around the blood vessel. Mural thrombi, which occur in cardiac chambers associated with low-flow states and/or a coagulopathy, also may occur in large animals, although they have been rarely diagnosed antemortem in the heart.[245] Thrombosis usually occurs when intimal disease is present, but it may occur in arteries with no intimal disease when a hypercoagulable state exists, such as with dehydration, endotoxemia, anemia, hypotension, stress, or stasis.[246–248] This type of thrombosis is frequently a complication of acute infectious disease (particularly acute toxic enteritis or colitis), neoplasia, or any chronic debilitating disease.

An *embolism* is foreign material carried in the bloodstream. Emboli frequently arise from an arterial or venous thrombus, but unusual emboli include catheters and other foreign bodies inadvertently introduced into the circulatory system. In

large animals, emboli occur most commonly in bacterial endocarditis, thrombophlebitis, omphalophlebitis, and parasitic arteritis. Aortoiliac thromboembolism has been reported as a complication of valvular endocarditis in a calf and mural endocarditis in a cow.[249,250]

Clinical Signs and Differential Diagnosis

Sites of thrombosis associated with thrombophlebitis are likely to have pain, swelling, redness, and palpable thickening of the involved vein. These signs frequently occur within 12 to 24 hours after catheter removal when the thrombus is associated with catheterization. If there is bilateral jugular venous thrombosis, sudden, marked swelling of the head may occur. If the thrombosis involves the terminal aorta and iliac arteries in horses, the signs are frequently a vague hindlimb lameness, exercise intolerance, or poor performance. These nonspecific signs make it necessary to rule out lameness from other causes, cardiac disease, or respiratory problems. Failure to ejaculate has been reported in breeding stallions with aortoiliac thrombosis.[251] Aortoiliac thrombosis in horses is also characterized by heavy sweating after exercise, except over the hindlimbs, which are cool. With severe aortoiliac thrombosis the affected limb can be cool to the touch at rest or can be cold with no palpable femoral arterial pulse. Saphenous vein filling is slow or nonexistent in affected horses, and the metatarsal and other peripheral arterial pulses of the hindlimbs are weak. Rectal examination may be normal, or weak, absent, or asymmetric iliac pulses may be palpated. Fremitus of the iliac arteries or terminal part of the aorta may be palpated. The terminal part of the aorta may feel larger or firmer than normal, or an aneurysmal dilation may be detected. Hindlimb weakness, inability to bear weight on the affected limb(s), and cold limbs with weak or absent femoral arterial pulses occur in affected calves.[252] With verminous arteritis of the cranial mesenteric artery, a thickened, dilated cranial mesenteric artery or aorta may be palpated that may be firmer than normal and have a weak pulse, or fremitus may be palpated. In calves with aortic or aortoiliac thrombosis weakness, lameness, knuckling, paresis or paralysis of the hindlimbs, inability to rise, and cold hindlimbs lacking a femoral arterial pulse have been described.[249,253–255]

The signs attributable to embolism and thrombosis may be identical. Embolism is usually manifested by an acute episode of pain or fever, abnormal pulsation in a peripheral vessel, or a change in skin temperature. If there is peripheral vessel showering, superficial veins may be collapsed and muscular

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weakness may be present. Embolic showering usually occurs in animals suspected of having or known to have thrombus formation.

Clinical signs associated with an aneurysm depend on its location and may vary from being asymptomatic to being a noticeable enlargement or mass associated with a blood vessel or causing colic, syncope, seizures, or sudden death on rupture. In a peripheral artery, a pulsatile expansile mass may be visualized or palpated. Other considerations for this finding are a false aneurysm and an arteriovenous fistula. A false aneurysm is clinically indistinguishable from a true aneurysm but can be distinguished ultrasonographically. A false aneurysm is caused by a break in the continuity of all three coats of the arterial wall rather than in the tunica media alone. This results in extravascular accumulation of blood in adjacent tissues. Signs attributable to low blood flow (e.g., lameness, colic, edema) may be present with arterial aneurysms. Aneurysms of the cranial mesenteric artery frequently manifest as chronic episodes of colic. With involvement of major cardiac vessels, there may be pain, an auscultable heart murmur, rapid tachycardia, signs of CHF, acute onset of pulmonary edema, or sudden death when the aneurysm ruptures. The latter signs make aneurysms difficult to distinguish from the clinical signs of a horse with valvular heart disease or cardiomyopathy. One cause of an aorticocardiac fistula in horses is the result of rupture of an aneurysm of the sinus of Valsalva.[87,94–96] Aortopulmonary rupture and fistulation occur in young to middle-aged Friesians, resulting in similar clinical signs in some horses, along with collapse, coughing, intermittent lameness, and fever.[256,257]

Clinical Pathology

Aneurysms or pseudoaneurysms may be visualized radiographically as soft tissue density masses continuous with a vessel wall (true aneurysm) or extending outward from a vessel wall (false aneurysm).[242,243] However, the majority of the aneurysms involving the aorta and aortic root are not visible radiographically. Echocardiography is useful in the diagnosis of aneurysms involving the aortic root (Fig. 30.27).[86,87,94–96] Echocardiographic diagnosis of rupture of aortic arch with pseudoaneurysm or aortopulmonary fistulation requires obtaining additional echocardiographic views, following the aorta and pulmonary artery cranially and dorsally.[257] Recently aortic arch rupture has also been diagnosed with transesophageal echocardiography.[257] Angiography can be used in the

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diagnosis of peripheral vessel swelling or suspected thrombosis but is of little use in diagnosis of aneurysms of major vessels in adult animals. Ultrasonography may be used for the diagnosis of aneurysms or thrombosis of major arteries and peripheral vessels. In aortoiliac thrombosis of horses, ultrasound has been used to determine the origin of the thrombus and the extent of occlusion of the involved arteries (Fig. 30.28).[258] Abdominal ultrasonography of the upper left flank dorsal to the left kidney has been used to diagnose aortoiliac thrombosis in calves.[253] Diagnostic ultrasound has been used to detect thrombi in the caudal vena cava in cattle.[259,260] Although the occluding thrombus is not imaged, detecting a distended oval or round caudal vena cava rather than the normal triangular vessel in the eleventh and twelfth intercostal spaces is consistent with this diagnosis in cattle. Thrombi have been detected ultrasonographically in the hindlimb in both horses and cattle.[261–265] Jugular vein thrombophlebitis has also been diagnosed ultrasonographically in both horses and cattle (Fig. 30.29).[128,266] Similarly, diagnostic ultrasound has been used to image the cranial mesenteric artery, its branches, and the aorta in horses with verminous arteritis.[267] Aneurysms appear as dilated vascular structures or vascular outpouchings continuous with the vessel wall,[86] whereas a thrombus is apparent as a hypoechoic to echogenic mass within a blood vessel.[128] Cavitation of an occlusive thrombus is suggestive of septic thrombophlebitis (see Fig. 30.29), whereas a nonseptic thrombus usually has a homogeneously hypoechoic to echoic appearance.[128] Complete occlusion of the vessel can be determined ultrasonographically, or flow within an aneurysm or alongside a thrombus determined. Doppler ultrasound provides a more sophisticated method for determining blood flow and vessel patency.

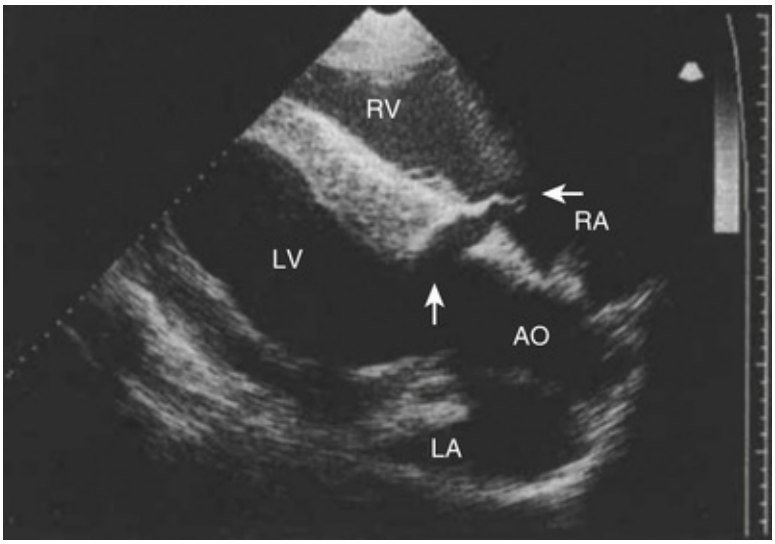


FIG. 30.27 Two-dimensional echocardiogram of a horse with a ruptured sinus of Valsalva aneurysm. Note the defect in the right side of the aorta at the sinus of Valsalva *(vertical arrow)* extending into the right atrium *(horizontal arrow).* The right atrium *(RA),* right ventricle *(RV),* left ventricle *(LV),* left atrium *(LA),* and aorta *(AO)* can be seen in this left ventricular outflow tract view.

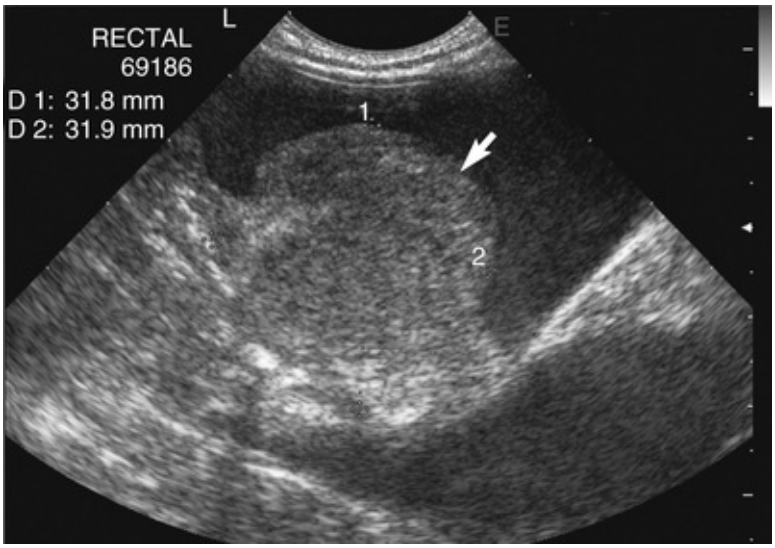


FIG. 30.28 Transverse transrectal sonogram of a large, somewhat heterogeneous thrombus *(arrow)* in the terminal portion of the aorta measuring 31.8 mm by 31.9 mm in diameter.

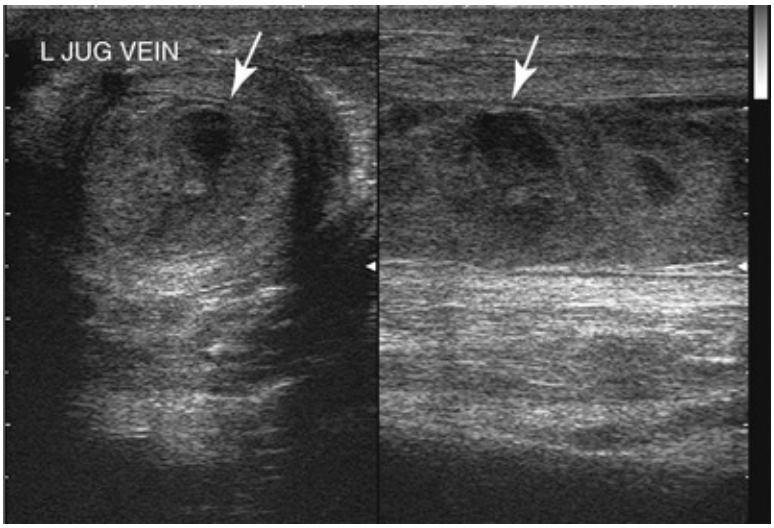


FIG. 30.29 Sonogram of the left jugular vein from a horse with septic thrombophlebitis. Note the cavitary appearance in the center of the thrombus *(arrows)* consistent with infection.

In the case of catheter-associated thrombosis, a positive catheter tip culture (>10^3 colony-forming units) along with a positive blood culture provides evidence of septic thrombophlebitis.[268] An aseptic ultrasound-guided aspiration of the cavitary lesion within a heterogeneous thrombus can be performed, and the aspirate submitted for culture and sensitivity testing.[128] Septic thrombophlebitis from any cause or embolic showering of septic thrombi may be accompanied by neutrophilic leukocytosis and elevation in fibrinogen concentration or SAA.

Pathophysiology

Irritation of the intimal lining of a blood vessel, stasis of blood flow, or existence of a hypercoagulable state triggers the clotting cascade and sets the stage for development of thrombosis. Further injury causes hemorrhage, more thrombosis, ulceration, and calcification. These in turn can compromise the media of the vessel, predisposing to aneurysm formation, and impinge on the lumen of the vessel, causing obstruction to blood flow. Either aneurysm or thrombosis can occlude blood flow to vital structures or organs, resulting in ischemia.

Thrombosis in any sizable vein causes venous hypertension, passive congestion, and subsequent edema and pain of the structure. As the thrombus matures, it adheres to the wall more, but with clot retraction and lysis, recanalization may occur. However, parts of the thrombus may protrude into the

moving bloodstream and serve as the source of embolic showering, even during thrombus organization. The most common site for an embolus to lodge has not been established in large animals; the femoral and iliac arteries are common locations in humans. Emboli usually lodge at bifurcations, where the caliber of the artery is suddenly reduced.

The most common outcome of aneurysm of a major vessel is thought to be rupture. Rupture of sinus of Valsalva aneurysms into the right atrium, right ventricle, and interventricular septum has been reported in the horse.[94–96] VT often occurs with rupture of an aortic sinus of Valsalva aneurysm and dissection into the interventricular septum.[95,96] Unruptured aneurysms may have other complications, such as thrombosis or embolization of the thrombus. The frequency of rupture or embolic showering from thrombosis is unknown in animals. In Friesians, rupture of the aorta occurs into the pulmonary artery at the level of the ligamentum arteriosum and into the surrounding perivascular structures.[256,257]

Epidemiology

The significance of thromboembolism in large animals is poorly defined. Spontaneous thromboembolism is commonly associated with parasitism in horses, and the aorta and cranial mesenteric arteries are the sites most frequently involved.[162] Aortoiliac thrombosis is also a recognized syndrome diagnosed most frequently in heavily exercised horses. Although historically parasitism has been associated with aortoiliac thrombosis in horses, other causes of this syndrome are probable but have not been elucidated. Thrombotic disease can occur in any animal having repeated IV injections or being catheterized for administration of medication or fluids, but it is particularly common in horses with acute toxic enteritis, colitis, or sepsis. Careful skin preparation and aseptic technique are important factors in minimizing the likelihood of the patient developing catheter-related thrombophlebitis. Low doses of heparin have been effective in limiting the development of catheter-related thrombophlebitis in cattle.[269] Large intestinal disease, hypoproteinemia, endotoxemia, salmonellosis, fever, diarrhea, and locally produced fluids have all been identified as risk factors for catheter-associated thrombophlebitis.[248,270,271]

Arteriosclerosis is recognized in horses and in cattle. In cattle the lesion is most frequently caused by excessive vitamin D_3 supplementation or ingestion of

calcinogenic plants, such as *Solanum malacoxylon, Cestrum diurnum*, or *Trisetum flavescens*.[272] In horses the arteriosclerotic lesions were caused by lesions induced by *Strongylus vulgaris*.[97] Ingestion of calcinogenic plants also occurs in horses, resulting in lesions in the aorta.

Aneurysms are uncommon in large animals but have been documented as the cause of sudden death in breeding stallions and racing Thoroughbred and Standardbred horses.[96,97] Aneurysms of the sinus of Valsalva are one cause of aortic rupture in older horses and are probably congenital in horses, as they are in humans.[86,94–96] Aortic root rupture also occurs without the presence of a preexisting aneurysm and has been associated with medial necrosis of the aorta. Psuedoaneurysm of the aorta in young Friesians is at the level of the ligamentum arteriosus, is a breed problem, and can result in sudden cardiac death, although many horses have a more chronic course.[256,257]

Necropsy Findings

Aneurysms are detected grossly as dilations of the involved blood vessel. Aneurysms of the sinus of Valsalva are characterized by an absent tunica media in the wall of the aorta, causing the aneurysmal dilation.[76,86] Rupture of a sinus of Valsalva aneurysm may occur into the right atrium, right ventricle, or interventricular septum, resulting in an ACF and volume overload.[76,86,87,95,96] Rupture through the tricuspid valve or chordae tendineae may also occur. Subendocardial dissection of blood down the interventricular septum may occur. Subsequent ruptures into the left ventricle and of the mitral chordae tendineae have also been reported. Pseudoaneurysms of the aorta with rupture at the ligamentum arteriosum and into the pulmonary artery occur in the Friesian breed.[244,256,257] Aneurysms of the major vessels leaving the heart may involve more than one vessel by dissection and hemorrhage. Aneurysms may contain thrombi or parasites, and there may be evidence of embolic showering of thrombi into peripheral vessels or other organ systems, especially the lungs. Histologically there may be necrosis and inflammation at the site of the aneurysm with foci of mineralization.

Thrombosis and arteriosclerotic lesions are recognized as rounded, well-demarcated fibrous plaques frequently located in the thoracic and cranial abdominal aorta (Fig. 30.30). The plaques may contain a central calcified core or parasitic larvae. Microscopically there is a thin layer of fibrin, platelets, and

inflammatory cells in early lesions, whereas older lesions have a greater fibrous component. Thrombotic lesions may be associated with proliferation of the underlying aortic intima. In horses, parasitic larvae may be found.



FIG. 30.30 Ascending aorta from a horse that experienced an acute onset of uniform ventricular tachycardia after exercise and died within 3 hours of onset. Note the irregular calcified surface of the aorta, consistent with atherosclerosis.

Treatment and Prognosis

Aneurysms of major vessels carry a guarded to grave prognosis because surgical correction is rarely attempted and spontaneous rupture is thought to be relatively common. Intact aneurysms of the sinus of Valsalva can be detected echocardiographically, and once an aneurysm has been detected, the horse should be removed from all athletic competition because of the risk of rupture.[86,118] The occlusion of an ACF has been successfully performed with an Amplatzer occluder device in a breeding stallion.[273] This stallion survived to discharge but was euthanized a month and half later due to worsening of his underlying heart disease.

Treatment of thrombosis consists of removal of the catheter, if present, and resting the affected vessel. Warm compresses or hydrotherapy may be helpful in some animals. Topical NSAIDs (diclofenac sodium) may also be useful. Support wraps may be useful to control swelling. The effectiveness of anticoagulant

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therapy (clopidogrel usually at 2 mg/kg twice daily PO in horses, aspirin at 100 mg/kg once daily PO, ruminants; 10 mg/kg once daily, horses; or sodium heparin at 30 to 40 units/kg SC twice daily) or antiinflammatory drugs for dissolving a thrombus is questionable. Anticoagulant therapy may be useful in preventing additional thrombus formation or propagation of the existing thrombus. Ultrasonographic guidance can be used to obtain a sterile aspirate of the cavitated area of the thrombus for culture and sensitivity testing when septic thrombophlebitis is suspected.[128] Broad-spectrum bactericidal antimicrobial therapy should be instituted for suspected septic thrombophlebitis or when a cavitated thrombus is detected ultrasonographically and modified, if necessary, on the basis of the results of culture and sensitivity testing.[128] Bacterial endocarditis, particularly involving the tricuspid valve, is a potential complication of septic jugular vein thrombophlebitis. With the exception of a jugular venous thrombus or some horses with aortoiliofemoral thrombosis, surgical removal of an embolism or thrombus is rarely attempted in large animals. Surgical resection of a jugular vein with septic thrombophlebitis has been performed successfully when the surgeon could ligate the affected vein above and below the thrombus. Jugular vein thrombectomy with removal of the contents of the affected portion of the vein has been performed successfully in horses.[274] Although the prognosis for complete resolution of the thrombophlebitis is guarded, especially if the thrombus is infected, many veins do recannulate with complete resolution of the thrombus and without vascular stricture. However, the time course is slow, and persistent local induration and obstruction to blood flow may persist. The prognosis for nonracehorses to return to the same level of performance is good.[275] However, Standardbred racehorses in this same study had a decreased chance of returning to racing at the same level.[275]

The prognosis for horses and calves with aortoiliac thrombosis is guarded. Although most calves with aortoiliac thrombosis have died or were euthanized, two calves have survived. One calf received antithrombotic treatment with unfragmented heparin and aspirin, and the other was treated with ketoprofen, acepromazine, and local heat. A wide variety of medical treatments have been proposed for horses with aortoiliac thrombosis, including sodium gluconate, larvicidal deworming, phenylbutazone, and a controlled exercise program. Success has been variable. Surgical thrombectomy has also been successful in some horses.[276–278]

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Prevention and Control

Thrombosis and embolization from IV catheters can be prevented or their incidence reduced by aseptic insertion, stabilization of the catheter, use of topical antiseptics, application of a sterile dressing, daily inspection of the catheter and vein, and replacement of the catheter at another site (preferably in another vein) if phlebitis occurs. Dwell time is a significant factor in the development of thrombophlebitis, and catheters should be replaced by new ones at another site every 72 hours.[279] Attempts should be made to place long-term catheters in large peripheral or central veins where contact between the endothelium and catheter is minimized and medications administered are diluted by the large volume of blood flow. Catheters left in place for prolonged periods should be of silicone rubber or polyurethane.[268] Clopidogrel (2 mg/kg PO twice daily, horses), aspirin (100 mg/kg PO once daily, ruminants; 10 mg/kg/day, horses), and low-dose heparin (30-40 units/kg SC twice daily, ruminants and horses) therapy should be considered to prevent thrombus formation in septic or endotoxic patients. Horses are much more prone to jugular thrombosis than are ruminants.

Parasite control is important in the control of thromboembolic disease and aneurysm in horses. Aneurysms of the sinus of Valsalva may be detected by routine echocardiographic screening of horses but occur so infrequently that this is not practical. In cattle, arteriosclerotic lesions are prevented by proper calcium and vitamin D supplementation.

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Atrial Fibrillation

Definition and Etiology

Atrial fibrillation (AF) is a cardiac arrhythmia characterized by a lack of coordinated atrial electrical activity. It is caused by an abnormality of impulse conduction that results from multiple small rapid and random reentrant activation of the atria or by one or more discrete rotors. High resting vagal tone, commonly found in horses, shortens the action potential duration in atrial myocardial cells, making AF more likely to occur. AF can occur in the presence of atrial enlargement from atrial myocardial disease, atrioventricular valvular regurgitation, ventricular failure, myocarditis, endocarditis, autonomic nervous system imbalance, electrolyte or acid-base disturbances, anesthetic drugs or tranquilizer administration, unknown causes, or in the absence of detectable underlying cardiac disease ("lone" AF). Although "lone" AF has been a term used when no underlying cardiac disease can be found, in all likelihood, underlying atrial myocardial disease is present at the microscopic level that we are currently unable to detect.

Clinical Signs and Differential Diagnosis

Large animals with AF may be asymptomatic at rest, and AF may be detected as an incidental finding in an otherwise normal horse. Horses that perform in rigorous athletic events usually have a history of exercise intolerance or poor performance. Other complaints may be exercise-induced epistaxis, respiratory disease, weakness, syncope, myopathy, colic, or CHF. Cattle with AF usually have underlying GI disease.[280,281] Atrial premature depolarizations have also been reported in cattle with GI disease and may be a prelude to the development of AF.[281] Foot rot, pneumonia, and endocarditis have also been associated with AF in cattle. Anorexia and decreased milk production are common in cattle with AF. AF and the clinical signs associated with it in horses and in cattle can be paroxysmal. Paroxysmal AF usually lasts no more than 24 to 48 hours before spontaneous conversion to sinus rhythm occurs.[282] Spontaneous conversion usually occurs in horses with small atria and an otherwise normal heart or in cattle with correction of the underlying problem. Transient potassium depletion associated with the administration of furosemide is a common cause of

paroxysmal AF in horses. Administration of bicarbonate “milkshakes” has also been implicated in horses with paroxysmal AF. AF has also been associated with iatrogenic hyperthyroidism in horses due to the administration of Thyro L or supplements containing kelp or ground-up shellfish.

Animals with AF have an irregularly irregular cardiac rhythm. In horses with AF, there is a high degree of underlying periodicity.[283] Heart sounds vary in intensity, and no fourth heart sound is audible. The heart rate may be slow, normal, or elevated. In cattle with severe abdominal disease, the heart rate usually reflects the severity of the underlying disease. In horses the resting heart rate is usually normal to slightly elevated and is rarely above 50 beats per minute (bpm) unless there is underlying myocardial or valvular disease or the horse has another reason for tachycardia (colic, etc.). During exercise, horses with AF develop abnormally high heart rates that are usually 40 to 60 bpm higher than expected for each level of exercise, far exceeding the peak heart rate of 240 bpm at maximal exercise.[284–286] The arterial pulse varies in intensity. A pulse deficit occurs when two beats occur in rapid succession and is infrequent unless the heart rate is elevated. Cardiac murmurs of grade 3/6 or louder are present in less than 50% of the horses and in even fewer cattle with AF.[287–289] Signs of CHF (peripheral edema, jugular venous distention) may be present in some animals, but they are not caused by the arrhythmia. In these cases, AF occurs secondary to the atrial enlargement that occurs with the underlying valvular or myocardial disease.

Absence of an auscultable fourth heart sound in the presence of an irregular cardiac rhythm with no underlying regularity distinguishes AF from other cardiac arrhythmias. Sinus arrhythmia, which is also an irregular rhythm, has an audible fourth heart sound. Second-degree AV block, which is usually a regularly irregular rhythm, also has an audible fourth heart sound. However, underlying sinus arrhythmia is usually present in these horses, making it more difficult to distinguish second-degree AV block with sinus arrhythmia from AF. Any increase in sympathetic tone, such as occurs with exercise or excitement, should result in a regular rhythm in horses with second-degree AV block while those with AF will have persistent irregular rhythm. Ventricular and atrial ectopic beats usually occur with a relatively regular underlying rhythm. A complicated ventricular rhythm with more than one focus of activation may have characteristics similar to those of AF and must be distinguished from it by an ECG. Atrial tachycardia with varying degrees of atrioventricular block has similar auscultatory characteristics, and the underlying fourth heart sounds may

be missed if the animal is auscultated in a noisy environment.

Clinical Pathology

In cattle with AF, acid-base and electrolyte disturbances occur frequently and are most likely attributable to the underlying primary disease. Most cattle with AF have GI disease, and the most consistent acid-base disturbance is metabolic alkalosis.[289] Hypocalcemia, hypokalemia, and hypochloremia may also be seen in cattle with AF. Experimental induction of metabolic alkalosis with hypokalemia in cattle has been associated with development of AF.[290] Most horses with AF have normal electrolytes, although the fractional excretion of potassium may be low, particularly in horses that sweat excessively or are routinely receiving furosemide for exercise-induced pulmonary hemorrhage. cTnI may be elevated in horses with acute AF, particularly if the sample was obtained 4 to 6 hours after the onset of AF. In most horses, this will decrease rapidly in next day or two following the onset of AF. If the cTnI continues to climb or is very high, active myocardial disease should be suspected. Elevations of T3 or T4 may be present in horses that have been receiving supplements containing kelp, shellfish, or Thyro-L.

The diagnosis of AF is made by ECG. The arrhythmia is characterized by an irregular R-R interval. The ventricular response rate is low, normal, or high, depending on the presence of heart disease or the severity of the primary disease. The ventricular complexes have normal polarity and amplitude but vary slightly in appearance from beat to beat. Similarly, the QT interval and appearance of the T wave vary. P waves are absent, replaced by fine undulations of the baseline called *fibrillation* or *f waves.* In some leads the f waves are barely visible, particularly in cattle (Fig. 30.31). In some cases, atrial flutter may be present with larger saw-tooth baseline undulations called *flutter* or *F waves*.

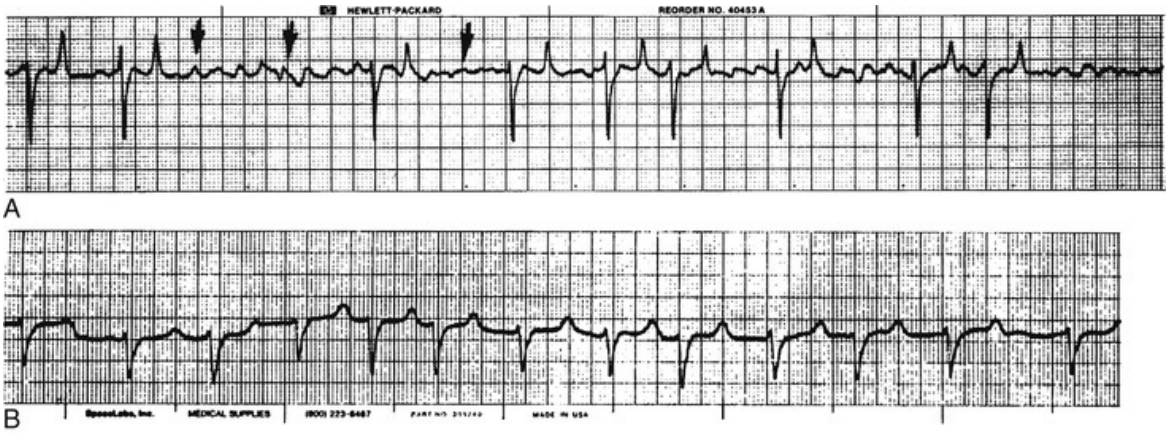


FIG. 30.31 Electrocardiograms showing atrial fibrillation in a horse **(A)** and cow **(B).** The irregular QT intervals and absence of P waves are apparent. *Arrows* point to fibrillation waves, which are apparent only in **A.**

The echocardiogram is used to determine whether cardiac disease is present. The most significant change associated with the arrhythmia is a mild reduction in shortening fraction (24% to 28%) that occurs, in part, secondary to the loss of the atrial contribution to ventricular filling.[291] Absence of the second (atrial) opening of the mitral valve, corresponding to atrial contractions, is also detected with AF.[292] Conversion to sinus rhythm usually results in these echocardiographic findings returning to normal within several days if there is no underlying myocardial disease.[291,293] Similar improvement occurs in horses with MR and AR after conversion to normal sinus rhythm.[293] In many large animals with AF, no evidence of heart disease can be detected echocardiographically; these animals are often considered to have “lone” AF. However, both electrical and structural remodeling of the atria occur in the horse with AF, which, although reversible early on, contributes to the persistence and recurrence of AF.[294–296]

Abnormal echocardiographic dimensions, if detected, indicate that underlying heart disease is present. Measurement of the maximal left atrial dimension in the two-chambered view of the left atrium and left ventricle from the left cardiac window should be performed in peak systole to determine whether there is left atrial enlargement. This measurement is a more sensitive indicator of left atrial enlargement than the M-mode left atrium–to–aortic root ratio. In normal Standardbred and Thoroughbred horses, the left atrial diameter in this view should be 13.5 cm or less. Measurement of the left atrium–to–aortic root ratio can be performed in the 2D short-axis view of the aorta across the maximal short-axis diameter of the left atrium to obtain additional information about left

atrial size.[24] Measurement of the maximal diameter and area of the left atrium can also be performed in the four-chambered view in peak systole if the heart can be imaged in its entirety.[24]

Cardiac catheterization reveals normal cardiac output and blood pressure measurements in most awake horses with AF, but conversion to normal sinus rhythm may induce a reduction in mean right atrial, pulmonary arterial, and aortic pressures.[297] Similar studies have not been reported in cattle.

Pathophysiology

Experimentally, rapid stimulation of the atrium can initiate AF, which can be sustained if the animal has a large heart and sufficient vagal tone.[281,298–301] In horses and cattle the normal atria may be large enough to support AF once it is established. In addition, both species have a high vagal tone at rest. This combination of factors may be responsible for the large number of benign or functional cases of AF in large animals. The ventricular response during AF results from rate-dependent concealment of AF wavelets bombarding the AV node.[283] Cardiac diseases such as endocarditis, atrioventricular valvular regurgitation, and CHF that result in atrial enlargement and rapid stimulation of the atria provide a setting in which AF can develop and can be sustained naturally. Microscopic cardiac pathology might also create the proper setting for the development of conduction block and reentry.

During AF there is no coordinated contraction of the atria, so ventricular filling is passive. Although this might be expected to reduce cardiac output, there is no evidence this occurs in resting horses without concurrent MR or AR.[297] In several horses with AR or AR with MR, a decreased cardiac output was detected compared with horses without valvular insufficiencies before conversion.[293] The cardiac output increased significantly in warmblood horses with valvular regurgitation after conversion. During exercise, however, the heart rate of horses with AF exceeds normal limits, often by 40 to 60 bpm for each level of exercise. This results in a decreased cardiac output and the resultant exercise intolerance that occurs in horses performing high-intensity athletic work. Even higher heart rates were reported in warmblood horses during lungeing exercise, with the majority of these horses exhibiting QRS complexes with abnormal morphology during exercise.[302] Blood flow to other organs and viscera, although not studied, may be altered in large animals with AF, resulting in reduced GI motility, colic,

reduced muscle blood flow, and poor milk production.

Atrial pressures are elevated in horses with AF.[297,303] Sustained high pressure is likely to produce dilation of the atria. With progressive dilation, secondary atrioventricular valve regurgitation may occur. During AF, blood flow to the atrial myocardium is reduced, and progressive fibrosis can also be a consequence of chronic AF. Sustained AF may result in progressive cardiac disease, although it is usually well tolerated in the horse.

Epidemiology

Standardbred, Thoroughbred, and draft horses have been reported to have the highest incidence of AF.[285,287,288] Racehorses have been diagnosed most frequently, but AF has been found in all types of horses.[287,288,293] Horses of all ages are susceptible to AF, but it occurs infrequently in ponies, foals, weanlings, and yearlings. Older horses, ponies, foals, weanlings, and yearlings with AF more frequently have underlying heart disease associated with the arrhythmia.

In cattle, AF is diagnosed more frequently in dairy cattle than in beef cattle, but there is no apparent breed predilection.[280,289] It is commonly associated with GI disease or abdominal pain in cattle.[280,281,289] Foot rot and pneumonia can also be associated with development of AF in cattle.

Necropsy Findings

Many cattle and horses have “lone” AF without apparent underlying heart disease, so the necropsy findings reflect the primary disease. Microscopic cardiac pathology has been found in horses with AF that consists of focal atrial myocardial fibrosis, microvascular alterations, and cardiac nerve abnormalities.[304–306] Multifocal or large areas of myocardial fibrosis were detected in dairy cows with idiopathic AF.[307] Whether these changes predisposed to the development of AF, were a consequence of AF, or were aging changes has not been established. A minority of horses and cattle have endocarditis, CHF, or valvular lesions, and the necropsy findings reflect these conditions. In horses with AF, mitral valve disease was the most common valvular lesion.[288] Pharmacologic and transvenous electrical cardioversion (TVEC) are both options for conversion of AF to normal sinus rhythm in horses.[288,308–319]

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Treatment and Prognosis

Quinidine is the drug of choice for pharmacologic conversion of AF to normal sinus rhythm in horses and cattle. The drug is a negative inotrope at high dosages, causes systemic hypotension, increases the ventricular response rate, and can produce undesirable side effects and toxicity—it must be used with caution. In animals with CHF, quinidine therapy has considerable risk.[288] Because most large animals have little or no underlying cardiac pathology, treatment with quinidine is usually successful in restoring normal sinus rhythm. Treated animals should be monitored frequently by physical examination, with careful auscultation and ECG recording. Continuous ECG recording using radiotelemetry should be performed throughout treatment.[311] Animals should have normal acid-base balance and electrolyte concentrations before treatment. They should be adequately hydrated, allowed to drink and eat, or given additional oral fluids (horses) or IV fluids (cattle) during therapy. IV administration of quinidine gluconate is successful in converting horses with recent-onset AF to sinus rhythm.[312] Quinidine gluconate is most successful when administered to horses with AF of 2 weeks or less. However, quinidine gluconate had been successful in converting horses with AF of 2 to 4 weeks' duration. Horses with longer durations of AF should be treated with quinidine sulfate via nasogastric intubation. Quinidine is poorly absorbed after oral administration to cattle, so it must be given by IV infusion to obtain therapeutic concentrations. Cattle should be given IV fluids during quinidine infusion. Quinidine therapy should always be discontinued when conversion to normal sinus rhythm occurs.

Quinidine sulfate is the preparation most economically used in large animals, although quinidine gluconate has resulted in successful conversion of a cow with AF.[320] Before therapy, a baseline ECG is recorded. Horses are given a dose of 22 mg/kg of body weight in a suspension of water via nasogastric tube. At 2 hours (when blood concentration of quinidine should have peaked), they are evaluated closely for idiosyncratic or toxic reactions, such as nasal edema, cutaneous reactions (urticaria or wheals), laminitis, colic, marked diarrhea, or ataxia. An ECG is recorded. If conversion to normal sinus rhythm has not occurred and the QRS duration is not greater than 25% of the pretreatment QRS duration, and none of the aforementioned abnormalities have occurred, another dose is administered. Two hours after each dose is administered via nasogastric intubation, an ECG is recorded. If there has been no conversion to normal sinus

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rhythm and the horse is not exhibiting toxic or adverse reactions to quinidine, another dose is administered, up to a maximum of four doses. A plasma quinidine concentration should be obtained 1 hour after the fourth dose administered every 2 hours to be sure the horse will be able to tolerate another dose without experiencing toxicity. If the QRS complex is prolonged by more than 25% of the pretreatment value or if a fast (>80 to 100 bpm) sustained supraventricular arrhythmia, ventricular rhythm, colic, marked diarrhea, ataxia, nasal edema, or laminitis develops, therapy should be discontinued. Although laminitis is a frequently reported complication of quinidine sulfate therapy in the older literature, the actual incidence of laminitis associated with quinidine administration is rare.[311] Nasal mucosal edema, neurologic signs, and prolongation of the QRS duration to greater than 25% of the pretreatment value are all signs of quinidine toxicity; if detected, the drug should be discontinued. Colic associated with high dosages of quinidine should also prompt discontinuation of treatment (at least for this attempt at conversion). If conversion has not occurred after a total of four to six doses (one every 2 hours) or after a cumulative dose of 88 to 132 mg/kg of quinidine sulfate has been administered, treatment intervals should be prolonged to every 6 hours (approximate half-life of quinidine).[311] Only four doses of quinidine sulfate should be administered every 2 hours before switching to every 6 hours if plasma quinidine concentrations cannot be obtained in a timely fashion. The every-6-hour treatment can be continued until the horse converts or shows toxic or adverse side effects or the owner elects to discontinue treatment. The advantage of this treatment regimen is that steady-state plasma and myocardial concentrations of the drug are usually achieved. There is less quinidine toxicity, a lower total dose of quinidine sulfate is used, and horses that did not convert after the standard every-2-hour administration may convert with this treatment regimen. Digoxin at 11 µg/kg PO twice daily can then be added to the therapeutic regimen if conversion has not occurred in 24 to 48 hours; it appears to be helpful in some horses.[311] Concurrent administration of digoxin and quinidine will result in an increased plasma digoxin concentration,[321] so to prevent digoxin toxicity, concentrations should be monitored beginning the second day of combined quinidine and digoxin therapy. If this is not possible, the horse should not receive more than 2 days of combined digoxin and quinidine therapy.

TVEC has been successful in converting horses to normal sinus rhythm and is the preferred treatment for equine AF in some hospitals with the necessary

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equipment and specialists trained in this procedure. TVEC is particularly useful in horses in which adverse or toxic reactions to quinidine prompted discontinuation of antiarrhythmic therapy with the result that conversion to normal sinus rhythm was not achieved.[316,319] TVEC is also the treatment of choice for horses that have marked resting tachycardia or excessively high heart rates. TVEC is also a good option for those with aberrant conduction or VA with sympathetic stimulation or exercise.

Quinidine sulfate at a dose of 48 mg/kg is suspended in 4 L of saline or lactated Ringer solution when cattle are treated for AF. This dose is administered at a rate of 1 L/h. IV fluids are administered simultaneously in the opposite jugular vein. Cattle should be monitored continuously during the infusion. Cattle frequently become depressed and develop diarrhea during the infusion of quinidine. These signs are side effects, and therapy can be continued. The infusion rate should be slowed if the ventricular response rate exceeds 100 bpm. If the QRS complex is visibly prolonged or a fast (>120 bpm) supraventricular arrhythmia or ventricular rhythm develops, therapy is temporarily discontinued. Just before conversion, some cattle have blepharospasm and are ataxic. The infusion should be discontinued as soon as conversion occurs. Therapy should be discontinued after the 4 L infusion even if conversion to normal sinus rhythm has not occurred.

During quinidine therapy the ECG shows predictable changes. The fibrillation waves become coarser and less frequent. The R-R interval becomes more regular as the heart rate increases. Before conversion there may be a rapid regular atrial rate with more than one saw-toothed flutter (F) wave or P wave for each QRS complex (atrial flutter or atrial tachycardia with atrioventricular block, respectively). At the time of conversion, a single P wave is present for each QRS complex. Frequently a large T_a wave is present and the ST segment is elevated. The ECG should be normal within 12 hours of conversion. A continuous 24-hour ECG is recommended in horses with AF after conversion to determine whether frequent atrial premature depolarizations are present. If the continuous ECG is normal and left atrial and ventricular function has returned to normal, the horse can be returned to training. If frequent trial premature complexes (APCs) are detected or left atrial contractile dysfunction persists, the horse should be rested and treatment with corticosteroids or antiarrhythmics considered. The horse should not be returned to work until the APCs have resolved and left atrial contractile function has returned to normal. IV amiodarone and flecainide have been used to convert horses with AF,[314,315,317] but amiodarone is less successful

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than quinidine for this purpose.[314,317] VA was common in horses given flecainide, limiting its usefulness as a treatment for AF in horses.[315]

The resting ventricular response rate should be less than 60 bpm in horses and 100 bpm in cattle before quinidine therapy. TVEC is the preferred treatment in horses with high resting heart rates and high heart rate responses to stimulation or during prior quinidine therapy. Digoxin is recommended before quinidine therapy in horses where TVEC is not an option and in cattle with fast heart rates. One or two doses of digoxin (11 µg/kg PO twice daily) are administered before initiation of quinidine therapy in horses with only mild tachycardia. In horses with very labile heart rates or problems with rapid ventricular response rate during a previous conversion, digoxin can be administered for up to 5 to 7 days before initiation of quinidine therapy. Cattle are given digoxin by IV infusion at 0.86 µg/kg/h or 11 µg/kg three times daily. The side effects of quinidine treatment (e.g., rapid ventricular response rate) may be decreased in animals pretreated with digoxin. Digoxin is also indicated as a pretreatment in horses with AF and very low FS (<24%), indicative of underlying myocardial disease. Because cattle with successfully treated primary GI disease frequently convert to normal sinus rhythm spontaneously—usually within 5 days of resolution of the primary problem—treatment is delayed for this period.[289] Cattle that do not convert spontaneously in 5 days, have chronic GI problems, or have AF with adverse hemodynamic effects (poor peripheral perfusion, weak arterial pulses, and/or pulse deficit) are selected for quinidine therapy. The prognosis for cattle with AF is good if the primary problem has been resolved and conversion to normal sinus rhythm occurs. Prognosis for cattle with chronic GI disease is guarded, but many show improved appetite and milk production when AF is resolved. Unless heart disease is present, few cattle experience a recurrence of AF. A small percentage of cattle fail to respond to quinidine therapy, and their prognosis is guarded to poor because milk production and appetite are intermittently poor and heart disease can be progressive.

Horses with paroxysmal AF have a good prognosis for return to performance, and few have a recurrence of the arrhythmia. If possible, predisposing factors such as transient potassium depletion should be removed by discontinuing furosemide administration or adding oral KCl to the diet. Oral bicarbonate milkshakes and thyroid hormone supplementation or supplements containing kelp or shellfish should be avoided. Horses with “lone” sustained AF have a good prognosis for conversion to normal sinus rhythm and a return to previous performance level.[287,288] Horses with sustained AF associated with mild to

moderate valvular regurgitation and atrial enlargement often have a recurrence of AF but can usually be successfully converted when indicated. Even mild MR is associated with an increased risk of recurrence of AF. Horses with heart rates over 60 bpm or with signs of CHF have a guarded to grave prognosis, and conversion to sinus rhythm is rarely warranted. Treatment of the underlying cardiac disease (if possible) is warranted, and the horse should be treated for CHF with digoxin, diuretics, and vasodilators as needed. Recurrence of AF and side effects of quinidine therapy are more frequent in horses that have had AF for longer than 4 months before treatment.[288] The recurrence rate for horses with recent onset AF is 15% and increases with longer duration AF up to 45% or more. This may be the result of atrial remodeling and the associated microscopic cardiac lesions that developed with chronic AF.

In horses with permanent AF or in those in which conversion of AF is not an option, an exercising ECG is indicated if ridden or driven exercise is desired, to be sure that these horses are safe to ride for an informed adult rider. The exercise test should be slightly more rigorous than their regular exercise, if possible. Their heart rates should not exceed 220 bpm at the maximal exercise desired. Heart rate control with oral digoxin or sotalol have been used to slow the ventricular response rate during exercise, but more work is needed to determine the efficacy and safety of this long term.[322] Those with aberrant conduction and multiform VA during exercise should be retired from ridden or driven work.[118]

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Ventricular Tachycardia

Definition and Etiology

Ventricular tachycardia (VT) is a cardiac arrhythmia characterized by a rapid rhythm originating in the ventricle. This rhythm originates below the bundle of His in the specialized conduction system, surrounding ventricular myocardium, or both.[323] VT may be caused by disorders in impulse formation, impulse conduction, or a combination of the two.[323] Ventricular reentry is an important mechanism in the genesis of sustained VT, whereas abnormal automaticity is probably responsible for idioventricular rhythms and parasystole. Changes in autonomic tone may also be important in the genesis of VT. Early afterdepolarizations are thought to be the mechanism responsible for ventricular tachyarrhythmias associated with sympathetic stimulation. Late coupled ventricular complexes or a very premature ventricular depolarization are usually required to initiate VT. VT can occur when there is myocarditis, myocardial necrosis, fibrosis, fibro-fatty infiltrate or neoplasia, bacterial endocarditis (especially involving the aortic or mitral valve), autonomic nervous system imbalance, hypoxia, ischemia, electrolyte or metabolic disturbances, anesthesia, drug administration, sepsis, endotoxemia, toxic myocardial injury, or aortic root rupture, or it may be associated with other, unknown causes.[96,233,248,324,325]

Clinical Signs and Differential Diagnosis

The clinical signs detected depend on the ventricular rate, type of VT (uniform or multiform), duration of VT, and severity of the underlying cardiac disease.[325] Large animals with VT may be asymptomatic at rest if the rhythm is relatively slow and uniform, or they may have severe CHF with rapid uniform or multiform VT.[325] Exercise intolerance is common and may be so severe that the animal has frequent syncope. Other complaints include depression, weakness, colic, respiratory distress, coughing, ventral edema, and pulmonary edema. Acute viral or bacterial respiratory disease with high fever may precede development of VT in horses or may occur concurrently with it. Gastrointestinal disease and primary myocardial disease are more common in horses with VT.[324,326] Horses with severe hemorrhage are also at increased risk for VA.[327] In

cattle, VT occurs most frequently secondary to sepsis and toxemia. Anorexia and decreased milk production are common in affected cows.

Animals with sustained VT have a rapid heart rate with a regular (uniform) or irregular (multiform) rhythm.[328–331] Heart rates as high as 300 bpm have been detected in horses with VT. Heart sounds vary in intensity, with some loud booming sounds ("bruit de cannon"). Arterial pulse may be variable or uniform, with normal (slower rate) or weak (rapid rate) intensity pulses. Pulse deficits frequently occur, particularly with rapid or multiform VT. Jugular pulses are commonly detected in large animals with VT. The large pulse waves seen in the jugular vein are cannon "a" waves that occur when the right atrium and ventricle contract simultaneously. Cardiac murmurs are not commonly detected. Signs of CHF are usually present when VT is rapid and sustained but are uncommon in animals with slower or paroxysmal VT.[328–330] Signs of right-sided CHF (ventral edema, venous distention) usually predominate with sustained uniform VT and increase in severity the longer the duration and more rapid the rate of the arrhythmia. Signs of left-sided CHF (coughing, expectoration of foamy fluid, respiratory distress) usually predominate with multiform VT.

The presence of jugular pulses and bruit de cannon in an animal with a rapid regular rhythm helps distinguish VT from sinus or supraventricular tachycardia. Multiform VT can be difficult to distinguish from AF, because both arrhythmias have an irregular rhythm with heart sounds that vary in intensity. Jugular pulses may also be detected in large animals with AF but are usually less prominent than in animals with VT. Although large animals with multiform VA usually have more severe clinical signs, an ECG is necessary to distinguish these arrhythmias.

Clinical Pathology

Electrolyte, metabolic, or toxic causes of VT may be present in large animals with primary GI disease. Hypomagnesemia and hypokalemia have also been associated with development of VT.[331] Serum creatinine and BUN may be elevated in horses and cattle in CHF associated with prerenal azotemia. Serum osmolality, BUN, and creatinine increase and urine osmolality decreases acutely in horses with experimental monensin toxicosis.[177] Initial decreases in serum potassium and serum calcium have also been reported in these animals. Marked elevations of cTnI have been seen in horses with VT.[195,196,326] cTnI is a more sensitive indicator of myocardial injury; therefore cTnI is currently preferred for

detection of myocardial injury in horses, cattle, South American camelids, and small ruminants. Cardiac isoenzymes of CK and LDH are often elevated if there is recent myocardial injury associated with VT. Elevation of the myocardial fraction of CK (CK-MB) in excess of 5% of the total CK is compatible with myocardial injury in horses.[177] A neutrophilic leukocytosis, elevated SAA, and hyperfibrinogenemia may be detected in animals with infectious myocarditis or bacterial endocarditis or may be elevated owing to the primary underlying disease. In most large animals with VT, however, hematologic findings are normal.

The diagnosis of VT is made from the ECG. A series of four or more ventricular premature complexes (VPCs) is diagnostic of VT.[324,332] The electrocardiographic appearance of the VPC may be widened and bizarre, or the QRS duration and appearance of the QRS and T may be near normal, especially in horses (Fig. 30.32).[324,325] Although the duration of QRS complexes that are ventricular in origin is usually within the normal range reported for horses, it is usually longer than the QRS duration of the horse's normal sinus beats.[324] The major direction of the QRS complex is usually oriented opposite to that of the T wave. The R-R intervals may be regular or irregular. The morphology of the QRS complexes may be similar (uniform) or may vary widely with multiform VT (Fig. 30.33). Atrioventricular dissociation is usually present, with an atrial rate slower than the ventricular rate. Fusion beats and capture beats may be detected. VT can be sustained or paroxysmal.

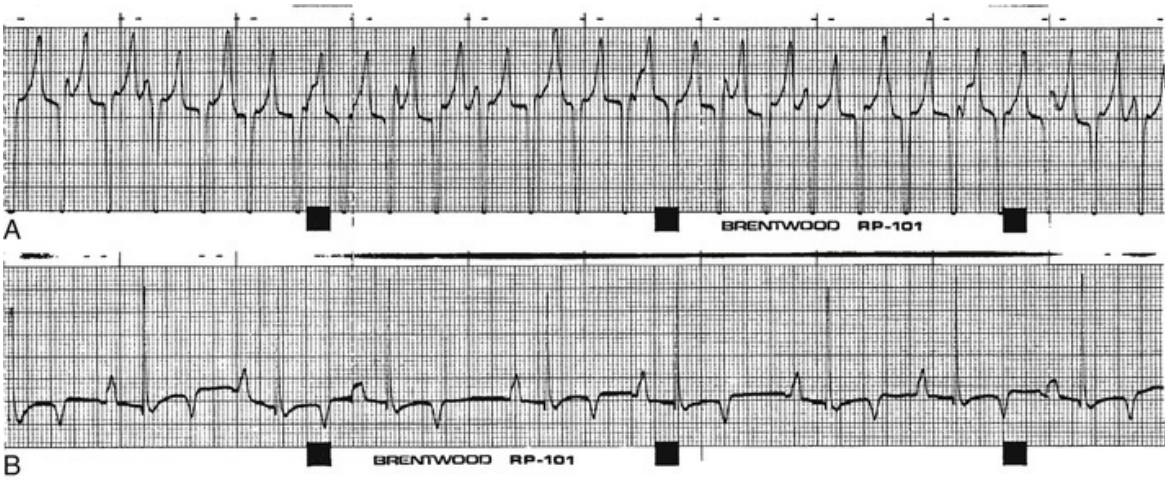


FIG. 30.32 Lead II electrocardiogram obtained from a horse with sustained uniform venticular tachycardia (VT) and congestive heart failure

before **(A)** and after **(B)** conversion to sinus rhythm. Note the abnormal QRS and T configuration and slower atrial rate during the sustained VT.

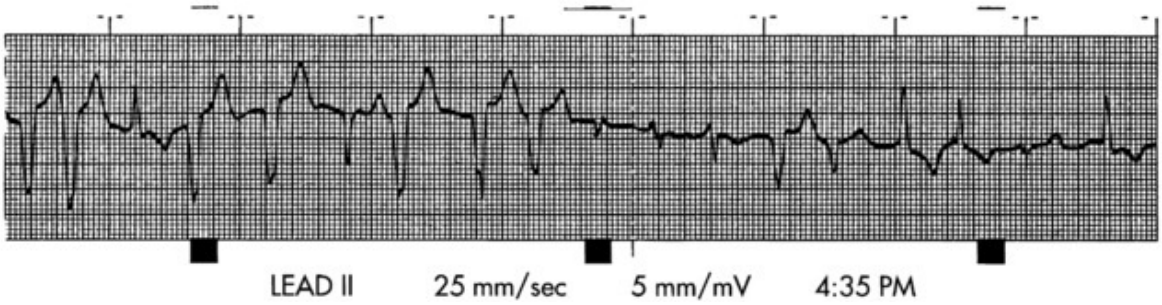


FIG. 30.33 Lead II electrocardiogram obtained from a horse with multiform ventricular tachycardia and acute onset of pulmonary edema. Note the multiple different QRS and T configurations and the elevated ventricular rate.

The echocardiogram is used to determine whether cardiac disease is present. The echocardiogram is usually abnormal in large animals with primary myocardial disease and normal in large animals with secondary VT, except for the changes associated with the VT itself (see Fig. 30.15). Abnormal echocardiographic findings that may be detected in large animals with primary myocardial disease include myocardial dyskinesis, hypokinesis, and akinesis; abnormal myocardial echogenicity; decreased FS, ET, and EF; loss of the normal systolic and diastolic undulations of the aortic root; and detection of spontaneous contrast, small aortic root, and large pulmonary artery. Occasionally the echocardiographic abnormalities created by VT may be difficult to distinguish from those of primary myocardial disease. Rupture of the aortic root at the right sinus of Valsalva should be considered in horses with acute onset of uniform VT and colic.

Cardiac catheterization may reveal severe hypotension and low cardiac output. In healthy ponies with pacing-induced VT, stroke volume decreased significantly when the ventricle was paced at 150, 200, and 250 bpm.[333] Mean left atrial pressure, mean pulmonary arterial pressure, and right ventricular systolic pressure increased significantly when the ventricle was paced at 220 and 250 bpm. Aortic pressure and cardiac output decreased in these ponies at 250 bpm, but the decrease from resting values was not statistically significant. Myocardial perfusion in the papillary muscles and subendocardium decreased significantly

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with pacing-induced VT at a rate of 250 bpm. Decreases in cardiac output, arterial blood pressure, and myocardial perfusion are even more marked in animals with underlying myocardial disease or multiform VT, as are the changes in left atrial, pulmonary arterial, and right ventricular pressure.

Pathophysiology

VT is probably initiated spontaneously by late coupled ventricular complexes, whereas one very early ventricular premature depolarization can often initiate VT electrically.[323] Sympathetic stimulation may also provoke VT by increasing the amplitude of the early afterdepolarizations, culminating in a run of VT.[323] This may be the mechanism of some of the exercise-induced VT in horses. Reentry in the ventricle is an important cause of sustained VT, particularly in human patients with dilated cardiomyopathy and ischemic heart disease. The area of reentry is reportedly small (<1.4 cm^2).[323] Reentry is also thought to be an important mechanism in horses with sustained VT.[330,334,335] Delayed afterdepolarizations may trigger VT in humans and dogs and may be the mechanism for digitalis-induced VT.[323] Abnormal action potentials have also been demonstrated in ventricular myocardium resected from human beings with recurrent VT.[323] Depressed automaticity and afterdepolarizations have been associated with acute myocardial ischemia, whereas automaticity and afterdepolarizations are enhanced in Purkinje fibers surviving myocardial infarction. Idioventricular rhythms and parasystole may be caused by abnormal automaticity.

Cardiac diseases such as endocarditis may result in septic myocardial emboli and myocardial ischemia. Aortic root rupture and dissection of blood into the interventricular septum disrupts conduction and usually results in a uniform VT. Myocarditis, myocardial necrosis, and fibrosis or a fibro-fatty infiltrate also may result in abnormalities of impulse formation and conduction, leading to VT.[336] The excitement of the high-performance situation (sympathetic stimulation) and the decreased myocardial perfusion that may occur at peak exercise may make exercise-induced VT more common in racehorses and other types of high-performance horses.

Epidemiology

VT has been reported in all large animals, although horses may have the highest incidence. VT leading to ventricular fibrillation is thought to be one of the leading causes of sudden cardiac death in horses when other causes of death cannot be found on postmortem examination.[335,337,338] Male horses are at increased risk for aortic root and sinus of Valsalva rupture and are usually middle-aged at the time of rupture. However, aortic rupture has been seen in horses as young as 3 years of age. VT is also more likely in large animals of any age with primary GI disease and in horses following severe hemorrhage.

Necropsy Findings

If VT is not associated with primary myocardial disease, necropsy findings reflect the underlying disease. Gross and microscopic cardiac pathology has been found in horses with VT (see Fig. 30.30), although in some horses no cardiac pathology is found. Areas of myocardial necrosis, inflammatory cell infiltrate, fibrosis, fibro-fatty infiltration, infarction, microvascular alterations, and cardiac nerve abnormalities have been reported in horses with VT.[305,330,335,336] CHF is most likely in large animal patients with multiform VT and heart rates in excess of 180 bpm. Bacterial endocarditis and secondary septic emboli dissemination through the coronary arteries as a result of VT occurs in a minority of large animal patients. Aortic root rupture and rupture of a sinus of Valsalva aneurysm with dissection of blood into the interventricular septum are infrequently detected in horses.

Treatment and Prognosis

Treatment and prognosis for VT depends on the suspected cause of the arrhythmia, severity of the animal's clinical signs, and electrocardiographic abnormalities detected.[324,325] Relatively slow, uniform VT often resolves or improves significantly with correction of the underlying electrolyte or metabolic imbalances, without requiring antiarrhythmic therapy. These animals usually have an excellent prognosis for conversion with correction of the underlying problem. Similarly, in large animals with sepsis or toxemia, hemodynamically and electrically stable VT often resolves with treatment of the underlying disease. Uniform, hemodynamically stable VT in animals with myocarditis may resolve with rest and/or corticosteroid therapy. A minimum of 4 to 8 weeks of rest is indicated in these patients before returning to work, once the VT has

resolved.

Treatment with antiarrhythmics is indicated in any animal with hemodynamically unstable or life-threatening VT. Treatment with antiarrhythmics is indicated if clinical signs of CHF or cardiovascular collapse are present or if the rate of sustained VT is extremely high. In horses with sustained uniform VT, a heart rate in excess of 120 bpm usually warrants antiarrhythmic therapy, whereas in cattle, antiarrhythmic therapy may not be indicated until the heart rate exceeds 140 bpm or greater. Horses with rapid sustained uniform VT (≥120 bpm) need antiarrhythmic therapy, because signs of CHF will develop after several days or weeks with this arrhythmia, if not already present. Rapidity of CHF onset is related to heart rate and type of primary myocardial disease, if present. These horses usually have a good prognosis for conversion and return to their previous performance level with appropriate antiarrhythmic therapy (many times three or more antiarrhythmic drugs must be tried before conversion occurs) and rest before the horse is returned to work.

ECG findings associated with life-threatening VT include a multifocal origin for the ventricular premature depolarizations, torsades de pointes (wide VT), and the presence of an R wave superimposed on the preceding T wave (“R on T”). Large animal patients with clinical signs of CHF and hemodynamic collapse with rapid (heart rate <120 bpm) multiform VT (±R on T) should be treated as a cardiovascular emergency; sudden death from ventricular fibrillation is likely without antiarrhythmic therapy. Large animals with multiform VT (±R on T) must be given a guarded to grave prognosis for survival because most have severe underlying myocardial disease. Often conversion to sinus rhythm may not be successful before the animal develops ventricular fibrillation and dies. If successfully converted to sinus rhythm, many of these animals die or are euthanized because of the severity of the underlying cardiac disease.

Several antiarrhythmic choices are available to the large animal practitioner for correcting life-threatening VT (see Table 30.3). Lidocaine hydrochloride—the most readily available drug for most large animal practitioners—is rapidly acting, administered IV, and has a short duration of action and minimal hemodynamic effects. However, this drug has central nervous system side effects in horses (hyperexcitability and seizures) and must be used at a lower dosage than in cattle. Quinidine gluconate (or quinidine sulfate in cattle) is effective in large animals but is less rapidly acting, has negative inotropic effects at large doses or if primary myocardial disease is present, causes hypotension, and can produce undesirable adverse or toxic reactions. Magnesium sulfate can cause

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hypotension but has no other recognized adverse cardiovascular effects. It is less rapidly acting than lidocaine, but in both normomagnesemic and hypomagnesemic patients it may be effective when other antiarrhythmics fail. IV procainamide, IV and oral propafenone, and IV flecainide have also been used successfully in horses with VT. IV propafenone is indicated for refractory VT and has been used successfully in several horses that did not respond to lidocaine, quinidine, procainamide, or magnesium sulfate. However, it is currently unavailable in the United States. Sotalol has been successful in several horses with VT and is available in an intravenous formulation.[339] Other antiarrhythmics such as propranolol have been used with less success but have converted large animals with sustained VT.

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• CHAPTER 31

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Diseases of the Respiratory System

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▪ Diagnostic Procedures for the Respiratory System

General Evaluation of the Patient With Respiratory Disease

Kara M. Lascola • Pamela A. Wilkins

History

As with any disease process, acquisition of an accurate and appropriate history is the first step undertaken in evaluating the patient with a complaint thought to be related to the respiratory tract. Animals with respiratory disease may have widely varied histories, so a thorough anamnesis is necessary. Age and breed may play a role in the development of respiratory disease, such as congenital defects or neoplastic disease, or in inherited or acquired immunodeficiency syndromes seen in certain breeds. The environment in which the animal is maintained can contribute to the development or severity of respiratory disease. For example, equine recurrent airway obstruction (RAO) and inflammatory airway disease (IAD) may manifest following a change to a new environment. Stressful events, such as weaning or long-distance transport, can predispose both horses and cattle to respiratory disease. It is important to know if certain diseases are either endemic or epidemic where the animal is kept or has recently resided. Any recent traumatic or potentially traumatic event should be noted. A thorough vaccination history should be obtained, as should an accurate history of any treatments or supplements and the patient's response.

Presenting Signs or Chief Complaints

Unilateral or bilateral nasal discharge is a common finding or complaint associated with respiratory disease. Respiratory noise at rest or during exercise is commonly associated with abnormalities of the upper airway and may accompany inequalities of airflow present at the nares. Normal animals may periodically cough or sneeze, but an increase in either activity may indicate involvement of the respiratory tract. Exercise intolerance or reduction in athletic

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performance should prompt evaluation of the respiratory system. Other clinical signs that should encourage the clinician to conduct a thorough evaluation of the respiratory tract include abnormal breathing patterns (tachypnea, hyperpnea, dyspnea), cyanosis, hemoptysis, epistaxis, unusual swellings (facial, pharyngeal, cervical), lymphadenopathy, ataxia or reluctance to move, foul smell to the breath, weight loss, and ventral abdominal, sternal, or limb edema.

Physical Examination

The initial physical examination occurs at some distance from the patient and involves evaluation of the demeanor, posture, mental status, and way of movement of the patient. It is important to note if the patient has an abnormal stance, such as standing with the head and neck extended. If the patient is unwilling to move or stands with elbows abducted, this suggests that pleural pain is present. Ideally the respiratory rate can be determined by observation, as can the respiratory pattern. Although some respiratory diseases are not manifest at rest, important clues can be gained from observation of the patient at rest in many others. The normal resting respiratory rate of an adult horse is 8 to 16 breaths/min, of adult cattle is 15 to 35 breaths/min, and of sheep and goats is 12 to 20 breaths/min. There is some small abdominal component during the expiratory phase. The normal rate for neonates is up to 60 breaths/min at birth and less than 30 breaths/min by 1 month of age; respiratory rate decreases toward the adult rate with age. High ambient temperature, fever, and excitement can all increase respiratory rate. Normal breathing, which is quiet and apparently effortless, is termed *eupnea.* The term *dyspnea* is a breathing pattern that is inferred by the observer to reflect difficulty in breathing; the animal will appear distressed, and the work of breathing is obviously increased, although the actual rate may be within normal limits. Other terms used to describe breathing patterns include *tachypnea*, characterized by rapid rate and shallow depth or low tidal volume; *hyperpnea*, with increased frequency and depth of breathing (an example would be during postexercise recovery); and *apnea*, in which there is no discernible breathing. Two additional terms include *hypoventilation* and *hyperventilation*, both of which require a change in arterial carbon dioxide partial pressure as a component of their definitions. Hyperventilation is a pattern that increases alveolar ventilation and causes arterial hypocapnia, whereas hypoventilation alters gas exchange in such a way to cause arterial hypercapnia, or retention of carbon dioxide.

Closer examination can reveal some of the physical manifestations of

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presenting complaints listed previously. Beginning with the head, the clinician should determine that airflow is even from both nostrils, as differences can indicate either congenital or acquired abnormalities ranging from choanal atresia to the presence of upper airway masses. Abnormal respiratory sounds can sometimes be present at rest and may be heard at the nares. Abnormal breath odors may be detected. The frontal and maxillary sinuses should be percussed; identification of abnormal resonance, usually dullness, may be made easier by performing this with the mouth held open. Palpation of the submandibular regions, larynx, and pharyngeal and cervical regions should be performed to identify any abnormal lymph node enlargement, masses, or areas of muscular atrophy. Both jugular veins should be checked for patency and the presence of any evidence of injection sites or infections that may contribute to abnormal upper airway function by interfering with normal recurrent laryngeal nerve or vagosympathetic trunk function.

Coughing represents a nonspecific irritation of receptors in the airway and can be induced by many mechanisms. It can be, and usually is, a normal protective reflex that allows the animal to clear material from the airway. Cough can be associated with increased mucus production, production of other respiratory secretions, or decreased mucociliary clearance. In older horses cough is often associated with severe RAO, whereas in younger horses cough is more commonly associated with infectious diseases and IAD (see discussion of these disorders later in this chapter). Normal animals should not cough when the larynx or trachea is palpated.

Nasal discharge can be unilateral or bilateral, scant or copious, clear, mucoid, mucopurulent, or even bloody. The nature and character of nasal discharge can provide some information about a possible source of the discharge, but this information should not be overinterpreted. Horses, for example, have a tendency to swallow excess airway secretions, and the volume of secretions may be underestimated. Whereas unilateral nasal discharge is often suggestive of a source in front of the larynx, bilateral nasal discharge can be of either upper or lower airway origin. Skin depigmentation of the ventral nares or presence of mucoid material in feed or water containers are clues to the presence of nasal discharge.

Hemoptysis is the coughing up of blood from the airways or lungs. It is important to determine conclusively that the blood has come from the respiratory system. Epistaxis is defined as blood seen at the nares and often originates in the nasal passages, sinuses, turbinates, nasopharynx, or equine guttural pouches,

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although the lung can be, and is, a source on occasion, as in exercise-induced pulmonary hemorrhage (EIPH) or following lung biopsy. Bilateral epistaxis generally indicates bleeding caudal to the choanae. Because animals tend to swallow excessive respiratory secretions, bleeding can be occult and may not be seen unless the animal drops its head toward the ground. Significant blood loss can occur in this manner, unseen by owners.

Examination of the oral mucous membranes may reveal cyanosis, which is bluish discoloration of the oral, nasal, or vulvar mucous membranes. Cyanosis does not become apparent until approximately one third of the total normal hemoglobin is deoxygenated; this reflects a profound decrease in oxygen saturation of hemoglobin and is suggestive of severe hypoxemia. Since the total quantity of deoxygenated hemoglobin lends the mucous membranes the bluish color, very anemic patients may lack sufficient deoxygenated hemoglobin to appear blue, which makes appreciation of cyanosis impossible in these patients. One caveat is that all newborns are cyanotic for the first few breaths and only become pink when they have established neonatal, as opposed to fetal, cardiorespiratory circulation and have fully inflated their lungs to allow for gas exchange.

It is important that auscultation of the thorax take place in as quiet an environment as possible. In addition, auscultation of the lung fields should be performed under two breathing conditions, eupnea and hyperpnea, with the latter induced by the use of a rebreathing maneuver (bag). The purpose of this technique is to cause the animal to rebreathe its own expired carbon dioxide. The resultant increase in Pa_{CO_2} stimulates deeper and more frequent breathing efforts, making recognition of abnormal lung sounds simpler. The rebreathing bag must be large enough to accommodate two to three times the normal tidal volume of the animal and should be held in such a manner as to prevent the bag from occluding the patient's nostrils. Once the bag is removed, the animal will usually take several very deep breaths, and the examiner should take advantage of these breaths to reexamine areas where suspicious sounds were heard during rebreathing. Coughing and prolonged time of return to baseline respiratory patterns should be noted. This technique is contraindicated in animals demonstrating increased respiratory effort at rest.

Normal breath sounds are those produced by turbulence within the tracheobronchial tree and may vary considerably depending on location within the lung, breathing pattern, and condition of the animal.[1] Only airways from the larynx to segmental bronchi contribute to sound generation. Vesicular sounds—

the quietest sounds, heard over the middle and diaphragmatic lung regions—correlate best with regional ventilation and mainly represent segmental bronchial sounds; they do not represent airflow in terminal conducting airways and alveoli, which is silent due to the nature of its flow. Bronchial sounds are louder and heard best over the trachea and base of the lung. Common abnormalities found during auscultation include ventral areas of dullness if pleural effusion is significant, dorsal areas of dullness or hyperresonance with pneumothorax, and dorsal harsh lung sounds. The degree of variation in normal lung sounds is large, and auscultatory findings do not always correlate well with the degree of lung abnormality. That said, abnormal lung sounds are always potentially clinically important.

Adventitious lung sounds are divided into short discontinuous sounds called *crackles* and longer continuous sounds called *wheezes*, replacing the older terms *rales* and *rhonchi*, respectively. Crackles are most commonly generated by sudden pressure equalization when collapsed airway segments open. Although an air-fluid interface is required, crackles do not necessarily imply excessive secretions or pulmonary edema. They are often end-inspiratory and associated with reinflation of atalectatic lung. Crackles may be normal when auscultated in the newborn or over the previously down-side lung of a laterally recumbent neonate. Disease processes that generate crackles include pneumonia, interstitial fibrosis, chronic obstructive lung disease, congestive heart failure, and atelectasis.[2]

Wheezes commonly represent oscillation of airway walls before complete closing (expiratory) or opening (inspiratory). Intrathoracic airways are usually involved in expiratory wheezes and include the lower trachea and main, lobar, and segmental bronchi. Disappearance of a wheeze after coughing indicates secretory rather than tissue component origin. Disease processes responsible for wheezes include airway stenosis or external compression, airway lumen compromise by a foreign body, purulent material, cyst or neoplasm, bronchoconstriction, and airway wall thickening as occurs in chronic bronchitis. Expiratory wheezes are a hallmark of obstructive lung diseases such as RAO. Crackles and wheezes may be variably present. A final category of adventitious sounds is the “rubbing” or “creaking” sounds generated by sliding or stretching of inflamed pleural surfaces, commonly termed *pleural friction rubs.*

Percussion of the thorax is performed by methodical tapping over the intercostal spaces of the thorax using a variety of instruments, including plexors, pleximeters, spoons, or fingers. It is of relatively low diagnostic sensitivity but

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may be useful particularly when thoracic ultrasound is not available. It should be performed when pleural effusion is suspected and in all ruminants to detect occult pneumonia. Percussion can reveal hyporesonance (dullness) ventrally when pleural effusion is present, reveal hyperresonance dorsally in pneumothorax, and cause some patients with pleurisy to exhibit pleurodynia (pleural pain). Other conditions that can alter resonance of the thorax include diaphragmatic hernia with intrathoracic intestine, pericardial effusion, pulmonary and pleural abscessation, and consolidated lung. It is usually impossible to fully delineate the lung field cranially because of body fat and triceps musculature. There is a distinct region of cardiac dullness for all species on the left side.

Additional Diagnostic Evaluation of the Respiratory Tract

Endoscopy

The upper airway can be directly examined with the aid of an endoscope, the only limitations being the size of the patient, the patency of the airway, available means of restraint, and the size of the available equipment. Standard flexible fiberoptic endoscopes allow direct examination of the nasal passages, ethmoid turbinates, nasal maxillary opening of the sinuses, pharynx, guttural pouch openings, larynx, and cranial trachea (Fig. 31.1). Smaller (8 to 10 mm in diameter) endoscopes can be readily introduced into the equine guttural pouches, with the aid of a biopsy instrument, and longer bronchoscopes (200 to 250 cm) are commonly used to examine main stem bronchi and their initial branches in large animals. Smaller species may require the use of a smaller diameter (3 to 5 mm) endoscope or bronchoscope. Small brushes, used for collecting exfoliated cells for cytologic study, and a variety of biopsy instruments can be used for sampling the airway.

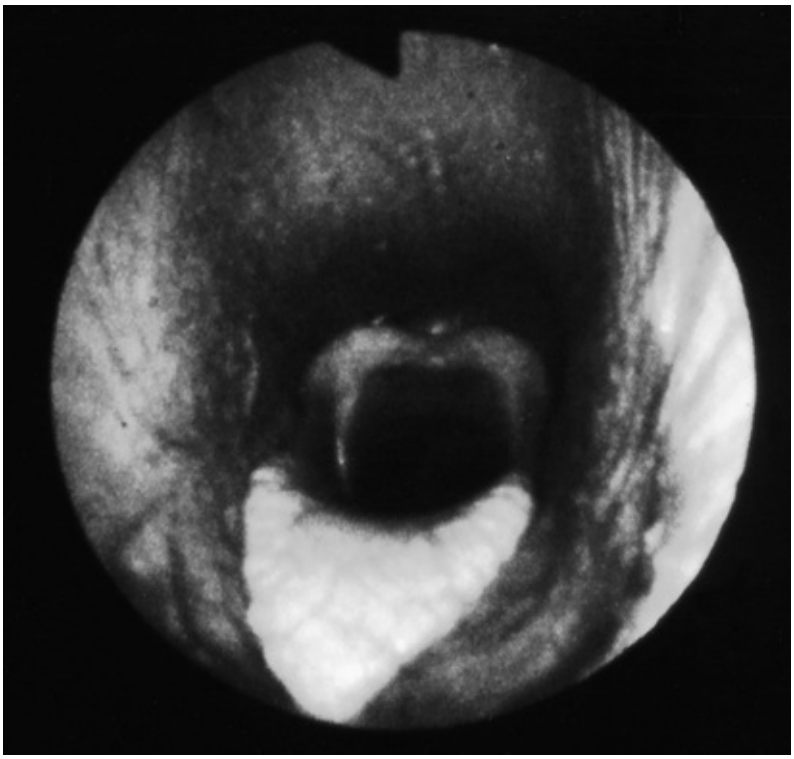


FIG. 31.1 Normal equine larynx. The larynx is directly visualized by endoscopy, with both structure and symmetry evaluated. (Courtesy Dr. Corinne Sweeney, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)

Airway endoscopy in the horse has evolved to include dynamic respiratory endoscopy (e.g., high-speed treadmill, overground endoscopy) during exercise to evaluate the dynamic function of the upper respiratory tract.[3-5] Objective measurements can be made using videoendoscopy with slow motion or freeze-frame features.[3] Treadmill endoscopy is available at specialty practices and typically is performed at high speed (12 to 14 m/s) using incremental standardized testing protocols. Overground telemetric endoscopy is performed during ridden exercise in the field with endoscopy equipment that is attached to the horse.[4,5] Advantages of overground endoscopy include the ability to evaluate the horse under saddle and in natural working conditions. However, standardizing exercise tests in the field may be more challenging. While resting endoscopy can detect many abnormalities involving the upper airways, dynamic upper airway obstructions that develop during exercise may be missed. In these situations dynamic endoscopy, if available, is the preferred diagnostic tool.[5] Sedation or tranquilization will aid many standing endoscopic examinations, but examinations aimed at evaluating pharyngeal and/or laryngeal function are best

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performed without any form of chemical restraint that might alter function. Most horses will allow standing examination of the upper airway with only physical restraint, such as judicious use of a nose twitch. Introduction of the endoscope into the trachea may elicit coughing. Small ruminants, such as sheep and goats, may require local tracheal administration of 2% lidocaine diluted to a 0.2% to 0.3% solution. If lidocaine is used in small ruminants, it must not reach a toxic dose (~6 mg/kg). Diluted lidocaine can similarly be used in horses and cattle for evaluation of the distal trachea, main stem bronchi, and larger bronchial tree branches. Horses are more sensitive to tracheal and bronchial stimulation and are more likely to require lidocaine than are cattle.

Guttural pouch diseases and upper airway abnormalities, such as pharyngeal lymphoid hyperplasia, laryngeal hemiplegia, epiglottic entrapment, dorsal displacement of the soft palate, pharyngeal cysts, retropharyngeal masses, and epiglottic deformities, are best diagnosed by endoscopic examination. Direct tracheobronchoscopic examination is useful for the diagnosis of tracheal diseases such as tracheal collapse or trauma as well as for the diagnosis of lower airway abnormalities such as EIPH and mild to moderate equine asthma (IAD). Bronchoscopy may also be useful for evaluating additional lower airway abnormalities, including severe equine asthma (RAO), tumors, or abscesses. The degree and nature of airway secretions accumulating in the trachea can be easily assessed with an endoscope, and scoring systems for tracheal mucus and blood have been developed for the diagnosis of mild to moderate IAD[6] and EIPH,[7] respectively. Accumulated secretions in the trachea and distal airways may be sampled by aspirating the secretions through small tubing introduced through the biopsy channel of the endoscope. Because the endoscope has passed through the nonsterile upper airway, samples collected without the use of a sterile, double- or triple-lumen guarded tube are best suited for cytologic, not microbiological, evaluation but may be fully compatible with evaluation using molecular diagnostic techniques.[8-11] Endoscopy has also been used to help remove foreign bodies from the airway, generally aided by the biopsy instrument.

Endoscopic evaluation of the thoracic cavity (thoracoscopy) can be performed in horses under sedation or general anesthesia[12] and has also been described in healthy cattle.[13] The procedure can be useful for the evaluation and treatment of conditions such as thoracic neoplasia, pleuropnemonia or other pleural disorders, and thoracic trauma. Thoracoscopic-guided lung biopsies can also be performed in the horse.[14] Thoracoscopy is performed using standard laparoscopic

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equipment, including a rigid endoscope, camera, monitor, light source, and insufflation systems when performed under general anesthesia. The provision of supplemental oxygen is essential, and ventilatory support may become necessary during standing procedures.

Diagnostic Imaging

Radiography.

Radiographs are indicated for evaluation of congenital abnormalities, diseases, or trauma involving the respiratory tract or thoracic cavity. Radiographs are frequently performed along with endoscopy or thoracic ultrasound for more thorough evaluation of the upper respiratory tract or lower respiratory tract and thoracic cavity, respectively. Portable equipment needed to perform radiographic evaluation of the upper airway is available in the majority of private practices, while most large referral and university practices have the equipment needed to perform thoracic radiography in larger patients such as adult horses and cattle. Portable systems are generally suitable for thoracic imaging in foals or calves, camelids, and small ruminants. Digital radiography has replaced traditional film-screen radiography in many practices and referral clinics. Advantages to digital systems include portability, speed of image acquisition and processing, and immediate on-site image display as well as a greater range of radiographic exposures and tools for image manipulation.[15,16]

Skull and cervical radiographs offer diagnostic information for evaluation of the upper respiratory tract, including the sinuses, pharyngeal and laryngeal structures, and the extrathoracic trachea. For large animal species, standing lateral skull films are easily obtained, whereas ventrodorsal and oblique projections often require sedation. Certain difficult patients may require general anesthesia. Sinuses affected by neoplasia or inflammation may show abnormal tissue density, a horizontal fluid line on a standing lateral film, bone lysis around the affected sinus, or alveolar periostitis. Thorough evaluation of the sinuses and nasal passages requires lateral, dorsoventral, and oblique views. Foreign bodies may be detected if they are radiopaque. The equine guttural pouches are evident on lateral skull projection, and abnormal fluid accumulation, distortion by enlarged retropharyngeal lymph nodes, and emphysema can be identified.

Radiographic assessment of the thorax of large animals remains preferable to ultrasonographic examination for detection of diffuse parenchymal diseases, such as interstitial pneumonia, pulmonary edema, equine multinodular

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pulmonary fibrosis, fungal pneumonia, acute respiratory distress syndrome (ARDS), chronic disorders, and deep parenchymal or mediastinal abscesses. Radiographic changes can be nonspecific for a particular disease or minimal to nonexistent in diseases such as EIPH or mild IAD. The thorax in adult horses and cattle is filmed as standing lateral, generally requiring a series of three to four separate but overlapping images to capture the entire lung field; thus the benefit of the ventrodorsal view, in which the two lungs may be compared, is lost. Bilateral standing radiographs may aid in localizing lesions to one hemothorax or the other. In neonates and small ruminants the entire lung field can be imaged in one to two views, and as these animals can be more readily handled and restrained, multiple recumbent views are possible. If significant accumulation of pleural fluid is suspected, ultrasonographic examination should be performed first and radiographs obtained following drainage of excess fluid, as fluid may obscure potentially important parenchymal disease.

Four types of radiographic patterns are described for the thorax: alveolar (airspace), interstitial, bronchial, and vascular. In the alveolar pattern, opaque areas coalesce and fully obliterate vessels and bronchi, and air bronchograms may be prominent. This pattern is commonly found in pulmonary edema, pulmonary hemorrhage, equine multinodular pulmonary fibrosis, ARDS, pneumonia with lung consolidation, and neoplasia. Interstitial patterns are the most common pattern noted in equine thoracic radiographs and are characterized by a blurring of the edges of pulmonary vessels, a diffuse increase in lung density, and variable reticular, linear, and nodular opacities. The *reticular* pattern is most commonly associated with more diffuse infectious lung diseases, pulmonary edema, interstitial pneumonia, and pulmonary fibrosis, whereas the irregular *linear* pattern is seen most commonly with resolving bronchopneumonia. *Nodular* opacities are consistent with abscesses, granulomata, and neoplasms. It is rare to see a pure bronchial pattern in a horse; it is usually seen in association with an interstitial pattern. An exception is paired linear opacities or numerous small circular opacities (donuts) representing thickening of large or medium airways in equine bronchitis or bronchiolitis. The vascular pattern is seen in horses radiographed immediately after exercise or in animals with left-to-right cardiac shunts. Finally, extraparenchymal problems such as pleural effusions or free gas may be seen on thoracic radiographs of large animals. Thoracic radiology is far less sensitive than ultrasonography for evaluation of potential rib fractures.

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Computed Tomography and Magnetic Resonance Imaging.

Advanced radiographic modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) have become increasingly available at academic and private referral practices and can aid in the diagnosis and characterization of certain upper airway disorders in large animal species. Advantages to these systems are that they provide high-resolution three-dimensional imaging and minimize superimposition of overlying structures that may complicate interpretation of skull radiographs. An additional advantage of CT is the high speed of image acquisition. Standing CT units allow for imaging of the head and proximal cervical region in sedated adult horses, thus eliminating the need for general anesthesia. CT provides excellent bone and soft-tissue contrast and is often used in the diagnosis of sinonasal disorders such as dental-related sinus disease, neoplasia, and ethmoid hematomas.[17] MRI provides superior soft-tissue detail, and its use is also described for the diagnosis of laryngeal and sinonasal disorders in adult horses.[18,19] MRI is currently more limited in its application toward routine use in large animal species because of the availability of equipment, time required for acquisition of images, and potential costs associated with the procedure.

CT imaging has also become a more desirable tool for the diagnosis of pulmonary and extrapulmonary thoracic disease in hospitalized veterinary species, particularly as the considerable reduction in image acquisition time often eliminates the need for general anesthesia. CT thoracic imaging in large animals is limited to small ponies, foals, calves, and smaller species such as camelids, where it has been described in healthy and sick animals with pulmonary and extrapulmonary disease.[16,20-22] Imaging of the thorax is not possible in larger animals due to restrictions in currently available CT gantry diameters and limitations associated with exposure settings needed to penetrate a larger torso.

Ultrasonography

Thoracic ultrasonography is useful for diagnostic, therapeutic, and prognostic evaluation of the extraparenchymal thorax, the pleural space, and the peripheral (superficial) parenchyma of the lung and should be considered for complete evaluation of any large animal with pulmonary disease. Unlike thoracic radiography in adult large animals, thoracic ultrasonography is an imaging technique readily available to most practitioners. In many instances it is superior

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to thoracic radiography; examples include evaluation of pleural effusions, assessment of thoracic trauma and rib fractures, evaluation of neoplasms or granulomata, detection of mediastinal masses or abscesses, and guidance of transthoracic lung biopsy.[23-25] Field ultrasonography has also become an important tool in monitoring dairy calves for bovine respiratory disease.[26]

Ultrasonography is generally performed with the patient standing, although in neonates lateral recumbency may be preferred or even necessary.

Although ultrasound waves will not penetrate the aerated portion of the lung, limiting the examination to extraparenchymal surfaces in normal horses, ultrasonography is superior to thoracic radiography for the evaluation of these areas of the chest. Small amounts of pleural fluid that would be missed on auscultation, percussion, or thoracic radiographs can be detected, and the amount and character of pleural effusion in each hemithorax can be evaluated separately.[23] Clear fluid is anechoic, but inflammatory cells, gas, and fibrin are echogenic, causing opacities that can be seen floating in pleural fluid and altering the general echogenicity of the fluid. Because of this, ultrasound is the method of choice for diagnosis and monitoring of pleural space disease. Ultrasonography should be used to guide catheter placement for thoracocentesis. The pleural surfaces are imaged well by ultrasound with thickened or roughened areas easily detected. Lack of normal independent movement of the visceral and parietal pleural surfaces during the respiratory cycle, suggestive of adhesion formation, can be readily monitored.[23,24]

Consolidated lung is a better acoustic medium than aerated parenchyma and can be well visualized. Pleuropneumonia with consolidation or atelectasis caused by compression of the ventral lung by pleural effusion can be evident. Pulmonary abscesses or masses extending to the lung surface can be imaged, and ultrasound can be used for guidance during transthoracic biopsy.[23,24] Thoracic radiography remains superior to ultrasound in the diagnosis of pulmonary parenchymal disease and pneumothorax; the two techniques can be combined to optimize diagnostic capacity.

Nuclear Medicine Imaging

Nuclear scintigraphy is a specialized technique available at a few specialty referral practices. Gamma-emitting radioisotopes, most commonly technetium-99m, can be used with an external detector (gamma camera) to assess regional pulmonary ventilation and perfusion in the horse. For perfusion scans, the

radioisotope is bound to albumin aggregates and injected into a peripheral vein. The aggregates become trapped in the pulmonary arterial vasculature, and the resulting image illustrates the perfusion distribution of the pulmonary arterial system. The ventilation scan is generated when the horse inhales aerosolized radioisotope particles through a closed circuit system.[27] The particles are small enough in diameter to be deposited in the alveoli and small conducting airways, with the gamma camera recording the sites of deposition. Together, the ventilation and perfusion scans allow for evaluation of the ventilation/perfusion (V/Q) ratio, important in evaluation of certain respiratory problems such as chronic EIPH (high V/Q areas), pulmonary thromboembolism (high V/Q areas), and RAO (low V/Q areas). Additional uses are in the evaluation of deposition in the lung of aerosolized radiolabeled medications such as albuterol[28] and in the evaluation of mucociliary clearance or tracheal mucus transport where the time required for a bolus of radioisotope to cover a given tracheal distance is evaluated.[29]

Arterial Blood Gas Analysis

Arterial blood gas measurement is the most sensitive indicator of respiratory function readily available to the clinician. The most easily accessed arteries for sampling are the metatarsal, temporal, facial, and brachial arteries (Fig. 31.2). In cattle the coccygeal artery on the ventral aspect of the tailhead is easily accessible. Heparin is the only acceptable anticoagulant for blood gas samples, and all gas bubbles must be removed and the syringe capped to prevent equilibration of the sample with room air. A short (1-inch), small-gauge (25-gauge) needle and a 1- to 3-mL syringe should be used. Preheparinized syringes with needles can be purchased, or regular syringes and needles may be heparinized by aspirating a small volume of heparin into the syringe via the needle and then forcefully expelling the air and heparin from the syringe three times. This minimizes the effect heparin might have on any reported values from the blood gas analyzer. Pulsation of blood from the needle, spontaneous filling of the syringe, and bright color of the blood all confirm a successful arterial puncture. If arterial puncture is questionable, a comparison sample may be drawn from the jugular vein. Once the sample has been drawn, the vessel should be manually compressed for 2 to 5 minutes to prevent hematoma formation. If the sample will not be analyzed within 10 minutes, it should be placed on ice to slow blood cell metabolism. The patient's body temperature at the time of

sampling should also be recorded, as results are frequently reported at both 37° C and as *temperature-corrected values* at the actual rectal temperature of the patient for pH, P_{O_2}, and P_{CO_2} because these values are known to be temperature variable. Clinically, either set of values may be used, but comparisons should be made only between samples reported similarly as either temperature corrected or not. The ranges of normal arterial blood gas values for nonneonates of various species are listed in Table 31.1.



FIG. 31.2 Arterial blood sample drawn from temporal artery for arterial blood gas analysis. (Courtesy Dr. Eric Birks, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)

TABLE 31.1

Normal Arterial pH and P_{CO_2} Values for Various Species (Nonneonate)

Species	Blood pH	P_{CO_2} (mm Hg)
Bovine	7.32-7.45	35-53
Ovine	7.32-7.54	37-46
Equine	7.32-7.44	38-46
Caprine	7.42-7.46	33-38

Portable blood gas analyzers are relatively inexpensive and easy to use and provide rapid return of results, making blood gas analysis in large animals more practical in the field.[30,31] Awareness of potential device-, species-, or age-related

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differences in reference ranges, as well as awareness of any limitations in accuracy, is critical for proper interpretation of results. Pulse oximetry is also used in some institutions and referral centers. These monitors measure oxygen saturation of hemoglobin, which is useful for diagnosing severe hypoxemia or recognizing desaturation events, but provide no measure of actual arterial oxygen and carbon dioxide partial pressures; as such, these monitors do not replace arterial blood gas evaluation for assessing adequacy of pulmonary gas exchange.

The most common abnormality recognized with arterial blood gas analysis in an animal that is breathing room air is hypoxemia with normocapnia, hypocapnia, or hypercapnia. Hypoxemia is defined as decreased oxygen tension of the arterial blood (decreased Pa_{O_2}), whereas hypoxia is defined as decreased oxygen concentration at the level of the tissue, with or without hypoxemia. Hypoxia results from hypoxemia, decreased perfusion of the tissue bed in question, or decreased oxygen-carrying capacity of the blood due to anemia or hemoglobin alteration. There are five primary means by which hypoxemia develops in any animal: (1) low partial pressure of oxygen in the inspired air, such as seen at high altitude or in an error mixing ventilator gas (altered Fi_{O_2}); (2) hypoventilation; (3) V/Q mismatch; (4) diffusion limitation; or (5) intrapulmonary or intracardiac right-to-left shunting of blood. Mild to moderate hypoxemia is not an uncommon finding in neonates, but it must be evaluated in terms of the current age of the foal and its position. The difficulty in obtaining the sample must also be considered, as severe struggling can variably affect the arterial blood gas results.

Hypercapnia (increased Pa_{CO_2}) develops in response to hypoventilation and may also represent respiratory failure if the lung is significantly involved in the underlying pathology, such as with severe pneumonia or ARDS. It is important to try to distinguish between acute and chronic hypercapnia. Acute hypercapnia is usually accompanied by a relatively dramatic decrease in blood pH of 0.008 pH units for each 1-mm Hg increase in Pa_{CO_2}. This respiratory acidosis can promote circulatory collapse, particularly in the concurrently hypoxemic and/or hypovolemic patient. The effects of more chronic CO_2 retention are less obvious as the time course allows for adaptation. The pH change is less, about 0.003 pH units per 1-mm Hg increase in Pa_{CO_2}, as it is balanced by enhanced renal absorption of bicarbonate by the proximal renal tubule. Most patients with acute respiratory distress are in the acute stages of respiratory failure, but chronic

adaptation will begin to occur within 6 to 12 hours and will be maximal in 3 to 5 days. An increase in bicarbonate will be noted, particularly if the acidosis is primarily respiratory in origin, and pH may be within the normal range.

Alveolar gas exchange is readily estimated by determining the alveolar-arterial (A-a) gradient for oxygen, computed by subtracting the Pa_{O_2} measured by the arterial blood gas from the calculated alveolar oxygen partial pressure (PA_{O_2}). The PA_{O_2} is effectively estimated using the partial pressure of inspired oxygen (Pi_{O_2}) as follows[32]:

$$PA_{O_2} = \frac{Pi_{O_2} - Pa_{CO_2}}{0.8}$$

The Pi_{O_2} equals the total barometric pressure (760 mm Hg) minus the partial pressure of water vapor (47 mm Hg) multiplied by the fraction of room air that is oxygen (0.21) and thus equals 150 mm Hg for room air at sea level. For patients on supplemental inspired oxygen, the practitioner must remember to recalculate the Pi_{O_2} with the new oxygen fraction (Fi_{O_2}) (or, if at altitude, the P_{O_2} in the inspired gas), which is only possible in patients receiving inspiratory gas through a closed system. The Pa_{CO_2} is obtained from the arterial blood gas measurement. The A-a gradient is normally only 4 to 10 mm Hg; an increase beyond this indicates impaired gas exchange within the lungs, most often the result of V/Q mismatching. Only an estimate of the A-a gradient can be calculated in patients receiving intranasal insufflation of oxygen, as neither the Fi_{O_2} nor the P_{O_2} is known.

A second useful measurement is the Pa_{O_2}/Fi_{O_2} ratio, a component of most definitions of ARDS.[33,34] The Pa_{O_2}/Fi_{O_2} ratio equals the Pa_{O_2} obtained from the arterial blood gas divided by the Fi_{O_2}. The normal Pa_{O_2}/Fi_{O_2} ratio in most adult animals is greater than 300 mm Hg. In nonneonatal veterinary species, a Pa_{O_2}/Fi_{O_2} ratio of 201 to 300 mm Hg is consistent with veterinary acute lung injury (VetALI), whereas a ratio of 200 mm Hg or less suggests veterinary ARDS (VetARDS). Modified definitions of VetALI and VetARDS exist for neonatal foals (EqNALI and EqNARDS) to account for the relative hypoxemia of normal neonatal foals compared with adults during the first week of life.[35] These conditions are described in greater detail in a later section of this chapter (Acute Respiratory Distress Syndrome).Respiratory Function Testing

Numerous techniques have been developed to evaluate respiratory function. Techniques already discussed in this section include arterial blood gas evaluation for assessing efficiency of gas exchange by the lung and videoendoscopy for the

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qualitative evaluation of upper airway function. Additional techniques that allow for quantitative measurements of upper airway and pulmonary mechanics that influence normal transport of gas from the periphery to the site of gas exchange are available. In most systems, measurements of pressure, flow, and volume allow for the computation of a variety of ventilatory parameters such as respiratory frequency, minute volume, and tidal volume as well as determination of airway resistance and impedance. Pulmonary function testing is performed in horses for the diagnosis and characterization of equine asthma[36-38] and has been described in healthy adult camelids.[39,40] These techniques are primarily limited to use as research tools.

A variety of techniques have been described for the evaluation of upper airway mechanics in exercising horses. In addition to acquiring measurements of ventilatory parameters, these systems may also allow for the construction of pressure volume curves to assess the work of breathing or tidal breathing flow-volume loops to detect and characterize airway obstruction.[41] Assessment of airway muscle activity using electromyography and respiratory sound analysis have also been described in exercising horses.[42,43] One of the major limitations associated with evaluating airway function in exercising horses is the equipment required for these tests. Face masks equipped with a pneumotachograph or pneumotachometer are required to obtain measurements of airflow, whereas nasotracheal or percutaneous tracheal catheters coupled to pressure transducers are used for measurements of airway pressures. These systems may be cumbersome for the exercising horse, may impede achievement of maximal speeds, or may introduce error into results by altering airway mechanics. Recently an ergospirometer has been described that holds promise for acquiring measurements of oxygen consumption (V_{O_2}) and ventilatory parameters in exercising horses under field testing conditions.[44]

Collection and Evaluation of Respiratory Secretions

Tracheal Aspirates and Bronchoalveolar Lavage.

Various spaces in the respiratory system can be aspirated or lavaged for diagnostic or therapeutic purposes. The most commonly performed procedure is the percutaneous tracheobronchial aspirate. By aspirating from the airways caudal to the larynx, a sample without pharyngeal contamination can be obtained. As discussed previously, endoscopically guided tracheobronchial

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aspirates can be obtained, and these compare favorably with traditional percutaneous tracheobronchial aspirates provided that a protected aspiration catheter is used.[8]

In both the horse and the ruminant, the procedure is performed with the animal standing. Sedation or restraint may be needed. A small area over the trachea in the middle third of the neck is clipped and routinely sterilely prepared. The skin is anesthetized using a local block of 2% lidocaine (2 to 3 mL subcutaneously), and a small stab incision is made. A sterile trocar or needle (10-gauge) is introduced on the midline between muscle bundles, with the beveled edge facing ventrally (pointed edge facing dorsally) to decrease the opportunity for inadvertent cutting of the tubing when it is introduced or manipulated, and the ventral tracheal wall is punctured between two cartilaginous rings. The distal end of the trocar or needle is then advanced distally in the trachea, taking care not to lacerate the dorsal tracheal mucosa. Sterile polyethylene tubing or catheter is introduced through the trocar or needle for about 30 cm. A needle or sharp trocar should be withdrawn to prevent severing the tubing or catheter, but a trochar with rounded edges may be left in place. Approximately 20 to 30 mL of nonbacteriostatic sterile isotonic saline solution is introduced quickly. Intermittent aspiration is performed as the tubing is gradually withdrawn. The tubing can be advanced again if a guarding cannula has been left in place to prevent introduction of skin contamination. Additional saline solution aliquots can also be introduced. Once an adequate sample has been obtained, the tubing is completely withdrawn, followed by the withdrawal of the needle or trocar. Commercially available tracheobronchial aspiration kits are also available for use with horses and foals. Injectable antimicrobial solution or suspension can be infiltrated at the skin incision site if a septic sample is suspected, and in horses and small ruminants a sterile dressing can be applied for 24 hours if desired.

Possible complications include subcutaneous emphysema (usually peritracheal but may extend into the mediastinum), local cellulitis, or cutting of the catheter at the needle and loss into the airway. The latter is usually resolved because the catheter is rapidly coughed up, but if necessary, the severed catheter can be retrieved endoscopically. This complication can be readily avoided by using commercially available kits that use a trochar instead of a needle (MILA [MILA International, Elanger, Ky.]), eliminating the needle point that can sever the catheter. The sample should be cultured for aerobic bacteria, and anaerobic cultures should be made if these organisms are suspected based on evidence of pleural effusion, lung consolidation, abscessation, fetid breath, or history of

aspiration. For patients with prior antimicrobial therapy, it is advised to discontinue antibiotics for 72 to 96 hours before culture when possible.

A direct smear and Gram stain can be used as an initial guide for antimicrobial therapy pending culture results. Cytologic evaluation can be extremely valuable in differentiating among infectious, allergic, parasitic, and neoplastic processes. If fluid evaluation cannot be performed shortly after collection, it should be stored at 4° C for no more than 24 hours to avoid neutrophil degeneration or bacterial overgrowth. Transtracheal aspirates from clinically normal horses contain columnar ciliated epithelial cells, a few neutrophils, and multiple mononuclear cells. The presence of squamous epithelial cells suggests oropharyngeal contamination, which may occur if the animal coughs during sample collection. Increased percentages of neutrophils and the presence of mast cells, eosinophils, giant cells, and hemosiderophages have been found in aspirates from normally performing Thoroughbred racehorses, indicating some airway inflammation in "normal" equine atheletes.[10] Mucus, large spores, and fungal hyphae may be found in the absence of airway disease and must not be overinterpreted. In cases of pneumonia, neutrophils may constitute 40% to 90% of the cellular sample. Bacterial pneumonia causes a more degenerate appearance of neutrophils, and intracellular bacteria may be found. Equine lungworm is characterized by the presence of large numbers of eosinophils and occasionally larvae. In ruminants, the most important information gathered in patients with bronchopneumonia is usually the result of culture and antimicrobial sensitivity testing.

Bronchoalveolar lavage (BAL) involves obtaining a sample from the terminal airways and alveolar region and is described in horses, cattle, and camelids.[40,45,46] BAL is performed using a long endoscope (200 to 250 cm) or BAL tube (e.g., double-lumen or cuffed Bivona [Smiths Medical, Norwell, Mass.] or MILA [MILA International, Elanger, Ky.]) introduced through the nares. Endoscopic BAL allows for more exact placement of the end of the endoscope, so a clear understanding of the anatomic location of the distal airway lavage is available. It also allows for the characterization of lower airway secretions and mucosal inflammation. Use of the BAL tube is a blind technique, but most frequently the right dorsal lung is sampled.[47] BAL is contraindicated in horses that are expected to exercise within 24 hours of the procedure and in any animal demonstrating signs of respiratory distress, marked tachypnea, paroxysmal cough, or significant hypoxemia.

Proper sedation and restraint is critical for performing BAL. In horses, the

addition of butorphanol may reduce cough that is typically associated with this procedure. Instillation of 0.2% to 0.3% lidocaine, particularly when passing the tube into the trachea or past the level of the carina, may also decrease cough. Passage of the tube into the trachea can be facilitated by stretching the head horizontally. The endoscope or tube should be passed until it is wedged in the most distal bronchus. If using a cuffed BAL tube, the cuff should be inflated to seal the airway once wedged. In adult horses, it is recommended to infuse a total of 250 to 500 mL of warm (37° C), sterile physiologic saline in aliquots of 60 to 250 mL. Smaller lavage volumes may be necessary in foals or smaller species. Fluid may be instilled via prefilled syringes or via a solution administration set using a pressure bag with fluid bag or pressure bulb with fluid bottle. The BAL fluid sample is collected via gentle continuous aspiration with syringes or a suction pump using low suction pressure. Cytologic interpretation does not appear to be influenced by method of fluid collection, but syringe aspiration may minimize the potential for barotrauma in certain horses.[48] Fluid aliquots recovered should be pooled for analysis. The presence of surfactant (foam) and turbidity on gross inspection is suggestive of a properly obtained sample.

BAL has the advantage of sampling the distal airways, but only a limited area of the lung is sampled instead of the pooled secretions from a tracheobronchial aspirate. Bronchoalveolar lavage is considered superior to tracheobronchial aspirate in evaluation of horses with diffuse chronic lung diseases of the peripheral airways. Molecular analysis of fluid can be performed for identification of certain viral or bacterial species. Cytologic findings of BAL and tracheobronchial aspirates correlate poorly, and the latter should be performed prior to BAL if bacterial pneumonia is suspected. Bronchoalveolar lavage cytology is valuable for evaluation of suspected fungal infections, equine asthma, and EIPH. Similar to tracheobronchial fluid, BAL fluid should be processed within a few hours or stored at 4° C. Normal cell distribution of BAL fluid in healthy horses (based on 250-mL lavage volume) reveals predominantly macrophages (50% to 70%) and lymphocytes (30% to 50%) with lower percentages of neutrophils (<5%), mast cells (<3%), and eosinophils (<0.1%).[38] Infused BAL volumes of less than 250 mL will not adequately lavage the distal alveoli and may correspond to falsely increased neutrophil and decreased macrophage numbers.[38] Macrophages are the predominant cell type (89%) in BAL fluid of healthy calves,[46] whereas alpacas may have a greater abundance of neutrophils (10%).[40]

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Bronchoscopically or endoscopically guided airway brushing can also be performed for the collection of airway epithelial cells. Cells should be obtained with gentle brushing to avoid trauma and can be collected at several locations along the airway. Cytologic analysis can be performed on direct smears or on cells preserved in fixative solution.

Thoracocentesis

Aspiration from the pleural space is a simple procedure that can be both diagnostic and therapeutic. In the horse with septic or neoplastic effusions, sedation is often unnecessary because the procedure causes only minimal additional discomfort. Following ultrasonographic evaluation of the thorax, a point is chosen where drainage or fluid sampling would seem most appropriate, frequently found in the sixth or seventh intercostal space 10 cm dorsal to the olecranon and above the lateral thoracic vein. The area should be clipped and surgically prepared. Multiple sites may be needed in horses with loculated pockets of fluid in the pleural cavity. The skin and intercostal tissue down to the pleura are anesthetized with lidocaine, and a stab incision is made. A sterile 2- to 3-inch teat cannula or bitch catheter is introduced immediately cranial to the rib border. The cannula should be attached to sterile intravenous (IV) extension tubing and a three-way stopcock. While the cannula is advanced bluntly through the parietal pleura, a sudden loss of the force required to advance is felt. Aspiration should be attempted at this time. The orientation of the cannula can be varied to reach as much fluid as possible. Normally only a few milliliters of straw-colored fluid are obtained. In cases of pleural effusion, as much as 30 L may be removed from each side of the chest (Fig. 31.3). If fluid is excessive, the tubing can be extended over a bucket for gravity drainage, or a vacuum pump with a fluid trap can be attached. When the procedure is complete, a purse-string suture is placed around the stab incision and the cannula is withdrawn while the suture is tightened. In cases where the effusion is large and expected to continue forming for several days, the drainage can be performed by placing a chest tube instead of a teat cannula. If a chest tube is to be left in place, it should be secured with a Chinese finger-trap suture and the end covered by a Heimlich valve to prevent aspiration of air into the thorax through the tube. If the thorax is being drained rapidly, the patient should be watched carefully for signs of distress, as draining of large volumes can alter cardiovascular parameters significantly.

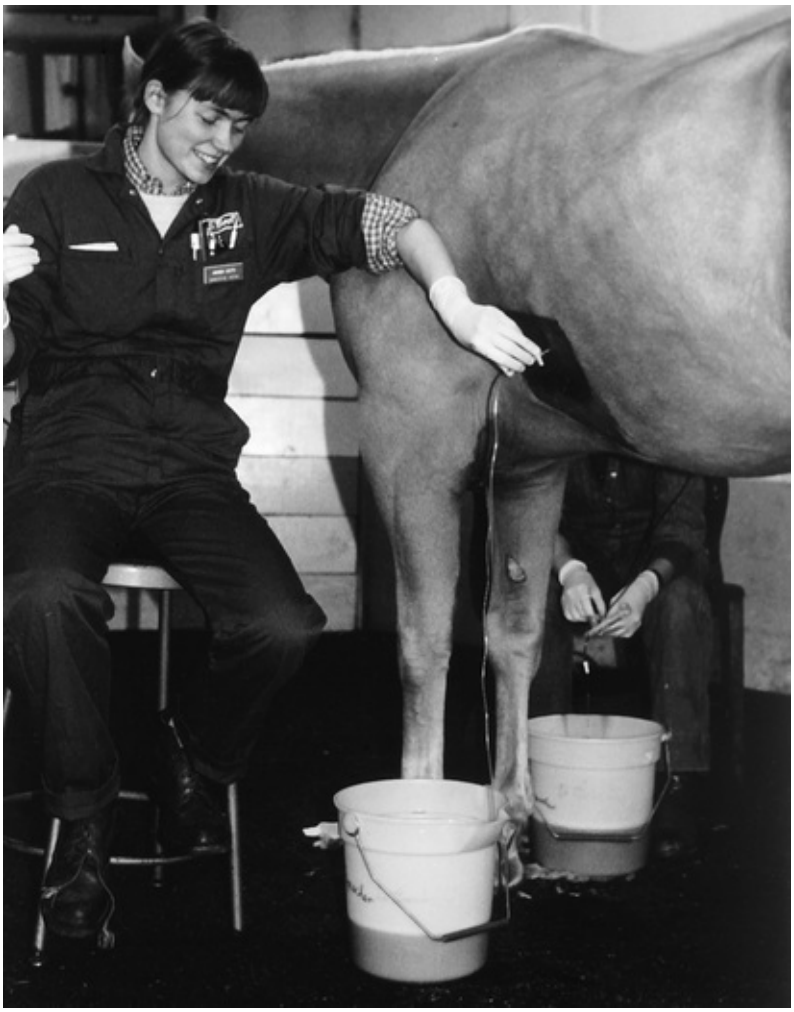


FIG. 31.3 Thoracocentesis and therapeutic drainage in the horse. Pleural effusion can be large and bilateral. Samples should be obtained for culture and cytologic examination at the time the chest is drained. (Courtesy Dr. Corinne Sweeney, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)

Increasing opacity, presence of fibrin clumps, and malodor of pleural fluid all suggest relative progression from transudate to septic exudate containing inflammatory cells and debris. A putrid odor suggests the presence of anaerobic bacteria. Samples should be cultured for aerobic and anaerobic organisms. A white blood cell (WBC) count of 10,000/mL or less is considered normal; fewer than 60% are normally neutrophils, the remainder being lymphocytes and macrophages. The proportion and total number of neutrophils increase with pleuritis. Erythrocytes are normally not present in the absence of a traumatic tap. The protein concentration is normally less than 3.5 g/dL, and pH should be approximately 7.4. Additional metabolic values that give early indication of

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sepsis can be obtained on pleural fluid samples collected after filtration through a blood administration set to remove fibrin and debris potentially detrimental to analytic equipment. Pleural fluid pH, P_{CO_2}, and concentration of glucose, lactate, and bicarbonate can be directly compared with similar analysis of venous blood from the patient. A septic pleural exudate is acidic, with decreased glucose and bicarbonate but increased lactate and P_{CO_2} compared with venous blood concentrations or tensions, apparently reflecting metabolic activity of phagocytic cells and bacteria and development of an anaerobic environment.[49] Of these values, low pleural fluid glucose concentration (<40 mg/dL) has the best correlation with sepsis.[50]

Neoplastic cells may be found in cases of lymphosarcoma, adenocarcinoma, or other neoplasms. Equine gastric squamous cell carcinoma occasionally presents with neoplastic pleural effusion. If neoplastic effusion is suspected but diagnostic cells do not exfoliate into the pleural fluid, thoracoscopy can be used directly to visualize and obtain biopsy samples of intrathoracic lesions.

Mediastinal fenestrations may be occluded by fibrin and cell debris; therefore each side of the thorax should be evaluated separately. In the horse, a transtracheal aspirate for culture should also be performed because of the common association of pleuritis with bacterial pneumonia and pulmonary abscessation. Although identical organisms are generally isolated from both samples, this is sometimes not the case.

Sinus Trephination

Sinus trephination is performed in horses or ruminants and may be indicated when serosanguinous or foul-smelling and purulent nasal discharge, facial malformation, exophthalmos, stertorous breathing, or epistaxis are detected on physical examination and when sinus percussion and imaging findings support it. Trephination is useful for diagnostic aspiration, drainage, and flushing of the sinuses. Sinoscopy may also be indicated, particularly when the true extent of the disease process is difficult to determine or if biopsy samples are needed.

In the horse the frontal, sphenopalatine, and ethmoidal sinuses communicate with the posterior chamber of the maxillary sinus and drain through the nasal maxillary opening into the middle meatus. The anterior chamber of the maxillary sinus is separated by an osseous septum that often breaks down with infection, making the posterior chamber of the maxillary sinus the most productive site for diagnostic aspiration. A line is drawn from the medial canthus of the eye

perpendicular to the facial crest. After tranquilization and local anesthesia, the sinus is approached with a Steinmann pin midway on this line. Once the sinus has been entered, it should be aspirated using a sterile 16-gauge needle or canine urinary catheter. One skin suture will suffice for closure. If purulent material or fluid within the sinus is under pressure, some leakage into the subcutaneous space may occur, with resulting cellulitis. The sample should be cultured for aerobic and anaerobic bacteria and examined cytologically for signs of septic inflammation or neoplastic cells.

The frontal sinus is trephined more often for flushing in chronic cases than for diagnostic purposes. The approach is 2.5 cm lateral to the midline of the face and 2.5 cm caudal to the point where the nasal bones begin to diverge.

In cattle the frontal sinus is most often affected, with septic inflammation as a consequence of dehorning. Purulent material frequently accumulates in the postorbital diverticulum of the sinus. The landmarks for sinus trephination in cattle are described later in this chapter.

Postdehorning sinusitis in goats can be a severe condition, especially in animals dehorned when mature. The frontal sinus contains numerous septae, creating poor drainage; the bony plate protecting the brain is thin, so that septic necrosis of bone leading to meningitis may occur. Therefore in mature goats with sinusitis, appropriate systemic antimicrobial therapy and vigorous curettage of the affected areas should be conducted.

Guttural Pouch Catheterization

When indicated by radiography and/or endoscopy, the equine guttural pouches are easily catheterized for diagnostic sampling and lavage. Sampling can also be achieved by placing thin tubing through the biopsy channel of the endoscope, as for tracheobronchial aspiration, and directly aspirating or aspirating after introduction of sterile saline. Lavage can also be performed through the biopsy channel. The patient should be heavily sedated so that the head drops, facilitating drainage of the secretions by gravity. A Chambers mare catheter can be passed blindly through the ventral meatus into the pharynx. The curved end is directed beneath the flap of the medial lamina of the pouch ipsilateral to the nostril used for passage. Successful passage is indicated by lack of resistance while the catheter is inserted deeper than if it were in the pharynx. The position of the catheter tip in the pharynx can be observed through an endoscope placed up the opposite nasal passage. Once the catheter is within the pouch, it can be used to obtain a sample, to drain excessive secretions, or to act as a conduit for flushing.

A self-retaining uterine catheter can be left in place for repeated flushing, but the Chambers catheter can be passed repeatedly with no complications.

Airway and Lung Biopsy

Biopsy of the airways or lung is most often performed in the horse and is indicated to obtain a histologic diagnosis or prognostic information primarily in cases of diffuse lung or airway disease. Endobronchial biopsy is performed for the collection of airway samples, whereas parenchymal samples are obtained by means of percutaneous or thoracoscopically guided collection techniques. For endobronchial biopsy, multiple samples can be collected along the upper and lower airways. Histologic analysis of endobrochial samples collected from peripheral airways may have clinical utility for diagnosis of RAO in horses.[51] Thoracoscopically guided pulmonary wedge resection is also an option for collection of a larger parenchymal tissue sample and enables direct visualization of the lung prior to biopsy. The procedure is relatively safe but is more invasive and requires specialized equipment and expertise.[14] For percutaneous biopsy, use of a spring-loaded biopsy instrument with a large-gauge (14-gauge), 15-cm or longer biopsy needle and a sample “slot” length of 22 mm is recommended. Discomfort is minimal, and sedation may or may not be needed. The site for biopsy should be determined following ultrasonographic evaluation and should be away from common locations of major pulmonary vessels. Caudal and dorsal locations are generally chosen. The site should be surgically prepared and infiltrated with local anesthetic down to the pleura. The biopsy needle is inserted through a stab incision just cranial to the rib and directed medially through the intercostal muscles and parietal pleura. The needle should be advanced the distance indicated by ultrasonographic measurement, then sharply advanced less than 1 cm to enter the lung parenchyma and the spring-loaded instrument “fired” to obtain the sample; the biopsy instrument is then withdrawn. After sufficient biopsy specimens have been obtained, a single skin suture can be placed at the incision site, but no additional aftercare is needed. A specimen should be placed directly in 10% formalin or glutaraldehyde for fixation with additional samples submitted for bacterial and fungal culture, and potentially for more advanced molecular diagnostic techniques. Complications of lung biopsy have been reported to range from transient epistaxis or hemoptysis, which is to be expected, to more severe pleural and parenchymal hemorrhage. Lung biopsy is not indicated for pleuropneumonia cases but is generally required to differentiate

between equine multinodular pulmonary fibrosis, discrete fungal lesions, and potential neoplasia, when accurate diagnosis is required for therapeutic and prognostic purposes.

Techniques for Identification of Respiratory Pathogens

Infectious respiratory disease can have significant individual and herd health implications. Timely and definitive identification of the causative agents is necessary to ensure that the appropriate therapeutic, prophylactic, and biosecurity protocols are instituted. Although infectious respiratory disease may represent a diagnostic challenge for the equine practitioner, technological innovations have improved the speed and sensitivity with which infectious organisms can be identified.[52] Culture, immunologic tests, and molecular techniques represent the most commonly used tools for pathogen identification. These techniques should not substitute for careful clinical evaluation, and an accurate diagnosis may necessitate the use of more than one diagnostic test. Regardless of the technique chosen, the practitioner should adhere to appropriate guidelines for sample collection and handling, as failure to do so can negatively affect the diagnostic accuracy of a given test.

Conventional culture methods represent indispensable diagnostic techniques when infectious respiratory disease (bacterial, viral, fungal) is suspected. Although these methods are sensitive, they are time consuming, often delaying pathogen identification days to even months, as in the case of certain viral organisms. Variable recovery of organisms from respiratory secretions and contamination may also negatively affect diagnostic accuracy. Matrix-assisted laser desorption/ionization–time-of-flight mass spectrometry (MALDI-TOFMS) is a novel technology that uses pathogen-specific mass spectra ribosomal protein profiles for the identification of fungal and microbial pathogens.[53] Extensive databases of organism-specific MALDI-TOFMS profiles have been generated, and when compared to conventional culture, MALDI-TOFMS can reduce the time required for pathogen identification from days to hours. This has important clinical implications regarding more timely institution of appropriate management.

Immunologic Techniques.

Immunoassays rely on interactions among bacterial, viral, and fungal antigens and radioisotope-, enzyme-, or fluorescent-labeled antibodies. The use of

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polyclonal antibodies tends to increase the sensitivity of the assay, as the preparation may contain antibodies to multiple epitopes on the target antigen, but at the same time it may also decrease assay specificity due to their heterogeneous nature. Test specificity can be improved by the use of monoclonal antibodies, as these antibodies interact with only a single well-defined epitope or very similar epitopes. Immunofluorescence, although labor intensive and time consuming, is considered highly sensitive and specific, particularly for virus-infected cells. The enzyme-linked immunosorbent assay (ELISA) is available for the diagnosis of a wide range of infectious respiratory diseases. For certain pathogens the ELISA has the advantage of rapid turnaround of results and minimal labor; however, these tests may be subject to false-negative and false-positive results. Virus neutralization (VN) assays are highly accurate and sensitive. Unfortunately, VN is more expensive, labor intensive, and time consuming compared to other diagnostics.

Immunohistochemistry is a standard diagnostic tool for the identification of viral, bacterial, and protozoal pathogens in tissue sections. This technique depends on polyclonal or monoclonal antibodies binding to a target antigen and the demonstration of this interaction by colored histochemical reactions visible by light microscopy or by emittance of fluorescence. Immunohistochemistry is highly versatile, and assays have been developed to detect a variety of equine respiratory pathogens in tissue sections.

Molecular Techniques.

Molecular-based technology, in particular polymerase chain reaction (PCR) techniques, have greatly advanced the diagnosis and management of viral, fungal, and bacterial respiratory disease. Advantages to these techniques include the speed with which results can be obtained, the superior sensitivity and specificity of these assays, and the ability to obtain quantitative results. Nucleic acid of both live and dead pathogens can be detected at very low concentrations and in a wide variety of specimens, and PCR is often useful to identify organisms that are difficult to grow in culture. The ability to perform parallel (“panel”) testing for multiple respiratory pathogens simultaneously from a single sample has greatly increased diagnostic efficiency, particularly when co-infection of multiple pathogens exists. Other advances that have expanded the clinical utility of PCR techniques include identification of virulence-associated genes, discrimination among different viral strains as well as between viable and nonviable organisms, determination of infectious risk, and the ability to

simultaneously test for multiple genes from the same organism.

Polymerase chain reaction involves amplification of a target region of DNA. Advances in PCR technology such as reverse transcription PCR (RT-PCR) and real-time, or quantitative, PCR (qPCR) have greatly expanded the applications of standard PCR. RT-PCR enables identification of viruses whose genome is composed of RNA (e.g., influenza, coronavirus) by reverse transcribing the viral RNA into complementary DNA (cDNA) for amplification. Commercially available kits have increased the diagnostic utility of this technique. Real-time PCR (qPCR) combines PCR amplification with simultaneous detection of the amplified products, allowing for quantification of PCR products in a closed tube system. Real-time PCR may also be combined with RT-PCR (qRT-PCR) for the quantification of messenger RNA (mRNA). Compared with traditional PCR, qPCR reduces the risk of contamination and increases the sensitivity and speed of detection.

Adhering to appropriate sample collection and handling protocols is essential for diagnostic accuracy of PCR. For example, sterile synthetic nasal or nasopharyngeal swabs (rayon or dacron tipped) are recommended for viral identification, whereas nasopharyngeal or guttural pouch lavage is recommended for identification of *Streptococcus equi* subsp. *zooepidemicus*. Regardless of the source, samples should not be frozen but refrigerated at 4° C for no more than 2 to 3 days before processing. False-positive results are often due to contamination, and false-negative results may occur from enzyme inhibitors that suppress DNA amplification. Molecular diagnostic techniques are covered in greater detail in Chapter 29.

Novel techniques that have the potential to further our understanding of the pathogenesis as well as the immunologic and genetic bases of respiratory disease include flow cytometry, genome-wide association study (GWAS), and respiratory microbiome analysis. Although these techniques currently are primarily used as research tools, they may have broader clinical applications in the future by contributing to improvements in the prevention, diagnosis, and management of respiratory disease. Flow cytometry is a laser-based technology that detects and quantifies light scatter and fluorescence emitted by fluorescent-labeled cells. Combinations of scattered and fluorescent light are identified and analyzed to derive information about the physical and chemical properties of a large number of cells at one time. It can be used to immunophenotype cells isolated from respiratory secretions and may thus improve characterization of the immunologic response associated with select respiratory diseases.

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The goal of a GWAS is to identify genomic features that may influence the risk of disease or the pathogenesis of a disease in animals or humans. The entire genome is evaluated in individuals with and without a particular disease to identify specific genetic variants found more frequently in individuals with disease. It is important to recognize that a GWAS does not determine causation, but only association. It may, however, facilitate identification of candidate genes that can be further investigated. In large animal species GWAS is being used to improve the understanding of genetic influences on susceptibility to severe RAO in warmblood horses,[54] equine viral arteritis in stallions,[55] and bovine respiratory disease in cattle.[56]

The role that the respiratory tract's resident microbial communities may have on respiratory health has received considerable attention through the field of respiratory microbiome analysis. In particular, the respiratory microbiome is thought to contribute to the prevention of colonization by pathogenic organisms, the mitigation of pathogenicity when infection is established, and the structural and immunologic maturation of the respiratory tract.[57] Important areas of ongoing respiratory microbiome research in large animals include characterization of different microbial communities throughout the respiratory tract, identification of factors influencing the development of the microbiota in maturing animals, and understanding how certain events (e.g., transport, physiologic stress, antimicrobial or glucocorticoid administration) may alter the microbiome and potentially influence susceptibility to or pathogenicity of respiratory disease.[58-61]

Pulmonary Function Testing

Daniela Bedenice

Pulmonary function testing (PFT) has emerged as an essential tool in equine referral practice and is largely aimed at describing the severity, anatomic pattern, stability (reactivity), and reversibility of bronchoconstriction caused by noninfectious airway obstruction and inflammation, such as is seen in RAO and IAD.[1] Clinical indications for noninvasive PFT include assessment of horses with intermittent cough, exercise intolerance, abnormal breathing pattern, and excess mucus, as well as early detection of subclinical disease, evaluation of treatment response, intensive care monitoring, and prediction of outcome. PFT is generally divided into the assessment of respiratory mechanics (mechanical properties of the respiratory system) and gas exchange. Analysis of gas exchange

investigates ventilation-perfusion matching, shunt, diffusion capacity, and dead space–to–tidal volume ratio (V_D/V_T). Lung mechanics, on the other hand, determine the static and dynamic properties of the lung, including resistance, compliance, functional residual capacity (FRC), and ventilatory parameters.[1]

Mechanics of Breathing

The mechanical function of the lung is essentially defined by static and dynamic properties. Tests that are performed with the respiratory system at equilibrium and zero flow are referred to as *static tests.* Examples include measurement of lung volume subdivisions (e.g., FRC) and compliance of the lung and chest wall.[1]

FRC is a measure of the amount of gas that remains in the lungs at end-expiration (end-expiratory volume). FRC is lower in patients with increased "lung stiffness" (reduced elastic recoil of the lung) as well as airway inflammation, whereas FRC increases in patients with expiratory airway obstruction and gas trapping.[2] This test can be easily performed in awake clinical patients via a helium dilution technique.[3] In short, the patient is connected to a reservoir bag at end-expiration to rebreathe a standard, commercial breathable gas mixture of 10% helium (He), 20% oxygen, and the remainder nitrogen for 90 seconds. The dilution of He (a nonexchangeable gas) gives a measure of end-expiratory lung volume.[3]

Measurements of static compliance or "elastic recoil of the lung" require breath holds and have applications only to the anesthetized patient. So-called *pressure-volume curves* are generated in the relaxed patient during lung deflation from total lung capacity (TLC), using an esophageal balloon technique. Compliance is defined as the lung volume change per unit of pressure change[2]:

$$\text{Compliance} = \frac{\Delta V}{\Delta P}$$

Reduced lung compliance (i.e., increased lung stiffness) may be associated with increased fibrous tissue (pulmonary fibrosis), atelectasis (e.g., underventilated lung), or an increased pulmonary venous pressure, in which the lung becomes engorged with blood. Emphysema and normal aging of the lung, which leads to alteration in elastic tissue, are causes of increased lung

compliance.[2]

In contrast to static tests, tests that are performed with the respiratory system in motion (e.g., during quiet breathing) are referred to as *dynamic.* An example of a dynamic measurement is resistance, a measurement that requires flow. Resistance arises from friction of air molecules against airway walls[1]:

$$\text{Resistance} = \frac{\text{Change in pressure } (\Delta P)}{\text{Change in flow } (\Delta V)}$$

The measurement of pulmonary resistance (R_L) using a flow meter attached to a face mask and an esophageal balloon catheter to measure transpulmonary pressure changes is conventional in the horse but rarely used in the clinical setting.[1] This technique allows computation of both R_L and dynamic compliance (C_{dyn}) at spontaneous breathing frequencies. Maximal transpulmonary pressure change ($\Delta P_{PL_{max}}$) and R_L both increase in cases of obstructive airway disease, whereas C_{dyn} decreases. However, this classic technique is fairly insensitive in detecting subclinical disease[4,5] and has greater utility in the diagnosis of IAD if coupled with a challenge test (i.e., histamine bronchoprovocation [see below]).[6,7]

Forced Oscillation Techniques

In contrast to the conventional methods, noninvasive measurements of total respiratory system resistance via forced oscillation techniques (FOTs) are used in the diagnosis of IAD in horses. In short, oscillometry is the study of lung mechanical function via the application of external forces to the respiratory system.[8] Either a loudspeaker (e.g., impulse oscillometry system [IOS]) or air pressure (e.g., monofrequency forced oscillation) is used to superimpose pulses of flow (4 to 5 L/s peak) through a face mask on the horse's respiratory system during spontaneous breathing. The generated reciprocal pressure waves are subsequently recorded at the airway opening (i.e., face mask). The magnitude and phase relationship between the input of flow and output of pressure are then used to perform the calculations of impedance (total opposition to airflow) and its components, resistance and reactance, at a variety of oscillatory frequencies (generally 1 to 7 Hz).[1] In most horses with IAD (equine asthma) there is a frequency dependence of resistance, with higher values for resistance recorded at

the lower oscillatory frequencies (1 to 2 Hz), indicative of bronchoconstriction.[9-11] Horses with moderate to severe lower airway obstruction commonly show high initial baseline values for respiratory resistance at 1 Hz (e.g., >1.0 cm H_2O/L/s).[1] Higher frequencies (≥2 Hz) provide information concerning central airway resistance (R_{aw}). Baseline respiratory resistance measurements using FOTs are often combined with bronchoprovocation tests for the early diagnosis of IAD. In addition, the use of an IOS has been advocated for separate analysis of inspiratory and expiratory impedance parameters, to allow the evaluation of both phases of the respiratory cycle in horses.12

Histamine Bronchoprovocation

Bronchoprovocation is a challenge test that assesses the response of the respiratory system to a bronchoconstrictor agonist (e.g., inhaled histamine).[1] The provocatory concentration necessary to cause a 100% increase in baseline respiratory system resistance is commonly termed $PC100_{RRS}$. Horses with a low $PC100_{RRS}$ (e.g., <8 mg/mL of histamine) are designated as having hyperreactive airways. Airway hyperreactivity (AHR) is an exaggerated narrowing response to a bronchoconstrictive stimulus, which was first found in horses with heaves[13] and is considered a hallmark of IAD. Some studies have documented a correlation between airway reactivity and mast cell percentage in BAL fluid in horses with a history of exercise intolerance.[14] The clinical symptoms associated with AHR are thought to include coughing (increased sensitivity) and exercise intolerance, whereas bronchoconstriction causes uneven ventilation and hypoxemia.[1] Both FOTs and respiratory inductive plethysmography (see below) have been used to assess AHR through histamine bronchoprovocation in client-owned horses. However, where different methodologies are used to assess AHR, comparison of histamine bronchoprovocation test results in horses should be made with caution.

Respiratory Inductive Plethysmography

The objective assessment of respiratory function and breathing pattern may also be obtained through the concurrent application of respiratory inductive plethysmography (RIP) and pneumotachography, which has been validated for the use in humans,[15,16] horses,[17] and sheep.[18] Two elastic bands, each containing a single sinusoidal conducting wire, are temporarily placed around the animal's

thorax and abdomen (Fig. 31.4). Stretch and contraction of the bands resulting from normal respiratory movements are measured as voltage changes, which is proportional to the change in circumference and volume of the thorax and abdomen. Simultaneously, measurements of nasal flow are obtained at the airway opening (face mask). This technique rapidly assesses the synchronicity of breathing pattern (e.g., thoracoabdominal asynchrony due to diaphragmatic paralysis)[19] and the individual contribution of the thorax and abdomen to respiration. It further quantifies changes in flow resulting from airway obstruction. Recently, the use of a novel respiratory ultrasonic plethysmography (RUP) system was proposed to detect circumference changes of rib cage and abdominal compartments in large and small animals.[20]



FIG. 31.4 Respiratory inductance plethysmography being performed in a horse. (Courtesy Dr. Andrew Van Eps, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)

Forced Maneuvers

Forced expiratory maneuvers are commonly performed in humans with suspected asthma. The patient is asked to blow out hard from TLC until the lung is empty. The volume of air expelled in 1 second (FEV_1) corrected for forced vital capacity (FVC) is used as a measure of lower airway obstruction.[1] Couëtil adapted the method of forced maneuvers for routine clinical application in

heavily sedated, nasotracheally intubated horses.[21] He further demonstrated flow limitation in horses with early signs of obstructive airway disease (IAD) that was worse in animals with heaves. Remission from heaves showed improvement in flow limitation.[1]

PFT is considered instrumental in the understanding of the pathogenesis, pathophysiology, epidemiology, diagnosis, and treatment of lung disease in the horse.[1] The described tests are aimed at quantifying airway obstruction, airway reactivity, and lung stiffness in the clinical setting. PFT will thus facilitate the diagnosis of subclinical disease and improve the clinician's assessment with regard to aggressive management of lung disease, decisions for ventilation, intensity of monitoring, and assessment of treatment response and prognosis.

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▪ Equine Respiratory System

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Disorders of the Lung

Bacterial Pneumonia and Pleuropneumonia in Adult Horses

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Bacterial infections of the lower respiratory tract are common in adult horses. Lower respiratory tract infections may be localized to the lumen of the airways (called bacterial bronchitis or septic IAD) or may involve the pulmonary parenchyma (called pneumonia). In equine medicine, the term *bronchopneumonia* is often used to refer to lower respiratory tract infection regardless of whether the infection is localized to the bronchi or whether the infection involves both the bronchi and the lung parenchyma. When there is subsequent extension of the infection from the pulmonary parenchyma to the visceral pleura and pleural space, the disease is referred to as pleuropneumonia. The spectrum of clinical signs shown by horses with bronchopneumonia is broad and reflects the severity of the disease process. Early identification of affected animals and immediate initiation of appropriate therapy are essential to prevent mortality and functional impairment of the respiratory system.

Infectious Agents Involved

Adult horses most commonly acquire bacterial pneumonia by aspiration of microorganisms that normally inhabit their nasopharynx or oral cavity.[1,2] β-hemolytic streptococci, particularly *Streptococcus equi* subsp. *zooepidemicus (S. zooepidemicus)* is by far the most common bacterial pathogen isolated from adult horses with bronchopneumonia.[3,4] Nonenteric gram-negative bacteria such as *Pasteurella* spp. and *Actinobacillus* spp. are also frequently isolated, either alone or in combination with *S. zooepidemicus*. Enteric gram-negative bacteria such as *Klebsiella* spp., *Escherichia coli*, *Enterobacter* spp., and *Salmonella enterica* may also be isolated. Other aerobic gram-positives such as *Staphylococcus* spp. and *Rhodococcus equi* or gram-negatives such as *Pseudomonas* spp. and *Bordetella bronchiseptica* are occasionally isolated. *Pseudomonas* spp. are rarely a primary cause of pneumonia in horses, and their presence often reflects contamination of equipment used for taking airway samples (such as endoscopes). *Streptococcus pneumoniae*, a common pathogen

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of humans, has been positively correlated with lower airway inflammation in young Thoroughbred racehorses in the United Kingdom.[5] The microorganism can also induce pneumonia in ponies following heavy intrabronchial challenge.[6] Its isolation from pneumonic horses in the United States appears to be rare.

Anaerobic bacteria are isolated from approximately one third of adult horses with severe bronchopneumonia, pleuropneumonia, or pulmonary abscessation. The most common anaerobes isolated are *Bacteroides* spp. (particularly *Bacteroides fragilis*), *Clostridium* spp., and *Peptostreptococcus* spp.; *Fusobacterium* spp. and *Eubacterium* spp. may also be isolated.[3,7] Isolation of anaerobes from horses with pneumonia or pleuropneumonia has been associated with a less favorable prognosis in some studies. In one study, the survival rate for 221 pneumonic horses with strictly aerobic isolates from tracheobronchial aspirates was 81.4% compared with 38.3% for the 81 horses in which anaerobes were cultured.[3] Mixed bacterial infections are very common and may represent synergy between aerobic or facultative aerobic and anaerobic bacteria.

The importance of *Mycoplasma* spp. in the development of equine bronchopneumonia and pleuropneumonia is controversial. Several *Mycoplasma* species have been isolated from the respiratory tract of both diseased and healthy horses, with *Mycoplasma felis* and *Mycoplasma equirhinis* being the most common isolates. In one study, isolation of *M. equirhinis* was positively correlated with lower airway inflammation in a group of young Thoroughbred racehorses in the United Kingdom,[8] whereas isolation of *Mycoplasma* spp. was not significantly associated with disease in a similar population in Australia.[9] An outbreak of lower respiratory tract disease caused by *M. felis* infection has been described.[10] *M. felis* has also been isolated from horses with pleuropneumonia, and experimental infection with *M. felis* has resulted in pleuropneumonia.[11,12]

■ Epidemiology

Bacterial bronchopneumonia may affect horses of any age and breed. In one retrospective study of 327 horses with pneumonia or pleuropneumonia, there was no sex predilection but 82% of the horses were younger than 5 years of age.[3] In a retrospective case-control study of risk factors for development of pleuropneumonia, Thoroughbreds were at greater risk and Standardbreds were at lower risk of developing the disease.[13] In the same study, the most significant risk factor for development of pleuropneumonia was long-distance transport

within the week prior to the onset of clinical signs.[13] In another study, 24.4% of 90 horses with pleuropneumonia had recently been transported over long distances, and 12.2% had recently undergone general anesthesia.[14] Five of the postsurgical cases had undergone upper airway surgery.[14] Whether these horses had preexisting lung disease or whether they developed aspiration pneumonia as a result of surgery and general anesthesia could not be ascertained.

Other factors significantly associated with increased risk of developing pleuropneumonia include recent viral respiratory tract infection or exposure to horses with viral infections and racing within 48 hours prior to developing clinical signs.[13] One study in the United Kingdom identified a higher incidence of pneumonia or pleuropneumonia in show jumpers, presumably reflecting the greater distance over which these horses are transported compared to racehorses in that country.[15]

■ Pathophysiology

Colonization of the lungs by opportunistic bacteria occurs when the pulmonary defense mechanisms are compromised or are overwhelmed by massive numbers of bacteria. Several factors can contribute to causing increased numbers of bacteria in the lower airways. Dysphagia or esophageal obstruction will lead to aspiration of large numbers of pharyngeal bacteria, and these disease processes often result in pneumonia. However, the vast majority of horses with bacterial pneumonia or pleuropneumonia do not have a history of dysphagia or esophageal obstruction. Other factors that have been shown to significantly increase bacterial contamination of the lower respiratory tract include confinement with the head elevated, transportation, and high-intensity exercise.[16-18] In one study, confinement of horses with the head elevated resulted in a significant increase in bacterial numbers as well as neutrophilic inflammation in the lower respiratory tract as early as 6 hours after initiating confinement.[17] *Actinobacillus* spp., *Pasteurella* spp., and β-hemolytic streptococci were the predominant bacterial isolates. Lowering the head for 30 minutes every 6 hours to facilitate postural drainage during a 24-hour confinement did not prevent multiplication of bacteria.[17] Clearance of accumulated secretions and bacteria occurred within 8 to 12 hours after release from confinement.[17] In similar confinement experiments, pretreatment with penicillin considerably reduced the number of β-hemolytic streptococci but did

not reliably reduce total bacterial numbers.[19] Cilia of many other species such as dogs and humans can transport mucus effectively against gravity, and posture has no effect on tracheal mucociliary transport in these species.[20,21] In contrast, periods of lowered head posture are absolutely essential for normal mucociliary clearance in horses.[22]

In one study, long-distance transport by road over 12 hours resulted in increased bacterial contamination and neutrophilic inflammation in tracheal aspirate fluid when the horses' heads were restrained in an elevated position.[23] This is in contrast to another study in which there was no significant cytologic or bacteriologic changes in BAL fluid from mares whose heads were not restrained in an elevated position during transportation for 12 hours.[24] Collectively, these findings suggest that duration of time with a raised head position is more important than the stress of transport alone in development of airway colonization. Finally, the last factor shown to increase bacterial contamination of the large airways of horses is exercise. In one study, a single bout of high-intensity exercise resulted in a tenfold increase in aerobic and hundredfold increase in anaerobic bacterial counts in tracheal aspirate samples compared to preexercise values.[16]

Pulmonary defense mechanisms can be compromised by numerous factors. These include stress (e.g., transport, intense exercise), viral infections, malnutrition, exposure to dust or noxious gases, immunosuppressive therapy, immunodeficiency disorders, and general anesthesia. Infections with influenza virus and equine herpesvirus 4 (EHV-4) have been shown to significantly decrease mucociliary clearance for up to approximately 30 days post infection in horses.[25] In one study, long-distance transport resulted in a significant reduction in phagocytosis by peripheral blood neutrophils for approximately 36 hours after transport.[23] The effects of long-distance transport on number, viability, and function of cells in BAL fluid have given conflicting results, with no clear pattern emerging.[24,26-28] Similarly, the effects of exercise on the immune system are complex and depend on a multitude of factors, including the intensity or duration of exercise, the specific immune function being analyzed, and the timing of the measurement in relation to exercise. In general, moderate exercise enhances immune function, whereas strenuous exercise tends to be detrimental to immune function.[29] High-intensity exercise in horses leads to a significant decrease in blood neutrophil and bronchoalveolar macrophage phagocytic activity, which may lead to decreased bacterial clearance from the lungs.[30-32]

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Exercise also affects the adaptive immune system, as lymphocyte proliferation responses and interferon (IFN)–γ production are decreased following high-intensity exercise.[33-35] Strenuous exercise has also been shown to increase susceptibility to experimental influenza virus infection in ponies compared with rested animals.[33]

Regardless of the exact mechanism predisposing to bacterial colonization, the inflammatory response induced by bacterial invasion results in infiltration with neutrophils and other inflammatory cells into the airways and pulmonary parenchyma. Inflammatory cells and their mediators cause damage to the airway epithelium and capillary endothelium, leading to flooding of the terminal airways with inflammatory cells, serum cellular debris, and fibrin. This process is generally more severe in the ventral portions of the lung. In early stages the lungs may be simply edematous, reflecting inflammation and early exudation, whereas in chronic, severe cases the airways may be consolidated or abscessed. These lesions interfere with gas exchange, and if severe enough, the resulting ventilation-perfusion mismatch leads to hypoxemia and clinical signs of respiratory disease.

In severely affected animals, inflammation will extend to the pleural space. The first stage of bacterial pleuropneumonia is an exudative stage, which is characterized by rapid outpouring of sterile pleural fluid into the pleural space in response to inflammation of the pleura. The associated pneumonic process is usually contiguous with the visceral pleura and results in increased permeability of the capillaries in the visceral pleura. If appropriate antimicrobial therapy is initiated at this stage, the pleural effusion may not become septic and may resolve. With progression, the bacteria invade the pleural fluid from the contiguous pneumonic process and the second, fibropurulent, stage evolves. This stage is characterized by the accumulation of large amounts of pleural fluid with many degenerate neutrophils, bacteria, and cellular debris. Fibrin is deposited in a continuous sheet, covering both the visceral and the parietal pleura adjacent to affected areas. As this stage progresses, there is often loculation and formation of limiting membranes. These loculations prevent dissemination of the infection but make drainage of the pleural space with chest tubes increasingly difficult. The last stage is the organization stage, in which fibroblasts grow into the exudate from both the visceral and the parietal pleura surfaces and produce a membrane called the pleural peel. This inelastic pleural peel encases the lung and renders it virtually functionless. At this stage the exudate is generally thick.

■ Clinical Signs and Physical Examination

The spectrum of clinical signs shown by horses with bacterial lung infection is broad and usually reflects the severity of the disease process. Horses with septic IAD and no or minimal involvement of the lung parenchyma may be completely normal at rest. Clinical signs may be limited to exercise intolerance and/or poor performance, or affected horses may cough or have bilateral nasal discharge during or immediately following exercise. Even in early cases of bronchopneumonia, clinical signs may not be obvious. As the disease progresses, clinical signs may include any combination of fever, anorexia, depression, bilateral nasal discharge, cough, weight loss, tachypnea, and respiratory distress. Nasal discharge is usually mucopurulent but may be hemorrhagic in some cases with pulmonary infarction and necrotizing pneumonia.[36] Halithosis and a foul-smelling nasal discharge may be present and have been associated with infection by anaerobic bacteria. However, the absence of a putrid odor does not rule out infection with anaerobic bacteria.

Because the parietal pleura is highly innervated and painful when inflamed, horses with acute pleuropneumonia often exhibit pleurodynia (pleural pain). Pleurodynia can often be detected by applying digital pressure to the intercostal space, resulting in grunts, intercostal muscle spasm, or even escape maneuvers by the patient when pain is present. Pleurodynia may also be manifested as pawing, stiff forelimb gait, abducted elbows, and reluctance to move. The condition may easily be mistaken for colic, exertional rhabdomyolysis, or laminitis. As more fluid accumulates in the pleural space and the disease becomes chronic, pain is less evident. A plaque of sternal edema is a common clinical finding in horses with pleuropneumonia. This is not a specific finding, as it can occur with many other disease processes.

Careful auscultation after application of a rebreathing bag (if not precluded by respiratory distress) is extremely valuable in defining the presence and sometimes extent of lung involvement. Horses with a large amount of secretions in the trachea often have an audible tracheal rattle. Most horses with bronchopneumonia will cough when the rebreathing bag is applied, whereas horses without bronchopneumonia will not. Occasional inspiratory or expiratory crackles and/or wheezes may be heard over affected areas, which are more commonly located ventrally. Because consolidated lung parenchyma is a good acoustic medium, mild consolidation sometimes results in only increased bronchial sounds. In contrast, the lung sounds may be diminished in areas of severe consolidation, extensive abscess formation, or pleural effusion.

Auscultation of horses with pleuropneumonia reveals normal lung sounds in the dorsal lung fields, with no sound or considerably decreased lung sounds ventrally. Pleural friction rubs are often not heard because they are present only in the acute stage of the disease. If they are heard, friction rubs are present predominantly at the end of inspiration and the early part of expiration. They disappear as inflammation decreases or as pleural fluids accumulate. Cardiac sounds are often heard over a wider area of the chest than normal, probably as a result of enhanced conduction of sound through the pleural fluid. Thoracic percussion is useful to detect and delineate pleural effusion with resonant sounds dorsal and dull sounds ventral to the horizontal line of effusion.

■ Differential Diagnosis

When physical examination and auscultation indicate pulmonary disease, the major clinical task is differentiating infectious from noninfectious causes. Among infectious causes, bacterial pneumonia is most common. Most viral infections are confined to the upper respiratory tract. The clinical presentation of equine multinodular pulmonary fibrosis may resemble that of horses with bacterial bronchopneumonia. Pulmonary aspergillosis most often follows severe gastrointestinal (GI) disease that had resulted in mucosal compromise.[37] Severe respiratory disease unresponsive to antimicrobial therapy might suggest fungal pneumonia or equine multinodular pulmonary fibrosis. Parasitic pneumonitis is rare in adult horses but may be seen in horses pastured with donkeys or mules. The two major noninfectious causes of pulmonary disease that may be confused with bacterial pneumonia include heaves (also known as RAO) and IAD. Other uncommon causes of noninfectious pulmonary disease that may result in similar clinical signs are pneumothorax, pulmonary edema, smoke inhalation, neoplasia, and idiopathic interstitial pneumonia. The diagnostic tests described below aid in the differentiation between infectious and noninfectious causes of lower respiratory tract disease.

When pleural effusion is present, several differentials should be considered. Bacterial pleuropneumonia is by far the most common cause of pleural effusion in horses. In one study, 90 of 122 horses (73.8%) with pleural effusion had pleuritis secondary to bacterial pneumonia or lung abscessation.[14] Other less common causes of pleural effusion in horses include hemothorax, penetrating chest wounds, esophageal ulceration or rupture, neoplasia, fungal pneumonia, pericarditis, congestive heart failure, diaphragmatic hernia, hypoproteinemia,

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and chylothorax.

■ Diagnostic Approach

Presumptive diagnosis of lower respiratory tract infection is generally based on clinical signs and careful auscultation of the lungs with a rebreathing bag. The need for additional diagnostic procedures is determined by the severity and duration of clinical signs, the number of affected animals, the value of the affected animals, and prior treatment used and response to such therapy. Bacterial pneumonia or pleuropneumonia most commonly affects an individual horse on a given farm. In horses suspected of having bacterial pneumonia, the goal of diagnostic evaluation is to rule out diseases of the upper respiratory tract and to determine the cause and severity of lung involvement.

Hematology and Biochemistry.

Horses with bacterial bronchopneumonia commonly have an inflammatory hematologic profile. Leukocytosis and absolute neutrophilia with or without a left shift are supportive of bacterial infection. Neutropenia with a toxic left shift may also be evident in the acute stages in severely affected animals. Increased fibrinogen and/or serum amyloid A concentrations, hyperglobulinemia, and mild hypoalbuminemia are common. Anemia of chronic inflammation may develop in chronically affected animals. There does not seem to be a good correlation between the severity of clinical signs and the presence or the magnitude of hematologic changes. When plasma fibrinogen concentrations are increased, their sequential measurement provides a useful means of monitoring response to treatment. It must be remembered that a normal hematologic profile does not rule out bacterial bronchopneumonia.

Endoscopy.

Endoscopy may be useful to rule out upper airway infection in situations where physical examination and auscultation of the lungs are not conclusive. Presence of mucopurulent secretions in the trachea and bronchi confirms lower respiratory tract disease. However, the presence of mucopurulent secretions does not necessarily indicate a bacterial infection, as this is also a common finding in horses with RAO and IAD. Bronchoscopy may also be useful in locating the affected lung segment in horses with focal pneumonia or draining pulmonary abscesses. It should be noted that exploration of the trachea and lower airways via bronchoscopy may contaminate subsequent samples taken for culture.

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Tracheobronchial Aspirate for Cytology and Culture.

Tracheobronchial aspirate (TBA) for cytologic examination and bacterial culture is one of the most helpful diagnostic procedures available when bronchopneumonia is suspected. BAL is not as useful as TBA in cases of bronchopneumonia because with BAL, only a small portion of a lung is sampled. In contrast to BAL, TBA samples contain a pooled sample of secretions from all portions of the lung, thus increasing the chances of culturing the pathogen of interest. In one study involving 22 horses diagnosed with pneumonia or pleuropneumonia based on thoracic radiographs or ultrasonography, BAL cytology was abnormal in only 10 horses despite attempts at selectively sampling the affected area.[38] In contrast, all horses had evidence of septic inflammation based on tracheobronchial aspirate cytology.[38] Whenever possible, antimicrobial therapy should be discontinued at least 24 hours before performing TBA. TBA is preferably obtained by sterile percutaneous transtracheal aspiration to avoid contamination from the upper airway. Alternatively, the sample can be collected with a sterile guarded aspiration catheter passed through the biopsy channel of a flexible endoscope.[39,40] Endoscopy has the advantage of allowing selective aspiration of exudate when it is present, which may therefore enhance recovery of bacteria. However, bacterial contamination of nasal or pharyngeal origin more commonly occurs in TBA samples collected via endoscopy. Airway fluid specimens should be submitted for cytology, Gram stain, and aerobic and anaerobic bacterial cultures. The fluid used for anaerobic cultures should be transferred to the laboratory immediately after collection in a manner that prevents or minimizes exposure to air. Anaerobic transport media are commercially available and should be routinely used. Specimens submitted for isolation of anaerobes should not be refrigerated because many anaerobes are intolerant to cold. In horses with pleural effusion, TBA should be obtained even if pleural fluid is available for bacterial culture. In one study, culture of the pleural fluid was negative in 43% of 111 horses with pleuropneumonia, whereas tracheobronchial fluid yielded growth in all cases.[3] Only approximately 5% of cases had growth from the pleural fluid but not from TBA.[3]

Macrophages and columnar ciliated epithelial cells predominate in TBA from healthy horses. The percentage of neutrophils in TBA from apparently healthy horses can be quite variable. In one study, approximately 75% of apparently healthy Thoroughbred racehorses in training had less than 20% well-preserved neutrophils.[41] Occasional plant spores and fungal hyphae may be present either

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free or in large mononuclear cells. Their presence does not necessarily indicate fungal infection and probably reflects the horse's environment. Degenerated neutrophils displaying karyolysis and cytoplasmic vacuolization are the predominant cell type in horses with bacterial lower respiratory tract infections. Bacteria may be found intracellularly or extracellularly. Presence of squamous epithelial cells indicates contamination with the upper respiratory tract or pharynx and is more common in samples obtained via the endoscope. The trachea is not a perfectly sterile site, and pathogenic bacteria potentially can be isolated from the trachea of normal horses.[39] Therefore culture results should always be interpreted in the context of clinical signs and cytologic examination. If small numbers of bacteria are cultured in the absence of cytologic evidence of sepsis, it is unlikely that they are the cause of the respiratory problem. Similarly, growth of various molds is common in TBA cultures, and the clinical signs, imaging data, and cytologic findings should be considered prior to initiating treatment with antifungal agents.

Thoracic Ultrasonography.

Thoracic ultrasonography can be performed using a range of transducers and machine types. The normal aerated lung parenchyma is not penetrated by the ultrasound beam, rendering only the pleural space and superficial lung surface available for study. Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas but may not be as useful as radiography to evaluate the full extent of lung lesions, since lesions with overlying aerated lung will not be detected. However, in most horses with bronchopneumonia the periphery of the lung is affected, enabling the clinician to successfully image some of the lesions. Early ultrasonographic lesions are nonspecific and may include only irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes. Consolidated lung varies in appearance from dimples of the pleural surface to large wedge-shaped areas of sonolucent lungs (Fig. 31.5).

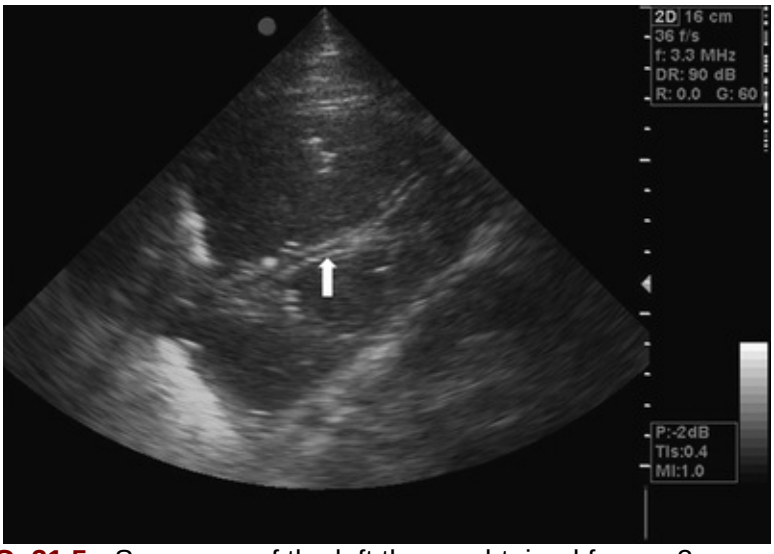


FIG. 31.5 Sonogram of the left thorax obtained from a 3-year-old Thoroughbred gelding. The ventral aspect of the lung is completely consolidated. Notice the liver-like appearance of the wedge-shaped area of the lung. Fluid bronchograms are indicated by a white arrow.

Ultrasonography offers a considerable advantage over radiographs in the study of the pleural surfaces and space. A small amount of pleural effusion that would otherwise be missed clinically or by radiography can be detected easily by ultrasonography. Ultrasonography can also be used to assess the nature and approximate volume of fluid, select the optimal site and depth for thoracocentesis, and detect sequelae such as fibrin deposition, pleural adhesions, abscess formation, and pneumothorax. Pleural effusion appears as hypoechoic to anechoic fluid between the parietal pleural surface and the lungs (Fig. 31.6). The echogenicity of the fluid typically reflects the degree of cellularity. Fibrin appears as filamentous strands floating in the effusion (see Fig. 31.6). The presence of small (<1 mm) bright echoes (gas echoes) often indicates anaerobic infections (Fig. 31.7).[42] Gas echoes may also be seen with gangrenous pneumonia or bronchopleural fistulas, or they may result from leakage of air during thoracocentesis.

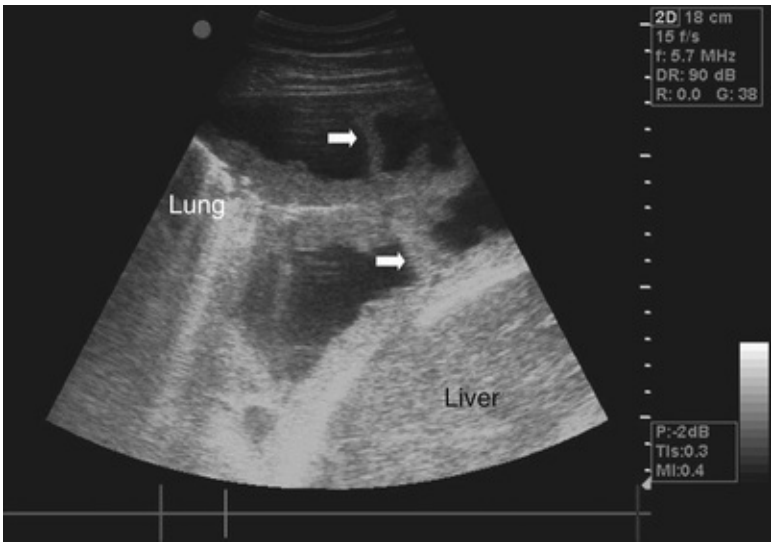


FIG. 31.6 Sonogram of the thorax obtained from a 4-year-old horse with pleuropneumonia. The ventral tip of the lung is atelectatic and covered with fibrin. There are adhesions between the tip of the lung and the diaphragm and chest wall *(white arrows).*

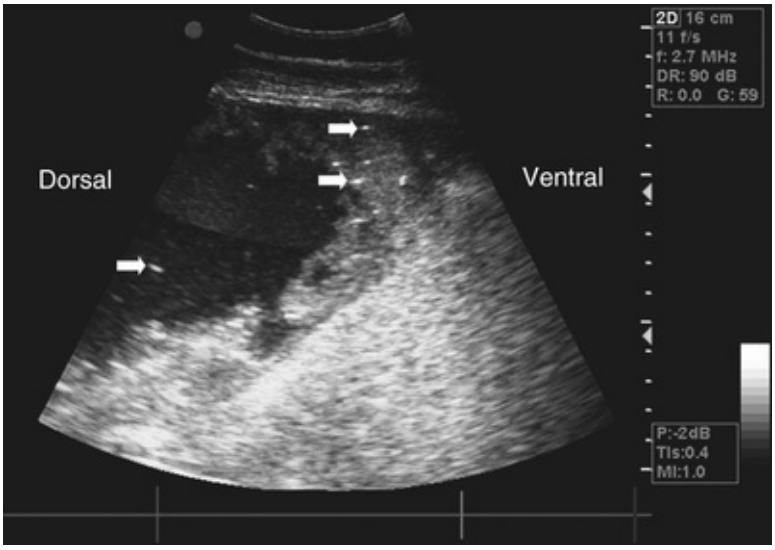


FIG. 31.7 Sonogram of the ventral thorax obtained from a horse being treated for pleuropneumonia. The sonogram shows a pleural abscess filled with fluid dorsally and with hyperechoic material ventrally. There are multiple gas echoes (some indicated by arrows). Multiple anaerobes were obtained on culture of an aspirate.

Radiography.

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In horses with mild septic IAD, thoracic radiographs may be normal or may reveal only mild bronchial or bronchointerstitial patterns. In more severely affected animals, radiographs demonstrate irregular opacities in the ventral thorax that may obscure the normal vasculature and cardiac silhouette (Fig. 31.8). Air bronchograms are sometimes visible. Abscesses are often present as circular soft-tissue opacities of varying sizes. In some cases they may be cavitated with thick walls and a distinct horizontal line representing fluid gas interface (Fig. 31.9). Pleural effusion appears as a horizontal line demarcating a ventral soft-tissue opacity that obscures the heart and ventral lung fields (Fig. 31.10). When severe pleural effusion is present, it is most efficient to perform thoracic radiographs after the pleural fluid has been drained. Although ultrasonography is superior to radiographs in horses with pleuropneumonia, radiography should still be performed when possible to detect and monitor resolution of deep pulmonary abscesses that may be missed during ultrasonography.

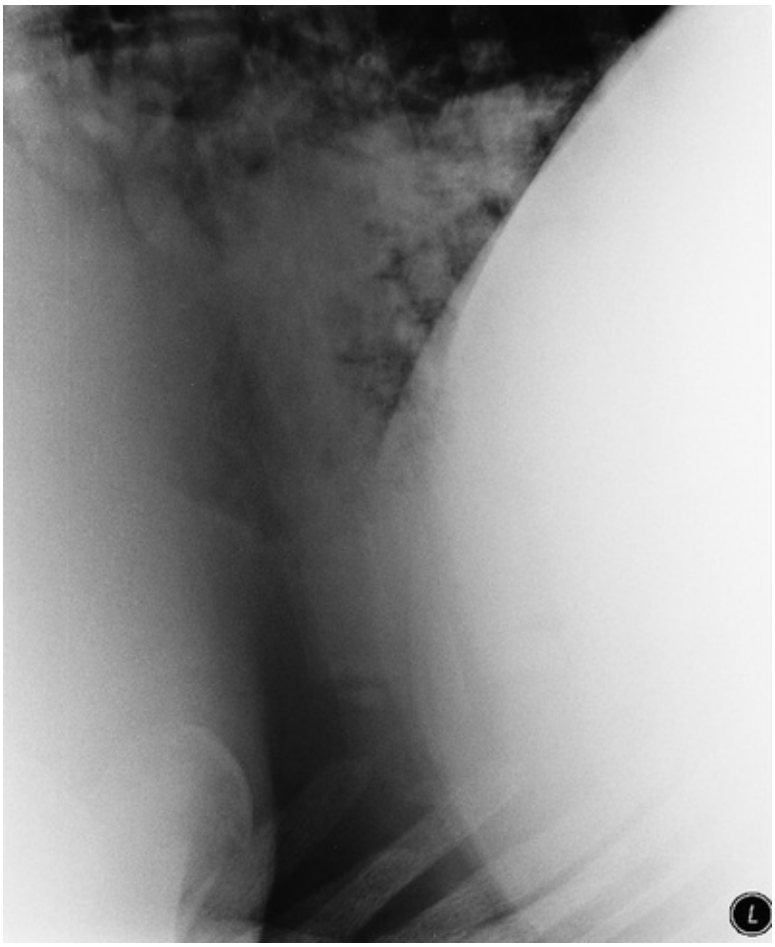


FIG. 31.8 Lateral thoracic radiograph of the caudoventral lung field from a 4-year-old Thoroughbred mare showing a pronounced alveolar pattern with air bronchograms. The caudal silhouette of the heart is almost completely obscured.

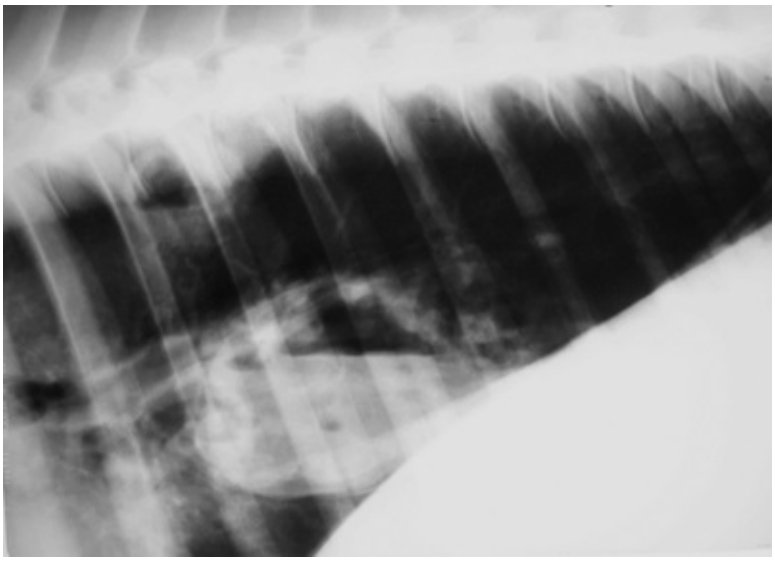


FIG. 31.9 Lateral thoracic radiograph of the caudodorsal lung field from a 3-year-old Thoroughbred filly showing two cavitary abscesses with distinct horizontal lines representing fluid-gas interface.

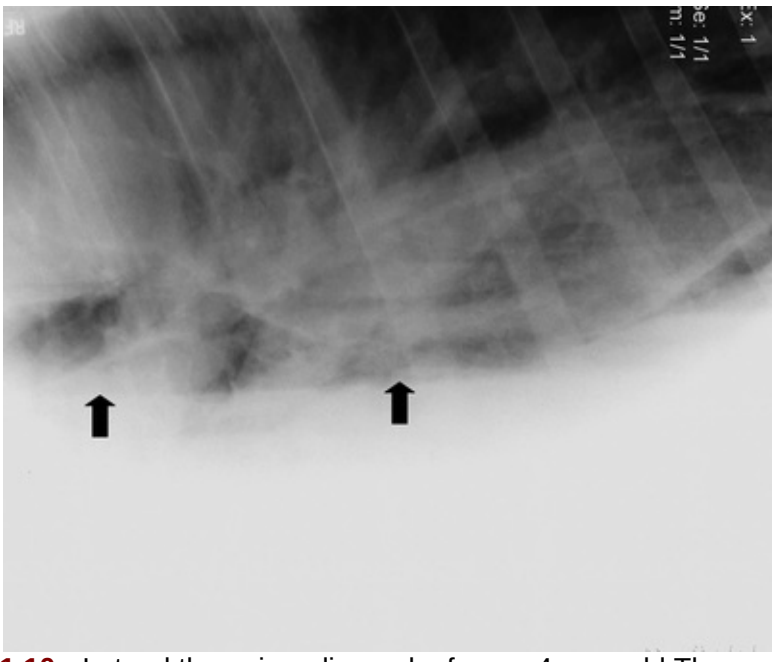


FIG. 31.10 Lateral thoracic radiographs from a 4-year-old Thoroughbred gelding with pleuropneumonia. A large amount of pleural effusion obscures the ventral lung fields. The dorsal aspect of the fluid line is indicated by black arrows. An interstitial pattern is noted in the caudodorsal lung fields.

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Thoracocentesis for Cytology and Culture.

Thoracocentesis should be considered in horses with pleural effusion. The procedure can be of diagnostic value by allowing differentiation of septic pleuritis from effusion caused by other disease processes. It can also be of therapeutic value via removal of excessive chest fluid, which allows pulmonary reexpansion and a reduction in respiratory distress. Thoracocentesis is best performed using ultrasound guidance to determine the most appropriate site. A blunt teat cannula is typically used if a small volume of effusion is being sampled strictly for diagnostic purposes. Depending on the volume of effusion, a 16-, 24-, or 32-French chest tube is used when pleural drainage is also indicated (see the Pleural Drainage section later). An aliquot of pleural fluid is placed into tubes containing anticoagulant solution (ethylenediaminetetraacetic acid, or EDTA) so that cytologic evaluation may be performed. Part of the fluid should be saved in sterile containers with appropriate transport media for subsequent Gram stain and aerobic as well as anaerobic bacterial cultures. The normal parameters for equine pleural fluid have been reviewed[43-45] and are described earlier in this chapter.

Thoracoscopy.

Thoracoscopy is rarely necessary in the initial evaluation of horses with pleuropneumonia. However, the technique might be of diagnostic and therapeutic value in more chronic cases that develop pleural abscesses or pleural adhesions (see the Thoracoscopy section later).[46]

■ Treatment

Systemic Antimicrobial Therapy.

Administration of appropriate antimicrobial agents is the most important part of the therapeutic plan. The choice of the antimicrobial agent depends on the severity of the clinical signs, cost, ease of administration, and, when available, results of bacteriologic culture and susceptibility testing of TBA or pleural fluid. Dosages for commonly used antimicrobial agents are presented in Table 31.2. In early cases of mild bronchopneumonia, the practitioner is justified in suspecting *S. zooepidemicus* as the likely causative microorganism and in treating accordingly. *S. zooepidemicus* is almost invariably susceptible to penicillin, ampicillin, and cephalosporins such as ceftiofur (Table 31.3). The possibility of a

mixed infection involving *S. zooepidemicus* and gram-negative microorganisms must be kept in mind when such empirical therapy is unsuccessful. Ceftiofur offers the advantage of having a good spectrum of activity against common nonenteric gram-negative pathogens (e.g., *Pasteurella* spp., *Actinobacillus* spp.) and against many enteric gram-negative pathogens (see Table 31.3). Ceftiofur is available as a sodium salt that requires daily intramuscular administration or as ceftiofur crystalline free acid. Two intramuscular doses of ceftiofur crystalline administered 4 days apart provide therapeutic concentrations of ceftiofur and desfuroylceftiofur-related metabolites in plasma and pulmonary epithelial lining fluid for approximately 10 days from the beginning of treatment.[47-49]

TABLE 31.2

Antimicrobial Agents Commonly Used to Treat Bacterial Bronchopneumonia in Adult Horses

Antimicrobial[a]	Dose	Frequency (h)	Route
β-Lactams			
Benzyl Penicillins			
Penicillin G (Na, K)	22,000 IU/kg	6	IV
Penicillin G (procaine)	22,000 IU/kg	12	IM
Aminobenzyl Penicillins			
Ampicillin sodium	20 mg/kg	8	IV
Ampicillin trihydrate	20 mg/kg	12-24	IM
Cephalosporins			
Cefazolin	10-20 mg/kg	6	IV
Ceftiofur sodium	2.2-4.4 mg/kg	24	IM
Ceftiofur crystalline free acid	6.6 mg/kg	[b]	IM
Aminoglycosides			
Amikacin	10 mg/kg	24	IV or IM
Gentamicin	6.6 mg/kg	24	IV or IM
Fluoroquinolones			
Enrofloxacin[c]	5.5 mg/kg	24	IV
	7.5 mg/kg	24	PO
Tetracyclines			
Oxytetracycline[d]	6.6 mg/kg	12	IV[d]
Doxycycline[e]	10 mg/kg	12	PO[e]
Minocycline	4	12	PO
	2.2	12	IV
Others			
Chloramphenicol	50 mg/kg	6	PO
Metronidazole	25 mg/kg	12	PO
	35 mg/kg	12	Per rectum
Rifampin	5 mg/kg	12	PO
Trimethoprim-sulfonamide	30 mg/kg (combined)	12	PO

[a]Pharmacokinetics data are available for horses, but in most cases safety studies have not been performed in the equine species.

[b]Two doses 4 days apart will provide 10 days of coverage. If a longer treatment period is necessary, weekly (q7days) administration is sufficient after the initial two doses.

[c]Should not be used in young growing horses because of the risk of arthropathy.

[d]Dilute and give by slow IV infusion.

[e]Administer orally only. Intravenous doxycycline has resulted in severe cardiovascular effects, including collapse and death in some horses.

IM, Intramuscular; *IV,* intravenous; *PO,* oral.

TABLE 31.3

In Vitro Antimicrobial Susceptibility of Aerobic Bacterial Isolates Commonly Isolated From Horses With Bronchopneumonia or Pleuropneumonia

	Antimicrobials[a]										
Microorganisms (n)[b]	**AMP**	**AMI**	**CHL**	**E**	**ENR**	**GM**	**P**	**TE**	**TMS**	**RIF**	**XNL**
Gram-Positives											
Streptococcus zooepidemicus (758)	99	1	88	94	50	55	99	16	63	98	100
Staphylococcus aureus (211)	41	96	95	76	89	89	44	83	81	95	57[c]
Other staphylococci (149)	41	96	95	76	89	89	44	83	81	95	57[c]
Gram-Negatives											
Escherichia coli (362)	52	95	88	1	94	85	—	71	53	—	92
Enterobacter spp. (132)	25	83	78	2	85	65	—	74	54	—	64
Klebsiella spp. (130)	2	91	74	1	88	71	—	76	60	—	82
Actinobacillus spp. (42)	79	71	86	15	95	91	54	88	71	—	100
Pasteurella spp. (28)	78	100	94	36	89	100	47	93	75	—	100
Pseudomonas spp. (232)	4	88	9	4	54	71	—	41	22	—	17

[a]Percentage of susceptible isolates.

[b]Approximate number of isolates (some isolates were not tested against every antimicrobial agent).

[c]Ceftiofur is rapidly metabolized to desfuroylceftiofur in vivo. Desfuroylceftiofur is as active as ceftiofur against most bacterial pathogens, but most coagulase-positive *Staphylococcus* spp. are resistant. Therefore despite in vitro susceptibility, ceftiofur is not the ideal choice for the treatment of staphylococcal infections.

—, Not tested or testing not warranted; *AMI,* amikacin; *AMP,* ampicillin; *CHL,* chloramphenicol; *E,* erythromycin; *ENR,* enrofloxacin; *GM,* gentamicin; *P,* penicillin; *RIF,* rifampin; *TE,* tetracycline; *TMS,* trimethoprim-sulfonamide; *XNL,* ceftiofur.

Adapted from Giguère S, Afonso T: Antimicrobial drug use in horses. In: Giguère S, Prescott JF, Dowling PM, editors: *Antimicrobial therapy in veterinary medicine,* 5th ed. Ames, IA: Wiley-

Blackwell; 2013, pp. 457–472. Isolates were obtained from multiple equine clinical specimens including but not restricted to tracheobronchial aspirates and pleural fluid.

Therapy of horses with mild lower respiratory tract infections should be continued for a minimum of 10 days or until clinical signs resolve. In some cases the duration of therapy needed may preclude continuous intramuscular therapy because of muscle soreness. Trimethoprim-sulfamethoxazole (TMS) combinations offer the advantage of oral administration. The usefulness of TMS combinations for the treatment of severe bacterial respiratory tract infections in horses may be limited by their apparent limited in vivo activity against *S. zooepidemicus*. In contrast to penicillin, TMS was ineffective in eradicating *S. zooepidemicus* in a tissue chamber model of infection in horses.[50,51] This failure of in vivo response was observed despite in vitro susceptibility of the isolate and high concentrations of TMS in the tissue chamber fluid.[50,51] However, in a recent study oral TMS was effective in the treatment of mild to moderate lower respiratory tract infections caused by *S. zooepidemicus*.[52]

In more severe cases of bronchopneumonia and in all cases of pleuropneumonia, antimicrobial therapy ultimately should be selected based on results of culture and in vitro susceptibility testing. Before obtaining these results, selection should be based on knowledge of the prevalence and susceptibility pattern of bacteria commonly isolated from affected horses (see Table 31.3). Polymicrobial and mixed aerobic/anaerobic infections are common; thus broad-spectrum antimicrobial therapy is initially required. A combination of gentamicin for gram-negative coverage and penicillin for gram-positive and anaerobic coverage is commonly used as initial broad-spectrum therapy for moderate to severe bronchopneumonia. Enrofloxacin can be used as a substitute to gentamicin for gram-negative coverage in adult horses. Advantages of enrofloxacin over gentamicin include greater activity against Enterobacteriaceae, better penetration in phagocytic cells and tissues, and better activity in purulent material. However, enrofloxacin should never be used as standalone initial therapy in horses with bronchopneumonia because of its lack of activity against anaerobes and variable activity against streptococci such as *S. zooepidemicus*. Ampicillin or cefazolin can replace penicillin for gram-positive coverage and offer the supplementary advantage of providing additional gram-negative coverage.

Treatment of anaerobic pleuropneumonia is usually empirical, as antimicrobial susceptibility testing of anaerobes is difficult because of their fastidious nutritive and atmospheric requirements. Thus familiarity with

antimicrobial susceptibility patterns is helpful in formulating the treatment regimen when an anaerobe is suspected. The majority of anaerobic isolates are susceptible to relatively low concentrations of penicillin. However, *B. fragilis*, a frequently encountered anaerobe in horses with pleuropneumonia, is routinely resistant to penicillin. Other members of the *Bacteroides* family are known to produce β-lactamases and are potentially penicillin resistant. Metronidazole has excellent in vitro activity against a variety of obligate anaerobes, including *B. fragilis.* Oral administration rapidly results in adequate serum levels and thus is an acceptable route of administration for horses with pleuropneumonia. Therefore if anaerobic infection is suspected, oral metronidazole is usually added to the combinations mentioned previously. Malodorous nasal discharge, halitosis, or the presence of gas echoes in pleural effusion seen during ultrasonography suggests the presence of an anaerobic infection. However, the absence of these findings does not rule out anaerobic bacterial infection. Horses with extensive lung consolidation and horses with pleuropneumonia may benefit from having metronidazole added to the treatment regimen. Metronidazole is not effective against aerobes and therefore should always be used in combination therapy. Chloramphenicol is active against most aerobes and anaerobes cultured from horses with bronchopneumonia or pleuropneumonia. However, because of human health concerns, its use should be limited to the treatment of horses with severe anaerobic bacterial infections refractory to metronidazole therapy in countries where its use is allowed. Rifampin is bactericidal and active against streptococci and some species of anaerobes. It penetrates well into abscesses and may be helpful in the treatment of infections with walled-off abscesses. Rifampin should always be used in combination with another antimicrobial agent to decrease the likelihood of emergence of resistant mutants.

In cases of severe bronchopneumonia, lung abscesses or pleuropneumonia long-term antimicrobial therapy ranging from 3 weeks to several months may be required. In the initial stages of therapy, IV antimicrobials are preferred to achieve higher serum concentrations. Oral antimicrobial agents can be used later in the course of the disease if appropriate based on in vitro susceptibility testing. Clinical signs, lung auscultation, fibrinogen concentrations, and repeated ultrasonographic and/or radiographic examination are useful in assessing response to therapy and deciding when to discontinue antimicrobial therapy. Stall rest must be enforced during therapy of pneumonia, and return to exercise should be gradual and permitted only after the horse is clinically normal and antibiotic therapy has been completed.

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Aerosolized Antimicrobial Agents.

Aerosolized antimicrobial agents might be a useful adjunct to oral or systemic antimicrobial agents, particularly in horses with chronic septic inflammatory airway disease and no or minimal involvement of the lung parenchyma. The rate and extent of penetration of a drug into most sites outside the vascular space, such as lung tissue, are determined by the drug's concentration in plasma, molecular charge and size, extent of plasma protein binding, and blood flow.[53] In other tissues such as the central nervous system and the eye, a lipid membrane provides a barrier to drug diffusion.[53] There is a similar barrier between blood and the bronchial epithelium, restricting penetration of some drugs into bronchial secretions and epithelial lining fluid of the lower airways.[54] Aerosol administration of antimicrobial agents can result in high drug concentrations in the respiratory tract while minimizing systemic concentrations and their resulting toxicity.

Antimicrobial delivery by inhalation is greatly influenced by the product formulation and type of nebulizer. Aerosol use of IV formulations can lead to exposure to potentially irritant or toxic additives and inappropriate pH or osmolality ranges. In one study, the particle size distribution and particle density of gentamicin sulfate and ceftiofur sodium aerosols were affected by the antimicrobial concentration of the solution.[55] Gentamicin concentrations of 50 mg/mL or ceftiofur concentrations of 25 mg/mL produced the optimal combinations of particle size and aerosol density when a medical ultrasonic nebulizer was used.[55] Development of a silent battery-operated nebulizer for horses (Flexineb [Nortev Ltd., Galway, Ireland]) has greatly facilitated delivery of antimicrobial drugs by inhalation in horses.

In healthy horses, aerosolization of 20 mL of the commercially available IV gentamicin sulfate solution (diluted to 50 mg/mL) using an ultrasonic nebulizer resulted in bronchial lavage fluid concentrations approximately 12 times higher than concentrations achieved by IV administration at a dose of 6.6 mg/kg.[56] In the same study, serum concentrations following aerosol administration were below 1 µg/mL at all times.[56] Once-daily aerosol administration of gentamicin to healthy horses for 7 consecutive days did not result in pulmonary inflammation or drug accumulation in the respiratory tract.[57] The major limitation to the use of aerosolized gentamicin in horses is its lack of activity against *S. zooepidemicus*, the most common bacterial pathogen of the equine respiratory tract. Nebulization of ceftiofur sodium (diluted to 50 mg/mL in sterile water) at a dose

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of 2.2 mg/kg with the Flexineb mask was well tolerated and resulted in drug concentrations in pulmonary epithelial lining fluid above the minimum inhibitory concentration of the drug required to inhibit the growth of 90% of *S. zooepidemicus, Pasteurella* spp., and *Actinocbacillus* spp. for approximately 24 hours after administration.[58] Additional studies are required to assess the efficacy of aerosolized antimicrobial agents for the treatment of bacterial respiratory tract infections in horses.

Ancillary Treatments.

The need for ancillary treatments depends on the severity of the disease and is most often necessary in horses with pleuropneumonia. Nonsteroidal antiinflammatory agents (NSAIDs) may be beneficial to minimize inflammation, provide analgesia, and control high fevers. Additional analgesia may be necessary in horses with severe pleurodynia. Adequate hydration should be maintained in patients receiving these agents for extended periods, especially if aminoglycosides are used concurrently. Intravenous fluid therapy may be necessary to correct hypovolemia in acute stages, but it is rarely required for chronic cases. Intrapharyngeal insufflation of oxygen is indicated in horses that remain severely hypoxemic despite adequate drainage of the pleural cavity. Adequate parenteral or preferably enteral nutritional support via a nasogastric tube is beneficial in horses that remain anorectic for several days. In horses with severe systemic illness, distal limb cryotherapy is indicated in an attempt to prevent development of laminitis.

Pleural Drainage.

Small amounts of pleural effusion may resorb quite readily with appropriate antimicrobial therapy. Therefore although a small sample of pleural fluid is useful diagnostically, pleural drainage is not necessarily indicated in all cases of pleuropneumonia. Drainage of pleural effusion results in removal of exudate and debris and allows for reexpansion of the lungs. Indications for drainage include a poor response to conservative therapy or the presence of pleural fluid with at least one of the following characteristics: (1) sufficient volume to cause respiratory distress, (2) fetid odor, or (3) cytologic or biochemical evidence of sepsis. Pleurocentesis and chest tube placement are described earlier in this chapter.

Pleural Lavage.

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Pleural lavage may be helpful to dilute thick, viscous pleural fluid and remove fibrin, debris, and necrotic tissue. Pleural lavage is most helpful in subacute stages before loculated pockets of pleural fluid develop. However, pleural lavage may help break down fibrous adhesions and establish communication between loculae. Pleural lavage is typically performed by using the same chest tube for infusion and drainage of lavage fluid. Alternatively, lavage can be performed by infusing fluid through a dorsally positioned tube and draining it through a ventrally positioned tube. Approximately 5 L of sterile, warm isotonic fluid solution is infused by gravity flow. After infusion, the chest tube is reconnected to the unidirectional valve for drainage. Allowing the horse to walk once the continuous flow has stopped will often result in drainage of additional fluid. Pleural lavage is probably contraindicated in horses with bronchopleural communications because it may result in spread of septic debris up the airways and into normal areas of the lungs.[59] Coughing and drainage of lavage fluid from the nose during infusion suggest the presence of a bronchopleural fistula (see the Complications of Pleuropneumonia section later).

Use of Fibrinolytic Agents.

The use of intrapleural fibrinolytics in the treatment of loculated pleural effusion remains controversial in human medicine.[60] Various fibrinolytic agents such as streptokinase, urokinase, and recombinant tissue plasminogen activators (rtPA; e.g., alteplase, tenecteplase) have been used.[60] Numerous case series in humans have shown that such therapy is fairly safe and may facilitate drainage. However, controlled trials are scarce and have given contradictory results regarding the ultimate benefit of intrapleural fibrinolytic therapy. Subgroup analysis of a meta-analysis of randomized controlled trials indicated that intrapleural fibrinolysis with urokinase might reduce the need for surgery and shorten hospital stay, whereas similar effects were not documented with streptokinase or rtPA.[61]

In recent years, rtPA has been increasingly used as an adjunct therapy for selected human patients with loculated pleural effusion. Several case series indicate a potential benefit for rtPA,[62,63] but large randomized placebo-controlled clinical trials are lacking.[60,62] Fibrinolytic drugs have negligible effects on decreasing the viscosity of purulent material because the viscosity of pus is attributable mainly to its DNA content. Therefore intrapleural recombinant human deoxyribonuclease I (rhDNase I) is sometimes used in combination with rtPA.[64] In a randomized clinical trial, intrapleural rtPA–rhDNase I therapy

improved fluid drainage in humans with pleural infection and reduced the frequency of surgical intervention and the duration of the hospital stay, whereas treatment with rhDNase I alone or rtPA alone was ineffective.[65]

Given that fibrinous pleural effusion has been associated with a less favorable outcome in horses with pleuropneumonia,[66] there has been increasing interest in the use of intrapleural fibrinolytic agents. There are isolated reports and a retrospective case series reporting the use of rtPA in horses with fibrinous pleuropneumonia. In one report, 12 mg of alteplase was infused in volumes of 0.9% saline ranging between 250 mL and 2 L.[67] In another report, tenecteplase (12 to 30 mg in 500 mL of 0.9% saline) was administered alone or in combination with 25 mg of rhDNase I.[68] In both reports there was a subjective decrease in the amount of fibrin in the thoracic cavity as assessed by ultrasonography. In a retrospective case series of 25 horses, altepase (0.4 to 20 mg per hemithorax in 10 mL to 2 L of polyionic solution) was administered 1 to 4 times per horse with no evidence of adverse effects and a subjective decrease in the amount of fibrin as assessed by ultrasonography after approximately 65% of treatments.[69] Controlled studies evaluating the safety and efficacy of rtPA and rhDNase I are required before the widespread use of these agents can be recommended in the management of fibrinous pleuritis in horses.

Thoracoscopy.

Thoracoscopy allows direct evaluation of the lungs and pleural cavity. In selected cases, thoracoscopy may be a useful tool to facilitate placement of thoracic drains in abscesses, transect pleural adhesions, and disrupt loculations.[46] The technique can also be used to biopsy or aspirate specific lesions affecting the periphery of the lungs. The procedure can be performed in the standing sedated horse with local anesthesia and is usually very well tolerated.[70]

Adhesions between the lung and the diaphragm or body wall may prevent complete collapse of the lung, making insertion of the instruments more difficult and sometimes limiting the view of the pleural cavity. Adhesions are easier to disrupt during the first week after formation when the tissue is fibrinous rather than fibrous. Transection of mature adhesions is more difficult and can result in severe hemorrhage. Creation of a pneumothorax is a necessary feature of thoracoscopy, and horses should be monitored carefully throughout the procedure. Transient exacerbation in clinical signs of pulmonary disease due to pneumothorax can be alleviated by reinflation of the lungs.

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Thoracotomy.

Surgical intervention in horses with pleuropneumonia is not a substitute for adequate medical management, but in carefully selected cases it can save the lives of horses that would have to be euthanized otherwise. The criteria for surgical interventions include (1) failure to respond to antimicrobial therapy, pleural drainage, and pleural lavage; (2) stable systemic medical condition; (3) presence of a large amount of fibrin, debris, or pus in the pleural space; and (4) either a walled-off lesion or presence of a complete mediastinum to avoid creation of a bilateral pneumothorax. Surgical intervention is most beneficial in chronic cases with large unilateral localized pockets of thick debris, especially if there is resolution or at least a significant improvement of the disease in the opposite hemithorax. Before surgical exploration, the nature and location of the lesion must be thoroughly characterized by ultrasonography or thoracoscopy to determine the ideal surgical site. When there is bilateral disease, thoracotomy is performed on the most severely affected side. If necessary, a second thoracotomy can be performed on the opposite side at a later time. Thoracotomy is typically performed with the horse standing. It is common practice to place a large chest tube into the targeted cavity and leave it open to atmospheric air for several hours before thoracotomy.[59] The onset of respiratory distress indicates development of bilateral pneumothorax, in which case standing thoracotomy is contraindicated and pneumothorax must be corrected. Unilateral pneumothorax is usually well tolerated.

The standing surgical procedures most commonly performed include thoracotomy via an intercostal approach and thoracotomy with rib resection. For the intercostal approach, the surgical site is prepared and infiltrated with local anesthetic. The lateral thoracic vein must be identified to avoid inadvertent incision. A vertical incision is made through the skin, intercostal musculature, and pleura. The length of the incision is dictated by the size of the pleural abscess and consistency of its content. When necessary, partial excision of the intercostal muscles will facilitate manual exploration of the cavity and removal of fibrin and necrotic debris. The major advantage of the intercostal approach over rib resection is preservation of thoracic wall integrity and compliance. Thoracotomy with rib resection is elected when the cavity is very large and it is anticipated that extensive manual débridement of fibrin and necrotic debris will be necessary. The advantage of the thoracotomy with rib resection over the intercostal approach is improved access to the thorax, allowing manual removal of large fibrin clumps and necrotic debris (Fig. 31.11). With both rib resection

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and intercostal approaches, the incision is left open and irrigated once or twice daily with a sterile isotonic fluid solution. The cavity is periodically débrided via gentle massage, taking care not to disrupt mature adhesions. After adequate formation of granulation tissue, tap water may be used. Depending on the size of the incision, it may take a few weeks to 2 to 3 months for complete closure by second intention. Complications during thoracotomy may include bilateral pneumothorax (if the cavity is not walled off and the mediastinum is not complete) and cardiac dysrhythmias (if the lesion is in close proximity to the heart). The most common long-term complication is the formation of a chronic draining fistula, but by itself this complication does not prevent the horse from returning to its usual occupation. In a retrospective study of 16 horses that had a standing lateral thoracotomy for pleural disease, 14 horses (88%) survived to discharge, and 46% of horses that survived returned to their previous level of athletic activity.[71] In another retrospective study, 9 of 11 horses that had a thoracotomy survived.[4]



FIG. 31.11 Thoracotomy with rib resection in a Thoroughbred filly with a large pleural abscess in the right hemithorax communicating with another abscess cranial to the heart. In this case, a rib resection was done to facilitate manual removal of purulent material and necrotic debris from both abscesses.

■ Complications of Pleuropneumonia

Several complications may occur during medical therapy of severe pneumonia and pleuropneumonia. These complications include jugular vein phlebitis or thrombosis from catheter placement, diarrhea resulting from antimicrobial therapy, pneumothorax or cellulitis secondary to thoracocentesis, coagulopathy, pleural abscesses, bronchopleural fistulas, pericarditis, and laminitis.

Pleural abscesses refractory to antimicrobial therapy are treated by thoracocentesis or thoracotomy (see earlier sections). In some cases of pleuropneumonia, the heart may act as a valve to trap effusion and inflammatory debris in the cranial thorax. Small cranial thoracic masses may result in nonspecific clinical signs such as fever, tachycardia, and sternal edema. Larger abscesses may result in jugular vein distention, forelimb extension (pointing), and caudal displacement of the heart. Diagnosis is made by ultrasonography (Fig. 31.12). It is necessary to pull a forelimb forward to successfully image the cranial thorax. Most horses with cranial thoracic masses will respond to conservative therapy with antimicrobial agents.[72] Drainage of the abscess should be performed in cases refractory to medical therapy or when the mass interferes with normal cardiac function. Cranial thoracic abscesses may be sampled in the standing horse with a front limb pulled forward. However, when drainage and lavage are required, the procedure is best performed under short-term general anesthesia to avoid damage to the heart and major blood vessels present in the cranial thorax. It is not recommended to leave an indwelling tube because the triceps musculature often causes the tube to kink. Repeated drainage and lavage may be necessary in some cases.

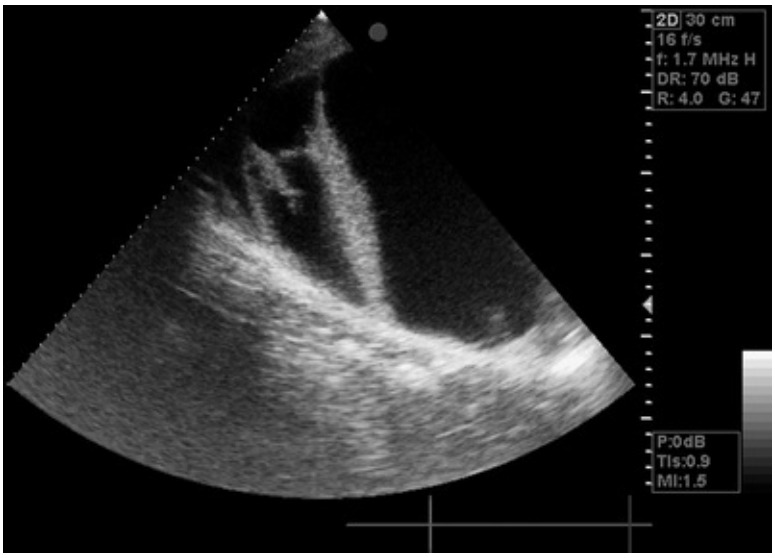


FIG. 31.12 Sonogram of the cranial thorax obtained from the third intercostal space of a 2-year-old Thoroughbred filly with distended jugular veins and pitting edema of the ventral thorax. A large, fluid-filled, loculated abscess was imaged.

Bronchopleural fistulas develop when necrosis of lung tissue leads to direct communication between the airways and the pleural cavity. Diagnosis may be confirmed by thoracoscopy or by injecting sterile fluorescein dye into the pleural fluid and looking for presence of dye at the nostrils or within the trachea by endoscopy. Horses with bronchopleural fistula will often cough during pleural lavage, and lavage fluid may be noted at the nostrils. Most bronchopleural fistulas seal spontaneously as a result of adhesions to the chest wall or fibrin deposition on the visceral pleura. Sealing may occur rapidly or take several weeks. In one case, partial pneumonectomy was successful at resolving a chronic bronchopleural fistula and pulmonary abscess.[73]

■ Prognosis

The prognosis for survival and return to normal athletic function depends on the severity and duration of clinical signs prior to therapy. Horses with septic inflammatory airway disease or mild to moderate bronchopneumonia have a very good prognosis for a return to previous athletic performance. The prognosis for horses with pulmonary abscesses and without concurrent pleuritis is also good. In one study, 45 of 50 (90%) adult horses with pulmonary abscesses survived.[74] In the same study, 92% of Standardbreds and 52% of Thoroughbreds raced after treatment of pulmonary abscesses.[74] For horses that returned to

racing, performance after successful treatment of lung abscesses was not significantly different from that before the illness.[74]

In a retrospective study of 327 horses with pneumonia or pleuropneumonia, the overall survival rate was 75%.[3] In the same study, the survival rate for 81 horses from which anaerobic bacteria were cultured was only 38.3%.[3] However, other studies failed to identify an association between the presence of anaerobic bacteria and decreased survival.[4,75] In cases of pleuropneumonia, retrospective studies have shown survival rates ranging from 43.3% to 87.6%.[4,14,75,76] Differences in survival rates among studies may reflect differences in referral populations as well as advances in therapy in more recent years. Many horses that would have been euthanized because of chronicity and lack of response to medical therapy several years ago are now successfully treated with the surgical approaches described above. This is evidenced by a retrospective of 153 horses with pleuropneumonia in which the survival rate was 95.7% when horses electively euthanized were excluded.[76]

The effect of pleuropneumonia on subsequent racing performance has not been examined extensively. In one retrospective study, 43 of 70 (61%) horses that had recovered from pleuropneumonia returned to racing, and 24 of those 43 (56%) won at least one race.[77] In the same study, horses that required placement of an indwelling thoracic drain did not have a worse prognosis for return to performance compared to horses that did require placement of a drain.[77] In contrast, horses that developed complications such as pulmonary abscesses, cranial thoracic masses, or bronchopleural fistulas were significantly less likely to return to racing.[77]

Rhodococcus equi Infections

Steeve Giguère

Rhodococcus equi, a gram-positive facultative intracellular bacterium, is one of the most common causes of pneumonia in foals between 3 weeks and 5 months of age. *R. equi* has also emerged as a significant opportunistic pathogen in immunosuppressed humans, especially those infected with the human immunodeficiency virus (HIV).[1,2] Although *R. equi* can be cultured from the environment of virtually all horse farms, the clinical disease in foals is endemic and devastating on some farms, sporadic on others, and unrecognized on still others. At farms where the disease is endemic, costs associated with veterinary

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care, long-term therapy, and mortality of some foals may be very high. This text reviews the clinical manifestations, pathogenesis, epidemiology, diagnosis, treatment, and control of infections caused by *R. equi* in foals.

■ Clinical Manifestations

Pulmonary Disease.

The most common clinical manifestation of disease caused by *R. equi* infections in foals is a chronic suppurative bronchopneumonia with extensive abscessation (Fig. 31.13). The slow spread of the lung infection combined with the remarkable ability of foals to compensate for the progressive loss of functional lung make early clinical diagnosis difficult. Early clinical signs often consist of a mild fever, occasional cough, or slight increase in respiratory rate that may not be apparent unless foals are exercised or stressed by handling. If pneumonia progresses, clinical signs may include decreased appetite, lethargy, fever, cough, tachypnea, and labored breathing characterized by nostril flaring and increased abdominal effort. Bilateral nasal discharge is an inconsistent finding. In a recent report of 161 foals affected with *R. equi* pneumonia, the most common clinical signs were cough (71%), fever (68%), lethargy (53%), and increased respiratory effort (43%).[3] A smaller percentage of affected foals present with a more devastating subacute form. These foals might be found dead or, more commonly, are presented in acute respiratory distress with a high fever and no previous history of clinical respiratory disease. Foals with the subacute form of the disease have a poor prognosis despite appropriate therapy.



FIG. 31.13 **A,** Left lung from a foal with severe pneumonia caused by *Rhodococcus equi*. There is marked consolidation of the cranial portion of the lung, and multiple abscesses are present caudodorsally. **B,** Cross-section of the same lung showing multiple abscesses filled with caseous material. (Courtesy Dr. William Castleman., University of Florida, College of Veterinary Medicine, Gainsville, Fla.)

Because ultrasonographic screening for early detection of pneumonia caused by *R. equi* has become routine practice at many endemic farms, the most frequently recognized form of *R. equi* infection at those farms is a subclinical form in which foals develop ultrasonographic evidence of peripheral pulmonary consolidation or abscessation without manifesting clinical signs.[4,5] At those farms, the cumulative frequency of ultrasonographically visible areas of focal pulmonary consolidation or abscessation considerably exceeds the historical frequency of clinical pneumonia attributed to *R. equi*, indicating that many subclinically affected foals might spontaneously recover without therapy. In two

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independent studies at breeding farms endemic for *R. equi* infections, 80% to 90% of foals with ultrasonographically visible lesions recovered without antimicrobial therapy.[6,7] The proportion of subclinically affected foals that progress to clinically apparent disease might vary by farm, geographic region, and age at which foals are examined.

Extrapulmonary Disorders.

Extrapulmonary manifestations of rhodococcal infections are common.[8] In a study of 150 foals with *R. equi* infections admitted to a teaching hospital, at least 1 of 39 different extrapulmonary disorders (EPDs) were recognized in 74% of foals, although some EPDs, particularly abdominal lesions, can be difficult to recognize antemortem and were recognized only during necropsy.[8] Survival was significantly lower among foals with EPDs (43%; 48 of 111) than among foals without EPDs (82%; 32 of 39).[8] Some EPDs (e.g., polysynovitis, uveitis) might be the first clinical manifestation of *R. equi*–associated disease, detected prior to signs of pneumonia.

Intestinal lesions are present in approximately 50% of foals with *R. equi* pneumonia presented for necropsy.[9] However, the majority of foals with *R. equi* pneumonia do not show clinical signs of intestinal disease. In the same study, only 4% of the foals had intestinal lesions without pneumonia.[9] The intestinal form of *R. equi* infection is characterized by a multifocal ulcerative enterocolitis and typhlitis over the area of the Peyer's patches with granulomatous or suppurative inflammation of the mesenteric and/or colonic lymph nodes.[9] In some cases, the only abdominal lesion noted may be a single large abscess (usually in a mesenteric lymph node) that often adheres to the large or small bowel (Fig. 31.14). Foals with abdominal abscesses have a poor prognosis.[8]

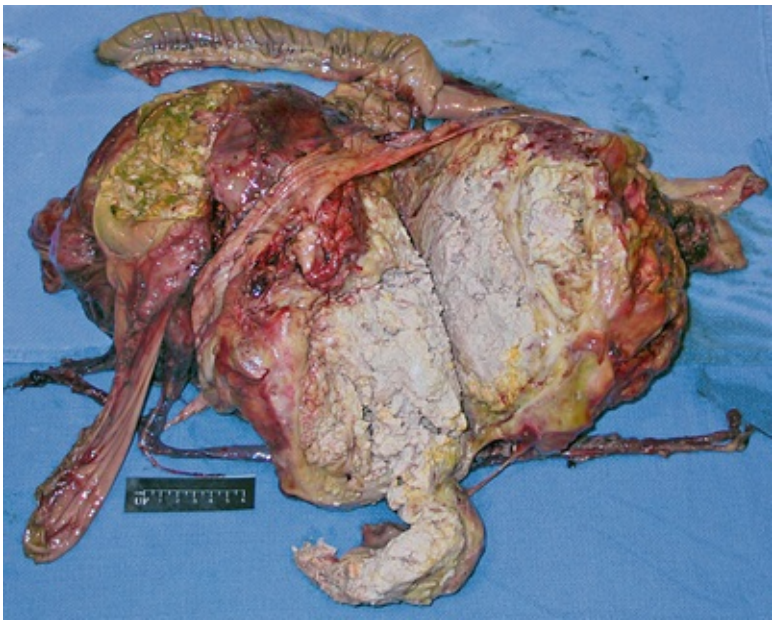


FIG. 31.14 Large abdominal abscess from a 4-month-old foal with a history of weight loss, fever, and mild intermittent episodes of colic. A portion of the small intestine and a portion of the small colon are adhered to the abscess. Culture yielded pure growth of *Rhodococcus equi*.

Clinical signs associated with the abdominal form of the disease may include fever, depression, anorexia, weight loss, colic, and diarrhea.[8,10] Diarrhea might occur in foals infected with *R. equi* either as an EPD caused by pyogranulomatous typhlocolitis or as a result of antimicrobial treatment. Of 31 foals with ulcerative enterotyphlocolitis identified at necropsy, only 12 foals had diarrhea, whereas 9 foals had diminished growth.[8] Marked GI lymphatic obstruction associated with increased protein concentration in the peritoneal fluid and systemic hypoproteinemia may lead to ascites, giving affected foals a pot-bellied appearance. Such foals have a poor prognosis because of the extensive granulomatous inflammation of the colonic mucosa and submucosa, and mesenteric lymph nodes.

Intermittent or persistent bacteremia with *R. equi* may be more common than recognized and may result in metastatic spread of infection. The proportion of foals that are blood culture–positive and the stages of disease during which bacteremia is most likely to occur are poorly defined. In one study, 6 of 10 foals with naturally acquired pneumonia had positive blood cultures.[11] More recently, *R. equi* was isolated from the blood of 11 of 19 foals, and foals with positive blood culture results were less likely to survive than foals that were culture-negative.[8]

Polysynovitis, characterized by effusion of multiple synovial structures and absence of lameness, occurs in approximately one fourth to one third of foals with naturally acquired *R. equi* infections.[8,12] Uveitis has also been described in foals naturally infected with *R. equi*.[8] Foals with uveitis might display epiphora, photophobia, aqueous flare, hypopyon, iris discoloration, miosis, and other ophthalmic abnormalities. Detection of immunoglobulins within the synovial membrane or iris by immunofluorescence in a small number of affected foals combined with the fact that *R. equi* is rarely isolated from these sites at the time of diagnosis or necropsy [8,12-14] have led to the widespread hypothesis that polysynovitis and uveitis are immune-mediated disorders.[13-15] However, experimental infection with virulent *R. equi* consistently results in polysynovitis and uveitis, and development of these conditions is associated with the severity of pulmonary disease.[16,17] Culture of synovial fluid and aqueous humor within days of the onset of clinical signs in these foals often yields *R. equi*, and histologic examination of the synovial membrane reveals suppurative inflammation with bacteria.[16,17] Therefore polysynovitis and uveitis are most likely septic processes resulting from bacteremia. However, the infection is eventually cleared from the synovial structures and the eye, resulting in chronic nonseptic inflammation at these sites at the time of diagnosis or necropsy. Regardless of the inciting cause, local therapy of the affected joints in clinical cases of *R. equi*–associated polysynovitis is usually not indicated because the effusion resolves without any apparent consequences if the primary infection responds to appropriate antimicrobial therapy. The presence of polysynovitis or uveitis in a foal between 3 weeks and 6 months of age is highly suggestive of *R. equi* infection and deserves further investigation (see the Diagnosis section later).

Bacteremic spread of the organism from the lungs or GI tract may occasionally result in severe septic arthritis of a single joint or, more commonly, osteomyelitis. However, foals can occasionally develop *R. equi* septic arthritis or osteomyelitis without apparent lung involvement or other source of infection. Foals with septic arthritis typically show moderate to severe lameness, whereas foals with polysynovitis are not lame or only minimally so. In addition to appropriate antimicrobial therapy (see the Treatment section later), foals with *R. equi* septic arthritis and osteomyelitis often require aggressive local therapy. *R. equi* vertebral osteomyelitis or diskospondylitis resulting in spinal cord compression has also been reported.[18-20] Clinical signs of vertebral osteomyelitis

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or diskospondylitis may include stiff gait, reluctance to move, palpable pain, and sometimes soft-tissue swelling associated with paravertebral abscessation.[8] If the infection or associated swelling extends to the epidural space, neurologic signs of spinal cord disease or nerve root compression might be apparent.[8] Specific neurologic signs vary according to the specific region of the spinal cord that is affected. Foals with vertebral osteomyelitis generally have a poor prognosis. However, there are reports of successful treatment with prolonged antimicrobial therapy alone or in conjunction with surgical débridement of infected bone.[18]

Other less common EPDs associated with metastatic spread of *R. equi* include pericarditis, endocarditis, cellulitis, dermatitis, subcutaneous abscesses, peripheral lymphadenopathy, guttural pouch empyema, pleuritis, sinusitis, ulcerative lymphangitis, myositis, stomatitis, pyometra, and omphalitis.[8,21] Other immune-mediated EPDs include immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, and telogen effluvium.[8,22]

Adult Horses.

Disease caused by *R. equi* in adult horses is rare, but there are sporadic reports of infection involving primarily the lungs or abdominal lymph nodes (similar to infection observed in foals) and, less common, of wound infection. In one adult horse, acquired combined immunodeficiency of unknown origin led to *R. equi* septicemia and lung abscessation.[23] Occasionally the microorganism has also been isolated from infertile mares and aborted fetuses.[9,24,25]

Other Domestic Animal Species.

R. equi has been isolated from many species other than people and horses. *R. equi* is frequently cultured from the submaxillary lymph nodes of pigs with granulomatous lymphadenitis. However, *R. equi* can also be isolated from the submaxillary lymph nodes of 3% to 5% of apparently healthy pigs, and experimental infection studies in pigs have failed to reproduce granulomatous lymphadenitis.[26,27] The causative role of *R. equi* in granulomatous lymphadenitis in pigs remains unproven. Isolation of *R. equi* from other domestic animal species is rare. *R. equi* can be isolated from lymph node granulomas in 0.008% of cattle at abattoir postmortem inspection.[28] *R. equi* has been cultured also from rare cases of bronchopneumonia, mastitis, metritis, ulcerative lymphangitis, and septic arthritis in cattle. In goats, *R. equi* has been cultured from cases of liver abscesses, bronchopneumonia, subcutaneous abscesses, osteomyelitis, and

disseminated infections involving multiple sites.[29,30] In dogs and cats, *R. equi* has been isolated from cases of pneumonia as well as from wound infections, subcutaneous abscesses, vaginitis, endocarditis, endophthalmitis, hepatitis, osteomyelitis, myositis, and joint infections.[31,32] A severe systemic form with suppurative to necrotizing pneumonia and multiple caseating abscesses in mediastinal lymph nodes, liver, and spleen has been observed in camelids (llama and dromedary).[33,34]

Virulence

The ability of *R. equi* to induce disease in foals likely depends on both host and microbial factors. *R. equi* is a facultative intracellular pathogen, and its ability to persist in and eventually destroy alveolar macrophages seems to be the basis of its pathogenicity. Knowledge of the virulence mechanisms of *R. equi* was largely speculative until the discovery of a virulence plasmid in the early 1990s.[35,36] Unlike most environmental *R. equi,* isolates from pneumonic foals typically contain an 80- to 90-kb plasmid. Plasmid-cured derivatives of virulent *R. equi* strains lose their ability to replicate and survive in macrophages.[16] Plasmid-cured derivatives also fail to induce pneumonia and are completely cleared from the lungs of foals within 2 weeks following heavy intrabronchial challenge, confirming the absolute necessity of the large plasmid for the virulence of *R. equi*.[16,37]

Sequencing and annotation of the virulence plasmid obtained from isolates of *R. equi* cultured from pneumonic foals revealed 73 coding sequences[38,39] divisible into four discrete areas based on open reading frame (ORF) amino acid sequence similarity and predicted protein function. The “backbone” sequence of the plasmid is highly similar to that of a plasmid found in the environmental microorganism *Rhodococcus erythropolis* and consists of regions for replication or partitioning, conjugation, and unknown functions.[38] The fourth plasmid region is a 21-kb pathogenicity island (PAI) that is crucial for virulence.[38,39] The 26 coding sequences of the PAI include the unique and *R. equi*–specific virulence-associated protein (Vap) family.[39] There are six full-length *vap* genes, (*vapA, vapC, vapD, vapE, vapG,* and *vapH*) and three truncated *vap* pseudogenes (*vapF, vapI,* and *vapX*).[38] To date, *vapA,* which encodes an immunodominant, temperature-inducible, and surface-expressed lipoprotein,[40,41] is the only *vap* gene with a demonstrated role in virulence,[42] whereas *vapsC, D,*

E, F, G, I, and *X* are dispensable.[42,43] *VapA* is required for intracellular growth in macrophages,[42] where it disrupts endolysosomes and contributes to preventing maturation of the phagosome to the stage of fusion of *R. equi*–containing vacuoles with lysosomes.[44,45] The functions of the other Vap proteins are unknown.

Although *vapA* is necessary for virulence, it is not sufficient.[16] Two additional regulator genes of the PAI, *virR* and *virS*, are required for intracellular growth in macrophages and virulence.[46-49] Loss of either regulator results in decreased transcription, not only of *vapA*, but also of several chromosomal genes.[46-49] These findings demonstrate the presence of molecular "crosstalk" between the virulence plasmid and the *R. equi* chromosome. All of the *vap* genes as well as five other ORFs within the PAI are upregulated when *R. equi* is grown in macrophage monolayers.[50] Regulation of expression of the genes in the PAI is complex and depends on at least five environmental signals: temperature, pH, oxidative stress, magnesium, and iron.[50-52] The precise role of each of these genes in the pathogenesis of *R. equi* infections remains to be determined. The entire virulence plasmid can be transferred by conjugation from plasmid-containing strains of *R. equi* to plasmid-free *R. equi* strains at a high frequency, and plasmid transmission restores the capacity for intracellular growth in macrophages.[53] Deletion of a putative relaxase-encoding gene *(traA)* located in the proposed conjugative region of the plasmid prevents plasmid transfer.[53]

Virtually all isolates of *R. equi* cultured from diseased foals contain the large circular plasmid described earlier (designated pVapA because it encodes *vapA*), whereas most isolates from swine with granulomatous lymphadenitis contain a similar large circular plasmid (designated pVapB) that encodes a 20-kDa antigen (VapB) that is related to but distinct from VapA.[54] Most isolates from cattle with granulomatous lymphadenitis and from goats with various infections contain a linear plasmid (designated pVapN, with "N" standing for "no-A no-B") unrelated to the circular virulence plasmids pVapA and pVapB.[55,56] In contrast, many environmental isolates of *R. equi* do not contain any of these three plasmids and are referred to as avirulent because they lack the ability to replicate in macrophages and in experimentally infected mice and they cannot induce disease in foals. Isolates carrying pVapB or pVapN have not been isolated from foals with naturally acquired *R. equi* infections. Experimentally, heavy intrabronchial challenge of foals with *R. equi* carrying pVapB results in pneumonia but at a dose much higher than that required for induction of

pneumonia with strains containing pVapA.[57] The observation that all *R. equi* isolates obtained from foals carry pVapA, most isolates from swine carry pVapB, and most isolates from ruminants carry pVapN-type plasmid has led to the hypothesis that plasmid type might dictate host species tropism. However, *R. equi* isolates from pigs, carrying pVapB, are able to replicate in a plasmid-dependent manner in macrophages obtained from a variety of species (murine, swine, and equine).[58] Similarly, equine isolates carrying pVapA are capable of replication in swine macrophages.[58] Plasmid swapping between equine and swine strains through conjugation does not alter the intracellular replication capacity of the parental strain.[58] These results demonstrate that, although distinct plasmid types exist among *R. equi* isolates obtained from different species, host tropism is not determined exclusively by plasmid type.

The plasmid profile of *R. equi* isolated from other species is not as straightforward as it is in horses, swine, and ruminants. Analysis of 65 *R. equi* isolates from humans with and without AIDS reveals that approximately 15% of isolates contain pVapA, approximately 17% contain pVapB, and approximately 25% contain pVapN.[59] Most isolates of *R. equi* cultured from humans do not contain pVapA, pVapB, or pVapN.[59-62] Therefore the pathogenesis of *R. equi* infection in immunocompromised human patients appears to be different from the pathogenesis in foals, in which pVapA is always found. Similarly, isolates from cats and dogs can be avirulent or contain any of the three plasmids.[31,63]

Another major advance in the understanding of *R. equi* virulence was the sequencing and annotation of the genome of *R. equi*.[64] The 5.04-Mb *R. equi* genome is most similar to that of the environmental bacterium *Rhodococcus jostii* and then to *Nocardia farcinica* and *Mycobacterium tuberculosis*.[64] As with these other actinomycetes, a large number of the 4598 genes of *R. equi* appear to be involved in lipid metabolism. Like *M. tuberculosis,* lipids are a key component of the outer cell envelope of *R. equi*.[65] This mycolic acid-containing glycolipid barrier might serve to protect the peptidoglycan and plasma membrane from the damaging effects of host-generated enzymes and immune-mediated reactive intermediates. Cell envelope mycolic acid carbon chain length varies among *R. equi* isolates, and notably it was observed that strains with longer mycolic acids were more lethal to mice.[66] This might be explained by the fact that mycolic acid chain length plays a key role in diversion of macrophage phagosome trafficking by *R. equi*.[67] Although it has been firmly established that the virulence plasmid is essential for infection of foals, several chromosomally

encoded genes have also been proven to play essential roles in intracellular survival and virulence, notably those involved in various metabolic functions such as fatty acid metabolism, anaerobic metabolism, aromatic amino acid biosynthesis, regulation of secreted proteins, iron acquisition, hydrogen peroxide resistance, and cholesterol catabolic pathways.[64,68-76]

■ Pathogenesis

Inhalation of virulent *R. equi* is the major route of pulmonary infection in foals. The incubation period following experimental intrabronchial challenge varies from approximately 9 days after administration of a heavy inoculum to approximately 2 to 4 weeks when a lower inoculum is administered.[16,77] Lung consolidation can be detected as early as 3 days following heavy intrabronchial challenge.[16] However, the incubation period under field conditions is unknown and likely varies depending on several factors, including the number of virulent bacteria in the air, the age of the foal, and host defense mechanisms. Ingestion of the organism is an important route of exposure, and likely also of induction of an immune response, but rarely leads to hematogenously acquired pneumonia unless a foal has multiple exposures to large numbers of bacteria.[78] Indeed, intragastric administration of live virulent *R. equi* to foals on day 2 and day 7 of life is highly effective in preventing development of pneumonia following subsequent heavy intrabronchial challenge.[79] Despite conferring protection, oral vaccination with live virulent *R. equi* would not be an acceptable strategy to immunize foals, since it would lead to progressive contamination of the environment with virulent bacteria. However, it undoubtedly shows that newborn foals have the ability to mount protective immune responses against *R. equi* (see the Immunity section later).

Epidemiologic evidence suggests that most foals on endemic farms become infected early in life.[80] The median age at the time of diagnosis is approximately 35 to 50 days on most endemic farms.[3,81] Given the fairly long incubation period of the disease, this finding would also support the fact that many foals become infected early in life. In one study, foals between 3 and 13 days of age (mean of 6.4 days) were more susceptible to experimentally induced *R. equi* pneumonia than foals between 14 and 36 days of age (mean of 25 days).[82] In another study, foals between 3 and 42 days of age were experimentally infected with various doses of virulent *R. equi* (10^3 to 10^7).[83] Whereas the youngest foals were highly susceptible to infection, the oldest foals were resistant to thousandfold higher

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challenge.[83] Collectively, these findings indicate that many foals on endemic farms become infected at a young age and that younger foals are more susceptible than older foals to infection caused by *R. equi*. However, these findings do not necessarily indicate that foals are only susceptible to *R. equi* during the neonatal period. Older foals are also susceptible to experimental infection with *R. equi*, but they require a higher inoculum. In one study, intratracheal administration of *R. equi* to 10 foals between 27 and 67 days of age (mean of 49 days) resulted in disease in all foals.[37] The relative resistance of older foals to infection caused by *R. equi* compared with younger foals is likely the result of immunologic priming after natural exposure to the pathogen.

■ Epidemiology

Although *R. equi* can be cultured from the environment of virtually all horse farms, the clinical disease in foals is endemic and devastating on some farms, sporadic on others, and unrecognized on still others. This might reflect differences in environmental and management conditions, as well as differences in the virulence of isolates, but the exact basis for the difference in the prevalence of the disease among farms remain unknown. Breeding farms with a large acreage, a large number of mares and foals, a high foal density, and a large population of transient mares and foals have greater odds of being affected by *R. equi* pneumonia.[84,85] In contrast, *R. equi* pneumonia does not appear to be associated with lack of attention to routine preventive health practices.[86]

R. equi is a soil microorganism with simple growth requirements. The highest numbers of *R. equi* are found in surface soil, and the organism cannot be found at depths exceeding 30 cm.[87] *R. equi* can be cultured not only from the soil of all horse farms but also from the soil of areas not inhabited by horses. In one study, *R. equi* was isolated from approximately 74% of soil samples collected from 115 parks and 49 household yards in Japan. The number of *R. equi* in those samples ranged from 10 to 10^5 colony-forming units (CFU) per gram of soil. None of the 1294 isolates from those samples expressed VapA or VapB.[27]

R. equi can be isolated from the feces of most adult horses at concentrations ranging from 10 to 10^4 CFUs/g of feces. The number of *R. equi* in the feces of mares on endemic farms does not increase in the weeks before or after foaling.[88] In one study, virulent *R. equi* could be isolated from the feces of all mares sampled, demonstrating that mares can be an important source of virulent *R. equi* for their surrounding environment.[89] However, dams of affected foals did not shed more *R. equi* in feces than did dams of unaffected foals, indicating that heavier shedding by particular mares does not explain infection in their foals.[89] In another study, *R. equi* could be isolated from the feces of only 19% of the foals at 1 week of age and from all foals by 4 weeks of age.[88] Foals can shed high concentrations of *R. equi* in their feces, reaching numbers up to 10^5 CFUs/g of feces.[90] Virulent *R. equi* present in the sputum of pneumonic foals will be swallowed, and as a result the manure of *R. equi*–affected foals is likely a major source of progressive contamination of the environment with virulent organisms.

In a survey of the prevalence of *R. equi* at horse breeding farms in Japan, the

organism was isolated from almost all soil samples, at numbers of 10^2 to 10^5 CFUs/g of soil.[91] Although virulent *R. equi* isolates containing pVapA were cultured from 24 of 31 farms examined, the vast majority of these isolates did not contain plasmids and were avirulent. On those farms, virulent *R. equi* represented 1.7% to 23.3% of all isolates.[91] However, neither the presence nor the concentration of virulent *R. equi* in soil is positively associated with increased cumulative incidence of *R. equi* pneumonia at breeding farms in North America or Australia.[92-94] In addition, soil geochemistry does not appear to be associated with occurrence of *R. equi* pneumonia at farms.[95]

In contrast, airborne concentration of virulent *R. equi* is associated with disease incidence at Thoroughbred breeding farms in Australia.[94] Factors associated with increased air concentration of *R. equi* at these farms included site (higher in holding pens and lanes relative to paddocks), warmer ambient temperature, less soil moisture, reduced grass height, and later date during the foaling season.[94] In Kentucky, concentrations of airborne *R. equi* were lower between midnight and 6 AM, and the presence of horses at the sampling site appeared to increase the airborne concentrations of virulent *R. equi*.[96] These findings suggest that airborne concentrations may be increased by greater activity and density of horses at sites where foals are housed. Also in Kentucky, foals were more likely to be exposed to airborne virulent *R. equi* when housed in stalls versus paddocks and earlier (January and February) versus later (May and June) during the foaling season.[97] Similarly, the odds of detecting airborne virulent *R. equi* at three breeding farms in Ireland were approximately 17 times greater in stables (stalls) than in paddocks of a given farm, and concentrations of virulent *R. equi* were also significantly higher in stables than in paddocks.[98] In a recent study at a breeding farm in Texas, exposure of foals to airborne virulent *R. equi* during the first 2 weeks after birth was significantly associated with subsequent development of *R. equi* pneumonia.[99] The fact that exposure to *R. equi* preceded development of pneumonia suggests that the higher concentration of airborne virulent *R. equi* is likely the cause of pneumonia rather than an effect of it.

In one study, air samples from the breathing zone of pneumonic foals had higher concentrations of virulent *R. equi* than environmental air samples collected from lanes and pens at the same farms.[100] However, concentrations of virulent *R. equi* from air samples collected from the breathing zones were not significantly different between pneumonic foals and healthy controls, indicating

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that affected foals do not represent a greater risk than other foals for aerosol transmission. In addition, there was no association between virulent *R. equi* in the breathing zone of foals and the subsequent diagnosis of rhodococcal pneumonia.[101] Thus, to date, there is no compelling evidence that *R. equi* infection is contagious among foals and that affected foals should be isolated from other foals.

Considerable genotypic variability has been found among isolates of *R. equi* obtained from the same farm and among isolates from various countries or continents.[102-104] Interestingly, multiple different *R. equi* strains were isolated in five of the six cases in which more than one isolate from a single foal was examined.[103] Similarly, six distinct genotypes were identified among nine *R. equi* isolates from one foal with pneumonia and concurrent abdominal lesions.[105] None of the four pulmonary isolates were identical; however, a pulmonary isolate was found to be identical to an isolate recovered from a small intestinal lymph node, and a second pulmonary isolate was identical to an isolate from a mesenteric lymph node.[105] Therefore foals can be infected with multiple strains of virulent *R. equi*, and with current techniques it is not possible to link infections to a given geographic site or region on the basis of analysis of isolate genotyping.

■ Rhodococcus equi–Phagocytic Cell Interactions

Once inhaled, *R. equi* is taken up by alveolar macrophages through a process of receptor-mediated phagocytosis. One of the receptors used by macrophages to engulf complement-opsonized *R. equi* is complement receptor 3 (CR3 or Mac-1).[106] In addition, *R. equi* might use the macrophage mannose receptor for entry, which may recognize lipoarabinomannan (LAM), an outer surface component of the bacterium, either directly or via mannose binding protein or surfactant molecules adhered to LAM.[107] Once engulfed by resident macrophages, virulent *R. equi* are able to modify the phagocytic vacuole to prevent acidification and subsequent fusion with lysosomes.[44,108-110] The ability of *R. equi* to disrupt endolysosome function depends on VapA,[45] and addition of soluble recombinant VapA restores the ability of avirulent *R. equi* mutant lacking the *vapA* gene to survive and replicate in macrophages.[111,112] Uncontrolled intracellular replication of *R. equi* leads to necrosis of the macrophage.[113] If bacteria are opsonized with *R. equi*–specific antibody, presumably promoting bacterial entry

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via the macrophage Fc receptor, the fate of the *R. equi*–containing phagosome is altered and lysosome fusion occurs.[114] This may explain how the presence of *R. equi* antibody might aid in the prevention of infection. Killing of *R. equi* by mouse macrophages is dependent on the presence of IFN-γ, which activates macrophages to produce both reactive oxygen and reactive nitrogen intermediates. These two radicals combine to form peroxynitrite, which efficiently kills *R. equi*.[115] Neither reactive oxygen nor reactive nitrogen intermediates alone are sufficient to mediate killing of *R. equi*.[115] Macrophage activation and nitric oxide synthesis act at least in part by increasing the ability of macrophages to store iron in a way that it cannot readily be accessed by *R. equi*.[116] Additional cytokines such as tumor necrosis factor (TNF)–α might have similar effects on restricting intracellular growth of *R. equi* in macrophages because both IFN-γ and TNF-α are required for clearance of virulent *R. equi* in mice.[117] In a recent study, priming of equine monocyte-derived macrophages IFN-γ, TNF-α, or IL-6 decreased intracellular survival of *R. equi*, whereas IL-1β or IL-10 enhanced intracellular survival.[118] Neutrophils also play an important role in early host defense against virulent *R. equi*.[119] As opposed to macrophages, neutrophils from foals and adult horses are fully able to kill *R. equi*.[120-122] As seen with macrophages, killing of *R. equi* by neutrophils is considerably enhanced by specific opsonizing antibody.[123,124]

■ Immunity

Antibody-Mediated Immunity.

Immunity to *R. equi* pneumonia in foals likely depends on both the antibody and cell-mediated components of the immune system, but its exact basis remains to be determined. The strongest evidence for a role of antibody in protection against *R. equi* is the partially protective effect of passively transferred anti–*R. equi* hyperimmune equine plasma (HIP; see the Control and Prevention of *R. equi* Infections on Farms Where the Disease Is Endemic section later) and the fact that maternal vaccination against poly-*N*-acetylglucosamine protects foals against intrabronchial challenge with *R. equi*.[125] The mechanisms by which antibody confers protection against facultative intracellular bacterial pathogens is an area of active investigation. Opsonization of *R. equi* with specific antibody has been shown to promote phagocytosis and killing of *R. equi* by alveolar macrophages, identifying antibody as a critical component of HIP.[114,126] In most

studies evaluating the protective effect of HIP, donors were immunized with whole cell vaccines or a mixture of several soluble antigens, making it impossible to determine the role of antibody against defined antigens of *R. equi*.

A number of studies have focused more specifically against the role of antibody against plasmid-encoded Vaps. First, monoclonal antibody to VapA and serum from horses immunized with partially purified VapA have opsonizing activity.[127] Moreover, purified immunoglobulins obtained from horses vaccinated with partially purified VapA protected mice against intraperitoneal challenge with virulent *R. equi* compared with mice administered immunoglobulins from nonimmunized horses.[128] Finally, intravenous administration of purified immunoglobulins obtained from horses immunized with recombinant VapA and VapC to foals was found to reduce the severity of pneumonia following heavy experimental challenge with *R. equi*.[129] In the same study, the degree of protection conferred by purified anti-VapA and anti-VapC immunoglobulins was similar to that provided by commercially available HIP.[129]

In adult horses, the concentrations of *R. equi*– and VapA-specific IgGa and IgGb antibodies (the IgG isotypes that preferentially opsonize and fix complement in horses) are dramatically enhanced following intrabronchial challenge with virulent *R. equi*. This occurs in conjunction with clearance of the bacteria from the lungs.[130] In foals, production of antibody to VapA and VapC, but not that to other Vaps, increases following natural exposure to *R. equi*.[129] Characterization of the subisotype response in naturally infected foals revealed mainly an increase in IgGa, IgGb, and IgG(T).[129,131,132] Experimental infection of young foals with a low inoculum of virulent *R. equi* that resulted in subclinical pulmonary lesions caused a marked increase in serum IgGa and IgGb levels, resulting in concentrations that were significantly higher than those of adult horses undergoing the same challenge.[133] Infection of foals of the same age with a higher inoculum leading to severe respiratory disease resulted in a switch from a predominant IgGa response to a striking IgG(T) response, indicating that the size of the *R. equi* inoculum can modulate immune responses.[134]

Cell-Mediated Immunity.

Because of the facultative intracellular nature of *R. equi*, cell-mediated immune mechanisms are thought to be of major importance in resistance to infection. A large part of the knowledge of cell-mediated immunity to *R. equi* infections comes from infection of mice. Deficiencies in the complement component C5

and in natural killer (NK) cells in mice do not impair the pulmonary clearance of virulent *R. equi*.[135] In contrast, functional T lymphocytes are absolutely required for the clearance of virulent (plasmid- and VapA-positive) *R. equi* in mice.[136-138] However, athymic nude mice (lacking functional T lymphocytes) clear plasmid-cured derivatives from their lungs within 1 week of infection, suggesting that, as opposed to virulent organisms, clearance of avirulent plasmid-negative strains in mice does not require functional T lymphocytes and depends mainly on innate defense mechanisms.[137]

The two major mechanisms by which T lymphocytes mediate clearance of intracellular pathogens are secretion of cytokines and direct cytotoxicity. Although both CD4+ (helper) and CD8+ (cytotoxic) T cells contribute to host defense against *R. equi* in mice, CD4+ T lymphocytes play the major role and are absolutely required for complete pulmonary clearance.[138-140] Studies in mice have clearly shown that a type I response, characterized by IFN-γ production by T-helper lymphocytes, is sufficient to effect pulmonary clearance of *R. equi*, whereas a type II response, characterized by IL-4 production, is detrimental.[136,141]

As opposed to foals, adult horses are typically resistant to *R. equi* infections. Thus immune adult horses have been used as a relevant model to better understand what responses are necessary for immunologic protection. Clearance of virulent *R. equi* in adult horses is associated with a significant increase in BAL fluid CD4+ and CD8+ lymphocytes, lymphoproliferative responses to *R. equi* antigens, development of *R. equi*–specific cytotoxic CD8+ T lymphocytes (CTLs), and IFN-γ induction by CD4+ and CD8+ lymphocytes.[130,142,143] *R. equi*–specific CTLs, which are apparently present in all immune adults, are major histocompatibility complex (MHC) class I–unrestricted and appear to recognize unique bacterial lipids from the cell wall.[143,144] The current thought is that these lipid antigens might be presented to T lymphocytes via the CD1 system, as has been well described in *M. tuberculosis*.[145] How these findings in mice and adult horses relate to the foal is an area of active research.

Immunity to *R. equi* in Foals.

Virtually all newborn mammals are immunologically immature and have an assortment of immunologic deficits compared with older animals. In general, neonates and perinates have diminished innate immune responses and decreased antigen-presenting cell function and are less able to mount type I immune

responses.[146] As a result, neonates of various species demonstrate an increased susceptibility to certain infections.

A number of relative immunologic deficits have been demonstrated in foals. In conjunction with the lack of immunologic memory in newborns, these deficits are postulated to account for the unique age-associated susceptibility of foals to rhodococcal pneumonia. Age-related deficiencies in *R. equi*–specific CTL activity has been documented in 3-week-old foals.[143] Activity of CTLs is improved by 6 weeks of age and is similar to that of adult horses by 8 weeks.[143] Antigen-presenting cells from foals have significantly lower CD1 and MHC class II expression compared with adult horses.[145,147] In addition, several studies have demonstrated that the ability of equine lymphocytes and neutrophils to produce and/or upregulate various cytokines is strongly influenced by age.[146-151] In particular, the finding that young foals are deficient in their ability to produce IFN-γ in response to mitogens has led to the hypothesis that an IFN-γ deficiency and type II bias might be at the basis of their peculiar susceptibility to *R. equi* infections.[148,149] However, foals are also deficient in their ability to produce IL-4 in response to stimulation with mitogens and stimulation with *R. equi* and after vaccination with a killed adjuvanted vaccine, suggesting that a clear polarization toward a type II response is unlikely in neonatal foals.[152-155] Consistent with these findings, experimental infection of young foals with virulent *R. equi* results in IFN-γ induction and antibody responses similar to, or greater than, those of adult horses undergoing the same experimental challenge.[133]

Several studies have investigated various immunostimulants that might enhance host defense mechanisms during the relatively narrow period of susceptibility to *R. equi*. Inactivated *Parapoxvirus ovis*, *Propionibacterium acnes*, and unmethylated CpGs all enhance ex vivo or in vitro phagocytic cell function or cytokine induction in foals.[156-159] However, despite successfully enhancing IFN-γ production in foals, inactivated *P. ovis* failed to decrease the cumulative incidence of pneumonia at an *R. equi*–endemic farm. In the same study, IFN-γ and IL-4 secretion at birth was not associated with subsequent development of pneumonia.[160]

Spontaneous resolution of *R. equi* pneumonia after experimental challenge has been recognized.[82,161,162] Many foals on farms where the disease is endemic do not develop disease or develop subclinical disease that resolves without intervention.[7,163,164] In addition, intragastric administration of live, virulent *R. equi* to newborn foals confers complete protection against subsequent heavy

intrabronchial challenge.[79,165] Oral inoculation with virulent *R. equi* results in accelerated development of *R. equi*–specific CTL,[166] providing a potential mechanism for the protection conferred by oral inoculation. Collectively, these findings unequivocally demonstrate that most foals have the ability to mount protective immune responses to *R. equi*. The basis for the peculiar susceptibility of foals to infection with *R. equi* is likely complex and multifactorial rather than involving a simple and single explanation. The number of virulent bacteria in the environmental air, the age of the foal, the level of prior exposure to *R. equi*, and genetic susceptibility likely play a role. Genetic susceptibility to *R. equi* is likely complex, with modest contributions from numerous genes involving various biological pathways and processes.[167]

■ Diagnosis

The distinction between lower respiratory tract infections caused by *R. equi* and those caused by other pathogens is problematic, especially at farms without previous history of *R. equi* infections. Measurement of WBC or fibrinogen concentrations, ultrasonography, and radiography may help raise the degree of suspicion that pneumonia in a given foal may be caused by *R. equi* rather than another microorganism. However, the definitive diagnosis of bronchopneumonia caused by *R. equi* should be based on bacteriologic culture or amplification of the *vapA* gene by PCR from a TBA obtained from a foal with (1) clinical signs of lower respiratory tract disease, (2) cytologic evidence of septic airway inflammation, and/or (3) radiographic or ultrasonographic evidence of bronchopneumonia. Amplification of *vapA* by PCR is done preferably in conjunction with bacterial culture because the former test does not permit identification of other bacterial pathogens and in vitro antimicrobial susceptibility testing of *R. equi* isolates.[168] The definitive diagnosis of extrapulmonary infections (e.g., abdominal abscess, osteomyelitis) caused by *R. equi* must rely on bacteriologic culture or PCR amplification of *vapA* from samples from the site of infection. The diagnosis of extrapulmonary disorders from sites at which *R. equi* cannot be detected (e.g., uveitis or polysynovitis) should be based on isolation of *R. equi* from TBA or other primary sites of infection. The diagnosis of enterocolitis caused by *R. equi* is problematic because isolation of *R. equi* from feces cannot be taken as evidence of enterocolitis caused by *R. equi*.[168]

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Clinical Laboratory Tests.

Hyperfibrinogenemia is the most consistent laboratory finding in foals with *R. equi* pneumonia, although rare cases may have normal fibrinogen concentrations. Neutrophilic leukocytosis with or without monocytosis is also common. One study showed significantly higher fibrinogen concentrations and WBC counts in nonsurvivors than in survivors,[169] whereas other studies showed no difference between the two groups.[12,170] In one study, WBC count higher than 20,000 cells/μL, fibrinogen concentration higher than 700 mg/dL, and evidence of pulmonary abscessation were more likely to be found in foals with pneumonia caused by *R. equi* than in foals with pneumonia caused by other bacteria.[171] However, there is considerable overlap in distributions, which precludes the use of fibrinogen concentrations and WBC counts for diagnosis or prognosis for an individual foal.[171] Similarly, serum amyloid A (SAA) concentrations are significantly higher in pneumonic than in healthy foals.[172] However, many foals with severe *R. equi* pneumonia have SAA concentrations within the reference interval, and there is a poor association between SAA concentration and the severity of pulmonary disease as assessed by radiography.[172]

Imaging Techniques.

Thoracic radiography is useful in evaluating the severity of pneumonia and in assessing response to therapy. A prominent alveolar pattern characterized by ill-defined regional consolidation is the most common radiographic abnormality.[169] The consolidated lesions are often seen as more discrete nodular and cavitary lesions consistent with pulmonary abscessation (Fig. 31.15). Severity of alveolar pattern and number of cavitary lesions are the radiographic findings significantly associated with a poor outcome in foals with *R. equi* pneumonia.[173] Although nonsurvivors tend to have more severe radiographic lesions than survivors, many survivors have very severe radiographic lesions; thus radiographs should not be used as the sole criterion for prognostication and euthanasia.[12,170,173] Ultrasonography is a helpful diagnostic tool when lung involvement includes peripheral areas but may not be as useful as radiography to evaluate the full extent of lung lesions because abscesses with overlying aerated lung will not be detected by ultrasonography. However, in most horses and foals with pulmonary abscessation the periphery of the lung is affected, enabling the ultrasonographer to successfully image some of the abscesses.[174] Early ultrasonographic lesions

are nonspecific and may include only irregularities of the pleural surface. These lesions may progress to form focal areas of consolidation of various sizes (Fig. 31.16, *A*). In more chronic cases, well-circumscribed, encapsulated abscesses can be detected (Fig. 31.16, *B*). Ultrasonography is very useful in evaluating the severity of pneumonia and in assessing response to therapy, especially for equine practitioners who do not have access to thoracic radiography. Ultrasonography is also a useful tool for detecting some abdominal abscesses (Fig. 31.17) and for screening for *R. equi*–infected foals on farms where the disease is endemic (see the Control and Prevention of *R. equi* Infections on Farms Where the Disease Is Endemic section later). Ultrasonographic or radiographic detection of lung abscesses raises the degree of suspicion that pneumonia in a given foal is caused by *R. equi*. However, detection of pulmonary abscesses, while commonly used as a screening test (see the Screening for Earlier Detection of Affected Foals section later), is not a definitive diagnostic test.

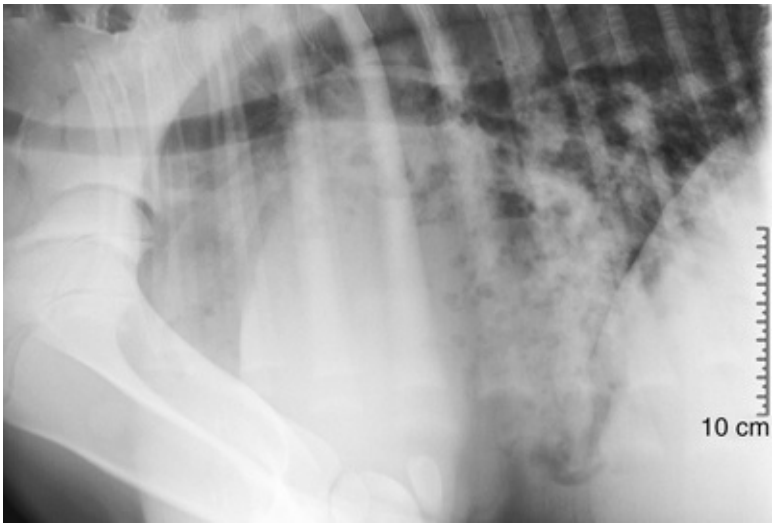


FIG. 31.15 Thoracic radiograph from a 2-month-old foal with pneumonia caused by *Rhodococcus equi*. The study shows a combination of alveolar and nodular interstitial patterns as well as cavitary nodular infiltrates, primarily in the cranioventral and caudoventral thorax. A mild interstitial infiltrate is present in the caudodorsal lung. The trachea is displaced dorsally, suggesting tracheobronchial lymphadenopathy. There is slight narrowing of the tracheal lumen at the thoracic inlet, likely indicating the presence of tracheal secretions.

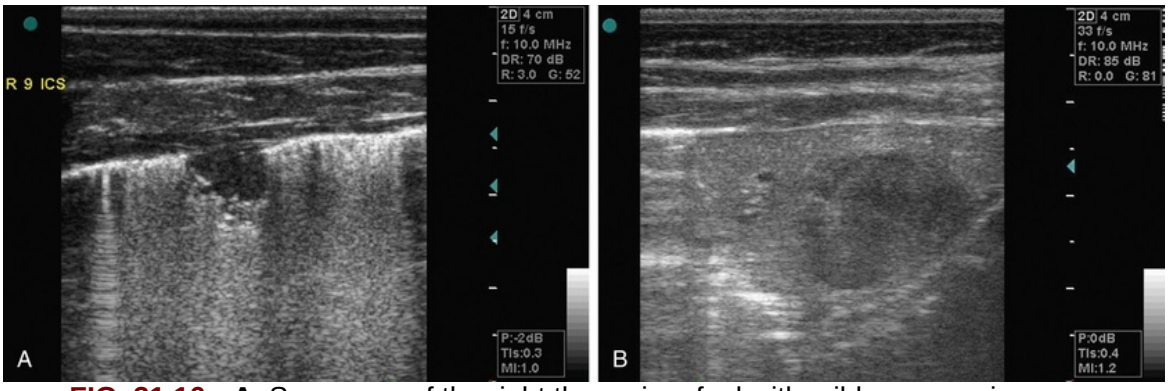


FIG. 31.16 **A,** Sonogram of the right thorax in a foal with mild pneumonia caused by *Rhodococcus equi*. There is an approximately 1 cm^2 area of focal consolidation. **B,** Sonogram of the left thorax in a foal with severe pneumonia caused by *R. equi*. There is consolidation of the ventral aspect of the lung surrounding a large encapsulated abscess.



FIG. 31.17 Sonogram of the abdomen obtained from a 3-month-old Thoroughbred foal with severe pneumonia caused by *R. equi* and multiple abdominal abscesses. The sonogram shows an abdominal abscess *(arrow).* The pneumonia resolved with therapy, but the abdominal abscesses persisted. The foal was eventually euthanized because of weight loss and intermittent episodes of colic. Postmortem examination confirmed resolution of pneumonia and the presence of abdominal abscesses caused by *Rhodococcus equi*.

Serology.

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Currently available serologic tests should not be used for the diagnosis of pneumonia caused by *R. equi*. Independent studies evaluating the performance of serologic tests available for diagnosis of infection caused by *R. equi* at endemic farms have demonstrated that these tests have low sensitivity, low specificity, or both.[175-178] Improving either sensitivity or specificity of ELISA assays by changing the cutoff value corresponding to a positive or negative test result could only be done to the detriment of the other. The presence of antibodies indicates exposure, subclinical infection, or maternal transfer of antibodies, but it does not necessarily indicate infection leading to clinical disease.

Cytology, Culture, and PCR Amplification.

Bacteriologic culture or PCR amplification of *vapA* from a TBA are the only acceptable ways of establishing a diagnosis of *R. equi* pneumonia. In one study, only 7 of the 11 (64 %) foals with positive *R. equi* culture at necropsy and 57 of the 89 (64 %) foals with radiographic evidence of lung abscessation yielded *R. equi* from culture of a TBA.[179] However, in two other studies, all 17 foals in which *R. equi* was isolated from lung parenchyma at necropsy yielded the organism from culture of TBAs obtained antemortem, suggesting that culture of a TBA is a valid method for diagnosing *R. equi* pneumonia.[180,181] Larger case series are required to more accurately estimate the sensitivity of TBA culture for diagnosis of *R. equi* pneumonia in foals. Specificity of the test must also be considered. Foals without clinical disease may have *R. equi* in their trachea as a result of subclinical disease or, incidentally, from inhaling *R. equi* in contaminated environments. At a farm with endemic *R. equi* pneumonia, 77 of 216 (35%) foals sampled had positive TBA cultures but remained free of clinical signs of respiratory disease throughout the season.[182] For this reason, culture or PCR amplification of *R. equi* from a TBA should always be interpreted in the context of cytologic and clinical findings. Detection of *R. equi* from a foal without clinical signs of respiratory disease, cytologic evidence of septic airway inflammation, or ultrasonographic or radiographic evidence of pulmonary lesions is likely an incidental finding, due to the ubiquitous nature of the organism on horse farms. Amplification of *vapA* by PCR has been shown to be more sensitive than bacterial culture in most but not all studies.[183-185] However, increased sensitivity may also result in a higher incidence of false-positive results due to the detection of very small numbers of *R. equi* present as environmental contaminants. Moreover, culture offers the advantage of detecting

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other bacterial pathogens present and permits in vitro susceptibility testing of recovered pathogens. As a result, PCR amplification of *vapA* may be done in conjunction with, but should not replace, bacterial culture. The use of PCR assays based on genes other than *vapA* is not recommended, as these assays would also detect environmental isolates lacking the virulence plasmid, which are not known to cause disease in foals.

Isolation or detection of *R. equi* from nasal or fecal swabs cannot be taken as evidence of disease due to infection with *R. equi*. *R. equi* can be cultured from the feces of healthy horses even if they live at farms without history of *R. equi* pneumonia.[90,186,187] Quantitative culture of the feces of foals at weekly intervals has been advocated to aid in early diagnosis of *R. equi* infections because the fecal concentration of *R. equi* increased at the same time as clinical signs of respiratory disease appeared in a few foals.[187] Similarly, concentrations of *R. equi* in feces at the time of clinical diagnosis, as assessed by quantitative PCR amplification of the *vapA* gene, were significantly higher in clinically affected foals than in healthy foals or foals with subclinical lesions at the same farm.[188] However, the assay is not commercially available and it is unknown if the cut-point used in the aforementioned study would be applicable to foals at other farms. Quantification of *R. equi* in a single fecal sample from a foal has little diagnostic value because of individual and farm-to-farm variation in the number of *R. equi* in feces.[90,186,187] Furthermore, a negative fecal culture may not be helpful in excluding *R. equi* infection because only 5 of 30 (17%) foals with confirmed *R. equi* pneumonia had positive fecal cultures.[182] Similarly, bacterial culture and PCR amplification of nasal swabs are insensitive for diagnosis of *R. equi* pneumonia.[183,184,189]

■ Treatment

Because ultrasonographic lesions in many foals that are clinically healthy will resolve without treatment (see the Screening for Earlier Detection of Affected Foals section later), it is important to consider separately treatment of subclinically affected foals and foals with clinical disease.

Foals With Severe Clinical Pneumonia.

A wide variety of antimicrobial agents are active against *R. equi* in vitro. However, many of these drugs are reported to be ineffective in vivo, possibly because of poor cellular uptake and resulting low intracellular concentrations.

Randomized, controlled clinical trials comparing the efficacy of various antimicrobial treatments in foals with severe clinical pneumonia caused by *R. equi* are lacking. The only data available regarding treatment comparisons are from retrospective cohort studies and studies using historical controls. In a retrospective cohort of 48 foals referred to a veterinary teaching hospital between 1978 and 1985, all 10 foals treated with erythromycin-rifampin survived compared to 2 of 4 with TMS, 2 of 6 with chloramphenicol, 0 of 4 with oxytetracycline, and 0 of 17 with penicillin-gentamicin.[12] In the aforementioned study, the combination of erythromycin-rifampin was introduced in 1981, and it is unknown if disease severity influenced treatment allocation. In another report, 50 of 57 (88%) foals with culture-confirmed pneumonia caused by *R. equi* and treated with erythromycin and rifampin survived between 1981 and 1986. These reports, in association with the previously reported in vitro activity and synergism of erythromycin and rifampin,[191] became the basis of recommended therapy with erythromycin and rifampin. Since the early 2000s, azithromycin and clarithromycin have replaced erythromycin in the combination with rifampin because of their higher oral bioavailabilities and considerably higher concentrations in pulmonary epithelial lining fluid (PELF) and bronchoalveolar cells.[192-196] The recommended dosages are listed in Table 31.4. Several formulations of erythromycin are commercially available. Although they all show slight differences in bioavailability and elimination, they all result in therapeutic concentrations at recommended dosages. However, the bioavailability of erythromycin in foals is considerably lower when foals are not fasted (mean ± SD: 26 ± 15% when fasted and 8 ± 7% when fed).[194]

TABLE 31.4

Recommended Dosages, Oral Bioavailability, and Serum Half-Lives of Antimicrobial Agents Commonly Used for the Treatment of *R. equi* Infections in Foals

Class	Drug	Dose (mg/kg)	Route	Frequency (h)	Oral Bioavailability (%)	Serum $t_{1/2}$ (h)	References
Macrolides	Erythromycin[a]	25	PO	6-8	8[b]-25[c]	1	193, 260
		5	IV	6	NA	1	261
	Clarithromycin	7.5	PO	12	57[b]	5.4	195
	Azithromycin	10	PO	24-48[d]	56[b]	18	191, 192
		5	IV	24-48[d]	NA	16	191, 192

Rifamycins	Rifampin	5	PO	12	49[c]	15	`262-264

[a]Erythromycin base, stearate, phosphate, estolate, or ethylsuccinate.

[b]Mean (± SD) bioavailability with ad libitum access to milk and hay.

[c]Mean (± SD) oral bioavailability after fasting.

[d]Administration q24h for 5 days and q48h thereafter.

IV, Intravenous; *NA,* not applicable; *PO,* by mouth.

Macrolides and rifampin are highly active against *R. equi* in vitro but only exert bacteriostatic activity.[197,198] As a result, macrolides and rifampin exert time-dependent activity against *R. equi* in vitro.[198] Of the three macrolides listed previously, clarithromycin is the most active against *R. equi* in vitro and against intracellular *R. equi* in cell culture.[198,199] The minimum inhibitory concentrations at which 90% of *R. equi* isolates are inhibited (MIC_{90}) are 0.06, 0.5, and 1.0 µg/mL, for clarithromycin, erythromycin, and azithromycin, respectively.[200,201] The combination of a macrolide and rifampin is synergistic both in vitro and in vivo, and the use of the two classes of drugs in combination reduces the likelihood of *R. equi* resistance to either drug.[191,197,198]

Randomized, controlled, prospective studies comparing the relative clinical efficacy of erythromycin, clarithromycin, and azithromycin in pneumonic foals have not been reported. In a retrospective study, the combination clarithromycin-rifampin was significantly more effective than erythromycin-rifampin or azithromycin-rifampin, especially in foals with severe pulmonary lesions.[202] Although data analysis was adjusted for disease severity and age, these results must be interpreted with caution because foals were not randomly allocated to treatment groups and because of potential biases inherent to retrospective data. Nevertheless, these data are the best available evidence to guide macrolide selection in foals with *R. equi* pneumonia.

The discovery that concurrent therapy with rifampin considerably decreases plasma, PELF, and bronchoalveolar cell concentrations of clarithromycin[203,204] has led to questions about the value of the combination. Despite the profound decrease in clarithromycin bioavailability caused by concurrent administration with rifampin, concentrations of clarithromycin in PELF and bronchoalveolar cells are well in excess of the MIC_{90} (0.06 µg/mL) and even the concentration of clarithromycin that prevents emergence of resistant mutants (0.24 µg/mL when combined with rifampin).[203,204] These findings likely explain the apparent clinical efficacy of the combination of macrolides with rifampin despite the

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decrease in bioavailability. Administration of rifampin 4 hours after administration of clarithromycin results in a statistically significant improvement in the bioavailability of clarithromycin, but the modest improvement is unlikely to be of clinical relevance.[205]

Studies in immunodeficient mice indicate that the combination of a macrolide with rifampin is superior to either drug used in monotherapy. In one study, the combination of erythromycin with rifampin was significantly more effective than either drug used alone.[206] Given that concurrent administration of rifampin considerably decreases bioavailability of clarithromycin in foals, a similar mouse infection model was used to compare the in vivo activity of clarithromycin and rifampin alone or in combination. Despite significantly lower clarithromycin concentrations in mice treated with the combination, treatment with clarithromycin and rifampin in combination significantly decreased the number of *R. equi* in the organs of nude mice compared to treatment with either drug alone.[207] The numbers of *R. equi* in the organs of mice treated with clarithromycin or rifampin alone were either higher or not significantly different from that of saline controls.[207]

A well-designed, large-scale clinical trial is needed to determine the benefit (or detriment) of combining a macrolide with rifampin for treating foals with severe *R. equi* pneumonia. However, such a study is unlikely to be performed because of the very large sample size needed and the logistical and financial requirements involved. In the meantime, we have more than 30 years of experience and retrospective data as well as animal models documenting the superiority of the combination of a macrolide with rifampin, compared to a complete lack of evidence that macrolide monotherapy is effective in foals with severe clinical pneumonia. Until there is solid evidence demonstrating that macrolide monotherapy is not inferior, the combination of a macrolide (erythromycin, azithromycin, or clarithromycin) with rifampin remains the recommended treatment of choice.[168,208]

Foals With Mild to Moderate Subclinical Lesions.

Only studies enrolling foals with lesion scores of 10 cm or greater (see the Screening for Earlier Detection of Affected Foals section later) have documented a significant difference in recovery between foals treated with antimicrobials (i.e., azithromycin with rifampin) and the placebo groups.[164,209] Therefore apparent recovery of foals with mild subclinical lesions with various treatments

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in uncontrolled studies cannot be taken as evidence of efficacy. In two separate, blinded, placebo-controlled studies, azithromycin alone (10 mg/kg PO q24h) or gamithromycin alone (6 mg/kg IM q7d) were found to be noninferior to the combination azithromycin and rifampin.[164,209] Monotherapy with tulathromycin also was more effective than a placebo, but not as effective as the combination of azithromycin with rifampin.[210] Despite a statistically significant difference between macrolide monotherapy and the control group in these studies, it is important to note that up to 78% of the foals receiving the placebo recovered without the need for antimicrobial treatment.[209] Therefore the apparent efficacy of macrolide monotherapy in foals with subclinical ultrasonographic lesions should not be interpreted as evidence of similar efficacy in foals with severe pneumonia. It is also unknown if macrolide monotherapy is more likely to induce and select for resistance than combination therapy in vivo. In vitro evidence indicates that resistance is less likely to occur with the combination of macrolide with rifampin.[211]

Treatment of Foals With Mixed Bacterial Infections.

Various bacteria and fungi are often isolated from TBA along with *R. equi.* The most common concurrent bacterial isolates are β-hemolytic streptococci and *E. coli*.[212] Isolation of multiple types of bacteria or fungi from a TBA does not negatively affect survival, and mixed infections are significantly more likely to be encountered in TBA than in lung tissue, suggesting that many bacteria isolated from a TBA colonize the trachea without necessarily contributing to pulmonary pathology.[212] Some clinicians advocate the addition of a third antimicrobial agent if heavy growth of a gram-negative pathogen is isolated along with *R. equi*. Retrospective data indicate that the use of additional antimicrobial agents with better gram-negative coverage (i.e., gentamicin or ceftiofur) is not associated with increased survival relative to the use of a macrolide with rifampin in foals from which both *R. equi* and gram-negative bacteria are isolated from a TBA.[212] The combination of an aminoglycoside (gentamicin or amikacin) with macrolides or rifampin in vitro is antagonistic against *R. equi* compared with either drug alone.[191,197,198] However, the clinical significance of this in vitro finding has not been established.

Treatment of Foals Infected With Isolates of *R. equi* Resistant to Macrolides and/or Rifampin.

Although the vast majority of *R. equi* isolates from foals are highly susceptible to macrolides and rifampin in vitro, strains resistant to either drug class have been encountered. Most foals infected with *R. equi* that do not respond to therapy are infected with isolates susceptible to macrolides and rifampin. Therefore failure to respond to antimicrobial therapy does not provide evidence that a given foal is infected with an isolate resistant to antimicrobial agents. The presence of an isolate resistant to macrolides or rifampin can only be confirmed by in vitro susceptibility testing done by a laboratory following the criteria established by the Clinical and Laboratory Standards Institute (CLSI).

In a recent study, the overall prevalence of macrolide- and rifampin-resistant isolates in Texas and Florida over a 10-year period was 4%.[213] In the same study, the odds of death were seven times higher in foals infected with resistant isolates.[213] In addition, the study demonstrated that isolates of *R. equi* susceptible to macrolides were sometimes misclassified as resistant; therefore it is reasonable to request retesting or validation of resistance by the testing laboratory. More recently, it has been documented that mass antimicrobial treatment of subclinically affected foals has selected for antimicrobial resistance over time, with isolates of *R. equi* resistant to all macrolides and rifampin being cultured from as many as 40% of the foals at some farms.[104] Macrolide resistance in *R. equi* is conferred by acquisition of a newly identified ribosomal RNA methylase gene designated *erm*(46).[214] This gene confers resistance to all macrolides, lincosamides, and streptogramins type B but not to other classes of antimicrobial agents.[214] The gene can be transferred from resistant to susceptible isolates of *R. equi* by conjugation.[214] Most macrolide-resistant isolates of *R. equi* that have been identified to date are also resistant to rifampin. Rifampin resistance in *R. equi* is the result of mutations in the *rpoB* gene.[201,215-217]

Therapy of foals infected with isolates confirmed to be resistant to macrolides, rifampin, or both is problematic because of the limited range of effective alternatives. Macrolide- and rifampin-resistant isolates of *R. equi* are susceptible in vitro to fluoroquinolones, gentamicin, linezolid, and vancomycin.[213,218,219] In one study, 18 of 24 isolates were also susceptible to chloramphenicol, minocycline, and TMS.[213] Currently there are no data to indicate the preferred antimicrobial agents for the treatment of foals infected with isolates resistant to macrolides and rifampin. Vancomycin, imipenem, or linezolid in foals should be used only for the treatment of life-threatening *R. equi* infections caused by isolates confirmed to be resistant to all other possible alternatives. The use of

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systemic and/or nebulized gentamicin is a reasonable consideration for foals infected with macrolide- and rifampin-resistant isolates. Historically, the efficacy of gentamicin in foals infected with *R. equi* has been widely reported as being poor. This belief is based on the results of a retrospective case series of foals with pneumonia caused by *R. equi* in which all 17 foals treated with gentamicin died, whereas all 10 foals treated with erythromycin in combination with rifampin survived.[12] In contrast, in another retrospective case series of 39 foals with pneumonia caused by *R. equi,* all 19 survivors were treated with gentamicin, whereas nonsurvivors were treated with a variety of other antimicrobial agents, including erythromycin, kanamycin, or chloramphenicol.[169] These studies were not controlled and did not account for lesion severity at the time of initiation of therapy. In addition, the dosages of gentamicin used in those studies were lower than dosages currently recommended based on the fact that gentamicin effectiveness is now known to be concentration dependent. Gentamicin is one of the few drugs that is bactericidal against *R. equi,* and it is highly active against intracellular *R. equi*.[220] Intravenous or nebulized gentamicin administered at a dose of 6.6 mg/kg once daily results in pulmonary epithelial and bronchoalveolar cell concentrations well in excess of the MIC_{90} for isolates of *R. equi*. Additional studies will be necessary to assess the clinical efficacy of gentamicin intravenous or nebulized in foals infected with *R. equi*.

Duration of Therapy.

Resolution of clinical signs and radiographic or ultrasonographic resolution of lung lesions are commonly used to guide the duration of therapy, which generally ranges between 2 and 12 weeks, depending on the severity of the initial lesions and response to therapy. Foals treated based on subclinical lesions identified during ultrasonographic screening typically do not require as long a treatment period as foals in respiratory distress with severe pulmonary lesions. In fact, as addressed later, many foals with subclinical ultrasonographic lesions clear the infection without therapy.[7,163]

Adverse Effects.

Although well tolerated by most foals, macrolides commonly cause diarrhea. The diarrhea is often self-limiting and does not necessitate cessation of therapy. However, affected foals should be monitored carefully because some may

develop severe diarrhea, leading to dehydration and electrolyte losses that necessitate intensive fluid therapy and cessation of oral macrolides. The incidence of diarrhea in foals treated with erythromycin-rifampin has ranged between 17% and 36%.[202,221] In one study, foals treated with clarithromycin had a higher incidence of diarrhea (28%) than those treated with azithromycin (8%), although in most cases diarrhea was mild and self-limiting.[202] In the same study, the incidence of severe diarrhea necessitating administration of IV fluids was not significantly different between groups of foals treated with azithromycin-rifampin, clarithromycin-rifampin, or erythromycin-rifampin.[202]

Hyperthermia and tachypnea have been described in foals treated with erythromycin during periods of very hot or humid weather.[221] Anecdotal reports suggest that these reactions occur occasionally with newer macrolides as well. Recent studies demonstrate that azithromycin, clarithromycin, and erythromycin suppress sweating in foals, with erythromycin inducing more severe sweating dysfunction.[222,223] In contrast, rifampin does not impair sweating.[222]

Severe enterocolitis also has been reported in mares whose foals are treated with erythromycin, presumably caused by disruption of the mare's normal colonic microflora following ingestion of small amounts of active drug during coprophagia or by contamination of feeders or water buckets with drug present on the foal's muzzle. This complication seems to be rare. Enterocolitis in mares has been reproduced experimentally by administration of subtherapeutic doses of erythromycin.[224] In some cases, the severe enterocolitis in the mares of treated foals is associated with *Clostridium difficile*.[225]

Ancillary Therapies.

Nursing care, provision of adequate nutrition and hydration, and maintaining the foal in a cool and well-ventilated environment are important. Humidified oxygen delivered by pharyngeal insufflation in moderately hypoxemic foals or by percutaneous transtracheal oxygenation in severely hypoxemic patients is indicated.[226] Judicious use of NSAIDs might reduce fever and improve attitude and appetite in febrile, lethargic, anorectic foals. Nebulization with saline, antimicrobial agents, or bronchodilators have been advocated, but there are no data to either support or refute these therapeutic practices. In addition to appropriate systemic antimicrobial therapy, foals with *R. equi* septic arthritis or osteomyelitis often require aggressive local therapy such as joint lavage, surgical débridement, and IV or intraosseous regional limb perfusion with antimicrobial

agents.

■ Prognosis

Prior to the introduction of the combination of erythromycin and rifampin as the treatment of choice in the early 1980s, the prognosis of *R. equi*–infected foals was poor, with survival rates as low as 20%.[227] Using erythromycin and rifampin, Hillidge reported a successful outcome (as assessed by survival) in 50 of 57 (88%) foals with confirmed *R. equi* pneumonia.[179] Studies from referral centers, where severely affected cases are likely more prevalent, have revealed survival proportions ranging between 59% and 72%.[170,202,228] The prognosis for foals with abdominal abscesses is poor, although rare cases will respond to long-term antimicrobial therapy.[8,229] Surgical removal or marsupialization have been attempted in some foals, but abdominal adhesions usually result in inability to resect the abscess.

In contrast, the survival rate at farms that use a screening program to identify and treat foals with subclinical lesions has resulted in survival proportions of nearly 100%.[4,230] However, recent evidence indicates that many of these foals would have recovered without therapy.[6,7,163,231] Controlled studies have shown that approximately 88% of foals with ultrasonographic lesion scores (sum of the diameter of each abscess) of 10 cm or less recover without antimicrobial therapy. In the same studies, treatment of affected foals with antimicrobial agents did not provide a clear benefit over administration of a placebo.[7,163]

The impact of *R. equi* infections on future athletic performance has been examined. No significant differences in total earnings, average earning index, or age at first race were observed when comparing 30 horses that previously had *R. equi* pneumonia with either their dams' other progeny or the North American averages.[232] In another study, 54% of 83 foals that survived *R. equi* pneumonia had at least one racing start as compared with 65% of their birth cohort, suggesting that horses contracting *R. equi* pneumonia as foals might be somewhat less likely to race as adults. However, consistent with a previous report,[232] the racing performance of those foals was not different from that of the U.S. racing population.[170] In summary, prognosis for performance after successful treatment of uncomplicated *R. equi* pneumonia should be regarded as very good.

Control and Prevention of *R. equi* Infections on Farms Where the Disease Is Endemic

Methods for control and prevention include using screening tests for early detection of *R. equi* pneumonia, environmental management, chemoprophylaxis, and prevention through use of either passive or active immunization. Currently there is inadequate evidence to recommend environmental interventions to control or prevent *R. equi* pneumonia.[233] Further evaluation of certain practices, such as foaling at pasture and reducing either airborne concentrations of virulent *R. equi* or density of mares and foals, is merited.

Screening for Earlier Detection of Affected Foals.

R. equi pneumonia is often not recognized until it is well advanced and therefore difficult to treat. To a casual observer, even severely affected foals may appear to suckle and behave normally. The rationale for screening is the assumption that detecting foals in the early stages of disease and implementing appropriate treatment of affected foals will improve outcomes. It is important to emphasize that screening methods are not diagnostic tests. A useful screening test is one in which the probability of disease is high with a positive test result (high positive predictive value) and very low with a negative test result (high negative predictive value). The higher the prevalence of disease is at a given farm, the higher the positive predictive value of a given test will be. Therefore depending on the prevalence of *R. equi* infections at a given farm, a positive result on a screening test could be a basis from which to perform a diagnostic test (low to moderate prevalence) or to initiate therapy (high prevalence). Uncontrolled studies suggest that screening may reduce the mortality attributable to *R. equi* pneumonia.[4,234] Thus in the absence of a vaccine or other effective methods for preventing this devastating disease, screening is a reasonable approach to control *R. equi* at endemic farms. Implementing screening testing at farms that are only sporadically affected by *R. equi* pneumonia may not be warranted.

A variety of screening techniques performed serially have been described, including visual inspection of foals for clinical signs of pneumonia, rectal temperature monitoring, hematologic variables, serology, and thoracic imaging using either radiography or ultrasonography, with empirical recommendation that screening begin around 3 weeks of age.[235] Systematic comparisons of these tests have not been performed. Thus a specific recommendation for any particular screening test cannot be made, and it is likely that the optimal

approach for screening may vary among farms on the basis of cumulative incidence of disease, resources available for control and prevention, and preferences of the attending veterinarians and farm management.

Studies have shown that serial PCR amplification of *vapA* in feces and serum measurement of serum concentrations of either antibodies against *R. equi*, serum amyloid A, or plasma fibrinogen are not useful screening tests.[172,176,178,236,237] WBC concentrations performed at monthly intervals had clinically acceptable sensitivity and specificity for early detection of *R. equi* pneumonia at one farm (sensitivity of 79% and specificity of 91% at a cutoff value of 15,000 cells/µL).[175] However, serial measurement of WBC or neutrophil concentrations resulted in limited performance for prediction of subsequent development of clinically apparent *R. equi* pneumonia at another farm.[238] In addition to conflicting data regarding the benefit of this approach, additional limitations of using WBC concentration for screening are the time and effort required to collect blood samples from foals, the lag from time of submission to availability of results, and the potential for false-positive results attributable to stress-associated leukocytosis or other infectious or inflammatory conditions that may be common among foals.

Over the past decade, control of *R. equi* infections at many farms where the disease is endemic has relied on early detection of subclinical pulmonary disease using thoracic ultrasonography and initiation of treatment with antimicrobial agents prior to development of clinical signs.[4,5,239] Ultrasonography of the chest offers several advantages over other screening tests: (1) results are specific for the presence of pulmonary pathology; (2) the procedure can be performed relatively quickly for an individual foal; (3) results are available immediately; and (4) the procedure may be more sensitive than radiography for detecting lesions in their early stages of development or in certain regions where soft-tissue structures are superimposed over regions of the lung.[174] Periodic ultrasonography of the chest has been reported to decrease mortality due to *R. equi* pneumonia at some farms relative to historical controls, but contemporaneously controlled studies are lacking.[4,5,239] Historically, antimicrobial treatment was recommended for all foals with pulmonary lesions 1 cm or greater in diameter.[4,5,239] This approach of ultrasonographic screening resulted in a considerabe increase in the number of foals treated for presumptive *R. equi* pneumonia. The temporal association between widespread use of macrolides and rifampin consequent to ultrasonographic screening and a

perceived increase in the frequency of detection of antimicrobial-resistant isolates of *R. equi* in the last decade suggests that this practice is not innocuous. Emergence of widespread macrolide and rifampin resistance at a farm after widespread use of these drugs was implemented on the basis of an ultrasonographic screening program has been documented.[104]

Several uncontrolled studies have reported the apparent efficacy of various antimicrobial agents in foals with mild subclinical lesions. Recently reported blinded, randomized, placebo-controlled studies, however, indicate that approximately 88% of foals with lesion scores (defined as the sum of the largest diameter of all pulmonary lesions ≥1 cm) between 1 and 10 cm recover without antimicrobial therapy.[7,163] Furthermore, antimicrobial treatment of foals with such ultrasonographic lesions does not significantly hasten lesion resolution compared to administration of a placebo.[7,163] In another study, 270 foals at an endemic farm were subjected to thoracic ultrasonography every 2 weeks for the entire season. The veterinarian making treatment decisions was unaware of ultrasonographic findings. Forty-six foals (17%) developed clinical signs of pneumonia and were treated; all 46 foals had ultrasonographic lesions.[6] Fifty-four foals (20%) remained clinically healthy and free of ultrasonographically visible pulmonary lesions, whereas 170 foals (63%) remained clinically healthy but had pulmonary lesions of various degrees of severity.[6] Optimal cut-point of the sum of the maximal diameters of all lesions observed sonographically at a given examination to maximize sensitivity and specificity in that study was 20 cm. This high sum of lesion diameters as a cut-point for lesion score would have yielded a relatively high sensitivity (89%) but poor specificity (62%) for the diagnosis of clinical pneumonia.[6] Despite using such a high cut-point to initiate therapy, the number needed to treat was 3, meaning that approximately three foals would be treated with antimicrobial agents unnecessarily for every one foal benefiting from therapy.

Because ultrasonography only allows the detection of lesions at the periphery of the lung and because of individual variation in disease susceptibility and host defense mechanism, there is no lesion score cut-point that will perfectly differentiate foals requiring therapy from foals that will spontaneously recover. Although it is probably indicated to treat foals with clinical signs of lower respiratory tract disease, the evidence reviewed earlier indicates that treatment of all foals with small subclinical pulmonary lesions is unnecessary. By being more selective and treating only foals with larger lesion scores (e.g., >10 cm) and

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monitoring the foals weekly or twice weekly both clinically and ultrasonographically, one farm was able to decrease antimicrobial drug use considerably without an increase in mortality.[209,210] Additional studies at multiple other endemic farms will be required to determine whether this approach should be widely recommended.

Passive Immunization.

Intravenous administration of HIP obtained from horses vaccinated against *R. equi* using various antigens has generally proved effective in significantly reducing the severity of *R. equi* pneumonia in foals following experimental challenge.[79,127,240,241] However, studies evaluating the efficacy of various HIP preparations under field conditions have given equivocal results. Although the data are conflicting and not all trials have shown a statistically significant reduction in the cumulative incidence of *R. equi* pneumonia, 5 of 7 studies have demonstrated reduction of relative risk, suggesting some benefit of HIP.[3,81,181,242-245]

Intravenous administration of purified immunoglobulins obtained from horses immunized with recombinant VapA and VapC to foals reduced the severity of pneumonia following high-dose experimental challenge with *R. equi* to a degree similar to that provided by commercially available HIP.[129] This demonstrates that immunoglobulins, predominantly against VapA and VapC, are responsible for the protection conferred by HIP. Therefore administration of plasma obtained from horses that are not hyperimmunized against *R. equi* is not recommended for protection against *R. equi*. Because endemicity of *R. equi* at farms does not appear to be explained by farm-specific isolates and because foals may be infected with multiple strains at once,[102] there is no need to administer plasma that is produced from immunizing horses with isolates of *R. equi* obtained from a given farm; transfusion of plasma from horses that have been immunized against any virulent (i.e., VapA-positive) strain of *R. equi* should suffice.[233] Use of HIP licensed as an aid in the control of *R. equi* pneumonia is recommended (rather than plasma simply obtained from horses hyperimmunized against *R. equi*) because licensure ensures standards of potency, purity, and safety. Currently there is insufficient information to recommend one brand of licensed antibody product over another.

The optimal amount of plasma to be transfused and the optimal age at which transfusion should occur remain to be determined. Administration of HIP 9 days

after aerosol infection of foals with *R. equi* did not confer protection,[246] suggesting that administration of HIP prior to infection is important. Because of evidence that many foals become infected early in life,[80] it is commonly recommended that foals receive transfusion of at least 1 liter of HIP no later than the second day of life. Because early administration may result in the decline of passively transferred antibody to a nonprotective level at a time when foals are still susceptible to *R. equi* and when environmental challenge is high, it is common practice to administer a second liter of HIP at 2 to 4 weeks of age.

Transfusion of HIP is not completely effective and therefore does not eliminate the need for careful monitoring of foals at risk. In addition to being incompletely effective, transfusion of HIP carries some risk to foals, such as trauma that may occur during handling and adverse reactions to transfusions. The process is also time intensive, labor intensive, and expensive. Thus the cost-effectiveness of transfusion depends on the value of the foals and the prevalence of disease at a given farm.

Active Immunization.

It would be convenient to control *R. equi* pneumonia on endemic farms by active immunization of mares or foals with a protective antigen. To date, however, this approach has been largely unrewarding. The role of antibody in partial protection against *R. equi* infection suggests that vaccination of mares could confer at least some degree of protection. However, in both a field study and an experimental challenge, vaccination of mares with live or killed whole cell *R. equi* did not provide protection against *R. equi* pneumonia despite a significant increase in colostral *R. equi*–specific antibody and transfer of these antibodies to foals.[244,247] Vaccination of a small number of mares with VapA associated with a water-based nanoparticle adjuvant led to high anti-VapA IgG concentrations in mares and foals and might have conferred protection against natural challenge compared with nonvaccinated controls.[248] More recently, vaccination of mares against poly-*N*-acetylglucosamine protected foals against intrabronchial challenge with *R. equi*.[125] Large-scale studies at endemic farms will be necessary to confirm these preliminary findings before widespread vaccination of mares can be recommended.

Because cell-mediated immunity is of paramount importance for protection against *R. equi*, active immunization of foals likely will be required for complete protection. Oral or nasal immunization with *S. enterica* serotype Typhimurium

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expressing the VapA antigen protects mice against *R. equi* infection.[249,250] Studies in mice indicate that DNA immunization with *vapA* protects against *R. equi* infection and that the IgG subisotype response is consistent with a type I–based immune response.[251] A similar DNA vaccine containing the *vapA* gene induced strong cell-mediated immune responses in adult horses, but responses were poor in foals.[252] Intrabronchial immunization of neonatal foals with a live, fully attenuated, riboflavin auxotroph strain of *R. equi* stimulated immune responses but did not confer protection against subsequent intrabronchial challenge with live *R. equi*.[253] The fact that live, avirulent plasmid-cured *R. equi* does not elicit adaptive immunity and is cleared rapidly indicates that bacterial replication is needed for induction of strong cell-mediated immune responses.[254] Intrabronchial immunization with a deletion mutant of *R. equi* lacking the chromosomal genes isocitrate lyase *(icl)* and cholesterol oxidase *(choE)* conferred protection against subsequent challenge in three foals.[255] However, two foals developed pneumonia caused by the mutant strain.[255] More recently, oral vaccination of foals with a live attenuated *R. equi* strain lacking genes involved in the steroid catabolic pathway elicited substantial protection against subsequent intrabronchial challenge with live virulent *R. equi*.[73] Collectively, the aforementioned studies indicate that there is a fine line between sufficient replication of *R. equi* for induction of strong cell-mediated immune responses and development of disease from the vaccine strain. Additional challenges are that immunization in foals will need to be initiated very early in life and an effective vaccine will have to overcome the relative immaturity of the naive neonatal immune system. Currently there is inadequate evidence to recommend active immunization of mares or foals to control or prevent *R. equi* pneumonia, but promising vaccine candidates are under development.

Chemoprophylaxis.

Because an effective vaccine is lacking, prophylactic administration of antimicrobial agents to all foals during the period when they are most susceptible to infection has been suggested as another approach for the prevention of *R. equi* infections on endemic farms. Azithromycin is an attractive choice for chemoprophylaxis because of good oral bioavailability, long half-life, and high and sustained concentrations in PELF, bronchoalveolar cells, and neutrophils. Two studies have evaluated the use of azithromycin for chemoprophylaxis. In a randomized, controlled trial conducted in the United States among 338 foals at

10 farms, the cumulative incidence of *R. equi* pneumonia was reduced from 21% among untreated foals to 5% among foals that received azithromycin (10 mg/kg PO q48h for the first 14 days of life).[256] In contrast, in a study conducted among 70 foals at a large breeding farm in Germany, the incidence of abscessing pneumonia was not significantly different between foals that received azithromycin (10 mg/kg PO q24h for the first 28 days of life) for prevention of abscessing pneumonia (cumulative incidence = 60%) and foals that did not receive azithromycin for chemoprophylaxis (cumulative incidence = 69%); however, the age at onset of abscessing pneumonia was delayed in treated foals.[230] The reason for the discrepancy between studies is unknown. Regardless, use of azithromycin is not considered an acceptable approach for chemoprophylaxis because widespread use of this drug would create greater pressure for emergence of macrolide resistance among bacteria.[168]

Gallium maltolate is a metal-based compound with antimicrobial properties that has been demonstrated to reduce replication of *R. equi* in pure culture[257] and within macrophages,[258] to reduce tissue concentrations of *R. equi* in mice following experimental infection,[257] and to be bioavailable[259] and safe in foals.[260] Unfortunately, chemoprophylaxis with gallium maltolate (30 mg/kg PO q24h for the first 14 days of life) failed to reduce the incidence of *R. equi* pneumonia in a placebo-controlled trial of 438 foals at 12 farms in the United States.[3]

Pneumonia in Foals

Daniela Bedenice

Equine pneumonia is a significant cause of morbidity and mortality in both the newborn and the older foal.[1-4] Although the causative agents and the mode of lung infection are generally different for each age-group, foal pneumonia is commonly associated with a compromise in the immunologic protection of the host. The exact immunologic basis of the foal's inherent susceptibility to opportunistic respiratory pathogens needs to be further elucidated.

Failure of passive transfer of immunity (FPT) is a well-known risk factor of neonatal infection, including respiratory disease,[4] because not only are affected foals deprived of specific maternal antibody protection but their neutrophil function is also seriously impaired.[5] Although foals can respond immunologically in utero to bacterial or viral infections, their ability to do so is

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less than that of adults. Reduced complement values and defective chemotaxis (directed migration of neutrophils or macrophages) and killing capacity of the neonatal neutrophil contribute to a relatively decreased defense against invading bacteria. Furthermore, an immature ciliary apparatus and the presence of fewer alveolar macrophages in neonates in comparison with adult horses lead to decreased bacterial clearance from the lungs.[6] The number and distribution of the bronchoalveolar cells approach adult levels only at approximately 3 to 6 weeks of age.[7]

It has been suggested that a natural cellular immunodeficiency may also occur in foals at 2 to 4 months of age.[8] Although the exact association between age-related cellular immunodeficiency and the defense against intracellular pathogens such as *Pneumocystis carinii (Pneumocystis jiroveci)* and *R. equi* of foals still needs to be clarified, CD4+ and CD8+ T-lymphocytopenia was documented in a filly with *P. carinii* pneumonia.[9]

■ Etiology

Neonatal Pneumonia (<1 Month of Age).

In contrast to the older foal, infectious lung disease in the neonate is usually part of a multiple-organ systemic infection or sepsis, which may be acquired via the placenta in utero or perinatally through environmental bacteria leading to hematogenous (ascending) infection (e.g., omphalophlebitis). *E. coli, Klebsiella* spp., *Actinobacillus equuli*, *Salmonella* spp., and *Streptococcus* spp. are some of the more common bacteria involved in neonatal foal pneumonia.[10]

Descending lung infections may be caused by inhalation of viral, bacterial, or opportunistic fungal agents. Furthermore, iatrogenic aspiration (oil, medication, oral supplements) or aspiration of gastric reflux, milk, meconium, or contaminated amniotic fluid after placental infection may seed the foal's lung. Meconium aspiration occurs in utero in foals that experience fetal distress (perinatal asphyxia). Although the meconium is commonly sterile at this time, it creates mechanical airway obstruction, surfactant inactivation, and pulmonary inflammation (caused by vasoactive mediators and chemotactic and inflammatory cytokines, including TNF-α, interleukin [IL]–1β, and IL-8).[11] The resulting edema and vasoconstriction may lead to hypoperfusion of the pulmonary parenchyma, with damage to type II pneumocytes and decreased production of surfactant.[12] This type of “secondary surfactant deficiency” also

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may be induced by other forms of generalized pulmonary inflammation, including diffuse bacterial pneumonia. Neurologic dysfunction, severe inflammation, or structural abnormalities of the upper airways (congenital cysts, dorsal displacement of the soft palate, laryngeal paralysis, pharyngeal weakness, etc.) may predispose to aspiration pneumonia postpartum. The prognosis of foals with dysphagia due to pharyngeal dysfunction is considered favorable for life and fair for athleticism, based on a 2012 study by Holcombe and colleagues.[13] In the latter report, 8 of 16 (50%) affected foals were premature and/or diagnosed with neonatal encephalopathy, and 12 of 16 (75%) had aspiration pneumonia.

Equine viral arteritis (EVA) and equine herpesvirus infections (EHV-1 and EHV-4) have been implicated in in utero viral infections leading to lung disease.[14] Although involvement of adenovirus in the pathogenesis of pneumonia has also been reported in a Thoroughbred foal, fatal adenoviral pneumonia is primarily related to severe combined immunodeficiency (SCID) in Arabian foals.[15,16] In addition, equine influenza virus (EIV) infection has been associated with fatal bronchointerstitial pneumonia in young foals that do not have maternal immunity.[17]

Pneumonia in Older Foals (1 to 6 Months of Age).

S. equi subsp. *zooepidemicus* and *R. equi* are the most important pathogens associated with pneumonia in older foals, although plurimicrobial infections (*Actinobacillus* spp., *B. bronchiseptica, E. coli, Klebsiella pneumoniae*, *Pasteurella* spp., *Pseudomonas* spp., *Salmonella* spp., and *Staphylococcus* spp.) are not uncommon.[18,19] *S. equi* subsp. *zooepidemicus* was isolated from 87% of uncomplicated lower respiratory tract infections in foals (1 to 8 months old) on selected farms[20] and was documented as the most common cause of pulmonary abscesses in a second study.[21] In contrast, anaerobes appear to be infrequently involved in primary pneumonia of foals.[20] *Corynebacterium* spp. pneumonia due to aerosol infection is a rare cause of diffusely increased interstitial and peribronchial radiographic densities, indicative of pulmonary abscesses in foals[22]; it is possible that the isolates in this study were *R. equi*. More recently, acute respiratory failure was associated with *Leptospira* spp. infection in five foals (3 weeks to 5 months of age). Pulmonary hemorrhage and interstitial pneumonia with infiltration of red blood cells, hemosiderophages, and inflammatory cells were observed at necropsy, similar to observations in people.[23]

Although respiratory viruses are often believed to be primary offending agents that lead to secondary bacterial lung invasion, they have limited importance in nursing foals.[20,24] Equine adenoviruses (EAdVs) and EHV-2 are ubiquitous in the general equine population, with little apparent pathogenicity in immunocompetent foals. Although adenoviruses are the most common respiratory pathogens in Arabian foals with SCID, the role of EHV-2 in the respiratory disease complex of foals remains unclear. It has been suggested that EHV-2 exerts its effects on the host indirectly through predisposition to secondary infections, such as *R. equi* pneumonia. Dunowska and colleagues evaluated serial blood samples from 43 foals on a single farm over a period of 10 months, where all but 2 foals were seropositive for EHV-2 on at least one occasion. The majority (88%) of these foals became infected with EHV-2 within the first 2 months of life.[25]

Because of the complexity of the disease, in-depth discussions of *Rhodococcus* pneumonia and ARDS are presented elsewhere in this chapter.

Interstitial Pneumonia.

Acute, severe interstitial or bronchointerstitial pneumonia is a sporadic, rapidly progressive disease of foals of 1 to 6 months of age that is characterized by a sudden onset of respiratory distress, tachypnea, fever, high mortality, and histopathologic evidence of severe, diffuse, necrotizing bronchiolitis, alveolar septal necrosis, and neutrophilic alveolitis on necropsy.[26-28] Although no definitive causative agents or factors of this disease have yet been identified, suspected causes include viruses, *P. carinii*, heat stroke, environmental toxins, and bacteria.[26-29] Enteric gram-negative organisms, *R. equi*, *Pseudomonas aeruginosa*, and *P. carinii* have all been cultured from the lungs of affected foals.

The reported cases are usually sporadic, affecting a single foal within a herd,[26] although rare clusters of cases have also been described.[28] The disease is generally rapidly progressive and may lead to sudden death as a result of fulminant respiratory failure. Severe respiratory distress, hypoxemia, hypercapnia, and respiratory acidosis are the most striking clinicopathologic signs. The hypoxemia of bronchointerstitial pneumonia is relatively resistant to supplemental oxygen therapy, indicating a pulmonary shunt. Thoracic radiographs commonly demonstrate caudodorsally distributed interstitial and bronchointerstitial pulmonary opacities. With advanced disease, the radiographic pattern progresses to include patches of a coalescing alveolar nodular pattern

with air bronchograms.[30] As with bacterial pneumonia, many foals demonstrate hyperfibrinogenemia and neutrophilic leukocytosis on hematology.

Therapy is symptomatic, including antiinflammatory therapy, broad-spectrum antibiotics, thermoregulatory control, bronchodilation, and supplemental oxygen. Surviving foals may develop a proliferative epithelial and interstitial response, including bronchiolar and alveolar epithelial hyperplasia, type II cell hyperplasia, and hyaline membrane formation.[30]

Chronic pulmonary disease (1 to 3 months' duration) with marked radiographic interstitial opacities was reported in 12 foals, ages 3 to 9 months, that were examined at a veterinary teaching hospital.[31] Evaluation failed to yield a consistent pathogen from tracheobronchial aspirates. The authors proposed that chronic interstitial pneumonia occurring in foals is associated with a good prognosis and considered corticosteroid therapy as a potentially useful treatment.

Pneumocystis jiroveci (carinii) Infection.

Rare opportunistic fungal pathogens of the lung may include *P. carinii* (renamed *P. jiroveci* in humans), *Aspergillus* spp., *Candida* spp., and *Mucor* spp. *P. carinii* is a unicellular eukaryote that has been classified as a fungus after DNA studies.[32] It is most commonly seen in humans and animals that suffer from a concurrent immunodeficiency. It was first recovered in Arabian foals with SCID.[33] It has since been recovered from foals of other breeds with no specific history of immunodeficiency, although for the most part no direct testing for immunocompetence was performed in the reported cases. However, one more recently documented case demonstrated a low number of circulating CD4+ and CD8+ lymphocytes in a filly with *P. carinii*.[33]

In several reports the onset of clinical signs in affected foals ranged from a 3-week history of weakness, weight loss, and nasal discharge to acute dyspnea. Half of the reported non-Arabian cases had concurrent infections with *R. equi*, *Enterobacter cloacae*, *E. coli*, or *S. equi* subsp. *zooepidemicus*. A severe interstitial, sometimes miliary and alveolar pattern was seen on radiographs of the lungs. The majority of the reported foals died, and the diagnosis of *P. carinii* was obtained at necropsy.[29,33-36] On postmortem examination the lungs were uniformly heavy and consolidated, and a diffuse interstitial pneumonia was found. Trophozoites and cysts were observed in the alveolar epithelial cells, and macrophages were observed within the alveoli. Fluorescent in situ hybridization, silver staining, and streptavidin-biotin immunolabeling of histologic sections

provide better identification of the organisms in the pulmonary tissue.[34] A few foals were also diagnosed by visualization of the organism on a BAL sample in the latter report. Two surviving foals responded to TMS therapy.

■ Clinical Presentation and Diagnosis of Foal Pneumonia

The clinical manifestation of pneumonia in the newborn foal can be variable and depends on the disease severity and underlying or associated problems. Early in life, localizing clinical signs of respiratory infection may be absent even in the presence of extensive disease. Dyspnea may be seen in severely affected foals and may manifest as an increase in respiratory rate, effort, or thoracoabdominal asynchrony (paradoxical breathing). However, signs of respiratory distress and hypoxemia are frequently vague. Even some severely hypoxemic foals may show only restlessness, considerable resistance, and struggling when being handled or restrained. Abnormal respiratory sounds (crackles or wheezes) may be heard on auscultation of ill foals. However, even normal foals may show crackles on the down lung after having remained in lateral recumbency for a prolonged period of time. Furthermore, foals with no auscultable abnormalities may still have extensive pulmonary disease.[37,38] Similar to other species, cyanosis is a sign of severe hypoxemia in foals. The arterial Pa_{O_2} (partial pressure of oxygen), however, must reach very low levels (35 to 45 mm Hg) before clinical cyanosis is observed. Approximately 5 g/dL of unoxygenated hemoglobin in the capillaries generates the dark-blue color that is appreciated as cyanosis in humans. Therefore severely anemic foals may never appear cyanotic even in the face of profound hypoxemia. Weakness, depression, anorexia, weak or absent suckle reflex, dehydration, and fever may also be noted in newborn foals with respiratory disease. Cough and nasal discharge are usually absent in the early stages of neonatal pulmonary disorders.[10] The older foal, on the other hand, will generally exhibit clinical signs that focus on the respiratory tract, such as abnormal auscultation of the lungs, nasal discharge, cough, fever, tachypnea, and increased respiratory effort.

Thoracic radiographs and arterial blood gas analysis are important in confirming the presence and evaluating the extent and distribution of foal pneumonia. Because radiographic findings may precede or lag behind alteration of respiratory function, repeated diagnostic imaging is recommended. A recent study documented that radiographic abnormalities involving the caudodorsal lung region were most common in neonatal foals admitted to a referral center.[39]

Bedenice and colleagues showed that the presence of dyspnea, tachypnea, a fibrinogen concentration greater than 400 mg/dL, systemic inflammatory response syndrome (SIRS), hypoxemia, or FPT in neonatal foals may be a predictor of underlying respiratory disease and should prompt an early radiographic evaluation of the thorax, even in the absence of other localizing clinical signs.[4,39] Thoracic ultrasonography has become a popular diagnostic tool for the assessment of equine lung and pleural disease and is particularly useful in determining the side(s) of the thorax affected, as well as the precise location of the lesion in many cases.[4]

Diagnostic sampling of the respiratory tract is less commonly performed in neonatal foals compared with older foals and adult horses. However, transtracheal aspirate, BAL, protected catheter brush (PCB), or protected aspiration catheter (PAC) sampling is important in stabilized patients, irrespective of age, to direct antimicrobial therapy and evaluate therapeutic efficacy. Lung biopsies are rarely performed and are limited to patients with chronic disease or suspected fungal pneumonia.[38]

■ Treatment

The treatment goals in dealing with bacterial pneumonia in either age-group are similar and directed at maintaining adequate gas exchange to ensure patient survival, limit progressive pulmonary damage, and ultimately eradicate infection. Long-term goals should aim to maintain optimal pulmonary function and conserve adult athletic performance. Specific treatment strategies for septic pneumonia may include goal-directed antimicrobial therapy, treatment of inflammation independent of antimicrobial therapy, respiratory therapy (oxygen therapy, ventilation, bronchodilation), and cardiovascular support.[37]

Broad-spectrum antimicrobial treatment, with consideration of the drugs' anticipated sensitivity and lung penetration, should be initiated before culture results are available. Third- or fourth-generation cephalosporins (ceftiofur and cefepime, respectively) show good penetration into lung tissues.[40] Ceftiofur administered intramuscularly at 6.6 mg/kg in weanling foals provided plasma and pulmonary epithelial lining fluid concentrations above the therapeutic target of 0.2 µg/mL for at least 4 days, and would thus be expected to be an effective treatment for pneumonia caused by susceptible pathogens such as *S. equi* subsp. *zooepidemicus*.[41] Alveolar delivery of antibiotics typically occurs via diffusion of a free, nonprotein-bound drug and is usually satisfactory if plasma

concentrations and alveolar perfusion are adequate.[42] Aminoglycosides penetrate lung tissue at 10% to 45% of serum levels. However, the acidic environment of infected airways may reduce the drug's activity below levels sufficient to eradicate the offending bacteria in some cases.[43,44] Antibiotic therapy should not be discontinued prematurely in neonatal foals because pulmonary infection is commonly well established before its diagnosis.[45]

■ Outcome

The survival of neonatal foals with septic pneumonia is contingent on the underlying disease conditions, a prompt diagnosis, and the cause and severity of lung dysfunction. Few studies have objectively evaluated the outcome of foal pneumonia.[38] One report documented that 65% of foals with radiographic evidence of pulmonary disease were discharged alive from the hospital, in contrast to 86% survival of foals without respiratory illness. The presence of diffuse radiographic infiltrates (caudodorsal, caudoventral, and cranioventral lung involvement) or concurrent alveolar patterns within the caudodorsal and caudoventral lung indicated lower survival rates.[38] Pneumonia is also considered one of the greatest causes of morbidity and mortality in foals older than 1 month of age.[2]

The long-term effects on athletic performance have thus far predominantly been evaluated in older foals that survived *Rhodococcus* pneumonia. *R. equi* infection in foals was associated with a decreased chance of racing as adults. However, the performance of foals that went on to race was not significantly different from that of the general U.S. racing population.[46] It remains speculative whether severe equine neonatal pneumonia will most likely limit future peak athletic performance. Human studies have shown that many hosts develop long-lasting or permanent lung changes after recovery from neonatal pneumonia, which may significantly affect quality of life and susceptibility to later infections. Case-based evaluations in horses have demonstrated that functional and structural pulmonary abnormalities may occur in survivors of severe neonatal pneumonia. However, the clinical significance of this finding currently remains unclear.

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Fungal Infections of the Equine Respiratory Tract

Allison Jean Stewart

■ Definition and Etiology

Fungi are eukaryotic organisms with a definitive cell wall made up of chitins, glucans, and mannans. Within the fungal cell wall, the plasma membrane contains ergosterol, a cell membrane sterol that is frequently targeted by antifungal agents. There are more than 70,000 species of fungi, but only 50 species are known to cause disease in people or animals. Pathogenic fungi can be divided into three groups: multinucleate septate filamentous fungi, nonseptate filamentous fungi, and yeasts. Dimorphic fungi are able to interchange between forms depending on environmental conditions. Examples of dimorphic organisms include *Blastomyces dermatitidis, Histoplasma capsulatum,* and *Coccidioides immitis*, which exist in yeast form in vertebrate host tissue and in hyphal or mycelial form in vitro. In soil and decaying matter, the mycelial form usually is present and is composed of a collection of hyphae. The mycelia produce infective spores that are capable of inoculating vertebrate tissue.

Fungal infections in horses are relatively uncommon, although geographic prevalence is highly variable. Fungi are ubiquitous, and their constant aerosol exposure to respiratory tissue is inevitable. Upper respiratory and pulmonary disease caused by fungi is frequently acquired by the inhalation route, with the sporular diameter small enough to allow penetration into the distal airways and alveoli. In most samples of stable air, more than 90% of particles visible under a light microscope are spores of fungi or actinomycetes.[1] One study found that if a horse stood quietly in its stable without access to hay, the mean concentration of dust was very low (approximately 12 particles/cm^3 [of particles less than 5 mm in diameter]). When the bedding was disturbed during the normal “bedding down” operation, the concentration of respirable dust increased sixfold.[2] Systemic fungal infections and some cases of fungal pneumonia are thought to arise through a compromised GI tract, by inhalation, or via open wounds.

Tissue invasion of pulmonary tissue usually occurs in the immunocompromised host, although on occasion the normal individual may be affected. Important predisposing factors for fungal pneumonia include (1)

qualitative and especially quantitative granulocyte abnormalities and (2) the presence of devitalized tissue. In most cases of upper respiratory tract fungal granuloma, there are no obvious predisposing causes.

Primary pathogenic fungi such as *B. dermatitidis, H. capsulatum, C. immitis, Cryptococcus neoformans,* and *Conidiobolus coronatus* usually infect immunologically normal horses. However, in a report of cryptococcosis in seven horses, five had a history of illness that may have predisposed them to cryptococcosis.[3] A separate group of fungal pathogens tends to infect only those equine patients with abnormal host defenses. Opportunistic fungi, including *Aspergillus* spp., *Candida* spp., *Fusarium* spp., *Emmonsia crescens,* and *P. carinii* (renamed *P. jiroveci* in humans), have caused fungal disease in horses that are immunocompromised or neutropenic; have neoplasia, colitis, enteritis, or bacterial pneumonia; or have been treated with corticosteroids.[4-15] In vitro studies support the critical role of phagocytic cells in host defense against opportunistic fungi.

■ Clinical Signs

Mycotic granulomas have been found in nasal passages, paranasal sinuses, nasopharynx, guttural pouch, trachea, bronchioles, lungs, and mediastinum of infected horses. The most common clinical signs of upper respiratory tract fungal infection include unilateral or bilateral serosanguineous or mucopurulent nasal discharge, as well as inspiratory or expiratory noise. Other clinical signs include coughing, facial deformation, and dyspnea caused by partial blockage of nasal passages by granulomatous masses. Differentials for fungal granulomas of the respiratory tract include ethmoidal hematoma, squamous cell carcinoma, amyloidosis, and exuberant granulation tissue.

Fungal plaques in the guttural pouch often are located over the arterial blood supply. Horses with guttural pouch mycosis usually present with episodic serosanguineous nasal discharge that may progress to potentially fatal epistaxis if there is erosion into an artery. The duration of clinical signs can vary from days to many months. Guttural pouch mycosis is discussed in detail later in this chapter.

Pulmonary fungal infections causing granulomas, diffuse pneumonia, or pleuropneumonia can present with signs similar to those of bacterial infection. There may be cough, nasal discharge, tachypnea, respiratory distress, hemoptysis, and, if chronic, weight loss. Radiographic appearance of fungal

pneumonia may reveal virtually any infiltrative pattern. Although miliary patterns are occasionally seen, the most common initial finding is a patchy bronchopneumonia. Multiple focal sites are common, and lesions tend to be peripheral in distribution. Differentials include bacterial pneumonia, equine asthma, silicosis, equine pulmonary nodular fibrosis (associated with EHV-5), granulomatous disease complex, and neoplasia.

Systemic infections can have variable clinical signs depending on the location and extent of the infection. Fungal infections can affect multiple organ systems and body cavities. Weight loss, colic, or diarrhea can often occur with infection within the abdominal cavity.

■ Diagnostic Sampling

Lesions in the nasal passages, nasopharynx, guttural pouch, trachea, and bronchioles usually can be observed directly during endoscopic examination. Masses in paranasal sinuses and lungs may be observed radiographically. CT or MRI provide detailed imaging of the equine skull (and thorax, depending on the size of the animal and gantry) and can be used to determine the extent of lesions and bony invasion. An 8- to 20-mm trephine (Michelle 8-mm trephine or 14- to 20-mm Galt trephine [Jorgensen Laboratories, Inc., Loveland, Colo.]) can be drilled into the nasal or maxillary sinus, through which a sterile rigid arthroscope or flexible endoscope can then be passed to directly view some lesions within the paranasal sinuses.

For nasal and nasopharyngeal lesions, specimens for cytology, histopathology, and culture can be obtained by using an endoscopically guided biopsy instrument; however, these samples tend to be small, superficial, and often nondiagnostic. Mucosal contaminants may overgrow the organism of interest. Larger biopsy samples from the nasal passages or nasopharynx often can be obtained by using a uterine biopsy instrument (Jorgensen Laboratories, Inc., Loveland, Colo.) passed nasally with visual guidance from a flexible endoscope. Excisional biopsy or surgical debulking may be performed through a sinus flap or via laryngotomy.

Fungal pneumonia may be diagnosed from samples obtained by tracheal wash or bronchoalveolar lavage fluid, or via a lung biopsy. Lung biopsy is associated with significant risk if a large pulmonary vessel is accidentally punctured. The biopsy should be performed ideally after radiographic evaluation or with concurrent ultrasound guidance and should be obtained from the periphery of the lung; however, some horses have experienced fatal hemorrhage associated with

puncture of a vessel only 2 cm from the periphery. The lung is rich in plasminogen, so bleeding complications may be severe. Spring-loaded biopsy needles (4-gauge × 20-cm biopsy needle [Temno Products Group International, Lyons, Colo.] or Magnum biopsy needle) are safer for lung biopsy compared with Tru-Cut biopsy instruments (Cardinal Health, Dublin, Ohio).[16] Ultrasound evaluation can be used to monitor for bleeding after the procedure.

Cytology.

Fungal hyphae may be identified in airway fluid or in impression smears obtained from biopsied masses. Clinicians must be careful in attributing significance to presence of fungal elements in a transtracheal aspirate. Fungal hyphae are often present either free or in large mononuclear cells in tracheal aspirates from healthy horses.[17] A study of healthy Thoroughbred racehorses showed that 70% had fungal elements detected in their tracheal aspirates without evidence of fungal pneumonia.[18] Barn fungus such as *Alternaria* spp. are nonpathogenic and rarely incite an inflammatory response in the host. The organisms often have a blocklike appearance and may be colored (Fig. 31.18). A normal predominance of macrophages, lymphocytes, and nondegenerate neutrophils (<5% to 10%) would be expected.

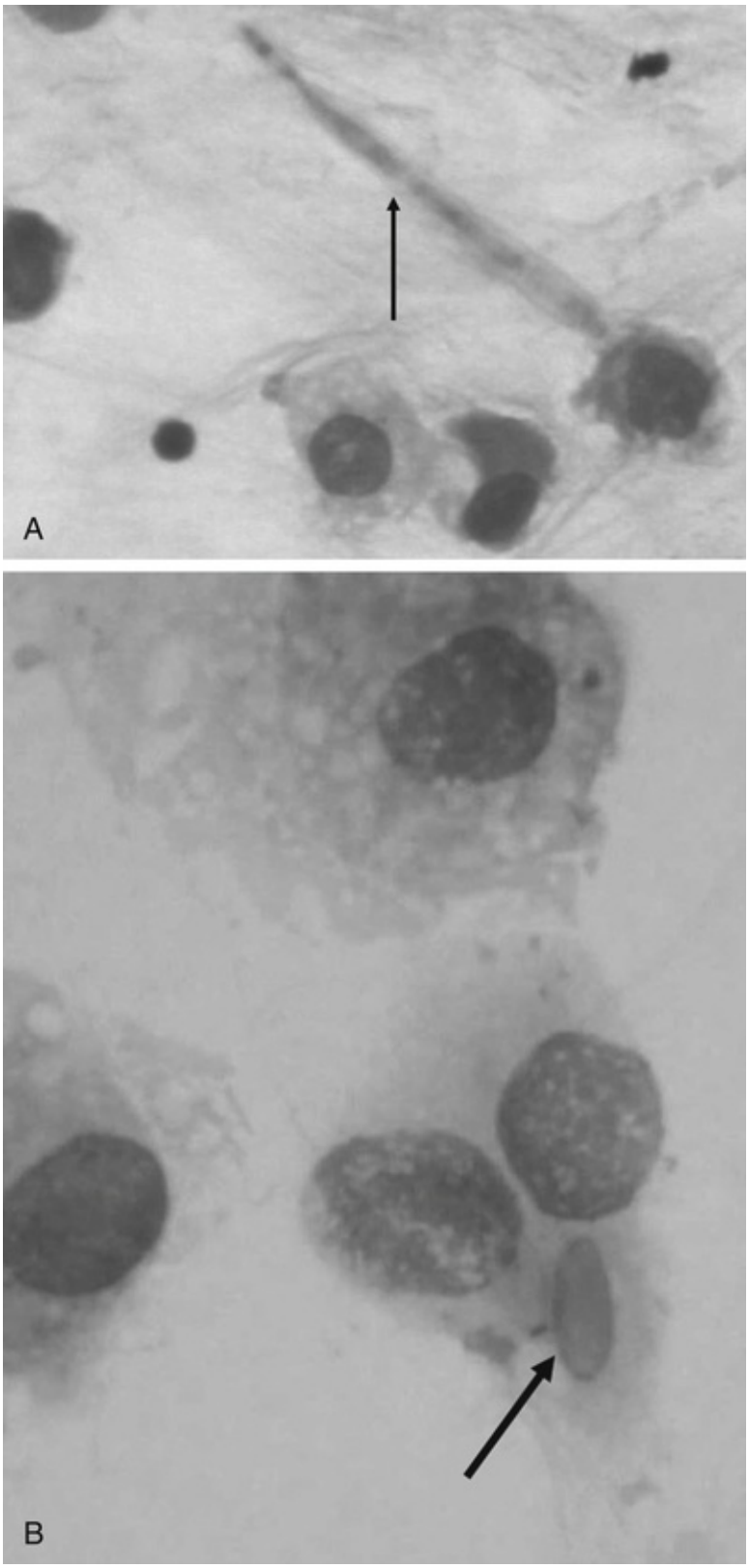


FIG. 31.18 *Alternaria* spp. from transtracheal wash specimens obtained from healthy horses. **A,** An extracellular spore *(arrow)* with several macrophages and squamous cells (indicative of pharyngeal

contamination). **B,** Intracellular spores *(arrow)* within binucleated macrophage. (Courtesy Elizabeth Welles, Auburn University, Auburn, Ala.)

To be significant cytologically, large numbers of fungi should be involved in the inflammatory process within the lung. With fungal pneumonia, aspirates may contain predominantly neutrophils that often are degenerate and may contain intracellular fungal hyphae. If processing of the sample is delayed, extracellular fungi may be phagocytized, and this makes interpretation more difficult. Some fungi have characteristic morphologic features that can give an early presumptive identification (Table 31.5).

TABLE 31.5

Characteristic Morphologic Features and Availability of Serologic Tests for Fungal Organisms Reported to Cause Fungal Granulomas in Horses (March 2018)

	Cytologic Appearance	Serologic Test	
Agent	**Tissue Form**	**Method**	**Veterinary Laboratory**
Cryptococcus neoformans	Round, thin-walled, yeastlike fungus (5-10 µm) with a large heteropolysaccharide capsule (1-30 µm in diameter) that does not take up common cytologic stains. Capsule is best stained using Mayer's mucicarmine stain. Organisms show narrow-based budding and lack endospores.	Capsular antigen ELISA (antigen) or latex agglutination (antigen)[26,58,61]	$41.00 UT $27.00 CU $23.00 CSU $18.00 UGA $29.50 NMDA $33.00 MDL
Conidiobolus coronatus	Broad, thin-walled, highly septate, irregularly branched hyphae (5-13 µm in diameter).[53,56] Often surrounded by acidophilic staining glycoprotein antigen-antibody complex known as Splendore-Hoeppli material.	Immunodiffusion is highly sensitive and specific. Decreasing titer is correlated to disease resolution in horses.[51,55]	Serologic testing not widely available.
Pseudallescheria boydii	Hyaline, nonpigmented, septate, randomly branched hyphae (2-5 µm in diameter) with regular hyphal contours. Asexual form has nonbranching conidiophores with terminal conidia. Sexual form in culture has cleistothecium (large, round body) and ascospores.[44]		
Coccidioides immitis	Spherules have a double-contoured wall, are variable in size, but can be large (20-80 µm, up to 200 µm). The mature spherules (sporangia) contain endospores (sporangiospores) 2-5 µm in diameter. In the environment, mycelium are thick walled with barrel-shaped arthroconidia.	AGID (antibody) for IgM and IgG[27,77,80,81] MVista Quantitative EIA (antigen)	$27.00 UT $20.00 CSU $21.00 CU $43.00 NMDA $60.00 MDL

Aspergillosis spp.	Broad (2-4 µm in diameter) septate hyphae with parallel sides and acute right-angled branching.	Platelia *Aspergillus* Galactomannan EIA (sandwich immunoassay) Some reactivity to *Penicillium, Alternaria*, and *Paecilomyces*. AGID (antibody) *Aspergillosis fumigatus* only *Aspergillus* spp. panel	$60.00 MDL $27.00 UT $20.00 CSU $21.00 CU $48.00 NMDA $105.00 UT (send out)
Blastomyces dermatitidis	Yeasts are spherical (15-17 µm in diameter) with basophilic protoplasm and unstained, uniformly shaped refractile walls. Unilateral, broad-based budding is characteristic. Yeasts are often located within multinucleated giant cells.	AGID (antibody)[23] MVista Quantitative EIA (antigen)	$27.00 UT $20.00 CSU $21.00 CU $48.00 NMDA $60.00 MDL
Histoplasma capsulatum	Yeasts (2-4 µm in diameter) have a thin, clear halo surrounding a round or crescent-shaped basophilic cytoplasm.	AGID (antibody)[74] MVista Quantitative EIA (antigen) Antigen	$27.00 UT $20.00 CSU $21.00 CU $48.00 NMDA $60.00 MDL $80.00 UT
Acremonium strictum	Mononuclear cells contain single, spherical, intracytoplasmic encapsulated spores 3-5 µm in diameter.[5]		
Candida spp.	Ovoid budding yeast cells (2-4 µm in diameter) with thin walls, or they can occur in chains that produce septate pseudohyphae when blastospores remain attached after budding division. Filamentous, regular, true hyphae also may be visible.		
Pneumocystis carinii	Trophozoite (yeast form) is a 2- to 5-µm in diameter ameboid with filopodia that attach to the surface of type I pneumocytes. Sporangia (cystic form) are encapsulated spores (4 to 6 µm in diameter) containing 8 uninucleate spores (intracytic bodies).[14,15,20,85]		
Fungal serology panel	Antibody to *Histoplasma, Blastomyces, Coccidioides, Aspergillus* (AGID) The CU panel also includes *Cryptococcus* antigen		$69.00 CU $68 CSU $48.00 NMDA
Fungal culture			$52.00 CU $30 CSU
Fungal susceptibility	Per isolate		$73.00 CU $168 UT

AGID, Agar gel immunodiffusion; *ELISA,* enzyme-linked immunosorbant assay; *Ig,* immunoglobulin.

CSU, Colorado State University, P (970) 297-1281, F (970) 297-0320, http://csu-cvmbs.colostate.edu/vdl/Pages/default.aspx; *CU,* Cornell University, Animal Health Diagnostic Center, P (607) 253-3900, F (607) 253 3943, http://ahdc.vet.cornell.edu/; *MDL,* Miravista

pdflibrary.net

Diagnostics Laboratory, Indianapolis, Ill., P (317) 856-2681, F (317)-856-3685, http://miravistalabs.com/fungal-infection-diagnostic-testing/; *NMDA,* New Mexico Department of Agriculture Veterinary Diagnostic Services, P (505) 383- 9299, http://www.nmda.nmsu.edu/vds/; *UGA,* University of Georgia, College of Veterinary Medicine, P (706) 542-5812, F (706) 583-0843, http://www.vet.uga.edu/idl/tests; *UT,* University of Tennessee, College of Veterinary Medicine, P (865) 974-5639 (mycology) or 974-5643 (serology), http://www.vet.utk.edu/diagnostic/index.php.

Histopathology.

Hyphae of certain fungi may be poorly visualized using routine hematoxylin and eosin (H&E) stains; therefore special stains such as periodic acid–Schiff (PAS), Gridley fungus, and Grocott-Gomori methenamine–silver nitrate (GMS) can be useful to stain histopathologic specimens. With chronicity, there is often evidence of extensive fibrosis.

Microbiological Culture.

Fungi can be found in tracheal aspirates from healthy horses. Sixteen percent of healthy horses are reported to have fungal growth on the tracheal aspirate bacterial culture plates; therefore results of fungal culture must be interpreted with caution.[19] Some fungi have fastidious growth requirements. They may be outcompeted by contaminant bacteria and may take up to several weeks to grow on culture media. For transport of tissue for microbiological culture, the sample should be placed in a prepared culture medium (BBL Port-A-Cul Vial [Becton, Dickinson and Company, Sparks, Md.]) and transported at room temperature. Specific culture media such as Sabouraud dextrose agar (Remel, Inc., Lenexa, Kan.), inhibitory mold agar, or Mycobiotic (Neogen, Lansing, Mich.) containing cycloheximide and chloramphenicol are useful.

Molecular Techniques.

Serologic tests that use immunodiffusion, radioimmunoassays, complement fixation, and ELISAs are available to detect circulating antibodies against several fungal organisms (see Table 31.5). These titers often decrease with resolution of disease; therefore repeated measurements can be used to help monitor response to treatment. Immunohistochemistry,[10,20-22] fluorescent in situ hybridization,[21] and DNA probes[23] can be used to positively diagnose fungal organisms in histopathology sections. A panfungal RT-PCR assay (University of California, Davis, Calif.) can be used to detect a variety of fungal organisms in body fluids and fungal isolates, followed by species-specific RT-PCR to

positively identify the organism.[5]

Immune Function Testing.

Several fungal infections have been associated with host immune suppression caused by severe malnutrition, congenital immunodeficiency, or acquired immunodeficiency.[13-15] Blood can be tested for immunoglobulin quantification by radial immunodiffusion (Cornell University, Ithaca, N.Y.) and lymphocyte subpopulation phenotyping via flow cytometry (Kansas State University, Manhattan, Kan.).[15,24]

■ Treatment

Treatment of fungal granulomas of the upper respiratory tract may involve surgical options (debulking, laser therapy, or cryotherapy) and/or medical therapy (systemic, topical, or intralesional). Treatment of *Aspergillus* spp. pneumonia is usually frustrating, as diagnosis is often late in the course of disease and the horse frequently has severe underlying illness. Successful therapy has been reported for other causes of fungal pneumonia.[5,25-28] Several pharmacokinetic studies on antifungal drugs have been performed,[29-34] and as these medications become more affordable, the success rate of therapy is likely to increase. The drug of choice depends on the site of infection, the fungus involved, and the financial resources of the owner. Specific antifungal agents used in horses have been reviewed.[35] Therapy may not be attempted because of the severity of the primary disease, the expense, or the poor prognosis.

Prevention of invasive fungal pneumonia is difficult. It is impossible for the horse to avoid large inhaled inocula, given its environmental conditions. Improving ventilation and minimizing exposure to inspired spores are most beneficial in immunocompromised patients. The most important methods of disease prevention are treating predisposing illnesses promptly and effectively and judiciously avoiding overuse of corticosteroids and broad-spectrum antibiotics.

Antifungal Therapeutics (Table 31.6)

Amphotericin B.

Amphotericin B deoxycholate is a polyene antibiotic that combines with ergosterol in the fungal cell membrane, resulting in an increase in cell

permeability. Intravenous amphotericin B can cause nephrotoxicity and phlebitis. Other possible side effects include anorexia, anemia, cardiac arrhythmias, hepatic and renal dysfunction, and hypersensitivity reactions.[36] Amphotericin B also has been used successfully to treat histoplasmosis and pulmonary aspergillosis and cryptococcosis.[25,26,37] A high dose of oral amphotericin B successfully treated mucormycosis caused by *Absidia corymbifera*.[38] Topical amphotericin B has been successful in treatment of nasopharyngeal *C. coronatus*.[39-42]

TABLE 31.6
Pharmacokinetic Studies of Antifungal Drugs Performed in Horses

Drug and Relative Cost	Dosage	Source	Susceptible Organisms, Equine Reports, Comments
Ketoconazole $ = Moderate	30 mg/kg q12h mixed with 0.2 normal HCl via nasogastric intubation[29]	LH Tablets (200 mg) (Nizoral [Janssen, Raritan, N.J.])	*Scopulariopsis*,[28] *Coccidioides, Cryptococcus, Candida, Malassezia, Histoplasma, Sporothrix, Microsporum, Trichophyton*
Itraconazole $ = Very expensive	5 mg/kg/day solution PO[31] (bioavailability 60%, compared to 12% for capsules)	Sporonox solution (10 mg/mL oral or injectable solution) Sporanox capsules (100 mg) (Janssen, Raritan, N.J.)	*Aspergillus*,[45,68] *Histoplasma, Bastomyces, Coccidioides, Cryptococcus, Candida, Paracoccidioides, Paecilomyces, Scopulariopsis, Sporothrix, Alternaria, Sporotrichum, Prototheca.* Not active against *Fusarium, Mucor, Rhizopus.* Very unstable and lipophilic, therefore compounded substances are not recommended.
Fluconazole $ = Inexpensive	14 mg/kg PO loading followed by 5 mg/kg/day PO[30]	LH Injectable solution (2 mg/mL) (Bedford Labs, Bedford, Ohio) Tablets (200 mg) (Pfizer, New York, N.Y.)	*Histoplasma, Bastomyces, Coccidioides*,[27] *Cryptococcus*,[60,61] *Mucor, Rhizopus, Candida*,[12] *Conidiobolomycosis*,[54,56] *Parracoccidia, Paecilomyces, Scopulariopsis, Sporothrix, Alternaria, Sporotrichum, Prototheca.* Minimal activity against *Aspergillus* and *Fusarium.*

		Generic available Powder (100 g) (Spectrum Chemicals, New Brunswick, N.J.)	
Voriconazole $ = Very expensive	4.0 mg/kg/day PO[32-34]	Vfend (Bedford Labs, Bedford, Ohio) Tablets (200 mg)	Drug of choice for invasive *Aspergillus*,[67] *Candida*, *Cryptococcus*, *Scedosporium apiospermum*, *Bipolaris*, and *Fusarium* species in human patients that are unable to tolerate or are refractory to other therapeutic agents.

HCl, Hydrochloride; *LH,* local wholesaler; *PO,* by mouth.

Azoles.

Benzimidazole derivatives in the class *azoles,* such as miconazole, enilconazole, ketaconazole, itraconazole, fluconazole, and voriconazole, destroy fungi by inhibition of ergosterol biosynthesis in the fungal cell membrane. Azole antifungals inhibit cytochrome P450–dependent 14 α–sterol demethylase, which is essential for the formation of ergosterol. Topical 2% miconazole was used in the resolution of four cases of guttural pouch mycosis[43] and as part of successful multimodal therapy against nasopharyngeal *Pseudallescheria boydii.*[44] Enilconazole is not commercially available in the United States but has been used topically in the successful treatment of guttural pouch mycosis.[45-47] Aerosolization of 1.2 mg/kg enilconazole q12h in 125 mL saline resolved *Scopulariopsis* pneumonia.[28] Ketoconazole is absorbed poorly in the nonacidified form[29] but can be acidified for better absorption (30 mg/kg via nasogastric tube q12h mixed with 0.2 normal HCl).[28]

Itraconazole (Sporanox solution [Janssen, Titusville, N.J.]) is absorbed well orally (bioavailability 60%). A dose of 5 mg/kg PO q24h maintains concentrations above mean inhibitory concentration (MIC) for susceptible yeasts (*Histoplasma* spp. and *Blastomyces* spp.) and *Aspergillus* spp., with no detectable side effects.[31] The use of compounded itraconazole is not recommended. It is very unstable (requires low pH), and owing to its lipophilic nature it is difficult to formulate in aqueous solution.

Oral fluconazole at a loading dose of 14 mg/kg, followed by 5 mg/kg q24h, yields concentrations in plasma, cerebrospinal fluid (CSF), synovial fluid,

aqueous humor, and urine above the MIC reported for several equine fungal pathogens.[30] Fluconazole, however, reportedly has minimal activity against filamentous fungi (*Aspergillus* spp. and *Fusarium* spp.). Low-dose oral fluconazole (1 mg/kg PO q24h) for at least 10 to 15 days anecdotally has been successful in treatment of fungal keratitis. Compounded fluconazole formulations are very stable. The cost of fluconazole has been markedly reduced since the availability of generic products.

Voriconazole, a broad-spectrum triazole antifungal agent, was approved for use in human medicine in 2002. It is now considered the drug of choice for initial treatment of invasive aspergillosis, candidiasis, cryptococcosis, *Bipolaris hawaiiensis*, and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* spp. in patients that are unable to tolerate or are refractory to other therapeutic agents.[46-49] An initial single-dose pharmacokinetic study in horses recommended a dose of 4 mg/kg PO q24h.[32] Voriconazole distributes widely into body fluids and reached therapeutic concentrations in peritoneal, synovial, and cerebrospinal fluids; aqueous humor; periocular tear film; epithelial lining fluid; and urine.[33-34]

Systemic Iodide Therapy.

The exact mode of action of iodides is unknown; however, they seem to have a beneficial effect on the granulomatous inflammatory process. Iodides have very little if any direct in vitro antibiotic effect.[50] Although several successful cases are reported in which iodides were used as primary or adjunctive therapy, overall efficacy is considered limited at best. Treatment is inexpensive, but iodide toxicity can occur and is characterized by excessive lacrimation, nonproductive cough, increased respiratory secretions, and dermatitis.[50] The recommended dose of 20% sodium iodide is 20 to 40 mg/kg/day IV for 7 to 10 days.[39,42,51,52] Orally administered iodine is available in two forms. Inorganic potassium iodide (10 to 40 mg/kg/day) is available only as a chemical grade and is unstable in the presence of light, heat, and excessive humidity.[42,52] Organic ethylenediamine dihydriodide (EDDI) (0.86 to 1.72 mg/kg of EDDI is equivalent to 20 to 40 mg/kg/day of the 4.57% dextrose powdered form [Butler Co., Columbus, Ohio]) is commercially available.[52] Administration of iodine in the diet of pregnant mares may cause congenital hypothyroidism in foals and thus should be avoided.

Etiologic Agents

Conidiobolomycosis.

Conidiobolus coronatus is a saprophytic fungus that causes granulomatous lesions of the upper respiratory tract in horses. Single to multiple granulomatous lesions in the nasal passages, trachea, or soft palate can be observed endoscopically (Fig. 31.19). Histologic appearance of conidiobolomycosis is similar to that of pythiosis and of basidiobolomycosis. Hyphae of *C. coronatus* are thin-walled, highly septate, and irregularly branched (see Table 31.5).[53] The lesions typically have large numbers of eosinophils and fewer macrophages, neutrophils, plasma cells, and lymphocytes surrounding hyphae. Definitive diagnosis is based on microbiological culture, immunodiffusion, or PCR.[54] Detection of serum antibodies by immunodiffusion is considered highly sensitive and specific[51,55] and can be used to monitor response to treatment.[55]



FIG. 31.19 Endoscopic image of mycotic granulomas caused by *Conidiobolus coronatus* in the nasopharynx of a horse.

Conidiobolomycosis lesions can be treated with surgical excision, laser therapy, cryotherapy, or long-term administration of iodides or antifungals.[39,51,54] Amphotericin B has been administered intralesionally or topically in combination with dimethyl sulfoxide (DMSO) to treat *C. coronatus*.[39-42] It is important to remember that long-term therapy and reevaluation are essential, as recurrence can occur.[42] Oral fluconazole would be considered the drug of choice for the treatment of conidiobolomycosis, with

treatment length varying between 4 and 16 weeks based on endoscopic reevaluation.[56] A vaccine using *C. coronatus* antigen from broth cultures was unsuccessful in treating seven horses with conidiobolomycosis.[54]

Cryptococcosis.

Cryptococcosis is caused by *Cryptococcus neoformans* (var. *neoformans* and var. *gattii*) and is a ubiquitous, saprophytic, round, basidiomycetous yeastlike fungus with a large heteropolysaccharide capsule that does not take up common cytologic stains (see Table 31.5; Fig. 31.20). The capsule forms a clear halo when stained with India ink. The capsule is immunosuppressive and antiphagocytic. A relatively high frequency of equine cryptococcosis occurs in Western Australia.[3,57,58] There is an epidemiologic relationship between *C. neoformans* var. *gattii* and the Australian river redgum tree *(Eucalyptus camaldulensis),* whereas *C. neoformans* var. *neoformans* has historically been associated with bird (particularly pigeon) excreta.[3] Cytologic or histopathologic identification is very reliable for diagnosis because of the characteristic morphology.[59] Serologic testing with latex agglutination to identify cryptococcal capsular antigen is useful, with resolution of lesions correlated with declining serum titers.[26]

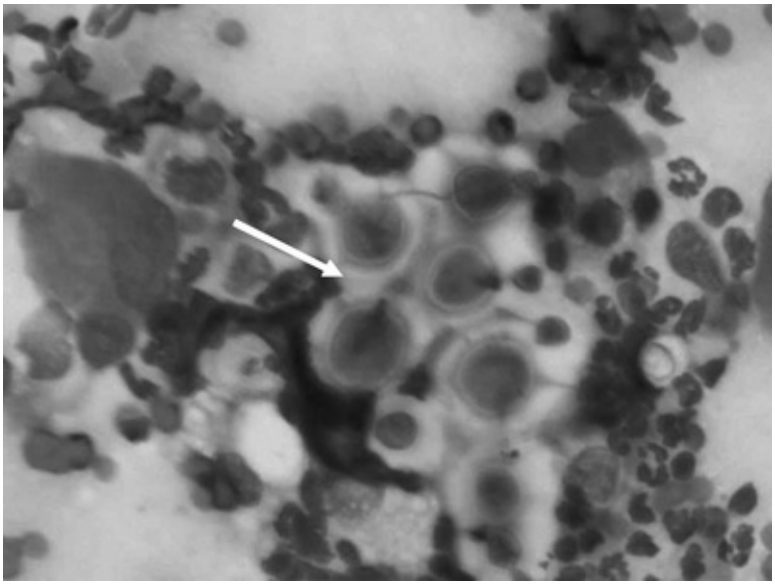


FIG. 31.20 Photomicrographs of an impression smear from a biopsy of a mass in the nasal passage of a horse. The smear is extremely cellular with abundant neutrophils and macrophages. Round yeast cells with large

nonstaining capsules and occasional narrow-based budding consistent with cryptococcal organisms *(arrow)* are shown. (Modified Wright stain, ×100.) (Courtesy Elizabeth Welles, Auburn University, Auburn, Ala.)

Cryptococcosis in horses is associated primarily with pneumonia, rhinitis (Fig. 31.21), meningitis, and abortion. Pulmonary *Cryptococcus* has been successfully treated with daily intravenous infusions of amphotericin B over 1 month.[26] However, four more cases from the same institution were recently successfully treated with oral fluconazole for 7 to 18 months, with declines in cryptococcal antigen titers corresponding to disease resolution.[58] Sinonasal cryptococcosis was successfully treated in two horses after extensive surgical débridement and long-term treatment with oral fluconazole.[60,61]

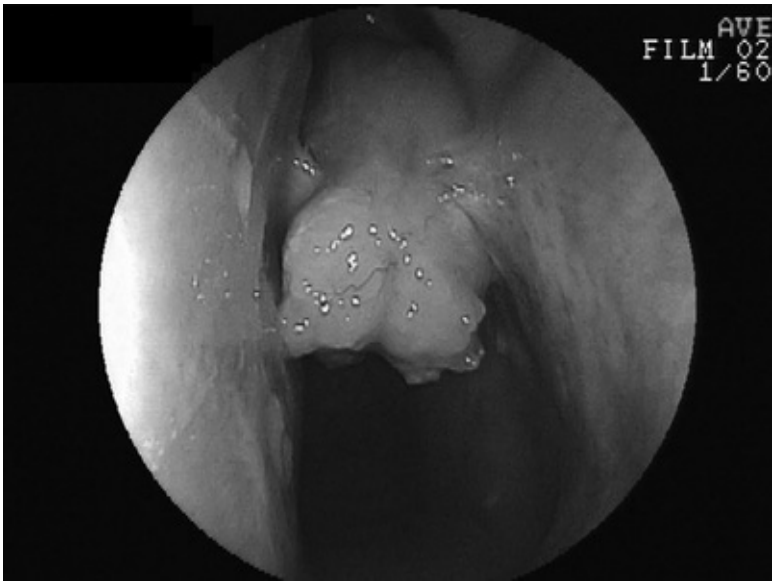


FIG. 31.21 Endoscopic image of a *Cryptococcus* granuloma in the nasal passages of a horse.

Cryptococcosis should be treated with fluconazole, amphotericin B, or voriconazole (Table 31.7).

TABLE 31.7

Treatment of Common Fungal Infections in Humans and Horses

Infection	Recommended Treatment in Humans[87]	Treatments Tried in Horses	Comments
Cryptococcosis	Induction with amphotericin B 0.7-1 mg/kg, plus 5-fluorocytosine 100 mg/kg/day for 2 weeks then consolidation with fluconazole 400 mg/day for >10 weeks.	Daily infusions of amphotericin B (initially 0.35 mg/kg, increasing over 8 days to 0.5 mg/kg in 1 L 5% dextrose in water over 1 h IV for 1 month) successfully used to treat pulmonary cryptococcosis. Flunixin meglumine (0.25 mg/kg IV) was administered before each treatment.[26,61] Successful treatment with long-term fluconazole (14 mg/kg loading then 5 mg/kg PO q24h) for sinonasal cryptococcosis after surgical débridement[60,61] and pulmonary infection.[58]	Reported dosages range from 0.3-0.9 mg/kg in saline IV over 1 h. Long-term oral fluconazole is recommended as sole treatment or after 2 weeks of IV amphotericin B.
Histoplasmosis	Amphotericin B 0.7-1.0 mg/kg/day for 2 weeks then itraconazole 200-400 mg/day for 4-18 months.	Successful treatment of histoplasmosis in a filly using amphotericin B (0.3-0.6 mg/kg eod IV infused over 1 h) with a total cumulative dose of 6.75 mg/kg administered over 1 month. After each treatment the filly became lethargic for 18-24 h. Polyuria and polydipsia occurred during the fourth week, but urine-concentrating ability was maintained and azotemia did not occur.[25]	In vitro susceptibility to fluconazole is poor.
Blastomycosis	Amphotericin B 0.7-1.0 mg/kg/day to 1.5-2.5 g total or to 0.5 g total then itraconazole 200-400 mg/day		
Aspergillosis (invasive pulmonary)	1. Voriconazole 200-400 mg PO q12h, 3-6 mg/kg IV q12h 2. Amphotericin B 1.0-1.5 mg/kg/day until desired response, then itraconazole 400 mg/day when disease progression slows	Voriconazole 4 mg/kg PO q24h. Successful treatment of a neonatal foal with pulmonary aspergillosis after lung lobe resection.[67]	Fluconazole has limited efficacy. Oral itraconazole or voriconazole would be the drugs of choice, possibly after 2 weeks of IV amphotericin B.
Candidiasis	1. Amphotericin B 0.7-1.0 mg/kg/day for 2 weeks 2. Fluconazole 6 mg/kg for 2 weeks 3. Caspofungin 70 mg ×1, then 50 mg/day for 2 weeks 4. Voriconazole	Two foals were treated with IV amphotericin B for 8 days (total dose 2.6 mg/kg) and 29 days (total dose 10.3 mg/kg), respectively. Fluconazole (5.5 mg/kg PO q24h) for 6 weeks and (4 mg/kg PO q24h) for 28 days was used to treat two other foals.[12]	Fluconazole is generally considered the drug of choice against *Candida* spp., although *Candida krusei* is resistant to fluconazole.
Pneumocystis	1. TMS 2. Pentamidine isethionate 3. Trimetrexate	TMS (25-30 mg/kg PO q12h) is the treatment of choice.[86] Dapsone[a] (3 mg/kg PO daily for 2 months) was used to successfully treat a foal with *Pneumocystis carinii* that developed *Salmonella* enterocolitis after treatment with TMS.[24]	Lacks ergosterol, therefore antifungals are not effective.

[a]Jacobus Pharmaceutical Co. Inc., Princeton, N.J.

eod, Every other day; *IV,* intravenous; *PO,* by mouth; *TMS,* trimethoprim-sulfamethoxazole.

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Pseudallescheriosis.

Pseudallescheria boydii is a saprophytic ascomycete. Infection most commonly involves the extremities, and in human patients it is known as Madura foot. Hyphae within tissue cannot be differentiated from *Fusarium* spp. or *Aspergillus* spp. unless cultured. *P. boydii* cultured from the nasal cavity and sinus of a horse with chronic, malodorous nasal discharge was susceptible in vitro to miconazole, ketaconazole, natamycin, and clotrimazole. After débriding and flushing the plaque, miconazole cream was infused twice daily for 4 weeks through lavage tubing that had been passed into the nasal passage through a hole drilled in the frontal bone and sinuses. Adjunctive iodide therapy was also administered and the lesions resolved.[44]

Nasal mycosis caused by *P. boydii* has been reported in two other horses, both of which were euthanized.[62,63] *P. boydii* has also been isolated from the pharynx of 2 of 60 normal donkeys.[64]

Aspergillosis.

Aspergillus spp. have broad septate hyphae with parallel sides and acute right-angled branching (see Table 31.5). They have a propensity for vascular invasion. Definitive diagnosis is by culture or staining by immunohistochemistry or immunofluorescence. *Aspergillus* spp. are very common in the environment, especially in moldy feed and bedding.[37] They are opportunistic pathogens and often cause disease in horses that are immunosuppressed from debilitating disease such as enterocolitis, septicemia, neoplasia, Cushing's disease, and equine protozoal myeloencephalitis (EPM); that have undergone surgery; or that have been treated with immunosuppressive drugs[4,6,8-10] (Fig. 31.22).


A
B

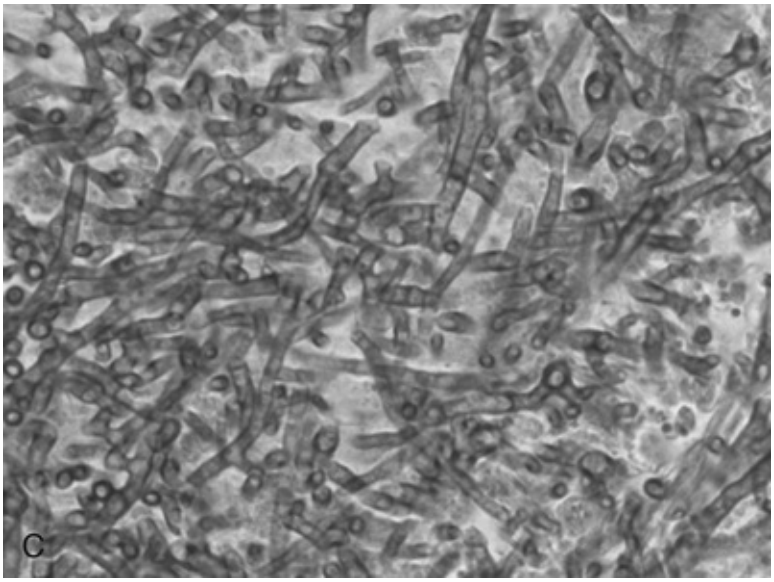


FIG. 31.22 One-month-old foal with *Escherichia coli* septicemia and secondary *Aspergillus* pneumonia. **A,** Dyspneic foal being supported with intranasal oxygen. The foal had eight septic joints and severe pneumonia and was subsequently euthanized because of the guarded prognosis. **B,** Photomicrograph of the pleural surface of the lung *(black arrows)* with extensive superficial and deep fungal growth. *Aspergillus* spp. characteristically have parallel-sided, regular septate hyphae with acute-angled dichotomous branching. They are seen reasonably well with hematoxylin and eosin stain. **C,** *Aspergillus* spp. hyphae within pulmonary parenchyma stained metachromatic with specific fungal stain (Gridley stain). (Courtesy Calvin Johnson, Auburn University, Auburn, Ala.)

Infection is by inhalation of an overwhelming number of spores, resulting in fungal proliferation and invasion of the small airways, or by translocation of organisms across an inflamed GI tract leading to lesions centered around large blood vessels as a result of hematogenous spread. In two retrospective studies of invasive pulmonary aspergillosis, 41 of 49 cases were associated with enterocolitis.[4,6] *Aspergillus* spp. pneumonia is almost uniformly fatal, often with no or mild respiratory signs. Antemortem diagnosis of pulmonary aspergillosis is made rarely. In a retrospective study of 30 cases of *Aspergillus* spp. pneumonia, only 2 cases were diagnosed or suspected antemortem.[6] Transtracheal aspirates or bronchoalveolar lavages may not be helpful because hyphae and spores are often present extracellularly or within macrophages in aspirates and lavages from healthy animals.[4] False-negative results also can occur. Cytologic examination of a transtracheal wash specimen obtained from the foal shown in Fig. 31.22, *A* 2 days prior to euthanasia failed to identify *Aspergillus* spp. hyphae. Serologic diagnosis occasionally has been useful,[65] but it is often

unreliable because many horses have titers to *Aspergillus* spp. Development of a commercially available ELISA is promising.[8,37]

In human medicine, 50% to 90% of patients with invasive aspergillosis die despite treatment. Amphotericin B has been the mainstay of treatment for invasive aspergillus for decades, but it is associated with nephrotoxicity in about 50% of human patients. Nephrotoxicity is reduced with the use of liposomal amphotericin B. Voriconazole, an azole antifungal, is now considered the drug of choice against human aspergillosis, and caspofungin (in the new class of echinocandin antifungals) shows promising results in patients with refractory infections.[66] Oral voriconazole and itraconazole are currently the treatments of choice for aspergillosis in horses. In human medicine, itraconazole has shown comparable response rates to those of amphotericin B.[66] *Aspergillus* spp. are usually resistant to fluconazole. There are limited reports of horses surviving pulmonary aspergillosis.[37] A neonatal foal with pulmonary aspergillosis was successfully treated by lung lobe resection followed by treatment with systemic voriconazole.[67]

Treatment of mycotic aspergillus rhinitis and sinusitis in horses has been more successful. It is important, however, to rule out concomitant invasive pulmonary aspergillosis. Oral itraconazole,[68] topical natamycin (flushed via an endoscope or indwelling catheter placed into the sinus), nystatin powder (insufflated up the nostril), and topical enilconazole have been curative.[69,70]

Blastomycosis.

Blastomycosis is caused by inhalation of conidiae of the thermally dimorphic saprophytic fungus *Blastomyces dermatitidis. Blastomyces* yeasts can be identified on cytologic examination, often within multinucleated giant cells. They are spherical, with basophilic protoplasm and unstained, uniformly shaped refractile walls. Unilateral, broad-based budding is characteristic (see Table 31.5).

Blastomycosis was reported to cause pyogranulomatous pleuropneumonia, pulmonary abscessation, peritonitis, and abscesses in a 5-year-old horse.[23] *B. dermatitidis* was positively identified from transtracheal wash fluid by use of a DNA probe, and serologic testing was strongly positive. The horse was euthanized without treatment.[23] Disseminated blastomycosis was diagnosed in a miniature horse with subcutaneous infections associated with a chronic pectoral wound. The pony had pulmonary consolidation and pleural effusion. Yeasts were

observed histologically in many tissues, and *B. dermatitidis* was cultured after 6 weeks.[71] Disseminated blastomycosis was diagnosed in a mare with unresponsive mastitis that progressed to subcutaneous lesions on the ventrum.[72]

Treatment with amphotericin B, itraconazole, or fluconazole is recommended (see Table 31.7).

Histoplasmosis.

Histoplasmosis is caused by the saprophytic, dimorphic fungus *Histoplasma capsulatum* and is most prevalent in moist soil containing bird or bat waste. Yeast organisms are 2 to 4 µm in diameter, with a thin clear halo surrounding a round or crescent-shaped basophilic cytoplasm. *H. capsulatum* has been reported in fewer than 10 equine cases,[25] and thus horses are considered to be relatively resistant to disease. *H. capsulatum* may occur in an enteric, pulmonary, or disseminated form.[25] *H. capsulatum* was identified in pulmonary granulomas in a horse dying of chronic *Yersinia* colitis.[73] It has also been associated with abortions and severe granulomatous pneumonia in neonatal foals (Fig. 31.23) and a yearling.[74] Successful treatment with amphotericin B was reported in a filly with pulmonary histoplasmosis diagnosed by cytologic identification of the organism on a tracheal wash smear and from a lung aspirate.[25] Treatment with amphotericin B or itraconazole is recommended (see Table 31.7).

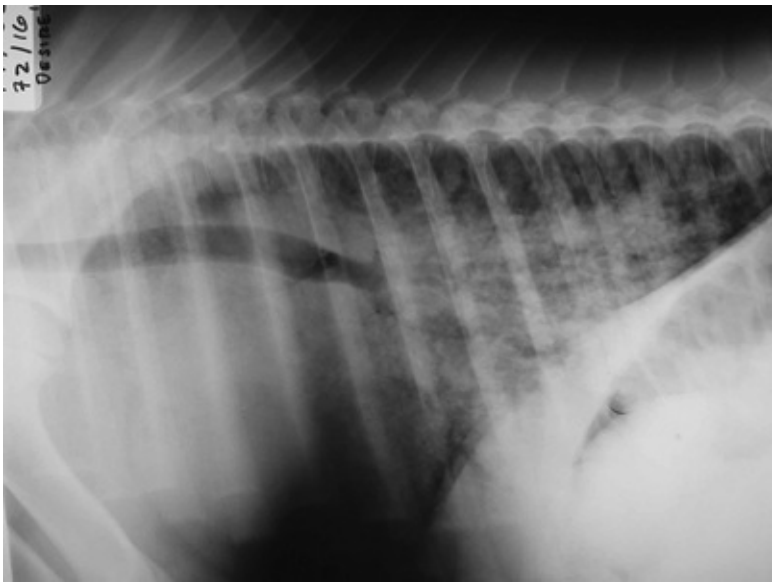


FIG. 31.23 Lateral thoracic radiographs from a foal with *Histoplasma* pneumonia. (Courtesy Carol Clark, Peterson and Smith Equine Hospital,

Ocala, Fla.)

Epizootic lymphangitis is caused by *Histoplasma capsulatum* var. *farciminosum*. It was eradicated from a number of European and Asian countries by slaughter, but it is still considered an economically important disease in Ethiopia, Senegal, South Africa, Chad, and Gambia, and it is likely still endemic in other African countries and parts of the Middle and Far East.[75] Although four forms of the disease—ocular, cutaneous, respiratory, and asymptomatic—are described, they are not distinct clinical entities, and combinations can occur.[75] The respiratory form can involve nodules in the mucous membranes of the nares and extend up the nasal passages, down the trachea, and into the pulmonary parenchyma. There is often a mucopurulent nasal discharge, with stertorous noise during respiration in advanced stages. This form causes cough, progressive weakness, and weight loss and is difficult to differentiate clinically from glanders. Control of the disease is gained usually by destroying infected horses and through application of strict hygiene practices to prevent spread of the organism. Organisms can be identified cytologically and definitively diagnosed by culture, but the organism is slow growing, and overgrowth by contaminants is common. Culture on Sabouraud dextrose agar supplemented with glycerol and chloramphenicol is recommended.[75] There is a skin test known as the "Histofarcin" test that is useful for field diagnosis, with a sensitivity of 90.3% but a specificity of only 69%; however, the false-positives may be due to subclinical disease.[76] Serologic tests were developed but are not commercially available. PCR testing shows promise but is currently not very practical in the field.[75] Treatment with systemic iodides, surgical excision, and topical treatment with amphotericin B is variably successful. A cost-effective and currently recommended protocol in impoverished areas consists of lancing all visible nodules under sedation and flushing with 4% tincture of iodine daily; in addition, oral potassium iodine (30 g for a 200- to 250-kg horse by stomach tube or orally in feed is administered daily for 5 days, then every other day for 3 to 4 weeks). This protocol is effective in early cases, but would be unlikely to resolve pulmonary disease.[75] Fluconazole would likely be effective, but would be economically prohibitive in most cases.

Coccidiomycosis.

Coccidioides immitis is a soil saprophyte that grows in semiarid areas with

sandy, alkaline soils.[77] Inhaled arthroconidia enlarge to form nonbudding spherules, which incite an inflammatory reaction in the lungs and lymph nodes.[78] Horses infected with this fungus have weight loss, fever, abdominal pain, and signs of respiratory disease. Localized, recurring nasal granulomas also have been reported.[79] Diffuse infections, with granulomas in the lungs, liver, kidney, or spleen, have a grave prognosis.[78] Przewalski's horses may be more susceptible.[79]

C. immitis is difficult to culture, and spherules may not be observed histologically from antemortem lung biopsies. However, serology is very useful for diagnosing infection, and decreasing titers are associated with clinical improvement.[27,77] Serum antibodies are detected rarely in healthy horses.[80] Higher serologic antibody titers are associated with a poorer prognosis for survival.[81] Horses with disseminated disease and pneumonia with thoracic effusion usually have severe clinical disease and frequently die (19 of 21 cases).[81] Antifungal agents successful in treating infected horses include itraconazole and fluconazole.[27]

Scopulariopsis.

Scopulariopsis pneumonia was diagnosed by culture of bronchoalveolar lavage fluid in a 2-year-old Quarter Horse filly with pleuropneumonia. The infection resolved following multimodal therapy with ketaconazole and aerosolization of enilconazole.[28]

Adiaspiromycosis.

Adiaspiromycotic miliary fungal pneumonia caused by the saprophytic soil mold *Emmonsia crescens* was diagnosed in a horse by percutaneous lung biopsy. Euthanasia was performed without treatment.[11]

Acremonium strictum.

A diagnosis of interstitial fungal pneumonia caused by *Acremonium strictum* was made based on cytologic evaluation, culture, and PCR testing of bronchoalveolar lavage fluid in a 10-year-old horse. The horse made an uneventful recovery with supportive treatment that included 1 month of fluconazole.[5] In general, fluconazole has been shown to have poor activity against *A. strictum* in vitro.[82] The isolate cultured from the horse was found to be resistant to fluconazole

based on in vitro sensitivity testing that was performed after the course of treatment. It is therefore uncertain if the fluconazole assisted in disease resolution.[5]

Candidiasis.

In human medicine, candidemia is the most common fungal infection in burn patients, neutropenic patients with malignancies, patients undergoing complex abdominal surgery, and patients receiving total parenteral nutrition and long-term corticosteroid therapy.[67] In humans, *Candida* spp. account for 8% to 10% of all blood culture isolates and rank fourth in the list of most frequently isolated pathogens from blood cultures.[67] The mortality rate in patients with candidemia is 40% to 75%.[67] More than 60% of isolates are *Candida albicans*.[67] Fluconazole is generally considered the drug of choice against *Candida* spp., although *Candida krusei* is resistant to fluconazole. Itraconazole, amphotericin B, caspofungin, and voriconazole are alternative antifungal agents (see Table 31.7).[67]

Systemic candidiasis was diagnosed and successfully treated in four neonatal foals. Each foal had prior sepsis attributable to gram-negative bacteria that had been aggressively treated with numerous antibiotics and parenteral nutrition. *C. albicans* was cultured from a transtracheal wash from one of the foals. Three of the foals had *Candida* glossitis, and one had panophthalmitis and fungal keratitis. Two of the foals were treated with intravenous amphotericin B, and oral fluconazole was used on the other two foals.[12]

Superficial *Candida* spp. infections of the mucous membranes (thrush)[83] can occur in isolation or as part of a systemic infection, and further microbiological culturing of the blood, tracheal wash, urine, or joint fluid may be indicated to rule out systemic infection.[12] *Candida* spp. glossitis can be treated by rinsing the mouth either with potassium permanganate (0.025% q24h) or nystatin (0.3 g in 10 mL of water q8h).

Pneumocystosis.

Pneumocystis carinii (renamed *P. jiroveci* in humans) has been reclassified from a protozoan to a saprophytic fungus based on the DNA sequence of its 16S-like RNA subunit, but some researchers consider it to be a plant because it lacks ergosterol, the major fungal sterol.[84] It exists as an ameboid yeast or as a cystic sporangia. *P. carinii* cannot be cultured, and diagnosis is based on the cytologic

identification of characteristic morphologic features using specimens obtained by bronchoalveolar lavage rather than tracheal wash. A fluorescent in situ hybridization method with an oligonucleotide probe that targets the 18S ribosomal RNA has been developed recently to detect *P. carinii* in histologic sections.[21] Immunohistochemistry also can be used.[20]

P. jiroveci is the most common organism to cause opportunistic infection in people with HIV, and people undergoing immunosuppressive therapy after organ transplantation are predisposed. *P. carinii* causes diffuse interstitial pneumonia, especially in immunocompromised patients such as Arabian foals with SCID.[13] It also has been diagnosed in immunocompromised adult horses,[14,15] as well as in an immunocompetent foal.[20] TMS (25 to 30 mg/kg PO q12h) is the treatment of choice (see Table 31.7).[85,86] Dapsone (3 mg/kg PO daily for 2 months; Jacobus Pharmaceutical, Princeton, N.J.) was used to successfully treat a foal that developed *Salmonella* enterocolitis after treatment with TMS.[24]

Streptococcus equi subsp. *equi* Infection (Strangles)*

Ashley G. Boyle

The highly contagious *S. equi* subsp. *equi* infections in horses, commonly referred to as *strangles,* were first described in early veterinary science literature by Jordanus Ruffus in 1251.[1] The causative organism will be referred to as *S. equi* in this section.

■ Clinical Signs

Strangles is characterized by sudden onset of fever followed by upper respiratory tract catarrh, as evidenced by mucopurulent nasal discharge and acute swelling with subsequent abscess formation in submandibular and retropharyngeal lymph nodes (Fig. 31.24). The term *strangles* was coined because affected horses sometimes suffocated as the lymph nodes became enlarged and obstructed the airway. Strangles is currently a reportable disease in many U.S. states.

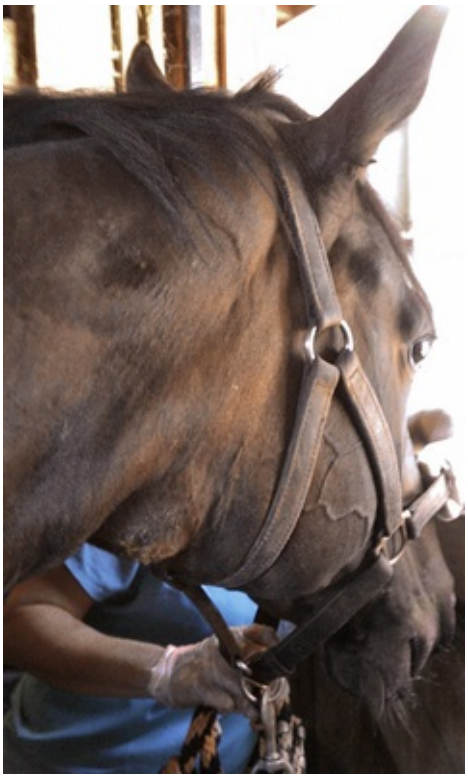


FIG. 31.24 Horse with retropharyngeal lymphadenopathy resulting in head and neck extension characteristic of *Streptococcus equi* infection.

Fever is the first clinical sign and remains as lymphadenopathy develops and abscesses mature. Pharyngitis makes swallowing painful, and affected animals may become anorectic or reluctant to eat and stand with the neck extended.

Lymphadenopathy is a major clinical sign. The submandibular and retropharyngeal lymph nodes are about equally involved in *S. equi* infections. They usually become swollen and painful approximately 1 week after infection. Other lymph nodes of the head region (parotid, cranial, and cervical) are also frequently involved and may abscess. Retropharyngeal lymph nodes may drain into and cause empyema of the guttural pouch (Fig. 31.25). Periorbital abscesses can cause marked swelling of the eyelids and result in ocular discharge that will culture positive for *S. equi* if sampled (Fig. 31.26). Abscesses of the lymph nodes at the thoracic inlet can cause severe tracheal compression, asphyxia, and death. Clinical severity and progression varies greatly depending on the immune status of the animal.

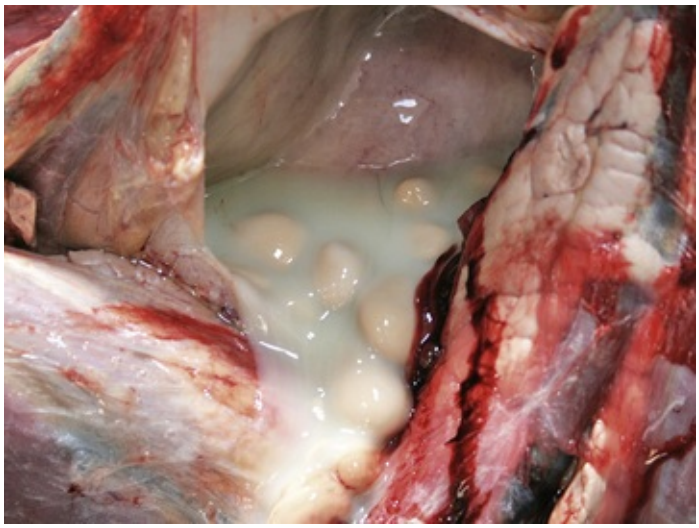


FIG. 31.25 Guttural pouch *Streptococcus equi* empyema with chondroids at postmortem. (Courtesy Dr. Julie Engiles, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)



FIG. 31.26 Horse with the unique presentation of periorbital abscessation with concurrent ocular discharge that cultured positive for *Streptococcus equi.* (Courtesy Dr. Erica Koch, Wentworth Equine Veterinary Services, Wolfeboro, N.H.)

■ Pathogenesis

S. equi is of the Lancefield group C streptococcal diseases and enters via the

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mouth or nose and attaches to cells in the crypt of the lingual and palatine tonsils and to the follicular-associated epithelium of the pharyngeal and tubal tonsils. There is no evidence of colonization before penetration. After a few hours, the organism is difficult to detect on the mucosal surface but is visible within cells of the epithelium and subepithelial follicles. Translocation to the mandibular and suprapharyngeal lymph nodes that drain the pharyngeal and tonsillar region occurs in a few hours.[2]

Complement-derived chemotactic factors attract large numbers of polymorphonuclear neutrophils (PMNs), although gross evidence of abscessation is not visible for 3 to 5 days after *S. equi* enters the lymph nodes. Failure of neutrophils to phagocytose and kill the streptococci appears to be a result of a combination of the hyaluronic acid capsule, antiphagocytic SeM protein, Mac protein, and other undetermined antiphagocytic factors released by the organism. Depending on the immune status of the patient and the degree of exposure to *S. equi* bacterial load, clinical signs may develop 3 to 14 days after exposure.[1]

Although strangles involves predominantly the upper airways, including the guttural pouches and associated lymph nodes, metastasis to other locations occasionally occurs. Spread may be hematogenous or via lymphatic channels, which results in abscesses in lymph nodes and other organs of the thorax and abdomen. This form of the disease is known as *bastard strangles.*

Nasal shedding of *S. equi* usually begins 2 to 3 days after onset of fever and persists for 2 to 3 weeks in most animals. Some animals never shed. In others, nasal shedding may last at least 6 weeks after purulent discharges have stopped. Persistent guttural pouch infection may result in intermittent shedding for years.[3,4] Systemic and mucosal immune responses are evident 2 to 3 weeks after infection and coincide with mucosal clearance.

As long as they were not treated with antimicrobials, approximately 75% of horses develop a waning immunity to strangles that lasts about 5 years after recovery from the disease. A small percentage of these horses become susceptible to a second attack of the disease within months, which probably represents a failure to produce or maintain an adequate level of the appropriate mucosal and systemic antibodies. Older horses with residual immunity have limited susceptibility and develop a mild form of strangles often called *catarrhal strangles.* These animals shed virulent *S. equi* that will produce severe disease in more susceptible, often younger horses. Colostral antibodies ingested during the first 24 hours of life have also been shown to recirculate to the nasopharyngeal

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mucosa, thus providing an additional source of protection to the foal during its first weeks. Foals that suckle immune mares are usually resistant to *S. equi* infection until weaning.[1]

■ Epidemiology

Transmission.

Outwardly healthy horses that still shed organisms are a source of infection when introduced into a new population of horses. Definitive determination of carrier status requires endoscopic examination of the guttural pouches as well as PCR testing of guttural pouch lavage fluid.[1,5,6] *S. equi* may originate from outwardly healthy horses such as the following:

- Horses that are incubating the disease and go on to develop signs themselves
- Horses that are recovering from recent disease but that continue to harbor the organism after full clinical recovery for some weeks
- Horses that are fully recovered from the disease but continue to be potentially infectious for prolonged periods through periodic shedding of *S. equi* (carriers)

Environmental Persistence of *Streptococcus equi*.

Currently there is a lack of definitive field-based evidence for prolonged environmental persistence. *S. equi* is known to be sensitive to bacteriocins from environmental bacteria and does not readily survive in the presence of other soil-borne flora. Modeled environmental field conditions revealed that the organism was found to persist for less than 4 days, but moist environments (e.g., water buckets) may allow the organism to persist for extended periods (up to 34 days) when protected by cold conditions.[7,8]

■ Diagnosis

Early definitive diagnosis is essential for containing this highly infectious

disease. Sampling may be unsuccessful during the incubation and early clinical phases. *S. equi* is normally not present on the mucosa until at least 24 to 48 hours after the onset of fever, so infection in horses monitored by daily measuring of rectal temperatures during an outbreak may be recognized early and isolated to limit transmission of *S. equi*. Samples can be obtained via nasopharyngeal swab, nasopharyngeal wash, and guttural pouch wash. A comparison of *S. equi* sample type is found in Table 31.8.[1] Cytologic evaluation reveals gram-positive extracellular cocci in long chains, supporting a general diagnosis of a β-hemolytic streptococcus organism. Common hematologic findings of horses with *S. equi* are hyperfibrinogenemia, neutrophilic leukocytosis, and mild anemia.[9]

TABLE 31-8

Comparison of Sample Type for Diagnosis of *Streptococcus equi*[1]

***S. equi* Sample**	**Pros**	**Cons**
Aspirate of mature abscessed lymph node	High yield of bacterial organisms	Requires this stage of disease
Moistened rostral nasal swab[a]	Ease of sampling	Animal needs to have active mucopurulent discharge
Moistened nasopharyngeal swab[a]	Ease of sampling	False negatives possible in early febrile state (not shedding yet)
		False negatives possible due to intermittent shedding from guttural pouch
Nasopharyngeal wash	Ease of sampling	False negatives possible in early febrile state (not shedding yet)
	Sampling more surface area	False negatives possible due to intermittent shedding from guttural pouch
	Was found to be more sensitive than nasopharyngeal swab[9]	
Guttural pouch lavage[b]	Best for detection of carrier animals	Special equipment needed
		Experience needed entering the guttural pouch
		More time consuming
		False negative if lymph nodes have not yet ruptured into the pouch

[a]Synthetic microfiber flocked swabs have not shown increased detection rates over traditional rayon or cotton swabs.

[b]The committee recommends guttural pouch lavage quantitative polymerase chain reaction (qPCR) for the detection of carriers with concurrent visual inspection of the guttural pouch via endoscopy. To limit the contamination of the environment and the veterinarians, we recommend collection directly from the guttural pouch, rather than via free catch from the nasal passage.

Culture.

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Culture is the preferred method on aspirates of mature abscesses, but it takes a minimum of 24 hours to obtain results. Culture is inexpensive, sensitive, and accurate for samples that have large numbers of bacteria, such as those collected from animals with obvious disease. Unfortunately, up to 40% of samples can be falsely negative on culture, especially in patients sampled too early in the course of disease or during convalescence.[10]

Polymerase Chain Reaction.

Multiple gene targets are available for the detection of *S. equi* via quantitative polymerase chain reaction (qPCR), and this technique has been shown to be more sensitive than culture as a diagnostic tool.[1,9-12] Nasopharyngeal washes (Fig. 31.27) are preferable to nasopharyngeal swabs due to a larger sampling area,[1] but guttural pouch sampling is 50 times more likely to detect carrier animals.[1] Absence of obvious guttural pouch pathology on endoscopic evaluation combined with negative guttural pouch lavage qPCR is recommended to remove a horse from quarantine.[1] To prevent contamination of the environment, it is recommended to aspirate the sample via polyethylene tubing through the instrument channel of a 1-meter endoscope.[5,6] The endoscope should be sterilized after and between sampling of suspect horses.



FIG. 31.27 Infusing 50 mL of 0.9% saline for a nasopharyngeal wash on a sedated horse with a uterine pipette. The pipette is punctured through one side of the rectal sleeve.

Serology.

Serologic testing involves the use of ELISA to detect the SeM protein. Serology is useful for detecting recent but not current infection; assessing the need for vaccination; identifying horses that may be predisposed to purpura hemorrhagica; and diagnosing *S. equi*–associated purpura hemorrhagica and metastatic abscessation (SeM titers often are = 1 : 12,800 but have been seen as low as 1 : 3200 and 1 : 6400 in confirmed cases).[1,10] It has been suggested that horses with high serum SeM-specific antibody titers (≥1 : 3200) may be predisposed to developing purpura hemorrhagica when vaccinated against *S. equi*.[1] A 2009 study reported safely vaccinating horses with SeM titers of 1 : 1600[13] or less with the Pinnacle® I.N. (Zoetis, Parsipanny, N.J.) vaccine. A 2017 study suggested that horses should be tested with the SeM serology for 1 year after a strangles outbreak to determine when it is safe to vaccinate.[14]

The Animal Health Trust in the United Kingdom has developed a combined serologic test that detects two surface antigens, Antigen A (SEQ_2190 N-

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Terminal Fragment) and Antigen C (SeM N-Terminal Fragment), and has similar sensitivity but greater specificity when compared to the whole SeM antibody titer.[15] This test can be used to identify unvaccinated horses with strangles exposure as recent as 2 weeks previously and to identify animals without clinical signs that may be carrying *S. equi* for the purposes of isolation and further evaluation via endoscopic guttural pouch examination.[1,15,16]

Vaccination.

Most horses develop a solid immunity during recovery from strangles, which persists but wanes in more than 75% of animals for up to 5 years as long as the animal was not treated with antimicrobials during the primary infection. This indicates that stimulation of a high level of immunity is biologically feasible given appropriate presentation of protective immunogens. There is evidence that immunity in horses resistant to reinfection is mediated at the mucosal level and functions to block entry of *S. equi*. However, systemic immunity after parenteral inoculation of avirulent live *S. equi* is also protective. Together these findings indicate that optimum immunity may require both systemic and mucosal responses.

Vaccine should be administered only to healthy nonfebrile animals free of nasal discharge. Although controversial, vaccination should be considered only in horses with no known contact with animals with strangles during an outbreak.[1] The American Association of Equine Practitioners (AAEP) Infectious Disease Committee does not recommend vaccination during an outbreak due to the increased risk of purpura hemorrhagica.

Use of Extract Vaccines.

Extract vaccines (Strepvax II [Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Mo.]) are given intramuscularly and elicit serum antibody responses 7 to 10 days later. Naive horses and foals require a schedule of two or three doses at an interval of 2 weeks. Booster doses are given once annually. Pregnant mares may be boostered a month before the expected date of foaling. Extract vaccines have been associated with cases of purpura hemorrhagica.[17]

Use of Attenuated Live Intranasal Vaccine.

Attenuated live vaccine (Pinnacle I.N. [Zoetis, Parsipanny, N.J.]) is given in a schedule of two doses at 2- to 3-week intervals. Annual booster doses are

recommended. The mode of application should be such that an adequate amount of vaccine reaches the pharyngeal and lingual tonsils but does not enter the trachea. Careful handling of live vaccine is recommended to prevent inadvertent injection intramuscularly via either the vaccine directly or contamination of other vaccines given at the same time. A temporary pharyngitis is possible secondary to administration of this vaccine, and it is not recommended in horses younger than 1 year of age because of the possibility of them developing vaccine-associated clinical disease.[18]

Future Vaccines.

It is likely that more effective and safer vaccines will be developed based on genomic sequence information from *S. equi* and other *Streptococcus* species, *and* there is a need for vaccines that are DIVA (differentiating infected from vaccinated animals) in order to identify recently infected horses from those already vaccinated via serology. Recent experimental trials in Europe have evaluated the use of recombinant multicomponent subunit vaccines that may be promising for broader clinical applications in the future.[19,20]

Control of Outbreaks.

Most outbreaks are thought to originate from introduction of an infected horse to a naive population. All new horses should be isolated for 3 weeks and monitored for any signs of disease, including fever. Many farms with repeated infections have resorted to screening for infection via a single endoscopic evaluation and PCR testing of guttural pouch lavages, a procedure considered by many as the "gold standard" for carrier detection.[5,6] A series of three nasopharyngeal swabs, collected 1 week apart, will result in detection by a positive culture on at least one of the swabs in only 60% of carrier animals. Concurrent testing of these swabs by PCR increases the likelihood of detection to more than 90% of carrier animals.[6]

A practical disease-control strategy should then be agreed on and implemented. The general aims and measures for such a strategy are outlined in Table 31.9, and a flow chart is shown in Fig. 31.28.[1,21]

TABLE 31.9

Aims and Measures Used to Control Transmission of *Streptococcus equi* on Affected Premises

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Aim	Measure
1. To prevent the spread of *S. equi* infection to horses on other premises and to new arrivals on the affected premises	Quarantine new arrivals for 3 weeks. Additional screening for subclinical carriers by guttural pouch endoscopy, culture, and qPCR testing should be part of any screening program. Stop all movement of horses on and off the affected premises immediately and until further notice.
	Horses with strangles and their contacts should be maintained in well-demarcated "dirty" (i.e., *S. equi*–positive) quarantine areas.
	Clustering of cases in groups should allow parts of the premises to be allocated as "dirty" (red), "exposed" (amber), and "clean" (green) areas.
	Perform twice-daily monitoring of rectal temperatures of the amber and green groups to identify temperature increases in horses early and move them to the red area prior to the start of shedding.
2. To establish whether convalescing horses are infectious at least 3 weeks *after* clinical recovery	Testing horses that have been treated with antibiotics should not commence prior to 3 weeks after the cessation of antibiotic treatment. If nasal discharge persists longer than 2 weeks, guttural pouch examination is indicated to identify horses that may have empyema and require additional treatment. A single endoscopically guided guttural pouch lavage qPCR on cases and their contacts to screen for carriers provides increased efficiency and sensitivity over three nasopharyngeal washes over 3 weeks. All equipment must be disinfected between horses when sampling multiples on a farm.
	Horses are considered safe to move out of isolation on the basis of absence of obvious guttural pouch pathology in conjunction with negative guttural pouch lavage qPCR results.
3. To eliminate *S. equi* infection from the guttural pouches	Remove pathology through a combination of flushing and aspiration with saline, and remove chondroids using endoscopically guided instruments.
	Perform topical and systemic administration of antimicrobials to eliminate *S. equi* infection.
	A minimum of 3 weeks should pass before retesting a treated, previously positive guttural pouch via qPCR.
4. To prevent indirect cross-infection by *S. equi* from horses in the "dirty" area to those in the "clean" area of the premises	Personnel should use dedicated protective clothing when dealing with infectious animals and should not deal simultaneously with susceptible animals.
	If this is unavoidable, infectious horses should be dealt with *after* susceptible animals.
	Strict hygiene measures are introduced, including provision of dedicated clothing and equipment for each area, disinfection facilities for personnel, and use of thorough stable cleaning and disinfection methods.
	When cost is not a factor, consideration should be given to destruction of the dedicated equipment after eradication of the infection.
	After removal of organic material from stables, all surfaces should be cleaned first with detergent and then be thoroughly soaked in an appropriate liquid disinfectant (bleach, phenols, quaternary ammonium compounds) and allowed to dry.
	Manure and waste feed from infectious animals should be composted (disinfected by heat) in an isolated location.
	Pastures used to hold infectious animals should be rested for 4 weeks.
	Care should be taken to clean and disinfect water troughs at least once daily during an outbreak.
	Horse vans should be cleaned with detergent and then disinfected after each use.

qPCR, Quantitative polymerase chain reaction.

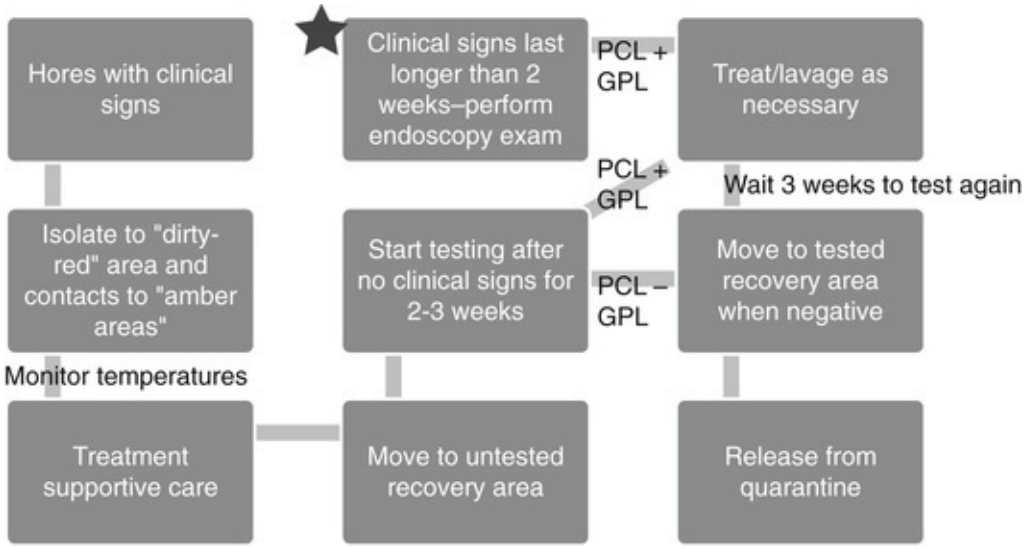


FIG. 31.28 Flow chart of recommended steps in the management of an outbreak of *Streptococcus equi*. Briefly, horses that present with clinical signs of strangles will be isolated to a “dirty” or “red” zone and all of these horses’ contacts should be in placed in an “amber” zone. Temperatures are monitored, and horses are moved to the “dirty” zone if the temperature is 101.3° F (38.5° C) or higher. Supportive care and treatment of affected animals should be provided. Once clinical signs have resolved in affected horses, they are moved to a recovery area for untested horses. It is recommended that guttural pouch endoscopy and *S. equi* polymerase chain reaction *(PCR)* and culture combination testing of the guttural pouch lavage *(GPL)* should start a minimum of 2 to 3 weeks after the resolution of clinical signs. If a horse is positive on GPL or has an abnormal endoscopy, copiously lavage the guttural pouch and treat with topical and possibly systemic antibiotics. If the GPL is negative, move the horse to a tested recovery area (“green” zone). If a horse remains clinical for longer than 2 weeks, perform a guttural pouch examination at that time to determine if the horse has significant empyema and requires lavage to remove physical contamination of the pouch in order to shorten time to resolution.[20]

■ Treatment

The goal of treating strangles is to control transmission and eliminate infection while providing future immunity to the disease. Appropriate treatment of horses with strangles usually depends on the stage and severity of the disease, and veterinary opinion as to whether to use antibiotic treatment remains markedly divided.[22]

Horses With Early Clinical Signs.

During an outbreak, immediate antibiotic therapy for new cases in the early

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acute phase with fever and depression may be curative and may prevent focal abscessation and shedding. Because abscesses have not developed at this early stage, the antibiotics have adequate access to the bacteria. Immediate treatment of horses that show the earliest clinical sign, fever, could be an effective way of controlling strangles outbreaks in racing stables or riding barns, although the disadvantages of treatment should be weighed.[1]

Horses With Lymph Node Abscessation.

Uncomplicated cases of strangles are often left to run their course with supportive care, providing lasting immunity. Affected horses should be isolated in a clean, dry stall and fed moist, palatable food. NSAIDs should be used judiciously to decrease swelling and promote eating. Hot compresses or topical 20% ichthammol can be used to accelerate maturation of abscessation. Mature external abscesses should be lanced to allow drainage, followed by daily lavage of open abscesses using dilute povidone-iodine solution. This speeds resolution of abscessation as well as alleviation of compression of the pharynx.

Although the use of antimicrobials for treating strangles is controversial, if the horse is febrile, depressed, anorectic, and particularly if manifesting dyspnea, antibiotic therapy is indicated to decrease abscess size and prevent complete airway obstruction. In rare cases, affected horses may require intensive supportive therapy, including IV fluids, feeding by nasogastric tube, and tracheostomy. An animal requiring a tracheostomy should be given systemic antimicrobial drugs to prevent secondary bacterial infections of the lower respiratory tract.

Drugs of Choice for Therapy.

Penicillin G (procaine penicillin [22,000 to 44,000 IU/kg IM q12h] or aqueous potassium penicillin [22,000 to 44,000 IU/kg IV q6h]) is considered the drug of choice for the treatment of nonpneumococcal streptococcal disease, with alternative drugs used depending on ease of administration or the site of infection. Other agents for therapy include cephalosporins and macrolides. Anecdotally, trimethoprim-sulfadiazine treatment failure has been seen, and there are no studies determining its effectiveness against *S. equi*.[23] Use of antimicrobials during any phase of the disease may prevent the development of lasting immunity.

Complications

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Guttural Pouch Empyema and Carrier Status.

The percentage of carriers per outbreak could be as high as 10%. Endoscopic examination is required for identification of guttural pouch empyema. The SeM ELISA and the combined indirect ELISA (iELISA) do not detect empyema or carrier status.[5] Elimination of guttural pouch empyema requires repeated lavage with a solution of 20% acetylcysteine in buffered saline via polyethylene tubing through an endoscope or via a Chambers catheter. Chondroids are particularly difficult to remove, possibly requiring manual removal with endoscopic equipment such as a memory helical polyp retrieval basket, repeated lavage via indwelling catheters, or surgical removal. Successful elimination of *S. equi* in these carriers requires local treatment of the guttural pouch with a penicillin gel after removal of the material within the guttural pouch in addition to systemic treatment with procaine penicillin or potassium penicillin for 7 to 10 days. Eradication of this disease will not be possible until the subpopulation of carriers is eliminated.[24]

Complications Associated With Metastatic Spread of Infection.

S. equi spreads hematogenously or lymphatically, resulting in metastatic abscessation that can affect any organ system in 2%[25] to 20%[26] of cases. Aspiration of mucopurulent discharge or hematogenous or lymphatic spread to the lungs can cause pneumonia. Abscessation in the mesentery, liver, spleen, and kidneys is common, leading to peritonitis and clinical signs of colic. Abscessation of the cranial mediastinal lymph nodes can cause tracheal compression and respiratory distress. Neurologic signs are present when abscessation occurs in the brain.[1] The mortality rate of horses with strangles is less than 2%, but the presence of bastard strangles can increase the mortality rate to as high as 62%.[27,28] Attempted culture and sensitivity from the affected body cavity provides direction for the appropriate antibiotic treatment, which has included penicillin, ceftiofur, chloramphenicol, and doxycycline. An average of 2.5 months of antibiotic treatment was needed for resolution.[27] Some horses have been treated via surgical drainage along with systemic antibiotics.[28]

Purpura Hemorrhagica.

Purpura hemorrhagica is an aseptic necrotizing vasculitis that can occur in mature horses after repeated natural exposure to infection or after vaccination of horses that have had strangles. The actual incidence of this type III

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hypersensitivity response secondary to strangles or vaccination is unknown. Clinical signs range from mild to life-threatening, including pitting edema of the head, trunk, and distal limbs, as well as petechiae and ecchymoses. In some cases, antigen-antibody complexes affect other sites, including the GI tract, muscles, lungs, myocardium, and kidneys. In addition to prolonged treatment with penicillin, cases of purpura hemorrhagica also require the use of systemic corticosteroids (dexamethasone, 0.1 to 0.2 mg/kg IV or IM q12-24h; prednisolone, 0.5 to 1 mg/kg PO q24h) for an average of 3 weeks to reduce systemic vasculitis.[13] Significant rhabdomyolysis with progressive atrophy has been identified in some Quarter Horses, after exposure to *S. equi*, without other signs of purpura.[17]

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Acute Respiratory Distress Syndrome and Acute Lung Injury (Acute Bronchointerstitial Pneumonia)

Bettina Dunkel

■ Definition and Pathophysiology

Acute respiratory distress syndrome (ARDS) describes a condition of severe pulmonary dysfunction and respiratory failure caused by physical or chemical injury or an exaggerated pulmonary immune response. In human medicine, the current definition, the so-called Berlin definition, defines ARDS as respiratory distress that is acute in onset (within a week of a known insult) and combined with the presence of bilateral pulmonary opacities and respiratory failure not fully explained by cardiac failure or fluid overload. Based on the degree of hypoxemia, measured by the ratio of partial arterial oxygen pressure (Pa_{O_2}) to fraction of inspired oxygen (Fi_{O_2}), three severities of ARDS are differentiated: mild (Pa_{O_2}/Fi_{O_2} >200 and ≤300 mm Hg), moderate (>100 and ≤200 mm Hg) and severe (≤100 mm Hg).[1-3]

In the first definition from 1994, the term *acute lung injury (ALI)* was used to describe a less severe form of the disease, now corresponding to the mild form of ARDS.[4] This term is no longer used in human medicine. It still features in the current definitions for veterinary acute lung injury (VetALI) and veterinary acute respiratory distress syndrome (VetARDS) that were developed during a consensus meeting predating the Berlin definition (Box 31.1).[5] Due to lack of available data, no species-specific definitions were established, but the physiologic differences in arterial oxygenation in foals younger than 1 week of age were addressed by introducing different inclusion criteria for this age-group (Table 31.10). The consensus definition also acknowledged the disease presentation in neonatal foals, with presumed pulmonary surfactant deficiency (called neonatal equine respiratory distress syndrome) secondary to very early gestational age, induction of parturition, or cesarean section as an entity distinct from VetALI and VetARDS.[5]

Box 31.1

Veterinary Acute Lung Injury (VetALI) and Veterinary Acute Respiratory Distress Syndrome (VetARDS)

At least one each of the first four criteria must be met; criterion 5 is recommended but optional (Wilkins et al., 2007).

1. Acute onset (<72 hours) of tachypnea and labored breathing at rest
2. Exposure to a known risk factor
3. Evidence of pulmonary capillary leak without increased pulmonary capillary pressure[a] (any one or more of the following):
    a. Bilateral/diffuse infiltrates on thoracic radiographs (>1 quadrant/lobe)
    b. Bilateral dependent density gradient on computed tomography
    c. Proteinaceous fluid within the conducting airways
    d. Increased extravascular lung water
4. Evidence of inefficient gas exchange (any one or more of the following):
    a. Hypoxemia without PEEP or CPAP and known Fi_{O_2}
        i. Pa_{O_2}/Fi_{O_2} ratio
            1. <300 mm Hg VetALI (Pa_{O_2} ≤63 mm Hg at room air[b])
            2. <200 mm Hg VetARDS (Pa_{O_2} ≤42 mm Hg at room air[b])
        ii. Increased arterial-alveolar (A-a) gradient
        iii. Venous admixture (noncardiac shunt)
    b. Increased “dead-space” ventilation
5. Evidence of diffuse pulmonary inflammation
    a. Transtracheal wash/bronchoalveolar lavage cytologic neutrophilia
    b. Transtracheal wash/bronchoalveolar lavage biomarkers of inflammation
    c. Molecular imaging (positron emission tomography)

CPAP, Continuous positive airway pressure; *Fi_{O_2}*, fraction of inspired oxygen; *Pa_{O_2}*, partial arterial oxygen pressure; *PEEP*, positive end-expiratory

pressure.

[a]No evidence of cardiogenic edema (one or more of the following):
Pulmonary arterial occlusion pressure <18 mm Hg (adult horse)
No clinical or diagnostic evidence supporting left heart failure, including echocardiography

[b]FiO_2 room air: 21%.

Adapted from Wilkins PA, Otto CM, Dunkel B, et al.: Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: The Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. *J Vet Emerg Crit Care* 17:333; 2007 with permission.

TABLE 31.10

Equine Neonatal Acute Lung Injury/Respiratory Distress Syndrome (Eq NALI/NARDS)[a]

Postnatal Age	Normal PaO_2	Normal PaO_2/FiO_2 Ratio	Eq NALI	Eq NARDS
60 minutes	60.9 ± 2.7 mm Hg	>300 mm Hg	<175 mm Hg	<115 mm Hg
12 hours	73.5 ± 3.0 mm Hg	>350 mm Hg	<200 mm Hg	<140 mm Hg
24 hours	67.6 ± 4.4 mm Hg	>350 mm Hg	<200 mm Hg	<140 mm Hg
48 hours	74.9 ± 3.3 mm Hg	>350 mm Hg	<200 mm Hg	<140 mm Hg
4 days	81.2 ± 3.1 mm Hg	>400 mm Hg	<250 mm Hg	<160 mm Hg
7 days	90.0 ± 3.1 mm Hg	>430 mm Hg	<280 mm Hg	<190 mm Hg

[a]As for VetALI/VetARDS but adhering to the following age-dependent adaptation of the PaO_2/FiO_2 ratio in term foals in lateral recumbency breathing room air (FiO_2 = 0.21) based on age-dependent normal values for PaO_2 under similar conditions (Wilkins et al., 2007).

FiO_2, Fraction of inspired oxygen; *PaO_2,* partial arterial oxygen pressure.

Adapted from Wilkins PA, Otto CM, Dunkel B, et al.: Acute lung injury and acute respiratory distress syndromes in veterinary medicine: consensus definitions: The Dorothy Russell Havemeyer Working Group on ALI and ARDS in Veterinary Medicine. *J Vet Emerg Crit Care* 17:333; 2007 with permission.

ARDS arises as a complication after major infectious or noninfectious bodily injury. The triggering event can be an intrapulmonary (viral or bacterial pneumonia, smoke inhalation, near drowning, or food aspiration) or extrapulmonary (trauma, multiple transfusions, systemic inflammatory response,

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or sepsis) insult. During injury or infection, the body mounts a protective response that involves controlled activation of the inflammatory and coagulation system.[6,7] The pathophysiology of ARDS centers around dysregulation of this initially protective response. Uncontrolled pulmonary inflammation and coagulation lead to accumulation and activation of leukocytes and platelets in the lungs, altered permeability of the pulmonary endothelial and epithelial barrier, and ultimately accumulation of extravascular protein-rich edema fluid within the alveoli and airways.[7,8] Although not temporally distinct and largely overlapping, the pathophysiologic events can be divided into an initial exudative phase, a fibroproliferative phase, and if the patient survives, a resolving or fibrotic phase.[9] The exudative phase is characterized by uncontrolled released of inflammatory mediators and influx of inflammatory cells into the pulmonary tissue. Activated platelets, neutrophils, and alveolar macrophages marginate in the microcirculation and extravasate into the pulmonary tissue where they release oxidants, reactive oxygen species, proteases, and cytokines, amplifying and perpetuating inflammation and coagulation.[10] A variety of mediators, pathways, and molecular systems ultimately contribute to the breakdown of the alveolar endothelial and epithelial barrier, causing flooding of the alveoli once the edema safety factors are exhausted. The barrier tends to collapse suddenly, resulting in rapid filling of the alveoli with proteinaceous exudate, leukocytes, and red blood cells and destruction of the surfactant layer.[11] The fast onset of pulmonary edema may correspond with the clinically observed acute onset of respiratory distress in foals. The prothrombotic and anti-fibrinolytic environment favours formation of thrombi in the pulmonary microvasculature and deposition of intraalveolar fibrin-rich hyaline membranes.[12] The fibroproliferative response, which can begin within 24 hours of the onset of ARDS, is characterized by type I pneumocyte necrosis and proliferation of the more resilient type II pneumocytes in an attempt to restore the epithelial surface.[11,13] Fibroblasts invade the pulmonary interstitium and alveolar walls and deposited collagen, which can result in fibrosis and significant impairment of pulmonary mechanics and gas exchange. The extensive pulmonary pathology leads to severe hypoxemia with hypocapnia or hypercapnia caused by ventilation-perfusion (V/Q) mismatch and decreased pulmonary compliance. Alveolar edema creates areas of a low V/Q ratio (adequate perfusion but no ventilation) causing hypoxemia, whereas areas with deceased perfusion generate hypoxemia and eventually hypercapnia by increasing dead space ventilation (high V/Q ratio;

adequate ventilation with minimal perfusion).[11] The coexistence of areas with high and low V/Q ratios adjacent to normal lung tissue makes mechanical ventilation of patients with ARDS extremely challenging and predisposes the patient to ventilator-induced lung injury.

The resolution of ARDS requires repair of endothelial and epithelial barriers, reabsorption of alveolar edema, and removal of inflammatory exudate and cellular debris.[7] Transepithelial ion flux generates an osmotic gradient, allowing water absorption through aquaporin-5 channels located on type I epithelial cells. If damage to the pulmonary epithelium is minor, pulmonary edema can be cleared swiftly, pulmonary function improves rapidly, and chances of survival increase. If large areas of alveolar epithelium are destroyed, gradual re-epitheliazation by proliferation of type II cells and potentially also by recruitment of progenitor cells must occur first.[7,14] Severe damage to the epithelium corresponds to prolonged respiratory failure, slow recovery, and high mortality.[15] Recovering patients may have complete resolution of pulmonary compromise or may suffer from residual functional impairment such as muscle weakness, decreased pulmonary function, restrictive or obstructive changes, and low diffusion capacities.

Environmental and individual risk factors may predispose certain patients to the development of ARDS. Recently identified environmental factors in people include long-term ozone exposure and vitamin D deficiency.[16] Individual gene variants regulating inflammation, coagulation, and endothelial cell function and genetic polymorphism predisposing individuals to the pathogenic effects of specific bacteria and viruses are also thought to influence the development and outcome of ARDS in humans.[7]

VetALI and VetARDS, in earlier reports also referred to as acute interstitial or bronchointerstitial pneumonia, have been described in foals and weanlings up to 7 months of age and other small and large animal species, including an alpaca cria.[17-25] Extensive searches for a common pathogen were conducted until with increasing understanding of the pathophysiology it became evident that multiple infectious and noninfectious agents are capable of initiating the inflammatory response.[19-22] In foals the most common risk factor appears to be intrapulmonary injury, namely bacterial or rarely viral pneumonia.[19-22,24-26] There are no clinical reports of VetALI and VetARDS in adult horses, although descriptions in case reports and small studies suggest its occurrence. Buergelt and colleagues[19] reported respiratory distress in six adult horses, but the description better fits the

heterogenous group of interstitial pneumonias than VetALI and VetARDS. Two adult horses with respiratory distress after near drowning met the criteria for VetALI,[27,28] and two horses affected by smoke inhalation experienced fulminant pulmonary inflammation and most likely VetALI.[29] Experimentally, VetARDS has been induced by IV injection of perilla mint ketones[30,31] and was observed after experimental gram-negative sepsis.[32] However, most of the animals in the latter study were in an agonal state, making interpretation of the observed pulmonary changes difficult.[32] Further risk factors recognized in other species that may also occur in the horse include systemic inflammation, severe trauma, multiple transfusions, aspiration of stomach content, drugs, and toxins.[5] The discovery of genetic predispositions to dysregulation of inflammation and coagulation in people is intriguing, as a similar predisposition in equids could potentially explain why of many foals affected by infectious pneumonia, only very few develop VetALI and VetARDS.

■ Clinical Signs and Differential Diagnoses

Clinical signs include profound depression, fever and respiratory distress with tachycardia, tachypnea, nostril flare, and cyanotic mucous membranes. Auscultation of the lungs can reveal a variety of abnormal sounds or complete silence over nonventilated areas. Clinically it is almost impossible to differentiate foals with VetALI and VetARDS from foals with severe bacterial, chiefly advanced *R. equi*, pneumonia, particularly as the syndrome can be triggered by an underlying bacterial infection.

■ Clinical Pathology and Necropsy Findings

Laboratory findings include severe hypoxemia with hypocapnia or hypercapnia and, depending on the underlying disease process, leukocytosis or leukopenia and hyperfibrinogenemia. Abnormal coagulation parameters may be observed, and signs of disseminated intravascular coagulation were present in two foals with VetALI and VetARDS in one report.[21] Transtracheal lavage fluid demonstrates neutrophilic inflammation with or without signs of infection, depending on the underlying cause. Thoracic radiographs show a diffuse, dense bronchointerstitial pattern often coalescing to a focal or diffuse alveolar pattern with prominent air bronchograms. The initial radiographic appearance of the lungs may worsen dramatically within hours due to rapid progression of pulmonary edema. On the other hand, absorption of the alveolar fluid may result

in impressive improvement of the radiographic appearance within days.[21,22] A thoracic sonogram is useful in foals that cannot be safely transported to a radiography unit and reveals multiple coalescing comet-tail artefacts predominately in the caudodorsal lung field.

On gross pathologic examination, the affected lungs are wet and firm and fail to collapse, and airways contain variable amounts of pink, foamy liquid. Histologically, necrosis of alveolar and terminal bronchial epithelium is observed with extensive filling of the alveolar spaces with neutrophils, macrophages, hemorrhage, protein-rich edema fluid or hyaline membranes. Occasionally microthrombi can be detected in interstitial capillaries. In more chronic cases, diffuse proliferation of cuboidal pneumocytes and fibroblasts and beginning fibrosis may be present.[19-22]

■ Diagnosis

The diagnosis can be established if the criteria outlined in Box 31.1 and, depending on the age, Table 31.10 are met, cardiac disease is absent, and the extent of the respiratory distress cannot be attributed solely to a primary disease process (e.g., almost complete destruction of the pulmonary parenchyma by a primary disease process). CT has been described in heathy foals and will allow more detailed assessment of lung pathology.[33,34] However, risks and benefits of the procedure need to be carefully assessed in these precarious patients. Presence of bacterial or viral pneumonia does not rule out concurrent VetALI or VetARDS.

■ Treatment and Prognosis

A recent reduction in mortality in human ARDS has largely been attributed to more widespread use of lung-protective ventilation with lower tidal volumes (6 mL/kg) and airway pressures and conservative fluid therapy.[35] Antiinflammatory, antioxidant, anticoagulant, and surfactant therapy and treatment to enhance alveolar edema removal (aerosolized or intravenous β-adrenergic agonists such as salmeterol, terbutaline, or epinephrine to stimulate active transepithelial ion transport) have largely failed to improve survival.[7] A recent meta-analysis showed promise for anti-platelet drugs, including clopidogrel, but whether this will be confirmed in future studies remains to be seen.[36] However, considering that, in contrast to human medicine, most equine patients die as a direct result of respiratory failure, some of those therapeutic

options may still benefit the equine patient. Because mechanical ventilation is, with few exceptions,[37] feasible only in neonates, the most important treatment remains intranasal insufflation of humidified oxygen via unilateral or bilateral intranasal cannulas. Large-bore tubing systems minimize the resistance to airflow, and Fi_{O_2} as high as 70% and 75% has been measured at the carina in adult horses and foals, respectively, using bilateral flow rates of 15 L/min (10 L/min in foals; combined 30 L/min in adults or 20 L/min in foals).[38,39] Alternatively, use of intratracheal oxygen insufflation has been described, achieving results similar to high bilateral intranasal flow rates.[40] Administration of methylprednisolone at 1 to 2 mg/kg/day is much debated but still frequently used in acute cases of human ARDS for up to 2 weeks, followed by a gradual decrease of the dose.[16] Considering that ventilation is rarely an option and that in two reports all but two foals surviving ARDS received corticosteroids, anecdotal evidence is in favour of steroid administration (IV prednisolone sodium succinate or methylprednisolone at 1 to 2 mg/kg/day divided in 2 to 4 doses). Antimicrobial treatment, if required, should be directed against the underlying disease process. Bronchoconstriction is not a prominent feature of ARDS, and therefore bronchodilators are most likely of limited use. Care should be taken when administering bronchodilators, as they can induce sudden worsening of V/Q mismatching and can lead to acute decompensation of the severely hypoxic patient. Judicious IV fluid therapy may be necessary in dehydrated patients, but overhydration or rapid changes in circulating blood volume should be avoided, as capillary hydrostatic pressure is the main determinant of pulmonary edema formation when endothelial and epithelial permeability is increased. On the other hand, a suboptimal hydration status decreases cardiac output and worsens oxygen delivery to the peripheral tissue. Measurement of central venous pressure may aid in determining the patient's hydration status. If foals are too depressed to nurse or eat, nutritional support is essential.

Based on the limited information available, the prognosis for survival and future athletic performance is guarded, with survival rates ranging from 60% to 69% in two clinical reports.[21,22] It is difficult to extrapolate long-term outcomes of pulmonary function from human patients due to the extensive use of mechanical ventilation with associated injury and the frequent presence of preexisting morbidities such as smoking.[41] Experimental induction of ARDS in horses did not result in any lasting histologic changes or fibrosis despite severe clinical signs.[30] The few long-term reports of equine survivors have so far

suggested little noticeable lasting respiratory compromise, and successful careers as racehorses have been reported even in severely affected animals.[22] More information is clearly needed to determine the long-term effects of severe pulmonary injury in horses.

Interstitial Pneumonia and Endogenous and Toxic Conditions

Pamela A. Wilkins

Interstitial pneumonia is an uncommon cause of acute or chronic disorders of the lower respiratory tract of horses.[1-8] However, because of the severity of the process, it becomes important to recognize and definitively diagnose this entity as early as possible in its clinical course. The term *interstitial pneumonia* defines a number of diseases that are acute to chronic and progress to pulmonary fibrosis. The course is insidious and morphologically characterized by alveolar structural derangements that lead to loss of functional gas exchange units of the lung and altered mechanical properties of the lung, characterizing the pneumonia as a restrictive lung problem.

■ Etiology

Multiple agents have been implicated in the genesis of interstitial pneumonia in animals, but fewer than 20 have been confirmed in horses (Box 31.2). Chief among these are infectious agents and ingested toxins. Frequently the etiologic agent cannot be identified due to the insidious nature of the process, and the final diagnosis is idiopathic interstitial pneumonia. The lung responds in a rather stereotypical manner to injury, and our limited ability to identify infectious, toxic, and immunologic causes frequently hinders our current ability to make an accurate identification of a specific etiology. All efforts should be made to identify an etiologic agent early in the course of the disease, but the practitioner needs to be aware that treatment frequently will be nonspecific and supportive.

Box 31.2

Causes of Interstitial Pneumonia in Horses

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Acute

- Infections (systemic viral, bacterial, parasitic)
- Inhaled chemicals
  - Oxygen (FiO_2 >50%)
  - Smoke
- Ingested toxins or precursors
  - Perilla mint *(Perilla frutescens)*, Crofton weed *(Eupatorium adenophorum)*, *Crotalaria* spp., *Senecio* spp.
- Adverse drug reactions
  - Uncertain
- Hypersensitivity
  - Acute hypersensitivity pneumonitis
- Endogenous metabolic or toxic conditions
  - Shock—particularly endotoxic (acute respiratory distress syndrome, or ARDS)
  - Disseminated intravascular coagulation (DIC)
  - Uremia
- Idiopathic or cryptogenic

Chronic

- Infections (systemic viral, bacterial, parasitic)
- Inhaled inorganic dust (pneumonoconioses)
  - Silicosis
- Hypersensitivity
  - Hypersensitivity pneumonitis
- Ingested toxins or precursors
  - Perilla mint *(P. frutescens)*, Crofton weed *(E. adenophorum)*, *Crotalaria* spp., *Senecio* spp.
- Collagen-vascular disorders
  - Uncertain
- Idiopathic or cryptogenic

Infectious Agents.

Infectious causes of interstitial pneumonia in horses and foals include viral,

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bacterial, parasitic, protozoal, and fungal agents. Typically the pneumonia is acute and severe, characterized by severe damage to the lung parenchyma (alveolar region).

Viral agents are frequently implicated or suspected but rarely identified by the usual serologic, histopathologic, and virus isolation methods. The advent of more sensitive and specific techniques, such as in situ PCR and monoclonal antibody immunohistochemistry (IHC), may partially resolve the current diagnostic challenge. Most recently, a novel gamma equine herpesvirus, equine herpesvirus 5 (EHV-5), has been found to be associated with a nodular form of interstitial pneumonia of horses characterized by pulmonary interstitial fibrosis, suggesting that these rather unusual cases may have an underlying infectious etiology.[9-11] This disease has been called equine multinodular pulmonary fibrosis (EMPF) by the authors describing the pathology of the disease (Fig. 31.29). Horses affected generally have a history of fever, cough, and weight loss accompanied by exercise intolerance and finally respiratory distress. They can present as acutely affected animals or as having a more chronic, progressive problem. Typical radiographs reveal multiple discrete to coalescing nodular densities overlying a diffuse interstitial pattern. Histologic appearance is diagnostic of this disease (Fig. 31.30). EHV-5 has been identified in both BAL fluids and lung biopsy samples from affected patients by both PCR and IHC. Influenza infection resulting in severe, fatal interstitial pneumonia in unvaccinated or naive horses and foals has been described in single case reports and as outbreaks.[12-14] There is a single report of a fatal pneumonia in a young horse secondary to EHV-1 infection.[15] Both adenovirus and equine arteritis virus have been described as causes of severe bronchointerstitial or interstitial pneumonia in foals and adult horses.[16-19]

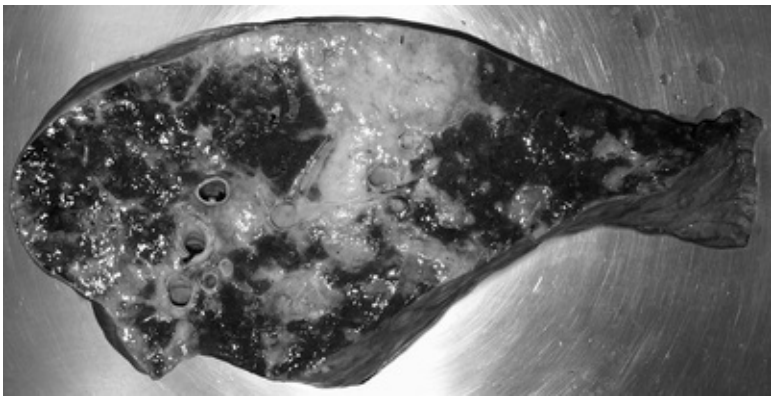


FIG. 31.29 Cut section of lung from a horse with equine multinodular pulmonary fibrosis (EMPF). Note the large areas of fibrous tissue within the pulmonary parenchyma. (Courtesy Dr. Fabio Del Piero, Louisiana State University, Baton Rouge, La.)

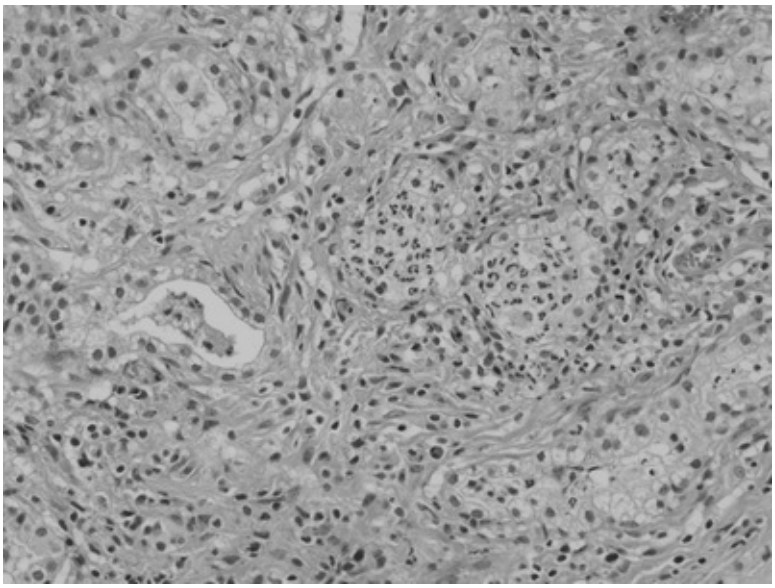


FIG. 31.30 Postmortem histopathology specimen from a horse with severe equine multinodular pulmonary fibrosis (EMPF). This is the histologic appearance of one of the fibrotic nodules. The alveoli are constricted within dense neoformed fibrotic tissue. Alveoli have an abnormal cuboidal epithelium (type 2 pneumocytes), and the lumen contains macrophages, sloughed epithelial cells, and neutrophils. Denser and diffuse fibrotic areas are present. (Courtesy Dr. Fabio Del Piero, Louisiana State University, Baton Rouge, La.)

In some horses with bronchointerstitial pneumonia of unknown cause, bacterial agents have been isolated from the lung. The usual distribution of

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bacterial bronchopneumonia in the horse is cranioventral, frequently associated with transportation, whereas the distribution in interstitial pneumonia is diffuse. In the latter cases the bacteria may be either opportunistic or primary pathogens and may not represent the primary causative agent.[20,21] An exception is *R. equi* pneumonia of foals, which can cause ARDS in older foals. *R. equi* has been cultured from foals with severe, acute bronchointerstitial pneumonia with a diffuse pulmonary distribution.[22] Interstitial pneumonia associated with *P. carinii* has been described in the foal, and *Mycoplasma* spp. have been isolated from the respiratory tract of adult horses.[23-25] The significance of the *Mycoplasma* isolates remains a matter of debate.[25] *P. carinii* pneumonia is thought to occur primarily in immunocompromised foals as a complication of some other serious disease, such as infectious pneumonia or SCID. It is characterized by a plasmacytic, lymphocytic interstitial pneumonia with flooding of alveoli with foamy acidophilic material.

Parasitic pneumonia, an uncommon cause of chronic bronchointerstitial pneumonia, usually occurs in young foals secondary to migration of *Parascaris equorum* larvae through the pulmonary parenchyma.[26]

Ingested Chemicals.

Ingested chemicals rank second only to infectious agents as potential causes of interstitial pneumonia in horses. Ingestion of pyrrolizidine alkaloids from a variety of plants (mostly genera *Crotalaria, Trichodesma,* and *Senecio*) can cause interstitial pneumonia in horses.[27] This toxicity is associated with production of a toxic metabolite activated in the liver that then circulates to the lung. The toxic alkylating agents damage capillary endothelial cells, although the amount of alkyloid required to damage the lung is generally less than that required for hepatotoxicity. Crofton weed *(Eupatorium adenophorum),* a poisonous plant found primarily in Australia and Hawaii, produces interstitial pneumonia in horses.[28] Toxicity is associated with ingestion of the flowering plant, but the nature of the toxin is not known. Perilla ketone, derived from the plant *Perilla fructans,* produces acute respiratory distress within 1 week of ingestion in ponies.[29] The lesions include diffuse alveolitis and Type II pneumocyte proliferation with sparing of the bronchioles. Toxicity depends on additional metabolism of the 3-substituted furan by the mixed function oxidase system, which occurs directly in the lungs of the horse.

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Inhaled Chemicals.

Direct pulmonary injury by inhaled chemicals is an uncommon cause of interstitial pneumonia in horses. In humans this type of pneumonia is primarily related to occupational exposure. Smoke inhalation causes acute, diffuse interstitial pneumonia in horses, frequently followed within a few days by opportunistic bacterial pneumonia.[30] Oxygen toxicity can theoretically produce interstitial pneumonia and alveolar Type II cell proliferation. This problem is more likely to be seen in neonatal foals mechanically ventilated with increased levels of oxygen (Fi_{O_2} >50%) for several days, although this may in fact be a form of ventilator-associated lung injury (VALI) related to mechanical stretch of the airspaces. Damage is thought to be due to production of reactive oxygen metabolites, which attack a lung that may already have been injured by barotrauma, resulting from a ventilator-driven increase in airway pressure. Agrichemicals or herbicides, such as paraquat, may cause acute interstitial pneumonia (AIP) in horses and should be considered in horses with a history of possible exposure.[31] Silicosis is a specific chronic granulomatous pneumonia of horses associated with inhalation of silicon dioxide crystals.[32] This syndrome has been described in horses originating from the Carmel Valley region of California. The inhaled particles are ingested by alveolar macrophages and result in lysis of the macrophage, chronic alveolitis, and fibrosis. Multiple granulomas are present, and submicron intracytoplasmic crystalline particles can be identified in macrophages.

Hypersensitivity Reactions.

In the most specific sense, hypersensitivity pneumonitis refers to pulmonary disease caused by inhalation of organic antigens. Lymphocytic, plasmacytic bronchitis and bronchiolitis, combined with lymphocytic interstitial pneumonia, characterize the disease in the horse lung. Granuloma formation and fibrosis can be observed. Chicken dust and fungi have been implicated as a cause of severe, chronic bronchointerstitial pneumonia, but the syndrome itself is quite rare.

Endogenous Metabolic and Toxic Conditions.

A variety of conditions cause acute pulmonary injury with inflammatory edema or severe alveolar wall damage and serofibrinous exudation similar to that described for AIP. Acute uremia, shock, burns, and trauma can produce an acute pulmonary injury called acute lung injury (ALI) or acute respiratory distress

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syndrome (ARDS), depending on severity. Although endotoxin does not directly injure the lung, endotoxemia in the horse initiates inflammatory and metabolic cascades that can lead to pulmonary injury. Activation of these pathways produces vasoactive and chemoattractant molecules that increase vascular permeability, activate complement, produce proinflammatory cytokines, and release neutrophil enzymes that can adversely affect the lungs of horses. Horses, as a species, are quite sensitive to the negative effects of endotoxemia, and their lungs are particularly sensitive, perhaps due to the presence of intravascular macrophages, which further amplify the inflammatory cascade. Both ALI and ARDS have been defined for veterinary patients but require updating.[33]

■ Pathophysiology

Interstitial pneumonia progresses through four phases.[7,11,34] During the first phase, the initial insult causes parenchymal injury and alveolitis. This is followed by a proliferative phase characterized by cellular and parenchymal alterations in tissues of the lung. Chronic cases progress to the development of interstitial fibrosis, and the final stage results in end-stage irreparable fibrosis of the lung.

The structural changes that occur in the lung reduce the number of functional alveoli, adversely affecting ventilatory function of the lung and altering V/Q relationships. There is reduced lung compliance associated with the loss of distensible alveoli, presence of pulmonary edema, and fibrosis. Total and vital lung capacity are decreased in association with the loss of functional gas exchange units and reduced lung compliance. The work of breathing is increased, resulting in exercise intolerance and difficulty breathing. Pulmonary hypertension and cor pulmonale may present as complications of interstitial pneumonia and fibrosis. Although the origin of pulmonary hypertension is unclear, hypoxic vasconstriction and generation of vasoactive compounds (such as endothelin-1) that alter pulmonary vascular resistance acutely, and vessel anatomy chronically, may play a role.

■ Clinical Signs

Horses affected with interstitial pneumonia frequently present with fever, cough, weight loss, nasal discharge, exercise intolerance, severe dyspnea, cyanosis, and a restrictive breathing pattern. A “heave line” may be present; nostril flare and an anxious expression are usual. The history can be acute or chronic. Although

affected foals are frequently depressed and anorectic, adults may be bright and alert with a variable appetite. The disease proceeds toward death in many cases, with progressive respiratory compromise, although some may also slowly improve with time. More than one foal at a farm may be affected.

■ Diagnosis

In older horses, the primary differential diagnosis of RAO may be excluded by the leukocytosis and hyperfibrinogenemia that commonly occurs in horses with interstitial pneumonia and fibrosis but does not occur in horses with heaves. However, these abnormal features are common in horses with infectious bronchopneumonia, and thoracic radiography is of paramount importance in establishing a definitive diagnosis. Typically, thoracic radiographs reveal extensive interstitial and bronchointerstitial pulmonary patterns (Fig. 31.31). Nodular infiltrates, either large or miliary, may be present but are always diffusely distributed.

Culture of transtracheal or BAL aspirates often yields no significant growth of viral, bacterial, or fungal pathogens. Cytologic evaluation of tracheal or BAL fluid shows increased numbers of neutrophils and macrophages. If *P. carinii* is involved, BAL fluid may reveal trophozoites or intracystic bodies with special stains, such as toluidine blue or methenamine silver. Using PCR, EHV-5 has been found in BAL fluid from horses with EMPF.[9] EHV-5 PCR has been found to be closely associated with EMPF in BAL fluid or a combination of whole blood and nasal secretions.[35]

Histologic examination of a transthoracic lung biopsy specimen is the definitive diagnostic test for chronic interstitial pneumonia and fibrosis and for EMPF (see Fig. 31.30) . Care must be taken to ensure that the biopsy is obtained from a representative area, and ultrasound guidance has been useful in the hands of the author. Clinically important complications from this technique are uncommon but can occur. Biopsy can both define the causative agent and confirm the clinical diagnosis in EMPF when evaluated for EHV-5.

Additional diagnostics could include arterial blood gas analysis, abdominocentesis, and thoracocentesis to rule out metastatic neoplastic disease; pulmonary function testing; viral isolation; serologic testing for antibody to fungi and chicken serum if hypersensitivity pneumonitis is suspected; and immunohistochemical evaluation of lung tissue for suspected infectious agents. A complete cardiac evaluation should also be conducted, as pulmonary

hypertension and cor pulmonale are not uncommon sequelae.

■ Treatment

Treatment of these cases is often unrewarding. Therapeutic goals are (1) treatment of any underlying or secondary infection; (2) suppression of inflammation; (3) maintenance of tissue oxygen delivery within appropriate limits; (4) relief of any associated bronchoconstriction; and (5) prevention or treatment of complications. Environmental management, with appropriate temperature and humidity control and good ventilation, is beneficial.

Parenteral corticosteroid therapy is the mainstay of treatment, with early and aggressive therapy providing the best long-term outcome, particularly in foals. In one report of 23 foals affected with acute bronchointerstitial pneumonia, 9 of 10 treated with corticosteroids survived, whereas none of those not receiving steroid treatment lived.[4] Foals with a diagnosis of ARDS have the best prognosis when treated with corticosteroids and antimicrobial therapies as indicated by diagnostics.[36]

Broad-spectrum antimicrobial treatment should be instituted initially, particularly in foals, as described for the treatment of infectious bronchopneumonia. The choice of antimicrobial and duration of therapy should be dictated finally by the culture and sensitivity results from the transtracheal aspirate and by the patient's clinical course. Anecdotally, horses with EMPF have responded to treatment with acyclovir or other antiviral agents and corticosteroids. The course of therapy is generally prolonged, 6 to 12 weeks; clinical and radiographic improvement has been noted in a few cases to date.

Foals, in particular, and adults with severe respiratory distress may benefit from nasal insufflation of humidified oxygen, with flow rates of 5 to 15 L/min for foals and 15 L/min for adults.[37] If necessary, as determined by persistent hypoxemia in the face of intranasal insufflation at the rates given, a second nasal canula can be placed in the opposite nostril to increase the Fi_{O_2}. Care must be taken to avoid obstruction of the nasal passages. Alternatively, intratracheal or transtracheal insufflation can be considered to further increase Fi_{O_2} and improve oxygenation (see Fig. 31.31).[38]

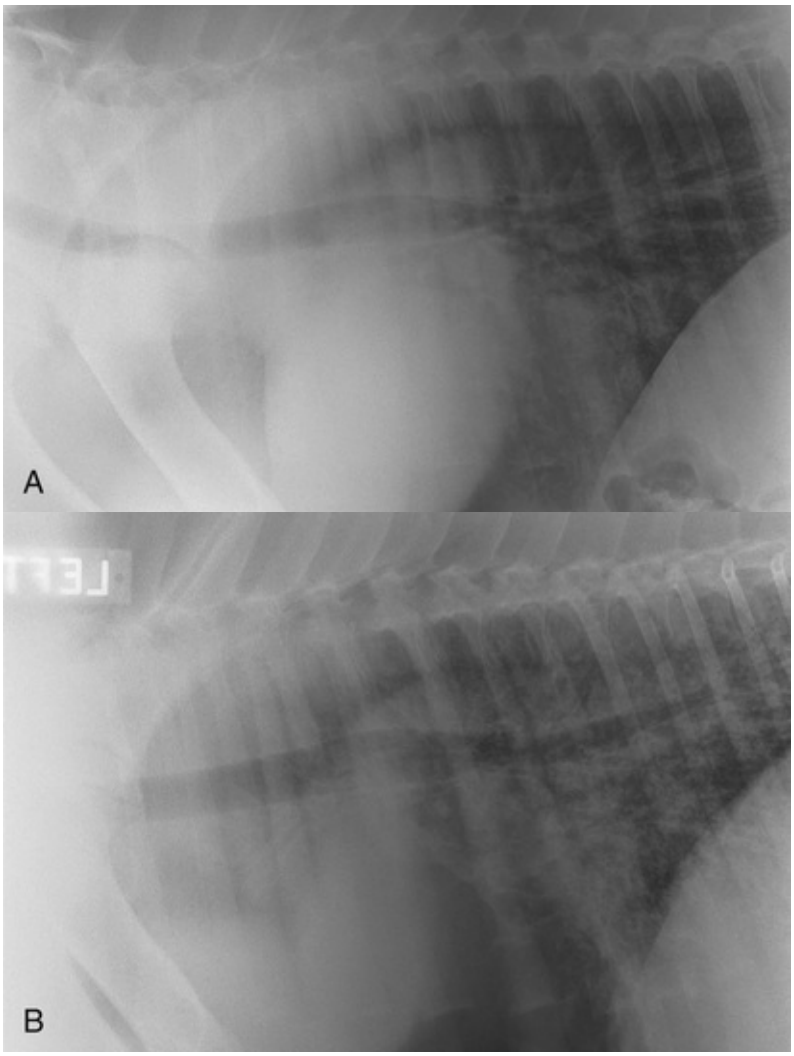


FIG. 31.31 **A,** Midthoracic/caudal dorsal thoracic radiograph of a foal younger than 2 months that presented with *Pneumocystis* spp. pneumonia and acute respiratory distress syndrome (ARDS). Immune function testing was within normal limits. Note the predominant interstitial pattern with patchy alveolar component. **B,** Similar radiographic view of the foal in A following 4 weeks of treatment with antimicrobials and corticosteroids. This foal was also treated with inhaled antimicrobials, inhaled corticosteroids, and intranasal oxygen insufflation over the first 2 weeks of treatment. The foal was significantly improved clinically and radiographically.

Systemic bronchodilator therapy may or may not be indicated in these cases. If used, bronchodilators may worsen V/Q inequalities. Thus bronchodilator therapy should be accompanied by supplemental oxygen, and the effects should be monitored with serial blood gas measurements and discontinued if hypoxemia worsens. Nebulized or aerosolized bronchodilator therapy may be more judicious, and beneficial effects are evident in some foals with respiratory

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distress. Aminophylline and theophylline should not be used due to their narrow therapeutic range. Furosemide may be appropriate for its bronchodilator effect and its effect on reducing pulmonary artery pressure, particularly if cor pulmonale develops.

■ Prognosis

The prognosis of interstitial pneumonia in horses is generally poor to guarded. Affected foals, when treated early and aggressively with corticosteroid and antimicrobial therapy, have the best outlook for life. The disease is usually progressive in adults and eventually results in the demise of the horse, although the occasional horse recovers sufficiently to return to previous performance levels. A fair number of adult horses, with continuous intense management, will live for a period but be severely compromised,. Exceptions to the poor prognosis may be seen in cases of *P. carinii* and parasitic pneumonia in foals if they are treated early and aggressively and, possibly, also in cases of idiopathic interstitial pneumonia/EMPF in adult horses that are treated early with corticosteroids and antivirals. A trial of treatment for peracute interstitial disease for 48 hours is warranted, and chronic interstitial pneumonia should be treated for a minimum of 6 weeks before discarding the possibility of recovery.

Equine Respiratory Viruses

Gabriele A. Landolt

Viral respiratory infections in horses are major causes of respiratory disease resulting in impaired health, poor performance, and financial losses. Although vaccines are available for many of the etiologic agents, viral respiratory disease has remained among the most commonly encountered equine health concerns worldwide.

Infection with equine respiratory viruses can lead to serious respiratory illness with potentially fatal consequences, yet the clinical significance of some of the viruses that have been detected in equine respiratory tract secretions remains largely unknown (e.g., EHV-2, EHV-5, equine coronavirus).[1] The severity of equine viral respiratory disease depends on the agent, virulence of the circulating virus, infectious dose, management and environmental conditions, and degree of immunity of the individual animal. In a group of susceptible horses, equine viral respiratory disease is often characterized by the rapid spread of an acute, febrile respiratory disease that may be accompanied by a cough and serous nasal

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discharge. Therefore a presumptive diagnosis of viral respiratory disease can often be made based on history and clinical signs. However, to confirm and differentiate among the potential etiologic agents, laboratory diagnosis is required.

■ Diagnosis of Equine Respiratory Viruses

The basic approaches for the laboratory diagnosis of equine viral respiratory disease are the isolation of the etiologic agent (virus isolation); demonstration of the virion, the virus genome, or the viral products in clinical specimens (detection of virus particles by electron microscopy; detection of viral antigens by immunofluorescence, ELISA, or immunoperoxidase; detection of the viral genome); and the detection of virus-specific antibodies (serology). Because each of these methods has merits as well as disadvantages (e.g., lack of sensitivity, long turnaround time, high costs), it may be necessary to combine several of them to identify the etiologic agent accurately and rapidly. The World Organisation for Animal Health (OIE; http://www.oie.int) publishes the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals*, which provides an in-depth review of current diagnostic testing strategies.

Virus Isolation.

Virus isolation from clinical samples is crucial for epidemiologic investigation and for vaccine production and generally is carried out in cell culture. The notable exception is equine influenza virus, for which embryonated chicken eggs have remained the culture system of choice. Because virus shedding in secretions of the respiratory tract is typically greatest within the first few days after infection, the best results for virus isolation are often achieved by culturing nasal or nasopharyngeal swab samples collected in the first 24 to 48 hours after onset of clinical disease. Because the duration of nasal virus shedding is often brief in partially immune animals, it may prove useful to sample immunologically less protected individuals in a group (e.g., younger horses, poorly vaccinated or unvaccinated animals) to increase the likelihood of demonstrating infectious virus. Nasopharyngeal or nasal swab samples are best collected using polyester-tipped swabs instead of cotton swabs because certain viruses (e.g., influenza A virus) have been found to adhere to the cotton fibers. Preferably, the swab samples should be placed in a small amount of sterile viral transport medium and kept on ice.

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Antigen Detection.

The most important advantages of diagnostic tests aimed at the detection of viral antigen over traditional virus isolation are the faster turnaround time as well as the ability to detect virions that have lost their infectivity. Immunofluorescence (fluorescent antibody [FA] test) is based on the detection of virus-infected cells using virus-specific fluorochrome-labeled antibodies. The technique is used to detect viral antigen in a broad range of clinical samples (e.g., frozen sections of tissues, tissue imprints, cells obtained from nasal scrapings or tracheal washes) and has been shown to be highly sensitive. A number of antigen-capture ELISA-based assays have been developed for the detection of equine respiratory viruses.[2-6] Frequently, a solid-phase system is used for virus detection. Specific antibody is first adsorbed to the surface of a microtiter plate, and the sample containing the suspected virus is then added. If the virus is present, it binds to the adsorbed antibody. After washing, specific enzyme-labeled antibodies are added. Detection of virus in the sample is achieved by addition of the enzyme substrate, which results in a color reaction. Commercially available ELISA-based test kits (e.g., Flu OIA® assay [Biostar, Boulder, Colo.]; Directigen Flu-A assay® [Becton Dickinson Microbiology Systems, Cockeysville, Md.]) have been validated for the rapid, stall-side detection of equine influenza virus. Many investigators found these commercial diagnostic kits to be highly specific and rapid, and their sensitivity approaches that of egg-based virus isolation.[7-11] Since the discovery of PCR, the technique has found wide application in diagnostic laboratories. By choosing appropriate oligonucleotide primers, a selected region of the viral genome can be amplified. PCR-based assays are extremely sensitive and theoretically can detect a single copy of the target nucleic acid in a sample.[12-14] Due to the assay's high sensitivity, the greatest challenge facing the diagnostic application of PCR is the production of false-positive results. Nevertheless, PCR-based techniques offer a more sensitive tool for the diagnosis of equine respiratory viruses than conventional techniques such as culture or immunoassays. To increase the diagnostic capacity of PCR, multiplex PCR assays have been developed. By including more than one pair of primers in the reaction mixture, these assays are designed to simultaneously detect a panel of respiratory pathogens. RT-PCR–based assays are widely used for the detection and quantification of equine respiratory pathogens.[15-17] By using a target-specific fluorescent probe, RT-PCR–based assays eliminate the need to distinguish the target by PCR fragment size on electrophoresis or hybridization

with probes post PCR. The advantages of RT-PCR include high specificity, sensitivity, and a rapid turnaround time.

Antibody Detection.

Detection of virus-specific antibodies has been and continues to be a key tool in the diagnosis of equine viral respiratory disease. Detection of specific antibody can provide support that an animal has been exposed to a given antigen. Although this is often used as circumstantial evidence of infectious disease, a diagnosis of active infection requires the demonstration of at least a fourfold increase in antibody titers (seroconversion) in samples collected during acute infection and during convalescence. Therefore serology typically provides only retrospective information. Yet as most serologic assays are fairly easy to perform and cost-effective and because large numbers of samples can be collected and tested simultaneously, serologic testing is particularly useful for large-scale population surveillance. Commonly used techniques for antibody detection include ELISA-based assays, virus neutralization tests, single radial hemolysis, complement fixation tests, and hemagglutination inhibition assays. Due to the inherent variability of immunoassays, paired samples always should be run by the same laboratory. Lastly, it is important to recognize that antibody is not always detected in the presence of active infection. The most common reason for a negative result despite infection is that insufficient time has passed between infection and measurement of an antibody response. Alternatively, immunocompromised horses may fail to produce a detectable antibody response despite active infection.

■ Treatment

The treatment of horses suffering from viral respiratory disease is primarily symptomatic. It is important to ensure that sick animals are kept in a clean, well-ventilated, and stress-free environment. Morbidity caused by pyrexia and myalgia may be reduced by administering NSAIDs. It is important to monitor affected horses for development of complications such as pneumonia and myocarditis, and animals exhibiting signs of respiratory disease beyond 10 days should be reevaluated to rule out secondary bacterial infections.

Antiviral drugs, such as amantadine, rimantadine, oseltamivir, and the chain-terminating nucleoside analogs (e.g., acyclovir, valacyclovir, cidofovir), have been evaluated for prophylaxis and treatment of horses during outbreaks of equine influenza and EHV-1, respectively. In addition, there are several

published reports describing the use of acyclovir in horses diagnosed with EMPF.[18,19]

Clinical trials with the influenza virus M2 ion channel blockers amantadine and rimantadine have shown that both drugs appear to be equally effective in reducing the severity and duration of clinical illness.[20,21] In addition, oral administration of rimantadine (30 mg/kg q12h) was shown to reduce the virus load in nasal secretion, although the duration of nasal virus shedding was similar to that in the untreated controls.[20] However, the therapeutic and prophylactic benefits of M2 ion channel blocker antiviral therapy during outbreaks of equine influenza may be limited due to the potential for the rapid development of drug resistance. In vivo and in vitro studies have demonstrated that drug-resistant influenza virus mutants can develop as early as 1 day after start of treatment.[22] Subsequent isolation of the drug-resistant virus from susceptible contacts showing signs of clinical disease indicates that acquisition of drug resistance is not associated with attenuation of the virus.[23,24] Treatment of horses with amantadine has also been associated with adverse effects and poor oral bioavailablity.[25] Oseltamivir, a neuraminidase inhibitor with demonstrated antiviral activity against equine influenza in vitro, was also found to reduce the magnitude of nasal virus shedding and severity of clinical signs in horses following experimental inoculation.[26] In addition, oseltamivir administration reduced the counts of *S. equi* subsp. *zooepidemicus* in bronchoalveolar fluid samples collected 7 days after influenza infection compared to the untreated controls.[26] Despite these findings, the use of antivirals during an equine influenza outbreak should be carefully deliberated, as their use can result in the development of antiviral resistance among influenza A viruses.[27-29] Hence the indiscriminate use of these drugs can possibly reduce the effectiveness of treatment during an outbreak.

Acyclovir, valacyclovir, ganciclovir, valganciclovir, and other chain-terminating nucleoside analogs have been shown to be efficacious against various strains of abortigenic and neuropathogenic EHV-1 viruses in vitro.[30-33] Despite the fact that the oral bioavailability of acyclovir in horses is low,[34] anecdotal reports suggest a potential benefit of acyclovir administration (10 mg/kg PO five times daily) in horses with clinical signs of EHV-1 infection (e.g., herpes myeloencephalopathy and neonatal infection).[35-37] Studies examining the effectiveness of oral valacyclovir, a prodrug of acyclovir with enhanced oral absorption, in the treatment of horses infected with EHV-1 have demonstrated

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controversial results. Although administration of valacyclovir (27 mg/kg q8h followed by 18 mg/kg q12h) to aged mares either prior to experimental EHV-1 inoculation or at the onset of fever reduced the severity of clinical signs, virus shedding, and viremia in one study,[38] another study found no effect on clinical signs, nasal virus shedding, or viremia in ponies treated (40 mg/kg q8h) compared to the untreated control ponies.[39]

Equine Influenza Virus

Equine influenza is the most frequently diagnosed cause of viral respiratory disease of the horse.[40,41] It is a highly infectious disease that affects horses, donkeys, mules, and zebras. Outbreaks of a disease resembling influenza have been reported as early as 1751; however, the etiologic agent was not isolated until 1956.[42,43]

■ Etiology

Equine influenza viruses are members of the family *Orthomyxoviridae,* which contains enveloped viruses with segmented, single-stranded, negative-sense RNA genomes.[44] The *Orthomyxoviridae* comprise the following genera: influenza A, B, and C viruses; thogotoviruses; and isaviruses.[44] Influenza D virus was isolated from pigs and cattle,[45,46] and serologic evidence for influenza D virus infection in humans and horses has recently been established.[47,48] Despite this, the clinical significance of this finding is currently unknown.

Equine influenza viruses are members of influenza A viruses. In contrast to influenza B and C viruses, which appear to have a fairly narrow host range, influenza A viruses can infect a wide variety of species (e.g., horses, humans, wild and domestic birds, pigs, sea mammals, dogs, and cats). It has long been recognized that influenza A viruses exhibit partial restriction of their host range,[43] indicating that viruses from one host species occasionally can transmit to infect another host. Although horses have often been regarded as isolated or "dead-end" hosts for influenza,[43] events of recent years clearly indicate that the species barrier for viruses jumping either to or from horses is not absolute. For example, the severe influenza epidemic in horses occurring in 1989 in the Jilin and Heilongjiang provinces in the northeast of the People's Republic of China was caused by a virus with avian-like genetic features, suggesting that the virus

had spread directly to horses from birds.[49] Another, more recent example is the transmission of an equine-lineage H3N8 virus to dogs in the United States.[50]

Although the viral and host factors that determine the host range of influenza viruses and the mechanisms by which species barriers are overcome are not completely understood, a large body of research highlights the importance of the viral hemagglutinin (HA) glycoprotein in determining host specificity.[43,51,52] The HA serves as the viral receptor-binding protein and is embedded, along with the neuraminidase (NA) and the ion channel M2 protein, in a host cell–derived lipid envelope. Mediated by binding of the HA to sialic acid residues on the host cells, the virion envelope and the host cell membrane fuse. This interaction subsequently promotes the release of the viral genome into the cytoplasm of the host cell. The NA is responsible for the cleavage of the α-ketosidic linkage between a sialic acid molecule and an adjacent sugar D-galactose or D-galactosamine. Biologically, the NA facilitates the mobility of the influenza virus virion by assisting in the release of the budding virus particle from the host cells.[53,54] Both HA and NA are major surface antigens of the influenza virus virion. Partly due to the host immune pressure, these proteins can undergo substantial antigenic variation (antigenic drift), which allows the mutant viruses to escape neutralizing antibodies.

Based on antigenic properties of the HA and NA, influenza A viruses are divided into subtypes. To date, eighteen HA subtypes (H1 to H18) and eleven NA subtypes (N1 to N11) have been described.[55,56] With the exception of two HA and NA subtypes (H17, H18, N10, N11) that have been isolated only from bats, all other subtypes have been isolated from wild waterfowl.[55,57-59] In contrast, only a limited number of subtypes have been associated with infection of mammals. In humans, only viruses of H1, H2, H3, N1, and N2 subtypes have circulated widely in the population,[43,60] and only H1, H3, N1, and N2 subtypes have been consistently isolated from pigs.[61-63] In horses, two influenza subtypes have been described: H7N7 (A/equine/1) and H3N8 (A/equine/2).[42,64,65] Although there are a few reports of horses with serologic evidence of H7N7 exposure,[42,66,67] the H7N7 viruses have not been isolated from horses since the late 1970s[11,57,68] and are considered to be extinct. In contrast, despite intensive vaccination programs, equine H3N8 viruses continue to circulate in large parts of the world. Since the 1980s, a number of severe, widespread influenza outbreaks in horses have occurred in South Africa,[69] India,[70] the People's

Republic of China,[49,71] the United Kingdom,[72] and most recently South America.[73,74] In 2007 an equine influenza outbreak occurred for the first time in Australia, a country previously considered to be free of the disease.[75] The outbreak was caused by an equine-lineage H3N8 virus that was thought to have been introduced by importation of influenza-infected horses from Japan.[75,76] Stringent control measures, consisting of movement restrictions and vaccinations, allowed for the eradication of the virus from the Australian horse population, and Australia regained its equine influenza–free status in December 2008.[77,78]

Since the early to mid-1980s, the equine H3N8 viruses have diverged into two distinct evolutionary lineages: Eurasian and American. Although the circulation of both lineages initially centered largely on their geographic origin,[79] introduction and apparent maintenance of American lineage viruses in horses in Europe initially resulted in the co-circulation of both lineages in Europe. In contrast, only a few reports support sporadic infection of horses in North America with viruses originating in Europe.[80-82] Continued genetic divergence of the American lineage viruses resulted in the formation of three antigenically distinct American-like sublineages (a South American lineage, a Kentucky lineage, and a Florida lineage).[82] Since the early 2000s the Florida sublineage has further evolved into two antigenically distinct groups, referred to as Florida sublineage clades 1 and 2. Whereas clade 1 viruses primarily circulate in North America, clade 2 viruses have mainly been identified in Europe and parts of Asia.[80,82] Despite the fact that the rate of genetic diversion of equine viruses is small compared to human and swine influenza viruses, this sustained genetic and antigenic evolution continues to have an impact in terms of immunization.

■ Epidemiology

Experimentally, horses of all age-groups are susceptible to infection.[83] However, although sporadic infection in foals has been described, there exists only one published report of a widespread influenza outbreak in foals younger than 6 months of age.[84] The lower incidence of disease in young foals is most likely due to the presence of maternally derived antibodies. Influenza-specific serum antibody concentration (particularly antibody titers measured by single radial hemolysis) is often used as a correlate for protection against infection and disease, and animals with high concentrations of homologous antibody are by

and large protected against experimental challenge.[85,86] After natural infection, ponies were reported to be protected from infection for 8 months, with partial protection persisting for more than 1 year.[87] Although vaccination does not always provide full protection against clinical disease, immunization has reduced the frequency of influenza outbreaks and the frequency and severity of clinical signs when influenza occurs among vaccinated animals.[83,88,89]

Equine influenza outbreaks occur most often when susceptible animals are congregated and housed in close contact with each other (e.g., horse shows, racetracks, sale barns). It is thought that spread of virus among susceptible animals occurs through three modes: direct contact with infected animals or fomites, droplet transmission (droplets larger than 10 µm and capable of being projected over moderate distances by coughing and sneezing), and aerosol transmission (droplet nuclei smaller than 5 µm, capable of wide dissemination and of reaching the lower respiratory tract).[90] Although aerosol transmission clearly has the greatest impact in regard to influenza virus infection control, the importance of bioaerosol transmission in the spread of influenza virus is poorly understood. Depending on the prevailing environmental conditions (humidity, temperature, exposure to sunlight, etc.), the virus can remain infectious for days on contaminated surfaces.[91] Meteorologic factors associated with an increased risk of spread of equine influenza virus between premises during a recent outbreak were relative humidity of less than 60% and wind speeds greater than 30 km/h from the direction of a barn with infected horses.[92]

Once the virus has been introduced into a group of immunologically naive animals, disease can spread rapidly (in a matter of hours to days). Such effective spread is enhanced by a short (~2 days) incubation period, high concentrations of virus shed in nasal secretions, a forceful cough, as well as the practice of housing horses in confined spaces.[91] In partially immune animals, the spread of disease is often considerably slower, and outbreaks may last as long as 3 to 4 weeks.[93] Following experimental infection, horses typically shed virus for 6 to 7 days.[94-97]

■ Pathogenesis

Influenza A viruses replicate and induce pathologic changes throughout the respiratory tract, with the most significant lesions typically occurring in the lower airways. After inhalation of the virus, the virion attaches to sialic acid receptors on the surface of the respiratory epithelial cell and enters the cell by

receptor-mediated endocytosis. Following replication and release from the host cell, the virus spreads quickly throughout the respiratory tract. Largely through apoptosis,[98-100] influenza virus replication leads to cell death. The loss of the ciliated respiratory epithelium in the trachea and bronchial tree[101] results in the impairment of tracheal mucociliary clearance.[64,102,103] In addition, the disruption of the superficial layers of the respiratory epithelium allows opportunistic bacteria to invade the deeper tissues of both the upper and the lower respiratory tract. The combination of reduced airway clearance and erosion of the respiratory epithelium predisposes affected horses to the development of secondary bacterial complications such as bacterial bronchopneumonia.[101,104] In uncomplicated cases, regeneration of the respiratory epithelium begins about 3 to 5 days after onset of illness,[104] yet resolution of the epithelial damage takes a minimum of 3 weeks.[103,105]

■ Clinical Presentation

Clinical signs of influenza virus infection in horses are often seen 48 hours after exposure to the virus. In vaccinated animals, the disease is rarely fatal, but deaths have been reported during some epidemics, particularly in donkeys and rarely in neonatal foals.[42,106] The typical clinical presentation of equine influenza consists of pyrexia, anorexia, lethargy, nasal discharge, and cough. Pyrexia is often the first symptom present, with body temperatures peaking somewhere between 48 to 96 hours after infection. In some cases, a second peak of pyrexia may occur around 7 days after infection. Nasal discharge is typically serous in the first few days of illness but may become mucopurulent by 72 to 96 hours after infection. Concurrently, a dry, hacking cough develops. Coughing tends to persist long after pyrexia and nasal discharge have resolved and may still be present 3 weeks post infection. The majority of affected animals are anorexic during the initial pyrexia. Uncomplicated cases of equine influenza can resolve within 7 to 14 days post infection. Complications of equine influenza can be severe and include secondary bacterial pneumonia, myositis, myocarditis, and limb edema.[65,102,103] Neurologic disease as a result of a nonsuppurative encephalitis has also been described.[107] Finally, it has been hypothesized that influenza infection may predispose horses to the development of equine asthma and exercise-induced pulmonary hemorrhage.[65,101,102] The effects of influenza virus infection can be significantly exacerbated by even moderate exercise.[108]

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Hemogram abnormalities associated with equine influenza infection can include a moderate normocytic, normochromic anemia and a leukopenia, which may result from both a neutropenia and lymphopenia. Monocytosis during early convalescences is a variable finding.

■ Control

Control of equine influenza primarily is based on adequate husbandry procedures and vaccination. Introduction of equine influenza virus into a group of horses likely can be prevented by following the biosecurity guidelines (e.g., isolation of horses for 4 weeks prior to introduction into the horse population) published by the OIE (published in the *Terrestrial Animal Health Code,* Volume II, 2013; http://www.oie.int/). Because these biosecurity measures may be difficult to implement for most barns, 2 weeks of strict isolation and adequate vaccination may serve as an adequate compromise. Unfortunately, even these measures are often not taken, and vaccination is the primary modality used for infection control.

Although a wide variety of vaccine formulations, including modified live and recombinant vaccines, are commercially available, inactivated vaccines remain the most common type of vaccine used. Despite the fact that the vaccines are generally very efficacious, outbreaks of equine influenza continue to occur. One of the reasons for this is that the virus undergoes antigenic drift, which results from the accumulation of amino acid changes in the antigenic sites of the hemagglutinin protein. Studies have shown that even a single amino acid difference in one of the five antigenic sites of the hemagglutinin protein between the vaccine and infecting virus strain can result in a reduction of the protection induced by the vaccine.[109,110] In addition, vaccination seldom induces the same immunity as natural infection, and vaccine-induced antibodies may not persist for very long.[100] This is particularly true for vaccines that are based on inactivated whole virus. In contrast, vaccines using modified live virus and recombinant vectored virus technologies (e.g., canary poxvirus–based vaccines) stimulate both humoral and cellular immune responses and mimic immunity elicited by natural infection more closely.[100]

Similar to human influenza virus vaccines, equine vaccines need to be updated periodically to include relevant contemporary virus strains. Vaccine strain recommendations are based on epidemiologic, genetic, and antigenic data that are analyzed by a panel of equine influenza specialists overseen by the OIE.[111]

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With the divergence of the Florida sublineage, current recommendations are that killed vaccines should include strains representative of both Florida clade 1 and clade 2.[112] Because the sustained genetic evolution of the equine H3N8 viruses will continue to result in vaccine failures in the future, inclusion of viral antigens representative of contemporary circulating viruses must remain a priority.

Studies have demonstrated that an intranasal, cold-adapted, modified live virus vaccine was able to confer protection for up to 12 months after a single administration. Despite this, only a 6-month claim is made on the product data sheet.[97,113] While the vaccine contains only one modified life virus strain, which is based on the H3N8 A/Eq/KY/91 isolate, the vaccine appears to protect against both European and American lineage isolates.[114] Lastly, a recombinant canary poxvirus vector-based vaccine has also shown excellent performance against recent influenza virus strains.[115]

Recommendations for equine vaccination are available from a variety of sources. Due to the presence of maternally derived antibodies, foals should not be vaccinated before at least 6 months of age.[116-118] For inactivated vaccines, initial vaccination series should include three doses even when the data sheets recommend only two initial doses.[117] An interval of 3 to 4 weeks between the first and second doses is recommended, but a longer interval of 3 to 4 months between the second and third doses is preferred. This results in the third dose of the initial series being administered when the antibody response to the second vaccine dose has waned, and the amplitude of the antibody response to the third dose is consequently much greater.[119] For high-risk populations (show horses, racehorses, etc.), booster vaccinations should be given at 6-month intervals.[117,120] Additional booster doses may be administered 1 to 2 weeks prior to potential exposure if a higher risk of infection is anticipated. The modified live intranasal vaccine requires only a single initial dose, followed by booster doses at 6-month intervals.

Equine Herpesviruses

Equine herpesvirus infection is a common infection of equids throughout the world, with at least nine herpesviruses identified to date.[121,122] The equine herpesviruses with the most clinical importance are the *Alphaherpesvirinae* EHV-1 and EHV-4, which both cause respiratory disease. EHV-1 commonly infects horses, donkeys, and other equids and occasionally infects domestic

cattle, captive camelids, cervids, and zebras; EHV-4 is restricted to horses.[121] EHV-3, also a member of the subfamily *Alphaherpesvirinae*, is the cause of equine coital exanthema, a venereally transmitted disease characterized by superficial lesions on the epithelium of the external genitalia of mares and stallions.

Members of the *Gammaherpesvirinae* subfamily, both EHV-2 and EHV-5 have been associated with a range of clinical diseases, including respiratory disease. Whereas EHV-2 has been associated with poor athletic performance, respiratory disease, and keratoconjunctivitis,[123-126] EHV-5 has been hypothesized to be the causative agent of EMPF and equine lymphoma.[127-129] EMPF is a progressive pulmonary disease characterized by coalescing nodules of fibrosis and interstitial pulmonary fibrosis and pneumonia.[127] Results from a recent study in which EMPF was experimentally induced after inoculation of horses with virus isolated from EMPF lesions provides added support for the causal relationship between EHV-5 infection and the disease.[130]

Studies aimed at determining the clinical significance of EHV-2 and EHV-5 infection are complicated by the ubiquitous nature of infection in the equine population. EHV-2 and EHV-5 have been detected in horses throughout the world.[131-133] As both viruses can frequently be detected in samples obtained from healthy horses as well as from horses with clinical disease, the relevance of the finding remains unknown.[134-137]

■ Etiology

Both EHV-1 and EHV-4 are members of the *Alphaherpesvirinae* subfamily of herpesviruses, in the genus *Varicellovirus*. These two viruses have very similar antigenic and genetic characteristics, although they are quite distinct from the gammaherpesviruses EHV-2 and EHV-5.[121] Both viruses are easily inactivated by solvents, detergents, disinfectants, and other common veterinary means of decontamination but in favorable environmental conditions can persist for as long as a month and in refrigerated liquids for much longer.

Both EHV-1 and EHV-4 have a linear double-stranded DNA genome of 145 and 150 kbp encoding 79 and 80 open reading frames (ORFs), respectively,[138-140] which can code for 77 proteins. Amino acid homology of EHV-1 and EHV-4 is 55% to 96%.[138] The gene products of EHV-1 and EHV-4 are classified as immediate early, early, or late (which include the major glycoproteins).[141-144] In

recent years, a single nucleotide polymorphism (N752/D752) in the EHV-1 ORF 30, encoding the catalytic subunit of the viral DNA polymerase, was suggested to be significantly associated with the neuropathogenic potential of EHV-1 strains.[145,146] In support of the increased neuropathogenic potential of the N to D substitution at position 752 are the results of a recent study using recombinant viruses with either genotype.[145] Although results of several recent studies indicate that the less virulent genotype (N752) appears to be more prevalent in the equine population at this time,[147-149] viruses with D752 have increased in prevalence in recent decades.[150] It has been hypothesized that the link between the substitution of asparagine (N) and aspartic acid (D) at position 752 and its neuropathogenic potential is due to the higher magnitude and duration of viremia that was found after experimental infection of horses with virus carrying this mutation.[151] In contrast, a recent study found no significant difference in viral loads in nasal secretion and blood between the two genotypes in horses with natural EHV-1 infection.[149] The discovery of this mutation and its association with neuropathogenic potential led to the development of PCR-based diagnostic assays that are able to detect strains carrying the N752D mutation. Despite this, it should be taken into consideration that infection with an EHV-1 strain encoding D at position 752 does not inevitably result in neurologic disease. Likewise, although D752 is present in the large majority of EHV-1 viruses causing neurologic disease, equine herpesvirus myeloencephalopathy (EHM) has also been caused by strains with N at position 752. Lastly, glycoprotein D, an essential protein in the viral entry process, has recently been shown to be another important virulence factor of EHV-1 in horses.[152]

■ Epidemiology

EHV-1 infection causes significant suffering in horses and extensive economic losses through frequent outbreaks of a range of diseases, including respiratory disease, abortion, neonatal foal death, EHM, and chorioretinopathy.[121] EHV-4 can cause respiratory disease outbreaks but only sporadic cases of abortion rather than abortion storms. Infections caused by EHV-1 and EHV-4 are particularly common in young performance horses and frequently result in establishment of latent infection within the first weeks or months of life.[153] Establishment of latency with subsequent viral reactivation resulting in clinical disease and viral shedding during periods of stress is a characteristic of

herpesviruses in general, including EHV-1 and EHV-4,[121] and makes eliminating these pathogens from the equine population a difficult if not impossible endeavor. Latency and reactivation are critical features of the epidemiology of EHV-1 and EHV-4 infection, allowing the virus to persist for lengthy periods, and in all likelihood as a lifelong infection, in the majority of previously infected horses before reactivating. Reactivation and subsequent nasal virus shedding can result in infection of new susceptible horses and possibly in disease in the latently infected horse itself. Although the true prevalence of latent equine herpesvirus infection is unknown, as more sophisticated methods of detecting latent infection with EHV-1 and EHV-4 are developed,[154] the detectable prevalence of infection continues to rise with the implication that EHV-free horses are a very rare occurrence.

■ Pathogenesis

The pathogenesis of EHV-1 infection has been comprehensively reviewed.[121,155,156] Primary EHV-1 or EHV-4 infection occurs at the respiratory epithelium, resulting in erosion of the upper respiratory mucosal surface and viral shedding for 4 to 7 days post infection; shedding can occur for longer at lower levels and possibly beyond 14 days. Cell-to-cell spread results in the presence of virus in respiratory tract lymph nodes within 24 to 48 hours post infection. In contrast to EHV-4 infection, which is mostly limited to the respiratory tract, EHV-1 establishes a lymphocyte-associated viremia, which is responsible for the delivery of virus to the pregnant uterus and other tissues. Spread of virus from leukocytes to endothelial cells at these secondary sites results in vasculitis, hemorrhage, thrombosis, and ischemic tissue necrosis. Viremia can persist for up to 21 days and is a prerequisite for abortion, chorioretinopathy, and EHM. Moreover, there appears to be a positive correlation between the development of EHM and the magnitude and duration of viremia.[157] Despite this, only a small percentage of horses with viremia develops EHM, indicating that the clinical outcome of infection in the individual animal is influenced by other factors (e.g., age, sex, breed, virus strain).[146] In pregnant mares, EHV-1 infection can result in abortion subsequent to vasculitis of the small arteriolar branches of the glandular layer of the endometrium with subsequent thrombosis, microcotyledonary infarction, perivascular cuffing, and transplacental spread of virus.[121] Abortion typically occurs in the last 4 months of pregnancy but has been reported to occur as early as the second trimester.

There are usually no signs of impending abortion, and the foal is typically expelled in the amniotic membrane, having just died from asphyxia due to placental separation. Some fetuses survive initially but then die from respiratory failure due to infection of the lungs. EHV-1 myeloencephalopathy results from widespread vascular injury after damage to the vascular endothelium of the blood-brain barrier and thrombo-ischemic necrosis in the spinal cord and the brain. It is possible that the immunopathologic response to EHV-1 infection of the vascular endothelium of the central nervous system may play a part in the etiology of the thrombo-ischemic necrosis. In this regard, a recent study has found an increased concentration of D-dimers in the bloodstream during EHV-1 viremia, suggesting that viremia can result in activating the coagulation cascade and the fibrinolytic system.[158] EHV-1 chorioretinopathy is also caused by a vascular endotheliopathy with subsequent ischemic injury to the chorioretina, and it is characterized clinically by focal or multifocal "shotgun" lesions.[159] While the incidence of ocular lesions has been reported to be more than 50% following EHV-1 infection, most ocular infections remain subclinical.[159] Moreover, these lesions are typically not detectable in acute disease and take weeks following infection to become visible. Latency is established in the lymphoreticular system and in the trigeminal ganglion.[121,147,160] Reactivation of latent virus frequently results in reinfection of the upper respiratory tract and shedding of virus in nasal secretions.

Immunity to EHV-1 and EHV-4 has been extensively reviewed.[161] The protective immune response following infection is short lived (3 to 6 months), although this may increase with age and repeated exposure. High titers of virus-neutralizing (VN) antibody before infection can reduce the amount and duration of virus shed from the nasopharynx[162] but fail to prevent infection or the development of EHM or abortion.[163] The reason for this failure is likely to be related to the rapid intracellular translocation of the virus,[164,165] thereby escaping the effects of VN antibody. However, intracellular virus is susceptible to cytotoxic T lymphocytes (CTLs), which can lyse virus-infected cells. This CTL activity is MHC class I restricted and mediated by CD8+ lymphocytes.[166] Ponies with high frequencies of CD8+ CTLs show a reduction in the clinical and virologic outcome of infection[167] and are protected against abortion.[168] Control of EHV-1 infection requires an immune response that not only limits primary infection but also controls reactivation of latent infections.[163] Although circulating and mucosal antibodies each play some role in protection,[162,169] the

most important component of a protective immune response to EHV-1 is the CTL response.[168,170,171] Another important aspect of EHV-1 pathogenesis and immunity is the capacity of the virus to evade the immune response.[172] Strategies of immunoevasion used by EHV-1 include modulation of cytokine responses with subsequent effects on T- and B-cell responses, modification of the CTL responses, interference with antigen presentation by downregulation of MHC class I expression, inhibition of antibody-dependent cytotoxicity, alteration of NK-cell lysis, and loss of efficient chemoattraction of professional antigen-presenting cells.[173-176]

■ Clinical Presentation

Clinical diseases associated with EHV-1 and, to a lesser extent, EHV-4 infection include respiratory disease, abortion, EHM, chorioretinopathy, and neonatal foal death. Infection with both EHV-1 and EHV-4 causes respiratory signs, but clinical signs are likely more severe for EHV-1, as is the likelihood of viremia. Respiratory disease is often more severe in young horses than in older, previously exposed horses. Clinical signs of EHV-1 or EHV-4 respiratory tract infection include pyrexia, which may be biphasic, with a first peak at 24 to 48 hours associated with upper respiratory tract infection and a second peak occurring at 4 to 8 days if viremia develops. Lethargy and anorexia are often mild, and nasal discharge, serous at first, becomes mucopurulent by days 5 to 7. Conjunctivitis, lymphoadenopathy of the submandibular lymph nodes, and edema or vasculitis of the distal limbs are variable findings. Respiratory disease, particularly affecting a large number of animals, is uncommon in horses older than 2 years of age presumably due to recurrent exposure to the virus and development of sufficient immunity to suppress clinical signs of airway disease.

Neonatal foals infected with EHV-1 in utero may be normal at birth but quickly become weak, lethargic, and develop profound respiratory distress. Prognosis is poor for survival. The abortion and EHM forms of EHV-1 are discussed elsewhere under the appropriate system.

The clinical signs resulting from infection with EHV-2 and EHV-5 remain poorly described and established, although these viruses may be a cause of acute respiratory tract disease with clinical signs of nasal discharge, reactive submandibular lymph nodes, and coughing.[123,177] There is mounting support of a potential association of EHV-5 infection and EMPF. However, the exact nature of the relationship between the virus and the disease has not yet been fully

elucidated.[127,128,178-180]

■ Prevention

Due to the ability of equine herpesviruses to establish latency within their host, the elimination of these pathogens from the equine population is not a feasible approach to infection control. Therefore strategies that prevent dissemination of the virus from horses undergoing active virus shedding must be used. Vaccines are an attractive tool for this, but currently there are no products that can provide comprehensive protection against equine herpesvirus infection and its potential sequelae. Inactivated EHV-1 vaccines are capable of eliciting circulating VN antibody responses, which can limit respiratory disease and nasal viral shedding, and the use of some of these vaccines has been associated with a reduction in the incidence of abortion storms.[161-163,181] Vaccines containing higher antigen loads, and typically those licensed for control of abortion, can generate high-titered VN antibody responses and even EHV-1–specific interferon-gamma responses.[181] Such vaccines are likely to outperform other inactivated products with lower antigen loads. Using an optimized vaccination regime (vaccination was performed on days 0, 27, and 97) and virus challenge at the peak of the resulting immune response, a recent study was able to demonstrate a significant reduction in days of viremia in addition to a reduction of clinical signs and nasal virus shedding after administration of a commercially available high-antigen load killed vaccine.[182] A commercially available modified live EHV-1 vaccine (MLV) generates limited EHV-specific cellular immunity[183] and has been demonstrated to reduce respiratory disease and viral shedding but no protection against viremia.[184] The use of current commercial vaccines of proven efficacy is recommended at 6-month intervals for control of respiratory disease and shedding of EHV-1 and EHV-4. Generally, vaccines effective against EHV-1 will cross-protect against EHV-4. There is no evidence that any commercial or experimental vaccine can prevent the occurrence of EHM.

No attempts are made to control EHV-2 or EHV-5 infection with vaccination. However, the proposal that concurrent EHV-2 infection may play a role in the etiology of *R. equi* pneumonia has led some clinicians to attempt vaccination of foals with killed EHV-2 vaccines.[185]

Biosecurity measures following detection of EHV-1 and EHV-4 infection should include the use of strict hygiene and barrier precautions as well as isolation of affected and in-contact horses for periods of up to 28 days. The virus

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is thought to spread primarily through contact, with limited airborne droplet spread compared to equine influenza virus. Extensive codes of practice have been described for control of the spread of EHV-1 in facilities both in publications[121] and in online resources (http://www.hblb.org.uk; http://www.aaep.org).

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Equine Arteritis Virus

Equine viral arteritis (EVA), named after the characteristic inflammatory changes found in the walls of small arteries, is a contagious disease of horses caused by equine arteritis virus (EAV).[186] While EVA is a disease with worldwide distribution, the seroprevalence varies substantially between countries and equine populations. Despite the fact that the vast majority of EAV infections are subclinical, occasional outbreaks occur that result in respiratory disease in adult horses, abortion, and fatal pneumonia in foals. These disease outbreaks have significant costs in terms of animal suffering and economic loss. Recent examples of larger outbreaks with substantial impacts on animal health and economic losses include a multistate EAV outbreak in 2006–2007 in the United States as well as a 2007 outbreak in the Normandy region of France.[187-189]

■ Etiology

EAV is an enveloped positive-strand RNA virus and is a member of the family *Arteriviridae*, order *Nidovirales*.[190] The *Arteriviridae* comprise the following genera: *Equartevirus* (equine arteritis virus [EAV]), *Rodartevirus* (porcine reproductive and respiratory syndrome virus [PRRSV], lactate dehydrogenase-elevating virus [LDV] of mice), *Simartevirus* (simian hemorrhagic fever virus [SHFV] and others), and *Dipartevirus* (wobbly possum disease virus [WPDV]).[191] The polycistronic genome of EAV is approximately 12.7 kb and contains at least 10 functional ORFs.[192-194] ORFs 1a and 1b encode two replicase polyproteins that are posttranslationally processed by three proteinases to produce at least 13 nonstructural proteins. The remaining eight ORFs encode eight structural proteins, two (M and GP5) of which serve as the major viral envelope proteins. The GP5 envelope glycoprotein carries the major neutralization determinants of the virus, and four neutralization sites (A to D) have been identified.[195] Based on phylogenetic analyses of the EAV-ORF5, the viruses are divided into two distinct clades: North American and European clades that share approximately 85% nucleotide identity.[196,197] Despite the fact that only one serotype has been identified, there are extensive variations in virulence of different isolates of the virus. While the molecular determinants of EAV virulence have not been fully elucidated, recent data suggest that amino

acid substitutions in the replicase and/or the structural proteins (GP2, GP4, GP5, and M) result in attenuation of a virulent strain of EAV.[198] The virus is readily inactivated by lipid solvents and disinfectants, although it can remain infectious for 75 days at 4° C, for years in tissue samples stored at –20° C, and for decades in semen, embryos, and tissue samples stored at –70° C.[199]

■ Epidemiology

EAV is spread by the respiratory and venereal routes, and the persistently infected carrier stallion is central to the persistence of the virus in the horse population.[186] As a consequence, disease outbreaks frequently follow the importation of carrier stallions or their semen. With the increasing internationalization of the horse industry, this has become an important factor in the spread of the virus throughout the world in recent years and highlights the fact that identification of the carrier stallion is a key component of EVA control programs.[187,200] Virus transmission may also occur through direct or indirect exposure of seronegative animals to aborted fetuses and fetal membranes, by carrier stallions to susceptible stallions by masturbation, and from EAV-infected donor mares to naive recipient mares via embryo transfer.[201,202]

Following infection, a variable percentage (10% to 70%) of stallions infected become carriers and shed the virus for a variable period, ranging from several months to years, in their semen.[200,203] The virus persists primarily in the ampulla of the vas deferens, and the carrier state has been shown to be testosterone dependent, as castration resolves infection.[200] Some carrier stallions spontaneously eliminate the virus from their reproductive tract. During replication of the virus in the carrier stallion, genetically and phenotypically distinct variants of the virus can emerge, and these variants subsequently can be found in the semen of these stallions.[188,204,205] When one of these variants is transmitted to a mare through breeding, or occasionally through contaminated fomites, a new outbreak can occur.[186] Transmission by the venereal route is associated with infection rates in mares as high as 85% to 100%, and disease outbreaks often result from breeding a seronegative mare with EAV-containing semen.[190] Subsequent spread of the virus to other horses on the premises is by respiratory droplets and the airway route.[190] During these outbreaks the EAV strain remains stable with minimal genetic change.[186] Seroprevalence varies among breeds and between countries and geographic regions, with a reported

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seroprevalence of up to 85% in U.S. Standardbreds but less than 6% in Thoroughbreds in the United States.[206] While it has been hypothesized that differences in seroprevalence are due to genetic susceptibility to EVA, it is likely that the difference is a consequence of the number of actively shedding carrier stallions in different breeds. The virulence of strains in specific breeds can vary, however, and the strains shed by Standardbreds are typically highly attenuated, causing minimal disease.[186] Interestingly, recent research suggests that a correlation exists between the host's genotype (i.e., CD3+ T-cell susceptibility to EAV infection) and the clinical outcome of infection, including the potential to become a carrier of the virus.[207-209]

The immune response to infection is strong, leading to protective immunity with a duration of several years.[190] Foals born to immunized mares are protected by colostral antibodies for 2 to 6 months.

■ Pathogenesis

Virus transmission occurs via both the venereal and the respiratory routes. After respiratory infection the virus invades the respiratory epithelium and infects bronchial and alveolar macrophages, reaching bronchial and other regional lymph nodes by 48 hours post infection.[190] Nasal virus shedding is typically detected for 7 to 14 days after infection but can last for up to 21 days.[210] The establishment of viremia leads to dissemination of the virus throughout the body and further replication of the virus in the adrenals, thyroid, liver, and testes. Following infection, virus can be detected in the buffy coat for 2 to 21 days and in the plasma and serum for 7 to 9 days. The virus infects and replicates in endothelial cells, causing direct injury to the vascular endothelium and adjacent muscularis media, and subsequently gains access to the media of affected vessels. Vasculitis is characterized by fibrinoid necrosis of small muscular arteries, leukocyte infiltration, and perivascular hemorrhage and edema. With the exception of the carrier stallion, virus is eliminated by 28 days post infection and coincides with the appearance of virus-neutralizing antibodies.[211] Reports exist where virus has been recovered for up to 180 days post infection from the accessory sex glands of prepubertal colts.[190,212,213]

■ Clinical Presentation

The great majority of infected horses are asymptomatic. When disease does

occur, the clinical signs of EAV infection can vary from fever and leukopenia to severe disease and death. In general, the severity of EVA tends to be greater in very young and old horses. The incubation period is 2 to 14 days (6 to 8 days following venereal exposure). Horses may show some of the following signs. Typically the affected animals are pyrexic, with temperatures reaching 40.5° C (105° F) for 1 to 5 days. Anorexia, lethargy, serous nasal and ocular discharge, and coughing may occur. Conjunctivitis ("pink eye") with ocular discharge and periorbital and supraorbital edema; dependent edema of the limbs, prepuce, scrotum, and mammary glands; urticaria (localized to the sides of the neck and face or generalized); photophobia; petechial hemorrhage in the nasal, conjunctival, and oral mucous membranes; and submandibular lymphadenopathy have also been reported.[190]

In stallions, acute infection can cause short-term subfertility characterized by reduced libido, decreased sperm motility, sperm concentration, and normal sperm morphology. These changes in semen quality are transient but can persist for up to 16 weeks.[187] In contrast, persistent infection does not appear to have an effect on sperm quality in carrier stallions.[187]

Abortions in pregnant mares occur in the acute or early convalescent phases of infection and are often not preceded by premonitory signs. It is thought that abortion occurs as a consequence of placental dysfunction secondary to vasculitis affecting myometrial blood vessels.[214] Abortion can occur from 2 to 10 months of gestation, with abortion rates ranging from 10% to 70%. Fetuses are typically partially autolyzed at the time abortion occurs. Commingling of mares recently bred by an infected stallion with pregnant mares is a common scenario leading to abortion.

Neonatal foals infected with EAV show severe respiratory signs and high mortality. In foals that survive more than 24 hours, fever and leukopenia or thrombocytopenia are present. Interstitial pneumonia, lymphocytic arteritis or periarteritis, renal tubular necrosis, and fibrinoid necrosis of the tunic media are seen on pathologic examination.[186]

■ Prevention

EVA control programs are aimed at eliminating the risk of abortion, neonatal foal death, and the establishment of the carrier status in stallions.[199] Control measures include identification of carrier stallions, isolation and testing of horses prior to introduction into the resident horse population, segregation of pregnant

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mares and newborn foals, vaccination, and the establishment of biosecurity measures. Prevention of the development of carrier status in future stallions can be accomplished through vaccination of all colts with breeding potential in the first year of life and annual revaccination thereafter.[190] Identification of the carrier stallion can be accomplished by virologic and serologic testing (taking into account previous vaccination history) and should be carried out prior to introducing a stallion to a new premises.[199] Serologic testing should be performed in all stallions prior to the breeding season, and if seropositivity is detected in a stallion with no known vaccination history, virologic testing of the semen should be conducted. If the carrier status has been identified, these stallions should be managed separately under strict hygiene protocols to prevent spread of the virus to naive in-contact animals.[187,200] Mares being bred to carrier stallions should be vaccinated against EAV. Fresh and frozen semen from carrier stallions is also infective, and negative mares receiving this semen should be vaccinated. Extensive codes of practice have been produced by both the U.S. Department of Agriculture (http://www.aphis.usda.gov) and the Horserace Betting Levy Board (http://www.hblb.org.uk) to assist in control of EVA. Moreover, guidelines for vaccination of horses against EAV have been established by the American Association of Equine Practitioners (AAEP; http://www.aaep.org).

Both a modified live and a killed vaccine against EAV have been developed.[186,190] In the United States, the MLV vaccine has been available since the mid-1980s. The vaccine was derived from an experimental vaccine that was created by serial passage of the virulent Bucyrus strain in primary horse kidney and primary RK cells. The MLV vaccine provides complete or partial protection against the clinical signs of EVA, but viral replication still occurs after challenge. Despite the fact that only a single serotype of EAV has been described, recent in vitro studies demonstrated that antibodies raised subsequent to vaccination with the MLV vaccine do not neutralize all strains with equal efficiency.[215,216] The duration of vaccinal protection appears to be as long as 2 years, although annual revaccination of breeding stallions is recommended before the start of the breeding season. The MLV vaccine has been used successfully to limit outbreaks of infection in racecourses after initial diagnosis.[190] The manufacturer does not recommend the use of this vaccine in foals younger than 6 weeks of age and in pregnant mares. Vaccination of pregnant mares during the last 2 months of gestation has been associated with the risk of abortion.[217]

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Equine Rhinitis Virus

■ Etiology

Equine rhinitis viruses (formerly equine rhinoviruses) are a known cause of clinical and subclinical respiratory infections in horses worldwide. The viruses are classified as members of the family *Picornaviridae*, which includes small ("pico"), nonenveloped, single-stranded RNA viruses. Among the equine rhinitis viruses, at least two serotypes have been isolated from horses: equine rhinitis A virus (ERAV) (formerly equine rhinovirus 1 [ERV-1]), and equine rhinitis B virus (ERBV) (formerly equine rhinovirus 2 [ERV-2]).[218,219]

Considerable uncertainty has surrounded the classification of the equine rhinitis viruses. Because the illness caused by these viruses resembles the common cold brought about by rhinoviruses in humans, they initially were included in the genus *Rhinovirus*. However, subsequent studies demonstrated that ERAV differed from other members of the *Rhinovirus* genus as well as from ERBV.[219-222] For example, while rhinoviruses generally demonstrate a narrow host-cell range in vitro and in vivo, ERAV is able to infect and replicate in a broad range of cell types and host species. For instance, intranasal inoculation of a human volunteer with ERAV resulted in pharyngitis, lymphadenitis, fever, and viremia.[223] Furthermore, the presence of systemic signs and viremia during ERAV infection, the occurrence of persistent infections, and the physical properties of the virus are all more reminiscent of foot-and-mouth disease virus (FMDV). Based on these characteristics, along with similarities in protein sequences, ERAV was placed alongside FMDV in the *Aphtovirus* genus of the picornavirus family. Subsequently, ERBV has been reclassified as the sole member of the new genus *Erbovirus*. To date there are three known serotypes of ERBV: ERBV1, ERBV2, and ERBV3 (acid-stable equine picornavirus).

■ Epidemiology

First isolated from horses in the United Kingdom,[224] ERAV infection occurs worldwide and is a recognized cause of acute respiratory disease.[218,225-227] The incidence of neutralizing antibody to ERAV varies according to the age of the horse, and most horses appear to become infected during their second year of life. In a study by Studdert and Gleeson, only 16% of horses between the age of 6 and 12 months were seropositive.[221] However, studies conducted in older horses found that a high percentage (50% to 90%) of horses 5 years of age have

antibodies to equine rhinitis virus.[225,228-230] As with many other respiratory pathogens, young horses entering a large population in frequent contact with other horses are most susceptible to infection.[225] In addition, there appears to be a seasonal distribution, with most of the ERAV infections occurring in late winter and spring.[231,232] Stress (e.g., transportation and training) and concurrent disease resulting in immunosuppression may predispose to infection.[233] The virus is fairly resistant to inactivation and is thought to survive in the environment for a considerable time. As for human rhinoviruses, virus spread occurs most likely through direct and indirect contact (fomites).[234]

The clinical significance of ERBV1, ERBV2, and ERBV3 is not well defined. Several recent surveillance studies indicate that the prevalence of ERBV1- and ERBV2-neutralizing antibodies is between 24% and 80% of horses.[123,229,230,235] However, the consequences of infection with ERBV1 and ERBV2 are unclear, as these viruses have been isolated from horses both with and without signs of acute respiratory illness.[229,236,237]

■ Clinical Presentation

Although ERAV is generally considered a respiratory pathogen, the clinical signs associated with infection may be quite variable. Following experimental infection with ERAV, horses may develop pyrexia, anorexia, nasal discharge, pharyngitis, and lymphadenitis involving at least the submandibular and pharyngeal lymph nodes.[238] On some occasions, laryngitis or mild bronchitis can develop.[228] Based on serologic studies, subclinical ERAV infection may also occur and may be important in the dissemination of the disease.[221,231,234,238,239]

Horses infected with ERAV may also develop viremia. On average, viremia lasts for 4 to 5 days, and the disappearance of virus from the blood coincides with the appearance of neutralizing antibodies.[238] Although the relationship between antibody levels and protection against disease has not been established, immunity is thought to be solid, and antibodies persist for a long time.[234]

Infection with ERAV may be accompanied by long-term urinary and fecal shedding as well as virus persistence.[238,240] The recognition of the potential for ERAV persistence has important implications for disease diagnosis. Highly sensitive diagnostic methods (e.g., immunofluorescent antibody [IFA] or RT-PCR) may be able to detect persistent ERAV in horses suffering from respiratory disease, which may not be associated with the observed illness. This notion is

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underlined by the recent finding that the ERAV genome was detected by RT-PCR in nasopharyngeal swab samples obtained from two clinically healthy horses 1 year after acute ERAV infection.[219]

■ Control

Similar to other respiratory viruses, infection control should be based on adequate husbandry and biosecurity measures. Recently, a conditionally licensed ERAV vaccine has become available in the United States. Based on data provided by the manufacturer, the initial vaccination series should include three doses administered with a 3- to 4-week interval between each dose. Booster vaccinations should be administered at yearly intervals or prior to an anticipated virus exposure.

Equine Adenovirus

■ Etiology

Adenoviruses (family *Adenoviridae*) comprise a group of nonenveloped, icosahedral DNA viruses. Although most vertebrate species harbor an adenovirus, the viruses are highly species specific. In humans, adenoviruses are extremely prevalent and represent a significant cause of acute respiratory, ocular, and GI disease. Infections of immunocompetent individuals usually stay localized and often take a mild or subclinical course.[241] Similarly, equine adenoviruses have been isolated from clinically healthy adult horses[242] and foals.[243,244] Equine adenoviruses consist of two species, equine adenovirus 1 (EAdV1) and equine adenovirus 2 (EAdV2), which appear to have evolved from separate lineages within the adenoviruses.[245] EAdV1 has been implicated as the cause of acute respiratory tract disease[246,247] and conjunctivitis, as well as a progressive, fatal pneumonia in Arabian foals with SCID.[248-250] EAdV2 has been incriminated as a cause of intestinal infection[251,252] and diarrhea in immunocompetent foals.[253,254]

■ Epidemiology

First isolated in 1969 from a foal with respiratory disease,[255] equine adenoviruses have a worldwide distribution.[256] While serologic evidence from Australia, the United Kingdom, the United States, the Netherlands, and Nigeria

indicates that adenovirus infection occurs at a high frequency in the general horse population,[257-260] the role of equine adenovirus in respiratory disease in adult horses remains unclear. In this regard it is interesting that a number of studies found no apparent association between clinically apparent respiratory disease in young adult horses and infection with adenovirus, as diagnosed by subsequent seroconverison.[237,239,261]

In contrast, fatal and nonfatal adenovirus pneumonia has been well documented in foals, particularly of the Arabian breed. Fatal respiratory disease is predominantly seen in foals with SCID. Other foals may develop respiratory disease but usually do not succumb to disease.

In general, adenovirus transmission is thought to occur via direct contact with secretions from infected animals or indirectly via fomites or infected premises. In adult horses, the virus can persist in the upper respiratory tract, and these animals can act as a reservoir host for the virus. Adenoviruses are highly stable and have been found to remain infectious at 4° C for up to 1 year.

■ Clinical Presentation

The clinical signs recorded after experimental intranasal infection of a Thoroughbred yearling were confined to a serous nasal discharge that lasted from 4 to 12 days post inoculation. Peak levels of serum antibodies were found at 13 days after inoculation and dropped by approximately 2 months after experimental infection.[262]

In foals, clinical signs generally occur between 10 and 35 days of age.[263] After experimental inoculation at 24 hours of age, clinical signs appeared 3 to 5 days after infection and consisted of intermittent pyrexia, nasal and ocular discharge, tachypnea, and cough. All foals recovered by day 10 post inoculation. The majority of foals developed a mild and transient lymphopenia that was followed by lymphocytosis. Typically, about 25% of infected foals also develop diarrhea.[263] Gross pulmonary lesions found in animals euthanized at 14 to 21 days post inoculation included atelectasis, involving up to 25% of the pulmonary parenchyma, and suppurative bronchopneumonia. Histologically, swelling and hyperplasia of the airway epithelium, as well as intranuclear inclusion bodies in the respiratory epithelial cells, were a consistent finding up to 11 days post infection.[264]

Foals with SCID show a progressive decline in health despite intensive therapy. In necropsy, conjunctivitis, rhinitis, tracheitis, and bronchopneumonia

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are present. Intranuclear inclusion bodies are readily demonstrated in the respiratory epithelial cells. Areas of interstitial pneumonia surround affected bronchi. Acute pancreatitis characterized by inclusion bodies in acinus and ductal cells, as well as adenoviral sialoadenitis involving labial and parotid salivary gland can often be demonstrated.[252,265]

■ Control

No vaccine is available to control adenovirus infection in horses. However, except in immunocompromised animals, the virus appears to be of little clinical importance.

Hendra Virus

Hendra virus is described in detail later in this chapter.

Equine Lungworm

Scott M. Austin

Dictyocaulus arnfieldi is a nematode parasite that affects donkeys, mules, horses, and asses. Infection occurs most frequently in cold, damp climates. This parasite appears to be well adapted to the donkey, as large numbers of parasites are associated with minimal clinical signs.[1] In contrast, infections in horses produce intense tissue reaction to parasites, resulting in clinical signs of a cough and arrested development of the adult worms. It has been suggested that donkeys are the natural host and that horses require cohabitation with donkeys to acquire the infections. Although it is true that patent infections are rare in the horse, horses may be infected without any history of exposure to infected donkeys.[2,3] *D. arnfieldi* has a direct life cycle. Infection begins with the ingestion of infective L3 larvae from contaminated pastures. Larvae migrate from the intestines to the lungs via the lymphatics and then infiltrate the alveoli. Adult worms may reach 8 cm in length and can block smaller airways. There is no evidence that links infection in donkeys to pulmonary fibrosis; however, lungworm infections may exacerbate other coexisting pulmonary disease.[1] The lungworms have a prepatent period of about 8 to 13 weeks.[3,4] Embryonated eggs produced from patent infections are coughed up, swallowed, and passed in the feces. The eggs hatch into first-stage larvae in the feces and spread onto pastures

with the assistance of the fungus *Philbolus*.[1] The larvae congregate on or in the sporangiophore of this fungus, which colonizes the surface of the manure. Fluid within the sporangiophore increases in pressure until it explodes at midday, spreading parasitic larvae up to 3 meters from the site of origin. The dispersion of larvae away from feces increases the odds of ingestion by a susceptible host. The L1 larvae can survive for up to 7 weeks in the environment with suitable warmth and moisture but die rapidly in the cold.[5,6] Maturation of L1 larvae into infective L3 larvae can happen in as little as 5 to 7 days under permissive conditions. In contrast to infections in donkeys, larval development is usually arrested in the early fifth stage in horses, and patent infections are rare.[7,8] In horses, infections are more frequently encountered when pastured with donkeys, but infections have been identified in closed horse herds without exposure to donkeys or mules.[1,6,9,10]

Although *D. arnfieldi* infections have been common in donkeys, more recent surveys indicate a significant decline in the prevalence of this parasite.[11] Three decades ago, a survey of horses and donkeys in central Kentucky identified an infection rate of 54% for donkeys and 25% for horses.[9] In a separate study of a single Kentucky farm, lungworm larvae were found in 93% of donkeys and 50% of Thoroughbreds.[12] A more recent survey of 735 new donkeys at admission to a sanctuary in the United Kingdom (2004-2008) demonstrated a prevalence of only 4% in donkeys.[11] Necropsy surveys of horses in central Kentucky from 2000 to 2001 failed to identify any *D. arnfieldi* infections.[13] The macrocyclic lactones, which are highly effective against *D. arnfieldi*, were introduced after these initial studies and are probably responsible for the decline in incidence of this parasite.[1]

Donkeys rarely show clinical signs associated with infection, and pathology is usually limited to areas of overinflation surrounding affected bronchi and to the tip of the caudal lung lobe. In contrast, more significant lesions are seen in infected horses and are associated with a more robust inflammatory response to lungworm infections.[1] In the horse, larvae within the bronchi stimulate a marked eosinophilic and lymphocytic exudate.[14] Damage from the adult worms causes focal edema and hemorrhage and results in hyperplasia and thickening of occupied bronchi.[15] The adult parasites also impair local defenses as they disrupt the mucociliary apparatus and cause a decrease in alveolar macrophage numbers, allowing for opportunist bacterial infections.[7] Exudate, adult parasites, and

airway hyperplasia cause obstruction of small bronchioles and secondary air trapping. Examination of affected lungs demonstrates interstitial pneumonia, focal necrosis, and areas of pulmonary overinflation in the lung periphery.[4,14]

Parasitic pneumonitis can affect horses of any age, but clinical signs are most frequent in horses between 5 and 8 years of age.[9] Clinical signs can develop as rapidly as 12 days after ingestion of infective larvae.[7] Chronic cough is the most common manifestation in the horse, along with exercise intolerance and mucopurulent nasal discharge.[10] Affected horses are rarely inappetant or dull.

Diagnosis in donkeys relies on the modified Baermann technique to detect larvae in the feces. Fifty grams of feces are required for this test. Accurate results require the feces to be evaluated quickly or to be kept cool, as temperatures greater than 16º C are associated with the loss of 50% of the larvae in 24 hours and the loss of 80% in 48 hours.[15] Since patent infections are rare in horses, endoscopic or transtracheal examination for larvae or proof of eosinophilic inflammation may be required to make a diagnosis. Hematologic and serum chemistry results are frequently normal in horses with uncomplicated parasitic pneumonitis. Mature neutrophilia and hyperfibrinogenemia are usually seen only when there is a secondary bacterial infection.[16] Supportive evidence for parasitic pneumonia can be obtained by transtracheal wash, BAL, and possibly direct visualization through an endoscope. Cytology of aspirates demonstrates abnormally elevated eosinophil counts (greater than 2%). Eosinophil percentages as high as 88% have been recovered from horses with *Dictyocaulus* infections. Larvae or eggs can be found during examination of the fluid.[16] Radiographic examination is nonspecific and may reveal a mixed bronchointerstitial pattern.[5,16] Centrifugal flotation, modified McMaster technique, and Baermann technique have all been used to identify eggs or larvae in the feces of infected animals. Confirmation of infections in horses is difficult, as patent infection is rare.

Historically, thiabendazole (440 mg/kg/day for 2 days) and mebendazole (20 mg/kg/day for 5 days) were effective in reducing parasite load and larval shedding, but neither product is currently available.[17] Fenbendazole, a benzimidazole that is still available, only reduces larval numbers in feces of donkeys by 50% to 70% when administered at 15 mg/kg PO once.[18] The larvicidal dose of fenbendazole (10 mg/kg/day for 5 consecutive days) is not effective against adult *D. arnfieldi*.[18] Macrocyclic lactones such as moxidectin (400 µg/kg) or ivermectin (200 µg/kg) have been demonstrated to be effective

against mature and immature stages of *Dictyocaulus* spp., and these drugs are the most frequently used products to treat parasitic pneumonia.[19] It is recommended that new donkeys be tested for *Dictyocaulus* and treated accordingly before introduction to a herd. Horses that graze pastures shared with donkeys are more likely to acquire infections, so it is important to control infections in donkeys and limit exposure of horses to the parasite.[20]

Thoracic Trauma

Scott M. Austin

Thoracic injuries in the horse are uncommon but are often associated with high mortality. These injuries result from either penetrating or blunt trauma.[1,2] Collision with fences is the most common cause of penetrating thoracic wounds, but running into trees and farm implements, gunshots, goring by horned animals, and impalement by high-velocity debris during tornadoes have also been reported.[3,4] While penetrating wounds are usually obvious, blunt force injuries can be more difficult to diagnose and may occur after collisions with stationary objects, kicks from other horses, and athletic mishaps such as falls. Significant internal injuries may be present in the absence of external wounds.[5] Frequently, damage occurs to both internal and external structures, and a complete physical examination and ancillary diagnostic tests are necessary to determine the extent of the damage. Potential trauma includes pectoral or axillary lacerations, penetrating wounds or impalement of the thorax, rib fractures, flail chest, and lung contusions or lacerations and leads to potentially life-threatening complications such as pneumothorax, pneumomediastinum, hemothorax, pleuritis, and diaphragmatic hernia.[6,7]

External injury can cause extensive muscle damage, rib fractures, laceration of large vessels, and significant shock and pain. Internal injuries such as pneumothorax and thoracic hemorrhage will have the additional signs of respiratory distress characterized by nostril flaring, dyspnea, tachypnea, and exaggerated thoracic excursions.[1,2] In addition, horses with diaphragmatic hernias may present with signs of abdominal discomfort.[1-3] Patient stabilization to alleviate life-threatening complications must be undertaken first. Initial treatment ensures a patent airway, restores ventilation and oxygenation, controls hemorrhage, addresses shock, and reestablishes circulatory volume.[7]

After the patient is stabilized, a complete examination of the thorax will

include careful auscultation and percussion, chest wall palpation, wound exploration, blood gas analysis, diagnostic thoracentesis, radiography, and ultrasonography. Decreased lung sounds with increased resonance over the dorsal lung field is characteristic of pneumothorax, whereas diminished lung sounds with decreased resonance over the ventral thorax is characteristic of hemothorax or pleural fluid accumulation.[2] Ultrasonography is extremely valuable for evaluation of the pleural space and lung surface and can detect air, blood, or fluid. Thoracentesis can be used in conjunction with ultrasound to further characterize any abnormalities. Arterial blood gas provides information regarding ventilation and oxygenation, and serial samples can be used to evaluate response to therapy. Because of the size of the equine chest, radiography usually requires referral to a hospital with equipment sufficient to image the equine thorax.

Wounds of the Axilla

Deep wounds of the axilla occur frequently because of wire cuts, running into fences, or being impaled by sharp objects.[6] Axilla wounds may cause direct penetration of the thorax or develop significant subcutaneous emphysema potentially leading to pneumomediastinum and pneumothorax.[6,7] Wounds should be explored and thoroughly lavaged, but excessive pressure is discouraged, as this may drive contaminants further into the wound.[6] To limit subcutaneous emphysema, wounds should be packed with gauze and a stent applied to hold packing in place. Packing should be changed every 24 to 48 hours until a granulation bed has formed.[7] As with any wound, broad-spectrum antibiotics, pain relief, and tetanus prophylaxis are recommended. Activity should be restricted, and cross-ties have been recommended. If severe subcutaneous emphysema develops, secondary pneumomediastinum and potentially pneumothorax may occur weeks after the initial injury.[3]

Penetrating Thoracic Wounds

When penetrating chest wounds are suspected, the clinician must perform careful auscultation and observe the respiratory cycle for several breaths. Splinting, paradoxical movement of a chest wall segment, and obvious incongruities of the chest wall suggest serious problems in ventilation.[6,8] Careful palpation may identify local pain, fractures, flail segments, or subcutaneous emphysema. Ultrasound can confirm abnormalities detected during physical

examination.[6] Serial exams are necessary, as signs of pneumothorax may take time to develop. If full-thickness penetration of the chest wall is suspected, arterial blood gases should be performed to evaluate oxygenation. Chest radiographs can be used to determine if pneumothorax, pneumomediastinum, or rib fractures are present.

Pneumothorax

Pneumothorax is an uncommon event and is classified as open, closed, or tension.[2,3,9,10] Penetrating wounds through the chest wall result in an open pneumothorax, and air moves freely into and out of the chest during inspiration and expiration. In contrast, the chest wall is intact in closed pneumothorax, and air entering pleural space originates from lung parenchyma secondary to infection, rib fractures, or ruptured lung bulla.[6] Tension pneumothorax occurs when a one-way valve develops in either the chest wall or lacerated lung parenchyma. Air is drawn into the pleural space upon inhalation but does not escape during exhalation, resulting in intrapleural pressures that surpass atmospheric pressure and causing compromise of ventilation and cardiopulmonary collapse.[5]

In a review of 40 cases of pneumothorax in horses, the causes were divided between open and closed trauma and surgery of the upper and lower respiratory tract.[10] Closed pneumothorax secondary to pleuropneumonia (17 of 40 cases) and blunt force trauma of the thorax (7 of 40) accounted for the majority. Penetrating wounds resulting in open pneumothorax accounted for 9 of 40 cases. Pneumothorax was bilateral in 19 of 40, unilateral in 17 of 40, and not stipulated as unilateral or bilateral in 4 of 40.[10] Bilateral and tension pneumothorax compromise ventilation and result in obvious clinical signs, whereas unilateral pneumothorax is well tolerated in the horse.[7] Unilateral pneumothorax is more likely encountered secondary to pleuropneumonia, whereas trauma usually results in bilateral pneumothorax.[3,10] The survival rate was 69.6% for traumatic causes of pneumothorax as opposed to 35.3% for infectious causes.[10] Clinical signs of pneumothorax include tachypnea, cyanosis, lack of lung sounds upon auscultation in the dorsal lung fields, fever, tachycardia, decreased activity, depression or anxiety, and cough. While history and clinical signs are suggestive, the diagnosis can be confirmed with radiography and ultrasonographic examinations.[10] Thoracic radiographs are often not possible in the field, but

ultrasonography can be used effectively. Radiographic signs of pneumothorax include retraction of normal pulmonary parenchyma, hyperlucency within the caudodorsal thorax, and visualization of the dorsal margin of the lung lobes below the bodies of the thoracic vertebrae (Fig. 31.32). Radiography and ultrasonography have been reported to have 74% agreement, with most discrepancies occurring when the volume of air in the thorax was small.[11] Ultrasonography is superior to radiography for detecting small volumes of air in the pleural space.[12]

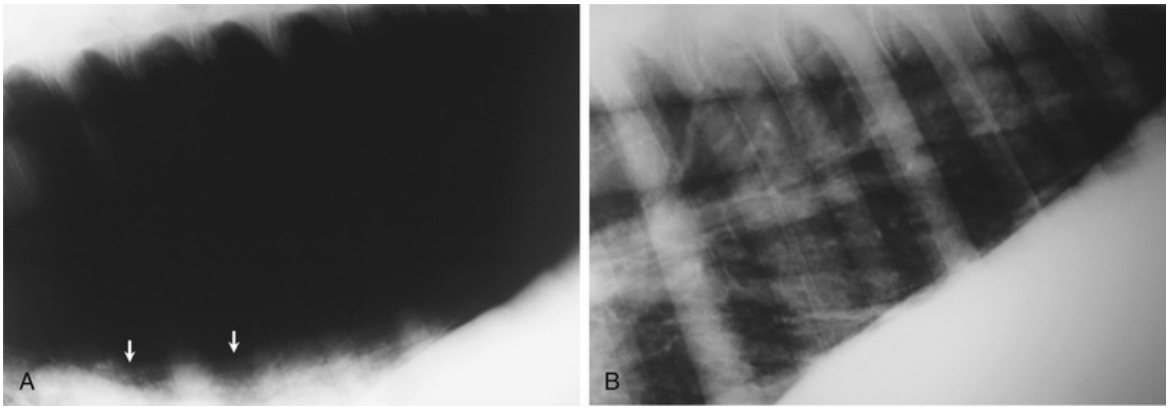


FIG. 31.32 **A,** Lateral radiograph of the caudodorsal thorax of a horse with bilateral pneumothorax. The dorsal borders of the lung margin are marked by arrows. **B,** Same view as A after thoracocentesis and resolution of the pneumothorax.

Normal aerated lung is characterized as a hyperechoic line on the ultrasound image. Ribs are visualized as hyperechoic curved lines that cast acoustic shadows. The appearance of two ribs with acoustic shadowing in the superficial plane and the pleural line deep is defined as the “bat sign.”[12] Absence of the bat sign is characteristic of subcutaneous emphysema. Static images of air within the pleural space and the normal air-filled lung may appear similar; however, synchronous movement of the pleural line relative to the chest wall or “gliding lung sign” is characteristic of normal lung. Air that doesn't move with the respiratory cycle is seen with pneumothorax. M-mode ultrasonography can also be used to evaluate the pleural space. Normal lung on M-mode ultrasonography is represented by a series of horizontal lines representing the skin, muscular layers, and pleura. Below the pleura the normal lung appears as a granular layer. With pneumothorax, the granular layer is replaced by a continuum of horizontal

lines above and below the pleura line.[12] In experimentally induced pneumothorax, two-dimensional ultrasonography can detect as little as 50 mL of air within the pleural space and is superior to M-mode ultrasonography and radiography for identification of pneumothorax.[12]

Arterial blood gas analysis should be performed when pneumothorax is suspected. Severe alterations indicate the need for immediate support of perfusion and ventilation. Pulse oximetry can provide a continuous indicator of response to treatment.[6] Common complications include hypoxemia and possible metabolic and respiratory acidosis.[13]

Treatment for pneumothorax focuses on eliminating air from the pleural space and preventing recurrence. Obvious penetrating chest wounds should be sealed with a sterile, airtight dressing.[2,4,7] Temporary wound closure, packing, petroleum dressings, and application of plastic wrap have been recommended to stop air leakage (Fig. 31.33). Stent bandages or complete circumferential bandages should be applied for added security of closure. However, bandages around the chest should not be used when flail chest is present.[14] In most instances, pain is significant and can cause inadequate ventilation and hypoxemia (Pa_{O_2} <80 mm Hg).[1-3] Nasal or tracheal insufflation of oxygen is necessary in hypoxemic or cyanotic patients until correction of ventilation can be accomplished.[1,2,15,16] Intratracheal oxygen has been demonstrated to be superior to intranasal oxygen for increasing inspired oxygen concentrations but may also provoke coughing, which can be counterproductive.[7] Treatment of pneumothorax includes dorsal chest tube placement (10- to 14-gauge) in the twelfth intercostal space and suction of air. All wounds should be explored, cleaned, and packed. Removal of air allows reestablishment of ventilation and helps control hemorrhage from low-pressure pulmonary vessels.[2,7] Antibiotics, pain relief, and tetanus prophylaxis are indicated in most cases.[3,6,10] Simple observation of spontaneously occurring pneumothorax indicates that air is slowly resorbed with time. Approximately 1.25% of the volume of a hemithorax is resorbed in 24 hours, which means that a 20% pneumothorax would take 16 days to eliminate.[5]



FIG. 31.33 Emergency stabilization of a horse with an open thoracic wound and subsequent pneumothorax. Plastic wrap has been placed around the chest to prevent air from entering the thoracic cavity, and a Heimlich drainage valve has been attached to the dorsally placed chest tube. Intravenous fluids and intranasal oxygen are being administered.

Pleuritis or pleuropneumonia are potential sequelae to open chest wounds and necessitate culture and sensitivity to guide antimicrobial selection and ventral drainage to manage fluid accumulation. Mixed bacterial infections are expected after penetrating wounds. In a case series evaluating acute and chronic pleuritis or pleuropneumonia, pleural fluid accumulation secondary to penetrating injury was rare (3 of 43 cases).[17] Prognosis is satisfactory in most cases, with a reported 73% survival rate; however, horses that develop secondary pleuropneumonia have a guarded prognosis of 50% survival.[3,6,17,18]

Pneumomediastinum

Contents of the mediastinum include the trachea, esophagus, heart and great vessels, nerves, lymph nodes, and thoracic duct. Pneumomediastinum occurs secondary to extensive subcutaneous emphysema secondary to axillary wounds or trauma to the trachea or esophagus at the thoracic inlet. Classic radiographic features include visualization of the thoracic esophagus, great vessels, and outer

margins of the trachea.[4,6] Specific treatment is not described except for limiting aspiration of air through an axillary wound, broad-spectrum antibiotics, and monitoring for pneumothorax.

Hemothorax

Bleeding secondary to thoracic trauma may be sufficient to cause hemorrhagic shock in addition to compromising ventilation. Expected clinical signs include tachycardia, tachypnea, pale mucous membranes, weakness, trembling, and respiratory distress. Occasionally a systolic murmur may be present. It should be noted that the degree of tachycardia may not correlate with severity of pain. If heart rate is higher than expected for the apparent pain level, hemorrhage should be suspected.[7] In a survey of horses with thoracic trauma, hemothorax was identified in 40% and was not life threatening, indicating that minor vessels are most often involved.[3] Hemorrhage is severe when the heart and great vessels are damaged, and most horses with massive hemothorax do not survive.[1,2] Treatment of blood loss consists of arresting hemorrhage, restoration of circulatory fluid volume, and if indicated, whole blood transfusion.[19-21] Intravenous, polyionic crystalloids are administered at a rate of 20 to 80 mL/kg over several hours to restore circulatory volume, improve cardiac output, and increase tissue perfusion. The goal is normal to slightly low blood pressure (permissive hypotension) if hemorrhage can be stopped. Hypertonic saline (7.2%) can be administered at 2 to 4 mL/kg in horses with hemorrhagic shock but should not be used in horses with uncontrolled hemorrhage, as the increase in blood pressure may disrupt clot formation.[7] Hypertonic saline will need to be followed by isotonic fluid therapy. Colloids such as hetastarch are not recommended in horses with acute hemorrhage due to potential interference with coagulation.[21] When severe bleeding persists and signs of hypotension ensue, blood transfusion is often necessary. Losses of up to 20% of the blood volume (8% to 10% of body weight) can be tolerated without a significant drop in blood pressure. Acutely, alterations in packed cell volume (PCV) and total protein will not be evident, so the need for transfusion must be based on clinical signs such as tachycardia, poor pulse quality, pale mucous membranes, cool extremities, depression and anxiety, and weakness.[7] Alterations in blood lactate (>4 mmol/L), venous oxygen tension (<30 mm Hg), venous hemoglobin saturation (<50%), and blood pressure may further indicate the need for transfusion.[4,20] The recommended volume of blood to transfuse is 6 to 8 L in an adult horse,

which represents 30% to 40% of the estimated or calculated blood loss.[20] Blood loss estimation can be conducted using the following formula:

$$\text{Liters of blood lost} = \frac{\text{Normal PCV} - \text{Patient PCV}}{\text{Normal PCV}} \times 0.08 \times \text{Patient weight (kg)}$$

When the hemorrhage is controlled or originates from smaller vessels, removal of blood from the thorax improves ventilation and avoids secondary septic pleural effusion, pleural adhesions, and constricting fibrothorax. Patient stabilization prior to removal is necessary.[7]

Rib Fractures

Rib fractures are most commonly seen in foals and occur during birth. In a postmortem review of 760 foals, thoracic trauma was evident in 8.8%. Nineteen had fractured ribs that were believed to be the cause of death.[22] Asymmetry of the chest wall was seen in 55 of 263 foals in another study, and dystocia and a primiparous dam were identified as factors that increased the risk of thoracic trauma.[23] The percentage of rib fractures in foals admitted to referral centers may be as high as 65%.[22,24] The most common site of rib fractures in foals appears to be the costochondral junction and involves ribs 3 through 8.[22] Death in foals is usually secondary to hemothorax with respiratory collapse, myocardial lacerations, pneumothorax, diaphragmatic hernia, and hemopericardium.[22] Clinical signs of rib fractures include lethargy and recumbency, groaning and grunting, plaques of subcutaneous edema over the affected area, flinching upon palpation, and audible or palpable crepitus or clicking upon digital palpation or simultaneous auscultation.[4,24] Ultrasonography is very useful in identifying fractures and assessing underlying pulmonary injury (Fig. 31.34). Fractured ribs in foals may be reduced and stabilized using plates, self-tapping cortical screws, cerclage wire, or zip ties.[25,26] Foals with rib fractures that do not overlie the heart may be managed by complete stall rest for 2 weeks. If injuries are more severe, analgesia, thoracentesis, nasal insufflation of oxygen, whole blood transfusions, sedation, and positive pressure ventilation may be necessary.[6]

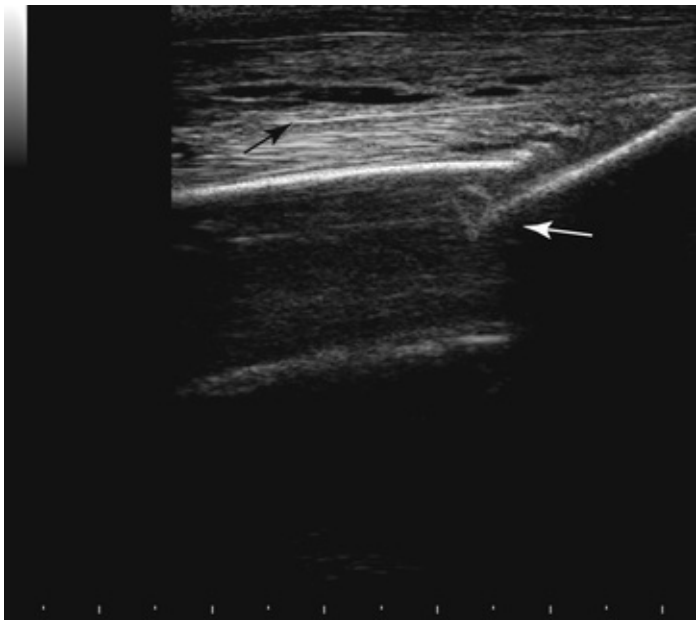


FIG. 31.34 Fractured rib *(white arrow),* saggital view. Note the edema surrounding tissues *(black arrow)* and around the fracture site.

Rib fractures in adult horses generally occur after blunt force or penetrating trauma. Thirty percent of horses with penetrating wounds may have concomitant rib fractures.[3] Radiographic identification of minimally displaced rib fractures in adult horses may be difficult because of the large mass of the horse and superimposition of ribs on the opposite side. Indeed, in many instances, rib fracture may not be apparent until a callus has formed. Fortunately, single fractures appear to heal well without surgical intervention.[2] Surgical intervention is reserved for displaced fractures that are a risk to lacerate lung, heart, or diaphragm.

Flail chest, while more common in neonates, is rarely observed in adult horses. Flail chest is defined as fracture of three or more ribs in at least two sites allowing a free-floating rib segment and a characteristic paradoxical movement of the rib segment during respiration. The segment of chest wall moves inward during inhalation and outward during exhalation.[6] Diagnosis is rare in the adult horse, as the trauma sufficient to cause a flail chest is often fatal. Flail chest causes severe respiratory compromise and often leads to severe hemorrhage due to trauma to the underlying heart and lung. Stabilization of the flail segment is essential, and suturing ribs in the affected segment to an external splint provides stability during healing.[7]

Abdominal Injury

When there is extensive thoracic trauma, the abdominal cavity should also be thoroughly evaluated. The cupula of the diaphragm can extend as cranial as intercostal space 6 during expiration, making the diaphragm vulnerable to injury with thoracic trauma. Diaphragmatic hernias can occur secondary to thoracic trauma but are rare.[27] Clinical signs may include exercise intolerance, respiratory compromise, and tachypnea. In some horses, abdominal discomfort may dominate and be consistent with either a strangulating or nonstrangulating obstruction of the intestine.[28-31] Thoracic radiography and ultrasonography may identify herniation of the diaphragm, and abdominocentesis may identify intestinal perforation or bowel rupture. Often tears are not identified until exploratory laparotomy, and they frequently occur along the ventral midline just dorsal to the xiphoid process.[4] Conservative management of diaphragmatic hernias often results in euthanasia, so surgical repair is recommended.[32,33] Multiple methods of surgical repair have been reported, and all require mechanical ventilation intraoperatively.[27,32] Aftercare is similar to that for patients with colic; however, pneumothorax should be resolved before recovery.[4]

Summary

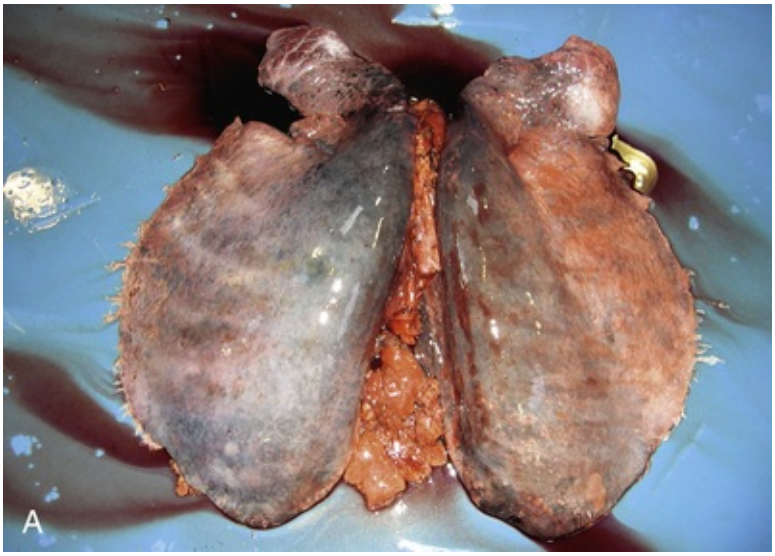
Injuries to the thorax of the horse can be managed with surgical or conservative strategies.[3,7,18,34] Initially patients require stabilization, and the extent and complicating factors of the wounds must be defined. Horses with simple rib fractures, small chest wounds, and modest pneumothorax or hemothorax are candidates for conservative management. Medical therapy includes broad-spectrum antibiotics and appropriate pain relief, thoracentesis or thoracic drain placement, second intention wound healing, and bandaging. More severe wounds require surgical intervention to exploration, lavage of wounds and body cavities, stabilization of fractures, control of hemorrhage, and removal of foreign bodies.[34]

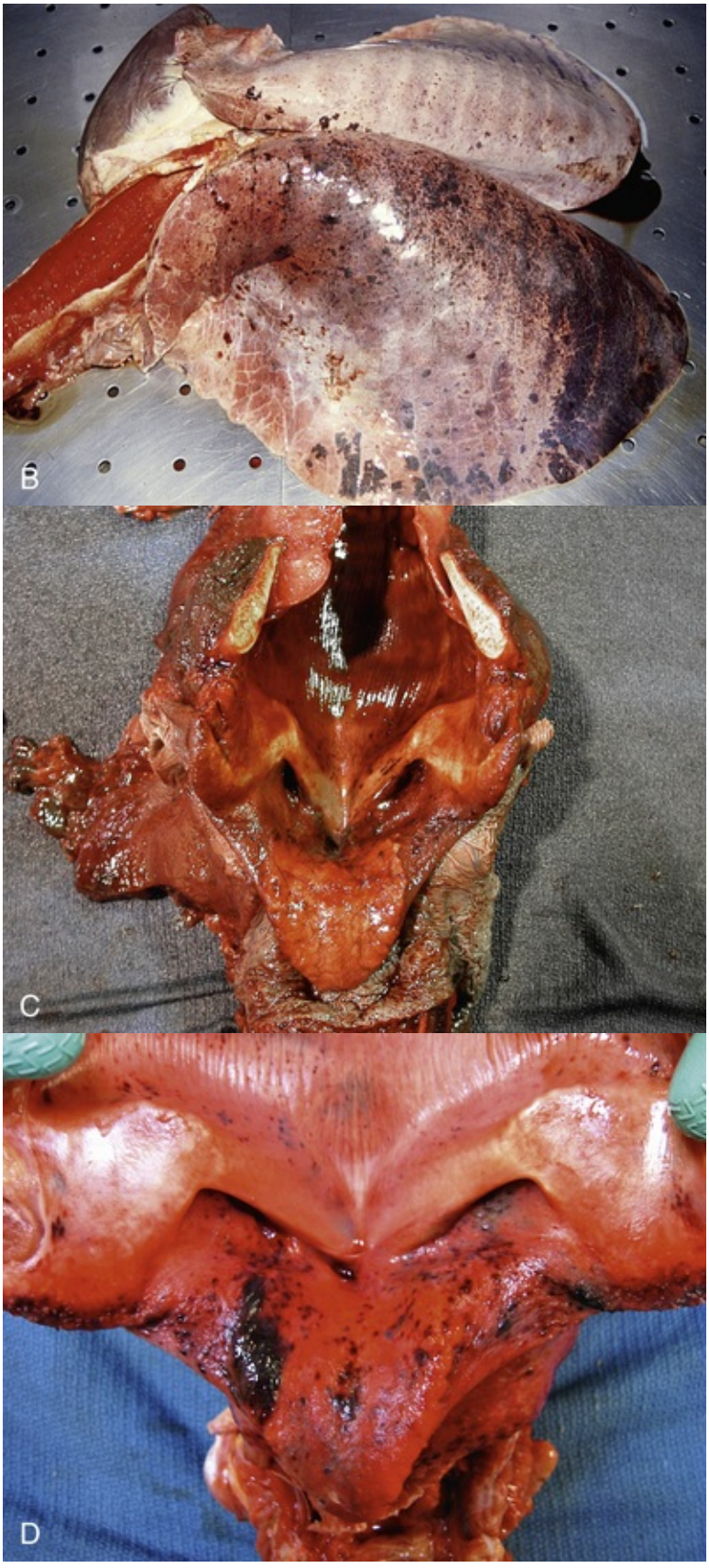
Pulmonary Edema

Pamela A. Wilkins

Pulmonary edema rarely occurs as a primary event in the horse and, when present, is usually secondary to some other pathologic process. Extravascular

fluid accumulates within the lung after events that alter hydrostatic and colloid osmotic interstitial and vascular forces change the surface area and pore size of the blood-gas barrier or diminish lymphatic drainage.[1] Pulmonary edema can be classified as cardiogenic or noncardiogenic. Pulmonary capillary pressure can be increased by any increase in left atrial or pulmonary artery pressure. In horses, this can occur secondary to acute renal failure, left heart failure, or very high cardiac output conditions, such as extreme exercise. Increases in microvascular permeability may occur with sepsis, disseminated intravascular coagulation, hypoxic acidosis, allergic responses such as transfusion reactions, or primary pulmonary pathology, resulting in the release of mediators of inflammation that increase vascular endothelial or alveolar epithelial permeability. Pulmonary edema associated with airway obstruction has been termed *negative pressure pulmonary edema* (NPPE) and has been reported in horses.[2-7] NPPE occurs secondary to inspiratory efforts against a closed glottis that result in a precipitous fall in intrathoracic pressure. The large decrease in intrathoracic pressure increases the transmural pressure gradient for all intrathoracic vascular structures, favoring movement of water into the extravascular space. Transient pulmonary obstruction may be a root cause of fatal exercise-induced pulmonary hemorrhage (EIPH) in racehorses and other horses performing at maximal exercise; these horses are predisposed because of already large transmural pulmonary vascular pressures and large intrathoracic pressure swings associated with breathing (Wilkins and Del Piero, unpublished data) (Fig. 31.35).




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FIG. 31.35 **A,** Lung from a horse that suffered sudden death on the racetrack caused by fatal exercise-induced pulmonary hemorrhage (EIPH). Note the dorsal acute hemorrhage, diffuse edema, and rib impressions present on the dorsal surface of the lung. **B,** Lung from a horse that suffered documented upper airway obstruction at maximal exertion on a treadmill. This horse experienced fatal EIPH. Note the severe pulmonary edema with hemorrhage, bloody froth in trachea, and ecchymotic hemorrhages in trachea. **C,** Larynx of a horse that suffered from fatal EIPH. Note the widespread diffuse subepithelial hemorrhage, ecchymoses, and petechia, supporting negative airway pressure as the cause. Upper airway occlusion due to left laryngeal hemiplegia is supported by the significantly decreased muscle mass of the left cricoarytenoideus dorsalis muscle bodies. **D,** Larynx from a horse found dead in stall with evidence of hemorrhagic pulmonary edema. Negative pressure pulmonary edema secondary to airway occlusion is supported as the cause of death because of its presence throughout the larynx and upper airway. (Courtesy Dr. Fabio Del Piero, Louisiana State University, Baton Rouge, La.)

Diagnosis is based on clinical examination, history of predisposing causes, and radiographs. Horses have a shallow rapid respiratory pattern and may be dyspneic. Arterial blood gas analysis may reveal hypoxemia and hypercapnia. Fine crackles or wheezes may be audible on auscultation. Patients with volume overload (associated with renal failure or, rarely, too-rapid fluid administration) or primary cardiac problems may have an increased central venous pressure with pronounced venous distention. Fluid (clear or slightly yellow or pink-tinged) may drip from the nostrils and can increase in volume without necessarily becoming frothy. Continuous coughing and production of frothy blood-tinged or bloody fluid production warrants a very grave prognosis. Radiographic findings are nonspecific but include peribronchial and perivascular cuffing, increased prominence of vessels, and a hazy reticular interstitial pattern (Fig. 31.36). Underlying pulmonary disease may obscure signs of edema, and radiographs of sufficiently high quality to show relatively subtle changes may not be obtainable in mature horses. Numerous diffuse comet-tail artifacts are seen with thoracic ultrasound examination (Fig. 31.37). Noncardiogenic pulmonary edema (capillary leak) is a component of the definition for VetALI and VetARDS (see the Acute Respiratory Distress Syndrome and Acute Lung Injury [Acute Bronchointerstitial Pneumonia] section earlier).

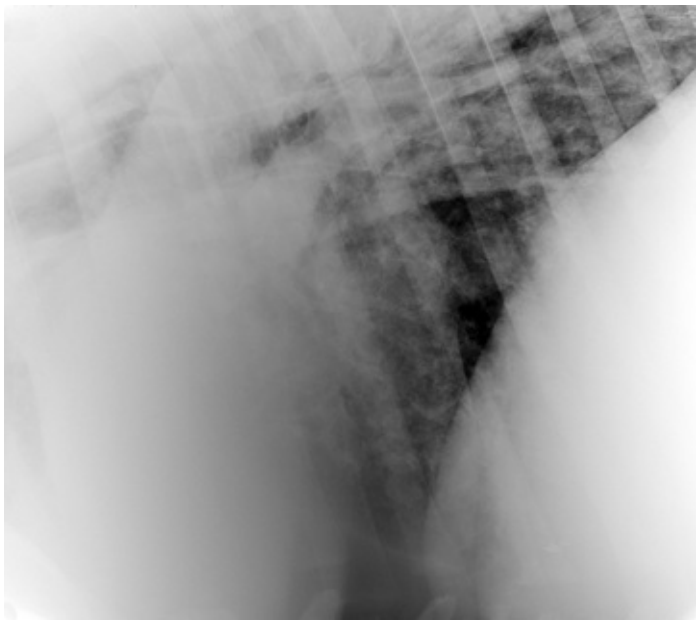


FIG. 31.36 Radiograph of caudal ventral lung of a horse with pulmonary edema. Note the mixed hazy reticular interstitial pattern. Bronchiolar cuffing is also evident. (Courtesy Dr. Midge Leitch, University of Pennsylvania, New Bolton Center, Kennett Square, Penn.)

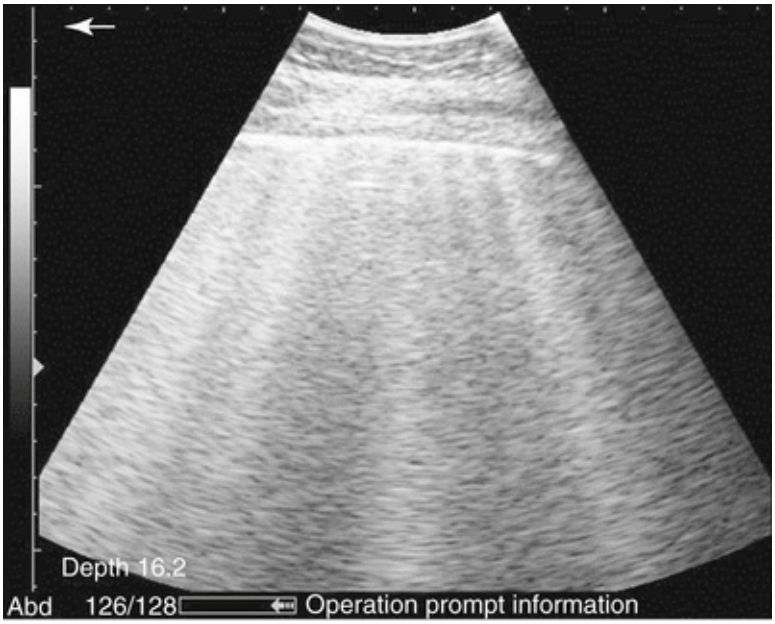


FIG. 31.37 Ultrasound image of lung of a horse with pulmonary edema. Note the multiple diffuse comet-tail artifacts. (Courtesy Dr. Kim Sprayberry, California Polytechnic State University, San Luis Obispo, Calif.)

■ Treatment

Treatment consists of correcting the cause, reversing hypoxemia, decreasing plasma volume and left atrial pressure, and increasing plasma colloid osmotic pressure. Intranasal oxygen and even positive ventilation may be needed in severe cases. Improvement in oxygenation can be monitored by sequential arterial blood gas analysis or by using transcutaneous oxygen saturation monitoring equipment (pulse oximetry) applied to the nasal mucosa, tongue, or other available nonpigmented mucous membrane. In cases of NPPE, maintaining an adequate, low-resistance airway is very important to prevent further damage, and tracheostomy may be necessary. IV fluid therapy should be guided by the patient's needs and monitored by serial measurement of central venous pressure if necessary. Furosemide may be given intravenously or intramuscularly at a dose of 1 to 2 mg/kg and repeated in 1 hour (Table 31.11). If helpful, the dose can be titrated for each patient. At a dose of 1 mg/kg, approximately 8 L of urine is produced in approximately 1 hour.[8] A few studies have been conducted on the effects of furosemide on pulmonary hemodynamics in the horse.[8-12] Furosemide provides some relief to RAO-affected horses within 20 minutes of administration, increasing dynamic compliance without affecting Pa_{O_2}.[13] The beneficial effects appear to be mediated by prostaglandin E2 (PGE2), derived from either the renal or the airway epithelium, resulting in bronchial smooth muscle relaxation. Prior treatment with flunixin meglumine prevents the furosemide-induced bronchodilation.[14] The effect in horses with pulmonary edema has not been reported. Colloid solutions should be administered cautiously or in conjunction with use of diuretics because they can initially increase vascular pressure. Plasma may be safer than other colloid preparations such as dextrans or hetastarch. Colloid solutions may be of little benefit in raising intravascular osmotic pressure in patients with increased microvascular permeability.

TABLE 31.11
Pharmacologic Treatments for Pulmonary Edema in Horses

Treatment	Reason	Route	Dose/Rate	Comments
Oxygen	Hypoxemia	Intranasal insufflation	5-15 L/min	Aim for Pa_{O_2} >85 mm Hg, O_2 sat >90%
Furosemide	Diuresis	Intravenous	1 mg/kg	Repeat as needed; monitor acid-base status, hydration, and

				electrolyte concentrations
Furosemide	Bronchodilation	Nebulization		Will not be effective with concurrent NSAID administration
Bronchodilators (various)	Bronchodilation	Nebulization Oral Intravenous	See the Summer Pasture–Associated Obstructive Pulmonary Disease section	Many will be effective, described in depth elsewhere
Flunixin meglumine	Antiinflammatory	Intravenous	1 mg/kg	bid; monitor renal function
Diphenhydramine	Antihistamine	Intravenous	0.1-1 mg/kg	bid; monitor for excessive drowsiness
Epinephrine	Anaphylaxis	Intravenous	3-5 mL IM for 450-kg horse	Use ONLY for treating anaphylaxis

bid, Twice a day; *IM,* intramuscularly; *NSAID,* nonsteroidal antiinflammatory drug; *O_2 sat,* percentage oxygen saturation; *PaO_2,* partial arterial oxygen pressure.

Antiprostaglandin drugs (flunixin meglumine, phenylbutazone) and antihistamines may help and are indicated particularly in cases of anaphylactic reaction, as are diphenhydramine and epinephrine (see Table 31.11). Bronchodilators may be of benefit (see Table 31.11). The use of corticosteroids remains controversial; if they are used, antimicrobial coverage is advisable, as pulmonary edema has been shown to impair pulmonary bacterial defense mechanisms.

Smoke Inhalation

Peggy S. Marsh

Smoke inhalation injury is typically associated with exposure to fires, and there are often concurrent problems in other body systems from thermal injury. Thermal injury, along with smoke inhalation, leads to both local and systemic lesions. Diffuse tissue edema may occur and can create organ dysfunction. Severely affected patients may develop complex problems, including life-threatening sepsis, systemic inflammatory response syndrome, and in some cases, multiple organ system failure.[1]

Insult to the respiratory system by smoke inhalation depends on the fuels that burned, the completeness of combustion, the heat intensity, and the duration of exposure. In general, lesions are initiated by three mechanisms. The first is direct thermal injury, which is often limited to the upper respiratory tract by laryngeal reflexes and efficient heat exchange within the nasal passages.[2] Second, toxic chemicals in the smoke can cause damage, both directly and indirectly, through inflammatory mediators. Carbon monoxide intoxication is commonly associated

with human injuries from smoke and is a product of incomplete combustion.[3] Finally, with combustion there is consumption of oxygen, and the resulting low Pa_{O_2} can lead to pulmonary vasoconstriction as well as generalized hypoxia.

Three phases of pulmonary dysfunction have been described in the horse.[4,5] The first stage is acute pulmonary insufficiency caused by several mechanisms. Carbon monoxide may be present in sufficiently high concentration to cause toxicity within a short time after exposure. Carbon monoxide combines with hemoglobin to form carboxyhemoglobin. Hemoglobin has a 200 to 250 times greater affinity for carbon monoxide as compared with its affinity for oxygen.[3] High levels of circulating carboxyhemoglobin result in a shift of the oxyhemoglobin dissociation curve to the left, thereby decreasing oxygen release at the tissue level and leading to tissue hypoxia. Other processes occurring during this acute phase include progressive edema and necrosis in the upper respiratory tract, leading to airway obstruction; bronchoconstriction in the lower respiratory tract, caused by the irritating effects of noxious products; and altered pulmonary blood flow.[6]

These insults produce the second stage: formation of pulmonary edema, lower airway obstruction, and pulmonary parenchymal lesions. Within 48 to 72 hours after exposure, driven by pulmonary macrophages, neutrophils are called into the area of insult. They release cytokines, proteolytic enzymes, and oxygen-derived free radicals. Expression of the inflammatory cascade in excess of balance causes microvascular damage, leading to increased extravascular lung water. Local insult also results in the release of tissue factor, initiating the coagulation cascade to produce fibrin. Debris from the inflammatory cascade, along with fibrin and material directly deposited from smoke inhalation, create pseudomembranous casts, which may obstruct the small airways. Widespread plugging of the airways may significantly increase airway pressure, causing barotrauma and alveolar damage.[6] The last stage, bronchopneumonia, occurs as a result of local and systemic impairment of the host immune system. This phase may take up to 1 to 2 weeks after the initial injury to develop.

It is common for horses with smoke inhalation injury to also have burn injury. A complete description of this process in horses has been reported.[7] Thermal injury causes a local response that includes microvascular insult and direct tissue coagulation leading to inflammation, local edema, and finally necrosis. Extensive local injuries will drive a systemic response. An initial decrease in systemic organ blood flow is followed by the formation of generalized edema.

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The pathophysiology of edema formation is complex and involves protein shifts, endothelial damage, and alteration of the interstitial architecture, all leading to a net accumulation of fluid in the interstitial spaces.[8] Over time, major thermal injury is characterized by high cardiac output, increased oxygen consumption, and protein and fat wasting, all of which may create a hypermetabolic state.[9,10] Loss of skin as a barrier, release of inflammatory mediators, and hypermetabolism play a role in the development of immunosuppression. Other features noted with burn injury in the horse include acute hemolysis, renal failure, laminitis, and myositis.[11]

Horses exposed to smoke will have a variety of clinical signs depending on the duration and type of exposure and the length of time from the insult. Acutely in more severe cases, within the first 6 hours, signs of carbon monoxide toxicity and shock may occur. The patient shows signs of severe hypoxemia and may be depressed, disoriented, irritable, ataxic, or even moribund. As edema and necrosis progress in the upper respiratory tract, dyspnea and stridor may develop. Auscultation of the thorax may reveal decreased air movement, crackles, or wheezes, but these may not become apparent for 12 to 24 hours. If edema of the airways is sufficiently severe, airflow may be severely restricted. Edema fluid may be visible at the nostrils and later may be replaced by inflammatory exudate. Concurrent edema formation may be occurring systemically. Hypoxia and generalized edema may lead to dysfunction of distant organs such as the kidneys and muscles. Signs of infection may be difficult to ascertain from other signs. All that may be noticed is a fever and a worsening of respiratory signs after initial improvement. As noted in a recent report, clinical signs may become more complex when there is thermal injury.[12] Exposure to smoke without thermal injury can also occur, as with unhealthy air created by large wildfire smoke and associated debris. Clinical signs of an irritated respiratory tract are seen, similar to horses with chronic inflammatory airway disease.[13]

Diagnosis is typically based on history and physical examination. A normal initial examination does not rule out exposure because the onset of clinical signs may be delayed several days. Within a short time after exposure, carboxyhemoglobin concentration in venous blood can be measured. A level above 10% is consistent with carbon monoxide toxicity.[3] Various diagnostic tests are useful in determining the extent of respiratory injury. These tests include endoscopy of the upper respiratory tract and tracheobronchial tree, thoracic

radiographs, blood gas analysis, hematology, and cytologic evaluation of tracheal aspirates. Any or all of these tests can be performed on a serial basis as prognostic aids. Diagnostic tools for other organ injury include blood pressure monitoring, measurement of central venous pressure, serial hematologic and serum chemistry analyses, and monitoring of urine production.

Treatment depends on the stage and extent of injury. Initially, oxygen support is of benefit. It is a treatment for carbon monoxide toxicity and helps reduce hypoxemia.[14] Humidified oxygen can be supplied by nasal insufflation or via transtracheal catheter. Upper respiratory tract obstruction may necessitate a tracheostomy. Attention should be paid to keeping the airways clear, and nebulization may help. Bronchodilators may be useful in counteracting reflex bronchoconstriction. Decreasing inflammation and pulmonary edema may necessitate the use of diuretics and NSAIDs. Use of corticosteroids is controversial because of the potential for immunosuppression and laminitis.[4] Where available, hyperbaric oxygen therapy has been used.

Secondary complications require attention. Cardiovascular compromise and burn-induced edema may necessitate the judicious use of intravenous fluids. To prevent infection, strict hygiene, meticulous nursing care, and optimal nutritional support should be provided.[1,7] Prophylactic antimicrobial use is not recommended in human patients. Documented infection should be treated with appropriate antimicrobial agents based on results of culture and sensitivity patterns.[1,7] Proper management of chronic smoke exposure includes limiting exercise and a full veterinary examination of the respiratory tract before return to work.[13]

Recurrent Airway Obstruction

Dorothy M. Ainsworth

In a recent American College of Veterinary Internal Medicine (ACVIM) consensus statement, it was suggested that because of their similarities to human asthma, recurrent airway obstruction (RAO), summer pasture–associated obstructive pulmonary disease (SPAOPD), and equine inflammatory airway disease (IAD) now be classified under the umbrella term *equine asthma*.[1] In recognizing that differences in the clinical severity of these three inflammatory conditions exist, it was further suggested that horses with RAO or SPAOPD (either symptomatic or in remission) be referred to as having severe equine

asthma; those horses with IAD should be diagnosed as mild or moderate equine asthmatics.[2] For simplicity, the terms RAO and SPAOPD are used in the following sections.

■ Definition and Etiology

RAO is a pulmonary inflammatory condition that affects mature horses usually older than 7 years of age. It is characterized by excessive mucus production, airway neutrophilia, bronchial hyperreactivity, and in most cases, reversible bronchospasm. Previously, the condition has been called heaves, chronic obstructive pulmonary disease (COPD), broken wind, hay sickness, and small airway disease.[3]

RAO typically occurs in adult horses residing in the northeast and midwest regions of the United States and Canada, as well as in Great Britain and in Europe—locales where the climate is wet and cool and horses are stabled and fed hay. RAO also occurs in horses pastured outdoors but fed dusty hay, especially from round bales. It rarely occurs in horses maintained in warm, dry climates, such as those found in California or in Australia.[4] In North America the prevalence of RAO diagnosed at veterinary teaching hospitals positively correlated with rainfall, minimum temperatures, and total pollen and mold counts occurring 1 to 3 months previously.[5] These findings suggest that environmental conditions are integral to the development of the disease in genetically susceptible horses.

RAO reflects a hyperreactivity to inhaled molds and organic dusts contained in the feeds, hay, and straw. It resembles occupational (neutrophilic) asthma found in humans exposed to organic dusts typically found in animal husbandry operations.[6] Identifying the *specific* causative agents within the hay dust that induce the equine disease has been a challenge, as stable dust contains more than 50 species of molds, large numbers of forage mites, endotoxins, and other inorganic components.[7] Inhalation challenge with endotoxin induces airway neutrophilia but not all of the characteristic pulmonary function changes of RAO.[8,9] Likewise, inhalation challenge with aqueous extracts of *Aspergillus fumigatus, Faenia rectivirgula (Micropolyspora faeni),* or *Thermoactinomyces vulgaris* partially induces RAO in susceptible horses.[10-12] Complete experimental induction of RAO in susceptible horses requires inhalation of hay dust particulates either by natural challenge (hay feeding) or by nebulization of a hay dust solution or a solution containing fungal spores, endotoxin, and silica

microspheres.[13-17]

Development of Pulmonary Inflammation

Within hours of hay dust exposure, airway neutrophilia and excessive mucus production are evident endoscopically and cytologically.[18,19] Alveolar macrophages, isolated from RAO-susceptible horses just 6 hours after nebulization of a hay dust solution,[20] have upregulated gene expression of TNF-α, IL-1β, and IL-8. The trigger for gene transcription may reflect activation of nuclear factor kappa B (NF-κB) by Toll-like receptors 2 and 4 (TLR2 and TLR4) following exposure to fungal wall components, endotoxin, or other bacterial cell products.[21] The expression of hypoxia-inducible factor 1α (HIF-1α) is thought to enhance TNF-α, IL-8, and vascular endothelial growth factor (VEGF) expression through the NF-κB pathway.[22]

Macrophages.

The initial upregulation of macrophage-derived proinflammatory gene transcription is to be transient, with mRNA levels returning to preexposure levels 24 hours after hay dust challenge.[20,23,24] With continuous, chronic hay dust exposure, protein and the gene expression levels of IL-8, IL-1β, and TNF-α in the BAL cells remain upregulated, which probably reflects contributions from recruited neutrophils and other cells.[25-28] The net effect of these proinflammatory cytokines (and others such as IL-17, see below) is to enhance the chemokinetic gradient existing within the airways and to promote neutrophilic extravasation.[29,30] The neutrophil intracellular signaling pathways required for extravasation into the airways involve mitogen-activated protein kinases (MAPKs) and/or phosphoinositide 3-kinase (PI3K) as inhibition of these pathways attenuates neutrophil chemokinesis.[30] In RAO-affected horses, at least one mechanism that tempers neutrophil chemotaxis, secretoglobin production, is attenuated. These are mucosal epithelial-derived proteins that reduce IL-8–stimulated chemotaxis of blood-derived neutrophils. They also sequester calcium and phosphatidylcholine, a cofactor and substrate, respectively, both of which are required for phospholipase A2 activity.[31] RAO-affected horses have reduced secretoglobin concentrations in their BAL, suggesting an absence of an inflammatory braking mechanism.[31-33]

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Lymphocytes.

The role of lymphocytes, especially T-helper cells, in the development of the pulmonary inflammatory response remains uncertain. Data that support the hypothesis that RAO is an IgE-mediated (T-helper type 2 [Th2]) disorder include the findings of elevated allergen-specific IgE concentrations in the serum[34] and in the BAL fluid of RAO-susceptible or affected horses,[35,36] increased numbers of IL-4 and IL-5 (mRNA-positive) BAL fluid cells (detected by in situ hybridization techniques) in RAO-affected horses,[37,38] and genetic studies that suggest a phenotypic association (at least in one family of Swiss Warmblood horses) with a locus on equine chromosome 13 that contains the IL-4 receptor gene.[39] Although Th2 disorders are typically characterized by eosinophilic infiltrates, it has been hypothesized that IL-4 activates its receptor on neutrophils to inhibit neutrophil apoptosis, to increase protein synthesis, and to upregulate the expression of the IL-9 receptor.[40] This results in enhanced IL-8 production and neutrophil influx.[40,41] Although the gene expressions of IL-4 and IL-9 receptors are upregulated in peripheral blood neutrophils isolated from RAO-prone and RAO-affected horses, linking this pathway to the Th2 limb in horses requires additional investigation and confirmation.

Other data suggest that RAO does *not* reflect a polarized Th2 immune response. There are no significant differences in IgE-protein–positive cells in the lung tissue samples or in the BAL cells of RAO-affected horses compared with control horses.[42,43] Second, in those two well-studied Swiss Warmblood families classified as healthy or RAO-affected (based on a horse owner assessed respiratory signs index [HOARSI]), no significant differences in serum IgE concentrations against recombinant *A. fumigatus* antigen were found.[44] Third, results of IgE serologic and intradermal testing failed to detect a difference between RAO-affected and control horses.[45] Fourth, cytokine profiles of BAL cells[27,28] or of pulmonary CD4+ and CD8+ cells[46] isolated from RAO-affected horses during the first 24 or 48 hours after hay dust exposure fail to demonstrate an upregulation of IL-4, IL-5, or IL-13. Furthermore, chronic (3-week) hay dust exposure is associated with an increase in the gene expression of IFN-γ in the BAL fluid cells,[26,27] although in one trial, but not in the second trial of the same chronically affected horses, the gene expression of IL-4 was upregulated.[26] Fifth, GATA3, the transcription factor required for IL-4 gene expression, is not upregulated in the bronchial cells of RAO-affected horses.[47] Sixth, IL-4 gene

expression in the pulmonary lymph nodes isolated from chronically affected RAO horses is significantly downregulated compared to controls.[48] Importantly, these data *do not* provide evidence that RAO is a Th1 immune response because (1) concomitant increases in the gene expression of T-bet, the transcription factor for IFN-γ expression in CD4+ cells, does not occur.[27] Interestingly, in other species TLR stimulation leads to the production of proinflammatory factors, including IL-12, and subsequent IFN-γ synthesis.[49,50]

In RAO-affected horses there is evidence that, as occurs in human asthmatics, Th17 cells (a subset of T-helper cells) contribute to the immunopathogenesis of RAO.[28,29,48] IL-17, secreted by Th17 cells and some granulocytes, promotes maturation, chemotaxis, and activation of neutrophils. IL-17 also upregulates the gene expression of IL-8 in the airway epithelium and promotes airway neutrophilia. Following chronic (≥2 weeks) hay dust exposure, IL-17 gene expression in BAL cells is upregulated in RAO-affected horses.[28,29] Increased IL-17 protein expression, detected immunohistochemically, is also found in the pulmonary lymph nodes of RAO-affected horses compared to controls.[48]

Currently little is known about the role of regulatory T cells (Tregs) in the immunopathogenesis of RAO. In mice and humans, this subset of CD4+ cells helps control immune responses to viral, bacterial, fungal, and parasitic infections.[51] In a study of RAO-affected horses during remission and exacerbation (4 days of hay challenge), the percentage of Tregs (CD4+, CD25+, Foxp3+) in the BAL increased from a baseline value (remission) of 1.5% to 4% (exacerbation).[52] Investigators hypothesized that the increase in Tregs may help resolve immune-mediated bronchial inflammation.

Epithelial Cells.

The airway epithelium not only serves as a physical barrier but also plays a key role in the secretion of cytokines needed to recruit inflammatory cells, to direct tissue-resident or circulating antigen-presenting cells, and/or to promote lung remodeling. It is likely that the inhaled microbial components bind to the airway epithelium via pattern recognition receptors and initiate an innate immune response with synthesis of inflammatory cytokines and chemokines.[17] In RAO-affected horses, bronchial epithelial IL-8 gene and protein expression is upregulated at least 24 hours after hay challenge,[28,53] potentially contributing to airway neutrophilia. Bronchial gene expression of other chemokines (CXC chemokine ligand 1 [CXCL1], granulocyte-macrophage colony-stimulating

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factor [GM-CSF], granulocyte colony-stimulating factor [G-CSF]) or cytokines (IL-5, IL-6, IL-10, IL-17, and transforming growth factor [TGF]–β1) is not different between control and diseased horses.[28,53] In a recent transcriptome analysis of endobronchial biopsies from affected horses, investigators reported an upregulation of genes involved in neutrophil chemotaxis (IL-8, CXC chemokine receptor type 2 [CXCR2]) and immune and inflammatory responses (matrix metalloproteinase [MMP]–1, MMP-8), suggesting that bronchial epithelium is an important contributor to the inflammatory process of RAO.[54]

Other Inflammatory Mediators.

As airway neutrophils and other cells accumulate, other inflammatory mediators are released and contribute to the inflammation. Histamine, released by degranulated mast cells, increases vascular permeability and produces bronchoconstriction. Although mast cell degranulation is typically attributed to IgE-mediated crosslinking of high-affinity receptors (FceRI) on mast cells, leukotrienes, prostaglandin E, acetylcholine, substance P, endothelin, and peptidoglycan induce mast cell degranulation.[55,56] Despite increased histamine concentrations in the BAL of RAO-affected horses, histamine-1 receptor antagonists provide little therapeutic relief for affected horses, suggesting that it is not a predominant inflammatory mediator in RAO.[57] The potential role of prostaglandins, with their bronchoconstrictive ($PGF_{2\alpha}$, PGD_2, thromboxane A2 [TXA2]) and/or bronchodilatory capabilities (PGE2, PGI_2), has also been examined. In a differential gene expression study of lung tissue from RAO-affected horses, PGF synthase, an enzyme that reduces PGD_2 and PGH_2 to $PGF_{2\alpha}$, and PTGDR, a PGD_2 receptor, were upregulated.[58] In diseased horses, increases in BAL PGE2 and $PGF_{2\alpha}$[59,60] and in serum TXB2 (a metabolite of TXA2) occur.[61] Although administration of a cyclooxygenase inhibitor prevents the increase in the serum TXB2 in RAO-affected horses, it does not inhibit the development of airway hyperresponsiveness or bronchospasm in susceptible horses. This suggests that eicosanoids are not the major contributor to clinical signs. Lipoxygenase metabolites have also been investigated in RAO-affected horses. In humans, these compounds are bronchoconstrictors (leukotriene [LT] B4, LTC4, and LTD4), mucus secretagogues (LTC4 and LTD4), and chemokines (LTB4).[62] Inhalation of LTB4 or LTD4 induces airway neutrophilia and bronchoconstriction, respectively, in normal and RAO-affected horses.[63] BAL

cells isolated from RAO-affected horses during the first 48 hours of hay dust exposure and stimulated ex vivo produce increased concentrations of LTB4 and LTC4.[62] However, actual BAL concentrations of LTB4 and LTC4 are not elevated in chronically affected horses[60] despite the finding of the enhanced gene expression of LTA4 hydrolase (which metabolizes LTA4 to LTB4) in RAO-affected horses.[58] Pretreatment of RAO-susceptible horses with either a 5-lipoxygenase inhibitor or a LTD4 receptor antagonist before hay dust exposure does not prevent the development of airway neutrophilia or alterations in lung mechanics.[64,65] In addition, treatment of clinically affected horses with the leukotriene receptor antagonist montelukast (LTC4, LTD4, LTE4 antagonist) also fails to improve pulmonary function test results, clinical scores, or arterial blood gas tensions.[66]

Reactive oxygen species derived from pulmonary macrophages and granulocytes contribute to the inflammatory process of RAO.[67] Oxidative stress occurs when enzymatic (superoxide dismutase, glutathione peroxidase, glutathione *S*-transferase) and nonenzymatic antioxidants (glutathione [GSH], ascorbate, α-tocopherol, bilirubin, albumin, and transferrin) are depleted.[68] Evidence of an oxidant stress within the airways of RAO-affected horses is based on the findings of (1) increased levels of oxidized glutathione (glutathione disulfide [GSSG]), (2) increased glutathione redox ratios (GSSG/GSSG + GSH), and (3) decreased ascorbic acid concentrations in the pulmonary epithelial lining fluid of RAO-affected horses.[67-69] Tan and colleagues also reported that both red blood cell and white blood cell glutathione peroxidase activities were significantly increased in RAO-affected horses during exacerbation compared with controls, suggesting a systemic response to the pulmonary inflammation.[68] (Systemic responses are discussed below.) Changes in these indices of oxidant stress correlate with lung dysfunction parameters (pulmonary [R_L], C_{dyn}, and Pa_{O_2}) in RAO-susceptible and RAO-affected horses.[70] Although reactive oxygen species (ROS) are well recognized for their microbicidal activities, they also upregulate proinflammatory gene expression by activating NF-κB.[71]

Proteases derived from airway phagocytes, lymphocytes, and epithelial cells may propagate the inflammatory reaction of RAO. MMPs with elastolytic and collagenolytic activities have been identified in the respiratory tract secretions of RAO-affected horses and include MMP-1, MMP-8, MMP-9, and MMP-13.[72-77] The degradative effect of MMP-9 on the basement membrane and on the

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extracellular matrix components facilitates the extravascular movement of neutrophils into the airways. The collagenase activity of MMP-8 and MMP-13 contributes to airway remodeling during disease exacerbation.[76] In vitro, tetracycline derivatives effectively inhibit MMP activity detected in tracheal epithelial lining fluid,[77] but their efficacy in ameliorating or preventing the inflammatory response of RAO-susceptible horses exposed to hay dust remains to be determined.

■ Epidemiology and Genetics

RAO occurs in both ponies and horses, but no gender or breed predisposition has been identified.[78,79] The prevalence of RAO is dependent on the geographic region examined. Bracher reported that 60% to 80% of Swiss horses older than 8 years of age suffer from some degree of this disease. In North America and in Europe the prevalence of RAO is estimated to range from 12% to 50%.[78] Although exposure to hay particulates is integral to the development of the disease, the role of a prior viral (or bacterial) infection in inducing susceptibility to hay dust hypersensitivity remains to be established. Horses with IAD (mild to moderate equine asthma) share some of the clinical features of RAO,[80] yet the relationship of IAD to the development of RAO is unknown. Currently there is no evidence that IAD progresses to RAO.[1,3]

A heritable component of RAO disease susceptibility exists. Marti and colleagues examined families of RAO-affected warmblood and Lipizanner horses and found that the risk of developing RAO was 3.2 times higher when one parent (dam or sire) had RAO and 4.6 times higher when both parents did.[81] In segregation and genomic analyses of two families of Swiss Warmblood horses, the mode of inheritance of RAO is characterized by major gene effects but the potential candidate genes differ between the two families.[39,82] In one family of Swiss Warmblood horses, RAO was transmitted in an autosomal recessive mode with the major association of microsatellites or single nucleotide polymorphisms and affected cases being found on equine chromosome 13 (ECA13).[83] In the other family of Swiss Warmblood horses, an autosomal dominant mode of inheritance was found, with the major association found on ECA15.[82] Investigators suggested that the observed genetic heterogeneity between the two families of Swiss Warmblood horses may reflect etiologically distinct subgroups of RAO that are not distinguished phenotypically. Proposed

potential candidate genes on ECA13 were those encoding receptors for IL-4 *(IL4R)* and IL-21[39]; on ECA15, a potential gene of interest was *SOCS5* (suppressor of cytokine signaling 5). Using a high-density SNP chip to re-genotype a subset of that same Swiss Warmblood family, Schnider identified an association (single SNP) located in an intron of *TXNDC11;* this locus was separate from the other previously identified regions.[84] *TXNDC11* encodes a thioreductase involved in the degradation of glycoproteins and, in cell cultures, mucin expression by *MUC5AC* gene. However, this SNP association failed to reach Bonferroni corrected genome-wide significance threshold. Although the results are intriguing, it remains to be determined if RAO genetic susceptibility maps to loci on ECA13 and ECA15 in other horse breeds. Lastly, as copy number variations may help identify candidate genes involved in disease processes, Ghosh and colleagues investigated this in a genomic analysis of RAO-affected and control horses (multiple breed types). Although 20 RAO-specific copy number variant regions were identified in 9 of 16 horses, they were distributed on 15 autosomes, and none was on ECA13.[85]

■ Clinical Signs and Differential Diagnosis

The severity of clinical signs in RAO-affected horses is variable and is exacerbated by stabling, exposure to dusts, hay, and ammonia fumes. Winter is considered a risk factor for disease exacerbation. However, RAO-susceptible horses kept outdoors during hot, humid summer weather—which may reflect a period of high concentrations of airborne pollen and spores—also exhibit a worsening of clinical signs.[86] In a study of 148 cases of RAO presented for evaluation to a veterinary referral hospital in the United Kingdom, the chief complaints (median duration of which was 7 months) were coughing (84% of cases), bilateral nasal discharge (54%), exercise intolerance (51%), and postexercise breathing difficulty (23%).[87] In a review of 16 cases presented to a veterinary teaching hospital in western Canada, the most common historical complaint (88% of cases) was coughing.[88] In a review of 65 cases presented to a veterinary teaching hospital in the northeastern United States, the primary problems were abnormal breathing effort (68% of cases), nasal discharge (50%), and a spontaneous cough (46%).[89]

On physical examination, mildly affected horses are typically afebrile and exhibit a bright demeanor and a normal or slightly accentuated (abdominal) breathing effort, respiratory rate, and heart rate. Nasal discharge may not be

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evident in all cases, perhaps because horses swallow excessively the expectorated exudate. When the horse is exercised, a thick white nasal discharge and a cough become apparent. The frequency of coughing increases when horses are stabled, often exceeding 10 to 15 coughs per hour.[90] More severely affected horses exhibit tachypnea (respiratory rate >40 breaths/min), nostril flaring, and a markedly accentuated expiratory effort (heave). The thoracic expiratory component may precede that of the abdominal compartment, producing a "double effort."[91] Abdominal pressure swings may be large enough to cause the anus to protrude with expiration. Paroxysmal coughing, bilateral nasal discharge, anxious facial expression, flatulence during coughing, reluctance to move, inappetence, and weight loss occur in the most severely affected cases.

Although RAO is a diffuse lung disease, auscultation of mild cases may not reveal abnormal lung sounds unless a rebreathing bag is used to induce a hyperpnea. In one survey, abnormal thoracic (47% of cases) and tracheal (63% of cases) auscultation occurred.[87] In the latter, abnormal lung sounds and "mucus clicks" (tracheal exudate) were detected by tracheal auscultation. In mildly affected horses, only regional areas of adventitious lung sounds (crackles or high-pitched expiratory wheezes) may be detected. In contrast, in severely affected horses, wheezes and mucus clicks may be heard at the horse's nostrils without the use of a stethoscope. Depending on the severity of the disease, thoracic percussion may be normal or may reveal expansion of the caudal lung fields beyond the normal line of pleural reflection.

Researchers have developed clinical scoring systems to categorize the severity of RAO. In moderately to severely affected horses, there is a very good correlation between the clinical signs and alterations in R_L or C_{dyn},[92] but in mild cases, clinical scores underestimate the severity of changes in the pulmonary function tests. In another study of 30 RAO-affected horses and 10 controls, investigators found that the severity of some clinical signs (e.g., cough, nostril flare, abdominal lift but not breathing frequency, thoracic auscultation, exercise intolerance) correlated with tracheal mucus scores, BAL neutrophil percentages, and thoracic radiographic evidence of bronchial and tracheal thickening.[93]

In rare cases, horses with long-standing RAO develop cor pulmonale, evidenced by jugular distention, pulsation, ventral edema, and tachycardia.[94,95] Although RAO-susceptible horses exhibit echocardiographic alterations during acute episodes of RAO (characterized by an increase in pulmonary artery diameter, a decrease in left ventricular diameter, and an abnormal septal motion),

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serum troponin measurements remain normal.[96] Because the echocardiographic parameters (reductions in the circumferential ratio of the aorta to the pulmonary artery and in the mass ratio of the left ventricle and septum to the right ventricle) return to normal when horses are in remission, it is likely that the reversibility of the airway disease reduces the risk of permanent myocardial disease.[95,97]

■ Laboratory Aids and Diagnostic Tests

The diagnosis of RAO is based on the history, the clinical signs, demonstration of the reversibility of airway obstruction following bronchodilator administration, and the response to therapy. A definitive diagnosis may be challenging in asymptomatic or mildly affected cases necessitating a “hay challenge” to precipitate clinical signs. Endoscopic examination of the respiratory tract of RAO-affected horses demonstrates excessive amounts of tracheobronchial secretions (mucus) that originate from most of the bronchial segments. Distal airways are edematous and inflamed, and airways easily collapse during expiration. Expectorated secretions from the lower respiratory tract coat the pharynx, larynx, and other structures of the upper respiratory tract. Cytologic analysis of lower respiratory tract secretions (BAL) is helpful in symptomatic cases. During periods of clinical remission, BAL cell populations obtained from RAO-susceptible horses consist predominantly of mononuclear cells (90% macrophages and lymphocytes) and do not differ from those found in healthy horses.[98] BAL from symptomatic horses contains more than 25% nondegenerative neutrophils and often exceeds 90% of the total nucleated cell count. Yet the extent of pulmonary neutrophilia alone is not correlated with severity of clinical signs.[99] In most cases the percentage of eosinophils or mast cells is not increased in affected horses. Thus cytologic analysis of BAL in RAO-affected horses reflects a suppurative nonseptic inflammation with increased mucus concentrations, distinguishing this disorder from lungworm infections (pulmonary eosinophilia), bacterial pneumonia (degenerative neutrophils, intracellular bacteria), or fungal pneumonia (degenerative neutrophils, hyphae, erythrocytes). In rare cases, infectious bronchitis may complicate RAO.

In general, the complete blood cell count (CBC) and serum biochemistry profiles are usually normal in RAO-affected horses.[89] In severely affected horses, a mature neutrophilia and lymphopenia may be evident on the leukogram. The “stress leukogram” reflects the effects of increased plasma

cortisol concentrations that occur at least 6 hours after RAO-susceptible horses are exposed to a high-dust environment.[100] Significant increases in serum haptoglobin, amyloid A, and functional fibrinogen concentrations in RAO-affected horses (maintained in dusty environments for >30 days) occur, challenging the conventional idea that RAO is a compartmentalized inflammatory response.[101,102]

Arterial blood gas analyses are normal in approximately 25% of the cases[103]; other cases exhibit hypoxemia (Pa_{O_2} <85 mm Hg) with or without evidence of arterial hypercapnia.[104] In symptomatic horses that are exercised, at a given work effort the arterial oxygen tensions are reduced compared with blood gas values obtained from the same horses during clinical remission.[105] The prognostic value of arterial blood gas alterations in RAO-affected horses has not been examined.

Digital thoracic radiographs of RAO-affected horses demonstrate an unstructured interstitial and/or bronchointerstitial pattern. The diaphragmatic silhouette may be flattened or concave in some horses, presumably due to lung hyperinflations.[106] Yet radiographs are of limited value in diagnosing RAO because the accentuated bronchointerstitial pattern can be detected in healthy aged horses. Radiographs are useful in *ruling out* thoracic neoplastic or infectious disorders (e.g., interstitial or bronchopneumonia pneumonia, equine multinodular pulmonary fibrosis) in horses that have clinical signs resembling RAO (cough, nasal discharge, abnormal breathing effort). In severely affected horses that repeatedly fail to respond to medical interventions, radiographs should be taken to determine if bronchiectasis (dilation or deformation of the bronchi or bronchioles) exists.[107] Bronchiectasis causes irreversible airway obstruction due to collapse of affected airways; it is a relatively uncommon complication of RAO.

Ultrasound evaluation of RAO-affected horses confirms a shift of the caudal lung border caused by alveolar hyperinflation.[108] However, gas in the large colon (left side) or in the cecum (right side) may preclude complete imaging of the most caudal extent of the lung fields at the sixteenth intercostal space. Thoracic ultrasonograms demonstrate small hypoechoic areas of irregularity on the lung surface. Ultrasonography is not useful in detecting airway inflammation.

Lung biopsies, although not typically performed to diagnose RAO, demonstrate bronchiolar goblet cell metaplasia, bronchiolar luminal exudate,

peribronchiolar lymphoplasmacytic cell infiltration, and accumulations of neutrophils within the airways.[88] The potential disadvantages of performing a lung biopsy include the risk of inducing hemorrhage (hemothorax, epistaxis) and the chance of obtaining a nonrepresentative tissue sample.

Intradermal skin testing of RAO-affected horses has been investigated extensively with the aim of diagnosing RAO and identifying the offending allergens. In separate studies, Evans and Jose-Cunilleras found that the total number of positive intradermal skin tests evaluated at 0.5, 4 to 6, and 24 hours after allergen injection was greater in RAO-affected horses compared to controls but that this difference in skin reactivity did not permit discrimination between a diseased horse and a healthy horse.[109,110] In contrast, others have failed to find a significant difference between RAO-affected and control horses in the number of positive skin responses to a variety of molds at either the early (0.5, 4 hours) or the late (24 hours) phases.[111-113] Wong and colleagues, evaluating the skin responses to intradermal histamine and *Aspergillus* antigens, found that compared with the controls, the RAO-affected horses had a heightened response to histamine (evaluated at 0.5 hours post injection) and a delayed resolution of the skin wheal (after 24 hours) to the *Aspergillus* antigens.[114] In general, positive skin tests and serum precipitins to fungal and thermophilic actinomycete antigens are found in many normal as well as RAO-affected horses, reflecting a level of exposure of the horse rather than a susceptibility to disease. Skin testing does not allow identification of RAO-susceptible or RAO-affected horses or of the specific inhaled particulate that is inciting the pulmonary inflammation.[115]

Serum allergy tests such as the radioallergosorbent test (RAST) or IgE-based ELISA, which aim to identify the allergen that is inciting the hypersensitivity, are of limited value in the diagnosis of RAO. Lorch and colleagues compared the results of three serum IgE quantitation assays—the spot test (a RAST), an ELISA that uses a recombinant human FceRIα chain as the IgE readout reagent (Allercept [Heska, Loveland, Colo.]), and an equine ELISA that uses a polyclonal antiserum to detect equine IgE—with intradermal skin test responses in RAO-affected horses. They concluded that based on the poor performance of all three tests, none should be used as a screening test for allergen hypersensitivity.[116] Similar conclusions were reached by Tahon and colleagues, who compared the Allercept test and the CAST test (Alpco [Windham, N.H.]), which measures IgE-mediated release of sulfidoleukotrienes from peripheral blood basophils, with intradermal testing in RAO-affected horses and controls.

None of the tests showed a significant difference in responses between diseased and control horses, and thus these tests did not support an IgE-mediated basis for RAO.[45]

Conventional pulmonary function tests (PFTs), used primarily in research investigations to confirm the diagnosis of RAO, require measurements of transpleural pressure changes (obtained via an intrathoracic esophageal balloon catheter system) either alone or in combination with airflow measurements (detected by a flow meter attached to a sealed face mask worn by the horse). Horses with RAO exhibit a decrease in dynamic lung compliance or lung distensibility (C_{dyn}), an increase in pulmonary resistance (R_L), an increase in maximum pleural pressure changes (ΔP_{plmax}), and an increase in peak inspiratory and expiratory flow rates.[117] In general, C_{dyn} reflects changes in peripheral airway function, whereas R_L reflects central, larger airway function. RAO-affected horses also exhibit bronchial hyperreactivity: The dose of aerosolized histamine or methacholine required to reduce C_{dyn} to 65% of its baseline value is much less in diseased horses than in controls.[118] During periods of clinical remission, PFTs are not different from those of healthy age-matched horses. Yet when using more sensitive tests of airway disease, horses in remission still maintain some degree of bronchial hyperreactivity and airflow obstruction,[119,120] demonstrating that conventional PFTs lack sensitivity.[121,122]

The changes in respiratory mechanics and the development of clinical signs are consequences of the influx of inflammatory cells, the contraction of smooth muscle in the airways, the production and accumulation of mucus, and possibly remodeling of the lung parenchyma (see below). Bronchoconstriction probably results from the cumulative effects of (1) released inflammatory mediators (histamine, serotonin, eicosanoids, leukotrienes, endothelin) and (2) activation of muscarinic receptors on the smooth muscle by released acetylcholine.[123] In addition to their direct effects on smooth muscle tension, histamine and serotonin also augment the release of acetylcholine from parasympathetic nerves.[124] Based on in vitro muscle bath studies, there is evidence that RAO-affected horses lack inhibitory nonadrenergic-noncholinergic innervation of the peripheral (but not central) airways, further contributing to the development of bronchospasm.[125] However, the expression or distribution of airway muscarinic receptor subtypes (M_1, M_2, M_3) is unaltered in RAO-affected horses.[126]

As noted earlier, excessive mucus is evident endoscopically and cytologically

in RAO-affected horses. This may be the result of increased mucus viscoelasticity[127,128] and an impairment of the mucociliary apparatus damaged from epithelial cell destruction.[129,130] An increase in the number of mucus cells and their delayed apoptosis may also be contributory.[122] An upregulation of two mucin-producing genes, *MUC5AC* and *MUC2*, in airway tissues of RAO-affected horses has not been detected.[131,132]

Airways that are narrowed, obstructed, or both (as a result of inflammatory cells, mucus, and alterations in pulmonary surfactant)[133,134] increase R_L and fail to participate in efficient gas exchange. Low ventilation-perfusion lung regions contribute to a widening of the alveolar-arterial oxygen-difference ($AaDO_2$) gradient and the development of arterial hypoxemia.[135,136] High ventilation-perfusion regions (dead space) also increase in affected horses, but normal arterial $Paco_2$ levels can be maintained in some horses through increases in the total minute ventilation.[137] Changes in minute ventilation are usually due to an increase in breathing frequency, as tidal volume changes little with the disease. In general, there are no significant changes in cardiac output, heart rate, and mean systemic arterial pressure, but pulmonary artery systolic and mean pressures and pulmonary vascular resistances are significantly increased in diseased horses.[137] The combination of airway inflammation and hypoxemia, if severe enough, stimulates the respiratory controller in the ventral medulla to increase the respiratory drive and to activate inspiratory and expiratory muscles (abdominal heave). Recruitment of respiratory muscles increases the maximum pleural pressure excursion (ΔP_{plmax}), the work of breathing, and the total body oxygen consumption.[138] However, much of the increased expiratory effort (and increased intrathoracic pressures) collapses the noncartilaginous airways, further compounding gas trapping and impairing gas exchange.

■ Pathology

The lungs obtained from RAO horses in remission at the time of death appear normal.[135] In symptomatic horses, the lungs are pink, soft, hyperinflated, and imprinted with rib impressions. Lungs fail to collapse when the chest is opened because of gas trapping distal to occluded airways.[111] Emphysematous bullae are usually lacking, but accumulations of mucus and cellular debris occlude the small airways, forming spiral-shaped casts known as *Curschmann's spirals.* Light and electron microscopic examinations of lung segments from diseased

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horses demonstrate that the peripheral airways are the most severely affected but central airways are not spared.[129,130] Histologic changes include goblet cell hyperplasia, epithelial cell damage, bronchial and bronchiolar epithelial cell hyperplasia, smooth muscle hypertrophy and hyperplasia, increased collagen and elastin deposition in the lamina propria, and overinflation of the alveoli.[139-141] Pathologic changes occur in response to pulmonary inflammatory mediators (release of neutrophil-derived exosomes, ROS, MMPs)[142] and mechanical loads on the airways. Peribronchiolar infiltrates consist of lymphocytes and plasma cells, along with collagen deposition[143]; eosinophils are rarely observed either within the airways or in the lung parenchyma. Airway remodeling (changes in airway smooth muscle [ASM] mass and collagen) as a function of antigen exposure, avoidance (pasture), and/or antiinflammatory and bronchodilator therapy have been extensively studied. Compared to age-matched controls, the ASM mass in the peripheral airways of RAO horses in remission is increased two- to threefold.[144] When RAO-affected horses are treated with either pasture turnout (antigen avoidance) or daily inhaled fluticasone for 12 months, a 30% reduction in peripheral ASM mass is observed.[145] A similar reduction in ASM mass occurs when RAO-affected horses are maintained in an antigen avoidance environment (pasture) while receiving daily inhaled fluticasone/salmeterol for 3 months,[146] an effect attributed to the steroid and not the bronchodilator. In the central airways, fluticasone/salmeterol treatment reversed extracellular matrix remodeling (of which collagen is a component) both within the lamina propria (decreased thickness) and within the smooth muscle layer.[146]

■ Treatment and Prognosis

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Environmental Management.

Environmental management remains the single most important therapeutic and prophylactic intervention. RAO-prone and RAO-affected horses should be kept outside at all times, blanketed during inclement weather as needed, and provided access to a well-ventilated, two- or three-sided shelter free of manure and urine (ammonia) fumes. When pasture is limited, the diet is supplemented with complete pelleted feed or hay cubes. Some horses will tolerate hay that has been soaked in water, but this practice is often forsaken when the weather becomes cold. Steaming hay can prevent exacerbations of RAO in susceptible horses,[147] as this reduces bacterial and mold counts of the hay.[148] In affected horses that have been turned out to pasture, clinical remission and normalization of pulmonary function test results usually take 4 to 8 weeks depending on weather conditions.[149] Reductions in peripheral airway smooth muscle mass take 12 months.[145] Acute exacerbations of RAO occur in pastured, susceptible horses during periods of hot, humid weather.[86,150] Owners should provide an alternative clean, cool environment during these periods to reduce the risk of pulmonary crises in susceptible horses.

In addition to alterations in forage, horses that are stabled should be bedded on a material that has a low respirable dust particle count. Cardboard bedding has a significantly lower particulate concentration (dust, *A. fumigatus, F. rectivirgula,* and *T. vulgaris*) than do wood shavings, wheat, or flax straw, although cardboard may be difficult to obtain and store.[149,151] Auger and colleagues found optimal reductions in airborne respirable dust in barns when horses were bedded on shavings and fed steamed hay.[152] In affected horses that are bedded on shavings and fed pelleted rations, significant improvements in the PFT results occur within 3 days.[153] Complete resolution of clinical signs may take 30 days, although not all horses respond to only allergen reduction measures while stabled indoors.[154] When implementing changes for RAO-susceptible horses, attention should be given to making similar alterations to surrounding stalls within the common airspace.[122,155] At-risk horses should be removed from the barn when stalls or other areas are being cleaned. When environmental management changes are implemented, horses in remission can remain clinically normal for months and exhibit normalization of BAL fluid neutrophil percentages and other indices of airway inflammation such as exhaled ethane. Nevertheless, bronchial hyperreactivity and forced expiratory airflow in RAO-

prone horses still remain abnormal.[119,156-158] Therefore these horses will always be more susceptible to disease development than healthy horses.

Environmental management considerations should also be implemented when horses are transported. Their heads should not be tied in close proximity to the hay net, as this practice places their breathing zone near a concentrated source of organic dusts and molds and restricts their head position so as to further decrease mucociliary clearance of respiratory secretions.[159]

Bronchodilators.

During acute exacerbations of RAO, bronchodilators improve lung mechanics and are useful in establishing the reversibility (and thus diagnosis) of RAO. The three main classes of bronchodilators that have been used in RAO-affected horses are the anticholinergics (muscarinic antagonists), the β_2-agonists, and the phosphodiesterase (PDE) inhibitors.

Muscarinic antagonists such as atropine, ipratropium, and N-butyl-scopolammonium bromide block the smooth muscle–constricting effects of acetylcholine. These actions exert the greatest effects in the central as opposed to the peripheral airways. IV administration of 0.01 to 0.02 mg/kg of atropine sulfate improves clinical signs and pulmonary function parameters (ΔP_{plmax}, respiratory rate, R_L, E_L) within 10 minutes of administration.[160-162] Atropine's short duration of action (2 hours) and undesirable side effects (mydriasis, ileus, tachycardia, dry airway secretions) preclude its routine use in the treatment of RAO. In contrast, ipratropium bromide is poorly absorbed from either the respiratory or the GI tract, minimizing the development of systemic effects. The powder form is nebulized (2 to 3 µg/kg) and exhibits an onset of action within 30 minutes; effects last from 4 to 6 hours.[163] In resting horses it reduces R_L and ΔP_{plmax} and increases C_{dyn} but produces no further improvement if horses are exercised.[164] N-butyl-scopolammonium bromide, when administered at 0.3 mg/kg IV, improves clinical scores and pulmonary function tests of RAO-affected horses within 10 minutes of its administration; effects last for 30 to 60 minutes.[162,165] No clinically adverse effects were noted following its use in research trials.

The β_2-adrenergic agonists—clenbuterol, albuterol, levalbuterol, and salmeterol—produce relaxation of smooth muscle by increasing the intracellular levels of cyclic adenosine monophosphate (cAMP). The bioavailability of

clenbuterol is greater than 90%, and when administered orally at a dose of 1.6 µg/kg of body weight twice per day (bid), a significant improvement in the clinical signs of affected horses can occur.[166] The effective dosage of clenbuterol varies among horses. If clinical improvement is not observed within 3 days of initiating treatment, the dose is increased stepwise (e.g., 2.4 µg/kg for 3 days, 3.2 µg/kg for 3 days). Adverse side effects (anxiety, shivering, sweating, and tachycardia) occur at higher dosages but may be minimized if clenbuterol is increased in a stepwise manner. Reports of fatal overdoses of clenbuterol in horses estimated to have received 100 µg/kg orally of a compounded product have occurred.[167] In addition to its bronchodilatory effect, clenbuterol also exerts an antiinflammatory effect: IV administration (0.75 µg/kg bid) to RAO-susceptible horses prior to hay dust exposure attenuates BAL fluid neutrophilia and TNF-α and IL-1 gene transcription.[168] Prolonged administration of clenbuterol (0.8 µg/kg bid for 3 weeks) may result in tachyphylaxis[169] due to downregulation of β-adrenoceptors, but this phenomenon may be reversed with concurrent corticosteroid administration.[170]

Aerosolized β_2-agonists are used to treat RAO-affected horses and permit direct delivery of the drug to the respiratory tract, minimizing the total amount of drug needed and reducing the prevalence of unfavorable systemic effects. The metered dose inhaler containing the drug is attached to a delivery system such as the Equine Haler (Equine Health Care, Inc., Hørsholm, Denmark) or Aerohippus (Trudell Medical, Inc., London, Canada). Both devices exhibit similar efficacy in drug delivery and clinical improvement.[171] Albuterol sulfate and levalbuterol improve pulmonary function by 60% to 70% in RAO-affected horses for approximately 1 to 3 hours, necessitating frequent administration of the drugs.[172,173] They are poorly absorbed, so systemic effects are uncommon. These drugs are typically used in “rescue” protocols to treat horses in respiratory distress. The recommended dose of albuterol is 1 to 2 µg/kg q1-4h and of levalbuterol is 0.5 µg/kg q4h.[174] Salmeterol, a long-acting β_2-agonist, is administered at a dose of 0.5 µg/kg q6-8h. Clinical improvement develops within 2 hours of administration, and significant decreases in pulmonary resistance last for 6 hours.[175]

Aminophylline and pentoxifylline are examples of the PDE inhibitors that produce smooth muscle relaxation by inhibiting the breakdown of intracellular cAMP. PDE inhibitors also exert antiinflammatory properties.[176] Administration of 12 mg/kg IV of aminophylline (in 1 L of 5% dextrose) improved clinical signs

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and reduced ΔP_{plmax} in approximately 50% of RAO cases[161] but caused hyperexcitability, hyperesthesia. and trembling. Because of the narrow range between therapeutic efficacy (serum concentration of 10 µg/mL) and toxicity (serum concentration of 15 µg/mL), aminophylline is not routinely used for the treatment of RAO. Pentoxifylline is well absorbed after oral administration (32 mg/kg q12h), improves some indices of pulmonary function, but does not improve BAL fluid neutrophilia.[177]

Antiinflammatory Drugs.

NSAIDs, in contrast to corticosteroids, are not beneficial in the treatment of RAO.[61] Of the glucocorticoids evaluated, oral prednisone is not used because of its poor bioavailability and lack of conversion to the active metabolite prednisolone.[178,179] Liquid and tablet forms of prednisolone are rapidly absorbed from the equine GI tract (bioavailability is approximately 50%), achieve peak concentrations 45 minutes post administration, and exert pharmacologic effects (based on changes in serum cortisol levels) for 8 hours.[179] Oral prednisolone (2 mg/kg PO once per day [sid] for 7 days) improved R_L, E_L, and ΔP_{plmax} within 3 days of its administration to RAO-affected horses stabled and continuously exposed to dusty hay. It was less efficacious than dexamethasone administered by intravenous (1 mg/kg q24h)[178] or oral (0.05 mg/kg q24h)[180] routes.

In RAO-affected horses receiving dexamethasone, within 2 hours of IV administration (0.1 mg/kg) there is a 37% decrease in ΔP_{plmax} that is further reduced by 4 hours post treatment.[181] Oral administration of the parenteral formulation of dexamethasone (0.164 mg/kg q24h to account for bioavailability) improves lung function parameters within 6 hours of treatment, with peak effects occurring 24 hours later. When horses are maintained in dusty environments, IV dexamethasone (0.1 mg/kg q24h) or dexamethasone isonicotinate (0.04 mg/kg IM every 3 days for three treatments) improves pulmonary function within 3 days of initiating therapy[178,181] and reduces airway inflammation (BAL fluid neutrophilia) within 10 days of treatment.[178,182] As might be predicted, a single dose of dexamethasone isonicotinate (0.06 mg/kg IM) administered to RAO-affected horses maintained in a dusty environment fails to provide discernible improvements in the clinical score, the PFT results, the BAL cytologic findings, or the activities of the transcription factors NF-κB or activator protein 1 (AP-1) evaluated 10 days post treatment.[183] In general, the rapid onset of action of IV

dexamethasone makes it an antiinflammatory of choice in horses exhibiting respiratory distress caused by RAO.[184]

Long-acting corticosteroids have also been evaluated in RAO-affected horses maintained in a dusty environment. A single IM dose of triamcinolone acetonide (0.09 mg/kg) markedly improved lung mechanics for 4 weeks. Cytologic changes (evaluated 14 days post treatment) demonstrated a reduction in airway neutrophilia (from 62% to 32%), but this change was not statistically significant.[185] Adverse effects of triamcinolone administration were not reported. In another study, RAO-affected horses received isoflupredone acetate for 14 days (0.03 mg/kg IM q24h) while being maintained in a dusty environment. Significant improvements in pulmonary function indices occurred within 3 days of initiation of the treatment,[186] and beneficial effects continued 7 days beyond the cessation of drug therapy. The only adverse effect noted was the development of hypokalemia.

Inhaled corticosteroids such as beclomethasone and fluticasone have been used with success to treat RAO. In a 3-week study, fluticasone proprionate (2 mg q12h) was administered to RAO-affected horses while they were stabled and fed "good"-quality hay. By day 21, marked improvements in PFTs and normalization of BAL neutrophil counts occurred.[26] Robinson and colleagues compared the effects of inhaled fluticasone (6 mg bid) and IV dexamethasone (0.1 mg/kg q24h) on PFTs and BAL cytologies in RAO-affected horses.[184] They found that (1) no adverse effects, including laminitis, were associated with a 3-day course of fluticasone at 6 mg bid; (2) greater reductions in ΔP_{plmax} in RAO-affected horses were achieved with dexamethasone than with fluticasone treatment; and (3) prophylactic (3-day) and continual (4-day) administration of fluticasone (6 mg bid) to RAO-susceptible horses subjected to stabling and dusty hay exposure were more efficacious in preventing the disease than was dexamethasone. They recommended that dexamethasone should be used for "rescue" therapy and fluticasone used as a preventive agent. Fluticasone is approximately 18 times more potent than another inhaled corticosteroid, beclomethasone dipropionate. Nasal or oral administration of fluticasone has no effect on circulating glucocorticoid levels, suggesting that its bioavailability across nasal and intestinal epithelium is poor.[187] However, daily aerosolization of fluticasone (dose of 1.5, 3, or 6 mg bid) significantly reduces serum cortisol measured 72 hours after initiating therapy.[184,187] The effect of long-term fluticasone administration on immunologic parameters has also been

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investigated. Administration of fluticasone (2 mg bid for 11 months) to RAO-affected or susceptible horses had no significant effect on (1) peripheral blood leukocyte, neutrophil, or lymphocyte numbers; (2) percentages of lymphocyte phenotypes; (3) blood neutrophil chemokine (IL-8, TNF-α) and glucocorticoid receptor gene expression; (4) IgG vaccine titers induced by immunization against tetanus toxoid or an inactivated infectious bovine rhinotracheitis (IBR) vaccine; or (5) mitogen-induced lymphocyte proliferative responses.[188] These data suggest that fluticasone is a relatively safe drug for use in the treatment of RAO.

Another inhaled corticosteroid that has been widely investigated in RAO-affected horses is beclomethasone dipropionate. When administered at a dose of 1320 to 1500 µg bid for 7 to 10 days to diseased horses continuously stabled and fed dusty hay, investigators noted that by day 7 of treatment there was a significant improvement but not a complete normalization of pulmonary function test results and BAL fluid neutrophil percentages.[182,189]

Inhaled steroids are often used in conjunction with inhaled bronchodilators for maximal therapeutic effects. When separate formulations are used, it is recommended that the bronchodilator be administered first so as to improve subsequent glucocorticoid deposition in the peripheral airways.[190] As suggested earlier, when administering glucocorticoids, adrenal gland atrophy, immunosuppression, and precipitation of laminitis remain a concern. All of the previously discussed parenteral and inhaled glucocorticoids reduce endogenous serum cortisol levels, but despite prolonged treatment protocols with glucocorticoids, adrenal gland responsiveness to adrenocorticotropic hormone administration remains.[185,186,189,191] Despite the improvement in clinical signs and in PFTs achieved with glucocorticoid therapy, BAL neutrophilia remains evident until environmental management changes are implemented.

Other Therapies.

In horses that develop respiratory distress because of the bronchospasm and airway inflammation, additional therapies are required. Administering nasal oxygen at flow rates as low as 5 L/min improves arterial oxygen tension by as much as 30 mm Hg in some severely affected horses.[192] Flow rates of 30 L/min (delivered by 2 nasal cannulae at 15 L/min) are associated with coughing and gagging in horses. Nasal oxygen supplementation does not reduce breathing frequency, suggesting that stimulation of vagally mediated afferents (perhaps

responding to inflammatory mediators) is responsible for the tachypnea.

Furosemide (1 mg/kg IV or nebulized) provides beneficial effects to RAO-affected horses within 20 minutes of its administration, decreasing R_L and increasing C_{dyn} without affecting Pa_{O_2}.[193] The beneficial effects appear to be mediated by PGE2, derived from either the renal or the airway epithelium, which promotes smooth muscle relaxation. Prior treatment with the cyclooxygenase inhibitor flunixin meglumine prevents the furosemide-induced bronchodilation.[194] Furosemide may have a local effect on vagal sensory afferent discharge independent of reflex anticholinergic bronchodilation.[195]

Another therapeutic agent proposed for the treatment of RAO is tamoxifen. This is a selective estrogen receptor modulator that, when administered at 100 mg PO every other day for three treatments, reduced airway neutrophilia in RAO-affected horses.[196] Tamoxifen also enhances apoptosis of peripheral blood and BAL neutrophils. Long-term studies of its efficacy and safety remain to be conducted.

Finally, Barussi and colleagues reported that in a clinical trial with only four horses, intratracheal instillation of autologous bone marrow–derived mononuclear cells improved clinical scores and reduced BAL neutrophilia.[197] Larger studies need to be completed before this approach can be recommended.

Additional therapeutic approaches that have *not* been found to be efficacious in the treatment of RAO-affected horses include a single acupuncture treatment,[198] the oral administration of an herbal preparation containing thyme and primula,[199] the rapid IV administration of 30 L of isotonic saline,[200] treatment with a constant rate infusion of IV lidocaine,[201] and sound-wave physiotherapy.[202]

■ Prognosis

RAO-prone horses are likely to develop acute exacerbations of the disease when husbandry practices lapse or when weather conditions become adverse. Horses do not “outgrow” the disorder, and in fact some clinicians believe that the inflammation becomes more difficult to manage as the horse ages. The basis for the lack of clinical response is unknown but may be the result of lung remodeling or potential downregulation of the glucocorticoid receptor.

If proper environmental management changes are implemented and if the appropriate therapy is initiated, clinical remission occurs in most cases. In a

follow-up survey conducted by Naylor of RAO-affected horses that had been examined and treated at a referral center 2 to 4 years previously, it was found that 20% of the original cases (3 of 15) had been euthanized, 33% were still receiving bronchodilators on an as-needed basis, and athleticism had not decreased in 92% of the horses.[88] Similarly, in a follow-up survey conducted by Aviza and colleagues,[89] 13% of the horses that had been diagnosed with RAO 3 to 4 years earlier had been euthanized. However, in contrast to Naylor's findings, Aviza noted that more than 50% of the respondents in that survey stated that the athletic performance of the horse had been compromised by the disease. Perhaps this difference between the two surveys simply reflected a failure of the owners to comply with environmental management recommendations. When queried about the husbandry practices, 77% of the respondents still stabled the horse for part of the day, and 84% still fed the horse dry hay.[89]

Because the effects of repetitive episodes on the development of irreversible changes in lung structure have yet to be determined, clients should be encouraged to implement effective husbandry changes that minimize the recurrences of RAO and prevent pulmonary parenchymal damage.

Summer Pasture–Associated Obstructive Pulmonary Disease

Dorothy M. Ainsworth

■ Definition and Etiopathogenesis

A condition clinically similar to RAO develops in mature horses in the southeastern United States that are kept outdoors on pasture. It is called *summer pasture–associated obstructive pulmonary disease* (SPAOPD), pasture asthma, or more recently severe equine asthma. As with RAO, this new term applies to horses that are exhibiting clinical exacerbations or are in remission. Clinical signs typically occur in June through September when the weather is warm and humid[1]; clinical signs resolve partially or completely when the horse is removed from the pasture. Winter manifestations of the disease are uncommon. Clinical signs parallel increases in environmental fungal spore (basidiospore, *Nigrospora*, and *Curvularia*) and grass (Bermuda grass and Johnson grass) pollen counts,[2] suggesting that aeroallergens (and potentially others) trigger the disease. SPAOPD has also been reported in horses in the United Kingdom, although

some of those cases may represent horses with underlying RAO whose condition is exacerbated by hot weather and airborne particulates.[3-6]

As with RAO, the immunopathogenesis of SPAOPD is uncertain. In one study, neither the total nor the antigen-specific IgE and IgG titers to certain fungi (*Aspergillus* spp., *Cladosporium herbarum*, *Penicillium* spp.), to thermophilic actinomycetes species *(Faenia rectivirgula*, *Saccharomonospora viridis*, *Thermoactinomyces thalpophilus)*, or to the forage mite *Lepidoglyphus destructor* in the tracheal lavage fluid were increased in SPAOPD-affected horses relative to controls.[7] Cytokine mRNA profiles in BAL cells and in peripheral blood mononuclear cells (PBMCs) isolated from SPAOPD-affected and control horses fail to provide consistent support for a polarized response. Increased IL-4 and IFN-γ copy number in BAL cells and PBMCs isolated from affected horses relative to controls was reported in one study.[8] In another investigation by the same group,[9] the gene expression of IFN-γ and IL-13 (but not IL-4) in BAL cells and peripheral blood lymphocytes isolated from symptomatic horses exceeded that of controls.

In a gene expression study of peripheral lung tissue isolated from affected and control horses,[10] 18 genes of known function were differentially expressed and found to be involved with lung protection, defense, mediation of proinflammatory or antiinflammatory responses, promotion of or protection from oxidative stress, cell recovery and repair, and mitogenesis. Of the 18 genes, only secretoglobin was downregulated in diseased horses—similar to what occurs in RAO horses.[11-13] In addition to blocking phospholipase A2 activation, secretoglobin reduces IL-8–enhanced neutrophil chemotaxis. Venugopal also reported upregulation of eight genes that encode proteins associated with cell repair and proliferation[10] involved in lung repair and airway remodeling, supporting histopathologic changes previously described in affected horses.[14] Differential expression of immune cytokines (IL-4, IFN-γ, IL-17, TGF-β) was not reported in their transcriptome study of lung tissue.

Because of its role in the pathophysiology of human obstructive pulmonary disorders, investigators have also evaluated endothelin-1 (ET-1) concentrations in horses with SPAOPD. This 21–amino acid peptide induces bronchoconstriction; enhances mucus secretion; promotes DNA syntheses and cell proliferation in airway smooth muscle cells; and facilitates airway inflammation by upregulating IL-1, IL-4, IL-8, TNF-α, and IFN-γ expression.[15,16] Compared with control horses, SPAOPD-affected horses have

increased ET-1 protein concentrations in the venous blood, BAL, and pulmonary epithelial lining fluid.[16] This finding, coupled with the observation that endothelin receptors A and B in the bronchial smooth muscle of affected horses are increased,[15] suggests that ET-1 is just one of many mediators involved in the pathophysiology of SPAOPD.

■ Clinical Signs and Differential Diagnoses

The clinical signs of SPAOPD are seasonal, reversible, and vary in severity. As with RAO, initial signs can be subtle and include exercise intolerance, intermittent cough, intermittent nasal discharge (serous or mucoid), and tachypnea. Horses are afebrile. As the disease progresses, accentuated expiratory efforts (heave line), nostril flaring, frequent coughing, and even respiratory distress can occur.[1] Crackles, wheezes, and "silent areas," suggesting the absence of air movement, may be auscultated.[1,14] Differential diagnoses include bacterial, viral, or fungal respiratory infections (ruled out by evaluation of blood work and culture and examination of tracheal aspirates) and anhidrosis (ruled out by assessing sweat production in affected animals).

■ Diagnosis

Historical and physical examination findings, along with the temporal development of clinical signs, support the diagnosis of SPAOPD. As with RAO, endoscopy of the lower respiratory tract reveals an accumulation of mucopurulent exudate within the tracheobronchial tree, evidence of bronchial epithelial hyperemia and dynamic collapse of intrathoracic airways during expiration. Cytologic analysis of BAL fluid demonstrates neutrophilia (>25%), the absence of intracellular bacteria, and excessive mucous production.[14] Microbial culture of pulmonary secretions is typically negative. Thoracic radiographic examination may reveal mild to moderate bronchointerstitial patterns with evidence of lung field hyperexpansion (flattened diaphragm). Ultrasonographic findings, although not specifically described in SPAOPD-affected horses, would be expected to be similar to those in horses with RAO. Postmortem examination of the lungs from affected horses reveals overinflation, the presence of rib impressions, and a failure to collapse. Histopathologic changes include accumulation of mucus and neutrophils in the small airways, peribronchiolar smooth muscle hypertrophy, peribronchiolar submucosal fibrosis, epithelial hyperplasia, goblet cell hyperplasia or metaplasia, and

peribronchial neutrophilic and lymphocytic infiltrates, similar to RAO. There is usually minimal evidence of emphysema and fibrosis.[14,17] Collectively these changes represent airway remodeling similar to what occurs in RAO.

■ Treatment

The most important management change to implement is to move the horse from the offending pasture either to another pasture or to a cool, dust-free stall that is bedded with shavings. Hay should be moistened or steamed and fed to the horse from the ground to reduce inhalation of organic dusts. When stalls and barn areas are being cleaned, the horse should be removed from these areas. Medical therapies include administration of glucocorticoids and bronchodilators, as described for horses with RAO (see the Treatment and Prognosis section for RAO).

■ Prognosis

Recurrence of the condition is likely to develop when susceptible horses are exposed to environmental triggers. Longitudinal studies have not been performed to ascertain the risk of permanent (irreversible) lung remodeling in recurring cases. The heritability of SPAOPD has not been established.

Inflammatory Airway Disease in the Horse

Melissa Mazan

What Is Inflammatory Airway Disease?

Inflammatory airway disease (IAD), small airway inflammatory disease, small airway disease, and *allergic airway disease* are often used interchangeably, but the once-fluid definition of IAD is slowly taking form. Although low-grade inflammation of the small airways is recognized as a common cause of poor performance in young to middle-aged athletic horses, it is only recently that a clear distinction has been made between heaves, or recurrent airway obstruction (RAO), and IAD. Workers in the field continue to debate whether IAD is a discrete disease entity or whether it is merely part of the continuum of airway inflammation that, if left untreated, will progress inexorably to the better characterized syndrome of RAO.[1] The recent Revised Consensus Statement on IAD[1] suggests that the term *equine asthma* better covers the spectrum of

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diseases that are characterized by excessive mucus accumulation in the airways and extend from severe heaves to mild IAD. Horses with IAD are generally young, although middle-aged horses may also be affected; have impaired performance that may go unnoticed at rest or during light work[2-4]; have mild to moderate airway inflammation that may involve neutrophils, mast cells, eosinophils, or lymphocytes[2,4-7]; have variable clinical signs, including cough, nasal discharge, and abnormal lung sounds; may have endoscopic evidence of tracheobronchial mucus accumulation; and may have normal lung function at rest but show evidence of airway hyperresponsiveness on exposure to nonspecific agents such as histamine or evidence of low limitations on forced expiratory maneuvers.[3,8-12] In addition, these horses may have lung dysfunction, as evidenced by airway obstruction, airway hyperresponsiveness, or abnormal blood gas exchange. This definition specifically excludes horses that appear systemically sick or that have overt evidence of respiratory dysfunction, such as flaring nostrils or excessive thoracic or obvious abdominal breathing efforts.

The prevalence of IAD is somewhat of a guessing game. One study involving 965 Standardbreds in active racing found that 22% had evidence of mucopus at the trachea or bronchial bifurcation when examined endoscopically, although these horses were diagnosed as having chronic obstructive pulmonary disease (COPD); undoubtedly they properly belong in the IAD group.[13] Similarly, 27% of actively racing Thoroughbreds in one study had IAD.[14] A remarkable 55% of 2-year-old Thoroughbreds in training could be classified as having lower airway disease on the basis of finding mucus in the trachea on endoscopy and inflammation on examination of tracheal aspirate fluid, and abattoir studies have shown that up to 37% of horses have histopathologic evidence of airway inflammation.[15,16] Because a standard definition of IAD has only recently been agreed on, the prevalence of IAD has varied according to the individual researcher's case definition. Nonseptic airway inflammation, regardless of whether it causes overt signs of respiratory disease, appears to be very common in performance horses. This discussion adheres to the definitions of IAD and RAO as developed by the International Workshop on Equine Chronic Airway Disease and the recent ACVIM consensus statement on IAD.[1,17] With RAO, horses have demonstrable lower airway obstruction, characterized by peak pleural pressures of at least 15 cm H_2O, induced by an environmental challenge of moldy hay, largely reversible by use of a bronchodilator or return to a nonchallenge environment, and accompanied by an increase in BAL fluid

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neutrophils during challenge. In contrast, IAD refers to a nonseptic airway disease in athletic horses that does not have a clearly defined allergic cause. The data from the many studies involving horses with what was traditionally known as COPD and is now more properly referred to as RAO, or heaves, did not conform with these guidelines, and many of the horses would more properly be characterized as having IAD.

■ Clinical Findings

Although most investigators agree that IAD is a disease of younger horses expected to do athletic work, and as such is distinct from the picture of the dyspneic horses with overt RAO, there remains a plethora of clinical signs and case definitions for IAD. One of the most common findings in IAD is exercise intolerance, with or without overt signs of respiratory disease. Of 25 horses referred either for routine physical examination or for poor performance, and without any clinical signs or history of respiratory disease, 76% had evidence of airway inflammation according to an inflammation scoring system based on endoscopy and tracheal wash findings.[18] Subclinical airway disease may result simply in mild abnormalities on auscultation and endoscopy, and occasionally in coughing.[19] Signs such as nostril flaring and excessive abdominal effort at rest, however mild, are usually associated with horses that have true RAO, as clinical signs that can be reliably detected using clinical scoring systems usually are accompanied by significant mechanical dysfunction of the respiratory system.[20] The prevalence of cough in horses with IAD is difficult to estimate, as many studies use the presence of cough as an inclusion criterion. Other studies have shown that cough may be seen less than 16% to 50% of the time.[21,22] On endoscopic examination, excessive airway mucus is often seen, ranging from multiple specks to streams of mucus.[23] Other clinical signs that are frequently noticed include prolonged respiratory recovery; respiratory embarrassment at exercise; worsening of signs during hot, humid weather; and inability to perform work during collection. Racehorses with IAD are typically described as fading during the last quarter of the race (Mazan, personal observation). It is interesting to note that horses with dorsal displacement of the soft palate (DDSP) have a higher prevalence of IAD than do control horses. This brings into play a chicken-or-egg argument, as it cannot be determined whether IAD is a risk factor for DDSP or DDSP is a risk factor for IAD.[24]

How does IAD affect performance? The answer depends on the use of the

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horse and the expectations of the owner. A practitioner with a primarily pleasure-horse practice or with show-hunter clientele might report a very low incidence of IAD in younger horses, primarily because the level of exercise in these horses is not likely to force a diagnosis through signs of exercise intolerance. A racetrack practitioner, on the other hand, would be far more likely to detect exercise intolerance resulting from lower airway disease in young horses because the level of expected athletic output is much higher and the horses have a greater likelihood of being examined endoscopically. Indeed, in a National Hunt racing population, excessive mucus was detected endoscopically in 68% of horses,[25] and IAD was one of the top two reasons cited for horses not running.[26] As might be expected, cough is more common in sport horses than in racehorses, as is an elevated respiratory rate, reflecting the generally earlier diagnosis in racehorses. Indeed, racehorses with excessive tracheal mucus performed at a lower level than those with no mucus found on endoscopic examination.[11,13]

Low-grade nonseptic airway inflammation was found to have a negative impact on ventilatory capacity, but this was more pronounced in racehorses. Moreover, using bronchiolar biopsy, this group also demonstrated that oxygen uptake and pulmonary ventilation correlated inversely with the morphologic grade of small airway disease and the height of the bronchiolar epithelium—the last finding suggesting that the extent of obstruction may determine the extent of exercise impairment.[27] Racehorses with IAD have impaired gas exchange during exercise.[3] However, other studies have found that horses with obvious evidence of airway inflammation do not necessarily have a history of exercise intolerance.[28] However, this may reflect the difficulty of diagnosing low-grade respiratory impairment and the trainer's failure to recognize poorer performance than nature intended, rather than the benign nature of the underlying disease.

■ Diagnosis

Bronchoalveolar Lavage.

Varying levels of specificity are used when documenting the presence of airway inflammation. The least specific is the documentation of mucus in the trachea, although it is the method that best lends itself to large studies in the field. However, visualization of mucus in the trachea gives little information as to the nature and the exact origin of the inflammation. Many workers have used and continue to use tracheal aspirate cytology to describe the nature of inflammation

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in IAD. Although tracheal aspiration can be used to explore the presence of inflammation and has been used to document neutrophilia, mastocytosis, and eosinophilia in young performance horses, the question of the nature and exact origin again presents itself.[29] Studies have shown poor correlation between tracheal aspiration and BAL cytology in horses.[30,31] Whereas tracheal aspiration harvests primarily neutrophils and epithelial cells, BAL yields primarily alveolar macrophages and lymphocytes in normal horses. Moreover, there is no evidence of correlation between tracheal wash findings and performance. Consequently, to avoid the problem of neutrophil count sensitivity to the collection method, BAL is the best choice for sampling respiratory secretions in horses with IAD.

Different pictures of inflammation emerge from various BAL studies, leading to speculation that different genetic predispositions and environmental exposures are important to the inflammatory phenotype. In comparison with healthy horses, BAL cytology in horses with IAD has shown, variably, neutrophils, mast cells, eosinophils, or lymphocytes. In general, horses with IAD have airway inflammation that may involve increases in nucleated cells or may also involve lymphocytosis. This is distinguished from RAO by the relatively low percentage of abnormal cells in IAD; whereas horses with RAO may exhibit almost entirely neutrophils in the BAL fluid, horses with IAD seldom have more than 2% to 15% neutrophils.[1] It is problematic that all BALs are not created equal. Even when the infused fluid is within the usual recommendations of 250 to 500 mL, when larger volumes are instilled, the percentage of neutrophils decreases.[32] Thus it is important to note volume of fluid instilled when assessing any report of airway inflammation based on BAL cytology.

Histopathology.

A recent study has given us insight into the inflammation that exists in the lower airways even of horses that have not been identified to have respiratory disease.[33] Inflammatory cell infiltrates (primarily CD3+ T cells) and smooth muscle hyperplasia were identified in most of the horses, although epithelial changes were not noted. Bronchiolar biopsies of athletic young horses with lower airway inflammation have shown inflammatory mucosal cellular infiltrates and luminal exudates, bronchiolar hyperplasia, and goblet cell metaplasia.[8] It is interesting to note that 80% of supposedly normal horses had minimal evidence of peribronchiolitis; this raises the question of what constitutes normal. O'Callaghan, while directing his concern to exercise-induced pulmonary

hemorrhage (EIPH), nevertheless found plentiful evidence of multifocal, small airway–centered disease on postmortem examination of young racehorses.[34] These findings included thickened walls caused by increased quantities of mucosal and peribronchiolar connective tissue, mononuclear bronchiolar cuffs, and extension of nonciliated bronchiolar epithelial cells into alveolar ducts.[34] Lakritz,[35] looking at lung tissue of clinically normal, young Thoroughbred horses in training, found evidence of increased collagen, disruption of the epithelial basement membrane, and duplication of the epithelial basement membrane, suggesting previous airway inflammation and epithelial injury, which correlate with an increased interstitial pattern on radiographs. An ultrastructural study of young horses with "mild COPD" in one study found a decreased number of typical Clara cell granules and goblet cell metaplasia before the bronchioles began to show signs of inflammation typical of RAO.[36] Although the authors state that there was good correlation between histopathology and the results of a battery of PFTs, auscultation, bronchoscopy, blood gas analysis, and BAL in these horses, it is a lasting disappointment that the results of the ancillary testing remain unpublished. These data, in sum, suggest that the histopathologic lesion of IAD is not only local bronchiolar inflammation but also remodeling and thickening of the bronchioles themselves, which lends itself to at least low-grade airway obstruction.

Lung Function Testing.

The esophageal balloon and pneumotach method for measuring lung function tends not to detect airway obstruction even in horses with RAO in remission.[37] However, use of the forced oscillatory technique and forced expiratory maneuvers has shown the existence of low-grade obstruction of the small airways of some horses with IAD.[3,38] The mechanical behavior of the respiratory system has been shown to differ with sampling frequencies in asthmatic humans,[39] and a pattern of decreasing respiratory system resistance (RSR) with increasing frequency has been termed *negative frequency dependence of resistance* and has been interpreted as evidence of underlying small airway obstruction despite baseline measurements within the expected range. Similarly, horses with IAD as a group have significantly higher values for RSR at the lower frequencies (1 to 3 Hz) and mild frequency dependence of resistance compared with controls,[40,41] although the baseline measurement of RSR may still frequently fall within the normal range. A study finding that lower oxygen

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uptake capacity and tidal volume correlated to a reduced diameter of the bronchiolar lumen owing to epithelial hyperplasia is strongly supportive of the existence of airway obstruction in IAD.[27] Likewise, lung resistance decreases with increasing minute ventilation in control horses but not in horses with IAD.[42] Consequently, without dynamic, frequency-dependent tests of lung function, forced maneuvers, or bronchoprovocation, it seems that researchers are simply failing to document a common feature of small airway obstruction in horse with IAD because testing devices are not sufficiently sensitive to these changes.

Airway Responsiveness.

Horses with clinical signs compatible with IAD also exhibit signs of airway hyperresponsiveness (the threshold at which horses react) and hyperreactivity (the slope, which correlates to the magnitude, of the response) when they are exposed to nonspecific agents such as histamine aerosol. The basis for airway hyperresponsiveness remains hotly debated among pulmonary physiologists. It is likely a multifactorial phenomenon that has been associated with airway wall thickening undetectable by conventional lung function testing, airway inflammation, and autonomic nervous system dysfunction.[43] There is a paucity of information concerning the mediators of airway hyperresponsiveness in horses with IAD. In our laboratory, horses with a clinical history and signs compatible with IAD have significantly greater airway reactivity than controls, although some control horses display airway hyperresponsiveness (AWHR) as well. A study in Standardbred racehorses with unexplained poor performance or cough showed a discordance in some horses between positive BAL findings and positive airway hyperreactivity,[44] raising the idea that without testing for AWHR, some horses affected with IAD will be missed. This nonspecific airway hyperresponsiveness has been seen in humans and is associated with a greater risk of eventual development of asthma.[45] Although nonspecific airway hyperresponsiveness has been noted both in adult horses without signs of respiratory disease and in foals, the significance of this finding remains unclear.

Although radiography can be useful in helping exclude septic causes of lower respiratory tract disease, such as pneumonia, lung abscess, or pleuropneumonia, its sensitivity in IAD is too low for it to be useful for identification of this disease. Moreover, no correlation exists among thoracic radiographs, airway hyperresponsiveness, and BAL cytology.[46] However, the more frequent finding

of a bronchial pattern on thoracic radiographs supports the existence of airway obstruction in these horses.

Endoscopy.

Tracheal endoscopy is convenient and easily performed, and lower airway scoring correlates with lower airway inflammation; moreover, particulate levels in the air have been correlated with endoscopically visible mucus in the trachea. Thickening of the septum has been shown to be useful in distinguishing horses with RAO from horses with IAD. The accumulation of mucus in the trachea has been shown to correlate with neutrophil percentages, but there was no such correlation with thickening of the septum.[47-49]

Biomarkers.

Although there was no utility found in using the circulating acute phase proteins C-reactive protein, haptoglobin, or serum amyloid A (SAA) to distinguish IAD from other causes of unexplained poor performance in racehorses,[50] SAA was found to be useful in distinguishing horses with IAD from those with infectious airway diseases, thus demonstrating the use of SAA in ruling out subclinical infectious disease.[51]

■ Etiology

No single cause of IAD has been identified, although there has been plentiful speculation about the role of environment, viral disease, infection, air pollution, and genetic predisposition. Although horses with IAD do not seem to experience bouts of overt airway obstruction on exposure to an allergenic environment, organic dust associated with stabling likely contributes to the initial inflammation. Sweeney noted that the racehorses in her study lived in conditions of poor ventilation, and she speculated that covert IAD may be instigated by the organic dusts, especially mold, in hay.[52] Others have noted that there is more mucopus in the tracheas of horses kept in poorly ventilated conditions, and in one study Thoroughbred racehorses in training, housed on straw, were found to be twice as likely to suffer from lower airway disease as those kept on shredded paper.[23] More recently, Holcombe and colleagues[53] showed that yearlings had a significantly higher number and percentage of neutrophils (polymorphonuclear neutrophils as high as 18%) in BAL fluid when they were stabled versus when they were at pasture. In support of this finding, endotoxin concentrations are, as

expected, higher in stables than at pasture.[54,55] Although none of these horses had any clinical signs of respiratory disease or evidence of exercise intolerance, they were not in work, and subtle signs of performance impairment could easily have gone undetected. Dust levels in the horse's breathing zone can be as high as 25 mg/m^3 (a level that would be considered unacceptable in any human workplace), which can explain the development of airway neutrophilia as a nonspecific response to high levels of particulates.[56] It is also likely that increased levels of endotoxin in hay and grain dust contribute to the development of airway neutrophilia,[57-59] which is supported by the finding that hay eating is a risk factor for increased tracheal mucus in pleasure horses.[28] A recent study of Thoroughbred racehorses in training confirmed that feeding hay from a net resulted in a significantly higher concentration of particulates and respirable endotoxin in the horse's breathing zone as well as an increase in eosinophil numbers in the BAL fluid.[60] In addition, the horse's position in the stable may affect development of IAD. In one study there was a significant association between the presence of visible accumulation of mucus in the trachea and the stable, stall, and particulate concentration and numbers.[61] Moreover, even when unaffected horses are exposed to stable dust, the neutrophil chemoattractant, IL-8, increases in the BAL fluid.[62]

Previous viral disease is commonly invoked as a predisposing factor in the development of IAD, and the evidence needed to implicate virus is increasing. As in humans with asthma, viral respiratory disease has been shown to cause AWHR for a period of time after infection, perhaps because of denuding of the respiratory epithelium. In one study various equine herpesviruses were found with greater frequency in the tracheal aspirate of poorly performing horses with signs compatible with IAD,[63] and more recently both EHV-2 DNA and equine rhinitis B virus RNA were found in the tracheal fluid but not in the nasal fluid of young racehorses with cough.[64] Similarly, in a different laboratory, horses with IAD had higher titers to equine rhinitis A virus, and there was a significant association between nasal shedding of EHV-2 DNA and diagnosis of IAD.[65] Moreover, both alphaherpesviruses (EHV-1 and EHV-4) and gammaherpesvirus (EHV-2d) have been associated with more long-lasting airway inflammation.[66]

The role of bacterial infection in IAD, particularly in young racehorses, is unclear. In several studies there was a strong relationship between inflammation of the lower respiratory tract and the presence of streptococcal species; horses with greater evidence of airway inflammation on tracheal aspiration and

endoscopy had higher mean bacterial counts in tracheal aspirate,[23] and horses with bacteria found in the tracheal aspirate had a greater tendency to cough.[15] Recently, it has been shown that the respiratory microbiota differs between horses with IAD and those without respiratory disease, with streptococcal species being increased in horses with IAD. Moreover, treatment with dexamethasone exacerbated this difference.[67] However, it is important to remember that association is not necessarily causation, and so increased numbers of bacteria may reflect impaired airway clearance rather than a causative role for bacteria. The role of bacterial and viral infection in IAD remains unclear at this time.

Because horses sample the ambient air on a continual basis, it seems logical that air pollution might contribute to the development of IAD. In one study, clinically normal horses exposed to ozone had significant increases in the glutathione redox ratio as well as total iron levels in the pulmonary epithelial lining fluid (both markers of exposure to oxidizing agents), and there was a strong correlation between airway inflammation score and the glutathione redox ratio in horses examined for poor performance but without overt airway disease.[68] In contrast, horses living in urban environments have been shown to have less airway reactivity, although greater levels of iron in the BAL fluid, than do horses living in rural environments.[69]

There are multiple other possible contributors to the development of IAD. Cold air exposure is an important risk factor for the development of asthma in human athletes, and cold air exposure has been shown to be a risk factor for development of tracheal mucus accumulation in some horses.[28] In support of this observation, exposure of equine airways to cold air resulted in altered immunologic responses for at least 48 hours. Exercise may also play a role in the development of IAD, in that neutrophils are increased in the BAL fluid for at least 48 hours after exercise, and there is a corresponding increased late-phase expression of IL-8 and TNF-α in the BAL fluid.[70,71]

There is no convincing evidence of an allergic response in horses with IAD. However, the presence of increased numbers of mast cells in the BAL fluid of horses with poor performance,[2] the association of BAL mastocytosis with AWHR,[72] and immunohistochemistry studies showing more IgA-containing cells and occasionally increased numbers of IgM- and IgG-containing cells are suggestive of a degree of allergic response and a heightened immune response. Anyone looking at recent studies of gene expression profiles in the BAL fluid of

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horses with IAD should take note of whether the horses were diagnosed as having IAD on the basis of a generalized increase in inflammatory cells or if the study group was parsed more thoroughly into horses with increased mast cells or horses with increased neutrophils. One study of horses with a generalized increase in inflammatory cells revealed an upregulation of IL-1β, IL-23, and TNF-α but no evidence of a polarized cytokine response.[73] On the other hand, when horses are stratified into mast cell versus neutrophil groups, mRNA for IL-4 correlated with mast cells but not neutrophils, whereas for all groups, similar to the previous study, TNF-α and IL-1β were increased.[74,75] It is most likely that multiple factors contribute to the development of IAD in individual horses; a critical level of risk factors or exposure is probably necessary for the disease to manifest itself. Recently, measurement of cytokine concentrations in BAL fluid suggested that neutrophilic IAD involved activation of the innate immune system and a Th1 polarized response; at the same time, the study supported other emerging findings that different cytologic profiles are likely associated with differing immunologic pathways.[76]

■ Differential Diagnoses

The diagnosis of IAD often requires the exclusion of other diseases that may have a similar clinical picture. Whereas horses with RAO (heaves) or summer pasture–associated RAO (SPARAO) in remission may be very difficult to distinguish from horses with IAD, horses with RAO or SPARAO have a history of episodes of obvious breathing difficulty associated with exposure to either moldy hay or summer pasture. Upper airway disease, such as sinus infection or guttural pouch infection, may cause cough and nasal discharge, and both static and dynamic upper airway obstructions may cause poor performance and poor recovery from exercise. These may be largely ruled out by endoscopy. Horses with pneumonia, bronchopneumonia, or lung abscess commonly have abnormalities suggesting systemic disease, such as abnormal findings on CBC, recent history of fever, weight loss, or inappetence. In these cases tracheal wash can be very helpful in determining a septic cause of disease. Thoracic radiographs or ultrasound will also aid in the detection of these septic respiratory diseases. EIPH may be seen in conjunction with IAD, but the presence of epistaxis, blood on endoscopy of the trachea, or red cells or hemosiderophages on BAL confirm the diagnosis of EIPH. Overt viral respiratory disease is difficult to confuse with IAD, as it usually manifests with fever and malaise, but

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horses with viral respiratory disease may exhibit prolonged cough and AWHR for weeks to months after resolution of the primary disease.

■ Therapy

There is remarkably little evidence-based support for any particular therapy in treating IAD. However, the mainstay of treatment has become a combination of environmental remediation, corticosteroid therapy, and bronchodilators.

Environmental Remediation.

The barn environment is a hotbed of particulate matter, respirable endotoxins, molds, and volatile gases such as ammonia. The worst offenders appear to be hay and straw. A study looking at different management systems showed that when hay and straw bedding were replaced by pelleted feed and wood shavings, the respirable particulate levels were remarkably reduced.[55] Further improvements can be made by using cardboard bedding to reduce dust and mold levels.[77] Indoor arenas present another high-dust challenge to the horse, with respirable particulate levels 20 times the level recognized to cause respiratory dysfunction in humans.[61] Other fairly common-sense strategies can be used. We make the following recommendations to owners in addition to the suggestion to change to low-dust feeds and beddings:

- Sprinkle aisles with water before sweeping.
- Avoid storing hay overhead. If unavoidable, lay a tarp under the hay to avoid dust raining down on the horses.
- Use a humectant or hygroscopic agent to reduce dust in the indoor and outdoor arenas.
- Remove horses from the barn while cleaning stalls or moving hay.
- Do not use blowers to clean aisles.
- Wet hay before feeding or use Dengie or other baked hay products.

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- Remove cobwebs and other dust collectors routinely.

A recent study demonstrated that environmental control was by far the most important means of treating airway inflammation and dysfunction in horses with heaves (RAO), a more severe disease than IAD, and feeding hay in a net was shown to be the most important factor in high breathing zone particulate levels.[60,78] It is logical therefore to suppose that environmental management is equally important in the treatment of IAD.

Corticosteroid Therapy.

Either parenteral or inhaled corticosteroids form the mainstay of drug therapy for IAD. Although the utility of corticosteroids for preventing or ameliorating airway remodeling in human asthma is debated, corticosteroids have recently been demonstrated to prevent airway smooth muscle thickening in mice with experimental asthma.[79,80] The degree of efficacy in decreasing BAL neutrophilia is not completely known. Some studies show an obvious benefit of dexamethasone in improving clinical signs and lung function and reducing BAL neutrophilia,[81] whereas others show improvement primarily in lung function with little effect on BAL cytology for dexamethasone only or for both dexamethasone and fluticasone.[78,82] Corticosteroid treatment certainly causes adrenocortical dysfunction, but this is less pronounced with inhaled therapy versus systemic.[81] Although concerns about precipitating laminitis with corticosteroid therapy are frequently expressed, the actual risk of laminitis with corticosteroid therapy is completely unknown.[6] In our clinic we frequently treat with an initial course of parenteral corticosteroids, typically a 4-week decreasing course of prednisolone followed by inhaled corticosteroids. A recent study demonstrated that fluticasone propionate is detectable in blood and urine after delivery by inhalation.[83]

Bronchodilator Therapy.

Bronchodilators, especially the inhaled form, appear to be efficacious in treating IAD in conjunction with corticosteroids. The most commonly used bronchodilators in IAD include aerosolized β-adrenergics, such as albuterol, and aerosolized parasympatholytics, such as ipratropium. β-Adrenergic drugs such as albuterol also increase mucociliary transport. The use of systemic β-adrenergics

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such as clenbuterol is not advised, as the extent of bronchoconstriction in IAD does not warrant risking the adverse effect of cardiovascular remodeling, which has been shown to occur in horses.[84] Moreover, a recent study demonstrated that when clenbuterol is given to horses with AWHR, tachyphylaxis associated with increased airway reactivity develops by 21 days of treatment,[7] whereas no such increase in AWRH was noted when horses were given aerosolized albuterol over a 10-day period.[85]

Mast Cell Inhibitors.

Sodium cromoglycate can be efficacious in treating known mast cell–mediated IAD[9] but will not be of use for treating the majority of horses with neutrophil-mediated disease. The use of sodium cromoglycate requires considerable owner compliance, as the maximum response to this drug occurs at 1 to 2 weeks after beginning treatment.

Aerosolized Therapy.

Aerosolized therapy using a combination of inhaled corticosteroids and bronchodilators is well established clinically in the treatment of IAD; however, there are no clinical trials establishing the efficacy of these drugs. When using inhaled drugs, we use a spacer and mask in order to improve delivery of the drug. Regardless of the type of mask and spacer device used, actual delivery of particles to the lower airways is poor in horses, as indeed it is even in humans, and the least efficacious means of delivering aerosolized drugs is by nebulization.[86,87] Unfortunately, strategies that we know improve lung deposition of aerosolized drugs in humans, such as slow deep breathing and breath holding, are not practical in horses. Devices currently on the market include the Aerohippus (Trudell Medical, Inc., London, Canada), the Equine Haler (Equine Health Care, Inc., Horshølm, Denmark), and the Flexineb® (Nortev Ltd., Galway, Ireland). Individual horse and owner preference determines which device should be used. Inhaled corticosteroids commonly used in the treatment of IAD include beclomethasone and fluticasone.

Although there are no reported clinical trials using corticosteroids in horses with IAD, horses with RAO treated with 3750 µg of beclomethasone dipropionate twice daily showed improvement in both clinical signs and lung function.[88] Smaller doses (500 to 1500 µg twice daily) were shown to be efficacious in horses with heaves, and we commonly use small doses (500 to

1000 µg twice daily) with good clinical effect in horses with IAD.

Fluticasone is a more potent corticosteroid than beclomethasone and has been shown to be efficacious in treating horses with heaves when administered using a delivery device that is no longer on the market at a dose of 2000 µg twice daily.[89] Unlike with beclomethasone, fluticasone did not cause adrenocortical dysfunction.[89] We use a decreasing-dose regimen, starting at 1500 to 2000 µg twice daily, working down to 1000 µg once daily or every other day. The lowest dose is reached over a 3- to 4-week period. Although we previously advised use of a short-acting bronchodilator, such as inhaled albuterol, 5 to 15 minutes before treatment with inhaled corticosteroid to increase deposition of the latter by fully opening the small airways, the accepted practice in human medicine currently is to avoid this practice. The logic behind this is that it is important to get the most useful and costly drug administered first before compliance decreases. It is important that the owner understand that even with the higher doses of inhaled corticosteroid, it may require 1 to 2 months for the best therapeutic effects to be achieved.

The most commonly used inhaled bronchodilator is albuterol, a β_2-specific adrenergic drug. The onset of effect with albuterol is quite rapid, with maximum bronchodilation being seen within 15 minutes. However, it is important to note that the maximum effect lasts for only an hour in some horses, and there are side effects (such as anxiety, nervousness, trembling, and tachycardia) with higher doses of the drug, even in the inhaled form. There is no evidence to suggest that the oral form of albuterol is even absorbed in the horse, and it is not suggested as appropriate therapy. Longer-acting β_2-adrenergic agonists, such as salmeterol and formoterol, can also be used, with bronchodilation lasting for 6 to 8 hours. Parasympatholytic drugs such as ipratropium have a slower onset of action but longer duration (at least 6 hours) than albuterol and lack the severe side effects of parenteral use of drugs such as atropine. It is important to remember that these bronchodilators are symptomatic drugs only; they do not treat the underlying inflammation and therefore are unsuitable for single-drug therapy.

Mast cell inhibitors that can be administered by metered dose inhaler include Intal (cromolyn) and Tilade (nedocromil sodium). They are discussed in earlier sections. Many putative ancillary treatments have been touted as efficacious in the treatment of airway inflammation in the horse. The only one with good evidence for efficacy is the use of omega-3 fatty acids in the feed.[90]

In summary, IAD is a disease characterized by nonseptic inflammation, visible

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on BAL cytology as excessive neutrophils, mast cells, or eosinophils, and involving low-grade airway obstruction and AWHR. Clinical signs include variable cough, nasal discharge, and poor performance. Excessive amounts of mucus may also be visualized in the trachea during endoscopic examination. The cause of IAD is unknown, but the disease is probably best avoided by achieving a low-dust and low-endotoxin environment. Treatment logically begins with environmental remediation and is supplemented by anti-inflammatory drug therapy using systemic or inhaled corticosteroids and inhaled bronchodilators. IAD that involves an excess of mast cells in the airways can be further treated with inhaled mast cell inhibitors.

Tuberculosis

Peggy S. Marsh

Tuberculosis refers to any infectious disease caused by *Mycobacterium* spp. and associated with the formation of focal granulomatous lesions. In humans many forms of the disease exist, with the primary site of infection most commonly being the lungs. *Mycobacterium tuberculosis* is the typical causative agent in humans, whereas *Mycobacterium avium* or *Mycobacterium bovis* is usually implicated in animal cases.[1] Tuberculosis is extremely rare in horses, especially in the United States. Most cases in horses have reported isolation of *M. avium*[2-5]; however, there are reports of infection with *M. bovis*[6-8] and *M. tuberculosis*.[9] In equine cases it appears that the organism is usually ingested, although primary respiratory infection may occur. Spread is hematogenous, and the organism frequently settles in lymph nodes and the spleen.

The most frequent presenting complaint is chronic weight loss with ensuing weakness and lethargy. Terminally ill horses with the pulmonary form are febrile and dyspneic and have a cough. Radiographic or sonographic evaluation of the thorax may be helpful in defining the pattern and distribution of lesions. Other clinical signs may be noted depending on the organ systems affected; these signs include intestinal tract abnormalities, hepatitis, and osteomyelitis of the cervical vertebrae.[1-9]

Diagnosis, usually made after the horse's death, is based on the presence of tubercles and isolation of the organism. The intradermal skin test is not reliable in the horse because a majority of clinically normal horses may have positive test results.[9] Cytologic or histologic evaluation of a wash or aspirate of a lesion may reveal acid-fast bacilli. Biopsy of the lesion(s) is necessary for a definitive

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diagnosis. When tuberculosis is suspected, culture of an appropriate sample, such as a tracheal aspirate with primary pulmonary involvement, is advisable. However, this is a very slow-growing organism, and isolation may take multiple weeks to months.[6] PCR technology has proven to be a useful tool, often in conjunction with culture.[6,7,9]

Due to public health concerns, treatment is not usually attempted. If treatment is undertaken, the horse should be isolated, with precautions taken to prevent the spread of disease and in consultation with the public health officials and/or the horse handler's physician. Tuberculosis is a reportable disease in other species. In one case a horse was treated with a prolonged course of antimicrobial medications (enrofloxacin and potassium iodide) while it took 4 months to identify *M. bovis* from biopsy samples from a lung mass. The horse went on to live at least another 8 years with no further problems related to the *M. bovis* infection.[6] Because treatment is usually not a viable option in horses, prognosis is very poor.

Bacillus Calmette-Guérin vaccine has been used in humans with potential exposure, but the benefit of its use in horses to provide increased resistance after exposure to a tuberculosis infection is unknown.

Pneumoconiosis (Silicosis)

Peggy S. Marsh

Pneumoconiosis refers to lower respiratory tract disease associated with deposition of small particles (dust) within the lungs. In human medicine the majority of cases are related to occupation and include coal worker's lung, silicosis, and asbestosis.[1,2] There are two related reports of silicosis in horses.[3,4] The majority of the horses originated from the Monterey-Carmel Peninsula in California. Silicosis is a disease caused by inhalation of crystalline silica. There are several clinical forms of silicosis in humans, including simple and complicated chronic forms as well as acute silicosis (silicoproteinosis). Silicosis has been associated with mycobacterial diseases, airway obstruction, and pulmonary neoplasia.[5] Freshly fractured silica is more toxic to alveolar macrophages than aged silica. Crushing silica leads to the formation of reactive radials.[6] The small (0.5 to 5 mm) particles are deposited in small airways and alveoli, then subsequently phagocytosed, initiating a cycle of granulomatous inflammation, oxidative stress, and apoptosis leading to chronic fibrotic

interstitial disease.[1,5,6]

The clinical signs reported in horses are similar to those of severe equine asthma (heaves) and include weight loss, cough, exercise intolerance, and sometimes exercise-induced respiratory distress (sweating, nostril flaring, abducted elbows, reluctance to move, and shaking). Resting respiratory rates are often increased. Physical examination revealed a restrictive pattern of breathing with harsh breath sounds and exercise-induced wheezing on auscultation.

Diagnosis was based on the presence of birefringent crystalline inclusions within pulmonary macrophages from samples obtained via tracheal aspiration, BAL, lung biopsy, or at necropsy.[4] In some cases repeated tracheal sampling was required. Radiographs of the thorax revealed a variety of findings, including most commonly an interstitial pattern (miliary, reticulonodular, and linear) most severe in the caudodorsal lung fields. Other radiographic abnormalities noted included lymphadenopathy, pleural effusion or thickening, hyperinflation, and pulmonary consolidation.[4]

Gross pathologic analysis revealed interstitial granulomatous pneumonia and fibrosis. Histologic examination with both light and electron microscopy revealed peribronchitis, perivasculitis, and cellular infiltrates of refractile inorganic dust particles within macrophages and giant cells.[3,4]

In general the horses reported to have silicosis had a poor prognosis. The original report presented postmortem findings of nine horses diagnosed with silicosis.[3] In a later, related paper, a total of 19 horses were identified.[4] Short-term (2 to 12 months) follow-up evaluation was available in eight of these individuals, with a progressive loss of respiratory function noted in four of the cases, leading to euthanasia. Treatment consisted of environmental change and glucocorticoid therapy. Novel forms of therapy, including inhibition of inflammatory mediators as well as inhibition of apoptosis, may be seen in the future[6]; however, silicosis remains with no cure.[2]

Recent work has revealed a systemic osteoporosis in a group of horses associated with fibrosing pulmonary silicosis.[7] Also, there are reports of pneumoconiosis in other domestic species that was caused by environmental contamination.[8] It may be prudent to keep environmental contamination in mind when investigating chronic noninfectious forms of lower respiratory tract disease in the horse.

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Mycoplasma

Peggy S. Marsh

Mycoplasma spp. are a group of bacteria that differ from other bacteria because they lack a cell wall, are much smaller than most bacteria, and need cholesterol to survive. These organisms are proven to cause respiratory disease in humans, cattle, and pigs. *Mycoplasma felis* has been isolated as a pathogen causing pleuritis and pericarditis in the horse.[1-3] Experimental infection with *M. felis* in ponies induced pleuritis.[3] The relative importance of *Mycoplasma* spp. as a pathogen in acute respiratory disease of the horse has been debated. Several species of *Mycoplasma* can be isolated from the respiratory tract of healthy and diseased animals, both adults and foals. A report from Australia did not yield growth of *Mycoplasma* spp. in any of the samples from young racing horses with coughs.[4] However, a similar case control–type study from the United Kingdom showed an association between *M. felis* and inflammatory airway disease in young racehorses.[5] Also, a Canadian report demonstrated growth of *Mycoplasma equirhinis* and *M. felis*, along with other bacteria commonly thought of as respiratory pathogens, in horses with acute lung disease.[6] *M. felis* has been reported as a potential cause of an outbreak of acute respiratory disease in a stable of young racehorses, as well as of respiratory disease in foals.[7]

Clinical signs of pleuritis caused by mycoplasma infection, including fever, depression, and pleurodynia, mimic other bacterial pleural pneumonia cases. Auscultation of the thorax may reveal pleural friction rubs and dull lung sounds over the cranioventral thorax. Sonographic examination of the thorax reveals pleural effusion, often bilateral. Thoracocentesis should be performed for both diagnostic and, if necessary, therapeutic purposes. The fluid is most often an exudate, lacking any odor. Cytologic examination reveals large numbers of neutrophils within the pleural fluid.

Crucial to diagnosis of mycoplasma infection is the elimination of more common pathogens, such as streptococcal infections. Thus routine cultures for aerobic and anaerobic bacteria should be performed in any case of pleuritis. Culture for the presence of *Mycoplasma* bacteria is difficult to obtain, and *Mycoplasma*-specific media should be used. Seroconversion can also be an aid in diagnosis, with seroconversion occurring in a large number of the reported cases of *M. felis* infection.[1,2,7] Experimental infection revealed that once seroconversion has occurred, the organism can no longer be isolated from

culture samples.[3] Seroprevalence in the United States is not known. Diagnosis may be aided by the use of RT-PCR methods for the detection of *M. felis*.[8]

Experimentally infected ponies recovered without treatment in one study, so the requirements of treatment specific for mycoplasma are unclear.[3] Where available, sensitivity testing should be performed on any *Mycoplasma* spp. isolate to help with antimicrobial selection. Macrolides and tetracyclines are generally effective for infections in other species. The role these organisms play in equine respiratory disease is still unclear, and investigation continues.

Glanders (Farcy)

Faisal Ghazi Habasha

Glanders is a serious zoonotic bacterial disease that primarily affects horses, mules, and donkeys. Some animals die acutely within a few weeks. Others become chronically infected and can spread the disease for years before succumbing. Without antibiotic treatment, the case fatality rate can be as high as 95%. Glanders also occurs in other mammalian species, particularly members of the cat family, dogs, sheep, goats, camels, and humans. Swine and cattle appear to be resistant.[1,2] The term *farcy* is limited to the visible appearance of external lesions, but in the latter case internal lesions always exist, although they may not be evident.[3]

Glanders is one of the oldest diseases of horses described. Absyrtus, a Greek veterinarian in the army of Constantine the Great (CE 300), described the disease with considerable accuracy and recognized that it was contagious.[4]

■ Etiology

Glanders is caused by *Burkholderia mallei,* a nonmotile, nonsporulating, facultative intracellular gram-negative bacillus in the family Burkholderiaceae. The organism name comes from the Greek *melis* (“severe disease”) and its Latin derivative *malleus* (“depicting a malignant disease”). The organism was first identified in Germany by Loeffler and Schutz in 1882 and confirmed as the cause of glanders in 1886.[3] The organism was formerly known as *Pseudomonas mallei* before being reclassified into the new genus *Burkholderia* in 1992. Traditionally the *Burkholderia* spp. are known as plant pathogens and soil bacteria, with two important exceptions, *B. mallei* and *Burkholderia pseudomallei,* the latter of which causes melioidosis. These two organisms differ

in their survival in the environment. *B. mallei* is subject to inactivation in the environment, and it is not thought to persist outside equine hosts for long periods of time. Limited environmental survival, particularly in wet, humid, or dark conditions, may be possible for 3 to 5 weeks, and the organism can remain viable in 20° to 25° C (68° to 77° F) water for as long as a month.[4] It is inactivated by heat, direct sunlight, and commonly used disinfectants, including hypochlorites.[1-3]

Genome Structure.

The genome of *B. mallei* consists of two circular chromosomes. Chromosome 1 contains 3,510,148 base pairs (bp), and chromosome 2 contains 2,325,379 bp. A total of 5535 predicted protein-encoding open reading frames are identified in the genome.[5] The genome of this organism carries a large number of insertion sequences as compared with the related *B. pseudomallei*, with a large number of simple sequence repeats that may function in antigenic variations of cell surface proteins (National Center for Biotechnology Information [NCBI] genome project).

Geographic Distribution.

Glanders was a concern during the 2016 Olympic Games in Brazil. It was also reported in western Europe in 2016.[6] Glanders is thought to be endemic in parts of the Middle East, Asia, Africa, Central America, and South America. Between 1998 and 2012, cases were reported in Brazil, Turkey, Russia, Eritrea, Ethiopia, Iran, Iraq,[7,8] United Arab Emirates, India, Pakistan, Afghanistan, and Mongolia, with suspected cases in other parts of Africa.[1] Glanders was reported active recently in Iran and the Philippines.[1] The disease was eliminated from horses in the United States during the 1940s, although one human case of glanders was reported in a laboratory worker in 2000.[9] This was the first human case reported in the United States since 1945.

■ Transmission

Glanders is mainly transmitted by contact with skin exudates and respiratory secretions from infected equids. Both latently infected and clinically ill animals can spread the disease.[1,2]

Horses, mules, and donkeys often become infected when they ingest *B.*

mallei–contaminated food or water. The organism can also be spread in aerosols and via entry through skin abrasions and mucous membranes. Carnivores usually become infected when they eat contaminated meat. *B. mallei* is readily spread by fomites such as harnesses, grooming tools, and food and water troughs. Humans are infected by contact with sick animals, contaminated fomites, tissue, or bacterial cultures. Rare cases of person-to-person transmission have been reported in family members who nursed sick individuals. *B. mallei* has been weaponized and was used as a biological weapon against military horses and humans during World War I and World War II. Aerosols may be the major route of infection in bioterrorist attacks.[10]

Incubation Period.

The incubation period varies with the form of disease from a few days to several weeks. Septicemia or localized disease usually becomes apparent after 1 to 5 days, whereas the pulmonary form typically becomes clinically apparent after 10 to 14 days.[1,2]

■ Clinical Signs and Differential Diagnosis

In equids, glanders is traditionally categorized into nasal, pulmonary, and cutaneous forms (farcy).[1,2] In the nasal form, deep ulcers and nodules occur inside the nasal passages, resulting in a thick, purulent, yellowish discharge. This discharge may be unilateral or bilateral and can become bloody. Nasal perforation is possible. The regional (submaxillary) lymph nodes become enlarged and indurated and may suppurate and drain. Healed ulcers become star-shaped scars. In the pulmonary form, nodules and abscesses develop in the lungs. Some infections are inapparent, whereas others vary from mild dyspnea to severe respiratory disease. In more severe cases, the clinical signs include coughing, dyspnea, febrile episodes, and progressive debilitation. Diarrhea and polyuria may also be seen. Discharges from pulmonary abscesses can spread the infection to the upper respiratory tract.

In the cutaneous form, the skin contains nodules that rupture and ulcerate, discharging an oily, purulent yellow exudate (Fig. 31.38). The regional lymphatics and lymph nodes become chronically enlarged and are filled with purulent exudates. There may also be swelling of the joints and painful edema of the legs. Orchitis is a common symptom in males. Clinical cases are usually a combination of these forms and can occur as acute, chronic, or latent disease.

Donkeys and mules, as a general rule, manifest the acute symptoms, which progress rapidly, whereas horses usually have the chronic or latent disease.



FIG. 31.38 Typical cutaneous form of glanders (known as farcy) showing skin nodules.

Nasal and pulmonary signs are usually seen in the acute form. The symptoms include a high fever, decreased appetite, coughing, progressive dyspnea, nasal discharge, and ulcers and nodules on the nasal mucosa. Bloody crusting may be seen on the nostrils, and there may be a purulent ocular discharge. The submaxillary lymph nodes are usually swollen and painful. Central nervous system signs have been reported in experimentally infected horses, possibly as the result of secondary bacterial infection from a compromised blood-brain barrier.[11] Animals with the acute form of glanders usually die in a few days to a few weeks.

The chronic form develops insidiously and results in progressive debilitation. The symptoms may include coughing, dyspnea, intermittent fever, enlargement of the lymph nodes, a chronic nasal discharge, and ulcers, nodules, and stellate scars on the nasal mucosa. The skin and lymphatics may also be involved. The chronic form is often fatal, but affected animals may live for years before succumbing to the disease.

In the latent form, there may be few symptoms other than a nasal discharge and occasional labored breathing. Lesions may be found only in the lungs.

The differential diagnoses for glanders include strangles caused by *Streptococcus equi;* epizootic lymphangitis, which is a chronic granulomatous

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and suppurative fungal infection caused by *Histoplasma farciminosum;* sporotrichosis, a chronic subcutaneous lymphatic mycosis caused by a gram-positive fungus *Sporotrichum schenckii;* ulcerative lymphangitis, a bacterial disease caused by *Corynebacterium pseudotuberculosis;* and melioidosis (Whitmore's disease), which is caused by *B. pseudomallei.* Melioidosis is particularly difficult to differentiate because *B. pseudomallei* and *B. mallei* cross-react in many serologic and hypersensitivity tests.[1,2]

■ Diagnosis

A diagnosis of glanders based on clinical signs can be made when *B. mallei* is isolated from samples or an immunologic reaction to the organism is detected serologically or on the basis of hypersensitivity test results. Isolation and identification of *B. mallei* in cultures of samples from lesions or various exudates, including respiratory secretions, is regarded as a gold standard for the diagnosis of glanders. *B. mallei* can be stained with methylene blue, Wright's stain, or Gram stain, but the staining can be weak or irregular, and bipolar staining of the gram-negative organism may be observed. They can be pleomorphic in older cultures, but in clinical samples and young cultures they typically form straight or slightly curved rods that are 0.3 to 0.8 µm in width and 2 to 5 µm in length. Some authors report that, in tissues, the organism is identified best with Giemsa stain.[12]

B. mallei can be grown on routine culture media, including nutrient, blood, and MacConkey agars; growth is slow, but colonies are usually visible within 48 hours. Optimal growth occurs at 37° C (98.6° F).

Automated bacterial identification systems do not always correctly identify this organism. All isolations must be performed in biosafety level 3 laboratories. Inoculation into laboratory animals, particularly guinea pigs (the Strauss reaction) or hamsters, was used for identification of *B. mallei* in the past, but this technique is now rarely practiced.

A cell-mediated hypersensitivity reaction test (mallein intradermal skin test) was used extensively to screen horses for glanders. This test is still used to certify horses as negative for glanders during importation to some countries. It may also be used in the diagnosis of clinical cases. The mallein test is based on hypersensitivity reaction to mallein, a commercially available, purified protein derivative of *B. mallei.* The test is performed most often by intradermal palpebral injection. Reactors are identified by marked eyelid swelling that

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develops within 24 to 48 hours, accompanied by fever and occasionally by purulent ocular discharge. No reaction or minimal swelling of the eyelid develops in unsensitized animals. False-positive reactions can occur in animals that are sensitized to other closely related *Burkholderia* spp., including *B. pseudomallei,* and cross-reactions with *S. equi* have been described.

Serologic tests are sometimes used to screen horses for importation to glanders-free countries or to identify clinically affected animals. Measurable titers of serum antibody against *B. mallei* develop approximately 1 week after infection. Complement fixation was the preferred serologic test in past eradication programs because of its ability to detect subclinically or chronically infected animals. This test was most useful when the prevalence of disease was high. Complement fixation is still used by some countries to assess imported equids for glanders. Enzyme-linked immunosorbent assay tests are also used to screen animals for international trade. Other serologic tests include indirect hemagglutination,[13] counterimmunoelectrophoresis, immunoblotting, and indirect fluorescent testing, but these tests are not approved by the World Organisation for Animal Health (OIE) for use in international trade.[1,2] Rapid DNA tests, such as PCR assays, are now also used.

■ Treatment

Treatment of glanders is often not advised because infected animals may remain subclinically infected and shed *B. mallei*.[1,2] The risk of zoonotic transmission also discourages treatment. Systemic treatment with antibiotics, including penicillin and streptomycin, is usually ineffective in controlling the disease. Some evidence has accumulated that enrofloxacin, erythromycin, ampicillin, sulfonamide, gentamicin, and tetracycline might be effective against *B. mallei.* This evidence has emerged from in vitro antibiotic sensitivity testing and from treatment studies in experimentally infected guinea pigs. Experimentally, in lab animals effective treatments also include doxycycline, ceftazidime, gentamicin, and trimethoprim sulfas.[1]

■ Prevention and Control

Cases of glanders in animals must be reported to the OIE.[1] The occurrence of this disease in any country can result in restrictions on international trade in horses and other affected animals. The mallein test and complement fixation test are approved assays recommended by the OIE for international trade purposes.[1]

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If glanders is detected, control measures include strict quarantine of all infected and exposed animals, diagnostic testing of animals with clinical signs indicative of glanders, and assessment of apparently normal equids with the elimination of those that react positively in screening tests. Ill animals and those with positive results of mallein tests are euthanized. Horses exposed to *B. mallei* that yield negative results in mallein tests are isolated and retested 2 to 3 weeks later. Carcasses and contaminated bedding and feed should be burned or buried. Equipment or other items in contact with infected animals should be disinfected.

People who handle tissues from infected animals, bacterial cultures, or contaminated fomites should implement strict precautions to prevent infection. Protective clothing, including masks, gloves, face shields, and gowns, should be worn. In clinical and research laboratories, *B. mallei* requires biosafety containment level 3 accommodation. Precautions are indicated for activities that are likely to produce aerosols, droplets, or concentrations of bacteria. Currently there is no commercial vaccine against glanders for use in humans or any other animal species.

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Exercise-Induced Pulmonary Hemorrhage

Kenneth W. Hinchcliff

Exercise-induced pulmonary hemorrhage (EIPH) is a pervasive disorder of horses that perform strenuous exercise, well recognized in Thoroughbred and Standardbred racehorses and occurring in other breeds and uses of horses.[1-6] The disorder is associated with reduced performance of Thoroughbred racehorses and other breeds and costs the Thoroughbred and Standardbred racing industries in the United States and Canada between $100 million and $225 million (U.S. dollars [USD], year 1995 value) annually.

Management of EIPH in racehorses is the subject of much debate, especially within North America where the administration of furosemide is permitted on the day of racing.[7,8] The debate is fueled by concerns about the welfare of racehorses, the integrity of racing and use of medications on race day, and uncertainty about the etiology, pathophysiology, and optimal treatment of EIPH.[9] There are a number of recent reviews of EIPH.[10-12]

■ Definition and Etiology

EIPH is a disease that occurs only in horses during strenuous exercise.[10] It manifests as the presence of blood in the airways of horses after strenuous exercise. Definitions of EIPH vary from detection of blood using microscopic examination of BAL fluid or tracheal aspirates to observation of blood in the airways during tracheobronchoscopic examination.

The etiology of EIPH remains unclear, although the pathogenesis is now reasonably well described (see below).

Epistaxis and hemorrhage into airways can occur as a result of a number of diseases, including disorders of the upper airways and lungs (Table 31.12). Hemorrhage into the trachea or bronchi can be a result of EIPH, pulmonary abscess, fungal granuloma, trauma, pneumonia, pulmonary foreign body, or hemangiosarcoma or other pulmonary neoplasia. Epistaxis can be associated with all of these causes of hemorrhage into the lower airway and with diseases of the upper airway, including guttural pouch mycosis, ethmoidal hematoma, trauma, and neoplasia of the upper airways and associated structures. Thrombocytopenia can cause epistaxis.

TABLE 31-12

Causes of Epistaxis in Horses. (Reproduced With Modifications by Permission.[91])

Disease	Epidemiology	Clinical Signs and Diagnosis	Treatment and Control
Hemorrhage Into Trachea or Bronchi, Sometimes With Epistaxis			
Exercise-induced pulmonary hemorrhage (EIPH)	Horses after strenuous exercise Most common in Thoroughbred and Standardbred racehorses	Epistaxis is a rare but very specific sign of EIP; only occurs after exercise Endoscopic examination of the airways is diagnostic	Efficacy of various drugs used for treatment and control is debated Furosemide is used extensively before racing
Trauma	Sporadic; associated with trauma to head, neck, or chest	Physical examination reveals site and nature of the trauma; can require endoscopic examination of upper airways	Symptomatic treatment
Pneumonia	Recent transport or respiratory disease; can occur as outbreaks though usually individual animals	Fever, tachypnea, abnormal lung sounds, leukocytosis, radiography demonstrates lung lesions; cytological and microbiological examination of tracheal aspirate	Antimicrobials, NSAIDs, oxygen Control by vaccination and prevention of respiratory disease
Lung abscess	Sporadic; hemorrhage can occur after exercise	Sometimes no premonitory signs fever, depression, anorexia, cough hemogram demonstrates leukocytosis Hyperfibrinogenemia ultrasonography or radiography demonstrates lesion Tracheal aspirates	Antibiotics
Intrabronchial foreign body	Sporadic	Cough, hemoptysis, fever; endoscopy or radiography reveals foreign body	Removal of foreign body—often not readily achieved
Pulmonary neoplasia	Sporadic; often older horse, but not always hemangiosarcoma	Cough, hemoptysis demonstrate mass on ultrasonographic or radiographic examination	None
Epistaxis (in Addition to the Above Diseases)			
Guttural pouch mycosis	Sporadic; acute onset epistaxis	Severe, life-threatening epistaxis; tachycardia, anemia, hemorrhagic shock	Surgical ligation or occlusion of arteries in the guttural pouch
Ethmoidal hematoma	Sporadic	Epistaxis not associated with exercise Usually unilateral	Surgery or injection of mass with formaldehyde
Thrombocytopenia	Sporadic	Epistaxis, mild, intermittent Petechiation and ecchymotic hemorrhages Thrombocytopenia	Glucocorticoids

Coagulopathy	Sporadic, congenital or associated with ingestion of rodenticides	Epistaxis, increased bleeding from minor wounds, hemarthrosis,	Identify and correct underlying cause Vitamin K administration
Neoplasia	Sporadic	Neoplasia of upper airways	None
Trauma	Sporadic	Injury to head or pharynx	Symptomatic
Sinusitis	Sporadic	Endoscopic or radiographic examination of sinus	Drainage, antimicrobials

There is evidence of a heritable component to exercise-associated epistaxis in Thoroughbred racehorses (h^2 = 0.27 for lifetime risk of epistaxis and 0.5 for risk of a repeated episode during an individual race,[13] and h^2 = 0.23 for an individual and 0.40 for a sire).[14] While there is evidence of heritability of epistaxis, there are no reports of the specific genetic factors contributing to EIPH (of which epistaxis is one manifestation; see below), such as could be identified by genome-wide association studies or other techniques.[15]

■ Clinical Signs and Differential Diagnosis

Poor athletic performance and epistaxis are the most common presenting complaints for horses with EIPH. Although poor performance might be attributable to any of a large number of causes, epistaxis associated with exercise is almost always secondary to EIPH.

Epistaxis due to EIPH occurs during or shortly after exercise and is usually first noticed at the end of a race, particularly when the horse is returned to the paddock or winner's circle and is allowed to lower its head. It is usually bilateral and resolves within hours of the end of the race. Epistaxis might occur on more than one occasion, especially when horses are raced or exercised at high speed soon after an initial episode. It is important to recognize that epistaxis is an uncommon manifestation of EIPH, occurring in as few as 4% of horses with EIPH.[16]

Exercise-Induced Pulmonary Hemorrhage and Performance.

Failure of racehorses to perform to the expected standard (poor performance) is often, accurately or not, attributed to EIPH.[17] Many horses with poor performance have cytologic evidence of EIPH on microscopic examination of tracheobronchial aspirates or BAL fluid or have blood evident on endoscopic examination of the tracheobronchial tree performed 30 to 90 minutes after

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strenuous exercise or racing. However, it is important to recognize that EIPH is very common in racehorses, and it should be considered the cause of poor performance only after other causes have been eliminated. Severe EIPH undoubtedly results in poor performance and, on rare occasions, death of Thoroughbred racehorses.[10,17,18] Thoroughbred horses with EIPH have impaired performance compared to unaffected horses.[17,19,20] The severity of EIPH is negatively correlated to race performance, with more severely affected horses having a lower likelihood of finishing in the first three places; they are less likely to be elite money earners and finish further behind the winner than do unaffected horses.[17,19,20]

Results of studies in Standardbred racehorses indicate either a lack of effect of EIPH on performance or an association between EIPH and superior performance. There was no relationship between presence of EIPH and finishing position in 29 Standardbred racehorses with intermittent EIPH, each examined on at least two occasions, or in 92 Standardbred racehorses examined on one occasion. However, of 965 Standardbred racehorses examined after racing, those finishing first or second were 1.4 times more likely (95% confidence interval 0.9 to 2.2) to have evidence of EIPH on tracheobronchoscopic examination than were horses that finished in seventh or eighth position.

There is no clear association between EIPH and performance (time) in barrel racing Quarter Horses.[21]

■ Diagnostic Approach

Physical Examination.

Apart from epistaxis in a small proportion of affected horse, there are few abnormalities detectable on routine physical examination of horses with EIPH. Rectal temperature and heart and breathing rates might be elevated as a consequence of exercise in horses examined soon after exercise, but values of these variables in horses with EIPH at rest are not noticeably different from horses with no evidence of EIPH. Affected horses might swallow more frequently during recovery from exercise than do unaffected horses, probably as a result of blood in the larynx and pharynx. Coughing is common in horses recovering from strenuous exercise and after recovery from exercise; horses with EIPH are no more likely to cough than are unaffected horses.[10] Other clinical signs related to respiratory abnormalities are uncommon in horses with EIPH.

Respiratory distress is rare in horses with EIPH and when present indicates severe hemorrhage or other serious lung disease such as pneumonia, pneumothorax, or rupture of a pulmonary abscess. Lung sounds are abnormal in a small number of EIPH-affected horses and, when present, are characterized by increased intensity of normal breath sounds during rebreathing examination. Crackles may be auscultated over the trachea in horses with EIPH but are also heard in unaffected horses.

Tracheobronchoscopy.

Observation of blood in the trachea or large bronchi of horses 30 to 120 minutes after racing or strenuous exercise provides a definitive diagnosis of EIPH. The amount of blood in the large airways varies from a few small specks on the airway walls to a stream of blood occupying the ventral one third of the trachea. Blood might also be present in the larynx and nasopharynx. If there is a strong suspicion of EIPH and blood is not present on a single examination conducted soon after exercise, the examination should be repeated in 60 to 90 minutes. Some horses with EIPH do not have blood present in the rostral airways immediately after exercise but do have blood when examined 1 to 2 hours later. Blood is detectable by tracheobronchoscopic examination for 1 to 3 days in most horses, with some horses having blood detectable for up to 7 days.

Bronchoscopic examination can be used to estimate the severity of EIPH through the use of a grading system. The interobserver repeatability of tracheobronchoscopic assessment of severity of EIPH using a 0 to 4 grading scale is excellent, and this scoring system has been widely adopted (Table 31.13).[16,17,20-23]

TABLE 31.13

Validated System for Grading the Severity of Exercise-Induced Pulmonary Hemorrhage Detected on Tracheobronchoscopic Examination of Thoroughbred Racehorses[92]

Grade 0	No blood detected in the pharynx, larynx, trachea, or main stem bronchi
Grade 1	Presence of one or more flecks of blood or ≤2 short (<quarter the length of the trachea), narrow (<10% of the tracheal surface area) streams of blood in the trachea or main stem bronchi visible from the tracheal bifurcation
Grade 2	One long stream of blood (>half the length of the trachea) or >2 short streams occupying less than one third of the tracheal circumference
Grade 3	Multiple, distinct streams of blood covering more than one third of the tracheal circumference. No blood pooling at the thoracic inlet

Grade 4	Multiple, coalescing streams of blood covering >90% of the tracheal surface, with pooling of blood at the thoracic inlet

It is assumed that a higher score represents more severe hemorrhage, but while the repeatability of this scoring system has been established, the relationship between the amount of blood in the large airways and the actual amount of hemorrhage has not been established.

Radiography.

Thoracic radiography is of limited use in detecting horses with EIPH. Radiographs can demonstrate the presence of densities in the caudodorsal lung fields of some horses, but many affected horses have minimal to undetectable radiographic abnormalities.[10] Examination of thoracic radiographs of horses with EIPH can be useful in ruling out the presence of another disease process, such as a pulmonary abscess, contributing to the horse's pulmonary hemorrhage or poor athletic performance. The utility of thoracic ultrasound for detection of EIPH has not been extensively reported. One report of detecting EIPH in 81% of 157 horses in which EIPH was diagnosed by relatively liberal assessment of BAL fluid reported sensitivity of presence of comet-tail lesions for diagnosis of EIPH of 86% and specificity of 25%,[24] indicating that ultrasound examination of the thorax has limited utility in confirming the presence of EIPH.

■ Clinical Pathology

Examination of Airway Secretions or Lavage Fluid.

The presence of red blood cells or macrophages containing either effete red blood cells or the breakdown products of hemoglobin (hemosiderophages) in tracheal or bronchoalveolar lavage fluid provides evidence of EIPH.[25] Detection of red blood cells or hemosiderophages in tracheal aspirates or BAL fluid is believed to be both sensitive and specific in the diagnosis of EIPH, although in the absence of a gold standard for diagnosis, this claim is yet to be validated. Examination of airway fluids from a variety of breeds and uses of horses, including barrel racing horses,[21] indicates the presence of EIPH in a greater proportion of horses than does tracheobronchoscopic examination after strenuous exercise or racing. The greater sensitivity of examination of airway fluid is probably attributable to the ability of this examination to detect the presence of small amounts of blood or its residual products and the longevity of these products in the airways. Although endoscopic examination can detect

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blood in occasional horses up to 7 days after an episode of EIPH, cellular evidence of pulmonary hemorrhage persists for weeks after a single episode. Red blood cells and macrophages containing red blood cells are present in BAL fluid or tracheal aspirates for at least 1 week after strenuous exercise or instillation of autologous blood into airways, and hemosiderophages are present for at least 21 days and possibly longer.[26]

Recent studies have reported on the use of red blood cell numbers in BAL fluid as a quantitative indicator of EIPH.[21,25,27-29] The diagnostic cutoff has not been determined, although 1000 cells/μL was used in one study,[21] and there is only a weak correlation between EIPH score determined by tracheobronchoscopic examination and red blood cell count in BAL fluid (r^2 = 0.15).[21] However, this indicator of EIPH severity has not been validated nor demonstrated to be more reliable or repeatable than tracheobronchoscopic examination and visual scoring. Furthermore, considerable concern exists over the suitability of red blood cell counts in BAL fluid for assessment of severity of EIPH given that an unknown area, although presumably small, of the lung is examined by lavage and there is a risk that this area of lung might not be representative of the lung as a whole, similar to the situation of examination of BAL fluid of horses with pneumonia.[7] BAL of sections of both lungs, achieved using an endoscope, might obviate some of these concerns given that BAL results of each lung in a horse differ.[30]

Tracheal aspirates can be obtained any time after exercise by aspiration either during tracheobronchoscopic examination or through a percutaneous intratracheal needle. Aspirates obtained through an endoscope may not be sterile, depending on the collection technique. BAL fluid can be obtained through either an endoscope wedged in the distal airway or a cuffed tube inserted blindly into a distal airway. Collection of fluid through an endoscope has the advantage of permitting examination of the distal airways and selection of the area of lung to be lavaged. However, it does require the use of an endoscope that is longer (2 m) than those readily available in most equine practices. Use of a commercial BAL catheter does not require use of an endoscope, and this procedure can be readily performed in field situations.

■ Necropsy

EIPH is a rare cause of death of racehorses, but among racehorses that die during racing for reasons other than musculoskeletal injuries, EIPH is common.[18]

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Necropsy examination of horses is usually incidental to examination for another cause of death. Grossly, horses examined within hours of strenuous exercise, such as horses examined because of catastrophic musculoskeletal injuries incurred during racing, can have severe petechiation in the caudodorsal lung fields. Horses with chronic disease have blue/gray or blue/brown discoloration of the visceral pleural surfaces of the caudodorsal lung fields that is often sharply demarcated, especially on the diaphragmatic surface. The discoloration affects both lungs equally with 30% to 50% of the lung fields being discolored in severe cases. Affected areas do not collapse to the same extent as unaffected areas and in the deflated lung have a spleen-like consistency. On cut surface, the discolored areas of lung are predominantly contiguous with the dorsal pleural surface and extend ventrally into the lung parenchyma. Areas of affected lung can be separated by normal lung. There is proliferation of bronchial vessels, predominantly arteries and arterioles, in affected areas. Histologically, affected areas exhibit bronchiolitis, hemosiderophages in the alveolar lumen and interstitial spaces, and fibrosis of interlobular septa and pleura and around vessels and bronchioles.

■ Pathogenesis

The cause of EIPH is rupture of alveolar capillary membranes with subsequent extravasation of blood into interstitial and alveolar spaces. The source of blood in such instances is the pulmonary circulation. Bleeding from bronchial circulation during exercise has been suggested, based on histologic evidence of bronchial angiogenesis in horses that have experienced previous episodes of EIPH, but contribution of the bronchial circulation to EIPH has not been demonstrated. Regardless of the contribution of bronchial circulation to blood in the airways, the likely proximate lesion is in capillaries associated with the pulmonary circulation, with the causative lesion likely in the pulmonary veins. In other words, pulmonary capillaries rupture, allowing blood to escape into the alveoli (the proximate lesion) due to lesions in the pulmonary veins that increase pulmonary capillary pressure. There is increasing evidence that the primary lesion is arteriovenous remodeling of pulmonary veins and that this remodeling differs in severity among lung regions and with the intensity of training.[31-37] Remodeling of pulmonary veins results in loss of distensibility and partial occlusion to blood flow, with subsequent presumed increases in pulmonary alveolar capillary pressure.[31,38] Hemorrhage into the interstitial space and

alveoli, with subsequent rostral movement of blood in the airways, results in blood in the trachea and bronchi.

Rupture of alveolar capillaries occurs secondary to an exercise-induced increase in transmural pressure (pressure difference between the inside of the capillary and the alveolar lumen), which, as noted above, can occur as a result of venous remodeling and loss of distensibility of pulmonary veins.[35] If the transmural stress exceeds the tensile strength of the capillary wall, the capillary ruptures. The proximate cause of alveolar capillary rupture is the high transmural pressure generated by positive intracapillary pressures, which are largely attributable to capillary blood pressure, and the lower intraalveolar pressure generated by the negative pleural pressures associated with inspiration.

During exercise, the absolute magnitudes of both pulmonary capillary pressure and alveolar pressure increase, with a consequent increase in transmural pressure. Strenuous exercise is associated with marked increases in pulmonary artery pressure in horses. Values for mean pulmonary arterial pressure at rest of 20 to 25 mm Hg increase to more than 90 mm Hg during intense exercise because of the large cardiac output achieved by exercising horses.[39] The increases in pulmonary artery pressure, combined with an increase in left atrial pressure during exercise, probably result in an increase in pulmonary capillary pressure. Combined with the increase in pulmonary capillary pressure is a marked decrease (more negative) in pleural, and therefore alveolar, pressure during exercise. The pleural pressure of normal horses during inspiration decreases from approximately –0.7 kPa (–5.3 mm Hg) at rest to as low as –8.5 kPa (64 mm Hg) during strenuous exercise. Together, the increase in pulmonary capillary pressure and decrease (more negative) in intrapleural (alveolar) pressure contribute to a marked increase in stress in the alveolar wall. Although the alveolar wall and pulmonary capillaries of horses are stronger than those of other species, rupture may occur because the wall stress in the alveolus exceeds the mechanical strength of the capillary.[40-42]

Other theories of the pathogenesis of EIPH include small airway disease, upper airway obstruction, hemostatic abnormalities, changes in blood viscosity and erythrocyte shape, intrathoracic sheer forces associated with gait, and bit-induced asphyxia.[43,44] It is likely that the pathogenesis of EIPH involves several processes, including pulmonary hypertension, lower alveolar pressure, and changes in lung structure, that summate to induce stress failure of pulmonary capillaries.

Obstruction of either the upper or the lower airway has been proposed as a

cause of EIPH. Inspiratory airway obstruction results in more negative intrapleural, and therefore alveolar, pressures. This effect is exacerbated by exercise, with the result that alveolar transmural pressure is greater in horses with airway obstruction. The higher transmural pressure in such horses can increase the severity of EIPH, although this has not been demonstrated. Moreover, although inspiratory airway obstruction might predispose to EIPH, the prevalence of this condition is much less than that of EIPH, indicating that it is not the sole factor inducing EIPH in most horses.

Horses with moderate to severe EIPH have histologic evidence of inflammation of the small airways, and there is a clear association between the presence of EIPH and inflammatory changes in bronchoalveolar or tracheal aspirate fluid. However, instillation of autologous blood into the airways does not induce a marked inflammatory response in normal horses, and it is therefore unclear whether inflammation alone induces or predisposes to EIPH.[45,46] Theoretically, small airway inflammation and bronchoconstriction have the potential to produce intrathoracic airway obstruction and therefore a more negative alveolar pressure. Given that small airway disease is common in horses, there is the potential for an important effect of factors, such as viral infections, air pollution, and allergic airway disease, to contribute to the initiation or propagation of EIPH.

The characteristic location of lesions of EIPH in the caudodorsal lung fields has led to the proposal that hemorrhage is a result of tissue damage occurring when waves of stress, generated by forelimb foot strike, are focused and amplified into the narrowing cross-sectional area of the caudal lung lobes.[47] According to the theory, the locomotor impact of the forelimbs results in transmission of forces through the scapula to the body wall, from where they pass into the lungs and caudally and dorsally. As the wave of pressure passes into the narrower caudodorsal regions of the lungs, it generates progressively greater shearing forces that disrupt tissue and cause EIPH. However, studies of intrapleural pressures have not demonstrated the presence of a systemic pressure wave passing through the lung and do not provide support for this hypothesis. Furthermore, track surface is not associated with incidence of EIPH in Thoroughbred racehorses.[22,48]

Horses with EIPH have been suspected of having defects in either hemostasis or fibrinolysis. However, although exercise induces substantial changes in blood coagulation and fibrinolysis,[49] these is no evidence that horses with EIPH have

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defective coagulation or increased fibrinolysis.[50]

Regardless of the cause, rupture of pulmonary capillaries and subsequent hemorrhage into airways and interstitium cause inflammation of both airways and interstitium, with subsequent development of fibrosis and alteration of tissue compliance. Heterogeneity of compliance within the lungs, and particularly at the junction of normal and diseased tissue, results in the development of abnormal shear stress with subsequent tissue damage. These changes are exacerbated by inflammation and obstruction of small airways, with resulting uneven inflation of the lungs. The structural abnormalities, combined with pulmonary hypertension and the large intrathoracic forces associated with respiration during strenuous exercise, cause repetitive damage at the boundary of normal and diseased tissue with further hemorrhage and inflammation. The process, once started, is lifelong and continues for as long as the horse continues to perform strenuous exercise.[35]

■ Epidemiology

EIPH is primarily a disease of horses, although it also occurs in racing camels and Greyhounds.[51,52] EIPH occurs in horses worldwide, and there does not appear to be any geographic distribution. It is a disorder of horses that run at high speed, such as Thoroughbred, Standardbred, or Quarter Horse racehorses; Quarter Horses used for barrel racing; and polo ponies.[2,5,21,53-55] The disorder is uncommon in endurance horses and is rare in draft breeds.[11,56] There is increasing recognition of its importance in sport horses, including 3-day event and show jumping, but there are no reports of the disease in horses used for dressage, although it is thought to occur.[57,58]

EIPH is considered to be associated with death during racing or in the hours after completion of racing in Thoroughbred and Standardbred horses,[59,60] although there is minimal evidence of the relative risk of death during racing of horses with EIPH.[10] Estimates of the incidence of such “sudden” deaths associated with EIPH in two large studies were 38% (60 of 157) and 35% (50 of 143) of deaths not attributable to musculoskeletal injury in Thoroughbreds, Standardbreds, and Quarter Horses or in solely Thoroughbreds, respectively.[59,60] However, there is uncertainty among some pathologists in attributing the cause of death to EIPH, and the role of EIPH in causing death of horses during strenuous exercise is unclear. Recognizing the subjectivity of both the diagnosis and the attribution of cause of death, it is suggested that EIPH associated with

death during racing should be classified as “exercise-associated fatal pulmonary hemorrhage.”[59]

The prevalence of EIPH varies with the method used to detect it and the frequency with which horses are examined, as discussed later in this section. Epistaxis associated with exercise is almost always attributable to pulmonary hemorrhage and occurs only in a small proportion of racehorses. Epistaxis occurs in only 3% of horses that have blood detected in the trachea by endoscopic examination performed within 2 hours of racing. The prevalence of epistaxis in racehorses varies between 0.1% and 9.0%, with the frequency depending on the breed, age, and sex of horses selected for study; the type of racing; and the timing and frequency of observation of horses after racing. Epistaxis is more common in older horses. There are conflicting reports of a sex predisposition, although epistaxis might be more common in female Thoroughbreds.[61] Epistaxis is more common after races of less than 1600 m than in longer races, although not all sources agree on this point. However, horses in steeplechase races, which are typically longer than 2000 m, are at greater risk of epistaxis than are horses in flat races.[47,61-63] Incidence of epistaxis in steeplechase horses in the United Kingdom is 5.3 per 1000 starts and 3.6 per 1000 starts in hurdle racing.[1] Risk factors for horses in jumps races (steeplechase) include previous epistaxis (odds ratio [OR] 6.1 [4.4 to 8.3]), racing in a claiming race (OR 5.9 [1.4 to 25]), more than 9 starts in the previous 4 to 6 months (OR 10 [2 to 47]), and racing on firmer ground.[1] *In summary, epistaxis is relatively uncommon, and most horses with EIPH do not have epistaxis*.

There are a variety of other methods of detecting EIPH, including endoscopic examination of the airways and microscopic examination of tracheal aspirates or BAL fluid, and the incidence, or prevalence depending on the study design, is influenced by the method used to detect EIPH and the definition of the disease.[10]

Almost all Thoroughbred racehorses in active training, and a large proportion of other types of horses undergoing regular high-speed exercise, have hemosiderophages in BAL fluid, indicating that all have some degree of EIPH.[27,64-66] The prevalence of EIPH decreases when diagnosis is based on endoscopic examination of horses after exercise or racing.

EIPH is very common in Thoroughbred racehorses, with estimates of prevalence, based on a single endoscopic examination of the trachea and bronchi, of 43% to 75%.[16,17] The prevalence increases with the frequency of

examination, with more than 80% of horses having evidence of EIPH on at least one occasion after examination after each of three consecutive races.[67] There can be considerable variability in severity of EIPH within an individual horse on repeated examination over a racing season, with this variability being greatest in horses that have EIPH of the greatest severity.[16] Horses with evidence of EIPH on one examination are likely to have EIPH detected on subsequent endoscopic examinations, most commonly at low grade (Grade 1 or Grade 2).[16] The prevalence of EIPH in Standardbred racehorses is assumed to be lower, with 26% to 34% of horses reported to have blood in the trachea after racing. However, these studies were based on a single examination, and one study only reported as positive those horses with blood covering more than one half the tracheobronchial tree. When examined after each of three races, 87% of Standardbred racehorses have evidence of EIPH on at least one occasion, suggesting that EIPH is as common in Standardbred racehorses as it is in Thoroughbred racehorses.[68]

EIPH occurs in approximately 62% of racing Quarter Horses and in 54% of Quarter Horses used for barrel racing when the diagnosis is based on tracheobronchoscopy and 66% when the diagnosis is based on a red blood cell count exceeding 1000 cells/μL.[21,55] Approximately 11% of polo ponies are affected with EIPH.[5,6] The disease does not appear to occur with any important frequency in draft horses but is not well documented.[56]

Age is considered a risk factor for EIPH, with the prevalence of the disorder being higher in older horses, but the risk factor is the amount of racing a horse has completed, not its age.[69,70] There is no consistent association of sex with prevalence of EIPH. Among Thoroughbred racehorses there is an unclear relationship between the speed of racing and the risk of EIPH.[22,69] Lesions of EIPH are not detected in young Thoroughbred racehorses that have trained at speeds of less than 7 m/s.[71]

The risk of EIPH increases with racing at lower ambient temperatures[22,69] and with the wearing of bar shoes during racing.[22] There is no association between risk of EIPH and track hardness.[22,69]

■ Treatment

Prevention of EIPH is contentious, as it can involve the administration of medications on the day of racing.[8] The efficacy of various interventions and

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medications has recently been evaluated in two systematic reviews that concluded that there was moderately strong to strong evidence that administration of furosemide before racing reduces the frequency and severity of EIPH in Thoroughbred racehorses.[10,12] There is either weak evidence or no evidence of efficacy of other interventions. There is a recommendation for use of furosemide, but because of the regulatory issues related to its use, this is only a weak recommendation.[10] Were there not regulatory considerations, the recommendation for use of furosemide would likely be strong, based on evidence of efficacy. Clearly, the decision to permit administration of furosemide to horses on the day of racing is based not only on its clinical efficacy but also on considerations of the welfare of the horse, integrity of wagering, policies on medication use in racehorses, and opinions of owners, bettors, trainers, and the public.[9]

A comprehensive evaluation of the efficacy of medications putatively used to treat or prevent EIPH is available, including citations to research.[10] Common features of many studies of interventions to reduce the incidence or severity of EIPH are use of a small number of horses, use of horses with signalment that is not typical of those affected by EIPH, an exercise model other than that which causes EIPH (e.g., treadmill exercise instead of overground exercise or racing), and lack of adequate reporting of results.[10,72] A key shortcoming of small studies is that they might fail to detect a treatment effect when such an effect does exist – the so called Type 2 error rate of under-powered studies.[72]

Furosemide apparently reduces pulmonary capillary pressure in exercising horses and likely does so by reducing blood and plasma volume as a result of profound diuresis.[73-76] There appears to be a direct effect of furosemide on pulmonary vasculature in some species,[77] but prevention of diuresis by ligation of ureters abolishes the hemodynamic effect of furosemide in anesthetized horses, suggesting that this is not an important mechanism of its hemodynamic effect in horses.[78]

Furosemide administration as prophylaxis against EIPH is permitted in a number of racing jurisdictions worldwide, most notably in Canada, the United States, Mexico, and most of the South American countries.[73] Within the United States and Canada, almost all Thoroughbred, Standardbred, and Quarter Horse racing jurisdictions permit administration of furosemide before racing. The vast majority (>90%) of Thoroughbred horses racing in the United States receive furosemide before racing, at an estimated annual cost of between $6 million and

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$20 million (USD, 1995 value). Although accurate numbers are not available, it appears that a smaller proportion of Standardbred and Quarter Horse racehorses receive furosemide before racing.

Therapy of EIPH is usually a combination of attempts to reduce the severity of subsequent hemorrhage and efforts to minimize the effect of recent hemorrhage. Treatment of EIPH is problematic for a number of reasons. First, the pathogenesis of EIPH has not been determined, although the available evidence supports a role for stress failure of pulmonary capillaries secondary to exercise-induced pulmonary hypertension. Second, with the exception of furosemide, there is a lack of information using large numbers of horses under field conditions that demonstrates an effect of any medication or management practice on EIPH. There are numerous studies of small numbers of horses (<40) under experimental conditions, but these studies often lacked the statistical power to detect treatment effects, and furthermore, the relevance of studies conducted on a treadmill to horses racing competitively is questionable.[10] Treatments for EIPH are usually intended to address a specific aspect of the pathogenesis of the disease and will be discussed in that context, but they should be considered in the context of the amount and strength of evidence, which for most treatments is scant and weak.

Prevention of Stress Failure of the Pulmonary Capillaries.

There is interest in reducing the pressure difference across the pulmonary capillary membrane in an effort to reduce EIPH. Theoretically, this can be achieved by reducing the pressure within the capillary or increasing (making less negative) the pressure within the intrathoracic airways and alveolus.

Reducing Pulmonary Capillary Pressure.

Furosemide administration as prophylaxis of EIPH is permitted in a number of racing jurisdictions worldwide, most notably in Canada, the United States, Mexico, and most South American countries. Within the United States and Canada, almost all Thoroughbred, Standardbred, and Quarter Horse racing jurisdictions permit administration of furosemide before racing.

The efficacy of furosemide in treatment of EIPH is now well documented.[12,67] The mechanism by which furosemide reduces the severity of EIPH is unknown, although it is speculated that furosemide, by attenuating the exercise-induced increase in pulmonary artery and pulmonary capillary pressure of horses, reduces the frequency or severity of pulmonary capillary rupture. Whether this

occurs as a result of furosemide's direct effect on pulmonary vasculature or an indirect effect resulting from a reduction in blood volume is unknown.[78-82]

Furosemide is associated with superior performance in both Thoroughbred and Standardbred racehorses, which further complicates assessment of its efficacy in treating EIPH.[83]

An increase in pulmonary capillary pressure secondary to altered rheostatic properties of blood during exercise has been suggested as a possible contributing factor for EIPH.[84]

Increasing Alveolar Inspiratory Pressure.

Airway obstruction, either intrathoracic or extrathoracic, increases airway resistance and results in a more negative intrathoracic (pleural) pressure during inspiration to maintain tidal volume and alveolar ventilation. Causes of extrathoracic airway obstruction include laryngeal hemiplegia and other abnormalities of the upper airway, whereas intrathoracic obstruction is usually a result of bronchoconstriction and inflammatory airway disease. Horses with partial extrathoracic inspiratory obstruction or bronchoconstriction and airway inflammation associated with recurrent airway obstructive disease (heaves) have pleural (and hence alveolar) pressures that are lower (more negative) than those in unaffected horses or in horses after effective treatment. Hypothetical relationships between the horse's bit, airway obstruction, and EIPH are not supported to date by empirical evidence.[43,44]

Partial inspiratory obstruction, such as produced by laryngeal hemiplegia, exacerbates the exercise-induced decrease in intrapleural pressures with a consequent increase in transmural capillary pressures. These changes can exacerbate the severity of EIPH, although an association between upper airway obstructive disease and EIPH has not been demonstrated. Surgical correction of airway obstruction is expected to resolve the more negative intrapleural pressure, but its effect on EIPH is unknown.

Recently, the role of the nares in contributing to upper airway resistance, and hence lowering inspiratory intrapleural pressure during intense exercise, has attracted the attention of some investigators. Application of nasal dilator bands (Flair strips) reduces nasal resistance by dilating the nasal valve and reduces the red blood cell count of BAL fluid collected from horses after intense exercise on a treadmill.[28] Furthermore, application of the nasal dilator strips to horses in simulated races reduces red blood cell count in BAL fluid of some but not all

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horses.

The role of small airway inflammation and bronchoconstriction in the pathogenesis of EIPH is unclear. However, horses with EIPH are often treated with drugs intended to decrease lower airway inflammation and relieve bronchoconstriction. Beta-adrenergic bronchodilatory drugs such as clenbuterol and albuterol (salbutamol) are effective in inducing bronchodilation in horses with bronchoconstriction, but their efficacy in preventing EIPH is either unknown or, in very small studies, not evident.[10] Corticosteroids, including dexamethasone, fluticasone, and beclomethasone administered by inhalation, parenterally, or enterally, reduce airway inflammation and obstruction but have no demonstrated efficacy in preventing EIPH. Cromolyn sodium (sodium cromoglycate) has no efficacy in preventing EIPH.[85]

Water vapor treatment (inhalation of water-saturated air) has been proposed as a treatment for EIPH because of its putative effect on small airway disease. However, water vapor treatment has no effect on EIPH.[86]

The use of bedding of low allergenic potential (shredded paper) to prevent EIPH has no apparent effect on prevalence of the condition.[87] While it is suggested that preventing or minimizing small airway disease might reduce the severity of EIPH, studies to demonstrate such an effect have not been reported. However, optimizing the air quality in barns and stables and preventing infectious respiratory disease appear to be sensible precautions.

Interstitial Inflammation and Bronchial Angiogenesis.

Hemorrhage into interstitial tissues induces inflammation, with subsequent development of fibrosis and bronchial artery angiogenesis. The role of these changes in perpetuating EIPH in horses is unclear but is probably of some importance. Treatments to reduce inflammation and promote healing with minimal fibrosis have been proposed. Rest is an obvious recommendation, and many racing jurisdictions have rules regarding enforced rest for horses with epistaxis. While the recommendation for rest is intuitive, there is no information that rest reduces the severity or incidence of EIPH in horses with prior evidence of this disorder.

Similarly, corticosteroids are often administered, either by inhalation, enterally, or parenterally, in an attempt to reduce pulmonary inflammation and minimize fibrosis. Again, the efficacy of this intervention in preventing or minimizing severity of EIPH has not been documented.

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Coagulopathy and Fibrinolysis.

Exercise induces substantial changes in blood coagulation and fibrinolysis. However, there is no evidence that horses with EIPH have defective coagulation or increased fibrinolysis. Regardless, aminocaproic acid, a potent inhibitor of fibrin degradation, has been administered to horses to prevent EIPH. The efficacy of aminocaproic acid in preventing EIPH has not been demonstrated.[10] Similarly, estrogens are given to horses with the expectation of improving hemostasis, although the effect of estrogens on coagulation in any species is unclear. There is no evidence that estrogens prevent EIPH in horses.

Vitamin K is administered to horses with EIPH, presumably in the expectation that it will decrease coagulation times. However, because EIPH is not associated with prolonged bleeding times, it is unlikely that this intervention will affect the prevalence or severity of EIPH.

Platelet Function.

Aspirin inhibits platelet aggregation in horses and increases bleeding time. Seemingly paradoxically, aspirin is sometimes administered to horses with EIPH because of concerns that increased platelet aggregation contributes to EIPH. There is no evidence that aspirin either exacerbates or prevents EIPH. There is evidence of considerable variability between horses in the effect of aspirin on platelet function.[88]

Capillary Integrity.

Capillary fragility increases the risk of hemorrhage in many species. Various bioflavonoids have been suggested to increase capillary integrity and prevent bleeding. However, hesperidin and citrus bioflavonoids have no efficacy in prevention of EIPH in horses.[89] Similarly, vitamin C is administered to horses with EIPH without scientific evidence of any beneficial effect.

Summary of Treatment Options.

Selection of therapy for horses with EIPH is problematic.[10] Given that most horses have some degree of pulmonary hemorrhage during most bouts of intense exercise, the decision must be made as to not only the type of treatment and its timing but also which horses to treat. Moreover, the apparently progressive nature of the disease with continued work highlights the importance of early and effective prophylaxis and emphasizes the need for studies of factors such as air

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quality, respiratory infections, individual differences in susceptibility, and frequency and duration of high-intensity exercise in inciting the disorder.[35]

The currently favored treatment for EIPH is administration of furosemide before intense exercise.[10] Its use is permitted in racehorses in a number of countries but is contentious in many. A frequent practice is to administer furosemide before high-speed training, and not on the day of racing, in jurisdictions that do not permit race-day administration of medications. There is increasing interest in the effect of furosemide administered 24 hours before racing on the incidence or severity of EIPH.[90] Its efficacy in this situation remains to be determined, although a recent study found that furosemide administered 24 hours before simulated racing did not reduce the incidence or severity of EIPH compared to a saline placebo treatment.[29] However, the study did not have sufficient statistical power to detect important differences in EIPH grade or red blood cell count in BAL fluid; there is a high risk of type 2 error (failure to detect a difference when one actually exists), as is the case with many studies of treatments for EIPH that include small numbers of horses (in this case, 15).[10] The association between furosemide administration and superior performance in Standardbred and Thoroughbred racehorses should be considered when recommending use of this drug.

■ Prevention and Control

There are no documented preventive strategies. Rest is an obvious recommendation for horses with EIPH, but the hemorrhage is likely to recur when the horse is next strenuously exercised. The duration of rest and the optimal exercise program to return horses to racing after EIPH is unknown, although some jurisdictions require exercise no more intense than trotting for 2 months. Firm recommendations cannot be made on duration of rest because of a lack of objective information.

Although a role for lower airway disease (either infectious or allergic) in the genesis of EIPH has not been demonstrated, control of infectious diseases and minimization of noninfectious lower airway inflammation appear prudent.

Concern about the role of impact waves in the genesis of EIPH has led to discussion of “low-stress” training protocols, but these have not been adequately evaluated.

■ Prognosis

Horses that have experienced one episode of epistaxis are more likely to have a second episode. For this reason most racing jurisdictions do not permit horses with epistaxis to race for a period of weeks to months after the initial instance, with more prolonged enforced rest after a subsequent episode of epistaxis and retirement from racing after a third bout. The recurrence rate after one episode of epistaxis in Thoroughbred horses is 20% to 30%.[13,62] This high rate of recurrence suggests that the inciting pulmonary lesions have not healed.

Long-term examination of performance of horses with EIPH indicates that horses with Grade 4 EIPH have shorter racing careers, but it is not clear if this is a function of the biology of the disease or a management decision by owners and trainers.[70] There is no association between measures of long-term performance measured over 10 years and Grades 1, 2, or 3 of EIPH in Thoroughbred racehorses.[70] Racehorses in Hong Kong that are EIPH positive on one or more occasions do not have fewer starts than horses for which EIPH was not detected (18 versus 15, $P = 0.17$) on endoscopic examination.[16]

Equine Thoracic Neoplasia

Fabio Del Piero • Pamela A. Wilkins

Surveys of equine neoplasms indicate a low prevalence of thoracic neoplasia in the horse. In an abattoir survey in London of 1308 horses, only 2 horses had pulmonary tumors: one granular cell tumor and one bronchiolar adenoma.[1] Two other necropsy surveys of 155 and 687 equines reported no thoracic neoplasms.[2,3] A report on chronic pulmonary disease in the horse states that the practical importance of lung tumors in this species is negligible.[4] University of Pennsylvania researchers examined 5629 horses between 1968 and 1987. Thirty-five horses had neoplasia involving the thoracic cavity, corresponding to a prevalence of 0.62%.[5]

The prevalence of primary lung neoplasms of any type is reported to be less than 1% of all reported neoplasms in domestic animals.[6] The lungs are susceptible to tumor emboli because of the filter action of the capillary bed associated with small capillary diameter and, perhaps, specific adhesion factors. It can sometimes be difficult or even impossible to distinguish metastatic disease from primary pulmonary neoplasia; thus an important part of the diagnosis is exclusion of possible primary sites elsewhere in the body. Primary pulmonary tumors reported in the horse include granular cell tumor, bronchial myxoma,

adenoma, adenocarcinoma, anaplastic bronchogenic carcinoma, and pulmonary carcinoma (Fig. 31.39). Other primary thoracic tumors reported in the horse include pulmonary chondrosarcoma, pleural mesothelioma, thymoma, and lymphosarcoma. The majority of these neoplasms generally occurs in the mature or aged horse. The exception is lymphosarcoma, which may also be observed in young animals.

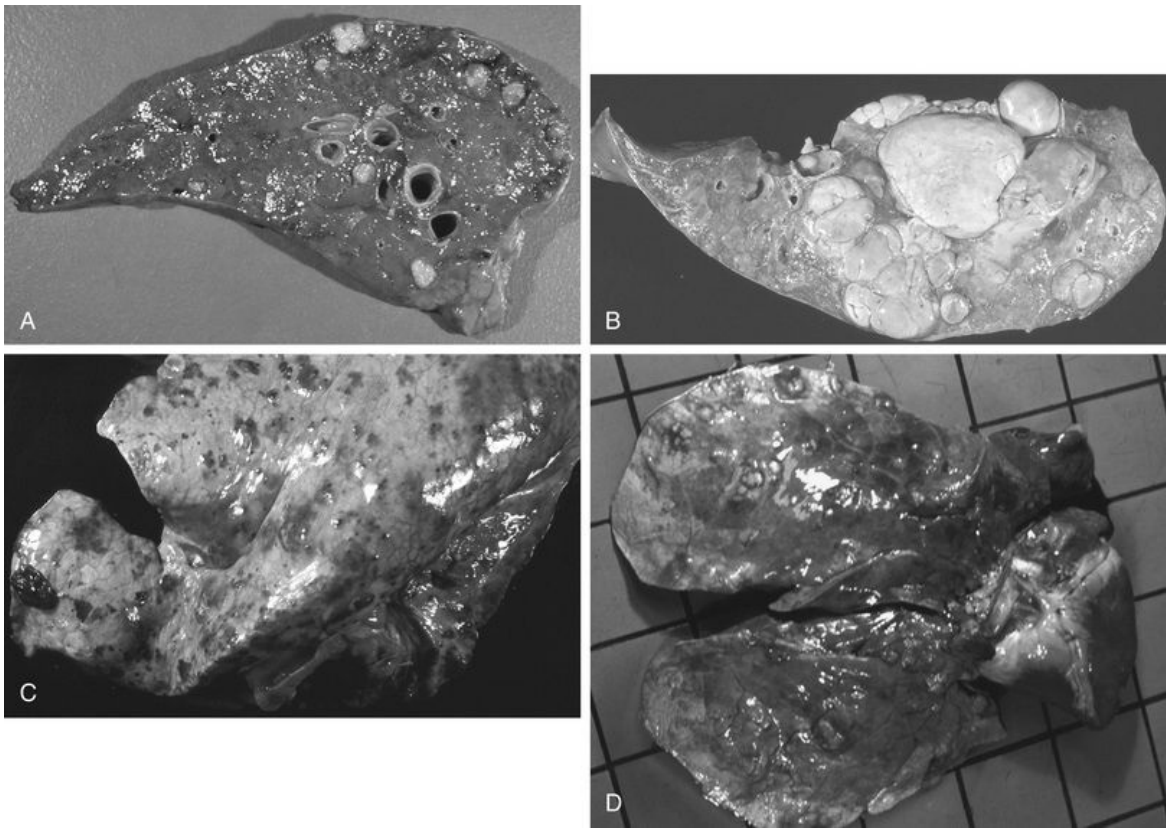


FIG. 31.39 **A,** Metastatic undifferentiated sarcoma. **B,** Granulosa cell tumor. **C,** Metastatic hemangiosarcoma. **D,** Metastatic squamous cell carcinoma.

Antemortem diagnosis of thoracic neoplasia depends first on recognition of thoracic disease. Most of the reported cases of thoracic neoplasia involve metastatic disease. The horses' clinical signs are generally related to the primary site of the neoplasm; therefore the clinician often has no reason to suspect thoracic involvement. When respiratory signs such as dyspnea, tachypnea, hemoptysis, cough, cyanosis, nasal discharge, and epistaxis are present, relevant diagnostic tests are more likely to be performed. Ultrasonography and

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bronchoscopy increase the frequency of antemortem diagnosis of thoracic neoplasia.

Granular cell tumors are the most frequently reported primary pulmonary neoplasm of the horse. They are usually confined to the lungs and are characterized by single to multiple well-defined, whitish, dense nodules associated with a major bronchus, often protruding into the bronchial lumen or more distally within the parenchyma. Most granular cell tumors have been diagnosed only at postmortem examination, often as incidental findings. These homogeneous growths of granular eosinophilic cells express S-100 and occasionally neuron-specific enolase.[7] The ultrastructural morphology of this tumor may suggest a neural origin as well. Primary pulmonary chondrosarcoma has been reported in the horse.[8] Cytologic examination of pleural fluid and antemortem needle aspirate of the pulmonary mass revealed neoplastic chondrocytes. Another report describes metastatic chondrosarcoma in the lungs of a horse with a primary tumor in a rib.[9] A primary bronchial myxoma, characterized by loose spindloid mesenchymal cells, was reported in a 25-year-old Arabian mare with a history of intermittent coughing, hyperpnea, and respiratory disease of 2 years' duration.[10]

Primary pleural tumors are also rare. The type reported in the horse is pleural mesothelioma. The tumor is frequently associated with a large volume of pleural effusion. Cytologic examination of the pleural effusion revealing numerous pleomorphic mesothelial cells may aid in the antemortem diagnosis.

Thymomas are neoplasms of thymic epithelial cells, regardless of the presence or absence of lymphocytes. They are infrequently reported in the horse.[11-13] Equine lymphosarcoma occurs in mediastinal, alimentary, multicentric, cutaneous, and generalized forms; combinations of one or more of these are not infrequent.[14,15] In a 1973 review of 54 cases of equine lymphosarcoma,[3] the lung was involved in 16.6% of the cases, whereas the thoracic lymph nodes were involved in 35.2%.[16] In the University of Pennsylvania survey, lymphosarcoma was the single most common neoplasia of the thorax and was present in 19 (54%) of the cases.[3] Pleural fluid cytologic evaluation was diagnostic in six (75%) of the eight horses. Diagnosis was made by biopsy of a peripheral lymph node in several cases. In a report from the University of Bristol, thoracic malignant lymphoma accounted for 74% of the cases of thoracic neoplasia.[16] Metastatic adenocarcinoma accounted for 20% of the cases in the University of Pennsylvania study[5] and 11% of the cases in the University of Bristol study.[16]

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The primary sites of the tumor were thought to be kidney, uterus, thyroid, and ovary.

Gastric squamous cell carcinomas commonly metastasize to the thoracic cavity. Cytology of pleural fluid with identification of neoplastic epithelial squamous cells has allowed for antemortem diagnosis of the carcinoma in several cases. Metastatic squamous cell carcinoma of the thorax was found in 14% and 5% of the cases in the University of Pennsylvania[5] and University of Bristol[16] surveys, respectively. Neoplastic epithelial cells may also be identified in biopsy specimens via indirect immunohistochemistry using antibodies recognizing cytokeratins of various molecular weights.

Hemangiosarcoma with pulmonary involvement was found in 9% of the horses in the University of Pennsylvania survey.[5] Hemothorax, anemia, and dyspnea were commonly seen with this type of neoplasm. Tentative antemortem diagnosis of the hemangiosarcoma can be made by transcutaneous direct thoracoscopy and observation of hemorrhages over the visceral and parietal pleural surfaces as well as tissue biopsy of these sites. Identification of neoplastic endothelial cells demarcating irregular, sometimes blood-filled cavities allows diagnosis from the biopsy specimen.

Malignant melanoma in a 20-year-old gelding had widespread infiltration of many organs, including the lungs and pleura.[16] This pattern of distribution is not uncommon in malignant, less pigmented melanomas. Amelanotic melanomas are rare in the horse, and microscopic identification of melanin simplifies the diagnosis of these tumors. Equine melanocytes express S-100 and PNL2 proteins, and their detection can be used to diagnose melanocytic neoplasms.

Other pulmonary metastatic tumors reported are mammary carcinoma,[17] seminoma,[18] and malignant pheochromocytoma.[19] Pulmonary hamartomas are occasionally observed in the newborn foal. Although they are nonneoplastic growths, they appear as tumorlike masses that can compress the surrounding parenchyma and cause systemic passive congestion and hydrops of the amnion in the fetus. Their histologic characterization is that of bronchiolar-like structures lined by cuboidal epithelium with lack of alveolar development or by normal alveoli, bronchi, and blood vessels but with an alveolus/artery ratio greater than normal. Generally they are not compatible with a long period of extrauterine life.

An unusual progressive idiopathic multifocal granulomatous pneumonia of adult horses may resemble neoplasia behaviorally and morphologically during clinical examination.[20,21] Pulmonary biopsy may allow the identification of

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equine multinodular pulmonary fibrosis (EMPF), which has been associated with EHV-5 infection[21] (see Figs. 31.29 and 31.30).

Clinical signs of thoracic neoplasia are often inapparent or nonspecific—for example, depression, inappetence, weight loss, and pyrexia. More specific signs include cough, epistaxis, and dyspnea. Cytologic examination of tracheobronchial aspirate, BAL fluid, or pleural fluid and histologic examination of a thoracic mass tissue biopsy with ancillary histochemistry and indirect immunohistochemistry may allow for antemortem diagnosis of the neoplasm. Occasionally, electron microscopy may provide additional information. In equine patients with respiratory signs, all causes of infectious or allergic lung disease should be eliminated before neoplasia is considered in the differential diagnosis.

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Diseases of Lymph Nodes, Vasculature, and Pharynx

Retropharyngeal Lymph Node Abscessation

John R. Pascoe

■ Definition and Etiology

In horses, the retropharyngeal lymph nodes consist of medial and lateral lymphoid chains. The lateral chain (8 to 15 nodes) is located ventral to the atlas and along the lateral sides of the guttural pouches. These lymph nodes are covered by the parotid gland and are not clearly distinguishable from the medial retropharyngeal lymph nodes (20 to 30 nodes). The medial retropharyngeal lymph nodes are located ventral to the lateral chain on the dorsolateral aspect of the pharynx and the caudoventral aspect of the guttural pouches.[1]

Retropharyngeal lymph node abscesses in horses are generally caused by *Streptococcus equi* subsp. *equi* infection (see the *Streptococcus equi* subsp. *equi* Infection [Strangles] section earlier) or are secondary to trauma.[2,3] Other bacterial isolates have included *S. equi* subsp. *zooepidemicus, Corynebacterium pseudotuberculosis, Actinomyces denticolens,* and *Actinobacillus* spp., including *Actinomyces denticolens*.[4,5] An unusual case of granulomatous infection of the guttural pouch caused by *Mycobacterium avium* complex was believed to have originated from the retropharyngeal lymph nodes.[6] Extension of guttural pouch infections into the retropharyngeal space has been suggested as another source of infection.[7] Lymphadenopathy of the retropharyngeal nodes may also occur during viral respiratory infections, including equine herpesvirus (EHV), influenza, and equine viral arteritis.[8] Retropharyngeal abscesses not associated with regional lymph nodes can result from perforation of the oropharynx or nasopharynx by ingested foreign bodies,[9] passage of a nasogastric tube,[10] or use of a balling gun.

In ruminants, the medial retropharyngeal lymph nodes are located on the dorsolateral aspect of the pharynx, one on each side of the midline. One to three lymph nodes may be present in cattle. The lateral retropharyngeal lymph nodes are located caudal to the medial retropharyngeal lymph nodes in the cranial neck

region and are caudal to the retropharyngeal space.[11]

Abscessation of the medial retropharyngeal lymph nodes in cattle may result from pharyngeal actinobacillosis, foreign body penetration, or traumatic perforations by balling guns or dose syringes.[12-14] *Trueperella pyogenes* or *Actinobacillus* spp. are frequently isolated.[8] Cattle with abscessed pharyngeal lymph nodes often have a small ulcer in the mouth, most frequently at the junction of the base and shaft of the tongue. This is more likely to occur when cattle are eating dry scabrous roughage. In addition to traumatic perforations and foreign bodies, caseous lymphadenitis (CLA) caused by *C. pseudotuberculosis* frequently results in abscessation of the retropharyngeal lymph nodes in sheep and goats.

■ Clinical Signs and Differential Diagnosis

Clinical signs associated with retropharyngeal lymph node infection or abscessation in horses include dysphagia, odynophagia (painful swallowing), nasal or oral regurgitation, excess salivation, difficult and often noisy breathing, painful throatlatch swelling, mucoid to mucopurulent nasal discharge, extension of the head and neck, and weight loss. In 46 horses with retropharyngeal lymph node abscessation, common clinical signs were fever and increased heart and respiratory rates (80%), unilateral or bilateral throatlatch swelling (65%), respiratory stertor or distress (35%), purulent nasal discharge (20%), inappetence and signs of depression (15%), and dysphagia (9%).[3] Other signs observed endoscopically include decreased cross-sectional area or collapse of the pharyngeal lumen, asymmetry of the dorsal pharyngeal wall, and deviation of the laryngeal aperture away from the retropharyngeal mass.[2,3] Differential diagnosis for a retropharyngeal mass should include abscess, cellulitis, guttural pouch empyema or tympany, parotiditis, lymphadenopathy, neoplasia, and hematoma.

Clinical signs observed in cattle with infection or abscessation of the medial retropharyngeal lymph nodes include difficult breathing, excessive salivation, extension of the head and neck, anorexia, enlarged submandibular lymph nodes, nasal discharge, and swelling in the retropharyngeal space.[12] Other disease conditions that affect the oropharynx and surrounding lymph nodes should be considered in the differential diagnosis. These include actinobacillosis, lymphosarcoma, sialolithiasis, and necrotic laryngitis, laryngeal edema, or severe tracheitis caused by infectious bovine rhinotracheitis (IBR) virus.[8,12]

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Affected sheep and goats may exhibit excessive salivation, increased respiratory rate, stertorous breathing, mucopurulent nasal discharge, regurgitation, gagging, depression, subcutaneous crepitation, weakness, and fetid breath. A false carotid aneurysm in the retropharyngeal space has been reported; on external examination it may be confused with abscessation of the medial retropharyngeal lymph nodes.[15] Enlarged retropharyngeal lymph nodes are usually easily palpated and identified in sheep and goats. CLA (see Chapter 37) is the most frequent cause of enlarged retropharyngeal lymph nodes in these species.

■ Clinical Pathology

Collection of purulent material from abscessed lymph nodes may assist in identification of the causal agent. Neutrophilic leukocytosis may be evident on the hemogram.

■ Laboratory Aids and Definitive Diagnostic Tests

Lateral radiographs of the pharynx, ultrasonography, and endoscopy facilitate the diagnosis of retropharyngeal infections or abscesses. In horses, radiography may reveal a large soft-tissue mass impinging on the guttural pouch from a caudoventral direction (Fig. 31.40, *A*), as well as thickening of the pharyngeal roof. The soft-tissue swelling may contain gas (Fig. 31.40, *B*). Compression of the larynx and trachea with ventral displacement may be evident (Fig. 31.40, *C*).[2] A gas-fluid interface on radiographs of the pharynx generally indicates abscessation, but care should be taken to distinguish a retropharyngeal abscess from guttural pouch empyema.[6] Foreign bodies associated with pharyngeal trauma are not typically radiopaque and thus not visible unless outlined by contrast medium. Exceptions include small wire foreign bodies likely ingested from baled hay that can perforate the tongue or oropharynx and cause cellulitis and dysphagia[9] and, in cattle, magnets that have been inadvertently placed retropharyngeally.

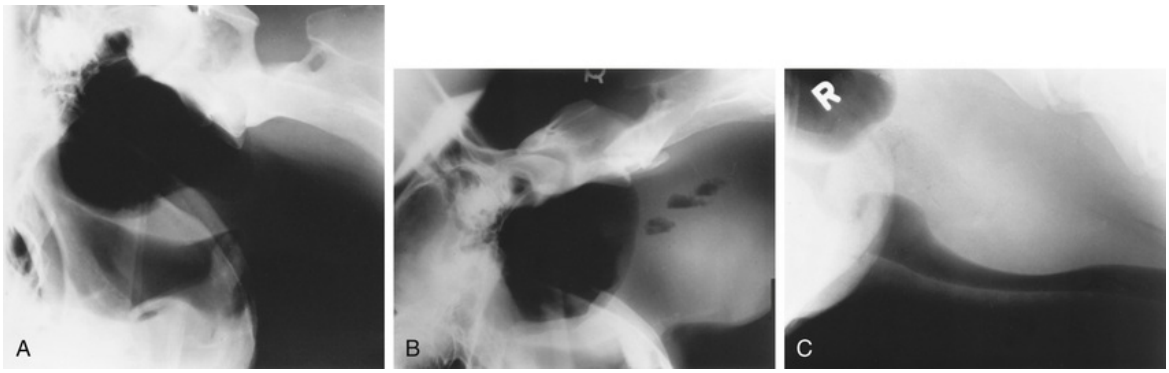


FIG. 31.40 **A,** Lateral radiograph. A soft-tissue density (retropharyngeal abscess) is distorting the floor of the guttural pouch. **B,** Lateral radiograph. There is increased soft-tissue density with gas shadows ventral to the cervical vertebrae. These changes are consistent with abscessation of the retropharyngeal lymph nodes. **C,** Lateral radiograph. There is increased soft-tissue density ventral to the cervical vertebrae, with compression of the dorsal border of the trachea. These changes were caused by cellulitis and abscessation of the retropharyngeal lymph nodes.

On endoscopy, asymmetry or collapse of the pharyngeal lumen, or both signs, suggests a retropharyngeal space-occupying mass. Recognition of drainage from the guttural pouch openings or examination of the guttural pouches may be necessary to differentiate between guttural pouch empyema and retropharyngeal lymphadenopathy or pharyngeal neoplasia. Occasionally the pharyngeal wall ruptures, allowing endoscopic observation of retropharyngeal drainage into the pharynx, usually near the esophageal entrance. Percutaneous needle aspiration of the mass may yield purulent material. Ultrasonography improves diagnostic precision by permitting more accurate identification of the abscess and highlighting its anatomic relationships to facilitate surgical drainage.[16]

Clinical examination, radiography, ultrasonography, endoscopy, and percutaneous centesis may all prove helpful in making a diagnosis of medial retropharyngeal lymph node infection or abscessation in ruminants. In cattle, localized swelling cranial to the larynx may be detected by digital palpation of the oropharynx.[12] Oropharyngeal examination must be performed carefully in animals with respiratory distress to prevent further airway compromise.

■ Pathophysiology

Upper respiratory tract disease, trauma, and foreign body penetration with resulting infection and drainage to local lymph nodes result in clinically apparent infection and abscessation of the retropharyngeal lymph nodes. In horses, the

retropharyngeal space is occupied primarily by the guttural pouches. Because the vagus, glossopharyngeal, hypoglossal, spinal accessory, and sympathetic nerves traverse this area, their function can be affected by infectious or inflammatory processes involving the retropharyngeal space.[2] If such infections are contained within the lymph nodes or are confined within the fibrous capsule of the abscess, cranial nerve dysfunction is not usually evident.[2] Clinical evidence of dysphagia or odynophagia, such as the presence of feed and saliva at the external nares, may result from angina and from inflammation or injury of the glossopharyngeal nerve or pharyngeal branch of the vagus nerve, compression, or obstruction of the pharynx or esophagus. It has been suggested that retropharyngeal lymphadenitis may result in neuritis of the pharyngeal branch of the vagus nerve in young horses and contribute to the pathogenesis of dorsal displacement of the soft palate.[17]

Respiratory distress may occur when retropharyngeal lymph node enlargement compresses or obstructs the nasopharyngeal, laryngeal, or tracheal lumen, and the disease caused by *S. equi* subsp. *equi* in horses is appropriately called *strangles.*

The most common cause of pharyngeal inflammation and infection in cattle is pharyngeal trauma associated with balling guns, dose syringes, paste wormer guns, esophageal feeders, or nasogastric tubes. A careful history to determine whether any of these devices were used is important in determining the source of pharyngeal abscessation. Such infections usually involve mixed bacterial flora, because the trauma is directly related to the oropharynx.

■ Epidemiology

Infection with *S. equi* usually results from contact (inhalation or ingestion) with pasture, feed, or water contaminated with nasal discharge from infected horses or asymptomatic carriers.[18] The likely bacterial reservoir in carrier horses is the guttural pouch, particularly if chondroids are present[18-20] or if there are swollen or discharging lymph nodes in the floor of the medial compartment of the guttural pouch. Infection of the pharyngeal and nasal mucosa results in an acute pharyngitis and rhinitis, and drainage to regional lymph nodes results in lymphadenopathy and possible abscessation.[8]

CLA is spread through discharges from ruptured lymph nodes. The causal agent, *C. pseudotuberculosis*, may persist in the environment for long periods, and infection results from inhalation or from contact of shearing, docking, or

castration wounds with contaminated soil, equipment, or freshly ruptured abscesses. Sheep dips have been reported as another source of infection.[8] Spread of infection from skin wounds often leads to involvement of local nodes and abscess formation.

■ Necropsy Findings

Fatalities are rare and typically occur from respiratory compromise or septicemia. Necropsy lesions include cellulitis with compression and ventral displacement of the larynx and cranial aspect of the cervical trachea. Abscesses are variable in size and may contain either caseous *(C. pseudotuberculosis)* or liquid *(S. equi* subsp. *equi)* material. A thick, fibrous capsule may occur in response to the infectious process and may account for the surrounding tissue compression. Occasionally, draining tracts may connect the abscess to the pharynx, guttural pouch, or skin.[10,21]

■ Treatment and Prognosis

Treatment goals are relief of respiratory distress and control of infection. Temporary tracheotomy may be needed for relief of respiratory distress and may be prudent, before percutaneous drainage is attempted. After surgical drainage, appropriate systemic antibiotics are administered, and supportive therapy to further reduce swelling may be beneficial.

Surgical approaches include percutaneous drainage, intraoral drainage, and marsupialization.[2,12] Percutaneous drainage is commonly used in horses because the long narrow oral cavity makes an intraoral approach very difficult. For abscesses visible through the mucosal lining of the guttural pouch, endoscopically assisted drainage into the pouch can be considered. Surgical access to the retropharyngeal space includes dorsal, ventral, and lateral approaches and access through Viborg's triangle.[3] A ventral surgical approach is recommended because of the relative lack of vital structures encountered and because excellent ventral drainage can be achieved. In standing sedated horses, less invasive drainage can be established by ultrasound-guided percutaneous needle placement into abscessed lymph nodes. Affected nodes can have a wall thickness of 1 to 2 cm and a diameter of 5 to 11 cm.[16] Aspiration of purulent matter and cavity lavage with antiseptic solutions and concurrent administration of parenteral antibiotics may be sufficient for resolution. If aspiration is not possible because the purulent material is too viscous, incision directly along the

needle shaft, after careful consideration of regional anatomy, provides adequate exterior drainage and access for cavity lavage with antiseptic solutions or use of a seton or gauze packing. If the abscess is endoscopically visible beneath the guttural pouch mucosa, drainage into the guttural pouch and subsequent lavage of the purulent material can be accomplished. Before or at the time of abscess drainage or excision, the horse should be started on broad-spectrum antimicrobials, followed by the appropriate specific antimicrobial drug when results of microbial susceptibility testing are known.

Occasionally, medical management alone may resolve infection; however, this is less likely if abscessation has occurred. Because the most common bacterial isolate in horses is *S. equi*, parenteral antimicrobial therapy with procaine penicillin G (22,000 IU/kg IM twice daily) or potassium penicillin (22,000 IU/kg IV four times daily) is recommended. Systemic NSAIDs are useful to reduce inflammation and swelling, and fluid and electrolyte therapy may be necessary if there is odynophagia or dysphagia. Aspiration pneumonia can occur with dysphagia or if there is oral or nasal regurgitation associated with painful swallowing.

In cattle with pharyngeal trauma, an existing wound is often draining from the retropharyngeal area into the oropharynx, making surgical drainage unnecessary, and response to parenteral broad-spectrum antimicrobial therapy is typically favorable.[22] Parenteral antimicrobial therapy alone has been ineffective in treating retropharyngeal abscesses when there is no draining tract.[12] Intraoral or percutaneous drainage has been used successfully in conjunction with broad-spectrum, parenteral antimicrobial therapy. After drainage, the abscess cavity is flushed daily with an antiseptic or antibiotic solution[12] with the head lowered so that exudate or flush solution is not aspirated; inspection of the granulating abscess cavity is necessary if feed impaction is suspected.[2,12] Aspiration pneumonia may be a serious complication when dysphagia is present.

In sheep and goats, walled-off *C. pseudotuberculosis* abscesses can be safely drained by marsupialization before opening the capsule, which prevents contamination of other retropharyngeal structures and markedly reduces postsurgical cellulitis. Although *C. pseudotuberculosis* is susceptible in vitro to a number of antimicrobial agents, these abscesses are typically not well controlled by antimicrobial therapy. Walled-off *C. pseudotuberculosis* abscesses are difficult to eliminate solely with antimicrobial therapy, and drainage or removal of the entire lymph node gives optimal results.

■ Prevention and Control

Preventive measures to limit infection and abscessation of retropharyngeal lymph nodes include isolation of horses affected with viral or bacterial upper respiratory tract disease, vaccination against strangles, vigorous treatment in the early stages of streptococcal infection, and correct administration of therapeutic agents with balling guns and dose syringes. Reducing environmental sources of contamination and preventing contamination of shearing equipment, dipping vats, and feeders with *C. pseudotuberculosis* are important to limiting spread in sheep. Culling affected sheep and goats may also help reduce the incidence of CLA.

Pharyngitis

John R. Pascoe

■ Definition and Etiology

Pharyngitis is inflammation of the pharyngeal tissues. It is not generally considered to be a specific disease entity but rather a response to other diseases, particularly viral and bacterial respiratory disease, and to a lesser extent to local physical, chemical, or allergic causes. Acute and chronic forms are recognized.

Although physical and chemical causes of pharyngitis may be identified with certainty, the role and specificity of microbial pathogens as causative agents remain controversial. In horses, *Streptococcus* spp. and various viral respiratory diseases have been incriminated as specific causes of pharyngitis, but given the ubiquitous nature of some virus groups in horses, a direct causal association remains unsubstantiated.[1,2] In cattle, *Trueperella pyogenes*, *Actinobacillus* spp., and *Fusobacterium necrophorum* are frequently isolated.[3]

Synonyms for chronic pharyngitis in horses include pharyngeal lymphoid hyperplasia (PLH), chronic pharyngitis, chronic lymphoid follicular hyperplasia, follicular pharyngitis, and follikelkatarrh.[4-6]

■ Clinical Signs and Differential Diagnosis

In acute pharyngitis, signs are associated with pharyngeal pain (odynophagia, dysphagia), nasal discharge (serous, seromucous, mucopurulent, purulent, feed-contaminated), regional lymphadenopathy (submandibular, retropharyngeal nodes), ptyalism (especially in cattle), respiratory noise (often inspiratory),

pharyngeal swelling, and cough. Mouth breathing may occur in cattle when there is increased resistance to breathing associated with excessive exudate, diphtherous membranes, and lymphadenopathy. Pharyngitis from local pharyngeal trauma or incarcerated foreign bodies may be associated with odor of nasal discharge or the breath. Cattle with necrotic laryngitis, pharyngitis, and stomatitis have a characteristic malodorous breath. Acute laryngeal inflammation and edema of unknown cause can occur in horses and ruminants and is characterized by marked inspiratory difficulty and stertor without malodorous breath. Treatment of acute edema with dexamethasone (0.05 mg/kg IM; avoid in pregnant heifers or cows) and broad-spectrum antimicrobials has produced rapid clinical improvement.

Signs observed on endoscopic or oropharyngeal examination in cattle include pharyngeal hyperemia and edema, lymphonodular swelling, and either a moist appearance of the pharyngeal surface or the presence of exudate or a diphtherous membrane adhering to the pharyngeal surface. Focal necrosis or ulceration of the mucous membrane and tonsillar tissue may occur; signs associated with rhinitis and laryngitis may be evident. Signs of chronic pharyngitis are similar. In horses, there may be endoscopic evidence of more marked hyperplasia of the lymphonodular follicles within the pharyngeal mucosa, and single or multiple lymphonodular masses may be within, or protrude from, the pharyngeal mucosa. Biopsy and cytologic evaluation are recommended to rule out neoplasia, particularly squamous cell carcinoma, lymphoma, and lymphosarcoma. Differential diagnostic possibilities include rhinitis and laryngitis, and in cattle, rabies should be strongly considered before oropharyngeal examination. If the predominant sign is dysphagia (see Chapter 7), other diagnostic rule-outs include foreign bodies in the tongue, fractures of the hyoid apparatus or jaws, and in the horse, diseases of the guttural pouches. If exercise intolerance is the primary complaint in a horse, pharyngitis should be considered only after other possible causes of impaired performance have been eliminated (see Chapter 5).[7-11] Pharyngitis is not a risk factor for poor racing performance in racing Thoroughbreds[12] or Standardbred trotters.[10] More severe PLH grades were found in poorly performing endurance horses (primarily Arabian horses); however, more definitive causes for poor performance were identified in these horses.[11]

Upper airway inspiratory pressures recorded during strenuous exercise in horses with grade IV PLH are not different from those of normal horses under

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the same exercise conditions.[8] Assuming that airflow in both groups of horses was comparable, severe PLH does not appear to cause functional upper airway obstruction. It is conceivable that pharyngeal pain associated with PLH may contribute to impaired performance; however, this effect remains unproven.

■ Clinical Pathology

Changes in the hemogram and serum biochemical profiles are likely to result from concurrent respiratory disease (increases or decreases in absolute or differential leukocyte counts, hyperfibrinogenemia, anemia) or to reflect abscess formation (neutrophilia, hyperfibrinogenemia) or dehydration and fasting associated with dysphagia. Electrolyte losses associated with drooling may alter serum electrolyte and acid-base status.

■ Laboratory Aids and Definitive Diagnostic Tests

Although a presumptive diagnosis can be made from clinical signs, definitive diagnosis requires observation of the pharynx (Fig. 31.41) and, more important, exclusion of other conditions that have similar signs. Radiography of the pharynx can provide information on pharyngeal anatomy, radiodense foreign bodies, soft-tissue masses, fractures, and in horses, guttural pouch disorders. Ultrasonography of the pharyngeal region and, if indicated by the clinical examination, both radiographic and ultrasonographic examination of the thorax may help define the extent of concurrent pulmonary disease.



FIG. 31.41 Endoscopic view showing the nodular appearance of pharyngeal lymphoid hyperplasia.

Microbial culture of pharyngeal secretions can be considered, but interpretation is difficult because (1) the pharynx normally has resident microflora with considerable individual variation, and (2) many of the microorganisms isolated are capable of opportunistic infection. In horses with grades III and IV PLH, the number of bacteria recovered per gram of pharyngeal secretion was almost 100-fold greater than in normal horses.[9] The pattern of microbial isolation was not consistent among horses, suggesting that these organisms were not the source of the pharyngitis but rather that other factors had made conditions for colonization more favorable.

Biopsy and cytologic examination are indicated in refractory cases and when abnormal masses are present to rule out neoplasia.

■ Pathophysiology

Acute pharyngitis occurs as a sequela to inflammation of regional lymphoid tissue (see Kumar and colleagues[13] for a description of the morphologic and

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histochemical features of the normal equine nasopharyngeal tonsil).[14] In horses, the pharyngeal tonsil consists of discrete lymphoid follicles diffusely distributed in the dorsal and lateral walls of the pharynx. In ruminants, the pharyngeal tonsil is located caudal to the pharyngeal septum in the caudodorsal wall of the pharynx and is bounded by long ridges and grooves into which mucous glands open. In response to local or lymphogenous spread of infection, the tonsillar tissue becomes inflamed and the tonsillar crypts become filled with desquamated epithelium, leukocytes, and bacteria. Clinically this is seen as hyperemia and edema of the pharyngeal tonsil with diffuse white or yellow tips to the lymph nodules. The edematous appearance is associated with hyperplasia of the lymph nodules and sequestration of perinodular inflammatory fluid.

If extensive destruction of the lymphoid cells or subsequent invasion of the nodules or supporting soft tissue is evident, the result is focal or diffuse necrosis, which may be seen as pinpoint areas of follicular necrosis or diffuse necrosis with associated purulent or fibrinonecrotic exudate. With resolution, atrophy of some follicles and increased fibrosis are present. Follicular atrophy also occurs with aging.

■ Epidemiology

No specific epidemiologic data are available. When pharyngitis occurs as a sequela to respiratory tract infection, the population demographics should be similar to those known for the specific respiratory disease. For example, grade II PLH was identified in 60% of foals with distal respiratory tract infection and in only 13% of control foals.[15] Because physical and chemical injury to the pharynx occurs sporadically, no universal epidemiologic characteristics would be anticipated.

PLH is prevalent in horses younger than 5 or 6 years of age, and the severity of PLH grades[5] is inversely correlated with age.[4,12,16,17] In endoscopic surveys of primarily Thoroughbreds in race training, prevalence of PLH ranges from 29% to 34%, with grade II PLH observed in 45% to 63% of 2-year-olds and less than 12% to 20% of horses older than 5 years affected.[16] Similar results are reported from Japan in racing Thoroughbreds with a history of cough or abnormal respiratory noise[18] and in a mixed population of horses in Calgary, Canada.[17] Pharyngeal mucus scores are not correlated with PLH, transtracheal wash aspirate, or BAL fluid variables, suggesting that PLH is not directly a manifestation of lower airway inflammation or disease.[17,19]

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■ Treatment and Prognosis

Approach to treatment is largely symptomatic and directed at palliation of pharyngeal pain and maintenance of unobstructed breathing until the initiating disease process has abated. In many instances, the signs are sufficiently mild that treatment is unnecessary. When pharyngeal angina is causing inappetence or dysphagia, administration of NSAIDs should be considered. Dehydration should be corrected by either parenteral or enteral fluid administration. Enteral fluid therapy may be difficult because passage of a nasogastric tube may elicit too much pain. For inappetent animals, nutritional support may be necessary until pharyngeal pain subsides sufficiently for normal eating to resume. Soft feeds, especially green grass, should be offered when available to encourage animals with pharyngeal discomfort to eat.

Antimicrobial therapy is probably not indicated, but it is often given to limit development of secondary bacterial infection. Infections caused by foreign body injury should be treated with antibiotics that have a broad aerobic and anaerobic spectrum of activity. Daily lavage of any cavitary wounds, débridement, and removal of feed material may be necessary to prevent additional abscess formation and hasten healing.

Custom topical preparations, usually containing an antibiotic, an antiinflammatory drug, and a hygroscopic agent (glycerin) or DMSO, are often used for palliation of clinical signs, especially in horses with PLH. These preparations are usually administered two or three times daily and sprayed onto the pharyngeal surface through a transnasal catheter. Despite frequent use, the efficacy of this therapy is unknown, and response may reflect natural resolution of the predisposing cause.

Treatment of PLH is empirical and generally palliative. Rest from training for 4 to 8 weeks is commonly recommended, and although some horses have recurrence when training resumes, this enforced rest is beneficial as convalescence for any concurrent subclinical respiratory disease. Horses kept in training are often initially treated empirically with sulfa compounds and topical throat preparations. With continued clinical signs, penicillin or broad-spectrum antibiotics are often administered. If PLH does not improve or resolve after therapy, pharyngeal cautery may be used. Techniques for pharyngeal cautery include topical application of trichloroacetic acid, electrocautery, freezing with liquid nitrogen or Freon, and photoablation by neodymium:yttrium aluminum garnet (Nd:YAG) laser with either a contact or a noncontact technique.[20] Although cauterization techniques have received considerable testimonial

support, it is likely that cautery does not effect a cure but simply obliterates reactive tissue so that it is no longer clinically evident.

Routine immunization for known viral respiratory pathogens is also recommended for treatment and prevention of PLH.[21]

■ Prevention and Control

Methods used to control and prevent most of the common viral and bacterial respiratory diseases (see Chapter 48 for vaccines) should limit herd problems with acute pharyngitis. Non–respiratory disease–related causes such as trauma from balling guns, nasogastric tubes and dose syringes, foreign objects, and chemical burns can be minimized by improved husbandry practices.

Prevention of PLH in horses by prophylactic immunization against common equine viral respiratory agents at regular intervals has been discussed at length, but there is no evidence to support this practice. Nevertheless, racetrack veterinarians maintain that frequent immunization (60-day intervals) against influenza and rhinopneumonitis markedly reduces the severity of PLH and improves exercise tolerance.[21] Considering the mobility of racing and show horse populations, this approach should at least be beneficial for limiting outbreaks of viral respiratory disease and consequently perhaps limiting chronic PLH. Until more is understood about the clinical appearance of the pharyngeal tonsil in horses, along with normal variations that occur with aging in exercised and nonexercised horses, and these findings can be correlated with immunopathologic events and indices of performance, it will remain difficult to treat, control, and prevent pharyngitis in a systematic manner.

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Guttural Pouch Diseases

John R. Pascoe

■ Definition and Etiology

The guttural pouches are paired, air-filled diverticula of the eustachian tubes that communicate between the middle ear and the pharynx. Located ventral to the atlas, dorsocaudal to the pharynx, and rostrodorsal to the retropharyngeal lymph nodes, they occupy a large part of the retropharyngeal space. Each pouch has a capacity of approximately 300 mL and is divided into medial and lateral compartments by a stylohyoid bone that courses through the caudolateral aspect of each pouch. The larger medial compartment accounts for approximately two thirds of the volume, and they appose each other on the midline, separated by a membranous septum. The medial compartment contains cranial nerves IX (glossopharyngeal), X (vagus), XI (spinal accessory), and XII (hypoglossal); the cranial cervical ganglion; and the cervical sympathetic trunk. The internal carotid artery lies deep to the caudolateral wall of the medial compartment. The pharyngeal branch of the vagus nerve and the cranial laryngeal nerve are immediately ventral to the floor of the medial compartment. In the lateral compartment, the facial nerve (VII) is located caudodorsally, and the external carotid artery and its branches, notably the maxillary artery, are associated with the roof of the lateral compartment.[1] The intimate relationship of these vessels and nerves with the mucous membrane lining the guttural pouches explains why epistaxis and nerve dysfunction frequently accompany guttural pouch disease. Communication with the pharynx occurs through a slit-like opening rostral and ventral to the pharyngeal recess. This funnel-shaped pharyngeal opening is wider rostrally than caudally. A mucous membrane fold within the pouch, the plica salpingopharyngea, contributes to the caudal narrowing of the opening and makes catheterization of the guttural pouch difficult. Redundancy of this tissue fold may contribute to guttural pouch tympany.[1]

Lined with pseudostratified ciliated epithelium containing goblet cells,[2] the guttural pouch is an extension of the pharynx and is not a sterile environment. In 30 normal horses, 59% of percutaneous guttural pouch lavage aspirates had bacterial growth, although only 7% had bacteria considered to be pathogenic; no fungi were isolated.[3] Aspirates were considered normal if they had less than 5%

neutrophils; typical cell distribution was primarily ciliated columnar epithelial cells, a few nonciliated cuboidal epithelial cells, and less than 1% monocytes, lymphocytes, and macrophages.[3] Inflammatory cell counts and altered cell distribution were correlated with recovery of bacteria. Horses exercised strenuously on a regular basis had lower total cell counts, lower neutrophil counts, and fewer bacteria isolated.[3] Preventing horses from head lowering for 12 to 24 hours increases the frequency of bacterial isolation, especially at 24 hours, including an increase in neutrophil counts, likely indicating a reduced ability to clear guttural pouch secretions.[4] Interpretation of microbial isolates from guttural pouches requires correlation with cytologic characteristics of guttural pouch fluid and clinical signs.[5]

Three disease conditions commonly affect the guttural pouches: tympanitis, empyema, and mycosis. Less common conditions include neoplasia,[6] fractures of the hyoid bone, temporohyoid osteoarthropathy, foreign bodies,[1] and cystic structures.[7]

Guttural Pouch Tympany

Tympany of the guttural pouch occurs infrequently. It can be recognized in foals from birth to 1.5 years of age[8-10]; affected foals are usually identified within the first 2 weeks of life. Fillies are more commonly affected, with the ratio of females to males ranging from 2 : 1 to 4 : 1. Familial and complex inheritance of guttural pouch tympany occurs in Arabian horses and German Warmblood horses, and sex-specific quantitative trait loci have been identified.[11]

Tympany is characterized by unilateral or bilateral distention of the guttural pouch with air. The exact cause is unknown, but congenital redundancy of the plica salpingopharyngea has been suggested. This mucosal fold acts as a one-way valve apparently permitting airflow into but not out of the pouch. Upper airway infection or inflammation has been postulated to result in enlargement of the fold or neuromuscular dysfunction contributing to air trapping.

■ Clinical Signs and Differential Diagnosis

Affected foals usually have a nonpainful, soft, fluctuant swelling in the retropharyngeal space (Fig. 31.42, *A*) with variable respiratory distress, extension of the head and neck, nasal discharge, signs of dysphagia, and possible development of aspiration pneumonia.[8,9] Guttural pouch fluid accumulation and

empyema can occur. Mild tympany may not result in signs other than swelling of the throatlatch (retropharyngeal) region. Respiratory distress occurs when continued distention of the pouch compresses the pharyngeal area. The differential diagnosis for throatlatch regional swelling should include guttural pouch empyema and retropharyngeal abscesses or cellulitis.

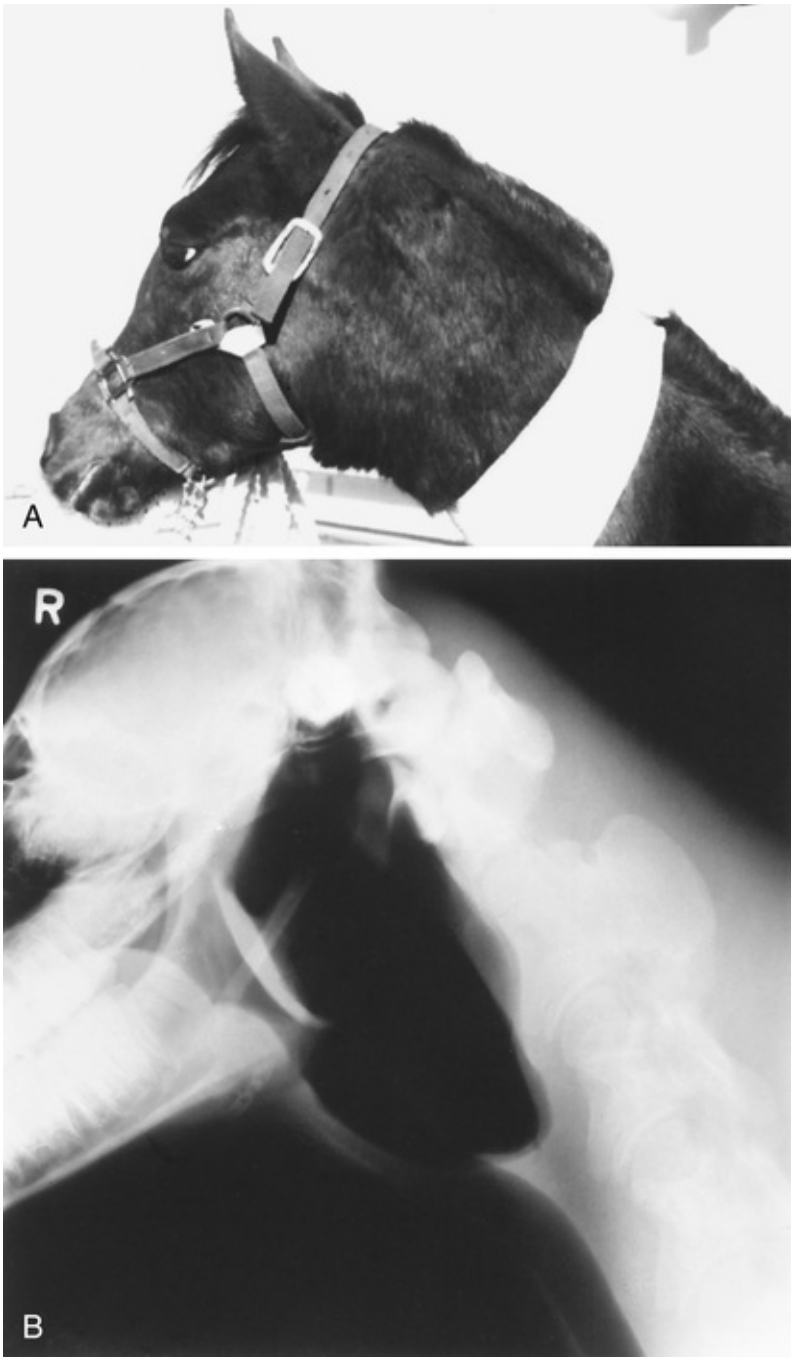


FIG. 31.42 *A,* Foal with guttural pouch tympany. Note the protrusion of the soft tissues over the lateral and ventral aspects of the throatlatch. **B,** Lateral radiograph of a foal with tympanitis of both guttural pouches.

■ Clinical Pathology

Stress leukocytosis may occur if there is marked respiratory distress.

■ Diagnostic Aids

Diagnosis of guttural pouch tympany is based on recognition of characteristic swelling in the retropharyngeal space and confirmation by clinical examination. Although distention is most often unilateral, extreme distortion of a single pouch may give the impression of bilateral involvement. Differentiation between unilateral and bilateral involvement can be difficult and may require deflation of the affected guttural pouch by catheterization or percutaneous needle aspiration combined with external compression. Other adjunctive diagnostic procedures include radiographic demonstration of gas distention of one or both pouches (Fig. 31.42, *B*) and endoscopic observation of pouch distention and pharyngeal distortion.

■ Treatment and Prognosis

Guttural pouch tympany and respiratory distress can be alleviated temporarily by aspiration of air from the affected pouch by percutaneous decompression at the point of greatest distention through Viborg's triangle or by introduction of a catheter through the pharyngeal opening of the guttural pouch. These measures are palliative, and the pouch rapidly refills after decompression. Treatment methods include surgical excision of the plica salpingopharyngea and part of the medial lamina of the eustachian tube; partial resection or photoablation of the plica; fenestration of the median septum between the two pouches by excision, electrosurgery, or photoablation; or creation of a salpingopharyngeal fistula by photoablation and temporary stenting of the fistula.[8-10,12-15] The latter technique is similar to an older, successful approach that involved incising the floor of the guttural pouch into the pharynx.[16] If the condition is bilateral, fenestration of the median septum alone is usually insufficient, and excision of one or both plica salpingopharyngea, in combination with septal fenestration or septal fenestration and salpingopharyngeal fistula formation, must be performed. After surgery the

prognosis for resolution of guttural pouch tympany is generally favorable[10] unless complicating factors such as aspiration pneumonia exist.[9] Early recurrence after surgery can range from 15% to 30%, but further resection of the plica salpingopharyngea or refenestration of the median septum or enlargement of the fenestration typically results in resolution of signs.[9,10]

Guttural Pouch Empyema

Guttural pouch infections are introduced directly through the pharyngeal opening or by lymphatic spread. Accumulation of purulent material (empyema) is considered to be a secondary, chronic, localized manifestation of a more generalized ascending respiratory infection. Empyema is usually unilateral and often a sequela to respiratory disease, especially infection by *S. equi* subsp. *equi*.[17-19] Typically a horse with guttural pouch empyema has continued nasal discharge after recovery from streptococcal infection.[19] In a case control study of foals with lower respiratory tract infection, 21% had concurrent mucopurulent drainage from the pharyngeal openings of the guttural pouches.[20] *S. equi* subsp. *zooepidemicus* was isolated from respiratory secretions of most infected foals and from exudate collected from guttural pouches.[21] Rupture of retropharyngeal abscesses into the guttural pouch has also been associated with empyema, suggesting that strangles or other upper respiratory tract infections may have an important role in the development of guttural pouch infection in horses.[17]

■ Clinical Signs and Differential Diagnosis

Clinical signs include intermittent nasal discharge that may worsen when the head is lowered, retropharyngeal swelling, cough, fever, parotid swelling and pain, dysphagia, difficult breathing, and pneumonia.[22] Nasal discharge can be unilateral or bilateral, even if only one pouch is affected, because the pharyngeal openings of the guttural pouches are located caudal to the nasal septum. Nasal discharge is generally nonodorous, white, and opaque. Altered breathing may result from gradual collapse of the pharynx as the guttural pouch distends. Signs of dysphagia may occur from pharyngeal compression or paresis. Inspissation of the purulent material results in chondroids (hard concretions of inspissated pus). Differential diagnosis of guttural pouch empyema should include diseases with chronic mucopurulent nasal discharge such as pneumonia, sinusitis, upper respiratory tract infections, and guttural pouch tympany.

■ Clinical Pathology

Leukocytosis is often present. Plasma fibrinogen concentration is often increased[22]; changes occur in parallel with development of leukocytosis, pyrexia, and clinical signs of strangles or primary guttural pouch empyema. Analysis of fluid from the guttural pouch often yields a β-hemolytic *Streptococcus* spp.,[17] although other bacteria have been isolated.[22-24]

■ Diagnostic Aids

Guttural pouch empyema should be considered when there is a chronic, nonresponsive nasal discharge. Diagnostic aids include endoscopy, radiography, percutaneous centesis, and aspiration of material from the pouch through the pharyngeal opening. Recognition of fluid (Fig. 31.43) or radiodense masses (chondroids) within the pouch on standing lateral radiographs supports a diagnosis of empyema. Physical and endoscopic examination or oblique radiographic projections may be needed to identify which pouch is involved. Endoscopic examination permits identification of the affected pouch and evaluation of the character of the fluid. Endoscopic examination of the lateral compartment is important to avoid missing sequestered fluid or chondroids.[23] Absence of fluid at the pharyngeal ostium does not preclude the possibility of guttural pouch empyema, as the fluid may be inspissated or the ostium may be sealed.[24] Fluid identified on radiographs should be characterized by endoscopic examination of the pouches or aspiration of the fluid with cytologic and microbial analysis. Fluid samples can be aspirated through the pharyngeal ostium using a sterile artificial insemination pipette, Chambers catheter, or tubing advanced through the biopsy channel of an endoscope. Alternately, fluid can be aspirated percutaneously but should be performed cautiously to minimize the likelihood of bacterial contamination along the needle tract and development of cellulitis.

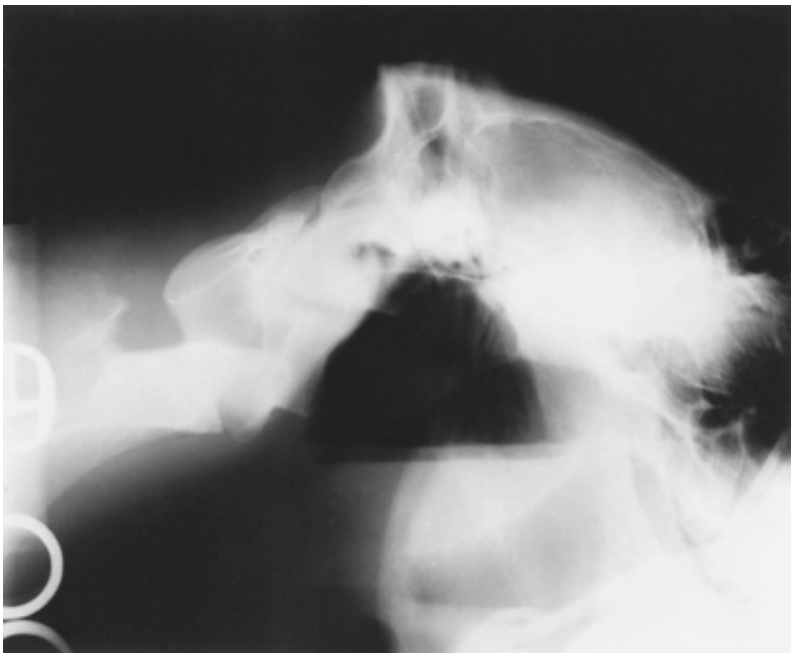


FIG. 31.43 Lateral radiograph demonstrating distinct fluid lines in both guttural pouches.

■ Pathophysiology

Guttural pouch empyema may result from extension of the upper respiratory tract infection with *S. equi* subsp. *equi* (strangles) to the guttural pouches or from rupture of retropharyngeal lymph node abscesses into the guttural pouch.[17] Commonly isolated bacteria from guttural pouch empyema include *S. equi* subsp. *equi, S. equi* subsp. *zooepidemicus, E. coli,* and *Klebsiella* spp.[22] Not all horses with empyema have a history of strangles or previous respiratory infection, and empyema seemingly can occur by many of the same mechanisms as middle ear infection; that is, fluid accumulates in the area, and uncontrolled growth of bacteria normally present results in inflammation and exudation.

■ Treatment and Prognosis

Treatment of guttural pouch empyema is complicated by poor drainage from the affected pouch. The pharyngeal opening of the guttural pouch is located rostrodorsal to the floor of the guttural pouch, and drainage can be achieved only by lowering the horse's head; however, adequate drainage may not occur if there is ventral distortion of the pouch. Inflammation of the lining mucosa may result in swelling of the tissue surrounding the pharyngeal opening, further

compromising normal drainage.

Treatment approach depends on the duration and nature of the empyema and the presence of chondroids. Parenteral antimicrobial therapy may reduce the quantity of the nasal discharge, but relapse often occurs after treatment stops.[22] The early stages of empyema may respond to daily lavage of the affected guttural pouch. Because of the thin nature of the mucosal lining and the proximity of cranial nerves VII and IX to XII and the cranial sympathetic trunk, it is important to use nonirritating solutions (e.g., physiologic or saline antibiotic solutions) to avoid neural inflammation or neuritis. Large volumes have caused guttural pouch rupture. Typically, 500 mL should be flushed into the pouch under moderate pressure to create contact with as much of the interior of the guttural pouch as possible. During lavage the head should be lowered to prevent aspiration of fluid and facilitate drainage. Purulent fluid from the affected guttural pouch should be aspirated on initial catheterization and submitted for microbial culture and antimicrobial susceptibility testing. Fluid collection can be accomplished with most flexible uterine culturettes under direct endoscopic observation. Parenteral antimicrobial drugs should be administered on the basis of susceptibility testing results. Streptococcal isolates may be resistant to potentiated sulfonamides and sulfadimethoxine.[22] Although medication may be of benefit in treating empyema, adequate drainage and local therapy are of primary therapeutic importance.

Indwelling catheters in normal guttural pouches cause increasing purulent discharge over time, which diminishes after catheter removal and is typically resolved within 3 days. Although indwelling catheters are convenient, daily catheterization and irrigation using an artificial insemination pipette or Chambers catheter should be considered when treating an already inflamed guttural pouch to diminish the inflammatory response associated with indwelling catheters. However, daily catheterization must be weighed against the stress, possible tissue trauma, and time requirements for intermittent catheterization.

Treatment with parenteral antimicrobials and local lavage is successful and requires a patent opening for adequate drainage, but the course of treatment may be protracted. Povidone-iodine (1% available iodine) diluted to a 10% solution (0.1% available iodine) for lavage of the guttural pouch caused considerable reaction, including inflammatory infiltrates, hemorrhage, necrosis, and lymphoid reaction.[25] Likewise, antimicrobial concentrations of chlorhexidine gluconate are not recommended.[26] Although acetylcysteine, a mucolytic, has been used to

resolve inspissated empyema,[27] subsequent reports have shown lack of efficacy and concern for added mucosal inflammation.[28] If response to lavage is poor or if secretions reaccumulate and empyema returns, surgical drainage of the guttural pouch should be considered.

Surgery is generally indicated when purulent material becomes inspissated or chondroids have formed,[29] although resolution was reported in one horse after prolonged lavage (14 days) through an indwelling catheter.[30] Surgical approaches include percutaneous drainage through standard approaches to the guttural pouches in anesthetized recumbent or standing sedated horses and creation of a nasopharyngeal fistula by use of an Nd:YAG laser.[31] Other approaches when chondroids are present include removal by retrieval devices passed endoscopically, standing removal through a modified Whitehouse approach,[32] and removal from the contralateral pouch after fenestration of the median septum when the ipsilateral ostium is closed.[24]

The prognosis for guttural pouch empyema is generally favorable if it is recognized promptly and treated appropriately.[22] Likewise, removal of chondroids typically has a good prognosis.[22]

Guttural Pouch Mycosis

Guttural pouch mycosis is a fungal disease of the guttural pouch that typically affects the dorsocaudal region of the medial compartment, although lesions affecting larger areas, including the lateral compartment, occur.[33-35] Fungal invasion of neurovascular structures coursing through the walls of the guttural pouches results in clinically apparent disease. The exact cause is unknown, although a number of fungi, especially *Aspergillus (Emericella) nidulans* and *Aspergillus fumigatus,* have been isolated from lesions.[35-39]

■ Clinical Signs and Differential Diagnosis

Lesions are usually unilateral but can occur bilaterally. The wide spectrum of clinical signs that can occur with guttural pouch mycosis reflects the degree of fungal invasion and subsequent inflammation of vascular structures or nerves beneath the mucous membrane lining the guttural pouch; however, the size of the lesion is not correlated with the severity of clinical signs. Intermittent spontaneous epistaxis and dysphagia are the common clinical signs that

stimulate owners to seek veterinary care; however, the earliest clinical sign in most affected horses is nasal discharge (serous to mucopurulent).[40] Epistaxis generally results from fungal erosion of the wall of the internal carotid artery in the roof of the medial compartment and less commonly from erosion of the external carotid artery (or its branches; e.g., caudal auricular artery) and maxillary artery in the lateral compartment. Epistaxis is usually unilateral from the ipsilateral nostril, but it can be bilateral because the pharyngeal openings of the guttural pouches are located caudal to the caudal border of the nasal septum.[34] Episodes of epistaxis typically occur at rest and vary from mild to severe, with several premonitory bleeds that generally culminate in a fatal episode of epistaxis.[34,35] Occasionally a horse dies from a single episode of epistaxis without previous clinical signs. Epistaxis may recur at intervals varying from 24 hours to 3 weeks.[34]

Dysphagia, the second most common clinical sign, likely results from damage to the pharyngeal branches of the vagus and glossopharyngeal nerves and generally occurs later than epistaxis in the course of the disease.[34] Horses with dysphagia cough during attempts to eat solid food, and in addition to food material in the nasal discharge, a considerable quantity of food is coughed from the mouth. Recovery from dysphagia may occur,[34] but in general the prognosis for full recovery is poor.

Other clinical signs include parotid pain, abnormal head posture, unilateral or bilateral nasal discharge, head shyness, abnormal respiratory noise from pharyngeal paralysis or laryngeal hemiplegia, sweating and shivering, Horner's syndrome, visual disturbances, colic, and facial paralysis.[34,35] These signs are the result of angina and dysfunction of cranial nerves and the sympathetic nerves.

The differential diagnosis for a horse with epistaxis should include EIPH, ethmoid hematoma, guttural pouch or pharyngeal neoplasia, tracheobronchial foreign bodies, and guttural pouch mycosis.[34] Differentiation of these diseases is aided by a thorough history and endoscopic examination. Differential diagnosis for dysphagia should include fractures of the hyoid apparatus; pharyngeal and guttural pouch fistula; cleft palate; esophagitis; pharyngeal paralysis; foreign body entrapment in the mouth or esophagus; pharyngeal neoplasia; lead poisoning; bacterial, viral, and mycotic central nervous system infections; and guttural pouch mycosis.[34]

■ Clinical Pathology

If epistaxis is the presenting complaint, moderate to severe anemia with accompanying hypoproteinemia may also be present. Differential white cell distributions may be normal or may indicate a stress response. If dysphagia becomes a dominant clinical sign, other hematologic changes indicative of infection secondary to aspiration pneumonia may be evident.

■ Diagnostic Aids

Clinical signs of epistaxis or cranial nerve dysfunction are suggestive of a diagnosis of guttural pouch mycosis. A thorough physical examination may reveal abnormal sensitivity on digital palpation of the parotid area on the affected side.[33] A definitive diagnosis of guttural pouch mycosis requires endoscopic observation of the characteristic diphtheritic lesion in the dorsocaudal aspect of the medial compartment, typically covering over the temporohyoid joint and internal carotid artery, or elsewhere within the guttural pouch.[34] Aneurysm of the internal carotid artery is rarely present. A healed lesion may be identified by presence of scar tissue within the mucous membrane.[34] Lesions vary in color (brown, yellow, black, or white) and size (from discrete nodules to diffuse irregular patches covering the roof of both the medial and the lateral compartments)[35]; erosion with fistula formation can occur into the opposite guttural pouch or pharynx. Occasionally the characteristic lesion is obscured by clotted blood, so that the diagnosis is based on the clinical signs of epistaxis correlated with blood present in the guttural pouch. Because hemorrhage may originate from the internal carotid, external carotid, or maxillary arteries, it is important to identify the source of bleeding before therapy, particularly if surgical intervention is being considered. Care should be taken not to dislodge a thrombus and produce further hemorrhage. If dysphagia is apparent, food and saliva may be identified during endoscopy of the pharynx and nasal passages.

In guttural pouch mycotic infections, radiographs are of limited value because only minimum suppuration is associated with mycotic infections; however, a lateral projection may allow assessment of the degree of fibrous reaction and loss of normal air space. Radiography may also aid in diagnosing some of the long-term sequelae, such as fibrous deposits in the pouch and associated bony changes.

Serum titers to *A. fumigatus* are not diagnostic; however, reactivity to 22-kd

and 26-kd serum antigens measured by immunoblot analysis may be diagnostic for guttural pouch mycosis.[37]

■ Pathophysiology

The pathogenesis and predisposing factors leading to guttural pouch mycosis and arterial erosion are unknown, but it is believed that the disease is initiated by some stress (inflammation, trauma, vascular insult) to the soft tissues where the mycotic plaques are generally found.[35] Aneurysm formation is not well correlated with the severity of the plaque formation. Although the nature of the initiating lesion remains unclear, it is generally agreed that the later stages are associated with deep fungal infections.[37] Fungal plaques have been induced experimentally after systemic and topical (guttural pouch) corticosteroid administration within 2 days of pouch inoculation with *A. fumigatus;* however, lesions resolved spontaneously within 15 to 28 days without apparent vascular or nerve involvement or induction of clinical signs.[38] *A. nidulans* and other *Aspergillus* spp. have been isolated and may be the causative agents[35-41]; *A. nidulans* is rarely pathogenic but may grow as an opportunist in the warm, humid environment of the guttural pouch.[35] The mycotic lesions show no predilection for either the right or the left guttural pouch.[34] Fungal infection of the pouch, erosion of major blood vessels, and involvement of nerves (IX, X, XI, XII, cranial cervical ganglion, and postganglionic sympathetic fibers) that traverse the area account for the epistaxis, local pain, and neurologic signs associated with guttural pouch mycosis.[34,35]

■ Epidemiology

No apparent age, sex, breed, or geographic predispositions have been observed. Guttural pouch mycosis is a sporadic disease that tends to arise during the warmer months of the year and rarely affects more than one horse in a particular stable.[34] Affected horses are afebrile; infection is diagnosed when clinical signs such as epistaxis and dysphagia occur, although nasal discharge is often the earliest reported sign.[34]

■ Necropsy Findings

Lesions are confined to the pharyngeal muscles, guttural pouch, and bones of the skull.[33] Gross findings may include large blood clots in the nasal passages and at

the pharyngeal opening of the guttural pouch. Unilateral denervation atrophy of the ipsilateral pharyngeal or laryngeal muscles may occur if there is involvement of the pharyngeal and recurrent laryngeal branches of the vagus nerve.[33] Examination of the guttural pouch generally reveals clotted blood and a diphtheritic plaque in the dorsocaudal aspect of the medial compartment that is firmly adherent to the underlying tissue and is clearly demarcated from surrounding tissue.[35] The lesion may be localized or may affect the entire roof of the pouch. If hemorrhage has occurred, the lesion may be obscured by clotted blood, pus, or mucus.[35] An intense inflammatory reaction may be evident in response to acute fungal infection, whereas the inflammation may subside with chronic healing lesions so that scar tissue is evident.[35] Active inflammation may also predispose to osseous lesions of the petrous temporal and stylohyoid bones.[33,35] Some cases of guttural pouch mycosis may not have associated clinical signs and may be diagnosed only on necropsy.[34]

■ Treatment and Prognosis

Without treatment a poor prognosis is warranted because affected horses are at risk for a fatal episode of epistaxis. Both medical and surgical treatments have been recommended, with variable results; however, surgical treatment by an intraarterial occlusion technique is generally considered to yield the best prognosis.[42-44] Although apparently uncommon, spontaneous regression of guttural pouch mycosis can occur and must be considered when the various medical or surgical treatments are being evaluated.[34]

Medical treatment is topical therapy of the mycotic lesion through the pharyngeal opening of the guttural pouch by means of a catheter. Bathing the lesion in medication may be facilitated by anesthetizing the horse and positioning it in dorsal recumbency. Instilling fungicidal and fungistatic drugs, topical enzymes, and organic iodine compounds into the guttural pouch has been attempted with variable success.[45,46] The necessity and efficacy of these treatments are unknown, and systematic treatment is hampered by a lack of knowledge of the pathogenesis of guttural pouch mycosis.[47] Parenteral administration of antibiotics, corticosteroids, thiabendazole, ketoconazole, and iodine compounds also has questionable efficacy.[47] The response of guttural pouch mycosis to local and parenteral treatment is protracted; thus the risk of fatal hemorrhage exists long after initiating treatment.[48,49]

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Surgical treatment of guttural pouch mycosis appears to offer the best prognosis for eventual cure. The internal carotid artery is not an end-artery, and blood can enter this vessel from the bifurcation of the common carotid or return from the cerebral arterial circle. Various surgical techniques have been described,[50] and use of a balloon-tipped catheter inserted into the distal internal carotid artery combined with proximal ligation of the internal carotid artery,[48-51] transarterial coil embolization,[43,52,53] or transarterial nitinol vascular plugs[54] induces thrombus formation and prevents hemorrhage from normal and retrograde blood flow. Thrombosis sufficient to prevent hemorrhage may develop in the distal internal carotid artery within 10 days of catheter placement.[51] Mucosal healing and complete regression of the fungal plaque have been reported to occur as early as 5 weeks after arterial catheterization[49] and as early as 15 days after coil embolization.[43] Insertion of a balloon-tipped catheter successfully prevented fatal epistaxis in 13 horses.[48] Topical or systemic treatment of the mycotic plaque is considered unnecessary after arterial catheterization.[48] Intraarterial insertion of latex balloons, embolization coils, or nitinol vascular plugs also results in lesion resolution,[54-57] although progression of a mycotic plaque after coil embolization and subsequent development of neurologic signs have been reported.[58] Complications associated with each of these arterial occlusion techniques have been reported.[59]

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Diseases of the Paranasal Sinuses

Sinusitis

John R. Pascoe

■ Definition and Etiology

Sinusitis, inflammation of the paranasal sinuses, results from primary microbial infection or from secondary bacterial infection associated with dental or other sinus disease. Lined by respiratory mucosa, the paranasal sinuses are at risk for developing diseases affecting the respiratory tract. Sinus empyema, accumulation of pus within a sinus cavity, may result from bacterial or viral infection.

Incidence of sinusitis is relatively low, likely less than 0.5% of disease in equine practice.[1] In two longitudinal retrospective studies, covering 25 years, of 477 horses referred with sinonasal disease, the distribution of causes was primary sinusitis (subacute or chronic; 33%), dental-associated sinusitis (21%), sinus cysts (13%), sinonasal neoplasia (7%), ethmoid hematoma (6%), sinonasal trauma (6%), mycotic lesions (4%), dental-related oromaxillary fistula (3%), and miscellaneous causes (6%).[2,3] The caudal maxillary, rostral maxillary, ventral conchal, and conchofrontal sinuses are more commonly involved, and the sphenopalatine sinus is affected less often.[4] The median age of horses affected with sinonasal disease is 7 to 11 years.[2]

Acute or chronic upper respiratory tract infections of viral or bacterial origin can result in primary sinusitis; *Streptococcus* spp. infection is the most common. Maxillary sinusitis caused by disease of the third (caudal roots) through sixth cheek teeth (modified Triadian numbers 109 to 111, 209 to 211) often results from alveolar periostitis, patent infundibula, fractured or split teeth, or deep diastemata between caudal maxillary teeth. Dental defects can permit access of food material or bacteria to the tooth root and sinus cavity, with extension to the frontal sinus likely through the frontomaxillary opening. Reported neoplasms include osteoma, osteosarcoma, adenocarcinoma, lymphosarcoma, squamous cell carcinoma, neuroendocrine tumors or neuroblastoma, fibroma, and chondrosarcoma.[5-7]

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■ Clinical Signs and Differential Diagnosis

Signs vary depending on cause, location, and extent of sinus involvement, with unilateral nasal discharge (serous, mucoid, mucopurulent, purulent) being the most frequent sign.[2,3] Physical examination of a horse with sinusitis should include observation for epiphora, facial asymmetry, altered nasal airflow, abnormal breath odor, mandibular lymphadenopathy, and sinocutaneous fistula.

Nasal discharge is typically unilateral because the nasomaxillary opening is located rostral to the caudal edge of the nasal septum. Intermittent or continuous nasal discharge need not be related to a previous upper respiratory tract infection. Although malodorous discharge is commonly associated with dental sinusitis and sinonasal mycosis, it has been reported to occur in 14% to 27% of primary sinusitis cases.[2,3] Mucopurulent discharge is more commonly associated with sinus cysts.[2] Sanguineous discharge is common with ethmoid hematoma and sinonasal trauma; however, guttural pouch mycosis, pulmonary hemorrhage, nasal turbinate necrosis, and neoplastic or granulomatous lesions should also be considered. Other differential diagnoses of nasal discharge should include guttural pouch empyema or mycosis, acute pharyngitis (strangles, rhinopneumonitis, influenza, trauma), neoplasia or necrosis of the turbinates, ethmoid hematoma, and pulmonary disease.

After nasal discharge, submandibular lymphadenopathy is the most common sign, particularly when microbial infection is a component of sinusitis.[3] Facial swelling occurs with frequency similar to that of lymphadenopathy, typically when sinus drainage is obstructed, there is an expansile mass within the sinus, or as an acute sign after facial trauma. Occasionally exophthalmos can occur with marked sinus distortion.

Patency of the nasomaxillary opening generally precludes facial distortion. Loss of patency occurs when inspissated exudate accumulates or mucosal lining tissue reaction obstructs the opening. Expansion of the sinus may result in reduced ipsilateral nasal airflow caused by distortion of the architecture of the nasal passages. In these cases abnormal respiratory noise rather than nasal discharge may be the primary presenting sign.

Epiphora occurs if there is nasolacrimal duct involvement from trauma, compression, or destruction of the duct associated with sinus disease. Approximately 20% to 50% of horses with dental sinusitis, sinus cyst, or sinonasal trauma have epiphora as a presenting sign.[2,3]

Percussion of the affected sinus may reveal dullness or pain, although normal

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resonance does not preclude the possibility of sinusitis. If there is bone thinning over gas above a fluid line (as can occur with some maxillary sinus cysts), percussion may elicit increased resonance.

Careful examination of the oral cavity for signs of dental or periodontal disease should be performed when any of these signs are present. Particular attention should be paid to examination of the occlusal surface of the teeth with a very fine dental pick (e.g., 22-gauge needle); however, it should be recognized that periapical abscess formation can occur without defects in the occlusal surface. Accuracy of diagnosis of dental disease is substantially enhanced by use of intraoral endoscopy and computed tomography (CT).

■ Clinical Pathology

The hemogram generally remains within the normal range, although acute sinusitis of infectious origin may be associated with neutrophilia with or without hyperfibrinogenemia. With chronic sinusitis, there may be concurrent hyperfibrinogenemia and hyperglobulinemia. Sinus fluid obtained by percutaneous centesis should be examined cytologically (including a Gram stain) and submitted for microbial culture and susceptibility testing to differentiate among bacterial, fungal, and neoplastic disease. Flecks of feed material indicate sinusitis secondary to dental abnormalities.

■ Laboratory Aids and Definitive Diagnostic Tests

A presumptive diagnosis of sinusitis can be made from the physical examination and associated clinical signs.[2,3,8] Procedures most helpful in establishing a diagnosis are sinonasal endoscopy, oral cavity examination, imaging (radiography, CT, scintigraphy, magnetic resonance imaging [MRI]), sinus centesis, and sinoscopy.[4,8,9]

Nasal cavity endoscopy may permit identification of exudate draining from the nasomaxillary opening or, in advanced cases, may reveal distortion of the nasal cavity secondary to sinus enlargement. Middle meatus examination is an important component of endoscopic examination. Diagnosis beyond recognition of the potential source of the nasal discharge is limited unless an obvious mass or abnormal tissue is observed. Sinoscopy can be accomplished by using an arthroscope[10] or flexible endoscope[11] inserted through small trephine holes in either the maxillary or the frontal sinus.[9] Examination of the rostral compartment of the maxillary sinus requires a separate portal unless the bony septum between

the rostral and caudal compartments has been destroyed. Observation may be limited by fluid or tissue, especially in the rostral compartment of the maxillary sinus, but can potentially be enhanced after sinus lavage and aspiration. Alternately, fenestration of the ventral conchal bulla can be used to facilitate endoscopy of the rostral compartment of the maxillary sinus.[4]

Standard radiographic projections include standing lateral, dorsoventral, and right and left oblique views.[12,13] Radiographic findings include fluid lines within the sinus, space-occupying soft-tissue densities, areas of decreased bone density, fractures, or dental abnormalities. Dental root disease is identified radiographically by a loss of continuity of the lamina dura and lysis of the tooth root or surrounding bone, combined with new bone formation and cement deposition.[12] Anatomy of normal equine skulls as demonstrated by CT and MRI has been described.[14-18] Diagnostic accuracy, especially determination of the extent of involvement of structures within the skull, can be enhanced by CT.[19,20] MRI may be useful in some sinonasal disorders.[21,22]

Findings associated with dental caries include hypoattenuation of cementum, destruction of enamel, and filling of the infundibular cavity with gas, whereas with dental decay there is gas accumulation in the root area or fragmentation of the root and sinus mucosal thickening. Additional changes with sinusitis typically involve the maxilla with endosteal sclerosis, thickening, periosteal reaction, and deformation, especially involving the facial crest.[20] Scintigraphic examination may improve specificity in identifying dental involvement in sinusitis.[23,24]

Percutaneous sinus centesis may provide a definitive diagnosis and allow an avenue for subsequent therapy. Cytologic evaluation, with concurrent microbial culture and antibiotic susceptibility testing, may elucidate the cause of the sinusitis. Isolation of a single organism such as *Streptococcus* spp. generally indicates a primary sinusitis, whereas polymicrobial infection is more compatible with sinusitis of dental origin. Visual examination of the oral cavity, especially intraoral endoscopy, and careful probing of the occlusal surfaces with a dental pick may help identify dental abnormalities.

■ Necropsy Findings

Affected sinuses contain fluid or tissue of variable color and consistency. Fluid character ranges from clear and odorless with cystic sinus disease to white, yellow, or green purulent fluid with a variable but often putrid odor in sinusitis

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resulting from other causes. Sinusitis of dental origin has a characteristically pungent and unpleasant odor. Granulomatous lesions often appear as large, lobular, gelatinous masses filling the sinus cavity. The gross appearance of neoplastic lesions within the sinus cavity depends on the type of neoplasm. Neoplasia may cause surrounding soft-tissue and bony destruction, whereas large, benign space-occupying lesions may result in distortion of the nasal turbinates and nasal septum, as well as visible facial bone distortion.

■ Treatment and Prognosis

Not infrequently, horses with a chronic mucopurulent nasal discharge from sinusitis have a history of response to antimicrobial therapy, followed by recurrence of the discharge after antibiotic therapy ceases. Definitive diagnosis of sinusitis can be accomplished using the techniques described earlier. Sinoscopy permits examination of the paranasal sinuses and in some instances facilitates treatment.[25,26]

Suggested treatment for primary sinusitis or empyema involves daily lavage of the sinus through a percutaneous centesis site with 1 L of saline, to which a broad-spectrum antibiotic or antiseptic has been added. Once the results of microbial culture and susceptibility testing are available, the appropriate antibiotic should be administered locally in the flush solution, as well as systemically, for 14 days. Resolution or reduction in the volume of nasal discharge is an indication of successful therapy. Sinus lavage often fails to remove inspissated material, which is often the nidus for continuing sinusitis and must be removed for resolution.[8] If little progress is made after 10 to 14 days of lavage or if drainage recurs, sinusotomy (trephination or bone flap technique, standing or recumbent anesthetized) is recommended to remove inspissated material[22] or identify other causes. The prognosis is generally favorable if primary sinusitis is not chronic and if the mucous membrane is not markedly thickened.[26,27] Chronic sinus disease (longer than 6 months) carries a poor prognosis, and for resolution to occur, surgical removal of the thickened, infected mucous membrane is required; creation of sinonasal drainage by sinus fenestration is also recommended.

Sinusitis that results from secondary factors is generally not responsive to medical management. Such conditions include diseased teeth, granulomas, or neoplasia; surgical removal of the inciting cause is required, and adjunctive treatment may be required. The prognosis for sinusitis associated with dental

abnormalities is usually favorable once the diseased tooth has been removed.[26,27] Complications are lower with oral extraction than with repulsion of diseased teeth.[27] Generally, failure of oral extraction and subsequent tooth or tooth fragment repulsion results in lower morbidity than initial repulsion.[27] If the periodontal ligament is intact, endodontic therapy can be used to save the tooth. This is accomplished by surgical apicoectomy and retrograde occlusion of the root canal after débridement of the pulp. In geriatric horses with dental-associated sinusitis, when economic constraints limit surgical options, sinusotomy and periodic sinus lavage and antibiotic therapy have been used successfully to manage nasal discharge.

The prognosis for resolution of granulomatous lesions is generally guarded and depends on surgical access and extent of the lesion. Neoplastic lesions are often well established and have metastasized, either locally or regionally, by the time they become clinically apparent; the prognosis for resolution is generally guarded to poor.[4]

■ Prevention and Control

Prevention of sinusitis in horses is difficult because of the variety of causes. Isolation of horses from those with upper respiratory bacterial or viral diseases may be of benefit in preventing primary sinusitis. Regular dental care and a proper diet may help circumvent sinusitis caused by dental abnormalities, although many cases most likely result from a variety of causes not yet defined or over which the owner or veterinarian has no control.

Ethmoid Hematoma

John R. Pascoe

■ Definition and Etiology

Ethmoid hematomas (progressive ethmoidal hematoma[1]; hemorrhagic nasal polyps[2]) are slowly expanding angiomatous masses (median dimensions: 3.8 × 9 × 13 cm)[3] originating principally from the mucosal lining of the ethmoid conchae. Smaller hemangiomas arising from the mucosal lining of the frontal, maxillary, and sphenopalatine sinuses have been recognized, but the relationship between these benign endothelial tumors and ethmoid hematoma remains uncertain. Ethmoid hematoma is a relatively uncommon condition of unknown

cause. Distinctly different histologic features characterize ethmoid hematoma and paranasal sinus cysts,[4] which makes it unlikely that these lesions are variants of each other with a common cause.[5] Although ethmoid hematomas have been reported in a 4-week-old foal and in 3-year-old horses, most affected horses are older than 8 years and are generally Thoroughbred, Arabian, or warmblood horses[6,7]; males (geldings) seem to be more commonly affected.[3]

■ Clinical Signs

A blood-tinged nasal discharge with intermittent epistaxis from one or both nostrils is the most common clinical sign. Unilateral or bilateral epistaxis varies from blood-tinged, mucoid, or mucopurulent discharge to blood spots or a trickle of blood. Fulminant or fatal epistaxis is uncommon. If the hematoma occupies the choanae or nasal cavity, a mucopurulent, occasionally malodorous nasal discharge with some blood discoloration is more commonly seen. Typically there is a history of abnormal respiratory noise, both inspiratory and expiratory, especially during exercise. With nasal cavity involvement, airflow may be reduced or absent on the affected side. Facial distortion or asymmetry is uncommon and more likely to occur with involvement of the frontal and maxillary sinuses. Secondary mycotic infections and empyema may be associated with intraparanasal sinus ethmoid hematoma.[8] Less commonly there may be an associated history of coughing, choking, ptyalism, increased respiratory effort during resting breathing, and either head shyness or headshaking.[1] If the hematoma has expanded into the paranasal sinuses, percussion yields a dull sound.

■ Laboratory Aids and Definitive Diagnostic Tests

Confirmation requires endoscopy of the ethmoid conchae and diagnostic imaging (Fig. 31.44). Although survey radiography is useful to identify the mass, its origin and extent are delineated more accurately with CT, which is also more reliable than a combination of clinical examination, endoscopy, and conventional radiography.[3] Limited information is available to assess the value of MRI for diagnosis of ethmoid hematoma.[9,10] In the absence of CT, sinoscopy may be of diagnostic value when the ethmoid hematoma involves the paranasal sinuses without nasal cavity protrusion. Rarely, ethmoid hematoma infiltrates the nasal conchae; these lesions, identifiable by CT, may be missed on sinoscopy. Definitive localization of ethmoid hematoma involving the sphenopalatine sinus

is unlikely by radiography or sinoscopy.[3]

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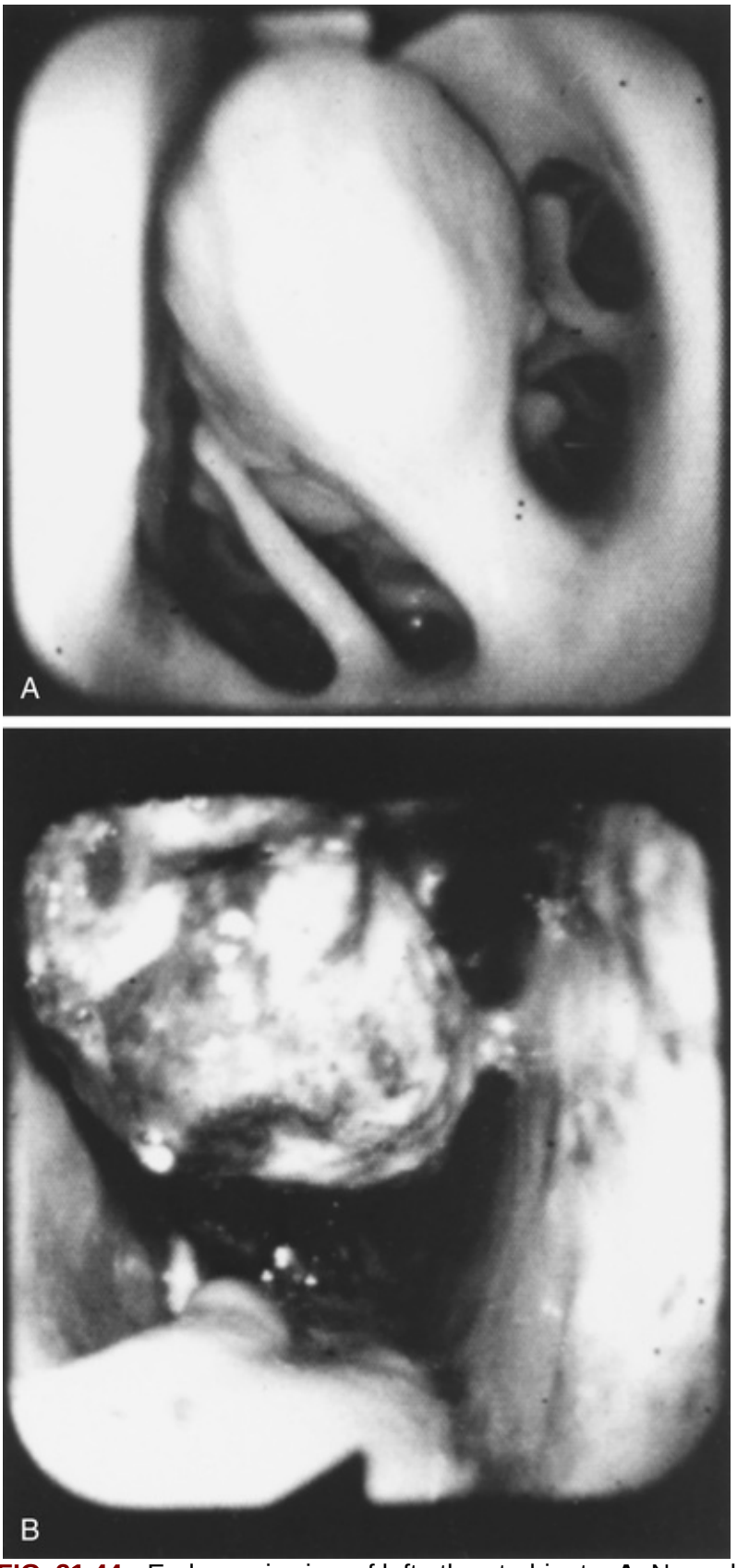


FIG. 31.44 Endoscopic view of left ethmoturbinate. **A,** Normal

appearance. **B,** Ethmoturbinate obscured by an ethmoid hematoma.

Ethmoid hematomas are bilateral in 30% to 50% of affected horses, so it is prudent to examine both ethmoidal conchae. The ethmoidal labyrinth is visible approximately 25 cm from the nares, with the endoscope positioned in the ventral nasal meatus and the viewing tip deflected dorsally. The rostral surface of the ethmoidal concha does not protrude beyond the caudal aspect of the nasal cavity; it has a bulbous shape and a moist pink to pale red mucosal covering. Distal to the rostral surface are numerous pillars that form the ethmoidal conchae and separate the ethmoidal spaces (cellulae ethmoidales). Ethmoid hematomas that project into the ventral meatus or through the choana into the nasopharynx often obscure the ethmoidal concha. Unilateral ethmoid hematomas that expand into the nasopharynx may extend into the contralateral ventral meatus and obscure that ethmoidal labyrinth.

The origin of hematomas that expand dorsally into the frontal sinus may not be visible on endoscopy, but hemorrhage that originates deep to the visible portion of the ethmoidal conchae may be evident or noticed from the region of the nasomaxillary opening in the middle meatus. Visible ethmoid hematomas vary in color from deep red to red-purple or may have a yellow-brown or yellow-green-brown to bronze color. The surface is irregularly rounded, with small punctate hemorrhages or erosions, and may be partially covered in yellow-white mucopurulent material that may be admixed with blood. Often the floor of the ventral meatus and regions of contact with the nasal cavity have pooled exudate (blood and mucopurulent matter). Manipulation of the hematoma surface with the endoscope may cause bleeding or oozing.

Radiographic recognition of a discrete, often smooth-surfaced homogeneous radiodensity originating from the ethmoidal conchae and extending into the frontal, maxillary, or sphenopalatine sinuses, or into the pharynx or nasal cavity, is suggestive of ethmoid hematoma. Precise definition of the hematoma origin is difficult to determine from radiographic projections, and small hematomas contained within the ethmoid labyrinth may not be visible.

CT examination allows more accurate assessment of the origin of the ethmoid hematoma,[3] allows determination of the extent of involvement of the paranasal sinuses (especially the sphenopalatine sinus) and conchae, and facilitates surgical planning. On CT scans, masses are often associated with bone destruction, especially of the ethmoturbinates and infraorbital canal, and typically abut the cribriform plate in 50% of cases. Masses commonly have mild

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to moderate signal heterogeneity and a hyperdense swirling appearance consistent with recent hemorrhage or mineralization, which are also common morphologic features.[3]

■ Necropsy Findings

Morphologic features have been described from surgical specimens, but few skulls with intact ethmoid hematomas have been examined.[2,3] Except in regions with necrosis or secondary infection associated with contact with the sinus or nasal cavity walls, the hematoma is a smooth-surfaced saclike structure containing blood in various stages of organization. The sac lining is generally healthy respiratory mucosa originating from a pedunculated region of the mucosal covering of the ethmoturbinate or sinus wall. On section, contents are amorphous red-black to chocolate brown, and in larger masses some evidence of irregular compartmentalization by fibrous tissue exists, especially on the inner surface of the sac.

Morphologic features include an outer covering of respiratory epithelium (flattened columnar or cuboidal ciliated epithelium-containing glands, and occasionally stratified squamous epithelium[4]) overlying an irregular zone of submucosal fibrous tissue, containing hemosiderophages, occasional plasma cells, and lymphocytes, less commonly neutrophils, that forms a pseudocapsule around hemorrhage in varying states of organization. There is variable organization of the fibrous tissue components. Endothelial cells do not show evidence of neoplasia. Thin endothelium-lined sinuses are often present within the myxomatous stroma. The respiratory epithelium is sometimes focally ulcerated and infiltrated with neutrophils, and occasionally there are squamous metaplastic changes. Ethmoid adenocarcinoma with a similar gross appearance to ethmoid hematoma has been reported.[3,11]

■ Treatment and Prognosis

Ethmoid hematomas slowly and progressively increase in size and can cause skull distortion if there is paranasal sinus involvement, so removal is recommended. Treatment method depends on location and size. Surgical ablation has been the preferred method; however, destruction of the hematoma by intralesional injection of formaldehyde solution is associated with less morbidity, although recurrence rates are similar to those achieved by other methods.[6-8,12,13] Surgical access is achieved by sinusotomy and then hematoma

ablation by curettage, cryosurgery, or use of an Nd:YAG laser[13]; photoablation can be achieved through the biopsy channel of an endoscope. If sinusotomy is necessary, the pedunculated origin of the hematoma is identified by digital palpation and then dissected, frozen, or photoablated, and the hematoma is removed. If the hematoma is friable, intact removal may not be possible, and hemorrhage may make observation of the origin of the mass difficult. After removal, the paranasal sinuses and nasal cavity are packed with gauze to control postoperative hemorrhage.

Surgical curettage can be associated with marked intraoperative blood loss typically from the turbinates or sinus mucosa rather than the hematoma. Temporary occlusion of both carotid arteries[14] can reduce blood loss until the sinus cavity is packed with gauze. Blood loss is minimized with cryosurgical extirpation and photoablation techniques, but these approaches are not always practical with large hematomas. Although blood loss is minimal with transnasal photoablation, this technique requires multiple procedures to destroy large masses but can be performed in the standing sedated horse. Photoablation (Nd:YAG laser, 100 W in noncontact technique) is effective in controlling remnants after surgical extirpation or subsequent regrowth.[15] A complication of severe epistaxis, subarachnoid hemorrhage and peracute, severe neurologic signs that occurred during laser photoablation of an ethmoid hematoma in the right nasal cavity have been reported in one horse.[16]

Destruction of ethmoid hematomas by endoscopically guided intralesional injection of formalin in standing sedated horses may reduce the need for surgical ablation.[12,17] A catheter passed through the endoscope biopsy channel is advanced through the rostral surface of the mass toward its origin, then 10% formalin (4% formaldehyde solution) is injected intralesionally. Commercially available catheters with a beveled needle tip are available, but relatively stiff plastic tubing that slides through the biopsy channel will penetrate the hematoma capsule. Sufficient volume (10 to 100 mL) is injected until fluid leaks back alongside the catheter or from the mass. For visibly pedunculated masses, formalin should be injected at the origin or neck of the mass. Tissue necrosis and slough occur within 5 to 10 days and may be associated with nasal discharge. Repeat injections, typically at no longer than 10- to 14-day intervals, may be needed to destroy the mass. Removal of necrotic tissue can be facilitated by use of long, grasping forceps and hydropulsion. Mycotic plaques may cover the treated site during healing but typically resolve without treatment;

endoscopically delivered topical natamycin has been used if mycotic plaque is extensive and associated with malodorous, purulent discharge.[18] If the hematoma has a paranasal sinus extension, necrosis of that tissue within the sinus, after destruction of the ethmoturbinate origin of the hematoma, may result in sinus empyema, mycotic infection, or both,[8] requiring ancillary treatment.

Occasionally progression of the ethmoid hematoma may result in weakening or loss of the cribriform plate or roof of the sphenopalatine sinus.[18] During mass removal, loss of this protective bony covering may result in intraoperative or postoperative neurologic complications. Recognition of loss of the integrity of these bony plates may not occur until sinus lavage. In a rare complication, death occurred after intralesional formalin injection in a horse where the cribriform plate had been eroded by the ethmoid hematoma.[19] Erosion of calvarial bone is rare, but careful CT evaluation of these regions in horses with extensive hematoma formation involving the frontal or sphenopalatine sinuses is warranted.[3]

Irrespective of treatment method, recurrence of the hematoma occurs in 17% to 50% of cases from several months to years after the initial surgery.[2,3,6-8,12,13,18] Increased use of CT to guide surgical planning and for postoperative evaluation is likely to contribute to a reduction in recurrence rates.

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Disorders of the Equine Soft Palate

Safia Z. Barakzai • Padraic Martin Dixon

■ Anatomy and Physiology of the Soft Palate

The equine soft palate extends caudally from the hard palate and completely divides the pharynx into nasal and oral compartments. Because the horse is an obligate nasal breather, the caudal border of the soft palate normally fits snugly around the base of the epiglottis, and the soft palate remains in this subepiglottic position at all times except during deglutition. The soft palate consists of the oral mucous membrane, palatine glands, palatine aponeurosis, palatal muscles, and nasopharyngeal mucosa. The soft palate is relatively thick (>2 cm) rostrally and tapers caudally as the amount of glandular tissue within it reduces considerably.[1] The paired muscles that control palatal position include the *palatinus* muscles (running rostrocaudally on either side of midline), the *palatopharyngeus* muscles (running from the palatine aponeurosis and lateral aspect of the *palatinus*, sweeping laterally up the walls of the nasopharynx), the *tensor veli palatini* muscles that tense the rostral aspect of the soft palate, and the *levator veli palatini* muscles that elevate the soft palate during deglutition.

The dorsal aspect of the soft palate forms the floor of the nasopharynx and has longitudinal ridges that become more apparent endoscopically when the palate is flaccid. Horses that resent endoscopic examination of the upper respiratory tract often tense their soft palate, giving its rostral aspect a dorsally “domed” appearance.

Dysfunction of the soft palate presenting as dorsal displacement of the soft palate (DDSP) or palatal instability (PI) at fast exercise is by far the most frequent palatal abnormality that clinicians are presented with in equine practice. Other palatal disorders are relatively uncommon.

Dorsal Displacement of the Soft Palate and Palatal Instability

Palatal dysfunction, which includes the two syndromes of DDSP and PI, is the most commonly diagnosed cause of upper airway obstruction in racehorses, with a reported prevalence of around 10% to 20%.[2,3] It also affects other types of

horses, particularly those that are exercised with their head and neck in a flexed position, such as dressage horses, showjumpers, and Saddlebreds.[4,5] Intermittent DDSP is a disorder that characteristically occurs in horses toward the end of fast work, when the caudal border of the soft palate becomes displaced dorsal to the epiglottis (Fig. 31.45). A definitive diagnosis of intermittent DDSP or PI can only be made using exercising endoscopy on a treadmill or using overground endoscopy. Palatal instability is seen as wavelike dorsal billowing of the rostral and caudal aspects of the soft palate but without actual displacement of the caudal border of the soft palate dorsal to the epiglottis. Palatal instability commonly precedes DDSP.[6-9] Swallowing may temporarily halt PI, but instability usually recurs within a few seconds and may then progress to true DDSP. As the soft palate "billows" dorsally, it may lift the epiglottis, changing the epiglottic conformation and causing the aryepiglottic folds to deviate medially.[9,10] It is unclear what degree of soft palate instability is "normal" and what percentage of horses diagnosed with PI would experience DDSP under different conditions, such as training versus racing. When PI is observed in isolation, it has been described as equivalent to a "presumptive" diagnosis of DDSP[11] and has also been suggested as a "prodromal" sign of impending DDSP.[9,12]



FIG. 31.45 Dorsal displacement of the soft palate seen in a horse undergoing exercising endoscopy. The epiglottis can no longer be visualized.

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"Rostral palatal instability" is another form of palatal instability that has been reported in horses and ponies, associated with neck flexion during exercise.[13,14] As the name suggests, the condition is characterized by dorsoventral billowing confined to the rostral aspect of the soft palate. Rostral palatal instability causes inspiratory nasopharyngeal obstruction and respiratory noise. Experimentally this condition has been produced by bilateral *tensor veli palatini* tenectomy.[15]

■ Pathophysiology

Horses that have other abnormalities of the palate or larynx, such as epiglottal entrapment, pharyngeal paralysis, and palatal cysts, are predisposed to DDSP. If no such abnormalities are present, the etiology of the disorder is currently unknown despite research efforts to improve understanding of the condition, with the ultimate goal of developing more effective treatments.[15-20] Current theories include neuromuscular dysfunction of the intrinsic soft palate muscles,[20-22] variations in the anatomic positioning of the laryngohyoid apparatus and the role of the thyrohyoid muscles in laryngeal "elevation,"[19,23,24] and the role of the distal hypoglossal nerve in maintaining nasopharyngeal stability.[25] Epiglottic hypoplasia or flaccidity was previously thought to be associated with intermittent DDSP. However, clinical and experimental data show that the epiglottis is not required to maintain the palate in a normal position and that the majority of horses that experience DDSP during treadmill endoscopy have an epiglottic length that is within normal limits.

■ Clinical Signs

Most horses with DDSP make a rough "snoring" or "gurgling" noise at exercise and may either pull up abruptly or slow down significantly after the palate has displaced. DDSP results in a flow-limiting expiratory obstruction, leading to decreased airflow, increased tracheal expiratory pressure and impedance, reduced minute ventilation and subsequent hypoxia, hypercapnia, and impaired athletic performance.[17,26,27] Conversely, once the soft palate has displaced, minimal obstruction is observed during inspiration as the upper airway inspiratory pressure maintains the soft palate in close apposition to the dorsal aspect of the epiglottis. During expiration, because a proportion of the exhaled air is directed ventral to the displaced palate and into the oral cavity, some horses are reported to exhibit "fluttering" of the cheeks during exhalation. Palatal

instability has also been shown to have a negative effect on ventilatory parameters if moderate to severe.[28] Low-frequency fluttering of the caudal border of the palate is believed to be the source of the loud expiratory and inspiratory “gurgle” or “snore” reported in 70% to 80% of affected horses[29]; however, up to 30% of horses can experience DDSP yet make no audible abnormal respiratory noise (“silent displacers”).[30-32]

■ Diagnosis

An accurate history that includes details of reduced exercise performance and of abnormal noise production, including the type of noise made and the stage of exercise when it occurred, can be very helpful. A thorough resting endoscopic examination of the nasopharynx should be performed to rule out other causes of palatal dysfunction such as pharyngeal or palatal cysts, epiglottic entrapment, or pharyngeal paralysis. The lower portion of the respiratory tract should also be examined for evidence of lower airway disease. DDSP and PI are dynamic conditions, and findings of resting endoscopy have been shown to correlate poorly with dynamic endoscopic findings.[12,31,32] Horses that displace their soft palates at rest are often normal during exercising endoscopy, and conversely many horses that are normal during resting endoscopic examination can develop DDSP at exercise.[12,32] One study reported that use of a characteristic history of gurgling and poor racing performance plus findings of resting endoscopy alone resulted in a 35% misdiagnosis rate of palatal dysfunction, as compared to findings of treadmill endoscopy.[32]

Exercising endoscopic examination, either on a high-speed treadmill with a standard videoendoscope or during ridden or driven exercise using a portable telemetric endoscopic system, is the gold standard for diagnosis of DDSP and PI.[3,6-8,12,31-34] Clinically normal horses may transiently displace their soft palates during exercise and particularly when pulling up. However, a normal horse typically swallows and replaces the palate to its normal subepiglottic position within a few strides, whereas DDSP is typically diagnosed if the palate remains dorsal to the epiglottis for a longer period of time (several seconds) or if DDSP occurs repeatedly.

Sound analysis has also been used as a research tool for diagnosis of DDSP,[30] but it has not been reported in significant numbers of clinical cases and its accuracy is therefore unknown. A significant relationship has been reported between the depth of the basihyoid bone measured using percutaneous

ultrasonography at the caudal aspect of the lingual process at rest and the occurrence of DDSP at exercise.[35] A more ventrally located basihyoid at rest was associated with an increased probability of DDSP occurring during treadmill endoscopy. This test had a high negative predictive value (89%) but a low positive predictive value (36%),[35] meaning that DDSP could be ruled out with reasonable certainty but that care should be taken when making a positive diagnosis of DDSP using this method.

■ Treatment

Many treatments are available for horses with DDSP, and this probably reflects both the unknown etiology of the disorder and the fact that most treatments have a similar success rate. Concurrent respiratory disorders, including upper or lower airway inflammation or infections, should be addressed fully, prior to resorting to surgical remedies, and if the horse has only just been brought into work, improving its fitness can resolve palatal issues. The use of systemic corticosteroids, NSAIDs, and topical antiinflammatory nasopharyngeal ("throat") sprays has been advocated to try to reduce upper airway inflammation.[2,31] One study showed that in young 2- and 3-year-old Thoroughbred racehorses, 56% of horses with DDSP were reported to show spontaneous resolution of the disorder within 3 months of their initial exercising endoscopic diagnosis, without receiving any specific treatment.[35] Spontaneous resolution was less common in older racehorses, with only 12% no longer experiencing DDSP on repeat overground endoscopic exam.[36] Tack changes, including use of a tongue tie,[36,37] dropped or crossed noseband,[36-39] and "W" or "Serena Song" bits, have also been reported anecdotally to be of benefit in affected racehorses. The laryngohyoid support device ("Cornell collar") has been advocated as a nonsurgical "tie-forward" procedure for horses with DDSP and was effective in 100% (7 of 7) of horses with experimentally induced DDSP.[40] In horses with naturally occurring DDSP, the Cornell collar was reported to be effective in around 60% of horses by one study.[36]

Surgical treatments for DDSP are numerous and include insertion of a thyrohyoid prosthesis (the laryngeal "tie-forward" procedure), staphylectomy, myectomy of the sternothyrohyoideus muscles, epiglottic augmentation with Teflon™, tension palatoplasty, thermocautery of the oral surface of the palate, laser cautery of the nasopharyngeal surface of the palate, in addition to multiple combinations of these procedures. A systematic review of treatments for palatal

dysfunction in the horse[41] concluded that “the low level of evidence makes it difficult to draw firm conclusions as to the efficacy of procedures used to treat DDSP.” The use of combinations of surgeries usually represents a “belt and braces” approach but arguably may provide a multimodal approach to a disorder with a multifactorial etiology. However, the use of multiple treatments in scientific studies also means that we are often left unsure as to which of the reported treatments, if any, may have had a beneficial effect.[41]

Failure of surgical remedies for DDSP is not uncommon. As a surgical principle, it is unwise to repeat a surgical procedure that the animal did not respond to the first time, unless the surgical procedure can be documented to have been performed suboptimally or has technically failed (i.e., broken or loose tie-forward suture).[42] Furthermore, the morbidity associated with certain procedures such as staphylectomy makes their repetition risky.[42] Few studies have analyzed the effects of surgery for DDSP using the “gold standard” of postoperative exercising endoscopy. A study that performed overground exercising endoscopy on 20 racehorses after laryngeal tie-forward showed that the surgery eliminated DDSP in 65% of horses but that 70% still exhibited a degree of palatal instability.[43] However, this study population was biased toward horses that had a suspected problem after the tie-forward (60% of cases presented had trainer-reported ongoing respiratory noise and/or poor performance).[43] Causes of failure of laryngeal tie-forward include not having a definitive diagnosis of the palatal issue preoperatively, migration of the larynx caudally after surgery, and suture pull-through or failure.

Persistent Dorsal Displacement of the Soft Palate

Persistent DDSP, where the soft palate is permanently positioned dorsal to the epiglottic cartilage, is rare compared to intermittent DDSP. It is observed in the resting horse and is often secondary to underlying structural abnormalities such as subepiglottic cysts, epiglottitis, epiglottic entrapment, intrapalatal cysts, pharyngeal paralysis, pharyngeal neoplasia, or pharyngeal foreign bodies,[13,41] but it can also be idiopathic. Persistent DDSP is seen most commonly after surgery to release epiglottal entrapment[44-46] if a large fold of the subepiglottic mucosa is resected but has also been reported after many other types of laryngeal surgery, including laryngoplasty and ventriculocordectomy.[47] Horses affected

with persistent DDSP make a loud gurgling noise at exercise, have poor exercise tolerance, and can be dysphagic, often coughing when eating.[44,47]

■ Diagnosis

Diagnosis is easily made by endoscopic examination of the nasopharynx in the resting horse where the epiglottis is never visible because the soft palate lies dorsal to it. Horses should be prompted to swallow several times during the examination to see if any transient relocation of the palate occurs. Ulceration of the caudal border of the soft palate can sometimes be observed. Observation of persistent DDSP with the endoscope passed per nasum, is an indication to perform endoscopy of the oropharynx (with a full dental speculum in place) to examine the epiglottis and associated structures for abnormalities. If 60-cm broncho-oesophageal forceps are available, the larynx and caudal soft palate can be desensitized by application of topical local anesthetic and the forceps then used to manipulate the palate to a subepiglottic position and to elevate the epiglottis to examine its ventral aspect (Fig. 31.46).

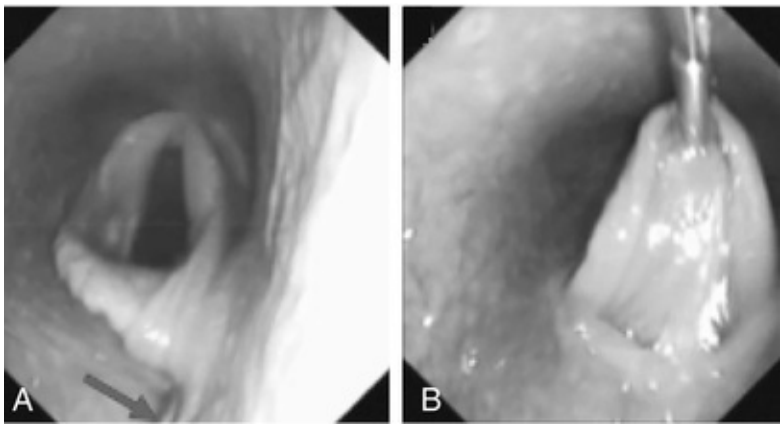


FIG. 31.46 Case of persistent dorsal displacement of the soft palate (at rest). **A,** A 60-cm broncho-oesophageal forceps *(arrow)* is used to manipulate the soft palate ventral to the epiglottis (topical local anesthetic has been applied). **B,** The forceps is then used to elevate the epiglottis and view the ventral surface.

■ Treatment

In most cases, persistent DDSP is secondary to some other disorder, and treatment should therefore be directed at the initiating cause. If no primary

disorder is found, the tie-forward procedure (laryngohyoid prosthesis) has been reported to be effective in alleviating idiopathic persistent DDSP in 7 of 15 affected horses.[44] In the same case series, the remaining 8 of 15 horses additionally required laser staphylectomy after the tie-forward procedure to resolve persistent DDSP.[44] A subepiglottic “releasing” incision, which may include a hyoepiglottic myotomy, has also been described for treatment of cases where it was felt that the epiglottis could not be manually repositioned dorsal to the palate due to subepiglottic adhesions.[47]

Congenital Palatal Defects

Congenital defects of the palate (cleft palate or palatal hypoplasia) are rare in horses, having a reported prevalence of 0.01% to 0.02%.[2] True cleft palates arise from incomplete embryologic closure of the palatal folds, but often there is a tissue deficit that should correctly be called palatal hypoplasia. Tissue defects or clefts may involve only the caudal aspect of the soft palate (Fig. 31.47) or both the hard and the soft palates. Affected foals should be examined carefully for other congenital defects such as cardiac, GI, and nasal septum abnormalities.

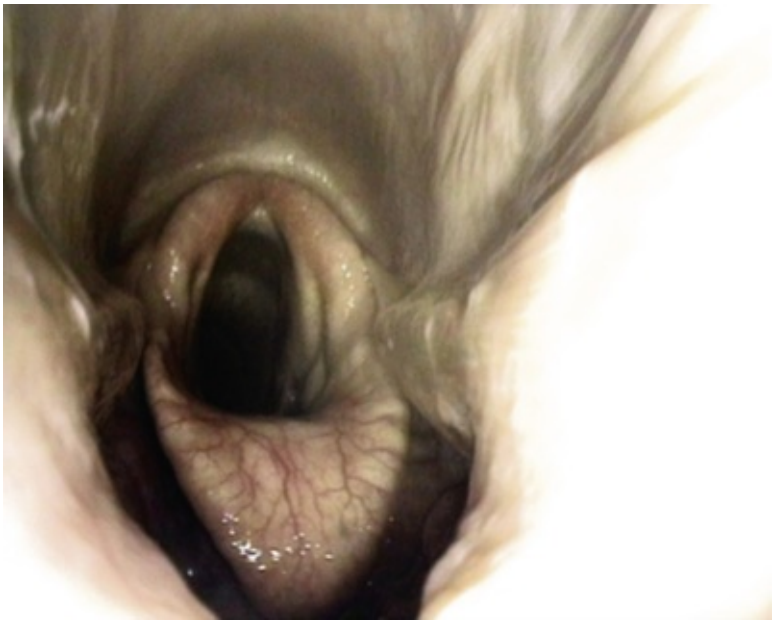


FIG. 31.47 Congenital midline defect (“cleft”) of the soft palate.

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■ Clinical Signs and Differential Diagnosis

Clinical signs of cleft palate include nasal regurgitation of milk (in foals) or other feed material in older horses, coughing, poor growth, and signs indicative of aspiration pneumonia such as cough during eating and persistent nasal discharge.[48-52] If the defect is small, abnormal respiratory noise due to PI or DDSP may be the only presenting sign, or the foal or horse may be asymptomatic. Endoscopic examination of the nasopharynx (using a small-diameter endoscope) reveals an abnormal outline to the caudal soft palate and food material within the nasopharynx, larynx, and trachea. The defect can be characterized by a midline cleft where there is an almost normal amount of tissue but failure of fusion of the left and right sides, a unilateral (Fig. 31.48) or bilateral soft palate hypoplasia. Defects of both the hard and the soft palates are less common (7% to 18%[48,52]), and these animals are usually presented as foals,[48] probably due to the increased severity of clinical signs. Differential diagnoses for dysphagia with aspiration of food material in foals includes subepiglottic cysts, pharyngeal paralysis or dysfunction (which can be transient in neonatal foals,[53] particularly if premature or dysmature), and in older horses, oesophageal obstruction (choke), guttural pouch mycosis, severe arytenoid chondritis, complications of laryngeal surgery (e.g., laryngoplasty or arytenoidectomy), and large pharyngeal cysts or pharyngeal or laryngeal foreign bodies or neoplasms.

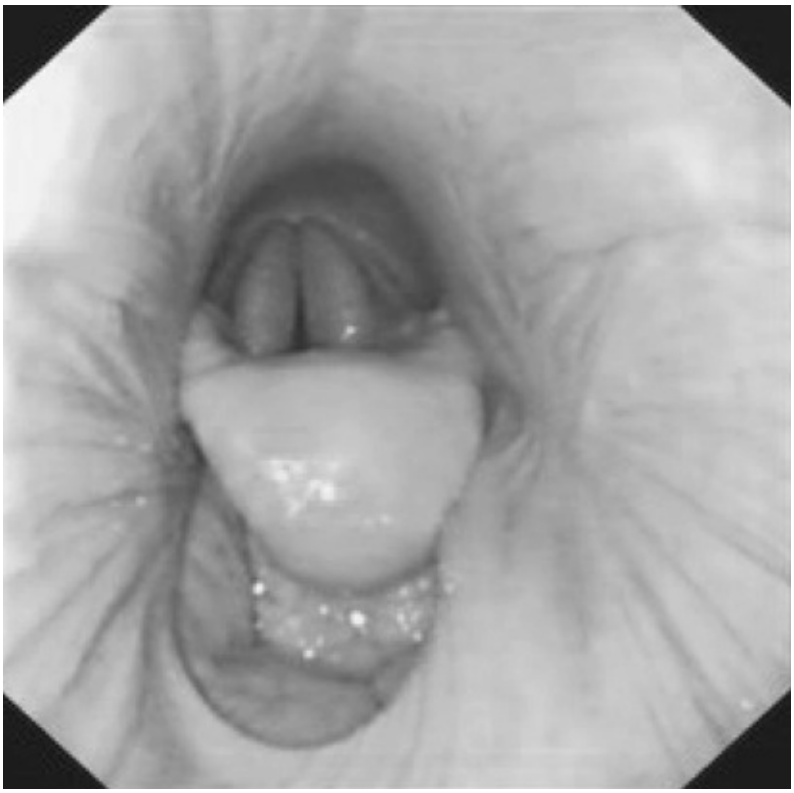


FIG. 31.48 Unilateral right-sided hypoplasia of the caudal soft palate.

■ Treatment

If signs associated with the palatal defect are confined to noise during exercise, occasional coughing after eating and/or nasal discharge (i.e., there are no or minimal systemic signs), affected foals can survive to adulthood and may be capable of ridden work if left untreated or treated symptomatically.[48,51,52] Surgical repair is possible for foals with less than 20% to 30% of the palatal tissue missing, but this is generally a salvage procedure only, and only a few go on to perform athletically to a high level when older, even if surgery is successful.[2,52] Surgical repair of soft palate defects is extremely challenging and has a high prevalence of complications and failure. Therefore if signs of severe aspiration pneumonia or a large palatal defect are present, euthanasia of affected foals should be considered as an alternative. Surgical approaches to the soft palate include transoral, pharyngotomy, laryngotomy, and mandibular syphysiotomy, and laryngeal tie-forward has been described to close small palatal defects.[49,50-52]

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Palatal Cysts

These rare lesions usually occur in young horses and may be a cause of abnormal respiratory noise and airway obstruction if they become large or if they disrupt the normal palate-epiglottic relationship. Palatal cysts probably form as the result of the obstruction of mucus-secreting glands within the soft palate, or they may have a traumatic aetiology.[54] The presence of palatal cysts predisposes horses to DDSP.

■ Clinical Signs and Diagnosis

Clinical signs include respiratory noise (at rest or during exercise), coughing, exercise intolerance, nasal discharge, dysphagia, and signs of aspiration pneumonia. Diagnosis is made by endoscopic examination of the nasopharynx where a raised intrapalatal mass can be seen. Oral endoscopy (as described above) may also be of value. Obtaining an “open-mouthed” straight lateral radiograph (with the incisors held apart with a gag) will cause the soft palate to move dorsally away from the tongue and allows focal thickening of the palate to be visualized more easily than on a standard closed-mouth lateral view. Differential diagnoses include palatal neoplasia and intrapalatal abscesses, the latter being usually associated with intrapalatal foreign bodies or strangles infection. Transendoscopically guided aspiration of the cyst should yield clear, viscous fluid.

■ Treatment

Treatment involves surgical excision or laser ablation of the cystic structure, if it is large enough to cause abnormal respiratory noise or airway obstruction. If the cyst is simply drained and some of the lining is left in situ, it is likely to recur.

Neoplasia

Neoplasms of the soft palate are rare. Lymphosarcoma and squamous cell carcinoma occur most frequently, and lesions may vary markedly in appearance. Surgical excision of pharyngeal neoplasms is rarely successful because total excision with wide margins is almost impossible to achieve. Radiotherapy may provide an alternative for treatment of pharyngeal neoplasms but is not widely available for horses.

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Disorders of the Trachea

Safia Z. Barakzai • Padraic Martin Dixon

Anatomy of the Trachea

The equine trachea extends from the caudal larynx to the carina where it divides into the two mainstem bronchi at the level of the fifth to sixth intercostal spaces and is about 75 to 80 cm long in a 500-kg horse.[55] The trachea occupies a midline position in the neck and also in the rostral thorax, where it lies in a fold of mediastinum, but at its termination it becomes slightly displaced to the right by the adjacent aortic arch.[56] It is composed of 48 to 60 individual tracheal rings of hyaline cartilage, which are incomplete dorsally.[55] In the cervical trachea, the free ends of the tracheal rings usually overlap, but in the thoracic trachea, the free ends rarely meet.[56] Each individual tracheal ring is 10 to 12 mm wide, being 2 to 3 mm thick dorsally and 5 to 7 mm thick ventrally. The dorsal tracheal ligament completes the dorsal aspect of the tracheal lumen, attaching to the inner surface of the tracheal rings. The cartilage rings vary a little in shape in the normal horse; the first few rings are slightly dorsoventrally flattened but more distally the rings become more circular in shape. Finally, at the level of the aortic arch, the rings can become slightly laterally flattened, particularly on the left side.[55] The tracheal ligament contains the transversely oriented trachealis muscle, and this elastic structure allows the trachea to expand slightly during times of increased respiratory effort.

Each tracheal ring is covered by and connected to adjacent rings by an intimately attached fibroelastic ligament called the annular ligament. This arrangement of semirigid cartilaginous rings and elastic annular ligaments, along with the loose attachment of the tracheal adventitia to other tissues, allows much flexibility of the trachea during head and neck movement while retaining its rigid cross-sectional shape. The cricotracheal ligament, which attaches the first tracheal ring to the cricoid cartilage, is of similar structure to the annular ligaments but is wider (craniocaudally) and under less tension.

Running bilaterally along the dorsolateral aspects of the trachea are many vital structures, including the carotid artery, vagus and recurrent laryngeal nerves, sympathetic truck, tracheal lymph ducts, and cervical lymph nodes. The trachea

is lined by a pale mucosa, containing numerous mucus and serous glands, and may contain fine longitudinal folds. Ciliated epithelial cells are the predominant cell type,[57] with each cell containing about 200 cilia that beat 15 to 20 times per second. These cilia transport mucus from the lungs proximally to the nasopharynx. In the equine trachea, mucus is transported at a velocity of 13 to 20 mm/min.[57] The "sump-like" depression in the rostral thoracic trachea is a common place for excessive respiratory secretions to accumulate in horses.[58]

Primary tracheal disorders are relatively uncommon in horses, but abnormal pooling of respiratory secretions in the "sump" of the trachea is often seen as a consequence of lower airway inflammation or exercise-induced pulmonary haemorrhage.[59] Primary lung disorders are not discussed further in this section.

Cricotracheal Ligament Prolapse

A limited number of clinical reports describe this disorder in Thoroughbred racehorses during fast exercise.[60-63] The cricotracheal membrane is normally longer (rostrocaudally) and under less tension than the tracheal annular ligaments. It is suggested that an abnormally long and/or slack cricotracheal ligament may prolapse dorsally, ventrally, or circumferentially into the airway lumen as a result of the very negative inspiratory airway pressures that are generated during fast exercise. One case series reported that cricotracheal ligament collapse can reduce the cross-sectional area of the tracheal lumen by 36% to 52%.[63] Concurrent upper and lower airway disorders may increase the severity of cricotracheal ligament prolapse by further increasing the negative pressure generated within the upper respiratory tract.

■ Clinical Signs and Diagnoses

Clinical signs include abnormal respiratory noise during exercise and reduced exercise performance[61-63] due to the dorsally displaced ligament causing turbulent and restricted airflow. Differential diagnoses must include all forms of dynamic upper airway collapse, in particular those that are associated with inspiratory noise, including recurrent laryngeal neuropathy, medial deviation of the aryepiglottic folds, vocal fold collapse, ventromedial luxation of the apex of the corniculate cartilages, epiglottic retroversion, and nasopharyngeal collapse. Diagnosis requires exercising endoscopy, either overground[63] or on a high-speed treadmill, with a specific effort made to examine the caudal laryngeal area by

having the endoscope tip positioned caudally and a good light source. In most reports of this disorder, multiple concurrent dynamic upper airway abnormalities are present.[62-63] Presumably, cricotracheal collapse is exacerbated with head and neck flexion, as this position will reduce tension on the cricotracheal ligament; however, this has not been discussed in any of the case reports to date. Palpation of the ventral aspect of the cricotracheal ligament in the resting horse can subjectively reveal flaccidity, and much of the overlying tracheal lumen can be occluded with digital pressure. Ultrasonography of the ventral aspect of the cricotracheal ligament with the horse's head extended may be useful to measure the length and thickness of the ligament, but the range of these ultrasonographic measurements in normal horses has not yet been reported.

■ Treatment

Conservative management of cricotracheal ligament collapse (7 days of oral phenylbutazone therapy) is reported to be successful in young (~2 years old) Thoroughbred racehorses that had other concurrent dynamic abnormalities noted on exercising endoscopy at the time of diagnosis.[63] Horses in which cricotracheal ligament collapse spontaneously resolved had evidence of nasopharyngeal inflammation (grade 3 pharyngeal lymphoid hyperplasia) at the time of initial diagnosis. This inflammation decreased or resolved at the time of follow-up exercising endoscopy, when the cricotracheal ligament collapse was noted to have resolved.[63]

For persistent cases, treatment is via imbrication of the ventral aspect of this ligament after closing the space between the cricoid cartilage and the first tracheal ring.[61,63] The dorsal half of the ligament cannot be accessed without risk of damaging the recurrent laryngeal nerves; however, Pollock and colleagues[63] report that imbrication of the ventral aspect only appeared to prevent prolapse in two mature horses.

Tracheal Collapse

Tracheal collapse is commonly recorded in many breeds of toy dogs[64-66] and can also occur in goats,[67] sheep, and cattle (P.M. Dixon, personal observations). In Equidae, this developmental disorder is often reported in small ponies and miniature horses[68-73] but also occurs in larger breeds of ponies[74] and donkeys.[71,75] In many small ponies, the disorder remains undiagnosed due to

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their low workload. There is a high prevalence of tracheal deformities in donkeys; in one postmortem study, 68.8% of tracheal rings did not have an oval or circular shape. Affected donkeys are usually asymptomatic unless severe tracheal deformity or intercurrent pulmonary disorders, such as advanced pulmonary fibrosis, are present.[75]

■ Pathophysiology

Tracheal collapse is usually caused by a cartilage ring deformity, including where the normal rounded or oval tracheal ring is replaced classically by a flatter tracheal ring with a greatly reduced dorsoventral diameter (Fig. 31.49). In some cases, a slack and enlongated dorsal tracheal ligament can exacerbate the dynamic tracheal collapse.[68,69,74] A more recent study also showed that most cases of tracheal collapse in donkeys were caused by grossly misshapen tracheal cartilages,[75] and perhaps a term other than *tracheal collapse* should now be used.

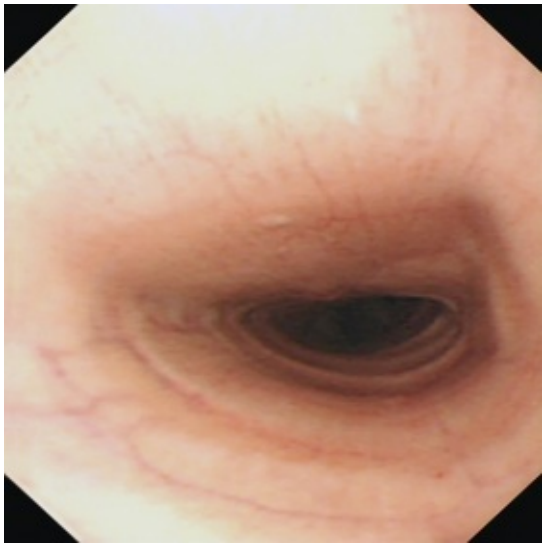


FIG. 31.49 Endoscopic view of a dorsoventrally collapsed trachea.

Many ponies and donkeys with tracheal collapse will have some dorsoventrally flattened tracheal rings (especially in their lower cervical trachea) but will also have other types of ring deformities (Fig. 31.50) at more caudal thoracic sites.[71,75] In other cases with relatively normal-shaped tracheal rings, there appears to be separation of the dorsal ligament from the dorsal aspect of

the tracheal rings (Fig. 31.51). This defect usually involves the mid and distal cervical as well the intrathoracic trachea and may occasionally involve the mainstem bronchi. Some affected equids may also have a degree of tracheal rotation, with the dorsal aspect of trachea facing dorsolaterally (authors' personal observations).



FIG. 31.50 Severe structural abnormality of an equid trachea.

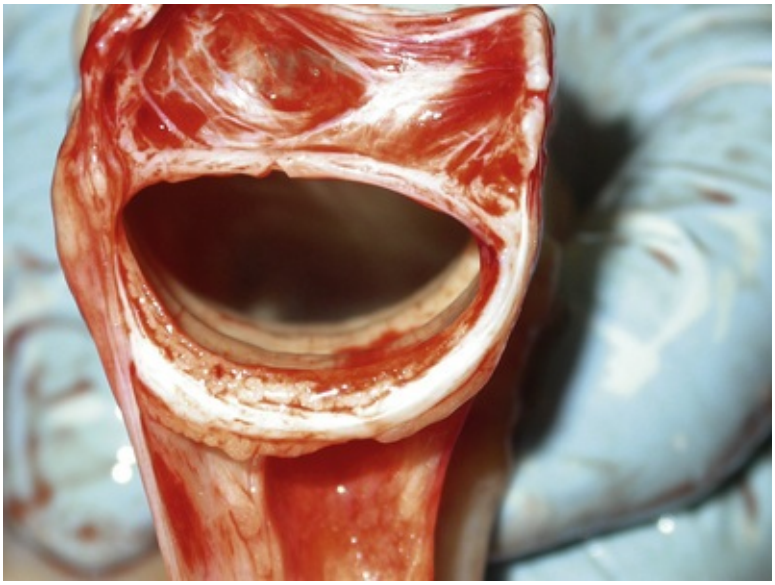


FIG. 31.51 This tracheal ring is a normal C shape, but the dorsal tracheal ligament has separated from the dorsomedial aspect of the tracheal rings.

Most ponies and miniature horses develop clinical signs of tracheal collapse in middle age,[73,75] thus indicating that some degenerative process of the tracheal cartilage or connective tissue also plays a role in the pathogenesis of this disorder. In one case series of 13 American Miniature Horses, all 4 horses that had tracheal histopathology performed on them had chondromalacia, which varied from mild multifocal hyalinization of the extracellular matrix to marked multifocal coalescing areas of chondromalacia characterized by complete degradation of the cartilaginous matrix and loss of chondrocytes.[73] The presence of chronic respiratory disease that may cause tracheal mucosal thickening and also increase intrapleural pressure swings, and neuromuscular problems causing loss of tone of the trachealis muscle have also been implicated in the pathogenesis of this disorder in donkeys.[75]

Temporary Tracheal Collapse

Horses with severe expiratory dyspnea due to pulmonary disease have increased positive intrathoracic pressure during expiration, which can cause a temporary collapse of the intrathoracic trachea, particularly of its dorsal ligament. Such temporary and often near-total tracheal collapse can also be observed transiently in all horses if they cough during bronchoscopy.

■ Clinical Signs

The typical clinical signs in affected equids are dyspnea and stridor, which commonly occur in hot or humid weather and may regress in autumn. Aleman and colleagues[73] report that clinical signs were initially intermittent and often associated with stressful events, exercise, dusty environment, and eating, but that all owners reported increasing severity of clinical signs with age. Stridor may be very loud, with Delahanty and Georgi[68] reporting a pony that made sounds like a truck horn that could be heard more than 800 m away. The stridor is loudest when auscultated directly over areas of tracheal obstruction. Severe dyspnea may occur even at rest because hyperventilation will exacerbate the partial tracheal obstruction in a self-perpetuating cycle. Affected horses can also exhibit tachycardia (60 to 130 bpm) and hyperthermia (38.2º to 40.0º C).[73]

Exercise-induced pulmonary hemorrhage may occur in severe cases, presumably because of increasingly negative intrathoracic pressures. Coughing may also occur, and it is unclear if this is due to tracheal inflammation caused by abnormal contact of dorsal and ventral tracheal mucosa or due to underlying

pulmonary disease that may have precipitated the clinical tracheal problem.

■ Diagnosis

Palpation of a collapsed cervical trachea may reveal sharp lateral protrusion of the deformed cartilage rings. However, palpation of the lateral edges of the flattened trachea can be difficult, as the deeper, distal cervical trachea is most commonly affected. In addition, some small ponies such as Shetlands have very thick skin and much subcutaneous fat, which makes tracheal palpation difficult.[54]

Endoscopy of affected cases will show the normal circular or oval appearance of the tracheal lumen to be replaced by a wider, flatter, or otherwise restricted lumen. In addition, excessive dynamic movement of the dorsal tracheal wall and even airway occlusion may be observed during deep breathing, with inspiratory narrowing of the cervical tracheal lumen and expiratory narrowing of the intrathoracic tracheal lumen. The mucosa may be red and inflamed.

Lateral radiographs of the distal cervical and thoracic trachea may be diagnostic, demonstrating the flattened appearance of the trachea,[69,73] but must be taken during inspiration for the cervical trachea and during expiration for the intrathoracic trachea. Radiography can be misleading in cases where tracheal rotation is present along with collapse, where the affected trachea may actually appear wider than normal on lateral radiographs.

■ Treatment and Prognosis

Treatment of such cases should initially be conservative, by restricting exercise, keeping affected cases indoors in cool boxes with an adequate water supply in hot weather, and treating any concurrent pulmonary disease. Acutely affected horses will benefit from intranasal oxygen therapy that reduces hyperventilation and thus decreases the degree of tracheal collapse. Tracheostomy usually does not provide relief because it does not bypass the affected region (usually distal cervical and intrathoracic trachea). Therefore insertion of an endotracheal tube via the tracheotomy to keep the collapsed trachea patent is usually necessary to provide a temporary functional airway in severely affected animals. Hyperthermia, if present, increases the metabolic rate and thus increases the respiratory demand further, causing a vicious cycle of events. Cooling down such ponies with a cold-water hose can be beneficial. Parenteral corticosteroids are also indicated in severely affected cases to reduce the secondary tracheal

mucosal inflammation or edema that is likely to be present. The long-term prognosis for severely affected miniature horses appears to be poor, with 10 of 13 horses in the largest case series to date either dying of this disorder or requiring euthanasia.[73]

Surgical correction of affected cartilaginous cervical tracheal rings (as is commonly performed in miniature dogs), such as placing external stents over deformed tracheal rings[70,76,77] or inserting stainless steel sutures into every third tracheal ring along with imbrication of the slack dorsal membrane,[68] has been performed in horses and ponies with varying success. The use of a metallic intraluminal stent has also been reported to have been successful in one miniature horse, but intratracheal granulation tissue formation and lower airway infection was associated with the stented area.[72] In some ponies, surgically altering the shape of the tracheal rings may not be successful because separation of the dorsal ligaments from the cartilage rings is the primary problem. In addition, careful evaluation will usually reveal involvement of the intrathoracic trachea, and because only 3 to 4 intrathoracic rings can be exteriorized cranially to the distal cervical area for surgical correction, this type of surgery may be of limited benefit to the horse. Although intrathoracic surgery to correct more caudal tracheal deformities is technically feasible, it is not practical.

Other Congenital Defects of the Trachea

Congenital defects of the trachea, other than tracheal collapse, are rare in horses, with only a few other types of deformities recorded, including a few reports of accessory or ectopic pulmonary tissue, including by Davis and colleagues,[78] who recorded an accessory cervical tracheal bronchus in a 3-day-old foal. The foal presented with a large, air-filled sac in its cervical region caused by rudimentary accessory lung that contained cartilaginous tissue and ciliated epithelium. Peek and colleagues[79] reported a combined tracheal and esophageal duplication cyst in a 4-month-old Arabian foal with a slowly developing cervical swelling that was successfully resected.

External Tracheal Trauma.

Tracheal trauma is usually caused by blunt trauma, such as kicks to the neck region that can cause severe tracheal damage, particularly if the trachea is compressed between a hoof and the overlying cervical vertebral body. Tracheal trauma can cause tearing of the mucosa (Fig. 31.52) and of the overlying annular

ligaments, and fracture of tracheal rings. Penetrating tracheal injuries occur less commonly.



FIG. 31.52 Tracheal trauma: oval-shaped tear in the tracheal mucosa showing separation of the underlying tissues.

■ Clinical Signs and Diagnosis

A common presenting sign in horses with tracheal rupture is extensive subcutaneous emphysema and swelling over the cranioventral aspect of the neck.[80-82] External skin wounds are not always present. The emphysema may later spread to involve the head, trunk, mediastinum, and even limbs. Horses will later become stiff and possibly febrile from secondary infection, and epistaxis and coughing may occur.[81] In addition to possibly having a ruptured trachea, horses with emphysematous cervical swellings should always be suspected of suffering from a ruptured esophagus[83] (authors' personal observations). Because the esophagus may lie lateral to the trachea at around the level of the sixth cervical vertebra in some horses, it is prone to trauma at this site.[54]

Cervical radiography of horses with tracheal or esophageal rupture will show extensive gas infiltration along the fascial planes of the neck, in addition to variable soft tissue or fluid-filled swellings of the cranial and ventral neck regions. Thoracic radiography may also reveal pneumomediastinum and possibly pneumothorax. Endoscopy (tracheoscopy) will confirm if tracheal

trauma has occurred, by evidence of mucosal tears, prolapse of submucosal tissue into tracheal lumen, distortion or partial occlusion of the lumen due to cartilage ring fractures, and/or local inflammation.[81,82] Esophageal endoscopy to examine the integrity of the esophagus should also be performed with the greatest of care in horses with neck swelling and emphysema.

■ Treatment and Prognosis

If the esophagus is ruptured, the prognosis is poor, as compared to tracheal rupture, where the prognosis is usually good. Small tears of the tracheal mucosa will usually heal spontaneously. In addition to tetanus prophylaxis, NSAIDs should be administered to such cases to decrease the traumatic inflammation, along with broad-spectrum antibiotics to reduce the potential spread of pathogenic bacteria with entrapped air along the fascial planes of the neck and into the mediastinum. The emphysema present in such cases will usually resolve in 1 to 2 weeks but may remain for up to a month in some horses.[81] Large rents in the tracheal mucosa with extensive herniation of soft tissue into the tracheal lumen can be sutured as described by Fubini and colleagues.[82] Structural damage to the tracheal rings has been corrected using an extraluminal titanium mesh.[76]

Fractures of the cartilaginous tracheal rings with gross distortion of the trachea may also occur, and it may be difficult to evaluate the degree of cartilage ring damage in the presence of severe local inflammation and emphysema. If available, CT or MRI of such lesions is the optimal method of assessing cartilage damage. If life-threatening tracheal obstruction occurs, a temporary tracheostomy may be performed with insertion of an uncuffed endotracheal tube through the tracheostomy to open up the collapsed section of trachea if the obstruction is distal to the mid-cervical region.

Intraluminal granulation tissue and subsequent development of circumferential fibrotic bands of tissue can be long-term sequelae of tracheal trauma. Occasionally such rings of tissue may eventually (months later) reduce the tracheal lumen to a significant extent, leading to respiratory obstruction with stridor. Transendoscopic laser resection of the protruding stricture can be attempted, but the site should be monitored postoperatively for recurrence of the lesion. The use of topical corticosteroid after laser surgery may be of use in preventing recurrence of strictures. Complete resection of the affected cervical tracheal rings (up to four rings maximum) with end-to-end tracheal anastomosis

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can also be attempted,[84] but such procedures can be very challenging. If the stricture is in the cranial cervical trachea, a permanent tracheostomy can be placed at a more distal site for horses that are not required for competition.

Intraluminal Tracheal Trauma

There have been several reports of intraluminal tracheal damage associated with the use of endotracheal tubes for maintaining general anesthesia, including inflammation,[85] focal perforation,[86] and severe ischemia of the tracheal mucosa if excessive cuff pressure is applied.[87] An experimental study showed that histologic evidence of tissue damage was present in all horses at the site of cuff contact with the trachea, at pressures that are commonly used in clinical practice (up to 120 cm H_2O).[87] The use of ethylene oxide for sterilizing endotracheal tubes between patients may also pose a risk, as this chemical can be retained in rubber and plastic and can result in tissue necrosis if tissue comes into contact with the sterilized item.[88]

Recommendations for tracheal intubation in horses include flushing the horse's mouth before anesthesia, using a clean endotracheal tube, gentle intubation technique, minimal head and neck movement after the tube cuff is inflated, and disconnection of the endotracheal tube from the anesthesia machine while moving the horse.[88] Measurement of cuff pressure should also be performed to identify excessive inflation.[88]

Focal Intraluminal Tracheal Lesions Including Neoplasia

Apart from granuloma formation post tracheostomy (Fig. 31.53) or after tracheal trauma, focal intraluminal tracheal lesions are rare in horses (although many horses and especially ponies have multiple small cartilaginous nodules that are of no clinical significance). Charlton and Tulleners[89] reported infected or necrotic mid-cervical tracheal proliferative lesions in two adult horses following intratracheal antibiotic administration in one and following a transtracheal aspiration in the other. The masses were resected using a transendoscopic laser in one horse and a combination of transendoscopic laser and conventional surgery in the other.

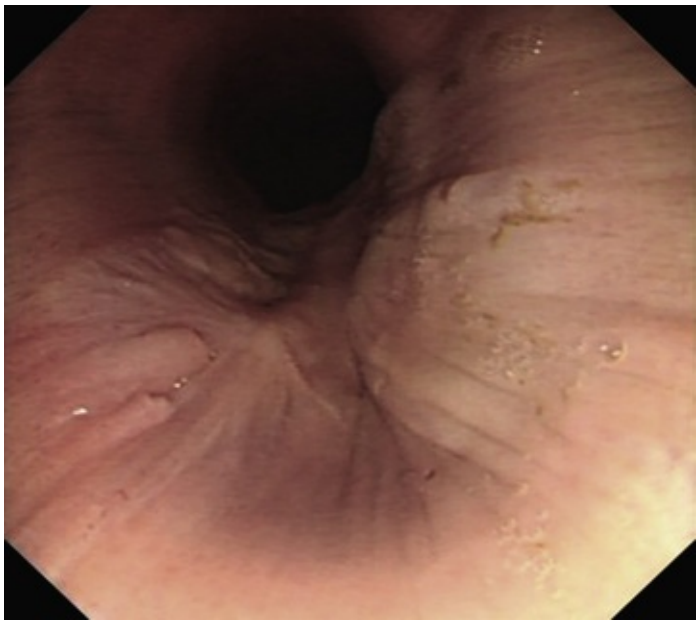


FIG. 31.53 Intraluminal scar tissue formation and cartilage deformity after tracheostomy tube removal.

Malignant tracheal tumours are rare in horses, but squamous cell carcinomas have been reported in the trachea of aged horses.[90] Benign lesions including papillomas, fibromas, eosinophilic polyps, chondromas, and adenomas are more common[91,92] and often can be successfully resected using a distal cervical tracheostomy and/or a transendoscopic laser excision. Transnasal retrieval of excised masses is usually possible using a transendoscopic grasping or "basket"-type forceps.

Extramural Tracheal Compression

Occasionally, enlarged lymph nodes compress the trachea, causing stridor. Severe lymphadenopathy is usually associated with *S. equi* subsp. *equi* ("strangles") infection[93] and may involve the upper cervical chain, compressing the proximal cervical trachea. They can also involve the distal cervical chain that compresses the trachea at the thoracic inlet.[54,93-95] Diagnosis usually can be made from the history and clinical signs, which are indicative of strangles, and confirmation can be made by needle aspiration and/or ultrasonography of cervical swellings. Treatment of strangles is reviewed in the *Streptococcus equi* subsp. *equi* Infection (Strangles) section earlier in this chapter.

Mediastinal tumours, mainly lymphosarcomas; other cranial thoracic tumours, including primary lung tumours; or grossly abscessed mediastinal lymph nodes

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can cause compression of the intrathoracic trachea or of one or both mainstem bronchi, leading to stridor and dyspnea. Such an endoscopic finding should lead to a careful thoracic examination, including radiography and ultrasonography. Thoracic tumours are usually untreatable in the horse.

Tracheobronchial Foreign Bodies

Inhaled foreign bodies are common in man and dogs but less common in horses, possibly due to their height. O'Connor[96] described a range of laryngeal and tracheal foreign bodies in horses and stated that a fatal bronchopneumonia could develop if the foreign body was not expelled by coughing. Inhaled foreign bodies seldom bypass the larynx, but if they do, they will usually become entrapped at the carina or in the mainstem bronchi,[97-100] predominantly in the right mainstem bronchus.[76]

A history of sudden onset of persistent coughing is a very prominent finding in these cases, and malodorous breath will often be present. Other signs of pulmonary disease, such as increased respiratory rate or the presence of abnormal lung sounds, are usually absent, at least initially, unless secondary lung infection occurs. If significant pulmonary infection develops, abnormal lung sounds and possibly purulent or blood-tinged nasal discharge may occur. No or only a temporary response (decreased coughing and nasal discharge) may occur following antibiotic therapy. Radiography may show a localized interstitial pattern caudal to the vena cava.[99]

Endoscopically, local airway inflammation and purulent respiratory secretions may obscure a foreign body. Even small foreign bodies may significantly obstruct airflow if they become lodged in a bronchus, and the induced local bronchial inflammation may also obstruct normal drainage of respiratory secretions from the affected bronchus, inducing severe, focal pulmonary infection. Transendoscopic lavage of the area may help determine if a bronchial foreign body or tumour is present. When identified, bronchial foreign bodies may be removed using transendoscopic grasping or basket forceps. Cranially facing leaves, branches, or thorns will make the recovery of such vegetation difficult, but with persistence, most bronchial foreign bodies will eventually become loose and retrievable. If this is unsuccessful, a distal cervical tracheostomy can be performed, and long, rigid, grasping instrumentation (such as broncho-oesophageal grasping forceps) can be used under endoscopic guidance to grasp and retrieve the foreign body.[98,99]

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Epiglottic Entrapment

Santiago D. Gutierrez-Nibeyro

■ Definition and Etiology

Epiglottic entrapment, persistent or intermittent, refers to the dorsal displacement of the aryepiglottic folds and subepiglottic mucosa over the epiglottis. The aryepiglottic folds attach to the free margins of the epiglottis and blend with both the dorsal epiglottic and the subepiglottic mucosa. Normally the subepiglottic mucosa is loosely attached to the epiglottis to allow movement of the cartilage during swallowing. The etiology of the disease is unknown, but inflammation of the subepiglottic mucosa and submucosa, redundant subepiglottic mucosa, and epiglottic hypoplasia or flaccidity have been reported as predisposing factors.[1-4] Epiglottic entrapment has a reported prevalence of 8% to 27% in Thoroughbred and Standardbred racehorses,[5-8] although it has been reported in nonracing Thoroughbreds and other breeds.[9] Epiglottic entrapment is often an incidental finding in weanlings and yearlings.[10]

■ Clinical Signs and Differential Diagnoses

Clinical signs are variable and depend on the severity of the entrapment and the presence of other diseases of the upper respiratory tract. Some racehorses can be asymptomatic and compete successfully with an entrapped epiglottis.[8,11] However, affected horses most commonly have a variable degree of abnormal respiratory noise and/or exercise intolerance due to partial airflow obstruction.[1,2,12] Clinical signs may also include coughing and nasal discharge.[9,13] Severe inflammation and ulceration of the entrapping tissue can exacerbate airway obstruction and noise production; rarely it may also cause dysphagia.[1,12] Potential endoscopic differential diagnoses include subepiglottic cysts, epiglottitis, epiglottic granulomas, and dorsal displacement of the soft palate.[5,13,14]

■ Definitive Diagnostic Tests

Endoscopic examination of the nasopharynx with the horse at rest is frequently diagnostic. Typically the scalloped edge of the epiglottis and the vessels on its surface are not evident on endoscopy because they are obscured by the

entrapping aryepiglottic fold (Fig. 31.54). Most epiglottic entrapments are persistent and thick, and approximately half of them are ulcerated.[2,12] If the epiglottis is not entrapped during the initial endoscopic evaluation but intermittent entrapment is suspected, overground endoscopy or endoscopy during a high-speed treadmill test is necessary for definitive diagnosis.[5,8]



FIG. 31.54 Endoscopic image of the nasopharynx of a 3-year-old Standardbred racehorse with a history of increased respiratory noise and chronic epiglottic entrapment. The entrapping membrane was thick, wide, and mildly ulcerated, and the epiglottis had moderate hypoplasia once the entrapment was corrected surgically. As in this case, most epiglottic entrapments are persistent and thick, and approximately half are ulcerated.

Although radiography is not used to diagnose the disease, an epiglottic entrapment can be detected using this diagnostic technique.[4] Epiglottic hypoplasia can be determined with both subjective endoscopic evaluation and radiographic measurement of the epiglottic length (determined by thyroepiglottic length).[4,15]

■ Treatment and Prognosis

Intermittent epiglottic entrapment may be treated conservatively with topical and systemic anti-iflammatory therapy and exercise restriction. Persistent epiglottic entrapment is typically treated surgically.[2,12] Surgical techniques to correct epiglottic entrapment include transendoscopic axial division using a Nd:YAG or diode laser,[2] transnasal or transoral axial division using a curved bistoury,[1,12,16-18] transnasal axial division using a shielded curved bistoury,[19] transendoscopic axial division using monopolar electrocautery,[20] transoral wire-snare resection of redundant subepiglottic mucosa,[21] and surgical excision via a laryngotomy.[3] Currently axial division of the entrapping aryepiglottic folds and subepiglottic mucosa is the preferred technique because the tissues are simply transected avoiding “debulking” of the epiglottis and excessive scarring postoperatively, which can cause dorsal displacement of the soft palate.[22] Resection of the entrapping tissues through a ventral laryngotomy is typically reserved for excessively thickened, ulcerated, or fibrotic-appearing entrapping membrane.[3] Postoperative care consists of topical and systemic antiinflammatory therapy and exercise restriction.

The prognosis is generally good; however, postoperative complications include recurrence of the entrapment, intermittent or persistent dorsal displacement of the soft palate, and epiglottis deformity.[2,12,17,23] The recurrence rate after surgical correction of an entrapped epiglottis using laser axial division is 5%[2]; it is between 0% and 15% using a curved bistoury[12,16,18,19] and as high as 40% using electrosurgical division.[20]

Pharyngeal Cysts in Horses

Santiago D. Gutierrez-Nibeyro

■ Definition and Etiology

Pharyngeal cysts are uncommon in the horse[1-3]; however, they are occasionally diagnosed in young Thoroughbreds, Standardbreds, and Quarter Horses.[4-8] Pharyngeal cysts occur most commonly in the subepiglottic region (Fig. 31.55) and occasionally in the soft palate (see the Congenital Palatal Defects section earlier in this chapter) or dorsal wall of the nasopharynx (Fig. 31.56).[4,6,8] Some authors believe that subepiglottic cysts are embryonic remnants of the thyroglossal duct (precursor of the thyroid gland), but others believe that these

cysts are secondary to inflammation and obstruction of the mucus-secreting glands that line the pharynx.[5] Cysts formed within the dorsal nasopharyngeal wall are thought to be embryonic remnants of the craniopharyngeal duct (precursor of the adenohypophysis).[4] The origin of soft palate cysts has not been elucidated; however, histopathologic examination of these cysts is consistent with a mucocele.[6]

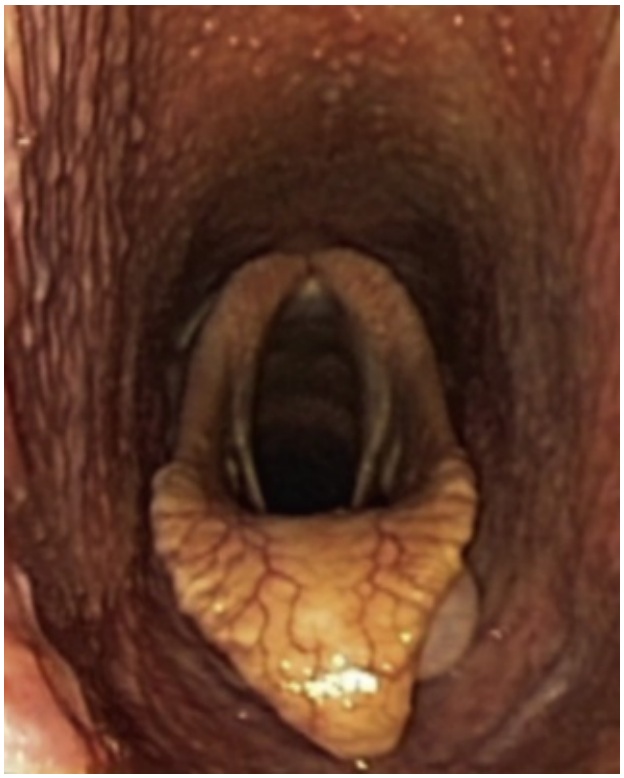


FIG. 31.55 Endoscopic image of the nasopharynx of a 2-year-old Standardbred horse with a small, smooth, and rounded subepiglottic cyst. The horse had a history of abnormal respiratory noise during training.



FIG. 31.56 Endoscopic image of the nasopharynx from a 1-week-old foal with a large cyst attached to the dorsal wall of the pharynx and a nasogastric tube in place. The cyst was resected with a cyst snare under endoscopic control.

■ Clinical Signs

In foals subepiglottic cysts are frequently asymptomatic,[3] but many cause increased respiratory noise, cough, nasal discharge, persistent dorsal displacement of the soft palate, dysphagia, and aspiration pneumonia.[5,6] The most common presentation in the adult performance horse is partial obstruction of the upper respiratory tract, abnormal respiratory noise, exercise intolerance, coughing, dysphagia, and in rare cases, complete obstruction of the upper respiratory tract.[4,7-9]

■ Clinical Pathology

CBC and biochemistry profiles are typically within normal limits unless concurrent inflammatory airway disease, pneumonia, or acute upper respiratory tract obstruction exists.

■ Definitive Diagnostic Tests

Endoscopic examination of the nasopharynx confirms the diagnosis and may

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also detect concomitant pathology such as epiglottic entrapment.[4,5,8] Occasionally a lateral radiographic view of the pharynx or transoral endoscopic examination of the oropharynx with the patient anesthetized is needed if the cyst is within the soft palate or beneath the epiglottis protruding into the oropharynx. Although contrast pharyngography has been described to help delineate cysts in the oropharynx,[6] in the authors' opinion the use of contrast is unnecessary if digital radiography is available. The use of ultrasound has been described to delineate the cyst from the adjacent structures before surgery, if necessary.[10]

■ Treatment and Prognosis

Pharyngeal cysts can be surgically removed, ensuring complete removal of the secretory lining without excessive excision of surrounding pharyngeal mucosa in the case of a subepiglottic cyst, which may lead to cicatrization and epiglottic dysfunction.[8] Subepiglottic cysts can be removed by a ventral laryngotomy,[4] via an oral or transnasal approach using an endoscopically guided laser, electrocautery snare, or cyst snare constructed with obstetric wire loop threaded through a Chambers catheter.[8,9] More recently, intralesional administration of 10% formalin has been reported, which provides an economically suitable alternative to surgical treatment[11]; however, multiple treatments may be required for complete resolution of the cyst.[11] Postoperative care consists of topical and systemic antiinflammatory therapy and exercise restriction. The prognosis following removal of subepiglottic cysts is good, and most horses return to full athletic function.[4,8] Less information is available regarding the prognosis after removal of other pharyngeal cysts.

Nasopharyngeal Cicatrix Syndrome

Ben Buchanan

The nasopharyngeal cicatrix syndrome is an inflammatory condition that was first described in 1987 in horses from south Texas[1] and continues to be a common finding of horses grazing pastures in certain areas of Texas. It is also sporadically reported in other U.S. Gulf Coast states. The syndrome is a combination of inflammation and scarring of the nasal passage, pharynx, larynx, arytenoid cartilages, and proximal trachea. Severity ranges from incidental findings during endoscopy to airway obstruction that requires permanent tracheostomy.[2,3]

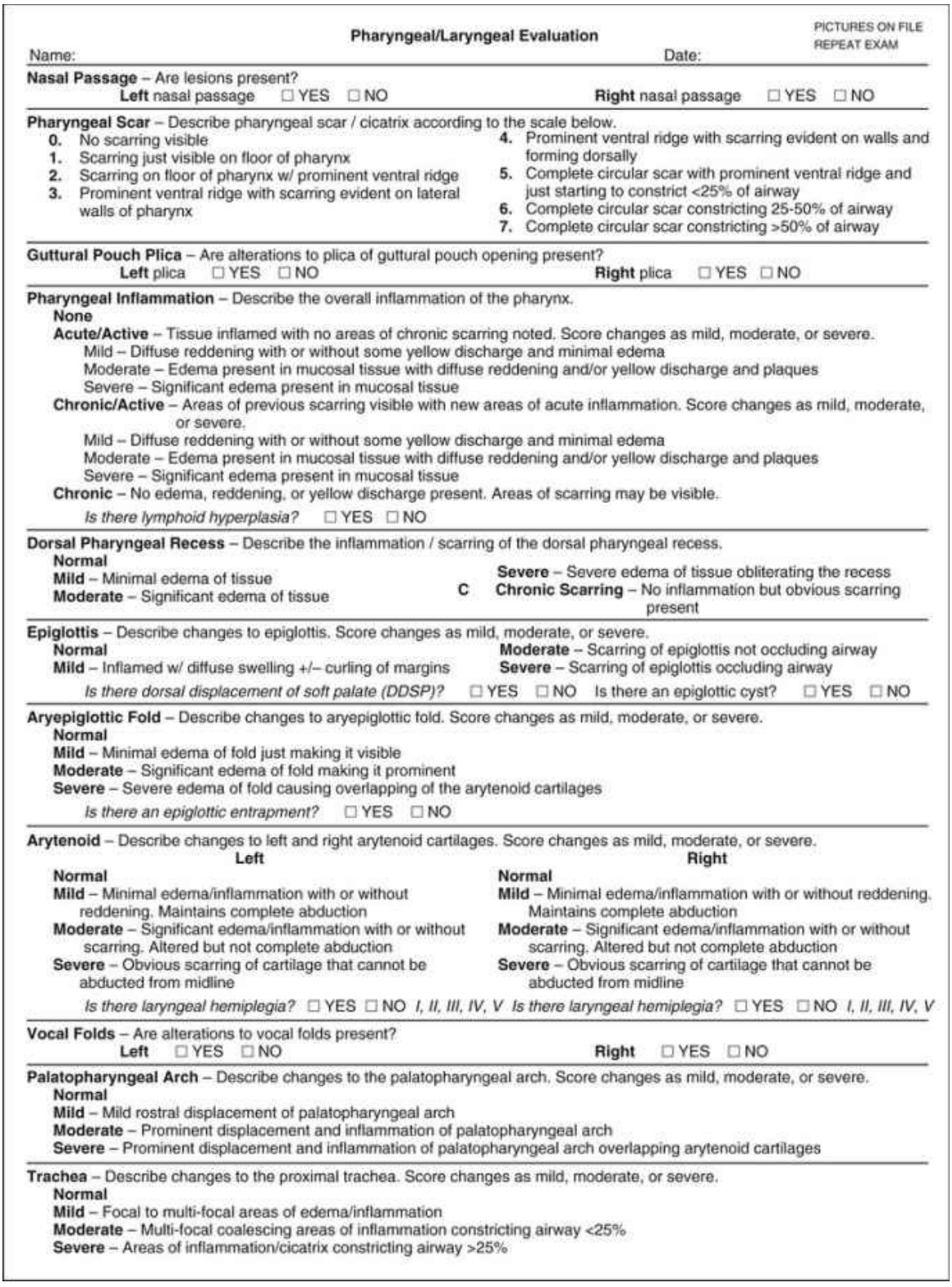
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■ Clinical Signs

Clinical signs include abnormal respiratory noise, nasal discharge, exercise intolerance, coughing, respiratory distress, and abnormal vocalization.[4] The character of the nasal discharge is frequently clear and mild. When compared with a case-controlled population in a retrospective study, affected horses made up 118 of 1236 horses examined endoscopically for any reason.[4] Of these affected horses, 97% had some degree of pharyngeal inflammation or scarring, of which 50% had a circumferential scar. In addition, 91% of affected horses had some inflammation or scarring of the larynx, and 39% had an airway obstruction, with the majority being at the level of the larynx. In this same study, horses with endoscopic evidence of acute nasopharyngeal cicatrix syndrome were more likely to have nasal discharge and respiratory distress, whereas horses with endoscopic evidence of chronic nasopharyngeal cicatrix syndrome were more likely to make respiratory noise or suffer from respiratory distress.

■ Endoscopic Signs

A scoring system used by the author is presented in Fig. 31.57 and builds on a system previously proposed by Rakestraw.[5] This system was developed to provide practitioners with a concise, simple, and complete system to document any abnormality of the upper respiratory tract seen on standing endoscopy.



Pharyngeal/Laryngeal Evaluation

PICTURES ON FILE
REPEAT EXAM

Name: Date:

Nasal Passage – Are lesions present?
Left nasal passage ☐ YES ☐ NO **Right** nasal passage ☐ YES ☐ NO

Pharyngeal Scar – Describe pharyngeal scar / cicatrix according to the scale below.
0. No scarring visible
1. Scarring just visible on floor of pharynx
2. Scarring on floor of pharynx w/ prominent ventral ridge
3. Prominent ventral ridge with scarring evident on lateral walls of pharynx
4. Prominent ventral ridge with scarring evident on walls and forming dorsally
5. Complete circular scar with prominent ventral ridge and just starting to constrict <25% of airway
6. Complete circular scar constricting 25-50% of airway
7. Complete circular scar constricting >50% of airway

Guttural Pouch Plica – Are alterations to plica of guttural pouch opening present?
Left plica ☐ YES ☐ NO **Right** plica ☐ YES ☐ NO

Pharyngeal Inflammation – Describe the overall inflammation of the pharynx.
None
Acute/Active – Tissue inflamed with no areas of chronic scarring noted. Score changes as mild, moderate, or severe.
Mild – Diffuse reddening with or without some yellow discharge and minimal edema
Moderate – Edema present in mucosal tissue with diffuse reddening and/or yellow discharge and plaques
Severe – Significant edema present in mucosal tissue
Chronic/Active – Areas of previous scarring visible with new areas of acute inflammation. Score changes as mild, moderate, or severe.
Mild – Diffuse reddening with or without some yellow discharge and minimal edema
Moderate – Edema present in mucosal tissue with diffuse reddening and/or yellow discharge and plaques
Severe – Significant edema present in mucosal tissue
Chronic – No edema, reddening, or yellow discharge present. Areas of scarring may be visible.
Is there lymphoid hyperplasia? ☐ YES ☐ NO

Dorsal Pharyngeal Recess – Describe the inflammation / scarring of the dorsal pharyngeal recess.
Normal
Mild – Minimal edema of tissue
Moderate – Significant edema of tissue
Severe – Severe edema of tissue obliterating the recess
Chronic Scarring – No inflammation but obvious scarring present

Epiglottis – Describe changes to epiglottis. Score changes as mild, moderate, or severe.
Normal
Mild – Inflamed w/ diffuse swelling +/– curling of margins
Moderate – Scarring of epiglottis not occluding airway
Severe – Scarring of epiglottis occluding airway
Is there dorsal displacement of soft palate (DDSP)? ☐ YES ☐ NO Is there an epiglottic cyst? ☐ YES ☐ NO

Aryepiglottic Fold – Describe changes to aryepiglottic fold. Score changes as mild, moderate, or severe.
Normal
Mild – Minimal edema of fold just making it visible
Moderate – Significant edema of fold making it prominent
Severe – Severe edema of fold causing overlapping of the arytenoid cartilages
Is there an epiglottic entrapment? ☐ YES ☐ NO

Arytenoid – Describe changes to left and right arytenoid cartilages. Score changes as mild, moderate, or severe.

Left	**Right**
Normal	**Normal**
Mild – Minimal edema/inflammation with or without reddening. Maintains complete abduction	**Mild** – Minimal edema/inflammation with or without reddening. Maintains complete abduction
Moderate – Significant edema/inflammation with or without scarring. Altered but not complete abduction	**Moderate** – Significant edema/inflammation with or without scarring. Altered but not complete abduction
Severe – Obvious scarring of cartilage that cannot be abducted from midline	**Severe** – Obvious scarring of cartilage that cannot be abducted from midline
Is there laryngeal hemiplegia? ☐ YES ☐ NO *I, II, III, IV, V*	*Is there laryngeal hemiplegia?* ☐ YES ☐ NO *I, II, III, IV, V*

Vocal Folds – Are alterations to vocal folds present?
Left ☐ YES ☐ NO **Right** ☐ YES ☐ NO

Palatopharyngeal Arch – Describe changes to the palatopharyngeal arch. Score changes as mild, moderate, or severe.
Normal
Mild – Mild rostral displacement of palatopharyngeal arch
Moderate – Prominent displacement and inflammation of palatopharyngeal arch
Severe – Prominent displacement and inflammation of palatopharyngeal arch overlapping arytenoid cartilages

Trachea – Describe changes to the proximal trachea. Score changes as mild, moderate, or severe.
Normal
Mild – Focal to multi-focal areas of edema/inflammation
Moderate – Multi-focal coalescing areas of inflammation constricting airway <25%
Severe – Areas of inflammation/cicatrix constricting airway >25%

FIG. 31.57 Pharyngeal/laryngeal scoring system.

Nasal Passage.

Both nasal passages should be examined. Lesions in the nasal passage appear as ulcerations and occur in less than 10% of cases.[4]

Pharyngeal Scar.

Schumacher and Hanselka first proposed a scoring system for this syndrome that focused on the pharyngeal scar.[1] This system has been adapted into a 7-point scale, with 0 indicating no visible scarring. A score of 1 indicates a scar just forming on the ventral floor. A score of 2 indicates a consistent ventral scar. A score of 3 indicates a prominent ventral ridge with scarring just evident on the lateral walls of the pharynx. A score of 4 indicates a ventral scar with evidence of a dorsal scar just forming. A score of 5 indicates a complete ring with less than 25% reduction in the size of the airway. A score of 7 indicates a severe case with a complete ring that has reduced the airway more than 75% (Fig. 31.58).

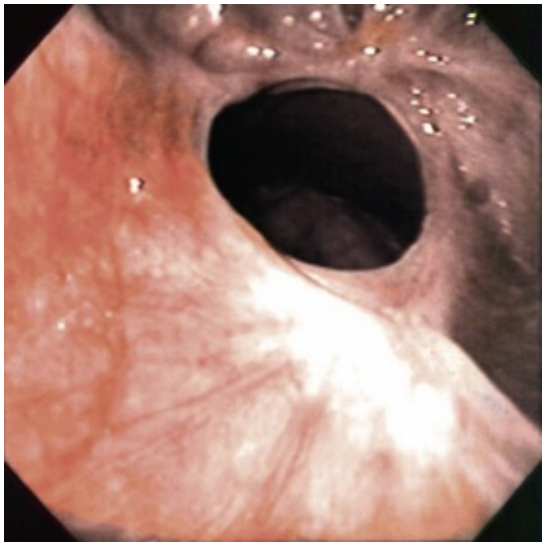


FIG. 31.58 Endoscopic image of nasopharyngeal cicatrix. This is an example of a grade 7 cicatrix.

Guttural Pouch Plica.

Occasionally, scarring of the external guttural pouch plica is observed as a deformity to the guttural pouch openings.

Pharyngeal Inflammation.

The overall appearance of the pharyngeal walls should be graded with attention to degree of redness, edema, and chronic scarring. Acute/active is indicated by erythematous edematous tissue with or without discharge and no areas of scarring noted (Fig. 31.59). The level of inflammation should be graded as mild, moderate, or severe. Chronic/active is similar, with areas of active inflammation mixed with areas of previous scarring (Fig. 31.60). The degree of inflammation should be graded as mild, moderate, or acute. A chronic description is indicated when there are areas of scarring with no active inflammation (Fig. 31.61). Any level of pharyngeal lymphoid hyperplasia should be noted.



FIG. 31.59 Endoscopic image of acute pharyngeal inflammation and swelling consistent with nasopharyngeal cicatrix syndrome.

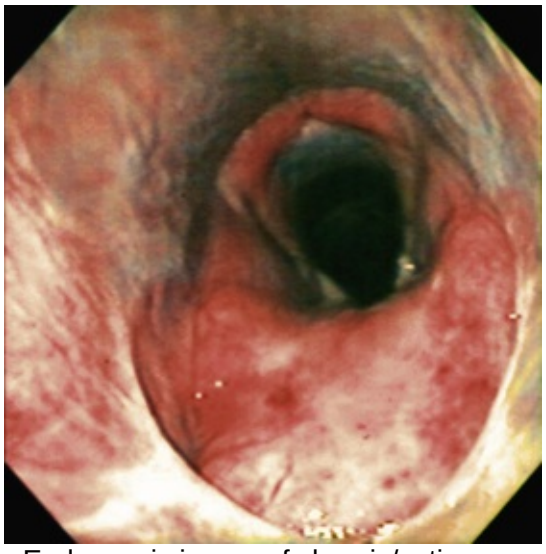


FIG. 31.60 Endoscopic image of chronic/active nasopharyngeal syndrome. There is both inflammation and swelling with a grade 3 cicatrix.

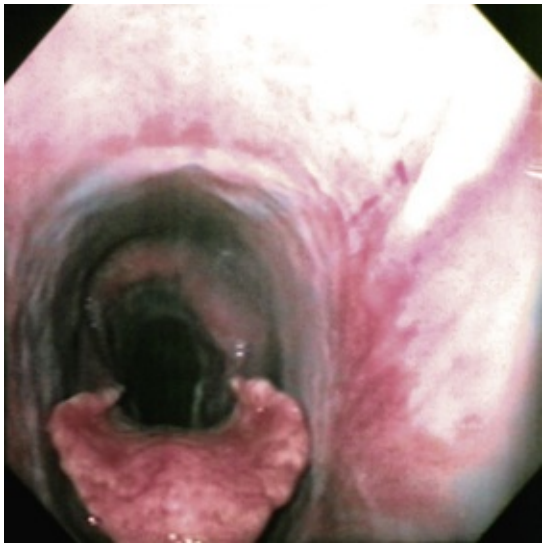


FIG. 31.61 Endoscopic image of chronic nasopharyngeal syndrome. There is scarring of the epiglottis and left arytenoid cartilage and a grade 3 cicatrix.

Dorsal Pharyngeal Recess.

The dorsal pharyngeal recess should be examined for inflammation and areas of previous scarring. Occasionally this area is the only area of inflammation noted in the pharynx. The recess should be graded as mild, moderate, severe, or

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chronic.

Epiglottis.

The epiglottis should be examined for swelling, scarring, displacement, occlusion of the airway, and cysts. Mild changes of the epiglottis include diffuse swelling with some curling of the margins. Moderate changes, although more severe, do not occlude the airway. Severe changes are noted as scarring of the epiglottis with occlusion of the airway. Any displacement of the soft palate or epiglottic cysts should be recorded.

Aryepiglottic Fold.

The aryepiglottic fold should be examined for edema and entrapment of the epiglottis. The abnormalities should be described as mild, moderate, or severe. Mild abnormalities are noted as minimal edema just making the fold visible. Severe changes are noted as significant edema causing the fold to overlap the arytenoid cartilages.

Arytenoids.

The left and right arytenoid cartilages should be evaluated for swelling, reddening, scarring, and abnormalities of abduction. Each cartilage is graded separately as having mild, moderate, or severe changes. Mild changes are noted as minimal edema or inflammation with or without reddening of the cartilage, with complete abduction. Moderate changes are noted as significant edema or inflammation with or without scarring, causing altered abduction of the cartilages. Severe changes are noted as obvious scarring of the cartilage that cannot be abducted from midline. Any laryngeal hemiplegia should be recorded.

Vocal Folds.

The vocal folds should be evaluated for edema and scarring. Changes in this area are common and should be recorded as present or absent.

Palatopharyngeal Arch.

The palatopharyngeal arch should be examined for edema and rostral displacement. The abnormalities should be described as mild, moderate, or severe. Mild abnormalities are noted as minimal edema causing minimal displacement. Moderate changes are noted as significant edema causing a prominent rostral displacement. Severe changes are noted as significant edema

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causing overlap of the palatopharyngeal arch over the apex of the arytenoids. Rostral displacement of the palatopharyngeal arch was noted in 36% of cases.[4]

Trachea.

The proximal trachea should be evaluated for areas of edema, inflammation, and scarring, as lesions in the proximal 6 to 10 rings of the trachea are common. Changes in this area should be graded as mild, moderate, or severe. A mild change involves multifocal areas of inflammation not reducing the size of the airway. A moderate change involves areas of inflammation causing a reduction in the airway of less than 25%. A severe change causes airway reduction greater than 25%. Abnormalities in the trachea have been reported in 75% of cases.[4]

■ Progression

This syndrome is rarely seen in horses younger than 4 years of age, and the length of time for an acute case to develop respiratory distress is unknown. In the author's experience the most severe cases occur in older horses.

■ Pathogenesis

To date no specific etiology has been identified, although some risk factor analysis has been completed. A retrospective case-control study of 121 horses[2] with nasopharyngeal cicatrix syndrome found a high association with housing on pasture or part time on pasture and with increased age. Cases of nasopharyngeal cicatrix syndrome were more likely to be presented in the summer months, with acute cases also being seen in the spring and fall. No breed or sex risk factor was noted. Cases seem to be more prevalent in years with higher rainfalls, although a few new cases may be seen during times of drought.

Inhalation of larger sized particulate matter (>5 microns) is suspected to be the inciting cause, as these particulates are deposited in the nasal mucosa, pharynx, larynx, and proximal trachea. This corresponds to the anatomic areas where the inflammation and subsequent scarring are noted. Whether these particulates include bacteria, fungus, allergen, or some other irritant is not known. There is some discussion of the oomycete *Pythium insidiosum* as a possible cause, although in the author's experience this is not likely a primary pathogen in these cases.

■ Treatment

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Because the agent or combination of agents causing this syndrome has not been identified, a single effective therapy has not been found. In addition, identification of effective treatments is complicated by the chronicity of the syndrome when it is typically first identified, the cyclical or seasonal nature of the clinical signs, and the response to changes in environmental factors. Current therapy consists of reducing exposure to pasture and reducing inflammation. No treatment has been effective if the horse remains on pasture. Surgical resection of affected areas frequently leads to excessive granulation tissue, especially after arytenoidectomy. If the airway is compromised, a permanent tracheostomy is the therapy of choice. If surgical reduction of the affected tissue is elected and the horse is not moved to a new environment, the lesions will recur.

■ Outcome

In acute cases, simply removing the horse from pasture and feeding in a dry lot or stall resolves most of the condition. It is believed that repeat or continual exposure of acute cases leads to the chronic scarring. Once the chronic scarring has developed, it will not resolve.

Equine Influenza in Australia*

Brett Tennent-Brown • Andrew W. Van Eps

Until 2007, Australia was one of a small number of countries that had never experienced an outbreak of equine influenza (EI). EI has never been reported in New Zealand. However, in August 2007 a consignment of horses, all of which had been vaccinated in accordance with Australian quarantine requirements, was admitted into the quarantine station in Sydney. At least one of these horses was subclinically infected with EI, and the virus subsequently spread among horses within the quarantine station. Following a break in biosecurity, EI virus escaped and spread rapidly through the naive horse population, affecting more than 76,000 animals on 10,600 premises in New South Wales and Queensland. Control of the outbreak and eradication of the virus from Australia cost an estimated US$1 billion.

As soon as EI had been confirmed in the general horse population, a control and eradication program based on movement restrictions and subsequently vaccination was initiated. Although only two states were affected, a complete national ban on all horse movements was put in place immediately, and all race meetings and other horse events were cancelled. Horses already at events were

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not permitted to leave until cleared by government veterinarians. Movement restrictions were highly effective in preventing the spread of virus beyond those areas affected in the first week of the outbreak but were extremely damaging financially to horse-related businesses. To alleviate some of the economic hardship, especially among the breeding industry, some movement restrictions were eased to allow the breeding season to proceed.

At the time of the outbreak in August 2007, there were no EI vaccines registered for use in the Australian general horse population. When additional measures were required to contain the outbreak, an emergency-use permit was issued for a canarypox-vectored recombinant EI vaccine (ProteqFlu, ProteqFlu-TE [Merial, Lyon, France]). This vaccine was selected for several reasons, including rapid onset of immunity,[1] the ability to differentiate vaccinated horses from those naturally infected, and reports of efficacy in the South African 2003–2004 outbreak.[2] Vaccination was initially used to create buffer zones around infected areas to contain spread of the epidemic. Horses inside the infected areas on unaffected properties were subsequently also vaccinated. Most horses received a primary course booster at the recommended interval of 4 weeks; however, some horses received an accelerated primary course schedule with the interdose interval reduced to 14 days.[3,4]

The last reported detection of EI occurred approximately 4 months after the outbreak began. Provisional freedom from disease was declared in March 2008, and EI-free status was confirmed by the World Organisation for Animal Health (OIE) the following year.

The EI virus isolated from horses in the quarantine station and horses in the general population was named A/equine/Sydney/2888-8/2007 (H3N8).[5] Following molecular characterization, the virus was classified as an American lineage, Florida sublineage, Clade 1 type[6] and is phylogenetically similar to the EI viruses that were circulating in Japan and the United States at the time.[7]

Clinical disease caused by the EI virus in adult horses was considered mild in the vast majority of cases; however, secondary bacterial bronchopneumonia was described as a complication and occasional cause of death in predominantly mature horses.[8] Infection of late-gestation mares was associated with increased severity of clinical signs in the infected mare and neonatal morbidity.[8,9] A fatal bronchointerstitial pneumonia associated with EI virus infection was reported in several foals from infected properties.[10]

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Hendra Virus

Brett Tennent-Brown • Andrew W. Van Eps • Gabrielle Landolt

Hendra virus (HeV) was first identified in September 1994 following the deaths of 14 Thoroughbred horses and 1 human during an outbreak of respiratory disease at racing stables located in Hendra, Queensland, Australia.[1] Severe, acute respiratory disease due to HeV occurred sporadically over the subsequent 14 years; however, neurologic signs have predominated in cases since 2008. In 2011 there was a marked increase in HeV incidence, and disease occurred over a wider geographic area than previously reported. At the time of writing, infection has been confirmed in more than 100 horses, 7 humans (with 4 human fatalities), and at least 1 dog (seroconversion without clinical signs) in the states of Queensland and New South Wales.

■ Etiology and Epidemiology

HeV and the closely related Nipah virus together form the genus *Henipavirus* in the family Paramyxoviridae. *Henipavirus* infection is dependent on the G and F viral glycoproteins. The G glycoprotein is a receptor binding protein that binds ephrin-B2 and ephrin-B3, whereas the F protein mediates fusion of the viral and host cell membranes.[2] Ephrin-B2 and ephrin-B3 are widespread on host's vascular endothelial cells, and as a consequence, HeV infection results in a vasculitis that particularly affects the respiratory and central nervous systems.[3,4]

HeV causes natural disease in horses and humans,[1] and disease has been experimentally induced in cats, guinea pigs, and mice.[5] The natural reservoirs for HeV are four species of pteropid bats (fruit bats or flying foxes) that are widely distributed throughout northern and eastern Australian.[6] HeV infection of bats is asymptomatic and apparently widespread; serologic surveys indicate a high prevalence of HeV antibodies in bats, including those in areas where equine or human disease has not been documented.[7] Following experimental infection of bats, virus can be detected in blood, saliva, urine, feces, placental tissues, and aborted pups.[8] Transmission between bats is thought to occur by exposure of naive animals to virus-contaminated urine or feces within the roost.[9]

Most equine cases have occurred between June and December, although the reason for this apparent seasonality is unclear. On many occasions the index case has been a horse that is kept outdoors in an area attractive to fruit bats. The mechanism of virus transmission to horses is not completely understood but

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likely follows ingestion of contaminated feed or water.[10] Horse-to-horse transmission requires close contact with body fluids (particularly respiratory secretions) and appears to occur infrequently in horses kept at pasture but more efficiently in stabled horses.[9]

HeV poses a serious zoonotic risk to animal caretakers and attending veterinarians. All reported human HeV infections have been linked to close contact with infected horses, and direct bat-to-human or human-to-human transmission has not been reported.[1,11,12] Although the risk of viral transmission appears to increase as the disease progresses, virus is shed at low levels prior to the appearance of clinical signs in experimental infections. Horse-to-human transmission is thought to require direct physical contact with nasopharyngeal secretions[13]; however, the virus can survive for several hours in the environment, and transmission by fomites might be possible. The risk of human infection is particularly high in the terminal stages of disease, and postmortem examinations should be postponed in suspect cases until HeV infection has been ruled out by appropriate testing.

■ Clinical Signs

The incubation period in experimentally infected horses ranges between 5 and 16 days and in humans appears to be between 5 and 21 days.[13-15] Prior to 2008, signs of acute severe respiratory disease predominated in equine HeV infections. However, since 2008, neurologic signs have been described more commonly and might be the result of a minor genetic change to the virus. Approximately 75% of cases are fatal, and these typically progress rapidly. although recently several HeV-positive horses have been described with a more gradual disease progression. Sudden death of one or more horses without obvious signs of illness should raise suspicion of HeV infection. Clinical signs in animals that survive beyond the peracute stages include pyrexia, depression, and signs of respiratory and/or neurologic disease. Signs related to respiratory tract involvement include tachypnea, respiratory distress, and a frothy nasal discharge. Commonly described neurologic signs include weakness, collapse, and an inability to rise; ataxia; altered mentation; central blindness; head tilt and circling; and urinary incontinence. Additional clinical signs may include tachycardia, frequent weight shifting or restlessness, muscle fasciculation, colic, and facial swelling or edema.

■ Pathology

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Gross changes at postmortem include edematous (submandibular and bronchial) lymph nodes, dilated pulmonary lymphatics, subpleural hemorrhages, and pulmonary consolidation and edema. Edema of other tissues may also be apparent. Histologically, HeV infection is characterized by a systemic vasculitis, particularly of the respiratory tract, brain, and meninges. Perivascular lymphocyte cuffing, neuronal necrosis, and focal gliosis have been observed in the brain. Perhaps the most notable histologic finding in HeV infection is the presence of syncytial giant cells containing cytoplasmic inclusion bodies in the pulmonary vascular endothelium.[16] Using electron microscopy, pleomorphic enveloped particles containing the helical nucleocapsid characteristic of the paramyxoviruses can be observed within cytoplasmic inclusions.[17,18] Hendra virus has unique morphologic characteristics that can be useful for diagnosis; the envelope is covered with spikes of 10 and 18 nm length, which gives the particle a unique “double fringed” appearance.[17,19]

■ Diagnosis

In regions where the virus is known to occur, HeV infection should be considered in any horse exhibiting a high fever and signs of acute lower respiratory tract or neurologic disease. It should be noted that not all infected horses have a fever when evaluated. HeV infection should also be considered in cases of sudden death. Differential diagnoses for HeV infection include plant (e.g., Crofton weed, avocado) or ionophore toxicity, bacterial pneumonia, and viral encephalitis or meningoencephalitis.

Laboratory testing is essential for confirmation or exclusion of HeV infection and includes virus isolation, detection of viral nucleic acid in body fluids or tissues, and demonstration of specific serum antibodies. Blood, nasal swabs, oral swabs, or vaginal or rectal mucosal swabs are suitable for quantitative real-time reverse transcriptase PCR (qRT-PCR) testing of both living and dead horses. However, samples collected very early in the disease incubation period can be negative by qRT-PCR testing. Furthermore, not all samples are positive simultaneously, and so collection of multiple samples for PCR is recommended. Detailed guidelines for sample collection, handling, and submission are available from local government sources such as the Queensland Government Department of Agriculture and Fisheries (http://www.daf.qld.gov.au). Appropriate personal protective equipment (protective eyewear, particulate mask, impervious gloves and gown) must be worn when collecting samples from suspect horses.

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Postmortem examinations pose the highest transmission risk for humans, and necropsies of suspect cases should be postponed until HeV infection has been ruled out.

■ Treatment and Prevention

In regions where HeV occurs, owners are advised to reduce contact between fruit bats and horses. Recommendations include to avoid placing feed or water beneath trees in which fruit bats might roost, limit horse access to flowering or fruiting trees that might attract fruit bats, and stable horses at dusk and overnight when fruit bats are most active. Since HeV contains a host cell–derived lipid envelope, inactivation of the virus is possible using compounds that disrupt the lipid envelope (e.g., lysol, sodium dodecyl sulphate [SDS], acetone, methanol).[18]

In November 2012, a subunit adjuvanted vaccine containing soluble HeV G proteins was released under a "minor permit" requiring strict conditions for its use.[2] The vaccine, Equivac® HeV (Zoetis, Parsippany, N.J.), is now fully registered, and the dosing schedule has been adjusted based on studies evaluating the duration of immunity.[20] The vaccine can be administered to healthy horses older than 4 months of age; the initial vaccination and booster are administered 21 to 42 days apart, followed by an additional booster at 6 months with annual boosters thereafter. Effective antibody levels are present 21 days after administration of the second dose. All vaccinated horses must be identified by microchip prior to vaccination and are registered in a central database. Vaccination has prevented infection in limited experimental trials, and since its release, all confirmed cases of HeV infection have occurred in unvaccinated horses. Several drugs (e.g., ribavirin, chloroquine) have been tested for their activities against HeV[9,21]; however, treatment of confirmed HeV cases is not permitted in Australia, and infected horses must be euthanized.

Crofton Weed Poisoning (Numinbah Horse Sickness, Tallebudgera Horse Disease)

Andrew W. Van Eps • Brett Tennent-Brown

The plant *Eupatorium (Ageratina) adenophora* is native to Central America but now appears as an intractable weed in many countries, including Australia and New Zealand.[1] Ingestion of large quantities of *E. adenophora* causes a pneumotoxicosis characterized by increased respiratory effort and rate.

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Outbreaks of respiratory disease caused by *E. adenophora* were reported in Southern Queensland and New South Wales in the 1940s and have occurred periodically since then.[1] Respiratory disease caused by *E. adenophora* has also been reported in New Zealand. The related species *Eupatorium riparium* is a perennial weed in Queensland and New South Wales and causes a similar syndrome in feeding trials. However, field cases of disease caused by *E. riparium* have not been reported.[2]

■ Epidemiology

Respiratory disease caused by *E. adenophora* has been described in horses between ages 18 months and 12 years with no gender predilection. Horses appear to be the only large animal species affected. Flowering stages are more toxic than nonflowering stages, and most cases occur during the summer after ingestion of the plant in spring.[1,3] There is typically a minimum of 2 months between plant ingestion and the appearance of clinical signs.[2]

■ Clinical Signs

The earliest clinical sign noted in affected animals is coughing that is exacerbated by exercise.[1,3] Respiratory rate and effort are markedly increased, and in some cases a double expiratory effort is apparent. Affected horses have reduced exercise tolerance, and adventitial sounds may be appreciated on thoracic auscultation. Severely affected horses experience weight loss and may be cyanotic. Cardiac arrhythmias that can result in sudden death develop in some horses.[1,3]

■ Pathology

The toxic principle of *E. adenophora* is unknown.[2] Pyrrolizidine alkaloids are suspected because of the condition's similarity to *Crotalaria*-associated lung disease (“jaagsiekte”) seen in South African horses. The toxin (or toxins) appears to be absorbed from the GI tract, and inhalation of plant material (e.g., pollen) is not required for disease.

At necropsy, the lungs are firm and do not collapse on opening the thorax. Pulmonary fibrosis is widespread, and there may be cavities containing necrotic material within the parenchyma. The visceral pleura are often thickened and white in appearance, with focal adhesions to the parietal pleura. Hydrothorax,

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pulmonary edema and emphysema, hydropericardium, and cardiac dilation may be found in horses that die suddenly.[1,3]

Sheets of epithelial-like cells lining the alveoli are apparent on histologic examination. Accumulations of inspissated protein are present within the alveoli of most chronic cases, and eosinophils and neutrophils commonly fill the bronchioles and surrounding alveoli.

■ Treatment

No effective treatment is known; once diagnosed, the condition is irreversible, although antimicrobials and corticosteroids have improved clinical signs in some cases.

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▪ Ruminant Respiratory System

Amelia R. Woolums

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Upper Respiratory Tract Diseases*

Amelia R. Woolums

Diseases of the Nasal Cavity

Amelia R. Woolums

Mycotic or Bacterial Nasal Granuloma

Infectious granulomas in the nasal cavity of ruminants are not common. Documented causes include the fungal organisms *Rhinosporidium seeberi* and other *Rhinosporidium* spp. (which cause rhinosporidiosis), *Helminthosporium* spp. (which cause maduromycosis), *Drechslera rostrata, Aspergillus* spp., *Phycomycetes* spp., *Stachybotrys* spp., and *Bipolaris* spp. Nasal granuloma caused by *Nocardia* spp. bacteria has also been reported. There is no apparent age, breed, or seasonal predilection, and cases are sporadic. The major clinical signs are upper respiratory noise (stridor), dyspnea, and mucopurulent nasal discharge, sometimes with epistaxis. Affected animals may rub the nose, suggesting pruritus or irritation. Nasal airflow may be reduced, and open-mouth breathing may occur in advanced cases. Hot or dusty weather may accentuate the signs, giving the appearance of seasonal exacerbation, but the lesions are progressive. The granulomas may be single or multiple, unilateral or bilateral, and located anywhere in the nasal cavity. They consist of 0.5- to 5-cm yellow to yellow-green or red nodules or polyps, which may be sessile or pedunculated. Rhinosporidiosis tends to be a single, unilateral polyp in the posterior nasal cavity, and maduromycosis tends to occur in the anterior cavity, but these distinctions are not consistent. Red and black spots (spores) may occur on the masses, and some may become secondarily infected with bacteria and ulcerate. Differential diagnoses include allergic rhinitis, foreign bodies, tumors, nasal actinobacillosis, nasal actinomycosis, and *Oestrus ovis* infection in small ruminants.

Endoscopy, biopsy, and culture of the lesions aid in the diagnosis. Histopathologic analysis reveals granulation tissue containing eosinophils, mononuclear cells, round sporangia, and sometimes hyphae or filamentous bacteria. The pathogenesis of the disease involves inoculation of eroded nasal

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mucosa with fungal spores or filamentous bacteria from the environment. The infectious agent causes a chronic delayed (type IV) hypersensitivity reaction, which eventually leads to the formation of a granuloma. Fungal granulomas can be more common in warm, wet climates. The granulomas can be difficult to treat, and although rarely fatal, the disease is chronically debilitating, with salvage often being the most practical solution.

Recommended treatments include surgical removal of the granulomas when possible and long-term sodium iodide (NaI) therapy. NaI can be administered at a dose of 66 mg/kg IV as a 20% solution, repeated at 10- to 14-day intervals until remission or iodism occurs. Iodism is characterized by lacrimation, cough, and scaling of the skin. The use of antifungal drugs to treat this condition in ruminants has not been reported.

Allergic Rhinitis and Enzootic Nasal Granuloma

Allergic rhinitis occurs in cattle and in its chronic stages may lead to the formation of granulomas. A similar condition may occur in sheep. The inciting antigen is frequently a plant pollen or more likely a fungal spore. Once homocytotropic antibody (IgE or possibly other classes in cattle) to the allergen has developed, subsequent exposure results in a localized, ongoing, immediate (type I) hypersensitivity reaction. If recurrent exposure to the allergen occurs, repeated tissue damage by mast cell factors results in chronic epithelial, duct, and goblet cell hyperplasia and metaplasia, as well as mucous hypersecretion and granulomatous inflammation, suggesting that a type IV hypersensitivity reaction contributes to the chronic lesion.[1]

Any breed may be affected, but Channel Island breeds and Friesians seem most susceptible. The disease occurs sporadically in the United States. A familial predisposition has been reported.[2] Most affected animals are between 6 months and 2 years of age. The signs are initially seasonal, usually occurring in warm, moist conditions; they include rhinorrhea, sneezing, nasal pruritus, a sudden onset of dyspnea, and stertorous inspiration. There is a profuse bilateral nasal discharge. Intense pruritus is characteristic and associated with sneezing, headshaking, and nose rubbing. In severe cases facial swelling, tachypnea, hyperpnea, and ulceration of the nasal mucosa may occur. Nasal foreign objects may result from the animal's attempts to scratch the nasal mucosa. Lacrimation, chemosis, and blepharitis may also be present. In the chronic stages (the “enzootic nasal granuloma”), the signs are more constant, with seasonal

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exacerbations. The granulomas tend to be multiple, firm, white, raised nodules 1 to 2 mm in diameter with an intact mucosa, or pale pink, flat plaques scattered throughout the nasal cavity. Differential diagnoses include fungal granulomas, foreign bodies, respiratory viruses, nasal actinomycosis or actinobacillosis, tumors, *O. ovis* infection (small ruminants), and irritation caused by inhalation of hot or irritant gases.

Endoscopy; biopsies; cultures; antigen detection tests for viruses, bacteria, or fungi; and serologic analysis can be used to rule out these differential diagnoses. Eosinophil counts in nasal secretions correlate with the susceptibility of the animal and activity of the disease, but no absolute level is diagnostic. Intradermal allergen testing has been suggested to aid in diagnosis, but interpretation of results needs to be done in conjunction with historical and clinical findings.[3] This condition should be differentiated from fungal or bacterial granuloma because the therapy is different.

Treatment and control entail removal of the allergen, or removal of the animal from the allergen, and therapy to block the hypersensitivity reaction. Recommended drugs include various antihistamines, meclofenamic acid, and corticosteroids at standard antiinflammatory doses (0.05 to 0.2 mg of dexamethasone per kilogram IM or IV or 1 to 2.2 mg of prednisolone per kilogram IM or IV daily). Topical corticosteroid therapy can be considered in severe, acute occurrences of the disease. The adverse effects of corticosteroids on milk production and their potential to induce abortion or parturition should be considered before their use. Antihistamine therapy has had equivocal results.[3]

Nasal Foreign Bodies

Cattle are more prone than small ruminants to the acquisition of nasal foreign bodies. Foreign objects may be acquired as a result of attempts to scratch the nose in cases of allergic rhinitis or because of the cow's aggressive eating habits. Depending on the size and duration of residence of the object, signs may include headshaking, stridor, sneezing, snorting, frequent nose licking, unilateral decreases in airflow, foul odors, and serous, mucopurulent, or hemorrhagic discharges. Differential diagnoses include fungal granulomas, allergic rhinitis, tumors, nasal actinomycosis or actinobacillosis, and *O. ovis* infection (small ruminants). Many objects can be visualized on careful examination of the nasal cavity with an adequate light source, but some may require endoscopy for diagnosis and removal.

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Nasal Trauma and Fractures

Trauma to the facial bones, sinuses, and turbinates may result from fighting, accidents caused by improper restraint, farm machinery accidents, human maliciousness, and passage of excessively large nasogastric tubes. Severe fractures can lead to facial swelling, subcutaneous emphysema, obstruction of airflow, stertor, and epistaxis. Secondary infection causes foul odors and mucopurulent nasal discharge. Differential diagnoses for the acute external swelling of the head with stertor include snakebite, actinobacillosis, actinomycosis, and phlegmon (*Fusobacterium, Clostridium* spp.). Unless the development of severe depression fractures, formation of sequestra, or severe obstruction of airflow occurs, surgery is usually not indicated. Radiographs confirm the diagnosis and help determine the need for surgical removal of potential sequestra or elevation and fixation of large displaced segments. Prophylactic antibiotics (typically penicillin, 22,000 IU/kg IM q12-24h) are recommended to prevent fracture infection and sinusitis, and NSAIDs (flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily) may help relieve pain, swelling, and stridor. The prognosis is usually good.

Nasal Tumors and Polyps

Tumors and polyps of the nasal cavity and sinuses are rare in ruminants. Nasal tumors reported in cattle include osteomas and osteosarcomas of the sinuses, squamous cell carcinomas, neuroblastomas, and adenocarcinomas of the ethmoid mucosa. Ethmoid adenocarcinomas are speculated to be caused by viruses on the basis of an endemic pattern in some cases. They tend to occur in cattle 6 to 9 years of age and are frequently unilateral. Metastasis occurs to the lymph nodes and lungs. Signs common to all nasal tumors include mixed or inspiratory dyspnea, stridor, nasal discharge, epistaxis, foul breath odors, unilateral decreases in airflow, open-mouth breathing, and distortion of the facial bones. Differential diagnoses include fungal granulomas, atopic granulomas, foreign bodies, sinusitis, fractures, and nasal actinobacillosis and actinomycosis. Treatment has not been investigated.

The majority of nasal neoplasms in sheep and goats are adenopapillomas, adenomas, or adenocarcinomas. Squamous cell carcinoma has also been reported. An enzootic form of nasal adenocarcinoma occurs in both sheep and goats and is associated with ovine nasal adenocarcinoma virus (ONAV)[4] or caprine nasal adenocarcinoma virus (CNAV),[5] respectively. These agents are β-

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retroviruses that are closely related to but distinct from jaagsiekte sheep retrovirus (JSRV), the cause of ovine pulmonary adenocarcinoma (OPA). Although nasal adenocarcinoma has been difficult to consistently reproduce experimentally, inoculation of kids with concentrated cell-free and bacteria-free filtrate containing virus from naturally infected goats has resulted in disease.[6] Neoplastic transformation is limited to secretory epithelial cells of the nasal turbinates, but CNAV appears to have a wider tissue tropism than ONAV; in one study viral provirus incorporated into host DNA was found in many tissues of infected goats but was largely confined to tumor tissue of infected sheep.[5] There is no breed or sex predisposition for enzootic nasal adenocarcinoma; affected animals are most commonly young adults, but the tumor has been identified as early as 4 months of age. Signs include progressive inspiratory dyspnea; stridor; exercise intolerance; mouth breathing; serous, mucoid, or mucopurulent nasal discharge, which is typically profuse; tachypnea; decreased airflow; headshaking; sneezing; exophthalmos; and facial asymmetry. The lesions may be unilateral or bilateral, originating in the olfactory region of the ethmoid turbinates. The neoplasia arises either from Bowman's glands or serous glands of the nasal mucosa. The tumor begins as a small nodule that can grossly resemble the mucoid polyps that occur in animals with chronic rhinitis. Over time the adenocarcinoma grows into a soft, gray to grayish-pink, mucoid, nodular, cystic mass. The tumor is benign but locally expansive, often entering the sinuses and eroding overlying bone. Histologically the tumor is typically classified as a low-grade adenocarcinoma, but it may also be identified as an adenopapilloma or adenoma. Initially affected animals eat and drink normally and maintain body condition, but as the tumor expands, the animal begins to lose condition, and death eventually occurs as a result of inanition, asphyxia, or aspiration pneumonia. Necrosis or secondary bacterial infection of the tumor can occur and may lead to the production of foul-smelling, purulent discharge and systemic signs related to bacterial infection, such as fever, depression, and hyperemic mucous membranes.

Differential diagnoses for nasal neoplasia in small ruminants include nasal fungal or bacterial granuloma, actinobacillosis, actinomycosis, *O. ovis* infection, and sinusitis. Endoscopy and radiology are helpful in establishing an initial diagnosis of a nasal mass. Preoperative or antemortem pinch biopsies and exfoliative cytologic analysis frequently are nondiagnostic, and findings may be misleading. Identification of tumors in multiple animals in a herd or flock supports a diagnosis of enzootic nasal adenocarcinoma. Definitive identification

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of infection with ONAV or CNAV can be difficult. Serologic tests are not reliable because animals do not consistently produce antibody to the viruses, possibly because of the presence of endogenous retroviruses that share epitopes with ONAV and CNAV and induce the development of immunologic tolerance. PCR has been used to specifically identify and differentiate ONAV, CNAV, and JSRV in tissues of affected animals. Surgical management of nasal adenocarcinoma in sheep has been described.[7]

Oestrus ovis Infestation

Amelia R. Woolums

■ Definition and Etiology

Oestrus ovis is a parasite of the nasal passages and sinuses of sheep and, less commonly, goats. Goats are relatively resistant to infection and, even when housed with sheep, tend to have a lower prevalence of infection. Occasionally humans and other animals are accidentally infected, with conjunctival infection the most common form of disease in humans.[8] The pathogenic stage of the parasite is the larval stage. The first instar larvae are deposited near the nostrils of sheep by the adult female fly and migrate into the nasal and ethmoid turbinates; in the ethmoids the larvae molt to second instars, which migrate to the sinuses before molting again and becoming third instar larvae. Third instar larvae, which are yellow-white in color and have a dark dorsal stripe with rows of spines on the ventrum of each segment, return to the nasal passages and are sneezed out onto the ground, where they pupate and eventually develop into adult flies. The adult is active during warm months, and the parasite may overwinter either as a first instar larva in the host or as a pupa in the ground. Larvae can persist in the upper airways for weeks to months and appear to be able to arrest development for a period if necessary to avoid climate extremes. Adult flies have a rudimentary mouthpiece and are not able to feed; thus the larvae must ingest adequate nutrients while in the host to support the life of the adult fly.

■ Clinical Signs

The larvae cause irritation of the nasal passages and sinuses, leading to mucoid to mucopurulent and sometimes blood-tinged nasal discharge, sneezing, nose

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rubbing, and inspiratory stridor. Adults flies cause annoyance by flying around the heads of animals; thus both stages can lead to decreased productivity by decreasing the time spent grazing by affected animals. Occasionally the larvae may cause sinusitis or pneumonia owing to secondary bacterial infection associated with irritation caused by the larval infestation. Differential diagnoses to consider include nasal foreign bodies, allergic rhinitis, nasal adenocarcinoma, fungal rhinitis, trauma, sinusitis, actinobacillosis, and actinomycosis.

■ Pathogenesis

The larvae cause direct irritation to the nasal passages and sinuses, and this irritation may predispose animals to the development of secondary bacterial rhinitis, sinusitis, and/or pneumonia. Interstitial pneumonia has also been seen on occasion in affected sheep, presumably induced by inhalation of parasite antigens and inflammatory mediators from the upper respiratory tract.

■ Epidemiology

Infection is more common in warm climates. European surveys have identified *O. ovis* in 35% to 91% of sheep surveyed,[9,10] with seroprevalences of 46% to 69%.[11] A majority of flocks surveyed had at least one infected animal. No North American reports describing the prevalence of *O. ovis* infestation have been published in recent decades.

■ Diagnosis

Diagnosis is usually presumptive, based on typical clinical signs. The larvae can also be identified via radiographs of the head or by endoscopy, but these tests may not be practical for field use. Serologic diagnosis has been used for research studies of the epidemiology of *O. ovis* infection, but these tests are unlikely to be available at most diagnostic laboratories.

■ Treatment and Prevention

The larvae are susceptible to ivermectin at 200 µg/kg PO. Moxidectin at 0.2 mg/kg as a 0.1% oral drench was not effective against *O. ovis*[12]; these investigators found that the same dose given as a 1% injectable solution was effective, but this route is not approved in the United States. Pour-on eprinomectin at 0.5 mg/kg (applied immediately after shearing)[13] and injectable

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doramectin at 200 µg/kg IM[14] have also been shown to be effective in sheep, but these treatments are also not approved for use in sheep or goats in the United States. Because the adult fly should be killed by freezing weather, in areas with a season of freezing weather it is logical to treat after the first hard freeze, when sheep will no longer be susceptible to infection until warm weather returns. Prevention is aimed at regular strategic treatment with effective anthelmintics to prevent long-term infection with the larvae.

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Diseases of the Sinuses*

Gretchen P. Grissett

Sinusitis

■ Definition and Etiology

The paranasal sinuses of ruminants consist of the following sinuses: sphenoid, lacrimal, conchal, palatine, frontal, and maxillary.[15] The maxillary sinus lies on the upper jawline and contains the roots of the premolar and molar teeth. The frontal sinus consists of a rostral and caudal compartment, with the caudal being the largest and expanding into the horn core. In sheep and in goats, the frontal sinus consists of a medial and lateral compartment, with the lateral compartment being analogous to cattle's caudal compartment.[15] Despite the potential for infection in any sinus, the maxillary and frontal sinuses are the ones of most clinical significance.[15]

Frontal sinusitis most commonly occurs secondary to a dehorning procedure that entered the sinus. Other common causes include traumatic fracture or injury of the horn, horn tipping, bone sequestrum secondary to dehorning, facial fracture,[16] or *O. ovis* infection in sheep (in goats less commonly). Bucking bulls were more likely to present with horn and sinus disorders than nonbucking bulls in one study.[17] Maxillary sinusitis most commonly results from an infected tooth root. Other causes of maxillary or frontal sinusitis include extension of actinomycosis or neoplasia, hematogenous extension of respiratory pathogen,[18] sinus cysts,[19] and lymphosarcoma.[20] One study evaluated the paranasal sinus microbial flora of clinically normal cattle and cattle presented for portmortem examination, finding that 83.5% of the study individuals did not contain detectable microbes. The organisms isolated from the paranasal sinuses in this study included bovine respiratory disease pathogens *Haemolytica, Trueperella pyogenes*, *Pasteurella multocida, Bibersteinia trehalosi,* and parainfluenza virus type 3 (PIV-3).[18]

■ Clinical Signs and Differential Diagnosis

Acute or chronic sinusitis can result following dehorning. Generally only one

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sinus is affected. Clinical signs associated with acute sinusitis include lethargy, inappetence, pyrexia (39.4° to 41.1° C), unilateral or bilateral mucopurulent discharge, head pressing, and head tilt. Typically, purulent discharge and/or foul-smelling crusting is present at the cornual portion of the sinus. With chronic sinusitis, clinical signs can occur weeks to months after dehorning. Chronic frontal sinusitis can also occur unrelated to dehorning. One study found 4 of the 12 individuals presented for chronic frontal sinusitis had horns, had no record of dehorning, or were dehorned as calves without entering the sinus, but 3 of the 4 did have a recent history of respiratory disease.[21] Clinical signs potentially associated with chronicity include the aforementioned signs, as well as intermittent or consistent pyrexia, stridor, alterations in airflow (typically unilateral), halitosis, reluctance to move, abnormal posture, extended head and neck, partially closed eyes with tendency to rest the head on stationary objects as a sign of pain, frontal bone distortion, exophthalmos, and intolerance of head manipulation. Neurologic signs may result if extension causes impingement or infection of the central nervous system with possible sequelae, including intracranial abscess and septic meningitis.[21]

Maxillary sinusitis is uncommon. Clinical signs include facial swelling and possible deformation over the affected sinus, unilateral mucopurulent discharge, and occasionally decreased appetite secondary to pain during mastication.[16] Maxillary sinusitis is usually associated with a tooth root infection. However, in one report a cow with maxillary sinusitis unassociated with a tooth root fracture or infection was successfully treated. Bacteria cultures were negative, and the etiology was idiopathic.[22] Differential diagnoses for sinusitis include facial fractures, actinomycosis, actinobacillosis, retrobulbar abscess, lymphosarcoma, nasal or sinus neoplasia, and sinus cysts.

■ Diagnosis

Typically, diagnosis can be reached based on history and clinical signs. Certainly, a history of recent dehorning or chronic nasal discharge (especially unilateral) should create a high suspicion of sinusitis. Percussion of the affected sinus may reveal a dull, full resonance and may be painful to the individual. A hyperresonant sound may occur if gas is present under severely thinned bone. Radiographs reveal fluid in the sinuses and may reveal lysis and/or deviations of bony septa (Fig. 31.62). In cases of maxillary sinusitis, radiography will determine if dental disease is involved. In addition, radiography will diagnose

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presence of facial fractures, masses, and actinomycosis. Endoscopy can assist with localization and etiology of the clinical signs. In one report endoscopy was used to confirm maxillary sinusitis by visualizing purulent drainage from the ostia of the nasomaxillary opening, as well as visualizing the sinus after sinus trephination to rule out diagnoses such as sinonasal cyst or neoplasia. CT gives the most precise localization and definition, especially with regard to cysts, masses, and dental disease.[23] Sinocentesis can be performed for culture and cytologic examination.[19] For sinocentesis, a Steinmann pin is used to create a hole into the sinus to facilitate fluid aspiration.[19] A culture and sensitivity of the fluid should be performed to direct antibiotic selection. *T. pyogenes* is isolated most commonly with dehorning-associated sinusitis.[21] *P. multocida* is most commonly isolated in individuals with sinusitis not associated with dehorning.[21] However, a multitude of other agents have been reported, including *Proteus*, *Pseudomonas, E. coli*, *Moraxella* spp., *Aerococcus viridans, Bacillus* spp., *Fusobacterium* spp., *Prevotella* spp., *Porphyromonas levii*, and *Bacteriodes* spp.[17,21] A CBC and serum biochemical profile is often variable and offers minimal assistance with definitive diagnosis.

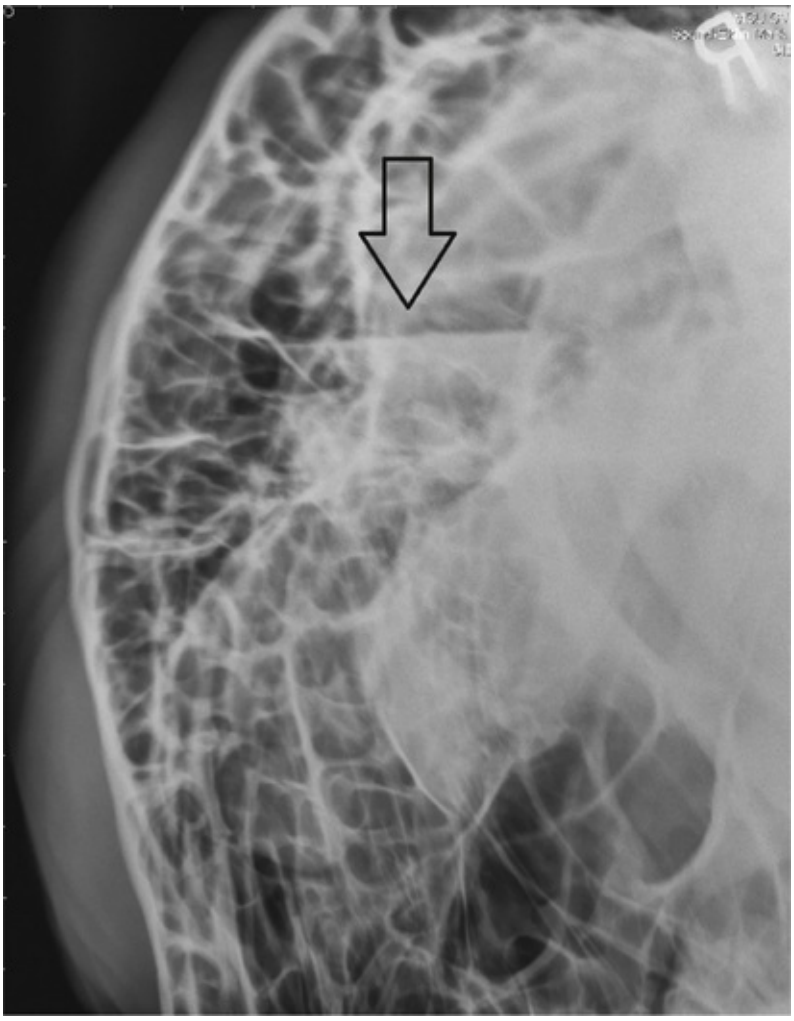


FIG. 31.62 Right lateral radiograph with a horizontal fluid line *(arrow)* in the right frontal sinus of a mature Brahman bull with sinusitis secondary to horn tipping. (Courtesy Dr. Gretchen Grissett, Mississippi State University, Starkville, Miss.)

■ Treatment and Prognosis

Establishing drainage and sinus lavage are the treatment goals for sinusitis. For acute sinusitis associated with dehorning, conservative management can be used by thorough cleansing; débridement; removal of sequestered, devitalized bone; and lavage of the cornual wounds. If cornual drainage is inadequate, placement of a 4-mm Steinmann pin into the caudal frontal sinus is another conservative technique for treatment of acute sinusitis.[16] After local anesthesia and a stab incision, a hand chuck or drill is used to create the hole into the affected sinus with the Steinmann pin. Polyethylene tubing (Foley catheter, fluid administration

set) is used for daily sinus lavage.

For chronic cases, access to the paranasal sinuses is achieved with trephination or bone flap over the affected sinuses.[16] Trephination is ideal because it can be performed standing with sedation and local anesthesia under field conditions, whereas a bone flap requires general anesthesia. Unfortunately, a bone flap may be necessary in cases with pyogranulomatous inflammation that would be insufficiently lavaged with trephination alone. In addition, the numerous septa of the frontal sinus and high location of the nasomaxillary opening in the maxillary sinus may necessitate a bone flap to allot adequate access and drainage.[15] Sinusotomy locations for trephination include the dorsal frontal sinus, postorbital diverticulum, rostral frontal sinus, turbinate portion of the frontal sinus, and the maxillary sinus (Fig. 31.63).

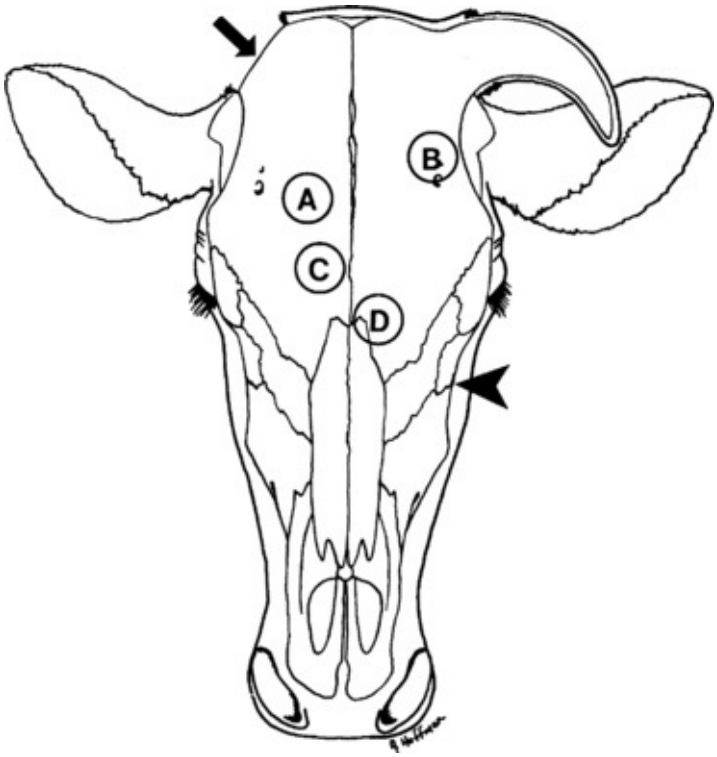


FIG. 31.63 Trephine sites for sinusotomy. **A,** Dorsal frontal sinus. **B,** Postorbital diverticulum. **C,** Rostral frontal sinus. **D,** Turbinate portion of frontal sinus. The maxillary sinus is trephined ventral to a line from the infraorbital foramen to the medial canthus *(arrowhead).* If draining tracts are present at the poll, an additional sinusotomy can be made in the cornual portion of the frontal sinus *(arrow).*

Frontal sinusotomy sites are based on known anatomic landmarks and modified as needed to accommodate frontal bone distortion and dehorning wounds.[21] The individual should be restrained appropriately in a chute and sedated. The sinusotomy location is 3 to 4 cm from midline intersecting a line drawn between the caudal aspect of the orbits. The proposed site should be surgically prepared and instilled with 2% lidocaine HCl for local anesthesia. A full-thickness circular area of skin large enough to accommodate the trephine (approximately 2 cm in diameter) extending to the periosteum should be excised. A Galt trephine should then be used to remove a section of bone to access the sinus. After entering the sinus, samples should be obtained for culture and cytology. If draining tracts are present, a second sinusotomy can be performed at the cornual portion of the sinus. The postorbital diverticulum is accessed approximately 4 cm caudal to the dorsal rim of the orbit just above the temporal crest of the frontal bone.[24,25] The rostral frontal sinus is entered just caudal to a line drawn between the center of the orbits and just off midline, with the turbinate portion of the frontal sinus entered just rostral to this line and to either side of midline. The numerous septae in the frontal sinus can often make drainage difficult, especially with postoribital diverticulum involved, meaning that one trephination can be insufficient. Often two trephination sites are required for an ingress and egress lavage system. For sheep and goats, the frontal sinus is even more compartmentalized than cattle, making effective drainage very difficult. In addition, sheep and goats have a thin calvarium, meaning that chronic sinusitis leads to meningitis more easily than in the bovine patient. Therefore early, aggressive treatment in sheep and goats is essential, including consideration of a bone flap procedure and two trephination sites. Preferred trephination sites are rostral to the horn or medial to the middle of the orbital rim, avoiding risk of injury to the frontal vein.[15]

The maxillary sinus is accessed by drawing a line from the medial canthus to the infraorbital foramen. The trephine is positioned just ventral to this line, lining up just dorsal and caudal to the facial tuberosity.[22] If an infected tooth cannot be removed orally, the sinusotomy site should be positioned over the affected tooth to allow axial alignment and repulsion of the tooth.[25] In immature animals, the tooth roots are longer and occupy much of the maxillary sinus. Therefore care should be taken and the trephine site should be positioned higher to avoid the tooth roots.[16] If a tooth is repelled, a roll of gauze or methyl methacrylate plug should be used to pack the alveolar socket to prevent feed material entering the

side. If rolled gauze is used, the gauze can be passed from the socket, into the sinus, and out the trephine hole and secured to the individual's face. The packing should be changed with each lavage. Since the maxillary sinus has fewer septae than the frontal sinus, typically one sinusotomy site is sufficient for drainage and lavage. With chronic maxillary sinusitis, damage to the lacrimal and infraorbital canals and infraorbital nerve is possible.[15,23]

Drains can be placed in communicating trephination sites to prevent premature closure and facilitate lavage and drainage of the affected sinus. Sinus lavage should occur once to twice daily with saline, dilute povidone-iodine, or dilute chlorhexidine solution. One study evaluated sinus lavage solutions and found that individuals treated with the 5% diluted povidone-iodine solution had better clinical resolution that the individuals lavaged with saline alone.[26] A stent bandage can be used to cover the trephination sites to prevent debris and environmental contamination entering the sinus until sufficient granulation has occurred.[16] Parenteral antibiotics and NSAIDs are indicated in individuals with systemic signs. Flunixin meglumine (1.1 mg/kg IV q24h) is recommended for individuals in the acute phase of the disease course and those that are perioperative. For individuals with chronic sinusitis treatment, meloxicam (0.5 to 1 mg/kg PO q48h) is recommended for protracted treatment. Since sinusitis caused by dehorning is most commonly associated with *T. pyogenes*, penicillin G procaine (22,000 U/kg IM q12h, or 44,000 U/kg IM q24h) is the empirical antibiotic choice.[21] *P. multocida* is most commonly isolated in frontal sinusitis not associated with dehorning.[21] Penicillin may be effective against some *P. multocida* isolates, but oxytetracycline (11 mg/kg IV q24h for 5 days, or 20 mg/kg SC long-acting oxytetracycline q72h) can be administered with nondehorning-related sinusitis. Florfenicol (40 mg/kg SC q96h) is also a reasonable choice, as it has bacteriostatic activity against both *T. pyogenes* and *P. multocida*. Antimicrobial therapy should always be modified to culture and sensitivity results when available. Prognosis is good for individuals early in the disease course, usually resolving in 7 to 14 days with appropriate therapy and systemic antibiotics. For chronic cases the prognosis is fair to guarded, with weeks of aggressive therapy required for a successful outcome. Individuals with neurologic signs typically have a grave prognosis, and humane euthanasia should be considered.

■ Prevention and Control

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The best prevention for frontal sinusitis in ruminants is dehorning as neonates prior to communication of the horn with the frontal sinus. Ideally, dehorning occurs with electrocautery (dehorning iron) or a Barnes dehorner prior to communication with the frontal sinus. For mature cattle, a surgical (cosmetic) dehorn using aseptic technique is recommended. A cosmetic dehorn allows primary skin closure, minimizing environmental contamination and expediting healing time.[27] If a surgical dehorn is not performed, avoid dehorning during fly season or windy or rainy conditions to help prevent mydriasis and sinusitis. Disbudding of sheep and goats should occur in the first week of life due to the rapid growth of horns. For mature sheep and goats, cosmetic dehorning can also be performed, minimizing the risk of sinusitis and expediting healing time.[28] Without cosmetic dehorning, dehorning of mature sheep and goats requires intensive bandage management and 4 to 6 weeks for healing by second intention.[29]

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Diseases of the Pharynx, Larynx, and Trachea*

Amelia R. Woolums

Pharyngeal Trauma, Abscesses, Cellulitis, and Granulomas

■ Definition and Etiology

Pharyngeal trauma may result in hematomas, foreign body granulomas, cellulitis, or abscesses. Trauma usually results from careless use of balling guns, dose syringes, paste-type anthelmintics or calcium preparations, specula, and stomach tubes. Rough, stemmy feeds (especially when chopped), grass awns, briars, and foreign objects (e.g., nails, baling wire) may also cause punctures. Migrating foreign objects or medications (e.g., mineral oil, anthelmintics) may cause pharyngeal granulomas. Hematomas and puncture wounds often result in abscess formation. Diffuse cellulitis may also result. Common bacteria involved include *Arcanobacterium pyogenes*, *Actinobacillus* spp., *Pasteurella* spp., *Bordetella* spp., *Fusobacterium necrophorum*, and *Streptococcus* spp. In cases of particularly virulent bacterial invasion, the condition can become rapidly fatal. *C. pseudotuberculosis* (caseous lymphadenitis) may localize in the pharyngeal nodes of sheep and especially goats. Caseous lymphadenitis is discussed later in this chapter and also in relation to the hemolymphatic system in Chapter 37.

■ Clinical Signs and Differential Diagnosis

Signs of pharyngeal trauma vary with the severity of the resulting reaction (e.g., peracute cellulitis versus chronic abscess or granuloma). Prominent signs include inspiratory dyspnea with stertorous inspiratory sounds and a prolonged inspiratory phase; extended head and neck; ptyalism, which is often profuse; quidding; evident pain on swallowing or reluctance to swallow solid feed but willingness to drink liquids; prolonged chewing of boluses; regurgitation of food or saliva through the nostrils caused by pharyngeal paresis; mucopurulent to bloody nasal discharge and fetid odors, usually bilateral; cough; bloat; and visible or palpable swelling in the pharyngeal area. Megaesophagus has been

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reported subsequent to pharyngeal trauma. Palpation of the pharynx may increase the stertor and cause pain. In severe cases, systemic signs of fever, anorexia, depression, dehydration, and forestomach stasis may be present. Aspiration pneumonia may be a secondary complication.

Differential diagnoses include pharyngeal tumors; lymphosarcoma; sialoliths; rabies; botulism; actinobacillosis; necrotic laryngitis; laryngeal abscesses, trauma, edema, or paralysis; and laryngeal tumors.

■ Diagnosis

A thorough manual examination of the oropharynx or a visual examination with an adequate speculum and light source usually confirms the diagnosis of a pharyngeal swelling and often reveals a puncture that is discharging pus. Cases in which the infection is diffuse can be more difficult to recognize, and endoscopy or radiography can be particularly helpful. Restraining the jaws with a McCallum speculum allows a guarded needle attached to a length of tubing and a syringe to be inserted into the swelling for aspiration of any swelling identified. This helps differentiate localized abscesses from granulomas, hematomas, cellulitis, and tumors; allows culture and sensitivity determinations on abscesses; and may aid in cytologic diagnosis of granulomas or tumors. Radiographs may reveal foreign bodies (Fig. 31.64) or air densities (Fig. 31.65) in the pharyngeal tissues. The CBC usually reflects an inflammatory process, with a neutrophilic leukocytosis and a left shift, or a neutrophil-lymphocyte reversal. Dehydration is frequently evident. If the animal is unable to swallow, large amounts of bicarbonate may be lost through the saliva, which may lead to evidence of metabolic acidosis on blood gas analysis or serum biochemical profile.

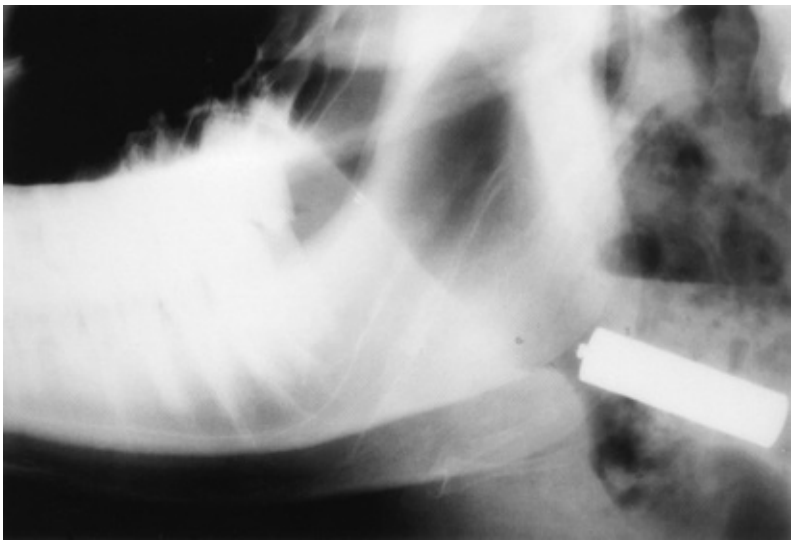


FIG. 31.64 Radiograph of the pharyngeal area of a cow. Note the magnet located in the retropharyngeal tissue.

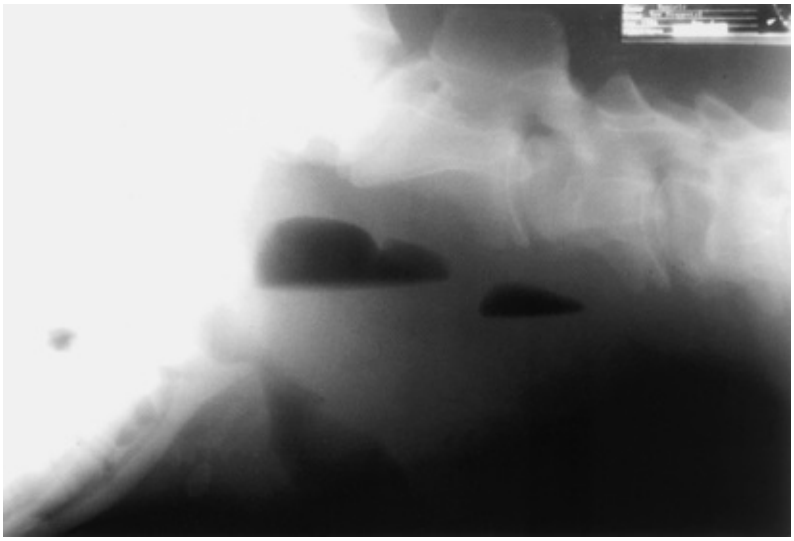


FIG. 31.65 Radiograph of the pharyngeal area of a cow. Note the air densities in the tissue, suggestive of abscess formation.

■ Treatment and Prognosis

Discrete pharyngeal abscesses are usually best drained into the pharynx. Whenever possible the procedure should be done on the standing animal without sedation to preserve the cough reflex and prevent aspiration. A good oral speculum and excellent restraint are needed. The head should be kept lowered. A

guarded blade such as a hook blade from a fetotomy set is introduced into the pharynx, and the abscess is lanced. The cavity is flushed with a mild antiseptic such as 0.2% povidone-iodine in saline solution, again taking care to prevent aspiration. Other options include drainage to the exterior, drainage and flushing with a large-gauge needle and tubing, and extirpation.[2] Removal of a bacterial granuloma from the pharynx of a cow via electrocautery has been described.[4] Systemic antibiotics are administered in accordance with culture and sensitivity results, or in their absence, procaine penicillin G (22,000 to 44,000 U/kg IM q12-24h) or tetracycline (11 mg/kg IV or SC daily, or 20 mg/kg of long-acting oxytetracycline SC q72h) are used. NSAIDs (flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily) help relieve pain, swelling, and stertor. In animals with severe, persistent dyspnea, tracheostomy may be necessary. Granulomas and diffuse cellulitis are likewise treated medically with appropriate antimicrobials and antiinflammatory drugs. Supportive therapy such as IV fluids or feeding through a rumenostomy site may be necessary if the animal refuses to eat or drink. The prognosis for most pharyngeal abscesses, hematomas, cellulitis, and granulomas is usually good with appropriate therapy.

Dorsal Displacement of the Soft Palate

Although rare, dorsal displacement of the soft palate has been reported in cattle.[30] Respiratory noise is apparent on inspiration and expiration but is loudest on inspiration. Diagnosis can be made by endoscopic examination. Treatment is similar to that used in horses and can include conservative therapy, which consists of antiinflammatory drug therapy and rest, or the condition can be surgically corrected.

Necrotic Laryngitis (Calf Diphtheria, Laryngeal Necrobacillosis)

■ Definition, Etiology, and Epidemiology

Acute to chronic infection of the laryngeal mucosa and cartilage of young cattle is very common, particularly in feedlots. Laryngeal contact ulcers probably provide a damaged mucosal surface, which then allows invasion of the cartilage by *F. necrophorum*, which is the proximate cause of the lesions. Alternatively, *Histophilus somni* may be the primary agent inducing a perilaryngeal vasculitis,

with *F. necrophorum* representing a secondary bacterial invader.

The disease is most common where cattle are housed in dirty or crowded conditions and in feedlots. Most feedlot cases occur in animals on feed for longer than 30 days. The incidence is sporadic. Cases occur year round, but there appears to be a higher incidence in fall and winter. The disease has a worldwide distribution.

■ Clinical Signs and Differential Diagnosis

The problem occurs most commonly in calves from 3 to 18 months of age, up to about 24 months. It is characterized by an acute onset of a moist, painful cough, which the animal may attempt to suppress because of pain. Frequently a severe inspiratory dyspnea with a loud guttural stertor and open-mouth breathing with the head and neck extended are observed. The animal may salivate, make frequent painful swallowing movements, and stand and sip water continually. Signs of systemic disease, including anorexia, depression, fever (as high as 106° F [41.1° C]), and hyperemic mucous membranes, are present. There is often a bilateral nasal discharge and a fetid odor to the breath. The larynx may be visibly or palpably swollen, and palpation may elicit a cough, cause pain, and markedly increase the dyspnea and stertor. If untreated, many calves will die in 2 to 7 days as a result of systemic effects of bacterial toxins and upper airway obstruction. Recovered cases may have a chronic roaring respiration and a harsh, dry cough because of the misshapen larynx. Aspiration pneumonia and chronic “poor doers” are common sequelae. Differential diagnoses include pharyngeal trauma (abscess, cellulitis), severe viral laryngitis (e.g., IBR), actinobacillosis, and laryngeal edema, abscesses, trauma, paralysis, and tumors.

■ Diagnosis

The diagnosis is usually made presumptively based on clinical signs alone. A laryngoscopic or endoscopic examination can help confirm the diagnosis, but care must be taken to prevent further stress and respiratory embarrassment. Acute cases show changes in the CBC consistent with any acute septic condition: leukopenia caused by neutropenia with a left shift. In chronic or ongoing cases, leukocytosis with neutrophilia, monocytosis, and hyperfibrinogenemia may be present.

■ Pathophysiology

F. necrophorum normally does not penetrate intact mucous membranes. Laryngeal contact ulcers are thought to provide the portal of entry for *F. necrophorum*, which is ubiquitous. Laryngeal contact ulcers are also very common in slaughter cattle and are speculated to be caused by the following combination of factors: (1) an acute mucositis from mixed upper respiratory infections; (2) reflex coughing and swallowing, which accelerate the rate of laryngeal closure; and (3) resulting erosion of the swollen membranes over the vocal processes and medial angles of the arytenoid cartilages. Necrotic laryngitis can alter pulmonary function such that the growth rate is impeded and also predisposes to secondary bacterial pneumonia.

■ Necropsy Lesions

The lesions are typically located over the vocal processes and medial angles of the arytenoid cartilages. Acute lesions consist of marked edema, hyperemia, and swelling of the mucous membrane around a necrotic ulcer, with accumulated exudate. The lesions spread along the vocal processes and vocal folds and may extend into the cricoarytenoideus dorsalis muscles. In chronic cases the lesions consist of a focus of necrotic cartilage surrounded by purulent exudate, which may be inspissated. The tract opening may be surrounded by granulation tissue and may drain pus. The arytenoid cartilage may be rotated into the lumen or may contain mucosal cavities lined with thin, hyperemic epithelium.

■ Treatment, Prognosis, Prevention, and Control

Oxytetracycline (11 mg/kg IV or SC q24h, or 20 mg/kg of long-acting oxytetracycline SC q72h), procaine penicillin G (22,000 to 44,000 U/kg IM q12-24h), or florfenicol (20 mg/kg IM q48h or 40 mg/kg SC q96h) are appropriate. NSAIDs (flunixin meglumine, 1.1 to 2.2 mg/kg IV once daily or divided twice daily) may reduce swelling, inflammation, and fever. Cases with severe respiratory distress may benefit from one or two doses of steroids (dexamethasone, 0.05 to 0.2 mg/kg IV or IM once or twice), but repeated doses of steroids are not recommended. A tracheostomy may be necessary in severe cases to relieve dyspnea and rest the larynx. Good nursing and supportive care are also important, including shelter, adequate ventilation, easy access to feed and water, and oral or IV fluids if needed. The prognosis is guarded; even when the condition is detected early and treated vigorously, cattle sometimes relapse. When extensive cartilage necrosis occurs, a fatal outcome or chronic ill-thrift is

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expected. There are no specific control measures. The proposed pathogenesis would suggest that measures to control other respiratory diseases may reduce the incidence of necrotic laryngitis.

Laryngeal Papillomatosis

Papillomas of the larynx have been reported in feedlot cattle. They are caused by a papovavirus, which is thought to enter laryngeal contact ulcers (see the previous Necrotic Laryngitis section). Characteristic signs of laryngeal papillomatosis are stertorous respiration and cough. Differential diagnoses include necrotic laryngitis, pharyngeal trauma, abscess, or granuloma; actinobacillosis; and laryngeal abscesses, trauma, edema, paralysis, and tumors. The lesions are sessile to pedunculated, yellow, frondlike, 1- to 10-mm growths over the vocal processes of the arytenoid cartilages.Treatment usually is not indicated but involves surgical removal. Measures to decrease other respiratory infections and thereby decrease contact ulcers may lower the incidence of papillomas.

Laryngeal Abscesses

Abscessation of the arytenoid cartilages caused by *A. pyogenes* has been reported in calves and sheep. Clinical signs include tachypnea, extension of the head and neck, cyanosis, and a severe progressive dyspnea with marked stertor that can be localized to the larynx. Many affected animals remain alert and afebrile and continue to eat until the terminal stages of severe dyspnea. Endoscopy reveals generalized edema and hyperemia of the laryngeal mucosa and obstruction of the rima glottidis by swelling of one or both arytenoids. Radiographs may demonstrate soft-tissue swelling of the larynx. The condition has been speculated to be initiated by grass awns, trauma, hereditary predisposition, or congenital cavitations in the cartilages. In sheep, rams appear to be more commonly affected than ewes, and two reports found a breed predisposition in Texels and Southdowns, although other reports have indicated that various breeds are affected.[31] The necropsy lesions consist of encapsulated abscesses containing pus and necrotic debris in the arytenoid cartilage, usually in the vicinity of the vocal cord. A tract from the abscess typically opens in an area of granulation tissue in the laryngeal mucosa. Treatment consists of tracheostomy, antibiotics (usually penicillin at 22,000 to 44,000 U/kg IM q12-

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24h), and antiinflammatory drugs (flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily). The prognosis for recovery is considered guarded unless the condition is detected in the earliest stages and treated vigorously; however, one affected heifer lived for at least 1 year and was bred successfully after permanent surgical tracheostomy for chronic arytenoid abscessation.[32]

Other Laryngeal Obstructions (Laryngeal Trauma, Edema, Paralysis, and Foreign Objects)

Other laryngeal obstructions are all sporadic and may manifest with similar signs. Trauma to the larynx may result from roping or injury in restraint devices. Inappropriate placement of an endotracheal tube can potentially damage the larynx. The respiratory system is the main target organ for anaphylaxis in ruminants, and laryngeal edema can be a prominent component of this syndrome. Inhalation of smoke or other noxious gases also may cause laryngeal edema. Laryngeal hemiplegia has been reported in association with *Sarcocystis* species infection of the muscles of the larynx and pharynx in a ram.[33] Foreign objects more commonly lodge in the pharynx, but sharp objects and food materials may be aspirated and lodge in the larynx. Signs common to these laryngeal obstructions include inspiratory dyspnea, prolongation of the inspiratory phase, mouth breathing, stertor, cyanosis, salivation, and extension of the head and neck. Palpation of the larynx may reveal swelling and may exaggerate the dyspnea and stertor. Differential diagnoses include necrotic laryngitis, laryngeal abscesses, severe viral laryngitis, actinobacillosis, and tumors. Endoscopy and radiology are required in most cases to differentiate these conditions. Hematologic analysis may give some indication of the presence of bacterial infection; a stress leukogram may also be seen. Tracheostomy is indicated in all severe cases. Surgical correction of laryngeal obstruction by tracheolaryngostomy has been described in cattle.[34]

Laryngeal trauma and paralysis may resolve spontaneously or may require reconstructive surgery. The therapy of anaphylaxis is discussed in the Anaphylaxis section later in this chapter. Foreign objects should be removed surgically or endoscopically. NSAIDs (flunixin meglumine, 1.1 to 2.2 mg/kg IV daily or divided twice daily) may help reduce swelling, edema, and respiratory embarrassment in all forms of obstruction.

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Tracheal Collapse and Stenosis

■ Definition and Etiology

Tracheal collapse or stenosis is infrequently reported in cattle and goats.[35] The cause is usually unknown, but the problem may result from cranial thoracic trauma, roping, tracheostomies, or possibly congenital defects. In cattle the majority of reports have described tracheal collapse in calves in which signs were usually first evident at several weeks of age. The majority of these cases also involved the thoracic trachea (Fig. 31.66), suggesting a congenital lesion. However, in most calves with tracheal collapse the condition has been a result of dystocia at birth, especially breech presentations, which suggests a traumatic cause. In contrast to reports in cattle, tracheal collapse has been reported in a mature goat that showed no previous signs of respiratory abnormality.[36]



FIG. 31.66 Radiograph demonstrating collapse of the thoracic trachea in a calf.

Tracheal collapse has also been reported in Texel-cross lambs with inherited chondrodysplasia[37]; affected lambs were normal at birth but developed exercise intolerance as early as 1 week of age. Severely affected lambs developed fatal respiratory compromise when exercised. Tracheal stenosis can also occur in lambs born to ewes that ingest *Veratrum californicum* root and rhizome material at days 31 through 33 of gestation.[38]

■ Clinical Signs and Differential Diagnosis

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Clinical signs of tracheal collapse may include fever, tachycardia, tachypnea, cyanosis, and mucosal hyperemia with vessel engorgement, but affected animals may have normal vital signs and are otherwise alert and in good condition. Dyspnea is usually induced or exacerbated by excitement or exercise or may be severe at rest. Stertorous respiration is usually evident, is frequently worse on inspiration, and can often be localized to the trachea on auscultation. The inspiratory phase is prolonged, and a “honking” cough is characteristic, especially with intrathoracic collapse. Palpation may reveal or induce the collapse when the cervical trachea is involved. Tracheal palpation or elevation of the head may increase the stertor or induce the honking cough. In some cases there may be other evidence of trauma (fractured ribs, sternebrae), and in some animals pneumonia may be present. There is no response to antibiotics, steroids, or tracheostomy.

Texel-cross lambs with tracheal collapse resulting from inherited chondrodysplasia also exhibited retarded growth, forelimb varus, and reluctance to walk. Severity of signs varied among affected individuals; some died or were euthanized within weeks because of respiratory compromise, whereas others survived to breeding age.[37] Animals that survived for several months often developed arthritis characterized by severe erosive lesions of the articular cartilage of major joints, including the shoulder, hip, and stifle. Lambs with congenital tracheal stenosis resulting from maternal ingestion of *V. californicum* died within 5 minutes of birth after signs of severe respiratory distress.[38]

Other possible disorders with signs similar to those seen in animals with tracheal collapse or stenosis are tracheal foreign bodies, tracheal actinobacillosis, neoplasms, bronchopneumonia, necrotic laryngitis, and extratracheal compressive lesions (e.g., abscesses, tuberculosis, hematomas).

■ Diagnosis

Any deviation of the hemogram from normal is probably a reflection of associated pneumonia or stress. Endoscopy and radiography are the most helpful ancillary aids. Care must be taken when restraining, sedating, and passing the endoscope in these animals; oxygen should be available. In cattle with idiopathic tracheal collapse, radiography and endoscopy usually reveal a dorsoventral flattening, most typically in the caudal cervical and cranial thoracic trachea, although lateral collapse and collapse in other locations (cranial cervical, intrathoracic) are occasionally encountered.

■ Pathophysiology

Proposed causes of tracheal collapse in other species include congenital malformations, genetic or nutritionally induced weakness of cartilage, deficient innervation of the trachealis muscles, trauma, ischemic lesions from endotracheal tube cuffs, and primary pulmonary disease. No histologic differences were noted in tracheal rings from collapsed and normal segments when this has been assessed. As previously mentioned, most calves with tracheal collapse have a history of dystocia at birth. During delivery, compression of the chest wall with fracture of the first pair of ribs may cause injury at the thoracic inlet. However, signs of tracheal collapse are not immediately evident at birth but develop over time.

Lambs with tracheal collapse associated with inherited chondrodysplasia had clinical signs most similar to a condition in humans that results from a mutation in the diastrophic dysplasia sulphate transporter gene,[39] but the causative mutation in sheep has not yet been reported. Preliminary data indicated that the chondrodysplasia was inherited via a recessive mode of inheritance.[37] Tracheal stenosis in lambs born to ewes fed *V. californicum* was presumed to be caused by cyclopamine, a steroidal alkaloid that is the toxic principle in highest concentration in *V. californicum.* It was notable that lambs developed tracheal stenosis when ewes were fed *V. californicum* at 31 to 33 days of gestation, whereas craniofacial defects typically recognized in lambs born to exposed dams are seen when the ewe ingests the toxic plant by day 14 of gestation.[38]

■ Necropsy Lesions

At necropsy, affected animals may have either a laterally or dorsally compressed trachea; typically several centimeters of the trachea are affected. Necropsy of sheep with inherited chondrodysplasia reveals a trachea that is flaccid, flattened, and sometimes irregularly kinked. Tracheal rings are markedly thickened, and the lumen is narrow, possibly extremely so. Diffuse pulmonary congestion and edema, with epidcardial ecchymoses, may occur as a result of terminal anoxia and respiratory distress. Other lesions include exaggerated convex curvature of the ribs, anglular limb deformities, and erosive arthritis with exposure of the subchondral bone in one or more joints. Histologically, hyaline cartilage in affected organs is hypercellular and disorganized, with foci of apparent chondrolysis. Chondrocytes are larger than normal, although shrunken, apparently necrotic chondrocytes are also seen. Necropsy of lambs with

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congenital tracheal stenosis resulting from maternal ingestion of *V. californicum* reveals pronounced lateral flattening of the trachea. Tracheal rings are reduced in number, with abnormal size and shape and irregular spacing. Histologically, the cartilage rings in affected lambs were flattened and thin and had a thinner zone of proliferating chondrocytes on their outer surface compared with normal age-matched controls.

■ Treatment and Prognosis

Mild cases may respond to confinement sufficiently to be fed out for slaughter. A number of surgical treatments have been proposed in other species, including anastomosis, bisection of tracheal rings, internal and external prostheses, and plication of the dorsal membrane. External prostheses have been used successfully in calves,[35] adult cattle, and a goat.[40] A favorable prognosis for surgical correction is estimated at approximately 30%.[23] A detailed description of surgical repair in calves by external prostheses has been published.[23] Successful management of lambs with congenital tracheal collapse or stenosis has not been reported, although mildly affected lambs with congenital chondrodysplasia survived into adulthood. Because of the apparent genetic basis for the disease, breeding of affected animals should not be recommended.

Tracheal Foreign Bodies and Masses

Ruminants may occasionally inhale foreign objects that lodge in the trachea. Tracheal actinomycosis has been reported to result in signs of tracheal obstruction.[41] Signs include a chronic cough, inspiratory dyspnea, audible stridor that can be localized to the trachea, extension of the head and neck, open-mouth breathing, and salivation. Differential diagnoses should include pharyngeal trauma; necrotic laryngitis; laryngeal abscesses, trauma, edema, or paralysis; tracheal collapse; and extratracheal compressive lesions. Endoscopy and radiology are important aids to diagnosis. Care must be exercised in restraint and in passage of the endoscope. Some small objects may be retrieved by a snare passed through an endoscope; others may require tracheostomy. When possible, the tracheostomy should be performed below the object. The actinomycotic masses are soft, pedunculated lesions with a granular surface containing small yellow foci.

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Tracheal Edema Syndrome of Feedlot Cattle

Tracheal edema syndrome has also been referred to as *tracheal stenosis* in feedlot cattle. In this condition extensive edema and hemorrhage in the dorsal wall of the trachea result in coughing, dyspnea, and stertor, which has given rise to the term *honker cattle*.[42] Tracheal edema syndrome occurs in two forms, characterized by either acute dyspnea or a chronic cough. It is not known whether the two forms are related. Although the syndrome has been recognized for years, no controlled research has been undertaken to determine the cause or risk factors of this syndrome, and the cause is unknown. Theories regarding possible causes include infections with upper respiratory viruses or bacteria such as *P. multocida* or *H. somni*, trauma to the trachea from feedbunks, passive congestion and edema from excessive fat accumulation in the thoracic inlet, hypersensitivity reactions, and mycotoxins.

The acute dyspnea syndrome occurs mainly in heavy feedlot cattle in the latter two thirds of the feeding period and is most common in Southern Plains feedlots. It is sporadic and more common in summer, possibly because of exacerbation by hot weather. At one extreme, sudden deaths without the onset of noticeable clinical signs have been reported, and at the other extreme subclinical disease was evidenced by lesions in animals at slaughter that did not have clinical signs. Other factors that increase respirations also may cause signs to appear. Signs include an acute onset of dyspnea and loud guttural inspiratory sounds that can be localized to the lower trachea. Open-mouth breathing, extension of the head and neck, and cyanosis, leading to recumbency and death by asphyxiation, are present. Differential diagnoses for this form include pharyngeal trauma or abscess; necrotic laryngitis; IBR; laryngeal abscess, tumor, foreign object, edema, or paralysis; tracheal foreign object, mass, or collapse; and AIP.

The chronic form occurs in lighter cattle (135 to 400 kg [300 to 900 lb]) and is more common in western plains feedlots. It is also sporadic but less seasonal. Affected animals may have a history of IBR or pneumonia. The main sign is a continuous, frequent, deep, hacking, nonproductive cough. The animal may be unthrifty but is otherwise normal in appearance. The main differential diagnoses are necrotic laryngitis or mild, chronic suppurative pneumonia. Endoscopy and visualization of the lesions subsequently described aid in the diagnosis. Necropsy of the acute form reveals an edematous thickening of the submucosa and mucosa of the dorsal trachea (Color Plate 31.1), as much as 5 cm thick and extending 20 to 30 cm from the midcervical area to the thoracic inlet or tracheal

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bifurcation. There is also extensive mucosal, submucosal, and peritracheal edema and/or hemorrhage, possibly related at least in part to agonal breathing. There may be no other lesions of the airway or lungs, or abnormalities (e.g., pulmonary edema, bronchitis, interlobular edema and emphysema, alveolar hemorrhage) may be seen. Lesions in the chronic form consist of hyperemia of the mucosa of the caudal third of the trachea, with a thin layer of mucopurulent exudate. The mucosa may have a cobblestone appearance or even large, fiberlike projections and polyps. No effective treatment exists for the chronic form. Corticosteroids (dexamethasone, 0.05 to 0.2 mg/kg IM or IV; prednisolone, 1 to 2.2 mg/kg IM or IV daily) are recommended for the acute form, as are such practices as preventing stress, providing shade, and cooling with water sprays and fans. Opinions are divided regarding the value of antimicrobial therapy. However, because animals with tracheal edema syndrome may be difficult to distinguish clinically from animals with conditions that could respond to antimicrobials (such as necrotic laryngitis), antimicrobials are often administered. Because withdrawal times associated with antimicrobial administration could delay shipment of affected animals to slaughter, drugs with a short withdrawal time should be used if salvage is an option. Tracheostomy may not be helpful if placed proximal to the obstruction, and relief of dyspnea via tracheostomy may require insertion of an endotracheal tube to the tracheal bifurcation. Oxygen administration could be beneficial if available. Recovered patients tend to relapse and should be salvaged.

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Lower Respiratory Tract Diseases*

Amelia R. Woolums

Clinical Classification of Pneumonia

Amelia R. Woolums

In an effort to simplify the differential diagnosis of the array of lower respiratory diseases of cattle, a classification system based on pathophysiology and clinical signs can be used:

1. Bronchopneumonia is characterized pathophysiologically by invasion of pathogenic organisms that gain access to the lung through the pulmonary tree. It is characterized clinically by depression, fever, and other signs of sepsis such as hyperemic mucous membranes or scleral injection and by an anterior-ventral distribution of abnormal lung sounds and lesions. Bronchopneumonia is the final outcome of the *respiratory disease complex* of ruminants, and because viruses play an important role in this disease complex, viral causes of respiratory tract disease in ruminants are placed in this category.
2. The interstitial pneumonias are a very diverse group of (usually) noninfectious diseases. Although it is difficult to make generalizations, these diseases are characterized pathophysiologically by an interstitial reaction that usually results from ingestion or inhalation of toxins or allergens. Clinically affected animals tend not to be as depressed and septic, although dyspnea may be severe and disease can be rapidly fatal. Abnormal lung sounds and lesions are diffusely distributed, and there is little or no response to antibiotic therapy.
3. Metastatic pneumonia is characterized pathophysiologically by septic embolization of the lungs from other foci in the body, classically liver abscesses and postcaval thrombi. Clinically, cases of metastatic pneumonia exhibit signs of sepsis as with bronchopneumonia, but with widespread pulmonary lesions and abnormal lung sounds, and the eventual development of hemoptysis (see the Vena Caval Thrombosis and Metastatic Pneumonia section later).

The Bronchopneumonias (Respiratory Disease Complex of Cattle, Sheep, and Goats)

Amelia R. Woolums

The respiratory disease complex of ruminants consists of the single clinical entity of bronchopneumonia or pleuropneumonia but is caused by numerous combinations of infectious agents, compromised host defenses, and environmental conditions. Bronchopneumonia causes greater economic losses than any other disease of feedlot cattle or lambs and is one of the most common causes of mortality in other ruminant populations.

In dairy calves, bronchopneumonia, sometimes called *enzootic pneumonia*, is most common in group-housed calves. It is called *shipping fever* in beef calves because the greatest incidence of bronchopneumonia occurs after shipment to stocker operations or feedlots; the term *bovine respiratory disease* (BRD) or *bovine respiratory disease complex* (BRDC) is also used to describe bronchopneumonia in cattle. Bronchopneumonia also occurs in nursing beef calves, in mature beef or dairy cows, and in young or mature sheep and goats, sometimes in outbreaks that can have significant morbidity and mortality. The infectious agents and risk factors of bronchopneumonia of sheep and goats are similar to those of calves.

Bronchopneumonia of ruminants is a disease of multifactorial causation that occurs when a certain combination of host, environment, and infectious agent characteristics (risk factors) is active. The numerous infectious agents (Boxes 31.3 and 31.4) associated with bronchopneumonia are ubiquitous in ruminant populations, and the bacteria most often associated with pneumonic lesions are part of the normal resident flora of the ruminant nasopharynx. In addition to recognition of the microbial agents that contribute to the development of bronchopneumonia in ruminants, an understanding of the management practices and host factors that also play a role is necessary for developing successful programs of prevention. Management practices and other risk factors for bronchopneumonia are discussed in the Host and Environmental Risk Factors for Undifferentiated Ruminant Respiratory Disease section later.

Box 31.3

Viral Agents Associated With Respiratory

Tract Diseases in Ruminants

Bovine

Viruses of Major Importance (Commonly Isolated or Generally Accepted to Be Important Contributors to Ruminant Respiratory Disease)

- Bovine herpesvirus type 1 (BHV-1, also known as infectious bovine rhinotracheitis virus [IBRV])
- Bovine respiratory syncytial virus (BRSV)
- Bovine viral diarrhea virus (BVDV)
- Bovine parainfluenza virus type 3 (PIV-3)
- Bovine respiratory coronavirus
- Alcelaphine herpesvirus types 1 and 2/ovine herpesvirus type 2 (malignant catarrhal fever)

Viruses of Minor Importance (Uncommonly Isolated or of Uncertain Importance in Ruminant Respiratory Disease)

- Bovine herpesvirus type 4 (BHV-4)
- Bovine adenovirus
- Bovine rhinitis virus
- Bovine reovirus
- Calicivirus
- Influenza virus

Ovine and Caprine

- Bovine respiratory syncytial virus (BRSV)
- Parainfluenza virus type 3 (PIV-3)
- Adenovirus
- Bluetongue virus
- Ovine progressive pneumonia (maedi-visna) virus of sheep[a]
- Pulmonary carcinoma of sheep[a]

[a]Cause of chronic progressive respiratory disease.

Box 31.4

Bacteria, Mycoplasma, Ureaplasma, and Chlamydophila Species Associated With Bronchopneumonia of Cattle, Sheep, and Goats

Bacteria of Major Importance (Commonly Isolated or Generally Accepted to Be Important Contributors to Ruminant Respiratory Disease)

Mannheimia haemolytica
Pasteurella multocida
Histophilus somni
Mycoplasma bovis
Bibersteinia trehalosi
Mycoplasma dispar
Ureaplasma spp.
Mycoplasma ovipneumoniae (sheep and goats only)
Mycoplasma mycoides subsp. *mycoides*, large colony variant (goats)
Trueperella pyogenes (formerly *Arcanobacterium pyogenes*) (secondary opportunistic pathogen)

Bacteria of Minor Importance (Uncommonly Isolated or of Uncertain Importance in Ruminant Respiratory Disease)

Pseudomonas aeruginosa
Escherichia coli
Streptococcus spp.
Staphylococcus spp.
Moraxella spp.
Salmonella spp.

Bacteroides spp. (anaerobe)
Peptococcus indolicus (anaerobe)
Fusobacterium spp. (anaerobe)
Chlamydophila spp.

Infectious Agents Associated With the Respiratory Disease Complex of Cattle, Sheep, and Goats

■ Etiology

Numerous infectious agents have been isolated from cases of bronchopneumonia in ruminants. Although infectious bronchopneumonia of ruminants is usually caused by two or more infectious agents acting together, some agents can also cause significant disease alone. Therefore the clinical and epidemiologic characteristics, means of diagnosis, and treatment and prevention of the infectious agents will be first considered individually. A description of epidemiology, diagnosis, and treatment of "undifferentiated" bronchopneumonia (bronchopneumonia with no specific causative diagnosis attempted) will then follow. The clinical signs, gross pathologic lesions, and recommended methods of diagnosis for the major infectious causes of ruminant respiratory disease are listed in Table 31.14.

Table 31.14

Clinical and Gross Pathologic Characteristics of Common Infectious Agents That Cause Respiratory Disease in Ruminants

Agent	Species	Clinical Signs[a]	Gross Pathology[a]	Diagnosis
Viruses				
BHV-1 (IBR)	Cattle	Fever, depression, anorexia, serous to mucopurulent nasal discharge, muzzle hyperemia, nasal plaques, coughing, inspiratory stridor (conjunctivitis ± keratitis, abortion)	Congestion; fibrinopurulent exudate of nasal passages, larynx, trachea; in young calves, pneumonia and involvement with other organs	VI or IFA nasal swabs, conjunctival scrapings
				PS
				VI, IFA, or IHC of tissue from upper airways or lungs collected at necropsy
BRSV[b]	Cattle, sheep, goats	Fever, depression, anorexia, tachypnea, nasal discharge (±), coughing, expiratory	Lobules in cranioventral lung collapsed, firm, dark red; caudodorsal lung fails to	IFA or RT-PCR of nasal swabs (VI unreliable)

		dyspnea, harsh bronchovesicular sounds over cranioventral lung, crackles and wheezes rarely, quiet lung sounds caused by pneumothorax, subcutaneous emphysema	collapse, rubbery texture (suggestive of acute interstitial pneumonia); dorsocaudal emphysema	PS IFA or IHC of lung at necropsy (most reliable in acute stage of disease)
PIV-3	Cattle, sheep, goats	Like BRSV but more mild, commonly asymptomatic; contributes with other agents to enzootic calf pneumonia or shipping fever	Scattered lobules of cranioventral lung collapsed, firm, dark red	VI or IFA of nasal swabs PS VI, IFA, or IHC of lung at necropsy
BVDV	Cattle	Fever, depression, anorexia, nasal discharge, tachypnea, coughing (±); contributes with other agents to enzootic calf pneumonia or shipping fever (diarrhea, abortion, congenital defects, persistently infected calves, hemorrhagic syndrome)	Scattered lobules of cranioventral lung collapsed, firm, dark red	VI, ELISA. or PCR of peripheral blood buffy coat PS VI, IFA, or IHC of lung at necropsy
Respiratory coronavirus[b]	Cattle	Contributes with other agents to enzootic calf pneumonia or shipping fever	Not yet well characterized, probably as for PI3	VI (need special cells) or RT-PCR of nasal swabs PS VI or IFA of lung at necropsy
Bacteria				
Mannheimia haemolytica	Cattle, sheep, goats	Fever, depression, anorexia, signs of endotoxemia, tachypnea, evidence of pleural pain, mucoid to mucopurulent nasal discharge, harsh bronchovesicular sounds over cranioventral lung ± crackles (coughing not prominent)	Cranioventral lung lobes firm, dark red to gray-brown; fibrin on pleura; yellow pleural fluid that may be gelatinous; infarct-like (wedge-shaped) lesions sometimes seen	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) Culture from characteristic lesions at necropsy
Pasteurella multocida	Cattle, sheep, goats	Fever, tachypnea, cough, depression, mucoid to mucopurulent nasal discharge, harsh bronchovesicular sounds over cranioventral lung ± crackles	Cranioventral lobules (sometimes lobes) firm, dark red to purple; purulent exudate in airways; fibrin on pleura not expected	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret) Culture from characteristic lesions at necropsy
Histophilus somni[b]	Cattle, (uncommon in sheep, goats)	As for *P. multocida;* possibly also evidence of pleural pain (joint effusion, infertility or abortion, otitis, conjunctivitis, neurologic signs)	As for *M. haemolytica*, although fibrinous pleuritis not as consistent; fibrinopurulent arthritis, myocarditis often seen in respiratory cases	Culture from aseptic TTA from animal with signs of disease (nasal swabs difficult to interpret); culture from characteristic lesions at necropsy
Mycoplasma bovis[c]	Cattle	Fever, anorexia, tachypnea, cough, nasal discharge;	Cranioventral lobules collapsed, firm, dark red;	Culture from aseptic TTA from animal with

		chronic or ongoing pneumonia that fails to respond as expected to therapy (joint or tendon sheath effusion, otitis, conjunctivitis)	multiple grossly visible raised nodules filled with caseous material (abscesses or caseous necrosis); (fibrinopurulent arthritis, tenosynovitis, or otitis common in respiratory cases; myocarditis or pericarditis)	signs of disease (nasal swabs difficult to interpret; more meaningful if several in group have positive culture from characteristic lesions at necropsy)

[a]Clinical signs not related to the respiratory system but possibly also prevalent are listed in parentheses. Note that respiratory disease is often caused by two or more agents, so clinical signs and gross pathology in an individual or herd may be any combination of those listed for individual agents.

[b]Agent does not survive transport well or can be difficult to isolate; requires special handling or culture techniques to maximize likelihood of isolation.

[c]Usually need to specifically request tests to isolate mycoplasmas and to specifically identify the species *M. bovis.*

BHV-1, Bovine herpesvirus type 1; *BRSV,* bovine respiratory syncytial virus; *BVDV*, bovine viral diarrhea virus; *ELISA*, enzyme-linked immunosorbent assay; *IBR*, infectious bovine rhinotracheitis; *IFA*, immunofluorescent assay; *IHC*, immunohistochemistry, most commonly used on formalin-fixed lung tissue collected at necropsy; *PCR*, polymerase chain reaction; *PIV-3*, parainfluenza type 3; *PS*, paired serology; *RT-PCR*, reverse transcriptase PCR; *TTA*, transtracheal aspirate; *VI*, virus isolation.

Viral Agents

Many different viruses have been identified in nasal secretions or respiratory tissues of cattle, sheep, or goats with or without respiratory disease. Recent development of next-generation sequencing approaches that allow identication of all viral genomes present in a sample (the “virome” or “viral metagenome”) has revealed even more, sometimes newly recognized respiratory viruses.[1] Historically, five viruses have been considered the most important contributors to the bovine respiratory disease complex: bovine herpesvirus type 1 (BHV-1), bovine respiratory syncytial virus (BRSV), bovine viral diarrhea virus types 1 and 2 (BVDV1 and BVDV2), and parainfluenza virus type 3 (PIV-3). In sheep and goats, BRSV and PIV-3 have been considered important. However, in some recent surveys of cattle or cattle populations with respiratory disease, other viruses have been more prevalent than these five viruses. Also, anecdotal reports suggest that, at least in North America, BHV-1 and PIV-3 are less commonly found in cattle with respiratory disease than they were in the second half of the twentieth century. This may be related to broad population immunity induced by widespread use of vaccines containing these viruses. Thus the relative

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importance ascribed to the viruses described below may be changing.

Bovine Herpesvirus Type 1 (Infectious Bovine Rhinotracheitis Virus)

■ Definition and Etiology

Bovine herpesvirus type 1 (BHV-1) is an enveloped DNA virus of the family *Herpesviridae*, subfamily *Alphaherpesvirinae*, genus *Varicellovirus*. It is associated with multiple, distinct disease syndromes of cattle that include infectious bovine rhinotracheitis (IBR), conjunctivitis (see Chapter 39), infectious pustular vulvovaginitis (IPV), balanoposthitis, abortion (see Chapter 43), encephalomyelitis (see Chapter 35), and mastitis. Two subtypes have been identified on the basis of restriction endonuclease cleavage patterns. These subtypes are referred to as BHV-1.1 and BHV-1.2; BHV-1.2 can be further divided into BHV-1.2a and BHV-1.2b. Either subtype can cause respiratory or genital disease; only the respiratory manifestations of infection are discussed here. The respiratory form is characterized by rhinitis, tracheitis, and pyrexia and is referred to as IBR. BHV-1 can also cause pneumonia as part of a severe generalized infection in young calves.[2,3] The virus is also of importance in the bovine respiratory disease complex because of its role in enhancing secondary bacterial bronchopneumonia by causing respiratory injury and immunosuppression, as discussed later.

■ Clinical Signs

Clinical signs from infection with BHV-1 alone can range from inapparent to severe. Clinical signs can include any combination of pyrexia, anorexia, sharp drop in milk production in dairy cattle, increased respiratory rate, a slight degree of hyperexcitability, ptyalism, coughing, and nasal discharge that progresses from serous to mucopurulent. Clinical signs of lower respiratory tract infection may be caused by secondary bacterial pneumonia, which is a common sequela to BHV-1 infection. Severe hyperemia and reddening of the muzzle can occur, which is the reason for the common name of “red nose” to describe BHV-1 infection. Pustules may develop on the nasal mucosa and later form diphtheritic plaques. Conjunctivitis with excessive ocular discharge may be present. Conjunctivitis with corneal opacity can also occur as the principal manifestation of BHV-1 infection and may be misdiagnosed as infectious bovine

keratoconjunctivitis (pink eye). Abortions may occur concurrently with respiratory disease, but they can also occur well after infection. Abortions may also occur in cattle that escape serious respiratory disease.

On rare occasions, neonatal calves may suffer from an acute respiratory and/or systemic form of BHV-1 infection characterized by rhinitis, marked lacrimation, inflammation and necrosis of the soft palate, laryngotracheitis, and ulceration of the GI tract.[2,3] Vaccination of calves within 3 days of age with modified live viral vaccines has also been associated with severe, fatal systemic BHV-1 infection.[4] The severity of disease in vaccinated calves was suspected to be caused by lack of maternal antibody and resultant widespread multiplication of the vaccine virus.

■ Pathogenesis

The route of infection is by direct contact with infected cattle or aerosol; apparent transmission by aerosol has been recognized among calves separated by as little as 4 m.[5] At least three of the surface glycoproteins of BHV-1, gC, gD, and gB, mediate attachment to host cells and entry through interaction with heparan sulfate proteoglycans and other host cell proteins. Epithelial cells of the respiratory tract are the initial target of infection after respiratory exposure, and after initial infection the virus can spread intracellularly to neighboring cells. Lymphocytes and monocytes are also susceptible to infection; although infection with these cells produces little virus, they appear to be a means by which the virus reaches extrarespiratory sites after respiratory infection. In severe field cases of BHV-1 infection the virus can be found in multiple organs, including the esophagus, spleen, and liver.[6]

Respiratory disease caused by BHV-1 is mediated by two major mechanisms: (1) direct injury and destruction of infected epithelial cells in the upper respiratory tract and bronchi, with resultant inflammation and increased susceptibility to infection with secondary opportunistic pathogens; and (2) immunosuppression resulting from dysfunction of neutrophils, lymphocytes, and macrophages. Immunosuppressive actions of BHV-1 include decreased neutrophil chemotaxis and mitogen-induced blastogenesis of lymphocytes, decreased expression of MHC class I molecules, and induction of apoptotic death of lymphocytes and monocytes.[7]

Another important mechanism of pathogenesis of BHV-1 is the ability to establish latent infection.[8] After acute infection, BHV-1 can be found in a latent

state in the trigeminal ganglia; the virus may also persist latently in the tonsil.[9] During latent BHV-1 infection, virus is not actively produced in infected cells; thus latently infected cattle do not shed virus. However, an RNA molecule called the *latency related transcript* (LRT) is abundantly produced in latently infected cells, which prevents apoptosis in cells receiving signals that should trigger apoptosis.[8] One or more proteins encoded by the LRT appear to be required for the virus to reactivate from latency. Stress or administration of glucocorticoids causes reactivation of the latent virus, leading to shedding of virus and the possibility of infection of in-contact susceptible animals. Latency appears to occur in effectively all cattle that are infected with BHV-1, thus ensuring that the virus can be spread during times of stress by animals that have been free of clinical disease from BHV-1 infection for months to years. Modified live BHV-1 vaccines are also capable of causing latent infections.[10] Calves that are exposed to BHV-1 when they have moderate levels of circulating maternal antibody can develop latent infection while never showing signs of clinical disease.[11] Latency of BHV-1 is thus an important mechanism by which the virus can persist and spread in a group of cattle.

■ Epidemiology

Studies of antibody prevalence to BHV-1 indicate that infection is widely distributed in the cattle population. Latently infected adult cattle are thought to be the principal reservoirs of infection. Infections of the respiratory tract by BHV-1 are prevalent when large concentrations of beef or dairy cattle are assembled, although BHV-1 does not appear to have an important role in enzootic pneumonia of calves. Decreaed milk production has been linked to subclinical BHV-1 infection in dairy cows.[12] In feedlots, “late breaks” of BHV-1 infection and disease can be seen to occur in cattle previously vaccinated against BHV-1.[13] Although BHV-1 is a relatively genetically stable virus, there is evidence that mutations are occurring in BHV-1 isolates currently circulating in cattle populations, which may help the virus escape host immunity.[13] Although commercially available vaccines can still prevent disease resulting from experimental challenge with modern BHV-1 isolates, viral shedding is increased relative to cattle challenged with older BHV-1 isolates that are more similar to the strains included in vaccines.[13,14] Repeat vaccination later in the feeding period has been recommended to decrease risk of late BHV-1 breaks.[15]

■ Necropsy Findings

IBR is rarely fatal in mature cattle unless it is complicated by secondary bacterial infection of the lung. Lesions include rhinitis, laryngitis, and tracheobronchitis. The mucosa of the nasal passages and trachea can be congested or hemorrhagic. Pustular lesions (sometimes referred to as “plaques”) may be observed, and these lesions may coalesce to form adherent necrotic material on respiratory (Color Plate 31.2), ocular, and reproductive mucosa. Usually the inflammatory lesions induced by BHV-1 do not extend into airways contained within the lung, but secondary bacterial bronchopneumonia with the expected pathology is common. Conjunctivitis and, less commonly, keratitis may be present. Esophageal erosions have been identified in severe natural outbreaks.[6] Perinatal infection of calves can lead to fatal systemic disease, with necrotic foci found in the liver, adrenal glands, kidneys, and other organs.[3,4] Although intranuclear inclusion bodies are a feature of herpesvirus infections, they are not a common histologic feature of BHV-1.

■ Diagnosis

BHV-1 can be diagnosed by PCR, virus isolation, immunofluorescent antibody (IFA) testing, or immunohistochemistry (IHC) to identify virus or viral nucleic acid in nasal swabs or conjunctival scrapings antemortem or in tissues collected postmortem. Infection can also be diagnosed by paired serology, with tests for serum neutralizing (SN) antibodies most commonly used.

■ Treatment and Prevention

Cattle infected with BHV-1 should receive supportive care. Good-quality feed and water should be made easily available, and additional stressors such as transport, castration or dehorning, or introducing new cattle to the group should be avoided or postponed. NSAIDs such as flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) may help severely affected individuals maintain water and feed consumption. Administration of antimicrobials to treat or prevent secondary bacterial pneumonia may be appropriate (Table 31.15), although these are not invariably required. Steroids should not be administered. Because protective immunity develops rapidly after either intranasal or IM vaccination,[16,17] BHV-1 vaccination in the face of an outbreak may help limit disease, although the efficacy of this practice has not been tested in a controlled study.

Table 31.15

Antimicrobials Approved by the U.S. Food and Drug Administration for Treatment of Bovine Respiratory Disease

Antimicrobial	Label Dose	Route of Administration	Treatment Interval	Slaughter/Milk Withdrawal	Approved for Control of BRD? (Metaphylaxis)	Appr for Sh and Goats
Long-Acting Preparations						
Ceftiofur crystalline free acid[a] (Excede)	6.6 mg ceftiofur equivalent/kg (1.5 mL/45 kg)	SC in the ear	Once	13 days/0 days	Yes	No
Danofloxacin[b] (Advocin)	8 mg/kg	SC	Once	4 days/not approved	No	No
	6 mg/kg	SC	48 h (no more than 2 doses total)	4 days/not approved	No	No
Enrofloxacin[b] (Baytril 100)	7.5-12.5 mg/kg	SC	Once	28 days/not approved	Yes (7.5 mg/kg dose only)	No
Florfenicol (Nuflor)	20 mg/kg	IM	48 h	28 days/not approved	No	No
	40 mg/kg	SC	Once	38 days/not approved	Yes	No
Florfenicol (Nuflor Gold	40 mg/kg	SC	Once	44 days/not approved	No	No
Gamithromycin (Zactran)	6 mg/kg	SC	Once	35 days/not approved	Yes	No
Oxytetracycline (Liquamycin LA-200	20 mg/kg	IM, IV, SC	48-72 h	28 days/96 h	No	No
Oxytetracycline (Tetradure 300)	30 mg/kg	IM, SC	Once	28 days/not approved	Yes	No
Tildipirosin (Zuprevo)	4 mg/kg	SC	Once	21 days/not approved	Yes	No
Tilmicosin (injectable: Micotil 300)	10-15 mg/kg	SC	Once	42 days/not approved	Yes	Sheep toxic goats
Tulathromycin (Draxxin)	2.5 mg/kg	SC	Once	18 days/not approved	Yes	No
Preparations for Daily Use					No	
Ampicillin (Polyflex)	4.4-11 mg/kg	IM	24 h	6 days/48 h	No	No
Ceftiofur sodium[a] (Naxcel)	1.1-2.2 mg/kg	IM, SC (cattle) IM (sheep and goats)	24 h for 3 days, with 2 more days allowed if not yet recovered	Cattle: 4 days/0 days Sheep and goats: 0 days/0 days	No	Yes
Ceftiofur HCl[a]	1.1-2.2	IM, SC	24 h for 3	3 days/0 days	No	No

(Excenel RTU)	mg/kg		days, with 2 more days allowed if not yet recovered			
	2.2 mg/kg	IM, SC	48 h for 2 doses total	3 days/0 days	No	No
Enrofloxacin[b] (Baytril 100)	2.5-5 mg/kg multiday therapy	SC	24 h for 3 days, with 2 more days allowed if clinical improvement	28 days/not approved	No	No
Erythromycin (Gallimycin-100)	9 mg/kg	IM	24 h	6 days/not approved	No	Sheep
Oxytetracycline(various preparations)	6.6-11 mg/kg	IV,[c] IM,[c] SC[c]	24 h	Varies with preparation	No	Not fo inject
Procaine penicillin G (various preparations)	6600 U/kg (22,000 U/kg)[e]	IM	24 h	Varies with preparation	No	Sheep
Sulfadimethoxine (Albon, Di-Methox)	55 mg/kg, initial treatment 27.5 mg/kg thereafter	IV, PO	24 h	Varies with preparation	No	No
Tylosin (Tylan-200)	17.6 mg/kg	IM	24 h	21 days/not approved	No	No

[a]In cattle, use of an extralabel dose level, frequency, duration, or route prohibited by law.

[b]Extralabel use in food animals prohibited by law.

[c]Varies with preparation.

[d]Oxytetracycline is labeled for administration to sheep in feed; not a recommended route for treatment of respiratory disease.

[e]Dose that has been shown to be more effective than label-approved dose. Higher dose can be given by the same route of administration and with the same treatment interval, but use of extralabel dosages must comply with the Animal Medicinal Drug Use Clarification Act (AMDUCA) and withdrawal times must be extended.

Note: Many of the drugs listed in this table are not approved for use in veal calves; some are not approved for use in lactating dairy cattle.

BRD, Bovine respiratory disease; *IM*, intramuscular; *IV*, intravenous; *PO*, oral; *SC*, subcutaneous.

Efforts to prevent BHV-1 infection should include practices that optimize host immunity and avoiding management practices that put cattle at risk, such as mixing newly introduced cattle with established populations. Many brands of inactivated and attenuated BHV-1 vaccines for SC or IM administration are commercially available; products that contain BHV-1 alone or in combination with other pathogens are available. Modified live vaccines are also available for

intranasal administration; intranasal vaccines also include PIV-3 with or without BRSV. Vaccination to prevent disease due to BHV-1 infection is discussed in detail in Chapter 48. It is important to remember that vaccination can complicate efforts to identify viruses that may be causing outbreaks of bovine respiratory disease. It appears that live virus is more likely to be shed from cattle vaccinated with modified live vaccines given intranasally, as compared to vaccines given by injection.[18] However, viral DNA can be identified by PCR of nasopharngeal swabs or transtracheal aspirates for 28 days after cattle are vaccinated either intranasally or subcutaneously with modified live virus vaccine.[19] This makes it difficult to interpret the results of PCR testing of respiratory samples when trying to diagnose BHV-1 infection in cattle that have been recently given modified live vaccines.

Other Herpesviruses

Bovine Herpesvirus Type 4

Bovine herpesvirus type 4 (BHV-4) is in the subfamily *Gammaherpesvirinae,* genus *Rhadinovirus;* therefore it is serologically distinct from BHV-1. The seroprevalence of BHV-4 is high in the cattle population of the United States, and it has been implicated in several disease conditions of cattle, including reproductive disorders (abortions and metritis), mammillitis, enteric disease, and respiratory disease. However, BHV-4 can also be isolated from apparently healthy cattle. The role of BHV-4 in bovine respiratory disease has not been well defined.

Herpesviruses Causing Malignant Catarrhal Fever

Malignant catarrhal fever (MCF) is a sporadic disease of cattle with systemic manifestations that can include signs of respiratory disease. In North America, MCF is usually caused by ovine herpesvirius type 2, a gammaherpesvirus acquired by cattle exposed to sheep shedding the virus. MCF can also occur in cattle infected with alcelaphine herpesvirus types 1 and 2 or other related viruses, which can be acquired by exposure to infected exotic hoofstock. MCF is discussed in detail in Chapter 32.

Bovine Respiratory Syncytial Virus

■ Definition and Etiology

Bovine respiratory syncytial virus (BRSV) is an enveloped RNA virus recently moved from the family *Paramyxoviridae* to the new family *Pneumoviridae,* genus *Orthopneumovirus.*[20] This virus is named for the characteristic cytopathic effect it produces in vitro and in vivo, which is the formation of syncytial cells. BRSV shares many similarities in its biology and epidemiology with the human respiratory syncytial virus (HRSV), a common respiratory pathogen of humans with particular importance in disease of young children and the elderly. Although BRSV and HRSV are closely related, they are distinct viruses. BRSV has also been isolated from sheep and goats with respiratory disease. Research suggests that ovine respiratory syncytial virus (also known as ovine pneumovirus) may be distinct from HRSV and BRSV, whereas caprine respiratory syncytial virus (also known as caprine pneumovirus) may be more closely related to BRSV.[21] A European serologic survey undertaken to determine whether nonbovine species were likely to harbor BRSV infection found that only goats, in addition to cattle, were commonly seropositive.[22] These results indicate either that goats are commonly infected with BRSV or that antigenic similarities between caprine respiratory syncytial virus and BRSV led to production of cross-reactive antibodies in many goats. In spite of minimal to moderate differences among BRSV isolates at the genetic level, isolates can differ notably in their reactivity, with monoclonal antibodies directed against individual BRSV proteins; this indicates that apparently minor genetic differences could lead to changes that allow the virus to evade host immunity. Genetic variability is evident in BRSV isolates collected over several decades, and BRSV isolates commonly included in commercial vaccines can differ a relatively large amount from isolates collected from recent natural outbreaks.[23,24] Studies have also shown that genetic differences in BRSV isolates can be grouped by geographic origin, with some European isolates differing to a notable degree from isolates from the United States or Japan.[23] These changes appear to be driven by vaccination; thus commercial vaccines may need to be reformulated periodically to include BRSV similar to isolates currently circulating.

■ Clinical Signs

Clinical signs of BRSV infection alone can vary from inapparent to severe in an infected group of cattle. Signs of disease are limited to the respiratory system. Infected animals may display elevated rectal temperature, depression, decreased

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feed intake, elevated respiratory rates, ptyalism, cough, and nasal and lacrimal discharges. Signs of disease may progress rapidly, and early signs may be missed. Thoracic auscultation may reveal increased bronchial and bronchovesicular sounds; fine crackles or wheezes may be heard, particularly in the middle or dorsocaudal lung fields. Absence of bronchovesicular sounds may be noticed in the dorsal or dorsocaudal lung fields if an emphysematous bulla is present, or if a bulla has ruptured, leading to pneumothorax. In later stages of the disease, dyspnea can become pronounced and is characterized by increased expiratory effort and mouth breathing. Subcutaneous emphysema and intermandibular edema are sometimes noted. Dramatic reduction in milk production has been reported in dairy cattle. Duration of disease is variable (1 to 2 weeks). A biphasic clinical course has been described but does not appear to be a consistent finding. Infection can also cause clinical signs of respiratory disease in sheep, goats, and deer; however, the severe clinical signs, including dyspnea and subcutaneous emphysema, which are sometimes seen in cattle and suggest AIP, do not seem to be seen in small ruminants or cervids.

■ Pathogenesis

The means of transmission appears to be contact with infected cattle and aerosols. Fomites such as bottles and buckets are also a likely means of transmission, as HRSV is spread by fomites. The incubation period is 3 to 5 days. Infection with BRSV can cause bronchitis, bronchiolitis, alveolitis, and interstitial pneumonia, leading to clinical signs referable to small airway and alveolar disease, including expiratory dyspnea, auscultable wheezing, and hypoxemia. The virus causes epithelial cells to fuse, resulting in the characteristic multinucleated cells, or syncytia, which are seen in airways and alveoli. Epithelial cells, which may undergo apoptosis after BRSV infection, slough into the lumen of airways and are phagocytized by neutrophils or alveolar macrophages. Infection of alveolar macrophages and circulating peripheral blood mononuclear cells occasionally occurs,[25,26] and BRSV infection of macrophages decreases important functions of these cells, including Fc receptor expression, phagocytosis, phagosome-lysosome fusion, and production of factors that induce neutrophil chemotaxis.[27,28]

The severity of disease after BRSV infection is related to host immunity. Both humoral and cell-mediated immunity contribute to protection. Clinical signs of infection are less severe in animals with moderate to high levels of serum

antibody against BRSV,[29,30] and more extensive pathology is seen in calves depleted of CD8+ T cells before infection.[31] Protection after intranasal vaccination is related to rapid onset of BRSV-specific IgA production in nasal secretions,[32] indicating that mucosal immunity is likely also important in protection against naturally occurring disease. Host immunity after exposure to BRSV can minimize disease, and clinical signs are usually the most noticeable in calves younger than 6 months of age. However, very young calves are not necessarily most likely to have the most severe disease; clinical signs after experimental infection were less severe in 1-day-old calves than in 6-week-old calves, apparently due to a less robust inflammatory response in younger calves.[33] Ruminants appear to be susceptible to reinfection with BRSV throughout their lives, and adult cattle can develop severe disease after BRSV infection.[34,35] Because genetic variability among BRSV isolates is not great, reinfection does not seem to be largely due to viral strain variation. It appears that natural infection does not confer lifelong immunity, and some cattle may be reinfected annually,[36] although clinical signs are not always apparent.

Although host immunity can protect ruminants from severe disease after BRSV infection, the host immune response can also contribute to disease. Cattle with severe disease after natural infection have a higher proportion of degranulated mast cells in their lungs than less severely affected cattle,[37] indicating that mast cell mediators contribute to physiologic and pathologic changes seen in severe cases. In experimentally challenged cattle, BRSV-specific IgE has been associated with disease severity.[38] Exposure to the fungus *Saccharopolyspora rectivirgula* (formerly *M. faeni*), the spores of which induce pulmonary hypersensitivity in cattle and other species, enhanced BRSV-specific IgE production in calves,[38] indicating that environmental allergens can affect the immune response to BRSV infection. Calves infected with BRSV before infection with *Histophilus somni* developed higher levels of *H. somni*–specific serum IgE than did calves infected with *H. somni* alone.[39] Thus BRSV infection can lead to production of virus-specific IgE, which may be enhanced by coexposure to allergens, and BRSV infection may also increase IgE production in response to infection with other agents. Crosslinking of IgE bound to mast cells by binding of BRSV or other specific antigen is expected to lead to mast cell degranulation and subsequent bronchoconstriction, pulmonary edema, and other sequelae of mast cell mediator release and immediate hypersensitivity.

Other evidence that BRSV can trigger immunopathogenesis is the fact that

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certain BRSV vaccines have on rare occasion been shown to cause enhanced disease when vaccinated animals are subsequently infected with BRSV. Vaccine-enhanced disease has been seen after both natural[40,41] and experimental infection.[42,43] It appears that the dose of BRSV protein, the adjuvant included in the vaccine, and probably also other factors related to the formulation of the vaccine and the genetics of vaccinated cattle determine whether enhanced disease is likely after infection of cattle given a particular BRSV vaccine. Apparent vaccine-enhanced disease was reported in cattle that received a modified live vaccine in the early stage of a natural BRSV outbreak, which suggests that BRSV vaccination in the face of a BRSV outbreak could be harmful.[40] It is important to note that BRSV vaccines are commonly used, and vaccine-enhanced disease is rarely reported; thus vaccination is still recommended as part of any plan to control disease caused by BRSV. Many gaps exist in our understanding of what aspects of the immune response contribute to disease severity after BRSV infection or vaccination. Most research completed to date has focused on enhanced disease in calves that received formalin-inactivated BRSV. The data suggest that when enhanced disease occurs in calves vaccinated with formalin-inactivated BRSV, it is related to a relatively strong response by T-helper type 2 (Th2) cells, as evidenced by decreased production of the Th1 prototype cytokine interferon gamma,[44] increased production of BRSV-specific IgE,[45] and pulmonary eosinophil infiltration.[42] The association of BRSV-specific IgE production with disease severity in some experimental studies indicates that at least some individual ruminants will produce IgE after BRSV vaccination or infection, which may contribute to severe disease in these individuals.

The presence of co-infection with other pathogens such as *M. haemolytica* or bovine viral diarrhea virus (BVDV) can also increase the severity of disease after BRSV infection. Although genetic variation among BRSV isolates is not extensive, experimental challenge with certain isolates of BRSV can lead to serious disease, whereas challenge with other isolates leads to only minimal disease. This indicates that, despite limited differences among viral isolates at the genetic level, variation among BRSV isolates may still contribute to variations in disease severity.

■ Epidemiology

Prevalence of antibodies to BRSV in the cattle population of the United States

ranges from approximately 60% to 80%. Seropositive sheep, goats, and deer are commonly identified in domestic or wild populations, confirming that infection occurs in these species. Cattle of any age are susceptible to disease following BRSV infection. BRSV was demonstrated to be involved in 14% to 71% of respiratory disease outbreaks in North American and European studies of calf pneumonia outbreaks involving several farms. In a recent survey of more than 1300 dairy herds in Norway, herd size, geographic location, and closer proximity to neighboring herds were related to increased risk for a herd to have evidence of BRSV exposure, based on antibodies in bulk tank milk.[46] Herds that were positive for BRSV antibodies in bulk tank milk were more likely also to be positive for antibodies to bovine coronavirus. Seroconversion to BRSV has been significantly associated with treatment for respiratory disease in feedlot cattle,[47] and cattle with low antibody titers to BRSV at feedlot entry have increased risk of developing disease.[48] Although feedlot cattle are commonly infected with BRSV after arrival, a survey of necropsy findings at 72 Canadian feedlots found BRSV at postmortem of only 11% of the cattle that died or were euthanized because of pneumonia.[49] The low rate of isolation at necropsy suggests that if the virus contributes to disease in feedlot cattle, it is often no longer present by the time the animal dies or is euthanized. In general, morbidity rate tends to be high in outbreaks of BRSV, whereas case fatality rate is variable, ranging from 0% to as high as 20%.[50]

Cattle are most likely the principal reservoirs of infection, although a European serologic survey of different species found that goats were also often seropositive,[22] indicating that goats may be a source of BRSV infection for cattle, and vice versa. The mechanism by which BRSV persists in the cattle population is not known. Possibly a similar epidemiologic pattern to that described for HRSV also exists for BRSV. HRSV is capable of reinfecting the host throughout his or her life, with the most severe disease occurring in the very young or elderly. Subsequent exposure results in mild upper respiratory tract disease. Similarly, adult cattle may periodically undergo subclinical to mild infections and serve as a source of infection for susceptible young stock. However, one study concluded that transmission among seropositive cattle was not a plausible mechanism of BRSV persistence in a dairy herd.[51] These authors suggested that persistent BRSV infection in individuals is a more plausible explanation of population persistence of BRSV. BRSV has been identified in B lymphocytes in tracheobronchial and mediastinal lymph nodes of calves 71 days

after experimental infection,[52] so it may be that individual cattle harbor the virus long term and periodically begin shedding it, allowing it to periodically reappear in herds even if they are closed to new introductions.

■ Necropsy Findings

Grossly, in cattle that die or are euthanized after BRSV infection, individual cranioventral lobules may appear dark and collapsed because of atelectasis or consolidation. Dorsocaudal lung often fails collapse and may have a rubbery texture suggesting AIP. In severe cases, interstitial or bullous emphysema is often present in the dorsocaudal lung (Color Plate 31.3). Pathologic emphysema must be differentiated from that sometimes caused by agonal breathing of cattle. Histologic lesions depend on the stage of infection. Neutrophilic and later mononuclear bronchitis, bronchiolitis, and alveolitis are present in infected animals. Syncytial cells may be seen in the airways or alveoli; intracytoplasmic inclusion bodies are rarely present. BRSV infection can cause lesions consistent with AIP; therefore differential diagnoses for the typical gross lesions include other causes of AIP (see the Feedlot Acute Interstitial Pneumonia section later in this chapter). Histologic changes consistent with AIP include alveolar epithelial hyperplasia, hyaline membrane formation, and interstitial inflammatory cell infiltrate, hemorrhage, and edema. Later, evidence of chronic bronchitis and bronchiolitis obliterans can be found.

■ Diagnosis

Infection is diagnosed by identification of the virus in nasal secretions, tracheal aspirates, or lung lavage fluid from live calves or in lung tissue collected postmortem. BRSV is difficult to isolate, as it does not survive transport well; thus methods of identification that do not require the virus to be alive (such as IFA, IHC, and RT-PCR) are preferable to virus isolation for the identification of BRSV. IHC of formalin-fixed tissue is convenient because the virus can be identified in tissue processed for histopathologic evaluation. Although virus is readily identifiable in the first days after infection, virus is less likely to be found by 10 to 15 days postinfection, even when lung tissue collected postmortem is tested by IHC.

Seroconversion as evidenced by paired serology also supports a diagnosis; virus neutralization or ELISA assays are most commonly used to identify BRSV-specific antibody. In live cattle, the arterial partial pressure of oxygen (PaO_2) is

highly negatively correlated with the extent of lung pathology.[53]

■ Treatment and Prevention

Treatment of BRSV is supportive and aimed at limiting the inflammatory response in bronchioles and alveoli and preventing secondary bacterial infection. Antiinflammatory therapy with NSAIDs (such as flunixin meglumine at 1.1 to 2.2 mg/kg IV daily or divided twice daily) is considered appropriate. Administration of one or two doses of steroid therapy (dexamethasone, 0.05 to 0.2 mg/kg IV or IM once or twice) is appropriate in selected individuals with severe respiratory distress or evidence of AIP. Antimicrobials to treat or prevent secondary bacterial infection may be indicated, although these are not invariably required. For rare individuals with severe signs suggesting AIP, insufflation with intranasal oxygen, if available, and diuretic therapy with furosemide (0.5 to 1 mg/kg IM or IV once or twice daily) may be helpful. Although the prognosis for animals with uncomplicated BRSV infection is good, the prognosis for animals with AIP is guarded. Animals with severe respiratory distress should be handled with care, as even careful manipulation to administer treatment can lead to rapid respiratory decompensation and death.

Both modified live and inactivated BRSV vaccines for intramuscular or subcutaneous administration are commercially available, as are modified live multivalent vaccines for intranasal administration. More information on the use of vaccines to prevent disease due to BRSV is presented in Chapter 48. There is no respiratory syncytial virus vaccine licensed for use in small ruminants, although BRSV vaccines ares sometimes administered to sheep or goats in an extralabel manner. Controlled studies of the effects of BRSV vaccines licensed for cattle on respiratory disease in sheep or goats have not been published.

Bovine Viral Diarrhea Virus

BVDV is an enveloped RNA virus of the genus *Pestivirus* in the family *Flaviviridae*. A wide spectrum of disease has been associated with BVDV infection, including subclinical infection, bovine viral diarrhea and mucosal disease (see Chapter 32), immunosuppression, repeat breeding problems, abortion, fetal mummification (see Chapter 43), congenital defects, immunotolerance, and persistent infections. Only the contribution of this virus to respiratory disease is discussed here.

Historically the role of BVDV in the bovine respiratory disease complex was

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controversial, but research provides good evidence that the virus contributes to bovine respiratory disease and related decreased productivity of cattle in the field in at least some cases. Experimental challenge of cattle with BVDV alone can lead to mild pneumonia,[54] and occasionally herd outbreaks of BVDV are first identified by the presence solely of signs that are likely to be interpreted as evidence of respiratory disease, such as fever, tachypnea, and loud bronchovesicular sounds.[55] Experimental infection studies have also shown that respiratory disease caused by *M. haemolytica,* BHV-1, or BRSV is significantly more serious when cattle are co-infected with BVDV. This synergistic effect of BVDV with other respiratory pathogens is believed to be a result of immunosuppression caused by BVDV, which is discussed in detail in Chapter 32. The ability of BVDV to cause respiratory disease appears to depend in part on the strain of infecting virus.[56,57]

Studies of naturally occurring bovine respiratory disease have shown that in some situations BVDV can be isolated from a majority of cattle affected with shipping fever pneumonia, particularly in association with *M. haemolytica*[49] or in association with *Mycoplasma bovis* in animals with chronic pneumonia.[58] Seroepidemiologic studies have also indicated an association of BVDV with respiratory disease. The most convincing data have come from studies of calves purchased and assembled at sale barns for shipment to feedyards across several states.[59] In 2 consecutive years BVDV was significantly more likely to be isolated from calves that were treated for respiratory disease than calves in the same group that were not treated; calves treated for respiratory disease were also significantly more likely to seroconvert to BVDV than penmates who were not treated for respiratory disease.

In addition to contributing directly to bovine respiratory disease by infecting the respiratory tract and enhancing the pathogenicity of co-infecting bacteria or viruses, BVDV may also contribute to respiratory disease by impairing the ability of cattle to respond properly to vaccination against other respiratory pathogens. Calves infected with BVDV before BHV-1 vaccination shed BHV-1 longer after subsequent BHV-1 infection than calves that were not co-infected with BVDV.[60] In another study, calves persistently infected with BVDV failed to develop a serologic response to a *M. haemolytica* vaccine, in contrast to control animals not infected with BVDV.[61]

In summary, BVDV infection is significantly associated with the development of bovine respiratory disease in some cases. Although experimental challenge

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studies indicate that BVDV may cause mild respiratory disease when acting alone, the virus appears to contribute most importantly by impairing the host's ability to resist infection and limit disease caused by other pathogens.

Bovine Parainfluenza Virus 3

■ Definition and Etiology

Bovine parainfluenza virus 3 (PIV-3) (also known as bovine respirovirus 3) is an enveloped RNA virus classified in the family *Paramyxoviridae*, genus *Respirovirus*. The virus has been associated with respiratory tract disease in cattle, sheep, and goats. It hemagglutinates and hemadsorbs red blood cells of certain species, which means that serum antibodies can be identified by hemagglutination inhibition assays. Variation in virulence among strains of PIV-3 has been reported, with types A, B, and C being characterized.[62] Naturally circulating isolates appear to be diverging genetically from strains in vaccines, likely due to immune pressure associated with vaccination.[62,63] Significant similarities between bovine PIV-3 and human PIV-3 have led to efforts to use bovine PIV-3 as a modified live intranasal vaccine for humans.[64]

■ Clinical Signs

Uncomplicated PIV-3 infections result in mild signs of disease at most. Clinical signs, if present, may include fever, cough, nasal and ocular discharge, increased respiratory rate, increased bronchovesicular sounds, and wheezes. The most important role of PIV-3 is in predisposing the respiratory tract to subsequent infection by other viruses and bacteria such as *Mannheimia (Pasteurella) haemolytica.* Severity of signs increases with the development of secondary bacterial pneumonia, and if death occurs it is usually the result of secondary bacterial infection. Infection with PIV-3 is widespread in sheep and goats. Only one serotype of ovine PIV-3 has been identified, and it is related to but distinct from the bovine strain. Most infections are inapparent to mild.

■ Pathogenesis

Infection with PIV-3 can lead to signs referable to both upper and lower respiratory tract infection. After experimental infection of calves, clinical signs are evident by 2 days post infection, and signs peak at 4 days post infection. Virus is found in the nasal passages, trachea, and bronchiolar and alveolar

epithelial cells. The virus damages the pulmonary mucociliary apparatus[65] and depresses several important functions of alveolar macrophages such as Fc receptor expression, phagocytosis, and microbicidal activity,[66] which likely predisposes infected animals to secondary bacterial pneumonia.

■ Epidemiology

The widespread prevalence of antibodies to PIV-3 indicates that it commonly circulates in ruminant populations. A recent survey of unvaccinated ungulates in one U.S. state indicated that circulating PIV-3 strains may be diverging antigenically from the strains included in vaccines.[63] Inapparent or subclinical infections with PIV-3 are common; in one report, 28 groups of calves seroconverted to PIV-3 over 8 months, but respiratory disease was seen in association with PIV-3 infection in only four of these groups.[67] Infection appears to spread rapidly in susceptible cattle housed at high population densities and in close contact. Feedlot cattle commonly seroconvert to PIV-3 soon after feedlot arrival, and seroconversion has been associated with treatment for respiratory disease in some[48] but not other[47] cases. In spite of the fact that feedlot cattle frequently become infected with PIV-3 after feedlot entry, a survey of necropsy findings at 72 Canadian feedlots found PIV-3 at postmortem examination in only 4% of the cases with pneumonia.[49] The low rate of isolation at necropsy suggests that if the virus contributes to the development of pneumonia, it may no longer be present by the time the animal dies.

■ Necropsy Findings

Lesions of PIV-3 infection alone are rarely seen during postmortem examination of naturally affected cases. Experimental PIV-3 infection results in congestion of the respiratory mucosa, swelling of lymph nodes associated with the respiratory tract, and lobular consolidation concentrated in the cranioventral lung.[68] Bronchiolitis and alveolitis are seen histologically with both proliferative and degenerative changes in the epithelial cells of the bronchioles and alveoli. Syncytia and intranuclear and intracytoplasmic inclusion bodies may be seen. In many respects, pathologic features of experimental PIV-3 infection are similar to but more mild than those caused by BRSV.

■ Diagnosis

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PIV-3 can be identified by virus isolation or RT-PCR of nasal swabs from infected animals. Unlike BRSV, which is also a paramyxovirus, PIV-3 is not particularly difficult to isolate. Diagnosis can also be confirmed with paired serology, with virus neutralization or hemagglutination inhibition assays most commonly used.

■ Treatment and Prevention

There is no specific treatment for infection with PIV-3; as described for BHV-1 and BRSV, supportive care is indicated. Other management practices to prevent or control respiratory disease in calves or feedlot cattle are also appropriate.

Both inactivated and modified live multivalent vaccines containing PIV-3 with other viruses are available for parenteral administration, and modified live vaccines containing PIV-3 and BHV-1, with or without BRSV, are available for intranasal administration; these vaccines are labeled for use in cattle but not in sheep or goats. More information regarding the use of vaccines to control disease due to parainfluenza virus infection is presented in Chapter 48.

Bovine Coronavirus

■ Definition and Etiology

Bovine coronavirus (BCoV) is an enveloped positive-sense RNA virus in the family *Coronaviridae*, genus *Betacoronavirus*, species *Betacoronavirus 1*. Other coronaviruses also classified in the species *Betacoronavirus 1* include equine coronavirus, porcine hemagglutinating encephalomyelitis virus, and human coronavirus OC43, one of the causes of the common cold. Although BCoV is not zoonotic, the virus is thought to have evolved from a human coronavirus, possibly in the late nineteenth century.[69] BCoV causes calf diarrhea and winter dysentery, and the virus also has been associated with respiratory disease outbreaks in calves and feedlot cattle. Sequencing of the gene encoding the spike (S) protein, which the virus uses to attach to and enter host cells, indicates that recent isolates from outbreaks of respiratory disease, winter dysentery, and hemorrhagic colitis in postweaned calves are divergent from older calf diarrhea isolates, including one BCoV included in a modified live virus vaccine currently marketed for control of calf diarrhea.[70,71] It has been postulated that BCoV is evolving over time and now is more prone to causing respiratory disease while also causing enteric disease—a “pneumoenteric” tropism. Outbreaks of

respiratory disease associated with BCoV infection are usually due to a single dominant genotype. Recent studies in Scandinavia indicate that strains circulating on farms in a region can be genetically closely related, with more than 95% similarity in the sequence of the S gene.[69]

Antibodies to older BCoV isolates can cross-react with more recent isolates but incompletely; thus animals vaccinated with the modified live vaccine for control of calf diarrhea may not be completely protected from newer genetically divergent isolates.

■ Clinical Signs

Infection with BCoV has been associated with outbreaks of calf diarrhea (Chapter 20) and winter dysentery (Chapter 32), as well as respiratory disease in dairy and beef calves and feedlot and stocker cattle. Although it has long been known that BCoV can be identified on nasal swabs collected from calves with signs of respiratory disease or diarrhea, the role of BCoV as a "cause" of bovine respiratory disease has been controversial. Calves with diarrhea due to BCoV infection can shed the virus in nasal secretions as well as feces (though not always from both sites at the same time) in the absence of signs of respiratory disease. Moreover, experimental infection of seronegative naive calves can reliably cause diarrhea but inconsistently leads to respiratory disease, with respiratory signs being mild at most. This failure to clearly fulfill Koch's postulates has contributed to skepticism regarding BCoV as a cause of bovine respiratory disease. However, one group of researchers used Evans' criteria of causation to support a role for BCoV in feedlot respiratory disease.[72] A relevant role for BCoV in bovine respiratory disease has also been inferred by identification of BCoV in multiple animals during acute respiratory disease outbreaks,[72,73] by identification of BCoV infection or seroconversion as a significant risk factor for respiratory disease in individuals or herds,[74-76] or by finding cattle with preexisting serum antibodies to BCoV to be protected from respiratory disease when seronegative cattle are not.[77] However, other studies have failed to identify a relationshiop between BCoV infection or seroconversion and respiratory disease. At this time it seems that BCoV is likely a contributor to bovine respiratory disease outbreaks in some cases, but finding the virus may not mean that it is the primary cause of disease. Variation in respiratory virulence among BCoV strains may be important, but if so the features that make a strain more or less likely to cause respiratory disease have

not yet been defined.

Clinical signs of respiratory disease attributed to BCoV are nonspecific and may include fever, nasal discharge, rapid respiratory rate, and coughing. Rectal temperatures may be high (up to 107° F [41.7° C]). Although mortality rates in uncomplicated outbreaks are usually low, secondary bacterial infection due to *Mannheimia haemolytica*, *Histophilus somni*, or other opportunistic respiratory pathogens can lead to fatal disease in multiple individuals.[78,79] Coinfection with other respiratory viruses may also occur.

■ Pathogenesis

The lack of a reliable experimental model of respiratory disease following BCoV infection, as well as the fact that fatal, naturally occurring cases are typically affected by secondary bacterial infection, makes it difficult to clearly define the pathogenesis of respiratory disease specifically due to BCoV infection. The virus infects respiratory epithelial cells, presumably inducing a host response that leads to clinical signs of airway inflammation. Infection of respiratory epithelial cells may increase susceptibility of cattle to secondary bacterial infection through inhibition or the mucociliary elevator.

■ Epidemiology

Respiratory disease has been attributed to BCoV infection in dairy calves,[74] preweaning beef calves,[75] and feedlot and stocker cattle.[79] Coronaviruses similar to BCoV have also been identified in wild ruminants, cervids, and camelids,[80] suggesting that cross-infection among different species may be possible. In dairy calves and preweaning beef calves the virus appears to contribute to enzootic pneumonia as well as to epizootics (outbreaks) of variable morbidity and usually low mortality. Two naturally occurring outbreaks of respiratory disease (shipping fever) attributed to BCoV in feedlot cattle were described in a detailed report.[79] In these outbreaks, characterized by high morbidity and mortality, BCoV was isolated from the nasal passages of more than 80% of the cattle in the early stages of the outbreaks. No other respiratory viruses were identified in most of the cattle, but *M. haemolytica* was also isolated from a majority of cattle as the two epizootics progressed. In another report, calves with low antibody titers to BCoV at feedlot entry were more likely to be treated for respiratory disease than calves entering the feedlot with higher titers.[77] Other researchers have commonly found the virus when cattle are sampled soon after feedlot entry.[81]

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Moreover, it is common for a majority of cattle to have serum antibody titers to BCoV at feedlot arrival or to seroconvert soon after arrival; therefore it is clear that cattle are often infected with BCoV shortly before or after feedlot entry.[81-83] However, seroconversion or viral shedding has not always been significantly associated with treatment for respiratory disease.[83]

Surveys of antibodies in pooled milk samples or bulk tank milk on dairies indicated that large herd size, geographic location, and closer proximity to neighboring herds were risk factors for BCoV exposure.[46,84] Dairy herds positive for BCoV antibodies in bulk tank milk were more likely also to be positive for antibodies to BRSV. Genetically identical isolates can be isolated from different dairies in a region in the same period, suggesting that the BCoV may transfer between some farms by the sale of cattle or on fomites.[71] However, it has also been shown that farms in an area may remain free from BCoV infection when the virus is circulating on nearby farms.[84]

■ Necropsy Findings

Following experimental infection, BCoV can be found in epithelial cells of the nasal passages and lung.[85] Grossly, small areas of cranioventral lobular collapse may be seen.[86] In naturally occuring cases of fatal disease, pathologic changes consisent with secondary bacterial infection will likely obscure any changes primarily attributable to BCoV.

■ Diagnosis

BCoV is most commonly identified by PCR in respiratory secretions or tissues collected at postmortem. The virus is not easy to isolate; standard cell lines used for isolation of other respiratory viruses are often not permissive to BCoV, but the virus can be isolated on human rectal tumor-18G cell lines.[87]

■ Treatment and Prevention

As for other respiratory viruses, there is no specific treatment for BCoV infection; supportive care as described for BHV-1 and BRSV is indicated. Although licensed vaccines labeled for the prevention or control of respiratory disease due to BCoV are not currently marketed in the United States or Canada, vaccines labeled for control of calf diarrhea due to the virus are available. A research trial tested the extralabel intranasal administration of a modified live

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bovine coronavirus and rotavirus vaccine (Calf-Guard [Zoetis, Parsippany, N.J.]) to control respiratory disease in feedlot cattle.[88] Vaccination significantly decreased the subsequent rate of treatment for respiratory disease in cattle that had relatively low serum antibody titers against coronavirus at arrival. Recently a modified live coronavirus vaccine was approved for intranasal adminstration to aid in the reduction of enteric disease due to BCoV (Bovilis Coronavirus [Merck Animal Health, Madison, N.J.]). Anecdotal reports indicate that this vaccine is also administered to control or prevent outbreaks of respiratory disease, an extralabel use; no published clinical trials have yet described benefits of this application.

Infectious BCoV can be identified on boots and clothing of personnel 24 hours after they have handled infected calves, indicating that fomites could be a means of transmission.[89] Thus boots and other fomites should be disinfected or changed after examining calves or cattle likely to be infected with BCoV. Other management practices to prevent or control respiratory disease in calves or feedlot cattle are also appropriate.

Influenza Viruses

Influenza viruses are enveloped RNA viruses in the family *Orthomyxoviridae.* Currently there are four genera in this family: *Alphainfluenzavirus, Betainfluenzavirus, Gammainfluenzavirus,* and *Deltainfluenzavirus,* which contain the influenza A, B, C, and D viruses, respectively. Influenza A viruses (IAV) circulate widely in various avian reservoir hosts and cause important seasonal disease in humans; IAV also cause important disease in poultry, swine, horses, and dogs. With IAV, influenza B viruses (IBV) contribute to seasonal disease in humans; influenza C viruses (ICV) primarily cause respiratory infection in young children. Humans appear to be the primary reservoir hosts for IBV and ICV, but infection with either IBV or ICV has occasionally been identified in other species. Antibodies to IAV, IBV, and ICV have been identified in cattle, indicating that cattle can be infected with these viruses.[90-92] Seroconversion to IAV has followed outbreaks of respiratory disease in cattle when no other respiratory pathogens could readily be found,[91] suggesting that IAV infection may rarely cause disease in cattle. However, only IDV have been commonly identified in surveys of respiratory viruses in cattle.

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Influenza D Virus

In 2011, an influenza virus was isolated from a pig with respiratory disease that was initially thought to be ICV.[93] However, the isolate was subsequently shown by in vitro testing to fail to reassort genome segments with confirmed ICV isolates, indicating that it was not a member of the genus *Gammainfluenzavirus*. The new virus was classified as IDV of the genus *Deltainfluenzavirus.* Seroprevalence to IDV was found to be low when serum samples from humans or swine were tested but high when serum samples from cattle were tested, suggesting that cattle but not swine or humans are a reservoir host. IDV infection appears to occur commonly in cattle around the world. Serum or other samples from cattle have been found to be positive for IDV or antibodies to IDV in the United States, Europe, and Japan.[94-96] Surveys to date have found that many herds contain at least one seropositive animal, with the percent of seropositive cattle within a herd typically in the range of 30% to 50%, although this varies with location of the herd and age of the animals.[94,96] In some cow-calf herds, more than 90% of young calves have been found to be seropositive, suggesting that most calves receive antibodies to IDV from colostrum.[94,97] A survey of historically banked samples indicated that herd level seroprevalence in Nebraska was likely greater than 90% in 2004.[97] IDV currently circulating in North America have been defined to occur in one of two genetic clades[93,94]; antibodies to viruses in one clade react partially to viruses in the other clade. European IDV isolates to date have been antigenically similar to North American isolates,[95] whereas Japanese isolates have been more distinct.[98]

Horses, sheep, and goats have also been shown to be seropositive to IDV at low prevalence[99,100]; poultry have not yet been reported to be seropositive. An early report found only 1.3% of 316 human serum samples from the United States and Canada to be seropositive to IDV,[93] suggesting that infection of humans is uncommon. However, a recent small survey testing 35 people who have regular contact with cattle and 11 people who do not found 91% of the people with cattle contact to be seropositive versus 18% of the people without cattle contact.[101] Thus the information available to date suggests that humans are not a reservoir for IDV, but they are susceptible to infection, which may occur commonly in individuals with frequent contact with cattle. This is relevant because of the known possibility of species to share influenza viruses, with reassortment of gene segments leading to development of new, possibly more

virulent variants. The importance of this in the ecology of IDV is not yet known.

The importance of IDV as a contributor to bovine respiratory disease is still under investigation. Seroconversion has been associated with development of bovine respiratory disease,[94] and IDV has been found in materials collected from cattle with respiratory disease.[94,95,102] Viral metagenomic sequencing of nasal or nasopharyngeal swabs identified IDV as significantly associated with respiratory disease in dairy calves,[103] and IDV tended to be associated with respiratory disease in feedlot cattle.[1] When IDV is found in respiratory secretions or tissues of cattle with naturally acquired disease, it is common to find other respiratory pathogens also present, making it difficult to particularly ascribe disease to IDV alone. IDV and BCoV, another virus commonly isolated from cattle during respiratory disease outbreaks, can both use the same cellular receptor, 9-*O*-acetyl-*N*-acetylneuraminic acid (Neu5,9Ac2), to attach to and enter cells. The significance of this in the ecology of these viruses in cattle populations is not clear.

Experimental challenge of seronegative cattle with IDV alone has induced disease that is mild at most, with viral replication and inflammation generally confined to the nasal passages and trachea.[104,105] In this regard, IDV is also similar to BCoV, which is commonly identified in cattle with respiratory disease but causes little if any respiratory disease when seronegative cattle are purposely exposed to the virus alone. This is currently interpreted to indicate that infection with IDV alone is unlikely to cause identifiable respiratory disease in cattle, but IDV infection can contribute to disease when it occurs concurrently with other factors that that impair or challenge respiratory defense. For example, IDV infection of nasal and trachea epithelial cells may impair function of the mucociliary elevator, increasing the likelihood of secondary bacterial infection by *M. haemolytica* or other opportunists.

No vaccine for IDV is currently marketed. An experimentally developed inactivated vaccine decreased clinical signs and virus shedding following experimental challenge of cattle.[105]

Bovine and Ovine Adenovirus

Adenoviruses are nonenveloped DNA viruses of the family *Adenoviridae*. At least 10 serotypes of bovine adenovirus (BAV) have been identified. BAV infection is widespread and frequently subclinical; adenoviruses are also often

isolated in association with other viruses and bacteria, making it difficult to assign causation in naturally occurring disease outbreaks. However, a recent survey of viral metagenomes in dairy calves with respiratory disease recently identified adenoviruses as one of the viruses significantly associated with respiratory disease.[103] Adenovirus infection has also been associated with enteritis, conjunctivitis, keratoconjunctivitis, and “weak calf syndrome.”

At least six antigenic types of ovine adenovirus and two types of caprine adenovirus have been identified. It appears likely that these viruses cause widespread infection. The majority of isolations of adenovirus have been from young lambs, and it has been isolated in association with respiratory and enteric disease. Experimental infections result in mild disease with anorexia, pyrexia, increased respiratory rates, coughing, and diarrhea. Ovine adenovirus serotype 6 has been shown under experimental conditions to act synergistically with *M. haemolytica* in the production of pneumonia in lambs.

Bovine Rhinitis Virus

Bovine rhinitis virus is a nonenveloped RNA virus in the family *Picornaviridae*. There are two serotypes of bovine rhinitis virus: bovine rhinitis A virus and bovine rhinitis B virus. A recent surveys of viral metagenomes from nasal or nasopharyngeal swabs from dairy calves with and without clinical signs of respiratory disease found bovine rhinitis A virus to be significantly associated with disease.[103] A similar study that evaluated viral metagenomes in U.S. and Mexican feedlot cattle with and without signs of respiratory disease found the viruses to be present in nearly all feedlots sampled, but their presence was not significantly associated with clinical signs of respiratory disease.[1]

Bacterial and Chlamydial Agents

■ *Mannheimia haemolytica*

Definition and Etiology

M. haemolytica is a gram-negative aerobic bacteria of the family *Pasteurellaceae.* There are at least 12 serotypes of *M. haemolytica,* and some ruminant isolates are untypable with currently available laboratory tools. Some serotypes of *M. haemolytica* are pathogenic, whereas others are nonpathogenic commensals of the ruminant nasopharynx, and the serotypes that are pathogenic

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for cattle are not the same as those that are pathogenic for sheep or goats. Serotype A1 is the most common isolate from pneumonic lungs of cattle, and serotype A6 is the next most common; serotype A2 is the most common isolate from the nasopharynx of normal cattle. Serotype is also relevant to pathogenicity of isolates from sheep and goats; serotype A2 is the most common isolate from sheep and goats with pneumonia, and serotypes A7, A9, and several others have also been associated with disease.

■ Clinical Signs

Cattle, sheep, or goats infected with *M. haemolytica* display a dull or depressed attitude and lose interest in eating. Fever, tachypnea, and depression are often the only abnormal signs early in the course of infection; coughing is not a prominent sign in the acute stage of disease unless co-infection with another agent such as BHV-1 or BRSV is present. Animals may display evidence of thoracic pain, such as standing with elbows abducted or catching the breath before expiration; these signs are a result of the painful fibrinous pleuritis caused by *M. haemolytica.* Because *M. haemolytica* is a gram-negative organism, endotoxin (lipopolysaccharide) is produced by the agent, and thus cattle with mannheimiosis may show signs of endotoxemia, including fever, tachycardia, tachypnea, salivation, respiratory distress, pale or dark mucous membranes with prolonged capillary refill time, and cool extremities. Thoracic auscultation may reveal harsh or loud bronchovesicular sounds consistent with pulmonary consolidation, particularly over the cranioventral lung. Disease after *M. haemolytica* infection can be fatal, particularly if it is not treated; it can also lead to chronic pneumonia associated with secondary invasion with agents such as *Pasteurella multocida*, *Mycoplasma bovis*, or *Trueperella pyogenes.*

It is important to remember that naturally occurring disease caused by *M. haemolytica* is commonly preceded by infection with a viral agent such as BHV-1, BRSV, or BCoV; therefore the clinical signs described previously for these or other respiratory viruses may also be present in animals infected with *M. haemolytica*.

■ Pathogenesis

M. haemolytica is a normal inhabitant of the nasal and pharyngeal mucosa and is considered an opportunistic pathogen. Ruminants appear to become infected at an early age and carry *Mannheimia* as a minor part of the upper respiratory tract

flora. Only a small percentage of nasal swabs yields positive results for *M. haemolytica* serotype A1 in healthy, unstressed calves,[1] but if several areas of the nasal mucosa are cultured at necropsy, it is often possible to isolate *M. haemolytica* from animals that previously had negative findings on nasal swabs.[2] The stress of transportation or viral infection causes a breakdown of the defense mechanisms that limit normal bacteria flora, resulting in a rapid proliferation of virulent *M. haemolytica* serotype A1. The number of calves yielding a positive nasal swab *M. haemolytica* culture increases after transport, and there is a large increase in the numbers of *M. haemolytica* in positive samples.[1] BHV-1 and PIV-3 viruses have been shown to have the same effect as transportation on *Mannheimia* populations of the nasal mucosa. *M. haemolytica* has been demonstrated in the tracheal air of stressed, healthy calves harboring the organism on their nasal mucosa. Some of these inhaled organisms are deposited deep within the lung and normally are cleared within hours. However, under conditions of impaired pulmonary defenses caused by insults to the upper respiratory tract, preexisting viral infection, or other factors, *M. haemolytica* is able to proliferate rapidly within the lung and, with the aid of its virulence factors and toxins, to produce a severe lobar necrotizing fibrinous pleuropneumonia. Calves infected with respiratory viruses or *Mycoplasma* species have increased susceptibility to severe bronchopneumonia when exposed to *M. haemolytica.* Similarly, infection of lambs with PIV-3 or adenovirus followed in several days by *M. haemolytica* causes severe pneumonia.[3]

Once *M. haemolytica* becomes established in the lungs, interactions between the bacteria and the host defenses result in tissue damage and elimination of the bacteria. A major virulence factor of *M. haemolytica* is an exotoxin that is lethal to ruminant leukocytes, the leukotoxin. Leukotoxin, which is produced by *M. haemolytica* during the logarithmic phase of growth, causes cytolysis of ruminant platelets, lymphocytes, macrophages, and neutrophils.[4] There is diversity in the gene encoding the leukotoxin molecule among *M. haemolytica* serotypes, and genetic diversity is related to differences in toxicity. Leukotoxin binds to cells via CD18, the beta subunit of the β_2 integrins CD11a/CD18 (LFA-1), CD11b/CD18 (Mac-1), and CD11c/CD18 (CR-4); although leukotoxin can bind to cells from nonruminant species, only ruminant cells are killed by the toxin. Contact with leukotoxin increases expression of LFA-1 on ruminant leukocytes, making the cells even more sensitive to injury by leukotoxin. At low concentrations, leukotoxin induces leukocyte death by apoptosis, whereas at

higher concentrations the toxin causes cell lysis.[5] *M. haemolytica* expressing a mutant nontoxic leukotoxin induced less lung pathology in calves as compared with *M. haemolytica* producing functional toxin, but clinical signs were not different between the two groups of calves, indicating that leukotoxin is not the only virulence factor of importance in causing disease.[6]

Another virulence factor that contributes to disease resulting from *M. haemolytica* is lipopolysaccharide, or endotoxin. As in other species, exposure of ruminants to endotoxin from gram-negative bacteria induces a multitude of responses leading to inflammation, including initiation of the complement and coagulation cascades, activation of endothelial cells and recruitment of neutrophils, and activation of neutrophils and alveolar macrophages, leading to their production of proinflammatory cytokines, which further amplify the inflammatory response. The proinflammatory cytokines TNF-α, IL-1β, and IL-8 are expressed in the lungs of cattle within 48 hours of *M. haemolytica* infection.[7] Calves exposed to a preparation containing *M. haemolytica* endotoxin develop leukopenia, fever, tachypnea, diarrhea, and dyspnea as early as 2 hours after exposure.[8] Endotoxin potentiates the effects of leukotoxin by inducing increased expression of β_2 integrins on leukocytes, which contain CD18, the receptor for leukotoxin. Bovine alveolar macrophages first exposed to endotoxin were susceptible to death induced by concentrations of leukotoxin too low to cause cell death alone, and macrophages exposed to both endotoxin and leukotoxin produced more of the proinflammatory cytokines IL-8 and TNF-α than did macrophages exposed only to leukotoxin.[9] These data indicate that leukotoxin and endotoxin work in synergy to cause disease in ruminants. The production of IL-8 is of particular importance because IL-8 is a major inducer of neutrophil chemotaxis. The massive influx of neutrophils induced by IL-8 and other inflammatory mediators is a key factor in lung tissue destruction caused by *M. haemolytica.* Calves experimentally depleted of neutrophils can be completely protected from gross and microscopic lesions of the severe fibrinonecrotic bronchopneumonia that is induced by intratracheal inoculation of *M. haemolytica* in calves with normal neutrophil levels.[10] Lysis of neutrophils results in the release of lysosomal products, including elastase, collagenase, and reactive oxygen intermediates. These chemicals are bactericidal but also capable of destroying the neutrophils themselves and surrounding tissues. Neutrophil-mediated damage to the endothelial cells results in exudation and thrombosis, which produce the classic lesions of necrosis and fibrinous exudation.

In addition to leukotoxin and endotoxin, *M. haemolytica* possesses other factors that contribute to its virulence. The bacteria have a polysaccharide capsule that aids in attachment and prevents phagocytosis by neutrophils and iron-regulated outer membrane proteins (IROMPs) that bind transferrin and alter the function of neutrophils. The bacteria produce adhesins that mediate attachment to host cells, and neuraminidase produced by the bacteria may aid in host colonization by decreasing the viscosity of respiratory mucus and decreasing the repellant negative charge on host cells by cleaving sialic acid residues.

■ Epidemiology

In many studies over several decades, *M. haemolytica* has been found to be a common bacterial isolate from feedlot cattle with fatal fibrinous bronchopneumonia.[11,12] *M. haemolytica* was isolated postmortem from 25% to 30% of cattle that died or were euthanized because of pneumonia in two studies evaluating causes of mortality in feedlot cattle.[12,13] An assessment of bacteria isolated from transtracheal aspirates of live feedlot cattle with respiratory disease and healthy cattle found that *M. haemolytica* was significantly more likely to be isolated from aspirates from cattle with BRD, compared to healthy controls.[13] In contrast, an older study that used BAL to identify bacteria present in the lungs of feedlot cattle before antimicrobial treatment for acute pneumonia found that *M. haemolytica* was not identified more frequently in the lungs of cattle with pneumonia than in normal controls, whereas *P. multocida* was significantly associated with bronchopneumonia.[14] In this study, none of the calves died or were euthanized because of the naturally occurring disease, indicating that disease was not severe. Because *M. haemolytica* is relatively more likely to cause acute fatal pneumonia than other bacterial pathogens of the ruminant lung, it may be overrepresented in necropsy surveys in which only fatal cases of disease are sampled. Seroconversion to *M. haemolytica* or *M. haemolytica* leukotoxin has been significantly associated with treatment for respiratory disease or “undifferentiated fever” in feedlot cattle in some[15,16] but not others.[17]

In contrast to the situation in feedlot cattle, *M. haemolytica* is less commonly associated with pneumonia in dairy calves. In one study, *M. haemolytica* was less frequently isolated from guarded nasopharyngeal swabs collected from dairy calves with acute respiratory disease than *P. multocida* or *Mycoplasma* spp.[18] Isolation of *M. haemolytica* on nasopharyngeal swabs was not significantly

associated with clinical signs of respiratory disease or pulmonary consolidation identified by transthoracic ultrasound in dairy calves in another study.[19] Magnitude of serum antibody titers, or changes in serum antibody titers, to *M. haemolytica* were not significantly associated with treatment for respiratory disease in a third report.[20] Although *M. haemolytica* is not as commonly associated with respiratory disease in dairy calves as other bacteria, it can be a cause of clinical and sometimes fatal bronchopneumonia in dairy calves, as well as in preweaning beef calves, adult dairy or beef cows, sheep, or goats.

■ Necropsy Findings

Infection with *M. haemolytica* causes grossly evident fibrinopurulent bronchopneumonia (Color Plate 31.4). The infection is aerogenous, so disease occurs primarily in the cranioventral lung, but in severe cases caudoventral and even dorsal lung may be affected. Affected areas of lung are dark red to purple or gray-brown, firm, and heavy; discolored areas may be wedge-shaped owing to thrombosis of a vessel supplying the affected region during the severe inflammatory response. The interlobular septa are expanded by clear to yellow gelatinous material that represents proteinaceous fluid that has leaked from blood vessels in the lung. The inflamed areas of lung may be covered with yellow fibrin that may adhere to the pleura of the thoracic wall, and the pleural cavity usually contains straw-colored fluid, which may be voluminous. In cases that have been ongoing for a few days, firm, gritty lumps that are dry and crumbly on sectioning may be identified; these represent areas of necrotic tissue. *M. haemolytica* may also produce pneumonia characterized by firm, dark red pulmonary consolidation without fibrinous pleuritis; this is especially common in dairy calves or sheep and goats. Animals that survive the acute stage of pneumonia caused by *M. haemolytica* may have multiple abscesses and pleural adhesions; in these cases other bacteria such as *P. multocida*, *Mycoplasma bovis*, or *Arcanobacterium pyogenes* may be contributing to pathology.

Histopathologic evaluation of tissues from cattle with pneumonia due to *M. haemolytica* reveals that alveoli are filled with edema and fibrin and that there is massive infiltration of neutrophils and macrophages. Foci of coagulative necrosis may be present; hemorrhage is also often present both within and between alveoli. Bronchioles are filled with leukocytes and may have foci of epithelial necrosis.

■ Diagnosis

Diagnosis of pneumonia due to *M. haemolytica* is most reliably made by culture of lungs with typical gross pathology at postmortem evaluation of animals that die or are euthanized as representative cases in outbreaks. Once bacteria colonies are isolated, MALDI-TOFMS or traditional biochemical methods can be used to identify the bactera; MALDI-TOFMS can also be used to identify the serotype.[21] Some laboratories offer PCR testing to identify the bacteria, which may be more sensitive than culture.[22]

A presumptive antmortem diagnosis in individual animals with clinical signs of bacterial pneumonia can be made by identification of the bacteria by aerobic culture of nasal swab, guarded nasopharyngeal swab, transtracheal aspirate (TTA), or BAL. There is good to very good agreement between the results of culture of nasal or nasopharyngeal swabs and TTA or BAL at the level of the genus and species in calves with respiratory disease.[18,23] Because *M. haemolytica* is a commensal of the upper respiratory tract, finding the bacteria does not necessarily mean it is the only or even the most important cause of disease. However, if the agent is found in respiratory materials collected from an animal with clinical signs consistent with bacterial pneumonia, it is appropriate to assume that *M. haemolytica* is contributing to disease in the patient. Cytologic evaluation of TTA or BAL samples would be expected to reveal septic purulent inflammation characterized by large numbers of neutrophils that may be degenerate, exhibiting toxic change, and possibly containing intracellular bacteria. Thoracocentesis can be used to identify fluid accumulation in the thorax; fluid collected shows a high percentage of neutrophils with a high (>3 g/dL) total protein content if bacterial pleuropneumonia is the cause of fluid accumulation. If an ultrasound machine is available, transthoracic ultrasound evaluation can be used to confirm the presence of consolidated lung tissue, possibly with pleural effusion and fibrin. Thoracic radiography, if possible, is expected to show evidence of consolidation of the cranial lung and possibly pleural fluid accumulation. Evidence of pneumonia identified by either radiography or transthoracic ultrasound evaluation has been shown to correlate strongly with findings on postmortem examination of calves with bacterial bronchopneumonia.[24]

Serologic tests can be used to identify serum antibodies to *M. haemolytica*, and seroconversion identified by paired serologic testing could be used to confirm infection with *M. haemolytica* in one or more ruminants. However, these

tests are most commonly used for research applications, and they may not be available at all diagnostic laboratories. Moreover, seroconversion to *M. haemolytica* has not been consistently associated with disease.

■ Treatment and Prevention

Treatment of *M. haemolytica* requires administration of an antimicrobial that is effective against the organism. Many antimicrobials are currently labeled for the treatment of *M. haemolytica* (see Table 31.15). The decision to choose any one of the many approved products is based on multiple factors, including regional susceptibility of *M. haemolytica* isolates, the number of times it is possible to treat animals, withdrawal times, and cost. Recently, *M. haemolytica* that are resistant to multiple antimicrobial classes (multidrug resistant, or MDR) have been identified in lung collected at postmortem from feedlot and stocker cattle in the United States and Canada[25-27] and by guarded nasopharyngeal swabs of some populations of stocker and feedlot cattle.[28-30] Currently, evidence-based guidelines for management of cattle with bronchopneumonia attributed to MDR *M. haemolytica* are lacking; anecdotally it has been reported that cattle can recover despite the presence of *M. haemolytica* resistant to the antimicrobial with which they are treated. This may indicate that the host response can resolve infection and repair pathology in at least some cases of MDR infection.

In addition to appropriate antimicrobial therapy, treatment to prevent the adverse effects of endotoxin should be considered for ruminants suspected or confirmed to have pneumonia caused by *M. haemolytica*. The NSAID flunixin meglumine can ameliorate the inflammatory response to endotoxin, and treatment with flunixin meglumine has been shown to improve outcome in individual animals infected with *M. haemolytica*. However, administration of NSAIDs may not be cost-effective in the treatment of large numbers of cattle with respiratory disease. Thus a consideration of the cost versus expected benefit is appropriate before NSAID therapy is administered to an entire group.

Prevention of infection and disease caused by *M. haemolytica* is approached by three avenues: administering antimicrobials prophylactically to animals at high risk of disease; increasing host immunity by ensuring adequate passive transfer and administering vaccines against *M. haemolytica;* and minimizing factors such as viral respiratory tract infection, mixing of animals from various sources, and long-distance shipment, all of which increase the susceptibility of animals to disease caused by pathogenic serotypes of *M. haemolytica*.

Administration of antimicrobials effective against *M. haemolytica* to an entire group of calves at high risk for disease because of recent weaning, uncertain immune status, mixing with cattle from a variety of sources, and long-distance shipment ("metaphylaxis") has been a reliable means of decreasing morbidity and mortality associated with respiratory disease in such populations. Administration of tilmicosin to groups of such high-risk calves either before shipment or on arrival at feedlots decreased the proliferation of *M. haemolytica* serotype A1 in the nasopharynx of calves and was associated with decreased treatment for respiratory disease as compared with calves not treated with tilmicoson.[31] In a later study, administration of florfenicol at arrival decreased colonization of the nasopharynx with *M. haemolytica* A1 and delayed treatment for respiratory disease.[1] However, recent reports have described a high prevalence of MDR *M. haemolytica* following metaphylactic antimicrobial administration.[28,30] The degree to which MDR *M. haemolytica* negatively affect outcome in infected cattle is not yet clear, but dissemination of MDR *M. haemolytica* in cattle populations may begin to decrease the benefit of metaphylaxis. Further discussion of the role of metaphylactic administration of antimicrobials to control bovine respiratory disease can be found in the Metaphylactic Antimicrobial Therapy section later in this chapter.

Mixing recently weaned calves from multiple sources and shipping them long distances is a well-known precursor to outbreaks of fibrinous pneumonia[32]; thus efforts to minimize stresses and improve immunity for calves moving through the marketing chain should lessen disease caused by *M. haemolytica.* Preconditioning, wherein vaccination and stressful procedures such as weaning and castration are carried out well in advance of mixing and shipment, can decrease costs associated with fibrinous pneumonia in feedlot cattle.[33] However, preconditioning should not be considered a guarantee against all respiratory disease; severe disease can sometimes occur in preconditioned calves. Further discussion of the role of preconditioning to prevent bovine respiratory disease can be found in the Preconditioning section later in this chapter.

Vaccination can be used as part of a plan to decrease disease caused by *M. haemolytica.* Bacterins, toxoids, and at least one modified live vaccine are currently available in the United States and Canada for the prevention and control of respiratory disease due to *M. haemolytica* in cattle; additional information is presented in Chapter 48. At the time of this writing, it appears that only one vaccine containing *M. haemolytica* and *P. multocida* is specifically

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labeled for vaccination of sheep and goats in the United States and Canada (Mannheimia Haemolytica–Pasteurella Multocida Bacterin [Colorado Serum Company, Denver, Colo.]). Vaccination of sheep or goats with vaccines labeled for use in cattle may not reliably provide protection against disease, as serotypes of *M. haemolytica* that most commonly cause disease in sheep and goats are not included in vaccines for cattle. However, a recent study found that one licensed cattle vaccine decreased disease in sheep following experimental challenge of sheep with PIV-3 followed by challenge with serotype A2 *M. haemolytica*.

■ Definition and Etiology

Pasteurella multocida

P. multocida is a gram-negative aerobic bacteria of the family *Pasteurellaceae.* Like *M. haemolytica, P. multocida* can be found in the nasopharynx of healthy ruminants. Although *P. multocida* is regularly isolated from the lungs of ruminants with bronchopneumonia, there has been debate over the years as to whether this species is a primary pathogen (i.e., capable of causing disease alone) or whether some other primary stressor or insult is required to occur before this agent can participate in disease. As with *M. haemolytica,* experimental challenge of calves with *P. multocida* alone does cause clinical signs and pathologic change in the lung similar to that seen in natural outbreaks of disease,[34-36] but large numbers of the bacteria must be administered in a way that bypasses the upper respiratory tract (most commonly by intratracheal or intrabronchial instillation). Alternatively, exposure to a viral respiratory pathogen a few days before exposure to *P. multocida* makes ruminants more likely to develop disease. These findings indicate that some insult that weakens respiratory defense is necessary for most if not all cases of naturally occurring disease to occur.

P. multocida is a diverse species of bacteria that is classified into five serogroups (A, B, D, E, and F) based on antigenic differences in the bacterial capsule. Serogroups B and E cause hemorrhagic septicemia, a disease predominantly seen in Asia and Africa; these serogroups are rarely described in North America. Serogroup A is the predominant serogroup associated with ruminant respiratory disease,[37,38] although serogroups D and F may be common in some regions, particularly in sheep.[39] In addition to the alphabetic serogroup designation, isolates may also receive a numeric designation based on cell wall

antigen types (for example, *P. multocida* A3 is commonly isolated from cases of bovine pneumonia). A report characterizing 153 *P. multocida* isolates from cases of pneumonia and mastitis in cattle in England and Wales indicated that relatively few strains of *P. multocida* cause the majority of disease in cattle. Moreover, although a few strains isolated from cattle had also been associated with disease in swine and poultry, the majority of strains were uniquely associated with their host species of origin.[38] Other research indicated that certain strains of *P. multocida* had a predilection for the respiratory tract of sheep, whereas others were associated with the reproductive tract.[39] Taken together, these data suggest that differences among strains of *P. multocida* are related to the type of disease caused and the host likely to be affected. Therefore merely isolating *P. multocida* without further characterizing the isolate could make it difficult to know with confidence whether the bacteria isolated was actually contributing to disease. It has been suggested that strain variation is related to differences in severity of respiratory disease occurring in ruminants infected with *P. multocida*.[35]

■ Clinical Signs

Calves infected with *P. multocida* display clinical signs of fever, increased respiratory rate, and sometimes depression, coughing, and mucoid to mucopurulent nasal discharge. Loud or harsh bronchovesicular sounds may be heard over the cranioventral lung fields owing to pulmonary consolidation, and coarse crackles may be heard as a result of air moving through exudate in large airways. Because *P. multocida* is a gram-negative organism that produces endotoxin, signs of endotoxemia (such as tachypnea, tachycardia, and/or fever) may also contribute to signs that accompany infection with the organism. Compared with calves infected with *M. haemolytica*, calves infected with *P. multocida* tend to have less severe signs, and signs of disease last for a shorter time.

■ Pathogenesis

Little is known regarding the pathogenesis of *P. multocida* in ruminant respiratory disease. In addition to lipopolysaccharide (LPS), the organism has a capsule that allows it to resist phagocytosis. Outer membrane proteins, particularly IROMPs, are likely to contribute to the ability of the bacteria to establish and proliferate within the host.[40,41] The prominent role of *P. multocida*

in dairy calf pneumonia relative to its role in acute fatal bronchopneumonia of feedlot cattle suggests that prolonged impairment of the respiratory defense mechanisms may be necessary for this organism to establish in the lungs in sufficient numbers to cause pathology. *P. multocida* has been shown to overgrow *M. haemolytica* in challenge studies using large doses of pure cultures of *M. haemolytica*.[34] This may be related to the fact that *P. multocida* can inhibit growth of *M. haemolytica* in vitro.[42] Thus when *P. multocida* is identified in lung tissue or other materials from cattle with respiratory disease, it is possible that in at least some cases, the agent has displaced *M. haemolytica* that actually initiated disease.

■ Epidemiology

P. multocida is commonly isolated from the lungs of dairy calves that die or are euthanized because of bronchopneumonia, with mycoplasmas being the only bacteria isolated more often in surveys of farms experiencing outbreaks of calf pneumonia.[43,44] Recent studies evaluating respiratory pathogens in individual live dairy calves have also found *P. multocida* to be the agent most commonly identified.[18,19] Although *M. haemolytica* is more commonly isolated than other bacteria from lung tissue of feedlot cattle that die of acute bronchopneumonia,[11] it is interesting to note that two different studies comparing the bacteria identified in transtracheal aspirates or BALs collected from live feedlot cattle with respiratory disease, and also from normal control cattle, found *P. multocida* to be most strongly associated with respiratory disease.[13,14] This may indicate that *P. multocida* is an important contributor to feedlot respiratory disease but *M. haemolytica* is more likely to lead to disease that ends in death, causing *M. haemolytica* to be overrepresented in surveys of bacteria in tissues collected at postmortem.

■ Necropsy Findings

P. multocida produces a purulent bronchopneumonia with plum-colored cranioventral consolidation and purulent exudate on cut section within the airways; when calves are experimentally infected with *P. multocida* alone, the lesion is usually not extensive and is typically confined to the cranioventral lung lobes. Histologically, bronchopneumonia characterized by infiltration of neutrophils and macrophages into alveoli and airways is seen. Microscopic evidence of abscesses may be present. Fibrin deposition with expansion of

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lymphatics and interlobular septa with edema, and focal areas of coagulative necrosis, can be seen in calves infected with *P. multocida,* but this lesion is more typical of infection with *M. haemolytica.*

■ Diagnosis

Bronchopneumonia caused by *P. multocida* is diagnosed as described for *M. haemolytica.* The species is most commonly identified by culture of lung lesions identified at postmortem examination of affected animals or from guarded nasopharyngeal swabs or other respiratory materials collected antemortem. Because of the association of *P. multocida* with chronic or ongoing pneumonia, identification of this agent may indicate that the animal has been affected with bronchopneumonia for several days to weeks.

■ Treatment and Prevention

Treatment of *P. multocida* is as described for *M. haemolytica.* Several antimicrobials are labeled specifically for the treatment of *P. multocida,* and products labeled for the treatment of *M. haemolytica* are also likely to be effective against this organism (see Table 31.15). Because *P. multocida* seems to be associated with chronic or ongoing pneumonia, effective treatment of infection may require longer therapy than the 3 to 5 days historically recommended for ruminants with bronchopneumonia, but this recommendation has not been tested in controlled studies and would be an extralabel use of some antimicrobials. Although antimicrobial resistance has historically been uncommon in *P. multocida* associated with ruminant respiratory disease, recent surveys of bacteria recovered from lung tissue or other respiratory materials collected from feedlot cattle have revealed *P. multocida* isolates that are resistant to multiple classes of antimicrobials.[25,26,29] MDR in *P. multocida* as well as *M. haemolytica* has been attributed to genetic elements called integrative conjugative elements (ICEs), which are integrated into the bacterial genome, include multiple genes encoding resistance to multiple antimicrobial classes, and can be transferred between bacteria of different genera.[45] The clinical significance of MDR *P. multocida* is not clear at this time, but these findings suggest that respiratory disease due to *P. multocida* may become more difficult to treat effectively if resistant bacteria become widely distributed in cattle populations.

Because prior insult to respiratory defense mechanisms appears necessary for

P. multocida to cause disease in cattle, prevention of disease is likely to be aided by undertaking efforts to prevent other primary respiratory injury. This could include efforts to prevent infection with viral respiratory pathogens and to establish management practices that help minimize respiratory tract disease.

Relatively little is known about protective immunity that limits respiratory disease due to *P. multocida* in ruminats. Modified live vaccines can protect calves from disease caused by experimental challenge.[46,47] Antibody responses to several outer membrane proteins were associated with protection in one study, and these were induced by live but not inactivated vaccine.[47] Several commercial vaccines are marketed for administration to cattle that contain *P. multocida* in combination with *M. haemolytica*, with or without other agents. It appears at present that one vaccine is licensed for administration to sheep and goats (Mannheimia Haemolytica–Pasteurella Multocida Bacterin [Colorado Serum Company, Denver, Colo.]). At this time no properly designed clinical trials have been reported that allow identification of any beneficial effect of the *P. multocida* component of available vaccines for ruminant respiratory disease in the field. More information about vaccination against *P. multocida* is presented in Chapter 48.

■ Definition and Etiology

Histophilus somni

H. somni is a gram-negative aerobic bacteria of the family *Pasteurellaceae. H. somni* can be found on the genital and upper respiratory mucosa of normal ruminants,[48-51] but it can also cause a variety of diseases, including septicemia, thrombotic meningoencephalitis (TME), endometritis, abortion and infertility, pneumonia, pleuritis, laryngitis, otitis, conjunctivitis, myocarditis, mastitis, and polyarthritis.[52] Only pneumonia and pleuritis resulting from this organism are considered here. Two bacteria very similar to *H. somni, Haemophilus agni* and *Haemophilus ovis,* have been isolated from sheep with septicemia, meningitis, mastitis, and reproductive abnormalities; DNA hybridization studies have indicated that these three organisms should all be classified as *H. somni.* Although specific serotypes of *H. somni* have not been associated with disease as is the case for *M. haemolytica* and *P. multocida,* differences in virulence among different strains have been demonstrated in experimental challenge studies.[53] Moreover, differences in expression of molecules considered to be

virulence factors have been demonstrated when strains from healthy animals are compared with strains from diseased animals.[54] Thus it appears that some isolates of *H. somni* are more likely to cause disease than others, but more research is needed to confirm the characteristics that define a pathogenic isolate.

■ Clinical Signs

H. somni can cause disease in a variety of organ systems, and the clinical signs of infection will depend on the organ system affected. The possibility of concurrent infection of multiple systems should be considered in patients suspected to have disease caused by *H. somni.* In a Canadian retrospective study from the early 1990s, the majority of animals presented to a regional diagnostic laboratory for necropsy as a result of haemophilosis had disease in more than one organ system.[55] Signs of respiratory tract infection can range from mild to severe and can include fever, tachypnea, cough, nasal discharge, and depression. Severe cases of disease can be fatal.[53,56] Harsh or loud bronchovesicular sounds may be heard on thoracic auscultation because of pulmonary consolidation, particularly over the cranioventral lung fields. Affected animals may have signs of pain owing to fibrinous pleuritis,[56] including reluctance to move, standing with elbows abducted, and catching the breath before expiration. The cell wall of *H. somni* contains lipooligosaccharide (LOS), which induces inflammatory responses identical to those induced by LPS from *E. coli*[57]; therefore animals with pleuritis or pneumonia caused by *H. somni* could also have clinical signs referable to endotoxemia, including tachypnea, tachycardia, dark or pale mucous membranes with prolonged capillary refill time, salivation, or dyspnea.

■ Pathogenesis

H. somni can live on respiratory or genital mucous membranes without causing disease, and it is not entirely clear what factors related to the pathogen or host must change for disease to occur. The physical and immunologic barriers presented by the upper respiratory tract are apparently of major significance; calves exposed to *H. somni* by aerosol did not develop disease,[58] whereas instillation of the bacteria directly into the trachea or bronchi led to disease that could be severe.[53,56] As has been shown for *M. haemolytica* and *P. multocida*, primary infection by a viral respiratory pathogen is likely a predisposing factor that allows *H. somni* to advance and establish in the lower respiratory tract in many cases. Calves infected with BRSV before infection with *H. somni* had

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disease of greater severity than that seen in calves infected with either BRSV or *H. somni* alone.[56,59]

H. somni has many features that help the bacteria escape the immune response.[60] The bacteria have outer membrane proteins that bind to the Fc region of antibody, allowing them to escape opsonization.[54] When the bacteria are ingested by neutrophils or macrophages, they are able to resist being killed.[61] The bacterial LOS induces inflammatory responses similar to the LPS of other gram-negative bacteria,[57] and *H. somni* is able to periodically change the structure and antigenicity of its LOS, which is likely to be important in evading the host immune response.[62]

An important aspect of the pathology caused by *H. somni* is the formation of vasculitis and vascular thrombi. *H. somni* can induce programmed cell death (apopotosis) of vascular endothelial cells, stimulate endothelial cell tissue factor activity, and disrupt intercellular junctions.[63] These effects lead to exposure of the vascular basement membrane, activation of platelets and the coagulation cascade, and thrombosis. These processes presumably contribute to pathology through release of inflammatory mediators by activated platelets and endothelial cells and through impaired blood flow due to microscopic thrombi.

Another important aspect of *H. somni* is the propensity of infection to induce IgE production by the host.[59,64] Infection with BRSV before infection with *H. somni* led to production of high levels of *H. somni*–specific IgE, which was associated with disease of increased severity as compared with control calves.[59] Cattle vaccinated with four different *H. somni* bacterins were all found to develop serum levels of *H. somni*–specific IgE that were significantly higher than levels seen in control unvaccinated cattle.[64] Because IgE mediates type I (immediate) hypersensitivity, animals that produce IgE against *H. somni* after vaccination or primary infection could have signs of an allergic or anaphylactic response on subsequent revaccination or reinfection. Such IgE-mediated hypersensitivity reactions have been proposed to contribute to the adverse reactions sometimes seen in cattle after vaccination for *H. somni*.[64] In addition to inducing IgE production, *H. somni* directly produces histamine,[65] which could further contribute to the development of hypersensitivity-like signs during *H. somni* infection. Among other actions, histamine increases permeability of bronchial epithelium; this may help the bacteria move out of the airways and into the lung parenchyma.

■ Epidemiology

Exposure to *H. somni* is common, with 25% to 100% of cattle in various populations having serum antibodies.[66] It is common for feedlot cattle to have measurable antibody titers to *H. somni* at feedlot entry,[16,67] indicating that cattle are commonly exposed on the farm of origin or in transit to the feedlot. Seroconversion is also common in the first few weeks after feedlot entry,[16,17] indicating that cattle also continue to be exposed to *H. somni* in the feedlot. Several Canadian reports have indicated that *H. somni* can be a significant contributor to the development of respiratory disease or undifferentiated fever in feedlot cattle.[13,68-70] A causative association is typically inferred either by the association of seroconversion with respiratory morbidity and mortality during the period of study or by the association of *H. somni* vaccination with decreased respiratory morbidity and mortality. By these measures it appears that most disease resulting from *H. somni* occurs within the first 2 months of the feeding period,[70] and perhaps even within the first 2 weeks.[17] High-quality field research on the role of *H. somni* in feedlot respiratory disease in recent years has come almost entirely from Canada; it is not clear whether this indicates that *H. somni* is a less significant contributor to disease in the United States or the research has just not been done.

H. somni is usually less prevalent than *P. multocida* and *Mycoplasma* spp. in surveys of the causes of pneumonia in dairy calves,[19,44,71] but it can cause bronchopneumonia that is significant; one necropsy survey found pneumonia in 12 of 15 calves younger than 8 weeks of age submitted because of disease resulting from *H. somni*.[55]

■ Necropsy Findings

H. somni usually produces lung lesions similar to those due to *P. multocida;* rarely it may produce lesions that resemble *M. haemolytica*, including fibrinous pleuropneumonia.[52,53,56] Grossly, plum or red to brown consolidated lobules are seen in the cranioventral lung, sometimes with abscesses containing brown-red fluid material. Interlobular septa can be distended with edema and fibrin (Color Plate 31.5), and hemorrhage may be grossly visible. Purulent material is seen within airways on the cut surface of lung. The surface of the pleura may be flecked with fibrin, or in some cases fibrin deposition may be extensive, with varying amounts of straw-colored fluid in the pleural cavity. Bronchial lymph

nodes may be enlarged, with ecchymotic hemorrhages on the cut surface.

Histologically, inflammatory cells predominately made up of neutrophils infiltrate the alveoli and airways. Edema, hemorrhage, and fibrin can be seen in alveoli and interstitial spaces, and areas of coagulation necrosis surrounded by inflammatory cells may be found. Interlobular septa are expanded with fibrin, and thrombi are seen in blood vessels.

A massive fibrinous pleuritis with pleural effusion sometimes results from septicemic spread of *H. somni.* This condition can be differentiated from the fibrinous necrotizing lobar pleuropneumonia of shipping fever caused by *M. haemolytica* because the *H. somni* lesion involves only the pleural surface, not the lung.

■ Diagnosis

Bronchopneumonia or pleuropneumonia caused by *H. somni* is diagnosed as described for *M. haemolytica.* The bacteria can be difficult to isolate, so samples collected for culture should be transported to the diagnostic laboratory without delay, and the diagnostic bacteriology laboratory should be specifically requested to attempt to isolate *H. somni* if involvement of the agent is suspected. PCR tests for the bacteria are available at some laboratories, and these may be more sensitive than culture.[22] Samples are ideally taken from animals before antimicrobial treatment, as *H. somni* is usually susceptible to a wide variety of antimicrobials and treatment makes it difficult to isolate the bacteria.[52] Serologic tests have been used to identify antibodies to *H. somni* for research,[16,17] and seroconversion could be used to confirm infection in a group of cattle, but these assays are unlikely to be available at most diagnostic laboratories. IHC has been used to identify *H. somni* in association with lesions in formalin-fixed tissues,[72] and this may be an additional test available at some diagnostic laboratories.

■ Treatment and Prevention

Historically *H. somni* has been found to be susceptible to a variety of antimicrobials, including tetracycline, penicillin, and sulfonamides, as well as newer antimicrobials, many of which are labeled for use in the treatment of *H. somni* (see Table 31.15). However, recent surveys of bacteria recovered from lung tissue or other respiratory materials collected from feedlot cattle have revealed some *H. somni* isolates that are resistant to multiple classes of antimicrobials, although MDR *H. somni* have not been as prevealent as MDR *M.*

haemolytica or *P. multocida* in these reports.[25,26,29] The impact of MDR on the efficacy of treatment of *H. somni* is not yet clear.

Several *H. somni* vaccines for use in cattle are commercially available; all are killed whole bacteria preparations (bacterins). More information about vaccination to control disease due to *H. somni* is presented in Chapter 48.

■ Definition and Etiology

Mycoplasma bovis

Mycoplasma bovis is a member of the genus *Mycoplasma* of the class Mollicutes, and as such it is among the smallest free-living organisms. *M. bovis* was first identified in 1961 in the United States, where it was isolated from a case of mastitis.[73] It has since spread worldwide. The bacterium was originally considered a subspecies of *Mycoplasma agalactiae*, and the two agents can be difficult to distinguish. However, *M. agalactiae* is a pathogen of sheep and goats and is rarely isolated in the United States, whereas *M. bovis* is regularly isolated in cases of pneumonia, respiratory disease, arthritis, tenosynovitis, and other disorders of cattle. *M. bovis* can rarely cause disease in sheep, goats, and other species.

■ Clinical Signs

The clinical syndromes associated with *M. bovis* and the approach to their treatment and prevention have been reviewed.[74] Respiratory infection with *M. bovis* causes fever, tachypnea, inappetence, and sometimes respiratory distress.[75] Coughing and nasal discharge are reported in some cases.[76,77] Respiratory disease caused by *M. bovis* can occur in outbreaks; in young calves, a subset of calves affected often develops otitis, characterized by unilateral or bilateral drooping of ears with purulent aural discharge, possibly with vestibular signs such as head tilt, nystagmus, and ataxia.[76-78] In weaned beef calves and cattle entering feedlots, a subset of affected animals may develop arthritis and tenosynovitis[79-81]; this syndrome is sometimes referred to as chronic pneumonia and polyarthritis syndrome.[81,82] Young calves can also develop arthritis or tenosynovitis.[77] A typical complaint by the producer experiencing a respiratory disease outbreak involving *M. bovis* is that cattle do not respond to therapy as expected, and a significant proportion of affected animals remain chronically ill

and unthrifty for weeks after the onset of disease.[79,80] In addition to respiratory disease, *M. bovis* can also cause mastitis, arthritis and tenosynovitis, conjunctivitis, otitis, sinusitis, and myocarditis and/or pericarditis. The bacteria can also be isolated from aborted fetuses and from semen, linking the agent to reproductive failure; infected semen can also be a vehicle for introduction of *M. bovis* into a herd.[83] North American bison *(Bison bison)* can develop severe and sometimes fatal disease following *M. bovis* infection, with mature adults often being predominantly affected.[84]

The ability of *M. bovis* to act as a primary respiratory pathogen has been debated. Classically the agent has been understood to be an opportunist, establishing itself after primary infection with viral pathogens or other bacteria. However, experimental challenge of gnotobiotic calves with *M. bovis* alone induced respiratory disease with clinical signs of fever, tachypnea, and inappetence and grossly evident lung lesions.[75] These findings indicate that *M. bovis* can cause disease while acting alone; however, as for other bacterial respiratory pathogens of cattle, it is likely that natural infection and disease often follows another primary insult.

■ Pathogenesis

Much is still unclear about the mechanisms by which *M. bovis* causes disease. In vitro studies suggest that pathogenicity is associated with the ability of *M. bovis* to attach to host cells.[85] Antibodies against several of the variable surface proteins (VSPs) expressed by *M. bovis* were able to partially but not completely block attachment, indicating that the VSPs play a role in attachment.[85] *M. bovis* is able to migrate between ciliated respiratory epithelial cells,[86] which likely facilitates transfer from the respiratory mucosa to deeper sites such as joints and tendon sheaths. *M. bovis* was found to colonize the tonsils of calves fed colostrum contaminated with the bacteria[87]; thus infected tonsils may serve as a reservoir leading to otitis media and possibly respiratory disease in calves fed milk or colostrum containing *M. bovis*. Caseous necrosis, often found in the lungs of calves with pneumonia associated with *M. bovis* infection, appears to be due at least in part to tissue damage induced by oxygen and nitrogen radicals released by leukocytes attempting to clear the infection.[88]

M. bovis has a variety of ways to evade the host immune response, which likely contributes to persistent infection and poor response to therapy. VSP

expression has been shown to be an important pathogenic mechanism.[89] *M. bovis* expresses at least three VSPs—VspA, VspB, and VspC—and isolates have been found that express some or all of these proteins.[90] *M. bovis* isolates show extensive variability in VSPs at both the genetic and the antigenic level. In addition, *M. bovis* can directly impair the activity of neutrophils[91] and monocytes[92] and can kill lymphocytes by inducing them to undergo apoptosis (programmed cell death).[93] Induction of proinflammatory cytokine production by the host may also contribute to disease caused by *M. bovis*.[94]

■ Epidemiology

M. bovis can be isolated from the respiratory tracts of normal cattle[95,96] as well as those of cattle with respiratory disease.[97-99] Surveys of nasopharyngeal swabs taken from dairy calves with no clinical signs of respiratory disease found *M. bovis* in 0% to 34% of the animals sampled.[99,100] A survey of multiple-source weaned beef calves sampled soon after arrival at nine different backgrounding or stocker operations identified nasal shedding of *M. bovis* in 0% to 6% of animals at each operation.[101] *M. bovis* can also be found in bovine lungs without evidence of disease at postmortem examination.[12] The fact that *M. bovis* can be isolated from animals with no clinical or pathologic signs of pneumonia has led some to question whether the agent is a true respiratory pathogen. However, a consistent association of *M. bovis* with a clinical syndrome of chronic nonresponsive pneumonia with or without otitis, arthritis, or tenosynovitis and with a pathologic syndrome of bronchopneumonia with multifocal caseous necrosis has led to general acceptance that *M. bovis* contributes importantly to significant morbidity and mortality in some situations.

M. bovis has been identified in dairy calves and feedlot cattle with respiratory disease in multiple reports. For example, in a survey of pathogens in calves in dairy herds in Quebec, only *M. bovis* was significantly associated with higher odds of clinical signs of respiratory disease, lung consolidation identified by transthoracic ultrasound, and decreased weight gain.[19] A survey of causes of death in cattle in Ontario feedlots identified caseonecrotic pneumonia caused by *M. bovis* as a cause of more fatalities within the first 60 days of the feeding period than acute fibrinosuppurative pneumonia typical of disease caused by *M. haemolytica* or *H. somni*.[12] A large proportion of cattle can be infected with *M. bovis* in the first weeks after feedlot entry,[102,103] and infection can be associated

with decrased weight gain.[102] *M. bovis* infection of the respiratory tract appears to persist for weeks in cattle, but data are mixed in terms of whether cattle clear one infection only to be infected with a new isolate[103] or a single isolate persists for several weeks.[104] In 49 chronically sick cattle from a single feedlot, *M. bovis* was identified in the lungs of 82% of the cases and in the joints of 45% of the cases.[105] BVDV was also present in 39% of the cases from which *M. bovis* was isolated. A later retrospective study by the same authors found BVDV in the lungs of 44% of cattle subjected to necropsy with a final diagnosis of pneumonia caused by *M. bovis;* these data led the authors to suggest that immunosuppression resulting from BVDV may predispose a subset of animals to chronic pneumonia and/or arthritis caused by *M. bovis*. In contrast, others found that BVDV infection was not more common in feedlot cattle with caseonecrotic lesions typical of *M. bovis* infection.[98]

Currently available data indicate that *M. bovis* can spread from a few animals carrying the bacteria to others until a large proportion of a group is infected; transmission in these cases is most likely via respiratory infection by direct contact or short-distance aerosol.[79,80,95] Long-term persistence of bacteria in pneumonic lung of a few individuals may facilitate transmission to others in the herd.[106] Feeding milk infected with *M. bovis* appears to be an important source of infection for dairy calves.[77-79] Multiple reports have indicated that outbreaks can be caused by a single genotype of *M. bovis*,[107,108] although more than one genotype of *M. bovis* can also be isolated during outbreaks.[109]

■ Necropsy Findings

Grossly, lungs of cattle with pneumonia caused by *M. bovis* have dark red, firm consolidated lobules of the cranioventral lung. Raised white to yellow, firm nodules that range from 0.5 to several centimeters in diameter are often but not invariably seen clustering in the cranioventral lung (Color Plate 31.6).[75,82,110] These nodules may appear to be abscesses, but in most cases they are actually foci of coagulation (caseous) necrosis (Color Plate 31.7).[75,98] Differential diagnoses for gross lesions of abscessing pneumonia in cattle include infection with *Trueperella pyogenes* and *Fusobacterium necrophorum* (both of which are more likely to be associated with a foul odor than *M. bovis*) and *Mycobacterium bovis* (tuberculosis). Other gross lesions include enlargement of interlobular septa by edema and fibrin. Fibrinous or fibrous pleural adhesions are unusual

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and if present may signal co-infection with *M. haemolytica* or *H. somni*. Animals with pneumonia typical of *M. bovis* may also have arthritis, tenosynovitis, myocardial abscesses, and/or otitis. Microscopic evaluation of affected lung reveals purulent pneumonia and bronchiolitis, with extensive infiltration of neutrophils in airways, and peribronchiolar cuffing with lymphocytes and mononuclear cells. Foci of eosinophilic coagulation necrosis are surrounded by a rim of dark pyknotic inflammatory cells and, farther out, a region of primarily macrophages and some plasma cells.[75,82] IHC staining for the organism may reveal large numbers surrounding the periphery of areas of coagulation necrosis as well as in association with bronchiolar and alveolar epithelial cells.[82,111]

■ Diagnosis

Confirmation of respiratory disease caused by *M. bovis* is most reliably made by identification of the agent by culture or PCR of respiratory materials collected antemortem from cattle with clinical signs of bronchopneumonia or in lung tissue with typical gross lesions collected postmortem. For antemortem diagnosis, materials are ideally collected from the lower respiratory tract (TTA or BAL). The reliability of nasal swabs or guarded nasopharyngeal swabs for confirmation of disease due to *M. bovis* is less certain; the agreement between the results of nasal swab culture and the presence of lung disease caused by *M. bovis* was good in one study[97] and only moderate to poor in two other studies.[14,112] A recent report indicated very good agreement between between the results of nasal swabs or guarded nasopharyngeal swabs and the TTA if mycoplasma culture was followed by PCR to specifically identify *M. bovis* but not when culture alone was used.[18] The reliability of nasal swabs or guarded nasopharyngeal swabs for identification of *M. bovis* in respiratory disease outbreaks may be greater if multiople animals in a group are sampled and found to be positive. When samples are submitted for identification of *M. bovis*, it is important to request that the diagnostic laboratory specifically identify this agent; diagnostic laboratories often characterize mycoplasmas only to the level of the genus based on results of mycoplasma culture. Because other mycoplasma such as *Mycoplasma bovirhinis, Mycoplasma dispar,* and *Mycoplasma alkalescens* can also be isolated from the respiratory tract of cattle with pneumonia, a report of "*Mycoplasma* spp." is not equivalent to a diagnosis of *M. bovis*. Species-specific identification of *M. bovis* is most commonly made by PCR testing, which is available on request at many veterinary diagnostic

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laboratories. MALDI-TOFMS can also be used to identify bacterial species once colonies are isolated by culture. Although either mycoplasma culture followed by PCR or direct PCR (without mycoplasma culture first) can be used to identify *M. bovis*, the agreement between both tests used in the same animal may not be strong.[101] One recent report found culture to be more likely positive than PCR when nasal swabs were tested, whereas PCR was more likely positive than culture when milk was tested.[113] Although available data suggest that *M. bovis* is less commonly isolated from healthy cattle than are other mycoplasmas, because the organism can be found in nasal swabs and lung tissue of apparently normal animals, isolation of the bacteria in the absence of evidence of disease is of uncertain significance.

Serologic assays have been used to identify seroconversion in epidemiologic studies or to identify evidence of recent or past infection, but the tests are not widely available, and their results have not been shown to reliably indicate active infection.[114] Serology is most commonly used to determine whether *M. bovis* is a likely cause of mastitis in dairy herds; the value of serology in the diagnosis of respiratory disease is not well established. A review article discussing the diagnosis of mycoplasmas in cattle in detail was recently published and should be consulted for more information.[115]

■ Treatment and Prevention

Several antimicrobials, including tulathromycin (Draxxin [Pfizer Animal Health, Parsippany, N.J.]), florfenicol (Nuflor Gold [Merck, Madison, N.J.]), enrofloxacin (Baytril 100 [Bayer Healthcare LLC, Pittsburgh, Pa.]), and gamithromycin (Zactran [Boehringer Ingelheim, Ingelheim am Rhein, Germany]), are currently labeled for treatment of disease due to *M. bovis*. However, multiple authors report that cattle with pneumonia caused by *M. bovis* respond poorly to antimicrobial therapy.[80,81,114] Because *M. bovis* can be seen in association with foci of coagulation necrosis in lungs of affected cattle,[82,98] it may be that antimicrobials are not maximally effective in this environment, or it may be that insufficient duration of treatment is carried out in at least some cases. Controlled trials indicating the duration of antimicrobial therapy needed for effective treatment of pneumonia caused by *M. bovis* are lacking, but anecdotal reports suggest that early treatment is critical for success[77,116] and that treatment should be continued for at least 10 to 14 days. Failure of antimicrobials that are predicted to be efficacious against *M. bovis* may also be

related to an inability of the immune response to effectively clear the organism due to immunosuppressive mechanisms described previously. Some veterinarians report that outbreaks of *M. bovis* cannot be stopped with any treatment but that outbreaks eventually terminate when chronically affected animals die or are shipped to slaughter.

Recently, multiple European reports have described increasing rates of antimicrobial resistance based on in vitro assessment of *M. bovis* isolates.[117] Although clinical trials under conditions typical of U.S. and Canadian cattle operations that confirm the efficacy of treatment in a field setting are lacking, antimicrobial resistance may begin to make treatment of cattle with disease due to *M. bovis* even more problematic.

Research indicates that vaccination can theoretically afford some protection against experimental challenge with *M. bovis*.[118,119] Vaccines for control of disease due to *M. bovis* vaccines are licensed for sale in the United States; for vaccines to be fully licensed, they must show evidence of safety and efficacy in experimental challenge studies. However, properly designed field trials provide better evidence of usefulness of vaccines in the field, and reports of field trials to test the efficacy of currently licensed *M. bovis* vaccines are sparse. Results from two trials testing the effect of *M. bovis* vaccines on respiratory disease in dairy or veal calves have been reported.[120,121] In one trial there was no difference in respiratory morbidity or mortality in the first 90 days of life for vaccinated calves, as compared to unvaccinated controls.[47] In the second trial, which evaluated the effect of two different commercially available *M. bovis* vaccines on lung lesions at harvest of veal calves at approximately 145 days of age, lung lesions were decreased in one vaccine group but not in the other group, as compared to unvaccinated controls.[48] Autogenous vaccines have been used for years, but no reports with large numbers of animals and appropriate controls are available to provide information about efficacy. More properly designed field trials are needed to determine the value of *M. bovis* vaccination as used in the field in different types of cattle populations. Issues contributing to the lack of an unequivocally effective vaccine to prevent disease due to *M. bovis* have recently been reviewed.[122]

■ Definition and Etiology

Mycoplasma mycoides subsp. *capri*

Caprine pneumonias that are not contagious among adults can be caused by several species of *Mycoplasma.* However, *M. mycoides* subsp. *capri* (Mmc; formerly *M. mycoides* subsp. *mycoides* Large Colony type) can be a very serious cause of mortality among goat kids, and it is so in North America.[123,124] *Mycoplasma mycoides* subsp. *mycoides* Small Colony type (MmmSC), which is related to Mmc, is the causative agent of contagious bovine pleuropneumonia, a serious cause of sickness and death in cattle in Africa. MmmSC has been eradicated from North America.

■ Clinical Signs

In herds with Mmc infections, goat kids usually appear clinically normal until 2 to 8 weeks of age, when the following three clinical syndromes occur:

1. A peracute illness characterized by high fevers (41.1° to 42.2° C [105.8° to 107.9° F]) and death within 12 to 24 hours;
2. A central nervous system syndrome with opisthotonos and death within 24 to 72 hours; and/or
3. An acute to subacute syndrome with high fevers, multiple hot swollen joints, and pneumonia.

The most common manifestations are swollen joints, lameness, and recumbency. About one half of affected kids have increased lung sounds on expiration and elevated respiratory rates. During an outbreak, 80% to 90% of kids die or are euthanized because of permanent recumbency. Mmc infection in adult is also life threatening.[125]

■ Necropsy Findings

The most common necropsy finding in goat kids that die of Mmc infections is a fibrinopurulent polyarthritis. Approximately half of field cases have pneumonia. One or more lung lobes have areas of patchy to diffuse red consolidation that is sometimes covered with a fibrinous exudate. Clear, golden-yellow to serosanguineous fluid is found in the thorax in half of the cases. In some patients there are fibrinous adhesions between the lungs and thoracic wall. Affected lungs have microscopic evidence of bronchopneumonia or interstitial pneumonia. Other common lesions include pericarditis, peritonitis, and enlargement of the kidneys, liver, and spleen.

■ Diagnosis

The definitive diagnosis of Mmc infection in individuals requires isolation of the agent from milk, joint fluid, blood, urine, or tissue. Infected goat herds can be readily identified by culturing bulk tank milk, because infected does shed up to 10^{10} Mmc organisms per milliliter of milk. Inapparent carriers can be identified by milk culturing, but false-negative results are a risk because organisms are shed intermittently. Goats can carry Mmc in their external ear canal, and PCR of auricular swabs has been shown to be a sensitive means of diagnosis of chronic carriers.[126]

■ Treatment and Prevention

Conventional antibiotic therapy for goats with Mmc infections is almost always unsuccessful. Tylosin or tetracyclines have been used; newer-generation antibiotics effective against *Mycoplasma bovis* could also be tried, although this would be an extralabel use of these drugs. A low percentage of kids make a clinical recovery from the septicemic illness but often have arthritis by the time they freshen. Does that recover from mastitis become chronic carriers.

Prevention is based on maintaining herds free of Mmc infection. Purchased does should originate only from herds that have no history of mortality in kids from arthritis and pneumonia and that have negative bulk tank cultures for Mmc. Purchased individuals should be held separate from the milking herd until they have an Mmc-negative milk culture result; treatment for ear mites may also be prudent. A vaccine is not commercially available.

Control of Mmc outbreaks centers on prevention of the systemic infection in kids and mastitis in milking does. Rapid prevention of new cases in kids can be expected from a program of feeding heat-treated goat colostrum (56° C [132.4° F] for 1 hour) or cow colostrum at birth, pasteurized milk up to 1 month of age, and pasteurized milk or a high-quality milk replacer from 1 month to weaning. All kids with swollen joints should be culled. Milking hygiene should be improved to prevent transmission of infection during milking. Milk samples from all does in the milking herd should be cultured to identify carrier does. Infected does should be kept in a separate string and milked last, or culled. Colostrum of dry does should be cultured as they freshen, and the does should be hand-milked separately until their milk is found to be free of Mmc. Monthly cultures of the bulk tank milk from the noninfected string should be performed to ensure that it is free of Mmc infection. The goal of control procedures is

eradication of Mmc from the herd.

Other Mycoplasmas

Mycoplasmas are isolated, usually in combination with other pathogens, from 50% to 90% of beef and dairy cattle pneumonias.[44,127-129] Mycoplasmas have been associated with peribronchial and peribronchiolar lymphoid hyperplasia, which is sometimes referred to as a "cuffing pneumonia," a common lesion in calves that die or are euthanized because of pneumonia.[130,131]

Mycoplasmas have also been recovered from lesions of acute and chronic bronchopneumonia in which a cuffing pneumonia was not apparent.

Other than *Mycoplasma bovis*, the species of mycoplasmas (see Box 31.4) prevalent in North America are generally considered to be mild respiratory pathogens, mainly causing subclinical infections unless coupled with environmental stresses or infections by other pathogens. Tracheobronchial aspiration performed on dairy calves at random found that calves with both *Mycoplasma* spp. and *Pasteurella* spp. present in the aspirate were at significantly greater risk of developing pneumonia than calves with only one organism or no organisms. A study of feedlot cattle found seroconversion to *M. alkalescens* to be significantly associated with undifferentiated fever, a clinical definition similar to undifferentiated respiratory disease.[16] Effects such as immunosuppression and inhibition of the mucociliary transport mechanism, which can be mediated by mycoplasmas, suggest that they may play an important contributory role in the pathogenesis of bovine pneumonia. *Mycoplasma ovipneumoniae* is often isolated from pneumonic lungs of sheep and goats, usually accompanied by *M. haemolytica*. On its own, *M. ovipneumoniae* is capable of causing mild, subacute to chronic bronchiolitis or bronchopneumonia that probably predisposes to *M. haemolytica* infections.

Bibersteiniia trehalosi

Bibersteinia trehalosi causes pneumonia or systemic disease with multiorgan infection in sheep. *B. trehalosi* has also been reported in association with severe peracute to acute bronchopneumonia in cattle and recently weaned calves.[132] Affected cattle died before they were noticed to be ill, and antimicrobial therapy did not seem to be very effective despite the fact that *B. trehalosi* isolates were susceptible to many antimicrobials in vitro. However, an effort to induce disease by experimental challenge of calves was not successful,[133] making it unclear

whether the bacteria alone can be assumed to be the primary cause of respiratory disease in field cases. In cases where *B. trehalosi* appears to be contributing to disease, therapy with antimicrobial drugs effective against *M. haemolytica* should be attempted. Vaccines against *Mannheimia haemolytica* may help limit the problem.[134] At this time it is not known what factors increase the risk of pneumonia due to *B. trehalosi* in cattle or domestic sheep.

Trueperella pyogenes

Trueperella pyogenes (formerly *Arcanobacterium pyogenes*) is a gram-positive rod-shaped species of bacteria that is a common cause of internal or SC abscesses in ruminants. *T. pyogenes* is occasionally isolated from the lungs of ruminants with pneumonia, typically from animals that have chronic pneumonia, possibly from grossly visible abscesses. This species is viewed as an opportunist that contributes to respiratory disease as a secondary or possibly "tertiary" invader after viral pathogens and other bacterial respiratory pathogens have become established. *T. pyogenes* has a variety of virulence factors, including a cytolytic toxin called *pyolysin*, as well as several molecules that aid in adherence to host cells.[135] Diagnosis of this pathogen is usually made as an incidental finding at necropsy of an animal with significant respiratory disease from other primary causes. Finding *T. pyogenes* during a respiratory necropsy should not induce efforts to directly treat or prevent this pathogen but rather should induce efforts to prevent other primary or secondary causes of pneumonia and to treat animals in a timely manner with appropriate therapy for an adequate duration in order to prevent chronic pneumonia.

Chlamydial Agents (*Chlamydophila* Species)

Chlamydial agents, most commonly *Chlamydophila abortus, Chlamydia psittaci,* and *Chlamydophila pecorum,* have been associated with a variety of disease syndromes in cattle and small ruminants, including abortion and infertility, conjunctivitis, polyarthritis, encephalomyelitis, and enteritis.[136] These agents are also occasionally identified in pneumonic ruminant lungs. Because chlamydial agents can also be identified in ruminants with no signs of disease and because seroprevalence is high, the importance of chlamydial agents in ruminant respiratory disease has been debated. Although experimental infection of calves with high numbers of *C. psittaci* via a route that bypasses the upper respiratory tract can lead to clinically evident respiratory disease that may be severe,[137] in

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the natural setting these agents are most likely to participate as one of mutiple factors necessary to induce important ruminant respiratory disease. Research indicates that calves are infected with chlamydial agents relatively early in life and that crowding enhances the likelihood of a high proportion of animals being infected.[138]

Approach to Diagnosis and Treatment of Respiratory Disease of Undetermined Cause (Undifferentiated Ruminant Respiratory Disease)*

Amelia R. Woolums

Information regarding diagnosis and treatment of individual infectious agents that can cause ruminant respiratory disease was presented earlier. However, it is common for more than one of these agents to be involved when a group of cattle, sheep, or goats has an outbreak of respiratory disease. Moreover, when a veterinarian is called to make an initial evaluation of a group of ruminants with respiratory disease, the etiologic agent or agents involved are not known, and efforts to diagnose the microbial agents involved may not in fact be necessary. The term *undifferentiated respiratory disease* has been applied to respiratory disease of uncertain cause. Thinking of an outbreak as “undifferentiated respiratory disease” before a causative diagnosis is confirmed is helpful to ensure that the veterinarian considers all possible infectious agents and management factors that may be contributing to disease in the animals in question.

■ History

Successful treatment of one or more ruminants with respiratory disease will require identification and alteration of the risk factors associated with ocurrence of the disease; this is particularly true when multiple animals are affected in an outbreak or when endemic disease occurs at an unacceptable rate. Evaluation of the problem begins with collection of a thorough history and is followed by examination of affected animals and the environment. The history questions are directed at management practices that predispose to respiratory disease. It is important for the veterinarian to directly observe as many management practices as possible to ensure that what is described is actually occurring. Examination of

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the environment includes evaluation of animal housing to determine whether poor ventilation, crowded or dirty housing, or temperature extremes are likely increasing the disease susceptibility of animals. The nutrition program should be assessed to determine whether nutritional deficiencies are likely contributing to disease susceptibility.

■ Clinical Signs

Once a thorough history is collected, several animals involved in the outbreak should be examined. The degree of fever and severity of abnormal lung sounds were correlated with risk for retreatement for respiratory disease in feeedlot cattle[1]; thus clinical examination may be important not only for accurate identification of sick cattle but also for improving estimates of outcome for cattle with respiratory disease. Scoring systems have been developed to aid in the assessment of clinically evident respiratory disease in individual dairy calves and in groups of dairy calves.[2,3] These scoring systems are suitable for use by laypersons trained to assess calves periodically, to facilitate timely diagnosis. A limitation is that the scoring systems do not differentiate between upper and lower respiratory tract disease. A veterinarian or trained technician can address this limitation by using transthoracic ultrasound evaluation (see the Thoracic Ultrasonography and Radiography section later) to determine whether lung lesions are present in calves with a clincial score indicating respiratory disease.

Ruminants affected by bronchopneumonia exhibit signs of respiratory tract inflammation and sometimes systemic inflammatory response. In early stages, animals stand off by themselves and do not readily approach feed. They hold their heads and ears lower than normal, appear depressed, and move more slowly than normal. As disease progresses, respirations become rapid and shallow, there may be frequent licking of the muzzle, and a moist cough is often present. Animals may have a fever of 40° to 41° C (104° to 105.8° F), and as the disease progresses they appear gaunt, have deep labored respirations, and may hold the head extended. Dyspnea may be both inspiratory and expiratory. Ocular and nasal discharges progress from serous to mucopurulent. The heavy chest wall of larger cattle may make it difficult to hear normal airway sounds. Auscultable lung changes may include increased harshness or loudness of inspiratory sounds (“large airway sounds” or “bronchial tones”). Auscultation may reveal crackles and wheezes. When ventral consolidation occurs, harsh breathing is still audible ventrally, but percussion reveals ventral dullness. Percussion is best

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accomplished on young calves and goats of any age. Recently shorn sheep can be readily percussed, but heavy wool makes percussion difficult. Animals in which a fibrinous pleuritis develops are reluctant to move because of pain, have shallow respirations, and sometimes have pleural friction rubs detectable on auscultation.

Nasal discharge, dyspnea, abnormal lung sounds, cough, and high fevers are cardinal signs of bronchopneumonia. Other respiratory tract conditions that must be considered as differential diagnoses include interstitial pneumonia, pulmonary edema, pleuritis, laryngitis, tracheitis, and lungworms. Rare conditions include thoracic neoplasia and diaphragmatic hernia. Nonrespiratory diseases that may result in abnormal respiratory signs include septicemia, heart failure, acid-base imbalances, and poisonings such as nitrate toxicity. In sheep and goats, ovine progressive pneumonia (OPP), caprine arthritis and encephalitis (CAE), and lung or mediastinal abscesses caused by *C. pseudotuberculosis* are additional differential diagnoses.

Because ruminants are often housed in groups and are often not acclimated to individual handling, signs of respiratory disease in one or more individuals are often first noticed from a distance rather than from “hands-on” examination. Early signs of bronchopneumonia include mildly depressed attitude and appetite; thus caretakers may first identify animals with bronchopneumonia when they are offered feed, at which time affected animals fail to come forward to consume feed with normal enthusiasm. A standardized system to improve recognition of sick calves can be used to enhance detection of calves with respiratory disease in group pens.[4]

Groups at particularly high risk for respiratory disease, such as animals that have been recently weaned and/or transported by truck or trailer, should be evaluated no less than once per day for at least the first week or two after weaning or transport to facilitate timely identification of new cases. Frequent evaluation of animals at high risk is important because the early signs of respiratory disease are nonspecific and subtle, and severe bronchopneumonia can advance rapidly, sometimes leading to death that is sudden and unexpected in as little as a few hours. For this reason, it is preferable to feed groups of ruminants at high risk for bronchopneumonia frequently, providing only what they will consume in 12 to 24 hours, rather than providing enough feed for several days in a self-feeder or via large amounts of hay. It is important to remember that once obvious signs of bronchopneumonia (such as coughing, profuse mucopurulent nasal discharge, and dyspnea) are evident from a distance, disease is often

advanced and animals are less likely to respond well to therapy.

■ Diagnostic Evaluation of Undifferentiated Ruminant Respiratory Disease

If clinical examination of an individual or group of cattle, sheep, or goats indicates that respiratory disease is present, it is not always necessary to pursue diagnostic testing. Occasional outbreaks of respiratory disease occur in groups of ruminants, and such occasional outbreaks can often be managed successfully with administrative symptomatic therapy alone. Similarly, individuals with a first-time clinical diagnosis of bronchopneumonia may respond completely to presumptive therapy in the absence of any diagnosis. However, if recurrent outbreaks occur or if animals do not respond appropriately to symptomatic therapy, then diagnostic tests are warranted to better characterize the nature of the problem and to help determine the reason for treatment failure. In such situations a careful evaluation of management practices and facility design is also warranted to ensure that all practices possible are in place to maximize the ability of animals to resist respiratory infection. Management practices important to minimizing respiratory infection are described in the Prevention and Control of Undifferentiated Ruminant Respiratory Disease section later.

Thoracic Ultrasonography and Radiography.

The use of transthoracic ultrasound to identify evidence of lung consolidation, pleural effusion or fibrin deposition, and other abnormalities consistent with bronchopneumonia is feasible and helpful if an ultrasound machine is available for use by an individual properly trained in ultrasonographic evaluation and if animals can be restrained for assessment. An ultrasound machine used for pregnacy diagnosis, one with a transrectal probe, is well suited for on-farm transthoracic evaluation. Seventy percent isopropyl alcohol can be used as a transducing agent; it is not necessary to clip the hair unless excessive mud is present. On-farm use of ultrasonography has been evaluated for the diagnosis of bronchopneumonia in feedlot cattle and dairy calves. The procedure is feasible in dairy calves, where evaluation of the tenth through first intercostal spaces on the right side of the thorax and the tenth through second intercostal spaces on the left side of the thorax is possible, and with some practice it allows the practitioner to assess all regions where lesions consistent with bronchopneumonia are likely to occur. While transthoracic ultrasonography can be used to identify lesions of bronchopneumnonia in feedlot cattle and other

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older animals, due to heavy forelimb musculature it is often not possible to evalute the first and second intercostal spaces, thus some disease is more likely to be missed. Chutes that are necessary to restrain beef cattle also make ultrasonography more logistically difficult, as the chute may obstruct sites where the probe must be placed and puts the operator at more risk of injury. The sensitivity of transthoracic ultrasound evaluation for the diagnosis of lung consolidation consistent with bronchopneumonia in dairy calves has been estimated to range from 66% to 94%, and the specificity ranges from 88% to 100%.[5,6] The reader is referred to a detailed review for more information regarding on-farm use of transthroacic ultrasonography for the diagnosis of lower respiratory tract disease in calves.[6]

When used in conjunction with clinical scoring systems, transthoracic ultrasonography allows identification and discrimination of calves with clinical disease limited to the upper respiratory tract, clinical disease including lung disease, or subclinical lung disease. In one study, the presence of lung consolidation identified by transthoracic ultrasonography in dairy heifers in the first 8 weeks of life was associated with a 525-kg decrease in their first lactation milk production.[7]

Although the value of ultrasonography for the diagnosis of bronchopneumonia in sheep and goats has not been extensively assessed, the technique should also be feasible for use in these species, assuming that the probe can be placed into contact with skin overlying intercostal spaces. This may be difficult for sheep in full fleece but should not be a problem for goats or sheep with little or no wool.

Thoracic radiography is useful for confirmation of pulomonary changes consistent with bronchopneumonia when suitable radiographic equipment is avaiable. For larger cattle this means that radiography is only possible in referral hospitals. On-farm radiography may be feasible for calves and sheep and goats, by use of portable equipment; however, it does carry the risk of radiation exposure to personnel and is likely only cost-effective for valuable individuals.

■ Clinical Pathology and Assessment of Passive Immunity

Complete blood cell counts or serum biochemical analyses are rarely of much value in diagnosis of respiratory disease in ruminants. Some viral infections may cause leukopenia, but when bacterial pneumonia is superimposed the WBC count may be elevated. Animals with bacterial pneumonia may have an inflammatory leukogram characterized by a leukocytosis with a mature

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neutrophilia, possibly with a left shift; hyperfibrinogenemia is likely to occur. Animals with chronic pneumonia may have a normal WBC count even when there is significant pulmonary pathology.

Failure of passive transfer is a major risk factor for pneumonia in calves,[8,9] so investigation of respiratory disease outbreaks in calves should include an evaluation of passive transfer status by measurement of immunoglobulins or total solids in the serum of a subset of calves 1 to 7 days of age. Measurement of serum total solids with an optical, digital, or Brix refractometer is a practical, satisfactory procedure for estimation of serum immunoglobulin concentrations in groups of calves.

■ Necropsy Findings

The value of necropsy findings to confirm the cause of death, particularly in animals that die unexpectedly, cannot be overemphasized. Much valuable information may be gained before a disease outbreak causes excessive mortality if early cases that die are subjected to timely necropsy. On a herd level, establishing a practice of subjecting all animals that die to at least gross necropsy can aid greatly in maintaining management practices that limit animal disease and death; this is because the actual cause of death identified at necropsy can sometimes be unexpected. For example, if an animal is assumed to have died of pneumonia, but it actually died of acute enterocolitis, then inappropriate control measures may be undertaken.

The cost of having animals sent to the local diagnostic laboratory for full necropsy may dissuade some owners from allowing necropsies. However, useful information can be gained simply by gross necropsy evaluation performed on the farm by the local veterinarian or, on larger operations, by staff members trained by the supervising veterinarian. With some practice veterinarians can develop confidence in identifying the major differentiating gross features of common diseases, and they can thus ensure that management is aimed at control of disease of the correct organ system. Moreover, there are some identifiable characteristics typical of the major infectious causes of bronchopneumonia. Gross necropsy can help the veterinarian make a more accurate list of differential diagnoses for outbreaks of bronchopneumonia, allowing the development of a more appropriate plan for treatment and prevention. Gross pathologic features of disease caused by infectious respiratory agents are described elsewhere in this chapter and are summarized briefly below. A review of the pathology of common pulmonary diseases of cattle is available for

additional information.[10]

A respiratory necropsy should include assessment of the upper airways and trachea. Fibrinopurulent material in the larynx is evident in cattle with necrotic laryngitis. Infection with BHV-1 (infectious bovine rhinotracheitis virus [IBRV]) causes generalized reddening (congestion) and small raised, red or pale plaques on the mucosa of the nasal passages and trachea; more severe cases have dark red, hemorrhagic changes, possibly with yellow-brown exudate adherent to the mucosa (fibrinopurulent tracheitis) (see Color Plate 31.2).

Bronchopneumonia in recently transported cattle (shipping fever pneumonia) is most commonly a fibrinopurulent bronchopneumonia. The cranioventral areas of affected lungs are dark red to gray-brown in color, firm, and heavy. Bronchial lymph nodes are swollen, wet, and dark red. The inflamed lung and parietal pleura are sometimes covered with variable amounts of yellow fibrin, and the pleural cavity may contain straw-colored fluid. Fibrinous pleuritis usually indicates the presence of *M. haemolytica* or *H. somni*, or possibly *B. trehalosi.* These species can also cause necrosis of lung, which will be firm and brown to gray, and which may contain dark red, wedge-shaped lesions (infarcts) that are caused by thrombosis of an artery supplying the region. Large amounts of straw-colored exudate are often present in the pleural space. Chronic cases have multiple abscesses and pleural adhesions. As much as 60% to 80% of the lung tissue is often involved in fatal cases of severe bacterial pneumonia. In severe cases the dorsal regions of the caudal lobes often are mottled by interspersed patches of inflammation and normal parenchyma. In some cases, forced respirations result in vesicular to bullous pockets of emphysema in the dorsal areas of the caudal lobe (see Color Plate 31.3). These changes can also be seen with primary BRSV infections or with AIP. Focal or multifocal areas of firm white to yellow material that look like abscesses may actually be caseous necrosis caused by *M. bovis* (see Color Plates 31.6 and 31.7). Abscesses containing caseous or liquid purulent material may also be caused by *T. pyogenes* or anaerobic bacteria; these findings indicate chronicity.

Bronchopneumonia in housed dairy calves is less often fibrinous, but rather is characterized by the presence of firm, collapsed, dark red lobules in the cranioventral and possibly the caudal ventral lung (Color Plate 31.8); in severe cases, whole lobes of the lung may be affected. Firm, dark red lobules without fibrin on the pleura are common in pneumonia caused by *P. multocida*, *M. bovis*, or other mycoplasmas. Infection with BRSV and PIV-3 can also cause lobular consolidation of the ventral lung. *M. haemolytica* or *H. somni* may also be

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isolated from such lesions even in the absence of fibrinous pleuritis.

Animals that die after chronic persistent coughing, dyspnea, and weight loss often exhibit lesions of chronic suppurative pneumonia. Bronchi and bronchioles are filled with purulent exudate, there are multiple mature lung abscesses, and greatly dilated bronchioles contain malodorous exudate. When bronchiectasis is severe, the lung lobes have a nodular appearance.

Although gross necropsy alone can be very helpful in generating an accurate list of differential diagnoses, histopathologic and microbiologic findings may add valuable information, particularly in situations where symptomatic treatment has failed. Gross necropsy findings alone are not always definitive; for example, in one study of AIP in feedlot cattle, only 67% of the cases that were diagnosed with AIP based on clinical and gross pathologic findings were confirmed by histopathology.[11] Therefore in outbreaks with relatively high mortality or in cases in which therapy is not yielding expected results, the cost of full necropsy of two or three typical cases is likely to be well worth the expense.

If full necropsy at a local diagnostic laboratory is to be undertaken, two or more animals showing signs that are typical of the early stages of the disease outbreak should be sent for euthanasia and necropsy. Although the producer may be reluctant to euthanize animals that may recover and would rather send animals with chronic, nonresponsive disease, the chronic cases are unlikely to yield information relevant to the primary problem.

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Microbiologic Tests

Samples for identification of viral and bacterial pathogens associated with cases of respiratory disease can be collected antemortem from live animals or at necropsy of animals that have died or been euthanized. It is important to remember that administration of modified live viral or live bacterial vaccines, particularly intranasal vaccines, in the 4 to 8 weeks preceding diagnosis may complicate interpretation of test results, as efforts to diagnose wild-type agents presumably contributing to disease may instead identify vaccine strains of virus or bacteria that are likely to be shed for some time after vaccination. Remember also that recent vaccination may induce seroconversion and can complicate the use of serologic testing to diagnose the cause of a respiratory disease outbreak.

Appropriate samples to collect from live animals include nasal swabs, guarded nasopharyngeal swabs, TTA, or BAL. Each of these samples has benefits and drawbacks. Nasal swabs are usually collected with a 6-inch (13.5-cm) swab that is not guarded (protected) from contamination. After sampling, the swab is put into transport medium that may come with the swab or may be obtained from a veterinary diagnostic laboratory. Guarded nasopharyngeal swabs are usually collected using a longer swab guarded by an outer sheath, such as is used for mare or cow uterine culture. While these swabs are unwieldy for sampling young calves, they allow the swab to be protected from contamination by commensal bacteria in the outer nasal passage, providing a theoretically more representative sample of viruses and bacteria in the nasopharynx that are more likely contributing to respiratory disease.

Although respiratory viruses can be shed by cattle without signs of respiratory disease, if viruses are identified in animals with respiratory disease they should be considered contributing factors. Identification of bacterial respiratory pathogens such as *M. haemolytica, P. multocida, H. somni,* or *M. bovis* from nasal or guarded nasopharyngeal swabs requires some interpetation. Because these bacteria are considered part of the normal flora of the upper respiratory tract, their identification in cattle without signs of respiratory disease is not significant. However, in calves with clinical signs of bronchopneumonia, identification of these agents on nasal or guarded nasopharyngeal swabs has been shown to agree moderately to strongly with the results of culture of materials from the lower respiratory tract, such as TTA, BAL, or materials collected at necropsy.[12-14] Guarded nasopharyngeal swabs are considered by

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many to be superior for the identification of bacterial pathogens because they are less likely to result in cultures that are overgown by contaminants. Others have suggested that BAL is superior to guarded nasopharyngeal swabs for identification of bacterial pathogens[15]; however, BAL is technically more demanding and time consuming. Overall, for sampling multiple individuals in a group of calves with respiratory disease, guarded nasopharyngeal swabs provide a reasonably good representation of the agents causing disease in the respiratory tract. However, for valuable individuals, TTA or BAL is the preferred method of sampling to identify infectious agents causing bronchopneumonia.

Proper handling and transport of the specimens collected from live animals or at necropsy is critical to maximize the chance of an accurate diagnosis. The veterinarian is encouraged to contact the diagnostic laboratory if he or she is uncertain about the proper methods of sample collection and transport; most laboratories now post this information on their websites, making it easy to find for those with internet access. See Table 31.14 for guidelines for identifying common infectious respiratory pathogens.

Viruses

A specific viral diagnosis requires laboratory confirmation. Most laboratories direct their diagnostic efforts toward the viruses for which vaccines are available. Diagnosis of other respiratory viruses may require the assistance of specialized laboratories.

Virus Isolation.

Virus isolation is time consuming and expensive, but it can be a sensitive method for identifying some viruses. Virus isolation is performed in cell culture, with subsequent use of PCR, immunofluorescence, or IHC to identify the specific virus isolated. A variety of specimens can be tested, including nasal, nasopharyngeal, conjunctival, and tracheal swabs; TTA; BAL; and a variety of respiratory tract tissues that can be obtained at postmortem examination. Fluids, tissues, and swabs may be frozen; however, freezing may kill some of the virus in the sample. Alternatively, swabs and tissue specimens may be placed in a viral transport medium and kept refrigerated or on ice packs until arrival at the diagnostic laboratory, preferably within 24 hours. In general, better success at virus isolation is obtained when specimens are collected in the acute phase of disease.

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Detection of Viral Antigens.

Immunofluorescent antibody (IFA) staining is a rapid method for identifying specific respiratory viruses. Antemortem identification can be made in cells in material obtained from nasal, nasopharyngeal, or conjunctival swabs or from cells obtained by TTA or BAL. Postmortem identification can be made from frozen tissue sections prepared from a variety of respiratory tract tissues. IHC can also be used to test cells from swabs or fixed tissue. This is a useful procedure that allows histologic examination of tissues in conjunction with specific identification of the causative agent.

Antigen capture enzyme immunoassay (EIA) provides a rapid means for detecting certain viruses. These tests can be performed on fluids or homogenates of tissues obtained from the respiratory tract. Commercially available antigen capture EIAs are available for diagnosis of HRSV infections in infants and young children; these are also capable of detecting BRSV[16] and are used in some veterinary diagnostic laboratories. The same technique has been developed for the detection of BVDV and is in use for screening serum samples to detect cattle persistently infected with BVDV.

Detection of Viral Nucleic Acids.

Testing material from swabs, fluids, or tissues for viral nucleic acid by PCR (for DNA viruses) or RT-PCR (for RNA viruses) is widely available at veterinary diagnostic laboratories. One benefit of using nucleic acid detection to identify pathogens is that the pathogen does not have to be viable to be identified; this can be a particular benefit for relatively labile viruses such as BRSV.

Serologic Diagnosis.

Retrospective diagnosis of viral infections can be made by determining antibody titers in paired sera from individual animals. The first sample is collected in the acute phase of the disease (the “acute” sample), and the second is collected 2 to 4 weeks later (the “convalescent” sample). In a respiratory disease outbreak, multiple animals should be tested to achieve a serologic diagnosis; it is typical for seroconversion to be identified in only a subset of animals tested in any outbreak. Serologic diagnosis is made by demonstrating at least a fourfold increase (i.e., at least two dilutions) in antibody titer in the convalescent sample as compared with the acute sample; a fourfold fall in titer from the acute to the convalescent sample also indicates recent infection. Because day-to-day variation in results of tests used for serologic diagnosis is typical, the acute and

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convalescent samples should be run by the laboratory on the same day. Thus the acute serum samples should be processed and stored in the freezer by the local veterinarian and later shipped together with the convalescent samples. Because infections in young ruminants can occur in the presence of passively derived antibodies, seroconversion may not always occur during outbreaks of bronchopneumonia involving young animals.

A variety of serologic tests are available for antibody determinations, but most laboratories use a serum neutralization (SN) test (also known as a virus neutralization [VN] test) for identification of antibodies to viruses. It is important to remember that SN tests take several days to run. Some laboratories use more rapid procedures such as ELISA or IFA for determination of virus-specific serum antibody titers. A hemagglutination-inhibition test can also be used for PIV-3, influenza D virus, and respiratory coronavirus.

Bacteria

A variety of bacteria have been isolated by aerobic culture of materials collected from the respiratory tract of ruminants with respiratory disease. However, the most frequent and important isolates are *M. haemolytica, P. multocida, H. somni,* and *M. bovis*. Other mycoplasmas such as *M. dispar* or *M. ovipneumoniae* may be important in some cases. The isolation of *T. pyogenes*, coliforms, or anaerobic bacteria often is indicative of chronic pneumonia or aspiration pneumonia and may be associated with lung abscessation.

Before bacterial culture is attempted, the status of any recent antibacterial therapy should be determined. If possible, specimens from untreated cattle should be collected. It is important to remember that *M. haemolytica, P. multocida, H. somni,* and mycoplasmas are normal inhabitants of the nasal passages of cattle and may be cultured from respiratory tissue in the absence of respiratory disease. Special culture methods are required to identify *H. somni* and mycoplasmas, and many diagnostic labs will not test for these organisms unless testing is specifically requested. Moreover, most laboratories will not identify the species of mycoplasmas cultured unless that is requested; thus an isolate may be identified only as "*Mycoplasma* spp." If involvement with *M. bovis* is to be confirmed, the veterinarian will likely need to specifically request species identification for any mycoplasmas isolated. Specific identification of *M. bovis* is most often done by IFA, IHC, or PCR. Some mycoplasmas are more hardy or easier to grow than others; for example, it is not unusual for *M. bovis* to overgrow *M. dispar* when both are present in the same sample. Culture of

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mycoplasmas typically takes at least 1 week, and laboratories often call a sample negative only after it has been subcultured at least once, which usually requires at least an additional week. Thus it takes longer to get the final results of mycoplasma testing than testing for other bacteria.

When sampling lung tissue for bacterial infection at necropsy, contamination of the sample with environmental agents can best be prevented by first searing the lung surface with a heated spatula or knife, then making an incision with a sterile scalpel, followed by sampling with a swab through the incision. However, it may not be practical to sear the surface of the lung in the field setting. Alternatively, sections of lung and other tissue samples can be sent in sterile, sealed containers on ice to the diagnostic laboratory for appropriate sampling for bacteria.

Detection of Bacterial Antigens or Nucleic Acids.

It is common for diagnostic laboratories to use IHC for identification of bacteria in formalin-fixed tissues. This technique offers many advantages, including correlation of the pathogenic organism with the lesion and detection of pathogens not found on bacterial culture because of overgrowth of other organisms such as *T. pyogenes* or *P. multocida.* The use of PCR for identification of bacterial agents in a variety of samples is also increasingly available, and this may be more sensitive than culture.[17] The veterinarian is encouraged to contact the diagnostic bacteriologist at the local diagnostic laboratory or check the laboratory website for information regarding which tests are available. MALDI-TOFMS is used by many diagnostic laboratories for rapid identification of bacteria once they have been isolated by culture.

Serologic Testing for Bacterial Pathogens.

Diagnosis of infection with bacterial pathogens can be attempted retrospectively through the use of serologic testing as described earlier for viral pathogens. However, the use of serologic tests for identification of infection by bacterial respiratory pathogens has mostly been limited to use in research. Thus these tests are not likely to be widely available in veterinary diagnostic laboratories.

Other Approaches to Diagnosis of Respiratory Disease.

The use of a computer-aided electronic stethoscope has been shown to have relatively good sensitivity and specificity, compared to pen checking, for identification of respiratory disease in feedlot cattle.[18]

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Remote assessment of feeding and drinking behavior, infrared thermography, and remote detection of fever by rumen boluses or ear tags have all been used in research settings to identify cattle that have signs of illness typical of BRD. At present these approaches are not yet practical, reliable, and cost-effective for the routine diagnosis of respiratory disease. However, they will likely be the focus of continued research, and one or more of these methods may eventually become applicable for routine use in the future.

Treatment of Undifferentiated Ruminant Respiratory Disease*

Amelia R. Woolums

Antimicrobial Therapy.

The basic principles of antimicrobial therapy for bacterial bronchopneumonia are to treat early enough, treat long enough, and treat with the appropriate antimicrobial agent. Because there are currently many effective antimicrobials marketed for the treatment of important bacterial respiratory pathogens in cattle (see Table 31.15), failure to treat early enough is more likely an important cause of treatment failure than failure to choose the correct antibiotic. If lung lesions becomes too advanced before treatment is initiated, it may not be possible to reverse lung pathology with a practicable course of any antimicrobial.

Treating early enough requires timely identification of animals with clinical signs of respiratory disease. Because individual ruminants in production agriculture settings often receive their first treatment for undifferentiated respiratory disease from a layperson caretaker and not from a veterinarian, it is appropriate for caretakers to be taught by the supervising veterinarian to recognize signs of respiratory disease. Caretakers should be trained to watch for these signs whenever they are in contact with ruminants in their care; clinical scoring systems have been developed for identification of respiratory disease in dairy calves.[2,3] Similarly, in cattle feedlots clinical signs are assessed by lay caretakers, including the pen riders who evaluate cattle in the feedlot pens and the “hospital crew” who examine individual cattle “pulled” or removed from feedlot pens by the pen riders and sent to a treatment area for individual assessment and treatment by the hospital crew. It is imperative that lay caretakers evaluating animals for clinical signs of disease receive training from the supervising veterinarian and that training be reviewed regularly so disease

identification and treatment is as accurate and timely as possible. In addition, treatment of affected animals by lay caretakers should be based on written protocols established by the supervising veterinarian and maintained for easy review on the farm or feedlot.

Ruminants with undifferentiated bronchopneumonia are often identified and treated presumptively based on clinical signs, without diagnostic testing to identify specific viral or bacterial etiologic agents. However, if animals fail to respond as expected to nonspecific therapy, diagnotic tests are warranted, as they may reveal an unexpected pathogen, a bacterial pathogen with unexpected antimicrobial resistance pattern, or another underlying disease that must be addressed.

Since bacteria often contribute to bronchopneumonia in ruminants, appropriate presumptive treatment includes an antimicrobial effective against the most common causes of bacterial bronchopneumonia. Selection of the appropriate antimicrobial tends to be what most veterinarians focus on when treating respiratory disease because this is the aspect of therapy over which they have the greatest control. Factors such as cost, route of administration, treatment interval, drug label restrictions, necessity of extralabel doses, and withholding times may exclude a number of antimicrobials, leaving a short list of suitable alternatives for use as a first-line antimicrobial agent. Only antimicrobials that are licensed and effective at label doses should be considered for routine use in food animals. Table 31.15 lists antimicrobials currently approved in the United States for the treatment of respiratory disease in cattle, sheep, and goats. If data regarding the MIC of bacteria isolated from untreated animals are available, the dose or duration of therapy can be rationally modified, but it is imperative that proper withdrawal times be observed when antimicrobials are used in an extralabel fashion. At the time of this writing, the Food Animal Residue Avoidance Databank (FARAD; www.farad.org or 1-888-USFARAD) is an invaluable resource for veterinarians who need to identify withdrawal times for drugs administered to food animals in an extralabel manner. The use of MIC data requires some understanding of the pharmacokinetics and pharmacodynamics of the drugs to be considered; published information is available regarding interpretation of MIC data, or veterinarians can contact FARAD, the diagnostic bacteriologist at their local diagnostic laboratory, or a veterinary clinical pharmacologist for assistance.

A decision regarding which antimicrobial to use to treat bronchopneumonia may be based on the results of antimicrobial susceptibility testing or MIC data

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for bacteria isolated antemortem or postmortem from animals in the group. However, such results must be interpreted carefully. The most relevant information is gained from testing samples collected from diseased lung at postmortem from animals that have not yet received any antimicrobial therapy. However, because animals are often treated presumptively before they die or are euthanized, it may be difficult to test animals that have not already been treated. Once an animal has been treated, bacteria isolated may be resistant to multiple antimicrobials.[19,20] However, bacteria isolated from the lungs of cattle that have been treated with antimicrobials are not always resistant to these drugs.[21] Currently, evidence-based guidelines for management of cattle with bronchopneumonia attributed to MDR bacteria are lacking; anecdotally it has been reported that cattle can recover despite the presence of *M. haemolytica* resistant to the antimicrobial with which they are treated. This may indicate that the host response can resolve infection and repair pathology in at least some cases of MDR infection. Management of cattle with respiratory disease associated with MDR bacteria is an active area of research.

The choice of which antimicrobial to use can also be based on records of efficacy for animals treated in the past. Producers who keep accurate records of drugs used, with results of treatment responses, relapses, and the proportion of treated animals that become chronic cases, may select first-line antimicrobials based on historical performance of a drug. This may be the best approach to antimicrobial selection. Guidelines for response to antimicrobial therapy for feedlot cattle with respiratory disease have been suggested: 70% to 80% of animals should respond to the first treatment they are given, the case fatality rate should be between 4% and 7%, and the ratio of chronic cases to cases that die should be 0.5 to 1.0.[22]

A final method of choosing a first-line antimicrobial drug is reliance on published treatment trials. Published trials give comparisons between responses for various antibiotics in cattle with naturally occurring bacterial bronchopneumonia. The outcomes of these trials are often expressed as both health and production values. When evaluating published treatment trials that use cases of naturally occurring bacterial bronchopneumonia, it is important to realize that the results may not be applicable to cattle and pathogens outside the operation where the trial was carried out. The highest-quality information comes from meta-analyses or systematic reviews, which incorporate information from multiple trials. Recent meta-analyses provide estimates of the relative efficacy of many of the antimicrobials currently labeled for treatment or control of bovine

respiratory disease.[23-25]

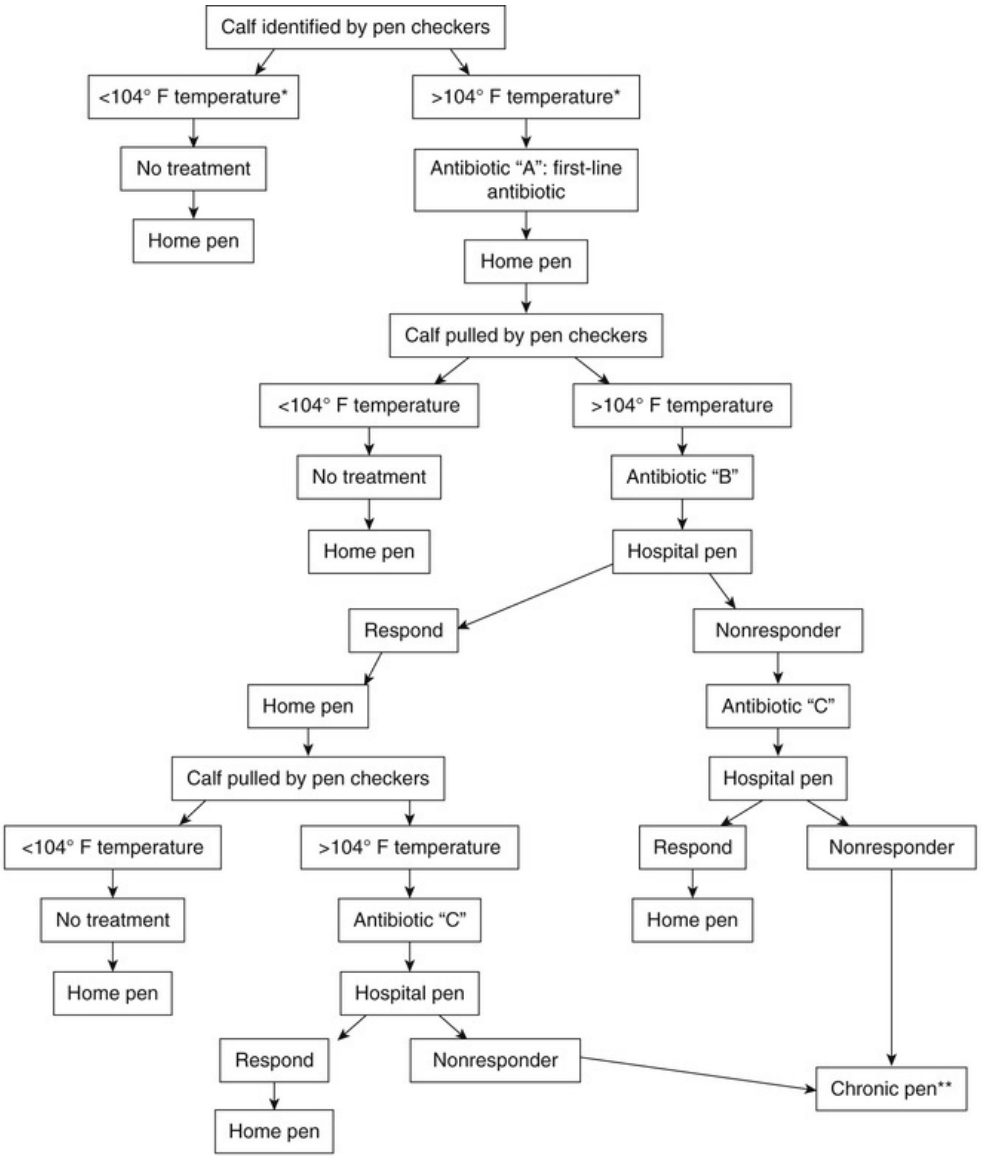
Mass medication of an entire group of cattle during an outbreak can curtail the daily number of new cases and improve outcomes. In the acute stages of an outbreak, whatever drug is chosen should be given by injection; therapeutic levels are not likely to be reliably maintained by administering drugs in feed or water because of suppressed feed intake by sick cattle. It is important to base a decision to mass-medicate on measurable criteria. Some feedlot veterinarians implement mass medication when the pull rate of sick animals is 10% on each of 3 consecutive days or 25% on a single day.[26]

Although little research has been undertaken to determine optimal duration of therapy for undifferentiated respiratory diease of ruminants, a general recommendation is that therapy should be continued for at least 48 hours after clinical signs of fever, dyspnea, and systemic inflammatory response have abated. Many of the antimicrobial drugs labeled for use in the treatment of pneumonia in cattle provide multiple days of therapeutic drug concentrations in lung tissue after only a single injection. These products decrease the time and stress associated with daily treatment; in feedlots, they also make it easier for caretakers to return animals to home pens rather than keeping them in hospital pens, which may be associated with poorer responses by treated animals. Although a 3-day course of antimicrobial therapy for undifferentiated bronchopneumonia was in the past considered adequate, the view is increasingly held that treatment for a longer duration may be more appropriate. This is particularly true for pneumonia caused by *M. bovis* in dairy calves or feedlot cattle, which may respond better to treatment for at least 7 to 10 days.[27,28] Although treatment for 7 to 10 days would be extralabel for some antibiotics, multiple drugs currently marketed have been shown to provide therapeutic drug levels for at least 7 days when used at dosages recommended on the label (see Table 31.15).

In some cases clinical signs of bronchopneumonia do not resolve following treatment with the first-line antimicrobial. In such cases, veterinarians must decide when to give a new drug and which drug to choose for second-line therapy. In the past, a standard recommendation was to administer a second antimicrobial if the animal was still febrile 72 hours after treatment with the first-line antimicrobial. However, recent research has suggested that, for cattle given a long-acting antibiotic as a first-line treatment, it may be acceptable to wait longer than 72 hours before administering a second antibiotic. For example, it has been recommended that cattle not responding to treatment with long-acting

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(200 mg/mL) oxytetracycline should be treated with a second drug after 2 to 3 days, whereas cattle treated with ceftiofur crystalline free acid (Excede® [Pfizer Animal Health, Parsippany, N.J.]) should be treated with a second drug if not responding after 5 to 7 days, and cattle treated with tulathromycin (Draxxin® [Pfizer Animal Health, Parsippany, N.J.]) should be treated with a second drug if not responding after 7 to 14 days.[29] It can be difficult for a veterinarian to withhold treatment with a second or even third drug if cattle are not improving quickly, but administering a different long-acting product every 3 days may not improve outcomes, although the practice will increase the cost of treatment and may also increase opportunities for the development of bacteria resistant to the antimicrobials. More research is needed to provide evidence-based guidelines regarding when a second or third drug should be given to nonresponding cattle. At this time, veterinarians often make recommendations based on past experience. A typical decision tree for treating feedlot cattle with antibiotics is shown in Fig. 31.67, but protocols such as these may be modified as more information about the use of long-acting antimicrobials is obtained from field research.



*Temperature at which cattle are treated can vary from 103.5° to 104.5°F ; cutoff is selected at discretion of supervising veterinarian.
**Calves in chronic pen should be monitored for weight gain, suffering, and withholding times, so that appropriate action can be taken (i.e., euthanize, sell, continue feeding).

FIG. 31.67 Decision tree for antibiotic treatment of feedlot cattle. (Input contributed by Dr. Robert A. Smith.)

The same principles of therapy described previously apply to the treatment of sheep and goats. Unfortunately, fewer drugs are labeled for the treatment of sheep and goats as compared with products used for cattle. Drugs labeled for use in sheep and goats are listed in Table 31.15. Note that whereas tilmicosin (Micotil 300 [Elanco Animal Health, Greenfield, Ind.]) is labeled for use in sheep, fatal reactions have occurred in goats treated with this drug. Goats should not be treated with tilmicosin. It is imperative to ensure that producers are given

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an appropriate meat and milk withdrawal time when antimicrobials are administered to sheep and goats at extralabel dosages; this is a particular concern in feedlot lambs or goats and in lactating dairy sheep or goats, from which products may enter the food chain in a relatively short time after treatment.

Antiinflammatory Therapy.

Viral or bacterial infection that leads to bronchopneumonia can cause significant tissue injury and inflammation. Moreover, many of the bacteria that cause bronchopneumonia are gram-negative bacteria that produce endotoxin, which can cause a systemic inflammatory response that can be harmful and even fatal. Treatment with NSAIDs could mitigate these effects; treatment should also decrease fever and discomfort, which should lead to improved feed intake and improved growth or milk production. A review of the published evidence for the use of NSAIDs in treatment of BRD is available.[30] Although NSAIDs often decrease fever and improve clinical appearance in cattle with BRD in the first few days after administration, a positive impact of NSAID treatment on other outcomes has not been as consistent. For example, average daily gain was improved for cattle with BRD given an NSAID as well as an antimicrobial in one study[31] but not in another.[32] Mortality was not decreased by NSAID treatment,[32,33] but lung consolidation at slaughter or necropsy was decreased in cattle receiving certain NSAIDs.[31,33] Therapy with NSAIDs might be justified on the grounds that they should improve animal comfort and therefore animal welfare, but the degree to which they actually improve comfort and welfare has not been quantified. It has also not been well established that NSAIDs are cost-effective; this will likely vary in different settings depending on the number of animals to be treated and the cost of the drug administered. If NSAIDs are to be used for treatment of BRD, in the United States and Canada flunixin meglumine (Banamine® [Merck Animal Health, Madison, N.J.]) is approved for control of pyrexia associated with BRD (1.1 to 2.2 mg/kg IV either as a single dose or divided into two doses at 12-hour intervals for up to 3 days). It is important to remember that flunixin meglumine is labeled only for IV use; administration via the IM or SC route can result in violative residues in tissues if longer withdrawal times are not observed. Phenylbutazone, which has been used in the past for antiinflammatory effect in ruminants, is now illegal to use in lactating dairy cattle in the United States, and because of prolonged tissue levels found in treated cattle its use is discouraged in all food animals. Recently meloxicam has

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received significant attention in North America for the control of pain and inflammation in cattle (1 mg/kg PO[34] or 0.5 mg/kg IM[35]). At the time of this writing, meloxicam is not specifically approved for the treatment of BRD in the United States or Canada; it is approved in Canada for treatment of calves with diarrhea or for pain control associated with disbudding. At the time of this writing, no NSAID is labeled in the United States or Canada for the treatment of respiratory disease in sheep or goats.

Because NSAIDs can be nephrotoxic and because nephrotoxicity is exacerbated by dehydration, dehydrated animals should be rehydrated before administration of these drugs. Care should also be taken not to overdose NSAIDs or use them for prolonged periods because they may also result in abomasal ulceration.

While corticosteroids have potent antiinflammatory effect and are sometimes used for treatment of severe inflammation associated with an infectious disease, they should not be used indiscriminately in the treatment of respiratory disease because of the potential for immunosuppression. Corticosteroids may have a place in treatment of respiratory diseases such as necrotic laryngitis or tracheal edema syndrome of feedlot cattle because edema of the larynx or trachea can cause life-threatening airway narrowing. The dose for dexamethasone in cattle is 0.05 to 0.2 mg/kg IM or IV, and the dose for isoflupredone acetate is 10 to 20 mg IM. Treatment with corticosteroids may cause recrudescence of BHV-1 infections.

There has been little research to support the use of antihistamines as an ancillary treatment for bovine respiratory disease. Tripelennamine HCl is labeled for cattle at a dose of 1.1 mg/kg, which can be repeated in 6 to 12 hours.

Antiviral and Immunomodulating Therapy.

Although antiviral drugs could be of theoretical benefit for treating ruminants with undifferentiated bronchopneumonia, they are not routinely used. Levamisole and isoprinosine have been used in attempts to stimulate the bovine immune system with equivocal success.[36] It is important to recognize that the immunostimulatory benefits of levamisole occur at doses in the 2 to 3 mg/kg range, compared with the anthelmintic dose of 6 mg/kg. A decreased immune response has been observed after an 8 mg/kg dose of levamisole. A DNA immunostimulant (Zelnate [Bayer Healthcare LLC, Pittsburgh, Pa.]) is available for use to aid in the treatment of BRD associated with *M. haemolytica* infection. Treatment with this immunostimulant decreased the percent of abnormal lung in

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calves experimentally exposed to *M. haemolytica*[37] and decreased mortality due to BRD in high-risk cattle.[38]

Supportive Therapy.

Supportive treatment may foster recovery of patients with respiratory disease. Sick animals should be provided with shelter that protects them from rain, cold, wind, and hot sun. They should not be crowded or housed in areas with excess mud and manure, and good-quality feed and clean water should be easily accessible. Mineral and vitamin deficiencies should be corrected with the use of injections or oral preparations if necessary.

Epidemiology of Undifferentiated Ruminant Respiratory Disease*

Amelia R. Woolums

Respiratory Disease in Dairy Calves.

Respiratory disease in dairy calves has been described to occur both in epizootics (outbreaks) and in an endemic (enzootic) pattern (“enzootic calf pneumonia”). At the farm level, the occurrence of producer-identified calf respiratory disease is skewed, with few or no calves being identified with respiratory disease on many farms and many calves being identified with respiratory disease on a few farms. The median (and range of) incidence for producer-identified respiratory disease in the first 90 days of life was 3% to 22% (0% to 52%).[39,40] Case fatality rates for respiratory disease in dairy calves have been reported to range from 2.6% to 9.4%.[40,41] Respiratory disease accounts for a significant proportion of the total mortality (proportionate mortality) in calves raised on dairy farms, with proportionate mortality rates of 24% to 52% reported.[41-43] Respiratory disease in dairy calves can be identified as early as the first week of life.[44,45] In reports describing dairy calf respiratory disease in the first 90 to 120 days of life, the median age at which calves were first identified by producers to have respiratory disease was between 27 and 37 days,[45,46] and the age at which the highest percentage of calves are treated ranged from 35 to 70 days[41,47,48] (5 to 10 weeks). In an assessment of calves in three Canadian dairies, weekly transthoroacic ultrasound in the first weeks of life indicated that 57% of calves were found to have lung consolidation on at least one

examination.[7] In a cross-sectional study of 39 dairies in which calves were examined by transthoracic ultrasonography once in the winter and once in the summer, the median calf-level prevalence of respiratory disease as defined by lung consolidation was 8% in winter and 15% in summer.[49]

The agreement between producers and veterinarians in identification of dairy calf respiratory disease was evaluated in two studies. Van Donkersgoed and colleagues[46] found that the risk of respiratory disease in Saskatchewan dairy calves was 39% as diagnosed by the farmer and 29% as diagnosed by the veterinarian. Virtala and colleagues[42] found that the risk of respiratory disease was 11% in New York dairy calves when diagnosed by producers and 26% when diagnosed by a veterinarian. In both sudies the agreement between veterinarian and producer diagnosis was poor at the level of the individual calf but moderate at the level of the herd. For calves subjected to necropsy, and using necropsy as the gold standard, the antemortem diagnosis of respiratory disease by producers was determined to have a sensitivity of 56% and a specificity of 100%.

Respiratory disease in dairy calves has a negative impact on their subsequent growth and productivity. In one study, calves treated for respiratory disease in the first 90 days of life were 2.5 times more likely to die before weaning than calves that were not treated.[50] Multiple investigators have shown that calfhood respiratory disease decreases calf growth.[51-53] Dairy heifers treated for respiratory disease weighed 10.6 kg less at 6 months of age than untreated calves.[51] Calves with signs of respiratory disease in the first 3 to 4 months of life are more likely to leave the herd before calving, calve later, and produce less milk in their first lactation compared to calves without respiratory disease.

Respiratory Disease in Preweaning Beef Calves.

Respiratory disease was reported to be the leading cause of preweaning death for beef calves 3 weeks of age or older on U.S. cow-calf operations.[54] Sixteen percent of deaths in beef calves born alive are attributed to BRD.[55] Two reports described the pattern of respiratory disease occurring over several years in beef calves still nursing their dams in a single large herd.[56,57] In 110,412 calves over 20 years, the annual incidence of preweaning calf BRD in the herd varied from 3% to 24%, with an average annual incidence of 11%. Annual mortality among calves with preweaning respiratory disease varied from 7% to 17%, with an annual average of 13%. In some years the incidence of preweaning BRD was higher than the incidence of respiratory disease after calves were weaned and

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transferred to the feedlot. Calves identified with preweaning respiratory disease weighed 7.7 kg less at birth than calves not identified with preweaning respiratory disease. A mail survey of cow-calf producers in Quebec found that 16% of respondents with fewer than 40 cows recognized calves with BRD, as compared to 36% of respondents with 40 cows or more.[58] In a mail survey of producers in six U.S. states, 21% of operations reported observing one or more calves with preweaning respiratory disease. Of these, 89% treated one or more calves, and 46% reported one or more calf deaths attributed to preweaning respiratory disease.[59]

Respiratory Disease in Feedlot and Stocker Cattle.

In U.S. and Canadian cattle production systems, weaned beef calves are typically transported from the farm where they are born (cow-calf operation) to feedlots where they are fed and managed until they have reached the appropriate weight for harvest. Calves may enter feedlots by direct delivery from their cow-calf operation of origin or through purchase at local or regional auction markets by an “order buyer” acquiring calves for feedlots. Alternatively, calves may not enter a feedlot directly but instead may be sent for temporary management to a “backgrounding” (also known as “conditioning”) operation, where they may receive vaccinations or other treatments such as anthelmintics and growth implants, with dehorning and/or castration if necessary. At the backgrounding operation calves may be reassorted based on their size, breed type, and/or gender into new groups before being sent to feedlots. Similarly, after sale, weaned calves are sometimes transported to “stocker” operations, where they are housed or “stocked” on pasture for weeks to months with supplemental feed given as needed, along with vaccinations and other treatments, before being transported to a feedlot at a later date.

Undifferentiated bovine respiratory disease is the most common cause of morbidity and mortality in feedlot and stocker cattle. The disease is also known as “shipping fever” because it commonly occurs after cattle have been transported. The pattern of BRD in North American feedlot cattle has been well characterized.[60,61] In a study by Alexander and colleagues,[61] data from 17,696 cattle in a single feedlot were evaluated, and factors related to respiratory disease morbidity were also evaluated. Respiratory disease was the cause of treatment for 50% of the cattle treated, with 58% of BRD cases developing in the first 40 days on feed. In a study by Ribble and colleagues,[60] data were collected on all

58,885 spring-born calves entering a single western Canadian feedlot over a 4-year period. Across the 4 years of the study, total (crude) mortality was fairly consistent, ranging from 2.4% to 4.8%, whereas the mortality caused specifically by BRD varied more than tenfold (0.25% to 2.73%). Across years, proportionate mortality caused by BRD ranged from 10% to 57%. Epidemic curves constructed for each of the 4 years showed that peak mortality occurred approximately 16 days after arrival at the feedlot and that at least 50% of BRD mortalities occurred within 3 weeks of arrival. Similar results were found in the Alexander study, where 58% of BRD cases were found to develop in the first 40 days on feed. The consistent onset of fatal disease in cattle within days of their arrival at the feedlot indicates that the disease process is often underway in affected animals before feedlot entry. Ribble and colleagues demonstrated that when the incidence of fatal BRD was high (greater than 2%), the disease clustered within truckload groups of calves and also, in 1 year, within pens.

Another study evaluated patterns of BRD in the first 100 days after feedlot entry in lots (cohorts) of cattle entering 10 U.S. feedlots over 8 years.[62] For 1.2 million cattle in 7553 lots, the cumulative within-lot BRD morbidity ranged from 0.3% to 84.3%, with a median of 4.2% and a mean of 8.8%. This study demonstrated that the pattern of BRD occurrence in the first 100 days on feed can vary greatly among lots of cattle. In some lots 80% of BRD cases occurred within the first 10 days on feed, whereas in other lots 80% of BRD cases had not occurred until the cattle had been on feed for more than 90 days. In some lots the proportion of cattle treated for BRD increased rapidly over relatively few days, and in others the proportion treated increased slowly over several weeks. In some lots a rapid increase in the proportion of cattle treated for BRD occurred relatively late, between 60 and 100 days on feed. The reasons for the different patterns of BRD occurrence that were observed in different lots of cattle were not determined, but they are likely related to a combination of factors related to the cattle and their environment.

Feedlot BRD has a significant negative impact on productivity of cattle. Numerous reports have demonstrated that BRD can decrease average daily gain, final weight at slaughter, and carcass quality, with these impacts decreasing producer profit.[63-67] Feedlot BRD has been shown to decrease average daily gain during the entire feeding period by 0.06 to 0.08 kg.[65,66] In one study, cattle treated once, twice, or three times for BRD yielded $41, $58, or $292 less, respectively, than cattle not treated for BRD.[63] Another study evaluating data

from more than 212,000 cattle entering Midwestern U.S. feedlots over a 5-year period similarly showed that increasing number of BRD treatments led to decreasing financial return; net returns for fall-delivered cattle treated three or more times were $72 less than cattle not treated.[68] Although the negative impacts of BRD are well established, affected cattle sometimes exhibit compensatory growth in the later phase of feeding period, so that cattle with BRD do not always perform more poorly than unaffected cattle when the entire feeding period is considered.[67] Therefore the exact impact of BRD on the performance and profit returned by a group of feedlot cattle will vary substantially depending on numerous variables, including the specific risk factors the cattle have encountered; the management of health and nutrition in the feedlot; the cost of feed, medications, and labor; and the value of the cattle at the time they are purchased and marketed.

The epidemiology of BRD in stocker cattle is similar to that described for feedlot cattle, although morbidity and mortality rates may be higher because cattle defined to be at “high risk” for BRD make up a large proportion of many stocker cattle groups. In high-risk cattle kept on native Texas range over 3 years, BRD morbidity ranged from 31% to 49%. Net returns for steers and bulls treated for BRD were decreased from 10% to 21%, and heifers treated twice or more for BRD had 19% lower conception rates at first breeding than unaffected heifers.[69] Many reports indicate that BRD is the leading cause of disease in stocker cattle.[69-71] And although Pinchak and colleagues reported death rates of less than 1% in stocker cattle on grass, anecdotal reports indicate that BRD mortality rates in high-risk stocker cattle can be alarmingly high, sometimes approaching 10% to 20%. In trials testing health practices designed to improve health outcomes for high-risk stocker cattle over a 28- to 84-day receiving period, BRD morbidity rates ranged from 62% to 72% and BRD mortality ranged from 0% to 13%.[72,73]

Respiratory Disease in Adult Dairy or Beef Cattle.

Although anecdotal reports indicate that adult beef or dairy cows can experience outbreaks of respiratory disease with high morbidity and an important impact on milk production in dairy herds, the epidemiology of respiratory disease in adult cows has not been well characterized. Surveys of U.S. producers indicated that respiratory disease is the cause of 3.4% of the deaths that occur in adult beef cattle[54] and 11.3% of deaths that occur in adult dairy cattle.[74] The lack of data regarding respiratory disease in adult cows is likely due to the fact that other

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diseases that affect reproductive performance and milk yield are of greater economic significance in this class of cattle. However, the few published descriptions of respiratory disease outbreaks confirm that the problem can on occasion be of major importance to individual herds.

Respiratory Disease in Sheep and Goats.

Little information is available regarding the epidemiology of respiratory disease in sheep and goats in North America. A survey of U.S. producers indicated that 7% of death in adult sheep is due to respiratory disease, whereas 12% of lamb deaths are due to respiratory disease.[75] Feedlots reported that shipping fever pneumonia accounted for 13% of feedlot lamb deaths, and other respiratory disorders accounted for 29% of lamb deaths.[35]

Host and Environmental Risk Factors for Undifferentiated Ruminant Respiratory Disease*

Amelia R. Woolums

In general, risk factors for respiratory disease in all ruminants are related to (1) factors that impair the host physiologic and immunologic responses that defend against respiratory infection, and (2) characteristics of the environment that overwhelm the ability of these physiologic and immunologic responses to prevent respiratory infection. More specifically, host risk factors are related to (1) mechanical respiratory defense by the anatomic features of the upper respiratory tract and the mucociliary elevator; (2) innate immune defense provided by soluble factors such as lysozyme and defensins and by cells such as granulocytes, macrophages, and natural killer cells; and (3) acquired immune defense provided by antibodies on mucosal surfaces and in serum and by cells such as T-helper lymphocytes and T-cytotoxic lymphocytes. Characteristics of the host that can impair these mechanisms include other concurrent disease, nutritional deficiency, genetics, pronounced or chronic stress related to events such as mixing animals from various sources, crowding, and/or long-distance transport. In young animals, failure of transfer of passive immunity is a cause of transient immunodeficiency that may contribute to respiratory disease.

Environmental factors can also contribute to the development of respiratory disease in ruminants. High concentrations of airborne particulates, infectious agents, or noxious gases impair the function of host respiratory defense mechanisms or enhance the transmission of infectious respiratory pathogens.

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Inadequate housing can lead to cold or heat stress, which may increase nutritional requirements beyond what is available and lead to increased disease susceptibility. Crowding or mixing animals of different sources and/or age-groups can increase opportunities for transmission of infectious respiratory pathogens. Long-distance transport is well known to predispose animals to respiratory disease; this is due to close contact with other animals, which enhances transmission of infectious agents, as well as to inhalation of particulates and noxious gases in truck exhaust. Mixing animals from multiple sources, such as occurs when animals are sold through livestock auctions, increases risk for respiratory disease by increasing opportunities for exposure to respiratory and other pathogens; psychological stress associated with the establishment of new social hierarchies may also contribute to immune suppression and increased rates of disease.

When respiratory disease occurs in any group of ruminants, a systematic evaluation of host and environmental factors that may increase risk of respiratory disease should be undertaken. The purpose of this evaluation is to identify modifications in management and husbandry that should help limit ongoing respiratory disease and should decrease risk of future respiratory disease. Although this approach is logical, there is unfortunately little research that confirms that management modifications decrease respiratory disease in ruminants; it is to be hoped that future work will address this knowledge gap. Specific risk factors relevant to various classes of ruminants are discussed below.

Dairy Calves.

In young calves, adequate transfer of passively acquired antibody and possibly also maternal cells from colostrum are very important for defense against respiratory and other infections. Nutritional deficiency, stress associated with weaning, mixing of calves from different sources, castration and/or dehorning, concurrent disease, and temperature extremes may all affect host defense mechanisms. Environmental risk facrtors are related to (1) air quality, including humidity and the concentration of bacteria, other particulates, and noxious gases in air; (2) ambient temperature extremes; and (3) opportunities for exposure of calves to respiratory pathogens through new introductions, mixing animals from different locations or age-groups on the same farm, or contact with older animals on the same farm. When dairy calves are affected by either epizootic respiratory disease (outbreaks) or enzootic calf pneumonia, careful evaluation of management practices that influence both host and environmental risk factors

may help prevent future disease.

Specific risk factors for respiratory morbidity and mortalitiy in dairy calves have been evaluated in many studies.[39-42,44,46,47,76-78] It is noteworthy that factors significantly associated with respiratory morbidity and/or mortality in some studies are not always associated with disease in other studies; this is likely because of differences in the populations studied or in methods of collection or analysis of data. Factors identified as signficant in more than one study may be relatively more important. Knowledge of factors associated with dairy calf respiratory disease can help veterinarians focus efforts to modify management to limit or prevent respiratory disease in herds where calf respiratory disease is a problem. Calf-level and farm-level factors that have been found to be significantly associated with dairy calf respiratory disease (morbidity or mortality) are presented in Box 31.5.

Box 31.5

Factors Associated With Respiratory Disease in Dairy Calves

Risk Factors Associated With Increased Respiratory Disease Morbidity in Dairy Calves

Calf-Level Factors

- Having diarrhea[39]
- Serum total IgG ≤1200 mg/dL[9] or serum total protein <5.7 g/dL[8]
- Calfhood in fall or winter[39,42,47]
- Being fed mastitic colostrum[9]
- Certain sires[47]
- Having the navel dipped[8,40]

Farm-Level Factors

- Shared housing with cows[9,77]
- Diarrhea occurring in calves[40,77]

Larger herd size[42,44,77]
Group housing of calves prior to weaning from milk[40]
More than 8-week age range among calves in same pen[77]
Leaving calves with dams for more than 24 hours after birth[77]
Manual (versus automatic) control of temperature in calf housing[8]

Risk Factors Associated With Decreased Respiratory Disease Morbidity in Dairy Calves

Calf-Level Factors

Being housed individually in outdoor hutch (versus any other housing)[40]
Having supervised calving[76]
Serum total IgG >800 mg/dL[46]
Receiving antibiotic preventatively[40]
Receiving supplemental antibody product to prevent diarrhea[8]

Farm-Level Factors

Decreased total bacterial counts in calf pen air[91]
Solid barriers between individual calf pens[91]
Bedding deep enough for calves to nest[91]
Antibiotics in feed or milk replacer[40]

IgG, Immunoglobulin G.

Preweaning Beef Calves.

As compared to dairy calf respiratory disease, less is known about factors that increase risk for respiratory disease in preweaning beef calves. Calf-level factors associated with preweaning respiratory disease over several years in a large U.S. herd included the year of the calf's birth, the location of the calf's group on the operation, whether or not the calf experienced dystocia requiring major assistance, the calf's sex (with male calves being at greater risk), and the age of the calf's dam (with calves born to heifers being at greater risk).[57]

A survey of cow-calf producers in Quebec[58] found that farms with fewer than 40 cows were less likely to report a problem with preweaning calf pneumonia than farms with 40 or more cows (16% versus 36% of producers recognizing nursing calf pneumonia). The rate of preweaning calf pneumonia was associated with calving season length, with a longer calving season being associated with more cases of calf pneumonia. Another study in Quebec found that the incidence of preweaning calf respiratory disease in the first month of life was decreased if the herd vaccinated cows for respiratory viruses, with a 13% incidence in herds not vaccinating cows versus a 6% incidence in herds vaccinating cows.[79]

More recent research has evaluated herd-level risk factors for preweaning calf respiratory disease in U.S. cow-calf herds. An analysis of U.S. Department of Agriculture National Animal Health Monitoring System (NAHMS) data collected by producer survey found that introduction of steers from outside sources, herd breed makeup, number of visits to the herd by outsiders, administration of antibiotics in feed to prevent calf respiratory disease, and the herd being the primary source of income for the producer were factors associated with preweaning calf respiratory disease treatment rate.[80] A mail survey of cow-calf producers in three eastern U.S. states and three Plains states found that the occurrence of preweaning calf respiratory disease was significantly associated with larger herd size, respiratory disease in cows, and diarrhea in calves.[59] Calving season length was associated with calf respiratory disease in Plains but not eastern herds. Cumulative treatment incidence was associated with winter calving, bringing calves into the herd from outside sources, giving calves supplemental feed, and use of a heat synchronization program. A case-control study of herd-level risk factors for respiratory disease in preweaning beef calves in three U.S. states found that herd size, use of an estrus synchronization program, and use of intensive grazing were associated with treatment of at least 5% of calves for respiratory disease.[81] Taken together, the available evidence suggests that factors that increase opportunities for introduction of respiratory pathogens new to the herd and factors that increase opportunities for close contact between calves, and among cows and calves, are important risk factors for respiratory disease in preweaning beef calves.

Feedlot and Stocker Cattle.

Risk factors for BRD in feedlot and stocker cattle include factors related to events on the cow-calf operation where cattle originate, events that occur while

cattle are in transit, and events that occur at arrival. On the cow-calf operation of origin, factors such as poor nutrition and uncontrolled parasitism are suspected to affect later BRD risk in the feedlot or stocker operation, but data confirming this are currently sparse. Cattle breed has been related to BRD risk.[82] Fetal programming, which refers to epigenetic effects driven by maternal experiences while the cow is pregnant but that affect the health of the calf long after it is born, is an active area of research; this may lead to clearer information about the relationship between events on the farm of origin and later BRD in stocker and feedlot cattle.

The mere fact that feedlot and stocker cattle are subjected to transport from the farm of origin increases their risk for BRD. Other factors related to increased rates of respiratory disease include sale through auction markets and prolonged time in market channels (sales barns, transport vehicles). Excessive dehydration or "shrink" from transport has been shown to account for significant morbidity and mortality in the feedlot. Movement through multiple auctions greatly increases the risk of respiratory disease. Several studies have confirmed that mixing cattle from multiple sources prior to or at feedlot entry is an important risk factor for feedlot respiratory disease.[61,83,84] Shipment for longer distances prior to feedlot entry has been associated with increased rates of respiratory disease in some studies[83,85] but not others.[86] Changes in weather have been associated with respiratory disease; Alexander and colleagues[61] found that a wide range between the high and low environmental temperatures in the first 2 weeks after feedlot entry was associated with increased respiratory disease. Cernicchiaro and colleagues[87] found that several weather-related variables such as maximum wind speed, mean wind chill, and temperature range were significantly associated with BRD risk, although the effect of weather was dependent on various characteristics of the cattle such as their average weight, risk category, and month of arrival and the number of cattle in the group. Heavier weight at entry has been shown to decrease feedlot BRD risk.[82,83] Castration at arrival has been shown in numerous studies to increase morbidity and mortality in feedlot and stocker cattle; it is preferable for male calves to be castrated or banded early in life to prevent the need for castration postweaning. Placement of water troughs so that cattle in adjoining pens shared them markedly increased risk for BRD in one study; the odds of BRD occurring was more than four times greated for cattle that shared water with cattle in adjacent pens compared to cattle that did not.[88] Metaphylactic antibiotic administration at

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arrival has been shown repeatedly to decrease risk for subsequent respiratory disease (see more discussion of metaphylaxis in the Metaphylactic Antimicrobial Therapy section later).

Calves that arrive in the feedlot with moderate concentrations of serum antibodies against respiratory viruses have sometimes been shown to have a decreased incidence of BRD, indicating that natural exposure or vaccination prior to arrival can be protective. Starting calves on diets containing 75% concentrate or greater or feeding corn silage as a major dietary component during the first month is associated with higher mortality and morbidity rates, possibly because of inhibition of certain immune functions by systemic acidosis. Feeding of nonprotein nitrogen, such as urea, is associated with increased rates of BRD.

Smith and Gill[89] have presented a helpful summary of risk classification of cattle in stocker and backgrounding operations. Stocker and backgrounding cattle can be grouped into one of three categories: (1) high risk, exposed: cattle with little or no history of vaccination, adaptation to hay or concentrate diet, and other preventative health management and with a history of mixing with cattle from multiple sources; (2) high risk, not exposed: as for high risk, exposed, but with no history of mixing with cattle from multiple sources; and (3) low risk: cattle that have been vaccinated, weaned, and turned out for a period before shipment. By nature most stocker and backgrounding cattle are in categories 1 or 2 and are thus at high risk for respiratory disease due to a variety of factors, including inadequate immunity, stress of recent weaning, and recent transport. Cattle may require dehorning and/or castration when entering the facility, which will further affect their health and productivity. Respiratory disease in high-risk, not exposed calves often peaks at 2 weeks post entry because these calves are not mixed with calves from other sources before they reach the stocker and backgrounding operation.

Adult Dairy and Beef Cattle.

Studies confirming risk factors for respiratory disease of adult dairy and beef cattle in modern North American production systems are lacking, but it is assumed that factors are similar to those described previously for calves and for cattle entering stocker operations and feedlots.

Sheep and Goats.

Many of the risk factors that have been found to predispose sheep and goats to

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undifferentiated respiratory disease are similar to those affecting cattle. Respiratory disease is more common in younger animals, after shipping or storms, and in crowded conditions. In addition, cold stress is an important risk factor for respiratory disase in young lambs and recently shorn adult sheep and goats. In contrast, heat stress may predispose to respiratory disease in unshorn sheep that do not have access to shade. Respiratory disease is also associated with semiconfinement or total confinement of sheep in poorly ventilated barns.

Prevention and Control of Undifferentiated Ruminant Respiratory Disease*

Amelia R. Woolums

Vaccines are available to prevent or limit disease due to several respiratory pathogens, and proper use of vaccines is an important component of any management effort to minimize ruminant respiratory disease. Information on the use of vaccines for ruminant respiratory pathogens is presented in the sections describing individual viral or bacterial agents.

Management Practices to Minimize Dairy Calf Respiratory Disease.

Efforts to minimize respiratory disease in calves should begin with assessment of factors that may be impairing host defense mechanisms, which were outlined above. Ensuring adequate transfer of maternal antibodies to newborn calves by appropriate colostrum handling and administration is one of the practices most important to ensuring calf health. On farms with high rates of calf respiratory disease, particulary in calves in the first month or two of life, efforts to address respiratory disease should include assessment of transfer of passive immunity in calves within the first week of life. If rates of failure of transfer of passive immunity are unacceptably high, management practices should be corrected to address the problem.

Although transfer of passive immunity is important to ensure calf health, groups of dairy calves with adequate transfer of passive immunity can still have high rates of respiratory disease. Thus other risk factors must also be assessed on dairies with unacceptable rates of calf respiratory disease. The method of calf housing has an important impact on risk for respiratory disease. Commonly used dairy calf housing includes individual calf hutches outdoors, super hutches for small groups of calves outdoors, individual calf pens inside a building, and group calf pens inside a building. Respiratory disease is less common in calves housed in individual hutches outdoors as compared to calves housed in

individual pens indoors or in group pens indoors.[9,40] In spite of this, many producers house calves in individual pens or group pens indoors because of the negative impact of weather extremes on calves housed outdoors in hutches and on their caretakers. Group pen housing also facilitates the use of automatic self-feeders to allow calves to nurse milk more frequently, and group pen housing allows calves to interact socially with other calves. These benefits of group pen housing must be weighed against the likelihood of increased rates of respiratory disease for group-housed calves. If calves are housed in group pens, respiratory disease is less common when the pens contain smaller numbers of calves (nine or fewer per pen).[76,90]

Standards for ventilation of calf housing have been reported (see Box 31.5). A study evaluating respiratory disease prevalence in calves housed in individual pens in naturally ventilated barns[91] found that respiratory disease prevalence was decreased on farms where pens had lower total airborne bacterial counts, solid barriers between calves, and bedding that was deep enough for calves to nestle into (so that their legs could not be seen when they were lying down). Because having four or more solid partitions around a calf increased total bacterial counts in pen air, solid partitions should be placed between calves but on no more than three sides; on the front, back, and top of calf pens, mesh barriers should be used.

Calf housing with stocking densities that are too high may result in increased transmission of pathogens, especially if there is mixing of calves of a wide age range. Overcrowding also puts additional stress on the building ventilation through buildup of noxious gases and pathogens. Cleaning of calf crates with high-pressure water sprayers is associated with new cases of pneumonia several days later. Bates and Anderson[92] have recommended standards for ventilation, including building location, fan capacity and location, intake location and design, temperature regulation, air space needed and airflow directions, and acceptable humidity levels. Sivula and colleagues[41] found that 80% of calf barns provided housing that failed to meet adequate standards of ventilation and housing regardless of whether calves were housed individually or in groups. In addition, calf housing in which calves shared the same air space as adults never met the adequate standards of ventilation and housing. A much higher percentage of calf housing that used calf hutches met these adequate standards of ventilation and housing, and virtually 100% would have been adequate housing if the hutches had been positioned correctly. Calves raised in inadequate housing

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have significantly poorer growth rates than do calves raised in housing that is considered adequate, which emphasizes the importance of adequate housing. A review of factors relevant to adequate ventilation of calf housing is available.[93] Ambient temperature is an important factor affecting dairy calf health. Calves must be protected from excessively cold, hot, wet, or humid conditions.

Nutritional problems that can predispose calves to disease include deficiencies of energy, protein, vitamins, or minerals necessary for the immune response. Deficiencies of copper, selenium, zinc, manganese, iron, and vitamins A and E are of special concern. Dairy managers sometimes create energy and protein deficiencies by feeding calves a low volume of milk during the first few weeks of life to minimize the incidence of neonatal diarrhea. Therefore it is important to evaluate feeding practices to correct factors that may be contributing to nutrient deficiency when attempting to limit dairy calf respiratory disease.

Veal calves are at great risk for respiratory disease because they are often reared in rooms that are filled to a high stocking rate with calves from multiple dairies that may put minimal effort into ensuring that the calves are fed adequate amounts of good-quality colostrum. Similar problems can occur on calf-rearing facilities where hundreds to thousands of very young dairy calves are raised until they are old enough to be returned to dairies to become lactating cows or sent on to feedlots. A high proportion of calves that enter calf-rearing facilities may have failure of transfer of passive immunity unless the operation managers uphold standards for passive immunity in calves they receive. Also, the accumulation of a large number of calves with a variety of histories and from a variety of sources causes problems similar to those encountered with older animals in feedlots.

Management Practices to Minimize Preweaning Beef Calf Respiratory Disease.

Relative to dairy calves, less is known about management practices that should prevent preweaning respiratory disease in beef calves. Risk factors identified include a longer calving season, concurrent neonatal calf diarrhea, and practices that increase opportunities for introduction of respiratory pathogens to the herd or that increase opportunities for close contact among calves and between cows, older calves, and younger calves. Thus in herds where preweaning calf respiratory disease is a problem, it may be helpful to decrease or prevent situations where preweaning calves and/or cows are brought together in close proximity. Improving immunity of preweaning calves by addressing factors that can lead to failure of transfer of immunity from colostrum (such as dystocia and

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hypothermia) may help mitigate preweaning calf respiratory disease, particularly in herds with a high incidence of respiratory disease in calves in the first month or two of life, when maternal antibodies should be most protective. Because occurrence of calf diarrhea has been associated with preweaning calf respiratory disease, efforts to control calf diarrhea, which usually precedes respiratory disease, should be undertaken in herds with both problems.

Administration of vaccines for viral and bacterial respiratory pathogens to preweaning beef calves may help decrease respiratory disease. Anecdotally, cow-calf operations with a history of perennial outbreaks of preweaning calf respiratory disease have reported decreased rates of disease when respiratory vaccines are administered to calves prior to the time that outbreaks are expected. Vaccination of beef calves still nursing their dams can be logistically challenging and may not have a favorable cost-to-benefit ratio on all farms. However, the perceived value of calf vaccination to decrease outbreaks of preweaning respiratory disease has led to adoption of the practice on some operations where the syndrome has been a problem.

Once an outbreak is underway, anecdotal reports suggest that vaccination with intranasal or injectable modified live vaccines containing IBRV, PIV-3, and/or BRSV may be helpful to shorten the outbreak, but this is not yet confirmed by controlled research. Moreover, BRSV vaccination in the face of a BRSV outbreak has been associated with apparent disease enhancement,[94] thus it is possible that administration of BRSV vacccine could make an outbreak of undifferentiated calf respiratory disease worse if BRSV is the cause of the outbreak.

Vaccination to prevent bovine respiratory disease is discussed in detail in Chapter 48.

Management Practices to Minimize Feedlot and Stocker Respiratory Disease

Preconditioning.

Preconditioning of calves is a practice undertaken to limit the impact of risk factors that influence the occurrence of BRD in feedlot cattle. Preconditioned calves are weaned well in advance of shipment to feedlots. They are trained to eat some grain from feed bunks and drink water from tanks; this is especially important for calves raised on rangeland where feed bunks or water tank may not be seen. Calves are castrated and dehorned, treated for internal and external

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parasites, and vaccinated against respiratory pathogens, with priming and booster vaccine administration timed to allow a full response to vaccination before calves are shipped to the feedlot. The exact details of a preconditioning program can be tailored to the needs and characteristics of the individual herd of cattle. A variety of preconditioning protocols have been described, and most of the major companies that sell vaccines have recommended standardized preconditioning programs. Also, in many areas of the United States and Canada, state, provincial, or regional groups may offer a standardized preconditioning program for local cattle producers. Typically some sort of validation that calves have received preconditioning is available through these organizations. Some of these groups also help the participating producers market the preconditioned calves in large, relatively uniform groups, which may help the calves bring better prices. In some cases, producers can retain ownership of their cattle after they enter the feedlot and receive data regarding health and performance of their animals throughout the feeding period and at slaughter. Information about local preconditioning programs usually can be obtained from agricultural extension agents or from faculty members who specialize in beef cattle management and health at colleges of animal science or veterinary medicine.

The value of preconditioning has been debated over decades. A summary of eight studies comparing the health of preconditioned calves with that of control calves indicated that, on average, preconditioning reduced the morbidity rate by 23% and the mortality rate by 50% in the feedlot.[95] However, preconditioned cattle do not always escape disease once they enter feedlots, and they sometimes experience outbreaks of high morbidity and mortality not unlike those seen in high-risk calves that are not preconditioned. Moreover, even when preconditioned calves experience less disease, their performance in the feedlot is not always better than that of nonpreconditioned calves,[96] or they may not always perform well enough that a profit that is greater than the cost of preconditioning is returned.[97] An evaluation of data collected over 8 years by the Texas A&M Ranch to Rail program showed that preconditioned cattle returned on average $90 more per head than nonpreconditioned cattle. However, in some years the return was better for preconditioned cattle than in other years. These data emphasize that preconditioning is likely to be cost-effective in the long run, but it may not always be cost-effective for an individual group of cattle in a single year. Also, while cattle that develop BRD in the feedlot often have decreased weight gain and/or feed efficiency and reduced carcass quality at

slaughter,[64-66] they sometimes exhibit compensatory gain after they recover from BRD, which allows them to “catch up” to cattle that do not develop BRD.[67] For this reason, some feedlot operators elect not to specifically purchase preconditioned cattle, which can cost more to purchase and may not consistently yield higher profits. Because of year-to-year uncertainty in the economic advantage of preconditioned cattle, producers who sell preconditioned calves may not always be able to sell calves at a price that provides a profit over the cost of preconditioning. If an individual producer or producer organization develops a good reputation for generating reliably healthy preconditioned calves, marketing these calves directly to cattle buyers may be the best way for the producer to realize a profit from preconditioned calves. Retaining ownership of calves sent to feedlots may also allow the producer to realize better profits, but this requires a relationship with a feedlot that will manage the calves in ways that will continue to optimize health once the calves enter the feedlot. It has also been shown that preconditionning can help the producer net greater returns simply because preconditioned calves weigh more when they are sold.[98]

Backgrounding.

Another practice similar to preconditioning is the practice of backgrounding. In backgrounding, weaned beef calves from a variety of sources (often purchased from multiple sale barns) are accumulated and processed in a manner similar to that carried out for high-risk calves at feedlot entry. Calves are then sorted by size and type and sold to feedlots, usually within a few days of arriving at the backgrounding operations. Backgrounding operations are sometimes referred to as “conditioning” operations. A variation of the backgrounding operation is the stocker operation; in stocker operations calves are processed and then “stocked” onto pastures, often with supplemental concentrate feeding, to graze and grow for a few weeks to months before shipment to feedlots. The difference between preconditioning and backgrounding is that preconditioning occurs on the farm where the calf is born or at least before the calf is mixed with other calves from different sources, with some aspects of treatment such as the first dose of vaccines ideally being administered before weaning. Calves that enter backgrounding or stocker operations often have uncertain health histories, they often have been weaned immediately before purchase, and when they arrive they have been mixed with calves with similar uncertain backgrounds from a variety of sources. Because of this, disease outbreaks of high morbidity and mortality are not uncommon on backgrounding and stocker operations, and respiratory

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disease is the leading cause of morbidity and mortality.[89] The backgrounding or stocker operator is thus taking on some of the risk of high-risk calves and is theoretically providing the feedlot with animals more likely to grow well with minimal disease than if the cattle entered the feedlot straight from the auction market.

Management at Feedlot Entry.

It is not surprising that preconditioning does not always influence the occurrence of respiratory disease in cattle after they enter the feedlot because it has no effect on many risk factors active during transit and in the feedlot. Therefore optimal control of feedlot respiratory disease should begin with preconditioning and continue with avoidance of auction yards, minimization of transport time to the feedlot, limited mixing of calves from different sources, limited number of calves per pen, and careful diet management in the feedlot. Correction of vitamin and/or mineral deficiencies if known or detected, using vitamin injections in entering calves, may be helpful to decrease disease associated with immunodeficiencies of nutritional origin.

Processing procedures on arrival at the feedlot can affect the incidence of BRD. General recommendations for handling incoming cattle (the “receiving program”) that are appropriate for any category of animals can be made.[26,89,99] In a receiving program, rest, rehydration, and ruminal restoration need to be addressed because cattle are physically and psychologically stressed by the marketing and transportation processes. It is recommended that these cattle be rested for 12 to 24 hours and that in the summer they be processed before the hottest part of the day. Prolonged holding before processing is associated with increased illness, and holding times over 48 hours should be avoided. Holding pens should be clean and dry or have dry bedding because this allows all cattle to lie down and rest. Shelter from wind, sun, rain, and dust should also be provided in the receiving pen.

It is important that incoming cattle have access to clean, fresh water. Raised spigots have been suggested as a way to teach incoming cattle to drink out of automatic watering devices because cattle that may not be familiar with water tanks will be attracted to the sound of splashing water. Incoming cattle should also be offered good-quality, long-stem grass hay on arrival. Hay is the best foodstuff for restoring or refilling the rumen. Hay can be put in the feed bunks as well as in feeders in the pen as a way of teaching cattle to eat out of bunks. Hay feeders may also be put along the pen perimeter to decrease walking the fence

line and encourage eating. The starter ration is an important source of energy and should be highly palatable. The proportion of the starter ration dry matter that is forage is not usually less than 50% to prevent problems of acidosis. Starter rations often contain a coccidiostat because coccidiosis can occur in calves after commingling.

Processing protocols may be tailored to the category of the incoming cattle. Pharmaceutical processing options can include vaccination (respiratory and other), vitamin injections, growth hormone implanting, treatment for internal and external parasites, long-acting antibiotic therapy, drugs for aborting pregnant heifers, and probiotic administration. Management procedures for processing include ear tagging, branding, tail trimming, castration, and tip dehorning. Some management procedures such as castration and dehorning could be left for a later time—for example, at reimplanting at 70 to 90 days on feed (if cattle are expected to be on feed for more than 150 days). Taking the rectal temperature of cattle at initial processing may be helpful in identifying sick cattle.

Although vaccination of cattle to prevent respiratory disease when they are first received by feedlot or backgrounding and stocker operations is a common practice, research has not found the practice to be consistently associated with decreased BRD risk.[83,100] In a recent study, delayed administration of multivalent modified live viral respiratory vaccine, in contrast to administration at arrival, was associated with a decreased rate of second treatment for BRD.[38] Failure of vaccination at arrival to protect cattle against later respiratory disease may be because cattle are already infected at the time of vaccination because they are not capable of mounting an adequately protective immune response in time, or because disease is caused by agents not included in the vaccines that are administered. Following on-arrival vaccination, cattle are sometimes given a second dose of respiratory vaccine 7 to 21 days after the initial dose at feedlot entry; it is not clear whether this is consistently beneficial. See examples of processing protocols for high-risk and low-risk cattle in Box 31.6.

Box 31.6

Examples of Processing Protocols for High-Risk and Low-Risk Cattle Entering Feedlots

Processing Protocol for High-Risk Cattle: Recently Weaned Cattle Purchased Through Auction Markets

1. Modified live BHV-1 (IBRV), BVDV1, BVDV2, BRSV, and PIV-3 vaccines[a]
2. Eight-way clostridial bacterin[a]
3. Antiparasitic
4. *Mannheimia haemolytica* ± *Pasteurella multocida* vaccine
5. *Histophilus somni* vaccine (if significant problem in past)
6. Growth implant
7. Ear tag identification
8. Bulls castrated (if needed)
9. Tip dehorning (if needed)
10. Metaphylactic antimicrobial treatment

Processing Protocol for Low-Risk Cattle: Healthy Yearlings Previously Fed in Backgrounding Operations

1. Modified live BHV-1 (IBRV), BVDV1, BVDV2, BRSV, and PIV-3 vaccines
2. Eight-way clostridial vaccine
3. Antiparasitic
4. Growth implant
5. Ear tag identification

BHV-1, Bovine herpesvirus type 1; *BRSV*, bovine respiratory syncytial virus; *BVDV*, bovine viral diarrhea virus; *IBRV*, infectious bovine rhinotracheitis virus; *PIV-3*, bovine parainfluenza virus type 3

[a]Experts are currently debating whether vaccines should be given to high-risk cattle at arrival or be delayed for some time.

Metaphylactic Antimicrobial Therapy.

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The term *metaphylaxis* refers to the administration of an antimicrobial to a group of animals that may be in the early stages of bacterial pneumonia or that are at significant risk of developing bacterial pneumonia. Thus the antimicrobial drug administered may have either therapeutic or prophylactic effect, depending on the state of each animal treated. Metaphylactic administration of antibiotics on arrival has been shown in many studies to decrease morbidity and mortality in groups of high-risk cattle.[101,102] Long-acting antibiotics have been reported to significantly alter the number of calves from which *M. haemolytica* can be cultured.[103,104] An additional rationale for metaphylaxis on arrival is based on the epidemic curve of fatal disease onset for bacterial bronchopneumonia, which shows that feedlot calves dying from fatal fibrinous pneumonia are already sick on arrival or become ill within days of arrival. Although metaphylaxis through feed and water was used in the past, it is currently recommended that metaphylaxis be administered by use of injectable antimicrobial agents. The ability of these drugs to reach therapeutic levels quickly in all animals gives them a clear advantage given the previously discussed rationale for bacterial bronchopneumonia metaphylaxis.

A number of trials that examine various antimicrobial agents and their effectiveness for bacterial bronchopneumonia metaphylaxis have been published. Most of these studies have examined both health and production values, and a variety of products have been shown to be efficacious in decreasing respiratory morbidity and mortality and sometimes in improving production parameters. Recent meta-analyses provide estimates of the relative efficacy of many of the antimicrobials currently labeled for treatment or control of bovine respiratory disease.[23-25] At the time of this writing, several antimicrobials are approved for administration to control BRD (metaphylaxis; see Table 31.15).

Similar use of long-acting antimicrobials in dairy calves may also be of value. The disease process does not have the same narrow windows of therapeutic intervention that occur in calves entering the feedlot. Dairy calves properly managed in maternity facilities and raised in hutches rarely experience any respiratory disease until they are moved to postweaning housing. Injectable mass medication is often used at the time calves are moved as a means of controlling postweaning BRD.[52]

Although metaphylactic antimicrobial administration has clearly been effective in decreasing BRD morbidity in high-risk beef cattle, recent reports have described a high prevalence of *M. haemolytica* resistant to multiple classes

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of antimicrobials on nasopharyngeal swabs collected from stocker cattle after metaphylactic antimicrobial administration.[105] The degree to which MDR *M. haemolytica* negatively affect outcome in cattle colonized by these bacteria is not yet clear, but dissemination of MDR *M. haemolytica* in cattle populations may begin to decrease the benefit of metaphylaxis.

Management Practices for Preventing Respiratory Disease in Sheep and Goats.

Prevention of pneumonia in sheep and goats is also based on altering the risk factors that predispose to pneumonia. Minimizing cold and heat stress, providing properly ventilated housing, avoiding overcrowding, and avoiding long transport in adverse weather aid in prevention. Mass medication can be used to control outbreaks of pneumonia in flocks. Injectable long-acting oxytetracycline is often used; tilmicosin can also be used for mass medication therapy for sheep, but it should never be administered to goats, as it can result in fatal reactions. Feedlot lambs are sometimes administered metaphylactic therapy (long-acting oxytetracycline) on arrival. See Table 31.15 for a list of antimicrobials approved for adminstration to sheep and goats.

The Interstitial Pneumonias*

Amelia R. Woolums

Understanding of the interstitial pneumonias of ruminants has evolved considerably over several decades. Unfortunately, lack of clarity still exists, particularly with regard to terminology. Terms such as *acute bovine pulmonary emphysema, atypical interstitial pneumonia* (AIP), *fog fever, pulmonary adenomatosis*, *farmer's lung*, and *acute respiratory distress syndrome* (ARDS) have been used interchangeably for all of the conditions that follow. This text uses a classification presented by Breeze,[1] which places the interstitial pneumonias into four groups: (1) ARDS, (2) hypersensitivity diseases, (3) chronic conditions that may be sequelae of ARDS or hypersensitivity diseases, and (4) parasitic diseases. BRSV infection can also cause AIP; this disease was discussed in relation to the respiratory disease complex of cattle, sheep, and goats in The Bronchopneumonias (Respiratory Disease Complex of Cattle, Sheep, and Goats) section earlier in this chapter.

Acute Respiratory Distress Syndromes

An ARDS is any respiratory condition characterized clinically by a sudden onset of (usually severe) dyspnea (Fig. 31.68) with gross and histopathologic findings consistent with AIP. The characteristic gross findings of AIP are lungs that fail to collapse when the thorax is opened (Color Plate 31.9) and that are heavy and have a firm, rubbery texture on palpation. Interlobular or bullous emphysema is usually present (see Color Plate 31.3), and sometimes the cut surface of the lung has a shiny or wet appearance because of edema. In some cases affected lobules, which are dark red to purple or sometimes grayish, are interspersed with normal-looking lobules, giving the lung a “patchwork” appearance. Although the gross findings are suggestive and often characteristic, other lung diseases can cause similar changes, so a diagnosis of AIP can be confirmed only by histopathologic evaluation. The histopathologic changes that confirm a diagnosis of AIP include alveolar hyaline membrane formation and fibrin deposition, alveolar and interstitial edema, and type 2 pneumocyte proliferation. Hemorrhage, emphysema, and interstitial inflammatory cell infiltrate can also be seen.



FIG. 31.68 Heifer exhibiting respiratory distress typical of acute respiratory distress syndrome (ARDS). Note the extended head, frothing at mouth, and wide-set front legs. (Courtesy Dr. Amelia Woolums, Mississippi State University, Starkville, Miss.)

The term *atypical interstitial pneumonia* has often been applied to describe the changes characteristic of AIP, but it has been pointed out that the clinical and pathologic changes in affected cattle are not “atypical” but rather are “typical” of acute lung injury (ALI).[1,2] Use of the term *acute interstitial pneumonia* to describe the characteristic pathologic changes and of the term *acute respiratory distress syndrome* to describe the clinical picture in an animal with AIP of as-yet undetermined cause is both accurate and all-encompassing. A diagnosis of AIP should be understood as a pathologic diagnosis rather than an etiologic diagnosis because a variety of insults can lead to the same lung lesion of AIP.

■ Definition and Etiology

Acute Bovine Pulmonary Edema and Emphysema

Acute bovine pulmonary edema and emphysema (ABPEE), classically known as *fog fever,* is an ARDS of adult (over 2 years old) cattle that occurs when these animals are changed from dry, sparse forages to lush, green pastures. It is caused by the conversion of L-tryptophan ingested in the lush forages to a pneumotoxic compound (3-methylindole [3-MI]), which leads to the development of pulmonary edema, alveolar epithelial hyperplasia, hyaline membranes, and emphysema.

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■ Clinical Signs

Adult brood cows are most commonly affected because this is the type of animal most likely to be subjected to the abrupt pasture change required to produce the condition. No breed is resistant. The type of pasture appears to be unimportant, as long as it is lush; ABPEE has been reported on a wide variety of grasses, alfalfa, rape, kale, and turnip tops.[3] Signs usually occur within 2 weeks of the pasture change. In severe cases there is an acute onset of very severe dyspnea with a loud expiratory grunt, frothing at the mouth, mouth breathing, and tachypnea. The animals are obviously distressed (as opposed to exhibiting the typical depression that occurs with infectious respiratory diseases) and stand with the head and neck extended and elevated and the nostrils dilated. Temperature and heart rate may be elevated secondary to the severe dyspnea and hypoxia. On auscultation the breath sounds are usually surprisingly soft in view of the gross dyspnea and tachypnea; a few crackles may be heard. Even mild exercise increases the dyspnea and may precipitate collapse and death. As many as 30% of severely affected patients may die, usually within 2 days. Those that survive typically show a dramatic improvement after 3 days. Recovering patients and those that are less severely affected exhibit tachypnea, harsh breath sounds, and crackles and wheezes, particularly in the caudal lung fields. Subcutaneous emphysema may develop. The demeanor of the entire group tends to become more tranquil. In cattle that have repeated episodes of nonfatal ABPEE, a chronic respiratory condition characterized by diffuse pulmonary fibrosis and alveolitis may develop.[4] For purposes of differential diagnosis, it is important to note that coughing is not prominent in the individual or the group. The main differential diagnoses are those diseases that cause ARDS in pastured adult cattle, usually in outbreak form. The association of ABPEE with typical management conditions (e.g., changes of pasture) and the absence of coughing, signs of sepsis, and adventitious lung sounds in early cases is also very important. Primary considerations should include the other plant toxicities (moldy sweet potatoes, perilla mint, and possibly others) that can be differentiated only by identifying the source. An outbreak of BRSV infection or parasitic bronchitis could cause similar clinical signs and pathology, but these are characterized by more coughing, signs of depression, and more prominent adventitious sounds; fever is common in animals with acute BRSV infection.

■ Pathophysiology

L-Tryptophan in lush forages is converted by ruminal microorganisms to indole-3-acetic acid and eventually to 3-MI, which is rapidly absorbed from the rumen into the blood. Metabolism of 3-MI by the cytochrome P450 mixed function oxidase system in the nonciliated bronchiolar epithelial (Clara) cells and type 1 pneumocytes results in one or more highly reactive intermediates that bind to intracellular proteins or other macromolecules and thus lead to damage or death of the cells. These intermediates are detoxified by conjugation with glutathione.[5] Cellular damage results in degeneration, necrosis, exfoliation of type 1 pneumocytes and Clara cells, and edema. These lesions in turn cause hyaline membrane formation, proliferation of type 2 pneumocytes, and to a lesser extent, proliferation of Clara cells.[6] The proliferation of type 2 cells is also known as *adenomatosis.*

■ Epidemiology

As indicated, ABPEE is consistently related to management practices in which hungry adult cattle are suddenly moved from sparse, dry grazing to lush green pastures. The British name “fog fever” arose from the association of the disease with “fog” pastures, which are the lush, green regrowth pastures that occur after hay or silage has been cut. The problem usually occurs in the fall. In the typical pattern in the western United States, cattle are moved from dry summer range onto irrigated or fertilized aftermath pastures. The disease usually appears as a herd outbreak, but individuals may be affected to widely varying degrees[7]; the morbidity rate commonly approaches 50%, with a case fatality rate as high as 30%.[8] Nursing calves typically are not affected.

■ Necropsy Findings

In animals that die of ABPEE, ecchymotic to petechial hemorrhages occur in the larynx, trachea, and bronchi, and frothy fluid is present in the airways. The gross and histopathologic lung lesions are consistent with AIP. Congestion, edema, and hyaline membranes cause deep red-to-purple coloration of the cranial lung lobes and a smooth, glistening appearance to the cut surface. Interstitial emphysema with large bullae and gelatinous yellow interlobular edema is common. Histologically, eosinophilic hyaline membranes line alveoli and alveolar ducts, and there edema and proliferation of type 2 alveolar epithelial cells are present. In animals that are killed after 3 to 4 days, emphysema and edema are less obvious, and the lungs tend to be light brown, firm, heavy, and

rubbery. There is severe diffuse alveolar epithelial hyperplasia (“adenomatosis”), and large mononuclear cells, multinucleated giant cells, and hyaline membranes are present in alveolar spaces. Edema, eosinophils, and inflammatory cells occupy the septa.

■ Diagnosis

Diagnosis is usually presumptive based on the history of recent exposure to lush green forage, typical clinical signs, and gross pathology and histopathology in fatal cases. Measurement of metabolites of 3-MI in blood or urine can be diagnostic, but this test is typically reserved for research applications.[9] Thoracic radiographs could be used to identify changes consistent with interstitial pneumonia in valuable individual animals. The results of TTA or BAL cytology have not been reported for cattle with ABPEE, but a nonseptic mixed inflammatory cell response would be expected. There are no unique hematologic or biochemical changes. A stress leukogram may be seen.

■ Treatment and Prevention

The stress of handling cattle can precipitate further deaths; because there is no specific treatment for ABPEE, moving cattle to attempt treatment may cause more deaths than it prevents. Some authors maintain that most cases in an outbreak occur within 4 days, that removing the herd from the pasture does not prevent additional cases, and that leaving the herd on the pasture does not result in additional cases; consequently the recommendation has been to handle severely affected cattle only if necessary to remove them to shade or to slaughter. Others recommend careful removal from the offending pasture. Antihistamines, corticosteroids, epinephrine, atropine, diethylcarbamazine, and diuretics are alleged to be of palliative value, but none of these has been confirmed to be effective in a properly designed trial. Recovery often occurs without therapy in less severe cases. In view of the dangers of handling affected cattle, the questionable efficacy of medical treatment, the probable irreversible nature of severe lesions, and the probability of spontaneous recovery in less severe cases, the best treatment may be no treatment. If treatment must be attempted, affected cattle should be handled very cautiously, and furosemide (0.5 to 1 mg/kg IM or IV once or twice daily) and flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) or steroids (dexamethasone, 0.05 to 0.2 mg/kg IM or IV once daily) may be given. Most fatalities occur in the first 2

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days. Severely affected animals that survive may develop chronic emphysema or heart failure secondary to cor pulmonale. Moderate to mild cases often show marked improvement after day 3, with recovery over about 10 days; relapses do not typically occur.

Prevention is based on modification of management and prophylactic drugs. Management strategies that have been recommended to prevent the exposure of susceptible cattle to potentially toxic pastures include the following[5-8,10]:

1. Place the cattle in a dry lot, feed palatable hay for several days, and turn them onto the lush pasture for 2 hours on the first day. Gradually decrease the amount of hay fed and increase the time on pasture over a period of 10 to 12 days.
2. Delay use of lush pastures until after a hard frost.
3. Mow and windrow the pasture before turning cattle out.
4. Use the pasture for young stock (younger than 15 months old) or sheep or other livestock; turn adult cattle out only after the pasture has been thoroughly grazed over.
5. Use the pasture before it becomes particularly lush.
6. Use continuous strip-grazing.

Because such management changes are frequently not feasible, prophylactic medication is a useful alternative. Monensin or lasalocid at 200 mg/head/day PO reduces the conversion of tryptophan to 3-MI.[3] Treatment with monensin should be started at least 1 day before pasture change and should be continued for an additional 10 days, whereas lasalocid requires a longer pretreatment period of 6 days.[11] Monensin or lasalocid is not expected to be beneficial after the onset of signs. Future possibilities include blockers of the mixed function oxidase system and enhancers of intracellular glutathione levels.

■ Definition and Etiology

Feedlot Acute Interstitial Pneumonia

In feedlot cattle an ARDS that is commonly referred to as *feedlot AIP* occurs. The exact cause of this syndrome is unknown, and it is probably multifactorial. Feedlot management practices typically do not include exposure of cattle to lush forages similar to those that cause ABPEE, and the feeding of moldy sweet

potatoes has not been associated with feedlot AIP.[12] A variety of causes have been proposed[13,14]; unfortunately, the amount of research done to confirm or refute the various hypotheses ranges from small to nonexistent. The most commonly suggested possible causes or predisposing factors are (1) feed-associated pneumotoxins such as 3-MI[9,15,16] or dietary factors related to protein metabolism,[17] (2) chronic bacterial pneumonia,[18,19] (3) gender[9,15] and hormonal influences,[20,21] (4) chronic small airway injury,[18,19,22] (5) BRSV infection,[19,23] (6) heat or dust exposure,[22,24] and (7) hypersensitivity reactions.[22,25,26] These possible causes could also work together in various combinations to cause feedlot AIP.

Support for 3-MI as a cause of feedlot AIP comes from research that showed that levels of a stable metabolite of 3-MI, 3-methyleneindolenine (3-MEIN), were significantly higher in the blood of cattle with AIP than in control cattle.[9,15] Increased levels of 3-MEIN may be a result of decreased clearance of the toxin. Loneragan and colleagues also found that 3-MEIN levels were higher in lung tissue of AIP cases as compared with animals without lung disease, but they were not higher than 3-MEIN levels in the lung tissue of cattle with bronchopneumonia; this suggested that 3-MI may contribute to the pathogenesis of both AIP and bronchopneumonia.[9] The mechanism by which 3-MI is generated and leads to lung damage was discussed in the Acute Bovine Pulmonary Edema and Emphysema section earlier. If 3-MI does contribute to the pathogenesis of feedlot AIP, it is not clear what about the feedlot diet predisposes cattle to produce high levels of 3-MI. Normal cattle produce some 3-MI through metabolism of dietary proteins. It may be that the protein composition (e.g., the tryptophan concentration) of foodstuffs sometimes added to feedlot rations can lead to spikes in 3-MI production. Cattle with feedlot AIP have been found to have higher ruminal pH values than expected for cattle adapted to a high-concentrate diet. Ruminal pH in AIP cases ranged from 5.6 to 7.2 in one study[19] and from 4.9 to 7.4 in another,[27] whereas the ruminal pH of cattle adapted to a high-concentrate diet is typically about 5.5 to 5.6.[28] Many proteins are relatively basic; therefore the high ruminal pH could be related to abnormal protein metabolism. However, the relatively high ruminal pH could also be caused by anorexia. The concept that abnormal ruminal protein metabolism could contribute to feedlot AIP was also supported by a small study that found increased ammonia levels in the ruminal gas cap of cattle with AIP.[29] An interaction between digestive health and AIP was also suggested by the

finding that in feedlot pens in which at least one animal had died from digestive disease, the incidence of AIP was approximately 70% greater than in pens in which digestive disease deaths did not occur.[17]

The hypothesis that bacterial bronchopneumonia contributes to feedlot AIP is supported by the finding by multiple authors that cattle with AIP frequently have superimposed gross and histopathologic lesions consistent with bacterial bronchopneumonia.[18,19,30] In a study evaluating the bacteria isolated from the lungs of cattle with feedlot AIP that had not received antimicrobial therapy, *P. multocida* and *Mycoplasma* spp. were significantly more likely to be isolated from the lungs of cattle with AIP than from the lungs of normal penmates.[19] An earlier study found that bacterial respiratory pathogens were not more likely to be isolated from cases of AIP as compared with controls, but the samples in this study were collected at necropsy of animals that received antimicrobial treatment before death in at least some cases.[31] It should be noted that no study has yet been able to confirm whether in cases with both lesions the bacterial bronchopneumonia was present before AIP occurred or the bacterial bronchopneumonia developed after the animals had AIP. If bacterial bronchopneumonia leads to the development of AIP, it is not clear how this happens. In humans with ARDS, bacterial infection is often a predisposing factor that appears to lead to ARDS through the induction of high local or systemic levels of proinflammatory cytokines.[32] The role of proinflammatory cytokines in cattle with feedlot AIP has not been investigated.

A role for gender and/or hormonal influences in the pathogenesis of feedlot AIP is related to the frequent (although not inevitable)[18] finding that the majority of affected animals are heifers.[15,17,19] Feeding of melengestrol acetate (MGA), which is fed to heifers to control estrus, has been suggested to contribute to AIP by some authors,[20] but others have not found evidence of any association between MGA and AIP.[33] Although one research study indicated that MGA could exacerbate experimentally induced AIP in sheep,[20] a well-controlled experimental study to determine the effect of MGA on AIP in cattle in the field is needed to clarify the involvement of MGA in AIP. It has also been suggested that growth hormone implants may contribute to development of feedlot AIP, although a survey of feedlot managers did not find data to support this.[33]

Infection with BRSV was linked to feedlot AIP in an early study.[23] Because BRSV infection can sometimes cause AIP, the possibility that a ruminant with lesions of AIP is simply a case of BRSV infection must always be considered.

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However, cattle with feedlot AIP do not always have a fever,[19] which is expected in animals with acute BRSV infection. Moreover, feedlot AIP can occur in outbreaks, but cases often occur sporadically, which would be less consistent with BRSV infection. Neither Sorden and colleagues nor Loneragan and colleagues found BRSV significantly more often in animals with feedlot AIP than in controls.[18,31] In another study the difference in frequency of identification of BRSV in feedlot AIP cases as compared with normal penmates approached significance ($P = .07$).[19] Although AIP is by definition "acute," it is interesting that several authors have reported histopathologic evidence of chronic airway injury (particularly, bronchiolitis fibrosa obliterans) in the lungs of animals with AIP.[18,19,22] In one study, the presence of bronchiolitis fibrosa obliterans was identified significantly more often in cattle with AIP than in penmates with no history of treatment for respiratory disease; this was in spite of the fact that AIP cases in the study also had no history of previous treatment for respiratory disease.[19] It is not known how past airway injury is related to the development of AIP, although chronic airway injury could be linked to the occurrence of chronic bacterial pneumonia, which has also been associated with feedlot AIP, as described previously. It may be that the chronic airway injury is related to dust exposure, although it is not clear why animals with AIP would be more likely to have airway injury caused by dust exposure than other penmates. Dust exposure has been anecdotally related to AIP,[22,24] and feedlot managers often report that efforts to control dust, such as spraying water lightly onto the surface of pens, decreases AIP occurrence when the disease is a problem. However, repeated exposure to feedlot dust or to fungal organisms from feedlot dust did not induce AIP in sheep or goats in experimental studies.[34,35] One study of the effect of dust on feedlot respiratory disease found only a weak association between airborne dust particles and respiratory disease.[36]

High ambient temperatures are thought to contribute to feedlot AIP because several investigators have found that the majority of cases occur in the summer,[17,22] but no mechanism by which hot weather might exacerbate AIP has been researched. Hypersensitivity reactions are often suggested to cause AIP. It is true that anaphylaxis can cause pulmonary edema, hemorrhage, and emphysema, with microscopic evidence of hyaline membrane formation.[37] However, animals that survive longer than a few hours after an episode of anaphylaxis do not have lung changes consistent with AIP, such as type 2 pneumocytic proliferation and interstitial inflammatory cell infiltrate.[38]

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Therefore an anaphylactic reaction may cause an occasional case of sudden death with lung changes typical of AIP, but anaphylaxis does not explain the majority of feedlot AIP cases. Other types of hypersensitivity-mediated lung disease have pathology that is unlike that seen in feedlot AIP, also making other types of hypersensitivity an unlikely cause of the majority of feedlot AIP cases.[1]

In summary, the cause of feedlot AIP is unknown, but the strongest support currently exists for some role for (1) factors related to feed, or ruminal metabolism, including 3-MI; (2) infectious respiratory disease, especially chronic bacterial pneumonia and possibly BRSV; (3) gender and/or other hormonal influences; and (4) chronic airway injury, which may be related to infectious respiratory disease. It seems likely that multiple factors can contribute to the development of feedlot AIP, and the factors may act in some as-yet unidentified combination in at least some cases. It is also possible that some causes predominate in some feedlots or individual cases, whereas other causes predominate in other feedlots or individual cases. A study evaluating the occurrence of bacterial respiratory pathogens in cattle with feedlot AIP found bacterial respiratory pathogens in the lungs of the majority of cases in one feedlot and in almost none of the cases in a second feedlot,[19] suggesting that bacterial infection played a role in the development of AIP cases in the first feedlot but not the second.

■ Clinical Signs

Feedlot cattle with AIP may be found dead in the pen. Clinical presentation includes rapid onset of expiratory dyspnea and tachypnea, although if the respiratory effort is great, the actual respiratory rate may not be greatly elevated. Cattle typically stand with their heads extended and front legs spread apart and exhibit open-mouth breathing (see Fig. 31.68). Frothing from the mouth may also be observed. Rectal temperatures are variable, ranging from normal to elevated.[19] Physical examination may reveal cyanosis, tachycardia, and subcutaneous emphysema that extends from the cervical to dorsal thoracic area. Auscultation of lungs reveals dull areas throughout the lungs, along with some crackles. Differential diagnoses of bronchopneumonia, tracheal edema, tracheal obstruction, and hypersensitivity pneumonitis should be considered.

■ Pathogenesis

Because the cause of feedlot AIP is unknown, the pathogenesis is also uncertain.

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If feed-related pneumotoxins cause at least a subset of cases with AIP, the pathogenesis will be similar to that described for ABPEE, 4-ipomeanol toxicity, and perilla ketone toxicity. If bacterial infection is a cause of some cases of feedlot AIP, as is true for some human cases of ARDS, then proinflammatory cytokine production and the resultant inflammatory cascades they initiate are likely involved. More research is necessary to determine the cause and the pathogenesis of feedlot AIP.

■ Epidemiology

In the 1999 NAHMS survey of feedlots, AIP was identified as the second leading cause of feedlot mortality, behind bronchopneumonia (shipping fever).[39] Mortality rates resulting from AIP of 0.03% to 0.15% have been reported.[17,22,30,33] An important feature of AIP is the tendency of the disease to occur most often in cattle on feed more than 60 days,[15,19,22,31] as opposed to shipping fever, in which mortality peaks by 45 days after feedlot entry. This means that losses due to AIP deaths are amplified by the fact that relatively more resources in feed and labor have been invested in cattle that die of AIP, as compared with cattle that die of shipping fever. Most cases of feedlot AIP occur in the summer,[17,33] but the disease can occur in any season of the year, and most studies report that heifers are disproportionately affected.[15,17,19] One survey found that the odds of an animal with AIP being a heifer were 3.1 times greater than the odds of the animal being a steer.[17] In feedlot pens in which an animal died from a digestive disorder, the relative risk of AIP occurring was about 1.7, indicating that pens with a digestive disorder death were about 70% more likely to also have an AIP death, as compared with pens with no digestive disorder deaths.

■ Necropsy Findings

The gross pathology of feedlot AIP is essentially the same as that described for ABPEE. If there is concurrent bacterial bronchopneumonia, there may be cranioventral consolidation, with fibrin deposition on the pleura, but in cases with no concurrent bacterial pneumonia, the pleura is free of fibrin. Grossly it is common to see a “patchwork” appearance of dark and light-colored lobules interspersed, and the lobules are freely movable (see Color Plate 31.9). Histologically, the most acute cases will have only hyaline membrane formation and alveolar edema, possibly with hemorrhage in the alveoli or interstitium;

cases that have been going on longer will have proliferation of type 2 alveolar epithelial cells and inflammatory cell infiltrate into the interstitial space (septa). It is not unusual to find evidence of chronic airway injury, such as peribronchiolar lymphoid cuffing, peribronchiolar vascular fibrosis, and bronchiolitis fibrosa obliterans.[18,19] Whether the chronic airway injury is related to the pathogenesis of AIP or is an incidental finding is unknown.

■ Diagnosis

Diagnosis of feedlot AIP can be confirmed only by histopathologic evaluation of lung from animals that die or are euthanized because of the disease. Clinical signs and even gross pathology are not definitive; only 65% to 80% of cases identified based on clinical signs were confirmed by histopathologic evaluation to have AIP in two studies.[6,15]

■ Treatment and Prevention

Recommended treatments are similar to those recommended for ABPEE. However, feeding monensin does not preclude development of feedlot AIP, as cattle that die of AIP are often consuming feed including monensin when they contract AIP.[15] Treatment is supportive and typically includes administration of antiinflammatory drugs such as steroids (dexamethasone, 0.05 to 0.2 mg/kg once or twice) or flunixin meglumine (1.1 to 2.2 mg/kg IV q24h) and diuretics such as furosemide (1 mg/kg IM or IV q12-24h). Antimicrobial drugs are appropriate given that cases often have superimposed bacterial pneumonia (see Table 31.15). There are no studies evaluating the response of cattle with AIP to any treatment, and such studies would be difficult because there is no perfect method of making an antemortem diagnosis of the disease. However, anecdotal reports indicate that the prognosis is guarded even with treatment. It is important to note that simply moving cattle out of the pen could lead to death from severe respiratory compromise. Because of the risks and uncertainties of treatment and the expected high case fatality rate, immediate salvage slaughter may be the most economic course to take; if salvage slaughter is attempted, remember to observe proper drug withdrawal times.

Because the cause of feedlot AIP is unknown, it is difficult to recommend control measures. Administration of aspirin and of vitamin E have been suggested as rational preventative strategies to counteract inflammatory pathways suspected to be involved in feedlot AIP; however, two trials showed

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no clear effect of these therapies on levels of 3-MI in treated cattle.[40,41] No cattle in these trials developed AIP, so an effect on disease could not be identified. The risk factors identified suggest that management strategies to minimize abrupt dietary changes and to control infectious respiratory disease may be helpful; anecdotal reports also suggest that efforts to control feedlot dust may be helpful.

■ Definition and Etiology

4-Ipomeanol (Moldy Sweet Potato) Toxicity

Moldy sweet potato toxicity is caused by the ingestion of a furanoterpenoid toxin produced by sweet potatoes *(Ipomoea batatas)* in response to infestation with the fungus *Fusarium solani (javanicum).* It should be emphasized that this disease is an intoxication and not an allergic response to the fungus.

■ Clinical Signs

There is an acute onset of tachypnea, tachycardia, hyperpnea, and dyspnea, with loud expiratory grunting, frothing at the mouth, extension of the head and neck, flaring of the nostrils, and frequent deep coughing. Crackles and harsh bronchial sounds are heard on auscultation. Signs usually occur within 1 day of exposure, and deaths may occur 2 to 5 days later. Differential diagnoses are as for ABPEE (see earlier discussion), which this condition closely resembles, except for the history of exposure and the more prominent cough and adventitious lung sounds.

■ Pathogenesis

When *F. solani* (or closely related species) grows on sweet potatoes, the potato produces several 3-substituted furans, including 4-hydroxymyoporone, which is hepatotoxic. This is converted by the fungus to a series of pneumotoxins, the most abundant of which is 4-ipomeanol. When ingested by cattle in sufficient amounts, this toxin is absorbed, carried to the lungs in the blood, and converted to a highly reactive metabolite by a cytochrome P450–dependent mixed function oxidase system. From this point the pathogenesis is similar to that of ABPEE—that is, the toxin binds to intracellular macromolecules in the cell, causing cellular damage, particularly in Clara cells, type I pneumocytes, and endothelium; edema, hemorrhage, cellular necrosis, hyaline membrane formation, and proliferation of cuboidal epithelium result, with secondary emphysema.

■ Epidemiology

The disease usually occurs in outbreak form when groups of cattle are fed damaged sweet potatoes. Morbidity and case fatality rates are high. Calves nursing affected cows are unaffected.[42]

■ Necropsy Findings

The lungs are wet, firm, and large and fail to collapse. Hemorrhages, yellow gelatinous edema fluid, and emphysema with bullae occur throughout. Lobules are dark-red and firm. Microscopic lesions include edema, emphysema, hyaline membranes, hemorrhage, mixed interstitial infiltrates, alveolar epithelial hyperplasia, peribronchiolar fibrosis, and bronchiolitis obliterans.

■ Diagnosis

Diagnosis is made based on a history of feeding sweet potatoes and identification of clinical signs and pathology consistent with AIP. Other diagnostic tests as described for ABPEE could also be attempted in valuable individual animals.

■ Treatment and Prevention

Treatment has not been investigated. Because the pathophysiologic mechanisms are similar to those of ABPEE, similar recommendations are suggested: handle affected animals with extreme care; if treatment is attempted, furosemide (0.5 to 1 mg/kg IM or IV q12-24h) and flunixin meglumine (1.1 to 2.2 mg/kg IV daily or divided twice daily) or dexamethasone (0.05 to 0.2 mg/kg IV or IM q24h) may be given. The prognosis for moderate to severe cases is grave, regardless of management. Because toxicity is difficult to predict and is usually severe and irreversible when it occurs, the feeding of mold-damaged sweet potatoes should be strictly prevented.

■ Definition and Etiology

Perilla Ketone (*Perilla frutescens*) Toxicity

Perilla ketone toxicity is an ARDS caused by ingestion of a pneumotoxin found in the leaves and seeds of *Perilla frutescens*, a common weed in the southeastern United States. This plant is also known as purple mint, perilla mint, wild coleus,

and beefsteak plant.[43] It is an erect herbaceous annual about 2 m high, with characteristic square stems, an aromatic odor, and opposite, coarsely serrated ovate leaves 5 to 10 cm long and 4 to 8 cm wide with a purplish tint at maturity. The seed and flower stage, which occurs in August to October, appears to be most toxic. The flowers are small, white to purple blooms on a long raceme. The plant prefers semishade, such as damp, open wooded areas.

■ Clinical Signs

Animals are often found dead.[43] Signs observed include a sudden onset of moderate to severe dyspnea, wheezing, frothing at the mouth, and an expiratory heave or grunt. In less severe cases the cow may pant. Exertion worsens the signs and may precipitate death. Mature cows are most often affected, but deaths have been reported in yearlings and calves. Death occurs in 3 to 7 days in experimental toxicity.[43] Differential diagnoses are as for ABPEE, which this condition closely resembles and from which it can be differentiated only by history of exposure.

■ Pathogenesis

The volatile oils of *P. frutescens* contain a number of 3-substituted furans that are chemically similar to 4-ipomeanol, the moldy sweet potato toxin. One of these, perilla ketone, predominates in the later growing season (when most toxicities occur) and has been shown to be pneumotoxic when given parenterally to mice, hamsters, goats, calves, and sheep.[43] The toxin is absorbed from the rumen, carried to the lungs through the blood, and probably metabolized to the toxic form by the mixed function oxidase system, as for 4-ipomeanol and 3-MI. The pathogenesis from this point parallels that of ABPEE or moldy sweet potato toxicity.

■ Epidemiology

P. frutescens seems to thrive in late summer, when pastures in the southeastern United States are frequently dry and dormant. This also corresponds with the more toxic stage of the plant. Cattle normally avoid the plant when other pasture is available but may be forced to consume it during this critical period. However, under experimental conditions calves were noted to prefer the mint.[43] The preseed stage appears to be of relatively low toxicity; the green seed–stage plant

is most toxic, especially the seed parts; dried hay from seed–stage plants is less toxic than green plants but is still potentially lethal; and frosted plants appear to have relatively low toxicity.[43] The exact toxic dose is unknown, but 2.3 kg of green seed–stage plant and 11.2 kg of hay were lethal for cattle in one trial.[43]

■ Necropsy Findings

The lungs are distended (often bearing the impressions of the ribs), fail to collapse, and are moist, heavy, edematous, and emphysematous. There are often bullae, pleural effusions, and froth in the airways. Histologic characteristics are edema, extensive alveolar epithelial hyperplasia, emphysema, and congestion.

■ Diagnosis

Diagnosis is based on history of exposure to perilla mint and characteristic clinical signs and lung pathology. Other diagnostic tests as described for ABPEE could also be attempted in valuable individual animals.

■ Treatment and Control

Treatment has not been investigated. On the basis of the similar pathophysiologic mechanisms, the recommendations for ABPEE should be followed. The prognosis for severe cases is grave, regardless of management. Cattle should be provided with sufficient forage that they do not seek out perilla mint; once they have begun to eat it, they should be fenced away from stands of the plant, and other forage should be provided.

Other Toxic Plants

Brassica spp. (rape, kale, turnip tops) are currently regarded as one of the types of pasture that can precipitate 3-MI–associated disease. The possibility that other specific toxins may be identified in these species has not been excluded. Morbidity and mortality rates appear to be much higher on *Brassica* spp. pastures than on other lush forages.[1] The hepatotoxic effects of pyrrolizine alkaloids are well known, but they also cause lung lesions. Lung lesions develop only in animals with chronic liver lesions, and the minimum dose necessary to produce lung lesions is never less than that which is hepatotoxic; therefore signs of liver disease usually predominate. *Crotalaria* and *Trichoderma* spp. are the most common offenders; to a lesser extent, *Senecio* spp. are a cause. Horses,

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sheep, cattle, and pigs have been affected. Pulmonary lesions include edema, congestion, hemorrhage, proliferation of bronchiolar and alveolar epithelial cells with megalocytosis, and interstitial fibrosis and cellular infiltration. As with 3-MI, 4-ipomeanol, and perilla ketone, the toxicity of the pyrrolizine alkaloids depends on activation by the mixed function oxidase system; in this case, however, the toxin is probably formed in the liver and spills over into the blood to reach the lungs. Vascular endothelium is probably the primary target for injury (versus the Clara cells and type 1 pneumocytes in the other ARDS).

Toxic Gases

Ruminants may be exposed to a variety of toxic gases in the environment. The most important are ammonia, hydrogen sulfide, carbon dioxide, and methane from excreta and respiration; these can be especially important when excreta is collected in pits or tanks. Other gases include nitrogen dioxide from silos; carbon monoxide from machinery exhausts and heaters; zinc oxide from welding of galvanized metal in barns; chlorine, formaldehyde, insecticides, and other fumes from agricultural chemicals and cleaners; and smoke from fires. In most cases concentrations usually remain below overtly toxic levels, and effects are very subtle. Such chronic low-level exposure may result in decreased disease resistance and depression of growth rates. Slightly higher levels of chronic exposure may cause clinically vague syndromes of lethargy, mild dyspnea, anorexia, depressed growth, excessive lacrimation and salivation, low incidence of sudden deaths over weeks or months, and stillbirths. Acute, severe outbreaks usually occur in tightly enclosed facilities and are related to accidents, power outages, agitation or pumping of manure pits, or other combinations of unusual circumstances. Such outbreaks are characterized by an ARDS of variable morbidity and frequently a high case fatality rate.

Nitrogen Dioxide.

Nitrogen dioxide (NO_2) is a yellow-orange to brown gas with an acrid odor that is produced by anaerobic fermentation of green plant material. It is a major component of “silo gas.” Acute exposure of farm workers to high concentrations of NO_2 causes a respiratory condition known as “silo-filler's disease,” characterized by severe acute edema and congestion and followed by bronchiolitis obliterans and progressive interstitial pulmonary fibrosis. A similar condition has been induced experimentally in cattle,[44] and apparent spontaneous

field cases have been reported.[45,46] Clinical signs in experimental and apparent field cases include cough, tachycardia, tachypnea, respiratory grunting, depression, anorexia, hypogalactia, extension of the head, open-mouth breathing, fever, salivation, lacrimation, and subcutaneous emphysema. Auscultation reveals decreased breath sounds and crackles. The primary differential diagnoses should include other ARDS of housed cattle that occur in outbreak form, especially exposure to other toxic gases (manure pit gases, zinc oxide, chlorine, carbon monoxide), and hypersensitivity pneumonitis from moldy hay. Nitrate toxicity should also be considered. Clinical pathologic evaluation is of limited benefit. Leukocyte counts remained normal in experimental cases; methemoglobin levels increased to a peak at 30 minutes after exposure and returned to normal in 12 to 24 hours.[44] The pathophysiologic mechanism probably involves the dissolution of the NO_2 in the water of the respiratory tract to form nitric acid. Nitrates and nitrites are also formed; these are irritating, and the nitrites cause methemoglobinemia. Nitrogen dioxide is also an oxidant itself and may contribute directly to the injury. The disease occurs as an outbreak, usually in housed cattle in proximity to a silo chute in a tight or poorly ventilated barn.[45,46] Nitrogen dioxide is heavier than air and layers on top of silage or spills out around the bottom of the silo. Corn silage produces more gas than hay, and a high nitrate content increases the danger. The levels are highest in the first 48 hours after filling the silo but may remain dangerous for 2 to 3 weeks.

Necropsy findings in experimental disease include hyperemia of the upper airways; hemorrhages, fibrinous membranes, and froth in the trachea; distended, noncollapsing lungs with rib imprints; a mottled appearance caused by consolidated lobules alternating with emphysematous lobules; and bullae. Microscopic lesions include alveolar epithelial hyperplasia, large foamy alveolar macrophages, hyaline membranes, hyperemia, hemorrhage, and edema.

Treatment involves the establishment of adequate ventilation; cows should be completely removed from closed buildings if necessary. Corticosteroids have apparently been beneficial in field cases, but no controlled studies have been performed to confirm efficacy. Because of the obvious differences in pathophysiologic characteristics, it would be unwise to extrapolate treatment regimens from those of ABPEE. Suggested empiric therapy might include corticosteroids (dexamethasone, 0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily or twice daily), and appropriate antibiotics to prevent secondary bacterial infections.

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Zinc Oxide.

Zinc oxide (ZnO) fumes have been associated with an ARDS in cattle.[47] Oxyacetylene cutting or arc welding of galvanized pipe results in production of white fumes of zinc oxide containing colloidal particles 0.3 to 0.4 mm in diameter, which can reach the terminal alveoli when inhaled. Construction activities in closed barns containing animals may result in toxicity in animals in close proximity to or in the path of ventilation. All ages may be affected.

Clinical signs in severe cases include acute onset of anorexia, frothing at the mouth, anxiety, extension of the head and neck, mouth breathing, expiratory grunting, tachypnea, tachycardia, mild fever, subcutaneous emphysema, and crackles on auscultation of the lungs. Death may occur within 12 hours. Less severely affected animals exhibit depression, mild fever, and tachypnea. Differential diagnoses include other ARDS of housed cattle that occur in outbreak form, such as exposure to other toxic gases (nitrogen dioxide, manure pit gases) or hypersensitivity pneumonitis. The pathophysiologic process presumably involves direct damage to cells by the ZnO and its products dissolved in the fluid lining the respiratory tract. Necropsy findings include purulent conjunctivitis; subcutaneous emphysema; congestion of the airways; tracheal hemorrhages; stiff, noncollapsing lungs; and pulmonary congestion, edema, and emphysema with bullae. Histologic lesions include pulmonary congestion, emphysema, edema, and mixed cellular infiltrates with a prominent eosinophil component. Treatment of severe cases with epinephrine, antihistamine, atropine, and corticosteroids had no effect in one outbreak, whereas mild cases recover spontaneously. Suggested empiric therapy could include ventilation of the area, dexamethasone (0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily or twice), and appropriate antibiotics to control secondary bacterial invaders.

Chlorine.

Chlorine is a greenish-yellow gas widely used in manufacturing. Animal exposure is usually the result of industrial accidents. Exposed animals may be found dead. Signs include depression, profuse nasal discharge, lacrimation, and dyspnea; crackles may be heard on auscultation.[48] The toxic effects are the result of the formation of hydrochloric and hypochlorous acids; the latter breaks down to hydrochloric acid and oxygen, both of which are toxic to tissues. Necropsy findings include congestion of the nasal mucosa, tracheitis, and pulmonary edema, hemorrhage, and emphysema. Histologic lung lesions include edema,

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emphysema, hemorrhage, atelectasis, hyaline membrane formation, and lymphocytic bronchitis. Treatment is empiric; suggestions include corticosteroids (dexamethasone, 0.05 to 0.2 mg/kg IM or IV daily), furosemide (0.5 to 1.1 mg/kg IM or IV daily to twice daily), and appropriate antibiotics to prevent secondary bacterial infection.

Manure Gases.

Manure gases include mixtures of hydrogen sulfide, ammonia, carbon dioxide, methane, and carbon monoxide.[1] Accumulation of these gases can result in asphyxiation of animals in enclosed barns over manure pits.

Smoke Inhalation.

Smoke inhalation injury may occur in animals that survive barn fires. Many clinical changes may not become evident for 24 to 48 hours after the fire. It is important to assess the degree of damage as early as possible and to attempt to anticipate sequelae so that early aggressive therapy can be instituted.[49] Common problems to check for include oral burns, conjunctivitis, and laryngospasm. Hoarseness, expiratory wheezes, and carbonaceous sputum indicate potentially serious sequelae. Crackles and wheezes on auscultation may occur very early or may be delayed for hours. Cough, stridor, and tachypnea may also occur. Bright red mucous membranes may indicate carbon monoxide poisoning or burns and may mask cyanosis. Carboxyhemoglobin determinations on iced venous blood (often available at human hospitals), serial arterial blood gas determinations, transtracheal wash, and bronchoscopy are useful in delineating the extent of damage and prognosis.

The pathophysiology of smoke inhalation is complex and involves two main mechanisms: carbon monoxide toxicity and smoke toxicity. Carbon monoxide toxicity results in tissue hypoxia in all organs, especially the brain; oxygen consumption in the fire and the pulmonary effects of smoke may aggravate this hypoxia. Heat damage in animals is usually limited to the upper airways. Smoke toxicity is related to the inhalation of soot, superheated particles, and a variety of noxious gases (e.g., aldehydes, oxides of sulfur and nitrogen, benzene from plastics), which results in the formation of dissolved acids, alkaloids, and other direct irritants in pulmonary fluids. These mechanisms eventually (usually 2 to 24 hours after inhalation) result in alveolar damage, interstitial edema, hypoxia, and secondary bronchopneumonia.

Treatment involves establishing a patent airway with intubation or

tracheostomy if necessary. Oxygen, up to 100% for short periods, is indicated; care must be exercised because 100% oxygen can also cause pulmonary damage. IV fluids should be given, with careful monitoring for pulmonary edema. The use of corticosteroids is controversial. Antibiotics are indicated to prevent secondary bronchopneumonia. Bronchodilators such as aminophylline at 6 to 10 mg/kg IV or PO three times daily may help relieve soot-induced bronchospasm.

Hypersensitivity Pneumonitis

■ Definition and Etiology

Hypersensitivity pneumonitis, also known as *extrinsic allergic alveolitis* (EAA) or “bovine farmer's lung,” is an allergic respiratory disease caused by inhalation of organic dusts. Several such conditions are recognized in humans, differing only in the nature of the antigen and the circumstances under which exposure occurs. The classic example, of which the bovine disease is probably the counterpart, is “farmer's lung.” EAA is caused by exposure to the dust from moldy hay, grain, or other plant matter containing spores and products of thermophilic actinomycetes such as *S. rectivirgula* (formerly *M. faeni*) and *T. vulgaris*.[50,51] Other unidentified forms of hypersensitivity pneumonitis probably occur in cattle.

■ Clinical Signs

EAA is a disease of confined adult cattle; consequently it is more common in dairy breeds than in beef breeds. Typically a succession of acute cases occurs during the winter housing period, so the clinician is presented with a group problem in which animals are in varying stages of the disease. The acute form is indicative of recent exposure and is characterized by a sudden onset of dullness, decreased appetite, hypogalactia, coughing, expiratory tachypnea, dyspnea, and cranial-ventral crackles on auscultation of the lungs.[50-52] There is a moderate transient fever, which is frequently missed. The chronic form is insidious at onset and may not be detected until there is considerable fibrosis. Animals with the chronic disease may have acute exacerbations as a result of heavy antigen exposure; some may not be detected until turned out in the spring, when increased exercise causes an acute crisis. There is a history of weight loss and coughing for several winters, with remission in the grazing season. Chronic signs include hypogalactia, weight loss, productive coughing, tachypnea,

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obvious hyperpnea, and widespread crackles and wheezes on auscultation of the lungs, especially in the rostral-ventral areas. Differential diagnoses should include respiratory diseases affecting groups of housed adult cattle in winter. Infectious diseases (viral and bacterial pneumonias) can usually be differentiated from farmer's lung by careful evaluation of factors such as clinical signs of fever and pulmonary consolidation. Therefore the main differential diagnoses are the toxic gases. It should be emphasized that hypersensitivity pneumonitis is not considered an ARDS and that no evidence exists for the involvement of hypersensitivity in the pathogenesis of the ARDS described previously. However, severe cases of EAA with prominent dyspnea and moderate, nonfatal cases of gas intoxication may appear clinically similar. If the group outbreak aspect of EAA is ignored, the clinician who examines one individual may be unable to distinguish this condition from fibrosing alveolitis.

■ Pathogenesis

The spores of the thermophilic actinomycetes are 0.7 to 1.3 mm in diameter and can easily reach the alveoli, where they induce both humoral (precipitating) and cellular immune responses. It is thought that repeated exposure results in the activation of a number of immunologically specific and nonspecific cellular and humoral effector mechanisms at the alveolar level, which results in tissue damage.

■ Epidemiology

EAA is a problem in areas with wet summers and severe winters, a situation characterized by the combination of moldy hay and housing of cattle in winter. In North America, EAA occurs primarily in the Great Lakes region of the United States and the eastern provinces of Canada.[3] Baling and stacking of hay with a high moisture content (over 30%) results in overheating of the stacks. Thermophilic molds become dominant and produce billions of spores, which are released when the hay is distributed for feeding. A similar situation can occur in stored grains. Affected hay is usually dry, friable, discolored, and dusty; however, it is not necessary for hay to be grossly dusty and poor in quality to release large numbers of spores.

■ Necropsy Findings

In acute cases the lungs are superficially grossly normal. Closer inspection

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reveals small gray spots in many lobules, which represent interstitial and peribronchiolar accumulations of lymphocytes. Other lobules exhibit dark red centers of atelectasis surrounded by pale pink raised edges of trapped air that are caused by narrowing of airways with lymphocytic infiltrates. Histologic evaluation confirms the presence of these lymphocytic infiltrates and aggregations, as well as epithelial granulomas, bronchiolitis, and bronchiolitis obliterans. The gross appearance in chronic cases is similar, with the addition of focal areas of interalveolar fibrosis and epithelial hyperplasia; epithelioid granulomas are absent unless a recent acute exposure has occurred.

■ Diagnosis

Precipitating antibodies to *M. faeni* are found in the serum in most cases. However, two precautions are necessary. First, the presence of precipitating antibodies only indicates exposure to the antigen; many normal animals also have antibodies. Second, it is possible that other as-yet unidentified antigens may cause allergic respiratory disease in cattle. The presence or absence of titers is therefore not necessarily diagnostic of the clinical status of the animal, and the magnitude of the titer does not reflect the extent of disease.

■ Treatment and Prevention

Treatment and control center around removing the offending antigen, which is frequently difficult from an economic and management standpoint. Corticosteroids (dexamethasone, 0.05 to 0.2 mg/kg IV or IM daily) may be beneficial in acute cases. Suggestions to decrease the molding of hay or degree of exposure include making silage instead of hay, ensuring proper drying before baling, and feeding hay outside. If the condition can be arrested before significant fibrosis occurs, the prognosis is good.

Anaphylaxis

In ruminants the lung is the major target organ in immediate (type I) hypersensitivity reactions. Precipitating antigens include vaccines, drugs, blood, *Hypoderma bovis* or *Hypoderma lineatum* larvae, insect bites, and bee stings. Signs of anaphylaxis usually develop in 10 to 20 minutes and include severe acute dyspnea, with flaring of the nostrils, extension of the head and neck, open-mouth breathing, frothing of the mouth, hyperpnea, and abduction of the elbows. Pharyngeal and laryngeal edema cause stertor and inspiratory dyspnea. Urticaria

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may occur in some cases, such as milk allergy in Jersey cows. Shivering, salivation, lacrimation, pruritus, diarrhea, fever, edema (eyes, muzzle, anus, and vulva), collapse, nystagmus, cyanosis, and discharge of froth from the nostrils also may occur. On auscultation there are harsh breath sounds, large airway sounds, and crackles. The primary differential diagnosis is peracute interstitial pneumonia. The pathogenesis involves an initial exposure to the antigen, which results in a genetically determined production of IgE. This antibody attaches to receptors on mast cells and basophils. On subsequent exposure to the antigen, bridging of the Fab parts of the antibody on these cells results in degranulation, with release of a variety of mediators such as histamine, bradykinin, 5-hydroxytryptamine, serotonin, slow-reacting substance of anaphylaxis (SRS-A), eosinophil chemotactic factor A, platelet activating factor, kinins, and prostaglandins. These mediators result in a cascade of vascular events, notably increased vascular permeability, which in turn results in acute severe edema. Pulmonary venous constriction, pulmonary artery hypertension, splanchnic pooling, increased mucus secretion, and bronchospasm also occur. Ruminants that die of anaphylaxis have severe pulmonary congestion and edema, laryngeal edema, and froth in the airways. Lung lesions of ARDS may be present.

The treatment of choice is epinephrine, 4 to 8 mg (4 to 8 mL of 1 : 1000 solution) IV or SC or 1 to 5 mg IV for an average 500-kg cow and 1 to 3 mg IV or SC for an average adult sheep or goat. Epinephrine has a short half-life, and animals should be observed closely for relapse. Ancillary therapy includes corticosteroids (dexamethasone, 0.1 mg/kg IM or IV; prednisolone, 2.2 mg/kg IM or IV daily). Other supportive therapies include shock doses of IV fluids (40 mL/kg/h), aminophylline, diuretics such as furosemide, oxygen therapy, and tracheostomy if necessary.

Miscellaneous Chronic Pneumonias

At least two chronic interstitial pneumonias of uncertain cause have been identified in cattle: fibrosing alveolitis and bronchiolitis obliterans. These are typically chronic diseases of individual animals.

Fibrosing Alveolitis

Fibrosing alveolitis is by definition a chronic disease of unknown and possibly multiple causes, characterized by diffuse inflammation of the lung beyond the terminal bronchiole. Approximately 50% of cases produce positive results for

precipitating antibody to *M. faeni,* and it is possible that these cases represent chronic farmer's lung, whereas others (that have negative *M. faeni* results) may be the chronic stage of hypersensitivity to other unidentified antigens.[1] Field investigations have failed to substantiate any connection between fibrosing alveolitis and repeated episodes of ARDS such as ABPEE. Furthermore, recovery from a single dose of 3-MI does not result in lesions typical of fibrosing alveolitis. However, repeated doses of 3-MI at weekly intervals experimentally cause fibrosing alveolitis–like lesions. Fibrosing alveolitis occurs in individual adult cattle (usually over 6 years of age) in both housing and pasture conditions. The history is usually that of a chronic progressive respiratory disease several weeks to 2 years in duration. Affected cattle remain bright and alert and continue to eat until the terminal stages of cor pulmonale and heart failure intervene. Signs include marked weight loss; consistent coughing; tachypnea; very marked hyperpnea, even at rest; and dyspnea after mild exertion. Auscultation may reveal crackles in the rostral-ventral lung field and widespread wheezes. Fever is not apparent. The primary differential diagnoses to consider are other chronic respiratory conditions of individual adult cattle. Chronic suppurative pneumonia and metastatic pneumonia can usually be differentiated from fibrosing alveolitis by careful physical examination and detection of depression, anorexia, shallow respiration, thoracic pain, and hemoptysis. ARDS caused by feed-associated pneumotoxins and lungworms are typically group problems, with at least some severe cases in the group. Differentiation from EAA may be impossible if the group outbreak nature of farmer's lung is not apparent; in fact, at least some cases of fibrosing alveolitis may represent chronic farmer's lung. At necropsy the lungs are very pale, firm, and heavy throughout. Scattered lobules are gray-red, slightly collapsed, and edematous. Thick mucus may be found in the airways, and there is frequently right ventricular hypertrophy as a result of cor pulmonale. Histologic changes are diffuse and include interalveolar fibrosis and infiltration with plasma cells, lymphocytes, mast cells, and interstitial cells; obliteration of alveolar spaces; mononuclear exudates in alveoli; alveolar epithelial hyperplasia; bronchitis; and bronchiolitis. The epithelioid granulomas characteristic of acute farmer's lung are absent. No treatment exists, and the lesions are irreversible.

Bronchiolitis Obliterans

Bronchiolitis obliterans is a chronic respiratory condition of yearling or young adult cattle characterized by a deep infrequent cough, tachypnea, hyperpnea, and

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an exaggerated expiratory effort. There is no fever. The cause is unknown; the condition is speculated to be a sequela to viruses (BRSV, PIV-3, IBR), parasites such as *Dictyocaulus viviparus*, or hypersensitivity pneumonitis. The lungs appear grossly normal at necropsy, except that they do not collapse. Histologic examination reveals extensive bronchiolitis and bronchiolitis obliterans, with epithelium-covered polyps with a connective tissue core projecting into and obstructing the lumen.[1]

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Chronic Progressive Pneumonias of Sheep and Goats

Jeanne Lofstedt • Emily John

Chronic progressive pneumonias are diagnosed with some frequency in mature small ruminants. In sheep, ovine progressive pneumonia (OPP) and *Corynebacterium pseudotuberculosis*–induced mediastinal lymph node and lung abscesses are the chief causes of chronic progressive pneumonia. Chronic progressive pneumonia in goats has been associated with the pneumonic form of caseous lymphadenitis (CLA) and occasionally with caprine arthritis encephalitis virus (CAEV)–induced lung lesions. Additional differential diagnoses that should be entertained in small ruminants that exhibit signs of chronic pneumonia include ovine pulmonary adenomatosis (OPA) in sheep and chronic bacterial pneumonia, verminous pneumonia, mycotic pneumonia, tuberculosis, and pulmonary neoplasia in sheep and goats.

Ovine Progressive Pneumonia (Maedi-Visna)

■ Definition and Etiology

OPP and *maedi-visna* (MV) are North American and European terms, respectively, for multisystemic diseases of adult sheep characterized by chronic, progressive, debilitating pneumonia; wasting; indurative mastitis; arthritis; and occasionally neurologic signs.[1-5] Synonyms are *Marsh progressive pneumonia*, *Montana sheep disease, zwoegerziekte, la bouhite,* and *Graaff-Reinet disease*.[2,4] The OPP virus (OPPV) and MV virus (MVV) are nononcogenic exogenous retroviruses that belong to the genus *Lentivirus,* which includes the human, simian, feline, and bovine immunodeficiency viruses; equine infectious anemia (EIA) virus; and CAEV.[4,5] These enveloped, single-stranded RNA viruses contain the enzyme RNA-dependent DNA polymerase or reverse transcriptase (RT). With this enzyme the viruses use cellular machinery to transcribe a segment of DNA from a template of single-stranded viral RNA; the DNA strand or provirus is then incorporated into the host genome. Close similarity of causal viruses, clinical signs, and lesions produced in tissues permits discussion of OPP and MV as a single disease entity.[3] Extensive mutation of the gene encoding for

envelope glycoproteins occurs in all lentiviral infections; this allows the mutated virus to escape elimination by the host immune response. Antigenic variation in the MVV has been documented.[4] The ovine lentiviruses (OvLVs) are closely related to the CAEV of goats, and cross-species transmission is possible through feeding of infected milk and colostrum.[5] These two viruses are now often referred to as *small ruminant lentiviruses* (SRLVs).[4,5]

■ Clinical Signs and Differential Diagnosis

The incubation period of OvLV infections is prolonged, and most infections are subclinical.[4,5] Approximately 25% to 30% of infected sheep eventually exhibit clinical symptoms.[1] Clinical disease is usually not evident until at least 50% of a flock is seropositive.[1] Conditions in sheep attributed to infection with OvLV include progressive emaciation (“thin ewe syndrome”), progressive respiratory failure, indurative lymphocytic mastitis (“hard bag”), posterior paresis, and chronic nonsuppurative arthritis.[1,4,5]

In North America, progressive pneumonia and aseptic indurative mastitis are the most common clinical manifestations of OvLV infections.[3] Clinical signs of disease are usually first observed in 2- to 3-year-old sheep, but most affected animals are 4 or 5 years old before they exhibit signs.[3,6,7] Emaciation, despite a good appetite, is one of the earliest symptoms. Tachypnea and respiratory distress develop gradually and initially are evident only on exertion.[3-5] Flared nostrils, neck extension, and open-mouth breathing are seen in advanced cases. Thoracic auscultation may reveal increased breath sounds, but crackles and wheezes are typically absent.[3] Pyrexia and purulent nasal discharge are uncommon and, if present, usually indicate concurrent secondary bacterial pneumonia.[5] Wool loss may be seen in advanced cases.[4] Affected ewes may give birth to small, weak lambs.[5] Death from anoxia or secondary bacterial infection ensues within 6 to 12 months of first appearance of clinical signs. In some flocks the disease appears to persist virtually unrecognized, whereas in flocks kept under harsh environmental conditions, mortality rates are quite high.[4]

The neurologic form of OPP is accompanied by weight loss and neurologic signs such as hindlimb ataxia, stumbling, and proprioceptive deficits, which progress over a period of months to paralysis or occasionally quadriplegia[3,5] (see Chapter 35). This form of the disease is encountered sporadically in heavily infected flocks and may occur separately or concurrently in sheep with

respiratory distress.[4,5] Indurative mastitis is often encountered in heavily infected flocks. The somatic cell count (SCC) in affected ewes is increased, but the milk is grossly normal; a firm udder may be detected with careful palpation.[4] The main consequence is poor weight gains in lambs suckling affected ewes, particularly if there are twins or triplets.[4] Arthritis, primarily affecting the carpal joints, is a rare manifestation of OvLV infection.[4,5]

Chronic pneumonias of sheep that have to be differentiated from OPP include chronic bronchopneumonia caused by *Mannheimia (Pasteurella) haemolytica,* OPA, verminous pneumonia, and pulmonary and thoracic lymph node abscesses caused by *C. pseudotuberculosis.*[1,2] Thoracic radiographs, culture of tracheal wash material, and fecal examination by the Baermann technique are useful for antemortem differentiation. Gross and histopathologic evaluations of pulmonary tissues obtained at necropsy are helpful for diagnosing a flock problem.

■ Clinical Pathology and Diagnosis

Hematologic changes in sheep with OPP are nonspecific and may include lymphocytosis early in the course of disease and mild hypochromic anemia and hypergammaglobulinemia in advanced cases.[3,7] A presumptive diagnosis of OPP can be made based on clinical signs of progressive weight loss and chronic pneumonia or, in rare cases, neurologic disease in adult sheep,[4,5] but the diagnosis is often overlooked if mildly affected sheep are culled for other reasons.[4] The majority of sheep infected with OvLV do not show obvious clinical signs and are essentially asymptomatic virus carriers serving as a reservoir of virus for other sheep in the flock.[4,5] For disease control purposes it is important to identify such animals as soon as possible after infection. Several tests, based on detection of antibodies or virus, have been used to identify subclinically infected sheep.

Serologic tests include the agar gel immunodiffusion (AGID) test, several ELISAs, and the Western blot assay.[3,4] The period from infection to seroconversion typically ranges from 3 weeks to several months but can take up to a year.[4] Some infected sheep never seroconvert, whereas others with advanced disease become transiently seronegative.[5] The AGID test has been the preferred serologic test for many years. It has good specificity but has gradually been replaced by a variety of ELISAs.[4,5] ELISAs are more sensitive than the AGID test and are useful when large numbers of samples need to be screened.[3-5] The

use of ELISAs to detect antibodies in milk offers the option of low-cost screening in milking sheep flocks.[4] The Western blot test is used on occasion to confirm ELISA results.[5]

Tests for virus include virus isolation in cell culture or viral genome detection by PCR.[5,8,9] These tests are usually reserved for select cases—for example, when infection is suspected in a seronegative animal or in young lambs that have received colostrum from seropositive ewes.[5] Milk or lung lavage samples are useful substrates for this purpose. Virus isolation, which is time consuming and expensive, is accomplished by coculture of infected fresh or frozen tissue with indicator cell lines. In culture, retroviruses form characteristic multinucleated syncytia.[7] Viral antigens can be detected in these syncytia by use of immunofluorescent staining.[7] PCR testing is more cost-effective than virus isolation.[3,4]

■ Pathophysiology

OvLVs gain access to the body via ingestion of milk or colostrum or through inhalation of aerosolized infectious particles. Infection is then established in the monocyte or macrophage cell line and spreads via these infected cells to the lungs, lymph nodes, choroid plexus, spleen, bone marrow, mammary glands, and kidneys.[7] The virus is able to persist in the face of humoral and cellular immunity through (1) latent infection of host cells by DNA provirus, (2) long-term nonproductive infection of blood monocytes (virus replicates only on differentiation of monocytes into macrophages), and (3) virus mutation with emergence of new antigenic variants that are not neutralized by preexisting antibody.[7] Because of the interaction of the virus with the macrophage monocyte series, a progressive multisystem chronic inflammatory process is initiated, primarily but not exclusively in the lungs and mammary gland.[4] Variations in genetic susceptibility, virus genotype, and the immune response of individual sheep influence target organ involvement and disease progression.[4]

■ Epidemiology

OPP and MV are present in many sheep-rearing countries but have not been diagnosed in Australia or New Zealand.[5] The seroprevalence of OPP in cull ewes in the United States has ranged widely and increases with advancing age.[2] With the exception of West Texas, which has an infection rate of 0.5%, serologic

surveys in cull ewes in other states have revealed infection rates of 30% to 67%. The low seroprevalence in Texas has been attributed to the hot, dry climate and extensive grazing practices.[7] Risk factors for increasing within-flock seroprevalence in North America include large flock size, purchase of more than 50 sheep, and maintaining flocks on nonfenced range.[10,11] Limited studies in large mixed-breed flocks have provided evidence that some sheep breeds may be more resistant to infection than other breeds are.[2] Additional research is required before a particular breed or line of sheep can be viewed as resistant to OvLV infection. The lung and mammary gland are believed to be the main sources of excreted virus.[2] Studies conducted in Europe and Iceland have shown that transmission from the ewe to her lambs commonly occurs through the ingestion of infected colostrum and milk.[2] In other studies, close confinement of diseased or seropositive sheep with healthy or seronegative sheep resulted in disease or seroconversion in the previously healthy or seronegative animals; these infections were presumed to have occurred via the respiratory route.[2] Concurrent OPA is believed to have a synergistic effect on disease transmission via the respiratory route.[4] OvLV transmission has been shown to occur through fecal contamination of drinking water.[2] Blood-contaminated placentas, contaminated milking equipment, and poor biosecurity practices have also been implicated as playing a role in the spread of infection.[2,4] Transmission through the uterine wall or via germ cells can occur but is of minor importance compared with other routes.[2,4]

■ Necropsy Findings

Lesions may develop in any or all of the following tissues of OPPV-infected sheep: lungs and regional lymph nodes, brain, joints, mammary glands, and blood vessels.[4] Changes are most obvious in the lungs, which do not collapse on opening of the thorax.[4,5,7] Vertical rib impressions may be seen on the exterior lung surface. Affected lungs are heavy and, after removal of any visible trachea, weigh more than 1 kg (normal lung weight is up to 500 g) and have a mottled to uniform pink-brown to gray-blue discoloration.[5] Secondary bacterial pneumonia may cause anterior-ventral pulmonary consolidation. Tracheobronchial and mediastinal lymph nodes are markedly enlarged (up to 10 times normal size), bulge on cut surfaces, and are homogeneous gray-white throughout.[4,5] Histologic examination reveals a diffuse lymphoproliferative pneumonia

characterized by prominent lymphoid follicle formation adjacent to bronchioles and small vessels; discrete nodules of lymphocytes, unrelated to vessels or airways, are also found in the lung parenchyma.[7] Lymphocytes, plasma cells, and macrophages infiltrate into interalveolar septa, and hyperplasia of alveolar epithelium and terminal bronchial smooth muscle may be seen.[4] A recent study has shown that proviral load of OPPV is correlated with histologic severity of tissue lesions in naturally infected sheep.[12] In some flocks uncomplicated OPP is the norm. In other flocks it may occur as a mixed infection with lungworm, bacterial bronchopneumonia, or pulmonary adenomatosis, which may result in the OPP lesions being overlooked on routine necropsy.[4]

■ Treatment and Prevention

OPP is not treatable. Antimicrobials can be used to control secondary bacterial pneumonia, but most sheep die within a year of first exhibiting clinical signs.[2,6] No effective vaccines are presently available for control of the disease. There is some evidence that vaccinating lambs born to seronegative ewes early in life may delay the onset of seroconversion when these lambs are maintained in an infected herd.[13]

OPPV is difficult to eradicate from a flock once infection has been established. Uninfected flocks should maintain strict biosecurity measures to avoid introduction of the disease. This may include not sharing rams, not mixing sheep with other flocks, and maintaining segregation at shows.[4] Breeding stock should be purchased from known OPP-free herds and quarantined and tested to ensure that they are seronegative before being introduced into the flock. Control methods that may be economically feasible for purebred flocks with a low seroprevalence rate include (1) a “test-and-cull” practice and (2) isolation of infected adults and artificial rearing of their offspring.[3] With the first method, all sheep are tested annually for antibody, and seropositive animals and their progeny younger than 1 year of age are culled or isolated from the negative flock; culling is preferred because of the risk of cross-contamination. New additions should be seronegative and originate from seronegative flocks. Annual testing should be performed until two consecutive negative test results are obtained to be reasonably confident that the flock is virus free. With the second approach, progeny are removed from their dams before they nurse and are fed cow's colostrum or colostrum from seronegative ewes and raised in isolation. The clean herd should be kept isolated from infected sheep and goats and from

humans and equipment in contact with infected sheep. Herd additions and annual testing should be handled as described for method 1. In flocks with well-established infections and a high seroprevalence rate, control options are limited.[4] The test-and-cull procedure and removal of lambs are impractical under commercial conditions. Increasing the flock replacement rate by strict culling of suspect cases and not keeping ewes beyond 4 to 5 years of age will assist in keeping the flock seroprevalence down and in reducing the incidence of clinical disease.[4]

Recent research has demonstrated that variation in the gene encoding transmembrane protein 154 (TMEM154) results in decreased susceptibility of sheep to infection with SRLVs.[14] Three main haplotypes of the TMEM154 gene have been identified: haplotype 3, the ancestral variant; haplotype 1, with a single amino acid substitution E35K; and haplotype 2, with a different single amino acid substitution N70I. Under natural exposure conditions, sheep possessing at least one copy of haplotypes 2 or 3 were 2.85 times more likely (95% CI 2.36–3.43) to be seropositive for OPPV than sheep possessing two copies of haplotype 1.[15] This suggests that marker-assisted selection of genetically resistant sheep may help decrease prevalence of OPPV infection within flocks.

Ovine Pulmonary Adenocarcinoma

■ Definition and Etiology

OPA, also known as jaagsiekte (South Africa), sheep pulmonary adenomatosis (United Kingdom), or pulmonary carcinoma (United States),[16] is a naturally occurring, retrovirus-induced bronchioloalveolar carcinoma of sheep and, in rare cases, goats that has been associated etiologically with a betaretrovirus called jaagsiekte retrovirus (JSRV).[17,18] OvLVs and herpesviruses have been isolated from OPA tumors; however, they are not consistently present and do not induce OPA when inoculated experimentally.[19] One theory is that these viruses may act as cofactors in tumor induction. Defining the role of JSRV in OPA has been complicated by the presence of 15 to 20 endogenous jaagsiekte retroviruses (enJSRVs) that are stably integrated into the genomes of sheep and goats.[20,21] Recent research has indicated that exogenous JSRV is likely not of endogenous origin. There has been speculation that the endogenous viruses may modify the genome of exogenous JSRV, either by inducing the expression of an oncogene or

by inactivating a tumor suppressor gene.[18] Sequence analyses of exogenous JSRV and enJSRV suggest that endogenous viruses do not directly contribute to the pathogenesis of OPA through large-scale recombination events, but small-scale recombination or complementation of gene function has not been definitively excluded.[20] There has been speculation that expression of enJSRV in the fetal or neonatal period may influence expression of OPA through induction of immunologic tolerance.[17,20] Endogenous JSRVs appear able to exert a protective effect on the host by blocking cellular entry of JSRV via receptor interference as well as by preventing proper cellular trafficking and, ultimately, release of virus particles.[22]

■ Clinical Signs and Differential Diagnosis

Symptoms normally appear in mature sheep between 2 and 4 years of age, although lambs as young as 3 months of age and sheep as old as 11 years have occasionally been diagnosed with OPA.[16] Signs include exercise intolerance, weight loss despite a good appetite, tachypnea, dyspnea, occasional cough, and high-pitched crackles on thoracic auscultation. A characteristic feature of OPA is the accumulation of abundant fluid in the respiratory tract that is frothy, clear, milky, or at times pink-tinged and may flow from the nostrils of affected sheep when the rear limbs are raised and the head is lowered ("wheelbarrow test").[16-18] Up to 400 mL of nasal secretions may be collected in a day, although 10 to 40 mL/day is more usual. Rectal temperature is usually normal unless secondary bacterial infection is present. Sheep with OPA typically succumb within a few weeks to months after first exhibiting clinical signs.

Chronic pneumonias of sheep that must be differentiated from OPA include chronic bronchopneumonia caused by *M. haemolytica*, OPP, verminous pneumonia, and pulmonary and thoracic lymph node abscesses caused by *C. pseudotuberculosis*.[1,2] Thoracic radiographs, culture of tracheal wash material, and fecal examination by the Baermann technique are useful for antemortem differentiation. Gross and histopathologic evaluations of pulmonary tissues obtained at necropsy are helpful for diagnosing a flock problem.

■ Clinical Pathology and Diagnosis

The only reported clinical pathologic abnormality in sheep with OPA is hypergammaglobulinemia. Advanced clinical cases in mature sheep can be presumptively diagnosed based on clinical signs of weight loss and respiratory

distress accompanied by copious nasal secretions, but in many cases the disease is subclinical.[16,17] To date, sensitive and specific tests for identifying apparently healthy animals that may be infectious are lacking. The absence of JSRV-specific antibodies in infected sheep have precluded the use of serologic tests for diagnosing infection.[17,18] PCR tests, capable of demonstrating viral nucleic acids of endogenous JSRV tissues in OPA-infected animals, have been developed but have a high false-negative rate and are not useful for identifying individual animals for eradication purposes.[17] The most successful approach for early diagnosis of OPA is PCR testing of bronchoalveolar fluid collected from live animals, but this is impractical for widespread testing, and saliva and nasal secretions of infected sheep often test negative for JRSV.[17] Recently, rapid transthoracic ultrasound has shown high sensitivity and specificity for antemortem identification of sheep with lung lesions consistent with OPA at postmortem examination, making this imaging modality potentially useful for flock-level screening for OPA.[23]

■ Epidemiology

OPA has been reported in sheep-rearing countries throughout the world but not in Australia, New Zealand, or the Falkland Islands.[17,18] Iceland is currently free of OPA as a consequence of implementing an aggressive slaughter policy in endemic areas in the 1950s.[17] The prevalence of OPA varies among countries in which the infection occurs; it is endemic in Scotland, Peru, and South Africa, where annual losses range from 2% to 10%. In contrast, OPA is infrequently diagnosed in the United States and Canada, where totals of 11 and 43 cases, respectively, have been reported.[18]

OPA has been reproduced experimentally by intratracheal inoculation of lung homogenates or pulmonary lavage fluids obtained from infected animals.[24] Lambs between birth and 5 weeks of age have been shown to be more susceptible to experimental infection than 10-week-old lambs.[24] This age-related susceptibility to OPA suggests that natural virus transmission occurs in the neonatal period.[17] Aerosol transmission and contamination of feed and water by respiratory secretions are likely methods of disease spread, particularly in confined sheep. Provision of diets deficient in selenium had no effect on development or progression of pulmonary tumors when compared to sufficient dietary selenium intake.[25]

■ Necropsy Findings

OPA lesions in the lungs are categorized as classical OPA or atypical OPA based on their appearance.[16,17] In classical OPA the lungs are heavy (two to three times normal weight) and exude clear fluid from the cut surface.[16-18] The trachea and bronchi often contain clear, foamy fluid. Large, firm, gray masses are commonly encountered in the cranioventral regions of one or both lungs. Smaller (1- to 2-cm) nodules are occasionally visualized in the caudodorsal lung regions. In atypical OPA the tumors consist of solitary or aggregated hard, white nodules that are clearly demarcated from normal lung tissue and have a dry cut surface.[16,17]

Metastasis to regional lymph nodes occurs in approximately 10% of cases, resulting in pulmonary lymph node enlargement.[16,17,26] Metastases to cardiac and skeletal muscles are infrequently reported.[16,17,26] Metastasis to solid abdominal organs as well as to the digestive tract and skin is also possible, although rare.[27] Secondary bacterial pneumonia caused by *M. haemolytica* may mask the lesions of OPA.[17]

OPA is classified by the World Health Organization (WHO) as a bronchioloalveolar carcinoma arising from alveolar type II pneumocytes or nonciliated bronchiolar cells.[26] Histologic lesions in the lungs consist of columnar or cuboidal cells arranged in an acinar or papillary pattern and are similar for classical or atypical OPA but with an exaggerated inflammatory response and fibrosis in the atypical form of the disease.[16]

■ Treatment, Prevention, and Prognosis

There are no known treatments for this disease. Antibiotics may prolong the life of OPA-affected sheep through control of secondary bacterial pneumonia.[18] There are no vaccines for OPA at this time.[17] Prompt culling of ewes suspected to be infected, as well as their offspring, has been used to decrease disease prevalence in endemic flocks.[16,17] OPA was eradicated from Iceland by slaughtering all sheep in endemic areas.[16-18] Contaminated areas where infected sheep were held should be left vacant for 2 months.[17] OPA has reportedly been eliminated from two flocks by removing the lambs at birth, depriving them of maternal colostrum, and raising them in isolation or by using embryo transfer.[16,17] This approach is impractical for commercial flocks. Until reliable

diagnostic tests for subclinically affected sheep are developed, control will remain problematic.

Caprine Arthritis and Encephalitis

CAE is a persistent lentiviral infection of goats with four possible clinical presentations: leukoencephalomyelitis in kids 2 to 6 months of age and chronic, hyperplastic polysynovitis, indurative mastitis, and interstitial pneumonia in mature goats.[28-30] Mild interstitial pneumonia, which is silent clinically, is a common postmortem finding in goat kids infected with CAEV.[31] Occasional kids with leukoencephalomyelitis may have diffuse involvement of one or more lung lobes.[30] In one study, 60% of adult goats serologically positive for CAEV had lesions of severe chronic interstitial pneumonia at slaughter.[31] In addition, chronic interstitial pneumonia, accompanied by exercise intolerance and dyspnea, was described in dairy goats originating from herds that had clinical cases of arthritis and leukoencephalomyelitis.[32] The lung lesions in these goats resembled those of OPP and MV and were positive for CAEV.[32,33] However, CAEV has been recovered from the lungs of goats with advanced arthritis but without interstitial pneumonia. In addition, goats inoculated intratracheally with purified CAEV did not develop pulmonary lesions.[32] This may indicate that there is no causal relationship between CAEV and interstitial pneumonia in goats or that an additional agent such as a helper virus is required for the lesions to develop.[30] The first signs of chronic progressive pneumonia associated with CAEV infection appear at times of stress such as kidding and include exercise intolerance, dyspnea, weight loss, and occasionally a cough.[30] Enlarged carpi may be present in some of the affected goats.[30] Radiographs in advanced cases demonstrate large areas of lung consolidation and sometimes bullous emphysema in the cranioventral or caudal lung lobes.[32] Histopathologic examination of lung biopsy samples may assist with an antemortem diagnosis.[30] Serologic testing is of no diagnostic value other than identifying the presence of CAE in the herd of origin. Lesions in the lungs at postmortem are as for sheep with the pneumonic form of OPP.[30] CAE is discussed in detail in Chapter 38.

Caseous Lymphadenitis

CLA, caused by *C. pseudotuberculosis* (previously known as *C. ovis*), is a

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chronic disease of sheep and goats characterized by the development of pyogranulomatous abscesses in lymph nodes and internal organs.[34-39] The disease affects small ruminants worldwide.[39] CLA most commonly presents as an external form characterized by abscesses in superficial lymph nodes.[37,39] The internal, or visceral, form of CLA manifests as internal abscesses in the mediastinal and mesenteric lymph nodes as well as internal organs, primarily the lungs, but also in the liver, kidneys, and central nervous system.[39] Small ruminants with the visceral form of the disease rarely have concurrent abscessation of external lymph nodes.[38] Goats are more commonly afflicted with external abscesses, whereas the visceral form of CLA appears to be more common in sheep.[34] Visceral CLA may be asymptomatic but is typically associated with progressive weight loss.[34,38,39] Specific clinical signs that may implicate visceral CLA of the lungs and associated lymph nodes include exercise intolerance, tachypnea, dyspnea, and chronic cough. Because of the encapsulated nature of pulmonary abscesses and the lack of exudate in airways, pulmonary crackles are rarely auscultated.[38,39] Nonspecific laboratory findings in sheep and goats with CLA include leukocytosis, hyperfibrinogenemia, hyperproteinemia, and hypergammaglobulinemia; however, laboratory findings are frequently normal in animals with chronic abscesses.[36,37] A definitive diagnosis of visceral CLA with pulmonary involvement may be achieved by thoracic radiographic and ultrasonographic findings of abscesses in the lungs and mediastinal lymph nodes or by isolating *C. pseudotuberculosis* from a transtracheal aspirate (TTA).[34,38] Failure to isolate the organism from tracheal wash fluid, however, does not rule out CLA as the cause of pulmonary disease. Characteristic postmortem findings of the respiratory form of CLA are one or more thick-walled, laminated, encapsulated, caseopurulent abscesses in the bronchial lymph nodes, mediastinal lymph nodes, and/or lung parenchyma.[36] Serologic tests have been developed for the detection of asymptomatically affected animals or those with internal abscess. They include the synergistic hemolysis inhibition (SHI) test and several ELISAs.[36,37] Most serologic tests are not specific enough to justify their use in culling programs. However, an ELISA developed in the Netherlands for disease eradication purposes has recently been improved to increase sensitivity (94%) and specificity (98%).[40] CLA is discussed in more detail in relation to the hemolymphatic system (see Chapter 37).

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Parasitic Bronchitis and Pneumonia*

Dwight D. Bowman

There is only a single lungworm, *Dictyocaulus viviparus*, that matures to the adult stage within the lungs of cattle. In sheep, the three main lungworms that may occur are *Dictyocaulus filaria*, *Muellerius capillaris*, and *Protostrongylus rufescens;* some other species mature in the lungs of sheep and goats around the world, but they are fairly rare compared to these other species. *Toxocara vitulorum* of cattle larvae undergo a liver to lung migration on their way to the intestine after infective eggs are ingested, and they can induce a transient pneumonitis during lung passage. In cattle, *Ascaris suum* of pigs can also cause signs similar to larval toxocariasis if cattle ingest large numbers of eggs; these infections do not develop to patency. In sheep and goats, *Toxocara canis* and perhaps other species from carnivores can cause transient pneumonitis as the larvae migrate through the liver and lungs on their way to arrest as larvae in other tissues such as muscle and nervous tissues.

Lungworms of Cattle: *Dictyocaulus viviparus*

■ Definition and Etiology

Dictyocaulus viviparus is a trichostrongylid nematode that is found in the bovine trachea and bronchi. These are robust white worms that can reach lengths of 8 cm; the slightly smaller males have very dark brown, stubby spicules that can often be visualized within the body of the worm just anterior to the copulatory bursa. The life cycle of *D. viviparus* is direct. The female produces larvated eggs that hatch in the lungs, and the larvae make their way up the respiratory tract, are coughed up, and are swallowed to be passed in the feces. The larvae on pasture ultimately develop to an infective third stage without feeding and can develop in the laboratory in aerated water into doubly sheathed infective stages. The larvae take 5 days or longer, depending on environmental conditions, to develop to the infective stage on pasture. The larvae then migrate to grass, where they are ingested by the feeding cattle. After ingestion, the larvae migrate through the intestinal wall and make their way into the mesenteric lymph nodes, where they molt to the fourth stage. It is the fourth-stage larvae that make their way to the lungs via the blood and lymph systems and initially are found in the terminal

capillaries of the ventral parts of the caudal lobes. At about 7 days after ingestion, the fourth-stage larvae enter the alveoli and then molt to the immature adult stage. The adults develop and mate, and eggs first appear in the bronchi, and subsequently larvae appear in the feces, some 3 to 4 weeks after the animal was initially infected. Clinically evident infection with *D. viviparus* typically occurs in young, nonimmune stock (younger than 12 months old) or in previously unexposed yearling or adult cattle. A reinfection syndrome can also occur when previously infected (and therefore immune) adults are subjected to massive challenge with infective larvae.[1,2]

■ Clinical Signs and Differential Diagnosis

Primary infection with *D. viviparus* can be broken down clinically into a prepatent phase, a patent phase, and a postpatent phase.[3] No signs are associated with the initial penetration of larvae until they reach the alveoli, where they provoke an eosinophilic exudate that blocks small airways. During the prepatent phase (approximately 7 to 25 days after ingestion) there is a gradual onset of coughing and tachypnea (35 to 60 breaths/min), which becomes increasingly apparent from day 14 to day 25. The severity of signs in this stage is proportional to the number of larvae ingested, the rate of ingestion, and the proportion of larvae reaching the lungs. Severe illness and death can occur in cases of heavy infection. In the patent phase (approximately 25 to 55 days after ingestion) a parasitic pneumonia with consolidation develops in the ventral areas of the caudal lung lobes as a result of aspiration of eggs and larvae into these areas. Tracheitis and bronchitis associated with the adult worms also develop. Clinical signs vary in severity and range from intermittent to marked coughing, tachypnea (respiratory rate may increase to more than 70 breaths/min), dyspnea, anorexia, and weight loss. Fever may develop with secondary bacterial infection. Auscultation reveals harsh breath sounds and widespread crackles and wheezes. In severe cases animals may exhibit open-mouth breathing, extended head and neck, protrusion of the tongue, and an expiratory grunt. Death is common in untreated, heavily infected animals.[2,3]

Recovery begins in the late patent phase, and the signs gradually resolve, sometimes over several months. During the postpatent phase (about days 55 to 90), adult parasites are expelled by a self-cure phenomenon. In approximately 25% of severe cases the postpatent phase is characterized by a sudden exacerbation of dyspnea at days 45 to 60 that is often fatal, after secondary

bacterial infection or alveolar epithelialization.[1,3] The reinfection syndrome occurs 14 to 16 days after adult cattle are placed on heavily contaminated pastures. Signs include acute hypogalactia; severe, frequent coughing; marked tachypnea; and depression. Auscultation reveals only harsh breath sounds with no crackles or wheezes.[1,3]

Relative to *D. viviparus,* an ancillary finding occurred as part of a 3-year study in Sweden that examined the effects of different parasite control strategies administered to cattle during their first grazing season on their weight gain in the three second grazing seasons when they were all handled equivalently.[4] Basically, during the second season of grazing, deficits acquired within each management group in the first year were maintained during the second year, but the first season of treatment had no effect on weight gain in the second season. During the second and third second-season grazing periods, *D. viviparus* entered the groups when additional contaminated pastureland was added to the grazing area in the final 2 years. The work then clearly showed that the presence of *D. viviparus* had a detrimental effect on all animals in both seasons and that during the second such season, signs of dictyocauliasis appeared in August and the cattle underwent dramatic weight loss (the trial precluded treatment without more serious signs of induced disease). Thus it was fairly clear that the larvae had overwintered on pasture, increased in number within the herd, and were there in sufficient numbers to cause significant effects in the second year.

Differential diagnosis should be straightforward if both clinical signs and epidemiologic characteristics of the disease are taken into account, especially in endemic areas. This is a disease of groups of cattle at pasture, typically in late summer or fall in northern temperate climates; the situation thus resembles ABPEE, which differs in clinical signs (i.e., less coughing and fewer adventitious lung sounds). The signs associated with lungworm infection are reminiscent of those of farmer's lung, which occurs in quite different circumstances. In typically nonendemic areas, outbreaks associated with climatic changes are frequently mistaken for acute bacterial bronchopneumonia.[1]

■ Diagnosis

Classically, diagnosis has been through the detection of the characteristic larvae passed in the feces. In cattle, this is the only nematode parasite routinely producing larvae found in the feces, and thus if the fecal sample is fresh, the finding of larvae is fairly diagnostic. Rectal fecal samples are preferred for

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parasite examination because samples picked up off the ground may contain free-living nematodes that can be difficult to differentiate from lungworm larvae. Recovery of larvae from fecal samples is substantially diminished if the sample is stored at room temperature for more than a few hours. The larvae are best detected by the Baermann test[5] and may be seen on a transtracheal wash. The larvae themselves are large (390 to 450 µm × 25 µm), have a somewhat pointed tail (compared to *Dictyocaulus filaria* of the sheep), and have an intestine filled with dark granules. The esophagus appears clear compared to the intestine under the microscope and is about one fourth of the total length of the larva. If the Baermann test cannot be set up soon after fecal collection, the sample can be safely refrigerated for 24 to 48 hours without serious larval loss.[6] No larvae are detected in the reinfection syndrome. In some European countries, ELISAs are used within various diagnostic laboratories to detect antibodies in cattle that have been exposed to infection.[7] An increase in eosinophils in the peripheral blood may also occur approximately 2 weeks after infection, peaking at 4 to 7 weeks after infection.[8] It has been suggested that with an average herd size of 73 (19 heifers and 54 cows), 9 heifers and 15 cows need to be sampled using the Baermann methods and 6 heifers and 10 cows need to be sampled when using the serum ELISA to be 95% confident that one test is positive if *D. viviparus* is present in the herd.[9]

In Europe, ELISA technology that is based on an antigen that is a recombinant product representing a major sperm protein of the adult male has now been developed to detect antibody in the milk and serum of cattle.[9-11] Examination in experimentally infected dairy cows revealed that the ELISA detected antibodies in the serum and milk some 30 to 32 days after infection and remained elevated for 112 to 138 days post exposure even though the cows had been treated for their infections with eprinomectin 49 days after infection and had ceased larval shedding.[11] However, if the cattle were treated during the prepatent period, larvae were never shed in the feces, and the animals remained antibody negative. This technique has now been adapted to determine the presence of antibodies in bulk milk and has been used to collect epidemiologic data. Of 810 dairy farms in Germany that were tested in January, September, and November, some 18% were positive on one occasion, and most positive samples were detected in January.[9] It was not known what percentage of zero-grazing herds were included in the bulk milk samples.

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■ Pathophysiology

Once the fourth-stage larvae enter the alveoli, they incite an eosinophilic exudate that blocks small bronchi and bronchioles, resulting in atelectasis and causing the cough and tachypnea of the prepatent phase. As these larvae mature and migrate up the airways, these lesions may resolve. However, the adult worms produce an inflammatory response in the larger airways, and aspirated eggs and larvae cause a marked macrophage and giant cell response, with consolidation of the ventral caudal lobes; these lesions are the cause of the signs in the patent phase. At any point in the pathogenesis (prepatent, patent, or postpatent stage), complications may occur that account for acute exacerbation and death. These complications are as follows:

- Development of pulmonary edema caused either by heart failure or by extensive alveolar epithelial damage and hyaline membrane formation
- Severe interstitial emphysema from the severe dyspnea
- Alveolar epithelial hyperplasia
- Secondary bacterial infection, which is relatively uncommon

In the reinfection syndrome, the immune response cannot completely overcome a massive challenge, and a small number of larvae reach the lungs. The signs are caused by the immune reaction to the migrating larvae. Lymphoid nodules develop around dead larvae in the bronchioles.[1-3]

■ Epidemiology

Parasitic bronchitis and pneumonia in cattle occur most often in temperate areas with high rainfall or intense irrigation. In the United States, lungworm infection is widely distributed, but disease outbreaks are uncommon, probably because periods of dry summer weather limit larval survival and accumulation on pasture.[2] In the southern United States, lungworm transmission is probably greatest in the cool winter months,[12] whereas autumn is probably the season of

most intense transmission in the northern United States.[13,14]

Dictyocaulus infections have been studied extensively in Europe, where the parasite is an important pathogen. Disease outbreaks occur most frequently in first season grazing animals. If large numbers of larvae are present on pasture at spring turnout of calves, disease may develop at that time. Often, however, levels of pasture larvae are too low to cause disease but lead to low-level primary infections in calves that result in the accumulation of additional larvae on pasture. This second wave of infection may lead to clinical lungworm disease when the primary infection did not produce adequate levels of immunity. If infection levels remain low, disease may not be observed until a third generation of parasites occurs. Immunity develops beginning about 10 days after heavy infection, and patent infections usually persist for only a few months. In the absence of continued exposure to parasites, immunity to reinfection will begin to decline after several months.[2,15]

Older animals without immunity also develop lungworm disease when exposed to high levels of pasture contamination with larvae. This can occur when animals from a nonendemic area are moved to an endemic area. In recent years outbreaks of primary parasitic bronchitis have become an important cause of respiratory disease in adult dairy cows in Europe. The increased prevalence of disease in this older age-group is likely the result of decreased levels of immunity after the widespread use of powerful suppressive anthelmintic regimens in first and second season grazing animals. Other management factors, such as isolation of calves from adult carrier animals and increased movement of livestock, may also contribute to a decline in levels of immunity.[7,16] Beef animals are less often affected than dairy cattle because management practices are more extensive and levels of infective larvae on pastures are generally lower.[2] The reinfection syndrome occurs in immune adult animals when, for example, immune cows are placed on a pasture previously contaminated very heavily by calves with patent disease.[1,2]

In northern temperate climates, the infection is carried from year to year by overwintering of larvae on pasture in some areas, by spreading of manure from infected housed calves in the spring, and by carrier cattle. Lungworm larvae also may be inhibited in the lungs of calves in winter (as with *Ostertagia* species in the abomasum) and mature in the spring.[1,3] It appears that over the last decade the disease is becoming more common in the more northern parts of the United Kingdom.[17]

■ Necropsy Findings

In the prepatent phase the lungs are largely normal, with a few atelectatic lobules in the ventral caudal lobes; adult worms are not present until late in this phase, but larvae may be detectable by microscopic examination of smears of bronchial exudate. In the patent phase there is usually bilaterally symmetric red consolidation of the ventral caudal lobes. Adult worms can be recognized on necropsy by their relatively large size and location in the trachea and bronchi. The lesions of the postpatent phase are similar, but no adult worms or larvae are present. In those patients that die of an acute exacerbation, there is extensive pulmonary edema and emphysema, with hyaline membranes and alveolar epithelial hyperplasia.

In the reinfection syndrome the pulmonary lymphoid nodules may be 3 to 4 mm in diameter and thus grossly visible as raised, gray-red to greenish-yellow nodules under the pleura. Initially these are composed of a core of eosinophilic parasitic debris surrounded by macrophages, multinucleated giant cells, hyperplastic bronchiolar epithelium, eosinophils, and plasma cells. The lesions eventually mature to lymphoreticular nodules with a germinal center. There is also greenish mucus in the airways and a greenish discoloration to the tissues, both caused by eosinophil infiltration. There is no edema or emphysema, and the rare lungworms that may be found are small and stunted.[1]

■ Treatment, Prognosis, Prevention, and Control

D. viviparus infection can be treated with a number of bovine anthelmintics available in the United States and other countries (Table 31.16). Macrocyclic lactone products also have residual efficacy against *D. viviparus,* and there is now an extended-release eprinomectin compound that will provide protection for 150 days.[18,19] Animals with only cough and tachypnea respond well, whereas those with dyspnea, fever, anorexia, and depression have a more guarded prognosis; some of these animals can be expected to die or remain chronically unthrifty.[1] Control (see also Chapter 49) involves appropriate pasture management and the strategic use of anthelmintics to prevent buildup of infection in the herd and on pastures. Several strategic deworming programs that effectively suppress lungworm infection throughout the grazing season have been developed in Europe. These programs include use of ivermectin at 3, 8, and 13 weeks after turnout and use of doramectin or eprinomectin at 0 and 8 weeks. Use of an oxfendazole pulse release bolus (not available in the United States)

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also provides strategic treatments. Alternatively, use of a continuous-release ivermectin or fenbendazole bolus (not available in the United States) will prevent development of lungworm infection during its period of efficacy.[16] A long-acting moxidectin injection product that provides protection from lungworm infection for 120 days is also now available in some countries.[20] Anthelmintic treatment with moxidectin or fenbendazole followed by movement of calves to safe pasture 9 weeks after turnout was also effective in controlling lungworm.[21] None of these control programs has been extensively tested under the variety of grazing conditions found in the United States.

Table 31.16

Anthelmintics Approved for Treatment of *Dictyocaulus viviparus* in the United States

Anthelmintic	Formulation	Efficacy of a Single Treatment	Approved for Dairy Cattle of Breeding Age
Levamisole	Drench, bolus, injection		
Fenbendazole	Paste, suspension, medicated feed, mineral		+
Oxfendazole	Suspension		
Albendazole	Paste, suspension		
Ivermectin	Injection, pour-on	28 days	
Eprinomectin	Pour-on	21 days	+
Eprinomectin	Injection	150 days	
Doramectin	Injection, pour-on	28 days	
Moxidectin	Pour-on, injection	42 days	+
			Pour-on only

Despite concern that suppressive programs may limit exposure to larvae and interfere with the development of immunity to lungworm, several studies conducted in Europe have shown that stimulation of the immune response still occurs, although relative levels of immunity may vary with different management systems and annual variation in the intensity of lungworm challenge.[7,22-24] In Europe, methods of control also include an effective irradiated larval vaccine.

Delay of spring turnout is an adjunct to control but should not be relied on as the sole means of control.[23] A targeted selective deworming program was successful in controlling lungworm infection in a dairy herd in Sweden. Only cattle testing positive for lungworm by the commercial ELISA were treated at each sampling date.[25] In an attempt to eradicate *D. viviparous* from two farms in

the Netherlands that had had lungworm-associated disease outbreaks, both herds were mass treated with eprinomectin at turnout.[26] From August to November of the first year after treatment, all first-year heifers remained lungworm negative as determined both by fecal examination and by monitoring for *D. viviparus*–specific antibodies. However, in the second year after treatment, one of the herds developed signs of parasitic bronchitis that was confirmed serologically. The other herd remained negative until at least the fourth year after treatment, but then signs of parasitic bronchitis were observed and the cattle were treated. The authors of this report believed that in both cases the *D. viviparous* was reintroduced into the herd from an outside source or perhaps that the reuse of pastures that may have lain fallow for an extended period provided the source of the new infections.

Toxocara vitulorum.

This parasite seems to be reemerging in prevalence within the developed world; there have been recent reports from a bison herd in western Canada, suckling beef calves in the Netherlands, and suckling Simmental cattle in the United Kingdom. In a closed cow-calf beef operation in north-central Florida, 17.6% of 105 calves under 3 months of age were found to be infected, and on a beef farm in Iowa, 40% of 34 calves were found to be infected after a calf died due to an ascarid intestinal impaction.[27-30] Infections in neonatal calves are acquired by fairly large larvae (0.75 to 1.5 mm in length) that are passed from cow to calf in the milk. In cows that ingest eggs, the larvae undergo a liver-lung migration before they make their way to the various tissues of the cow, where they are known to persist for at least 5 months.[31] There typically do not appear to be any signs associated with the lung migration of the larvae, but repeated passage of the larvae through the lungs on contaminated pasture could perhaps produce respiratory signs in older calves or adult animals.

Ascaris suum.

Cattle exposed to large numbers of *A. suum* eggs in areas contaminated by swine may have an interstitial pneumonia. Animals are typically affected approximately 10 days after exposure. Signs include depression, anorexia, fever, tachycardia, tachypnea, dyspnea with an expiratory grunt, variable coughing, ruminal stasis, and bloat. Auscultation of the lungs reveals increased breath sounds without adventitious sounds. Some deaths may occur. Differential diagnosis is difficult. Differentiation from the other interstitial pneumonias

depends more on history of exposure to the causative agents (e.g., lush pastures, sweet potatoes moldy with *Fusarium solani*, wild mint, *Perilla frutescens*, toxic gases, moldy hay). Differentiation from viral pneumonia (such as that caused by BRSV) and *D. viviparus* reinfection syndrome requires necropsy and demonstration of larvae. Ascarid larvae have characteristic lateral alae in histologic sections. Patent *D. viviparus* infection can be differentiated by Baermann examination of the feces. In fatal cases the lung lobes are firm and mottled blue, red, and gray. The cut surface oozes thin yellow exudate. There is emphysema in the dorsal diaphragmatic lobes and subpleural hemorrhage with neutrophil infiltration and necrosis of bronchiolar and alveolar epithelium. In chronic cases the cellular infiltrate is lymphocytic, and there is proliferation of bronchiolar epithelium and peribronchial fibrosis. Recommended treatments include corticosteroids (dexamethasone, 0.04 mg/kg IM or IV or prednisolone, 1 mg/kg IM or IV daily) and antibiotics to control secondary bacterial infection.[32] Clinical signs resolved after treatment with oxfendazole in one outbreak of suspected *A. suum* migration.[33] Cattle should not be exposed to areas heavily contaminated by swine.

Lungworms of Sheep and Goats

Three species of lungworms are of primary importance in sheep and goats: *D. filaria* and the two metastrongylid nematodes, *M. capillaris* and *P. rufescens*. Other genera of metastrongylid lungworms of minor pathogenic importance in sheep and goats include *Cystocaulus*, *Spiculocaulus*, and *Neostrongylus*. These parasites are rare or absent in North America.[34]

Dictyocaulus filaria.

D. filaria has a life cycle essentially identical to that of *D. viviparus;* the time from ingestion to the appearance of larvae in the feces is about 4 weeks. Mainly young animals are affected, but disease can also occur in adults. Dyspnea, tachypnea and coughing, and loss of condition occur in clinical cases.[32,33] Differential diagnosis includes the progressive viral pneumonias. Diagnosis is made by finding larvae in fresh feces by the Baermann test.[5] Samples should be tested soon after collection because larval recovery is significantly reduced in stored samples.[6] Larvae of *D. filaria* are similar in size and appearance to those of *D. viviparus* but also have a distinctive knob on the anterior end. The

pathogenesis is similar to that of *D. viviparus* (see earlier discussion). The adults are found largely in the dorsal-caudal regions of the diaphragmatic lobes. Bronchitis and peribronchitis, along with cone-shaped areas of pneumonia and atelectasis, and emphysema are present. Secondary bacterial infections may also occur.[34,35] Levamisole (8 mg/kg), fenbendazole (5 to 10 mg/kg), ivermectin (0.2 mg/kg PO),[33] and moxidectin (0.2 mg/kg PO or SC)[36-38] can be used for treatment. When outbreaks occur, all animals should be treated and moved to fresh pasture when possible. Clinical *D. filaria* infections seem to occur most frequently in areas with warm climates. In temperate areas the parasite overwinters either as arrested larvae in ewes or as larvae on pasture.[34]

Muellerius capillaris.

M. capillaris is probably the most common of the lungworms of sheep and goats. Infection is more pathogenic in goats than in sheep. Surveys in Maryland and Georgia detected the parasite in 64% and 68% of goats, respectively.[39,40] The life cycle is indirect. First-stage larvae are coughed up, swallowed, and passed in the feces. These larvae are relatively resistant and may survive for several months in the environment. After penetration of an appropriate molluscan intermediate host, the infective third stage develops in a minimum of about 12 days, is ingested with the snail, and passes to the mesenteric lymph nodes. The fourth-stage larvae proceed to the lungs, where adults develop in the alveoli. The prepatent period of *M. capillaris* infection is about 6 weeks.[41] Although many infections are subclinical, clinical disease may develop. Goats appear to be more likely than sheep to develop unthriftiness, coughing, and dyspnea. Infection may also predispose to secondary bacterial infection.[40] The difference in clinical signs between sheep and goats probably results from a difference in the pathogenesis of infection. The adult worms live in the pulmonary parenchyma, particularly the subpleural tissue. In sheep they produce grayish nodules typically 2 to 3 mm in diameter. On palpation at necropsy, these nodules have been described as feeling like “lead shot.”[40] Each nodule contains a worm and necrotic leukocytes and pulmonary tissue surrounded by a connective tissue wall and giant cells.[34] They may calcify or become secondarily infected with bacteria. Reports of lesions in goats indicate that *M. capillaris* causes an interstitial pneumonia. The lungs are resilient and firm, fail to collapse, and have tan, yellow, or gray patches located especially in the dorsal diaphragmatic lobes. The histologic lesion in goats is a diffuse thickening of

alveolar septa, with a mononuclear cell infiltrate and alveolar epithelial hyperplasia that extends far beyond the area immediately around the parasite. The local reaction around the worm is quite variable and does not appear to produce the nodules seen in sheep.[42] Diagnosis is made by Baermann examination of the feces. The larvae are smaller than those of *D. filaria* and have a kink at the end of the tail with a characteristic subterminal accessory spine.[5]

Several anthelmintics have been used in the treatment of *M. capillaris* infections. Moxidectin (0.2 mg/kg in oral or injectable formulation) is effective in treating sheep infected with *M. capillaris* and other small lungworms (*Cystocaulus ocreatus, Neostrongylus linearis,* and *P. rufescens*) and may be equally effective in goats.[43] Although larvae may initially disappear in the feces after treatment, they often reappear in fecal samples again after 1 to 2 months because anthelmintics are ineffective against immature worms and/or because inhibited larvae resume development.[5] Treatments that appear to eliminate adult parasites in goats include fenbendazole (15 to 30 mg/kg),[41,42,44-47] albendazole (10 mg/kg),[562] oxfendazole (7.5 to 10 mg/kg),[563] and ivermectin (0.3 mg/kg).[44,48] *M. capillaris* is largely resistant to levamisole.[35] Better control of immature or inhibited larvae with fenbendazole was achieved by administering the drug (1.25 to 5 mg/kg) for 7 to 14 days, although a regimen of 1 week on/1 week off/1 week on appeared to provide the most effective treatment. Albendazole (1 mg/kg PO daily for 7 to 14 days) was also effective.[46] Possible teratogenic effects of extended benzimidazole treatment in goats have not been thoroughly investigated, and albendazole should be used cautiously in the first 35 days of pregnancy.[44] Administration of ivermectin (0.3 mg/kg) or fenbendazole (15 mg/kg) two or three times at 35-day intervals has also been suggested for treatment.[35] Control methods include avoiding wet pastures and treating animals before the start of the grazing season to reduce infection levels in the intermediate host.[35]

Protostrongylus rufescens.

P. rufescens also uses molluscan intermediate hosts, and adults develop in the small bronchioles of sheep and goats.[41] Most infections are probably subclinical or produce only mild signs of chronic bronchitis or bronchopneumonia with nasal discharge and cough. Occasionally *P. rufescens* may produce severe or even fatal disease.[47] The diagnosis of *Protostrongylus* spp. infection is made by

finding larvae in the feces with the Baermann technique. The larvae are similar to those of *Muellerius* except that *Protostrongylus* larvae lack the subterminal accessory spine on the tail.[5] Fenbendazole, levamisole,[49] and moxidectin[43] can be used for treatment at the dosages used for *Dictyocaulus*. Other macrocyclic lactone products also may be effective but have not been tested. Control strategies are identical to those for *M. capillaris*. Few cases of infection have been reported in the United States, but nonspecific clinical signs, presence of subclinical carriers, and need for a special diagnostic technique may produce an underestimation of the prevalence of *P. rufescens* infection in sheep and goats.[49]

Larval Toxocariasis.

The dog ascaridoid *Toxocara canis* will infect and persist in the tissues of sheep and goats following the ingestion of infective eggs from pasture.[50-52] Migration of the larvae through the lungs does result in diffuse pulmonary inflammation, but there do not seem to be any clinical pulmonary signs accompanying the experimental infections.[53,54] Examination of sheep serologically using antibody detection tests has revealed that the prevalence of infection increases with age, with overall prevalences being 50% or more in the older animals sampled in Wales and Brazil.[55,56] More recent reports have found high levels of antibodies to *T. canis* in sheep from Brazil, Mexico, and Greece, and the report from Greece indicated that the seroprevalence in sheep was 7.71-fold higher than that found in goats from the same area.[57-59]

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Bovine Tuberculosis

W. Ray Waters

■ Definition, Etiology, and Epidemiology

Tuberculosis (TB) in animals and humans may result from exposure to bacilli within the *Mycobacterium tuberculosis* complex (i.e., *M. tuberculosis, M. bovis, M. africanum, M. pinnipedii, M. microti, M. caprae,* or *M. canetti*). *Mycobacterium bovis* is the species most often isolated from tuberculous cattle, and it is infectious to humans (zoonotic). Within the United States, bovine TB is nearly eradicated in cattle; however, sporadic cases are detected primarily due to ongoing importation of tuberculous cattle from Mexico, spillover from a wildlife reservoir host (i.e., white-tailed deer, *Odocoileus virginianus*) in the northeast region of the lower peninsula of Michigan, transmission from captive cervids infected with *M. bovis,* and herd-to-herd transmission in the United States. From 1998 to March 2017, there were 144 TB-affected herds within the United States (60.4% beef, 29.9% dairy, 0.7% bison, 1.4% mixed, and 7.6% captive cervid). In Great Britain the prevalence of bovine TB has been steadily rising despite continuous compulsory testing, with 10% of cattle herds in England (22.7% in the South West region) under movement restriction and nearly 25,000 cattle slaughtered at a cost of £91 million.[1] This dramatic and steady rise in TB prevalence is most likely due to the failure of the tuberculin skin test and slaughter strategy as applied in Great Britain and the presence of a wildlife reservoir (Eurasian badgers, *Meles meles*).[1] Wildlife reservoirs also hinder eradication efforts in New Zealand and Spain, with continual spillover from brushtail possums *(Trichosurus vulpecula)* and wild boar *(Sus scrofa)*/red deer *(Cervus elaphus),* respectively.[2,3] In Latin American and Caribbean countries, bovine TB is relatively common, with estimates of 70% of cattle being held in regions with *M. bovis* prevalence rates greater than 1%.[4] In underdeveloped regions of Africa and Asia, bovine TB is endemic, causing significant economic losses for producers and public health concerns due to the close contact of humans and animals and the frequent consumption of unpasteurized milk. Bovine TB in African free-ranging species (e.g., African buffalo *[Syncerus caffer]* and lions *[Panthera leo]*) threatens wildlife conservation efforts and ecotourism, affecting the balance of entire ecosystems.[5] Tuberculosis in goats

and sheep, primarily due to *M. caprae* or *M. bovis*, is uncommon in the United States but may occur in other regions of the world (e.g., Spain, Italy, New Zealand, Ireland, United Kingdom, Sudan, and Africa).[6,7]

In most countries with active control programs, affected cattle herds contain few infected animals suggestive of low rates of cattle-to-cattle transmission and a slowly progressive course of disease.[8] Transmission is generally by direct contact with TB-infected animals, as the organism may occur in exhaled droplets, saliva, feces, milk, urine, vaginal discharges, semen, or exudate from tuberculous lesions (e.g., lymph nodes with draining tracts that communicate to the exterior). Infection of the upper respiratory tract, pharyngeal area, and GI tract may also result from ingestion of infected feeds.[9] Housing (e.g., milking parlors, cattle sheds) and crowding increase the contact of naive animals with infected animals and enhance the spread of this disease. *M. bovis* is also transmitted by indirect contact through contaminated feed and water, feeding and watering equipment, cleaning equipment, or movements of personnel (i.e., anything that mechanically transfers the organism between locations). Movement of infected animals resulting from transfer of ownership, sharing of breeding animals, and fence-line contact with other herds is a common means of transferring the disease between herds and regions. In addition, global trade agreements are increasingly being implemented to promote international trade of livestock, thereby significantly increasing risks for interregional spread and distribution of TB over great distances.

Primary control strategies for bovine TB include diagnosis via tuberculin skin test and/or interferon-gamma release assays, isolation of affected herds, subisolation of infected animals within affected herds (i.e., Bang method), slaughter of infected animals, slaughter surveillance, and movement or border testing policies.[10] In addition to these traditional methods, antibody-based tests have recently emerged to detect *M. tuberculosis*–infected elephants,[11,12] *M. bovis*–infected captive cervids,[13] and on occasion *M. bovis*-infected cattle.[14] Also, molecular-based tools such as mycobacterial interspersed repetitive-unit–variable-number tandem-repeat (MIRU-VNTR), spoligotyping, and restriction fragment length polymorphism (RFLP) analysis of mycobacterial DNA are used to characterize mycobacterial isolates for epidemiologic investigations to determine potential links between new cases and prior outbreaks as well as the likely origin of infection. Most recently, high-throughput whole genome sequencing and rapid sequence analysis tools have been developed for a more

thorough comparison of relatedness between *M. tuberculosis* complex isolates obtained from livestock, wildlife, humans, and zoo species; this technology is rapidly replacing MIRU-VNTR, spoligotyping, and RFLP for determining relatedness of *M. tuberculosis* complex strains from livestock and wildlife.[15]

■ Clinical Signs and Antemortem Diagnosis

In most animals the disease is slowly progressive; however, bovine TB occasionally follows a more rapid, fulminating course with early dissemination. Most animals do not show clinical signs of *M. bovis* infection until late in the course of the disease. Clinical signs, when present, are often nonspecific (e.g., weight loss, inappetence, low-grade fluctuating fever) and vary according to the organs involved. Respiratory signs are generally mild and may include a soft, moist cough more noticeable during cold weather and after exercise. In advanced stages, animals may exhibit obvious dyspnea, emaciation, and respiratory distress. Enlarged lymph nodes may rupture and drain. Enlarged mediastinal lymph nodes may cause bloat. Enlarged retropharyngeal lymph nodes, a frequent sequela in cervids, may cause dysphagia, stridor, and salivation. Enlarged mesenteric lymph nodes may cause intestinal obstructions. Lesions occur less frequently in peripheral lymph nodes, the reproductive tract (causing infertility, abortion, metritis, and vaginitis), and mammary gland. Particularly with chronic cases, tuberculous mastitis may occur with the potential for transfer of *M. bovis* to humans, calves, cats, or other animals through ingestion of unpasteurized dairy products.

The tuberculin skin test remains the primary tool for the diagnosis of bovine TB. Specific applications of the tuberculin skin test, however, vary according to regional and country directives.[10] Primary screening tests may use a single injection of *M. bovis* purified protein derivative (PPD) applied either to the skin fold at the base of the tail (e.g., caudal fold test used in New Zealand, the United States, Canada, and Mexico) or to the skin of the midcervical region (e.g., in many European Union member states). Alternatively, a dual injection of *M. avium* and *M. bovis* PPD may be applied to separate midcervical sites as the primary screening test (in Great Britain, Ireland, and Portugal) or as a confirmatory test (in the United States and Canada). An interferon-gamma release assay (e.g., Bovigam™ [Prionics, Schlieren, Switzerland]; ID-Vet, Montpellier, France) is also used as a confirmatory test in many countries.[10,16] Bovine TB test specificity differs regionally, most likely due to variations in

application techniques (including differences in PPD usage), environmental factors, and co-infection (e.g., parasite burden[17]). In particular, it is widely recognized that exposure of cattle to various nontuberculous *Mycobacteria* spp. may confound interpretation of PPD-based tests. The use of dual injection of *M. avium* and *M. bovis* PPDs at separate sites was developed to address this issue, and comparative tests improve test specificity with only a slight loss in test sensitivity when compared to single-injection tests (e.g., caudal fold test). Recently, *M. tuberculosis* complex–specific antigens such as ESAT-6, CFP10, and Rv-3615c have been developed for use with interferon-gamma release assays and skin tests.[18] These antigens are generally not produced by nontuberculous *Mycobacteria* spp., including *M. avium* subsp. *paratuberculosis*[19]; thus they afford greater specificity with only minimal loss in test sensitivity.

■ Pathophysiology, Necropsy Findings, and Differential Diagnosis

While often viewed as a pulmonary disease in humans, TB is primarily a disease of the lymphatic system. With ruminants, tuberculous lesions are most commonly detected within pulmonary and cranial lymph nodes as well as lungs. In naturally infected cattle, 67% of tuberculous lesions are detected in lungs and pulmonary lymph nodes, 39% in cranial lymph nodes, and 8% in mesenteric lymph nodes.[20] Lesions are most commonly detected in the medial retropharyngeal lymph nodes of tuberculous white-tailed deer[21]; lungs, pulmonary lymph nodes, and pleura are also common sites of lesions in deer. In pigs (i.e., Eurasian wild boar and free-ranging domestic black pigs), tuberculous lesions are most commonly detected in the cranial lymph nodes, and dissemination is common.[22,23] With experimental infection, infectious dose affects disease severity and progression; animals exposed to high doses develop an earlier onset of lesions with greater severity than animals exposed to lower doses. The infectious dose of *M. bovis* for ruminants is quite low. For instance, intratracheal administration of one colony-forming unit (~6 to 10 bacilli) may cause disease.[24]

M. tuberculosis complex bacilli (including *M. bovis*) infect cells primarily of monocyte or macrophage lineage yet may also be found within type II alveolar epithelial cells, dendritic cells, neutrophils, and a few others. The pathognomonic lesion of *M. bovis* infection is the granuloma. Tuberculous

granulomas form in response to pathogen virulence factors and chronic antigen stimulation (due to persistent infection). Granulomatous inflammation is thought to limit the spread of tuberculous bacilli within the host by walling off the organism. The combination of the initial site of infection and the regional (i.e., draining this site) lymph node constitutes the primary complex commonly referred to as Ghon's complex with pulmonary *M. tuberculosis* infection in humans. Dissemination from the primary complex occurs via both lymphatic and hematogenous spread. Particularly in cases of prolonged or severe disseminated disease, determination of the primary complex may be impossible, confusing speculation on the initial route of infection. When infection occurs across mucous membranes, such as the oropharynx or intestine, the initial lesion in the mucous membrane may not be visible. whereas lymph node lesions are generally obvious.[25] From the initial site of entry, the organism invades local lymph nodes, where it causes necrosis surrounded by granulomatous inflammation consisting of primarily mononuclear cells. Localized lesions stimulate development of a fibrous capsule that varies in severity depending on the rate of development and chronicity of infection. Postprimary dissemination may occur, leading to spread of the organism and resulting in discrete nodular lesions in various lymph nodes and organs. Diffuse miliary TB may occur in severe cases. Latency, although a common sequela with *M. tuberculosis* infection of humans, is typically not considered a common stage of disease with *M. bovis* infection of cattle; however, *M. bovis* may be isolated from tissues without visible gross lesions, indicating a potential for “latent” infection.

Postmortem diagnosis is based on (1) gross and microscopic evaluation for tuberculous lesions, (2) detection of the organism by mycobacterial culture within tissues, with follow-up confirmation or characterization using molecular techniques, (3) direct detection of *M. tuberculosis* complex DNA within tuberculous lesions, and (4) detection of *M. tuberculosis* complex–specific DNA by PCR on histologic sections. Often multiple lesions are detectable on examination, although infected cattle may display no grossly visible lesions or only a single visible lesion. Macroscopic lesions appear as firm, encapsulated nodules and vary in size from barely visible to greater than 100 mm in diameter. Lesions may contain thick, white to yellow-orange, creamy to caseous purulent material. Lesions may be calcified. Lymph nodes, organs, and pleural or peritoneal serosa may be riddled with small miliary tubercles, and in the lungs these lesions may coalesce into a suppurative bronchopneumonia. Granulomas along the pleural serosa (i.e., pearl disease) often appear glossy. Chronic lesions

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are characterized by a discrete, thickened fibrous to calcified capsule, often containing thick caseous material. Lesion cavitation due to *M. bovis* infection in cattle is rare. Microscopically, lesions in lymph nodes or organs are granulomatous, generally consisting of caseous necrosis surrounded by infiltrates of epithelioid macrophages, Langhans-type multinucleated giant cells, and lymphocytes. Lesions with necrotic cores may contain dystrophic calcification. Detection of acid-fast bacilli within granulomatous lesions in tissue sections provides a preliminary diagnosis of mycobacterial infection that must be confirmed by mycobacterial culture and PCR. Acid-fast bacilli are often few in number and most commonly detected within the caseum of the necrotic core. Resolving lesions are thought to be rare. Lesion development can be divided into four different stages primarily based on the level of necrosis, fibrous encapsulation, and mineralization: stage 1 (no necrosis), stage 2 (minimal central necrosis, thin connective tissue capsule), stage 3 (central caseous necrosis with complete fibrous encapsulation), and stage 4 (extensive multicentric caseous necrosis with mineralization). Differentiation between the thickness of the fibrous capsule and the histopathologic stage of development may assist in determining the chronicity of the infection.

Mycobacterial culture is the gold standard for TB diagnosis. *M. bovis* grows slowly, and cultures are generally incubated for 8 weeks; growth usually becomes visible within 3 to 6 weeks. The identity of the organism in cultures may be determined with biochemical tests, colony morphology, and *M. tuberculosis* complex–specific PCR. Potential pathogens for consideration in differential diagnosis include nontuberculous *Mycobacteria* spp., *Nocardia* spp., *Arcanobacterium pyogenes*, *Corynebacterium pseudotuberculosis* (caseous lymphadenitis in goats and sheep), and mycotic infections. In particular, nontuberculous mycobacteria (e.g., *M. avium* subsp. *paratuberculosis*, *M. avium* subsp. *avium*, *M. kansasii*, and many others) are common isolates within tissues obtained from domestic livestock and wildlife. Johne's disease, caused by *M. avium* subsp. *paratuberculosis*, is common in domestic livestock, causing a mild to severe granulomatous enteritis. Other nontuberculous mycobacteria occasionally cause clinical disease resulting in granulomatous lesions in lymph nodes, lungs, and visceral organs.

■ Treatment, Prevention, and Control

Bovine TB is rarely, if ever, treated in domestic livestock. Particularly in developed countries, affected animals are slaughtered to limit potential

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transmission to other animals and to limit the duration and severity of regulatory restrictions. Antimycobacterial therapy may be indicated for rare or endangered animals or for those considered valuable as zoologic exhibits.[11] Antituberculous first-line chemotherapies include isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin. These agents have the greatest activity with the least undesirable side effects. Second-line agents include capreomycin, ethionamide, cycloserine, and thiacetazone. The fluoroquinolones (moxifloxacin, ciprofloxacin, levofloxacin, and enrofloxacin), although not considered first-line agents, have significant bactericidal activity against *M. tuberculosis* complex species. Outside of these rare cases, treatment for TB in animals is generally not considered practical on a cost basis.

Many countries have official bovine TB eradication or control programs, including uniform methods and rules for application of the programs. Prevention and control efforts are designed to identify affected herds and remove infected animals or depopulate the entire herd (stamping out). These efforts are generally achieved via routine slaughter surveillance to identify affected herds, targeted testing schemes to remove TB test–positive animals (reactors), movement restriction of affected herds, thorough epidemiologic investigations of reported cases to determine risks for other affected herds, and depopulation of affected herds. In addition, movement testing with certification of a negative TB tests may be required prior to entry of animals into certain countries or regions. In certain instances, entry of animals from known TB-affected regions may not be allowed. Specific regulations and rules concerning bovine TB control are provided within specific country and regional directives.[1,26,27] Due to limitations in the sensitivity of antemortem diagnostic tests for tuberculosis, depopulation of infected herds is thought to be the most effective means to ensure eradication of the disease from the target population. Surveillance and control of *M. bovis* infection in wildlife reservoirs, as well as mitigation efforts to limit spread from wildlife to livestock, are also critical for bovine TB control.

In instances where herds are depopulated and the owner intends to repopulate in the future, it is important to remove or thoroughly clean and disinfect facilities and equipment potentially exposed to the organism. The ability of *M. bovis* to survive for an extended period in the environment, and the ineffectiveness of disinfection of organic materials, necessitates that pastures and fields to be used in repopulation schemes be left vacant for a period prior to use. Instances of infection that are thought to originate from wildlife sources may precipitate changes in facilities, management and feeding practices, or wildlife control to

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prevent reinfection. Current experience with endemic *M. bovis* infections in wildlife in numerous countries has demonstrated that eradication of TB in free-ranging wildlife is difficult and a long-term proposition. Vaccines are rarely used for the control of bovine TB in regions with official control programs, primarily due to the potential for interference with traditional antemortem testing using PPD as antigen (i.e., tuberculin skin test and interferon-gamma release assays).[28] Bacillus Calmette-Guérin (BCG) is an attenuated *M. bovis* developed by Albert Calmette and Camille Guérin circa 1911 at the Pasteur Institute in Lille, France. Field efficacy trials performed in the early twentieth century demonstrated the partial effectiveness of BCG for the control of bovine TB.[28] Recent experimental trials with cattle have demonstrated that (1) subunit vaccines may boost immunity elicited by BCG in cattle, (2) BCG is particularly protective when administered to neonates, and (3) differentiation of infected and vaccinated animals is feasible in cattle using in vitro or in vivo methods.[18,28] In regard to wildlife reservoirs, the efficacy of BCG delivered orally has been demonstrated for brushtail possums (in field trials) as well as for Eurasian badgers, wild boar, and white-tailed deer (each in experimental challenge studies). The most practical route of vaccine delivery to wildlife reservoirs of *M. bovis* is via oral-delivered baits, although a parenteral route is being used for badgers in England. Additional research is needed in the areas of diagnostic testing, environmental sampling, vaccine development, and management practices that may decrease the risk of disease spillover from wildlife reservoirs to cattle.

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Other Pneumonias*

Amelia R. Woolums

Aspiration Pneumonia

Aspiration pneumonia is caused by inhalation of large amounts of foreign material, often liquids. The most common cause is careless drenching or passage of stomach tubes during administration of milk or liquid medication. It also occurs occasionally in pail-fed calves, animals with pharyngeal paresis, animals with necrotic laryngitis, lambs with nutritional myodegeneration, anesthetized animals, sheep that are dipped, cattle that have parturient paresis, and cattle that ingest crude oils or fuel oils. Meconium aspiration secondary to fetal distress has been recognized as a possible risk factor of neonatal calf mortality.[1]

If large quantities of fluid are aspirated, death may be almost instantaneous, but generally a gangrenous bronchopneumonia develops as a result of infection and the irritating properties of the inhaled material. Affected animals exhibit depression, tachypnea, dyspnea, coughing, and fever and may have putrid breath. Crackles, wheezes, and occasionally pleural friction rubs can be heard on auscultation.

A presumptive diagnosis is based on the history and clinical evidence of bronchopneumonia; definitive diagnosis can be confirmed by gross or histopathologic identification of feed, milk, or other aspirated material in airways. Differential diagnoses include acute bacterial bronchopneumonia and septicemia. Necropsy reveals consolidation of the anterior ventral areas of the lungs. Affected areas are severely hemorrhagic in acute cases and contain suppuration and liquefactive necrosis in subacute cases.

The prognosis is guarded in all cases of aspiration pneumonia, but some animals can be successfully treated. Antibiotics combined with antiinflammatory agents should be promptly administered, and long-term antimicrobial therapy (weeks) is required. Prevention of aspiration pneumonia centers on careful administration of medication and avoidance of other risk factors that may promote inhalation of foreign materials.

Mycotic Pneumonias

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Fungal pneumonia is a rare occurrence in ruminants. The clinical presentation is typically one of poor response to antimicrobial therapy. Cases of fungal pneumonia with metritis or placentitis have been reported.[2,3] Diagnosis is confirmed by identification of fungal organisms with an inflammatory reaction in tracheal aspirate or bronchoalveolar lavage, or at postmortem with fungal culture to confirm the identity of the agent. Little information is available regarding successful treatment of ruminants with fungal pneumonia. In other species such as horses, treatment requires weeks to months of therapy with antifungal agents such as ketoconazole or itraconazole; these drugs may be cost prohibitive for many ruminant cases, and their disposition in the rumen has not been described. Therapy with oral potassium iodide is an inexpensive alternative that may be attempted for some cases, but the efficacy of this therapy has not been confirmed. Prognosis for fungal pneumonia in all species is guarded to poor, depending on the severity of disease and the feasibility of treatment. Given these restrictions, treatment of fungal pneumonia in ruminants is likely reserved for valuable individuals. More guidelines regarding treatment for fungal pneumonia are presented in the section on equine respiratory diseases.

Vena Caval Thrombosis and Metastatic Pneumonia

■ Definition and Etiology

Metastatic or embolic pneumonia in cattle, also called *caudal vena caval thrombosis, pulmonary thromboembolism,* and *embolic pulmonary aneurysm,* is a distinct syndrome associated with multifocal abscessation of the lungs caused by septic thromboembolism of the pulmonary arterial system. The septic emboli arise from septic thrombi of the caudal vena cava (Fig. 31.69) or, less commonly, the cranial vena cava. Vena cava thrombi are in turn a sequela to various septic conditions such as jugular phlebitis, mastitis, metritis, foot rot, or, most often, liver abscesses secondary to rumenitis.[4] A variety of bacteria may be involved; those most frequently encountered include *F. necrophorum, A. pyogenes,* staphylococci, streptococci, and *E. coli.*



FIG. 31.69 Postmortem photograph of thrombus in caudal vena cava, which leads to embolic pneumonia demonstrated in Color Plate 31.10. (Photograph contributed by Feedlot Health Management Services, Okotoks, AB, Canada.)

■ Clinical Signs

Because of its association with rumenitis, this condition is most commonly seen in feedlot cattle, but any age, breed, sex, and class of cattle may be affected. The problem is unusual in cattle younger than 1 year of age. Cattle with metastatic pneumonia usually exhibit respiratory disturbance or weight loss or occasionally thoracic pain. The clinical signs in affected cattle have been described.[5,6] The classic presentation includes tachycardia, tachypnea, dyspnea, coughing, heart murmurs and pale mucous membranes (caused by anemia), widespread wheezes, epistaxis, and hemoptysis. The duration of signs is quite variable, ranging from acute respiratory distress to a chronic history of weight loss and coughing for weeks to months. Other signs, which are more variable, include fever, thoracic pain on deep palpation of the sternum and intercostal spaces, hepatomegaly (indicated by the ability to palpate the caudal edge of the liver in the right paralumbar fossa), subcutaneous emphysema, froth at the muzzle, and melena caused by coughing up and swallowing blood. Nonspecific accompanying signs include depression, anorexia, ruminal stasis, scant feces, and decreased milk production. In chronic cases, cor pulmonale may lead to signs of right ventricular failure such as jugular distention and brisket edema. The combination of respiratory signs with anemia, widespread wheezes, and especially

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hemoptysis is generally regarded as pathognomonic for this syndrome. Animals usually deteriorate rapidly once hemoptysis becomes evident, and death despite treatment is typical. Many patients die suddenly with an acute episode of severe intrapulmonary hemorrhage or hemoptysis after a variable course of respiratory disease. Some of these cases in which the respiratory signs were overlooked may account for the reports of sudden death attributed to vena caval thrombosis. Caudal vena caval thrombosis can also lead to hepatomegaly and extensive ascites, but most of these animals also have respiratory signs.[6] Sudden erosion of a large hepatic abscess into the caudal vena cava may also result in a massive embolic shower, with acute respiratory distress and death.

In patients with the pathognomonic signs (the majority of cases), no differential diagnoses need be considered. However, many patients are examined before the onset of hemoptysis, and a few may die without exhibiting these signs. Differential considerations in such cases, which usually manifest as acute dyspnea, should include anaphylaxis, various causes of ARDS, hypersensitivity pneumonitis, lungworms, and acute bronchopneumonia. Patients with right ventricular failure should be differentiated from those with pericarditis, lymphosarcoma, cardiomyopathy, and endocarditis.

■ Pathogenesis

The pathogenesis of this disease begins with the development of rumenitis secondary to lactic acidosis caused by highly fermentable diets such as those used in feedlots, some dairies, and some growing rations. Bacteria such as *F. necrophorum* and *A. pyogenes* are then able to penetrate the damaged ruminal epithelium and are transported to the liver in the portal drainage system, where they are filtered out and result in abscesses. If an abscess is located next to the caudal vena cava (where the vessel is closely applied to the left border of the liver), a septic thrombus may form in the vena cava as a result of infiltration of its wall by the abscess (see Fig. 31.69). Septic emboli detach from the thrombus and reach the lungs through the pulmonary arterial system. Alternatives to this classic pathway are rare; they include thrombosis of the cranial vena cava from primary lesions such as jugular phlebitis, thrombosis of the caudal vena cava from other subdiaphragmatic abscesses, right-sided endocarditis, and emboli arising from other septic foci such as mastitis, metritis, and foot rot. Large emboli may block lobar or larger arteries, causing an acute crisis and death. More typically, smaller emboli lodge in arterioles, where they cause arterial thromboembolism, arteritis, endarteritis, and pulmonary abscesses (Color Plate

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31.10). The widespread arterial embolism also results in pulmonary arterial hypertension. Arteritis and endarteritis weaken the vessel walls and, in combination with pulmonary hypertension, lead to the formation of aneurysms. In some cases a perivascular abscess not only erodes an arterial wall to produce an aneurysm but also simultaneously erodes a bronchial wall; when the aneurysm ruptures, the abscess cavity channels the blood into the bronchus, resulting in massive hemoptysis. In other cases, rupture of aneurysms results in large interstitial hematomas. Both processes result in anemia; when coughed-up blood is swallowed, melena may result. Coughing and wheezes are probably caused by blood clots in airways, peribronchial aneurysms and abscesses, and suppurative pneumonia. Pain results from dissecting aneurysms and hematomas.

■ Epidemiology

Metastatic pneumonia accounted for 1.3% of necropsy diagnoses in one large feedlot survey, with a rate varying between 1.6 and 7.3 cases per 100,000 head on feed. Cases occurred year round and during all stages of fattening, although 68% of cases occurred during the first 90 days on feed.[7] The case fatality rate is high.

■ Necropsy

Almost all patients with significant hemoptysis have a thrombus in the posterior vena cava between the liver and the right atrium. There is usually an adjacent hepatic abscess, varying degrees of venous congestion of the liver, and hepatomegaly. The lungs are large, uncollapsed, and firm. Aneurysms may occur in either lung or both. Hematomas associated with ruptured aneurysms are frequently 3 to 10 cm in diameter. Large blood clots may be found in the airways, aspirated blood may be found in the alveoli, and swallowed clots may be found in the rumen. Areas of suppurative pneumonia and multiple abscesses are present (see Color Plate 31.10).

■ Diagnosis

The CBC may reveal anemia and a neutrophilic leukocytosis with a regenerative left shift. Hyperglobulinemia is frequently present. Serum chemical analysis may reflect chronic passive congestion of the liver, with elevation of liver enzymes. Radiographs often reveal only an irregular increase in lung density. Small discrete densities (areas of embolic infarction and collapse); large, discrete,

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spheric opacities (hematomas); cavitating nodules, sometimes with gas-fluid interfaces (abscesses); bullae; and areas of consolidation may be observed in some cases.

■ Treatment and Prevention

The prognosis is grave, so treatment is rarely indicated, and salvage is the most feasible recommendation. In valuable individuals, antibiotics and supportive therapy may be attempted. Penicillin, oxytetracycline, or florfenicol may be effective; treatment should be administered for extended periods (weeks to months). Supportive therapy for cases with acute severe dyspnea includes furosemide (0.5 to 1 mg/kg IV or IM once or twice daily) and flunixin meglumine (1.1 to 2.2 mg/kg once or divided twice daily). One or two doses of corticosteroids (dexamethasone, 0.05 to 0.2 mg/kg IV or IM q24h) may be helpful in cases with severe respiratory distress.

Based on the assumption that rumenitis and liver abscesses are the first steps in the pathogenesis of most cases, measures to reduce the incidence of these problems are appropriate. Recommendations include slow adaptation of animals to high-energy rations and feeding of antibiotics to reduce the incidence of liver

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Diseases of the Thoracic Wall and Cavity*

Amelia R. Woolums

Pleuritis and Pleural Effusions

■ Definition and Etiology

Acute, primary pleuritis is rare in ruminants. It is almost always a secondary condition. The most common primary cause is most likely bronchopneumonia caused by *M. haemolytica* or *H. somni*. Other possible causes of pleuritis and pleural effusions include traumatic reticulopericarditis, extension from other causes of peritonitis, tuberculosis, liver abscesses, tumors (especially lymphosarcoma), external trauma, fractured ribs, gunshot, perforating injuries, various septicemic conditions, acorn toxicity and other causes of uremia, uroperitoneum, right ventricular failure, hypoproteinemia, ruptured thoracic duct, and hemothorax from trauma or hemangiosarcoma.

■ Clinical Signs

The signs depend on and may be overshadowed by the primary disease process. Pleuritis is a painful, septic process, whereas the signs associated with nonseptic effusions depend largely on the cause. Signs referable to pleuritis itself include anorexia, depression, fever, weight loss, decreased milk production, progressive dyspnea, and a characteristic stance and respiratory pattern, with the head and neck extended, elbows abducted, restricted excursion of the thorax, abdominal breathing, tachypnea, and a grunting or groaning with respiration. The animal may be reluctant to move. If a cough is present, it is often soft and suppressed because of pain. Jugular distention and pulsation may result from interference with venous return. Auscultation may reveal creaking or rubbing noises in dry pleuritis or a cranial-ventral masking of sounds caused by effusion. Percussion may reveal dullness ventral to the fluid line and may elicit pain. Differential diagnoses for dyspnea with abnormally quiet lung fields may include acute interstitial pneumonia, pneumothorax, and space-occupying lesions such as large abscesses, tumors, and diaphragmatic hernia. Once pleuritis or pleural effusion has been identified, the main differential diagnostic consideration is the

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determination of the underlying cause, as listed previously.

■ Diagnosis

A CBC helps separate infectious causes from noninfectious causes and distinguish relatively acute conditions (with significant left shifts) from those of a more chronic nature (with mature neutrophilia, hyperglobulinemia, and nonregenerative anemia of chronic disease). Serum chemical determinations and urinalysis identify hypoproteinemia and azotemia. A thoracocentesis should be performed and submitted to cytologic and cultural examination for bacteria, mycoplasma, and chlamydia. Nonseptic transudates indicate conditions such as neoplasia, heart failure, hypoproteinemia, and uremia. Septic exudates high in both cells and protein occur with pleuropneumonia, hardware, peritonitis, abscesses, penetrating trauma, and septicemias. A transtracheal wash is usually indicated because of the common association with pneumonia. Pericardiocentesis, abdominocentesis, and radiographs may indicate the primary source of an infection. Tuberculosis tests, leukemia virus titers, electrocardiography, echocardiographic examinations, ultrasonographic examination of the liver, and exploratory laparotomy may also help detect other primary processes.

■ Treatment

The primary problem should be treated. Effusions should be drained, either periodically or continuously through a Heimlich valve or a suction device fashioned from a syringe with the plunger transfixed with a pin. Effective drainage can be difficult in ruminants because of their propensity for fibrin formation and loculation of the fluid. Intermittent drainage is as effective as continuous drainage and simpler to maintain. Attempts at lavage have rarely been successful because of adhesions. Appropriate antibiotics are indicated in the presence of sepsis. NSAIDs (flunixin meglumine, 1.1 to 2.2 mg/kg IV or divided twice daily) are useful to relieve pain, ease respiration, and improve appetite. Rest and good nursing care are essential. The prognosis obviously depends on the extent and duration of the disease.

Pneumothorax

Pneumothorax is not common in ruminants. Most cases result from the rupture of an emphysematous bulla associated with pneumonia, straining, or coughing or

from puncture of the lung by a fractured rib. The bullae that occur in BRSV-induced pneumonia are a common source. Trauma to the pharynx or larynx can also lead to pneumothorax, presumably caused by air traveling from the cranial cervical regions through soft tissues and into the thoracic cavity. Penetration from the exterior is possible but less common. A case has been described in a postparturient cow with no other underlying cause found.[8] A retrospective study of 30 cattle with pneumothorax presented to a referral hospital found that 18 of the cases (60%) were associated with bronchopneumonia, 7 cases were associated with interstitial pneumonia, 3 cases were associated with laryngeal or pharyngeal trauma, and 2 cases were associated with neonatal respiratory distress.[9] Of interest was the finding that 13 of the 18 cases with bronchopneumonia were chronic, based on history and diagnostic findings; an association between pneumothorax and chronic bronchopneumonia had not been previously reported. The rate of survival for cattle with pneumonia and pneumothorax was lower than for cattle presented with pneumonia without pneumothorax, with an overall survival rate of 60% for cattle presented with pneumothorax.

Clinical signs of pneumothorax include inspiratory dyspnea, sometimes severe, with open-mouth breathing sometimes present. One side of the thorax may be relatively collapsed and immobile, with a compensatory increase in the size and excursion of the other side; however, this latter finding is often subtle and difficult to appreciate. Ruminants have a complete mediastinum; thus when pneumothorax occurs it is usually unilateral, and the animal is able to ventilate adequately using the opposite lung. Unless an infectious disease is responsible, affected animals are often alert and anxious. They may attempt to stand with the forefeet elevated. There is a pronounced abdominal component to the respirations. Cyanosis may occur, and airflow may be markedly reduced in severe cases. On auscultation there is an obvious disparity between the two sides; bronchovesicular sounds will be diminished dorsally on the affected side or may be entirely absent. Those lung sounds that are audible have a harsh, high-pitched, large airway character similar to those of a consolidated lung, especially over the carina; these sounds seem to be distant, as if the animal were breathing in a barrel. The point of maximum intensity of the heart may be displaced, and tachycardia is often present. Percussion may reveal an abnormal resonance when compared with that of the normal side, and simultaneous auscultation and percussion may produce a “ping” over the thorax. Subcutaneous emphysema is a fairly common feature, and pleuritis is often a sequela. Differential diagnoses of

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the inciting cause should include the various causes of ARDS, bronchopneumonia, viral pneumonias (especially BRSV), pleural effusions, diaphragmatic hernia, other space-occupying lesions (large abscesses, tumors), and clostridial infections. Pneumothorax can be diagnosed with radiographs, transthoracic ultrasound, or thoracocentesis; radiographs and ultrasound will also be useful to characterize the extent of any underlying lung disease. Other diagnostic tests to characterize underlying lung disease as described for infectious bronchopneumonia or interstitial pneumonia are appropriate.

If the affected animal shows signs of significant distress, the air in the pleural space should be evacuated. Evacuation can be accomplished by aseptically placing a teat cannula into the thoracic cavity at the dorsal aspect of the thorax at the tenth intercostal space and withdrawing air by use of an extension set, three-way stopcock, and syringe. In some cases this method can be successfully used to intermittently remove air; in other cases, continuous removal with a pleural evacuation device (Pleur-evac A-8000 [Deknatel Inc., Fall River, Mass.]) has been more effective.[10] If continuous evacuation is attempted, the animal must be adequately restrained; this is likely to be possible only with hospitalized animals. Other treatment includes therapy appropriate for underlying acute or chronic pneumonia as described previously for infectious bronchopneumonia or interstitial pneumonia. External wounds allowing air to enter the thorax should also be closed if present.

Diaphragmatic Hernia

■ Definition and Etiology

Diaphragmatic hernias are uncommon in ruminants. Hernias may be congenital, but most appear to be acquired, including those occurring in neonates. A congenital weakness in the diaphragm may predispose to some cases. Causes include difficult parturition, external trauma, and, by far the most common cause, traumatic reticuloperitonitis (TRP).

■ Clinical Signs and Differential Diagnosis

Affected animals can be asymptomatic for a prolonged period.[11] Most affected cattle are in late gestation or have calved recently. The history may include decreased milk production, weight loss, capricious appetite, difficulty in swallowing or regurgitation, previous signs of abdominal pain (possibly

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associated with acute TRP), vomiting, and abnormal posturing of the head and neck on swallowing or regurgitation. Respiratory signs are actually fairly uncommon, with the exception of large congenital hernias, in which there is obvious severe dyspnea and abdominal respiration from birth. Occasional cough and dyspnea have been reported, and auscultation may reveal asymmetric sounds, with lack of lung or heart sounds in the affected area, or splashing sounds similar to those heard with pericarditis. GI signs are actually more common and include bloat, signs consistent with TRP, difficulty or pain on passage of a stomach tube, diarrhea, constipation, and ruminal hypomotility. Some cows may retch or vomit on regurgitation. Pain is evidenced by odontoprisis or grunting on regurgitation. The primary differential diagnoses are TRP, pericarditis, esophageal stricture, esophageal foreign body (choke), neoplasia, and abscessation.

■ Diagnosis

Radiographs can be used to confirm the diagnosis. The normal outline of the diaphragm and heart may be obscured, and the honeycombs or foreign objects in the reticulum may be seen in the thorax because this organ is most commonly involved. Oral barium may also aid in the radiographic interpretation, particularly in early small hernias that will be missed on plain films. Pleuritis and other masses such as tumors and abscesses can also mimic hernias on plain films. If TRP is involved, the CBC, pleural effusions, and abdominocentesis may reflect the septic process. In cases not associated with TRP, the pleural effusion may be hemorrhagic in acute cases and normal in chronic cases.

■ Necropsy

The hernial ring is usually located at the junction of the musculotendinous portion of the diaphragm, about 12 cm ventral to the vena cava and slightly lateral to the midline. The ring is usually round to oval, with a diameter of 7 to 20 cm. The reticulum is usually herniated, most frequently to the right side of the chest. The liver, spleen, rumen, omasum, abomasum, intestine, and omentum may also be involved. Extensive adhesions usually develop between the herniated organs and the thoracic organs, and evidence of hardware can often be found.

■ Treatment and Prognosis

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Treatment is surgical. A two-stage approach is usually used. First, a standing left flank laparotomy and rumenotomy are performed; the defect is identified, foreign bodies are removed, and the ruminoreticulum is emptied. Because of the complete mediastinum, ventilatory assistance is rarely needed during this stage. Next, the animal is placed under general anesthesia with positive pressure ventilation. Various approaches have been used for this portion, including ventral midline, paramedian, semilunar postxiphoid, paracostal, and transthoracic with rib resection. The hernia is reduced, and the rent is repaired with sutures or mesh grafts. Mesh grafts are contraindicated if infection is present.

Pleural Mesothelioma

Mesotheliomas have been reported in cattle and goats,[12] including a congenital form in calves.[13] Most are peritoneal, but pleural mesotheliomas also occur.[14] Mesotheliomas result in the accumulation of large amounts of fluid in the involved body cavity; signs of pleural mesothelioma are therefore related to pleural effusion. They include dyspnea, tachypnea, decreased lung and heart sounds (sometimes unilateral, with a concomitant increase in sounds on the normal side), dullness on percussion, exercise intolerance, cyanosis, tachycardia, anorexia, weight loss, decreased production, cough, and weak pulses. If peritoneal lesions are also present, as is common but not universal, ascites is also present. Radiographs confirm the pleural effusion, and thoracocentesis yields a serous, sometimes blood-tinged or gelatinous fluid. Cytologic examination may reveal reactive mesothelial cells. At necropsy the pleura is thickened and contains multiple nodules of gray to yellowish-white tissue measuring several millimeters to several centimeters in diameter. Metastasis is uncommon. The tumor can be difficult to diagnose histologically and may resemble inflammation, pleural tuberculosis (“pearl disease”), or metastasis of another tumor.[13] There is no treatment.

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Miscellaneous Conditions*

Amelia R. Woolums

Lung Tumors

Lung tumors are uncommon in large animals. Those reported include pulmonary alveolar carcinomas, pulmonary adenomas, pulmonary adenocarcinomas, bronchogenic carcinoma, and pulmonary blastoma.[15,16] Malignant forms metastasize to regional lymph nodes and occasionally to other organs. Lymphosarcoma is the most frequent neoplasm to become metastatic to the lung, and uterine and ovarian adenocarcinoma may undergo metastasis to the lung. Because many lung neoplasms in cattle are incidental findings at slaughter or necropsy, clinical signs are therefore not well documented. The lesions are typically discrete, round, yellow to gray masses distributed throughout the lung tissue. Tumors are most likely to be detected antemortem by radiographic examination. Differential diagnoses in such cases include pulmonary abscesses, mycotic pneumonias, and tuberculosis.

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Color Plates

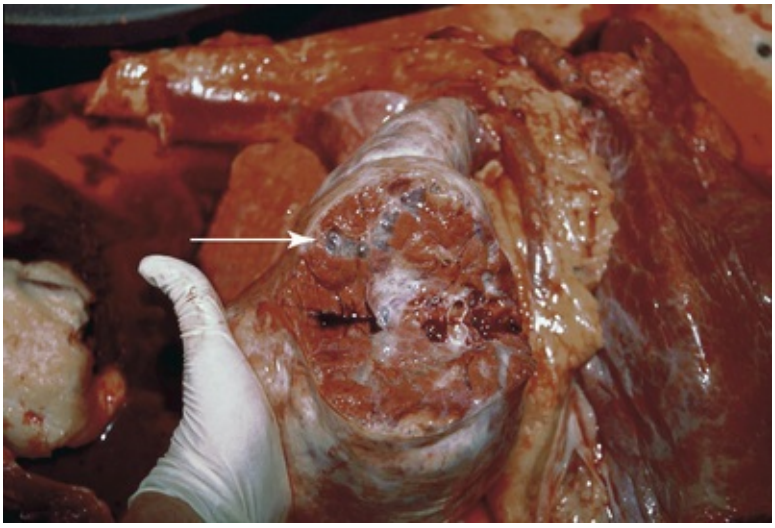


COLOR PLATE 31.1 Postmortem photograph of tracheal edema syndrome. Note the severe mucosal and submucosal thickening, which has obstructed the tracheza by approximately 50%. (Courtesy Feedlot Health Management Services, Okotoks, Alta., Canada.)



COLOR PLATE 31.2 Postmortem photograph of opened trachea from an animal infected with bovine herpesvirus 1 (BHV-1). Note the multiple white fibrinonecrotic plaques and, distal to the plaques, yellow fibrinopurulent

material on dark red tracheal mucosa. (Courtesy Feedlot Health Management Services, Okotoks, Alta., Canada.)



COLOR PLATE 31.3 Postmortem photograph of bovine lung with interstitial emphysema *(arrow)* often seen in severe bovine respiratory syncytial virus (BRSV) infection, as well as other causes of acute interstitial pneumonia. (Courtesy Dr. Amelia Woolums, Mississippi State University, Starkville, Miss.)



COLOR PLATE 31.4 Postmortem photograph of fibrinopurulent

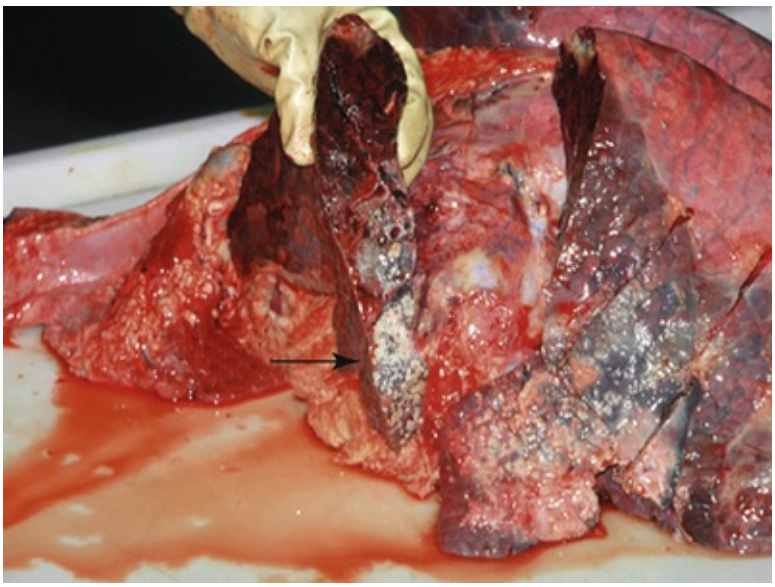
pleuropneumonia caused by *Mannheimia haemolytica*. Note the extensive dark red consolidated ventral lung, white fibrin on lung pleural surface, and red-tinged fluid in pleural space. (Courtesy Dr. Amelia Woolums, Mississippi State University, Starkville, Miss.)



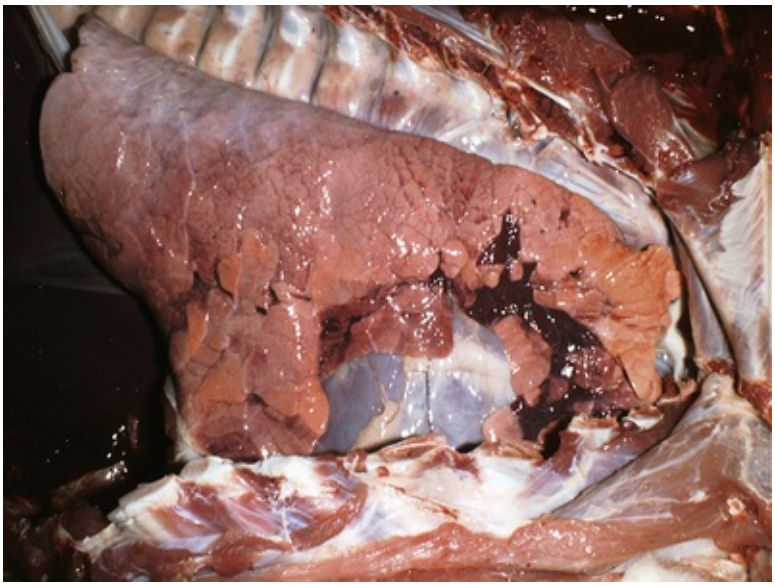
COLOR PLATE 31.5 Postmortem photograph of cross-section of lung tissue from feedlot steer with bronchopneumonia caused by *Histophilus somni.* Note that the interlobular space is expanded with fibrin and edema *(arrow).* (Courtesy Feedlot Health Management Services, Okotoks, Alta., Canada.)



COLOR PLATE 31.6 Postmortem photograph of lung from calf with bronchopneumonia caused by *Mycoplasma bovis.* Note the extensive nodular abscessation of the cranioventral lung. (Courtesy Dr. Tom Mullaney, Michigan State University, East Lansing, Mich.)



COLOR PLATE 31.7 Postmortem photograph of lung from calf with bronchopneumonia caused by *Mycoplasma bovis.* Note the dark red consolidated ventral lung with white caseous material visible on cut surface *(arrow).* (Courtesy Dr. Ricardo Rosenbusch, Iowa State University, Ames, Iowa.)

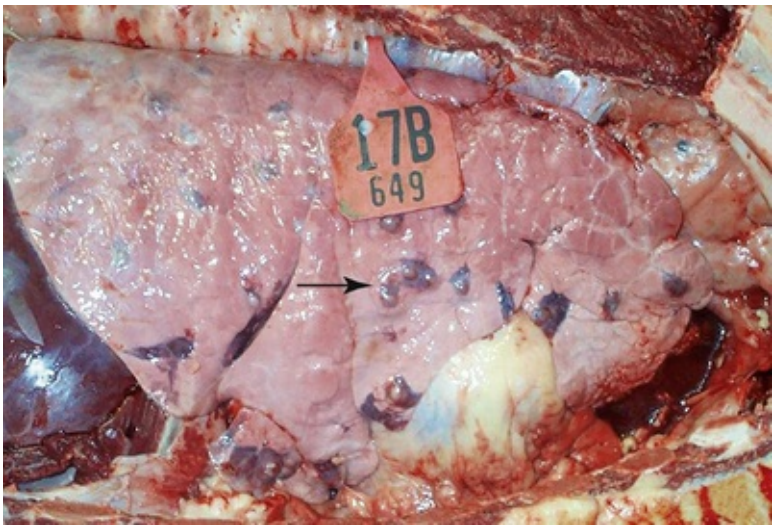


COLOR PLATE 31.8 Postmortem photograph of lung lesions typical of enzootic calf pneumonia. Note the scattered collapsed, dark red lobules in the cranioventral lung. This type of lesion could be caused by bovine respiratory syncytial virus (BRSV), parainfluenza virus type 3 (PIV-3), *Pasteurella multocida,* or mycoplasmas. (Courtesy Dr. Amelia Woolums, Mississippi State University, Starkville, Miss.)



COLOR PLATE 31.9 Postmortem photograph of lungs from heifer with acute respiratory distress syndrome (ARDS) caused by feedlot acute interstitial pneumonia (AIP). Note the expanded dorsocaudal lung and dark, collapsed lobules interspersed with pale, hyperinflated lobules. (Courtesy

Dr. Amelia Woolums, Mississippi State University, Starkville, Miss.)



COLOR PLATE 31.10 Postmortem photograph of lung from feedlot steer with embolic pneumonia caused by caudal vena caval thrombosis. Note the multiple dark red emboli *(arrow)* with raised abscesses scattered throughout lung. (Courtesy Feedlot Health Management Services, Okotoks, Alta., Canada.)

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• CHAPTER 32

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Diseases of the Alimentary Tract

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▪ Equine Alimentary System

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Examination and Imaging of the Equine Alimentary System

Samuel L. Jones • Michelle H. Barton

A thorough physical examination is compulsory, and tests that provide a minimum database (complete blood cell count [CBC], serum chemistry profiles, and urinalysis) are often indicated in horses with suspected alimentary tract disease. Once a differential diagnosis is compiled, a number of ancillary diagnostic tests are available to narrow the possibilities. Each diagnostic test or procedure is limited in the type and extent of information that can be obtained, and therefore the clinician should select the complement of procedures that is most likely to provide the information required to make a proper diagnosis and determine the appropriate therapy.

■ Rectal Examination

A systematic approach to examining the abdominal and retroperitoneal viscera should be established and applied during each examination to ensure that all pertinent regions and structures are examined. When feasible and if required, the patient should be sedated to allow a more thorough examination. In some cases, *N*-butylscopolammonium bromide administration or epidural anesthesia is required to obtain adequate access to structures during rectal examination. The principal goal of a rectal examination is to identify changes in size, texture, shape, or location of visceral organs, peritoneum, mesentery, and vasculature, or to detect objects that are normally not present. Rectal examination is often performed with ultrasonographic examination, and information derived from each must be considered in order to draw conclusions. Ultrasonographic examination is described in a later section of this chapter.

In the pelvic region of the normal horse, the urethra and accessory sex glands (male) or the vaginal vault and cervix (female) can be palpated. The urethra is usually not discernible in the female, but abnormalities such as uroliths may be detected. In the caudal abdominal cavity, the bladder, the uterus in females, and the pelvic flexure and small colon typically should be identified. The pelvic flexure and left ventral and left dorsal portions of the colon are normally located ventrally, on midline, or toward the left side of the abdomen. The small colon, in which formed fecal balls are palpable, courses throughout the caudal abdomen,

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mostly on the left side. In females the left ovary can be identified in the left dorsal, caudal region of the abdomen. Both ovaries should be palpated in conjunction with palpation of the uterus. The peritoneal surface should be detected along the surface of the abdominal wall and the surfaces of the viscera. It should feel smooth, with no crepitus or irregularities. Farther along the left side of the abdomen, the spleen is palpable as a smooth structure; the caudal border is well-delineated and tapered. The size and location of the spleen are variable because it can extend from the left body wall to the right ventral region of the abdomen. Farther cranially and dorsally, the left kidney can be palpated. The kidney should feel smooth and the renal pelvic fissure should be discernible, although in an overweight horse, extensive perirenal fat may obscure this detail.

From the left kidney, toward midline and extending from the abdominal aorta, the cranial mesenteric and ileocecocolic arteries may be palpated. Fremitus detected in these arteries may be associated with arteritis and thrombus formation secondary to *Strongylus vulgaris* larval migration; however, this association has been very inconsistent. Fremitus is frequently absent when severe arteritis exists, or the arteries may be entirely normal and fremitus felt. Fremitus can often be elicited by compression of the wall of the normal artery, which accelerates flow through the compressed lumen. The mesenteric root of the colon can be palpated ventral to the cranial mesenteric artery. This should feel like a mildly taut band of tissue extending from the dorsal midline ventrally. Excessive tension, displacement, thickening, or masses within the mesentery are abnormalities. It may be possible to palpate an enterolith, a fecalith, or a gravel impaction in the transverse colon, but this may be beyond the reach of the examiner because the transverse colon is cranial and medial to the left kidney.

On the right side of the abdomen, the base and cupola of the cecum can be palpated. The body of the cecum can be followed partially along the medial aspect of the cecum, cranially toward midline. The cecum has a prominent ventral band and sacculations. Gas, together with ingesta that is soft and mainly of a fluid consistency, can be identified within the cecum. Firm or excessive ingesta suggest an abnormality.

Findings that are different from normal often must be identified as either variations of normal or true abnormalities. Abnormalities of the peritoneal surface are common findings. Crepitus, or a “plastic wrap” texture, is indicative of gas secondary to trauma or infection. An irregular or rough surface may be indicative of fibrin on a visceral surface or neoplasia; with a perforated intestine, ingesta may be adhering to a visceral surface. There are many abnormal

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presentations of the large colon, most of which are associated with signs of colic. Thickening of the wall of the colon may be appreciated on rectal palpation and is indicative of edema or cellular infiltration of the colon. Abnormal masses palpated in the wall of the colon or in association with the colonic mesentery are indicative of infection, infarction, granulomatous colitis, or neoplasia.

The small intestine is not normally discerned by palpation. On occasion, however, peristaltic contractions may be felt in the small intestine as it courses across midline toward the base of the cecum. In some cases this causes the small bowel to feel firm and tubular. Relaxation of the peristaltic contraction should be discerned in such cases. Distention of the small intestine is abnormal. In some cases the bowel may feel thickened, which can occur with ileal muscular hypertrophy, edema, or inflammatory disorders of the small bowel.

Other abnormal findings that may accompany disorders of the abdominal alimentary system include masses, adhesions, enlarged and thickened mesenteric arteries, and caudal displacement of the spleen (secondary to gastric distention or neoplasia).

■ Paracentesis

Abdominal paracentesis is performed routinely in patients with suspected disorders of the abdominal viscera. Cytologic studies are used to quantitate peritoneal fluid; white blood cell (WBC) and red blood cell (RBC) counts; protein, fibrinogen, serum amyloid A, lactate, phosphate, and glucose concentrations; lactate dehydrogenase, creatine kinase (CK), and alkaline phosphatase (ALP) activity; and pH. The results of peritoneal fluid analysis may help establish a specific diagnosis but, of more importance, may help distinguish inflammatory from noninflammatory conditions, identify vascular obstructions or ischemic injury to the intestine, and determine whether surgical intervention is indicated.

■ Endoscopy

Two basic types of endoscopic equipment are available: equipment based entirely on a fiberoptic system and equipment based on a video system. Many affordable endoscopes are now available, and endoscopic examination of the proximal alimentary tract in horses is now common. A typical endoscope found in many private practices is a fiberoptic endoscope that has an insertion tube that is 100 to 110 cm in length and 10 to 14.5 mm in outer diameter. The larger-

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diameter tube can be inserted only through the nasal passages of older yearlings and adults and is not suitable for alimentary endoscopy, whereas a tube 10 mm in diameter can be passed through the turbinates of young foals. An insertion tube length of 110 cm is sufficient to reach the stomach of foals up to 40 days of age. A length of 150 to 180 cm is required for weanlings, and 200 cm is usually required for yearlings and adults. An insertion tube length of 200 cm is sufficient to reach the stomach of all adults of warm-blooded breeds, although 280 to 300 cm is required to examine the pylorus in adult horses. A 280- to 300-cm-long insertion tube enables duodenoscopy in adult horses.

Before a gastroscopic examination, suckling foals up to 20 days of age are not routinely kept from nursing for more than 1 hour. Older foals and mature horses, in contrast, should not have solid feed for 6 to 10 hours so that ingesta from the stomach may be adequately emptied. Longer duration of feed deprivation (12 to 18 hours) is desirable to view the antrum and pylorus of horses. Many foals less than 30 days old do not require sedation for gastroscopy, although sedation with xylazine (0.5 mg/kg) may facilitate the procedure. Sedation is required if the foal is to be placed in a recumbent position so that the entire glandular portion of the stomach can be examined. Older foals and horses must be sedated for gastroscopy. Xylazine (0.5 mg/kg given intravenously [IV]) usually provides adequate sedation. For greater sedation, detomidine (0.005 to 0.05 mg/kg IV) or a combination of xylazine and butorphanol (0.01 mg/kg IV) is effective.

After insertion of the endoscope, the stomach is distended with air until the nonglandular and glandular regions of the gastric surface can be observed. Distention with air is tolerated by foals and horses and has been associated only rarely with adverse effects. On occasion, sick neonates with poor intestinal motility have developed distention of the small intestine and experienced discomfort after gastroscopy.

More complete descriptions of techniques of gastroduodenal endoscopy can be found elsewhere.[1,2]

Endoscopy of the rectum and distal small colon can be performed with most flexible endoscopes in use in equine practice and should be preceded, as much as possible, by evacuation and saline lavage of the rectum and distal small colon. The mucosal surface should appear pink to pale red and should have a smooth, velvety appearance. Mucosal edema or thickening, hyperemia, irregularities, defects, tears, and intraluminal masses are abnormal findings. Because of the concern for trauma to the rectum and small colon, horses should be adequately sedated and restrained before preparation and examination of the distal

alimentary tract.

■ Laparoscopy

Laparoscopy can offer valuable diagnostic information regarding the abdominal cavity and is only minimally invasive.[3,4] It should always be preceded by a thorough physical examination, including abdominal rectal palpation, and by abdominal ultrasonographic examination, with particular attention to the sites for trocar insertion to ascertain the presence of adherent masses or viscera in the area. If abdominocentesis is to be part of the diagnostic workup, it should be performed before laparoscopy because laparoscopy can affect abdominal fluid values. In experimental animals undergoing diagnostic laparoscopy with carbon dioxide insufflation, both the abdominal WBC count and the abdominal total protein increased.[5]

The indications for laparoscopy include palpable abdominal masses, enlarged viscera, adhesions, acute or chronic colic, weight loss, and the need to obtain visceral biopsy specimens. Contraindications include adherent viscera or masses at the site of laparoscopic trocar insertion, diaphragmatic hernias, or extreme bloating. Horses with acute colic can be safely examined laparoscopically if the trocars and telescopes are inserted carefully.

The basic instruments for laparoscopic examinations include a laparoscopic telescope, laparoscopic cannula and trocar assembly, fiberoptic light source and cable, insufflator, and biopsy and manipulation instruments. Video cameras make visualization easier with less eyestrain but require more powerful light sources. The cost of laparoscopic instrumentation has decreased because laparoscopy has become popular in humans and animals, and the procedure is far more cost effective than in years past.

Horses should fast for 18 to 24 hours before most laparoscopic procedures; water is allowed on an ad libitum basis. Fasting increases intraabdominal visualization and decreases the possibility of penetrating a gas-distended viscus. The animal is restrained in standing stocks if the procedure is to be done while it is standing. Preoperative antibiotics, antiinflammatory drugs, tetanus prophylaxis, and a sedative analgesic combination are administered. It is important to administer the analgesics before abdominal insufflation. The flank areas are prepared for aseptic surgery. Local anesthetic agents are infiltrated subcutaneously (SC) and intramuscularly (IM) in the middle of the paralumbar fossa, slightly above the crus of the internal abdominal oblique muscle, for the

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insertion of the laparoscopic telescope. It is preferable to begin the laparoscopic procedure on the left side of the abdomen to minimize the chance of penetrating the cecal base. Additional ports may be created in the right paralumbar fossa to increase access to intraabdominal and retroperitoneal structures and enable the use of additional instruments. Ports are created with a stab incision, and a laparoscopic cannula and trocar assembly are inserted through the musculature and into the abdominal cavity. The trocar should be oriented toward the opposite coxofemoral joint when it is inserted. The trocar is exchanged for the telescope, and entry into the abdominal cavity is confirmed before insufflation begins. If the abdominal cavity has not been penetrated, a quick thrust with the telescope usually penetrates the peritoneum. Insufflation of the abdomen with CO_2 to 8 to 10 mm Hg is usually sufficient for most examinations.

The abdominal cavity is then examined systematically. On the left side of the abdomen, the spleen, left kidney, nephrosplenic ligament (Fig. 32.1), stomach, left side of the liver, diaphragm, and ventral portion of the colon are visualized cranially. A caudal view includes the root of the mesentery, the isolated small intestinal and small and large colon sections, the urogenital tract, the bladder, and the terminal rectum. The procedure is repeated on the right side of the abdomen. The liver, epiploic foramen, right kidney, descending duodenum, cecal base, and large colon are visualized cranially. The urogenital tract, root of mesentery, and intestinal segments are visualized caudally. Technical innovations have enabled extensive examination of intraabdominal structures. For example, it is possible to examine the entire small intestine via laparoscopy.[6] Depending on the pathologic condition, diagnostic laparoscopy may provide a diagnosis and allow access to surgically resolve the problem. Liver biopsy and right kidney biopsy samples are taken from the right side of the abdomen; left kidney and spleen biopsy samples are taken from the left side. Mesenteric lymph node biopsy samples are usually obtained via the left flank. Biopsy samples of other masses are taken from the more accessible side. At the end of the procedure, the abdomen is deflated, and the skin is closed with skin sutures only. The skin incision should not be closed until examination of both sides is completed, in order to minimize subcutaneous emphysema.

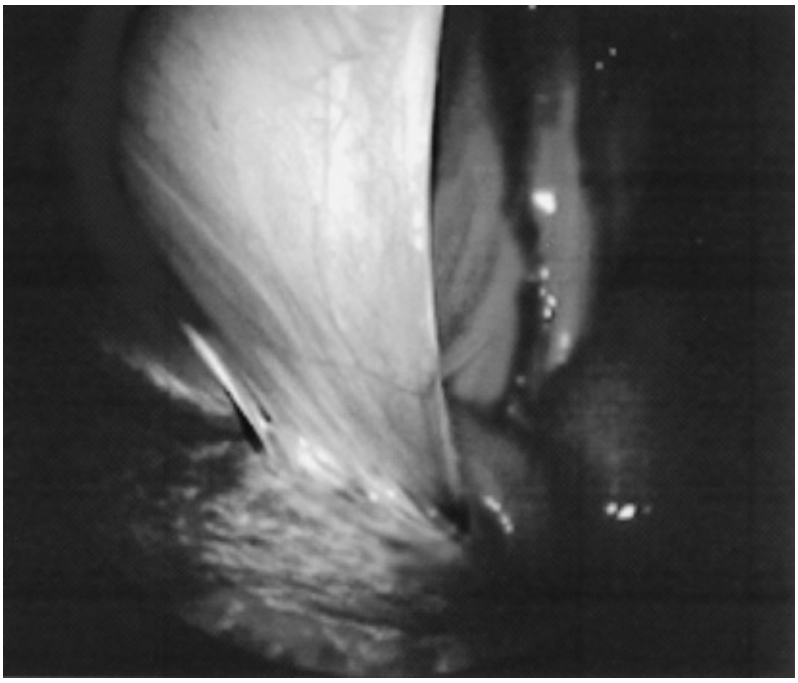


FIG. 32.1 Laparoscopic view of nephrosplenic ligament in a horse.

In some horses with ventral or cranial abdominal masses as determined with ultrasonography, the animal can be anesthetized and placed in dorsal recumbency for better characterization of the mass. Biopsy samples may be readily obtained. In horses with acute colic but without obvious signs indicating the necessity for surgery, laparoscopy can guide the decision to continue medical therapy or proceed to surgery. Strangulated sections of small intestine can be visualized, proximal enteritis can be diagnosed, and edema and vascular compromise to the large colon can be seen. No abnormalities may be detected in some animals with very localized lesions, or lesions may be inaccessible, depending on location.

Laparoscopic complications are similar to those of any other abdominal exploratory procedure. A viscus may be penetrated inadvertently; the left kidney may be perforated if the laparoscope is inserted too far dorsally; and the spleen may be penetrated if the laparoscope is inserted too far ventrally or is not aimed toward the opposite coxofemoral joint. The cecum may be perforated when the laparascope enters from the right side. If the horse has fasted and the laparoscopic trocars are inserted carefully, these problems are minimized. Subcutaneous emphysema occurs commonly but has not caused any clinical problems. The peripheral WBC count increased but stayed within normal limits in experimental animals undergoing laparoscopy.[5]

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■ Transcutaneous Ultrasonography of the Mature Equine Alimentary Tract

Michelle Henry Barton

Technique.

One of the most innovative, practical, affordable, and portable diagnostic tools introduced into the field of equine internal medicine since 2000 is transcutaneous ultrasonography. Although several different types of ultrasound transducers exist, adult equine abdomens are most completely imaged with a 2- to 5-MHz curvilinear array transducer, but a high-frequency (6- to 8.5-MHz) linear array transducer can be used to optimize resolution of superficial intraabdominal structures. Ideally, before the procedure, the patient's hair is clipped, the skin cleaned, and coupling gel applied. If clipping the hair is not an option, debris can be removed with grooming aids and the hair soaked in isopropyl alcohol. Most horses tolerate transabdominal ultrasonography without sedation. In patients sedated with α_2-adrenergic agonists, small intestinal and cecal motility can be transiently reduced, especially in horses that have fasted, and the luminal diameter of the small intestine may appear more dilated than in unsedated patients.[7,8] Likewise, administration of *N*-butylscopolammonium bromide will immediately reduce duodenal, cecal and left ventral colonic contractions for 30 (cecum and colon) to 120 minutes (duodenum).[9]

Detailed review of the physics of ultrasonography is beyond the scope of this section; however, several general principles should be kept in mind when transabdominal ultrasonography is performed. First, to ensure that all structures are properly assessed, the approach for covering the entire area to be evaluated must be consistent and systematic: for example, scanning one side at a time, dorsal to ventral, cranial to caudal. Using seven discrete locations in horses being evaluated for acute abdominal pain, the examiner can complete the fast localized abdominal sonography for horses (FLASH) method in less than 15 minutes; this method is extremely helpful in establishing the correct diagnosis.[10] The seven locations evaluated in the FLASH method are ventral, gastric, splenorenal, left middle third of the abdomen, duodenal, right middle third, and thoracic. Focused technique can be used to consistently identify the cecum, sacculated large intestine, spleen, liver, and right kidney. The left kidney is not always identified, and successful identification of small intestine may require repeated examination.[11]

Second, to ensure correct orientation of the anatomy being imaged, the examiner should be mindful of the position of the transducer and its orientation marker on the patient (Fig. 32.2). Because abdominal ultrasonography is often performed with the transducer over an intercostal space, the transducer should be oriented in a slightly oblique transverse plane (i.e., “slicing” across the long axis of the body). Careful attention should be paid to the spatial relationship of the viscera because this may be the only key feature distinguishing normal from abnormal.[12] Furthermore, the walls of some sections of the gastrointestinal tract appear strikingly similar and cannot be distinguishable unless information is provided about the probe's exact location on the patient.[13]

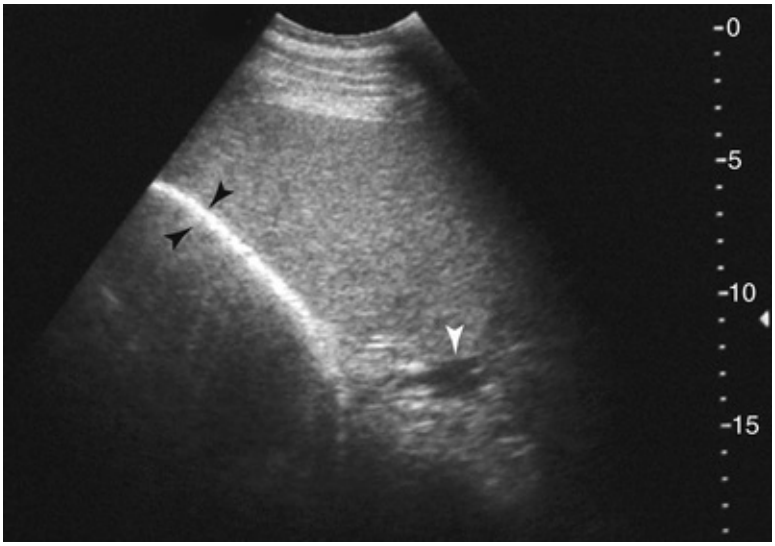


FIG. 32.2 Ultrasound view from the gastric window in the left eleventh intercostal space at the level of the shoulder in a horse. The left side of the image is dorsal. The *black arrowheads* mark the border between the serosal layer and the mucosal-luminal interface of the stomach wall, which appears as a curved hyperechoic line. The spleen is located in the near field between the stomach wall and the body wall. The *white arrow* marks the splenic vein. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 19 cm.

Third, in any ultrasonographic examination, it is important to be aware of the depth of the field of view. Selecting the appropriate frequency for the transducer is the key to producing high-quality images that are suitable for the depth of display. High-frequency probes provide sharp images, but the resolution is compromised as the depth of the viewing field increases.

A final general and helpful principle of ultrasonography is that more sound

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waves reflect to the transducer if two adjacent interfaces have markedly different acoustic impedances. The more sound that reflects to the transducer, the “whiter” the interface appears on the monitor; these tissue interfaces are called *echogenic* or *hyperechoic*. In contrast, less dense tissues reflect less sound, appear darker, and are referred to as *anechoic* or *hypoechoic* structures. The acoustic impedance of the soft tissue of the walls of the gastrointestinal tract is several thousand times greater than that of the free gas inside the adjacent lumen.[14] Consequently, the image at this soft tissue–to–gas interface appears as a fuzzy hyperechoic border (see Fig. 32.2). Because most of the sound waves at this interface are reflected and the free gas in the lumen has extremely low impedance, sound is neither penetrating nor reflecting from the lumen, and the rest of the lumen is therefore obscure.

Gas within a large luminal viscus is one of the greatest limitations to gastrointestinal ultrasonography in horses, inasmuch as it impedes visualization of deeper structures. While imaging a patient, the ultrasonographer should remember that gas rises to the nondependent portion of the abdomen, and fluid and heavier structures fall to the dependent locations. When a 3.5- to 5-MHz curvilinear transducer is used, the difference between anatomic layers of the intestinal wall in healthy horses is less distinct; the wall typically appears as a single hyperechoic line. Depending on the surrounding tissue and the contents of the lumen, three to five layers of the gastrointestinal wall may be visible when a high-frequency transducer is used; these five layers are the hyperechoic serosa, hypoechoic muscularis layer, hyperechoic submucosa, hypoechoic mucosa, and the hyperechoic mucosal interface with the lumen (Fig. 32.3).[15]

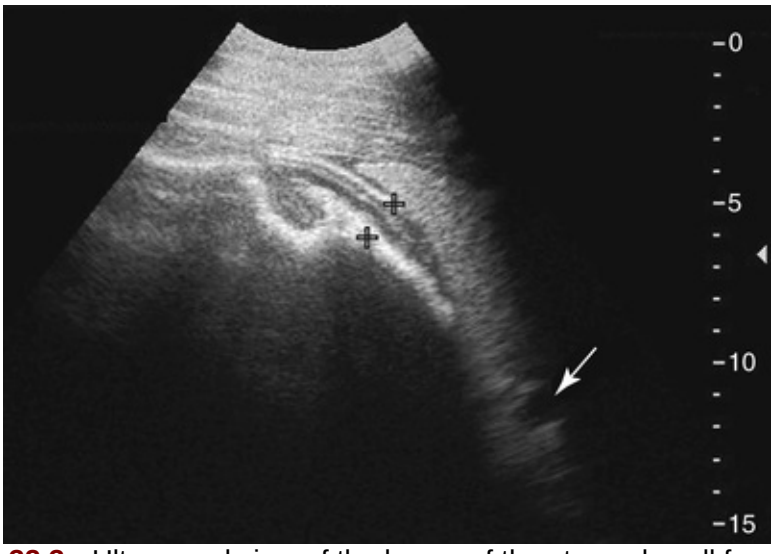


FIG. 32.3 Ultrasound view of the layers of the stomach wall from the gastric window in a horse. The left side of the image is dorsal. The *white arrow* marks the splenic vein. The electronic calipers (represented by *plus signs*) are placed at the border between the serosal layer and the mucosal-luminal layer and mark the stomach wall. The five ultrasonographic layers of the wall are visible, and it is abnormally thickened at 1.34 cm. Follow-up gastroscopy revealed that the horse had severe gastric ulceration.

In the following sections, transabdominal ultrasonography of the gastrointestinal tract is described with a systematic approach of scanning in a cranial-to-caudal direction. For the gastrointestinal tract, the ultrasonographer should be careful to document the following key elements: motility, presence of luminal distention, wall thickness and structure, luminal contents, and viscera position.

Ultrasonography of the Left Side of the Abdomen

Stomach.

When imaging is started on the left rostral side of the abdomen, the stomach should be located deep to the spleen between the ninth and thirteenth intercostal spaces at approximately the level of the shoulder. In this location, the only part of the stomach that can usually be seen is the wall of the greater curvature, which can be reliably identified as a smooth, curved, hyperechoic line adjacent to the spleen and the splenic vein (see Fig. 32.2).[16] The motility of the stomach is sluggish, and the ultrasonographer may get the impression that the greater curvature of the stomach remains stationary.[8] The stomach has the thickest wall in the gastrointestinal tract, measuring approximately 7 mm thick from the

serosal layer to the mucosal-luminal interface.[17] When the stomach is empty, the wall measures up to 1 cm thick, ill-defined loops of small intestine may appear between the stomach and the spleen, gastric rugal folds may be visible, and the gastric wall may be found only below the costochondral junction.[8,17]

Gastric Impaction and Ulceration.

Because only the dorsal portion of the greater curvature is visible and the lumen generally contains gas at this location, transcutaneous ultrasonography of the stomach is not a sensitive tool for diagnosing gastric ulceration, intramural gastric masses, or gastric impaction. However, if the wall of the greater curvature of the stomach extends beyond the fourteenth intercostal space in a horse that has not recently drunk or eaten, gastric distention should be suspected.[18] Furthermore, if excessive gastric fluid is present ventrally, a distinct hyperechoic gas–fluid interface may be apparent in the lumen (Fig. 32.4). If the stomach wall appears irregular or thickened, follow-up gastroscopy is indicated for a more definitive diagnosis (see Fig. 32.3).

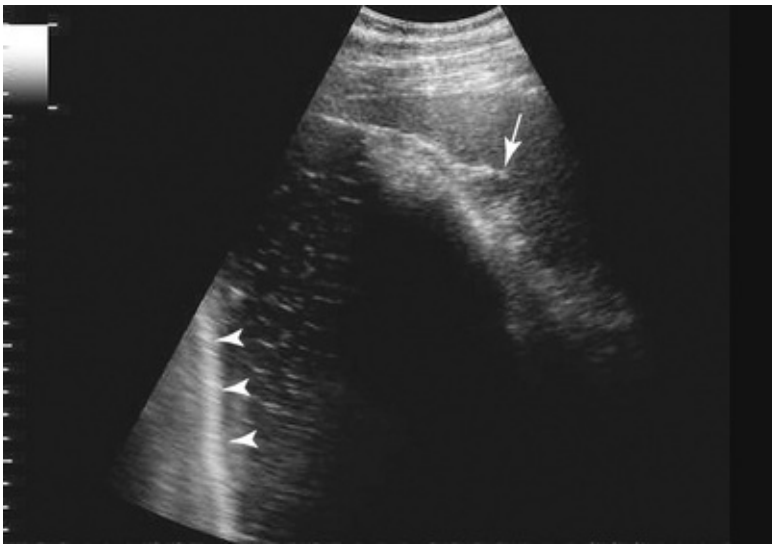


FIG. 32.4 Ultrasound view from the gastric window in a horse. The left side of the image is dorsal. The *white arrow* marks the splenic vein. The *white arrowheads* mark the interface between hyperechoic fluid in the dependent portion of the stomach *(right)* and gas dorsally. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 23 cm.

Spleen and Left Kidney.

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Although the focus of this section is gastrointestinal ultrasonography, the spleen and left kidney warrant brief review because of their proximity to the gastrointestinal tract. Caudad from the stomach, the spleen should be identifiable immediately adjacent to the body wall, from the left ventral eighth intercostal space to the paralumbar fossa. The size and location of the spleen vary greatly: The spleen can be left of the midline or extend slightly right of the ventral midline. In the rostral ventral left abdomen of some horses, the most rostral aspect of the spleen can appear either lateral or medial to the liver.[12] The spleen's ultrasonographic architecture is usually homogeneous, with vessels that are rarely visible. The echogenicity of the spleen is greater than that of the liver or kidneys.

The left kidney can be found between the fifteenth and seventeenth intercostal spaces and the first to third lumbar vertebrae, medial or deep to the spleen (Fig. 32.5), between the level of the tuber coxae and the tuber ischii.[19,20] In rare cases, the left kidney directly apposes the left body wall.[12] Gas in the small colon, left portion of the colon, or lung can preclude transabdominal viewing of the left kidney, which is normal, although colonic gas obscuring visualization of the left kidney may be adjunct evidence of dorsal displacement of the left portion of the colon.[21] The ultrasonographic dimensions of the left kidney vary according to the location from which the measurements are obtained. The longitudinal axis for craniocaudal length (i.e., the dorsal plane parallel to the spine) is difficult to measure because of interference by the ribs.[20] In Thoroughbred horses, the length of the left kidney varies from 9.6 to 15.6 cm.[19] The dorsoventral height in the slightly oblique transverse plane varies from 3.1 to 8.1 cm, and the lateromedial thickness varies from 6.6 to 9.1 cm.[19] The corticomedullary junction should be distinct, with the cortex being more echogenic. The adrenal glands are not usually identifiable via transabdominal ultrasonography.[12]

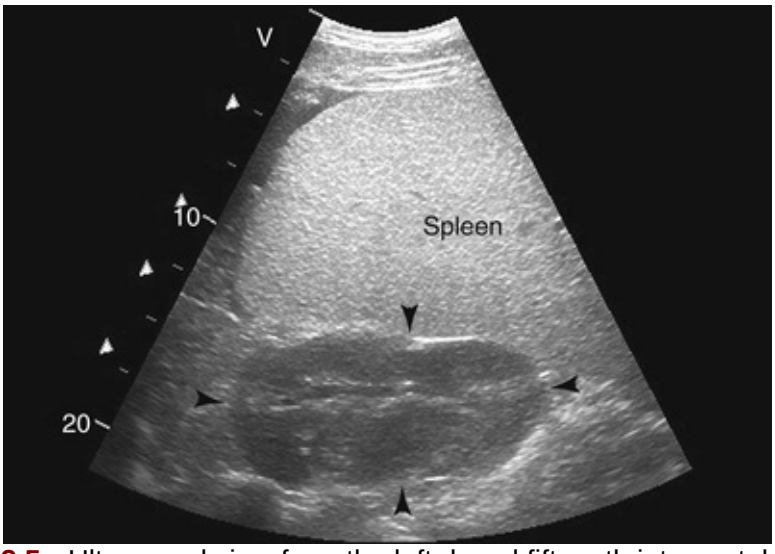


FIG. 32.5 Ultrasound view from the left dorsal fifteenth intercostal space in a horse, showing the normal adjacent orientation of the spleen to the left kidney *(black arrowheads).* The left side of the image is dorsal. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm.

Left Portion of Colon.

Many disorders of the large colon can be palpable by rectal examination, and thus transabdominal ultrasonography is an ancillary tool. Ventromedial to the spleen, the left ventral portion of the colon can be identified by its sacculated wall (Fig. 32.6) and sluggish but visible motility, normally contracting two to six times per minute.[8,13,15] Precise measurement of the colonic wall can be difficult because of the indistinct mucosal-luminal interface; in general, however, the wall of the colon should be less than 4 mm thick.[13,15,17] The left dorsal portion of the colon is not sacculated and can be dorsal, lateral, medial, or even ventral to the left ventral portion of the colon. Gas in the left ventral portion of the colon often precludes distinct identification of the left dorsal portion of the colon when the latter lies medial or dorsal to the left ventral portion of the colon. Gas in the colon typically generates a hyperechoic wall with an indistinct luminal border and intraluminal acoustic shadowing that precludes identification of the contents and the medial walls.

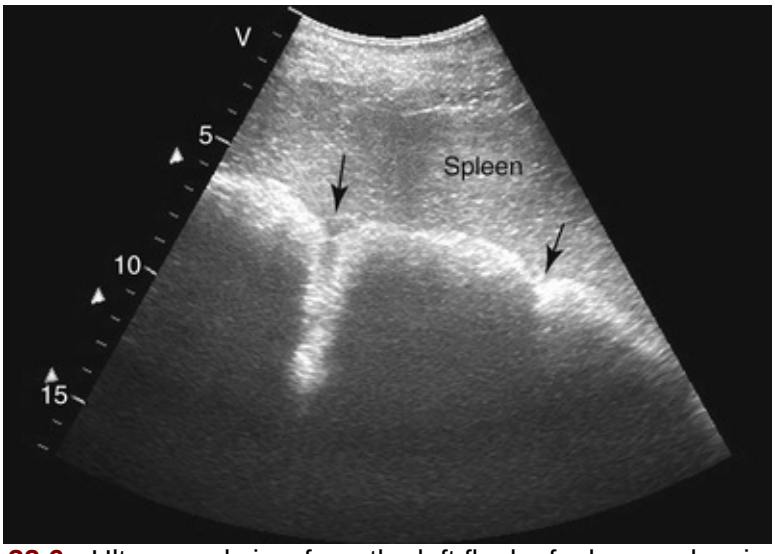


FIG. 32.6 Ultrasound view from the left flank of a horse, showing the spleen adjacent to the left ventral portion of the colon, identifiable by its location and the presence of sacculations *(black arrows).* The left side of the image is dorsal.

Colitis.

When visualized through ultrasonographic examination of the left portion of the colon, useful diagnostic characteristics include wall thickness and structure, orientation of the colon, and its contents. For example, thickening of colon wall can be caused by inflammation, infiltration by neoplastic cells, hemorrhage, or edema. Inflammation of the colonic wall (i.e., colitis) can result in mural widening, but the mucosal border often appears shredded, undulating, or wavy (Fig. 32.7). These later findings may be particularly helpful in identifying horses in the prodromal phase of colitis, before the onset of diarrhea. The contents of the colon can change from characteristic acoustic shadowing to that of swirling mixed echogenic fluid that may enable visualization of the distal colonic wall. With colitis, colonic motility can be increased or decreased, or it can remain unaffected.

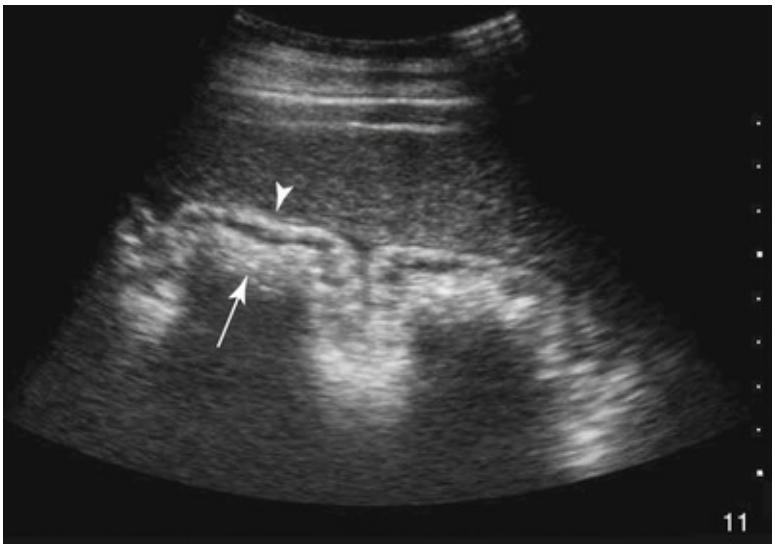


FIG. 32.7 Ultrasound view obtained from the same location as in Fig. 32.6 but from a horse with colitis. The left side of the image is dorsal. The left ventral portion of the colon is identifiable by its location medial to the spleen and by its sacculations. The wall of the colon was thickened to approximately 1 cm with three distinct layers: hyperechoic serosa *(white arrowhead),* hypoechoic muscularis, and submucosal, hyperechoic mucosal-luminal interface *(white arrow).* This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 11 cm.

Colonic Volvulus.

Colonic edema resulting from a volvulus of the colon also results in uniform hypoechoic mural thickening that is best identified with imaging along the ventral midline behind the xyphoid process. In one study in which colon wall edema was evaluated by transcutaneous ultrasonography through a ventral abdominal window, colon wall thickness of more than 9 mm had a sensitivity of 67% and specificity of 100% for colonic volvulus.[22] In addition, in some cases of colonic volvulus, nonsacculated colon tissue replaces sacculated colon tissue in the left ventral abdomen.[23] Furthermore, the blood supply to the ascending colon is located in the mesentery along its medial aspect, and thus major blood vessels are normally not visible ultrasonographically on the lateral surface (adjacent to the body wall) of the ascending colon. The ultrasonographic finding of distended vessels with reduced blood flow in colonic mesentery adjacent to the body wall implies that the colon is rotated along its long axis and is consistent with a diagnosis of displaced colon or a colonic volvulus.[24] Colonic motility is reduced with a volvulus.

Displacement of Left Portion of Colon.

On the left side of the abdomen, dorsal displacement of the left portion of the colon over the nephrosplenic ligament may obscure ultrasonographic visualization of the dorsal aspect of the spleen or left kidney, or the colon may appear lateral to the spleen (Fig. 32.8).[21] However, if gas is not present in the entrapped colon, the ultrasonographic diagnosis can be missed. Likewise, gas within the left portion of the colon can obscure the left kidney without entrapment of the colon. When ultrasonographic and other clinical findings support the diagnosis of left dorsal displacement of the colon, serial ultrasonography of the area can be a useful noninvasive method of determining whether the colon has relocated to its ventral position, as evidenced by successful ultrasonographic visualization of the left kidney.

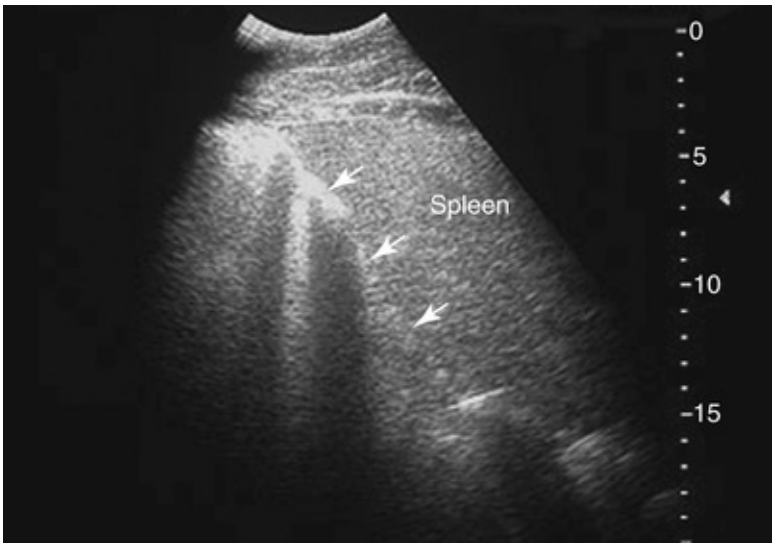


FIG. 32.8 Ultrasound view obtained from the same location as in Fig. 32.5 but in a horse with left dorsal displacement of the colon into the renosplenic space. The left side of the image is dorsal. The gas-distended colon *(arrowheads)* obscures visualization of the left kidney. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 20 cm. (Courtesy Science In 3D, Inc., and copyright 2002, University of Georgia Research Foundation, Inc.)

Colonic Impaction.

Gas within the colon often precludes accurate ultrasonographic diagnosis of colonic impaction. An impaction should be suspected in the ventral portion of

the colon when a hyperechoic border at the mucosal surface casts a strong acoustic shadow and when sacculations are flattened. Sand impactions are best visualized in the ventral abdomen and often compress the mucosal surface, create excessive acoustic shadowing or reverberation artifacts (Fig. 32.9), and significantly reduce visible motility of sacculations.[25]



FIG. 32.9 Ultrasound view obtained at the eleventh right intercostal space at approximately the level of the shoulder in a horse. The left side of the image is dorsal. Sand and gravel in the dependent portion of the right dorsal portion of the colon (*white arrowheads* on serosal surface) created reverberation artifacts in the lumen. The colon wall is thickened. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 13 cm. (Courtesy Science In 3D, Inc., and copyright 2002, University of Georgia Research Foundation, Inc.)

Small Colon.

The small colon is in the left paralumbar fossa, medial or ventral to the spleen. Because of its small diameter, sacculations, and packed serpentine loops that suspend from the dorsal mesocolon, often only small sections of the surfaces are visible ultrasonographically as short, sharply curving, hyperechoic lines (Fig. 32.10). As with the large colon, the motility of the small colon is slow (no more than three contractions per minute), and luminal surface gas typically prevents visualization of the contents and the distal walls.[15] Likewise, the dense contents of fecal balls in the small colon often generate anechoic shadows from the near

wall that precludes visualization of the distal wall (see Fig. 32.10).

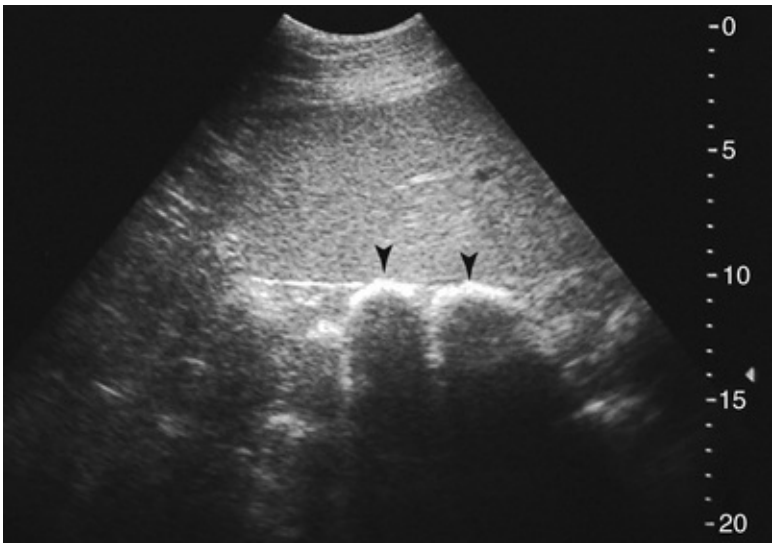


FIG. 32.10 Ultrasound view obtained from the left dorsal paralumbar fossa in a horse. The left side of the image is dorsal. The spleen is in the near field. The serosal surface *(black arrowheads)* of two adjacent loops of small colon are visible. Note the anechoic shadowing that precludes visualization of the distal small colon wall. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm.

Impaction in the Small Colon.

Impactions or enteroliths obstructing the lumen of the small colon can usually be readily diagnosed by transrectal examination; however, transabdominal ultrasonography may reveal loss of, or enlargement of, sacculations and intense anechoic shadowing (Fig. 32.11).



FIG. 32.11 Ultrasound view obtained from the left dorsal paralumbar fossa in a horse. The left side of the image is dorsal. The spleen is in the near field. The serosal surface *(black arrowheads)* of the small colon is visible and is bulging. Note the dramatic anechoic shadowing that was created by an intraluminal enterolith. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm. (Courtesy Science In 3D, Inc., and copyright 2002, University of Georgia Research Foundation, Inc.)

Small Intestine.

The jejunum can be identified in only approximately 10% of fed healthy horses.[8] The examiner must carefully watch for peristaltic activity that creates transient expansion of the lumen from movement of ingesta. Because of its medial location, the ileum cannot be identified distinctly by transcutaneous ultrasonography. The jejunum is most consistently found in the left inguinal area, medial to the spleen and the left ventral portion of the colon (Fig. 32.12). The small intestine has the most visible motility of any part of the gastrointestinal tract; peristaltic waves produce frequent rhythmic contractions. Fluid luminal contents typically enable accurate measurement of the wall (<3 mm) and visualization of the far wall along its long or short axis.[17] In healthy horses, jejunal luminal diameters rarely exceed 3 cm.[17] After complete contraction with peristalsis, a distinct lumen becomes difficult to discern. Fasting or sedation of the horse with an α_2-adrenergic agonist decreases motility of the small intestine, thereby significantly increasing the likelihood of visualization.[7,8]

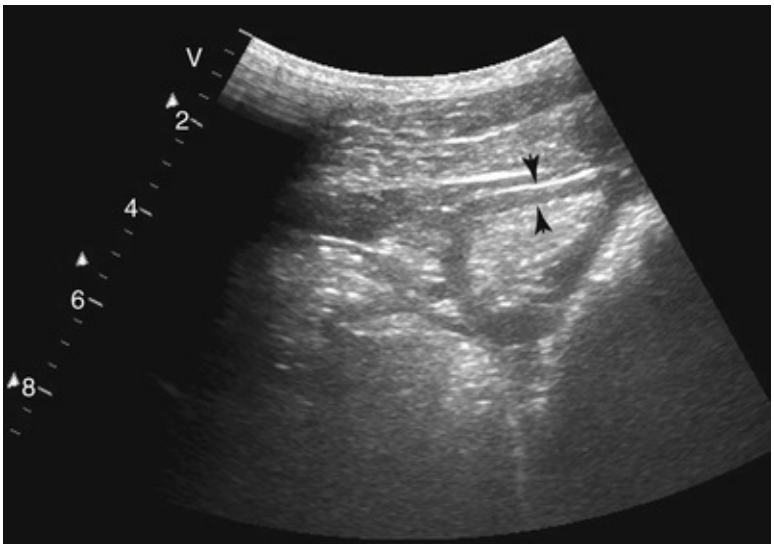


FIG. 32.12 Ultrasound view obtained of the left flank in a healthy, unsedated horse. A single loop of small intestine is visible between the body wall and the left ventral portion of the colon. The serosal to mucosal surfaces are most distinct in the near wall and are marked by the black arrowheads. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 8 cm.

Distended Loops of the Small Intestine.

Distended loops of small intestine often look the same on ultrasonography, despite the underlying cause. As mentioned, normal duodenum and jejunum are difficult to visualize in healthy fed horses; if the small intestine is found easily by ultrasonographic examination, the luminal diameter of small intestine exceeds 3 cm, or peristaltic contractions are notably reduced, the finding should be considered abnormal. Distention of the small intestine can result from paralytic causes, in which motility is reduced without physical luminal blockage or for mechanical reasons, in which a distal luminal or extraluminal obstruction impedes peristalsis. With either paralytic or mechanical ileus, small intestine distention can progress to the point at which the dilated segments of small intestine must fold back on themselves, creating the appearance of turns or curves within the lumen when viewed in long axis (Fig. 32.13). As ileus progresses, denser ingesta settles to the dependent portion of the affected segments (Fig. 32.14). In general, if small intestine distention progressively increases and motility decreases over serial examination, mechanical causes of obstruction that necessitate surgical intervention should be considered.[26,27] Scrutiny of the patient's clinical signs, ancillary diagnostic findings, and some

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distinguishing ultrasonographic features can be helpful in discriminating paralytic from mechanical causes of small intestine distention. In particular, the ultrasonographer should pay close attention to the small intestinal wall thicknesses and structure, progression of distention, degree of motility, and appearance of the intestinal contents.

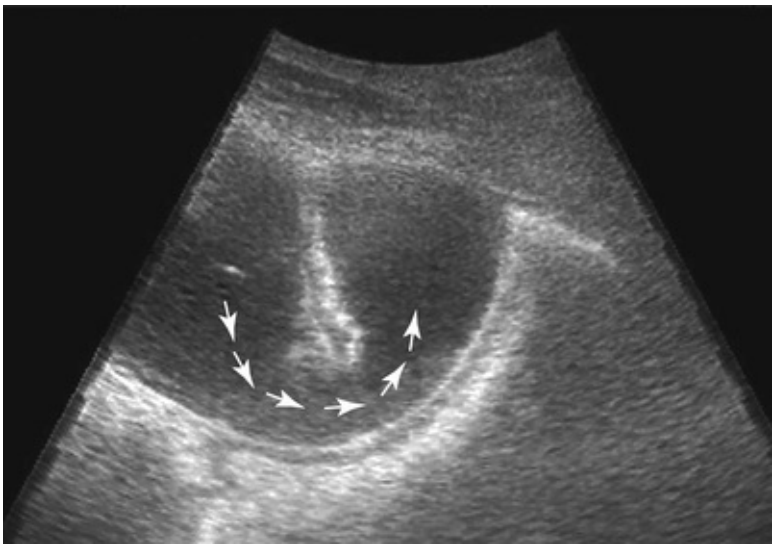


FIG. 32.13 Ultrasound view obtained from the left flank of a horse. A segment of distended small intestine is folding back on itself, creating the appearance of a "U turn" *(arrows).* This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 10 cm.

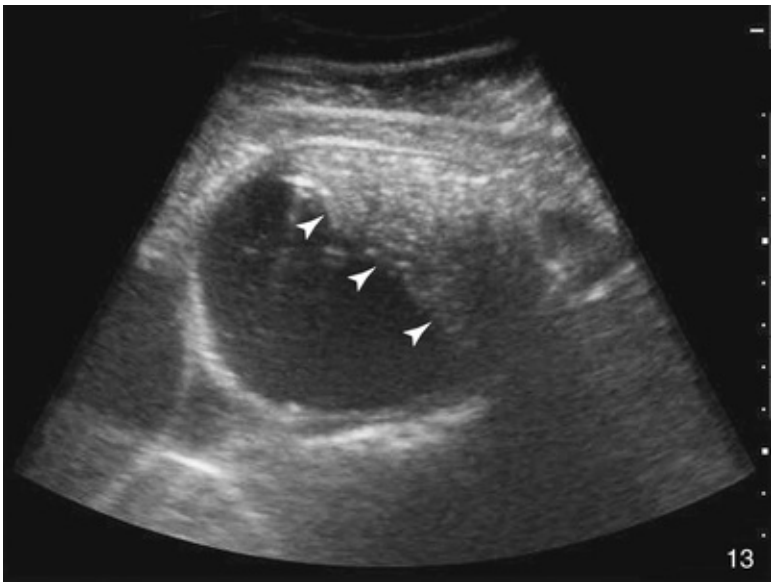


FIG. 32.14 Ultrasound view obtained from the left flank of a horse, showing a segment of distended small intestine in which hyperechoic ingesta settled dependently *(arrowheads).* The left side of the image is dorsal. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 13 cm.

Acute Enteritis.

The wall of the small intestine can be thicker than normal (i.e., >3 mm) as a result of inflammation, edema, hypertrophy, or neoplasia. Some causes of inflammation and edema are acute in nature, such as proximal or anterior enteritis, and some causes are chronic or insidious in nature, such as the inflammatory bowel syndromes or idiopathic intestinal hypertrophy. In addition to the clinical signs and other diagnostic features of proximal enteritis (low-grade fever, gastric reflux, inflammatory findings on leukogram, pain followed by depression after gastric decompression), on ultrasonographic examination, the mucosal wall of the small intestine may appear shredded,[17] corrugated, or wavy, resembling the edge of a lasagna noodle (Fig. 32.15). The proximal portions of the small intestine, especially the duodenum (see duodenum subsection later; Fig. 32.16), and the stomach may be distended with fluid. The movement in these loops can vary from apparently absent to hypermotile. For horses with enteritis, the expected response to medical therapy varies, but lessening degrees of luminal distention with progressive improvement in motility are expected. The appearance of hyperechoic gas bubbles within the wall of the small intestine is indicative of either necrosis or anaerobic bacterial infection..

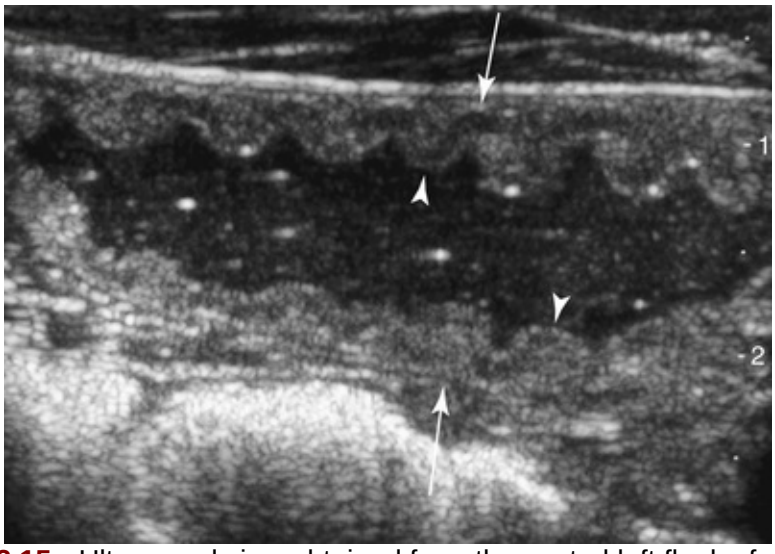


FIG. 32.15 Ultrasound view obtained from the ventral left flank of a horse with enteritis. The small intestinal wall is thickened (up to 6 mm in some areas), and the mucosa has a wavy or corrugated appearance. The *white arrows* mark the serosa, and the *arrowheads* mark the mucosal-luminal interface. This image was obtained with a linear probe set to a depth of 3 cm.

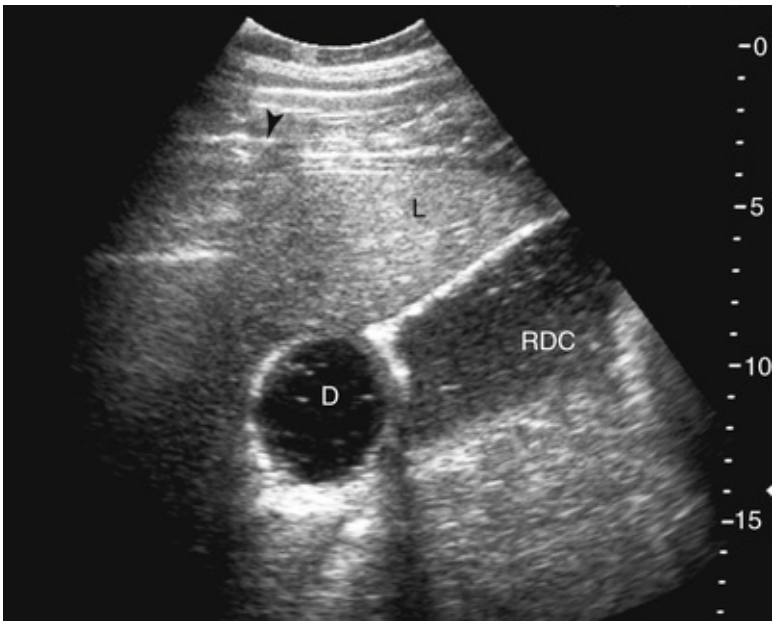


FIG. 32.16 Ultrasound view obtained from the right twelfth intercostal space of a horse with proximal enteritis. The duodenum *(D)* was distended to approximately 4 cm with reduced motility. The duodenal wall was mildly thickened (4 mm). The *black arrowhead* marks the ventral tip of the lung. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of

18 cm. *L,* Liver; *RDC,* right dorsal portion of the colon.

Inflammatory Bowel Disease and Ileal Hypertrophy.

If the signs of abdominal pain are more insidious, if an affected horse exhibits weight loss despite a good appetite, or if panhypoproteinemia is present, then symmetric and diffuse or regional thickening of the small intestine may be a sign of infiltrative or hypertrophic disease, such as inflammatory bowel disease, neoplasia (especially lymphosarcoma), or idiopathic ileal hypertrophy.[28] In these circumstances, the wall can be either uniformly or irregularly thickened, often with a narrow or obscure lumen (Fig. 32.17). In a study involving 35 horses with chronic wasting, a 5-mm cutoff value for patients with diffuse small intestinal wall thickness provided the best compromise between sensitivity (50%) and sensitivity (100%) for inflammatory bowel disease; rectal biopsy findings served as the reference standard.[29] Motility is usually preserved, unless mural thickening results in secondary mechanical obstruction. Definitive diagnosis of inflammatory bowel disease or idiopathic hypertrophy requires histopathologic evaluation.

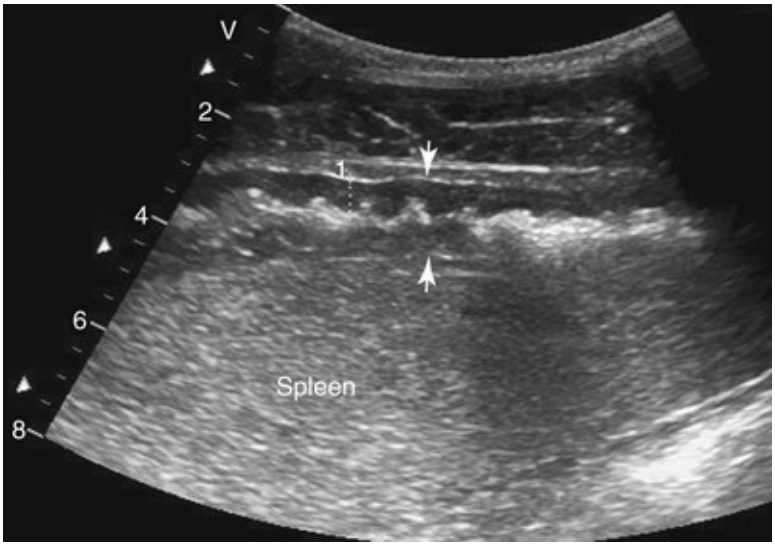


FIG. 32.17 Ultrasound view obtained from the left flank adjacent to the spleen, revealing the thickened and wavy wall of a longitudinally oriented segment of small intestine in a horse with chronic inflammatory bowel disease. The *white arrows* mark the serosal surfaces. The thickened walls are predominantly hypoechoic. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 8 cm.

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Nonstrangulating Obstructive Lesions of the Small Intestine.

Mechanical obstruction of the small intestine in which the adjacent blood supply remains intact—such as an ileal impaction, adhesions, mural hematoma, or that caused by severe chronic infiltrative disease of the intestinal wall—causes variable degrees of luminal distention proximal to the site of obstruction. In general, lack of significant changes in wall thickness or structure are features helpful for distinguishing simple nonstrangulating lesions of the small intestine from strangulating or severe inflammatory lesions. If serial ultrasonography reveals progressive severity of distention and lack of motility (see Fig. 32.17), surgical intervention should be considered.[26,27]

Strangulating Obstructive Lesions of the Small Intestine.

Progressive pain with poor response to medical intervention, lack of fever, and the presence of serosanguineous peritoneal fluid with increased or increasing lactate concentrations are clinical features that might help distinguish strangulating lesions of the small intestine from simple obstructions and enteritis. As with nonstrangulating obstructive lesions of the small intestine, ultrasonographically, the intestine proximal to strangulating obstructions is distended with either gas or fluid. The degree of distention and motility varies with the duration of strangulation; preobstruction segments may become turgidly circular and completely amotile loops of small intestine, and this development is highly correlated with mechanically obstructive lesions that necessitate surgical intervention (Fig. 32.18).[26,27]

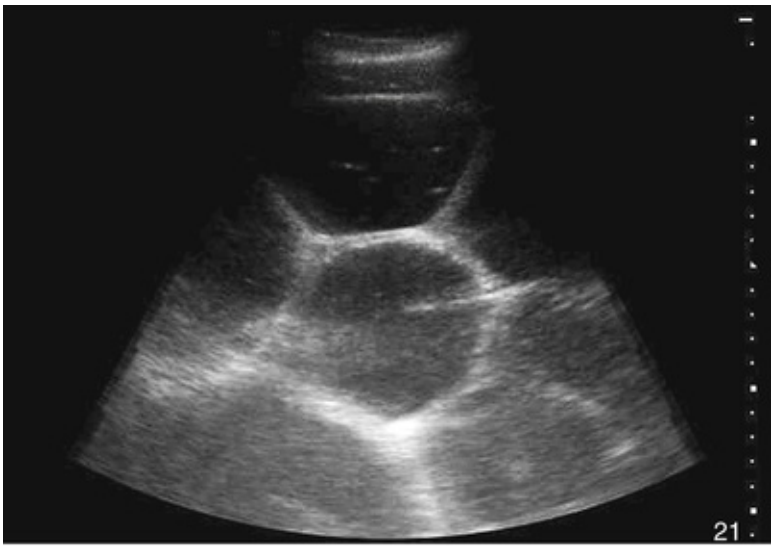


FIG. 32.18 Ultrasound view obtained from the left flank from a horse with a nonstrangulating obstruction that necessitated an exploratory celiotomy for correction. Note the numerous turgidly round and distended loops of small intestine. In real time, these distended loops had no appreciable motility. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 21 cm.

An important distinguishing feature of strangulated small intestine is the appearance of focally and usually uniformly thickened walls at the site of the strangulation (Fig. 32.19). Thus when regional uniform thickening of the small intestine is identified ultrasonographically, with other evidence of obstruction (hypomotile, hairpin-turn stacks of turgidly round and distended loops of small intestine with dependent ingesta), a strangulating obstruction should be the top consideration. Frequently the strangulated loops are identified in the ventral portions of the abdomen. In one study, the presentation of focal thickening and distention of the small intestine with no motility was 100% sensitive and 100% specific evidence of strangulating lesions of the small intestine.[26] If the affected segments are most readily visualized adjacent to the spleen and stomach on the left side of the abdomen (Fig. 32.20) or between the liver and right dorsal portion of the colon on the right side of the abdomen (Fig. 32.21), these respective locations are areas in which gastrosplenic and epiploic foramen incarcerations are readily found.

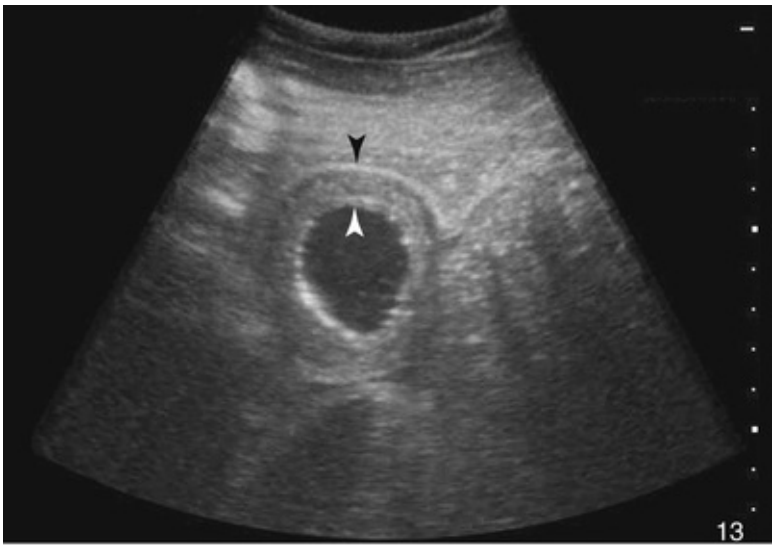


FIG. 32.19 Ultrasound view obtained from the left flank from a horse with a strangulating obstruction. A single distended loop of small intestine exhibits uniform thickening of the wall to approximately 8 mm (between *arrowheads*). In real time, this segment had no discernible motility. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 13 cm.

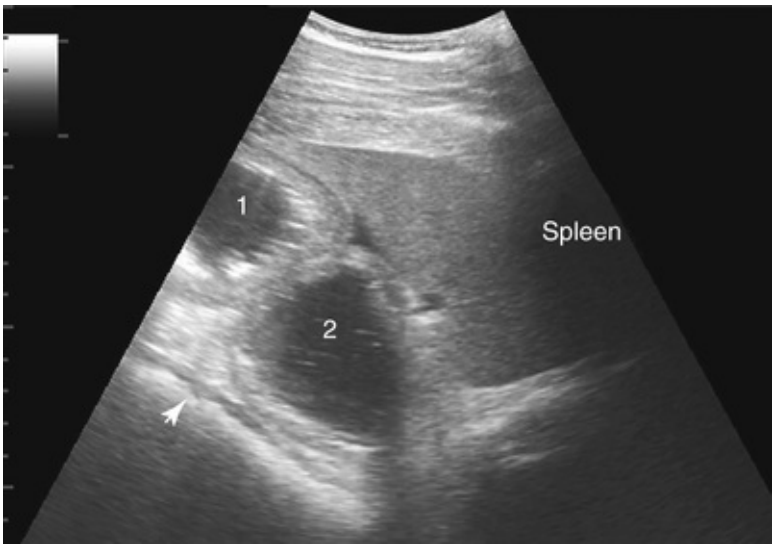


FIG. 32.20 Ultrasound view obtained from the gastric window from a horse with a strangulating gastrosplenic ligament entrapment. The left side of the image is dorsal. Two thickened, distended, and amotile loops of small intestine (labeled *1* and *2*) were found between the spleen and the stomach *(arrowhead).* This image was obtained with a 3.5-MHz probe set to a depth of 17 cm.

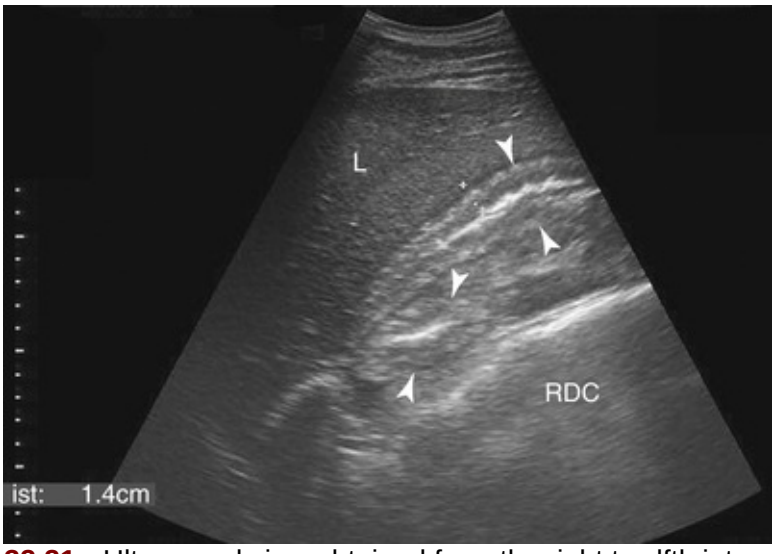


FIG. 32.21 Ultrasound view obtained from the right twelfth intercostal space from a horse with an epiploic foramen entrapment. *Arrowheads* mark the serosal surfaces of two thickened (14-mm wall) and compressed loops of amotile small intestine between the liver *(L)* and the right dorsal portion of the colon *(RDC).* This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 24 cm.

Intussusception.

Intussusceptions of the small intestine are most common in foals and young horses, and affected segments have a characteristic “bull's-eye” or target appearance in images across the short axis of the small intestine (Fig. 32.22).[30] The intussuscepted intestine tends to fall toward the dependent portion of the abdomen. As in other mechanical obstructive diseases, the proximal small intestine has normal wall thickness but is distended, with reduced motility and hairpin turns, depending on the degree of obstruction.



FIG. 32.22 Ultrasound view obtained along the caudal ventral midline in a horse with a jejunojejunal intussusception. The *arrowhead* marks the inner loop telescoped into the outer loop of jejunum *(arrow),* which created the classic “bull's-eye” appearance. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 10 cm.

Ultrasonographic Anatomy of the Right Side of the Abdomen.

Right-sided transabdominal ultrasonography is described with a systematic approach of scanning in the direction of cranial to caudal.

Liver and Pancreas.

The liver, descending duodenum, and right dorsal portion of the colon have characteristic locations and can be identified in the right rostral abdomen at the level of the shoulder (Fig. 32.23). The liver is located from the sixth to the fourteenth intercostal spaces, between the diaphragm and the right dorsal portion of the colon (see Fig. 32.23). Gas in the lung or the right dorsal portion of the colon can obscure identification of the liver dorsally or ventrally, respectively; ultrasonographically, the liver may thus be visible over only a few intercostal spaces. Only a small portion of the right side of the liver can be imaged, so its size is estimated on the basis of its expanse across the intercostal spaces.[12] It is unusual for the liver to be seen beyond the fifteenth intercostal space or in the same transverse plane as the right kidney, except at the most rostral aspect of the kidney. The ventral edges of a normal liver are distinctly sharp. Like that of the spleen, the architecture of the liver is relatively homogeneous, but more vessels are visible in the liver, and the general echogenicity of the liver is less than that

of the spleen.[17] Portal veins have more connective tissue in their walls and thus have more echogenic walls than do the hepatic veins.[12] Short segments of smaller portal veins often appear as hyperechoic parallel lines (see Fig. 32.23). In some small horses, the portal vein can be seen entering the hilus deep on the medial side of the image. The common bile duct and its branches within the liver are not normally visible.[12] The pancreas is not usually identifiable via transabdominal ultrasonography.[12]

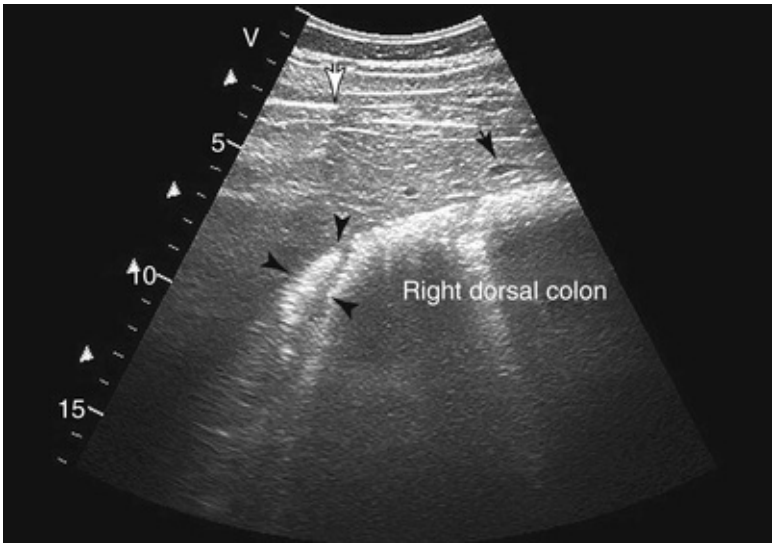


FIG. 32.23 Ultrasound view obtained at the eleventh right intercostal space at approximately the level of the shoulder in a horse. The left side of the image is dorsal. The *white arrow* marks the ventral tip of the lung. The *black arrowheads* mark the serosal surface of the duodenum with a hyperechoic lumen, between the liver and the right dorsal portion of the colon. Short hyperechoic parallel lines in the liver are the walls of portal veins *(black arrow).* This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 17 cm.

Duodenum.

The position of the duodenum is fixed by its suspending mesoduodenum; thus the duodenum can reliably be found descending the right middle abdomen at approximately the level of the shoulder, between the liver and the right dorsal portion of the colon (see Fig. 32.23), where it can be imaged transversely along its short axis. As with the jejunum, to locate the descending duodenum, the ultrasonographer must wait for a peristaltic contraction to deliver ingesta through

the lumen, thereby expanding the lumen; otherwise, the shape of the duodenum typically appears as a hyperechoic flattened or crescent-shaped line to a flattened oval. It is unusual for the duodenal diameter to exceed approximately 3 cm in healthy horses during peristaltic propulsion of ingesta.[31] The duodenum contracts one to four times per minute in fed horses,[31] but contractions are less frequent in anorexic, fasting, or heavily sedated horses. The duodenum can be followed on imaging to the level of the ventral right kidney (Fig. 32.24), where it crosses medially into the abdomen and is no longer distinguishable. The wall of the duodenum is less than 3 mm thick.[17]

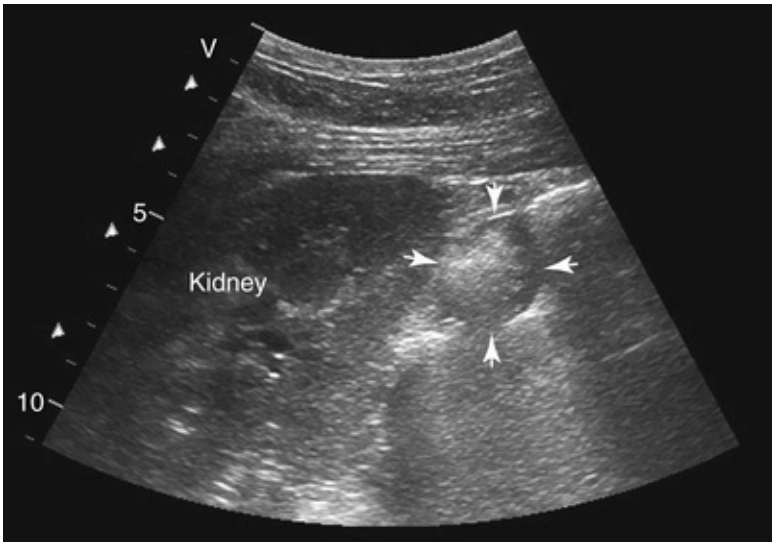


FIG. 32.24 Ultrasound view obtained from the right fifteenth intercostal space in a horse. The left side of the image is dorsal. The duodenum *(arrows)* can be seen ventral to the right kidney. This still image, captured when a peristaltic wave distended the luminal diameter to approximately 2.5 cm, was obtained with 3.5-MHz curvilinear probe set to a depth of 11 cm.

Right Portion of Colon.

The right dorsal portion of the colon, which has no sacculations, is immediately ventral to the liver and duodenum and is usually found from the right tenth to twelfth intercostal space, although it can extend to the fourteenth intercostal space.[32] The wall of the right dorsal portion of the colon consistently appears as a hyperechoic curved line, adjacent to the liver (see Fig. 32.23). Because of gas contents in the right dorsal portion of the colon, wall thickness is difficult to

measure accurately, and although thickness of up to 5.9 mm has been reported in healthy horses, less than 4 mm is typical.[32,] The walls of the right dorsal portion of the colon are significantly thinner in ponies and miniature horses than in large breed horses, typically measuring less than 3.2 mm.[33] If the ultrasonographer locates the right dorsal portion of the colon and slides the transducer ventrally, the interface between the right dorsal and right ventral portions of the colon is often identifiable, appearing as an indentation in the wall between the nonsacculated right dorsal portion of the colon dorsally and the sacculated right ventral portion of the colon ventrally. The right ventral portion of the colon has sacculations, and its contractions and wall thickness are similar to those of the left portion of the colon, although a wall thickness up to 5.1 mm has been reported in healthy horses.[32] The contents of the different portions of the right portion of the colon and their medial walls are normally obscured by luminal gas. The transverse colon is not usually identifiable via transabdominal ultrasonography.[12]

Right Dorsal Colitis.

When diarrhea in a horse is accompanied by panhypoproteinemia and a history of nonsteroidal antiinflammatory drug (NSAID) therapy, transabdominal ultrasonography of the right dorsal portion of the colon can be a useful diagnostic aide.[32] In patients with NSAID-induced right dorsal colitis, the wall of the right dorsal portion of the colon often appears thickened with mixed echogenicity and an irregular mucosal-luminal interface.

Displacement Right Dorsal Portion of Colon.

Identification of a large gas-distended viscus in the right caudal abdomen by transrectal palpation with accompanying taut colonic bands is consistent with a diagnosis of right dorsal displacement of the colon. The only major blood vessels normally visible ultrasonographically in the right caudal abdomen are those associated with mesentery of the lateral cecal band.[15] Thus the ultrasonographic finding of distended vessels with reduced blood flow in colonic mesentery adjacent to the body wall implies that the colon is rotated along its long axis and would be consistent with a diagnosis of right dorsally displaced colon or a colonic volvulus (Fig. 32.25).[24]

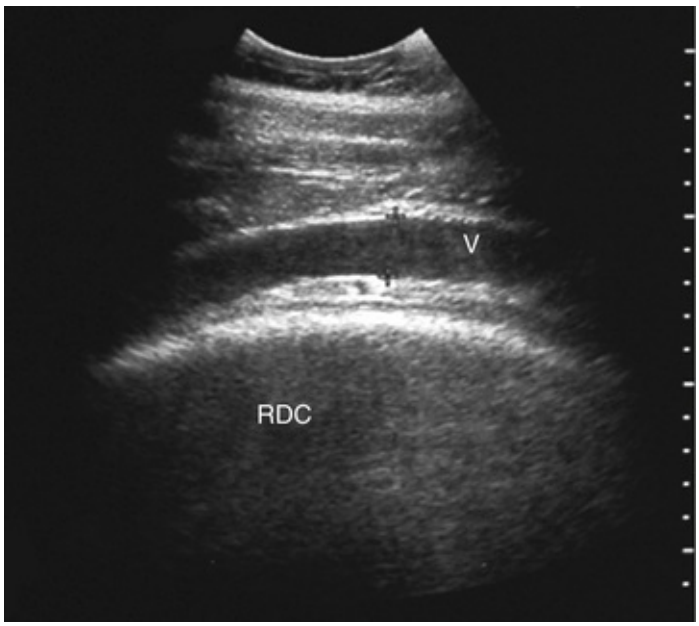


FIG. 32.25 Ultrasound view obtained from the right fifteenth intercostal space in a horse. A distended vein *(V)* is visible lateral to the wall of the right dorsal portion of the colon *(RDC).* The horse had a colonic volvulus. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 17 cm. (Courtesy Science In 3D, Inc. and copyright 2002, University of Georgia Research Foundation, Inc.)

Cecum.

The cecum has a sacculated wall that extends from the right paralumbar fossa to ventral midline, and its motility is similar to that of the different portions of the colon.[8,15] A unique characteristic that can be useful for distinguishing the cecum from the right ventral portion of the colon is that the lateral cecal band is oriented dorsoventrally and contains an associated artery and vein, whereas the lateroventral band of the right ventral portion of the colon is oriented caudocranially and does not have associated vasculature.[15] The cecal wall is less than 4 mm thick, and gas in the lumen precludes imaging the contents and far wall. Most diseases affecting the cecum can be sufficiently identified by transrectal palpation; however, transcutaneous ultrasonography can be helpful in confirmation of the diagnosis.

Typhlitis.

With acute inflammatory disease of the cecum, the cecal wall may be thickened, the mucosal surface may appear irregular or wavy, and movement varies from hypomotile to hypermotile. Gas normally present in the body or base of the

cecum precludes visualization of its contents and distal wall; however, with typhlitis, the cecum is often distended with fluid that is readily seen swirling inside of the lumen, and the distal wall can be visualized, especially toward the cecal apex.

Cecal Impaction.

Transrectal palpation is a better method of diagnosing cecal impactions, but transabdominal ultrasonography of cecal impactions may reveal loss of characteristic sacculations.

Cecocolic and Cecocecal Intussusception.

On transrectal evaluation, intussusceptions involving the cecum are often palpable as indistinct large, firm masses in the right or midcaudal portion of the abdomen. As with small intestinal intussusceptions, the characteristic ”bull's-eye” can be seen in the wall of the cecal apex or body within the lumen of the cecum or right ventral portion of the colon. In chronic intussusceptions, the walls are very thick and may appear abscessed or mass-like (Fig. 32.26).

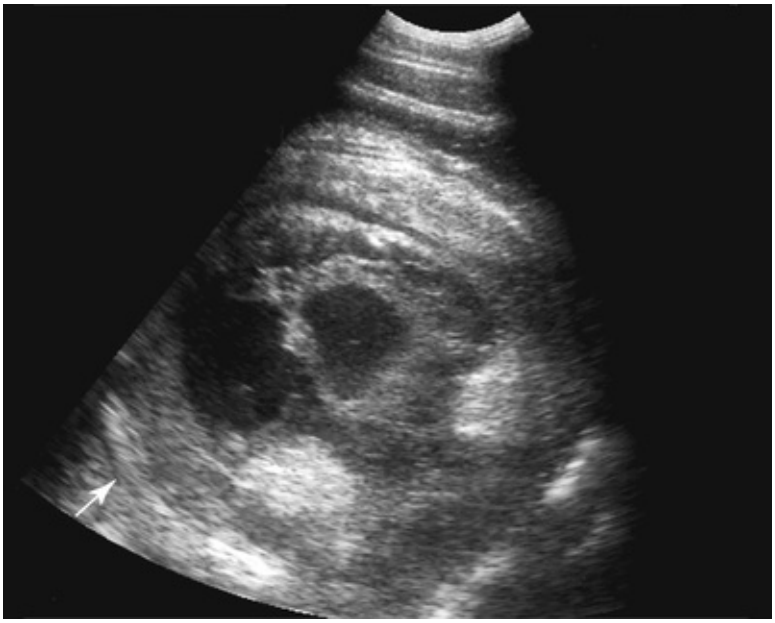


FIG. 32.26 Ultrasound view obtained from the right midflank in a horse with a cecocolic intussusception that appears as a large mass *(arrow).* The appearance of a “wall within a wall” is most apparent in the near field. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 24 cm.

Right Kidney.

Gas in the cecum, right dorsal portion of the colon, or lungs sometimes obscures visualization of the right kidney, which is normally found in the rostral fifteenth to seventeenth intercostal spaces[20] (see Fig. 32.24). In Thoroughbred horses, the right kidney measures 6.5 to 9.1 cm dorsoventrally (the slightly oblique transverse plane), 12.1 to 16.2 cm in length craniocaudally (the dorsal plane), and 6.5 to 8.4 cm lateromedially.[19] The ureters are usually difficult to identify, but the proximal right ureter sometimes appears as a hyperechoic circular structure at the hilus. The architecture of the right kidney is similar to that of the left kidney.

Peritoneal Cavity.

In a healthy horse, only minute pockets of peritoneal fluid should be identifiable in the rostroventral area of the abdominal cavity or adjacent to sacculations of the ventral portion of the colon. Excessive peritoneal fluid displaces organs and greatly facilitates visualization of structures not normally seen on ultrasonographic examination, such as the mesentery of the small intestine (Fig. 32.27).

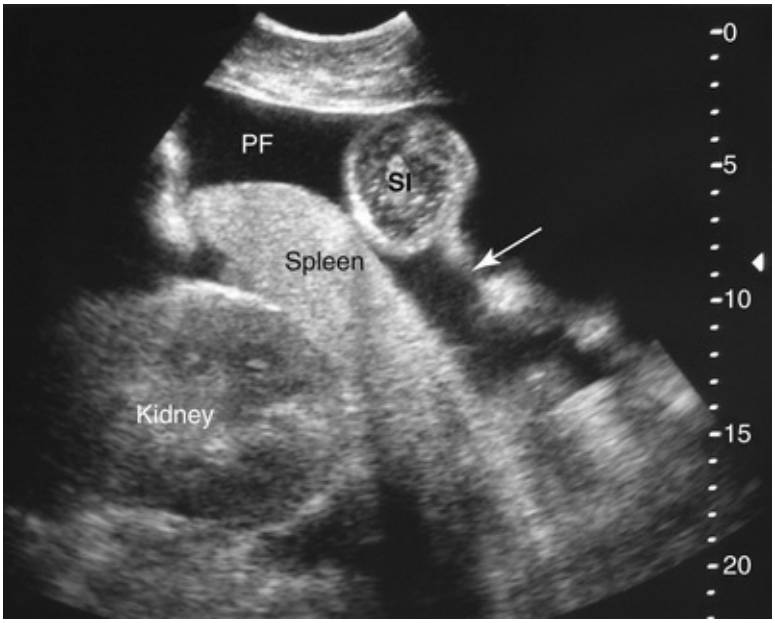


FIG. 32.27 Ultrasound view obtained from the left dorsal sixteenth intercostal space in a horse. The left side of the image is dorsal. Excessive

hypoechoic peritoneal fluid *(PF)* has displaced the spleen from the left body wall and enabled distinct visualization of a single loop of small intestine *(SI)* and its supporting mesentery *(arrow),* appearing as a "balloon on a string." The horse had metastatic mesothelioma. This image was obtained with a 3.5-MHz curvilinear probe.

Peritonitis.

Peritonitis should be suspected if volume or echogenicity of peritoneal fluid is increased. In some cases, free-floating or adherent fibrin or fibrous tags may be visible (Fig. 32.28). An abdominocentesis is an integral step for further characterizing the cause of peritonitis.

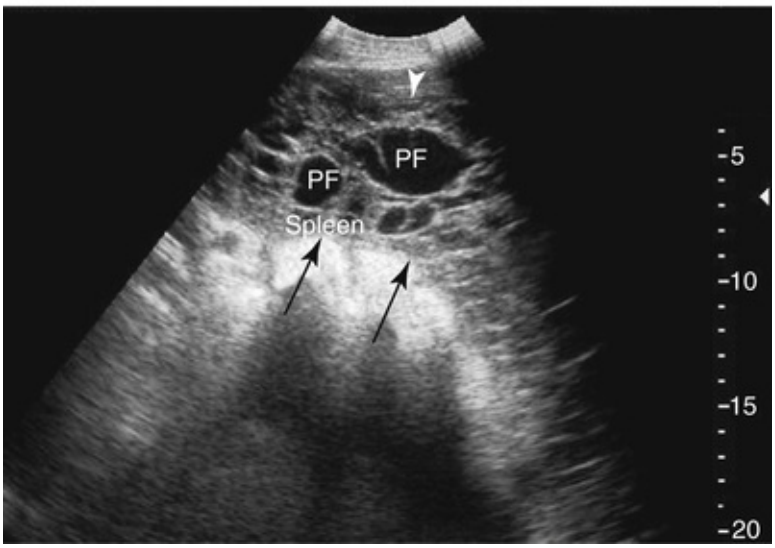


FIG. 32.28 Ultrasound view obtained from the lower right flank in a horse. The left side of the image is dorsal. Numerous hyperechoic fibrinous and fibrous adhesions trapping pockets of hypoechoic peritoneal fluid *(PF)* are present between the body wall *(white arrowhead)* and the serosal surface of the right ventral portion of the colon *(black arrows).* The horse had septic peritonitis. This image was obtained with a 3.5-MHz probe set to a depth of 21 cm.

Hemoabdomen.

Excessive blood in the peritoneal cavity displaces organs off the body wall. Blood in the peritoneal cavity appears as a mixed echogenic fluid that, in real time, often appears to swirl as it mixes with less echogenic peritoneal fluid (Fig.

32.29).[15] Abdominocentesis confirms the presence of blood.



FIG. 32.29 Ultrasound view obtained from the lower left flank of a horse with hemoabdomen. The left side of the image is ventral. Blood displaces the spleen from the left body wall and appears as swirls of mixed echogenicity between the spleen and left body wall. This image was obtained with a 3.5-MHz curvilinear transducer set to a depth of 24 cm.

Intraabdominal Masses.

Abscessation, hematoma, and neoplasia are the top potential diagnoses for intraabdominal space-occupying lesions, each of which can be located just about anywhere in the peritoneal cavity, in or attached to bowel, other intraabdominal viscera (i.e., spleen, kidney, liver), or the peritoneum. Space-occupying lesions appear as soft tissue densities of variable shapes and acoustic properties that distort normal sonographic architecture (Fig. 32.30). Although the definitive cause of an intraabdominal mass is often not discernible ultrasonographically, both abscesses and hematomas appear as either uniform echogenic or loculated space-occupying masses of mixed echogenicity. Chronic abscesses may be characterized by the presence of a thick echogenic capsule. Abscesses and hematomas are more commonly confined to a single location, whereas metastatic neoplasia should be considered if space-occupying lesions of varying sizes that distort normal ultrasonographic anatomy are visible in multiple locations. Although the ultrasonographic appearance of a space-occupying lesion may not help determine the cause, ultrasonography can be a useful guide for

biopsy or aspiration of the affected tissue.

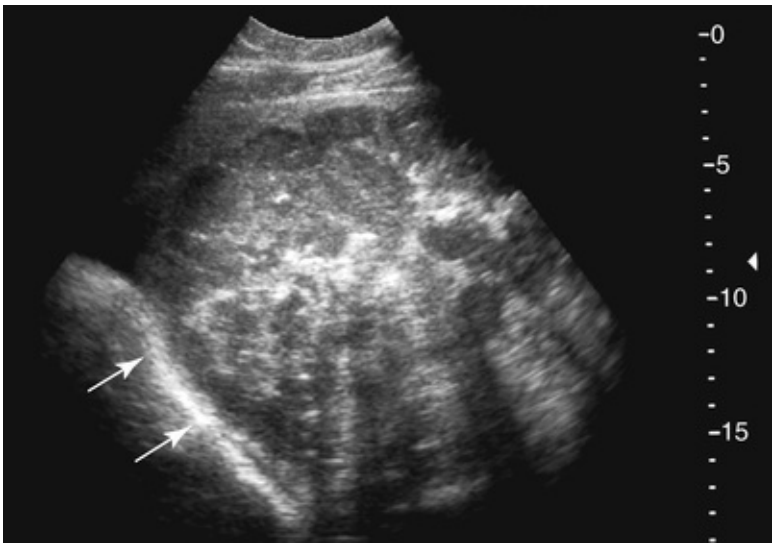


FIG. 32.30 Ultrasound view obtained from the gastrosplenic window in a horse. The left side of the image is dorsal. A large mass of mixed echogenicity occupies the space adjacent to the stomach wall *(arrows)* in the location normally occupied by the spleen. The horse had abdominal lymphosarcoma. This image was obtained with a 3.5-MHz curvilinear probe set to a depth of 19 cm.

■ Other Imaging of the Alimentary Tract

Radiography.

In horses the alimentary tract is a dynamic and complex environment to evaluate with any modality. Because of the size of the animal, as well as the distinct difference between air and soft tissue, radiographs are a useful diagnostic tool for evaluating the teeth, pharynx, esophagus, stomach, and intestinal tract. Portable radiographic units with maximal kilovolt peak (kVp) settings of 100 and maximal milliampere-second (mAs) settings of 30 make it possible for ambulatory practitioners to obtain diagnostic images of the head and cranial portion of the esophagus. However, to obtain images of the thoracic portion of the esophagus and abdomen, a referral clinic with a more powerful radiographic generator is usually required.

For average foals, exposures ranging from 80 to 88 kVp and 20 to 26 mAs have been used in radiography of the abdomen.[34] In adult horses, exposures

range from 60 to 140 kVp and 20 to 70 mAs.[35,36] To perform a complete evaluation of the abdomen, it is recommended that the abdomen be divided into four quadrants (cranioventral, midabdominal, caudodorsal, and caudoventral).[35] Large cassettes (35 cm × 43 cm) and fast screens are also needed to ensure that a diagnostic image is obtained. Because of the large amount of scatter radiation produced from the high exposure and thickness of tissue penetrated, an 8 : 1 to 10 : 1 grid should be used.[34-38] Alternatively, an air gap technique can be used to prevent image degradation.

The advent of computed radiography and digital radiography has greatly increased the diagnostic capabilities of conventional radiographic examinations. Both systems, available to equine practitioners, are considered indirect imaging modalities in which the x-ray photon interacts with an intensifying screen to convert the x-ray photon to light. This light then interacts with an imaging plate: film, as with a conventional radiographic system; within a photostimulable phosphor, as with computed radiography; or within a flat-panel detector, as with digital radiography. Regardless of the method, these images are considered "indirect" because the x-ray photon is first changed to light and then detected by the imaging medium.[39] The main benefits of computed and digital radiography are the increased latitude of the film. It is possible to change the contrast and grayscale levels after the exposure if the number of photons is adequate. The digital radiography systems also offer a rapid evaluation of the image because the cassette is directly connected to the computer. This allows the portable systems to show radiographic images within 10 seconds after the exposure is made. In contrast, the computed radiography system requires the cassette to be placed into a reader in order to display the image. Finally, because both computed and digital radiography are generally compliant with the Digital Imaging and Communications in Medicine (DICOM) standard, this allows any specialists with standard medical imaging software to view the images via a compact disk or via the Internet.

Survey radiography is generally helpful in evaluating the cervical portion of the esophagus for evidence of rupture, as well as in evaluating the abdomen. Esophageal ruptures secondary to an obstruction or vigorous placement of a nasogastric tube produce a small volume of gas that tracks just dorsal to the trachea (Fig. 32.31). This can be confused with a tracheal laceration; however, with tracheal lacerations, generally the gas accumulates around the trachea, and the volume of gas within the subcutaneous tissues and the cranial mediastinum is extreme. In addition, esophageal obstructions, also called *choke*, can sometimes

be identified on survey radiographs, depending on the material that is causing the obstruction and the amount of air or contrast medium that is able to surround the structure (Fig. 32.32). Although the nature of the obstruction cannot be determined, the extent of the abnormality can sometimes be identified.

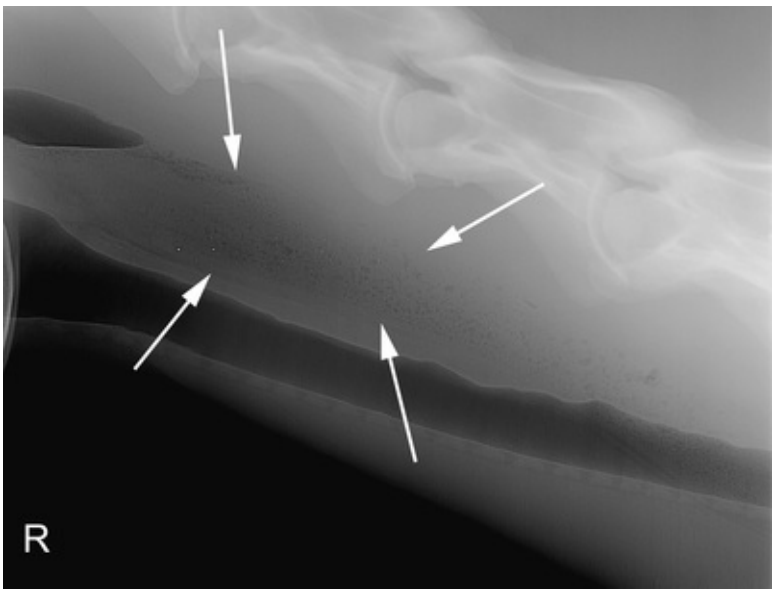


FIG. 32.31 Standing lateral radiograph of a 13-year-old Morgan gelding with an esophageal tear. Note the tubular region of small gas opacities caused by air trapped around the outer border of the esophagus *(arrows).* An esophageal perforation secondary to an ingested foreign body was confirmed with endoscopy.

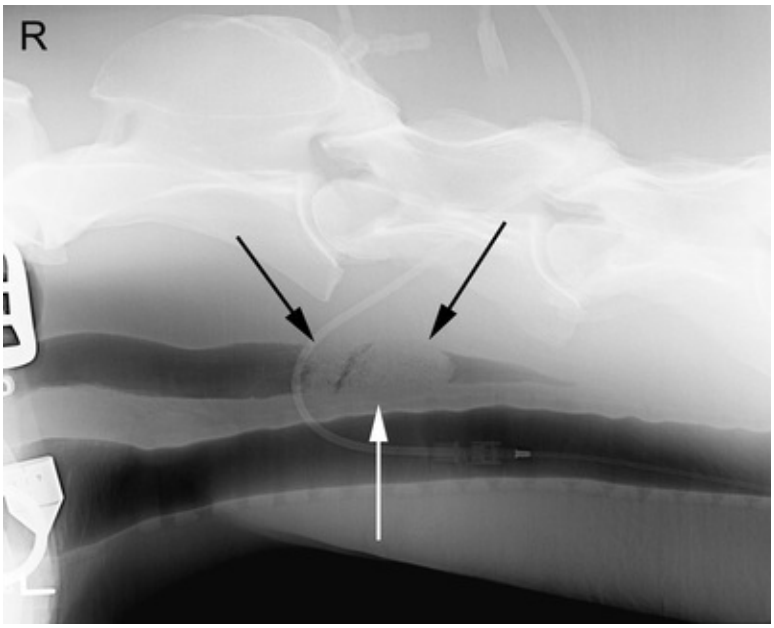


FIG. 32.32 Standing lateral radiograph of a 12-year-old Quarter Horse mare. Note the ovoid mass surrounded by gas just dorsal to the trachea *(arrows).* This lesion was a mixture of hay and grass.

Abdominal radiography is useful for evaluating the small and large intestines for sand accumulation, enterolithiasis, impactions, or small intestinal disorders in foals. When sand is ingested, it generally accumulates within the large colon along the ventral abdomen[10] (Fig. 32.33). Radiography is useful for monitoring the resolution of sand impactions after medical management; however, sequential examinations are needed to verify that the volume of sand has decreased.[36] If the volume of sand is large enough, it is difficult to determine whether an enterolith is present because of radiographic summation of the two lesions. Enteroliths are solid concretions of mineral that usually form around a nidus, such as a metallic foreign body (Fig. 32.34). The mineral composition is varied, as illustrated by the different opacities within the enterolith. Radiographs have a 96.4% positive predictive value for detecting enteroliths in high-prevalence areas. In one study, enteroliths were generally found to be within the midabdominal radiograph, and 67% of small colonic enteroliths caused large colonic distention, which was also identified on radiographs.[35] Impactions are more difficult to diagnose because radiography usually demonstrates only increased feed accumulation within the abdomen. Although no enterolith or obstruction is identified, granular material can be seen, usually within the ventral portion of the colon near the sternal flexure. This is because pelvic flexure impactions cause the feed material to accumulate orad, causing distention of the

left ventral portion of the colon (Fig. 32.35). Intestinal disorders such as functional ileus secondary to enteritis (Fig. 32.36) or obstruction secondary to intussusception or meconium impaction (Fig. 32.37) in foals can also be identified on abdominal radiographs. These images show large dilation of the small intestine, and differentiation between functional and mechanical ileus in foals is generally based on the size of the intestine and the volume of gas that is present.[37] Evaluation of the abdomen with ultrasonography may aid in qualifying the small or large intestinal motility, as well as identifying the source of an obstruction if it cannot be determined on radiographs.



FIG. 32.33 Standing lateral radiograph of a 4-year-old Arab mare with a history of colic. Note the large amount of opaque material within the ventral portion of the colon, probably secondary to sand accumulation.

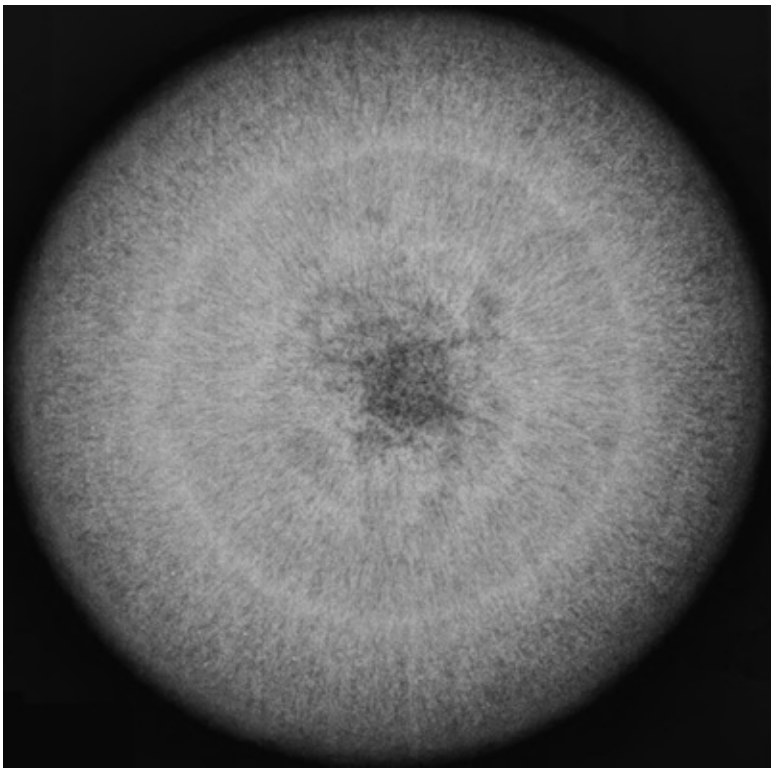


FIG. 32.34 Radiograph of enterolith obtained after surgical removal from the small colon. Note the variation in opacities caused by the various types of minerals that are contained within the enterolith.

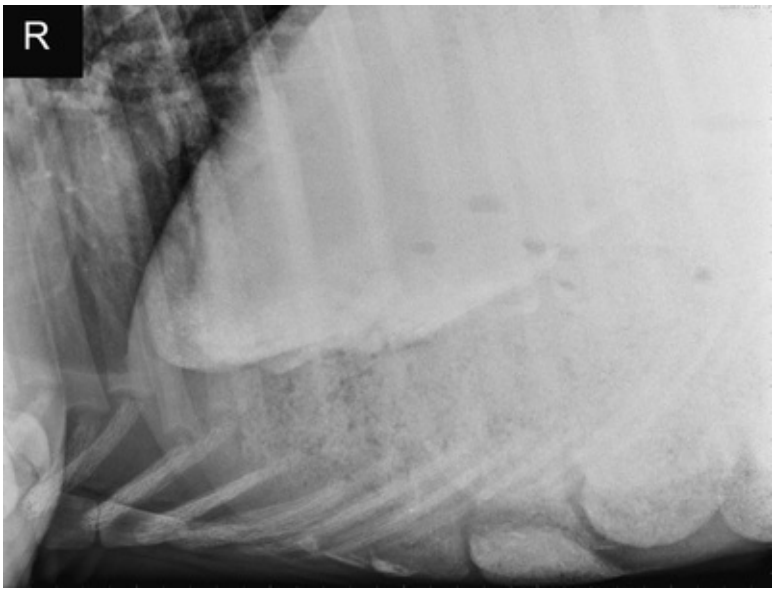


FIG. 32.35 Standing lateral radiograph of a 3-year-old Paint Horse gelding with a pelvic flexure impaction. The radiograph shows the sternal flexure with a large amount of granular material and a small amount of

sand accumulation in the ventral portion of the colon.

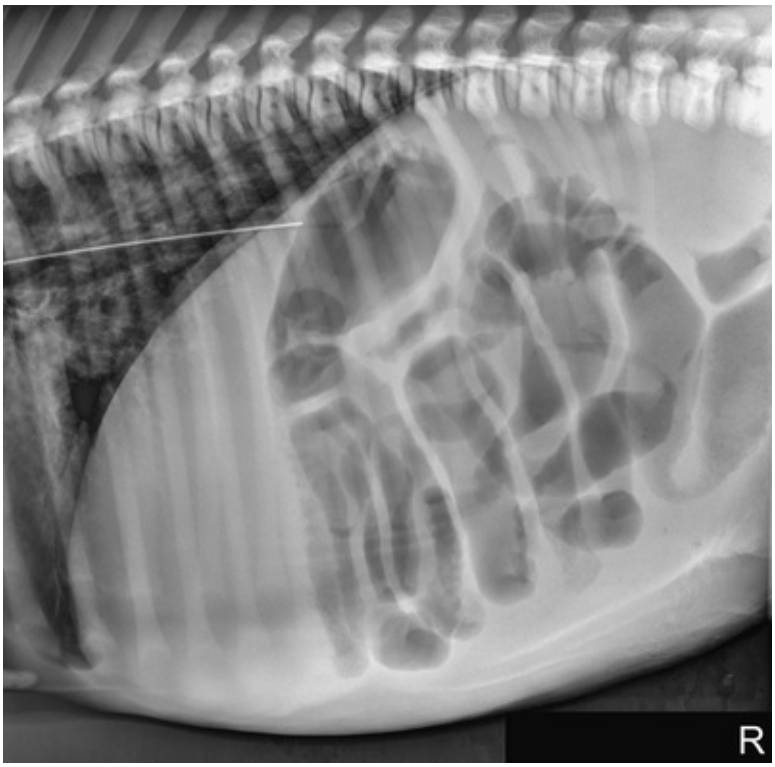


FIG. 32.36 Standing lateral radiograph of a 1-day-old, premature Quarter Horse filly. Note the large amount of gas-distended intestine. Because of the large amount of small intestinal distention, functional ileus was the primary differential diagnosis.

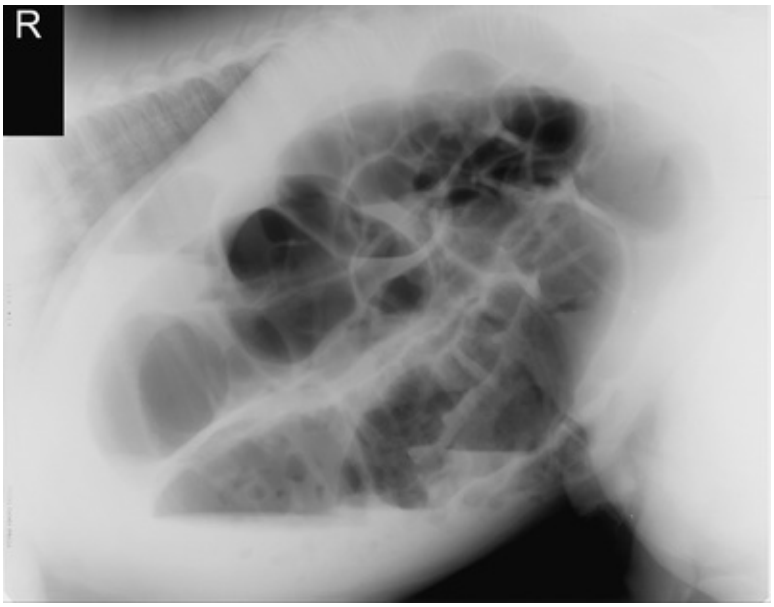


FIG. 32.37 Standing lateral radiograph of a 2-day-old Thoroughbred colt with a meconium impaction. Note the large amount of gas distention of the colon.

Radiography also allows for the use of contrast medium to further outline the alimentary tract and to evaluate pharyngeal function and esophageal motility.[40-42] Approximately 60 mL of barium sulfate paste or liquid, administered orally via a 60-mL dosing syringe, for radiographs of the laryngeal region and esophagus provides useful information about swallowing and large obstructions. If the barium liquid is identified dorsal to the soft palate, within the larynx or trachea, pharyngeal function is probably abnormal.[40] The barium paste coats the pharynx and esophagus, and this appearance is useful for identifying any ulcerations or irregularities in the mucosal surface. After those procedures have been performed, or if there is no evidence of an oropharyngeal dysphagia, esophagography is performed. For this procedure, water is added to approximately 200 to 500 mL of barium sulfate liquid to achieve a concentration of 1 : 1 or 2 : 1, which brings the total volume to 500 to 1000 mL. This liquid is administered through a nasogastric tube or cuffed endotracheal tube placed within the cranial portion of the esophagus to the level of C2 to C3. If a cuff is available, the cuff can be inflated with approximately 10 mL of room air. A radiograph is then made to verify that the tube is not within the trachea, and when it has been confirmed to be within the esophagus, the dose of barium is administered with a stomach pump. Toward the end of the dose, while the liquid is still being pumped, radiographs of the cranial, mid, and caudal portion of the

esophagus are obtained (Fig. 32.38). The use of the pump provides distention of the esophagus to help identify strictures or irregularities in the esophageal wall.

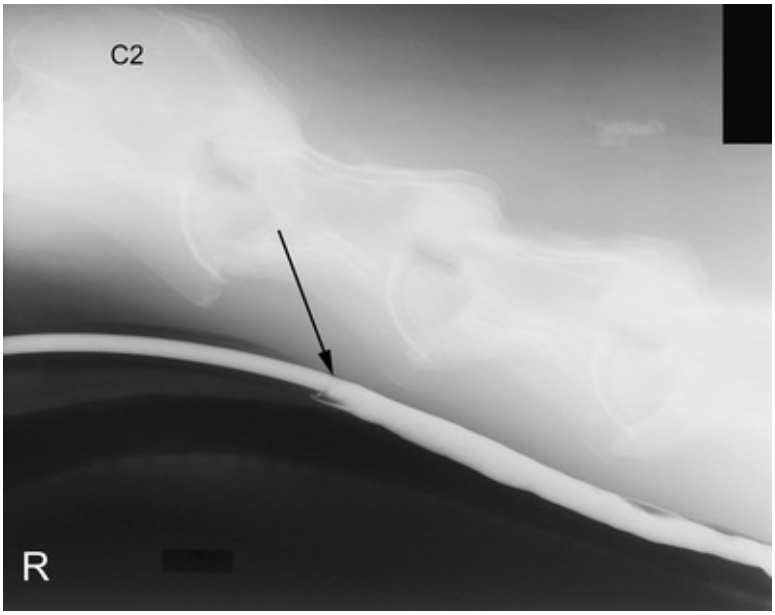


FIG. 32.38 Standing lateral radiograph, showing a normal esophagogram with barium liquid. The *arrow* marks the region where the nasogastric tube ends. This is approximately at the level of C3.

Positive (barium sulfate) and negative (room air) contrast media, administered orally, have also been used to evaluate the stomach and intestinal tract radiographically,[34,43,44] and the rectum and colon have been evaluated through retrograde administration of contrast medium.[44] These methods allow for the evaluation of the stomach, intestinal tract, and rectum for regions of obstruction, as well as ulcerations, tumors, motility disorders, and malformations. Although these methods have been described, ultrasonography has virtually eliminated the need to expose personnel and patients to the repetitive, high doses of radiation needed to obtain sequential radiographs of the abdomen.

Computed tomography (CT) and magnetic resonance imaging (MRI) are of little use for evaluation of the alimentary tract (except for the head). This is mainly because of the size of the patient in relation to the size of the gantry and bore in CT and MRI units, respectively. Dental disorders such as abscesses and fractures are clearly visible on CT images, especially on three-dimensional reconstructions (Fig. 32.39), and CT is also useful for detecting pharyngeal and esophageal masses that may not be fully identified with conventional

radiographs. CT and MRI can be used in foals that can be placed within the gantry or bore of the magnet; however, because of the motion of the gastrointestinal tract and the long acquisition times used with respiratory gating sequences, MRI has not been used widely to evaluate the thorax or abdomen. A single case report has been published about the use of contrast esophagography and CT to aid in the surgical planning of a persistent right fourth and left sixth aortic arch that caused a vascular ring anomaly in a foal.[45] However, the applications for these technologies have yet to be realized.

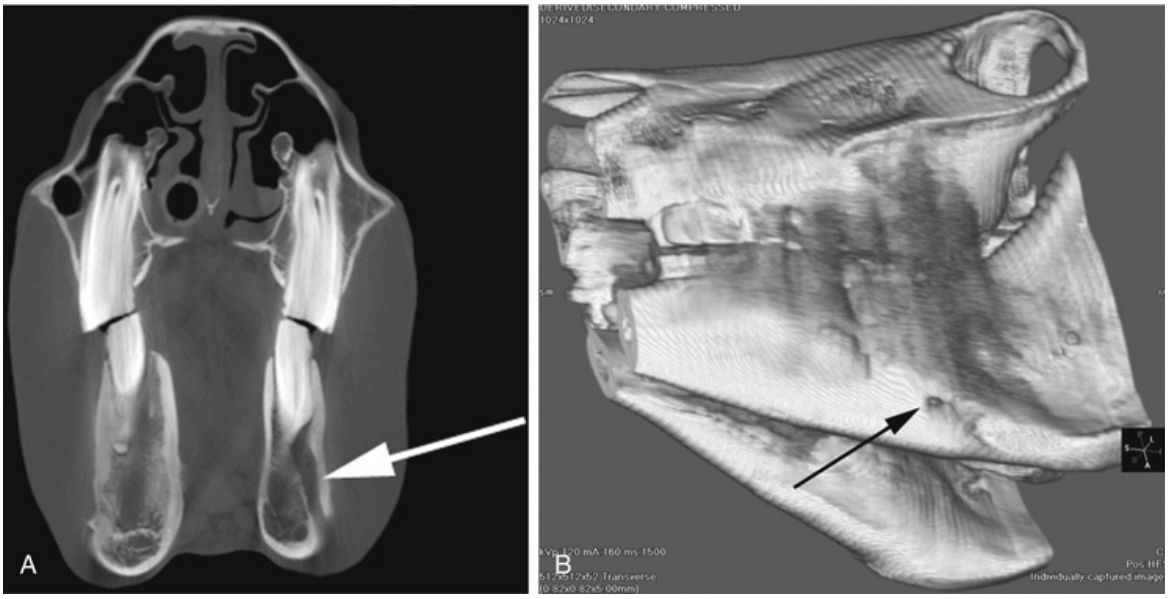


FIG. 32.39 Transverse **(A)** and three-dimensional **(B)** reconstructed computed tomographic images of the head of a 4-year-old pony mare with chronic draining tracts from the mandible. The *arrows* illustrate the tract through the mandible that communicates with the apical portion of the left mandibular first molar (tooth #309).

Scintigraphy.

Nuclear medicine is used widely for imaging the gastrointestinal tract in humans and animals. Although physical obstruction can be assessed with endoscopy, ultrasonography cannot delineate the pylorus in the normal horse because of the peripheral nature of the colon and colonic gas. Nuclear medicine provides a functional evaluation of the pylorus to determine whether gastric emptying is delayed in comparison with that in normal horses. This modality works better than gastric emptying with barium sulfate because of the minimally invasive

nature of the modality and ease of image acquisition. However, because of the need for a gamma camera to generate the images and the licensing requirements to handle radioactive material, this modality is less universally available. The primary use of scintigraphy in evaluating the gastrointestinal tract is to measure gastric emptying time.[46-49] Two protocols have been outlined in the references provided: The first entails the use of the readily available technetium-99m pertechnetate (^{99m}Tc) bound to disofenin or sulfur colloid.[47,50,51] This combination of radioisotope and radiopharmaceutical is fed in a pelleted ration alone or mixed with radiolabeled eggs. The normal range for the $t_{1/2}$ gastric emptying has been reported to be 1.49 ± 0.17 hours[26] and 1.56 ± 1.08 hours.[26] The other method is the breath test involving carbon-13 bound to octanoic acid (^{13}C-OABT). This method was compared with the ^{99m}Tc sulfur colloid method, and the solid-phase gastric emptying $t_{1/2}$ was found to be similar.[45] The main difference is that the ^{13}C-OABT is measured in the exhaled breath of horses and with spectroscopy, rather than with a gamma camera. The rationale for ^{13}C-OABT is that because a gamma camera is not needed, this test may be more portable and useful for field investigations.[50]

Another nuclear medicine procedure in the realm of alimentary tract evaluation involves the use of ^{99m}Tc with hexamethylpropyleneamine oxime (HMPAO). This procedure allows for radiolabeling WBCs in order to determine areas of inflammation.[52,53] The use of ^{99m}Tc is a matter of convenience because it is also used in equine bone imaging. Detection equipment, such as a low-energy, all-purpose collimator, is readily available in many practices. HMPAO is used because it binds to granulocytes and therefore should travel to areas of increased inflammation.[53] HMPAO also associates with the reticuloendothelial system, enabling localization within the lungs, liver, spleen, kidneys, and urinary bladder. The main drawback is that with the HMPAO bound to WBCs, there is a general lack of anatomic information, which can cause lesion localization to be difficult.[53] Although this technique is expensive and labor intensive, the results from the limited studies available appear encouraging.

■ Biopsy

The decision about whether to perform biopsy is often based on the ease of obtaining a sample and the relative value of the evaluation that can be made. Very small samples, such as those obtained with an endoscopy biopsy

instrument, are relatively easy to obtain, but they provide limited information. Full-thickness bowel specimens, obtained by means of ventral midline or flank laparotomy, are more difficult to obtain, but they provide much more information. Laparoscopic techniques to safely obtain full-thickness intestinal biopsy samples have been described[54] and may be more practical than laparotomy.

Obtaining a biopsy sample by endoscopy allows the practitioner to choose the biopsy site on the basis of the appearance of the mucosal surface, which most frequently reflects an inflammatory disorder. Conversely, when a biopsy sample is obtained through laparotomy, the serosal surface of the bowel may not reflect a disorder within the bowel wall. In such instances, obtaining several biopsy specimens may be helpful. Rectal mucosal biopsies are easily performed. Many instruments can be used to obtain the biopsy specimen, and a uterine biopsy forceps works well. A fold of mucosa can be pinched readily between two fingers, and a sample of this tissue is obtained this way. The size of such a sample is adequate for histologic or bacteriologic examination.

■ Fecal Examination

Cytologic, biochemical, bacteriologic, immunologic, and electron microscopic evaluations can be performed on fecal samples. In addition, the consistency and color, the presence of foreign material such as sand or gravel, and the presence of parasites should be examined in the examination of the alimentary system. In addition to fecal consistency, fecal particle size can be used to evaluate the efficiency of mastication or the colonic transit time. Increased particle size, with loose or watery stool, is suggestive of decreased colonic transit time.

Cytologic examinations are used primarily to evaluate the parasite burden of the animal. Ova of large and small strongyles, tapeworms, round worms, and *Strongyloides westeri* are most common. Coccidia are observed occasionally, but their presence is clinically unimportant. Examination of fecal WBCs has been advocated in the evaluation of horses and foals with enterocolitis. Because these cells are very labile, their presence in large numbers indicates that an inflammatory process is present and that the inflammation is in the distal portion of the colon or is associated with decreased transit time.

The presence of fecal occult blood should be determined so as to diagnose gastric ulcers, duodenal ulcers, and other potentially hemorrhagic disorders of the alimentary tract. However, the usefulness of this test has been shown to be quite limited because negative results can be obtained when blood is present in

the proximal portion of the gastrointestinal tract.[55] The sensitivity of most commercially available tests is poor; they may yield negative results in the presence of severe gastric bleeding.

Fecal culture is an essential component in the evaluation of many patients. In bacteriologic culture techniques for fecal samples, selective media that are designed to isolate *Salmonella* are routinely used. These media include selenite broth, tetrathionate broth, brilliant green agar, XLD agar, and *Salmonella-Shigella* agar. Less selective media, MacConkey agar, and eosin methylene blue agars are desirable for culture of other potential Gram-negative bacterial pathogens such as *Escherichia coli*, but the mere presence of *E. coli* in the feces does not determine its pathogenicity. Enterotoxigenic *E. coli* strains have been isolated from foals with diarrhea, but special tests, such as polymerase chain reaction (PCR) assays, must be performed to determine whether an isolate produces enterotoxin. Rapid enzyme-linked immunosorbent assays (ELISAs) are available at diagnostic laboratories for detection of enterotoxins of *Clostridium difficile* (*C. difficile* Tox A/B Test, TechLab, Blacksburg, Va.) and *Clostridium perfringens* (*C. perfringens* enterotoxin test, TechLab, Blacksburg, Va.) in fecal specimens.

The presence of rotavirus in a fecal sample can be determined by ELISA or an agglutination test. Both assays test for the presence of viral antigen in the feces. PCR assays are also available to detect rotaviral nucleic acids. ELISA is reported to be more sensitive than the agglutination test but is less specific. Therefore the agglutination test is likely to yield more false-negative results, and the ELISA test is likely to yield more false-positive results. The ELISA test is more time-consuming and inconvenient to perform than the agglutination test. When rotavirus is a concern, particularly as a farm problem, a reasonable approach is to screen fecal samples with the agglutination test and repeat testing of samples that yield negative findings with ELISA or PCR.

Some diagnostic laboratories have developed sensitive and specific multiplex PCR tests for panels of gastrointestinal pathogens (equine coronavirus and rotavirus, *Lawsonia intracellularis, Cryptosporidium, Rhodococcus equi, Neorickettsia risticii, Salmonella* spp., coronavirus, rotovirus, and *C. difficile* toxins A and B), that provide relatively rapid diagnostic information that can be used alone or in combination with culture or antigen detection methods.

■ Absorption and Digestion Tests

Tests of the ability of the equine intestinal tract to digest and absorb nutrients

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have a more limited clinical application in horses than in human or small animal medicine, but they can be useful in the evaluation of chronic weight loss, suspected small intestinal inflammation or neoplasia, gastric and small intestinal partial obstruction, and postoperative small intestinal malabsorptive disorders. For absorption tests to be diagnostic, the intestinal disorder must either be diffuse or affect the delivery to and transit through the small intestine.

Maldigestion tests are performed to evaluate exocrine pancreatic function and disaccharidase activity at the mucosal brush border of the small intestine. Pancreatic exocrine deficiencies have not been described in horses, probably because equine pancreatic secretions consist primarily of water and bicarbonate and have less enzymatic activity than in monogastric omnivorous species. Maldigestion related to disaccharidase activity at the mucosal brush border is relevant in viral and bacterial enteritides of foals, particularly rotavirus and coronavirus enteritides. As a result of these viral infections, there is loss of the superficial villous epithelial cells of the small intestine, in which the disaccharidases lactase, cellobiase, maltase, sucrase, and trehalase are located.[56] Lactase levels are highest in young suckling foals, and loss of this enzyme activity, secondary to loss of the mucosal villous cells, leads to lactose maldigestion. Lactose tolerance can be tested by administration of a 20% solution of D-lactose at a dose of 0.5 to 1 g/kg. This dose should result in an approximate doubling of the serum glucose level within 60 minutes of administration.[57]

Clinically applicable absorption tests include the D-glucose and D-xylose absorption tests. The glucose absorption test has the advantage of being relatively easy to perform and inexpensive. However, cellular uptake and metabolism of glucose, as well as intestinal absorption, influence the results and thus are undesirable variables. The D-xylose absorption test is therefore advantageous because it more directly measures intestinal absorptive capacity. The results of both tests, however, are affected by gastric emptying rate and small intestinal transit time. In the United States, D-xylose is available only through chemical suppliers and only for research purposes; its availability for clinical diagnostic use is restricted.

The D-glucose and D-xylose tests are performed similarly. After an 18- to 24-hour fast, a 10% solution of D-glucose or D-xylose, 0.5 to 1 g/kg, is administered through a nasogastric tube. For the measurement of glucose, blood is collected in sodium fluoride tubes, and for the measurement of D-xylose, blood is collected in heparinized tubes. Samples are taken immediately and 30, 60, 90, 120, 150,

180, 210, and 240 minutes after administration. Peak levels, which normally range from 20 to 25 mg/dL, are reached 60 to 120 minutes after administration and should decrease thereafter. The normal curve resembles an inverted V. Absorption curves vary as a function of each horse's age and type of feed given.[58] Delay or flattening of the absorption curve may reflect delayed gastric emptying, increased intestinal transit time, or impaired intestinal absorption.[59] Accurate interpretation of the results of these tests depends on the results of other diagnostic evaluations. In addition, different types of diets have been shown to affect the height, although not the shape, of the absorption curves significantly. In general, with diets that have higher digestible energy content, the curve has a lower peak.

■ Breath Tests

In humans, dogs, and cats, breath tests are used to assess a variety of intestinal disorders. The hydrogen breath test is used in assessments of intestinal bacterial overgrowth and in determination of carbohydrate digestion and absorption in the intestine. In patients with an abnormal intestinal bacterial population or carbohydrate malabsorption, bacterial fermentation of carbohydrate is excessive, one by-product being hydrogen. Because hydrogen is freely diffusible from the bowel into the blood and from the blood into the alveoli, measurement of exhaled hydrogen gas can be used to assess the status of intestinal bacterial fermentation of carbohydrates.

In horses, the hydrogen breath test is most applicable to conditions involving carbohydrate malabsorption and thus increased delivery of soluble carbohydrate to the large intestine for bacterial fermentation to occur. This technique has been used in horses: In one report, different carbohydrate substrates were evaluated in seven ponies,[60] and in another, the hydrogen breath test was used in conjunction with D-xylose absorption in nine horses with a variety of clinical disorders.[61] In the study with ponies, fasting resulted in negligible levels of breath hydrogen excretion. Sustained increases in breath hydrogen concentration to more than 10 parts per million (ppm) were observed in all ponies after they ingested oats or wheat flour, in three ponies after the administration of glucose and xylose, and in two ponies after the administration of lactulose and lactose. The pattern of breath hydrogen excretion varied among animals after the ingestion of identical test meals. In the clinical study, the diseased horses showed higher fasting breath hydrogen levels (range 7.5 to 61.5 ppm) than did normal horses (range, 0 to 5

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ppm). After xylose administration, none of the healthy animals showed an increase in breath hydrogen production, and five of diseased animals showed increases in breath hydrogen. In this group of patients, abnormalities in hydrogen breath measurement were more apparent than abnormalities in D-xylose absorption.

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Dentistry and Oral Disease

Jack Easley

The equine species has evolved as a continuously grazing animal, developing its own dental form and function over millions of years. The oral and dental structures provide horses with the ability to detect, prehend, masticate, and begin the digestion of mixed grass forage. As humans have domesticated and confined horses, their diet has been altered to consist of grazing improved pastures with more interval feedings of dry hay, grain, processed forages, and concentrates. Selective breeding and domestication practices have increased the incidence of equine dental and oral disease in modern equine populations.

■ Anatomy and Function

The structures that horses use in eating include tactile and prehensile lips, hypsodont incisors, premolars and molars, facial bones, muscles of mastication, tongue, hard palate, buccal mucosa, cheeks, olfactory organs, taste buds, salivary glands and ducts, blood vessels, lymphatic vessels, and nerves that support them. The equid oral cavity is long and cylindrical and is the entrance to the alimentary canal. The muscular lips form the entrance to the mouth, which is bound laterally by the cheeks, dorsally by the palate, and ventrally by the body of the mandible and the mylohyoid muscles. The caudal aspect of the mouth is composed of the soft palate, root of the tongue, and epiglottis and is continuous with the oropharynx.[1,2]

The blood supply to the mouth is derived from the maxillary, mandibular, labial, and sphenopalatine arteries. The venous drainage is chiefly through the linguofacial veins. Nerve sensation in the mouth, cheeks, and lateral aspect of the tongue is derived from the mandibular and maxillary branches of the trigeminal nerve (cranial nerve V). Motor function of the sublingual and mandibular salivary glands, lacrimal glands, and facial and labial muscles is activated by the facial nerve (cranial nerve VII). The hard palate has a central raphe, dividing the surfaces into right and left halves. The portion of the palatal mucosa just caudal to the upper incisors may appear swollen in 2- to 5-year-old horses when permanent incisor teeth erupt. Such mucosal enlargement is normal and has historically been referred to as *lampas*. Farther caudal, the hard palate becomes more concave and contains paired transverse ridges that traverse the cavity. These ridges are instrumental in moving a food bolus caudally in a spiral

manner as horses masticate forage.

The highly mobile, muscular tongue sits in the bottom of the mouth between the paired hemimandibular rami. It is covered by a tough, specialized squamous epithelium modified to form papillae. The tongue is supported in a sling formed by the mylohyoideus muscles. The root of the tongue is attached to the lateral aspect of the soft palate, pharynx, and hyoid bone. The lingual muscles receive their motor innervation from the hypoglossal nerve (cranial nerve XII) and sensory innervation from the lingual and glossopharyngeal nerves (cranial nerve IX). The rostral portion of the tongue is susceptible to injury from bits and other tack placed in the oral cavity. Injury from penetrating foreign body (usually wire) and neurogenic injury are possible.

The mandible is the largest bone of the face and is formed by the paired hemimandibles, which fuse rostrally at the mandibular symphysis when horses are approximately 2 to 3 months of age. Each hemimandible is composed of a horizontal and a vertical ramus. The horizontal ramus contains the alveoli of the teeth in the lower jaw. The vertical ramus terminates with the coronoid process rostrally and the mandibular condyle caudally. The temporalis muscle inserts on the coronoid process.

Between the incisors and the rostral aspect of the mandibular cheek teeth in the horizontal rami of the mandible is a large diastema: the interdental space or “bars” of the mouth. Canine teeth, if present, are located in this area. In young horses, the ventral border of the mandible is wide and round. Eruption swellings or “bumps” are often seen on the ventral border of the mandible of 2- to 4-year-old horses as the permanent mandibular cheek teeth erupt. With age and as eruption of the mandibular cheek teeth continues, the ventral border of the mandible takes on a sharper, angled appearance.

The paired incisive (premaxillary) bones form the rostral part of the upper jaw and contain the alveoli of the upper incisors. Caudally, the incisive bone becomes thinner and forms the rostral part of the hard palate. The suture line between the incisive bones and the maxillary bones is an anatomically weak area and a common site of facial fractures. The upper canines (if present) are situated just caudal to this suture line.

The paired, large maxillary bones extend from the incisive bone rostrally to the nasal bones dorsally and lacrimal bones caudally. The facial crest is a prominent ridge of bone on the lateral aspects of the maxillae. This crest continues caudally as the zygomatic process and joins the molar and temporal bones to form the zygomatic arch. The ventromedial aspects of the maxillary

bones join to form a horizontal shelf that provides rigid support to the majority of the hard palate. The alveoli of the upper canines, premolars, and molars are embedded in the maxillae. The positions of the alveoli of the upper cheek teeth are somewhat variable, but usually the alveoli of the first two cheek teeth lie rostral to the maxillary sinuses. The third and fourth cheek teeth lie within the rostral maxillary sinus in young and middle-aged horses. The caudal two cheek teeth lie within the caudal maxillary sinus. As the teeth continue to erupt with age, the maxillary sinus volume increases. More detailed anatomic relationships of the maxillary cheek teeth and the paranasal sinuses have been explored in horses of various ages with the use of CT.[3] Each alveolus is separated by transverse interalveolar bony septa.

Horses have seven paired paranasal sinuses: ventral conchal, dorsal conchal, frontal, sphenopalatine, caudal maxillary, rostral maxillary, and ethmoidal sinuses. The rostral and caudal maxillary sinuses are contained within the maxillae and are usually separated by a thin bony septum, although this septum often breaks down with sinus disease. The long infraorbital canals (one on each side of the head) traverse longitudinally through the maxillary sinuses, encasing the large paired infraorbital nerves.

Sinusitis can result from disease of the third, fourth, fifth, and sixth upper cheek teeth and classically results in a unilateral, malodorous nasal discharge. In a young horse, virtually the entire maxillary sinuses are occupied by dental alveoli. Therefore as the facial bones grow and reserve crowns of the upper cheek teeth erupt, the cheek teeth move forward and ventral in the sinus compartments. The maxillary sinuses drain into the back of the nasal cavity via a slitlike aperture, the nasomaxillary opening. The medial compartment of the rostral maxillary sinus is called the *ventral conchal sinus.* This compartment has poor drainage and is a common site in which inspissated pus accumulates. Its secretions must drain dorsally over the infraorbital canal into the lateral compartment of the rostral maxillary sinus. Drainage from these two sinuses courses into the caudal middle meatus adjacent to the drainage angle of the caudal maxillary sinus. The areas rostral to the paranasal sinuses are scrolled sections of the nasal cavities, referred to as the *dorsal* and *ventral nasal conchal bullae.* These structures have been shown to be an area in which inspissated pus accumulates in cases of chronic sinusitis.[4]

The temporomandibular joint is a synovial joint formed by the articulation of the squamous temporal bone and the condylar process of the mandible. The joint lies approximately 15 cm above the level of the occlusal surface of the cheek

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teeth. The joint cavity is large and divided in two by a cartilaginous intraarticular disk. The joint is bound by a tight capsule and lateral and caudal ligaments. The unique functional anatomy and age-related changes in the normal equine temporomandibular joint were described only as recently as the mid-2010s.[5,6] This joint can make a wide range of lateromedial movements (allowing the medially directed power stroke of mastication) but limited vertical and rostrocaudal movements.[7]

As a result of the wide lateromedial range of motion of the temporomandibular joint associated with the power stroke of chewing, the masseter and pterygoid muscles are the most highly developed muscles of mastication in horses. The powerful masseter muscle originates along the full length of the facial crest and zygomatic arch and has wide insertions along the caudolateral aspect of the mandible. The superficial masseter muscle fibers run almost vertically, whereas the deep fibers course in a ventrocaudal direction. The masseter pulls the jaw to the ipsilateral side and also contributes to closure of the jaw. The medial and lateral pterygoid muscles have origins and insertions similar to those of the masseter, and these lie on the medial aspect of the mandible. The digastricus muscle originates on the occipital bone and attaches to the caudal aspect of the mandible and is small in horses as a result of the minimal effort required to open the jaw with gravity assistance. The temporalis muscle, whose function is jaw closure, is also small and poorly developed in horses because vertical opening of the temporomandibular joint is limited. The muscles of mastication are innervated by the motor branch of the mandibular nerve, which originates from the trigeminal nerve (cranial nerve V).

■ Teeth

At approximately 6 months of age, 24 deciduous teeth have erupted in a foal. Development of the cranial and facial bones during the first 2 to 3 years of life allows room for the expansion of the dental formula from 24 deciduous to between 36 and 44 permanent teeth in a mature horse. The mature mouth of a horse contains six incisors each in both the upper and lower jaws, six permanent upper cheek teeth on each side of the mouth, and six lower cheek teeth on each side of the mouth (Fig. 32.40). The rostral three cheek teeth are premolars, and the caudal three cheek teeth are molars. Incisors and premolars have deciduous and permanent sets. Molars erupt at an older age and do not have deciduous counterparts. The cheek teeth of the upper jaw are broad and square, whereas the

lower cheek teeth are narrower and rectangular.

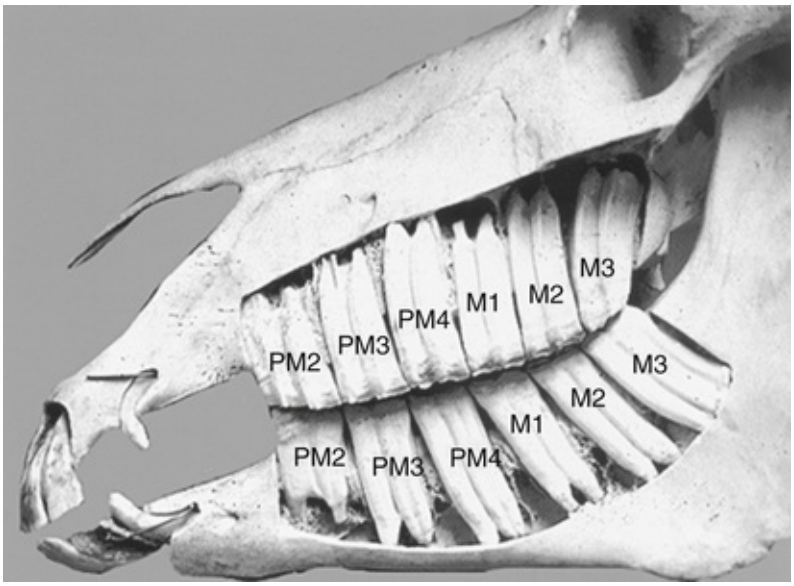


FIG. 32.40 Lateral view of equine cadaver skull. *M,* Molar; *PM,* premolar.

The cheek teeth in each quadrant of a horse's mouth are commonly referred to by number, from rostral to caudal (1 to 6). The inconsistent and vestigial first premolar, often referred to as a "wolf tooth," is not included in the 1-to-6 nomenclature. To help avoid confusion, the American Veterinary Dental College has endorsed use of the Modified Triadan System of tooth numbering for horses.[8] This three-digit tooth numbering system is based on a full phenotypic dentition composed of 44 teeth in total. The first digit designates the quadrant and arcade location and whether the dentition is deciduous or permanent. The numbering sequence for permanent teeth starts with 1 for the upper right, 2 for the upper left, 3 for the lower left, and 4 for the lower right. The corresponding deciduous teeth quadrants are numbered 5 to 8, respectively. In each dental quadrant, the first or central incisor is always 01; the other incisors are numbered 02 and 03. The canines, whether present or not, are designated 04 in this formula. The premolars are numbered 05 to 08 and the molars 09 to 11.

The equine incisor and molarized cheek teeth are hypsodont and have long anatomic crowns, which erupt throughout the life of the animal in a dynamic process of periodontal ligament and alveolar bond remodeling. The tooth crown is the enamel-containing portion of the tooth. When these hypsodont teeth first erupt, the occlusal surface is covered with cementum overlying the enamel. As

the teeth are subjected to masticatory forces and abrasive forage, the thin layers of occlusal cementum and enamel wear away, exposing the true or functional occlusal surface of the tooth. This process is termed *coming into wear.* The functional occlusal surface of hypsodont teeth is composed of thin, brittle sheets of hard enamel, sandwiched between softer but more stress-resistant layers of cementum and dentin. This three-textured occlusal surface is self-sharpening and very wear- and fracture-resistant. At the time of eruption, there are no true roots, and teeth are divided into apical and coronal regions, but most of the crown (reserve crown) lies within the alveolus. True roots are formed gradually over a period of 2 to 3 years after eruption.

The incisors and upper cheek teeth have enamel crown invaginations termed *infundibulae.* These invaginations partially fill with cementum that receives its blood supply from the occlusal soft tissues covering the tooth before eruption. A shallow infundibulum is present on each incisor tooth and has a wide opening at the occlusal surface referred to as a *cup.* As a tooth wears down over time, the small bottom portion of the infundibulum is exposed at the occlusal surface and is called the *spot.* Each upper cheek tooth has two deeper infundibulae: one rostral (mesial) and one caudal (distal). These extra enamel cones give the central area of these teeth a hard, serrated, but wear-resistant chewing surface. As these teeth develop but before the occlusal surface comes into wear, the infundibulae are supplied by infundibular arteries entering from the occlusal direction. Cementogenesis of the infundibulum starts first at distinct enamel infoldings in the occlusal part of the infundibula and advances in an apical direction.[9] The center of the cement lake that fills the infundibulum contains a hole of variable diameter. This channel is a remnant (“ghost”) of the central blood vessel that supplied nutrition to the now dead infundibular cementum. If the blood supply becomes compromised before cementogenesis is complete, infundibular cemental hypoplasia can develop, which predisposes affected teeth to infundibular caries and midsagittal fractures.

The interior of a tooth is composed primarily of dentine; primary dentine lines the walls of the common pulp chamber of a newly erupted tooth. The pulp chambers of hypsodont teeth are active throughout a horse's life, with primary and secondary dentine continually produced within the pulp cavity. This process of continuous secondary dentine production prevents pulp exposure at the occlusal surface as the tooth wears. The depth of secondary dentine at the occlusal surface of the pulp horns (seen as a brownish area on the occlusal surface of the tooth) varies in horses but is usually 5 to 7 mm thick. No age-

related increased thickness of occlusal secondary dentine has been found research, which supports the theory that secondary dentine deposition is at least partially regulated by occlusal stimulation.[10,11] The pulp cavity in the young equine permanent cheek tooth is very large. With increasing age, it divides into smaller pulp chambers (or horns) as dentine deposition increases. From 2 to 4 years after eruption, mandibular cheek teeth have a distinct, apically located, common pulp chamber that communicates with the pulp horns. The number of pulp horns has been well described: Five pulp horns are present in the 07 to 10 teeth, six pulp horns in the 06 teeth, and six or seven pulp horns typically present in the 11 teeth (Fig. 32.41).[12] Two to four years after tooth eruption, the dentine divides the endodontic system of most of the mandibular cheek teeth into two distinct compartments or roots. Each compartment consists of a root canal, a pulp chamber, and two or three pulp horns. The anatomic changes in pulps with age are quite complicated and slightly different between horses; thus endodontic treatments in this species are challenging.[13] The maxillary cheek teeth, as well as the 311 and 411, have three roots: one palatal and two buccal. Because of the continuous production of cementum around the apical or root portion of the tooth and continuous crown wear, old equine teeth wear apically past the infundibular enamel and peripheral enamel infolding that normally prevents crown attrition (senile excavation). When most of the crown enamel has worn away, the softer dentine and cementum are quickly worn away, which leads to a condition known as “senile excavation.” As the crown undergoes further wear, the peripheral enamel is lost, and the smooth dentine and cementum become the functional occlusal surface. When this condition involves multiple teeth in an arcade, it is referred to as *smooth mouth.*

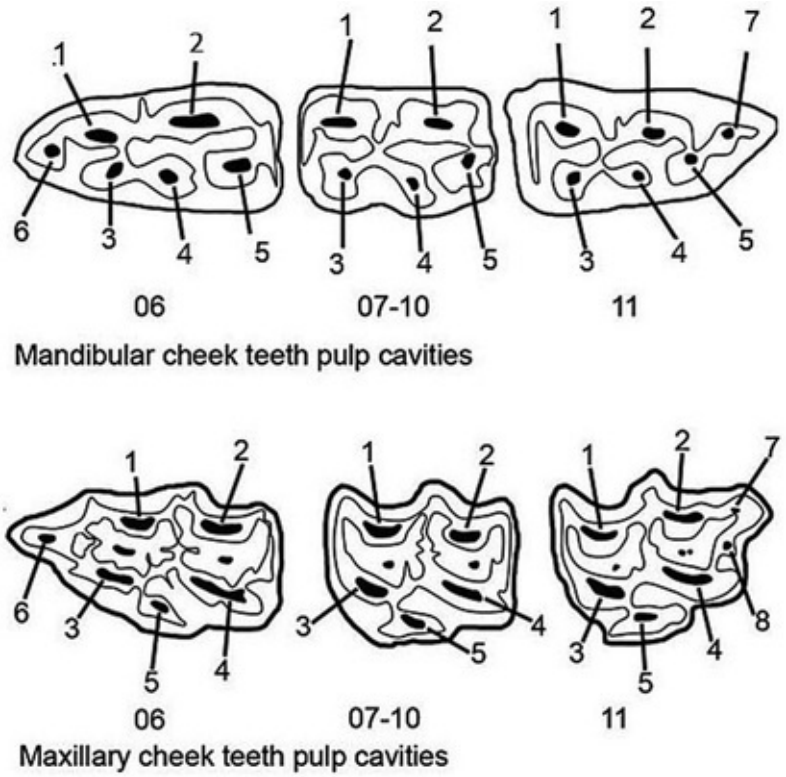


FIG. 32.41 Diagram of the premolar and molar pulp horns, seen as dark areas of secondary dentine on the occlusal surface.

Innervation of the dental structures is supplied by the trigeminal nerve (cranial nerve V), which exits the skull just below the ear. This nerve traverses rostrally and divides into the ophthalmic, maxillary, and mandibular branches. The maxillary nerve lies in the pterygopalatine fossa deep to the subperiorbital fat pad and enters the caudal maxilla ventral to the orbit via the maxillary foramen. It runs through the maxilla in the infraorbital canal, at which point it becomes the intraorbital nerve, and gives off branches to supply the maxillary cheek teeth and incisors. A branch of the infraorbital nerve exits the maxilla at the infraorbital foramen, just rostral and dorsal to the facial crest. The mandibular nerve runs medially along the mandible, becoming the lingual and inferior alveolar nerves, which arise as a common trunk and pass rostrally between the pterygoideus medialis and the ramus of the mandible. The inferior alveolar nerve enters the mandibular canal on the caudomedial aspect of the mandible, innervating the mandibular teeth. The mental nerve exits the mandibular canal via the mental foramen at the rostrolateral aspect of the mandible just rostral to the mandibular cheek teeth and supplies the ipsilateral soft tissues over the incisive portion of the mandible. These nerves and their branches are clinically

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significant in diagnostic procedures or procedures involving regional anesthesia in horses.[14]

Rudimentary first premolars (wolf teeth) are constant in fetal life in both upper and lower jaws. Many never develop to the point of eruption but instead degenerate and become incorporated in the maxilla or mandible. The upper wolf teeth erupt in 20 to 80% of horses; the lower wolf teeth rarely erupt (in 1% to 5%).

Equine males normally have two upper and two lower canine (bridle) teeth. This type of anatomic discrepancy is referred to as *sexual dimorphism*, inasmuch as as canine teeth are absent or rudimentary in most mares. The upper canine teeth erupt just caudal to the suture between the incisive and maxillary bones. The lower canine teeth lean forward, producing a long lower diastema or interdental space.

The horse is anisognathic: that is, the bottom jaw is narrower (by ≈25%) than the upper jaw. The lateral excursion of the jaw during mastication is conducive to occlusal wear of the buccal aspect of the lower and the lingual aspects of the upper molar arcades. The horse's jaw anatomy and jaw motion have an effect on the angle of the molar tables.[15] Cheek teeth occlusal angles have been found to range from 15 to 20 degrees in normal horses, according to three-dimensional models from CT images.[16] As horses chew, the jaw moves in rotational motion from side to side with some rostral-caudal excursion.[17] The construction of the molars with interdigitations of enamel, cementum, and dentine allows for uneven, continuous wear with a sharp, serrated surface when horses are grazing. The extent of lateral excursion of the mandible during normal mastication is affected by the length of the stem or roughage in a horse's ration. A horse on pasture or hay has a full or wide area of mandibular excursion. However, horses eating pellets or concentrates have a limited range of lateral jaw excursion. Horses with limited lateral jaw excursion have incomplete wear of the molar surfaces, which predisposes the arcades to sharp enamel edges, a vaulted ceiling of occlusion, or the serious problem of shear mouth. Malocclusion of the incisor or molar arcades perpetuates abnormal wear patterns that eventually predispose affected horses to diastema and secondary periodontal disease.[18]

Rostral or caudal molar malocclusions or eruption problems (displaced, deformed, delayed-eruption, missing, or supernumerary teeth) lead to uneven dental wear. Many horses with asymmetry between the upper and lower molar arcades (as a result of mandibular fracture, facial injury, congenital deformities

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such as brachygnathism [parrot mouth] and prognathism [sow mouth] or a mandible that is abnormally narrow in relation to the maxilla) have abnormal tooth wear in the form of sharp enamel points, dental overgrowths (hooks or ramps), shear mouth, step mouth, or wave mouth.

The dynamic change that takes place in the mature horse's head continues at a slower rate throughout life, with continual eruption and crown wear of the hypsodont premolar, molar, and incisor teeth, which retain their long reserve crowns and slowly-forming, short root structures. With continuous eruption and wear of the equine hypsodont teeth, all horses eventually experience senile attrition and wearing of their teeth “smooth” to the root.

■ Equine Dental Developmental Abnormalities

Equine dental developmental abnormalities can involve tooth number, structure, or position in the dental arcades. Abnormalities of dental development and eruption are quite common in horses and result in a wide range of clinical conditions. A congenital/developmental problem that manifests at the time of tooth eruption often leads to acquired dental problems as the teeth continue to erupt and wear. Some developmental abnormalities of the teeth of very young horses may not cause it to exhibit clinical signs until middle age. Consequently, several different dental abnormalities with interrelated pathogenesis are often present concomitantly at the time of clinical presentation.[19-21]

Supernumerary Teeth.

Supernumerary teeth are teeth in excess of the normal expected number in any of the dental arcades. This disorder has been referred to as *polydontia* or *hyperdentition.* Supernumerary teeth can be loosely categorized morphologically into two categories: (1) supplemental teeth that resemble teeth of the normal series in crown and root structure but not always in size, and (2) rudimentary or dysmorphic teeth that are abnormally shaped and smaller in size than normal teeth.

In general, these extra teeth are encountered at the caudal aspects of the molar arcades, but supernumerary teeth can also be lingual, buccal, or rostral to the normal arcades. Clinical signs most commonly associated with supernumerary cheek teeth are dental overgrowths and diastemata, which often lead to secondary periodontal disease.

Supernumerary incisors are reported more often in horses than are supernumerary cheek teeth. The main condition included in the differential

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diagnosis for supernumerary incisors or cheek teeth is retained deciduous teeth. In some cases, it may be clinically difficult to determine whether an extra tooth is a retained deciduous tooth or a supernumerary tooth. Examination with a radiograph that encompasses the entire affected dental arcade is often necessary to diagnose this condition. Radiographic examination of the affected jaw is often indicated to determine the identity of an extra tooth. A retained deciduous tooth has a more mature root and a shorter reserve crown than does the adjacent permanent teeth. Such distinguishing characteristics are visualized with radiographs.

Horses with supernumerary teeth should be managed on a case-by-case basis, but management in general is limited to regular assessment of the dentition, coupled with aggressive dental floating to minimize the opportunity for soft tissue damage by unopposed elongations. Dental elongations place abnormal orthodontic forces on the involved tooth. This can lead to shifting of teeth and diastema formation. In severe long-standing cases, deep periodontal pockets and oroantral fistulas predisposing to forage accumulation in the paranasal sinuses may develop. If complications such as severe periodontal disease or maxillary sinusitis occur, the supernumerary tooth or displaced adjacent tooth should be extracted or appropriate therapy undertaken to manage associated pathology, or both.[18-22]

Oligodontia.

Oligodontia is the congenital absence of a tooth germ or retention and inclusion of a tooth within the jaw. It is difficult to differentiate developmental oligodontia from tooth loss caused by damage to, or displacement of, a dental bud from injury. It is possible for permanent tooth germs of a young horse to be damaged, displaced, or removed when deciduous teeth or jaw bones are injured. Absence of a tooth in the dental arcade leads to dental drift or tipping of adjacent teeth. Lack of wear in the antagonist to the missing tooth can lead to dental elongations and abnormal mastication. Radiographic examination is often necessary to confirm a diagnosis of true oligodontia. Oligodontia may be associated with other epidermal defects such as poor development of hair and hooves.[23]

Dental Dysplasia or Hypoplasia.

Dental dysplasia (i.e., abnormal growth or development of a tooth or teeth) may result in an irregularly shaped tooth that does not fit well into a dental row. The poor fit may lead to diastemata, food entrapment and periodontal disease.

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Enamel hypoplasia has been associated with certain drugs or chemicals administered to the dam during gestation, or it may be idiopathic in origin. Dental dysplasia can involve the abnormal formation of the entire tooth structure or only a single tissue type. Abnormal enamel structure, such as branched pulp horns or abnormally shaped teeth, has been observed. Enamel acts as the scaffolding and template for the deposition of dentine and cementum. These tissues follow the abnormal enamel pattern, and consequently all three calcified tissues are dysplastic. Cemental hypoplasia usually involves the infundibular portion of the tooth, but it can also be a defect of the peripheral, coronal, or reserve crown or root cement.

Abnormal Dental Eruption.

Abnormal dental eruption, or maleruption, often results from trauma to developing teeth or surrounding bones, but it has also been reported to be congenital or idiopathic in origin. Cheek teeth can become vertically impacted when dental buds are developing in abnormal or crowded areas in the dental arcades. Teeth may become rotated or otherwise displaced as a result of developmental malpositioning of tooth buds or overcrowding before, during, or after eruption.

Most tooth displacements are developmental in origin as a result of overcrowding of the cheek tooth row at the time of eruption. These malocclusions are seen most often in miniature breeds and ponies and are often bilateral. Tooth displacements are also believed to be caused by abnormal positioning of a dental bud, which may result in impaction and delayed eruption or noneruption of the displaced teeth if they are sufficiently horizontal to the adjacent teeth. Developmental diastemata or abnormal spaces or gaps between cheek teeth are often caused by insufficient angulation of teeth to achieve interdental compression between adjacent teeth. Another cause for diastemata is the development of embryonic teeth too far apart.[21]

Malocclusions of incisors are congenital, developmental, or acquired in origin. Mandibular brachygnathism (parrot mouth) is a congenital incisor malocclusion, the origin of which is unknown but probably genetic. Many horses have some degree of overjet of the premaxillary incisors, but the overjet rarely causes a problem with prehension, unless the premaxillary and mandibular incisors totally lack occlusion. If brachygnathism is discovered when the foal is young, treatment may correct, or at least improve, the functional outcome for the animal.[24]

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A main consideration with an incisor overjet in adult horses is the cheek teeth malocclusions that accompany this condition. The maxillary cheek teeth arcades are usually positioned rostral to the mandibular cheek teeth, causing a rostral overgrowth of teeth 106 and 206 and a caudal overgrowth of 311 and 411. Check teeth elongations should be reduced to allow for proper rostrocaudal jaw excursion and mastication. The unopposed incisors can become elongated and limit lateral jaw motion, which can lead to abnormal dental wear and shear mouth.

Prognathism or undershot jaw occurs with less frequency in horses and is most common in miniature or dwarf breeds. Early detection and correction of the malocclusion in the foal may prevent the condition from worsening with age. The cheek teeth should be evaluated for malocclusion caused by overgrowths of teeth 111, 211, 306, and 406 and these should be corrected on a regular basis.

Bony malformations of the head can result in malocclusion of the incisors and cheek teeth. These bony skull curvatures or asymmetries usually result in an offset or diagonal incisor bite. Some bony malformations, such as campylorrhinus lateralis (wry nose) are obvious, and surgical correction may be necessary for a horse to be functional.[25] More subtle changes to the large bony plates in the head can be difficult to recognize and can be managed by correcting dental overgrowths and abnormal wear patterns.[26] Fractures secondary to trauma to the mandible or facial bones can also cause malocclusions and facial asymmetry. Care must be taken with correcting dental overgrowths associated with malocclusions, and they should be corrected gradually to prevent damage to pulp horns (which can lead to apical infection), dysphagia, and pain. Often, incisor malocclusion remains throughout a horse's lifetime, but regular maintenance may prevent it from worsening.

■ Acquired Dental Disease

Dental disease can be grouped into six basic categories:

1. Dental malocclusions and abnormal occlusal wear
2. Periodontal disease
3. Caries of the infundibulum or peripheral cementum
4. Endodontic disease
5. Tooth resorption and hypercementosis
6. Traumatic dental injuries

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These dental disease types are interrelated, and in most clinical cases, affected horses suffer from a combination of varying degrees of different dental disease types.

Alignment of the dental arcades is critical for the normal wear of continually erupting equine dentition, and any malocclusion can lead to abnormal occlusal wear. Historically, abnormal dental wear patterns have been described as dental crown elongations, descriptive terms for which include *hooks, ramps, waves, steps,* and *transverse ridges.* These elongations usually involve a normal tooth that is out of occlusion with an abnormality in the opposite arcade. The opposite diseased, damaged, misplaced, or missing tooth or jaw should be evaluated when elongations are found. Most dental elongations are addressed by reducing the crown height of the long tooth or portion of a tooth with a rasp or grinding instrument. In dental reductions, iatrogenic damage to the tooth, such as pulp horn exposure, thermal injury, or crown fracture, must be avoided. The viable pulp is usually covered by 7 to 10 mm of secondary dentine, but only 2 to 4 mm occlusal secondary dentine covers some pulp horns. Therefore crown reductions should be carried out in stages; no more than 3 to 4 mm of occlusal crown should be reduced in a session. Power grinding dental instruments generate heat that can cause damage to the pulp tissue. Shorter durations of grinding and water cooling have been found to mitigate this heating effect.[27,28] It is important to diagnose and treat the underlying malocclusion or dental disorder in horses with a diagnosis of abnormal dental elongations; otherwise, the elongation of the tooth will recur over time as the tooth erupts.

Periodontal disease is an altered state of the periodontium. The periodontium is the attachment apparatus of the tooth consisting of the gingiva, alveolar bone, periodontal ligament, and cementum. The periodontium is responsible for hypsodontic tooth eruption and for the distribution of masticatory forces from the teeth into the supporting bone. Periodontal disease is often a painful dental condition and is described as the leading cause of “quidding” in horses. Gingivitis is the mildest form of periodontal disease and is often associated with local irritants such as plant awns or bristles, botfly larvae, traumatic injury, or chemical exposure. Oral ulceration can be a reflection of systemic disease, such as vesicular stomatitis, which is a contagious reportable disease. Another mild form of periodontal disease affects primarily young horses 2.5 to 5 years of age when deciduous teeth (caps) are shed and permanent incisors and premolar teeth are erupting. A more progressive form of periodontal disease affects older horses as a result of the chronic effects of diastema or spaces that develop between teeth

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that are not aligned properly in the arcade. Diastema can form during tooth development when dental buds are spaced too far apart or abnormally angulated so that the teeth in a dental row are not properly compressed, which allows forage to become trapped between teeth. This is usually a progressive condition; left untreated, it becomes worse over time. As food becomes compressed deep between teeth, gingivitis and gingival recession develop. Deeper penetration of food causes periodontal disease to progress to affect all four periodontal tissues, along with proliferation of secondary bacterial infection with multiple species of bacteria that are also found in the normal equine oral cavity. Current molecular bacteriologic techniques help practitioners and scientists better understand this large pool of organisms that cannot be conventionally cultured.[29] Periodontal disease is the primary cause of tooth loss in mammals and is the most common reason for extraction of equine cheek teeth.

Management of periodontal disease involves treating both the cause and the effect of the problem. Diastema with feed trapped in the gingival margin often responds to thorough cleaning with dental picks, irrigation, or both. Reduction of any associated abnormal wear patterns is also indicated. In more refractory cases, it may be necessary to open or widen the diastema with a special burr or a right-angle grinder. This procedure may allow horses' masticatory actions to more easily channel food in and out of the gap, thus preventing or reducing entrapment of feed or stagnations and decay. This procedure is not without risk of pulp exposure and should be performed only by a professional with proper equipment and training.[30]

Some practitioners have had positive results using high-pressure irrigation to clean out periodontal pockets, followed by packing the area with a perioceutic agent such as doxycycline gel or a powdered antibiotic. This technique packs a high concentration of antibiotic in contact with the infected and inflamed tissues and acts as a temporary barrier to recontamination. This form of therapy may need to be repeated on a regular basis (every 4 to 6 months) in order to achieve long-term positive results. Severe periodontal disease that has resulted in bone loss and tooth mobility responds positively only to extraction of the involved teeth.

Dental caries is the macroscopic destruction of calcified dental tissues as a result of pH changes. These changes usually result when microorganisms within the oral cavity metabolize dietary carbohydrates to produce acids, which dissolve the mineral components of teeth. Because the mineral content of cementum (65% inorganic material) is lower than that of enamel (96 to 98%

inorganic material), the critical pH required for the demineralization process is higher (less acidic) than that for enamel; a pH of 5.5 is required for enamel, 6.2 for dentine, and 6.7 for cementum. Caries in horses can affect the exposed crown or infundibulum of the hypsodont teeth, the softer cementum being more commonly involved. Peripheral caries involving the cementum around the erupted tooth crown is poorly understood. This condition usually involves the distal cheek teeth and can progress to involve all three dental tissues. The prevalence is higher in particular regions of the world, and feeding on hay high in water-soluble carbohydrates, feeding on silage with a low pH, and drinking water with a low pH were found to be contributing factors. Equine peripheral caries does appear to be a reversible condition if the etiological agent is removed.[31]

Caries can also involve the infundibular portion of the incisor and maxillary cheek teeth. All infundibulae of incisor and cheek teeth show some evidence of cemental decay in the cup or open portion.[9,32] As the tooth wears, the portion of the infundibulum that is more apical fills with cementum (except for the small central vascular channel) and becomes exposed at the occlusal surface (referred to as the *spot* in the incisor teeth). Feed and other products of mastication can be compressed into a ghost of a vascular canal, and some degree of decay is always present. The infundibulum contains dead cementum and is lined with a layer of enamel. Therefore this decay does not usually lead to an inflammatory response or dental infection, and such superficial decay is innocuous in most cases. True dental disease secondary to infundibular decay can occur only if the protective enamel layer is penetrated. Developmental malformations of the infundibulum may weaken this enamel and predispose affected horses to dentine exposure and pulp disease. In upper cheek teeth with very large vascular channels or deformed infundibula, decay may weaken the tooth and predispose the tooth to excessive crown attrition or midsagittal crown fracture. A shallow infundibulum or senile attrition of the infundibulum can allow central occlusal excavation, which can lead to dental elongations on the opposite occlusal arcades (wave mouth). These abnormal wear patterns need to be reduced on a regular basis. To help strengthen the tooth and delay the progression of infundibular decay, some practitioners advocate cleaning out abnormally enlarged infundibular vascular channels and packing and sealing them with a dental composite material.[33] As advanced diagnostic methods such as CT become more readily available to equine practitioners, these abnormal-appearing infundibula can be better evaluated and treated.

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Disease of the dental pulp is referred to as *endodontic disease* and occurs primarily in horses between the ages of 4 and 10 years. This type of dental disease usually manifests as an infection and associated inflammatory changes at the apical region of the tooth. The clinical presentation depends on the structures adjacent to the apex of the affected tooth. Infections of the lower first four cheek teeth can manifest as ventral mandibular swellings with a draining tract. The last two lower cheek teeth are embedded in the portion of the mandible surrounded by the large muscles of mastication. These muscles are often enlarged or swollen, and ultrasound evaluation may reveal exudate accumulating between the mandible and muscle. The upper rostral two or three cheek teeth apices are closely associated with the facial bones and nasal passages. The caudal three or four upper cheek teeth are in the maxillary sinuses and can be associated with secondary sinusitis. Unilateral nasal discharge often occurs when the upper cheek teeth are affected. Because pulp disease compromises the tissue responsible for production of secondary dentine, the pulp horns and root canals on the affected teeth do not fill with secondary dentine as they should. In the later stages of pulp disease, the affected tooth usually shows some degree of pulp horn decay on the occlusal surface. This weakening and decay may predispose the affected tooth to crown fracture.[34,35] Medical therapy has been successful in the management of apical disease in the early stages. Chronic apical infections are usually treated by removal of the tooth and treatment of any associated bone or sinus disease.

Equine cheek teeth have classically been removed by several surgical and nonsurgical methods:

- Extraction via oral approach (with or without tooth sectioning)
- Repulsion via apical or retrograde approach
- Elevation via lateral buccotomy/alveolectomy approach

More recently, minimally invasive procedures involving the use of small radiographically guided pins for repulsion or an oral trocar approach to teeth through the cheek have been developed.[36,37]

A progressive dental condition involving the incisor, canines, and premolars of

aged horses has been described as equine odontoclastic tooth resorption and hypercementosis (EOTRH).[38] This disease is characterized by internal and external resorption of dental structures and is sometimes associated with excessive production of irregular cementum on the exterior and interior of the apical or root portion of the tooth. EOTRH is a progressive condition, but the pathophysiologic processes are still under investigation.[39] Clinical signs include sensitivity in the mouth to any manipulation, head shyness, periodic inappetence and weight loss, and decreased use of incisors for grasping or grazing. Oral examination reveals varying degrees of gingival secession, calculus deposition, and firm bulbous enlargement of the incisive bone over incisor reserve crowns. Radiographs are needed to confirm a diagnosis and evaluate the severity of disease. Radiographic changes can include various forms and depths of tooth resorption, cemental thickening, osteosclerosis, osteitis and tooth fracture. This condition can be a painful, progressively debilitating disease of aged horses. No medical or husbandry changes have been identified to slow or change the course of disease. Extraction of painful or fractured unstable teeth appears to be the best method of managing these cases.[40]

Traumatic injuries to facial and dental structures are more common in young horses. Bones that support to teeth are often involved in these injuries, and a good dental alignment in the repair of these fractures is often more important than good bone apposition. Jaw and facial fractures can also involve the deciduous teeth, the developing buds of the permanent teeth, or both. Damage to a deciduous tooth can lead to dental drift and crowding of the eruption pathway for the permanent tooth. Permanent tooth bud damage can result from direct trauma or oral contamination by the damaged deciduous tooth. Facial fractures often lead to bone growth disruption, which predisposes horses to dental malocclusions. Tooth avulsion, subluxation, and total luxation are also observed. Diseased teeth in the fracture line can lead to dental or bone sequestum, delayed union, malunion or nonunion, oronasal or orosinus fistula, and osteomyelitis. Teeth in the fracture site should be preserved in most cases to add to stability of the fracture repair. Problems associated with periodontal or endodontal disease may be observed soon after the fracture has stabilized or may not show up clinically until many years later.

Fractures of the mandible and maxilla involving the teeth can be repaired successfully, but the health of the dental structures must be maintained for good long-term results. Most of the jaw and facial fractures involving the dental bearing bones are best managed by the least invasive approach. Intraoral wiring,

alone or combined with a U-bar or acrylic splint, work wells and supports the compression side of the fracture. External fixation with a pinless external fixator provides less stability but is noninvasive and can be combined with oral wiring. Open reduction and internal fixation should be reserved for cases with few other options in stabilizing the fracture. Pins and screws should not be placed in the teeth because this often results in severe pulp damage.[37]

■ Salivary Glands and Ducts

Saliva hydrates and lubricates the oral cavity, facilitates swallowing, prevents tooth demineralization, and regulates the oral flora.[41] Diseases of the salivary glands and ducts, including sialoadenitis, salivary calculi, salivary mucocele, trauma, and neoplasia, are uncommon in horses. During oral examination, the openings of the salivary ducts should be noted. The parotid salivary duct communicates with the oral cavity via a flaplike, dorsally directed papilla, opposite the upper third or fourth check tooth. The mandibular salivary duct opens into the mouth on the lateral aspect of the sublingual caruncle. The sublingual salivary ducts (approximately 30 in number) are small pores in the sublingual recess.

Slobbering or drooling may indicate excessive accumulation of saliva in the mouth (sialism, ptyalism, or dysphagia). Heavy metal toxicity, parasympathomimetic poisoning, cholinesterase-inhibiting insecticides (organophosphates or carbamates), neurologic disease, and stomatitis may cause ptyalism. Slaframine is a cholinergic agonist that can cause “slobbers” in horses consuming forages, mostly commonly clover, contaminated with the fungus *Rhizoctonia leguminicola*. Tests for the presence of slaframine (1-acetoxy-6-amino-octahydroindolizine) are not readily available. Dysphagia can be caused by esophageal obstruction (choke), oral foreign body, rabies, or other neurologic disease.

Sialoadenitis may be the result of salivary duct obstruction caused by accumulation of exudate or mucus, by an ingested foreign body, or by a sialolith. Sialoliths develop in the parotid duct and can cause duct obstruction and salivary retention, which can lead to glandular atrophy or acute sialoadenitis, swelling, and rupture. On palpation, sialoliths are usually hard, smooth, and painless enlargements over the course of the parotid duct on the lateral aspect of the jaw. The diagnosis of sialolith is straightforward and differs from that of trauma, tooth abscess, and facial tumor. Surgical removal, usually orally, and primary

closure often yield good results.

Salivary mucocele is an accumulation of salivary secretions in a single or multiloculated cavity adjacent to a ruptured salivary duct. A ranula is a type of mucocele that is secondary to obstruction of the sublingual salivary duct. Treatment consists of creating a salivary fistula into the oral cavity or excising the mucocele and associated salivary gland.

Laceration or iatrogenic injury to the salivary ducts can lead to salivary cutaneous fistula. These injuries can be surgically repaired by reapposition of the severed duct and creation of an oral opening for the duct or by resection of the salivary gland. Oblation and sclerosis of the gland has been achieved by flushing of the duct with 1% formalin solution. Wounds involving the salivary glands can usually be handled by cleansing, débridement, and primary skin closure.

Benign mixed tumors, adenocarcinomas, and acinar cell tumors of the salivary glands have been reported in horses. Local invasion of a salivary gland by tumor originating in adjacent tissues and metastasis of melanomas to the parotid salivary gland in older gray horses are more common.

■ Equine Oral Tumors

Equine oral tumors are rare, making up a very small percentage of the facial or mandibular swellings. These tumors can be divided into three basic types: odontogenic, osteogenic, and secondary.[42,43]

Odontogenic tumors are derived from remnants of dental epithelium. Five types have been recorded in the maxillas and mandibles of horses: ameloblastomas, ameloblastic odontomas, complex odontomas, compound odontomas, and cementomas. Because of their rarity, ill-defined biological behavior, and poorly defined radiographic features, diagnosis can be difficult. Histopathologic findings can be confusing because their appearance varies at different sampling sites and because of age-related changes in tumor appearance.

Primary bone tumors are rare in horses and if present, they are usually benign. More than 80% of equine osteosarcomas occur in the head region. As is the case with odontogenic tumors, disagreement remains with regard to histologic classification, terminology, and nature of tumor. In addition to gross and histologic examination, clinicians and pathologists often must find a correlation between the history and clinical, radiologic, and some biochemical findings to establish a diagnosis. Ossifying fibroma can occur in young horses and usually involves the rostral mandible.

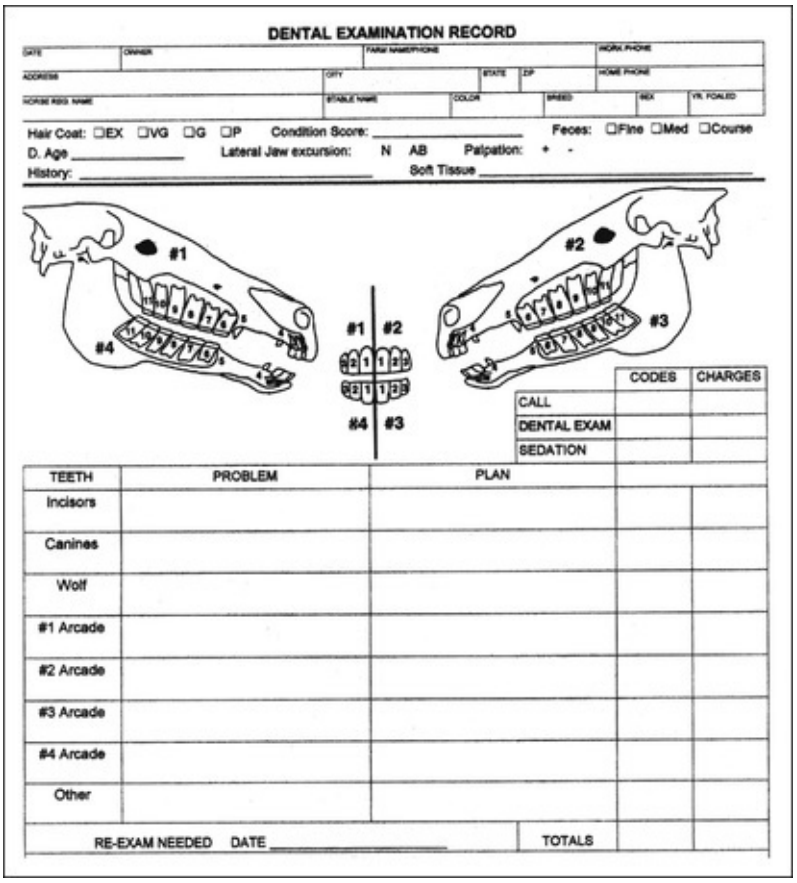
Secondary tumors of the head include extensions of oropharyngeal squamous

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cell carcinoma, lymphosarcoma, papilloma, and melanoma. Squamous cell carcinoma is the most frequently reported oral tumor in horses. In general, these tumors are seen in older horses and have no gender or breed predilection. There are many treatment options and methods of controlling the progression of oral tumors. Radiotherapy, hyperthermia, chemotherapy, cryosurgery, immunotherapy, autogenous vaccines, photodynamic therapy, laser therapy, and surgical resection have been used with variable success.

■ Dental Examination

Biannual dental examination of horses should be part of a routine health maintenance program. Improved eating efficiency and oral hygiene are the most important considerations from a medical standpoint. However, often owners are more enthusiastic about dental care because of its positive effects on a horse's sensitivity to the bit and athletic performance. Written documentation of dental examination findings is necessary to formulate a problem-oriented treatment plan and monitor age-related dental changes and progress after maintenance, treatment, or both (Fig. 32.42). A consistent routine followed by the examiner increases the efficacy and quality of the examination (Box 32.1).[44,45]



DENTAL EXAMINATION RECORD

DATE | OWNER | FARM NAME/PHONE | WORK PHONE

ADDRESS | CITY | STATE | ZIP | HOME PHONE

HORSE REG. NAME | STABLE NAME | COLOR | BREED | SEX | YR. FOALED

Hair Coat: ☐EX ☐VG ☐G ☐P Condition Score: _____ Feces: ☐Fine ☐Med ☐Course

D. Age _____ Lateral Jaw excursion: N AB Palpation: + -

History: _____ Soft Tissue _____

#1 #2 #3 #4

	CODES	CHARGES
CALL		
DENTAL EXAM		
SEDATION		

TEETH	PROBLEM	PLAN		
Incisors				
Canines				
Wolf				
#1 Arcade				
#2 Arcade				
#3 Arcade				
#4 Arcade				
Other				
RE-EXAM NEEDED DATE _____			TOTALS	

FIG. 32.42 Dental record form used to document dental examination findings and treatments performed.

Box 32.1

Recommended Timetable for Routine Dental Examinations and Common Corrective Procedures

Birth

1. Examine for congenital defects of lips or palate.
2. Assess tongue motion and strength.
3. Identify dental malocclusions.
4. Evaluate all body systems.

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Recommended Procedures

1. Provide genetic and orthodontic consultation, and perform corrective surgery if necessary.
2. Look for other problem signs such as underdeveloped carpal or tarsal bones, ruptured extensor tendons, and hernias.

6 to 8 Months of Age

1. Check incisor and premolar occlusions.
2. Check to see that all incisors have erupted.
3. Check for sharp enamel points or hooks.
4. Check tongue and buccal mucosa for ulcers.

Recommended Procedures

1. Provide orthodontic consultation, and float teeth if necessary.

16 to 24 Months of Age

1. Check for expanded eruption of lower wolf teeth.
2. Check points and hooks on premolars.
3. Look for bit lesions.

Recommended Procedures

1. Float teeth and round off rostral corner of premolar 2.
2. Extract wolf teeth.

2 to 3 Years of Age

1. Look for upper and lower wolf teeth.
2. Check corners of mouth and interdental space for bite injuries.
3. Evaluate incisors and molars for eruption and premolars for points and loose or retained deciduous teeth.

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Recommended Procedures

1. Float outside of upper and inside of lower cheek teeth.
2. Remove caps if present and ready.
3. Extract wolf teeth.

3 to 4 Years of Age

1. Check corners of mouth and interdental space for bit injuries.
2. Evaluate incisors for retained deciduous teeth or supernumerary teeth.
3. Evaluate molars for eruption and premolars for points and retained or loose deciduous teeth.
4. Evaluate size and shape of lower jaw and percuss sinuses.
5. Check for blind wolf teeth.

Recommended Procedures

1. Remove caps if present and loose.
2. Float teeth.
3. Remove wolf teeth.

4 to 5 Years of Age

1. Check all incisors for eruption and wear occlusion.
2. Check canine teeth for sharp edges or eruption delays.
3. Evaluate entire molar arcade for proper eruption and alignment (third cheek tooth).
4. Visually check upper rostral and lower caudal cheek teeth for hooks from malocclusion.
5. Digitally check for points on sharp edges of cheek teeth.
6. Percuss sinuses.

Recommended Procedures

1. Remove deciduous teeth if loose and ready.

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2. Reduce hooks if present.
3. Float teeth.
4. Remove mucosa over canines if gingival cysts are present.

5 Years and Older

1. Examine mouth visually and digitally, especially noting hooks and uneven wear.
2. Evaluate canines for sharp edges and tartar.
3. Percuss sinuses.
4. Use olfactory senses to detect evidence of oral decay or gingivitis.
5. Observe incisors for even wear.
6. Evaluate lateral jaw excursion.

Recommended Procedures

1. Float teeth.
2. Remove hooks.
3. Level or shorten incisors if indicated.

Several signs may be noted in the history or observed in a horse suffering from dental problems. A history of abnormal head carriage or head tossing when the horse is being ridden or eating, longer time taken to eat, halitosis, dysphagia, drooling or hypersalivation, dribbling feed (quidding), and eating hay before grain suggest that a dental problem exists. Indicators of dental problems in performance horses include tail wringing, headshaking, lunging in or out on the track, and fighting the bit (refusing to collect the head). Chronic colic or choke can result from improper mastication of feed. Reluctance to drink cold water may be a result of dental pain.[19,20,46]

Good dental health is extremely important to the equine digestive system. Proper mechanical digestion of feed allows better carbohydrate absorption in the small intestine and improved fiber fermentation in the cecum and large colon. Improperly masticated roughage and concentrate leads to poor digestibility in the small and large intestine because of large feed particles with decreased surface area per mass. This decreased surface area does not allow proper enzyme degradation or bacterial fermentation. Findings of whole grain or stem particles

longer than 5 mm during manure examination indicate improper mastication.

As a routine aspect of the dental examination, a horse's overall condition should be evaluated in view of its use and dietary intake. A body score should be assigned, as this is a more accurate way to subjectively record body condition[47] (Table 32.1). Objective assessment of body condition with the use of a scale, weight tape, or photographs is also beneficial and provides good data to assist in proper documentation and management.

TABLE 32.1
Principles to Guide Health Care Transformation in Canada

Condition	Neck	Withers	Shoulder	Ribs	Loin	Tailhead
1. Poor	Bone structure easily noticeable	Bone structure easily noticeable	Bone structure easily noticeable	Ribs protruding prominently	Spinous processes projecting prominently	Tailhead, pinbones, and hook bones projecting prominently
2. Very thin	Bone structure faintly discernible	Bone structure faintly discernible	Bone structure faintly discernible	Ribs prominent	Slight fat covering over base of spinous processes Transverse processes of lumbar vertebrae feel rounded Spinous processes are prominent	Tailhead prominent
3. Thin	Bone structure accentuated	Bone structure accentuated	Bone structure accentuated	Slight fat cover over ribs Ribs easily discernible	Fat buildup halfway on spinous processes, but easily discernible Traverse processes cannot be palpated	Tailhead prominent, but individual vertebrae cannot be identified visually Hook bones appear rounded but are still easily discernible Pin bones not distinguishable
4. Moderately thin	Neck not obviously thin	Withers not obviously thin	Shoulder not obviously thin	Outline of ribs faintly discernible	Negative crease (peaked appearance) along back	Prominence depends on conformation Fat can be felt;

						hook bones not discernible
5. Moderate (ideal weight)	Neck blends smoothly into body	Withers rounded over spinous processes	Shoulder blends smoothly into body	Ribs cannot be visually distinguished but can be easily palpated	Back is level	Fat around tailhead beginning to feel soft
6. Moderately fleshy	Fat beginning to be deposited	Fat beginning to be deposited	Fat beginning to be deposited	Fat over ribs feels spongy	May have a slight positive crease ?(a groove) down back	Fat around tailhead feels soft
7. Fleshy	Fat deposited along neck	Fat deposited along withers	Fat deposited behind shoulder	Individual ribs can be felt with pressure, but noticeable fat filling between ribs	Positive crease may be present down the back	Fat around tailhead is soft
8. Fat	Noticeable thickening of neck	Area along withers filled with fat	Area behind shoulder filled in flush with body	Difficult to feel ribs	Positive crease down the back	Fat around tailhead very soft
9. Extremely fat	Bulging fat	Bulging fat	Bulging fat	Patchy fat appearing over ribs	Obvious crease down the back	Bulging fat around tailhead

The age of a horse should be considered during evaluation.[48] Different conditions need to be addressed for each stage of the horse's growth, development, and maturity. The use of the horse should be considered during evaluation because dental care for horses that wear a bit might differ from dental care for horses that do not wear a bit. Stable surroundings should be carefully observed for evidence of vices (such as cribbing) or poor eating habits (such as quidding or dribbling grain).

The physical examination begins with observation of the horse's body condition, attitude, and temperament. The horse should be approached from the left side of the shoulder. Body and head conformation should be considered during evaluation of the masticatory system. Horses with small heads have more of an angle in the curve of the mandibular ramus (i.e., curvature of Spee) and are predisposed to dental crowding and ramps on the lower dental arcades. The head is observed from both sides and the front, and any asymmetries, protuberances, or swellings should be noted. The tongue is checked for proper movement, abnormal swellings, or signs of trauma or injury; the horse's ability to swallow is checked as well. Lacrimation should be noted, as well as any nasal discharge. Neurologic evaluation should be considered if any cranial nerve deficits are detected. Finally, the examiner assesses the head by palpating the mandibular rami, masticatory muscles, temporomandibular joints, and submandibular lymph

nodes to detect enlargements or asymmetry.

The frontal and maxillary sinuses should be percussed with the horse's mouth open. The width between the mandibular ramus should be noted because this is correlated with the room in the mouth for the bit. The sides of the head lateral to the upper dental arcade should be compressed from the orbit, moving forward to the first cheek tooth at the level of the nasal notch; any protuberances, depressions, asymmetry, or evidence of pain should be noted.

The commissures of the lip should be observed and palpated for signs of trauma from sharp teeth or improperly fitting bits. A loose-fitting halter is necessary to properly evaluate the mouth and oral cavity. If the horse is fractious or resists examination, a sedative should be administered before the oral portion of the examination. Sedation should be induced after a medical assessment of the animal (i.e., consideration of temperament, breed, age, body condition, mucous membranes appearance, central reaction time, heart rate and rhythm, and rectal temperature).

The mouth should be rinsed thoroughly with clean water. Impacted or trapped feed in the mouth should be removed manually or with the use of a dental pick and irrigation. Many horses with sharp buccal points on the upper dental arcade resist the full-mouth speculum. Floating the upper arcades before applying the speculum may decrease a horse's resistance. With a full-mouth speculum in place and the head properly restrained, a detailed visual and tactile oral examination can be carried out. A bright light source is necessary to illuminate the entire oral cavity for complete visual inspection. An examiner should manually inspect all hard and soft tissue in the oral cavity. Use of dental mirror, occlusal hook pick, and calibrated periodontal probe is often necessary to see and probe the occlusal surfaces and pockets between the cheek teeth. An oral endoscopic camera can aid in the completeness of the oral examination.[49]

■ Dental Imaging

Diagnostic radiology is a valuable aid in the diagnosis and management of equine dental disease. Because of the excellent contrast among air, bone, soft tissue, and tooth substance, the head is an excellent area for radiologic evaluation. Good-quality films can be obtained with portable x-ray machines and rare-earth intensifying screens without a grid. Digital and computed radiology have improved radiographic image quality and allow for high-quality images to be shared electronically for consultation with colleagues.

Indications for radiographic examination of the head include a suspicion of

dental infection, maleruption, diastema, or oral pain of unknown origin. Radiographs should be obtained before, during, and after dental extraction. Any abnormal dental finding, facial swelling, deformity, neoplasm, trauma, or fracture may warrant radiography to aid in diagnosis and management.

Radiographs can be taken in a standing, sedated horse. The technique for acquiring excellent images in the field has been reviewed.[50] The website of the American Veterinary Dental College also has a good example set of dental radiographs that can be viewed for reference (AVDC.com). The head and radiographic cassette can be placed on a stand to decrease motion distortion. A lateral view centered over the rostral edge of the facial crest demonstrates fluid lines, if present, in the sinuses. The lateral view superimposes the dental arcades and should not be relied on to diagnose diseases involving the dental reserve crown and roots. Lesion-oriented oblique films demonstrating the root or apical portion of the upper or lower cheek teeth are helpful in diagnosis of periapical disease. Open-mouth oblique films are beneficial in evaluating the exposed crown of the dental arcades. Special 4-inch × 8-inch (10 cm × 30 cm) flexible dental cassettes can be used to obtain intraoral radiographs of the maxillary dental arcades. Dorsoventral views centered over the tooth in question or area of concern can demonstrate periodontal disease on the buccal aspect of the upper cheek teeth, fractured teeth, or large area of infundibular decay. Intraoral occlusal films are useful in demonstrating incisor lesions or fractures rostral to the bars of the mouth. Other imaging techniques, such as ultrasonography, nuclear scintigraphy, CT, and MRI are useful in the diagnosis of many oral and dental diseases.[51,52]

■ Treatment

A plan for treatment should be based on the results of history, clinical findings, oral examination, and imaging before any dental work is begun. This problem-oriented approach ensures that the owner, the trainer, or both are informed of any abnormalities and are given a plan for treatment, as well as an estimate of the cost, before any corrective procedure is taken.

Therapy must be planned to ensure that all equipment is present to complete the prescribed task. The horse should be properly restrained and adequate help should be present to assist in performing and completing the corrective or surgical procedures. A dental record form should be used to document examination findings, treatment plan, and procedures performed (see Fig. 32.42).

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Routine Dental Maintenance

Floating (Odontoplasty of Enamel Points and Dental Crown Elongations).

Dental floating is an age-old and routine method of correcting the abnormal wear patterns associated with equine dental eruption and occlusal wear. Floating is also a procedure that allows the sculpting of the teeth to accommodate the bit. The main purpose of molar floating (leveling) is to remove points or sharp edges from the buccal aspect of the upper and lingual aspect of the lower molar arcades. Floating may also entail removing minor hooks or ramps from the rostral or caudal aspect of the arcades or leveling minor elevations on the occlusal surface of the arcades.

Proper equipment is necessary to reach all aspects of the cheek teeth molar surfaces completely, regardless of horse size. Smaller instruments are often needed to access the oral cavity of a miniature horse or pony. Longer, heavier instruments are often used to work in the mouths of large, Warmblood, or draft horse breeds. Sharp float blades made of carbide chips or tungsten carbide planning blades make the work of floating more efficient and less strenuous than in the past. The outward curve of the upper arcade makes the central buccal area involving premolar 3 (PM3) through molar 2 (M2) the easiest to reach with the float. For the area around PM2 and M3, an offset or angled head on the rasps is needed to reach all extremities. In most cases the lower arcade can be floated to remove the lingual enamel points with a flat, long-handled rasp. To correct rostral and caudal hooks, specialized tools such as carbide planing blades or power burrs may be required. The use of all dental equipment requires special training and skill to prevent iatrogenic injury to the horse's mouth.

Use of a full-mouth speculum aids in the oral examination and floating procedures, ensuring that the horse's mouth is kept in an open, safe (for the examiner as well as the animal) position for floating. In horses whose back teeth are slightly ramped back because of a greater curvature of Spee, a mouth speculum and a slightly curved or swivel-head float may be necessary to reach the table of the last molar.

In horses wearing bits, the rounding of the first upper and lower cheek teeth and lowering of the buccal cusps from upper PM2 and PM3 is referred to as a “bit seat” and usually requires an offset float or an S-shaped rasp. In theory, a bit seat is fashioned to prevent the soft tissue of the mouth from pressing against sharp points on the first premolars. To prevent pulp cavity exposure, care should

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be taken not to “overfloat” the occlusal surface of a tooth when bit seats are formed or overgrowths are corrected because this could lead to a direct pulp horn exposure.[5] Routine floating and other corrective measures in the mouth may require the added physical restraint of a dental halter and mild chemical sedation.

Wolf Teeth.

Wolf teeth are the first premolars to erupt and are present in 20 to 80% of horses. They are most often located in the upper arcade and seldom in the lower arcade. Horses that are worked with a bit in their mouth benefit from having the wolf teeth extracted. Some wolf teeth are naturally exfoliated at approximately 3 years of age when the first cheek teeth (or 06 caps) are shed and the permanent tooth erupts. Although not all wolf teeth cause problems, a loose or sharp wolf tooth can be a distraction or even cause pain of such severity as to lead to bad bitting habits. In some instances, diagnosis of wolf tooth problems is difficult and confusing. Sometimes they do not erupt in a normal downward path, penetrating the gum; rather, they may migrate rostrally under the gum and causing a subgingival enlargement, which in turn, is irritating to affected horses. Such unerupted first premolars have been referred to as “blind” wolf teeth and should be removed. Most wolf teeth are easily elevated with the horse sedated or after a small volume of local anesthetic is instilled around the tooth.

Canine Teeth.

Canine teeth are present in most male horses older than 4 years of age. Because of their unopposed position in the bars of the mouth, they are unlikely to cause problems. Some mares have small or rudimentary canines that do not seem to cause a problem but can become loose or accumulate tartar and must be removed. Long or sharp canines in a stallion or gelding can interfere with bitting, be a nuisance or a danger to the groomer/handler, or become an area of tartar accumulation. Erupting canine teeth in 4- to 6-year-old horses may cause an operculum to form and lead to subgingival pain and bit irritation, which may manifest as headshaking or other bad habits. The thin layer of tender mucosa should be removed over the canine if the gingival operculum is present. Severe calculus accumulation can be present on the lower canines, which predisposes horses to periodontal disease. Scaling calculus and frequent brushing of lower canines can control this problem in most horses.

The canine roots are long and curved, and thus this tooth is extremely difficult

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to extract in the male. If the canine becomes injured, infected, or involved in painful odontoclastic tooth resorption, surgical removal through a bone flap is indicated.[53]

Dental Caps.

As the developing permanent tooth (incisor or premolar) pushes toward the surface, it presses on the roots of the worn-down deciduous tooth, gradually cutting off that tooth's nutrition. The deciduous tooth becomes loose, its blood supply diminishes, the tooth dies, and it is displaced occlusally. The osseous alveolar wall adjusts to these changes by bone production and resorption, thereby providing a new socket for the embedded portion of the newly formed permanent tooth. The remaining cap portion of the deciduous tooth has up to four “legs” (root slivers) that cover the crown of the permanent tooth. If these slivers are broken off and remain subgingivally after the cap has been shed, gingivitis and periodontal disease often result.

The eruption pattern of permanent molarized dentition follows a sequence that predisposes to entrapment of deciduous PM3 and PM4.[54] Delayed shedding of deciduous premolars can predispose horses to gingivitis, periodontal irritation, or apical infection. Retained, split, or displaced deciduous premolars can be distracting in the training process of a young horse and may be a factor in dorsal displacement of the soft palate.

Retained caps can cause displacement or delayed eruption of permanent teeth. Clinically, they manifest as bony enlargements on the ventral mandibular ramus or on the maxilla, rostral to the facial crest. Often, such swellings are benign. However, they can become diseased if eruption is severely inhibited or bloodborne bacteria inhabit the inflamed dental pulp, which leads to anachoretic pulpitis and bony swelling with a draining tract. Caps should be evaluated visually as well as by manual palpation. A crease or indentation can be felt just above the gum line at the juncture of the separating deciduous and permanent tooth. Radiographs may be necessary to diagnose retained deciduous premolars.

Disorders of the Esophagus

Samuel L. Jones • Anthony T. Blikslager

■ Anatomic and Physiologic Considerations

The most cranial aspect of the esophagus is located on the median plane

immediately dorsal to the trachea. However, at approximately the midcervical region (C4 to C5), the esophagus typically shifts to the left of the trachea and lies just deep to the external jugular vein.[1,2] It is here that intraluminal obstructions or the tip of a stomach tube may be visualized, and this is the region where trauma can readily result in esophageal perforation. When a stomach tube is passed, it must be palpated to ensure that it is in the esophagus because jugular pulses can be confused with the appearance of the tip of the tube. In addition to its proximity to the external jugular vein, the esophagus is also adjacent to the vagosympathetic trunk and the common carotid artery.[1] The esophagus is innervated by branches of the vagosympathetic trunk, and blood is supplied to the cervical portion of the esophagus by branches of the carotid arteries. The thoracic portion of the esophagus—which lies ventral to the trachea until it reaches the tracheal bifurcation, where it resumes a dorsal position—receives its blood supply from the bronchoesophageal artery. Venous drainage is via the external jugular veins in the cervical portion of the esophagus, and the esophageal vein in the thoracic portion of the esophagus.

The muscular wall of the esophagus increases in thickness as the esophagus courses distally, whereas the lumen shrinks.[1] The esophagus is not covered by a serosa except for a very short segment that traverses the abdominal cavity between the diaphragm and the stomach.[2] Instead, the outer wall of the esophagus is composed of adventitia that is loosely attached to surrounding tissues. This loose connection allows movement of the esophagus during swallowing and during movement of the neck. The cranial two thirds of the esophageal wall consists of skeletal muscle, whereas the distal third of the esophageal wall is composed of smooth muscle. Although the muscular layers, like those in the remainder of the gastrointestinal tract, are composed of an outer and an inner layer, the skeletal muscle layers are oriented obliquely to one another.[1] This, and an abundant submucosa, enables extensive dilation of the esophagus as a bolus of food moves toward the stomach. In addition, the velocity of esophageal contraction is faster in the skeletal muscle segment of the esophagus than in the distal smooth muscle segment.[3] The muscle layers become oriented in more of an outer longitudinal and inner circular configuration in the caudal portion of the esophagus.[1] In the resting collapsed state, redundant esophageal mucosa and submucosa become oriented in longitudinal folds. The mucosa is composed of stratified squamous epithelium that is continuous with the stratified epithelium of the cardiac portion of the stomach.[1]

The cranial portion of the esophageal sphincter is formed by the cricopharyngeus muscle and maintains a resting intraesophageal pressure of approximately 85 mm Hg and a postdeglutition pressure as high as 200 mm Hg. Although the caudal portion of the esophageal sphincter is anatomically indistinct, resting intraesophageal pressure in this region is maintained at approximately 13 mm Hg, and postdeglutition pressure in the caudal portion of the esophagus may be as high as 100 mm Hg. The pressure in the caudal portion of the esophagus is maintained at approximately 10 mm Hg higher than the intraluminal pressure of the stomach.[3,4] Although the higher pressure in the distal esophagus has been implicated as the cause of the inability of most horses to vomit and for gastric rupture, other factors such as a poorly developed vomiting reflex may be more important.[5]

■ Diagnostic Considerations

Esophageal disease should be part of the differential diagnosis in any horse that demonstrates excessive salivation. Such signs also indicate the need to assess hydration, electrolyte levels, and acid-base status. In a study in which horses had continual loss of saliva via an experimentally placed esophagotomy, abnormalities included hypochloremia, hyponatremia, and hypokalemia.[6] This results from the relatively high levels of these electrolytes in saliva. Furthermore, because horses depend on dietary intake of potassium, hypokalemia would be exacerbated in a horse that was also unable to eat because of esophageal obstruction. Loss of salivary fluid and bicarbonate also results in dehydration and metabolic acidosis. However, metabolic alkalosis subsequently occurs, presumably as a result of renal compensation for loss of electrolytes, particularly chloride.[6]

Further examination of horses with esophageal disease may reveal evidence of swelling or emphysema in the region of the cranial or cervical portion of the esophagus that should prompt a thorough oral examination and further diagnostic studies such as radiography and endoscopy to define the nature of any esophageal abnormalities. If the esophagus has been perforated or ruptured, subcutaneous emphysema is usually evident. The lungs should be carefully auscultated for evidence of aspiration pneumonia. Radiographs of the chest are required for a full pulmonary assessment.

Radiographs of the esophagus should initially include plain films that may reveal evidence of an obstruction or areas of gas opacity within facial planes

indicative of esophageal perforation.[7] However, facial and subcutaneous emphysema must be differentiated from other causes, including tracheal perforation.[5] The esophagus is often distended with gas cranial to an obstruction up to the cranial portion of the esophageal sphincter. Plain radiographs may be diagnostic, but contrast radiographs are frequently necessary to fully define the nature of esophageal abnormalities.[7] Administration of barium paste or liquid helps reveal linear opacifications as a result of the linear mucosal folds and may help outline intraluminal obstructions or strictures (Fig. 32.43).[7] A double-contrast study is a useful radiographic technique for defining esophageal wall abnormalities, particularly postobstruction mucosal ulceration. For this study, a cuffed nasogastric tube is placed in the cranial portion of the esophagus, and 300 to 500 mL of liquid barium is injected, followed by a similar volume of air. Care should be taken in evaluation of such radiographs because swallowing can create the false impression that there is a stricture.[8] The incidence of swallowing can be decreased by administration of xylazine or detomidine. Liquid barium is preferable if swallowing function is compromised because it is less harmful to pulmonary tissues than is paste, and water-soluble iodinated contrast material is particularly damaging to the lung because of its hypertonicity.[5] However, if an esophageal perforation is suspected, water-soluble contrast material is preferable.[5]

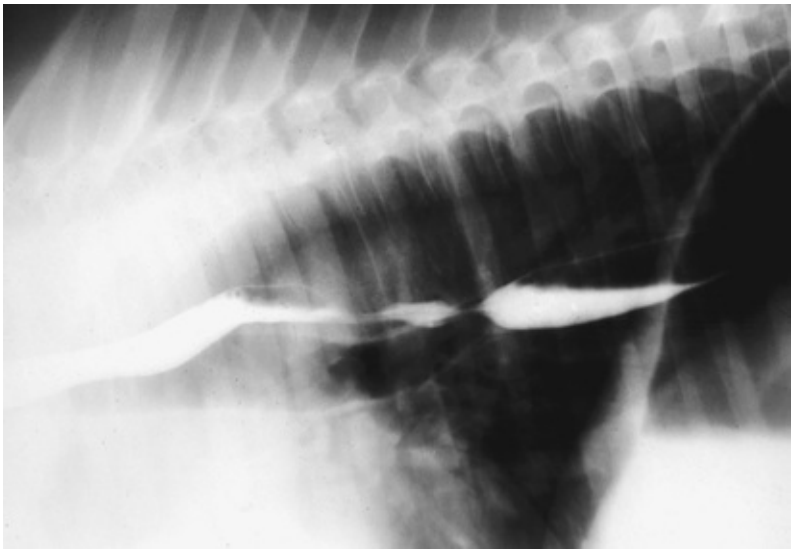


FIG. 32.43 Barium contrast medium–enhanced esophagogram outlining esophageal luminal structure. (Courtesy Dr. K.E. Sullins.)

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Ultrasonographic examination of the cervical portion of the esophagus is often helpful to identify the exact location of obstructions and to determine whether abnormalities of the esophagus are present. Perforations can be identified by periesophageal gas patterns. Whereas intraluminal contents often cannot be examined with ultrasonography because of the presence of air, abnormalities of the mucosal or muscularis layers can be identified. Intramural or extramural causes of esophageal problems (particularly obstructions) may be discovered through ultrasonography. The location and characteristics of masses (e.g., neoplasia, granulomas, abscesses) may be evaluated more readily with ultrasonography than with radiography or endoscopy. The thoracic portion of the esophagus, however, cannot be evaluated with ultrasonography.

The esophagus should be evaluated endoscopically as part of a complete evaluation of esophageal injuries and abnormalities. After the patient is sedated, the endoscope should be passed all the way into the stomach before the esophagus is examined; the esophagus is viewed more easily as the endoscope is withdrawn.[7] Inflation of the esophagus must also be performed intermittently because the wall of the esophagus periodically collapses around the end of the endoscope. The longitudinal folds of the esophageal mucosa are readily appreciated and can be flattened out as the esophagus is distended to view the entire circumference of the esophagus more clearly. Swallowing may create artifacts such as the appearance of strictures, so the esophagus should be carefully reinflated after each swallow to carefully evaluate such findings.[8]

The mediastinum, including the thoracic component of the esophagus, may be evaluated via thoracoscopy. Although this procedure caused pneumothorax in one case, a 15-minute period of evaluation allowed observation of numerous structures, including the esophagus.[9] Portals placed at the eighth, tenth, and twelfth intercostal spaces were useful for completion of this procedure and could provide additional information aside from radiographic and endoscopic evaluation of the thoracic portion of the esophagus.

■ Esophageal Obstruction

Esophageal obstruction, either primary (simple choke) or secondary to other disease processes, is the most common esophageal disorder in horses. Although primary obstructions may be caused by foreign bodies (including corncobs, potatoes, apples, carrots, medicinal boluses, stones, riding crops, or wood fragments), primary obstructions are most often caused by roughage, particularly

leafy alfalfa hay, coarse grass hay, bedding, and even grass.[10-20] Prior esophageal trauma or poor mastication caused by dental abnormalities may predispose horses to esophageal impaction. Obstructions from roughage may be precipitated by wolfing or gulping food, particularly if an affected horse is exhausted or mildly dehydrated (such as after a long ride) or weakened from chronic debilitation. Secondary impactions are caused by intramural or extramural abnormalities that mechanically impede food passage. Examples of intramural obstructions include tumors (squamous cell carcinomas), strictures, diverticula, cysts, and vascular ring anomalies.[21-27] Mediastinal or cervical masses (tumors or abscesses) may cause extramural obstructions.

Regardless of whether obstructions are classified as primary or secondary, the associated clinical signs are similar and are rarely specific. Many horses with esophageal obstruction are anxious and stand with the neck extended. Gagging or retching may be noted, particularly with acute proximal obstructions. Bilateral frothy nasal discharge containing saliva and food material, coughing, odynophagia, ptyalism, and dysphagia are usually the primary clinical signs, the severity of which varies with the degree and location of the obstruction. Distention of the cervical portion of the esophagus may be evident at the site of obstruction. Other clinical signs may be observed related to complications stemming from the obstruction, such as dehydration, weight loss, aspiration pneumonia, or esophageal rupture.

Thorough physical examination, including a complete oral examination, must be performed to rule out other causes of hypersalivation, dysphagia, and nasal discharge. Palpation of the jugular furrow may reveal a mass associated with the impaction. In most horses the esophagus is in the left jugular furrow, but it is in the right furrow in some animals. Crepitus or cellulitis may be evident, which suggests rupture of the esophagus. Auscultation of the lungs can determine whether pneumonia or pleural fluid is present because of aspiration or intrathoracic esophageal rupture. Passage of a nasogastric tube is a good way to determine whether and where an obstruction is present, but it provides little information about the nature of the obstruction or the condition of the esophagus.

Ultrasonography of the cervical region is extremely useful not only to confirm the presence of an impaction in the cervical portion of the esophagus but also to provide critical information about the location and extent of the impaction and esophageal wall thickness and integrity. Ultrasonography may also provide information about the cause of the obstruction. Radiography, particularly air or

barium contrast studies, are useful for assessing an esophageal impaction but may be more useful for evaluating the esophagus after, rather than before, relief of the impaction to demonstrate stricture, dilation, diverticula, esophageal rupture, or masses.[28,29] Care should be taken in interpretion of radiographic studies in sedated horses, particularly after passage of a nasogastric tube or other esophageal manipulations that may contribute to esophageal dilation.[30] Impacted food material can be detected in the esophagus as a typical granular pattern, and gas is often observed to accumulate proximal to the obstruction. Foreign bodies may be identified by contrast radiographic studies.

Definitive evaluation of esophageal obstructions often necessitates endoscopic examination. Most cases of esophageal obstruction occur at sites of natural narrowing of the esophageal lumen, such as the cervical portion of the esophagus, the thoracic inlet, the base of the heart, or the terminal esophagus; therefore an endoscope longer than 1 m may be required. The endoscope can be used to localize and investigate the nature of the impaction if a foreign body is suspected. Foreign bodies may be retrievable via transendoscopic tethering.[18] Critical diagnostic and prognostic information is obtained after resolution of the impaction to determine whether mucosal ulceration, esophageal rupture, masses, or strictures are present.

The primary goal of treatment for esophageal impaction is to relieve the obstruction. Parenteral administration of acepromazine (0.05 mg/kg IV), xylazine (0.25 to 0.5 mg/kg IV) or detomidine (0.01 to 0.02 mg/kg IV), oxytocin (0.11 to 0.22 IU/kg IM), esophageal instillation of lidocaine (30 to 60 mL of 1% lidocaine), or a combination of these may help reduce esophageal spasms resulting from pain or increased esophageal tone.[15,30-32] However, conclusive studies have revealed that detomidine, acepromazine, or a combination of xylazine and butorphanol had the greatest effect on esophageal motility when evaluated by a monomer in conscious horses.[33] In vitro studies revealed a relaxant effect of oxytocin on esophageal muscle, which suggests it may be useful for relief of esophageal obstruction.[34]

Resolution of an impaction may necessitate physical dispersal of the material. A nasogastric tube can be used to displace the impacted material in conjunction with external massage if the obstruction is in the cervical region. Often it is necessary to carefully flush the esophagus with water via an uncuffed or a cuffed nasogastric tube while the horse's head is lowered to aid in breaking up the impaction. Some clinicians advocate a dual-tube method whereby a tube is

placed through each nasal passage into the esophagus for ingress and egress of the lavage fluid. Because of the risk of aspiration of water, food, or both, esophageal lavage is sometimes done with a cuffed nasotracheal tube while the horse is under general anesthesia.

In refractory cases, intravenous administration of isotonic fluid containing 0.9% NaCl and KCl (10 to 20 mEq/L) for 24 hours at a rate of 50 to 100 mL/kg/day, in conjunction with an esophageal relaxant such as oxytocin, may promote hydration and softening of the impaction. Moreover, this helps prevent or alleviate any electrolyte or acid-base imbalances resulting from salivary losses of chloride, sodium, and potassium. Refractory cases may necessitate esophagotomy to relieve the impaction. Restriction of access to food, water, and bedding material must be enforced until the obstruction is resolved and the esophagus has regained function.

Dilation proximal to the site of obstruction, mucosal injury from trauma, and esophagitis are sequelae to esophageal impaction that predispose patients to reobstruction (Color Plates 32.1 and 32.2). The rate of reobstruction may be as high as 37%. Depending on the duration of the obstruction and the degree of trauma or dilation, the risk of reobstruction is high for 24 to 48 hours or longer; therefore food should be withheld for at least 24 to 48 hours after resolution of the obstruction. After 48 to 72 hours or when the esophageal mucosa has recovered as assessed by endoscopy, soft food (moistened pellets and bran mashes) can be fed to the horse. The patient can be returned to a high-quality roughage diet over a period of 7 to 21 days, depending on the degree of esophageal damage induced by the impaction and the nature of any underlying disease. The prognosis for survival is good (78%), but some horses may require permanent dietary modification if persistent chronic obstruction is a problem.[17]

Complications of esophageal impaction include esophageal ulceration, stricture, perforation, aspiration pneumonia, megaesophagus, and metabolic alkalosis from prolonged loss of salivary chloride and sodium. Esophageal endoscopy, ultrasonography, or both should be performed immediately after the impaction is relieved to determine whether any complications of the impaction have developed or whether an inciting cause of the obstruction is present. Endoscopic evaluation is critical to determine the postobstruction treatment and follow-up. Reevaluation should be performed intermittently every 2 to 4 weeks after resolution of the impaction if esophageal dilation or mucosal injury is noted. Additional evaluation with radiography may be warranted to assess motility and transit times.

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If the obstruction was present for 48 hours or longer, dehydration, hyponatremia, hypochloremia, and hypokalemia may occur and should be corrected with oral electrolyte solutions or intravenous administration of 0.9% NaCl and KCl (10 to 20 mEq/L). If aspiration is suspected, broad-spectrum antibiotics that are effective against Gram-positive and Gram-negative organisms, including metronidazole for anaerobes, should be administered. Sucralfate (20 mg/kg orally [PO] q6h) may hasten healing if esophageal ulceration is evident, but this is controversial. Some clinicians suggest that administration of an NSAID such as flunixin meglumine (1 mg/kg PO or IV q12h) or phenylbutazone (1.1 mg/kg PO or IV q12h) for 2 to 4 weeks after resolution of the impaction may limit the development of strictures.

■ Esophagitis

Inflammation occurs during many conditions of the esophagus. *Esophagitis* refers to a clinical syndrome of esophageal inflammation, which may or may not be ulcerative. Causes of esophagitis in horses include trauma (foreign bodies, nasogastric tube), infection (mural abscesses), and chemical injury (acidic medicines, cantharidin).[35,36] An important category of esophagitis is reflux esophagitis, caused by reflux or delayed clearing of gastric contents into the distal esophagus and subsequent chemical injury to the mucosa (Fig. 32.44). As with ulceration of the squamous portion of the stomach in horses, a major cause of ulcerative esophagitis is epithelial damage resulting from exposure to acid, which is synergistically exacerbated by bile salts.[11,37] The major protective mechanisms of the esophageal mucosa include salivary and food material buffers, normal peristaltic motility, and the barrier formed by the gastroesophageal sphincter. Thus esophagitis may accompany gastric ulcer disease, motility disorders, increased gastric volume from gastric outflow obstructions, gastric paresis, intestinal ileus, or impaired function of the lower portion of the esophageal sphincter.

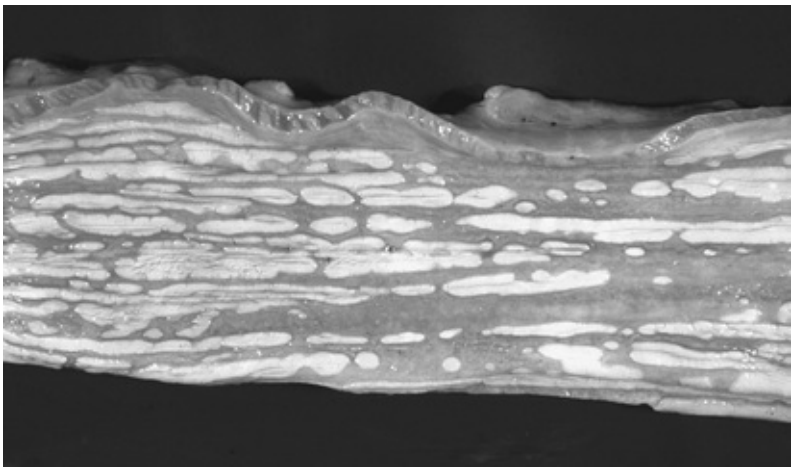


FIG. 32.44 Severe ulceration of the esophagus in a weanling foal that had severe duodenitis and gastric outflow obstruction. (Courtesy Dr. M.J. Murray.)

The clinical signs of esophagitis are nonspecific and similar to those of esophageal obstruction and gastric ulcer disease. In fact, esophagitis may occur concurrently with esophageal obstruction or gastric ulcer disease, so clinical signs may overlap extensively with those of these diseases. Gagging or discomfort when swallowing may be evident, and hypersalivation and bruxism are signs of esophageal pain. Horses with chronic esophagitis may have partial or complete anorexia to such a degree that they exhibit significant weight loss. Motility dysfunction secondary to esophagitis may cause recurrent esophageal impaction. Clinical signs of underlying disease that predisposes horses to esophagitis may predominate or mask the signs of esophagitis. Horses with gastrointestinal motility disorders such as anterior enteritis are at high risk for developing reflux esophagitis because of the presence of both gastric acid and bile salts in the fluid reflux. However, signs attributable to esophagitis secondary to ileus may not be noted because of the profound signs caused by the intestinal disorder. Foals with gastric outflow obstructions commonly have reflux esophagitis.

Diagnosis requires endoscopic examination of the esophagus. Diffuse, patchy, linear, or coalescing erosion or ulcerations may be noted. Significant edema or hyperemia may also be observed. It is important to determine whether underlying disease, such as infection, neoplasia, diverticula, or esophageal stricture is present. In addition, the stomach must be examined because reflux esophagitis is commonly accompanied by gastritis or gastric ulcer disease. If endoscopy is not available to detect esophageal ulceration, contrast radiography may be helpful for assessing esophageal motility and transit time.

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The principles of therapy for reflux esophagitis include control of gastric acidity and correction of any underlying disorder that is contributing to gastroesophageal reflux. Thus treatment with histamine-2 (H_2) receptor antagonists such as ranitidine or proton pump antagonists such as omeprazole is important for resolution of the disease. Some clinicians advocate sucralfate administration to aid healing of esophageal ulcers. However, the efficiency with which sucralfate binds to ulcerated mucosa in the squamous epithelium of the gastrointestinal tract has been questioned because low pH is optimal for the sucralfate polymers to bind ulcerated tissues. It is not clear whether reflux esophagitis provides the right pH environment for binding.

Foals with reflux esophagitis secondary to delayed gastric outflow caused by gastroduodenal ulcer disease or gastric paresis may benefit from prokinetic drugs that act on the proximal gastrointestinal tract. Metoclopramide (0.02 to 0.1 mg/kg SC q4-12h) reduces gastroesophageal reflux by increasing tone in the lower portion of the esophageal sphincter and increasing gastric emptying and gastroduodenal coordination. Metoclopramide should be administered to horses with caution because they are prone to extrapyramidal neurologic side effects. Continuous-rate infusion of metoclopramide (0.04 mg/kg/h) is one way to reduce the risk or severity of neurologic side effects. The rate can be reduced if side effects appear. Cholinergic drugs such as bethanechol (0.025 to 0.035 mg/kg SC q4-24h or 0.035 to 0.045 mg/kg PO q6-8h) may improve gastric emptying and are effective for treating reflux esophagitis. For esophagitis from trauma or pressure injury after esophageal impaction, judicious use of NSAIDs may be warranted to reduce esophageal inflammation and pain.

Dietary modification may be necessary in patients with esophagitis, depending on the degree of ulceration or if motility is impaired. Horses with less severe esophagitis should be fed frequent small meals of moistened pellets and fresh grass. Severe esophagitis may necessitate withholding food and complete esophageal rest for several days. Although the prognosis for esophagitis is good in the absence of underlying disease, the risk of stricture formation is high if severe circumferential or coalescing ulcerations are present. Animals with esophagitis caused by severe trauma or infection also may be prone to stricture formation.

■ Motility Disorders of the Esophagus

Esophageal hypomotility is the most common motility dysfunction of the equine esophagus and results in esophageal dilation or megaesophagus. Although

megaesophagus in horses is most commonly acquired, there are reports of idiopathic megaesophagus in young horses that is probably congenital (Fig. 32.45 and Color Plate 32.3).[38-43] Congenital megaesophagus appears to be more common in Friesian horses than in other breeds and is associated in some cases with smooth muscle hyertrophuy in the distal esophagus.[39,40]

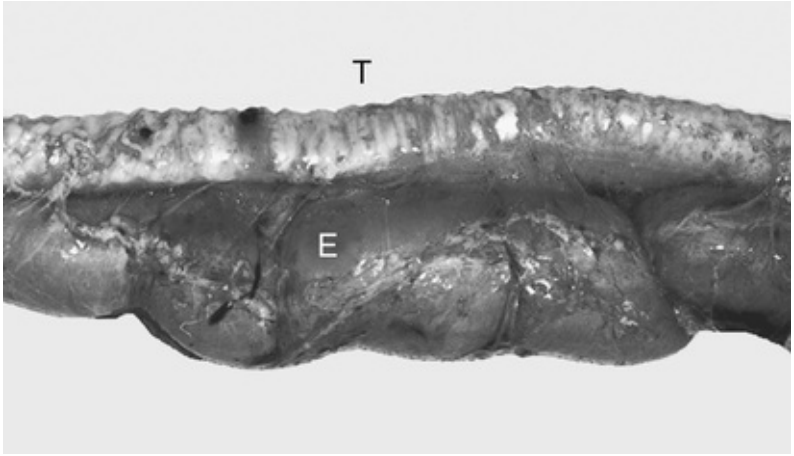


FIG. 32.45 Megaesophagus in a 10-month-old Paint Horse foal that had two duodenal strictures that appeared to have been present for several months. The trachea *(T)* lies dorsal to the dilated esophagus *(E).* (Courtesy Dr. M.J. Murray.)

Acquired megaesophagus in adult horses is usually caused by either primary or secondary esophageal obstruction. Esophageal impactions of relatively short duration cause proximal dilation of the esophagus that is generally reversible. However, if the duration of the obstruction is long, the motility of the esophagus may be permanently impaired. Acquired megaesophagus in foals is often secondary esophagitis resulting from gastric outlet or duodenal obstruction. Other causes of acquired megaesophagus include extraesophageal obstruction by tumors or abscesses, pleuropneumonia, and vascular ring anomalies. In addition, acquired megaesophagus may result from neurologic, neuromuscular, or muscular disorders. Neurologic diseases that cause vagal neuropathy, such as equine protozoal myeloencephalitis, equine herpesvirus myeloencephalitis, and idiopathic vagal neuropathy, have been associated with megaesophagus in horses. Pleuropneumonia may accompany vagal neuropathy and thus result in megaesophagus. Megaesophagus is also an early sign of equine dysautonomia[44] and may be noted in patients with botulism. Myasthenia gravis is a well-known

cause of megaesophagus in other species but has not been reported in horses. Also in other species, electrolyte disorders, cachexia, primary myopathies, myositis, and Addison disease may affect esophageal motility, but these have not been associated with megaesophagus in horses.

Esophageal inflammation, particularly reflux esophagitis, may affect motility and cause megaesophagus. However, because esophageal hypomotility may predispose to reflux esophagitis, it may be difficult to determine whether the esophagitis or the megaesophagus is the causative disorder (see Color Plate 32.3). Iatrogenic megaesophagus can be induced by the α_2-adrenergic agonist detomidine, but this is transient and reversible.[45] However, the use of this drug may complicate clinical evaluation of esophageal motility. Because esophageal hypomotility represents a functional obstruction, the clinical signs of esophageal hypomotility or megaesophagus are similar to those of esophageal obstruction. These clinical signs include ptyalism, dysphagia, and nasal discharge of saliva and food material. Dilation of the cervical portion of the esophagus may be evident externally. Weight loss is a common sign, and clinical signs attributable to an underlying disease may be evident.

Diagnosis of esophageal hypomotility requires transit studies. Transit time of a bolus from the cervical portion of the esophagus to the stomach can be measured by fluoroscopy or contrast radiography.[7,44] Other signs of esophageal hypomotility and megaesophagus include pooling of contrast material and an absence of peristaltic constrictions. Endoscopy may reveal a dilated esophagus and an absence of peristaltic waves. Evidence of underlying disease causing obstruction or esophageal dilation may be observed. The esophagus should be evaluated for evidence of esophagitis that is either causing esophageal motility dysfunction or is a result of impaired esophageal clearance of gastric fluid. Esophageal manometry may be useful for documenting abnormal postdeglutition contraction pressures, contraction time, and propagation times.[4,38] Other diagnostic tests such as a CBC and chemistry studies help identify an underlying cause. A careful neurologic evaluation should be performed. Signs of neurologic disease and abnormal cerebrospinal fluid analysis suggest an underlying neurologic disorder. Myopathy may be detected by electromyography.

Treatment of esophageal hypomotility or megaesophagus should be aimed at the underlying cause. Dietary modification should be aimed at improving esophageal transit of food. Slurries of pellets should be fed. In addition, it may be beneficial to feed from an elevated position to promote transit. In patients with reflux esophagitis associated with megaesophagus, metoclopramide or

bethanechol may be beneficial to increase lower esophageal tone, promote gastric emptying, and reduce gastroesophageal reflux. The prognosis depends on the underlying cause and the degree of dilation. Although many cases of megaesophagus associated with reflux esophagitis respond well to treatment, many other forms of megaesophagus, including congenital megaesophagus, have a poor prognosis.

■ Congenital Disorders

Congenital disorders of the esophagus are rare. Reported congenital abnormalities include congenital stenosis,[46] persistent right aortic arch, congenital strictures, esophageal duplication cysts,[47,48] and megaesophagus.[39,40,49] In the one report on congenital stenosis, double-contrast radiography revealed concentric narrowing of the thoracic portion of the esophagus in the absence of any vascular abnormalities at the base of the heart. Successful treatment included having the foal stand with the forelimbs elevated off the ground after each feeding.

Persistent right aortic arch is a congenital anomaly in which the right fourth of the aortic arch becomes the definitive aorta instead of the left aortic arch, which results in constriction of the esophagus by the ligamentum arteriosum as it extends between the anomalous right aorta and the left pulmonary artery.[24] Clinical signs may include dysphagia, drooling of saliva, and distention of the cervical portion of the esophagus as a result of partial obstruction of the thoracic portion.[50] Endoscopic examination typically reveals dilation of the esophagus cranial to the obstruction with evidence of diffuse esophagitis. In addition, evaluation of the thorax usually reveals the presence of aspiration pneumonia. Successful surgical treatment of persistent right aortic arch has been reported in one foal.

Esophageal duplication cysts cause typical signs of esophageal obstruction, including salivation, dysphagia, and swelling of the cervical portion of the esophagus as they enlarge. Such signs can make them difficult to differentiate from simple obstruction (choke). However, an aspirate of the mass may aid in the diagnosis by revealing the presence of keratinized squamous cells.[51] Cysts may communicate with the lumen of the esophagus. Surgical treatments have included complete surgical resection and surgical marsupialization. The latter appears to be more successful and to result in fewer complications. Complications of surgical resection have included (1) laryngeal hemiplegia

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secondary to surgical trauma to the recurrent laryngeal nerve in the region of the esophagus and (2) esophageal fistula formation.

■ Esophageal Perforation

Perforation typically occurs in the cervical region in response to external trauma or rupture of an esophageal lesion such as an impacted diverticulum. The esophagus is particularly vulnerable to external trauma in the distal third of the neck because it is covered by only a thin layer of muscle at this location.[52] Iatrogenic perforation may occur in response to excessive force with a stomach tube against an obstruction or a compromised region of the esophagus. Esophageal perforations may be open or closed and tend to cause extensive necrosis of tissues surrounding the wound because of drainage of saliva and feed material within fascial planes (Fig. 32.46). This may lead to extensive cellulitis and endotoxemia. Closed perforations of the esophagus are particularly troublesome because wound discharge may migrate all the way to the mediastinum and pleural space via fascial planes and may cause abscessation (Fig. 32.47). In addition, extensive subcutaneous and fascial emphysema frequently develops and is usually evident on cervical radiographs.

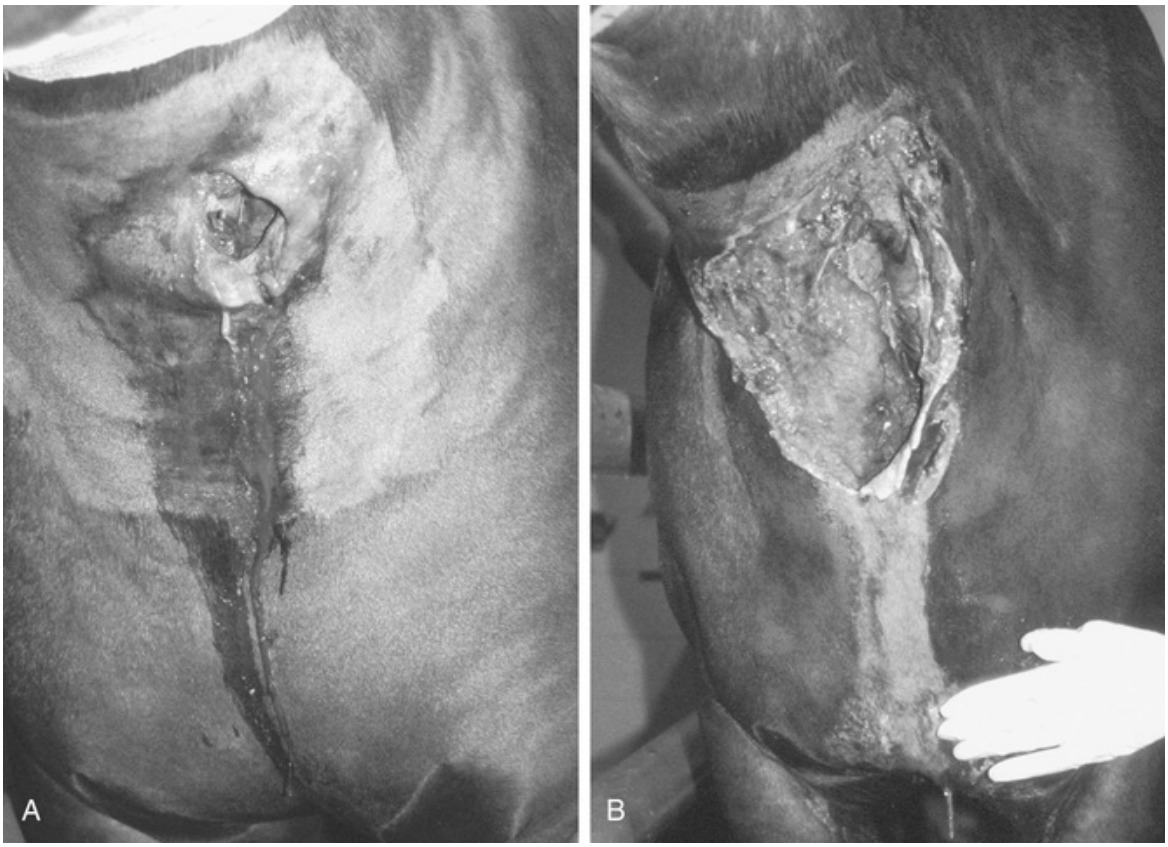


FIG. 32.46 Esophageal perforation in a horse. **A,** An open esophageal laceration was detected on presentation in the midcervical region. The wound was treated by lavage and débridement, and the horse was fed via a tube inserted into the esophagus through the wound. **B,** Approximately 14 days later, dissection of esophageal contents within surrounding fascial planes resulted in extensive sloughing of tissue.

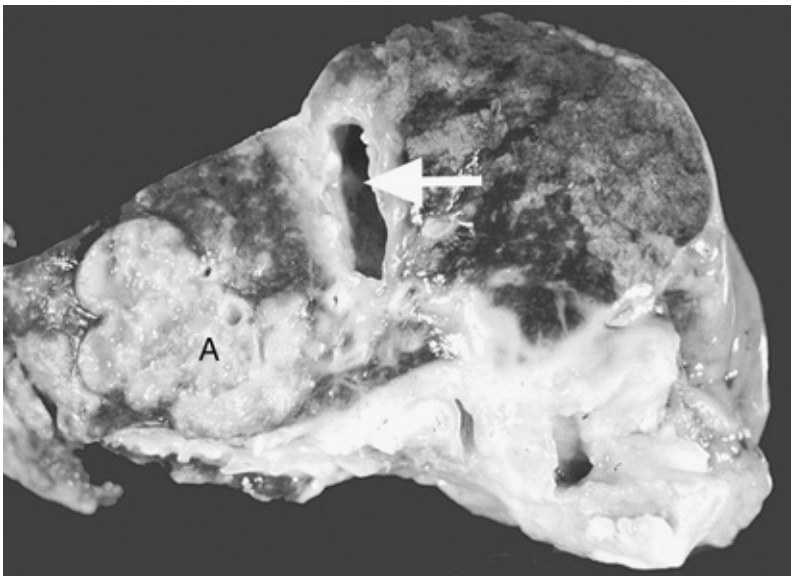


FIG. 32.47 Esophageal abscess *(A)* and cellulitis that developed secondary to an esophageal obstruction. The esophageal lumen is indicated by the *white arrow*. (Courtesy Dr. M.J. Murray.)

Treatment should include conversion of closed perforations to open perforations if possible,[53] extensive débridement and lavage of affected tissues, broad-spectrum antibiotics, tetanus prophylaxis, and esophageal rest. The latter may be achieved by placing a feeding tube into the esophagus via the wound. Alternatively, a small (12-French) nasogastric tube should be placed. For open perforations, once the wound has granulated and contracted to a small size, oral feeding may be attempted. Extensive loss of saliva via esophageal wounds may lead to hyponatremia and hypochloremia. In addition, transient metabolic acidosis occurs because of salivary bicarbonate loss, followed by progressive metabolic alkalosis. Although there are reports of esophageal wounds that healed well by second intention, it takes a prolonged period of time.[54] In addition, some perforations never completely heal and form permanent esophagocutaneous fistulas that may necessitate surgical correction. The development of esophageal strictures is not common because wounds are usually linear and not circumferential. However, traction diverticula may develop. Other complications of esophageal wounds include Horner syndrome and left laryngeal hemiplegia.

In a retrospective study on esophageal disorders, only 2 of 11 horses with esophageal perforations survived long term,[17] and in a report on esophageal trauma secondary to nasogastric intubation, 4 of 5 affected horses were euthanized.[35] The prognosis is therefore poor in horses with esophageal perforations, largely because of the extent of cellulitis, tissue necrosis, shock,

and local wound complications.

■ Esophageal Stricture

Strictures most commonly occur as sequelae to esophageal obstructions that result in circumferential erosion or ulceration of the esophageal mucosa; however, they may result from oral administration of corrosive medicinal agents and trauma to the neck.[55] Congenital strictures have also been reported. Strictures that result from mucosal and submucosal trauma are termed *esophageal webs* or *rings.* Strictures may also originate in the muscular layers and adventitia of the esophagus (mural strictures) or in all of the layers of the esophagus (annular stenosis).[56] Horses with these lesions have a presentation similar to that of horses with simple obstructions because strictures result in partial obstruction and accumulation of feed material in the lumen. Esophageal webs or rings can be observed endoscopically, whereas confirming the presence of mural strictures or annular stenosis may require double-contrast esophagography.

In one study on esophageal stricture after simple obstruction, maximal reduction in esophageal lumen occurred within 30 days of esophageal obstruction. Although surgery has been employed to reduce such strictures, initial medical management is warranted because strictures may resolve with conservative therapy, and the esophagus continues to remodel for up to 60 days after ulceration. In one report, seven horses with esophageal obstruction-induced stricture were treated conservatively by being fed a slurry diet and with antiinflammatory and antimicrobial medications; five of seven were clinically normal within 60 days. One of the five successfully treated horses had a 10-cm area of circumferential ulceration, which suggests extensive mucosal injury may resolve without permanent stricture formation.

If strictures do not resolve within 60 days, other methods to increase esophageal diameter should be investigated. Bougienage has been used successfully in small animal patients and human beings and is increasingly used to dilate strictures in horses. The technique involves passage of a tubular dilatable instrument down the esophagus and stretching of the stricture. Some authors have suggested that this may be accomplished by passing a nasogastric tube with an inflatable cuff (Fig. 32.48).[57] However, the procedure has to be performed frequently to achieve any success and is often not well tolerated by horses. Alternatively, several surgical techniques have been used to resolve

strictures, including resection and anastomosis,[58,59] temporary esophagostomy with fenestration of the stricture, esophagomyotomy for strictures of the muscularis layers and adventitia,[60,61] and patch grafting with local musculature.[62] However, such surgeries are fraught with complications, largely because of the propensity for stricture to recur in the traumatized esophagus. The esophagus lacks a serosal layer and does not rapidly form a fibrin seal, as does the remainder of the intestinal tract, and so anastomoses tend to leak. In addition, tension on the esophagus during swallowing and movement of the neck impairs healing of anastomoses.



FIG. 32.48 Attempted dilation of esophageal stricture with bougienage. In this case, a cuffed Silastic tube (Dow Corning, Midland, Mich.) was passed to the site of stricture under endoscopic guidance, and the cuff was then inflated to distend the site of stricture. (Courtesy Dr. M.J. Murray.)

■ Esophageal Diverticula

There are two types of diverticula: traction (true) diverticula and pulsion (false) diverticula. Traction diverticula result from wounding and subsequent

contraction of periesophageal tissues, with resultant tenting of the wall of the esophagus. Pulsion diverticula arise from protrusion of esophageal mucosa through defects in the muscular wall of the esophagus and usually result from trauma or acute changes in intraluminal pressure (Fig. 32.49). A traction diverticulum appears as a dilation with a broad neck on contrast esophagography, whereas a pulsion diverticulum typically appears as a flask shape with a small neck on an esophagogram.[63] Whereas traction diverticula are usually asymptomatic and of little clinical significance, pulsion diverticula may fill with feed material, ultimately leading to esophageal obstruction.[64] However, a movable mass in the midcervical region may be noticed before onset of complete obstruction.[5] Pulsion diverticula may be surgically corrected by inversion or resection of prolapsed mucosa and closure of the defect in the wall of the esophagus.[26,63,64] Inversion of excessive mucosa may predispose horses to esophageal obstruction and should therefore be reserved for small diverticula.

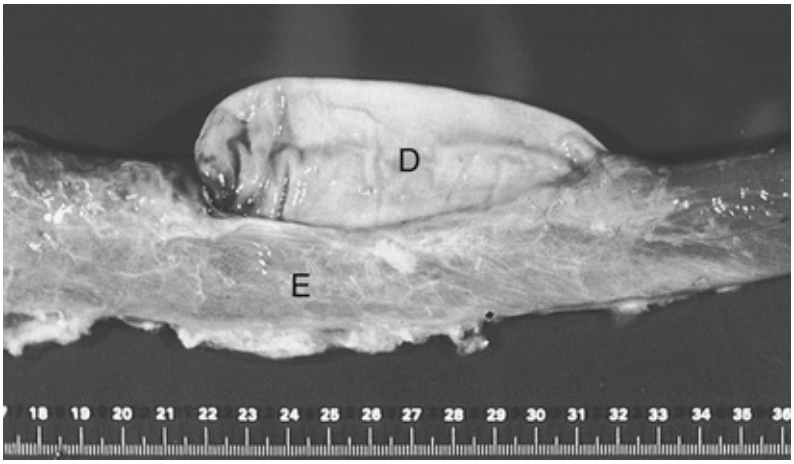


FIG. 32.49 Pulsion diverticulum *(D)* of the esophagus *(E)* in a horse that had intermittent episodes of esophageal obstruction. (Courtesy Dr. M.J. Murray.)

■ Neoplasia

Neoplasia of the esophagus is rare, but squamous cell carcinoma[65,66] and leiomyosarcoma[67] have reportedly affected the esophagus either as the primary site or in association with a lesion in the squamous portion of the stomach. The predominant clinical signs are weight loss, colic, and recurrent esophageal

obstruction. The tumor is typically detected on esophagoscopy and radiography during an affected horse's life, but a definitive diagnosis may necessitate a biopsy during laparotomy.[21,67] When neoplasia affects the lower portion of the esophageal sphincter, gastroesophageal reflux may contribute to ulceration of esophageal mucosa. The prognosis for malignant neoplasia of the esophagus is grave.

Disorders of the Stomach

Gayle D. Hallowell

Various diseases affect the equine stomach and include equine squamous gastric disease (ESGD), equine glandular gastric disease (EGGD), parasitic disease (*Gasterophilus* spp., *Habronema* spp., *Draschia* spp.), gastric impactions, gastric rupture, and squamous cell carcinoma. This section covers these conditions with a particular focus on EGGD, about which a number of reports have been published.

■ Equine Squamous Gastric Disease

Historically, this has been the most prevalent disease identified in the equine stomach. However recent personal communications and anecdotal reports suggest that the prevalence of this condition has fallen since 2005, particularly in sports and leisure horses.[1] This change in prevalence may be actual, secondary to an understanding of risk factors and subsequent changes in management, or different diseases are diagnosed instead because more veterinarians have longer gastroscopes and thus are able to examine the pylorus and pyloric antrum.

ESGD can be a primary problem or, occasionally, a secondary problem that results from obstruction of gastric outflow with subsequent backflow of acid gastric juices or alkaline biliary secretions. The focus of this section is on primary squamous disease. The management of secondary squamous disease is largely dictated by treatment of the primary disease causing delayed gastric outflow.

Pathophysiology.

ESGD results from increased exposure of the squamous mucosa, which has limited mechanisms of defense against highly acidic gastric contents. Horses constantly secrete gastric acid,[2,3] and hydrochloric acid is primarily responsible

for the damage to the squamous mucosa. Damage occurs rapidly; acid injury becomes evident within 30 minutes of exposure in vitro.[4] Horses are constant grazers, and in pasture conditions, the consumption of roughage creates a basketball-sized bolus of feed in the stomach that acts as a buffer to absorb gastric acid and physically prevents the splashing of gastric contents into the dorsal region of the stomach that is lined by squamous mucosa (Fig. 32.50). Any disruption in normal feeding or behavior results in breakdown of this protective mechanism and a resultant increase in the risk for ESGD. Short-chain fatty acids released during fermentation of soluble carbohydrates consumed in the diet are also likely to contribute directly to squamous mucosal injury[5] and disrupt the physical protective effect of a predominantly roughage-based diet. ESGD thus is largely a disease that results from the management changes imposed on horses for a variety of purposes.

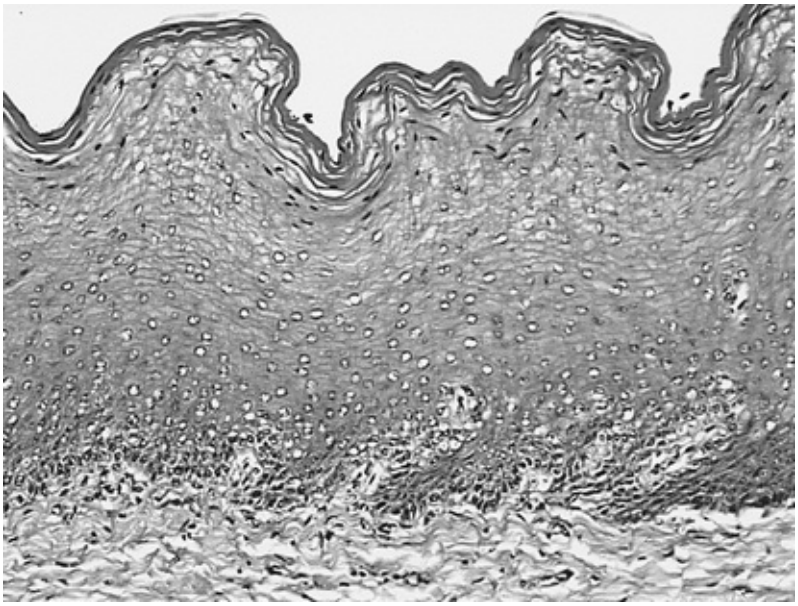


FIG. 32.50 Photomicrograph of equine gastric squamous epithelial mucosa. Multiple layers of epithelium are arranged in parallel with the luminal surface. The most superficial layers of cells are cornified, and superficial to these cells are layers of keratin. (Hematoxylin and eosin stain.)

Clinical Signs.

Clinical signs reported with ESGD include poor appetite, poor bodily condition,

and abdominal discomfort.[6] Other clinical signs loosely associated with ESGD include poor appetite or "picky eating,"[6-9] poor bodily condition or weight loss,[6,7,10] chronic diarrhea,[6,7] poor coat,[8], bruxism,[11] behavioral changes (including aggression and nerviousness),[7,12,13] acute or recurrent abdominal pain,[6,7,8,14-16] and poor performance.[7,8,17-19]

Prevalence and Risk Factors.

The prevalence of ESGD mirrors exercise intensity: The risk of disease development increases as the intensity of work increases. The highest prevalence of this disease has been reported in Thoroughbred racehorses, of whom more than 70% are affected across a wide range of studies.[8,11,20,21] However, it seems likely that these studies overstate the prevalence of clinically significant disease because many affected animals have only small focal lesions that are likely to be clinically insignificant but, by definition, meet the criteria for diagnosis of ESGD. This overrepresentation has led many clinicians to dismiss ESGD as a normal finding in a performance horse. It is proposed that mild (grade II/IV) ESGD may be an incidental finding and that although it may be associated with clinical signs, horses with grade III-IV/IV ESGD are more likely to have clinical disease.[22] The prevalence and significance of ESGD should be discussed in the context of the relative severity of lesions observed.

The Thoroughbred racehorse is the best studied of horse breeds regarding risk factors and effective treatments. However, ESGD is identified in a wide range of other horse breeds. In a Danish study, ESGD was observed in 69% of horses with varying activities, ranging from horses at pasture to horses in hard work, and there was no association between presence of ESGD and horse use.[23] Similar prevalence of ESGD has been reported in Standardbred (63% to 87%[3,24]), endurance (67% to 93% during competition[25,26]), show (58%[12]), and western performance (40%[27]) horses. The prevalence of ESGD in horses at rest is variable but typically lower and, when observed, tends to be less severe. However, in selected cases, severe (grade III-IV/IV) ESGD can be observed in horses at pasture, and ESGD should not be omitted in the differential diagnosis simply because a horse does not meet the typical risk profile.

The commencement of training, with the multitude of management changes imposed, including exercise[28] and high-concentrate/low-roughage diets,[29] can result in the development of ESGD within 7 days.[30,31] In addition to the overall

risk associated with the induction of training, specific risk factors that have been identified for ESGD include fasting,[32] transport,[31] stabling,[3] and time in work.[32] NSAIDs may induce ESGD experimentally; however, because of epidemiologic study results[21] and the lack of a direct link to the pathophysiology of squamous ulceration, it is unlikely that NSAIDs contribute to ESGD in the clinical setting.

Treatment.

Treatment of ESGD focuses on suppression of acid production and, when possible, changing management practices that may have contributed to the disease (Fig. 32.51). Acid suppression therapy does not contribute directly to healing, but the squamous mucosa has an enormous proliferative capacity, and the removal of ongoing insult is usually sufficient for the tissues to heal. Theoretically, removal of affected horses from the risk factors that caused disease and reestablishment of a normal pH gradient in the stomach should result in healing. However, a reduction in workload is often not possible, and treatment is required in the presence of ongoing exposure to risk factors. Furthermore, even when removal from the risk factors is possible (i.e., resting of an affected horse), acid suppression therapy is often necessary to restore a normal appetite so that enough roughage is consumed to reestablish the pH gradient in the stomach and thereby allow healing to occur. If removal from work is used to manage ESGD, then follow-up gastroscopy 4 to 6 weeks later is indicated to ensure that healing has occurred.

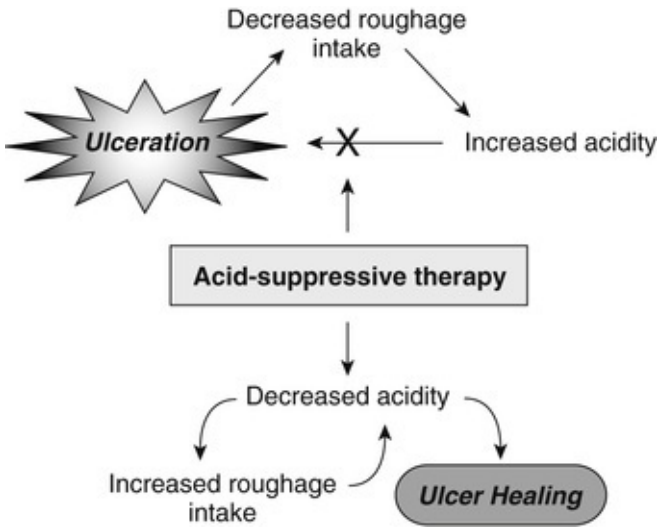


FIG. 32.51 Diagram representing the pathophysiologic process of

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ulceration in the equine gastric squamous mucosal epithelium and the permissive effect of acid suppression on ulcer healing.

Because the ability to remove risk factors, such as exercise and concentrate diets, can be limited, the use of acid suppression therapy remains a cornerstone in the management of ESGD. Various drugs have been used for this purpose, but oral omeprazole remains the most effective and best studied. Omeprazole inhibits the H^+, K^+–adenosine triphosphatase (proton) pump that secretes hydrochloric acid. Omeprazole is most commonly administered at a dose of 4 mg/kg PO q24h for 28 days, and its efficacy at this dose for treatment of ESGD has been well documented by several clinical trials.[33-37] The use of lower doses has been evaluated and, under certain conditions, doses as low as 1 mg/kg have been shown to be as efficacious as 4 mg/kg in the treatment of ESGD.[38] On the basis of experimental studies,[39-45] it is widely believed that once-daily administration of omeprazole results in 24 hours of acid suppression; however, one study has suggested that the duration of acid suppression after dosing at 4 mg/kg may be as short as 12 hours; thus in nonresponders, administration twice daily may be warranted.[46] As exercise is considered to be the peak risk period for ESGD development,[28] timing of omeprazole administration should be considered before exercise. However, one study revealed no advantage of administration of omeprazole 1 to 4 hours before exercise over administration after exercise.[47]

Reported healing rates at 28 days for horses that stay in work are typically around 70% to 80%.[33,34,37,47] Although the majority of affected animals improve by 28 days,[33,38,47,48] repeated gastroscopic examination is recommended before therapy is terminated to ensure that healing has occurred.

The H_2 receptor antagonists ranitidine and cimetidine are the other drugs that historically have been used for treating ESGD. Both drugs work by competitively blocking the H_2 receptor on the parietal cell, and their efficacy is dependent on maintaining plasma concentrations. Ranitidine, administered most commonly at 6.6 mg/kg PO q8h, has been shown to effectively suppress gastric acidity in experimental studies[2,14,49,50] and provides an alternative option for acid suppression. However, in a direct comparison of the efficacy of ranitidine with that of omeprazole, ranitidine was shown to be inferior,[35] and thus omeprazole remains the treatment of choice. Cimetidine has been poorly studied in this context, and its use is not justified.

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For nonresponding patients, which usually is only 10% of animals with ESGD, or those animals to which oral paste cannot be administered, long-acting injectable omeprazole (4 mg/kg IM q5-7 days) should be considered. It can be administered every 5 to 7 days, and studies have shown that it results in effective acid suppression during this period.[51] A small-scale clinical study demonstrated healing in 14 days in 100% of patients.[51] This drug should be administered via deep intramuscular injection into the gluteal mm. Transient swelling has occasionally been reported.[1]

Nonpharmaceutical methods, such as feed supplements and antacids, are popular among owners for the treatment of ESGD because of their low cost and availability. Although antacids can effectively reduce gastric acidity, their effect is short-lived (2 hours)[14,52] and so their use cannot be recommended. Mucosal protectants, such as pectin-lecithin complexes, may play a role in providing a physical barrier between the mucosa and acid, and short-term improvement in clinical signs associated with the use of antacids is often reported. Their use in selected cases may be sufficient for control of ESGD, but they should be considered alongside management changes to prevent recurrence, and alongside omeprazole in the treatment of ESGD, rather than as a primary treatment for ESGD.

Prevention of Recurrence.

To prevent recurrence of disease, management changes should be recommended. These changes include increased roughage and decreased concentrate in the diet; multiple, smaller feeds; increased turnout; and feeding a small amount of feed, such as a few handfuls of chaff, before exercise to act as a raft to protect the squamous mucosa from acid splash.[22] The use of mucosal protectants such as the pectin-lecithin complexes or administration of sugar beet, which contains pectin, should be recommended in the few months after treatment and may be required longer. Historically omeprazole has been used at 1.0 mg/kg PO q24h for prevention,[31] but 0.5 mg/kg PO q24h has been shown, under specific conditions, to be as effective.[47] Recent data in humans have revealed an association with long-term omeprazole therapy and acute kidney injury[53]; no such studies or association has been performed in horses, but this approach may not be innocuous. Gastric acid is produced for a reason!

■ Equine Glandular Gastric Disease (EGGD)

It is now widely accepted that EGGD is an entity separate from ESGD.[1] A series of studies have clearly demonstrated that the risk factors for EGGD[32] and response to its treatment[38,47,48,54] differ dramatically from those for ESGD, which is not surprising in view of the differences in the anatomy of the glandular mucosa (Fig. 32.52) and probable pathophysiologic features. EGGD is probably multifactorial in nature in horses.[1] Since 2005, the identification and reported prevalence of this disease have increased. Many authorities believe that this is a true change in disease prevalence; squamous disease is less common as a result of improved management based on risk factors and also is less likely to be diagnosed because of increased awareness of EGGD as an individual entity. Historically, some of the difference in prevalence reported may also relate to endoscopes available; those initially available in the 1990s were only 2.5 m in length, and therefore the pyloric antrum, where the majority of glandular disease occurs,[23,32,38,47,48,54] was rarely observed in clinical cases.

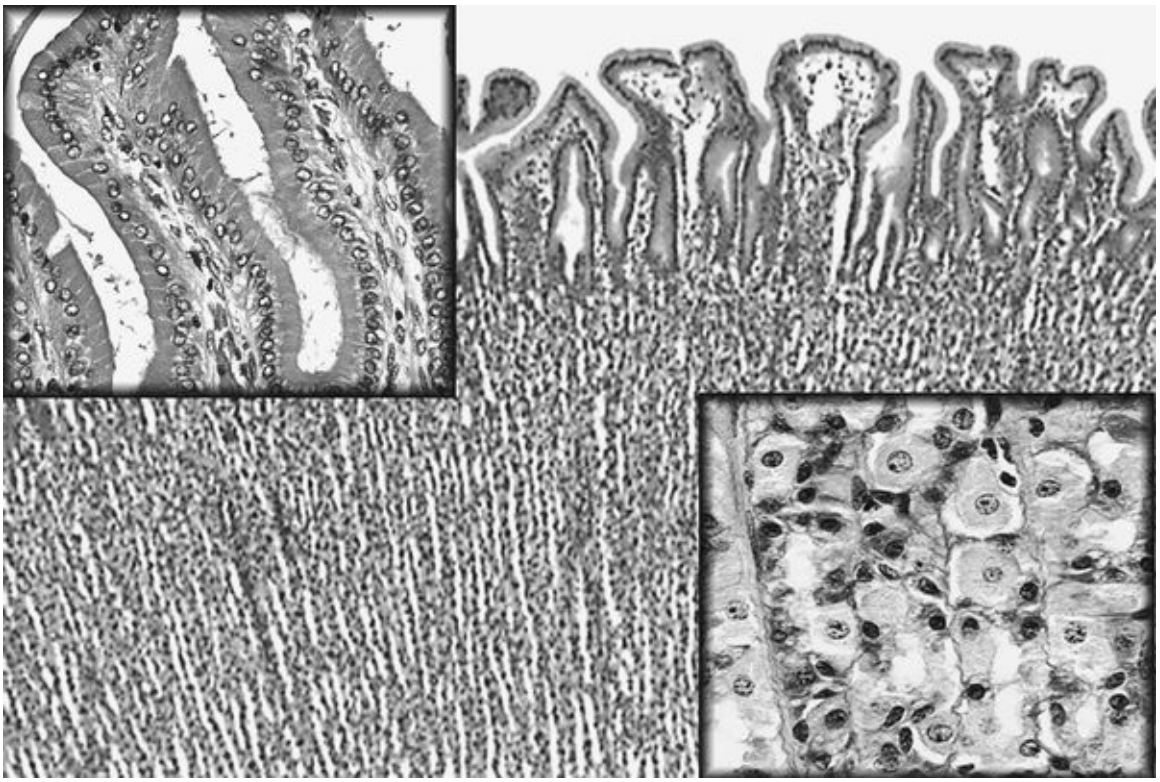


FIG. 32.52 Photomicrographs of equine gastric glandular mucosa. In contrast to the squamous mucosa, the glands are parallel to one another and perpendicular to the luminal surface. There are multiple cell types within the mucosa, with surface epithelial cells and mucus-secreting cells

toward the lumen, and parietal cells, chief cells, enterochromaffin-like cells, G cells, and D cells deeper in the mucosa. The *top left insert* is a high-power magnification of cells lining gastric pits on the surface of the epithelium. The *bottom right insert* is a high-power magnification of cells lining the gastric glands deeper in the mucosa. (Hematoxylin and eosin stain.)

Pathophysiology.

The glandular mucosa differs from the squamous mucosa in that under normal physiologic conditions, it is exposed to highly acidic gastric contents; the pH in the ventral portion of the stomach is relatively stable at between 1 and 3.[46] Whereas ESGD results from exposure of mucosa unaccustomed to acidity, EGGD may result from a breakdown of the normal defense mechanisms that protect the mucosa from acidic gastric contents, which includes bicarbonate and a layer of gastric mucus that is a mixture of glycoproteins, water, electrolytes, lipids, and antibodies.[55]

Lesions of the glandular mucosa are not ulcerative in most situations; they are erosive and inflammatory in nature. They often contain a mixed inflammatory population of lymphocytes, plasmacytes, and neutrophils and should thus be described as glandular gastritis.[56-58] Nodular lesions typically have a lymphocytic, plasmacytic infiltrate. Although lesions that have a fibrinosuppurative cap often have a predominance of neutrophils, their presence does not indicate an infectious cause.[1]

As mentioned, EGGD is probably a multifactorial condition. Different lesion types and location of lesions may have different causes, and thus responses to treatment may be different. The glandular mucosa in the pyloric, fundic, and cardiac regions differs in anatomy, physiology, and blood flow, which may be why most of the lesions identified in adult horses occur around the pylorus or in the pyloric antrum.[1]

Changes in blood supply may result in breakdown of normal defense mechanisms. Stress may influence gastrin production, reduce blood supply to the glandular mucosa, and thus initiate and perpetuate this condition. Blood supply to different areas of the glandular mucosa is thought to be uneven, and both exercise and feeding could result in initiation or perpetuation of disease.[1]

Acid injury is unlikely to be the initiator of these lesions, but it may perpetuate mucosal damage and prevent mucosal healing.[22]

Because these lesions contain an inflammatory infiltrate, it is entirely possible

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that some lesions are gastric manifestations of inflammatory bowel disease (IBD) and may necessitate similar treatment and management strategies, including evaluation of the remaining intestinal tract.[1]

Clinical Signs.

Clinical signs of EGGD are often nebulous, which makes assessing clinical significance of lesions challenging. According to a consensus statement,[1] clinical signs that are considered associated with EGGD include changes in temperament, including nervousness and aggression; changes in rideability, including reduced willingness to work and reluctance to go forward; unexplained weight loss, probably concurrently associated with reduced appetite or altered eating patterns; cutaneous sensitivity, manifested as flank-biting or resentment of girthing, leg aids, or rugging; and mild or recurrent abdominal pain.[1] It was deemed unlikely that changes in coat condition, stereotypical behavior, bruxism, and diarrhea were signs associated with EGGD.[1]

Although cutaneous sensitivity seems an implausible clinical sign of gastric disease, data from other species suggests that afferent pathways from abdominal viscera and the sixth to ninth thoracic spinal nerves are pooled, so that afferent signals from the skin may be affected by input and misinterpreted within the brain. In addition, viscerosomatic reflexes can result in pain and sensitivity in segmentally related structures such as the skin.[59]

Prevalence and Risk Factors.

EGGD prevalences of 47 to 62.5%[20,32] have been reported in Thoroughbred racehorses in Australia. Among a mixed population of horses in Denmark, the overall prevalence of EGGD was 57%[23]; in sports horses in the United Kingdom, 65%[60]; and in endurance horses, 27 to 33%.[25,26] Abattoir studies have reported prevalences of 57% to 67%[56-58] in a variety of horse types.

Information on risk factors for EGGD are limited and occasionally contradictory. What is obvious from these studies, however, is that risk factors for EGGD are different to ESGD. Warmbloods are at greater risk for developing EGGD than are other horse types.[61,62] In Thoroughbred racehorses, trainer was identified as a risk factor independent of other management factors.[32] Exercising for more than 4 or 5 days per week has been shown to be a risk factor in both Thoroughbreds using for racing[32] and in showjumpers,[63] whereas intensity of

exercise was not. Horse experience was inversely correlated with prevalence of EGGD in both polo ponies[64] and showjumpers,[63] which may suggest adaptation to type of work or differences in management of elite horses.[1] A study in endurance horses demonstrated a doubling in EGGD prevalence during the competition season in comparison with off-season activity,[26] which, as in human athletes, may be related to reduction in gastric and splanchnic blood flow during exercise.

Stress is an important risk factor in the development of glandular lesions in people.[65-67] Horses with severe EGGD have greater increases in cortisol in response to novel stimuli,[68] and in response to exogenous adrenocorticotropic hormone,[69] which suggests that these horses may be more sensitive to stress. There is controversy regarding the association with stereotypies; no association was found in one study,[32] whereas was an association with crib-biting was found in another.[70] These differences may be explained by the high prevalence of both conditions in a given population, particularly as stereotypies are often regarded as a coping strategy in horses. What would be more interesting to evaluate is disease prevalence in animals that are prevented from exhibiting stereotypical behavior. The lower prevalence in more experienced polo ponies and showjumpers[63,64] may relate to adaptation to physiological stress. Cortisol concentrations have been shown to be lower in more experienced show and showjumping horses than in less experienced horses.[71,72] It is challenging to know what is stressful to an individual horse; changes to minimize stress should be tailored to an individual and ideally kept consistent.

It is often perceived that there is an association between orthopedic and EGGD, but thus far no such association has been demonstrated,[32] and care is warranted because animals that present with poor performance often have multiple abnormalities that contribute to presenting signs.

There is currently no evidence to indicate an association between diet and EGGD, and thus making recommendations are challenging. However, grazing should be maximized (if this does not result in stress), and animals should not exercise on an empty stomach.[1]

In humans, bacterial agents and NSAIDs are the predominant causes of gastric disease; *Helicobacter pylori*–negative, NSAID-negative gastric disease is rare.[73] In horses, however, there is no evidence that bacteria are involved in the pathogenesis of EGGD. Several investigations in horses have failed to

consistently identify *Helicobacter*-like organisms in EGGD lesions.[56,57,74,75] Other bacterial species such as *Escherichia fergusonii*, *Streptococcus bovis*, and *Enterococcus faecium* are potentially pathogenic and have been associated with EGGD lesions, but their pathogenicity remains unproven; they may simply be colonizers. Studies on the gastric microbiota have failed to identify a difference between horses with EGGD and those without.[76] Thus no current data suggest that bacteria are an important cause of EGGD, although the potential for bacteria to cause this disease is plausible.

The theoretical potential for NSAIDs to cause EGGD is plausible as cyclooxygenase (COX) inhibition could reduce gastric and splanchnic blood flow. Glandular lesions can be induced if flunixin, phenylbutazone, and ketoprofen are administered at doses 50% higher than typically recommended,[62] whereas at clinical doses, phenylbutazone and suxibuzone did not induce gastric disease when administered for 15 days.[63] Moreover, the administration of NSAIDs has not been identified as a risk factor.[28,32,62-64,77,78] Thus at doses commonly used in clinical cases of horses that are otherwise healthy, the risk of EGGD associated with short-duration NSAID therapy is negligible.

Treatment.

It is widely accepted that ESGD and EGGD cannot be managed in the same way. In three studies, only 25% of glandular lesions healed with 28 to 35 days of omeprazole monotherapy at 4.0 mg/kg PO q24h, in direct contrast to an ESGD healing rate of 78%,[28,37,38] which suggests that this treatment is not appropriate for EGGD and that other treatment is required.

One plausible treatment option for EGGD is a combination of oral omeprazole (4 mg/kg PO q24h) and sucralfate (12 mg/kg PO q12h). Sucralfate is known to provide a physical barrier that prevents acid diffusion, stimulates mucus secretion (which blocks acid diffusion), inhibits pepsin and bile acid secretion, promotes epithelialization by preventing fibroblast degradation, stimulates epidermal and insulin-like growth factors, and increases mucosal blood flow through increased production of prostaglandin E. Data on its efficacy varies between studies. One study[79] demonstrated an 80% improvement and a 63% healing rate with this combination at 28 days, whereby healing was reported to represent grade 0 or 1 EGGD lesions, although improvement rates were lower for lesions around the pyloric antrum (67.5%). Another study,[80] in which the end point for healing was a completely normal appearance of the pyloric antrum,

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demonstrated a healing rate of only 22% at 28 days, although improvement rates were similar to those in the previously described study. If this combination is to be used, omeprazole should be administered on an empty stomach, and the animal should not be fed for 30 to 60 minutes after administration.[1] Sucralfate is not licensed for veterinary use, and so appropriate consent should be obtained before administration.

A second plausible treatment for this condition is administration of oral misoprostol (5 µg/kg q12h), which is licensed for treatment of refractory gastric disease in humans; however, it is not licensed for veterinary use. Misoprostol is a prostaglandin E analogue and as such probably improves mucosal blood flow. It has also been shown to effectively suppress acid production in horses[81] and inhibits neutrophilic inflammation.[82] One study[80] demonstrated healing, defined as return to normal appearance, in 73% of horses with significant pyloric glandular lesions that were treated with misoprostol; in contrast, the healing rate among those treated with combined omeprazole and sucralfate therapy was only 22%. Side effects are rare, but those reported with misoprostal administration include mild, transient diarrhea, mild abdominal pain, and urticaria. Care must be taken in administration to pregnant mares because this drug can induce abortion, although some safety data suggest that it can be safely administered to mares between 100 and 130 days pregnant.[83] Appropriate consent should be obtained before administration because this drug is not licensed for veterinary use and because of the potential for causing abortion in people, it should not be dispensed to women who are pregnant or planning to be pregnant. There is no rationale for combining this drug with oral omeprazole.

A third plausible option for the treatment of EGGD is long-acting injectable omeprazole. This drug administered at 4 mg/kg IM has been shown to be more effective than oral formulations in increasing pH in the ventral portion of the stomach[51]; acid suppression is maintained for 4 to 7 days, and so this drug should be administered at 5- to 7-day intervals. Thus far, the data available on the efficacy of this drug in clinical cases are limited. However, in a small study of Australian racehorses, 75% healing and 100% improvement was reported at 2 weeks after two injections.[51] Some unpublished data from sports and leisure horses demonstrated 64% healing, defined as mucosal appearance returning to normal and 96% healing at 2 weeks after two injections given 7 days apart.[1] Transient swelling has been reported in fewer than 10% of cases at the injection site, which is most common if administered into the pectoral muscle or neck. It

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is thus recommended that this drug be administered, after warming, as a deep intramuscular injection into the gluteal muscle. Appropriate consent should be obtained when this drug is used because it currently is not licensed for veterinary use.

If some of these lesions are extensions of inflammatory bowel disease, there may be some rationale in the use of glucocorticoids. Anecdotal reports indicate that they are beneficial in the subgroup of animals that do not respond to more conventional therapies listed previously. In a consensus, morning administration of prednisolone, 1 mg/kg PO q24h, or dexamethasone, 0.05 to 0.1 mg/kg PO q 24h, was suggested. Either dosage can be tapered over a 4- to 5-week period.[1] Other recommendations may include simplification of the diet (in view of underlying causes of IBD in other species, such as cereal proteins or alfalfa).

As stated previously, the role of bacteria in EGGD is unknown, but *Helicobacter*-like organisms are not consistently identified and are not considered an important factor in the initiation or perpetuation of EGGD.[22] In one study, the combination of omeprazole (4 mg/kg PO q24h) and trimethoprim-sulfadimidine (30 mg/kg PO q24h) failed to improve the treatment response in comparison with omeprazole therapy alone (4 mg/kg PO q24h).[54] In one consensus, investigators believed that antimicrobials were not an appropriate first-line treatment for EGGD; their use was deemed appropriate only if based on histologic and bacteriologic findings[1] and was necessary in fewer than 1% of cases.

There is no evidence that ranitidine, aloe vera, pectin-lecithin complexes, polysaccharides, kaolin, bismuth subsalicylate, sea buckthorn, acupuncture, or homeopathy is efficacious in the treatment of EGGD.[1]

If ESGD and EGGD lesions are found concurrently, treatment should be aimed at EGGD. No additional treatments are required because ESGD would be expected to heal with any of the first-line treatments discussed for EGGD (combined omeprazole-sucralfate, misoprostal, and injectable omeprazole).

Expectations for Healing and Monitoring.

Rates of healing are difficult to predict and probably vary by lesion. Raised, nodular, and fibrinosuppurative lesions probably take longer to heal than do flat, hemorrhagic lesions. Mucosal restitution can occur within 3 to 5 weeks, but complete resolution may take several months, especially where raised areas or nodules are visible.

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Affected horses should be evaluated monthly with gastroscopy until resolution is complete. Once lesions have resolved, treatment should be discontinued. There is no rationale for reducing the dose of the drugs discussed previously, with the exception of glucocorticoids. Affected horses should also be monitored for return of clinical signs. The need for follow-up gastroscopy depends on the case being managed.

Management of Refractory Cases.

Because many EGGD lesions are not healed in 28 to 35 days, it is prudent to have a rational plan of what to do when lesions are still present. The aims of treatment should be complete resolution with a mucosa that has a normal appearance. If treatment is prematurely discontinued, lesions may worsen again and clinical signs will recur.[1]

If first-line treatment yields no improvement at 28 to 35 days, or if an affected horse's condition deteriorates, an alternative first-line treatment should be used. If the alternative treatment produces improvement, it should be continued up to a maximum of 3 months. If the lesions have not resolved by 3 months, biopsy samples of the lesions should be obtained and investigations performed to establish evidence of concurrent intestinal disease.[1] If the biopsy reveals neutrophilia and if cultures of multiple sections yield a predominant bacterial species, treatment with an antimicrobial is warranted; many clinicians opt for oral doxycycline. If there is evidence of lymphocytic-plasmacytic inflammation or of IBD, then glucocorticoid treatment may be warranted. The finding of an eosinophilic infiltrate may be suggestive of parasitic organisms (*Habronema* spp. or *Draschia* spp.), and management with anthelmintics is warranted; these organisms, however, are extremely rare.

Prevention of Recurrence.

Prevention of EGGD, either as primary disease or as recurrence, is problematic. In a series of studies, worsening of EGGD grade was observed in 23% of horses despite omeprazole monotherapy at doses ranging from 1 to 4 mg/kg PO q24h.[38,47,48] Furthermore, it has been suggested that gastric hyperplasia may be present in a percentage of EGGD cases, and that in such cases omeprazole therapy is contraindicated.[84] As stated previously, no data are available as to whether long-term omeprazole therapy results in acute kidney injury, as it does in humans.[53]

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On the basis of the known risk factors for EGGD listed previously, which differ from those for ESGD, the following management changes are recommended. Ideally, horses should have a minimum of 2 rest days per week if possible. Stress should be minimized; for example, environments should be calm, and affected horses should have a minimal number of carers and the same equine field companions. Horses should be turned out, unless this is obviously stressful to a horse. Horses should be fed 2 L of chaff or equivalent of forage 30 to 60 minutes before exercise.[1] If IBD is suspected, diets should be simplified to include one straight and forage. Any irritant supplements (such as those containing magnesium sulfate) should be stopped.

In one study, the addition of corn oil, 0.3 to 0.45 mL/kg/day (150 to 225 mL/day for a 500-kg horse), decreased gastric acid output and increased prostaglandin E_2,[85] both of which are, in theory, beneficial in the treatment and prevention of EGGD. Thus addition of corn oil at a rate of up to 0.5 mL/kg/day may be beneficial. Lastly, in view of the fundamental role of failed mucosal defenses in the pathogenesis of EGGD, the use of mucosal barrier protectants is logical, and the use of pectin-lethicin at 150 g q12h or feeding sugar beet pulp (a cheaper alternative) may be beneficial.[84]

Diagnosis.

Gastroscopy remains the only reliable method for diagnosing ESGD and EGGD. Adequate patient preparation, plus some operator skill and patience, is required for a complete diagnostic evaluation of the entire stomach. A fasting period of at least 12 to 16 hours is required in most horses, and even small amounts of residual food hamper access to the pyloric antrum. In horses on low-roughage diets (e.g., racehorses), the duration of fasting may be shorter. Removal of water 1 hour before examination is advantageous but not mandatory. Examination of the stomach should be complete and methodical. Observation of the squamous mucosa is straightforward, whereas passage through to the pyloric antrum is more technically demanding. However, observation of the pyloric antrum is critical because the majority of glandular lesions in adult horses occur in this region.[32,38,47,48,86] Observation of the most ventral portion of the fundus is typically not possible because of the presence of fluid, but it can be possible with adequate patient preparation; however, disease in this region is rare.[84] The squamous and glandular mucosa should be assessed and scored separately and, although a variety of scoring systems have been described, the author prefers the

system first described by the Equine Gastric Ulcer Syndrome (EGUS) council,[87] shown in Table 32.2, for squamous disease. It is now widely accepted that the grading system for EGGD does not reflect severity of disease and until a better system is developed, lesions should be described according to the consensus statement by the European College of Equine Internal Medicine and the American College of Veterinary Internal Medicine.[22] These descriptors include *focal*, *multifocal*, and *diffuse; mild*, *moderate*, and *severe; nodular, raised, flat,* and *depressed;* and *erythematous, hemorrhagic*, and *fibrinosuppurative.* A more recent consensus statement focused on EGGD suggested that flat, erythematous lesions were likely to heal more rapidly than were those with a nodular, raised, and fibrinosuppurative or hemorrhagic appearance.[1] Examples of the normal appearance of the gastric and duodenal mucosa and lesions encountered in horses and foals undergoing gastroscopy are shown in Color Plates 32.4 through 32.12.

TABLE 32.2

Scoring System for Equine Gastric Ulcer Syndrome

Grade	Squamous Mucosa	Glandular Mucosa
0	Intact epithelium, no appearance of hyperkeratosis (yellow appearance to the mucosa)	Intact epithelium, no hyperemia (reddening) of the mucosa
I	Intact mucosa, but areas of hyperkeratosis	Intact mucosa, but areas of hyperemia
II	Small single, or multifocal lesions	Small single, or multifocal lesions
III	Large single or multifocal lesions, or extensive superficial lesions	Large single or multifocal lesions, or extensive superficial lesions
IV	Extensive lesions with areas of apparent deep ulceration	Extensive lesions with areas of apparent deep ulceration

Fecal occult blood tests[88] and sucrose permeability tests[89] for diagnosing gastric disease in adult horses have been shown to be unreliable and cannot be recommended.

■ Gastric Disease in Foals and Weanlings

Gastric disease is commonly identified in foals; the prevalence ranges from 21 to 98%.[90-94] Before weaning, the prevalences of squamous and glandular disease is similar,[94] whereas after weaning, the prevalence increases to levels similar to those among adults, and lesions are twice as likely to be found in the squamous mucosa as in the glandular mucosa.[94] As in adults, diagnosis is confirmed with gastroscopy. Results of one study suggested that a sucrose permeability test is a

useful screening tool for detecting gastric disease in weanlings; with a sucrose cut-off level of of 24 µmol/L, this test had excellent sensitivity (84 to 95%) and average to good specificity (47 to 71%).[94]

The pathophysiologic origins of this condition in foals are probably complex and, as in adults, probably differ between the squamous and glandular mucosa. Acid production is extremely variable in foals; in fact, gastric fluid is often alkaline,[95] which suggests that acid damage is unlikely to be a prevalent cause. Underlying diseases such as perinatal asphyxia syndrome, hypovolemia secondary to other disease and use of NSAIDs probably results in reduced gastric and splanchnic blood flow, and improvement of this should be the focus for prevention and treatment. Gastric disease in foals often co-occurs with lesions that extend into the esophagus and duodenum.

Clinical signs observed in this age group are nonspecific but are often more severe than in adults; they include diarrhea, abdominal pain (restlessness, rolling, lying on the back), excessive salivation, bruxism, and anorexia.[96] However, with such high prevalence, determining which lesions are clinically significant in the absence of clinical signs is challenging,[93] but because of the risk of intestinal perforation, which is fatal, many authors believe that these lesions should be treated.[96,97]

Because of the pathophysiologic process of this condition, the rationale for the use of sucralfate[98] or misoprostal[81,99] for prevention and treatment is significant. Omeprazole may play a role in the treatment of gastric lesions but should not be used for prophylaxis. Use of omeprazole prophylaxis in human patients was associated with an increased risk of pneumonia and *C. difficile* diarrhea,[100,101] and in foals in a multicenter study, it was associated with an increased risk of diarrhea.[102]

■ Gastric Impaction

Gastric impaction is relatively common. Clinical signs are diverse, with inappetence the most common manifestation and representing 50% of cases in one study.[103] Affected horses typically eat small amounts and have a significantly decreased total daily intake. Acute and recurrent colic are also common manifestations.[103,104] The causes of gastric impaction are unclear, and although poor dental care has been proposed as a predisposing factor,[105] cases commonly occur in horses with no dental abnormalities. Three types of gastric

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impaction are recognized: Type I is impaction of feed material without increase in the stomach size; type II is impaction of feed material with increase in the stomach size and, although difficult to prove, an underlying motility disorder is suspected in these cases on the basis of the poor response to treatment and prognosis; and type III impactions occur after the formation of a phytobezoar secondary to persimmon seed ingestion.[104,106] Classification of the type of gastric impaction is important because treatment and prognosis vary depending on the type. Distinguishing between types I and II can be difficult.

Diagnosis of gastric impaction in the field is difficult, but it should be part of the differential diagnosis in any horse with signs of mild abdominal pain that dramatically worsen after the administration of fluids via a nasogastric tube; in horses with unexplained inappetence; and horses with abdominal pain that appears to resolve with fasting, only to relapse with the reintroduction of feed. The clinical signs observed with type I impactions are typically mild, with a normal heart rate.[70] Signs may be more pronounced in type II impactions, and displacement of the spleen may be palpable on rectal examination. Type III impactions more commonly manifest with mild to severe colic, weight loss, or both.[104,106] Definitive diagnosis is made when, after an appropriate period of starvation, entry to the stomach with a gastroscope is obstructed by feed material. Alternatively, in type I, the stomach can often be entered and distended with air, but a clearly defined ball of feed material extending above the level of the margo plicatus is visible. In type III impactions a phytobezoar is typically visible once the stomach has been otherwise emptied of feed material. Ultrasonography can help distinguish between type I impactions, in which visualization of the stomach is difficult or limited, and type II impactions, in which the stomach distention often extends for several rib spaces.

In all cases, any concurrent systemic abnormalities such as hypovolemia, dehydration, and electrolyte derangements should be corrected, and resolution of the impaction should be confirmed by gastroscopic examination before food is reintroduced. The different types are treated as follows:

- For type I, the use of enteral fluids is highly effective; isotonic electrolyte solution (1 L/100 kg q2h) is administered via an indwelling large-bore nasogastric tube. Depending on the response, the rate

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and volume can be increased or decreased Administration of analgesia (e.g., flunixin meglumine, 1.1 mg/kg IV q12h) is recommended until resolution of the impaction, because signs of abdominal discomfort are common. The use of indwelling, small-bore nasogastric tubes for the administration of enteral fluids has been described[107]; in theory, the bolus administration of fluids should result in a more pronounced stimulation of the gastrocolic reflex, but the use of these tubes will probably cause less abdominal discomfort. With enteral fluid therapy alone, the prognosis is excellent (90% survival to discharge),[103] and so alternative therapies probably offer little advantage, although gastric lavage with water or the addition of carbonated cola drinks may be helpful.

• For type II impactions, treatment is similar to that of type I impactions, but caution should be exercised in the volume of fluids administered because the stomach wall is often friable and gastric rupture can occur. Concurrent intravenous fluid therapy should be considered if hypovolemia cannot be corrected and maintenance fluid requirements cannot be met with enteral therapy alone. The response of type II cases to treatment is often poor, and the addition of prokinetics may be beneficial in some cases; however, the response to prokinetic therapy is often disappointing.

Bethanechol (0.025 mg/kg SC q4-6h) is the prokinetic of choice,[17] but it is often difficult to obtain; erythromycin (1 mg/kg IV q6-8h) is a reasonable alternative. Surgery should be considered for types I and II impaction if the animal is showing signs of systemic deterioration or if the impaction does not resolve with medical therapy within 5 to 7 days; successful treatment by gastrotomy has been reported.[108] The prognosis for type II impactions has not been reported, but in anecdotal reports, it is guarded because gastric rupture can occur (even without enteral fluid therapy) and recurrence is common. The use of low-bulk diets during the refeeding stage is logical.

• Type III impactions by persimmon seed phytobezoars are generally refractory to standard enteral and intravenous fluid therapy. The use of carbonated cola drinks has been reported with a variety of techniques ranging from constant infusion of 1 L/h for 1 to 3 days to bolus administration of 700 mL q12h via nasogastric tube. The mechanism is believed to be a combination of the mucolytic effects of sodium bicarbonate, the acidifying effects of the cola, and mechanical disruption of the fibers of the phytobezoar by the stable carbon dioxide bubbles.[104] Constant infusion via a small-bore nasogastric tube appears to be the treatment of choice, and the use of

caffeine-free diet cola is recommended to reduce the risk of caffeine toxicosis or laminitis secondary to carbohydrate overload. The prognosis for type III impactions appears to be good; five of eight horses responded to medical therapy in one report.[104] In the same report, two additional horses were successfully treated surgically via laparotomy, with manual manipulation of the phytobezoar but without gastrotomy; the horse in which a gastrotomy was attempted was euthanized at surgery because of extensive contamination of the abdominal cavity.[104]

■ Miscellaneous Diseases of the Stomach

A variety of miscellaneous disease conditions, including gastric rupture, abscesses, tumors, and pyloric stenosis, also affect the stomach of horses.

Gastric Rupture.

Gastric rupture is most commonly secondary to obstruction of the small intestine or chronic gastric impaction. Idiopathic rupture accounted for 17% of cases in one report,[109] which suggests that a variety of other causes can result in rupture.

Gastric Abscessation.

These lesions are rare and are most common in foals. They can be secondary to gastric disease, *R. equi* bacteremia, foreign body penetration, and septic peritonitis. Signs are nonspecific and include fever, neutrophilia, increased serum concentrations of fibrinogen and serum amyloid A, anemia, weight loss, and, on occasional. abdominal pain. Diagnosis usually is made through gastroscopy and ultrasonography. Often a diagnosis is not made until a late stage of the disease, and although long-term antimicrobial therapy can be attempted, the prognosis is usually poor.

Gastric Tumors and Other Masses.

Squamous cell carcinoma (Fig. 32.53) is the most commonly reported of the tumors that affect the equine stomach, representing nearly 80% of cases in one report.[110] Other neoplastic conditions that affect the equine stomach include primary gastric adenocarcinoma, metastatic lymphoma, mesothelioma, and bile duct carcinoma. Gastric squamous cell carcinoma affects the squamous mucosa and can metastasize to other abdominal viscera or extend into the esophagus. As with other forms of neoplasia, presenting signs include chronic weight loss, abdominal pain, and spontaneous nasogastric reflux. No breed or sex predilection exists, and a wide range of ages are affected, although gastric squamous cell carcinoma usually affects older horses. Diagnosis is typically based on gastroscopic and ultrasonographic examination findings, and the prognosis is poor because there is no described treatment.

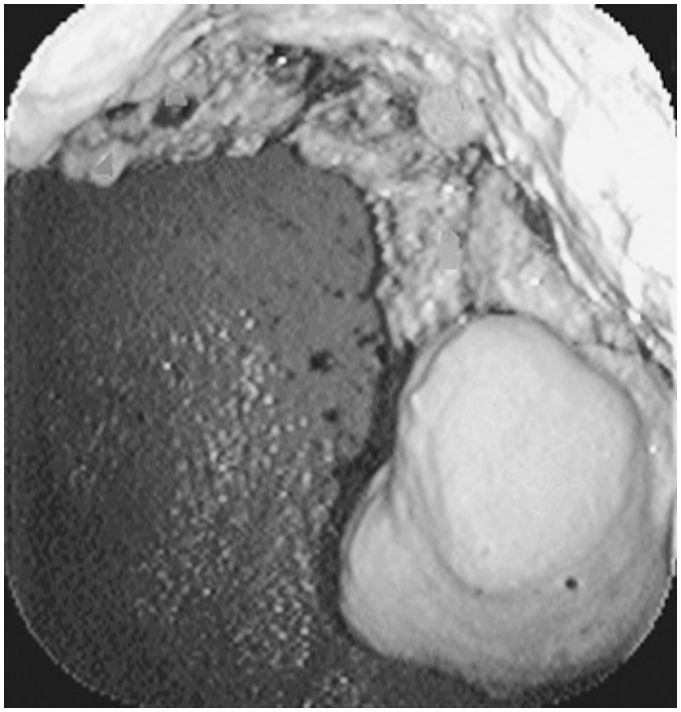


FIG. 32.53 Endoscopic view of a gastric squamous cell carcinoma.

Nonneoplastic masses that can be identified in the stomach include lesions associated with *Draschia megastoma*, *Habronema* spp. (Fig. 32.54), proliferative granulation tissue, and adenomatous masses in the antrum and pylorus. Lesions around the pylorus can be challenging to differentiate from EGGD.



FIG. 32.54 Images from the pylorus and pyloric antrum of a horse with recurrent colic. Biopsies of these lesions confirmed gastric habronemiasis. The horse was treated on several occasions with ivermectin, and within 3 months the lesions had resolved and clinical signs disappeared.

Pyloric Stenosis.

Pyloric stenosis is an uncommon condition that typically affects foals and young horses,[111] although horses of any age can be affected. It is thought to result most commonly from chronic gastric disease, although other space-occupying lesions may be the cause. Affected animals typically have a history of weight loss, poor appetite, postprandial abdominal pain, or recumbency.[111] Excessive ptyalism or spontaneous reflux of gastric contents from the nasal passages is common. Diagnosis is typically made via gastroscopy, although ultrasonography and contrast radiography can be useful adjunctive tests. Conservative management involves acid suppression therapy; omeprazole (4 mg/kg PO q24h) is effective in less severe cases. Intravenous fluid therapy and parenteral nutrition is indicated in patients with spontaneous reflux of gastric contents or in cases in which gastric emptying is significantly delayed. Long-acting injectable omeprazole at (4 mg/kg IM every 5 to 7 days) has not been reported for management of these cases, but it is likely to be more efficacious than oral medication.[51] Administration of bethanechol or erythromycin may be advantageous. Response to medical therapy is often disappointing and early surgical intervention is

indicated in such cases. Long-term survival rates of 50 to 69% have been reported for gastrojejunostomy,[112,113] which further supports early surgical intervention in nonresponsive cases.

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Endotoxemia and Sepsis

Kelsey A. Hart • Erin McConachie Beasley • Robert J. MacKay

■ Definitions

The term *endotoxin* was originally coined to describe toxic bacterial components that were contained within or on the bacterial cell, in comparison with exotoxins that were secreted from outside bacterial cells. The heat-stable endotoxic activity of *Vibrio cholera,* identified by Richard F. J. Pfeiffer in the late nineteenth century, resides in lipopolysaccharide (LPS), the principal component of the outer leaflet of the outer membrane of all Gram-negative bacteria[1] (Fig. 32.55). Today, the terms *endotoxin* (the activity) and *LPS* (the molecule) are used synonymously to refer to this specific Gram-negative bacterial membrane component, except when purified LPS is being referenced.[2] Each LPS molecule has three structural domains: a polar polysaccharide O region, which projects into the aqueous extracellular environment; a hydrophobic lipid A region, which is largely buried in the bacterial outer membrane; and a core acidic oligosaccharide region connecting the other two. The O-region is highly variable, consisting of repeating units each of one to eight glycosyl residues, and contains antigens specific for each bacterial strain; the core glycolipid region is relatively constant among bacteria and mediates most of the toxic effects of endotoxin. On bacterial death or during bacterial proliferation, large (molecular mass > 10^6 D) aggregates of LPS and membrane protein are released. It is these protein-lipid micelles that constitute native endotoxin.

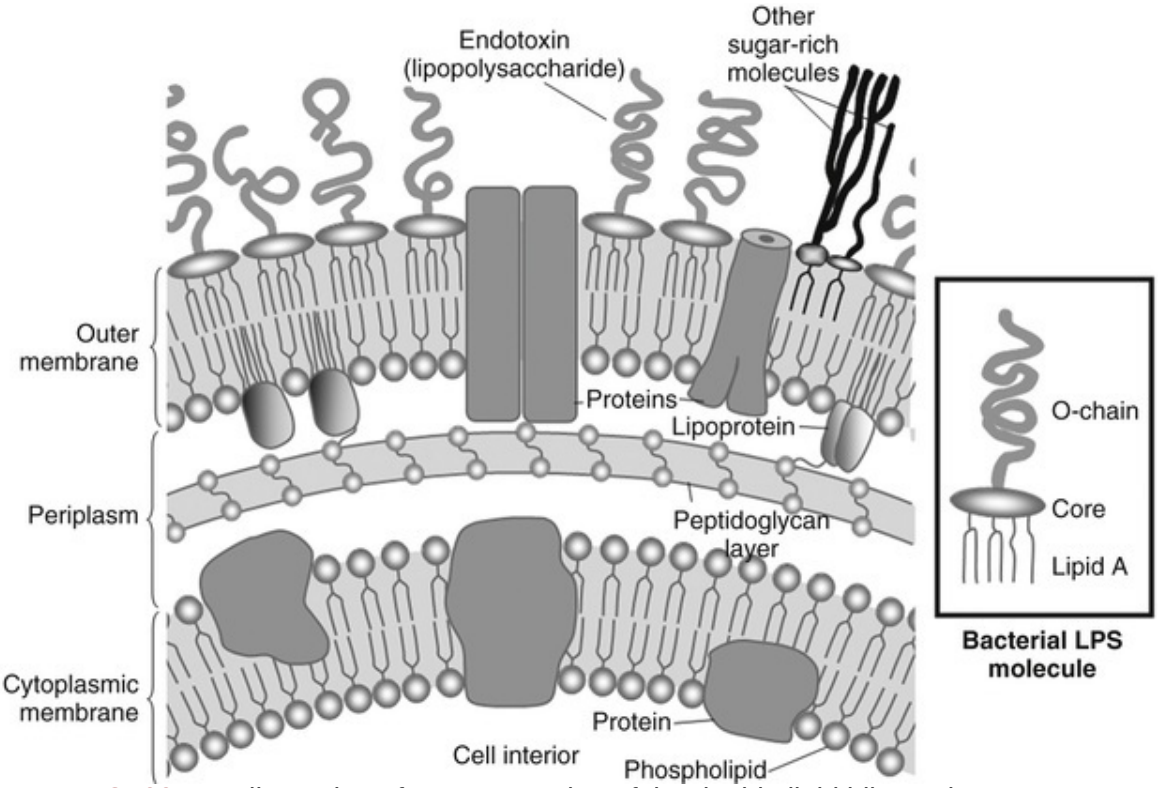


FIG. 32.55 Illustration of a cross-section of the double lipid bilayer that forms the cell membrane of Gram-negative bacteria. Lipopolysaccharide (LPS) is the principal component of the outer leaflet of the outer membrane. The *insert* shows a single LPS molecule with an O-polysaccharide chain, a two-part core oligosaccharide, and a hydrophobic lipid A phospholipid. R-mutant bacteria lack the O-chain and the phospholipid; varying amounts of the core oligosaccharide are present.

Endotoxemia literally is the presence of endotoxin in the blood. However, when the term is used clinically, it implies the presence of clinical signs typically caused by the inflammatory response to circulating endotoxin. Endotoxemia—actual circulating endotoxin or related clinical signs—can occur with Gram-negative bacterial infection in any tissue or through exposure to Gram-negative enteric bacteria any time the intestinal mucosal barrier is compromised.

The ability to respond to minute local concentrations of endotoxin by mounting vigorous inflammatory responses is well conserved across species.[3] Endotoxemia as a clinical syndrome in equine patients was first recognized in the mid-1960s.[4] The potential clinical importance of equine endotoxemia is clear from reports that intravenous infusion of LPS into horses reproduced many of the adverse clinical signs of diseases such as colitis, metritis, and strangulating intestinal obstruction.[5-10] Further evidence of the importance of endotoxemia

was the detection of circulating endotoxin in some horses with experimentally induced laminitis[11] or intestinal strangulating obstruction[12] and in horses with naturally occurring gastrointestinal diseases or septicemia,[13-17] hemostatic disorders,[16] and exhaustion associated with endurance[18] or racing[19] events. Since these original descriptions, a large body of review literature has documented the efforts that have been made to understand and, more importantly, treat equine endotoxemia.[20-23]

Endotoxemia should not be confused with either *bacteremia*, which refers only to the presence of viable circulating bacteria and can occur without clinical signs, or *septicemia*, which refers to systemic disease caused by any circulating microorganisms or their products, or both. *Sepsis* is a related term that is best defined as clinical evidence of an infection (documented or suspected) coupled with the presence of a *systemic inflammatory response syndrome* (SIRS).[24,25] SIRS is characterized in humans and animals by alterations in any two or more of the following: body temperature, heart rate, respiratory rate, and leukogram parameters (Table 32.3).[24-28] The presence of SIRS does not confirm infection, inasmuch as a variety of noninfectious conditions—such as trauma, hemorrhage, thermal injury, or toxin exposure—that result in the release of tissue damage-derived host molecules can also induce a systemic inflammatory of response. However, clinical findings consistent with SIRS should raise the clinician's level of suspicion that an infectious process is present and support a diagnostic search for a potential infectious process.

TABLE 32.3

Criteria for Diagnosis of Systemic Inflammatory Response Syndrome in Horses and Foals[28,30,41,44]

Criteria[a]	Adult	Foal
Alteration in body temperature	<98° F (36.7° C) or >101.5° F (38.6° C)	<99 °F (37.2° C) or >102.5°F (39.2° C)
Alteration in the leukogram	<4,500/µL or >14,500/µL or >10% band neutrophils	<4,000/ µL or >12,500/ µL or >10% band neutrophils
Tachycardia	>52 beats/min	>120 beats/min
Tachypnea	>25 breaths/min or $PaCO_2$ < 32 mm Hg	>30 beats/min Evidence of sepsis, cerebral ischemia or hypoxia, and or trauma

[a]For diagnosis, two or more criteria must be present. *$PaCO_2$*, Partial pressure of arterial carbon dioxide.

A scheme showing increasingly severe stages of SIRS and sepsis, from local infection to death, is shown in Fig. 32.56, and adapted definitions for SIRS in horses and foals are listed in Table 32.3. In general, *severe sepsis* includes sepsis (infection plus SIRS) and evidence of organ dysfunction, and *septic shock* includes severe sepsis plus acute circulatory failure (usually manifested by persistent hypotension after appropriate volume resuscitation).[25] Dysfunction of two or more organs in severe sepsis/septic shock is termed *multiple-organ dysfunction syndrome* (MODS) and has a high rate of mortality in human beings[29] and in horses with gastrointestinal disease.[30,31] The lethality of each grade increases from the base to the apex of Fig. 32.56; reported mortality rates for sepsis are 10 to 20%, those for severe sepsis are 20 to 50%[31] and those for septic shock are 40 to 80% in humans.[32] Comparable mortality data in horses are not currently available for increasing severity of sepsis. However, in horses with gastrointestinal disease, the presence of SIRS, increased severity of organ dysfunction and increased number of dysfunctional organs are all associated with an increased risk of death.[28,30]

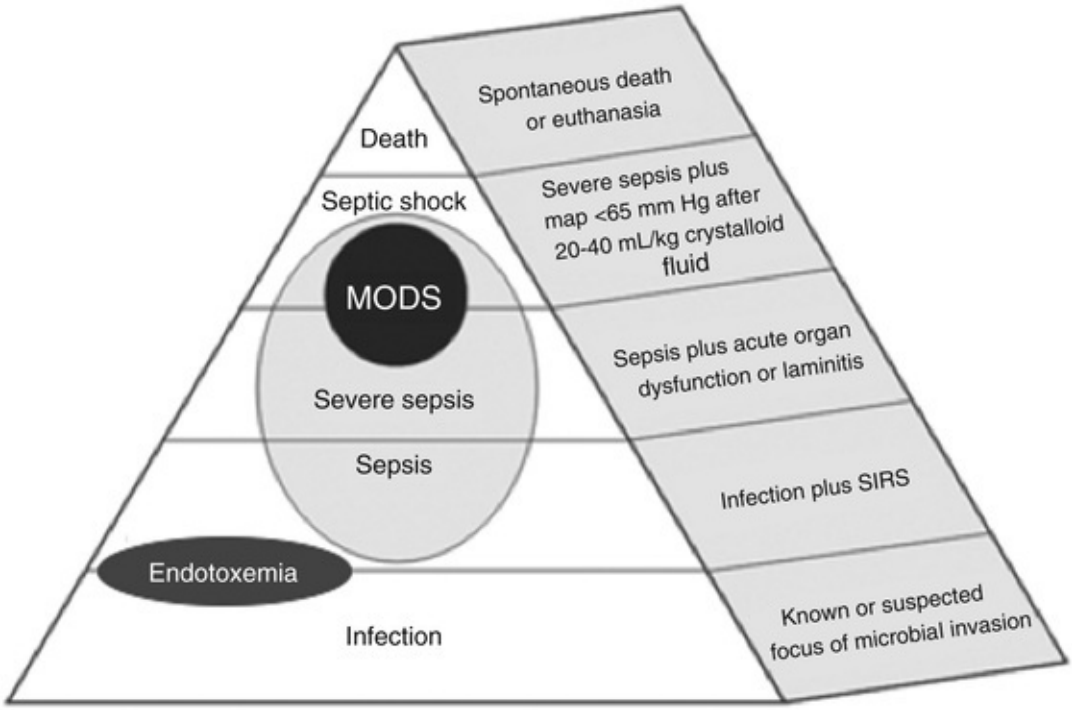


FIG. 32.56 Scheme for classification of the degree of sepsis. Systemic inflammatory response syndrome (SIRS) and organ dysfunction are defined in Tables 32.1 and 32.2 and in several studies.[28,30,41,44] *MODS*,

multiple organ dysfunction syndrome.

The fundamental difference between serious sepsis in humans and the syndromes seen in equids is the propensity for the latter to be associated with laminitis. In the context of sepsis, laminitis is often life-threatening. Moreover, it appears that the same types of global inflammatory and coagulation disorders that lead to MODS in patients with sepsis also are involved in the pathogenesis of both carbohydrate- and black walnut–induced experimental laminitis.[33-37] In view of their likely common pathogenesis, laminitis is considered—along with evidence of cardiac, renal, hepatic, neurologic, coagulation, or gastrointestinal compromise—part of the spectrum of MODS in equine sepsis.[30] Several researchers have utilized these or similar criteria for SIRS, MODS, or septic shock in horses or foals (Table 32.4; see Table 32.3 and Fig. 32.56).[28,30,38-44]

TABLE 32.4

Criteria for Multiple-Organ Dysfunction Syndrome in Neonatal Foals[41,44,a]

Neurologic	Clinical diagnosis of perinatal encephalopathy
Renal	Anuria, oliguria, or persistent azotemia (levels ≥ 2.2 mg/dL for ≥72 hours) after initial fluid resuscitation
Hemostatic	Clinical diagnosis of disseminated intravascular coagulopathy
Respiratory	Hypoxemia, hypercapnia necessitating intranasal oxygen insufflation or ventilation
Gastrointestinal	Persistent ileus necessitating withholding of enteral feeding for >24 hours
Cardiovascular	Vasopressor therapy for >24 hours

[a]For diagnosis, two or more criteria must be present.

The extraordinary ferocity of SIRS as triggered by endotoxin was nicely captured by Thomas[45]:

"The Gram-negative bacteria…display lipopolysaccharide…in their walls and these macromolecules are read by our tissues as the very worst of bad news. When we sense lipopolysaccharides we are likely to turn on every defense at our disposal; we will bomb, defoliate, blockade, seal off, and destroy all tissues in the area….Cells believe that it signifies the presence of Gram-negative bacteria, and they will stop at nothing to avoid this threat."

Although this modern conception of the early immune response to endotoxin is still accurate, it has become clear that a variety of other pathogen-derived

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molecules set off similar or identical host responses. For example, toxic shock syndrome resulting from *Staphylococcus aureus* infection[46] and streptococcal toxic shock[47] are examples of hyperinflammatory septic syndromes in horses that resemble diseases characterized by true endotoxemia (circulating LPS). Thus in sepsis—including putative endotoxemia in horses—it is likely that the clinical presentation is an aggregate of responses to multiple or varied microbial signals, as well as to certain "danger" signals generated by the host itself. In the case of horses, circulating endotoxin is not always detectable in horses described as "endotoxic"—in fact, it is typically found in fewer than 30%[48,49]—which suggests that other microbial components and host inflammatory molecules probably trigger similar clinical signs. Thus *sepsis* or *SIRS* is a more appropriate term than *endotoxemia* for the accurate description of the clinical findings usually attributed to endotoxin in horses (e.g., hyperemic or toxemic mucous membranes, fever, tachycardia, tachypnea, leukopenia). In this section, *sepsis* implies SIRS in response to any microbial infection, and *endotoxemia* refers specifically to the presence of endotoxin in the blood or to the specific clinical signs related to documented circulating endotoxin. However, the molecular basis of sepsis in horses via mechanisms other than endotoxemia is poorly understood at best, and so the majority of the following discussion centers on endotoxemia as an important component of equine sepsis.

■ Pathophysiology

Entrance of Endotoxin or Other Microbial Products Into the Circulation.

Although endotoxin and other microbial components are ubiquitous in the environment, both free and as a component of intact bacteria, these components normally are excluded from the body by the skin and mucous membranes. If the protective integument or mucosae are subjected to bacterial infection or otherwise damaged, bacteria or bacterial components such as endotoxin may reach the blood in sufficient amounts (<1 μg of purified LPS in experimental situations) to cause clinical signs. Gram-negative bacterial enterocolitis (e.g., salmonellosis), metritis, pleuropneumonia, and neonatal septicemia are common pathways to endotoxemia in horses. Because 1-g amounts of free endotoxin normally are safely sequestered within the intestine of adult horses, damage to the gut wall is particularly likely to result in endotoxemia. Such damage can occur as a result of tissue hypoxia, either local (e.g., intestinal volvulus,

infarction, incarceration) or systemic (e.g., hypovolemic shock); inflammation (e.g., duodenitis–proximal jejunitis [DPJ] or clostridial enteritis); mechanical trauma (e.g., rectal perforation, prolonged exercise); or intraluminal acidification (e.g., grain overload). In highly contaminated environments, potentially harmful amounts of endotoxin can be introduced into the lungs via inhalation.[50] Endotoxin may even be delivered directly into the blood via contaminated parenteral solutions (e.g., plasma/blood products or homemade intravenous fluids). Other microbes and microbial components (e.g., flagellin) or secreted toxins (e.g., staphylococcal exotoxins) can enter the circulation in similar ways, but these pathways in horses are not well understood.

Interaction With Pattern Recognition Receptors.

The mammalian immune system has the ability to recognize many distinctive patterns on molecules that signal potential danger. As a group, these molecules include microbial signals such as endotoxin, collectively termed *pathogen-associated molecular patterns* (PAMPs) and *damage-associated molecular patterns* (DAMPs, also called *alarmins*), which are host-produced molecules that originate from damaged or inflamed tissues (Table 32.5). A limited number of germ-encoded receptor types, both soluble and cell-associated, are dispersed throughout the body to detect potential threats (both septic and nonseptic). These are pattern recognition receptors (PRRs) and are exemplified by Toll-like receptors (TLRs) on (and in) cells and by complement receptor proteins and Hageman factor in plasma.[51-53] These and other PRRs are listed in Table 32.6. The interaction between PAMPs/DAMPs and PRRs is the initial event in the innate immune responses that result in the clinical presentation of endotoxemia or other forms of sepsis.

TABLE 32.5

Partial List of PAMPs and DAMPs[44,45,224,225]

PAMPs	DAMPs
LPS (endotoxin)	HMGB1
Lipoprotein	S-100 proteins[a]
Peptidoglycan	HSPs
Flagellin	Defensins
Lipoteichoic acid	Cathelicidins
Zymosan	Serum amyloid A
Viral double-stranded RNA	Genomic DNA
N-acetyl glucosamine	Mitochondrial DNA

[a]Proinflammatory proteins released by phagocytic cells during innate immune responses.

DAMPs, Damage-associated molecular patterns; *HMGB1,* high-mobility group box 1 protein; *HSPs,* heat shock proteins; *LPS,* lipopolysaccharide; *PAMPs,* pathogen-associated molecular patterns.

TABLE 32.6

Partial Listing of Pattern Recognition Receptors[44-46,224,226]

Cell-Associated	Soluble
Toll-like receptors (TLRs; e.g., TLR1 to TLR13 in mice)	Hageman factor
C-type lectin receptors (CLRs; e.g., Dectin-1)	MBL
Nucleotide-binding oligomerization domain receptors (NLRs; e.g., Nod1/Nod2)	C3b, Bb
AIM2-like receptors (ALRs, e.g., AIM2)	Ficolins
CD14 (membrane-anchored form)	CD14 (soluble form)

AIM, Absent in melanoma; *CD14,* cluster of differentiation 14; *MBL*, mannan-binding lectin.

Initially, endotoxin was widely believed to enter cells not via engagement of cell-surface receptors, as it truly does initiate innate immune responses, but by hydrophobic insertion into the membrane (Fig. 32.57). Since then, sequential discoveries of a plasma LPS-binding protein (1989 in humans,[54] 2005 in horses[55]), cluster of differentiation 14 (CD14; 1990 in humans,[56] 2003 in horses[57]), and TLRs (1998 in humans,[58] 2005 in horses[59]) have elucidated the molecular processes of endotoxin binding and signaling (see Fig. 32.57). LPS first interacts with LPS-binding protein, a normal plasma acute-phase protein; this interaction facilitates binding to the soluble or cell-associated co-receptor CD14. The LPS/LPS-binding protein/CD14 complex recruits and activates Toll-like receptor 4 (TLR4) dimer and an accessory component, lymphocyte antigen 96 (MD-2), in preparation for LPS signaling. On ligation of the receptor, the conserved intracellular domain of TLR4 (Toll–interleukin-1 receptor) initiates multiple downstream pathways that culminate in translocation to the nucleus of inducible transcription factors, including nuclear factor κB (NF-κB) and activator protein 1.[60] NF-κB binds to consensus sequences on the promoter or enhancer regions of an array of genes whose products are involved in the inflammatory response.[60] It has been argued that the global activation of TLR4 typical of sepsis also requires the actions of endogenous agonists (e.g., proteases).[61] Endotoxin also may activate NF-κB via TLR4-independent interactions with β_2-integrins, heat-shock proteins, and the intracellular Nod1 receptor.[62]

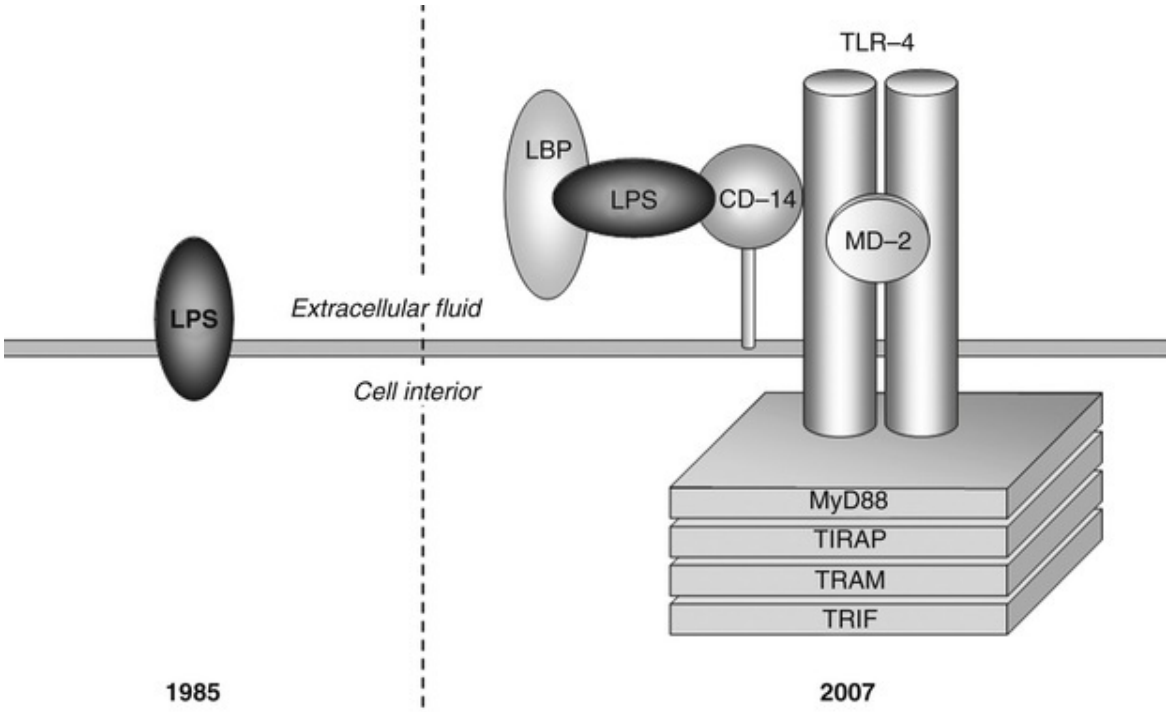


FIG. 32.57 Binding of lipopolysaccharide (LPS) to mammalian cell membranes. Initially (in 1985) it was widely believed that LPS initiated cellular signaling by hydrophobic interactions with the plasma membrane, but by 2007 the components of the signaling complex were more fully understood. In addition to the extracellular receptor components (discussed in the text), the intracellular Toll–interleukin-1 receptor (TIR) domain is shown interacting with four adaptor molecules (MyD88, TIRAP, TRAM, TRIF) to initiate a molecular signaling cascade that ultimately leads to gene activation. CD-14, cluster of differentiation 14; MD-2, lymphocyte antigen 96; TLR, Toll-like receptor.

Endotoxin engages TLR4 on cells of the innate and adaptive immune systems, especially mononuclear phagocytes (monocytes and macrophages), neutrophils, endothelial cells, and dendritic cells. Although endotoxin binds predominantly to TLR4, a number of TLRs (13 identified in mammals to date) are available to bind to other PAMPs/DAMPs (Table 32.7).[63] During sepsis, this diversity of TLRs allows redundant signaling of inflammatory cells. For example, non-LPS components of Gram-negative bacteria may bind other TLRs (e.g., flagellin binds to TLR5, lipoprotein and peptidoglycan bind to TLR2), whereas PAMPs from Gram-positive bacteria, viruses, or fungi bind different TLRs in the course of polymicrobial sepsis.[63] Equine TLR signaling has been characterized in many cells and tissues.[64-66] Of interest is that whereas LPS is a potent stimulator of equine monocytes via TLR4, flagellin (via TLR5) preferentially stimulates

neutrophils and induces little response from monocytes,[67] which suggests differential expression of these TLRs between cell types in horses that could play a role in clinical sepsis. Thus although TLR ligand-specificity appears to be well conserved across species, specific TLR expression varies among cells, tissues, and species and can result in varied responses to the same PAMP. Tissues subject to attack by mediators produced after the initial round of TLR binding can also amplify the inflammatory response by releasing DAMPs (e.g., high-mobility group box 1)[68], which in turn can bind to TLR or other PRRs.

TABLE 32.7

Seven Ligands for Human Toll-Like Receptors[56,226]

TLR1	Triacyl lipopeptides
TLR2	Lipoprotein Peptidoglycan (Gram-positive bacteria) Lipoteichoic acid (Gram-positive bacteria) Zymosan (yeast) Lipoarabinomannan (mycobacteria)
TLR3	Viral double-stranded RNA
TLR4	LPS Respiratory syncytial virus fusion protein HSP70
TLR5	Flagellin
TLR6	Diacyl lipopeptides Zymosan
TLR7	Viral single-stranded RNA
TLR8	Viral single-stranded RNA
TLR9	CpG oligodeoxynucleotide Herpes virus DNA
TLR10	Not determined
TLR11	Profilin-like protein (*Toxoplasma gondii*)
TLR12	Profilin-like protein (*Toxoplasma gondii*)
TLR13	23s Ribosomal RNA (bacteria)

CpG, Cytosine triphosphate deoxynucleotide followed by guanine triphosphate deoxynucleotide, linked by phosphodiester; *HSP,* Heat shock protein; *LPS*, lipopolysaccharide; *TLR*, Toll-like receptor.

During cellular activation, endotoxin and other microbial products can also interact with soluble PRRs normally present in plasma. Of particular importance is that endotoxin binds to complement proteins to initiate the lectin-dependent and alternative pathways of complement activation and activates coagulation factor XII (Hageman factor) to set off the “contact” system of coagulation.

Release of Mediators.

Endotoxin-induced NF-κB activation in peripheral blood and tissue leukocytes (and many other cell types) acts via multiple signaling pathways to induce the expression of more than 200 genes, many of which are involved in the pathogenesis of sepsis.[52,60,69] These include genes for proinflammatory cytokines (e.g., tumor necrosis factor [TNF], interleukins 1β, 6, 8, 12, and 18 [IL-1β, IL-6, IL-8, IL-12, IL-18]), chemokines (e.g., IL-8, macrophage inflammatory protein [MIP]), type 1 interferons (IFNs), procoagulants, adhesion molecules, immunoreceptors (e.g., TNF receptors), enzymes (e.g., elastase), and acute-phase proteins (e.g., fibrinogen). NF-κB activity is further amplified by the paracrine actions of these proinflammatory cytokines and by other DAMPs, cellular hypoxia, cellular necrosis, and chemical stress (including oxidant stress). Two of the cytokines secreted by macrophages, IL-12 and IL-18, stimulate IFN-γ synthesis and secretion from natural killer and other cells.[70] Because IFN-γ is a potent stimulator of both innate and acquired immune responses, it is considered a principal link between the two systems.

Endotoxin activates coagulation factor XII (Hageman factor), which leads both to liberation of bradykinin and to initiation of intravascular coagulation. Of even more importance is that complement is activated by alternative, lectin-mediated, and classical pathways to yield numerous active peptide products that play a role in opsonization, inflammatory cell trafficking, and microbial cell lysis. Other microbial structural components and products similarly stimulate inflammation, complement activation, and coagulation, although specific pathways and molecular mechanisms are less well characterized in humans than in horses.

Systemic Inflammatory Response Syndrome in Early Sepsis

The initial (early) phase of sepsis is often referred to as the “hot” phase and is characterized by inflammation, coagulation, and necrosis. The principal NF-κB–mediated events during early sepsis are summarized in Fig. 32.58. This phase has been described as a “cytokine storm,” during which there is flooding of inflammatory, procoagulant, and vasoactive mediators throughout the body. The net effects of these mediators promote microvascular injury and hypotension. The singular contributions of many mediators to sepsis is demonstrated by experiments with sepsis models in which blocking or deleting a single mediator has had a positive effect on outcome.

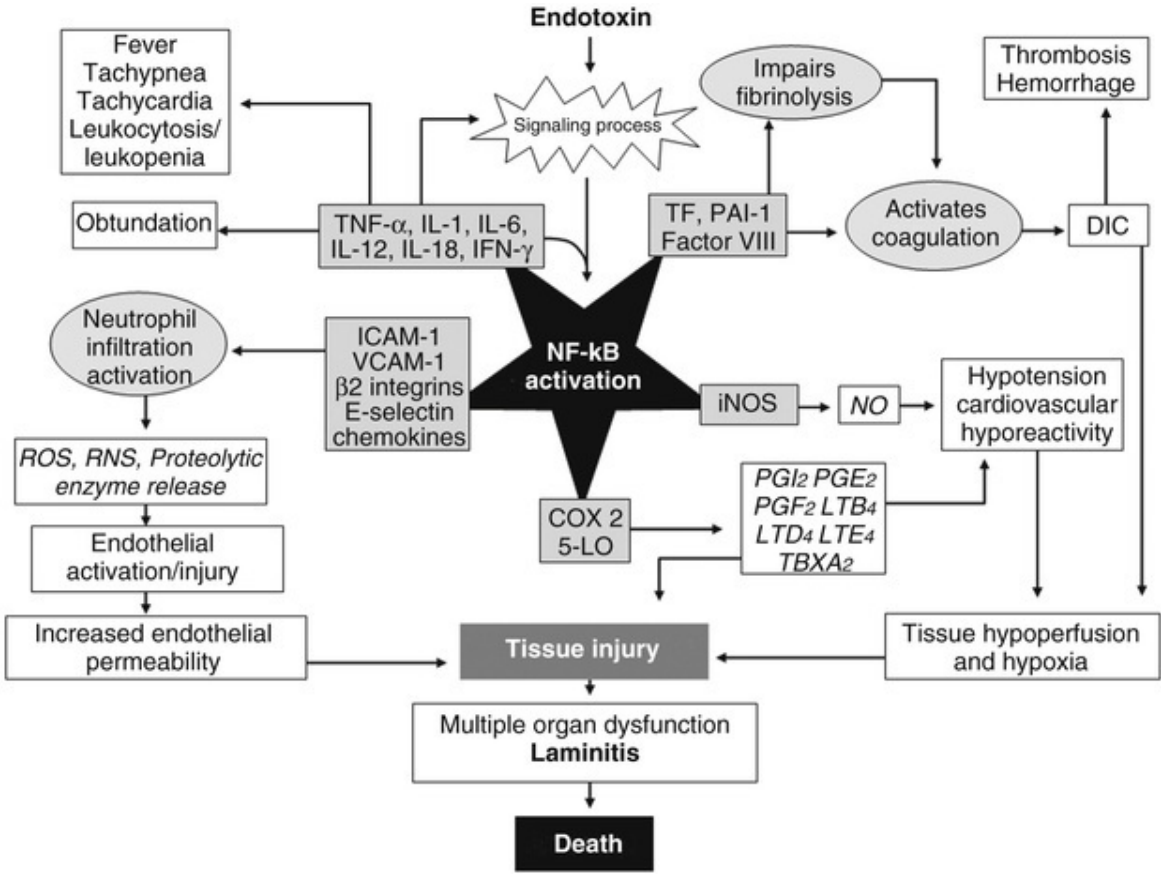


FIG. 32.58 Nuclear factor κB signaling plays a central role in the pathophysiology of septic shock. *COX 2,* Cyclooxygenase 2; DIC, disseminated intravascular coagulation; *ICAM-1,* intercellular adhesion molecule 1; *IFN,* interferon; *IL,* interleukin; *iNOS,* inducible nitric oxide synthase; *5-LO,* 5-lipoxygenase; *LT,* leukotriene; *NO,* nitric oxide; *PAI-1,* plasminogen activator inhibitor 1; *PG,* prostaglandin; *RNS,* reactive nitrogen species; *ROS,* reactive oxygen species; *$TBXA_2$,* thromboxane 2; *TF,* tissue factor; *TNF,* tumor necrosis factor; *VCAM-1,* vascular cell adhesion molecule 1. (Modified from Liu S, Malik A. NF-kappa B activation as a pathological mechanism of septic shock and inflammation. *Am J Physiol Lung Cell Mol Physiol* 2006;290:L622-L645, Fig. 3.)

In early stages of sepsis, large numbers of neutrophils accumulate on the endothelial surfaces of organs undergoing failure, and insult to one organ can trigger the widespread recruitment and sequestration of neutrophils in others. Such a scenario may contribute to the association of laminitis with severe intestinal disease,[71-74] although altered insulin and glucose dynamics,[75,76] vascular derangements,[72] or contributions of multiple inflammatory mediators[77] may also play a role in the development of laminitis in septic horses.

PAMPs (including LPS), inflammatory cytokines, and complement peptides

induce expression of selectins on endothelial cells, and neutrophils.[52] Selectins E and P on endothelial cells and selectin L on neutrophils reciprocally engage glycoprotein ligands to “tether” the neutrophil to the endothelial surface. A series of these transient interactions between ligands and receptors allows neutrophils to roll along the endothelial surface (Fig. 32.59). Neutrophil capture is most efficient in areas of low shear force such as the walls of postcapillary venules and in pulmonary capillaries. During rolling, neutrophils are activated by selectins, chemokines, and platelet-activating factor expressed on endothelial cells. The firm attachment or arrest step of the cascade is mediated by the avid interaction of neutrophil integrins with adhesion molecules of the immunoglobulin superfamily expressed on endothelial cells. During firm attachment the activated neutrophil spreads out and, in the healthy animal, squeezes between the intercellular junctions of adjacent endothelial cells and migrates into tissues up a gradient of chemotactic factors such as microbial chemotaxins, leukotriene B_4, IL-8, or complement component 5a (C5a). In contrast, in comparison with normal neutrophils, those found in septic animals have defective chemotactic responses but bind with greater avidity to the endothelium and to other neutrophils. When cultured, macrophages and neutrophils from patients with Gram-negative sepsis are hyporesponsive to LPS, which suggests a functional switch to LPS tolerance during the early stages of endotoxemia[78] (see Fig. 32.59). Sequestration of neutrophils on activated endothelium and in neutrophil aggregates accounts for the neutropenia found in most horses with endotoxemia. Of interest is that the life span of these sequestered neutrophils is prolonged during sepsis because normal apoptosis is prevented,[79] which might potentiate the inflammatory response during early sepsis.

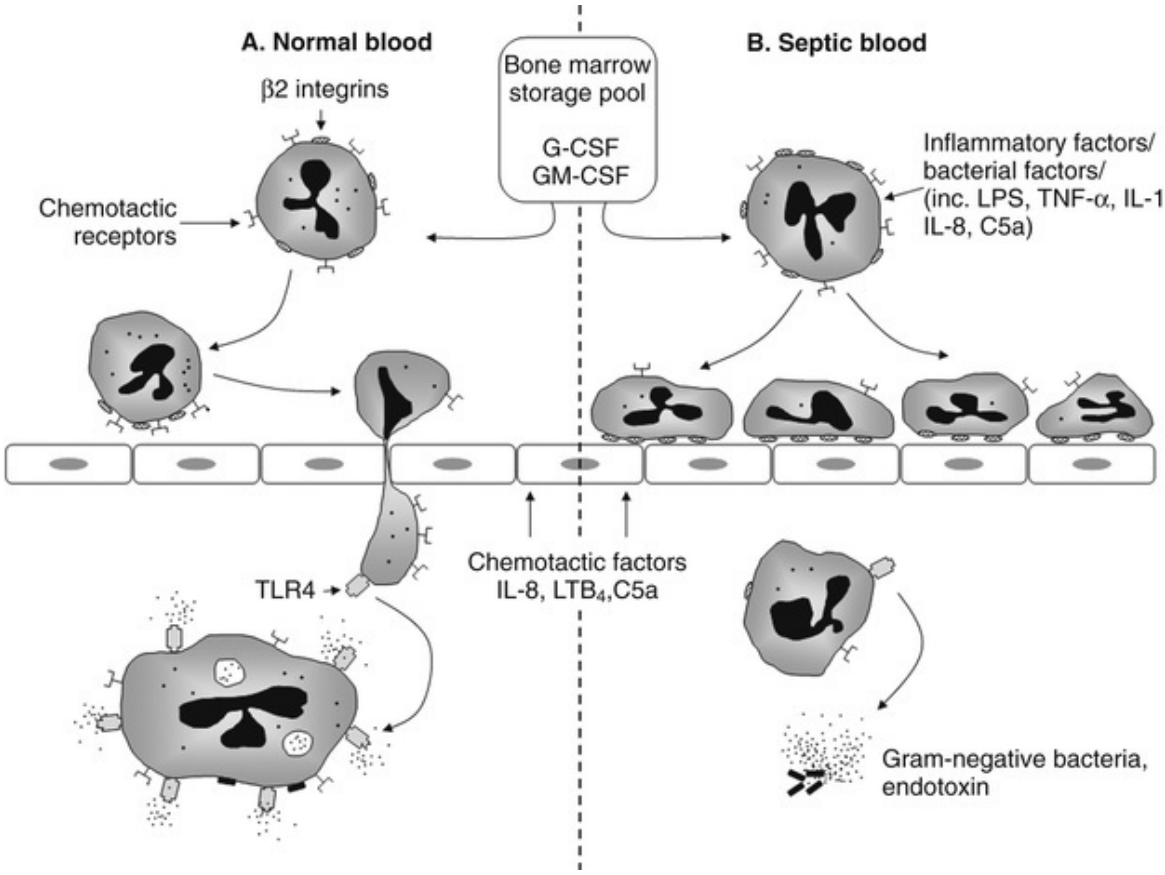


FIG. 32.59 Recruitment and activation of neutrophils in response to bacterial infection in healthy horses and septic or endotoxemic horses. In response to bacterial infection, cytokines are generated that induce the release of neutrophils from the bone marrow. In the normal state, large numbers of blood neutrophils enter sites of bacterial infection by first adhering to the activated endothelium of local postcapillary venules before migrating up a concentration gradient of chemotactic factors. Endotoxin is bound to Toll-like receptor 4 (TLR4), and bacteria are eliminated by phagocytosis. In patients with endotoxemia or sepsis, high levels of circulating inflammatory factors promote upregulation of surface integrins to promote firm endothelial adhesion to postcapillary venules. However, some of these factors also downregulate the expression of chemotactic receptors. Consequently, neutrophils are strongly bound but less responsive to underlying chemotactic factors. *C5a,* complement component 5a; *G-CSF*, granulocyte colony-stimulating factor; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IL,* interleukin; *LPS,* lipopolysaccharide; *LTB4,* leukotriene B_4; *TNF-α,* tumor necrosis factor α.

(Modified from Brown K, Brain S, Pearson J, et al. Neutrophils in the development of multiple organ failure in sepsis. *Lancet* 2006;368:157-169, Fig. 2.)

Tightly adherent neutrophil-endothelial conjugates formed during sepsis seal off microscopic pockets between the juxtaposed cells into which cellular

products can be concentrated. Of particular significance are the reactive oxygen species (ROS) produced as a result of the activation of the reduced forms of nicotinamide adenine dinucleotide (NADH) oxidase and of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in neutrophils (respiratory burst) and xanthine oxidase in endothelial cells.[51,69] Digital laminae of horses may be particularly vulnerable to the effects of ROSs because of low content of the endogenous oxidant scavenger superoxide dismutase.[80] In the presence of neutrophil granule myeloperoxidase and H_2O_2, highly toxic hypochlorous acid is formed on the endothelial surface. Superoxide anion generated as part of the neutrophil respiratory burst also reacts with nitric oxide (a reactive nitrogen species [RNS]) from endothelial cells to yield reactive peroxynitrite radicals (another RNS). Other potentially corrosive substances are contributed by neutrophil granules and include elastase, serine proteases, matrix metalloproteinases, and defensins. In addition to direct damage caused by membrane lipid peroxidation, ROSs and RNSs indirectly stimulate the expression of multiple inflammatory, procoagulant, and vasoactive mediators through activation of NF-κB in both neutrophils and endothelial cells.[51] Mediators such as bradykinin, platelet-activating factor, C3a, C5a, and leukotriene B_4 directly increase vascular permeability by promoting active retraction of endothelial cells via phosphorylation of the light chain of nonmuscle myosin.[51] Vascular leak then facilitates the movement of these potentially harmful substances into tissues.

In health, the antithrombotic phenotype of endothelial cells is maintained by the presence of low amounts of prostacyclin (prostaglandin I_2) and nitric oxide, and surface expression of thrombomodulin, protein S and protein C complex, and tissue plasminogen activator.[81] During endotoxemia, endothelium supports extrinsic pathway activation because of leukocyte-induced physical damage, expression of the procoagulant tissue factor, downregulation of antithrombin-III and protein C, and inhibition of fibrinolysis through expression of plasminogen activator inhibitor 1.[82-84] Additional procoagulant effect may be provided by deposition on the endothelial surface of all of the components of the intravascular coagulation system. Microvascular perfusion is further compromised by sepsis-associated increase in “stiffness” of both RBCs and WBCs,[85] which renders such cells less able to deform and squeeze through narrow capillaries.

The effect of endotoxemia and sepsis on vascular tone depends on the stage

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and severity of disease and the particular organ (vascular bed) considered. Neuroendocrine responses to sepsis lead to the upregulation of predominantly pressor mediators including arginine vasopressin, angiotensin II, serotonin, epinephrine, and norepinephrine. Inflammatory mediators are a mix of vasoconstrictors (thromboxane A_2, endothelin, C3a, C4a, C5a) and vasodilators (prostaglandins E_2 and I_2, adenosine, bradykinin, nitric oxide). In animals with serious sepsis, balances of constricting and dilating influences unique to each vascular bed, loss of vasoregulatory tone, and refractoriness of damaged endothelium to vasoactive substances causes maldistribution of blood flow among organs and systemic hypotension.

Because of poor perfusion pressure, direct microvascular injury, thrombosis, and loss of endothelial integrity (capillary leak), ischemia and hypoxia of organs and tissues occur.[33] In fact, the fundamental event in serious sepsis is the development of global tissue hypoxia, perhaps also complicated by *dysoxia*.[52] Global tissue hypoxia results when systemic oxygen delivery fails to meet the oxygen requirements of tissues, and dysoxia results when tissues are unable to effectively utilize delivered oxygen. During serious sepsis, widespread microvascular and mitochondrial injury decrease oxygen delivery and consumption at the cell, tissue, and organ levels.[51,86,87] Oxygen delivery to tissues is a product of cardiac output and oxygen content (which itself is a product of hemoglobin oxygen saturation and hemoglobin concentration). Systemic oxygen delivery multiplied by the percentage of oxygen extracted (normally ≤25%) by the tissues is the systemic oxygen consumption. The balance between systemic oxygen delivery and consumption is reflected by the mixed venous hemoglobin oxygen saturation (SVO_2). SVO_2 has been shown in other species to be a useful surrogate for cardiac index as a target for goal-directed therapy.[88] Central venous oxygen saturation, measured through a central venous line, is a reasonable and easily measurable substitute for SVO_2 (which must be measured via a Swan-Ganz catheter).

Various hemodynamic combinations may create a systemic imbalance between tissue oxygen supply and demand[52,89]:

- *Hypovolemia.* Because of decreased preload caused by hypovolemia, concomitant left ventricular dysfunction, and reflex systemic arterial

vasoconstriction, early endotoxemia is often characterized by low cardiac output (i.e., hypodynamic circulatory insufficiency).

• *Compensated but maldistributed perfusion.* After fluid-electrolyte resuscitation, compensatory mechanisms and low afterload drive transition to a hyperdynamic state. Even with normal or increased cardiac output, perfusion abnormalities may persist because of regional hypoperfusion associated with derangements in blood flow distribution, loss of vasoregulatory control to vascular beds, and endothelial dysfunction.[90] This state is often described as *distributive shock.*

• *Myocardial depression* secondary to effects of inflammatory mediators and apoptosis of cardiomyocytes is the predominant cause of death in severe sepsis and septic shock.[91] Myocardial injury—as indicated by increased cardiac troponin concentrations—was reported in horses undergoing emergency abdominal surgery,[92] which suggests that similar pathologic processes probably develop in horses with sepsis and SIRS.

• *Increased metabolic demands.* SIRS increases metabolic demands, as evidenced by increased splanchnic and total body oxygen consumption.

• *Impaired oxygen utilization.* The bioenergetics of cellular extraction and use, as well as respiration, may

be abnormal at least partially because of mitochondrial dysfunction.[51,86,87]

The effects of these hemodynamic derangements on clinical measures cardiovascular function and perfusion are detailed in Table 32.8.

TABLE 32.8
Effect of Hemodynamic State on Parameters of Cardiovascular Function

Pathologic State	MAP	CVP	$ScVo_2$	Lactate	CO	SVR
Hypovolemia	Variable	↓	↓	↑	↓	↑
Compensated but maldistributed	Normal to ↑	Normal	↑	Normal to ↑	↑	↓
Myocardial depression	Variable	↑	↓	↑	Normal to ↓	Normal to ↑
Increased metabolic demand	Variable	Normal	↓	Normal to ↑	Variable	Variable
Impaired O_2 usage	Variable	Normal	↑	↑	Variable	Variable

CVP, Central venous pressure; *CO*, cardiac output; *MAP*, mean arterial pressure; *$ScVO_2$*, central venous oxygen saturation; *SVR*, systemic vascular resistance.

Adapted from Otero R, Nguyen H, Huang D, et al. Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. *Chest* 2006;130:1579-1995.

In summary, the pathophysiologic mechanisms of early sepsis are currently thought to support development of a self-perpetuating imbalance in the systemic redox state, which results in oxidative stress that is believed to be at the root of SIRS and resultant organ dysfunction in sepsis.[51,86,87] Activation of local and systemic inflammatory responses results in production of ROS and RNS, which can directly and irreversibly damage cells and inhibit normal cellular activity, as described previously. In health, ROS and RNS production is tightly regulated by inducible antioxidant enzymes, production of which is regulated by the nuclear transcription factor Nrf2.[51] However, Nrf2 activity is impaired by excessive ROS and RNS production, which results in less activation of these antioxidant pathways and the generation of an overall oxidant environment.[51] Mitochondria are a key source of ROS and RNS but are also very sensitive to oxidative injury. Mitochondrial dysfunction and oxidative stress can result in tissue dysoxia and organ failure, as well as further stimulate inflammatory responses and NF-κB activation, creating the vicious cycle characteristic of SIRS and MODS.

Immunosuppression in Late Sepsis

It has become apparent that many horses with sepsis are profoundly immunosuppressed, as evidenced by lymphopenia, anergy, and susceptibility to opportunistic infections[51,52,93] (e.g., pulmonary aspergillosis in horses with enteric salmonellosis[94,95]). This immunosuppression, termed the *compensatory anti-inflammatory response syndrome* (CARS), has been explained by the reactive production of antiinflammatory mediators in response to the cytokine storm.[96] Although many such mediators are produced and actually can have favorable antiinflammatory effects when used as therapy in models of sepsis, it is now clear that three additional and primary mechanisms involving both innate and adaptive immune responses contribute to sepsis-associated immunosuppression: (1) widespread apoptotic death of lymphocytes (particularly B cells and $CD4^+$ T-helper cells) secondary to activation of intracellular caspases; (2) dendritic cell loss and dysfunction, which leads to inefficient or impaired antigen presentation; and (3) impaired phagocyte chemotaxis and killing responses.[51,93,97,98] Of interest is that macrophages and neutrophils are spared premature apoptotic death; neutrophils actually are prevented from physiologic apoptosis during sepsis and remain viable in sequestered sites.[79] In humans with sepsis, aspects of this immunosuppression are characterized by loss of cutaneous delayed-type hypersensitivity responses,[51] but this has not been investigated in horses to date. The relationship and interplay between SIRS and immunosuppression in sepsis is still unclear, and these phases may not always occur sequentially in the same patient.

■ Signs of Endotoxemia and Sepsis

Clinical Signs.

In horses given intravenous endotoxin experimentally, the clinical signs may range from fever without obvious malaise to multiple organ failure and death. Obviously, signs of the primary disease resulting in endotoxemia (e.g., severe pain caused by intestinal strangulation or diarrhea in horses with *Salmonella* colitis) may greatly influence the overall clinical presentation of horses with naturally acquired endotoxemia. The clinical signs of polymicrobial or Gram-positive sepsis are generally indistinguishable from the signs associated with endotoxemia/Gram-negative sepsis described later.[46,47,99,100]

Typically, in an adult horse given a moderate sublethal dose of endotoxin

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intravenously (e.g., 0.1 to 1 μg of LPS per kilogram of body weight), an early period of mild tachypnea peaks within 30 minutes and resolves within 2 hours. During this period, mucous membranes are pale. Beginning within 90 minutes after LPS injection, depression, restlessness, and inappetance are present and rectal temperature begins to rise. Auscultable intestinal sounds usually cease during this period and remain depressed for several hours. Intermittent signs of colic usually are seen, including recumbency (usually without rolling). Small amounts of loose feces usually are passed. The heart rate peaks during the stage of maximal abdominal discomfort (approximately 2 hours after administration of endotoxin) and then temporarily declines. During this time, mucous membranes become congested, the capillary refill time is prolonged, and a dark “toxic” line may become apparent around the gingival margins of the teeth. Beginning 4 to 6 hours after endotoxin administration, there is a secondary phase of tachycardia and tachypnea that is probably related to development of systemic hypotension and fever. This secondary phase persists for several hours. Horses that present clinically with mild to moderate endotoxemia or sepsis usually resemble experimental animals during the period 2 to 6 hours after intravenous endotoxin administration.

At higher LPS doses (e.g., 100 μg/kg) in experimental animals, or in patients with severe endotoxemia/sepsis, signs of circulatory failure and disordered hemostasis dominate the clinical picture. Usually affected horses are stuporous and totally anorexic. Signs of dehydration such as reduced skin turgor, dry mucous membranes, and sunken eyes are obvious. As systemic blood flow becomes more compromised, rectal temperature may drop into or below the normal range. Urine output is reduced or nonexistent. There are dark, congested mucous membranes, rapid and weak peripheral pulses, cold extremities, and sweating, and affected horses may have muscle tremors or become recumbent.

Vascular damage may be seen as petechial and ecchymotic hemorrhages on mucous membranes. A poor prognostic sign is the development of a hypercoagulation syndrome, during which routine venipuncture or catheter placement initiates thrombosis along the entire visible length of the jugular veins (or other superficial veins). If both jugular veins are thus occluded, there usually is massive swelling of the soft tissues of the head, and associated laryngeal edema may cause signs of upper respiratory tract obstruction. In some horses, thrombosed superficial vessels can easily be palpated through the skin of the legs and abdomen. Infarction of bowel segments or lungs may cause severe clinical signs that are unresponsive to treatment. A rare syndrome of thrombosis of major

limb arteries found in young foals is probably a result of sepsis syndrome.[101,102] At the time that hypercoagulation syndrome is recognized clinically, there is often also evidence of a secondary bleeding tendency (a consequence of platelet and clotting factor depletion and uncontrolled activation of fibrinolysis in disseminated intravascular coagulation), manifesting as prolonged hemorrhage from venipuncture sites and widespread mucosal petechiation. In cases with a severe pulmonary component, there may be hemorrhage into the respiratory tract with progressive tachypnea and dyspnea. Alterations in coagulation (both hypercoagulable and hypocoagulable states) were shown to be associated with incidence of SIRS and mortality in horses with acute gastrointestinal disease[30,40,103,104] and with mortality in septic foals.[105]

If moderately to severely affected animals survive for more than 24 hours, they usually exhibit visible edema of the ventral abdomen and limbs. Signs of MODS may first become apparent at this stage (see Table 32.2).[30] In adult horses, laminitis may develop or progress in severity as a result of mechanical failure of the lamina, even after improvement or resolution of other systemic signs of SIRS and sepsis. Of importance is that experimental endotoxin infusion does not reliably reproduce laminitis in horses, so other DAMPs or cellular responses in the sepsis syndrome probably play a role in laminar failure in equine sepsis.

Clinicopathologic Signs.

Profound leukopenia occurs early and is caused principally by neutropenia (usually accompanied by left shift and a toxic appearance of stained cells). Lymphopenia (<1000/μL) is found in the most severe cases and probably reflects sepsis-induced apoptosis and immunosuppression. Adult horses often are hyperglycemic at presentation, whereas neonates with sepsis are typically hypoglycemic. Other abnormalities are nonspecific and reflect altered tissue perfusion and variable organ dysfunction (see Table 32.2).[30]

In moderate and severe cases of endotoxemia, there also may be clinicopathologic evidence of disordered hemostasis, including any or all of the following: reduction in the circulating platelet count (<100,000/μL); reduction in plasma fibrinogen concentration; prolongation of the activated partial thromboplastin, prothrombin, or thrombin time; increased activity of plasminogen activator inhibitor 1; and increased concentration of fibrin degradation products. Studies in which viscoelastic coagulation testing was used

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to provide a more global assessment of coagulation function in horses with SIRS and foals with sepsis have provided further documentation of hypercoagulable and hypocoagulable states and of the association between coagulation derangements and increased disease severity and mortality in equine sepsis.[40,105] In horses with acute gastrointestinal diseases, there also is increased activity in peritoneal fluid of many of the elements of the fibrinolytic system, including tissue plasminogen activator. Depletion of key clotting factors can be detected most simply as prolongation of plasma recalcification time.[106]

Although the measured concentration of endotoxin in blood is not strongly correlated with incidence or severity of clinical signs, demonstration of circulating endotoxin obviously is definitive proof of endotoxemia. Of horses with acute gastrointestinal disease, 12 to 29% have detectable plasma endotoxin.[48,49] In experimental conditions, plasma endotoxin usually is assessed by some variant of the *Limulus* amebocyte lysate bioassay, which requires anticoagulation of samples with LPS-free heparin. A simple horse-side test for endotoxin that was marketed for use in clinical practice is no longer commercially available, but measurement of endotoxin activity in equine blood via neutrophil chemiluminescence has been described.[107] Tests for other microbial PAMPs that could play a role in equine sepsis (e.g., staphylococcal toxins, flagellin) are currently unavailable or limited to research settings.

Assessment of the Stage of Sepsis

Staging criteria for horses and foals with signs of SIRS/sepsis/endotoxemia are detailed in Fig. 32.56 and Tables 32.1 and 32.2.[26-28,30] Validated criteria for diagnosing and staging MODS in horses with GI disease are now available and may be applicable to horses and foals with other clinical conditions.[30] It is especially important to recognize that horses with serious sepsis need aggressive intervention in order to survive.

■ Treatment of Sepsis

There is no surefire treatment of sepsis or endotoxemia. Almost without exception, potentially novel treatments for Gram-negative sepsis that have been promising at the experimental level have failed when applied in clinical settings in human beings. A short list of treatments used in such trials includes anti–tumor necrosis factor α (TNF-α), IL-1 receptor antagonist, ibuprofen, platelet-activating factor antagonist, elastase inhibitor, nitric oxide synthase inhibitor,

antithrombin III (AT-III), tissue factor pathway inhibitor, and drotrecogin alfa (activated protein C).[108] It is clear that most experimental sepsis models do not replicate naturally occurring sepsis, at least as it occurs in humans and probably in horses. Even among sepsis models, results for the same candidate treatment are often inconsistent. For example, neutralization and inhibition of inflammatory cytokines such as TNF-α usually have salutary effects in LPS-infusion experiments; however, equivalent studies involving the cecal ligation-puncture model in mice (widely considered to be one of the best experimental sepsis models) usually have shown either neutral or negative effects on mortality.[109]

Several of many plausible explanations for the disparity among and between the results of experimental, single-center, and large clinical studies are (1) heterogeneity of presentations among enrollees in clinical studies; (2) diversity in genetic susceptibility to sepsis among outbred populations; (3) differences between experimental and clinical study species; (4) differences in timing of potential treatments in relation to the onset of sepsis between the two study populations; and (5) a preponderance of immunosuppressive states in naturally occurring sepsis, in comparison with the “cytokine storm” of early sepsis usually re-created in experimental models.

Fortunately, there is powerful evidence to support the use of early aggressive cardiovascular resuscitation in sepsis management in clinical settings. Previous work in humans documented a reduction in in-hospital mortality from serious sepsis, from 46.5% in the group that received standard therapy to 30.5% in the group that received early goal-directed therapy (EGDT; Fig. 32.60): oxygen, fluids, pressors, inotropes, and packed RBCs during the first 6 hours after admission to achieve a sequence of physiologic goals.[110] However, more recent studies have demonstrated conflicting results, with some failing to demonstrate any benefit of EGDT over standard therapy.[111-113] In view of the constant improvements in standard of care in human medicine, it seems possible that reaching the specific physiologic goals laid out in EGDT protocols is less important than general aggressive cardiovascular support and close monitoring during initial stabilization. Comparable aggressive cardiovascular resuscitation protocols for equine patients with SIRS, sepsis, and septic shock are detailed in the next section.

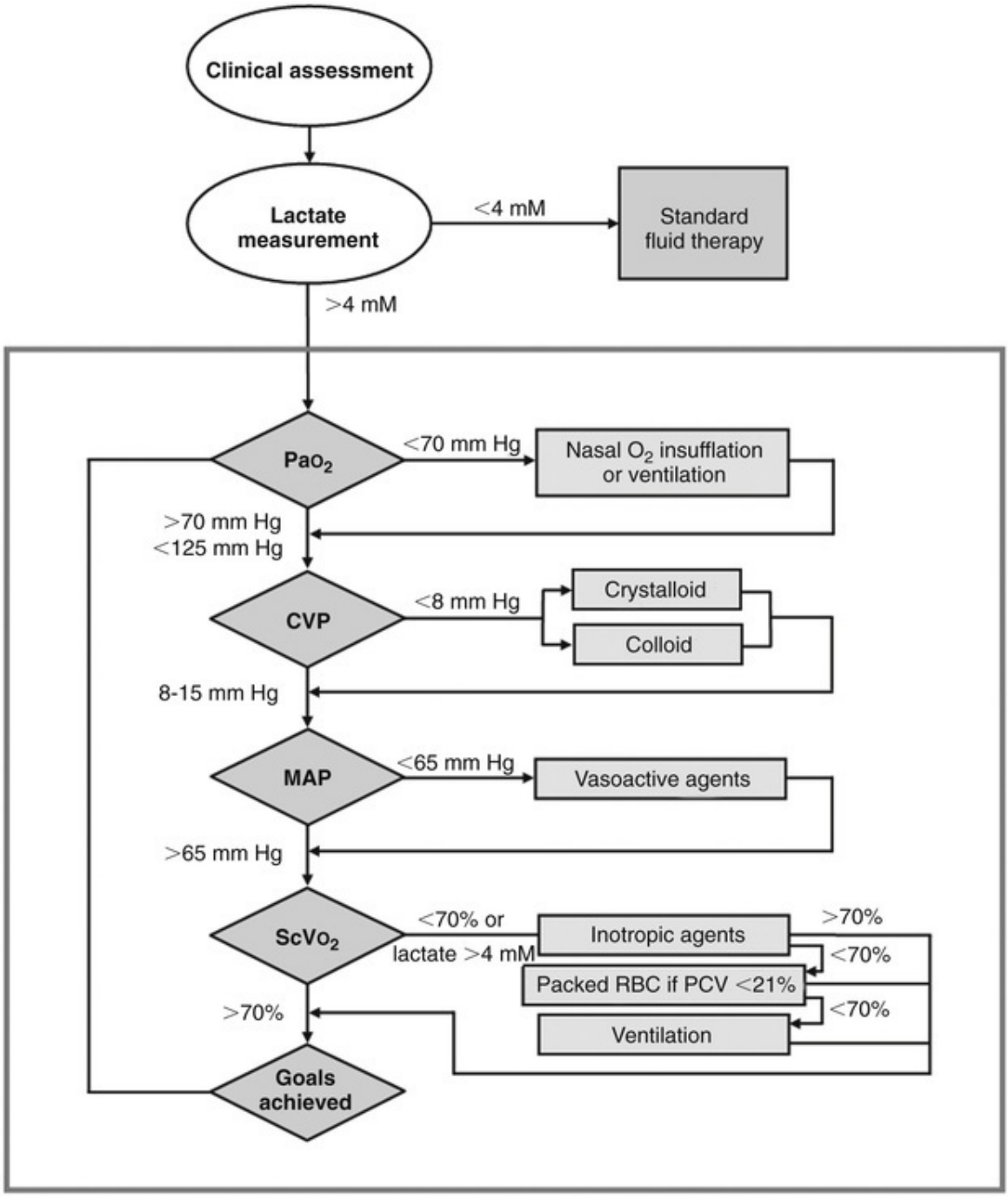


FIG. 32.60 Protocol for early goal-directed therapy. An initial 20-mL/kg bolus of isotonic crystalloid (or equivalent colloid) is given, followed by boluses of 10 mL/kg every 30 minutes until central venous pressure (CVP) reaches 8 to 15 mm Hg. If adjusted mean arterial pressure (MAP) at the heart base is still less than 65 mm Hg, vasopressors are given to effect. Norepinephrine, dopamine, or vasopressin can be used according to the clinician's preference. If the central venous oxygen saturation ($ScVO_2$) is still less than 70%, the continuous-rate infusion of dobutamine can be increased in increments up to 15 µg/kg/min. If the packed cell volume

(PCV) is less than 21% after the preceding steps and $ScVO_2$ is less than 70%, packed cells should be given to increase oxygen-carrying capacity. *PaO_2,* Partial pressure of arterial oxygen; *RBC,* red blood cells.

Improvements in cardiovascular support of horses with sepsis will continue to be of much more value than any single therapeutic agent available now or in the future. In fact, because clinical sepsis probably is almost always caused by multiple pathogen and host-derived DAMPs stimulating multiple, complementary, and redundant inflammatory pathways, management of sepsis is much more likely to be successful when therapy focuses on combatting the clinical sequelae of severe SIRS and subsequent immunosuppression rather than targeting a specific inflammatory mediator or PAMP. A prioritized strategy for management of horses with sepsis or endotoxemia should include (1) cardiovascular resuscitation; (2) laminitis prevention; (3) removal of the causes of sepsis; (4) neutralization of circulating endotoxin or other PAMPs; and (5) inhibition of PAMP-induced inflammation.

Cardiovascular Resuscitation.

Expansion of blood volume remains the cornerstone of treatment for horses with SIRS/sepsis/endotoxemia. Most cases can be treated successfully with intravenous balanced polyionic solution according to guidelines for estimating water deficits provided in the Fluid Therapy for Horses with Gastrointestinal Diseases section of this chapter. Urination should begin during the rapid replacement of estimated losses. Ideally, the fine control of fluid replacement is based on clinical evidence of blood volume and perfusion (e.g., mucous membrane color, heart rate, capillary refill time, pulse quality, jugular refill time, extremity temperature), as well as serial measurements of packed cell volume (PCV) or plasma protein concentration and blood lactate concentration. Some clinicians prefer the early use of compatible plasma (20 to 40 mL/kg) to replace the extravasated colloid lost as a result of vascular leak. Plasma has the advantage of providing immunoglobulin, acute-phase proteins, and anticoagulants and can provide antiendotoxin antibodies (described later). Synthetic colloids such as 6% hetastarch (hydroxyethyl starch solution) were advocated as excellent colloid replacement in sepsis and septic shock because of their superior oncotic activity. However, studies have demonstrated impairment of hemostasis and development of acute kidney injury in septic patients receiving some synthetic colloids, and the use of 6% hetastarch is now

considered contraindicated in human sepsis.[114]

In horses with severe sepsis, septic shock, or MODS, aggressive hemodynamic stabilization and monitoring is indicated. Owners should be informed that such treatment still carries at best a guarded prognosis for survival, substantial financial commitment, transfer to a referral center, and great risk of potentially life-threatening complications such as laminitis. However, early and aggressive intervention is essential in sepsis therapy; in critical care parlance, terms such as the “golden 6 hours” and the “silver 24 hours” exemplify this concept.[89]

Specific and critically evaluated guidelines for initial resuscitation and stabilization in equine sepsis are not available, but much has been extrapolated from human critical care. Initial fluid resuscitation should include a balanced polyionic crystalloid at 20 mL/kg as an intravenous bolus followed by reassessment of hemodynamic parameters; fluids with high chloride levels such as 0.9% sodium chloride should be avoided. Boluses of 10 to 20 mL/kg should be repeated until hemodynamic improvement is reached or three or four boluses have been given (total, 60 to 80 mL/kg).[115,116] Both clinical and clinicopathologic parameters should be monitored and at minimum should include heart rate, body temperature, mentation, capillary refill time, peripheral pulse quality, warmth of extremities, peripheral lactate, partial pressure of arterial oxygen, and mean arterial pressure (MAP). Central venous pressure (CVP) and central venous oxygen saturation can also be measured to guide resuscitation if suitable equipment is available.[117] Hypoxemic patients should receive nasal oxygen insufflation, and ventilation may be needed for severely hypercapneic or hypoxemic patients. Steady improvement in these parameters with return to reference values within the first 6 to 8 hours of therapy is ideal but not always possible. If the patient is still not improved after three or four fluid boluses, as mentioned, and oxygen/ventilatory support, additional therapy with colloids (plasma, or whole blood if anemia is also present), inotropes, vasopressors, or a combination of these should be considered.

Once the patient is stabilized, fluid management should continue according to standard protocols (see the Fluid Therapy for Horses with Gastrointestinal Diseases section) with adjustments made according to the results of continued monitoring of clinical signs of blood volume status and perfusion, blood acid-base status, partial pressure of arterial oxygen, central venous oxygen saturation, lactate, CVP, and MAP. If the blood bicarbonate concentration is less than approximately 16 mmol/L after volume restoration, sodium bicarbonate should

be given IV to replace calculated deficits. During correction of acidemia, intravenous fluids should be supplemented with potassium (10 to 20 mmol/L) to prevent correction-induced hypokalemia. A maintenance-rate infusion of glucose should be given to neonates with sepsis (4 mL of 5% dextrose–containing fluids per kilogram per hour) and hypoglycemic adults (2 mL of 5% dextrose or 0.2 mL of 50% dextrose per kilogram per hour). Glucose concentration should be regularly monitored, and the use of concurrent insulin therapy should be considered in persistently hyperglycemic animals.

Laminitis Prevention.

Adult horses with sepsis are at high risk for the development of laminitis. Among the clinical risk factors that are probably operative in the setting of sepsis are underlying endocrine disease, previous episodes of laminitis, a period of 24 hours or longer since onset of signs of endotoxemia or sepsis, fever, prolonged central reaction time, and cold extremities. The digital laminae are probably injured early in sepsis, potentially irreversibly, by processes associated with the cytokine storm and resultant global tissue hypoxia. Insulin resistance, hyperglycemia, microvascular injury and thrombosis, and protease activation all may also be involved in the pathogenesis of sepsis-associated laminitis. There is no ideal laminitis prevention strategy that is universally effective, but according to the current understanding of laminitis pathophysiology, a combination of prompt fluid resuscitation to restore appropriate digital perfusion, NSAIDs to decrease inflammatory mediators, and digital cryotherapy is generally accepted as the minimal standard of care, and some evidence supports their use in equine sepsis.[118,119] Laminitis prophylaxis must be implemented very early (preferably before an increase in digital pulses is detected) and is not universally protective.

The use of insulin infusions in septic horses may also be indicated to combat persistent hyperglycemia associated with sepsis-mediated insulin dysregulation, inasmuch as insulin dysregulation is associated with endocrinopathic laminitis. However, because insulin infusions at very high rates have been associated with laminitis development in healthy horses and ponies[120,121] and hyperinsulinemia is associated with endocrinopathic laminitis,[122] glucose or insulin infusions could possibly potentiate the development of laminitis in susceptible animals with sepsis. The use of insulin-sensitizing drugs such as metformin or pioglitazone could have potential in treating sepsis-mediated insulin dysregulation in horses, but to date these drugs have not been examined in clinical equine sepsis; current evidence suggests that their effects on insulin

sensitivity in horses may be variable at best.[123-125] If laminitis is already present, or if it develops during the course of treatment, it should be treated as described in Chapter 38.

Removal of the Cause or Causes of Endotoxemia and Sepsis.

Removal of the cause of sepsis usually involves both removal of the source of endotoxin or other microbial PAMPs, as well as correction of the abnormality that allows endotoxin or other PAMPs to enter the blood. In some cases, the source can be mechanically removed; for example, bacteria and associated inflammatory effusion can be drained from pleural or peritoneal cavities or lavaged from the postpartum uterus. Early and appropriate antimicrobial therapy also is essential. In general, broad-spectrum bactericidal drugs should be selected because septic horses may be immunosuppressed. In horses in which endotoxemia or sepsis is associated with diarrhea or other signs of colitis or typhlitis, the use of antimicrobial drugs is controversial because of their causal association with severe colitis. Antimicrobials should probably should be given to equids with colitis only in the following situations: (1) The affected horse is younger than 6 months of age; (2) clostridial or antimicrobial-associated enteritis is suspected (use of metronidazole should be considered); (3) the horse has a severe degenerative left shift or severe leukopenia with total neutrophil count of less than 1000 µg/mL; (4) the horse has concurrent peritonitis; or (5) the horse shows clinical evidence of dyshemostasis (e.g., jugular thrombosis or abnormal coagulogram). However, these recommendations and outcomes after treatment of equine colitis with and without antimicrobials have not been critically evaluated to date. Furthermore, effective antimicrobial therapy could temporarily worsen clinical signs by causing the release of endotoxin from killed bacteria. This possibility should be anticipated and minimized by the timely use of NSAID or other antiendotoxic therapy (see later discussion).

When intestinal strangulation is the cause of sepsis, surgical correction obviously is of paramount importance. For the purposes of perioperative management, however, it should be noted that resumption of intestinal blood flow could worsen endotoxemia and sepsis: Sequestered endotoxin and other microbial components may be flushed into the circulation through compromised intestinal walls. At least in the case of small intestinal ischemia, the mucosal barrier to endotoxin may be further compromised by ischemia-reperfusion injury when full blood flow is restored by luminal decompression or other manipulation. Prophylactic or intraoperative administration of NSAIDs, ROS

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scavengers, polymixin B, hyperimmune plasma or serum (as described later), or a combination of these before or immediately after correction of a strangulating intestinal lesion may be warranted.

Neutralization of Circulating Endotoxin

Hyperimmune Plasma and Serum.

An antiserum (Endoserum; Immvac Inc., Columbia, Mo.) and several hyperimmune plasmas (e.g., Equiplas-J, Plasvacc, Templeton, Calif.) produced by immunization of horses against R-mutant endotoxins are used in horses with suspected endotoxemia (in some cases, this is an off-label use). As is the case with studies in humans and small experimental animals, use of cross-reactive endotoxin antibodies in horses with either experimentally or naturally acquired endotoxemia has yielded conflicting results. Several studies demonstrated impressive reduction of mortality rate or improvement in clinical signs when antiendotoxin serum or plasma was given to horses[126-128]; in other studies, however, no improvement was demonstrated.[129,130] Pretreatment of foals with antiserum was associated in one report with significant worsening of clinical response to IV administered endotoxin in comparison with foals that received no pretreatment.[131] These disparate results probably reflect, at least in part, variation in the quality of antisera and experimental conditions; therefore no blanket recommendation can be made as to the clinical use of such products.

As evidence of the potential general value of hyperimmune plasmas, a reduction in mortality was achieved when antiendotoxin plasma raised against the *E. coli* mutant J5 was given to bacteremic humans (39% for controls versus 22% for those given antiendotoxin plasma) in a masked, well-controlled study at a single hospital.[132] In contrast, subsequent large multicenter studies of two different antiendotoxin monoclonals failed to show beneficial effects.[133,134] An equine study demonstrated no effect of hyperimmune plasma on clinical parameters or peak plasma TNF-α concentrations in horses undergoing an experimental low-dose endotoxin challenge, although peak plasma TNF-α bioactivity was reduced in horses receiving plasma in comparison with controls.[135] This suggests that hyperimmune plasma may contain factors such as soluble TNF-α receptor that could limit the activity of endotoxin-induced inflammatory cytokines. Hyperimmune plasmas (raised against any antigen) also contain colloid, anticoagulant, and increased amounts of substances such as

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acute-phase proteins, which might have nonspecific beneficial effect in the setting of endotoxemia and sepsis. Therefore the use of 5 to 40 mL of hyperimmune plasma (of any specificity) per kilogram can be justified in treatment of serious endotoxemia or sepsis in horses.

Polymyxin B.

Polymyxin B is a broad-spectrum cyclic peptide antibiotic with potent endotoxin-binding activity. Potentially lethal side effects (respiratory paralysis and nephrotoxicity) have precluded use of this agent as a systemic antimicrobial drug; however, polymyxin B retains endotoxin-neutralizing capacity at nontoxic dosages. Pretreatment of foals with polymyxin B at a dosage rate of 6000 U/kg significantly suppressed clinical and cytokine responses to intravenous endotoxin without causing toxic side effects.[131] Repeated administration to ponies of 15,000 U/kg also produced no sign of toxicity.[136] At a dose of 5000 U/kg, polymyxin B provided protection even when given 30 minutes after the start of LPS infusion.[137] The results of a pharmacokinetic and pharmacodynamic study of polymyxin B in horses suggested that the drug could safely be given at 6000 U/kg every 8 hours to maintain continuous endotoxin neutralization.[138] Lower doses (1000-2000 U/kg) also appear to have anti–TNF-α effects, but for shorter time periods.[137,139] Thus in horses with moderate or severe endotoxemia, IV polymyxin B (Polymyxin B sulfate; Bedford Laboratories, Bedford OH) can be given cautiously two or three times daily at a dosage rate of 1000 to 6000 U/kg. Each treatment should be diluted in saline and infused over at least 15 minutes. However, of importance is that although polymyxin B and the nontoxic polymyxin B–dextran 70 conjugate PMX-622 safely prevented signs of endotoxemia when given before LPS to otherwise healthy horses,[137,139,140] the drug has not advanced beyond phase 1 trials in human patients because experimental studies showed that it did not protect mice if given after intraperitoneal administration of endotoxin.[141]

Inhibition of Endotoxin-Induced Inflammation and Related Sequelae

Nonsteroidal Antiinflammatory Drugs.

Through inhibition of COX, NSAIDs reduce the formation of prostanoid metabolites (e.g., thromboxanes and prostaglandins) from arachidonic acid and thereby attenuate much of the adverse effect of endotoxin. Flunixin meglumine,

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phenylbutazone, ketoprofen, carprofen, meloxicam, firocoxib, and aspirin are examples of this class of drugs used in horses. When flunixin is administered at 0.25 mg/kg every 6 to 8 hours in horses, endotoxin-induced prostanoid production is prevented, and antiendotoxic effects are maximal in experimental situations without obscuring the signs of colic or increasing the risk of toxic side effects of the drug.[142] Flunixin, however, does not reduce endotoxin-induced leukopenia. Because there is evidence that aspirin does not prevent endotoxin-induced aggregation of equine platelets,[143] there appears to be no rationale for the practice of adding aspirin to the NSAID regimen. Most NSAIDs inhibit constitutive COX-1 activity (in addition to endotoxin-induced COX-2 activity), and so some morbidity is associated with their use. Gastric ulceration, right dorsal colitis, renal papillary necrosis, and possibly impairment of intestinal motility may develop.[144,145] Moreover, flunixin meglumine has been shown to slow mucosal healing and increase mucosal permeability by LPS in ischemic-injured equine jejunum,[146,147] although similar inhibition of mucosal barrier function does not appear to occur in the equine colon.[148] However, concurrent administration of misoprostol (a prostaglandin E_1 analogue)[149] or a constant-rate infusion of lidocaine[150] ameliorated these effects in an equine model, which suggests these drug combinations might be more appropriate than flunixin alone for horses with endotoxemia caused by intestinal ischemia.

In view of this toxic potential of equine NSAID use, it has also been suggested that administration of COX-2–selective drugs may minimize side effects while maintaining efficacy. Three NSAIDs with documented analgesic effect in horses—firocoxib, carprofen, and meloxicam—have been shown to be COX-2–selective.[151,152] Etodolac, a COX-2–specific drug in dogs and humans, is not COX-2–selective in horses when used at analgesic doses (23 mg/kg PO once or twice daily).[153] Firocoxib and meloxicam do not appear to retard small intestinal mucosal healing or increase LPS permeability in ischemic-injured equine jejunum as flunixin can.[146,154] Of importance, however, is that COX-2 activity may also have potentially beneficial effects in horses with sepsis; for instance, COX-2 products (e.g., prostaglandins E_2, and I_2) mediate epithelial restitution in damaged equine colon[144] and are thought to be important in maintaining the antithrombotic phenotype of normal endothelium. NSAIDs in the coxib class, which are potently COX-2 specific, have also been shown to increase the risk of atherosclerotic cardiovascular disease in humans.[155] Similar

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risks for coxibs in horses have not been described, but at present firocoxib and meloxicam are the only drugs in this class labeled for equine use, and neither is yet available globally.

Finally, although various NSAIDs have been shown to effectively prevent the clinical and molecular sequelae of equine endotoxemia in experimental models,[83,142,156-163] no study has shown convincingly that NSAIDs actually save lives in human or equine patients with naturally occurring sepsis. A large multicenter, controlled, masked, prospective study of ibuprofen in humans with sepsis syndrome showed no effect of this drug on the development of shock or the acute respiratory distress syndrome, and no improvement in survival.[164] Similar studies have not been conducted in horses to date.

Methylxanthine Derivatives.

Inflammatory cytokine production by macrophages is suppressed in dose-dependent manner by methylxanthine derivatives. This effect appears to be caused by phosphodiesterase inhibition and consequent elevation of intracellular cyclic adenosine monophosphate. Pentoxifylline, a drug that used widely by humans as a hemorheologic agent, has also been shown to increase RBC deformability in horses.[165] Pentoxifylline also inhibits TNF-alpha production in horse blood and in cultured equine macrophages while increasing secretion of prostacyclin.[166,167] Studies in other species suggest that pentoxifylline stimulates production of the antiinflammatory cytokine IL-10, suppresses neutrophil activation, and inhibits activation of NF-κB.[168] A pharmacokinetic study in horses has indicated that administration at 10 mg/kg PO two times daily provides serum concentrations equivalent to those used therapeutically in humans.[169]

Finally, intravenous pentoxifylline significantly, albeit only partially, reduced adverse signs in horses given LPS.[170] The usefulness of this finding is called into question, however, by the observation that the lethality-sparing effect of pentoxifylline in endotoxemic mice was removed if the drug was given in combination with indomethacin, a potent NSAID.[171,172] In this study, the investigators concluded that upregulation of prostacyclin production by pentoxifylline, which was prevented by concurrent indomethacin, reduced mortality in subject mice by preventing endotoxin-induced leukopenia. Of interest is that pentoxifylline alone increased WBC counts in horses, but this effect is prevented by flunixin.[167,170] Thus there might be a conceptual and potential beneficial effect of pentoxifylline therapy (10 mg/kg PO bid) in

endotoxic horses, although any effect could be partially or wholly neutralized by concurrent NSAID administration (as is commonly done in equine practice).

Corticosteroids.

The corticosteroid class of drugs theoretically has many useful actions in combating inflammation in endotoxemia and sepsis. These include reduced production of cytokines, inhibition of TNF-alpha production by macrophages, stabilization of cell membranes, and prevention of neutrophil activation. It is surprising, however, that neutral or negative effects of moderate or high-dose steroid use were found in large, multicenter studies of humans with Gram-negative sepsis,[173] probably in relation to immunosuppressive effects at these doses. Corticosteroids also are widely believed to increase susceptibility to laminitis in endotoxemic horses, perhaps by increasing the sensitivity of digital vessels to the constrictive actions of circulating catecholamines or by inducing insulin resistance and hyperglycemia.[174] Use of high-dose corticosteroids is currently contraindicated in the treatment of endotoxemia or sepsis in humans and horses.

Some human patients with sepsis appear to respond to low “physiologic” doses of hydrocortisone.[174-178] Most such patients have high baseline cortisol concentrations but are thought to be in a state of adrenal insufficiency termed *critical illness-related corticosteroid insufficiency* (CIRCI), a syndrome that also appears to occur in some septic neonatal foals and some horses with systemic illness and SIRS.[41,179-181] Low-dose hydrocortisone is associated with reduced need for vasopressor use and lower mortality rates in humans with septic shock, according to a number of reports,[175,176,182-184] but other studies have not demonstrated a beneficial effect.[185] At present, low-dose hydrocortisone therapy is recommended for humans with sepsis who meet criteria for CIRCI but not universally for all septic patients.[183] The use of low-dose hydrocortisone therapy has not yet been reported in septic equine patients, but a 3.5-day tapering regimen of low-dose hydrocortisone (1.3 mg/kg/day divided q4h IV) administered to healthy neonatal foals was shown to ameliorate LPS-induced inflammatory cytokine production from peripheral blood leukocytes without impairment of neutrophil function in an ex vivo model.[186]

Anticoagulant Therapy.

The use of anticoagulants such as heparin in horses with endotoxemia is

somewhat controversial. Heparin prevents microvascular thrombosis principally by promoting the anticoagulant activity of AT-III. Unfortunately, heparin cannot reverse existing thrombosis, and because AT-III is consumed during severe coagulopathy, it may not prevent additional intravascular coagulation in such cases. Fresh and fresh-frozen plasma are good sources of AT-III but also provide clotting factors that could potentiate intravascular coagulation. When given at the recommended intravenous or subcutaneous dose of 40 U/kg tid (fresh plasma) or 150 U/kg bid (fresh-frozen plasma), unfractionated heparin causes intravascular agglutination of equine RBCs.[187] Therefore it could be argued that the use of heparin might actually exacerbate intravascular cellular plugging, which is theorized to play a role in some cases of laminitis in equine sepsis. This side effect can be avoided with the use of *low-molecular-weight heparin* (LMWH), which is nonagglutinating but retains anticoagulant activity, principally via inhibition of factor Xa.[188] Two clinical studies have suggested that LMWH may have benefits over unfractionated heparin in the prevention of jugular thrombosis or laminitis in some equine patients with colic,[189,190] but this suggestion is not universally accepted. The use of heparin could be considered in horses with sepsis that have evidence of hypercoagulation syndrome (early evidence of dyshemostasis such as abnormal coagulogram or spontaneous venous thrombosis), or possibly in those that are at high risk for laminitis (e.g., DPJ, colitis, or grain overload). In general, heparin should be given with plasma (10 to 40 mL/kg) at a dose of either 200 to 300 IU/kg/day for unfractionated heparin (either divided bid-tid IV or SC or as a continuous intravenous infusion) or 50 IU/kg for LMWH (SC sid). Foals at risk for thrombosis may require a higher dose of LMWH, in the range of 100 IU/kg.[191]

Other anticoagulants that inhibit platelet function, including clopidogrel and aspirin, have also been evaluated in horses and are sometimes recommended in equine sepsis. Both clopidogrel (4 mg/kg PO once for loading dose and then 2 mg/kg PO q24h) and aspirin (5-10 mg/kg PO q24-48h) appear to be effective anticoagulants in horses by inhibiting platelet activation [192-194]; however, aspirin's effects are irreversible, which could be problematic if surgery or invasive diagnostic testing is required during sepsis treatment. Clopidogrel has been evaluated in horses with experimental endotoxemia, and attenuation of LPS-induced tachycardia was noted, but specific LPS-induced platelet hyperreactivity was not seen.[194]

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Scavengers of Reactive Oxygen Species.

ROSs are thought to cause corrosive tissue damage during endotoxemia and potentiate the production of inflammatory cytokines through activation of NF-κB. Surgical deflation of distended small intestine is thought to lead to ischemia-reperfusion injury, a process that generates ROSs from epithelial xanthine oxidase. The life-saving and necessary process of fluid resuscitation in horses with septic shock may even lead to whole-body ischemia-reperfusion and systemic release of ROSs. Despite these key associations between oxidant stress and sepsis, little effort has been made to intervene therapeutically at this level.

There is some evidence that allopurinol, a hydroxyl radical scavenger and inhibitor of xanthine oxidase activity, has positive clinical effect during sublethal endotoxin infusion in horses.[195] A recommended dose for allopurinol is 5 mg/kg IV. Because dimethyl sulfoxide (DMSO) has been shown to be a potent scavenger of hydroxyl radicals with efficacy in rodent sepsis models,[196] it has been considered for use in the treatment of equine endotoxemia, although effects in experimental models have been variable. DMSO is typically administered by rapid intravenous infusion (or by nasogastric tube) as a 10% to 20% solution in saline at dose of 0.02 to 1 g/kg every 6 to 12 hours. However, intravenous infusion of DMSO at the low and high ends of this dose range was recently shown to have little to no effect on clinical signs (with the exception of fever at the high dose), on clinicopathologic abnormalities, and on TNF-α production after endotoxin infusion in horses.[197] At high concentrations intravascularly, DMSO can cause hemolysis.

Ethyl pyruvate, a stable analog of pyruvate, has been shown to have remarkable protective efficacy in a variety of models of septic and nonseptic shock in rodents and other species; its beneficial actions are ascribed to its antioxidant effects.[198] Because this agent is inexpensive and can be given in intravenous crystalloid fluids, it could have potential for the treatment of endotoxemia and sepsis in horses. Reports about equine experimental endotoxemia support this theory, demonstrating beneficial effects on clinical manifestations of endotoxemia (except fever) and suppression of proinflammatory gene expression.[199-201] Use of ethyl pyruvate in clinical cases of equine sepsis or endotoxemia is not described to date, and other antioxidants that have shown benefit in rodent sepsis models and are considered for use in some human patients with sepsis (e.g., vitamin C, vitamin E, and *N*-acetylcysteine) have not been evaluated in equine sepsis.

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Miscellaneous Treatments.

A number of other treatments for endotoxemia and sepsis have been described in horses and other species, though on the whole, currently available data are less supportive of their use in clinical cases. Naloxone, a narcotic antagonist, at a dose of 0.2 mg/kg, blunted some of the cardiovascular effects of high-dose endotoxin in one study,[202] but a dose of 1 mg/kg had no effect in another.[203] Of importance, 0.75 mg/kg naloxone caused signs of colic in conscious horses,[204] probably by blocking the actions of endogenous β-endorphins at the high affinity μ-receptor. The detergent tyloxapol was remarkably effective in preventing the effects of endotoxin in anesthetized horses.[205] The mechanism of antiendotoxic action of tyloxapol is unknown, but the detergent has been shown to have wide-ranging effects on cells and proteins, some of which may preclude its use in clinical cases. For example, the detergent has been shown to inhibit cellular phagocytosis, clearly an important event in innate immunity and sepsis. Also, this agent induces marked hyperlipidemia (lipid levels up to 100-fold higher than in controls) in horses because of interference with lipoprotein metabolism. Similarly, a phospholipid emulsion effectively prevented adverse effects of subsequent endotoxemia; however, the treatment induced hemolysis sufficient to preclude its use in clinical cases.[206] A published report[207] on the use of the sulfonyl analog of the spin trap molecule alpha-phenyl-*N*-tert-butylnitrone suggests that this agent was effective in reducing clinical signs in horses given endotoxin. However, a cautionary note was the observation that in some rodents given the same agent at high doses, the endotoxin-induced mortality rate was actually higher.

Platelet-activating factor inhibitors have been effective anti-endotoxic agents in some species but have not yet shown much positive clinical effect in horses or humans.[208] In dogs and other experimental animals, inhibitors of nitric oxide production such as N^G-monomethyl arginine reverse endotoxin-induced (or more probably TNF-alpha-induced) hypotension;[209] however, nitric oxide synthase inhibitors generally have no protective effect in sepsis models. Furthermore, nitric oxide production may not be increased in horses with endotoxemia.[210] The antifibrotic pyridine compound pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) had no effect on endotoxin-induced clinical signs, leukopenia, or TNF-α production in horses.[211] Hyperbaric oxygen therapy also did not appear to have any protective effect on clinical or cytokine changes in experimental endotoxemia in horses.[212]

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Constant-rate infusion of ketamine has been theorized to have beneficial effects in equine endotoxemia after it was shown in vitro to suppress the production of inflammatory mediators by LPS-stimulated equine peritoneal macrophages.[213] Constant-rate infusion of ketamine at 1.5 mg/kg/h for 320 minutes achieves blood concentrations compatible with this inflammatory effect and has been shown to be safe and nonsedating in horses. However, pretreatment with ketamine had no effect on clinical signs, leukopenia, or inflammatory cytokine in horses after endotoxin infusion.[214] The putative antiinflammatory actions of ketamine appear to be mediated by the actions of adenosine on the adenosine A_{2A} receptor[215]; because the equine adenosine A_{2A} receptor was cloned and characterized pharmacologically, it itself may prove a potential direct target for antiinflammatory drugs in the future.

Future Treatment Considerations.

In summary, current research in horses, humans, and experimental animals suggests that a single therapeutic agent with universal benefit in endotoxemia and sepsis will be very hard (or impossible) to find. Most antiinflammatory approaches that show promise in experimental endotoxemia, even if they are aimed at the initiating steps of the inflammatory cascade (e.g., NF-κB activation), do not work consistently in severe sepsis models (e.g., cecal-ligation puncture) or in phase III clinical trials with human patients. A substantial proportion of the morbidity and mortality associated with sepsis may result as much from immunosuppression in the later stages of sepsis as from the cytokine storm in early sepsis. Immunosuppressed patients could be injured further by antiinflammatory therapy, which potentially explains some of the discrepancy between specific therapeutic efficacy in experimental sepsis and that in clinical sepsis. This emphasizes the need for accurate recognition of—and possibly tiered treatment protocols for—the various stages of sepsis. Plasma biomarkers such as adrenomedullin, procalcitonin, C-reactive protein, or high-mobility group box 1 levels have been used to diagnose sepsis, define sepsis categories, and provide prognostic information in humans,[216,217] but a universally reliable biomarker or combination of markers has yet to be identified. Similar markers need to be integrated more fully into equine sepsis diagnosis, staging and management, although several of the aforementioned human biomarkers (e.g., C-reactive protein) do not appear to be useful in equine sepsis diagnosis.[115]

Some different treatment approaches have the potential to be both effective

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and affordable. There is some indication that IFN-γ, a cytokine that is pivotal in both innate and acquired immunity, may be beneficial for combatting immunosuppression in bacterial sepsis.[218] Il-7, IL-15, and IL-17 may also prevent or modulate immunosuppression in sepsis by preventing leukocyte apoptosis and supporting both innate and adaptive immune function.[51,219] There also remains enthusiasm in human critical care for antioxidant strategies aimed at effective means to suppress or scavenge ROSs.[51,86,87] In this regard, the remarkable effects of ethyl pyruvate in multiple models of inflammation, which probably mediates through its antioxidant actions, offer considerable promise. So-called "metabolic resuscitation" with a combination of low-dose hydrocortisone, vitamin C, and thiamine appeared to have a beneficial effect on survival in one human study[220] and, if truly effective, might be both beneficial and cost-effective in the treatment of equine sepsis. Inhibition of complement activation with anti-C5a antibody show promise in some sepsis models and is currently in clinical trials in humans.[51,221] Finally, two of the most exciting possibilities in the distant future are the use of genotyping to target sepsis diagnosis and treatment and the potential use of even gene therapy to transiently transfect host cells in a targeted way with genes supporting immune and bactericidal function.[222,223]

Medical Disorders of the Small Intestine

Jennifer L. Davis • Nicola Pusterla

■ Ulcerative Duodenitis

Pathophysiology.

Ulcerative duodenitis is a rare condition that most often affects foals and, to a lesser degree, yearling horses. In one retrospective study, of 691 nonsurviving foals, 32 (4.6%) had ulceration of the duodenum, and only 1 of those foals (0.14% of 691) had duodenal involvement alone.[1] Lesions occur primarily in the proximal duodenum and may include erosions, focal ulceration, and diffuse inflammation with or without ulceration. The terms *duodenal ulceration* and *ulcerative duodenitis* may refer to differing clinical manifestations of the same problem, but they are considered the same entity in this section.

The pathophysiology of duodenal ulcer disease in foals is not understood as

well as gastric ulcer disease. The disorder is classically considered to be a peptic disease, similar to that seen in humans, in which damage to the duodenal mucosa results from excessive exposure to hydrochloric acid and pepsin. However, in humans, most cases of duodenal ulcer disease are associated with *H. pylori* infection,[2] whereas *H. pylori* bacteria have not been reported as a major cause of equine gastrointestinal diseases. In addition, in humans the incidence of duodenal ulcer disease increases with age,[3] in contrast to horses, in which duodenal ulcer disease occurs primarily in animals younger than 1 year of age.[4]

Ulcerative duodenitis and inflammation have occurred in geographic clusters (same farm) and in temporal clusters. All affected foals had moderate to severe gastric ulceration and extensive inflammation with varying degrees of erosion or ulceration in the proximal duodenum (see Color Plates 32.10 and 32.11). A similar temporal and geographic association was reported in two cases of ulcerative duodenitis in yearlings.[5] These findings seem inconsistent with a purely peptic insult as the cause for the ulcerative duodenitis. In one report of seven foals with ulcerative duodenitis,[6] lesions typically extended into a large area of the proximal duodenum and were characterized by mucosal necrosis, and areas of affected and more normal-appearing mucosa were often sharply demarcated. In the foals of that report, no common microbial organism other than *E. coli* was identified, and a cause for the ulcerative duodenitis was not determined. In most foals with duodenal disease, the lesions were not focal ulcers but rather appeared as more generalized inflammation. The origin of duodenal disease in foals is probably multifactorial and may involve a combination of breakdown of duodenal mucosal defenses, interaction of gastrointestinal peptides, and possible pathogenic agents.[7]

Clinical Signs.

The signs of ulcerative duodenitis have been classically described like those of gastric ulcer signs but more severe,[8] and in many cases, duodenal and gastric ulcers occur simultaneously. The gastric ulceration is probably secondary to physiologic or anatomic obstruction to gastric emptying, tends to be severe (see Color Plate 32.12), and potentially leads to gastroesophageal reflux, esophagitis and ptyalism. Until the gastric ulceration becomes severe, the primary signs of duodenitis can be nonspecific; they include fever, mild to moderate abdominal discomfort, mild obtundation, and diarrhea.

In general, the sequelae of ulcerative duodenitis are more severe than those of

primary gastric ulceration. Complications of ulcerative duodenitis include duodenal perforation with peritonitis or adhesions, duodenal stricture with complete or partial obstruction (Figs. 32.61 and 32.62), ascending cholangitis and hepatitis, and ascending pancreatitis.

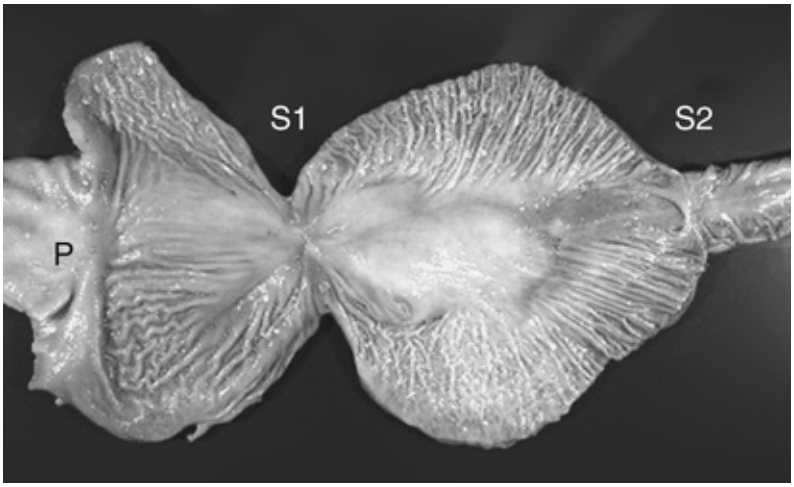


FIG. 32.61 Proximal duodenum of a 10-month-old horse with a history of chronic poor appetite and condition. The pylorus *(P)* is at the left. There are two strictures in the duodenum: *S1* is orad from the major duodenal papilla, and *S2* is aborad from the duodenal papilla. The segment of the duodenum between the strictures is dilated. (Courtesy Dr. M.J. Murray.)

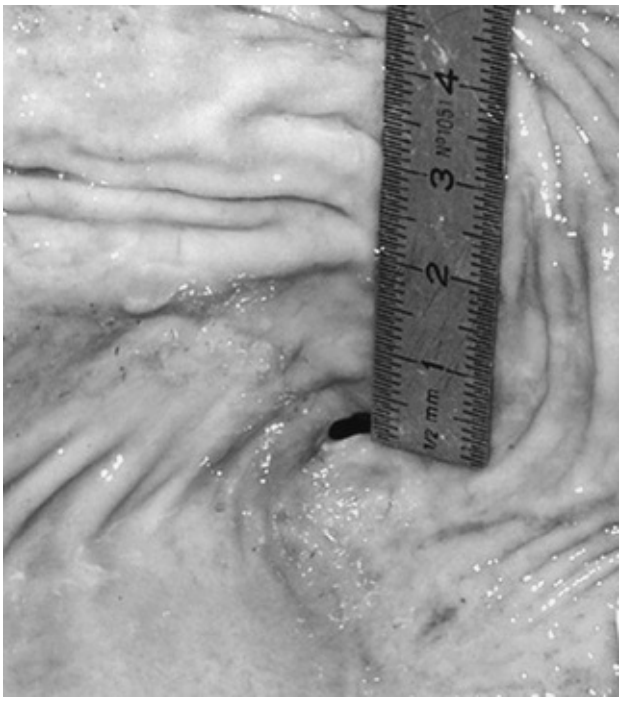


FIG. 32.62 Duodenal stricture *(S1)* in the horse described for Fig. 32.68. The diameter of the duodenal lumen at the stricture is only 3 mm. (Courtesy Dr. M.J. Murray.)

Diagnosis.

Duodenoscopy is the most specific means of diagnosis. An endoscope with at least a 200-cm working length is used in foals up to 6 months of age, and in older foals, a longer endoscope is needed to examine the duodenal mucosa. Because of the size of the stomach and the anatomic configuration of the duodenum in foals, it is usually not possible to advance the endoscope past the duodenal ampulla. Therefore a diagnosis is most readily made when lesions are diffuse or located within the ampulla. Excessive enterogastric reflux of bile through the pylorus is consistent with duodenal dysfunction. Ulceration at the pylorus or pyloric antrum may accompany ulcerative duodenitis and thus provide an indication of potential duodenal involvement.

The peritoneal fluid may show signs of inflammation, infection, hemorrhage, or a combination of these, depending on severity of disease. CBC often reveals peripheral blood leukocytosis and hyperfibrinogenemia. Serum chemistry studies may reveal elevations in liver enzymes, particularly biliary system–associated enzymes (γ-glutamyltransferase [GGT], ALP) and serum bile acids. With severe ulcerative duodenitis, survey radiographs of the cranial abdomen may reveal

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accumulation of fluid within the stomach and gas ascending the biliary ducts.[9] If barium contrast medium is placed into the stomach, complete emptying is usually delayed (>2 hours), and an irregular mucosal border may be noted in the descending duodenum. In most cases, however, radiography would not contribute to a diagnosis of duodenal ulcer per se, although duodenal stricture may be noted. If the descending duodenum is to be imaged, the volume of contrast medium placed in the stomach should not exceed 0.5 to 1 L in a foal and 1 to 2 L in a weanling or yearling; otherwise, the proximal descending duodenum will be obscured by contrast medium within the stomach.

Treatment.

The effectiveness of treatment of ulcerative duodenitis depends on the extent and severity of ulceration and the presence or absence of complications. Treatment objectives are to decrease duodenal inflammation, treat secondary gastric and esophageal ulceration, promote gastric emptying, and treat related problems such as peritonitis. If ulcerative duodenitis is confirmed or even suspected on the basis of clinical signs, treatment should be aggressive.

Inflammation may be an important part in the perpetuation of disease. In acute cases of ulcerative duodenitis, there usually is a pronounced lymphocytic infiltration of the mucosa. In more chronic cases, there is a mixture of neutrophils, macrophages, fibroblasts, and fibrinonecrotic exudate. Definitive antiinflammatory therapy has not been described for these cases, and the use of corticosteroids or NSAIDs is controversial because they may worsen gastric ulcer disease through inhibition of protective prostaglandin synthesis.

Suppression of gastric acid secretion is still an important objective in the treatment of ulcerative duodenitis in foals because most affected foals have gastric ulcers. Initially, acid suppression should be accomplished via parenteral administration of H_2 antagonists (cimetidine, 7 mg/kg IV q6h, or ranitidine, 1.5 mg/kg IV q8h) or proton pump inhibitors (pantoprazole, 1.5 mg/kg IV q24h). Oral medications are unlikely to be adequately delivered to, or absorbed from, the small intestine in the first days of treatment. Gastric emptying can be enhanced with bethanechol (0.02 mg/kg SC q6-8h or, when the foal can consume orally, 0.35 mg/kg PO q8h). In foals that have severe duodenal disease or that have required surgery, bethanechol has been given for up to 3 months. Once the foal can accept oral medication, it should be treated with the proton pump inhibitor omeprazole at a dose of 4 mg/kg orally once daily in the paste formulation. In the 24 hours after the first dose, acid suppression is incomplete,

and maximal suppression of acid secretion is achieved between days 1 and 5.[10] Therefore a common practice is to combine an H_2 antagonist IV for the initial 2 days of treatment with omeprazole in foals with duodenitis.

Misoprostol is a synthetic prostaglandin E_1 analog that has been used successfully in treating ulcerative duodenitis in humans. Doses of 2 to 5 µg/kg q8-12h can be used in horses, although side effects may include abdominal pain and diarrhea. Sucralfate promotes duodenal mucosal healing in humans.[11] The dose of sucralfate that is effective in humans with ulcerative duodenitis ranges from 1 to 2 g two to four times daily. Foals treated for ulcerative duodenitis that do not have impaired gastric emptying should be administered 2 to 4 g of sucralfate three times daily. Sucralfate, however, should not be used as the sole therapeutic agent for ulcerative duodenitis.

Foals with duodenitis must usually be prevented from nursing or eating for 1 to 3 days. During this time, parenteral feeding should be considered. Depending on the age of the foal, administration of parenteral nutrition should provide 40 to 60 kcal/kg/day.

If medical therapy is ineffective or if sequelae of ulcerative duodenitis cause complications, surgical intervention may be required. Gastroenterostomy has been reported to be effective in some cases through bypassing the affected portion of duodenum and allowing for an alternative route for gastric emptying.[9] However, short-term survival and long-term quality of life and use are often unsatisfactory. Patients that have a successful surgical outcome require long-term aftercare and usually require long-term maintenance acid suppression and treatment with a prokinetic drug until gastric emptying is normalized. Therefore an owner should be prepared to make a significant time and financial commitment before surgery is considered.

■ Duodenitis–Proximal Jejunitis

DPJ, also known as *anterior enteritis* or *proximal enteritis*, is a clinical syndrome characterized by inflammation and edema of the duodenum and proximal jejunum, excessive fluid and electrolyte secretion into the small intestine, and, consequently, large volumes of enterogastric reflux. The syndrome of DPJ was first described in 1982[12] and was more fully characterized in 1987.[13] A subsequent report[14] described clinical and clinicopathologic parameters in horses with DPJ that differed somewhat from cases in the 1982 report, which suggests that either the cases were of similar etiopathogenesis but

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of different severity or that the cases were of different etiopathogeneses whose only similarity was the segment of bowel affected. A diagnosis of DPJ is often applied when affected animals exhibit abdominal discomfort, small intestine distention, and excessive enterogastric reflux without obstruction; however, it is unclear whether all of these cases lie along a spectrum of severity of DPJ or whether they are several disease entities that affect the proximal small intestine and that share clinical features. The latter seems more likely.

Pathophysiology.

In horses with DPJ, lesions are consistently found in the duodenum, but the severity and frequency of lesions in the jejunum are variable. Serositis is a consistent finding, characterized by bright red to dark red petechial and ecchymotic hemorrhages on the serosal surface.[13] Histologic lesions include hyperemia and edema of the mucosa and submucosa, villous epithelial degeneration, epithelial cell sloughing, neutrophilic pleocytosis, hemorrhages in the muscular layers, and fibrinopurulent exudation on the serosa.

DPJ causes an increase in the volume of duodenogastric reflux, typically 50 to 100 mL/min. This reflux has been considered to result from increased intestinal fluid secretion and decreased motility. Mechanisms of intestinal fluid secretion include passive transmucosal exudation, secondary to mucosal and submucosal inflammation and characterized by a protein-rich fluid secretion, and active fluid secretion, caused by increased cyclic nucleotides and characterized by fluid with a high electrolyte content and low protein content. The components of fluid in the intestines of horses with DPJ have not been characterized, but they probably result from a combination of passive and active secretion. In some horses the hemorrhagic nature of the gastric reflux implies increased capillary permeability of the duodenal mucosa, whereas in other horses the watery nature of the reflux, the presence of serum electrolyte disturbances,[15] and the absence of peripheral hypoproteinemia are most consistent with an active secretory process.

Another potential source of the large volume of fluid secreted into the proximal small intestine and flowing back into the stomach is the pancreas. Normally there is periodic orad movement of duodenal contents into the stomach, which has been observed endoscopically and has been documented by collecting gastric contents with and without pyloric obstruction.[7] The duodenal contents have a large component of water, sodium, and bicarbonate, as well as bile salts from the liver. These secretions are presumed to originate from the pancreas, as well as the liver, and pathologic features of either of those organs

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may contribute to the pathophysiologic manifestations in cases of DPJ.

Suppurative cholangiohepatitis has been reported in cases of small intestinal inflammation secondary to DPJ.[16,17] The pathophysiologic origins of this observation may be related to an increased luminal pressure in horses with DPJ, which increases the likelihood of intestinal content regurgitation into the bile ducts. It is also possible that horses with DPJ absorb inflammatory mediators or bacterial products from the small intestine via the portal blood flow or systemic circulation.

Although the exact cause of DPJ is not known, several bacteria and toxins have been implicated. *C. difficile* has been frequently implicated in causing the disease. One prospective study cultured toxigenic species of *C. difficile* from the reflux of all 10 horses with a diagnosis of DPJ and only 1 of 16 horses with diagnoses of other causes of nasogastric reflux. Of the strains cultured, those in 8 of the 10 horses with DPJ produced both A and B toxins, whereas the those in the remaining 2 produced only toxin B.[18] This is significant in that toxin B may cause inhibitory electromechanical disturbances to smooth muscle in the small intestine, which may be a possible cause of ileus in these horses.[19] Toxin A has also been shown to promote inflammatory cell infiltration into the smooth muscle layers.[20] Influx of neutrophils and release of inflammatory mediators in the intestinal wall activate nitric oxide pathways, which results in inhibition of the enteric nervous system, increases in sympathetic tone, and a subsequent reduction of contractile activity in the gut.[21] Experimental intraduodenal inoculation of crude *C. difficile* toxins in fasting horses resulted in clinical signs of DPJ in 33% of cases; however, all cases had histopathologic changes consistent with DPJ.[22] *C. difficile* can also be cultured from the proximal intestinal tract in horses without evidence of gastrointestinal disease, however, and these strains can produce both toxin A and B.[23] *C. perfringens* and *Salmonella* spp. have also infrequently been associated with DPJ, but the significance of these pathogens remains unknown.

Feeding practices may be associated with the development of DPJ. In one study, horses with DPJ were fed significantly more concentrate and were significantly more likely to have grazed on pasture than were horses with other types of colic or horses with lameness.[24] This may indicate that these horses are exposed to some type of toxin or infectious agent through different types of feed. *Fusarium moniliforme* has been cultured from the feed of horses with naturally occurring DPJ. Under experimental conditions, *F. moniliforme* producing

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fumonisin B1 mycotoxins also caused lesions consistent with DPJ in two horses.[25] Neurologic lesions were present in those horses, however, and both died with lesions consistent with equine leukoencephalomalacia. Cantharidin toxins can also cause reddening of the mucosa in the small intestine, as well as excessive gastric reflux,[26] and may be a cause of DPJ in some cases. It is possible that this one syndrome has multiple initiating causes and that no one causative agent will ever be definitively identified.

Clinical Signs and Differential Diagnosis.

The differential diagnosis for DPJ includes simple or strangulating small intestinal obstructions. Differentiation can be extremely difficult in some cases and may delay surgical intervention in cases of small intestinal obstruction, to the detriment of the patient. The criteria used to discriminate between DPJ and obstructive lesions include degree of pain after reflux, presence of fever, and changes in hematologic parameters and abdominal fluid.

Horses with DPJ have a history of acute-onset moderate to severe abdominal pain, often followed by varying degrees of depression. Nasogastric intubation yields a large volume of enterogastric reflux, which is frequently orange-brown in color, with a fetid odor. Rectal palpation reveals multiple loops of mild to moderately distended small intestine. The initial volume of reflux may range from as little as 4 to 5 L to as much as 32 L. The duration of the reflux may be as short as 24 to 48 hours, but it usually lasts 3 to 7 days. Many affected horses are febrile (rectal temperature higher than 38° C [101° F]) and dehydrated and have injected mucous membranes, prolonged capillary refill time, diminished intestinal sounds, tachycardia (>60 beats/min), and tachypnea.[12-15,27,28] Horses with DPJ also tend to have a higher incidence of gastric ulceration than do horses with abdominal pain secondary to other causes.[29] Although abdominal pain usually abates after gastric decompression, most affected horses remain depressed, which perhaps is the most consistent and characteristic clinical sign of the disease. If the fluid that accumulates in the proximal intestinal tract is not removed periodically, signs of abdominal pain recur.

Assessments of the degree of small intestine distention and the thickness of the intestinal wall can be useful indicators. Many horses with DPJ have generalized distention of small intestine, but when palpated rectally, the intestine does not feel taut. In many cases of small intestinal obstruction, the bowel is tightly distended on palpation, but this is not universally true. Ultrasonography

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can be used, both transrectal and transabdominal, to determine the diameter of the small intestine, evaluate contractions, and measure the thickness of the wall of the intestine. With acute obstruction, several segments of small intestine that are 6 to 10 cm in diameter, have no contraction, and have a wall diameter of 3 to 5 mm are visible. With DPJ, small intestinal diameter may be less, and the thickness of the intestinal wall may exceed 6 mm.

Culture of the reflux for *Clostridium* and *Salmonella* spp. can be attempted. This can be difficult, however, given the special conditions required for anaerobic cultures, as well as the intermittent shedding of *Salmonella* spp. into the gastrointestinal tract of normal horses. Also, the large volume of reflux in these cases may dilute the bacterial population to the point at which isolating low numbers of bacteria is difficult.

Clinicopathologic Findings.

Clinical laboratory findings include increased PCV and total plasma proteins (hemoconcentration). Abdominocentesis often reveals an elevated total protein concentration in peritoneal fluid and a mild to moderate increase in the peritoneal WBC count (>5000 cells/μL).[27] The peritoneal fluid is usually yellow and turbid, but in severe cases, diapedesis of RBCs occurs, which results in a serosanguineous color. In abdominal fluid, a total protein concentration above 3.5 g/dL is associated with a poorer prognosis.[27] The WBC count in the peripheral blood may be normal, increased, or decreased.[13,14] In addition, hypocalcemia, hyponatremia, hypochloremia, hypokalemia, and acid-base alterations have been reported in horses with DPJ.[15] An elevated anion gap may be present, secondary to either decreased calcium and magnesium concentrations or increased lactate or albumin concentrations.[27] Increases in the anion gap to 15 mEq/L or higher have also been associated with a poor prognosis. Horses with enteritis have been found to have higher plasma D-dimer concentrations and more severe coagulopathies on admission than do horses with other types of colic.[30]

Activity of liver enzymes, particularly GGT, may be elevated in horses with DPJ, and such elevation may be a useful way to help differentiate between DPJ and strangulating lesions of the small intestine.[16,17] According to a retrospective study of a large series of DPJ cases to determine the prevalence of hepatic damage in horses with small intestinal inflammation, horses with DPJ had significantly higher hepatic enzyme activities than did the control group of

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horses with small intestinal strangulating obstruction (SISO).[17] More than 50% of horses with DPJ had biochemical evidence of hepatic disease (high GGT, aspartate aminotransferase, or ALP activity). In addition, horses with DPJ had a 12.1-fold higher risk of having high GGT activity and a 1.8-fold higher risk of having high aspartate aminotransferase activity than did horses with SISO. Aspartate aminotransferase activity in horses with proximal enteritis ranged from 133 to 2994 IU/L (reference range, 215.8 to 365 IU/L), GGT levels ranged from 7 to 117 IU/L (reference range, 6.2 to 19.1 IU/L), and ALP levels ranged from 86 to 1103 IU/L (reference range, 69.4 to 293.7 IU/L). Bile acid concentrations were rarely abnormal, which indicates that hepatic failure was uncommon. Histopathologic evidence of liver disease was a common biopsy and necropsy feature in the horses with proximal enteritis. Centrilobular necrosis and inflammation were noted in some cases.

Treatment.

Because the causative agent or agents of DPJ are unknown, treatment remains empirical and consists of aggressive supportive therapy. The continuous production of enterogastric reflux necessitates gastric decompression every 1 to 2 hours to relieve pain and to prevent gastric rupture. The stomach should be decompressed frequently, regardless of whether the horse is showing signs of abdominal pain, as these signs may be masked by severe depression or the administration of analgesic or antiinflammatory medications. Horses should receive nothing by mouth until small intestinal function has returned, recognized clinically by cessation or reduction of the nasogastric reflux to 1 to 2 L over a 4-hour period and increased frequency of borborygmi. The time necessary for gastric decompression varies with each patient. Repeated rectal examinations after the first day of therapy inconsistently reveal distended loops of small intestine, depending on the frequency of removal of the reflux and the severity of the initial lesion. Ultrasonography may reveal fluid-filled small intestine when the bowel is not discernible by rectal palpation. Loops of small intestine are most frequently visualized in the ventral flank area, near the udder or prepuce; therefore this area should be examined in all cases of suspected small intestine distention.

Intravenous administration of a balanced electrolyte solution is necessary to maintain intravascular fluid volume and cardiovascular performance. In some horses even rapid administration of fluid fails to adequately restore and maintain intravascular volume because of enteric fluid losses that can be as great as 8 L

per hour. In addition, the very large volume of isotonic crystalloid fluid that must be given intravenously to keep pace with enteric fluid losses in horses with DPJ may accelerate the flux of fluid from the vasculature into the intestinal lumen because of reduced intravascular oncotic pressure, increased capillary perfusion pressure, and increased capillary permeability in the inflamed intestine. Consequently, the balance between adequate hydration and the volume of enterogastric reflux obtained requires careful and frequent monitoring.

Administration of colloid solutions may be of benefit in preserving intravascular volume without promoting enterogastric reflux. The colloids most frequently used in horses include hyperimmune plasma and hetastarches. Plasma products require a large volume of administration to exert a colloidal effect, which is cost prohibitive in many cases. Smaller doses, however, may have a beneficial effect in horses with DPJ, particularly in animals showing signs of sepsis or endotoxemia. Hetastarches have been shown to significantly increase plasma oncotic pressure in ponies administered 10 mL/kg[31] and represent a reasonably priced alternative to plasma. These solutions have been associated with changes in the hemostatic profile in normal ponies at higher doses[32] and should be used with caution only in horses already at risk for coagulopathies, particularly with the higher-molecular-weight formulations.

During the initial hours of therapy, even aggressive intravenous fluid administration may result in only moderate clinical improvement. A positive clinical response—as evidenced by improved hydration status, decreased heart rate, decreased enterogastric reflux, improved attitude, and improvement in parameters reflecting kidney function (decreased blood urea nitrogen [BUN] and serum creatinine levels)—is correlated with resolving intestinal inflammation.

NSAIDs should be used judiciously to prevent the masking of the clinical signs of a potential surgical lesion. Flunixin meglumine can be used at a dose of 0.25 to 0.5 mg/kg PO every 6 hours to reduce the untoward effects of arachidonic acid metabolites.

Antimicrobial agents are typically administered to horses with DPJ, although the necessity for antimicrobial treatment in horses with DPJ is uncertain. Because of the association of DPJ with *C. difficile*, administration of intravenous penicillin G sodium or potassium (22,000 to 44,000 IU/kg IV q6h) is warranted. Metronidazole also has excellent activity against *C. difficile;* however, administration is difficult because nothing can be administered orally. Rectal administration of metronidazole has been studied[33] and can be used in these cases. The dose and frequency of administration should be increased because

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bioavailability after rectal administration is much less than after oral administration (30% vs. 74%, respectively). Broad-spectrum antimicrobial treatment may be indicated in horses with low WBC counts, but care must be taken in selecting an antimicrobial to avoid potential adverse effects, particularly nephrotoxicosis with aminoglycosides in a dehydrated patient with compromised renal function.

Horses with DPJ may have to be kept from eating for several days and are often in a hypermetabolic state; therefore they rapidly develop a negative energy and nitrogen balance. In these horses, parenteral nutritional support should be considered. Parenterally administered solutions containing glucose, balanced amino acid solutions, lipid emulsions, balanced electrolyte and trace minerals, and vitamins have been administered to adult horses with a variety of intestinal disorders, including DPJ. Part of a horse's nutritional requirements (8000 to 12,000 kcal/day) can be provided with glucose–amino acid solutions that are of moderate cost. The rationale for this treatment is that through provision of nutritional support to an anorexic, severely ill horse, the healing process is facilitated, complications are minimized, and the duration of hospitalization may be shortened. Thus the overall cost of providing nutritional supplementation, enteral or parenteral, to horses with DPJ may well be offset by quicker recoveries and diminished requirements for other costly treatments.

Prokinetic agents may also be useful in cases of DPJ. Of the available prokinetics, lidocaine is used most frequently.[34] A slow intravenous loading dose of 1.3 mg/kg in a bolus, followed by a continuous infusion of 0.05 mg/kg/min, has been shown to shorten the time of reflux and shorten the hospital stay of horses with DPJ.[35] It may do this by decreasing sympathetic tone, acting as an analgesic agent, affecting ion channels, or decreasing granulocyte infiltration in the intestinal wall. Its use should be reserved for horses in which a surgical lesion has been ruled out because it can effectively mask intestinal or foot pain. Horses should be refluxed frequently during the infusion and checked for other signs of complications, such as laminitis, routinely. Metoclopramide, erythromycin lactobionate, and cisapride are also used in cases of DPJ.[34] The efficacy of prokinetics in this disease is debated, mainly because the intestine must be healthy in order for the drugs to exert an effect. A more in-depth discussion of prokinetic agents can be found in the Gastrointestinal Ileus section.

Medical therapy is sufficient in most cases of DPJ; however, surgical exploration is sometimes necessary for definitive diagnosis; if horses show uncontrolled pain, have prolonged nasogastric reflux (>7 days), or have

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excessive fluid losses that cannot be corrected with conventional fluid therapy; or if clinical and laboratory findings are strongly suggestive of an intestinal obstruction. Retrospective comparisons of medical and surgical therapy of DPJ showed that in surgical cases, survival rates were significantly decreased and the nasogastric reflux lasted longer and continued in larger total volume. The horses in surgical cases were also more likely to develop complications such as diarrhea and showed a higher rate of incisional infection than did horses that underwent surgery for other types of colic.[36]

Complications.

Complications of DPJ include septic peritonitis, cholangiohepatitis, myocardial and renal infarction, aspiration pneumonia, adhesions of the proximal small intestine, and laminitis. In severe cases of DPJ, a segment of the small intestine may become infarcted, which necessitates surgical removal. The prognosis for surviving the initial intestinal insult is good in cases of DPJ. Death and function losses from this disease are more commonly related to the secondary complications such as laminitis and intraabdominal adhesions. In one report, laminitis occurred in 28% of horses with DPJ, and associated factors were high body weight and hemorrhagic gastric reflux.[37] Laminitis prophylaxis is routinely incorporated into the medical therapy and can include cryotherapy, NSAIDs, topical glyceryl trinitrate, and DMSO (200 mg/kg given as a 10% solution in normal saline). In one study, horses that received heparin as a prophylactic treatment for laminitis were less likely to develop clinical laminitis than were horses that did not receive heparin.[37]

■ Equine Proliferative Enteropathy

Nicola Pusterla

Equine proliferative enteropathy (EPE) is a disease of foals caused by the obligate intracellular organism *L. intracellularis.* It affects mainly weanling foals and occasionally young adult horses and is characterized by fever, lethargy, peripheral edema, diarrhea, colic, and weight loss. The diagnosis of EPE may be challenging and relies on the presence of hypoproteinemia resulting from hypoalbuminemia, thickening of segments of the small intestinal wall observed on abdominal ultrasonography, positive serologic findings, and molecular detection of *L. intracellularis* in feces. The disease occurs almost worldwide and has been reported in the United States, Canada, Europe, South Africa, Australia,

Brazil, and Japan.[38-42]

Epidemiology.

In pig populations, the chronic form of the disease is maintained by subclinically affected pigs or is established environmentally in some sites, allowing transmission of *L. intracellularis* to serial flows of pigs.[43] Mice and rats have been shown to be important reservoirs of *L. intracellularis* on pig farms; prevalences of animals with positive PCR assay results vary substantially between farms (4% to 83%).[44,45] Rodents appear to be suitable reservoir hosts because of their susceptibility to *L. intracellularis,* their close contact with domestic animals, and their high reproductive rate, and they maintain *L. intracellularis* across generations. The source of infection has not been determined for horses. Exposure to pig feces has been speculated as a potential source of infection for horses since cases of EPE were first reported. However, in most cases of EPE, no history or evidence of direct or indirect exposure to pigs or pig feces has been reported. Moreover, multilocus variable-number tandem repeat profiles of pig and equine isolates differ greatly. One experimental study demonstrated host specificity for *L. intracellularis* isolates cultured from pig or horse intestines.[46] The study showed that clinical signs, longer periods of shedding, and stronger serologic immune responses were observed in animals infected with species-specific isolates. Previous studies showed that a variety of wild and domestic animals (including dogs, cats, rabbits, opossums, skunks, mice, and coyotes) can shed *L. intracellularis* on farms with diagnosed EPE cases.[47,48]

Fecal-oral transmission of *L. intracellularis* has been documented in naive foals housed with foals clinically infected with an equine isolate of *L. intracellularis*.[49] One study showed that feces from rabbits experimentally infected with an equine isolate of *L. intracellularis* served as infectious material for weanling foals.[50] Although infected rabbits and foals remained asymptomatic, infection was supported by fecal shedding of *L. intracellularis* and detection of specific antibodies to *L. intracellularis*. Although the natural infectious dose for foals has not been determined, pigs receiving as low as 10^5 *L. intracellularis* organisms have been shown to develop infection.[51]

In piglets, large group size, weaning, transportation, diet change, and mixing have been associated with clinical disease. Predisposing situations such as the stress of weaning, overcrowding, decline in *L. intracellularis*–specific colostral

antibodies, endoparasitism, and introduction of new animals have been suggested as factors in the development of EPE in foals.[38] In pigs, infection and fecal shedding of *L. intracellularis* may persist for as long as 12 weeks.[51] This is in sharp contrast to experimentally infected foals, which show onset and duration of fecal shedding ranging from 10 to 14 days and 17 to 27 days, respectively.[49] Previous work has shown that *L. intracellularis* is likely to survive in environmental conditions for 1 to 2 weeks at 5° C to 15° C.[52]

Pathophysiology.

The mechanism of enteritis after infection with *L. intracellularis* involves invasion of the proliferating crypt cells in the ileum, causing excessive mitotic division and severe hyperplasia.[53,54] The hyperplastic mucosa becomes grossly thickened and develops a corrugated appearance. As would be expected, this thickening of the mucosa, along with the proliferation of immature crypt cells rather than mature villous cells, leads to a limited brush border development and a decreased absorptive capacity, which results in the weight loss and hypoproteinemia characteristic of these cases. The organism can divide within the infected cells and migrate up to the mucosal layers as the cells proliferate and advance. The differential diagnosis in these cases mainly includes *R. equi* enteritis, which can also cause ulceration in the areas of Peyer patches throughout the small intestine, cecum, and colon.

Clinical and Laboratory Findings.

EPE manifests in characteristic signalment, seasonality, clinical signs, and blood work abnormalities. The disease is generally manifested in foals younger than 1 year of age and, in North America, often between August and February.[39] Although the disease is common in weanling foals 4 to 7 months of age, cases of EPE have been seen in young adult horses.[42] Lethargy, anorexia, fever (>38.5° C), peripheral edema (ventrum, sheath, throatlatch, and distal limbs), weight loss, colic, and diarrhea are among the most common clinical findings in affected foals. Early clinical signs are generally unspecific and include mild depression, partial anorexia, and fever. Although diarrhea is common in affected foals and the character can vary from cow pie to watery, some affected foals produce normal feces. Fatal necrotizing enteritis associated with *L. intracellularis* has been reported in foals that developed acute onset of clinical signs, followed by rapid clinical deterioration and death caused by endotoxemia,

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bacteremia, or disseminated intravascular coagulation.[55]

Foals with EPE may also have concurrent disorders such as respiratory tract infections, gastric ulcerations, and intestinal parasitism. Signs of EPE may resemble those of more common gastrointestinal disorders such as parasitism, bacterial infections *(Clostridium* spp., *Salmonella* spp., *R. equi*, *N. risticii),* rotavirus, coronavirus, ulcerations, sand accumulation, intestinal obstruction, and intoxication with plants, chemicals, and pharmacologic agents such as NSAIDs or antimicrobials. As in pigs, the disease can be subclinical in foals and be manifested by a self-limiting and transient decrease in total serum protein concentration, coupled with decreased daily weight gain, in comparison with unaffected foals.[49] It remains to be determined whether growth retardation or unthriftiness are associated with subclinical infection.

The most consistent laboratory finding of clinical EPE is hypoproteinemia resulting from hypoalbuminemia. Total protein concentration is generally less than 5.0 g/dL, and albumin concentration is usually less than 2.0 g/dL. In one case report, hypoalbuminemia was the only consistent clinicopathologic abnormality of 57 affected foals; albumin concentrations ranged from 0.9 to 3.3 g/dL (normal reference range, 2.7 to 4.2 g/dL).[39] The exact mechanisms by which hypoalbuminemia develops in affected foals have not been investigated. It appears that decreased feed intake, coupled with malabsorption and protein-losing enteropathy resulting from the proliferative nature of the disease, may explain why albumin levels are low.[56] Affected foals may also demonstrate nonspecific blood abnormalities such as anemia or hemoconcentration, leukocytosis or neutropenia, hyperfibrinogenemia, increased activity of muscle enzymes, and electrolyte abnormalities (hypocalcemia, hypochloremia, and hyponatremia). Urine analysis to rule out protein-losing nephropathy and cytologic evaluation of abdominal fluid to rule out protein lost to a third space yields generally unremarkable results.

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Diagnostic Workup.

A presumptive diagnosis of EPE is generally based on age of the affected animal, clinical signs, hypoproteinemia/hypoalbuminemia, presence of thickened loops of small intestine on ultrasonographic evaluation, and absence of other causes of enteropathy and protein losses. Abdominal ultrasonography, although not very sensitive, may show segments of thickened small intestine and excessive abdominal fluid. In these cases, abdominocentesis yields a noninflammatory transudate. An antemortem diagnosis is generally confirmed through PCR detection of *L. intracellularis* in feces or rectal swab or serologic findings.

It is essential to perform both molecular and serologic diagnostic testing because these modalities have high analytical specificity but variable sensitivity, depending on the situation. Negative PCR results can be expected if the fecal samples are collected from foals that have received prior antimicrobial treatment or those in an advanced disease stage, when *L. intracellularis* organisms are no longer expected in the feces. Negative serologic results can be expected in the early stage of the disease, when humoral immune responses are not yet strong enough to be detectable by serology. Moreover, differences in sensitivity among different PCR and serologic assays can lead to divergent results. Among PCR assays, the use of a real-time platform has been shown to yield the best sensitivity and to reduce the likelihood of crossover or carryover contamination (i.e., false-positive results).[57-59] Several serologic assays, including indirect fluorescent antibody test, ELISA, and immunoperoxidase monolayer assay, have been validated and established for pigs.[60-62] A comparative study with equine serum samples has shown that various serologic assays yield accurate results; however, the immunoperoxidase monolayer assay is the most specific in determining the presence of anti–*L. intracellularis* antibodies in adult horses with EPE.[63]

Pathologic Findings.

Lesions are most frequently found in the distal jejunum and ileum, although diffuse thickening of the small intestine may occur.[53] A classical finding is pronounced mucosal thickening with varying severity of ulceration and transmural edema. The affected bowel appears to be stiff, and the mucosal surface has a corrugated appearance. Mucosal pleocytosis is a common feature,

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but in different cases the predominating inflammatory cell type differs. A lymphocytic or plasmacytic cellular infiltration may be present. Crypt proliferation is accompanied by crypt elongation and epithelial hyperplasia. The villi are blunted and may become fused. Silver staining with Warthin-Starry stain reveals elongated, curved bacilli in the apical zone of the crypt epithelial cells.

Treatment.

It is important to treat affected animals early, before lesions become advanced and result in marked weight loss and critically low serum protein values. Treatment of EPE in horses involves the use of antimicrobials such as macrolides, alone or in combination with rifampin, chloramphenicol, oxytetracycline, doxycycline, or minocycline, administered for 2 to 3 weeks. The choice of antimicrobial in the treatment of EPE should account for the risk of inducing disturbance of the gastrointestinal flora and renal toxicity. This is especially a concern in treating older foals with severe hypoalbuminemia. Supportive therapy with crystalloid fluids is necessary to correct dehydration, electrolyte imbalances, and azotemia secondary to fluid losses from profuse diarrhea. Colloidal support with plasma or hetastarch can help correct the edema and decreased colloid oncotic pressure. NSAIDs should be used with caution in foals showing signs of dehydration.

The prognosis in these cases is generally good with early and correct diagnosis of the problem. Therapy can be prolonged and should be continued until the diarrhea and hypoproteinemia have resolved and there is no longer evidence of thickened small intestine on ultrasonography.

Concurrent medical conditions should also be addressed. Clinical improvement after treatment is rapid; however, it may take weeks for the hypoproteinemia to resolve. Spontaneous recovery of clinically infected foals has not been documented, and up to 93% of treated foals survive the disease.[39] In general, nonsurvivors develop complications associated with gastrointestinal translocation, gastrointestinal perforation, or kidney failure.[55] Frazer reported that clinically affected and successfully treated foals sold for an average of 68% of the average price of unaffected foals by the same stallion.[39] However, their monetary earnings from racing were not significantly different from those of other horses.[64]

Monitoring and Prevention.

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Early recognition of clinical cases and separating affected animals from the rest of the susceptible foals until full recovery or cessation of fecal shedding appears to be a logical biosecurity measure to prevent spread and environmental contamination. The monitoring of a herd with endemic EPE status includes the regular physical evaluation of resident foals and the monthly or bimonthly assessment of total protein concentration and monthly serologic status. Monitoring for exposure to *L. intracellularis* and hypoproteinemia/hypoalbuminemia should begin at least 4 weeks before the historical first detection of clinical cases.

Because of the lack of epidemiologic data regarding potential natural reservoir hosts, as well as the lack of information pertaining to the biological processes of *L. intracellularis*, management changes should not be made on endemic farms. Moreover, maintaining good pest control and preventing nonequine domestic and wild animals from obtaining access to feed and feeding areas may potentially minimize the risk of disease spread.

Prevention strategies have been best described in pigs with in-feed antimicrobials and a commercially available *L. intracellularis* vaccine.[65-67] Detectable humoral and cellular responses can be measured in foals administered an avirulent live *L. intracellularis* vaccine.[68,69] The *L. intracellularis* vaccine has been shown to be safe and its administration well tolerated by the foals. A field efficacy trial performed on EPE-endemic farms in central Kentucky in 2008 showed that vaccinated foals maintained higher daily weight gains and higher total protein concentrations than did a nonvaccinated, naturally seroconverted group.[70] Under experimental conditions, weanling foals vaccinated intrarectally with an avirulent live vaccine against *L. intracellularis* were protected against clinical and subclinical EPE after challenge exposure with a virulent *L. intracellularis* isolate of equine origin.[71] This was determined by lack of clinical disease, absence of hypoproteinemia and ultrasonographic abnormalities compatible with EPE, and a significant reduction in *L. intracellularis* fecal shedding in vaccinated foals in comparison with nonvaccinated foals. Moreover, average daily weight gains from the vaccinated foals over the entire study period were similar to those of the control foals and significantly higher than those of the nonvaccinated foals, which highlights the benefit of the vaccine in the prevention of subclinical disease. The extralabel use of the *L. intracellularis* vaccine should be considered on EPE-naive and endemic farms in an attempt to reduce or prevent EPE. Timing of vaccine administration should again be synchronized with historical disease occurrence. Moreover, routine monitoring

for clinical signs and hypoproteinemia/hypoalbuminemia is still recommended even when vaccine prophylaxis is used.

■ *Rhodococcus equi* Enteritis

R. equi most frequently causes a severe pyogranulomatous pneumonia in foals 2 to 3 months of age. Extrapulmonary disorders have been associated with *R. equi* infection in foals, and the presence of these disorders is associated with an increase in mortality. Extrapulmonary disorders of the gastrointestinal system may occur in as much as 50% of cases. Diarrhea is reported to occur in up to 33% of *R. equi* cases. In one study of 150 affected foals, enterocolitis and typhlitis were reported in 31, intraabdominal abscesses in 25, abdominal lymphadenitis in 25, and septic peritonitis 11.[72]

Pathophysiology.

Intestinal infection with *R. equi* can occur through either fecal-oral transmission or swallowing of infected sputum. The organism invades and reproduces within the macrophages, causing a pyogranulomatous disease. In a survey of normal foals on two different farms, *R. equi* was shed in the feces of 16 of 17 and 19 of 26 foals, respectively.[73] Only 2 foals developed clinical signs of intestinal disease, and the shedding of bacteria in the feces increased threefold to fourfold during those times. Such foals, as well as adults, are probably the source of repeated contamination on endemic farms. The organism's ability to cause disease is based on the presence of virulence factors, particularly virulence-associated protein A (VapA), which has been most commonly associated with disease in pneumonic foals.

Clinical and Laboratory Findings.

Foals diagnosed with *R. equi* enteritis typically manifest the signs of pneumonia first, although foals in which the enteric form is the major pathologic process have been reported.[74] With the enteric form of the disease, diarrhea, weight loss, and colic are present. Many affected foals are febrile, anorexic, and depressed. Typical clinicopathologic findings include leukocytosis with neutrophilia and severe hyperfibrinogenemia. Ultrasonography of the abdomen may reveal pyogranulomatous abscesses in the lymph nodes.

A diagnosis of *R. equi* enteritis can be presumed in pneumonic foals showing signs of gastrointestinal disease for which cultures of transtracheal wash fluid

yield positive results for *R. equi*. *R. equi* can also be cultured from the feces, small intestinal luminal contents, or, occasionally, the peritoneal fluid of affected animals. A PCR based on the *vapA* gene has been developed and can be used as an adjunct diagnostic tool in these cases.[75]

Pathologic Findings.

The most common small intestinal lesion is multifocal ulcerative enteritis in the area of the Peyer patches of the ileum. Other parts of the small intestine may be affected, with lesions present throughout the entire small intestine.[75] These lesions frequently extend into the cecum and colon as well. A suppurative exudate is also present, along with pyogranulomatous inflammation of the mesenteric lymph nodes. Co-infection with *L. intracellularis* has also been reported to occur.[76]

Treatment.

Treatment of *R. equi* enteritis is similar to treatment of *R. equi* pneumonia. Erythromycin estolate (25 mg/kg PO q6-8h) or erythromycin phosphate (37.5 mg/kg PO q12h) combined with rifampin (5 to 7.5 mg/kg PO q12h) has been the traditional treatment for these foals, and it is still effective but requires a longer duration of treatment and is difficult for owners to administer because of the frequency of the treatments. Alternative treatments include azithromycin (10 mg/kg PO q24h for 5 days, followed by q48h) and clarithromycin (7.5 mg/kg PO q12h), with or without rifampin. To prevent relapses, it is very important to continue treatment until the hematologic abnormalities and radiographic or ultrasonographic examinations have returned to normal.

Complications.

Complications associated with *R. equi* enteritis include septic peritonitis and the development of intestinal adhesions. These may lead to death of affected animals or chronic abdominal problems in those that survive. Therapy is often prolonged in these cases, and owners should be warned that foals with extrapulmonary disorders associated with *R. equi* pneumonia have a more guarded prognosis.[72]

■ Enteric Pythiosis

Pythium spp. are protistal organisms that belong to a group of phycomycotic organisms that also includes *Conidiobolus* and *Basidiobolus* spp. They are a

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frequent cause of severely pruritic cutaneous granulomas in horses along the Gulf Coast and southern United States. Much less frequently, the disease can cause granulomatous lesions in the small intestine.

Pathophysiology.

Pythium spp. are presumed to be transmitted via contact with contaminated water. Once ingested, the organisms are thought to penetrate the intestinal mucosa through an existing lesion because necrotic tissue is considered chemotactic.[77] *Pythium* spp. may be able to penetrate healthy tissue, however, because some cases in dogs have been reported to have mesenteric lymph node involvement without any mucosal lesions.[78]

Clinical and Laboratory Findings.

Four reports of equine enteric pythiosis can be found in the literature.[79-82] In all cases, masses occurred in the middle to distal sections of the jejunum. One horse died suddenly, one was euthanized during surgery, and two were successfully treated with a jejunal resection. Organic iodide therapy was instituted in one horse postoperatively for 30 days. In three cases, clinical signs of intestinal disease had been present for several months before diagnosis. Chronic colic, weight loss, inappetence, and ill thrift have all been reported and could be related to the intestinal lesion. None of the reported animals had skin lesions. Hematologic evaluation was nondiagnostic in the three cases in which it was performed.

On gross examination, lesions appear caseous with discrete yellow foci (“kunkers”), and the intestinal wall is thickened because of a pyogranulomatous inflammation. On microscopic examination, a diffuse, mixed inflammatory infiltrate, along with granulation tissue, is found in the submucosa, tunica muscularis, and mesenteric attachments. Culture of the organism from these lesions is difficult; however, an indirect immunoperoxidase technique to stain for *Pythium*-positive hyphae is available in some laboratories.[81] Serologic testing for *Pythium* in canine and equine cases is available; however, it has been validated only for cutaneous disease in horses.

Treatment.

Treatment of phycomycetes is often difficult. They are not true fungi; therefore they are resistant to many antifungal drugs. Systemic amphotericin B is only

rarely effective in treating the cutaneous disorder. Organic iodides are inexpensive and safe when administered orally, but the mechanism of action as antimicrobial drugs is not understood, and the efficacy of this compound to treat this disease has not been proven. A vaccine can be formulated against the organism, and this has been shown to shrink the lesions in horses with cutaneous disease. Its efficacy against enteric disease is unknown at this time. In addition, premortem or presurgical diagnosis of the disease is extremely difficult, and so surgical resection with biopsy are the most effective treatment.

■ Inflammatory Bowel Disease

Several intestinal disorders characterized by inflammatory cell infiltration have been placed under the umbrella of IBD, including granulomatous enteritis, multisystemic eosinophilic epitheliotropic enterocolitis, eosinophilic enterocolitis, lymphocytic-plasmacytic enteritis, and basophilic enterocolitis.[83-89] IBD in humans is typically characterized by a neutrophilic inflammation, but neutrophils are only the effector cell in a highly complex disease process.[90] The syndromes described for equine inflammatory intestinal disorders therefore appear to differ from those of human IBD; because of the different types of cellular infiltrates found in affected horses, these disorders presumably reflect different pathophysiologic mechanisms. Thus use of the term *inflammatory bowel disease* is not intended to imply either a similarity to the condition described in human beings or similarity among the various syndromes described in horses.

Clinical and Laboratory Findings.

Horses with IBD typically have progressive weight loss despite a good appetite and have intermittent abdominal discomfort. If the disease predominates in the small intestine, diarrhea may not be a feature. In some cases, associated dermatitis is present.[91] Affected horses often present with peripheral edema secondary to hypoproteinemia from enteric protein losses. Ultrasonographic examination may reveal thickened walls of the small intestine (>5 mm in diameter).

Clinicopathologic abnormalities may include anemia, hypoalbuminemia, hypoproteinemia, and malabsorption of glucose and D-xylose. The results of a glucose tolerance test were abnormal in 70% of cases in one report.[92] Hypoalbuminemia in the absence of proteinuria or severe liver dysfunction is

consistent with protein-losing enteropathy. Some horses may have a relative gammopathy. Serum electrolyte concentrations and total CO_2 levels are usually normal. Subclinical disseminated intravascular coagulation with thrombocytopenia and increased fibrinogen degradation products have been identified in horses with chronic enteritis.[86,93] Serum antibodies to gluten have been detected in horses with IBD, as well as in those on a gluten-rich diet.[94] This suggests a potential pathogenic role of gluten in at least some cases of equine IBD, and dietary changes may play an important role in treatment.

In most affected horses, cellular infiltration can be found to varying degrees throughout the intestinal tract. Therefore rectal mucosal biopsy may be useful for identifying cases of IBD in horses.[95] If the proximal duodenum is involved, endoscopic biopsies can be used for diagnosis (Fig. 32.63). A definitive diagnosis often requires biopsy of the small intestine, large intestine, or both. With appropriate instruments, this can be done through laparoscopy, although an exploration via a ventral midline approach enables a more thorough evaluation of the abdomen.

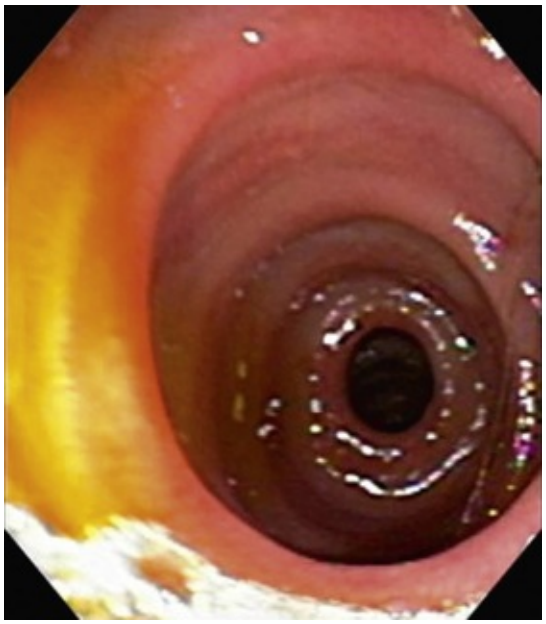


FIG. 32.63 Endoscopic view of the duodenum in a horse with lymphocytic-plasmacytic enteritis. Note the heterogeneous appearance of the duodenal mucosa.

Histopathologic evaluation of biopsy specimens can be used to differentiate

among the various IBDs reported in horses, according to the respective criteria.[87] A diagnosis of granulomatous enteritis is made when aggregates of macrophages and epithelioid cells are found in the mucosa, submucosa, or both, along with villous atrophy. In lymphocytic-plasmacytic enterocolitis, lymphocytes and plasmacytes are present in the lamina propria, and villous atrophy usually occurs. For multisystemic eosinophilic epitheliotropic disease, eosinophils, lymphocytes, and macrophages are found in the mucosa and submucosa. In rare cases, basophils have also been reported.

IBD syndrome, termed *idiopathic focal eosinophilic enteritis* (IFEE), involves focal areas of eosinophilic inflammatory infiltrates within the small intestine.[89,96-100] Affected horses typically are examined not because of chronic weight loss or diarrhea, but rather because of acute colic. Hypoproteinemia and malabsorption are not characteristic. The lesions are intramural masses or circumferential mural bands. Eosinophils with or without lymphocytes are seen infiltrating all layers of the intestine, with varying degrees of fibrosis.[100] Further characterization of the inflammatory lesions indicate that IFEE probably represents a focally exacerbated inflammatory reaction in horses with diffuse eosinophilic enteritis.[99] No underlying cause of the disease has been found, although food allergy, parasitism, and *Pythium* spp. have all been suggested.[100] The incidence, or at least the diagnosis, of this disease appears to be increasing.

Treatment and Prognosis.

Because the specific diseases included in the general category of IBD are quite different, a generalized treatment recommendation cannot be made, although corticosteroids are considered the mainstay of medical management. In one study, a lack of response to initial steroid therapy (prednisolone) was associated with a poorer prognosis for long-term survival, as was a lower peak xylose concentration.[101] The horses in this study were also treated with coadministration of anthelmintic drugs (fenbendazole) and reported a 3-year survival rate of 65%. The high survival rate may also be a result of case selection and case definition. Reported cases of eosinophilic, lymphocytic, and basophilic enteritis have classically failed to respond to treatment. If treatment is attempted, immunosuppressive doses of dexamethasone, up to 0.2 mg/kg IM or IV once daily, are recommended. Successful remission of granulomatous enteritis was reported in one patient that was treated with dexamethasone.[102] Cases of IFEE should be differentiated from other types of IBD with regard to treatment and

prognosis. These cases frequently respond to surgical decompression without resection if circumferential mural bands are the only lesion present.[100] In cases of intramural masses, surgical resection of the lesions usually resolves the problem.[98] Other treatments attempted include anthelmintic drugs with larvicidal activity, hydroxyurea, metronidazole, clioquinol (iodochlorhydroxyquin), and sulfasalazine.[103]

■ Neoplasia

Primary and secondary neoplasia involving the alimentary tract of horses is relatively uncommon, but several cases have been reported.[104] Typical signs associated with, but not diagnostic for, small intestinal neoplasia include colic and weight loss. In most horses with focal intestinal neoplasia, the problem becomes apparent only when lumen obstruction develops. Lymphosarcoma can be disseminated throughout a large portion of intestine, eventually resulting in a malabsorption and weight loss syndrome. Alimentary lymphoma is the most common intestinal neoplasia, and the small intestine is the most commonly affected intestinal segment.[105] Lymphosarcoma affects horses of all ages, although many of those with the alimentary form are older. The diagnosis of enteric lymphosarcoma is occasionally based on cytologic examination of fluid obtained by abdominocentesis, although multiple samples may be required before a positive sample is obtained.[106] In other cases, intestinal biopsy is necessary to diagnose the neoplastic disorder. Ultrasonography may reveal thickening and decreased echogenicity of the small or large intestinal wall or of both.[107] The prognosis is best if the tumor is discrete and can be removed surgically. A combination chemotherapy protocol of cytarabine (170 mg/m^2 IM), cyclophosphamide (142 mg/m^2 IV), and prednisolone (86 mg/m^2 PO q48h) has been reported to be effective in the treatment of mixed-cell thoracic lymphoma.[108] In other cases, corticosteroid therapy may induce clinical remission for several months, although it is not curative.

Other neoplasms affecting the small intestine are unusual; they typically arise from the wall of the bowel and include adenocarcinoma,[109] leiomyosarcoma,[110] and neurofibroma.[111] These tumors often result in intestinal obstruction and signs of abdominal discomfort. Discrete tumors may be surgically removed.

Paraneoplastic syndromes may be the first sign of neoplastic processes in a horse. Pemphigus, hypoglycemia, hypercalcemia, erythrocytosis, and

neuropathies have all been associated with tumors in horses.[112] Paraneoplastic processes may also lead to intestinal tract dysfunction in horses with extraintestinal tumors. Amyloid deposition secondary to multiple myeloma in a horse has been described.[113]

■ Small Intestinal Fibrosis

Small intestinal fibrosis is a rare syndrome that causes weight loss, chronic colic, and progressive debility in horses and ponies. Clusters of affected animals have been reported in Colorado[114,115] and Missouri.[116] The pathophysiologic origin of the fibrosis is not known, although ingestion of toxins (*Convolvulus arvensis* or common bindweed), inhibitors of 11β-hydroxysteroid dehydrogenase, and compounds with mineralocorticoid activity has been suggested.

Rectal palpation typically reveals thickening of the small intestinal wall, which may be confirmed by ultrasonography.[115] Gross examination may reveal that the overall length of the intestine is shortened by as much as 50%.[114,115] The histologic lesions include arteriosclerosis, capillary endothelial hypertrophy, extensive fibrosis of the submucosa, and hypertrophy of the muscularis mucosae and tunica muscularis.[114] The prognosis with the disease is determined by the length of the intestine that is involved. Surgical resection may be attempted.

■ Lymphangiectasia and Chyloabdomen

There are few reports of lymphangiectasia and chyloabdomen in the literature. Lymphangiectasia is dilation of the lymphatic channels of the small or large intestine (Fig. 32.64), usually caused by an abscess[117] or neoplasia. There are reports of chyloabdomen resulting from congenital lymphatic defects in a neonatal foal, intraabdominal abscesses in a foal, and abdominal adhesions in a miniature horse.[117-119] Typically, thickening of the intestinal wall and leakage of chyle into the peritoneal cavity result from obstruction or rupture of the lymphatic channels. Signs include abdominal discomfort, diarrhea, and chronic weight loss. Diagnosis is made on the basis of abdominal fluid analysis and ultrasonography. Chylous abdominal fluid appears milky and may contain a high percentage of lymphocytes. Ultrasonograms may reveal segments of thickened small intestine. Diagnosis is confirmed at surgery or postmortem examination, and treatment, if possible, is usually surgical, although in the author's experience, medical resolution of the effusion has been achieved.



FIG. 32.64 Section of small intestine from a foal with chyloabdomen and a *Rhodococcus equi* abdominal abscess *(arrow).* Mesenteric lymphatic channels are distended with white chyle, as are serosal lymphatic channels. (Courtesy Dr. M.J. Murray.)

Surgical Disorders of the Small Intestine

John F. Marshall • Anthony T. Blikslager

■ Simple Obstruction

Simple intestinal obstruction is a physical obstruction of the lumen without obstruction of mesenteric vascular flow (i.e., nonstrangulating obstruction). The most common causes are intraluminal masses composed of feed material (e.g., ileal impaction) and accumulation of parasites (e.g., ascarid impactions). Other instances in which the bowel is obstructed without associated compromise of blood supply include extraluminal compression by a mass or band of tissue in horses with intraabdominal adhesions and IFEE lesions. The large volume of fluid entering the small intestinal lumen on a daily basis[1,2] causes the obstructed intestine to become distended. Therefore although the mesenteric blood supply is not directly involved in simple obstructions, progressive and marked distention can result in decreased mural blood flow[3,4] and eventual necrosis of tissues.[5]

Ascarid Impactions.

Impactions caused by *Parascaris equorum* typically occur in weanling foals (median age, 5 months; range, 4 to 24 months) that have been on a poor

deworming program and that are administered an anthelmintic when they have a heavy parasite burden.[6] Products that cause sudden ascarid paralysis or death, including piperazine, organophosphates, and pyrantel pamoate, have been incriminated.[7] However, any effective broad-spectrum anthelmintic, such as the avermectins, probably has the same effect. Clinical signs include variable onset of colic after administration of an anthelmintic (usually within 1 to 5 days) and signs compatible with small intestinal obstruction, including nasogastric reflux.[6] The onset of the disease varies according to the degree of obstruction.[7] Diagnosis may be tentatively based on the history in a foal that appears unthrifty, has been recently dewormed, and has signs referable to small intestinal obstruction. The presence of dead ascarids in nasogastric reflux raises the index of suspicion of this particular form of obstruction.[6] Abdominal radiographs or ultrasonography may indicate the presence of multiple loops of distended small intestine, but neither imaging study is needed if clinical signs indicate the need for immediate surgery. Surgical treatment typically involves an enterotomy made over the intraluminal impaction and removal of ascarids.

Although simple intestinal obstruction tends to carry a favorable prognosis for survival, ascarid impaction is a notable exception. The mortality rate in these cases is high (up to 92% in one study) as a result of severe intestinal compromise, peritonitis, and development of adhesions. The severe intestinal compromise is almost entirely attributable to the duration of impaction, which, for unknown reasons, is not as readily recognized in foals as it is in adults. Reasons for this could include failure of the owner or farm manager to recognize colic in foals or failure on the part of the owner or veterinarian to recognize the implications of colic in foals. Although foals readily display signs of colic, other medical causes of colic such as gastric ulcer disease or enteritis might be more significant in the differential diagnosis than for adults. Second, the size of a foal may make episodes of colic appear more manageable than in adults, in which colic-induced trauma, especially to the head, may force the issue of referral and surgery at an earlier stage. This is speculative, but early intervention in foals with ascarid impaction would probably result in dramatic reductions in the reported mortality rate.[6] Improved survival rates have, in fact, been reported: For example one case series indicated that 12 (80%) of 15 horses studied survived to discharge, and 6 (60%) of 10 for which follow-up data were available survived for at least 1 year.[8] This improvement was related to changing the surgical technique to manually evacuating ascarids into the cecum rather than performing

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an enterotomy or resection and anastomosis.[8] However, many cases have multifocal and marked impaction by ascarids that are large and difficult to manipulate. The need for an enterotomy or resection probably relates to the initial severity of disease, and not all cases may be amenable to manual evacuation into the cecum.

Ileal Impaction.

Ileal impactions occur most commonly in adult horses in the southeastern United States. Although feeding of coastal Bermuda hay has been implicated in the regional distribution of this disease, it has been difficult to separate geographic location from regional hay sources as risk factors.[9] However, a study from the southeastern United States showed that the feeding of coastal Bermuda hay and failure to deworm with an anthelmintic with efficacy against tapeworms are significant risk factors for ileal impaction.[10] Furthermore, in a study performed in the United Kingdom, horses with evidence of tapeworm infection were at risk for developing ileal impaction.[11]

Typical signs in an adult horse with small intestinal obstruction include onset of moderate to severe colic and loops of distended small intestine rectally palpable as the condition progresses. Because the ileum is the most distal aspect of the small intestinal tract, nasogastric reflux may take a considerable time to develop and is found in only approximately 50% of horses requiring surgical correction of ileal impaction.[12,13] The diagnosis is usually made at surgery, although an impacted ileum may be palpated rectally.[14] However, multiple loops of distended small intestine frequently make the impaction difficult to palpate. Nonetheless, clinicians working in the southeastern United States who evaluate horses with cases of mild or moderate colic that have a history of eating coastal Bermuda hay, and in which distended loops of small intestine can be detected adjacent to the cecum, should strongly suspect ileal impaction.

Ileal impactions may resolve with medical treatment. In particular, horses with clinical signs compatible with obstruction of the small intestine and normal abdominal fluid should be treated medically unless pain is unmanageable or subsequent abdominal fluid samples indicate intestinal compromise. In cases in which surgery becomes necessary, fluids (2 to 3 L) can be directly infused into the mass, which allows the surgeon to break down the impaction. However, extensive small intestine distention and intraoperative manipulation of the ileum frequently leads to postoperative ileus (POI).[15] Therefore some surgeons now

elect to perform an enterotomy and to flush the contents from the intestinal lumen with minimal manipulation. Although early studies indicated a guarded prognosis,[13] a more recent study indicated that the prognosis is excellent for both medically and surgically managed ileal impactions.[16]

Ileal Hypertrophy.

Ileal hypertrophy is a disorder in which the muscular layers (both circular and longitudinal) of the ileum enlarge for unknown reasons. Parasitism has been implicated, particularly parasites that tend to localize to the ileum (such as tapeworms),[17] but this has never been proven. In some cases the jejunum may also be hypertrophied, either alone or in combination with the ileum.[18] It is clear from these findings that initial functional obstruction initiates this syndrome, causing the musculature of the intestine to hypertrophy in order to push intestinal contents aborally, but there is no evidence as to the mechanisms of this disease. Clinical signs include chronic intermittent colic as the ileum hypertrophies and gradually occludes the lumen. In one study, partial anorexia and chronic weight loss (1 to 6 months) were documented in 45% of affected horses.[19] The diagnosis is usually made at surgery, although in some cases the hypertrophied ileum may be palpated rectally or visible on ultrasonographic evaluation of the abdomen.[19] Treatment involves an ileocecal or jejunocecal anastomosis to bypass the hypertrophied ileum. Without surgical bypass, intermittent colic persists, and the thickened ileum may ultimately rupture. According to one report of 11 horses with hypertrophy of the ileum, only 1 horse survived, which indicates a poor prognosis. The most common reason for euthanasia was spontaneous ileal rupture.[18]

Meckel Diverticulum.

A Meckel diverticulum is an embryonic remnant that may become impacted. The diverticulum arises from the vitelloumbilical duct, which fails to atrophy completely and becomes a blind pouch projecting from the antimesenteric border of the ileum.[20,21] An associated mesodiverticular band occasionally extends from the diverticulum to the umbilical remnant and serve as a point around which small intestine may become strangulated. Mesodiverticular bands may also originate from the embryonic ventral mesentery and attach to the antimesenteric surface of the bowel, thereby forming a potential space within which intestine may become entrapped (Fig. 32.65).[22] Clinical signs range from chronic colic

for an impacted Meckel diverticulum to acute severe colic if a mesodiverticular band strangulates intestine. The diagnosis is made at surgery, and treatment entails resection of the diverticulum and any associated bands.[23]

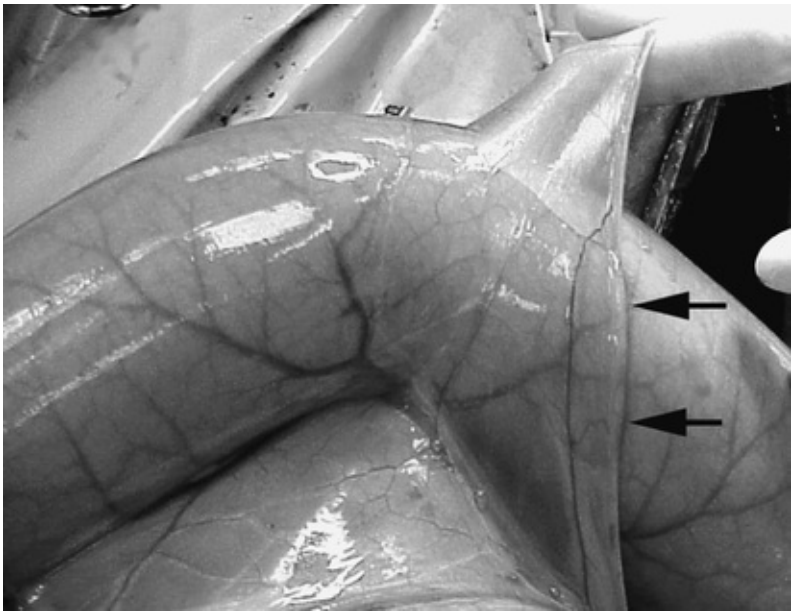


FIG. 32.65 Jejunal mesodiverticular band. This anomaly was an incidental finding during exploration of the horse's abdomen. Intestine may become entrapped within the mesenteric pocket formed by the attachment of the ventral to the dorsal mesentery *(arrows).*

Idiopathic Focal Eosinophilic Enteritis.

IFEE is a relatively recently described condition of the small intestine of horses. Since 2000, the condition has been reported in the United Kingdom and the United States, and although its diagnosis appears to be increasingly common, no causative agent or other etiology has been described.[24,25,26] The clinical presentation of horses with this condition is consistent with that of nonstrangulating small intestinal obstruction, and horses younger than 5 years of age are at increased risk.[26] IFEE is diagnosed during exploratory celiotomy when palpably thickened serosal plaques or circumferential constricting bands are identified in the jejunum. Multiple plaques or bands may be present throughout the jejunum. Early reports of surgical resection of the affected intestine revealed a fair prognosis; in one, 7 of 10 surgically treated horses survived to discharge.[24] In cases in which abnormal portions of small intestine

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has been resected, the diagnosis can be confirmed by histologic examination, which reveals severe transmural eosinophilic enteritis. However, pathologic and histologic examinations have not identified the cause of these lesions, and helminths have not been associated with them.[24] Although surgical treatment of this condition (resection and anastomosis) is frequently required, the majority of cases are treated by manual evacuation of impacted feed material into the cecum and parenteral administration of corticosteroids. An epidemiologic study of IFEE in the northwest of England revealed a seasonal pattern of the disease: The risk was highest between July and November.[26]

■ Strangulating Obstruction

Strangulating obstruction of the intestine is characterized by simultaneous occlusion of the intestinal lumen and its blood supply. Although strangulation of the intestinal lumen results in clinical signs similar to those of simple obstruction, occlusion of the blood supply results in a more rapid deterioration of the intestinal mucosa and subsequent onset of endotoxemia. Therefore clinical signs (including pain, heart rate, mucous membrane color, and capillary refill time) are typically more severe, and the prognosis is less favorable.

A great deal of work has been done to characterize mucosal injury that occurs during strangulation[27,28] and reperfusion.[29] In general, the lesion that develops during strangulation is severe: the small portion of bowel left viable is vulnerable to further injury during reperfusion.[30] The severity of the ischemic lesion is partly attributable to the fact that in most cases, initial occlusion of veins and partial occlusion of arterial blood supply during strangulation induces a hemorrhagic lesion. This results in extensive congestion and mucosal degeneration (Fig. 32.66).[27] Bowel peripheral to the strangulating lesion may also become injured as a result of distention.[31] In addition, distended small intestine that remains viable after surgical correction of strangulation may be subject to postoperative reperfusion injury through the generation of reactive oxygen metabolites.[32] Although attempts at reducing mucosal injury in a horse with antioxidants have met with some success,[33] their clinical use is limited.

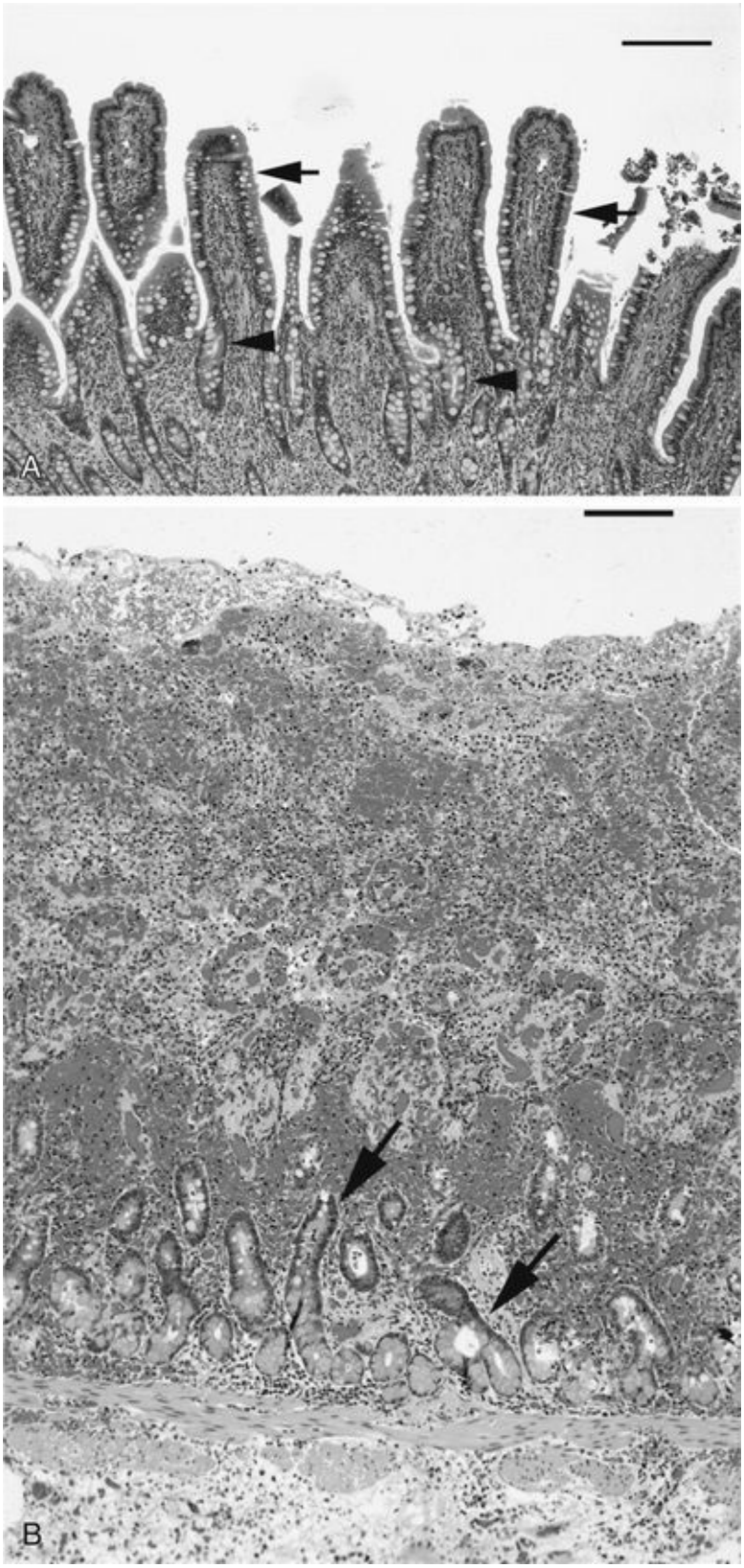


FIG. 32.66 Histologic appearance of normal and strangulated jejunal mucosa. **A,** Normal equine jejunal mucosa, with extensive villi *(arrows)* and

mucosal crypts *(arrowheads).* **B,** Hemorrhagic strangulating lesion of the jejunum, with complete loss of villi and extensive hemorrhage. Note the presence of crypts *(arrows),* which remain relatively undamaged. (Scale: 1 cm = 100 µm.)

The prognosis for survival in horses with SISO is generally poorer than those of most other types of colic. In a number of studies, rates of short-term survival of horses with SISO were between 55% and 84%. A large single-center study that included 147 horses with small intestinal disease demonstrated that short-term survival rate was significantly lower among horses with SISO (54.8%) than among those with a simple obstruction (79.6%).[34] In contrast, however, a review of 74 horses revealed no significant difference in short-term survival rate between horses with SISO (84%) and those with a simple obstruction (91%).[35] The importance of early referral and diligent assessment of intestinal viability was highlighted by a case series of 35 horses with strangulating small intestinal lesions that were managed without resection and anastomosis; the reported rate of survival to discharge was 100%.[36] It is important to discuss with owners the potential postoperative complications and long-term survival rates. Studies in which horses were monitored after discharge from the hospital have revealed significantly lower survival rates after 12 months, ranging from 47% to 68%.[37-39]

Episodes of colic are the most frequently reported complication after discharge[38,40] and are significantly more common in horses with small intestinal obstruction than in those with large colon disease.[38] A significant reason for repeated episodes of colic and reduced long-term survival in patients that have had small intestinal surgery is intraabdominal adhesions (Fig. 32.67). For example, in one study, 22% of horses undergoing small intestinal surgery required further surgery or were euthanized because of adhesions, and only 25% of horses that had a clinical problem with adhesions survived.[41] A more recent study of 99 horses requiring repeat celiotomy demonstrated that intraabdominal adhesions were the most common pathologic finding.[42] In that study, however, horses with small intestinal lesions were not more likely to develop adhesions than were those with large colon lesions, and horses with adhesions were no less likely to survive than those without.[42]



FIG. 32.67 Intraabdominal adhesion in a foal. Note the presence of a mature fibrous adhesion between two segments of jejunum *(arrows)* that resulted in kinking and partial obstruction of the affected intestine.

Epiploic Foramen Entrapment.

The epiploic foramen is a potential opening (because the walls of the foramen are usually in contact) to the omental bursa located within the right cranial quadrant of the abdomen. It is bounded dorsally by the caudate process of the liver and caudal vena cava and ventrally by the pancreas, the hepatoduodenal ligament, and the portal vein.[43,44] Clinical signs include acute onset of severe colic, and examination findings are compatible with small intestinal obstruction. Although the condition was reportedly more prevalent in older horses, studies have not revealed an age predilection.[45] However, a seasonal pattern for this disease has been detected. Specifically, more horses appear to suffer from epiploic foramen entrapment during the fall and winter months, which may reflect management practices.[46] An additional factor associated with epiploic foramen entrapment is crib-biting. One possible reason for this association is the development of negative intrathoracic pressure during cribbing, which might then result in cranial movement of intestine into the vicinity of the epiploic

foramen. The association between crib-biting and epiploic foramen entrapment has been shown in separate studies performed in the United Kingdom and the United States.[47]

The diagnosis is definitively made at surgery, although ultrasonographic findings of distended loops of edematous small intestine adjacent to the right middle body wall are suggestive of epiploic foramen entrapment.[43] Entrapped small intestine may enter the foramen from the visceral surface of the liver toward the right body wall or in the opposite direction. In most cases, however, the intestine enters the foramen in a left-to-right direction.[43,47] Small intestine entrapment may be limited to a portion of the intestinal wall (parietal hernia).[49] In addition, the large colon may become entrapped within the epiploic foramen.[50] In the treatment of epiploic foramen entrapment, the epiploic foramen must not be enlarged either by blunt force or with a sharp instrument because the vena cava or portal vein may be ruptured and fatal hemorrhage may occur. In addition, excessive force used to extract entrapped bowel during surgery may also result in rupture of a mesenteric branch of the cranial mesenteric artery. In some cases of epiploic foramen entrapment, intraabdominal hemorrhage found before surgery may result from compromise of the mesenteric blood supply rather than the major blood vessels that border the epiploic foramen. The prognosis has substantially improved since the 1990s, with short-term survival rates (discharge from the hospital) ranging from 74% to 95% in the most recent studies.[43,51,52]

Strangulation by Mesenteric Pedunculated Lipoma.

Lipomas form between the leaves of the mesentery as horses age, and mesenteric stalks develop as the weight of the lipoma tugs on the mesentery. The stalk of the lipoma and a loop of small intestine or small colon may become intertwined and lead to strangulation (Fig. 32.68). Strangulating lipomas should be suspected in mature horses (>10 years old) with acute colic referable to the small intestine.[53] In addition, geldings and ponies appear to be at risk for developing strangulating lipomas,[54] possibly because of differences in fat metabolism. One study documented a case of strangulating lipoma in a much younger patient, which indicates that although the aging process is associated with development of lipomas, this diagnosis cannot be ruled out preoperatively on the basis of age alone.[55,56] The diagnosis is usually made at surgery.

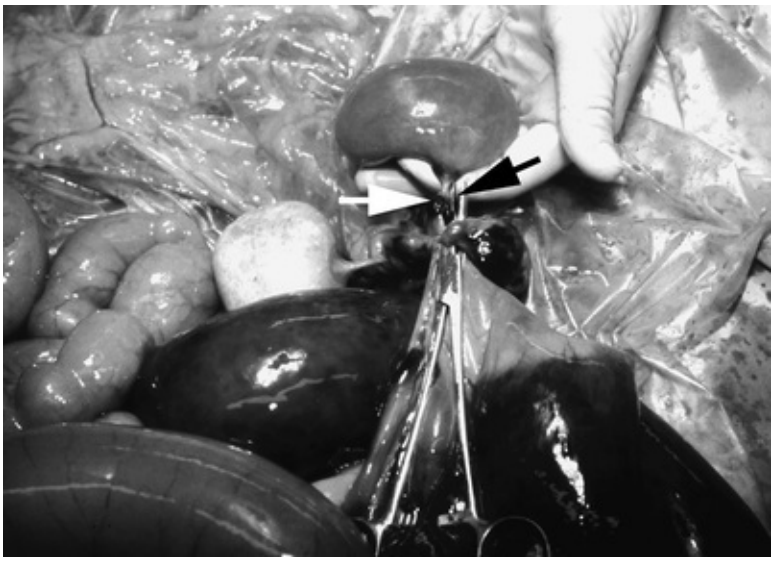


FIG. 32.68 Strangulating lipoma of the ileum. A lipoma, together with its mesenteric stalk *(arrows),* has become intertwined with a loop of the ileum, which resulted in a hemorrhagic strangulating obstruction.

Treatment involves surgical resection of the lipoma and strangulated bowel, although strangulated intestine is, on occasion, viable. Studies indicate that approximately 60% to 78% of horses are discharged from the hospital after surgical treatment.[53,57,58]

Small Intestinal Volvulus.

A volvulus is the twisting of a segment of small intestine more than 180 degrees along the axis of the mesentery. Small intestinal volvulus is theoretically initiated by a change in local peristalsis, but the mechanisms of this disease are unclear.[59] It is reportedly one of the most commonly diagnosed causes of small intestinal obstruction in foals.[60] It has been theorized that young foals may be at risk for small intestinal volvulus because of changing feed habits as they adapt to a forage-based adult diet. However, a report of 115 cases of small intestinal volvulus found that 74% of the affected animals were aged 3 years or older.[61] Onset of acute, severe colic, a distended abdomen, and radiographic or ultrasonographic evidence of multiple loops of distended small intestine in a young foal are suggestive of small intestinal volvulus. However, volvulus cannot be differentiated preoperatively from other causes of small intestinal obstruction.

In adult horses, volvulus frequently occurs in association with another disease process, during which small intestinal obstruction results in distention and subsequent rotation of the small intestine around the root of the mesentery (e.g.,

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in horses that have strangulation caused initially by a pedunculated lipoma). Although any segment of the small intestine may be involved, the distal jejunum and ileum are most frequently affected, probably because the mesentery is longer in the more distal portion of the bowel. The diagnosis is made on palpation of a twist at the origin of the cranial mesenteric artery during surgical exploration. Treatment includes resection of devitalized bowel, which may not be an option because of the extent of small intestinal involvement. For example, if complete volvulus of the small intestinal tract occurs, the only option would be to untwist the intestine and hope that the bowel was sufficiently viable to survive the disease process. This would in turn depend on the duration of disease and the extent of intestinal ischemia (i.e., how tightly the intestine twisted as the volvulus developed). Prognosis is based on the extent of small intestine involved and its appearance after surgical correction of the lesion.[62] For example, the degree of sepsis may be related to the surface area of devitalized tissue. In addition, the length of the time it takes to complete the surgery can become problematic, particularly in patients with sepsis, in which it is difficult to maintain adequate arterial blood pressure. Nonetheless, survival in patients with extensive small intestinal resection may not be related to the absolute length of intestine resected.[63] The prognosis for short-term survival is good; one study suggested that 80% of horses are discharged after surgery.[34]

Inguinal Hernia.

Inguinal hernias are more common in Standardbred and Tennessee Walking horses, which tend to have congenitally large inguinal canals. Inguinal hernias may also occur in neonatal foals, but they differ from hernias in mature horses in that they are typically nonstrangulating. Typical historical findings in mature horses with inguinal hernias include acute onset of colic in a stallion that has recently been used for breeding. A cardinal sign of inguinal herniation is coolness and enlargement of one testicle.[64,65] This is attributable to occlusion of the testicular blood supply in most cases rather than strangulated intestine within the scrotum itself. Inguinal hernias can also be detected on rectal palpation, and ultrasonography of the testicle is very helpful in determining the diagnosis, particularly of testicular torsion. The nature of the hernia (direct versus indirect) is determined by the integrity of the parietal vaginal tunic. In horses in which the bowel remains within the parietal vaginal tunic, the hernia is said to be indirect because the bowel remains within the peritoneal cavity. Direct hernias are those

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in which the bowel ruptures through the parietal vaginal tunic and occupies a subcutaneous location, followed by strangulation. Direct hernias most commonly occur in foals and should be suspected when a congenital inguinal hernia is associated with colic, swelling that extends from the inguinal region of the prepuce, and intestine that may be palpated subcutaneously.[66,67] Although most congenital indirect inguinal hernias resolve with repeated manual reduction or application of a diaper, or both, surgical intervention is recommended in foals with congenital direct hernias in order to reduce the hernia, as well as repair the parietal vaginal tunic.

In stallions with indirect inguinal hernias, the hernia is typically surgically reduced via combined inguinal and midline ventral abdominal incisions to allow visual inspection of the small intestine and, if necessary, resection and anastomosis. However, in many cases taken to surgery the short segment of herniated intestine improves markedly in appearance once it has been manually or surgically reduced, and in some cases the affected intestine can be left unresected. In these cases, subsequent laparoscopic closure of the internal vaginal ring is recommended to prevent recurrence and simultaneously retain the associated testicle.[68] In cases of nonreducible hernias, the affected testicle is congested because of vascular compromise within the spermatic cord, and although it may remain viable, it is recommended that it be resected and the external inguinal ring closed. If the testicle is retained, the inguinal canal should be partially closed at surgery to prevent recurrence, but the risk that this procedure will reduce spermatic cord vasculature is another problem. The prognosis in adult horses is good; 76% of horses in one study were alive 6 months after discharge.[65] Horses that have been unilaterally castrated during surgical treatment of inguinal hernias may be used for breeding. In these horses, the remaining testicle has increased sperm production, although an increased number of sperm abnormalities will be noticed after surgery because of edema and increased temperature of the scrotum.

Strangulating Umbilical Hernias.

Whereas umbilical hernias are common in foals, strangulation of herniated bowel is rare. In one study, 6 (4%) of 147 horses with umbilical hernias had incarcerated intestine.[69] The hernia sac is warm, swollen, firm, and painful in association with signs of colic. The affected segment of bowel is usually the small intestine, but herniation of the cecum or large colon has also been

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reported.[70] In rare cases, a hernia involves only part of the intestinal wall and is referred to as *Richter hernia.* In foals that have Richter hernia, an enterocutaneous fistula may develop. In one study, all 13 foals with strangulating umbilical hernias survived to discharge, although at least 3 died because of long-term complications.[70]

Diaphragmatic Hernias.

Herniation of intestine through a rent in the diaphragm is uncommon in horses, accounting for 0.3% of all cases of colic in a large multicenter study.[34] Any segment of bowel may be involved, although the small intestine is most frequently herniated.[71] Diaphragmatic rents may be congenital or acquired, but acquired hernias are more common. Congenital rents may result from incomplete fusion of any of the embryonic components of the diaphragm: pleuroperitoneal membranes, transverse septum, and esophageal mesentery. In addition, abdominal compression of the foal at parturition may result in a congenital hernia. Acquired hernias are presumed to result from trauma to the chest or a sudden increase in intraabdominal pressure, as might occur during parturition, distention of the abdomen, a sudden fall, or strenuous exercise.[72] In one study, of 40 horses diagnosed with diaphragmatic hernia, 19 (48%) had a history of recent trauma.[72] Hernias have been found in several locations, although large congenital hernias are typically present at the most ventral aspect of the diaphragm, and most acquired hernias are located at the junction of the muscular and tendinous portions of the diaphragm. In addition, a peritoneal-pericardial hernia has been documented in at least one horse.[73]

The clinical signs are usually associated with intestinal obstruction rather than respiratory embarrassment. However, careful auscultation may reveal an area of decreased lung sounds in association with obstructed intestine and increased fluid within the chest cavity. Such signs may prompt thoracic radiography or ultrasonography, both of which can be used to make a diagnosis. In one review, of 40 horses reported in the literature with diaphragmatic hernia, 7 (18%) had dyspnea.[72] Auscultation may also reveal thoracic intestinal sounds, but it is typically not possible to differentiate these from sounds referred from the abdomen. In another report, two of three horses with small intestinal strangulation by diaphragmatic hernia had respiratory acidemia, attributable to decreased ventilation.[74] Because of the difficulties in correcting diaphragmatic hernias and the associated complicating factors such as pneumothorax, these

cases are generally considered to have a poorer prognosis than are other causes of colic. Reports of 31 and 44 cases demonstrated that 46% and 27%, respectively, of affected horses undergoing surgical treatment survived to discharge, and the overall success rates were only 23% and 16%, respectively.[75,76]

Intussusceptions.

An intussusception involves a segment of bowel (intussusceptum) that invaginates into an adjacent aboral segment of bowel (intussuscipiens). The reason for such invagination is not clear, but it may involve a lesion at the leading edge of the intussusception, including small masses, foreign bodies, or parasites. In particular, tapeworms *(Anoplocephala perfoliata)* have been implicated.[77] Ileocecal intussusceptions are the most common intestinal intussusceptions in horses and typically affect young animals. For example, in one evaluation of 26 cases of ileocecal intussusception, the median age of the horses was 1 year.[78] Acute ileocecal intussusceptions are those in which the duration of colic is less than 24 hours, and they involve variable lengths of intestine that ranged in one study from 6 cm to 457 cm long. In acute cases the involved segment of ileum typically has a compromised blood supply. Chronic ileocecal intussusceptions typically involve short segments of ileum (up to 10 cm long), and the ileal blood supply is frequently intact.

Abdominocentesis results are variable because strangulated bowel is contained within the adjacent bowel. There is often evidence of obstruction of the small intestine, including nasogastric reflux and multiple distended loops of small intestine on rectal palpation. Horses with chronic ileocecal intussusceptions have mild, intermittent colic, often without evidence of small intestinal obstruction. A mass may be palpated in the region of the cecal base in approximately 50% of cases. Transabdominal ultrasonography may be helpful in discerning the nature of the mass. The intussusception has a characteristic target appearance on cross-section.[79]

Other segments of the small intestine, including the jejunum, may also be intussuscepted. In one study on 11 jejunojejunal intussusceptions, the length of bowel involved ranged from 0.4 to 9.1 m.[80] Attempts at reducing intussusceptions at surgery are usually futile because of intramural swelling of affected bowel. Jejunojejunal intussusceptions should be resected. For acute ileocecal intussusceptions, the small intestine should be transected as far distally

as possible and a jejunocecal anastomosis created. In cases of particularly long intussusceptions (lengths up to 10 m has been reported), an intracecal resection may be attempted. For horses with chronic ileocecal intussusceptions, a jejunocecal bypass without small intestinal transection should be performed.

In one study of the survival of horses with ileocecal intussusceptions, all 7 horses with chronic intussusceptions survived long term (>4 months), whereas only 5 (42%) of 12 horses with acute intussusceptions survived long term.[78] In a separate study of survival in horses with jejunojejunal intussusceptions, 6 (54%) of 11 horses were discharged from the hospital after surgery, and 4 (36%) of 11 horses survived long term (>16 months).[80]

Other Small Intestinal Strangulations.

Entrapment of the small intestine may occur through rents in the mesentery or in internal ligaments such as the gastrosplenic ligament,[81] the broad ligament, and the proximal aspect of the cecocolic ligament.[82] Entrapments may also occur through trauma-induced body wall hernias. For all of these conditions it is often necessary to enlarge the rent or hernia to allow reduction of entrapped small intestine. In the case of body wall hernias, the defect should be closed with suture or patched with mesh. Entrapment of small intestine within mesenteric rents can be particularly problematic because they can be difficult to reduce and the rents are often difficult to close. Mesenteric rents have been associated with an unfavorable prognosis, possibly because large lengths of intestine may become strangulated and because the mesenteric vasculature is frequently compromised to the extent that intraabdominal hemorrhage has been noted in some cases.[83] However, a case series involving 38 Thoroughbred broodmares with small intestinal mesenteric rents reported short-term survival rates of 76% overall and 88% among horses that recovered from anesthesia.[84] The inability to close the rent at surgery was associated with increased likelihood of colic after hospital discharge but did not affect overall survival. This study probably highlights the benefits of prompt referral before significant lengths of intestine are strangulated and the importance of making every effort to close the rent at surgery.

■ Nonstrangulating Infarction

Nonstrangulating infarction occurs secondary to cranial mesenteric arteritis caused by migration of *S. vulgaris*[85] and has become rare during surgery since

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the advent of broad-spectrum anthelmintics. Although thromboemboli have been implicated in the pathogenesis of this disease, careful dissection of naturally occurring lesions has not revealed the presence of thrombi at the site of intestinal infarctions in most cases. These findings suggest that vasospasm plays an important role in this disease.[85] Clinical signs are highly variable, depending on the extent to which arterial flow is reduced and the segment of intestine affected. Any segment of intestine supplied by the cranial mesenteric artery or one of its major branches may be affected, but the distal small intestine and large colon are more commonly involved. There are no clinical variables that can be used to reliably predict or differentiate this disease from strangulating obstruction. In some cases massive infarction results in acute, severe colic. In other cases intermittent colic develops as smaller emboli are released into the colonic blood supply. An abnormal mass and fremitus are occasionally detected on palpation of the root of the cranial mesenteric artery on rectal palpation. This disease should be considered part of the differential diagnosis in horses with a history of inadequate anthelmintic treatment and the presence of intermittent colic that is difficult to localize. Although fecal parasite egg counts should be performed, they are neither indicative of the degree nor specific for the type of parasitic infestation.

In addition to routine treatment of colic, dehydration, and endotoxemia, medical treatment may include aspirin (20 mg/kg q24h) to decrease the risk of thrombosis. Definitive diagnosis requires surgical exploration. Surgical treatment depends on the distribution of infarction. Unfortunately, these cases are difficult to treat because of the patchy distribution of the lesions and the possibility that lesions extend beyond the limits of surgical resection. In addition, further infarction may occur after surgery. The prognosis is fair for horses with intermittent mild episodes of colic that may be amenable to medical therapy, but horses that require surgical intervention have a poor prognosis.[85]

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Medical Disorders of the Large Intestine

Samuel L. Jones

Acute Diarrhea

Diarrhea in horses can be defined as the passage of fecal material that has increased water content. It can vary from soft, formed stools with a mild to moderate increase in water content to projectile fecal passages that contain little solid matter. The passage of excessive water in the feces reflects disruption of the normal balance of fluid and electrolyte secretion and absorption in the intestinal tract. In adult horses, diarrhea results almost exclusively from disorders of the large intestine, although it may be a feature of some disorders of the descending small colon. Diarrhea can result in significant losses of water, electrolytes, and plasma protein and is often accompanied by local and systemic inflammatory responses.

Diarrhea disorders in adult horses can be divided into those characterized by inflammation of the cecum and large intestine (typhlitis, colitis) and those in which there typically is no inflammatory response. Inflammatory disorders include those characterized by an acute inflammatory response (salmonellosis, Potomac horse fever [PHF], clostridiosis, and equine coronavirus, described later), disorders associated with endoparasitism (small and large strongyle larval migration or encystation), disorders arising from toxicity (cantharidin toxicity, described later, and NSAID toxicity), and disorders included under the umbrella term *inflammatory bowel disease* (IBD). Disorders that can manifest with diarrhea but are not characterized by colonic inflammation include those in which intestinal hydrostatic pressure is increased (congestive heart failure, cirrhotic liver disease), those in which intraluminal osmolarity is increased, and poorly defined disorders in which fluid secretion may be stimulated by the enteric nervous system.

Colitis is active inflammation within the colon that is usually associated with myriad local and systemic pathophysiologic events. Diarrhea is an important problem in horses with colitis, but sepsis resulting in impaired cardiopulmonary function, coagulopathies, and other sequelae of activation of inflammatory mediator cascades can be life-threatening. Other complications that occur in patients with colitis and sepsis, regardless of cause, include hematogenous organ colonization by bacteria, immune suppression and susceptibility to

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superinfection with bacteria or fungi, cecum or colon infarction, jugular vein thrombosis, and laminitis.

A variety of inflammatory cells and mediators affect the equine colon. In acute colitis the neutrophil is the effector cell, and the cascade of activation of inflammatory mediators associated with acute colitis is designed to bring neutrophils to where chemical signals indicative of bacterial infection have been detected. Signs of sepsis frequently accompany, or even precede, diarrhea in horses. Severe tissue inflammation can cause ulceration of the mucosal epithelium, which results in chronic malabsorption and protein-losing enteropathy. Malabsorption of volatile fatty acids (VFAs) and metabolic alterations that result from excessive production and release of inflammatory mediators can lead to an energy deficit and catabolism of body tissues.

Specific diseases affecting the equine large colon (e.g., salmonellosis, PHF, clostridial and equine coronavirus colitis, and cantharidin toxicity) may have different activators of local and systemic inflammatory responses, and they can produce unique toxins that further contribute to tissue injury. Regardless of the cause, the clinical problems of affected horses are often similar, and the clinician must consider treatments that modify inflammatory changes and replace losses of fluid, electrolytes, and plasma protein. In many cases, the cause of the diarrhea is not determined. Descriptions of important causes of diarrhea in horses are as follows.

■ Salmonellosis

Salmonella bacteria possess an array of virulence factors that confer attributes of mucosal adhesion and invasion, produce enterotoxins that stimulate intestinal fluid secretion, activate local inflammation (including recruitment of inflammatory cells and the release of their mediators), cause local cytotoxic effects, and initiate systemic responses attributable to LPS and other microbial molecules.

Epidemiology.

Numerous *Salmonella* serotypes have been associated with equine colitis, and overall more than 2500 serotypes of *Salmonella* have been described. *Salmonella enterica* serovar Typhimurium is the most frequently isolated serotype in horses; dozens of other serotypes are isolated sporadically. Many clusters of cases of equine salmonellosis in which specific *Salmonella* serovars predominate have been described. Nosocomial infections associated with *S.*

enterica serovars Krefeld,[1-3] Typhimurium,[2] Anatum,[4] Infantis,[5] and Newport[6] have been reported. Pertinent features of these bacteria are the ability to withstand a wide range of environmental conditions, the ability to rapidly invade and spread within the host (and thus be shed into the environment through the feces), and the range of severity of illness that results from infection.

Other key elements that influence whether clusters of cases will occur if an *S. enterica* serovar is present in the environment are availability and population density of susceptible hosts and the size of the infective dose of the pathogen. For these reasons, veterinary hospitals, breeding farms, and other facilities that may have a high density of horses are most vulnerable to the development of *Salmonella* outbreaks. In several studies at veterinary teaching hospitals, horses that were at greatest risk for developing salmonellosis or shedding *Salmonella* in their feces were those treated with antimicrobial drugs or admitted for treatment of colic.[7-9] Such horses are the majority of patients in any equine referral hospital and account for a significant biosecurity concern in equine hospitals and potentially in the home stables of shedding patients after discharge if susceptible animals have contact with discharged horses that are shedding.[10] Breeding farms are susceptible to *Salmonella* outbreaks (or other enteric infections) because of the concentration of large numbers of immunologically immature newborn animals. In either case the particular *Salmonella* organism involved in disease outbreaks may not have to be especially virulent because the inherent susceptibility of the host provides the microbe the opportunity to colonize and invade the host. Also of importance is the ability of the organism (inherent or acquired) to persist in the environment, lying in wait for both susceptible hosts and environmental conditions that favor its propagation and dissemination.

Serovars or strains of *Salmonella* that have newly acquired virulence plasmids can rapidly become established and spread among farms, sales areas, veterinary clinics, and veterinary teaching hospitals. Often the origin of these “new” bacteria is undetermined, but in some cases the organism can be traced to contaminated feed,[11] a specific shedder or index case introduced into the environment,[6] or domestic, feral, or wild animals.

Salmonella organisms are ubiquitous in the environment, and the prevalence of fecal shedding varies by the group of horses sampled and the method of detection. Prevalence of fecal shedding, based on fecal culture, in asymptomatic horses admitted to teaching hospitals varied from 1% to 5%.[12,13] In a nationwide survey of prevalence of *Salmonella* in fecal samples from horses on farms and

ranches, *Salmonella* bacteria were cultured from fewer than 1% of horses.[14] The incidence of *Salmonella* shedding in feces has been reported to be 17% among horses admitted to a teaching hospital for lameness examination and 35% to 60% or higher in hospitalized horses with gastrointestinal disease.[9,15] In these reports PCR was determined to be specific for *Salmonella* DNA, but the test cannot differentiate between shedding of live bacteria and that of DNA from dead organisms.

Horses are not considered to be carriers per se of *Salmonella* because no host-adapted *Salmonella* spp. have been identified in horses. *Salmonella abortus equi* has disappeared in the United States. Horses that shed *Salmonella* spp. in the feces usually do so transiently for several days to weeks; infrequently, horses shed *Salmonella* bacteria for several months.

In acutely affected horses, large numbers of highly infective *Salmonella* organisms can be shed in the diarrheic feces. Susceptible animals such as young foals, hospitalized horses receiving antimicrobial drugs, and horses under stress can become ill after becoming infected by the bacteria in numbers far lower (1% to 0.1%) than the number necessary to infect immunocompetent normal horses. Thus particular care should be taken in the management of horses and foals with diarrhea in environments in which there are other animals at risk (e.g., hospitals, breeding farms, show stables, racetracks). Asymptomatic shedders generally pass relatively small numbers of *Salmonella* organisms in the feces and do not appear to pose an important threat to healthy horses not being treated with antibiotics,[10] but asymptomatic shedders have been responsible for outbreaks of salmonellosis in hospitals and on breeding farms.

Clinical Findings.

Salmonellosis typically is characterized by an acute colitis that results in profuse diarrhea and occasionally abdominal pain. Many horses with salmonellosis have signs of sepsis and potentially cardiovascular shock, vascular leak syndrome, and coagulopathies. Horses are usually febrile, tachycardic, moderately to severely obtunded, and dehydrated. With other clinical syndromes of *Salmonella* infection, diarrhea is not a feature. These syndromes include fever and leukopenia, colic, and proximal enteritis with gastric reflux.

Diagnosis.

Salmonellosis is most commonly confirmed through bacteriologic culture or quantitative PCR detection of *Salmonella* bacteria. Other diagnostic tests such as

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lateral flow immunoassay and DNA hybridization are becoming commercially available and may become useful for rapid detection of *Salmonella* bacteria.[16] Multiple fecal cultures or quantitative PCR, or both, for *Salmonella* spp. should be performed on all horses with diarrhea, particularly if they have signs of systemic inflammation (fever, neutropenia or leukopenia, tachycardia, or tachypnea). It is recommended that at least three to five fecal samples collected 12 to 24 hours apart be submitted to increase the sensitivity of culture.[17] Samples with little solid matter often yield negative culture results, even when horses are infected with *Salmonella.* Formed fecal samples from infected horses are more likely to produce a positive culture result. A 5- to 10-g amount of feces should be submitted for culture in selective media such as tetrathionate broth or selenite broth and brilliant green agar or XLD agar. Culture of a rectal mucosa biopsy sample may be a useful adjunctive test for diagnosing salmonellosis. PCR is a sensitive screening tool for detection of fecal *Salmonella* DNA and is important for environmental monitoring and biocontrol measures in hospitals. Quantitative PCR is very sensitive and specific in comparison with conventional culture and has a high positive predictive value for individual patients that have clinical signs consistent with salmonellosis.[18]

Treatment and Prevention.

In most cases of salmonellosis, aggressive treatment facilitates resolution of the severe diarrhea and associated metabolic disorders within 7 to 10 days of the onset of illness. Intravenous administration of polyionic fluids is necessary to replace fluid and electrolyte losses and to augment preload in horses with poor venous return (see the Fluid Therapy for Horses with Gastrointestinal Diseases section in this chapter and also Chapter 44 for more comprehensive information about fluid therapy for diarrhea). Plasma may be needed to replace lost plasma proteins and increase plasma colloidal pressure. Alternative colloidal fluids, such as hetastarch, may be useful and more cost-effective than plasma in horses with vascular leak syndrome and hypoproteinemia. Flunixin meglumine is often used to treat inflammation in horses with signs of sepsis. Flunixin and other NSAIDs should be used with caution and at the lowest dose possible to prevent worsening of colonic mucosal damage or inhibition of mucosal repair.

Other antiinflammatory strategies may be used to treat sepsis associated with salmonellosis. Total or partial parenteral nutritional support is often indicated to provide adequate calories and amino acids during the most debilitating period of the illness. Antimicrobials are not universally administered to horses with

suspected or known salmonellosis, but antimicrobial administration may decrease the spread of *Salmonella* bacteria to other organs and may have some direct effect on *Salmonella* bacteria in the colon. Traditionally, use of antimicrobial drugs such as chloramphenicol, trimethoprim-sulfonamide, gentamicin, and cephalosporins has not appeared to accelerate resolution of signs of colitis. Fluoroquinolones, such as enrofloxacin, although potentially arthropathic in young horses, may be more effective because of high lipid solubility and bactericidal activity against *Salmonella* bacteria. The prevalence of infection with and shedding of multidrug-resistant *Salmonella* strains appears to be increasing in high-risk facilities such as equine veterinary hospitals, which potentially affects treatment success and zoonotic transmission.[6,19]

Horses that have severe diarrhea and sepsis for 10 days or longer are unlikely to survive, even with intensive therapy, because many have extensive ulceration of colonic mucosa and chronic, severe inflammation within the wall of the colon. Ulceration may be exacerbated by administration of NSAIDs. Complications such as catheter-associated thrombophlebitis, colonic infarction (Fig. 32.69), colonization of other organs by *Salmonella* spp. or other enteric bacteria, and laminitis can occur.



FIG. 32.69 Colonic infarction in a horse with salmonellosis. Tenesmus and rectal prolapse were early clinical signs of colonic infarction. (Courtesy Dr. M.J. Murray.)

Measures designed to prevent the spread of *Salmonella* in an environment with potentially susceptible hosts need not be excessively laborious or expensive. The goal is to minimize the size of the infective dose of an enteric

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pathogen to which a susceptible host may be exposed. Thorough cleaning of areas where fecal contamination is likely and prevention of mechanical distribution of contaminated material are the most important measures. Extensive use of disinfectants may not be necessary if cleaning measures are adequate. Cleaning must include removal of organic debris, which can be accomplished with several products designed for that task. Areas that require particular attention are stalls, including water buckets or automatic watering systems, drains, and cracks in the floors and wall; stall implements; surgical areas, including drains; and nasogastric tubes and pumps.

If a diarrheic horse is not hospitalized, it should be isolated to the greatest degree possible, and biosecurity measures should be instituted to prevent transmission and to detect and monitor any potential outbreak.[6] Bedding material should be removed frequently to minimize accumulation of potential enteropathogens. Personnel entering the stall should be restricted to the professional staff, and they should wear gloves, disposable coveralls, and disposable plastic boots. Footbaths with disinfectant are effective only if they are kept clean and fresh because they quickly accumulate organic material that interferes with the action of the disinfectant. Vacated stalls should be thoroughly cleaned, allowed to dry, and disinfected, and culture or PCR testing of selected sites in the stall (floor, drain, waterer) must yield negative results for *Salmonella*. Biosecurity protocol compliance is crucial for preventing an outbreak.

■ Potomac Horse Fever

PHF is an infectious enterocolonic disorder caused by *N. risticii* (formerly *Ehrlichia risticii*).[20-22] The organism is an obligate intracellular parasite, infecting peripheral monocytes and macrophages, colonic and small intestinal epithelial cells, and colon mast cells.[23] The pathophysiology of the disease is incompletely understood, although many horses infected with *N. risticii* have clinical signs and complications similar to those in horses with salmonellosis. Two to 4 days after experimental inoculation with *N. risticii,* horses had a mild, transient fever.[24] By 10 to 14 days after experimental infection, horses had become febrile, had a poor appetite, and exhibited mild to severe gastrointestinal signs ranging from mild colic and soft stool to profuse diarrhea.

In clinical cases of PHF, there are signs of sepsis, including fever, leukopenia, congested mucous membranes, and hypercoagulability. The early fever observed in experimental cases is usually not detected by owners, and when clinical signs

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are seen, it is presumed that the affected horse was infected 10 to 14 days previously. Hypoproteinemia is a frequent finding in horses with clinical cases of PHF, which reflects loss of serum protein through inflamed intestinal mucosa. Of interest is, however, that the magnitude of intestinal inflammation is typically much less than with salmonellosis, and yet the magnitude of hypoproteinemia (total protein concentration < 3 g/dL) can be as severe.

Laminitis is a frequent sequela and may occur in 30% in horses with PHF. *N. risticii* has also been associated with abortion in mares, although this is an unusual occurrence.[25] In some horses that show significant seroconversion to *N. risticii*, laminitis is the only clinical sign.

Mode of Transmission.

Although originally described as a disease of horses living near the Potomac River in Maryland and Virginia, horses with serologic evidence of exposure to *N. risticii* have been reported in most U.S. states. Because early research on PHF demonstrated that infection was readily transmitted through blood,[24] it was presumed that the natural mode of transmission involved an insect or arthropod vector. However, several studies have failed to demonstrate any such vectors.[26,27]

The association between an affected horse and proximity to a river (within 5 miles) remains strong. Investigators have found a possible link between this association and how the disease may be transmitted. *N. risticii* and *Neorickettsia helminthoeca* were found to share a high degree of DNA homology.[28] *N. helminthoeca* is transmitted to mammals by a trematode that parasitizes fish and aquatic snails.[28] This discovery prompted investigators to search for evidence that *N. risticii* might reside in trematodes and their hosts found in riverine inhabitants. *N. risticii* DNA was detected in operculate and pulmonate snails (*Juga* spp. and *Planorbella* spp., respectively) collected from stream water in northern California, where PHF is enzootic.[29,30]

Moreover, *N. risticii* was detected in trematode stages found in the secretions of freshwater snails and in aquatic insects.[31,32] The sequences of these genes were virtually identical to those of the genes of an equine *N. risticii* strain isolated from horses located on a property near the snail collection site. Further work demonstrated *N. risticii* DNA in two trematodes, *Acanthatrium* spp. and *Lecithodendrium* spp., found in bats and swallows, which suggests that these animals may serve as reservoirs and that trematodes are a vector for the

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organism.[33] Oral transmission of *N. risticii* with infected cell cultures has been produced experimentally,[34] which indicates that ingestion of *N. risticii*, rather than blood transmission, is the route of natural infection. Oral transmission and clinical signs of PHF were demonstrated in horses fed *N. risticii*–infected aquatic insects (caddisflies), which suggests that ingestion of infected aquatic insects may be the natural route of infection.[35,36] Ingestion of water containing infected trematode stages released from aquatic snails may also be a route of infection.

Diagnosis.

Accurate confirmation of PHF can be difficult because clinical signs of disease are nonspecific and available diagnostic tests are not entirely reliable. The conventional recommendation is that paired acute and convalescent blood samples be submitted for indirect fluorescent antibody or ELISA testing for antibodies to *N. risticii.* However, serologic evaluation to confirm the disease is not as straightforward as in many other infectious diseases. A fourfold increase in titer between acute and convalescent sera is considered to confirm infection with *N. risticii,* but failure to seroconvert does not rule out infection. Because the onset of clinical signs can be delayed as long as 14 days after infection, horses may seroconvert by the time an acute sample is obtained.[34] The magnitude of titer is not always correlated with active infection, inasmuch as many horses in endemic areas have high titers but no disease. Vaccination also can affect the titer. There is significant interlaboratory variability in results of indirect fluorescent antibody tests, and false-positive results occur frequently.[37] Therefore it has been suggested that indirect fluorescent antibody testing for antibodies to *N. risticii* not be performed in areas that are not endemic for *N. risticii.*[37]

The current standard for diagnosis of PHF used by most clinicians is quantitative PCR testing of whole blood samples to detect *N. risticii* DNA in leukocytes.[38] PCR testing appears to be sensitive and specific in horses with compatible clinical signs.

Treatment and Prevention.

Treatment with oxytetracycline (7 to 11 mg/kg IV twice daily for 4 days) effectively eliminates *N. risticii* from horses in experimental infections. Fever should resolve within 48 hours of beginning treatment with oxytetracycline, and diarrhea typically resolves within 24 to 72 hours of beginning treatment. In one

horse the author treated, clinical signs persisted until the dose of oxytetracycline was increased to 15 mg/kg twice daily. Orally administered doxycycline (10 mg/kg q12-24h) may be effective, although horses with severe gastrointestinal signs may not absorb doxycycline efficiently. Doxycycline must not be given intravenously because it will cause a horse to collapse. Some horses have had clinical relapses 2 to 3 weeks after initial resolution of clinical signs that were responsive to tetracycline. Horses do not remain chronic carriers of *N. risticii*.

In most cases of PHF, intravenous administration of polyionic fluids is necessary to replace fluid and electrolyte losses and to augment preload in horses with poor venous return. Plasma may be required to replace lost plasma proteins. Other colloidal fluids may also be used in patients with hypoproteinemia or sepsis. Because horses improve rather quickly once treatment with oxytetracycline has begun, parenteral nutritional support is usually unnecessary.

Vaccination has appeared to diminish the incidence and severity of disease, but PHF may still develop in vaccinated animals. Experimental results with vaccine were mixed, and the duration of immunoprophylaxis was very limited.[39] Disease severity has appeared to be less in vaccinated animals, although in the summer of 1994 many vaccinated horses developed severe cases of PHF. All of these horses were located in the area where PHF was originally described, and a new strain of *N. risticii* was identified.[40] PCR analysis has revealed multiple strains of *N. risticii*, which may account for the unreliability of the vaccine.[41] Horses in endemic areas should be vaccinated in the early spring and early to mid-summer on an annual basis.

■ Clostridial Diarrhea

Enteric clostridiosis was reported as a clinical problem in the 1970s, and clostridial bacteria were implicated as the causative agents of colitis X.[42] Difficulty in substantiating clostridial bacteria as the cause of enterocolitis in horses led to a deemphasis of this pathogen as a potential cause of diarrhea in adult horses. In the 1990s, with improved laboratory techniques for identification of clostridial toxins, clostridial bacteria were confirmed to be common causative agents of colitis in foals and adult horses.

The two most important clostridial species affecting the equine intestinal tract are *C. difficile* and *C. perfringens*. Most reported cases in adult horses have involved *C. difficile*, although in one report the prevalences of *C. difficile* toxin A and *C. perfringens* enterotoxin in fecal samples from horses with diarrhea

were similar, and in some horses toxins from both clostridial species were identified.[43]

Pathogenesis.

C. difficile is a Gram-positive sporulated obligate anaerobe responsible for most cases of antibiotic-associated diarrhea in many species, including horses, and for a substantial proportion of nosocomial infections in humans and horses.[44,45] *C. difficile* produces two important toxins, named A and B. Most isolates of *C. difficile* produce both toxins, but some isolates produce only one of these. Toxin A can elicit both fluid secretion and a pronounced inflammatory response in the bowel. Toxin A has intestinal secretory and cytotoxic effects,[46,47] increases intestinal permeability,[48] and can activate epithelial cells, neutrophils, mast cells, monocytes, and macrophages to release a multitude of proinflammatory cytokines and vasoactive mediators.[49-51] Two interesting features of toxin A are its induction of the neurotransmitter substance P in both the intestine and dorsal root ganglia and its apparent dependence on substance P for full expression of its pathologic effects in the intestine of rodents.[52] Thus the effects of toxin A appear to be mediated both through direct effects on intestinal cells and through the enteric nervous system.

Toxin B exhibits enterotoxigenic (secretory) activity and has also been shown to have potent cytotoxic effects on human colonic epithelium.[53] Toxin B has little relevance to the pathogenicity of *C. difficile* in animal models, however, and the roles of toxins A and B in the pathogenesis of equine clostridial enterocolitis are not known.

Strains of *C. perfringens* are classified on the basis of the toxins that are produced; at least a dozen have been identified to date.[54] *C. perfringens* type A and type C have been recovered from equine specimens,[55] and several *C. perfringens* toxins have been identified in equine specimens.[56,57] *C. perfringens* type A is the most frequently isolated type, and its enterotoxin is released on sporulation of *C. perfringens* within the intestine. Other exotoxins of *C. perfringens* have phospholipase activity (alpha-toxin), necrotizing cytotoxic effects (beta-, epsilon-, and iota-toxins), and hemolytic effects (theta-toxin).

Clinical Features.

Clostridial enterocolitis affects foals and adult horses. In some reports, toxigenic *C. perfringens* organisms were isolated from more than 50% of foals with

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diarrhea.[57,58] The clinical presentation in foals with *C. perfringens* is predominantly hemorrhagic diarrhea with sepsis. *C. perfringens* can cause septicemia and is often cultured from the blood of foals with hemorrhagic diarrhea. In some foals, classic necrotizing enterocolitis is manifested by gas- or fluid-distended intestines and thickened intestinal mucosa. These changes can be appreciated radiographically and ultrasonographically, and intramural gas produced by clostridial bacteria may be detected with ultrasonography as hyperechoic areas within the bowel wall. *C. difficile* infection is also a cause of acute enterocolitis in foals.[59]

Adult horses with clostridial enterocolitis frequently have diarrhea, but abdominal discomfort or fever may be the primary presenting problem. There are no clinical features that consistently distinguish clostridiosis from salmonellosis, and a spectrum of clinical signs exists, from moderate illness to severe toxemic colitis. Most horses with clostridial enterocolitis develop diarrhea, but in some cases enteritis manifested by ileus and gas distention of the small intestine may be the primary problem. Although both *C. perfringens* and *C. difficile* and their toxins have been detected in a significant number of adult horses with colitis, *C. difficile* appears to be more common.[60-62] In fact, *C. difficile* appears to be the most common cause of antibiotic-associated diarrhea and is a very significant cause of nosocomial diarrhea in horses.[45,63] The most common antibiotics associated with *C. difficile* colitis in horses are erythromycin, trimethoprim/sulfonamides, β-lactam antimicrobials, clindamycin, rifampicin, and gentamicin. Strain differences among isolates of *C. difficile* cultured from the diarrheic feces of horses in intensive care units are associated with toxigenicity, severity of disease, and metronidazole resistance.[45,64] *C. difficile* has been implicated in DPJ,[65] but a cause-and-effect association has not been proven.

Similar to salmonellosis, clostridial enterocolitis can develop into a widespread problem affecting several animals in a hospital or equine facility.[66] Risk factors for developing nosocomial clostridial enterocolitis are similar to those for nosocomial salmonellosis: antimicrobial administration, concurrent gastrointestinal disease, and age susceptibility (foals). In addition, *Clostridium* spp. are well suited to persist in the environment because of the production of spores that are resistant to environmental extremes and many disinfectants.

Diagnosis.

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Diagnosis of clostridial enterocolitis requires identification of toxigenic clostridia from intestinal contents or tissue. Several direct and indirect methods are used to detect toxigenic clostridia; these methods include culture, identification of toxins, and identification of toxin genes. Culture of *C. difficile* or *C. perfringens* requires anaerobic conditions, and the ability to culture these organisms from ingesta or fecal specimens rapidly diminishes with increased time from collection to arrival at a laboratory. It is recommended that samples be transported, chilled (not frozen) on ice, immediately or by overnight delivery for best recovery of clostridial organisms. Tissue specimens submitted for culture, toxin identification, or toxin gene identification should be handled similarly. Because nonpathogenic clostridia are common,[62,67] isolates should be tested for toxin production either by PCR or with bioassay before a definitive diagnosis is made in horses with clinical signs consistent with clostridial enterocolitis. Commercially available tests for clostridial toxins include an ELISA for *C. difficile* toxin A/B, a latex-agglutination test for *C. perfringens* enterotoxin, and an ELISA for *C. perfringens* enterotoxin. *C. difficile* A/B toxin tests have the advantages of being rapid, sensitive, and specific. Tests for *C. perfringens* enterotoxin are not as reliable for definitive diagnosis in most species. Also available is quantitative PCR for *C. difficile* toxin A/B genes and several *C. perfringens* toxin genes that can be applied directly to intestinal content or fecal samples without prior culture and isolation of the bacteria.[68]

Treatment.

Supportive care may be required, as with other cases of acute diarrhea in horses. Treatment with metronidazole (15 to 20 mg/kg PO q6-8h) appears to be effective in eliminating enteric clostridial infection in most cases. In one veterinary teaching hospital, isolates of *C. difficile* were resistant to metronidazole,[69] and vancomycin was used with reported success. Large-scale resistance to metronidazole has not been reported elsewhere, and it should be the first choice in the treatment of suspected clostridial enterocolitis. *Saccharomyces boulardii* is a nonpathogenic yeast used in the treatment of *C. difficile* diarrhea and colitis in humans. The yeast releases a protease that specifically degrades *C. difficile* toxins A and B, and this has been shown to be protective in experimental *C. difficile* colitis in rats and to prevent damage to human colonic epithelium by *C. difficile* toxins A and B in vitro.[70] Although *S. boulardii* (25 g PO q12h) has been shown to colonize the intestinal tract in horses,[71] its efficacy in preventing

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or treating enterocolitis in horses is not clear. *S. boulardii* decreased the severity and duration of enterocolitis in one small study[72] but not in a larger study of antibiotic-associated diarrhea in horses.[71] Di-tri-octahedral smectite has been shown to bind clostridial toxins[73] and may be useful for treating clostridiosis in horses. Di-tri-octahedral smectite is available as a powder or paste and should be administered according to the manufacturer's instructions for 3 to 5 days.

■ Equine Coronavirus Enterocolitis

Equine coronavirus is an enteric pathogen that causes fever, lethargy, colic, and diarrhea primarily in adult horses.[74] Infections have been reported in horses housed in boarding, racing, and show stables and on breeding farms. Rates of morbidity in outbreaks range from 10% to 83%.[75-78] Infections last a week or less and are usually self-limiting unless accompanied by potentially fatal complications such as sepsis or hypoammonemia. Equine coronavirus is shed in feces for several days; shedding may persist as long as 24 days.[77]

Pathogenesis.

Equine coronavirus is a primary pathogen in adult horses and appears to be involved in co-infections with other enteric pathogens in foals, at least in one study in the United States.[79]

Equine coronavirus infection in adult horses causes an acute necrotizing, neutrophilic inflammation that has been well documented in the small intestine.[80] Disease in the large intestine was not significant in a limited study,[80] but it presumably also occurs in the large intestine, at least in horses with diarrhea. Epithelial cell necrosis and intestinal inflammation result in damage to the mucosal barrier, and subsequent sepsis probably results from absorption of microbial molecules. Equine coronavirus can be recovered from the respiratory tract in infected adult horses, but it is not clear whether clinically relevant respiratory disease accompanies enteric infections.[81,82] Fatal hyperammonemia has been reported in some cases of equine coronavirus–infected horses,[77,78,80] probably as a result of changes in the mucosal barrier and intestinal microbiome.

Clinical Features.

The most common clinical signs in adult horses with equine coronavirus infection are fever, lethargy, and anorexia.[77] Encephalopathy characterized by

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circling, ataxia, head pressing, nystagmus, seizures, or a combination of these is a less common clinic feature and appears to be associated with hyperammonemia in at least some cases.[77] Clinicopathologic findings include neutropenia and band neutrophilia (especially early in the course of disease), hyperfibrinogenemia, elevated serum amyloid A concentration, electrolyte and acid-base changes typical of acute enterocolitis, elevated concentration of unconjugated bilirubin, transiently elevated liver enzyme activities, and prerenal azotemia.[74] Hyperammonemia may be present in encephalopathic patients.[77,78]

Diagnosis.

Diagnosis is currently based on quantitative PCR testing of feces while the animal is alive or intestinal tissues or contents after its death. Fecal quantitative PCR is quite sensitive.[77,78] Shedding of equine coronavirus begins after 3 or 4 days, at least in experimentally infected horses,[83] so quantitative PCR test results may be falsely negative very early in the course of disease. Fecal shedding can persist from 3 to 24 days, and so infected horses may test positive after clinical signs resolve.

Treatment.

Most cases are self-limiting and necessitate no specific treatment. Intravenous isotonic fluid administration with appropriate electrolyte supplementation may be required in some cases if diarrhea is persistent and severe. NSAID therapy may be indicated if fever and lethargy persist longer than a day or two. Analgesic drugs are indicated if colic is a problem. Complications such as sepsis and hyperammonemia may occur and necessitate intensive treatment and management as described elsewhere.

■ Cantharidin (Blister Beetle) Toxicity

Pathogenesis.

Cantharidin is the toxic principal found in beetles of the genus *Epicauta*, commonly known as blister beetles.[84-86] Ingestion of the beetles in contaminated alfalfa hay results in absorption of cantharidin through the gastrointestinal tract. Blister beetles feed on the flowers of alfalfa and are incorporated into baled alfalfa hay if the hay is cut and processed simultaneously.[84-86] Large swarms of beetles may be found in relatively small portions of hay. The lethal dose of

cantharidin is less than 1 mg/kg, but the concentration of cantharidin varies from species to species of blister beetles.[84,85] Therefore ingestion of as many as 100 to as few as 6 to 8 beetles may be lethal. Often more than one horse is affected. The fatality rate may be 50% or greater.[84,87]

Cantharidin is a potent irritant, causing cell damage and necrosis on contact.[84,86,87] The mucosa of the gastrointestinal tract is most commonly affected in horses because they ingest the toxin. Ulceration throughout the alimentary tract has been observed in natural and experimental cantharidin toxicity. Diarrhea probably results from the severe ulceration and inflammation of the large intestine, causing increased secretion of water, electrolytes, and protein. Large volumes of fluid and protein are lost in the gastrointestinal tract, which leads to hemoconcentration and profound hypoalbuminemia in some cases.[84,85,87] Cystitis, nephrosis, and myocarditis occur in natural and experimentally produced cases of cantharidin toxicity.[84,86,87] Cystitis and nephrosis result from the high concentration of cantharidin in the urine. The cause of the myocarditis and myocardial necrosis is unknown, but they may also be direct effects of the toxin on the myocardium. Plasma CK activity is often elevated, and this elevation has been postulated to arise from the damaged myocardium.[84,85] Affected horses have a characteristically stiff gait, but histopathologic evidence of skeletal muscle injury that explains the elevated plasma CK activity has not been observed.[85] Hypocalcemia and hypomagnesemia are characteristic features of cantharidin toxicity in horses that have not been explained.[84,85,87] Hypocalcemia may result from hypoalbuminemia, but the ionized calcium concentration is often decreased, along with the total calcium concentration, which indicates that hypoalbuminemia is not responsible for the hypocalcemia.[85]

Clinical Features.

Cantharidin toxicity can cause a range of clinical signs, from mild depression and abdominal discomfort to fulminant signs of toxemia and rapid death, depending on the ingested dose of toxin.[84,85,87] Most commonly, clinical signs include depression, sweating, irritability, abdominal pain, elevated heart and respiratory rates, fever, polyuria, polydipsia, and profuse diarrhea.[84,85,87] Blood is rarely seen in the feces. Affected horses frequently posture to urinate; indeed, stranguria and pollakiuria are characteristic of cantharidin toxicity.[84] Signs of

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hypocalcemia include synchronous diaphragmatic flutter and tremors. Gait may be stiff and stilted. Neurologic signs include head pressing, swaying, and disorientation.[87] Signs of systemic inflammation from sepsis may occur in severe cases. Some affected horses develop severe depression and toxemia and may die within hours after ingestion of cantharidin without developing diarrhea.[84,87] Hematologic abnormalities are similar to those of other causes of acute diarrhea, reflecting dehydration and sepsis. Hypocalcemia (both ionized and total calcium concentrations) and hypomagnesemia are characteristic biochemical features of cantharidin toxicity and may be profound. Azotemia with a urine specific gravity in the hyposthenuric range is common.[84,85,87] Microscopic hematuria and mild proteinuria may be evident.

Diagnosis.

Tentative diagnosis is based on clinical signs and the finding of blister beetles in the hay. Determining the species of the insects may be necessary to estimate the amount of cantharidin ingested. All species of *Epicauta* contain cantharidin, but some have small amounts. Definitive diagnosis requires the measurement of the cantharidin concentration in gastric or intestinal contents and urine.[84,88]

Treatment.

Fluid therapy and maintenance of electrolyte balance are important, as in all cases of acute diarrhea. Particular attention should be paid to the degree of hypocalcemia and renal function as a fluid therapy plan is developed. Specific therapy is limited. Administration of absorbent powders via nasogastric tube is important early to prevent further systemic absorption of cantharidin and local toxicity. Mineral oil administration may also help reduce absorption of the toxin. Pain control may be needed for colic or urinary pain. NSAID therapy should be used judiciously to avoid further injury to the intestinal mucosa and renal toxicity. Alternative analgesics, such as butorphanol or a lidocaine controlled-rate infusion, may be better choices.

■ Antimicrobial-Associated Diarrhea

The onset of acute diarrhea in horses has been associated with the use of several antimicrobial drugs. Lincomycin administered orally and tetracycline administered parenterally have been demonstrated to induce severe diarrhea in horses.[89,90] The oral administration of trimethoprim-sulfonamide, kanamycin,

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erythromycin, metronidazole, and penicillin and parenteral administration of ceftiofur and gentamicin have been implicated in onset of diarrhea, including fatal colitis, in horses. In one report there was no association between trimethoprim-sulfonamide and diarrhea.[91] However, in other reports, prior administration of antimicrobial drugs was positively associated with onset of colitis and negatively associated with prognosis for survival in horses with colitis.[92]

Antimicrobial-associated diarrhea is presumed to be secondary to disruption of normal colonic microflora and the proliferation of an enteropathogen, such as *Salmonella* spp., *C. perfringens,* and *C. difficile.* Of these, *C. difficile* is the most common cause of antimicrobial-associated diarrhea in horses.[45] Of interest, it was reported that mares whose foals were treated with erythromycin for *R. equi* infection developed severe, acute colitis, from which *C. difficile* and its toxins were isolated.[93] Erythromycin was detected in the mares' feces, and exposure to the erythromycin was presumed to have occurred when the mares licked erythromycin from the foals' faces.

■ Other Causes of Acute Diarrhea

NSAID toxicity has been associated with diarrhea secondary to damage to the colonic mucosa. Grain (carbohydrate) overload may cause overproduction of lactate in the colon, which leads to acute diarrhea. A combination of hyperosmolarity of the luminal contents and damage to the colonic mucosa account for the pathophysiologic process grain overload. The clinical signs are similar to those of other acute diarrheal diseases in horses and depend on the severity of the overload. Hyperlactemia, metabolic acidosis, and sepsis are key features of grain overload, and laminitis is a common sequela. Acute diarrhea in adult horses has also been associated with conditions such as lymphosarcoma enterocolitis and other IBDs, intestinal lymphosarcoma, peritonitis, heavy metal intoxication, anaphylaxis, and stress.

■ Clinical Assessments of Patients With Acute Diarrhea

The diagnostic evaluations performed on a horse with acute diarrhea are intended to provide the clinician with information to accurately assess the horse's condition and thus direct therapy toward specific requirements. The first part of the evaluation is a thorough physical examination, with particular attention to the horse's hydration status (skin turgor, gum moisture, capillary refill time),

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evidence of sepsis (fever or hypothermia, hyperemic mucous membranes, prolonged capillary refill time), cardiovascular system (heart rate and rhythm, character of peripheral pulse, capillary refill time), and signs of laminitis (lameness, digital pulse, palpable temperature of hoof walls). Many horses with colitis are moderately to severely dehydrated, with either purplish or brick-red mucous membranes. Purple mucous membrane color reflects venous congestion and poor venous return, whereas brick-red mucous membrane color reflects venous congestion and poor venous return plus arteriole and venule shunting and poor tissue oxygen exchange.

Blood pressure should be monitored; direct measurements via an arterial catheter are the most accurate, but indirect pressure measurements obtained with the use of a Doppler transducer placed over the coccygeal artery are satisfactory. Hypotension and hypertension occur in horses with colitis, and the blood pressure status of a patient often is unpredictable. Blood pressure can be monitored as frequently as labor allows and should be monitored hourly if vasoactive pharmaceutical agents are used.

Laboratory tests that should be performed include CBC and measurements of plasma protein and total solids. Total hemoglobin and PCV are used to assess hydration status. Total protein concentration is used to assess hydration status and degree of protein loss through inflamed intestinal mucosa and, in more chronic cases, through protein catabolism. Clinical hydration, PCV, and total protein concentration are compared to determine the extent of protein loss, and daily evaluations can be used to determine the rate of protein loss. Colloid oncotic pressure measurements are also useful, particularly if colloidal fluids other than plasma are given.

Total WBC count, WBC differential, and WBC structure are examined to assess severity of sepsis; plasma fibrinogen is examined to assess the severity of inflammation. Typically, the total WBC and neutrophil counts decrease initially. This is attributable primarily to bacterial endotoxins and the host's mediators of systemic inflammation, and it occurs in most cases of acute colitis, not just in those caused by *Salmonella* spp. The structure of the WBCs reflects the severity of the inflammatory response. “Toxic” changes such as basophilia, granulation, vacuolation of the cytoplasm, and scalloped borders of the cell membrane or adherence of neutrophils to RBCs do not reflect injury to the neutrophils by toxins but reflect the cells’ responses to stimulation by proinflammatory agents (TNF-alpha, IL-1) and the production of inflammatory mediators by the neutrophils that are toxic to bacteria. The degree of these changes in circulating

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neutrophils can be used to assess the severity of disease and also to assess the progress the horse is making. Often the initial sign that the horse is improving is a decrease in the “toxic” appearance of the neutrophils and a regenerative neutrophil response. A horse that continues to have severe neutropenia with a degenerating left shift or neutrophils, with cytoplasmic vacuolation, granulation, and basophilia, for more than 10 days has severe colitis that is unlikely to resolve.

Serum chemistry tests that should be performed include measurements of electrolytes (sodium, chloride, potassium, and calcium), BUN and creatinine, and blood lactate concentration, as well as assessment of acid-base status (blood pH and bicarbonate, or total CO_2). Many horses with diarrhea are hyponatremic, hypochloremic, and hypokalemic. With decreased feed intake, hypocalcemia occurs. A high–anion gap metabolic acidosis with hyperlactemia may be noted, particularly in horses with sepsis. The severity of these electrolyte disturbances should be monitored, in many cases daily, to allow for appropriate therapy. Parameters of renal function (BUN and creatinine) are frequently increased in horses with diarrhea for several reasons. Prerenal azotemia resulting from dehydration and decreased filtration across the glomerulus accounts for some of the increase in these parameters. Hyponatremia and hypochloremia can cause a decrease in glomerular filtration and an increase in BUN and creatinine levels that are secondary to tubuloglomerular feedback. Many horses that are adequately hydrated and yet moderately hyponatremic (serum sodium 120 to 128 mEq/L) remain azotemic until sodium levels increase above 130 mEq/L. In addition, many horses with toxemic colitis have damage to renal parenchyma, presumably the result of the effects of inflammatory mediators and alterations in renal blood flow.

The acid-base status can be evaluated by estimating serum bicarbonate on the basis of the total CO_2 or directly from a venous or arterial blood gas analysis. A venous blood gas sample helps in assessing perfusion and oxygen extraction. An increased venous oxygen partial pressure (>60 mm Hg) is indicative of poor capillary perfusion and oxygen delivery to the tissues. Affected horses usually have brick-red mucous membranes.

■ Principles of Therapy for Acute Diarrhea

Because the pathophysiologic process of equine colitis is complex, treatment is often multifaceted. Many of these treatments provide well-documented benefit,

whereas with others the efficacy is based only on empirical judgment. Outcome is determined not only by the severity of the primary disease causing colitis but also by complications that may arise from the disease.

In cases of acute colitis, fluid administration remains the treatment of primary importance. Most patients require intravenous administration in the early stages. The fluids used must replace fluid, sodium, chloride, and potassium losses. In many cases, large volumes are required for several days. (More specific guidelines for fluid therapy in colitis patients are covered in the Fluid Therapy for Horses with Gastrointestinal Diseases section and in Chapter 44.)

Most horses with colitis become hypoproteinemic as a result of protein leakage through the inflamed colon and catabolism of albumin secondary to negative energy balance. Hypoproteinemia frequently leads to edema formation in several areas of the body, including the intestinal tract, and can compromise the clinician's ability to keep the patient properly hydrated through fluid administration. Intravenous plasma therapy (6 to 10 L) is often beneficial as a colloidal fluid and as a protein replacement fluid. Other colloidal fluids may be more cost-effective for increasing colloidal oncotic pressures in hypoproteinemic horses but do not have the additional properties of plasma that may be beneficial. Plasma contains other proteins besides albumin and therefore can be of benefit beyond improvement of plasma oncotic pressure. Fibronectin is essential to the normal function of the monocyte-macrophage system in the processing of a variety of antigens. Other plasma proteins such as elastase and proteinase inhibitors, complement inhibitors, AT-III, and other inhibitors of hypercoagulability may be beneficial to patients with colitis.

The nutritional requirements of patients with colitis need to be considered, particularly in a case that may be protracted. Horses with colitis are typically anorexic, and the disruption of normal physiologic processes in the inflamed cecum and colon limits the effectiveness of these organs to digest and absorb nutrients. In addition, several mediators of inflammation and septicemia alter protein and calorie metabolism, which results in a catabolic state. Therefore even if an affected horse eats, it is likely to be in a severe caloric deficit for some time. Normally an average horse requires approximately 15 MCal/day. An septic horse may require 25 MCal/day. In a catabolic patient, muscle and fat tissue are mobilized and used in lieu of ingested nutrients. The plasma protein pool, including albumin and immunoglobulins, also is catabolized. In many cases of colitis, the decrease in plasma protein may be as much a result of catabolism as of leakage through the inflamed colon. A variety of products can be used for

enteral feeding (see Chapter 50).

Colitis is an inflammatory disease, and limiting inflammation is desirable when treating patients, particularly those with severe disease. Moreover, horses with acute colitis, regardless of the cause, have signs compatible with systemic inflammation associated with sepsis. Flunixin (0.25 to 0.5 mg/kg IV q6-8h) is the most commonly used antiinflammatory therapy in horses with colitis. However, the use of flunixin should be judicious and must be carefully monitored to avoid unwanted side effects on the gut mucosa and kidneys. Other antiinflammatory therapies, such as COX-2 selective firocoxib or lidocaine administered by controlled-rate infusion, may also be beneficial with less detriment to the gastrointestinal mucosa.

Sepsis is a common clinical feature in horses with acute colitis. Most of the clinical signs of sepsis are probably attributable to the effects of endotoxin. Therefore specific therapy for endotoxemia may be warranted.

The use of antimicrobial drugs in the treatment of colitis is controversial. In cases of colitis caused by *N. risticii,* the efficacy of tetracycline (6.6 to 11 mg/kg IV once or twice daily) is documented.[94,95] In other cases of colitis, including *Salmonella* colitis, in which specific antimicrobial sensitivities to the *Salmonella* spp. have been established, the efficacy of antimicrobial administration is not as well documented. Many clinicians believe that the use of an antimicrobial for which the *Salmonella* spp. have demonstrated sensitivity, such as chloramphenicol, enrofloxacin, gentamicin, amikacin, or a third-generation cephalosporin, does not significantly alter the course of the disease or hasten the elimination of the organism from the body. However, there is no published evidence either supporting or disputing the efficacy of antimicrobial treatment for salmonellosis, and the use of antibiotic therapy remains a judgment of the clinician. In patients with sepsis, the use of broad-spectrum antibiotics is justified to prevent bacteremia or organ colonization by *Salmonella* spp. or other enteric organisms. Antibiotics such as chloramphenicol and enrofloxacin that are lipid permeable or are concentrated in cells are a benefit because *Salmonella* reside, proliferate, and persist intracellularly in macrophages and other cells.

Medications that minimize or abolish colonic fluid secretion are of tremendous benefit in the treatment of equine colitis. Medications such as kaolin, bismuth subsalicylate, and activated charcoal are frequently used in cases of colitis in adult horses, but their efficacy as antisecretory agents in this context is unknown. These medications are more effective in foals with diarrhea, than in affected adult horses, probably as a result of an effect on the small intestine

rather than the colon. Absorbent powders such as activated charcoal or di-tri-octahedral smectite (Bio-Sponge) may be useful for absorbing bacterial toxins, particularly in horses with clostridiosis.

■ Chronic Diarrhea

Chronic diarrhea is one of the most frustrating disorders encountered by equine practitioners, with regard to both determining the cause and therapeutically managing the diarrhea.[96] Chronic diarrhea may be defined as persistent diarrhea of at least a month's duration. Although there are many causes of chronic diarrhea, these cases can generally be divided into two groups: diarrhea resulting from a chronic inflammatory condition and diarrhea resulting from a disruption in normal physiologic processes. Inflammatory conditions cause histologic changes in the colon mucosa, including pleocytosis (neutrophils, eosinophils, and lymphocytes), mucosal congestion, and mucosal erosion and ulceration. Submucosal edema, capillary congestion, and lymphatic congestion may be present. With physiologic disorders, there are no morphologic changes in the colon, and diarrhea is presumed to result from abnormal VFA synthesis or absorption. A small percentage of horses with chronic diarrhea have a primary disorder of a system other than the intestinal tract, such as congestive heart failure or hepatic disease. A thorough physical examination and evaluation of a minimum database (CBC, serum chemistry profile, urinalysis) should help establish whether a disorder is nonenteric.

Causes.

Inflammatory disorders that can cause chronic diarrhea include disorders caused by infectious agents such as chronic salmonellosis; chronic parasitism with *S. vulgaris*, *Strongylus edentatus*, and larval cyathostomiasis; abdominal abscessation; and, in weanling foals, equine proliferative enteritis caused by *L. intracellularis*, gastrointestinal *R. equi* infection, and rotavirus infection.

Noninfectious inflammatory causes include cellular infiltrative disorders such as granulomatous enteritis and lymphosarcoma, as well as sand enteropathy. Sand causes diarrhea through continued irritation of the mucosal lining of the colon. In weanling foals, gastric ulceration and gastric emptying disorders have been associated with chronic diarrhea that resolved when H_2 antagonist therapy was started. NSAIDs can cause chronic diarrhea, which is accompanied by varying degrees of pathologic change in the large intestine.

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Noninflammatory chronic diarrhea of colonic origin is thought to be a result of abnormal fermentation of cellulose by the resident bacteria in the large intestine. In vitro fermentation of feces from normal horses and horses with chronic diarrhea revealed that feces from the diarrheic horses produced more gas, acetate, and propionate than did feces from normal horses.[97] Whether this reflects fermentative activity within the colon is not known, but an abnormal increase in acetate could lead to fluid retention within the colonic lumen because acetate inhibits colonic absorption of sodium and water.

Diagnosis.

The diagnostic approach to cases of chronic diarrhea should be based on an attempt to differentiate inflammatory from physiologic causes. The evaluation can be extensive and expensive, and the owner should be prepared for the cause of the diarrhea to remain undetermined. Horses with chronic diarrhea may be adequately hydrated if water consumption has matched water losses; however, many such horses are brought to the veterinarian in a condition of mild to moderate dehydration. Moderate weight loss also has often occurred. On physical examination, signs of toxemia (injected mucous membranes, congested or hyperemic mucous membranes) should be noted.

A CBC should be evaluated for signs of chronic inflammation. Such changes include a decrease in the RBC count and PCV as a result of decreased erythrogenesis secondary to sequestration of iron by bone marrow macrophages (anemia of chronic inflammation). The WBC count may be normal or moderately increased. The fibrinogen levels can be normal or increased. Changes in WBC count and fibrinogen levels are influenced by the degree of inflammation and whether the inflammatory response is localized. Therefore a normal CBC does not rule out an inflammatory cause of the chronic diarrhea.

Peritoneal fluid analysis may reveal an increase in protein or WBCs, which is indicative of an inflammatory process within the peritoneal cavity. Often, however, colon inflammation is not reflected by alterations in the peritoneal fluid.

Serum chemistry values vary in horses with chronic diarrhea. Many affected horses have evidence of hyponatremia, hypokalemia, hypochloremia, azotemia, and metabolic acidemia. Other horses, particularly those with less severe chronic diarrhea, may have no serum chemistry abnormalities.

With a chronic inflammatory disorder of the colon, the total serum protein concentration is usually decreased because of protein leakage from the

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capillaries and disruption of the colonic mucosal integrity. This is usually reflected by hypoalbuminemia. In some cases, hyperglobulinemia occurs, and total serum protein concentration may be normal.

Increases in hepatic-associated enzymes, including sorbitol dehydrogenase, GGT, and aspartate aminotransferase, and serum bile acids indicate that hepatic disease is present. Hepatic changes and dysfunction such as inflammation, fibrosis or fatty infiltration, or biliary inflammation can be associated with diarrhea.

Feces should be examined for parasite ova; cultured for *Salmonella* spp., *C. difficile,* and *C. perfringens;* and tested for clostridial toxins. Weanlings should be tested for *L. intracellularis* and *R. equi*. In cases of acute diarrhea, it has been recommended that five consecutive fecal samples be cultured for *Salmonella* spp., but in cases of chronic diarrhea, many more are often necessary. As many as 15 fecal cultures may be needed to get a positive *Salmonella* spp. culture. In addition, a rectal mucosal biopsy sample should be cultured. In weanlings, the feces should be examined for rotavirus by transmission electron microscopy or ELISA. Although it is an unusual cause of diarrhea in weanlings, rotavirus should be considered when several foals on the same farm have chronic diarrhea.

An oral glucose absorption test can be done to determine whether there is small intestinal malabsorption, which would indicate a widespread small and large intestinal disorder if both diarrhea and glucose malabsorption are present.

A rectal mucosal biopsy may provide evidence of a widespread inflammatory disorder, such as one of the IBDs.[98] Biopsy specimens should be evaluated by a pathologist experienced in examining equine tissue specimens, and some caution should be used to avoid overinterpretation of the presence of few lymphocytes, plasma cells, and eosinophils.

Frequently the results of the previously mentioned diagnostic procedures do not determine the cause of the chronic diarrhea. In such cases, exploratory laparotomy may be warranted. This is particularly true if episodes of abdominal discomfort accompany the chronic diarrhea. In addition to exploration of the abdomen for the presence of masses or abscesses, the colon and cecum should be thoroughly examined. Biopsy samples from several sites of the colon, cecum, and mesenteric lymph nodes should be submitted for histopathologic study and culture for *Salmonella* spp.

Treatment.

Treatment of horses with chronic diarrhea is often empirical because either a

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cause has not been determined or the cause is not amenable to treatment. With inflammatory causes such as lymphosarcoma and granulomatous enteritis, the disease is usually untreatable. Some cases of eosinophilic colitis have been treated successfully with corticosteroids.

Chronic parasitism may be resolved with appropriate anthelmintic therapy, although damage to the mucosa may have become too extensive to allow normal absorption to occur. Administration of larvicidal doses of fenbendazole (15 mg/kg PO daily for 5 days) is usually effective in horses with nonresistant small strongyle infections. Treatment with ivermectin (0.2 mg/kg PO) or moxidectin (0.4 mg/kg PO) may be indicated when benzimidazole resistance is encountered. Concurrent administration of prednisolone (1 mg/kg PO once daily for 5 to 7 days) may minimize inflammation secondary to dying migrating larvae within the vasculature and mucosa of the colon.

Chronic salmonellosis does not lend itself to specific treatment because antimicrobial therapy generally does not resolve *Salmonella* infection in horses.

Administration of products containing bismuth subsalicylate is effective in some cases of chronic diarrhea. The action of bismuth subsalicylate is mediated through inhibition of prostaglandin synthesis and possibly by other undefined mechanisms. In full-size horses, a large volume, 1 to 4 L/day, must be administered to be effective.

Iodochlorhydroxyquin administered orally is effective in managing some cases of chronic diarrhea caused by maldigestion of cellulose by colonic microorganisms.[99] The actual mechanism of action of iodochlorhydroxyquin in resolving the diarrhea is not known. The drug was originally administered to horses with chronic diarrhea because an increase in fecal trichomonads was observed. However, this observation probably reflected the fact that trichomonads were washed out of the cecum and colon rather their being the cause of the diarrhea. Iodochlorhydroxyquin has minimal effect on colonic protozoal populations. It is not uniformly effective, and in many cases its effectiveness is only transient. Stools may initially become formed, but the diarrhea often recurs within several days. An initial dose of 20 mg/kg/day is recommended. If diarrhea recurs, decreasing the dose to 10 mg/kg/day is sometimes effective. If the medication is effective, it must be continued because if it is discontinued, the diarrhea resumes.

Changes in diet occasionally are helpful in horses with noninflammatory chronic diarrhea. A complete pelleted feed may positively affect the constituent VFAs produced in the colon and thus facilitate water absorption. Alternatively,

trying different types of roughage may result in selecting one that creates a more favorable metabolic environment in the large intestine.

The removal of sand from the colon by nonsurgical means is difficult, and in one report the administration of psyllium to remove experimentally introduced sand was not effective.[100] Other treatments used with anecdotal, but undocumented, success include fecal transfaunations, probiotics, cultured yogurt, and brewer's yeast.

Surgical Disorders of the Large Intestine

Anthony T. Blikslager • John F. Marshall

Simple Obstruction

Simple obstructions of the large intestine tend to have a more gradual onset than those of the small intestine and, in the case of large colon impactions, are frequently amenable to medical therapy.[1] Cecal impactions present much more of a dilemma because of the greater propensity of the cecum to rupture[2] and the relative difficulty of surgically manipulating it.[3]

■ Cecal Impaction

Cecal impaction may develop as a primary condition or may arise as a complication in horses with another disease state, particularly those that have been hospitalized and undergone surgery.[4,5] Reasons for development of cecal impaction in hospitalized horses are unclear, although motility disturbances arising from postoperative pain may play a role. Primary cecal impactions typically manifest as firm ingesta-filled impactions, whereas impactions that occur as an apparent secondary impaction tend to manifest as gross distention of the cecum with fluid ingesta. The latter has been termed *cecal dysfunction* and may be initiated by abnormalities in cecal motility. Evidence in favor of this supposition includes the fact that the right ventral portion of the colon is typically empty in horses with cecal dysfunction, which suggests a lack of aborad movement of digesta through the cecocolic orifice. However, clinical differentiation of cecal impaction and cecal dysfunction may be very difficult.[6] Horses with primary dry ingesta–filled cecal impactions tend to have a gradual onset of abdominal pain over a number of days. Such impactions have a propensity to rupture before the development of severe abdominal pain or

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systemic deterioration and therefore must be closely monitored.[5] In many horses with secondary cecal impactions, such as an impaction that arises in a horse hospitalized for surgery, it is very difficult to detect onset of colic because there is an expectation for horses to show some degree of depression after surgery and because many affected horses are already receiving analgesics such as NSAIDs or opiates. One potential method of detecting these cases is to closely monitor fecal output in the postoperative period.[7] Normal horses should produce six to eight piles of manure per day, whereas abnormal horses may produce no evidence of defection or a marked reduction in fecal production (less than three piles of manure per day). The latter should be carefully evaluated for both pain and intraabdominal evidence of an impaction and treated accordingly.

The diagnosis of cecal impaction is based on rectal palpation of a firm, impacted cecum or a grossly distended fluid-filled cecum. According to one study, such findings were detected in 89% of horses with cecal impaction that underwent rectal palpation of the abdomen.[6] However, there are cases in which only the cupula is impacted, and these are reportedly not palpable rectally.[8] Treatment for horses with dry ingesta–filled cecal impactions may include initial medical therapy, including aggressive administration of intravenous fluids, judicious use of analgesics, and administration of oral laxatives (e.g., 2 to 4 L of mineral oil per 500 kg).[9] Other oral laxatives have also been recommended, including magnesium sulfate (1 g/kg in 4 L of water PO up to twice daily for up to 3 days) and psyllium (1 kg q6-8h).

However, if the cecum is grossly distended or if medical therapy has had no effect within a reasonable period of time, surgical evacuation of the cecum via a typhlotomy is indicated. In one comparison of treatment of cecal impaction medically or by surgical intervention, horses that had surgery had a significantly improved prognosis for survival.[5] As far as surgery, it has been difficult to determine whether a cecal bypass should be performed. In some cases, if the cecum is not bypassed, cecal impaction recurs. This may be because the cecum becomes dysfunctional as a result of the impaction or because cecal dysfunction was the initial reason of impaction.[10] However, in another study in which horses that had had typhlotomy alone were compared with those that had had both typhlotomy and a cecal bypass via jejunocolostomy, there was no significant difference in outcome.[5] Nonetheless, this aspect of surgical treatment remains controversial.[11,12]

With regard to the prognosis, a study of 150 horses with cecal impaction

showed that horses treated medically had a short-term survival rate of 61%, which was significantly lower than that of horses treated surgically (82%). One year later, 57% of horses treated medically were still alive, whereas 70% horses treated with typhlotomy were still alive, as 73% of those treated with typhlotomy and jejunocolostomy.[5] As previously mentioned, there was no significant difference in prognosis with the two surgical approaches. However, clinicians should be aware that there may be regional differences in the types of cecal impactions and prognoses. For example, in a study from the United Kingdom, cecal bypass was preferred because of the authors' experience with recurrence of cecal impaction.[12]

■ Large Colon Impaction

Impactions of the large colon with ingesta occur at sites of anatomic reductions in luminal diameter, particularly the pelvic flexure and the right dorsal portion of the colon.[13] Although a number of reported risk factors have been reported, most have not been proven. However, a sudden restriction in exercise in association with musculoskeletal injury appears to be frequently associated with onset of impaction. In addition, one study of 120 horses with large colon impaction showed that 41% of cases were diagnosed in the winter,[14] possibly in relation to reduced water intake or changes in diet. Equine feeding regimens may be very important in the development of large colon impactions. For example, twice-daily feeding of concentrate are associated with secretion of large volumes of fluid into the small intestine, which results in transient hypovolemia (15% loss of plasma volume).[15] This leads to activation of the renin-angiotensin-aldosterone system; aldosterone stimulates absorption of fluid from the large colon, which may may dehydrate colonic contents.[15,16] Large concentrate meals may also decrease small intestinal transit time, which results in increased presentation of soluble carbohydrate to the cecum and large colon. Large amounts of fluid enter the colon occur as concentrates are readily fermented in the large intestine, which would also be expected to activate the renin-angiotensin-aldosterone system. This in turn also triggers net fluid absorption from the large colon. The effects of these large fluid fluxes on development of large intestinal disorders remains to be fully characterized, but undoubtedly they play some role in the syndrome of colic. From a practical standpoint, intestinal fluid fluxes may be reduced with frequent small feedings in horses requiring concentrate to maintain condition.[15]

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Clinical signs of large colon impaction include slow onset of mild colic that is typically well controlled with administration of analgesics but becomes increasingly more severe and refractory if the impaction does not resolve.[14] The diagnosis is based on rectal palpation of a firm mass in the large colon. However, the extent of the impaction may be underestimated by rectal palpation alone because much of the colon is out of reach. Adjacent colon may be distended if the impaction has resulted in complete obstruction. Initially, medical treatment should be attempted. Intermittent abdominal pain is controlled with administration of analgesics (flunixin meglumine, 0.25 mg/kg IV q6h to 1.1 mg/kg IV q12h; butorphanol, 0.05 mg/kg IV as needed; or xylazine, 0.3 to 0.5 mg/kg IV as needed). Detomidine (4 to 10 mg IV as needed) can be administered but with great caution because this agent readily masks severe pain. If there are concerns about use of nonselective COX inhibitors, including flunixin meglumine, COX-2 inhibitors such as firocoxib can be used. Considerations related to nonselective COX inhibitors relate to concerns about gastrointestinal mucosal integrity, or other organ systems such as the kidneys. In these instances, a COX-2 inhibitor may be indicated for control of pain. These drugs include meloxicam, which is not labeled for horses in the United States and only modestly targets COX-2, or the highly selective COX-2 inhibitor firocoxib, which is available in the United. States. Firocoxib must be administered in an off-label loading dose (0.3 mg/ kg), followed by the labeled dose (0.1 mg/kg, IV, q24h).[17]

In addition to analgesics, an oral laxative should be administered via nasogastric tube. Although mineral oil (2 L/500 kg to 4 L/500 kg PO) is commonly used as a laxative, hydration of the colonic contents can be better achieved by magnesium sulfate (1 g/kg in 4 L of water PO) or sodium sulfate (1g/kg in 3 L of water PO) by stomach tube.[18] Sodium sulfate has been shown to result in greater colonic content hydration than does magnesium sulfate, but it also results in significant thirst and hypocalcemia; therefore magnesium sulfate is preferred.[18] Access to feed should not be permitted, but water should be freely available. For impactions that persist, aggressive oral or intravenous fluid therapy, or both, should be instituted. One study demonstrated the increased efficacy of a continuously administered oral rehydration solution in softening feces in comparison with intravenous fluids, which are probably best suited to restoring the systemic extracellular fluid compartment.[19] If the impaction remains unresolved, if the pain becomes uncontrollable, or if extensive gas

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distention of the colon occurs, surgery is indicated. At surgery the contents of the colon are evacuated via a pelvic flexure enterotomy. The prognosis is good for horses in which impactions resolve medically (95% long-term survival in one study) and fair for horses that require surgical intervention (58% long-term survival in the same study).[1]

■ Enteroliths

Enteroliths are mineralized masses typically composed of ammonium magnesium phosphate (struvite).[20] One study has suggested that an increase in magnesium in the diet may predispose to the formation of enteroliths.[21] Enteroliths almost always form around a nucleus such as a silicon dioxide stone, a nail (Fig. 32.70), or a piece of rope that has been ingested and are most commonly found in the right dorsal and transverse portions of the colon. Although enterolithiasis has a wide geographic distribution, the incidence in California is high. In one California-based study, horses with enterolithiasis represented 28% of the surgical colic population. In addition, Arabian, Morgan, and American Saddlebred horses and donkeys are at risk of this disease.[22] A prospective, unmatched case-control study performed in California indicated that horses fed a diet composed predominantly of alfalfa hay are at risk for development of enterolithiasis, and allowing horses to graze on pasture was protective against this disease.[23]

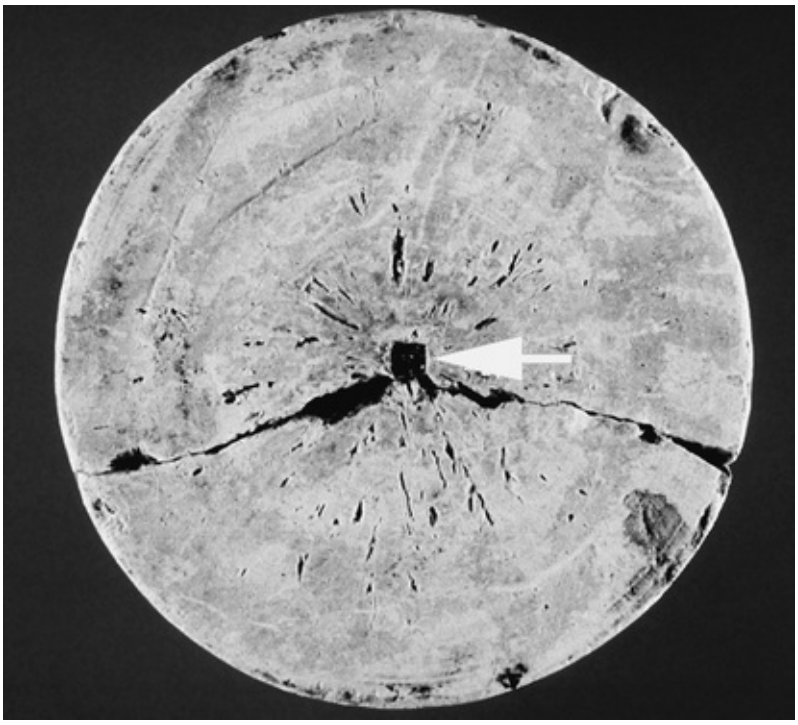


FIG. 32.70 Cut section of an enterolith. Note the presence of a nail head *(arrow)* that served as a nucleus for the formation of a struvite enterolith. (Courtesy Dr. David G. Bristol.)

Initially, clinical signs include intermittent abdominal pain in mature horses (almost always older than 4 years of age),[24] with few abnormalities on rectal examination. As enteroliths become larger, they may occlude the lumen of the colon and cause acute pain and large colon distention that necessitate surgical exploration. In some cases an enterolith is forced into the small colon, where it causes acute small colon obstruction. Enteroliths may be diagnosed on abdominal radiographs or at surgery. On rare occasions, an enterolith may be palpated rectally, particularly if it is present in the distal small colon.

In general, surgery is required for these cases, although there are reports of enteroliths being retrieved rectally. In fact, in one study, 14% of horses that presented for treatment of enterolithiasis had a history of passing an enterolith in the feces.[22] However, enteroliths are typically located in the right dorsal portion of the colon, transverse colon, or small colon. At surgery the enterolith is gently pushed toward a pelvic flexure enterotomy, but removal frequently requires a separate enterotomy of the right dorsal portion of the colon to prevent rupture of the colon. After removal of an enterolith, further exploration must be conducted to determine whether other enteroliths are present. Solitary enteroliths are usually round, whereas multiple enteroliths have flat sides. The prognosis is

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good (the rate of 1-year survival among 900 horses that underwent surgery in one study was 92%) unless the colon is ruptured during removal of an enterolith.[22] Colon rupture occurred in 15% of the 900 cases.[22]

■ Sand Impactions of the Large Colon

Sand impaction of the large colon is common in horses with access to sandy soils, particularly horses whose feed is placed on the ground. Sand accumulates in the large colon, particularly the right dorsal portion of the colon and pelvic flexure, but may be present in multiple locations.[25,26] In addition, sand may trigger diarrhea, presumably as a result of irritation of the colonic mucosa.[27] In horses with sand impactions, clinical signs are similar to those of horses with large colon impactions. In addition, sand may be found in the feces, and auscultation of the ventral abdomen may reveal sounds of sand moving within the large colon.[28] Radiography of the cranioventral portion of the abdomen may be useful for the detection of sand within the large colon and can serve to monitor resolution of sand accumulation.[29] In particular, one study showed that horses with a greater area of sand accumulation, multiple sand accumulations, and more gas on radiographs were significantly more likely to require surgery.[30] The diagnosis is definitively made at surgery but may be tentatively based on clinical signs compatible with a large colon impaction, together with evidence of sand in the feces. To determine the presence of sand, several fecal balls are placed in a rectal palpation sleeve or other container, which is subsequently filled with water. Sand, if present, will accumulate at the bottom of the container.

Initially, medical therapy should consist of a laxative such as mineral oil, magnesium sulfate, or psyllium in combination with enteral or intravenous fluid therapy; this is usually successful in the management of uncomplicated sand enteropathy.[29] Administration of psyllium hydrophilic mucilloid in water by stomach tube may facilitate passage of sand, although an experimental study failed to show a benefit of this treatment.[31] If colic becomes intractable, surgical evacuation of the large colon should be performed. Care must be taken to prevent tearing of the colon as a result of the weight of sand during exteriorization.[32] The prognosis is good; for instance, in one study, more than 94% of horses survived to discharge, regardless of whether they were treated medically or surgically.[30]

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Nonstrangulating Obstruction of the Colon

Several configurations of displacements, including nephrosplenic entrapment of the colon, obstruct the colonic lumen but do not compromise the colonic blood supply. Therefore these are technically simple obstructions. However, the lumen may not be completely obstructed, and some degree of venous congestion is common.[34] In some cases, nonstrangulating obstructions are difficult to differentiate from large colonic volvulus because a volvulus of less than 270 degrees does not result in strangulation of blood supply but can cause considerable abdominal pain and gas distention of the abdomen. In this regard, nonstrangulating obstructions represent early stages of strangulating obstructions. Clinical signs include mild to moderate colic with evidence of large colon distention on rectal palpation of the abdomen. The diagnosis is confirmed at surgery.[35] However, there is evidence that horses with suspected displacements can be successfully treated with a medical regimen, including fluids, analgesics, and exercise.[33] However, if pain is recurrent, particularly if it is of increasing intensity and frequency, or if there is evidence of intestinal compromise (particularly progressive changes in abdominal fluid and cardiovascular parameters indicating systemic deterioration), the horse should undergo surgery immediately. The prognosis for nonstrangulating obstructions of the large colon is good; more than 80% of horses in one report survived to hospital discharge.[36]

■ Right Dorsal Displacement of the Large Colon

With right dorsal displacement of the colon, the colon is displaced to the right of the cecum. Findings on rectal palpation typically include colonic bands coursing horizontally across the abdomen, with evidence of colon lateral to the cecum. In the most common configuration of right dorsal displacement, the large colon wraps around the cecum (pivoting counterclockwise around the cecum, in a view from above the horse), with the pelvic flexure lying in the left dorsal quadrant. Alternatively, the colon may wrap around the cecum in the opposite direction, with the pelvic flexure lying in the right dorsal quadrant.[37] One study suggested that although the prognosis for recovery after surgical correction of right dorsal displacement is good, this condition is associated with an increased risk of colic episodes in the postoperative period.[38] The reason for this has not been elucidated but may reflect an etiologic difference between right dorsal displacement and other simple obstructions of the large colon.

■ Nephrosplenic Entrapment (Left Dorsal Displacement) of the Large Colon

On the left side of the equine abdomen, colon displacements most commonly involve entrapment of the colon over the nephrosplenic ligament, although left dorsal displacements may be detected before the colon is fully entrapped. Clinical signs include gradual onset of mild to moderate colic as the entrapped colon fills with gas. Rectal palpation reveals gas distention of the ventral portion of the colon and displacement of the spleen toward the center of the abdomen. Careful palpation by following colonic bands up to the left dorsal quadrant often reveals the presence of colon between the left kidney and the spleen. Diagnosis may be based on rectal palpation of the colon traversing the nephrosplenic ligament. Alternatively, a tentative diagnosis can be reached with abdominal ultrasonography.[39] The spleen can be visualized on the left side of the abdomen, but the dorsal spleen and left kidney are obscured by gas-distended bowel, the dimensions of which may extend cranially from the paralumbar fossa. As with other examination techniques, ultrasonography is not uniformly reliable and occasionally yields false-positive results and false-negative results. A definitive diagnosis may necessitate surgery.

Treatment has traditionally been surgical intervention, during which the colon is gently rocked free of the nephrosplenic space. However, good success rates have been reported for nonsurgical intervention such as either light exercise (trotting) or physical manipulation (rolling) to return the colon to a normal location.[40,41] In addition, phenylephrine (3 to 6 µg/kg/min over 15 minutes) may be administered before exercise or rolling to decrease the size of the spleen.[42] In affected horses exhibiting mild pain and normal abdominocentesis findings, light trotting exercise for a period of 30 to 45 minutes may help correct the displacement.[40,43] Alternatively, the horse is anesthetized and placed in right lateral recumbency in preparation for rolling. The horse is rotated up to dorsal recumbency, rocked back and forth for 5 to 10 minutes, and then rolled down into left lateral recumbency.[44] One study showed that rolling is more effective than other medical treatments, including administration of phenylephrine and exercise.[45] Regardless of nonsurgical technique adopted, the resolution of displacement should be monitored by repeat rectal palpation of the nephrosplenic space and by ultrasonography to determine whether the entrapment has been relieved. If the entrapment remains, or there is any deterioration in clinical signs, the horse should undergo surgery.

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Regardless of technique, the prognosis is good. Several studies have demonstrated survival rates exceeding 90%.[40,46] Recurrence of left dorsal displacement has been described and may affect up to 23% of horses.[47] To prevent recurrence, laparoscopic closure of the nephrosplenic space may be performed after correction of the displacement.[47-49]

■ Atresia Coli

Atresia of any segment of the colon is a rare congenital abnormality in horses (Fig. 32.71).[50] The heritability and causes of the condition are unknown. One potential mechanism for development of the lesion is intestinal ischemia during fetal life, which secondarily results in necrosis of a segment of intestine. Clinical signs include a failure to pass meconium and colic within the first 12 to 24 hours of life. Secondary abdominal distention results from complete intestinal obstruction, and abdominal radiographs may reveal gas distention of the colon. The diagnosis is made at surgery. Any portion of the colon may be absent, but the distal segment of the large colon or the proximal small colon is usually most severely affected. If sufficient tissue is present, anastomosis to the proximal blind end of the colon may be attempted. The prognosis depends on which segment of the colon is absent but is usually poor because of an absence of distal portion of the colon.

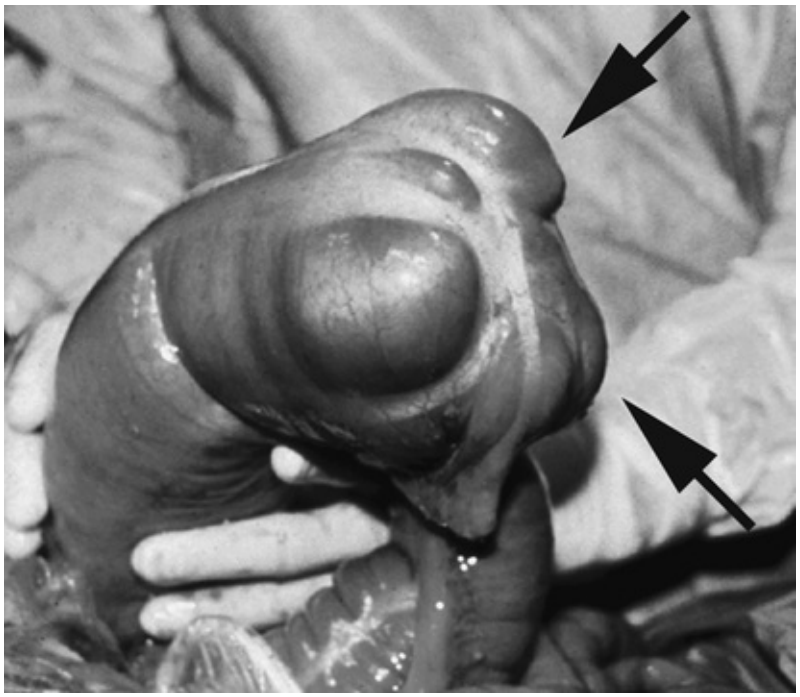


FIG. 32.71 Operative view atresia coli in a foal. Complete atresia of the pelvic flexure has resulted in a blind-ended ventral portion of the colon *(arrows),* which in turn resulted in gas distention of the colon. The ventral portion of the colon was subsequently anastomosed to the dorsal portion of the colon in this case.

Strangulating Obstruction

Although simple obstruction of the large colon carries a very favorable prognosis, strangulating obstruction of the large colon is associated with high fatality rates in most centers.[51] However, this is likely to be dependent on the duration of disease: In at least one referral center, early referral was associated with a marked increase in survival.[52] Two forms of strangulating obstruction are recognized: hemorrhagic strangulating obstruction, in which the arterial blood flow remains patent while veins are collapsed, and ischemic strangulating obstruction, in which both the arteries and veins are collapsed. The differentiating factor between the two is probably how tightly twisted the volvulus is. It has been suggested that ingesta-filled intestine is more likely to develop a hemorrhagic lesion during the development of volvulus because the intestinal contents prevent the intestine from twisting tightly.[53]

■ Large Colonic Volvulus

Clinical signs of large colonic volvulus include rapid onset of severe, unrelenting abdominal pain.[54] Although postparturient broodmares appear to be at risk, this association has not been conclusively determined. However, one study demonstrated that Thoroughbred horses are at significant risk for volvulus.[51] Once the large colon is strangulated (>270-degree volvulus), gas distention is marked, leading to gross distention of the abdomen, respiratory compromise as the distended bowel presses against the diaphragm, and visceral pooling of blood as the caudal vena cava is compressed. This condition is frequently refractory to even the most potent of analgesics. Affected horses may prefer to lie in dorsal recumbency, presumably to take weight off the strangulated colon. An abbreviated physical examination is warranted in these cases because the time elapsed from the onset of strangulation to surgical correction is critical.[52] In experimental conditions, the colon is irreversibly damaged with 3 to 4 hours of 360-degree volvulus of the entire colon.[55]

Despite severe pain and hypovolemia, the heart rate may be paradoxically slow, possibly in relation to increased vagal tone. A fast heart rate can be associated with a poor prognosis.[56] More accurate prognostic information can be obtained from plasma lactate. A plasma lactate concentration of 6.0 mmol/L or higher is 84% sensitive and 83% specific for predicting death.[57] In another study, preoperative PCV of more than 46% was associated with a significantly increased risk of death.[52] Results of abdominocentesis are often not indicative of the degree of colon compromise,[58] and in many cases abdominocentesis is not advisable because of extreme colonic distention. Rectal palpation reveals severe gas distention of the large colon, which often restricts access of palpation to the abdomen beyond the pelvic brim. In most cases, colonic bands can be palpated, which indicate that the ventral portion of the colon is uppermost and crossing the abdomen horizontally. The diagnosis may be tentatively based on signalment, severity of pain, and degree of distention.

At surgery the volvulus is typically located at the mesenteric attachment of the colon to the dorsal body wall, and the most common direction of the twist is dorsomedial with the right ventral portion of the colon as a reference point. However, the colon may twist in the opposite direction, twist more than 360 degrees (up to 720 degrees has been reported), or twist at the level of the diaphragmatic and sternal flexures. In all cases, the colon should be decompressed as much as possible, and in many cases, evacuation of colon contents via a pelvic flexure enterotomy helps correct the volvulus. However, in

horses in which colonic volvulus is diagnosed in the early stages, the volvulus can be corrected within the abdomen without evacuation of the colon.[52]

After correction of the volvulus, the colon should be assessed for irreversible injury. This determination is frequently based on mucosal color and bleeding (if an enterotomy has been performed), palpation of a pulse in the colonic arteries, serosal color, and appearance of muscular motility. However, determination of viability on the basis of these parameters is unreliable. Currently, one of the most reliable techniques for determining viability is histologic evaluation of frozen sections of colonic mucosa. Biopsy samples may be obtained at the pelvic flexure because it has been determined that mucosal changes are uniform throughout strangulated colon.[59] A prediction of viability can be based on the degree of luminal and crypt epithelial loss and the interstitium-to-crypt ratio (calculated from measurements of the crypt width and the width of interstitial space between crypts). In one study, morphologic changes consisting of an interstitium-to-crypt ratio of less than 3 and a 60% or less loss of glandular epithelium were predictive of survival with a sensitivity and specificity of 95% and 92%, respectively, in a population of 52 horses.[60]

In addition, it has been suggested that accuracy of viability determination can be increased by combining histologic evaluation with surface oximetry or laser Doppler determination of blood flow.[61] Unfortunately, frozen histologic sections are not available at most referral centers on an emergency basis. A retrospective study of formalin-fixed biopsy specimens of pelvic flexure from 28 horses found that morphologic scoring was not accurately predictive of short-term survival.[62] In another study, investigators assessed intraoperative colonic intraluminal pressure as a more practical potential indicator of outcome in horses with large colonic volvulus but found this measurement inaccurate for making this determination.[63] In a more recent study of formalin-fixed biopsy samples of pelvic flexure from a population of horses recovered from surgery for large colonic volvulus, a combination of both interstitium-to-crypt ratio and mucosal hemorrhage score was accurately predictive of survival.[51]

If the colon is judged to be irreversibly damaged, the feasibility of a large colon resection can be considered. Although 95% of the colon can be resected (that part of the colon distal to the level of the cecocolic fold), damage from the volvulus usually exceeds what can be resected. In these cases surgeons may advise euthanasia or may elect to resect as much damaged bowel as possible; however, resection of the colon has not been found to improve survival.[51]

Postoperative complications include hypovolemic and endotoxemic shock, extensive loss of circulating protein, disseminated intravascular coagulation, and laminitis. In addition, large colonic volvulus has a propensity to recur. The prognosis for survival to hospital discharge for cases of large colonic volvulus has been reported as between 58% and 88%.[52,64-67] Studies in which long-term follow-up has been completed have demonstrated that survival rates decline to between 34% and 66% after 2 years.[63,64] Although one study documented a recurrence rate of less than 5%,[58] some authors believe recurrence may be as high as 50%. Methods of preventing recurrence can be considered in patients considered at risk for recurrence.[68,69]

■ Intussusception

The most common intussusception of the large intestine is cecocolic intussusception, although in comparison with all forms of colic, it is a relatively rare condition of horses, accounting for 11 (1.3%) of 842 horses taken to surgery because of colic at one hospital.[70] The condition tends to occur in young horses (2 to 3 years of age) and may be associated with intestinal parasites, particularly tapeworms[71] and a heavy larval cyathostome burden.[72]

Clinical signs include acute onset of colic that varies in severity according to the degree of intussusception. Initially, the cecal tip inverts, creating a cecocecal intussusception, which does not obstruct flow of ingesta. As the intussusception progresses, the cecum inverts into the right ventral portion of the colon (cecocolic intussusception), which obstructs flow of ingesta and often causes severe colic. In one report on cecocecal and cecocolic intussusception, 26 of 30 horses presented with signs of acute colic.[71] However, the condition may also manifest as a chronic disease.[71] The cause of abdominal pain is often difficult to differentiate in these cases, although it is sometimes possible to detect a mass on the right side of the abdomen and the concurrent absence of a palpable cecum. Treatment involves manual surgical reduction by retracting the intussusceptum directly or via an enterotomy in the right ventral portion of the colon, with or without a partial typhlotomy.[71] The prognosis is usually regarded as poor because of severe compromise to the cecum and the risk of cecal rupture or severe contamination during surgery. However, a report of 18 horses without peritonitis that recovered from surgery showed that 15 survived long term.[71]

Colocolic intussusceptions are rare but have reportedly affected the pelvic

flexure and the left portion of the colon.[73-76] The condition is reportedly more common in young horses, but some older horses are affected. Clinical findings may include a palpable mass on the left side of the abdomen. Ultrasonography may also be useful. Treatment requires manual reduction of the intussusception at surgery, or resection of affected bowel.

Disorders of the Descending (Small) Colon

Nimet Browne • Vanessa L. Cook

Colic resulting from a problem with the small colon is comparatively rare: It has been identified in only 4.2% of cases of surgical colic but represents up to 18% of horses admitted to referral centers with gastrointestinal disease.[1-3] However, American Miniature horses seem to be at increased risk for obstruction of the small colon[2]; small colon lesions account for 60% of cases of surgical colic in that breed.[4] Arabian horses and ponies also appear to be predisposed to small colon disease.[2,5,6] Of interest is that horses older than 15 years of age also seem to be at an increased risk for small colon conditions,[2] especially strangulating lipoma, injury from foaling, and submucosal hematoma.[6] Mares may also be at increased risk for small colon lesions, possibly because of hormonal fluctuations affecting gastrointestinal motility,[2] because of the small colon's predisposition to injury during foaling, or because of the small colon could become entrapped by an ovary.

One of the biggest challenges with small colon lesions is that the associated clinical signs and rate of physiologic deterioration are less severe than those of a more orad obstruction, which often results in later referral.[2,6] Early clinical signs include lethargy and inappetance, whereas progression of disease typically results in abdominal pain, diarrhea, decreased fecal production, and abdominal distention. Gastric reflux occurs in 30% of cases with small colon strangulation.[7] A complete examination of abdominal distention with rectal examination and abdominocentesis provides useful information in determining the diagnosis and indicating surgical intervention.[6,8,9] However, because the small colon lies caudally in the abdomen, transabdominal ultrasonography may be less useful than it is for lesions in other sections of the intestinal tract. Transrectal ultrasonography, performed with care, may be a more sensitive method of detecting a compromised small colon and may aid in earlier diagnosis.[4]

Conditions affecting the small colon can be categorized as congenital diseases,

simple obstructions, vascular lesions, neoplasia, or strangulating lesions.

■ Congenital Diseases

Atresia Coli and Aganglionosis.

Atresia coli is much rarer in foals than in calves; the reported incidence is 0.44%.[10] There are several theories on the pathogenesis of this disease, but an ischemic vascular accident that results in atrophy of the affected segment is the most widely accepted one.[11,12] One study showed that fibroblastic growth factor 10 and its receptor are important in colonic development in mice; the lack or deficiency in growth factors could play a role in colonic atresia in foals.[13,14] There are four types of atresia.[15] Type 3, blind-end atresia, with no connection of the atretic segments, is the type most commonly found in foals.[10,14] Atresia coli may be confused with overo lethal white syndrome, in which affected foals have myenteric aganglionosis of the distal intestinal tract as the result of a mutation in the endothelin receptor type B gene.[16,17] In atresia coli, however, the intestinal tract is patent but nonfunctional. Loss of neurons in the myenteric plexus of the small colon can also be found in equine dysautonomia (grass sickness), although it is usually less severely affected than the ileum.[18]

Newborn foals with atresia coli usually appear normal but develop progressive abdominal distention and colic within 24 hours of birth. Atresia can be differentiated from other causes of colic in foals by the complete absence of feces with no meconium staining on digital rectal examination or even after an enema.[11] It may be possible to confirm a blind-ending rectum or distal small colon by digital palpation or passage of a soft catheter or endoscope. However, the defect is usually too proximal to visualize this way, and the friable colonic mucosa can be perforated easily; therefore this method is not recommended for diagnosis, but the use of *N*-butylscopolammonium can aid in diagnosis when colonoscopy is performed.[19] Plain radiographs do not usually identify the atresia but can help differentiate it from a meconium impaction. Retrograde contrast radiography, as described later in this section for meconium impaction, may give a more definitive answer.[20] A large volume of barium sulfate, up to 20 mL/kg, may be needed if the atresia is proximal to the transverse colon. If atresia is present, the path of the contrast agent is seen to end abruptly at the atretic segment.

The only chance for survival in cases of atresia is early exploratory celiotomy

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to assess the affected segment and determine whether surgical correction is possible. In calves with atresia, the prognosis is vastly improved if the diagnosis is made early and the animal is alert and is stabilized medically before surgery.[21,22] However, in foals, despite attempts at surgical resection of the atretic segment and anastomosis, the prognosis is grave; a 100% mortality rate has been reported in several studies.[10,14]

■ Simple Obstructions

Simple Impaction.

Small colon impaction is the most common abnormality of the small colon in adult horses, affecting 1.9% to 2.5% of all horses seen for colic at referral institutes.[3,9,23] Several studies report a strong association between small colon impaction and diarrhea. The most recent study documented that horses with diarrhea are 10 times more likely to develop a small colon impaction than are horses with a large colon impaction.[8,24] In other studies, diarrhea developed during hospitalization in 70% of all horses with small colon impaction, and 43% of those treated surgically yielded cultures positive for *Salmonella* spp.[23] These studies suggest that impaction of the small colon may be a sequela to colonic inflammation or colitis, such as *Salmonella* infection; therefore some hospitals use isolation protocols for all horses with a small colon impaction. Diarrhea, fever, leukopenia, and rectal mucosal edema are findings with small colon impactions and colitis; it is not known whether the underlying mucosal inflammation led to the impaction or whether the inflammation caused primarily by the small colon impaction predisposes horses to colitis.[2,8,9] A dramatic increase in the incidence of small colon impaction has been documented in the fall and winter, possibly because of decreased water intake or close housing that increases the incidence of infectious colitis, but a definitive reason is unknown. Of interest is that this seasonal incidence was not significant in the most recent study, possibly because of the milder winters in the southern United States.[8]

Diagnosis of a small colon impaction is most easily made by rectal palpation, with an accuracy of 79 to 87%.[8,23] A solid tube of ingesta with loss of the normal sacculations is found, but other rectal examination findings include gas distention of the large intestine and cecum and loose manure.[6,8,23] Great care should be taken in performing a rectal examination because the rectal mucosa may be edematous, and many horses will strain. [3] One of the best parameters for

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determining when surgical treatment of these cases is required is the presence of abdominal distention; affected patients are five times more likely to require surgical correction than are horses without abdominal distention.[8] In addition, increases in abdominal pain and alterations in abdominal fluid that are consistent with deterioration of the bowel are also indications for surgery.[2,6,8,23] Transabdominal trocharization in the right paralumbar fossa can be an effective and safe method of relieving gas accumulating orad to the impaction. This can be performed to relieve abdominal distention and improve the chance of success with medical therapy without the need to proceed directly to surgery.

Medical therapy should consist of intravenous fluid therapy to correct electrolyte abnormalities, in combination with enteral fluid therapy with a balanced electrolyte solution, and analgesics as necessary.[9,23] Because enteral fluids can iniate the gastrocolic reflex and gastric distention can stimulate contraction of the colon, typically 4 to 6 L of warm water with 1 oz of sodium chloride alternating with 1 oz of potassium chloride can be administered via nasogastric tube every 2 hours.[25,26] The administration of oral laxatives such as mineral oil, dioctyl sodium sulfosuccinate, or magnesium sulfate can be used to soften the impaction. The time it takes for the impaction to resolve with medical treatment is often longer than for large colon impactions; mean time to resolution is more than 2 days.[8] Affected horses that develop signs of systemic inflammation, such as fever, leukopenia, tachycardia, or tachypnea, may require treatment with antibiotics or antiendotoxin therapies.[9] Enemas may be administered in a standing horse to break down very aborad impactions but should be done so with extreme caution to avoid mucosal injury. Adequate sedation, epidural anesthesia, and the administration of *N*-butylscopolammonium bromide may decrease the risk of injury.[1,3,9,27]

Surgical correction of the impaction through exploratory celiotomy is usually performed with administration of a high enema and extraluminal massage by the surgeon. The impacted small colon is extremely friable, and the surgeon should be careful when manipulating the bowel in order to avoid serosal tears. Application of sterile carboxymethylcellulose to the serosal surface may help lubricate the intestine and reduce the trauma of manipulation. In severe cases, infusion of the impacted contents with isotonic fluids or an enterotomy in the small colon may be necessary to facilitate evacuation of the impaction.[3] An additional concern is the risk of reimpaction of the small colon as ingesta from the large colon move aborally after surgery. Therefore if there are ingesta in the

large colon at the time of surgery, a pelvic flexure enterotomy is also recommended so as to empty the large colon and reduce the risk of recurrence.[23] Surgical correction of the impaction can be time-consuming; to reduce anesthesia time, the items needed for high enema administration, such as a stomach tube with a rounded atraumatic end, a stomach pump, and buckets of warm water, should be assembled in the operating room before induction.

The prognoses with medical and surgical treatment appear to be similar in most studies.[8,23] Of interest is, however, that overall prognosis appears to have improved since the 1980s, increasing from approximately 75% in cases from 1986 to 1996 [23] to approximately 95% in cases from 1999 to 2004.[8] Therefore overall, the prognosis for small colon impaction is excellent, even if surgical intervention is necessary. However, because of the underlying inflammatory cause of this condition, length of hospitalization tends to be longer and associated costs higher than those incurred with a simple large colon impaction.[8]

Fecaliths, Enteroliths, and Foreign Bodies.

Simple obstruction of the small colon also involves inspissated feces (fecaliths), enteroliths, foreign bodies, or, less frequently, concretions of plant material (phytobezoars) or masses of matted hair (trichobezoars).

Fecaliths are improperly formed fecal balls, ranging in size from 4 to 6 cm, that are a result of poor diet, inefficient mastication, or reduced water intake.[28,29] They are a common cause of colic in young or old (>15 years) miniature horses; an occurrence rate of 63% was documented in a study of surgical colic in miniature horses.[4,29-31] Fecaliths that become lodged in the small colon usually cause complete intestinal obstruction and necessitate surgical removal, as described later. When colic is managed in a miniature horse, regardless of the cause, the serum triglyceride concentration should be monitored to allow early detection and treatment of hyperlipemia.[32]

Enteroliths are, as described previously, composed mainly of magnesium ammonium phosphate deposited in concentric layers around a nidus such as a small rock.[33] The incidence is very high in certain regions, such as California, where enterolithiasis accounts for 15.1% of all cases of colic seen at the University of California, Davis,[34] in comparison with less than 2% of colic cases at Texas A&M University.[35] Enteroliths can lodge in the large colon, transverse colon, or small colon. According to some studies, the transverse colon may be the most common site of obstruction; however, larger trials indicate that the

small colon is most commonly involved, with an incidence of 22%.[34,36-38] Horses with enteroliths were found to have certain changes in the composition of their colonic contents, in comparison with other surgical colic cases, which may predispose them to enterolith formation. These differences include a more alkaline pH, more colonic fluid, and higher mineral concentrations.[38] Certain management practices, including a high proportion of alfalfa in feed and less access to pasture, may also predispose a horse to enterolith formation.[35,38]

Clinical signs of enterolithiasis are similar to those seen with other nonstrangulating obstructions of the large or small colon. Many horses with enterolithiasis have a history of intermittent colic, but once the stone becomes lodged within the small colon, it can either be passed in the feces or become wedged.[34] Most enteroliths that obstruct the small colon lodge in the proximal third, presumably because of the change in lumen diameter between the transverse colon and descending colon.[38] Horses with an enterolith in the small colon are more likely to be tachycardic and leukopenic than are horses with an enterolith in the ascending colon.[38] Sensitivity of radiography for the diagnosis of enterolithiasis ranges from 41.6% to 62.5% for enteroliths located in the small colon and from 75% to 91.67% for enteroliths located in the transverse colon. Digital radiography has been shown to be more sensitive than computed radiography, which in turn is more sensitive than analog radiography. Enteroliths in the large colon are easier to identify than those located in the small colon, and increased gas distention negatively affects the sensitivity of radiographic images of enteroliths.[39-41]

Medical management aimed at reducing colonic pH has been suggested to try to prevent recurrence after surgery. However, when an enterolith lodges in the small colon, it usually causes complete obstruction and acute colic that necessitate surgical intervention, as described later. Rupture of the gastrointestinal tract is particularly common if the enterolith is lodged in the small colon and surgery is delayed.[34]

Ingestion of foreign material such as rope, twine, rubber fencing, cloth, or tires can also cause obstruction of the small colon.[31,42] This is usually a problem in younger horses, possibly because they are more inquisitive and will eat nonfood items found in their environment. It is possible for the foreign body to cause signs of small intestinal obstruction first, followed by a period of quiescence while it passes through the large colon before it finally causes complete obstruction of the small colon and causes acute onset of severe colic

and abdominal distention.[1,42] The fibers become covered in crystalline material during their transit through the intestinal tract, and the resulting irregular sharp projections cause pressure necrosis and mucosal ulceration,[6] which can be seen during exploratory celiotomy orad to the site where the foreign body has finally become lodged. These sharp projections make it virtually impossible to manipulate the foreign body orally or aborally within the lumen and thus make removal more complicated.

The majority of these obstructions necessitate exploratory laparotomy and an enterotomy to allow the obstruction to be removed.[29,34,42] Regardless of the cause of the obstruction, the overlying intestine is friable and can rupture easily either during induction of anesthesia or during surgical manipulation.[31,34,42] If possible, the mass should be gently manipulated more proximal or distal to the original site at which it lodged, so that the enterotomy can be performed in uninjured areas of the intestine.[6] However, foreign bodies in particular may be difficult to manipulate, and the enterotomy may have to be performed directly over the top of the obstruction. The site selected for the enterotomy should be isolated from the abdomen with sterile towels before the enterotomy incision is made. The incision should be made longitudinally through the antimesenteric taenia in order to preserve luminal diameter, reduce hemorrhage, and maximize speed and ease of the procedure.[43,44] The enterotomy can be closed in one layer with an inverting suture pattern.[44] Small areas of necrosis caused by transmural pressure from the obstruction can be managed by oversewing the affected segment.

Problems arise when intraluminal obstructions occur at the proximal portion of the descending colon, where the lumen narrows between the transverse and descending colon. Here, manipulation of the obstruction aborally into a section of small colon that can be exteriorized may be impossible. In such cases, an antimesenteric teniotomy, through the seromuscular layer alone, can be performed. This allows the obstruction to be advanced aborally into a section that can be exteriorized, while the intact mucosa prevents abdominal contamination.[45] The enterotomy and seromuscular incision are then closed as described earlier. An alternative approach is to administer a high enema to repulse the obstruction in an orad direction into the ascending colon, where it can be removed via a pelvic flexure enterotomy. Approximately 50% of horses with enteroliths in the descending colon have additional stones in the ascending colon; thus complete examination of the large intestine, especially the right

dorsal and transverse portions of the colon, is recommended after the removal of a stone through a small colon enterotomy.[34,38] The overall prognosis for horses with enteroliths of the descending colon is excellent. In one study, the short-term survival rate among horses that survived surgery was 94%.[38] Common postoperative complications include fever, anorexia, and diarrhea, which do not seem to worsen the prognosis but may prolong hospitalization. Recurrence has been identified in up to 7% of horses.[34]

Meconium Retention.

Meconium is composed of substances that are present in the intestinal tract at birth, such as glandular secretions, sloughed cells, and swallowed amniotic fluid, and is therefore sterile. Healthy foals pass meconium, which is a thick, tarry substance, within 48 hours; the presence of soft, yellowish stool is an indicator that meconium passage is complete.[30,46,47] Several studies indicate a higher incidence of meconium retention in colts than in fillies, presumably because the pelvis is longer and narrower in males.[30,47] Any factors that reduce intestinal motility (such as failure to ingest colostrum) and dysmaturity can result in difficulty passing meconium, which is described as *meconium retention.* Clinical signs include tail flagging, straining, and reduced suckling, which can progress to more severe signs of colic over time, such as rolling and abdominal distention. These signs are similar to those seen with ruptured bladder, and the two conditions can occur together; therefore a complete examination of an affected foal is important.

It may be possible to palpate meconium retained at the pelvic inlet by careful digital rectal examination. If the meconium is retained more proximally, it may be identified on a plain lateral radiograph. Presence of the obstruction may be confirmed by retrograde contrast radiography, which provides excellent sensitivity and specificity for evaluation of the transverse and descending colon.[20] Retrograde contrast radiographs may provide additional information when plain radiographs are inconclusive. A Foley catheter (28- to 30-French) is placed into the rectum, and up to 20 mL/kg (approximately 1 L) of 30% barium sulfate is carefully allowed to flow in by gravity until it squirts around the catheter or discomfort is observed.[20] Lateral and, of more importance, ventrodorsal radiographs are then obtained. If a meconium impaction is present, the path of the contrast agent stops before it reaches the transverse colon. Ultrasound examination can reveal gas distention of the large intestine and, in

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some cases, the meconium itself can be identified as a row of fecal balls in the small colon. The echogenicity of the meconium varies, but a typical “speckled” appearance has been described.[48-50]

Supportive medical management of all affected foals should be performed first, including correction of fluid and electrolyte imbalances, provision of nutritional support, and correction of failure of passive transfer if indicated.[51] Judicious use of analgesics such as flunixin meglumine or butorphanol and oral fluids may aid resolution of the impaction. The most effective treatment is administration of an enema. The enema can be a commercial phosphate enema or simply soap and water administered through a Foley catheter by means of gravity flow, as described previously. In cases that are refractory to simple enemas, an acetylcysteine enema may be effective. Acetylcysteine is a mucolytic, which acts by breaking disulfide bonds to make meconium less viscous. These enemas are available commercially (E-Z Pass Foal Enema Kit; Animal Reproduction Systems, Chino, Calif.) or can be formulated by adding 20 g of baking soda to 200 mL of water and then adding 8 g of acetylcysteine powder to make a 4% solution.[47] The solution is infused slowly through a Foley catheter, which is then clamped to allow the solution to be retained for up to 45 minutes to allow maximum activity of the acetylcysteine. The meconium retention was resolved successfully in all acetylcysteine-treated foals in one study, although 5% of foals required three enemas before resolution was obtained, and three foals in the study developed a bladder rupture.[47]

One report indicated that in approximately one third of foals with meconium retention, exploratory celiotomy is needed for resolution.[30] However, this study was carried out before the increased use of acetylcysteine retention enemas, and the current rate of surgical intervention is probably much lower. Because adhesions can develop in up to 33% of foals undergoing gastrointestinal surgery, long-term prognosis may be improved by reducing the number of foals undergoing exploratory celiotomy.[30,47,52]

Other Causes of Simple Obstruction.

Because of the proximity of the descending colon to the urogenital tract, it is possible for the descending colon to be obstructed by intraabdominal structures such as an ovary or retained testicle. Although such conditions occur infrequently, the most common is for the small colon to become entwined around an ovary.[6] The intestine can be freed and is not usually compromised, but the

ovary itself is usually nonviable and must be resected.[53] A similar problem has been reported from the spermatic cord of a retained teratoma that occluded the small colon.[54]

■ Neoplasia

With the exception of lipomas, neoplastic processes of the small colon are quite rare. In a study characterizing intestinal neoplasia in horses, lymphoma and adenocarcinoma were the most frequent neoplastic lesions located in the small colon.[55] Development of leiomyomas has been attributed to small colon intussusceptions, but they are also as incidental findings.[56]

■ Vascular Lesions

Intramural Hematoma.

Intramural or submucosal hematomas are rare, although some cases may not be diagnosed if they do not cause complete obstruction and if they resolve without intervention.[57,58] Blood hemorrhages between the mucosa and muscularis layers, which expand to occlude the lumen and cause complete obstruction. If left untreated, hematomas can lead to ischemic necrosis of the bowel wall and thus to septic peritonitis, endotoxemia, circulatory shock, and possible death.[57,58] The length affected has been reported to range from 24 to 65 cm. The cause is unknown, although blunt abdominal trauma has been associated with the condition in humans.[59] In one equine case series, iatrogenic rectal trauma was implicated as the cause. [58] There is an increased incidence among older horses; those affected had an average age of 11 years in one study.[6] Clinical signs include varying degrees of abdominal pain, as well as signs of vascular compromise from blood loss.[6,58] The presence of dark or clotted blood on rectal palpation may aid diagnosis, and in some cases, a mass within the small colon may be identified.[57,58]

Exploratory celiotomy with complete resection of the affected segment and end-to-end anastomosis (as described later) is necessary. Because of the length of the affected segment, it may be difficult to exteriorize and resect all damaged intestine. However, if the entire affected segment can be removed, the prognosis is good; one study demonstrated a 75% survival rate.[57]

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Mesocolic Tears and Rectal Prolapse.

Tears in the mesentery of the small colon can occur as a complication of parturition, especially in multiparous mares,[60,61] and result in segmental ischemic necrosis of the small colon. Trauma and straining during parturition can result in tearing of the mesocolon and devitalization of the associated descending colon, which may progress to an intussusception of the small colon, which manifests as a type III or IV rectal prolapse. In a type III rectal prolapse, the rectal ampulla prolapses, as with a type II prolapse, but in addition, a portion of the small colon intussuscepts into the rectum. In type IV rectal prolapse, part of the small colon and the rectum intussuscepts through the anus.[60,62] Gentle palpation around the prolapse can help determine the type of prolapse. Although a rectal prolapse is readily identifiable, devitalization of the small colon caused by tears of the mesocolon results in a more insidious onset of clinical signs, including depression and lack of feces.[60,61]

The mesocolic tear is frequently located caudally; as a result, the affected area is inaccessible through a midline celiotomy. Therefore it may be more prudent to first perform standing flank laparoscopy to determine the location and extent of the lesion.[63] This allows assessment of the lesion to determine whether resection and anastomosis of the affected segment via celiotomy are feasible or whether a permanent colostomy is required.[64,65] The prognosis is often poor because of the extent of the tear or delay in surgical intervention.[60,61,65]

■ Strangulating Obstructions

Strangulating Lipoma.

Pedunculated lipomas can cause a strangulating or nonstrangulating obstruction of the small colon, but this occurs much less frequently than in the small intestine. In a large retrospective study, lipomas were found to involve the descending colon in approximately 10% of cases.[2,7,66] The overall incidence of lipomas affecting any portion of the gastrointestinal tract is increased among older geldings and in Saddlebred and Arabian horses.[66,67] It is therefore likely that lipomas specifically affecting the descending colon have a similar distribution. Fig. 32.72 illustrates a pedunculated lipoma that had strangulated a short section of the small colon. Clinical signs typical of a strangulating obstruction include a significantly elevated heart rate, abnormal abdominocentesis findings, and distendtion of the large colon on rectal

examination.[6] Horses may only show mild to moderate signs of abdominal pain, in contrast to strangulating lesions in other parts of the gastrointestinal tract.[7] Rectal examination may yield unspecific findings, but a constriction of the lumen of the small colon caused by the lipoma may be palpated and feels like a blind end or narrowing of the lumen.[7]



FIG. 32.72 A short section of small colon that had been strangulated by a pedunculated lipoma.

Surgery is necessary to free the constricting lipoma, followed by resection and anastomosis if the intestine is nonviable (Fig. 32.73). Strangulating lipomas of the small colon are the most common reason for resection and anastomosis.[7] The prognosis is worse if resection is required, with a 50% survival rate in one study, in comparison with 100% survival for nonstrangulating lipomas.[6] However, a multicenter study documented a substantially better survival rate after resection and anastomosis of the small colon; the majority of patients were horses with a strangulating lipoma.[7] In that study, 84% of cases were discharged after hospitalization for a median of 8.5 days. The end-to-end anastomosis is usually sutured in two layers, with a simple continuous pattern in the mucosa followed

by closure of the serosa with an inverting suture pattern interrupted at 180 degrees. It is possible that failure of the anastomosis occurs more commonly in the small colon than the small intestine, but numbers are too low to definitively confirm this.[7] Diarrhea, fever, and delayed passage of feces are common postoperative complications, but long-term survival is good; of horses discharged in the aforementioned study, 93% were alive at 6 months.[7]

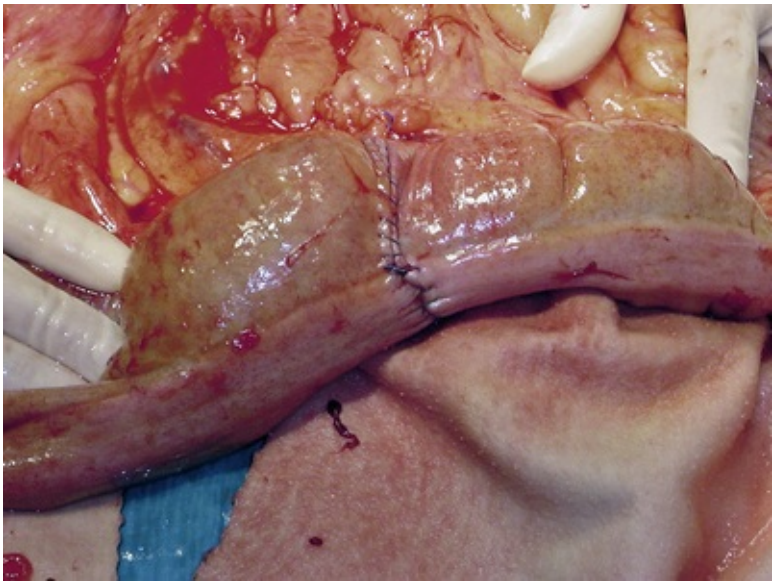


FIG. 32.73 The same case as in Fig. 32.72 after resection of the ischemic segment and end-to-end anastomosis.

Other Causes of Strangulating Obstruction.

Several other causes of strangulating obstruction can occur, but each condition is relatively rare. These include volvulus of the small colon[1] and strangulation through internal hernias such as a vaginal tear[2] or tears in the gastrosplenic ligament.[68] Intussusception can occur without rectal prolapse, and in some cases, the intussusceptum may protrude from the anus. Diagnosis can be made if a finger can be inserted between the protruding bowel and anal sphincter.[56,65,69,70]

■ Prognosis

A good survival rate was found in two large reviews of small colon disorders: 71% and 91% of patients were discharged from the hospital.[2,6] The main reason

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for euthanasia at the time of surgery was an inability to completely exteriorize the affected segment to allow adequate resection and anastomosis.[6] Previous reports have suggested that resection and anastomosis in the small colon may carry a poor prognosis because of a relatively poor blood supply, higher bacterial counts, the presence of solid fecal material, and increased collagenase activity in comparison with the small intestine.[1] However, among patients that survive surgery, short-term survival after surgery for a small colon lesion is excellent a rate of 100% survival was reported in one study.[71] In addition, horses that required resection and anastomosis did not have a worse prognosis for survival[2] and were less likely to develop the complications associated with small intestinal resection, such as postoperative ileus (POI).[71]

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Disorders of the Peritoneum in Horses

Tiffany L. Hall

■ Peritonitis in Horses

Anatomy and Physiology

The peritoneum consists of a single layer of mesothelial squamous cells covering the peritoneal cavity and abdominal organs. These cells rest on a thin basal lamina attached to a layer of loose connective tissue, which allows a variable degree of motion. The peritoneum is coated with a thin serous film that serves to minimize friction and facilitate free movement between abdominal viscera. In males the peritoneum forms a closed sac, whereas in females it communicates with the external environment via the fallopian tubes.

The peritoneum is divided into the visceral peritoneum and the parietal peritoneum. The visceral peritoneum, which encloses the intraperitoneal organs and forms the omentum and mesenteries, is supplied by the splanchnic vasculature and is innervated by the visceral autonomic nervous system. The parietal peritoneum lines the abdominal walls, pelvis, and diaphragm and receives its blood supply via branches of the lower intercostal, lumbar, and iliac arteries, which drain via veins into the caudal vena cava. Irritation of the parietal peritoneum gives rise to afferent stimuli that are perceived as somatic pain, which is transmitted by the intercostal and phrenic nerves and may manifest as splinting of the abdomen and a reluctance to move. In contrast, there are no pain receptors in the visceral peritoneum.

Peritoneal fluid is constantly being produced and absorbed through the passive diffusion of fluid and solutes across the semipermeable peritoneum. Transperitoneal fluid movement is increased during peritoneal inflammation and may cause a rapid, massive transudation of fluid into the peritoneal cavity that can lead to hypotension and shock.[1]

The peritoneal lymphatic channels, particularly the diaphragmatic lymphatic channels, play a major role in the removal of fluid and solutes from the peritoneal cavity, emptying primarily into the thoracic duct and providing the first line of defense against peritoneal contamination. Cellular defenses are provided by peritoneal macrophages, mast cells, mesothelial cells, and activated peritoneal T cells. Peritoneal macrophages have antimicrobial activity as a result

of their complement receptors, phagocytic ability, cellular recruitment, and T-cell–mediated immune responses. Peritoneal mesothelial cells are an abundant source of plasminogen activator, which is responsible for normal fibrinolytic activity on peritoneal surfaces.[1]

■ Pathogenesis

Peritonitis is inflammation of the peritoneum that results from a number of infectious and noninfectious causes. It is classified as primary or secondary, acute or chronic, and localized or diffuse. Common causes of peritonitis in horses are listed in Box 32.2. Primary peritonitis is uncommon in adult horses but may be diagnosed in foals with sepsis or young horses infected with *Streptococcus equi.* More commonly, peritonitis is secondary to translocation of bacteria from the gastrointestinal tract, occurs after urogenital trauma, or results from other inflammatory conditions. A subset of infectious peritonitis with a unique presentation and associated with *Actinobacillus equuli* has been described and is discussed at the end of this section.

Box 32.2

Causes of Peritonitis in Horses

Gastrointestinal

- Intestinal perforation
- Rectal tear
- Intestinal ischemia
- Proximal enteritis
- Colitis
- Intestinal parasites
- Intestinal neoplasia
- *Actinobacillus equuli* infection

Iatrogenic

- Celiotomy

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Enterocentesis
Chemical irritation (lavage solutions)
Colpotomy/castration

Foals

Bladder rupture/uroabdomen
Umbilical/urachal infection
Septicemia
Necrotizing enterocolitis
Rhodococcus equi infection

Extragastrointestinal

Neoplasia of abdominal organs
Hemorrhage of abdominal organs
Abscessation of abdominal organs
    Streptococcus equi
    Streptococcus zooepidemicus
    Corynebacterium pseudotuberculosis
Hepatic disorders
    Cholelithiasis
    Hepatitis
    Liver lobe torsion
Nephritis
Pancreatitis
Cystitis
Urolithiasis
Endometritis
Uterine/vaginal tears
Scirrhous cord
Systemic amyloidosis
Viral infection
    Influenza
    Equine viral arteritis
    Equine infectious anemia

Retrospective studies concluded that a cause of peritonitis is often not identified (as was the case in 50 of 65 horses and in 19 of 55 horses).[2,3] In both groups, cases of confirmed gastrointestinal rupture were excluded from analysis, and horses that had undergone abdominal surgery were excluded from one study. The conditions most commonly associated with peritonitis in these studies included recent abdominal surgery (18 of 55), postpartum complications (22 of 120), suspected cyathostomiasis (4 of 65), infiltrative bowel diseases (3 of 65), and internal abscesses (3 of 65).[2,3]

The local response of the peritoneum to insult is similar regardless of the cause. Initially, peritoneal mast cells and macrophages release histamine and serotonin, which results in vasodilation and increased vascular permeability with transudation of fibrinogen-rich plasma into the peritoneal cavity. The release of TNF-alpha and IL-1 stimulates neutrophil chemotaxis and degranulation, and the inflammatory response is promoted by the release of platelet-activating factor, prostaglandins, and leukotrienes. Damage to mesothelial cells results in release of tissue thromboplastin and decreased levels of plasminogen activator, which are conducive to fibrin formation and deposition.[4] Fibrin functions to confine bacteria and seal the peritoneal defect; however, if the immune system fails to clear the bacteria and foreign debris, the inflammation continues, and fibrin production results in abscess and adhesion formation.

■ Clinical Features

Clinical signs of peritonitis vary and depend on the cause and duration of the peritonitis. Localized infections often have limited systemic symptoms, whereas diffuse peritonitis can elicit generalized signs of endotoxemia and sepsis. Horses with peracute peritonitis caused by intestinal rupture show signs of acute, severe sepsis and cardiovascular collapse with tachycardia, tachypnea, sweating, varying degrees of abdominal discomfort, and death within hours.

According to two retrospective studies, the most common presenting clinical signs for peritonitis include colic, depression/lethargy, tachycardia, tachypnea, pyrexia, and altered mucous membrane character.[2,3] Much of the clinical presentation in acute colic reflects the degree of systemic inflammation and hypovolemia caused by third spacing. Colic symptoms may be related to inflammation of the parietal peritoneum and are characterized by guarding or splinting of the abdomen and a reluctance to move or defecate.[5] Sympathetic stimulation, hemoconcentration, or serosal surface trauma may decrease

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gastrointestinal motility, leading to ileus, which may result in gastric fluid accumulation and small intestine distention, thereby intensifying the abdominal pain. In addition, gastrointestinal impactions commonly develop as fluid is reabsorbed from the cecum and large colon in an attempt to replace intravascular fluid deficits resulting from extravasation of fluid into the peritoneal cavity. Chronic peritonitis generally manifests with more insidious signs, including lethargy, inappetance, and weight loss.

Rectal examination may identify either roughened peritoneal surfaces or an abnormally empty abdomen in cases of intestinal rupture. The bowel may become distended in association with the presence of adhesions or ileus. Abdominal masses, abscesses, or enlarged mesenteric lymph nodes are occasionally palpable; however, in many cases, no abnormalities are identified on rectal palpation. Animals with a recent history of foaling or castration should undergo urogenital examination to rule out vaginal, cervical, and uterine tears in mares or infected castration sites in males.

■ Diagnosis

Ultrasonography.

Ancillary diagnostic testing such as transabdominal and transrectal ultrasonography aid in diagnosis of peritonitis and identification of the source. The clinical utility of ultrasonography greatly depends on the quality of equipment and the experience of the practitioner; identification of abnormalities in cases of peritonitis ranges from 50% to 90%.[2,3] The most common finding on transabdominal ultrasonography is an increase in volume or altered echogenicity of peritoneal fluid. Other findings can include intraabdominal abscesses, lymphadenopathy, or dilation of the small intestine with or without increased intestinal wall thickness. Fibrinous strands or fibrin adhesions may also be identified by ultrasonography (Fig. 32.74) and a site for abdominocentesis selected. Perirectal masses may be observed on transrectal ultrasonography, particularly in cases associated with vaginal tears.

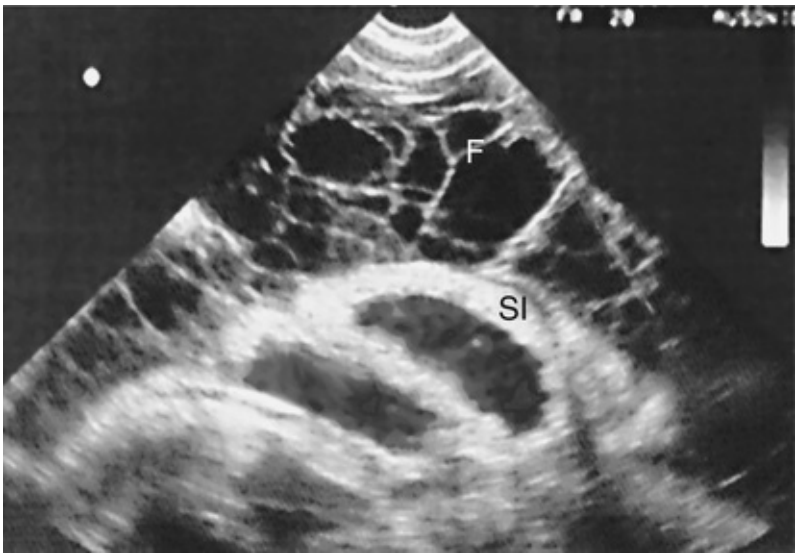


FIG. 32.74 Abdominal ultrasound image in an adult horse with chronic peritonitis, showing web of fibrin *(F)* surrounding anechoic fluid. The small intestinal wall *(SI)* is thickened. (Courtesy Dr. David Schmitz, Texas A&M University.)

Hematology and Biochemistry.

Alterations in laboratory values vary widely, depending on the cause and duration of peritonitis. Hematologic abnormalities seen in acute, severe peritonitis include elevated PCV secondary to transudation of fluid into the peritoneal cavity and severe neutropenia in association with endotoxemia and systemic inflammation. Initially, plasma protein levels increase, which reflects the degree of hypovolemia; in chronic cases, however, hypoproteinemia may be present. Peripheral cell counts can exhibit leukopenia or leukocytosis, and a left shift with more than 5% immature neutrophils is observed in approximately 40% of patients.[3] Hyperfibrinogenemia is a common finding; fibrogen levels ranged from 490 to 1120 mg/dL in a review of 65 cases.[2] Peritonitis of longer duration and internal abscesses may manifest with a normal or increased systemic neutrophil count, monocytosis, and elevated plasma protein levels, fibrinogen levels, or a combination of these.[6] In addition, peripheral and peritoneal levels of serum amyloid A may be greatly increased in cases of peritonitis.

Alterations in serum chemistry and blood gas values reflect the patient's cardiovascular status at the time of presentation, in association with the degree of systemic inflammation. Prerenal azotemia, hypokalemia, hyponatremia, and hypochloremia may be present, as may acidosis and an increase in unmeasured

anions, such as lactate, as the patient's condition declines. Other changes in serum chemistry values could indicate an underlying condition in a specific organ system.

Abdominocentesis.

Peritoneal fluid analysis confirms the diagnosis of peritonitis, although the cause may remain unknown. Expected values for peritoneal fluid in normal horses, as well as in horses that have undergone abdominal exploratory surgery and castration and in postpartum mares, are listed in Table 32.9.[7-10] The cytologic appearance of the leukocytes and mesothelial cells should be normal, although activated mesothelial cells with vacuolation are not an unusual observation in normal horses.

TABLE 32.9

Peritoneal Fluid Analysis in Normal Horses and After Conditions That Alter Peritoneal Fluid Values[7-10]

Parameter	Normal	After Celiotomy	After Castration	After Foaling	Dystocia
Fluid character	Clear, straw-colored	Clear, straw-colored	Clear to cloudy	Clear, straw-colored	Serosanguineous
Total nucleated cell counts (#/µL)	<5000	200,000 (postoperative day 4)	30,000 (postoperative day 5)	<5000	40,500 (postnatal day 1)
Cell structure	24 to 60% nondegenerate neutrophils	Nondegenerate neutrophils	85% neutrophils	Increased nondegenerate neutrophils	NR
Total protein	<2.0 g/dL	6 g/dL (postoperative day 6 post)	NR	<2.0 g/dL	4 g/dL (postnatal day 1)
Cytologic values	Mesothelial cells may be activated	NR	NR	NR	NR

NR, Not reported.

Evaluation of fluid character and quantity can aid in developing and prioritizing a differential list. Turbid, cloudy fluid indicates an increased cell count. Serosanguineous fluid indicates an increase in erythrocytes or free hemoglobin that may be caused by intestinal degeneration with transmural erythrocyte leakage, splenic puncture during abdominocentesis, abdominal viscera laceration, or skin contamination. Green fluid results from enterocentesis or intestinal rupture, and brown fluid is associated with late-stage tissue necrosis. The quantity of fluid varies among horses and can be increased in acute, diffuse

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peritonitis, or fluid may be absent in low-grade and localized peritonitis. The presence of large quantities of dilute, colorless fluid should alert the clinician to the possibility of ascites or uroperitoneum.

Cytologic examination of the peritoneal fluid should include Wright-Giemsa and Gram stains. Peritoneal fluid cell structure is an important diagnostic aid and can be evaluated wth the Wright-Giemsa stain. Neutrophils are evaluated for degenerative changes such as nuclear swelling and cytoplasmic vacuolation, which indicates activation associated with the presence of bacterial toxins. Identification of exfoliative cells from neoplasms, such as melanoma, is rare but diagnostic and aids in directing therapy and prognosis.[11] The Gram stain is used to identify bacteria and guide initial antimicrobial therapy until culture and sensitivity results become available.

Peritoneal fluid parameters consistent with peritonitis vary widely, depending on the disease process. Cytologic findings consistent with peritonitis include increases in total nucleated cell counts and protein with the predominance of degenerative neutrophils and intracellular bacteria. Nucleated cell counts ranged from 5800 to 350,000 cells/µL, and protein levels were as high as 8 g/dL, in one study,[2] but nucleated cell counts as high as 800,000 cells/µL have been reported in horses with peritonitis. Cytologic evidence of extracellular bacteria can result from skin contamination and should be interpreted in relation to the clinical signs and remainder of the fluid analysis.

Distinguishing between early, mild septic peritonitis and nonseptic peritoneal inflammation with clinical findings and routine fluid analysis alone may be difficult; however, peritoneal fluid pH and glucose concentrations have been found to be significantly lower in horses with septic peritonitis than in those with nonseptic peritonitis and in healthy horses. In a prospective study in 46 horses, serum-to-peritoneal fluid glucose concentration differences greater than 50 mg/dL were diagnostic for septic peritonitis. Peritoneal fluid pH less than 7.3, glucose concentration below 30 mg/dL, and fibrinogen concentration above 200 mg/dL were highly indicative of septic peritonitis.[12] A more recent study showed that peritoneal concentrations of L- and D-lactate were highest in horses with peritonitis, in comparison to other causes of colic; however, determination of the bacterial origin of D-lactate is not possible in the clinical setting.[13] In addition to these findings, other markers of inflammation and coagulopathy are altered in cases of septic peritonitis; alterations include significant elevations in peritoneal transforming growth factor β_3 in comparison with other causes of colic and

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significantly higher peritoneal D-dimer concentrations than in healthy horses or those with obstructive colic.[14,15]

Bacterial Culture and Sensitivity.

Microbiological culture and sensitivity testing are recommended to help identify bacterial agents and direct antimicrobial therapy. Serial cultures of the peritoneal fluid may be necessary to identify emerging or resistant bacterial strains. Optimal isolation of bacteria from peritoneal fluid requires the use of an enriching broth, blood culture medium, an antimicrobial removal device, or a combination of these.

Bacteria were cultured in cytologic study in 48 (71.6%) of 67 horses with peritonitis and identified in 28 (77.8%) of 36 cases of peritonitis. *E. coli*, *Staphylococcus epidermidis*, and *S. aureus* were the most common bacteria isolated from peritoneal fluid samples.[3,5] Anaerobes are frequently cultured from peritoneal fluid of equine peritonitis cases, *Bacteroides fragilis* being the most commonly identified.[16] Failure to identify or culture bacteria from peritoneal fluid does not rule out septic peritonitis.

■ Treatment

Many horses with peritonitis require early, aggressive therapy to address hypovolemia and dehydration, correct metabolic and electrolyte abnormalities, and reduce the effects of endotoxemia. The goals of therapy are to (1) stabilize the patient, (2) treat the inciting cause of peritonitis, (3) manage pain and inflammation, and (4) minimize complications.

Fluid Therapy.

Horses with peritonitis present with varying degrees of hypovolemia, dehydration, or both; thus fluid resuscitation with balanced, polyionic crystalloids should be the first step in treatment. Hypertonic solutions may be indicated in horses presenting with signs of hypovolemic shock, which may develop secondary to massive fluid shifts into the peritoneal cavity as a result of severe, acute inflammation. Because third spacing of albumin can lead to hypoproteinemia, administration of colloid solutions may be beneficial. Hetastarches (6%) are effective in fluid resuscitation and increase colloid oncotic pressure at doses of 8 to 10 mL/kg; however, caution should be used in patients with azotemia or underlying renal insufficiency because administration of those

solutions is associated with acute kidney injury in humans.[17] Large volumes of hyperimmune plasma may be used to raise plasma protein levels, whereas low doses (4.4 mL/kg) may aide in alleviating signs of endotoxemia.[18]

Acid-base disorders, as well as shifts in calcium, potassium, sodium, and chloride concentrations, may be observed in cases of peritonitis. Monitoring of acid-base status and electrolyte concentrations is recommended during the course of therapy with intravenous or oral supplementation as needed. See the Fluid Therapy for Horses with Gastrointestinal Diseases section for a more in-depth discussion of fluid resuscitation and selection.

Antimicrobial Therapy.

Antimicrobial therapy should be initiated in all cases of peritonitis, even when the inciting cause cannot be immediately identified. The site of infection, pathophysiologic features, pathogens probably involved, and concurrent patient conditions should be taken into consideration when an antimicrobial regimen is selected (Table 32.10). Lipophilic antibiotics (fluoroquinolones, potentiated sulfonamides) reach higher concentrations within the peritoneal cavity and in abscesses than do hydrophilic antibiotics (aminoglycosides, β-lactams); however, in the acute stages of the disease, inflammation of the peritoneal surfaces often causes hydrophilic antibiotics to reach therapeutic levels.[18] Moreover, intravenous administration is recommended as drug concentrations achieved are more reliable than those achieved with oral administration in horses suffering from dehydration or ileus.

TABLE 32.10

Antimicrobial Therapy for Peritonitis in Adults

Drug	Dosage	Route	Schedule
Potassium penicillin	22,000 to 25,000 IU/kg	IV	q6h
Ceftiofur sodium	2.2 to 4.4 mg/kg	IV/IM	q12h
Gentamicin	7 to 10 mg/kg	IV	q24h
Enrofloxacin	7.5 to 10 mg/kg	IV	q24h
	10 mg/kg	PO	q24h
Metronidazole	20 to 25 mg/kg	PR	q6-8h
Doxycycline	10 to 20 mg/kg	PO	q12-24h
Minocycline	4 mg/kg	PO	q12h
Trimethoprim-sulfonamide	30 mg/kg	PO	q12h
Chloramphenicol	50 mg/kg	PO	q6h
Rifampin	5 to 10 mg/kg	PO	q12h

IM, Intramuscular; *IV,* intravenous; *PO,* oral; *PR,* rectal.

A broad-spectrum antimicrobial regimen is recommended until culture and sensitivity results are available. Administration of a combination of a β-lactam and an aminoglycoside is appropriate; however, enrofloxacin may be substituted for gentamicin because of its increased lipophilicity or activity against *Staphylococcus*, or in cases of renal compromise. Metronidazole is often added on the basis of the frequency of *B. fragilis* isolated in horses with peritonitis. Oral antibiotic administration may be initiated after patients are stabilized and should be based on culture and sensitivity results.

Antimicrobial selection in foals is based on age and likely causes of peritonitis. Neonatal foals with peritonitis should be maintained on broad-spectrum intravenous antibiotics, as for septicemia, including a combination of a β-lactam (ampicillin, 20 mg/kg IV qid, or ceftiofur, sodium 5 mg/kg IV bid) and an aminoglycoside (amikacin, 20 to 25 mg/kg IV q24h). Older foals and weanlings have a higher incidence of *R. equi* and *S. equi* infection; thus antimicrobial regimens in these patients include either penicillin (procaine penicillin G, 20,000 IU/kg IM bid) or a macrolide/rifampin combination in the absence of other inciting causes.[19,20]

The duration of antimicrobial therapy is dependent on the inciting cause and the patient's response to treatment. Most peritonitis cases necessitate a minimum antimicrobial course of 7 to 10 days, and cases with intraabdominal abscesses may necessitate a 6- to 8-week course of antimicrobials. In cases of idiopathic peritonitis, antibiotics should be continued for several days after clinical signs resolve and peritoneal fluid counts return to normal. Other methods for monitoring progress and determining termination of therapy include serial ultrasound evaluation, CBCs, and measurement of fibrinogen levels in cases of internal abscesses.

AntiInflammatory Therapy.

All horses with peritonitis have varying degrees of local and systemic inflammation, and some may present with endotoxemia or endotoxic shock. Administration of medications with antiinflammatory properties, as well as those that bind and inactivate endotoxin, may be beneficial.

NSAIDs should be administered in all cases of peritonitis for both analgesic effects and ability to reduce the production of inflammatory mediators through COX inhibition. Flunixin meglumine is most often used for its antiinflammatory properties and may be administered at higher doses (1.1 mg/kg IV or PO bid) in

horses showing signs of discomfort or at lower doses (0.25 mg/kg IV or PO q6-8h) to minimize side effects. Other NSAIDs such as phenylbutazone (2.2 mg/kg IV or PO bid) or COX-2 selective firocoxib (0.1 mg/kg IV or PO q24h), may be used in place of flunixin meglumine.

Lidocaine has become widely used as an antiinflammatory agent. Research demonstrated that horses administered LPS intraperitoneally and treated with lidocaine (1.3 mg/kg IV bolus followed by constant-rate infusion 0.05 mg/kg/min) had significantly lower clinical scores of endotoxemia and lower concentrations of plasma and peritoneal TNF-α than did those receiving saline.[21]

Therapy targeted at binding and inactivating endotoxin includes the administration of hyperimmune plasma, endoserum, and polymyxin B. Polymyxin B (3000 to 6000 IU/kg IV bid) has been demonstrated to effectively bind circulating endotoxin; however, its use carries a risk of nephrotoxicity and is cautioned in cases with azotemia or preexisting renal insufficiency. The pathophysiologic features of and therapy for endotoxemia are discussed in depth in the Endotoxemia and Sepsis section.

Anthelmintics.

Peritonitis may develop in association with intestinal cyathostomiasis or verminous arteritis secondary to *S. vulgaris* migration; therefore anthelmintic administration is recommended when peritonitis is strongly suspected or in horses with a poor deworming history. Traditionally, fenbendazole (15 mg/kg PO for 5 days) or ivermectin (0.2 mg/kg PO) has been recommended after a horse with peritonitis is stabilized; however, resistance to both drugs has been reported. Alternative deworming protocols may include administration of moxidectin (0.4 mg/kg PO) or oxibendazole (10 mg/kg PO for 3 days).

Surgical Management.

Surgical intervention in peritonitis may be indicated to identify and correct the underlying cause, particularly when leakage or compromise of the intestinal or urogenital tracts is suspected. Ultrasonography occasionally reveals intraabdominal abscesses that could be drained via catheter or marsupialization. Peritoneal lavage and drainage should also be considered on the basis of peritoneal fluid analysis and are recommended when total nucleated cell counts exceed 100,000 cells/μL. The benefits of lavage and drainage include (1) reduction of bacterial numbers and concentrations of inflammatory mediators, (2) removal of foreign debris from the peritoneal/serosal surfaces, and (3)

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dilution of adhesion-promoting substances. Horses treated with peritoneal lavage must be monitored for dehydration, protein loss, and electrolyte imbalances. Complications associated with peritoneal drains include visceral puncture during insertion, ascending infection, subcutaneous leakage and edema, and herniation of intestine or omentum through the drain.[22]

Several techniques for peritoneal lavage and drainage have been described elsewhere, including the placement of ventral midline catheters in a standing horse, the use of active intraabdominal systems, and open peritoneal drainage.[18,23,24] Standing intraabdominal catheters, such as Foley, mushroom, or thoracic catheters, may be briefly placed aseptically under ultrasonographic guidance by insertion through the skin, subcutaneous tissues, and external muscle layers at ventral midline, then secured in place with a purse-string suture and several half-hitch knots. Catheters are either allowed passive drainage and connected to a Heimlich valve or are connected to an active-drain system, to prevent ascending contamination.

Balanced, polyionic solutions with a neutral pH are used to irrigate the abdomen. Antibiotics, antiseptics (povidone-iodine), and heparin have been suggested as additives to the lavage solution; however, no controlled studies have been performed to demonstrate any benefit. Severe inflammation of the peritoneal surfaces has been reported after the use of 3% or higher povidone-iodine lavage solutions. To perform peritoneal lavage, 10 to 20 L of solution is allowed to enter the abdomen via gravity flow through the ventral catheter. The catheter is then clamped and the patient is walked for 10 to 20 minutes to encourage distribution of the lavage fluid, after which the clamp is removed and the fluid is drained. This is repeated once or twice daily for 3 to 5 days or until fluid analysis findings normalize.

A retrospective evaluation of 67 horses receiving active intraabdominal drainage after celiotomy revealed a high incidence of minor complications (49%), including obstruction of the drainage system, leakage of fluid around the system, and subcutaneous fluid accumulation. Moreover, the incidence of incisional infection in this group was higher (32%) than in the control group (23.5%); however, this was attributed to the severity of the primary condition for which the patients had undergone surgery.[24]

Although open peritoneal drainage is preferred in humans and is reported to be successful in management of dogs and cats with peritonitis, this method has not been promoted in horses. In an experimental study, horses with induced peritonitis that received open drainage therapy with a plastic mesh sutured at the

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ventral abdominal wall had a significantly increased inflammatory reaction at the linea alba in comparison with those that were closed routinely. Moreover, all horses in the open drainage group developed incisional infections after removal of the mesh.[23]

Adhesion Prevention.

Development of intraabdominal adhesions has a significant effect on long-term outcomes for horses with septic peritonitis. Systemic administration of antimicrobials, dimethyl sulfoxide, and flunixin meglumine has been promoted because it reduces adhesion formation by decreasing peritoneal inflammation.[25] In addition, the systemic administration of heparin (20 to 40 IU/kg SC q8h) has been advocated for up to 72 hours in horses at risk of adhesion development or coagulopathy.[25] Heparin acts to decrease fibrin formation through its inhibition of thrombin.

Various intraperitoneal therapies have been evaluated in horses for the prevention of adhesions. Abdominal lavage, both intraoperatively and postoperatively, has demonstrated benefit in reducing the incidence of adhesion formation in horses undergoing exploratory celiotomy and those with peritonitis.[22,24] Introduction of heparin directly into the peritoneum during abdominal lavage may be beneficial; doses of 20,000 IU are recommended[26]; however, studies of the effects of concurrent systemic and local administration on systemic coagulation have not been reported in horses. Intraperitoneal administration of recombinant tissue plasminogen activator and 0.4% sodium hyaluronate has been shown to decrease adhesion formation; however, these are currently cost prohibitive in clinical cases.[25] The use of 1% sodium carboxymethylcellulose (2 L throughout the abdomen and applied to intestinal surfaces intraoperatively) has the most dramatic effect on adhesion formation, significantly decreasing the incidence of adhesions and the risk of death in experimental horses in comparison with untreated horses.[27,28]

■ Prognosis

Prognosis depends on the cause, severity, duration, and complications associated with peritonitis. Among horses with peritonitis, the prognosis is poorest for those suffering from gastrointestinal perforation or rupture and best for those with peritonitis associated with *A. equuli*. In two retrospective studies, rates of short-term survival were 86% (56 of 65) and 78% (43 of 55); however, both of these

studies excluded horses with a diagnosis of gastrointestinal rupture.[2,3] Another retrospective evaluation of 67 cases, including those with gastrointestinal rupture, demonstrated a higher mortality rate (40%).[5] In that study, serum creatinine levels, anion gap, and pH at the time of presentation were significantly different between survivors and nonsurvivors; however, more recent research has not confirmed these findings. Celiotomy was found to have a negative effect on survival, with an odds ratio of 9.87 for nonsurvival in horses undergoing exploratory within 2 weeks of diagnosis or as a part of the treatment for peritonitis.[3]

Complications are not uncommon, occurring in 40% (22 of 55) of cases, and can have a negative effect on long-term survival.[2,3] Reported complications include thrombophlebitis, ileus, diarrhea, drain site complications, intraabdominal adhesions, and laminitis. Monitoring and prophylactic therapy for these conditions may help reduce their adverse effect on outcome. With early diagnosis, correction of the inciting cause, aggressive medical therapy, and peritoneal lavage, the prognosis can be fair to good in acute cases of septic peritonitis in horses.

Actinobacillus Peritonitis

A subset of cases of peritonitis attributed to *A. equuli* infection has been reported among horses in Australia, New Zealand, and North America. Infection is generally thought to be secondary to translocation of the bacteria from the gastrointestinal tract or associated with *Strongylus* migration; however, the exact origin is unknown.[29-31] Affected horses present with symptoms of mild to moderate colic (60%), tachycardia (94%), tachypnea (90%), decreased to no borborygmi (88%), and elevated rectal temperature (77%). A chronic form of the disease with a history of progressive weight loss is also reported. A poor deworming history was noted in 9 of 18 horses tested in which elevated numbers of strongyle ova were found on fecal examination.[29,30]

As with other causes of peritonitis, hemoconcentration, an absolute left shift, and hyperfibrinogenemia are common. In addition, peritoneal fluid cell counts are markedly increased—100,000 cells/µL in 88% of samples (46,000 to 810,000/µL)—and protein levels are elevated in 98%. In contrast to other cases of peritonitis, cytologic findings are characterized by a predominance of nondegenerate neutrophils, and pleomorphic Gram-negative rods are identified in 53% of slides. A pure growth of *A. equuli* was obtained in 72% of cases.[30]

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These cases responded rapidly to antibiotic administration (100% short-term survival), and most isolates were sensitive to penicillin; however, it is recommended that therapy include penicillin/gentamicin or oral therapy with trimethoprim-sulfonamide until sensitivity results are available. Therapy should be continued for 7 days beyond return of peritoneal fluid analysis to normal values.

Peritonitis associated with *A. equuli* is characterized by mild to moderate signs of colic, lethargy, elevated heart and respiratory rates, and marked elevations in peritoneal fluid protein and cell counts. It does not progress to endotoxemia or shock, and it is characterized by a rapid response to antimicrobial therapy, which distinguishes peritonitis associated with *A. equuli* from other causes of peritonitis.

Hemoperitoneum

Hemoperitoneum is defined as the abnormal accumulation of blood within the abdominal cavity. In several retrospective case series, researchers have evaluated the causes, clinical presentations, and outcomes associated with the diagnosis of hemoperitoneum.[32-34] The various conditions diagnosed in horses with hemoperitoneum are summarized in Box 32.3. Clinical signs and prognosis depend on the cause and severity of the hemorrhage; however, most affected horses present with symptoms referable to abdominal discomfort/colic (78% to 79%) and hemorrhagic shock (60% to 85%), including tachycardia, tachypnea, pale mucous membranes, depression, weakness, and cool extremities.[33,34]

Box 32.3

Causes of Hemoperitoneum in Horses

Idiopathic: Trauma

Splenic rupture
Rib fracture
Pelvic fracture (iliac artery)

Neoplasia

Renal carcinoma
Granulosal cell tumor
Metastatic neoplasia

Female Reproductive Tract

Uterine artery
Broad ligament tear
Uterine tear/rupture
Ovarian hematoma
Ovarian dysgerminoma

Vascular

Aortic aneurysm
Mesenteric rents
Disseminated intravascular coagulation

Hepatic Rupture

Hepatic lipidosis

Splenic Rupture

Amyloidosis
Hemangiosarcoma

Antemortem diagnosis of hemoperitoneum is based on the identification of hemorrhagic effusion within the abdominal cavity by either ultrasonography or abdominocentesis. Characteristic swirling of echogenic fluid is noted on ultrasonography in cases of intracavitary hemorrhage, and a specific origin of hemorrhage may be identified on ultrasonography in 25% to 44% of cases.[33,34] Peritoneal fluid analysis confirms hemorrhage with findings of PCVs greater than 5%, elevated protein levels, and gross appearance. Hematologic and biochemistry values are often unremarkable; however, alterations in acid-base

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status, blood gas analysis, and plasma lactate concentrations reflect the severity of hemorrhagic shock.

Therapy for hemoperitoneum includes emergency stabilization of hemorrhagic shock, promotion of clot retention, and addressing the primary cause. Treatment of hemorrhagic shock includes conservative volume resuscitation with intravenous crystalloids, colloids, and blood transfusion (see the Fluid Therapy for Hemorrhagic Shock section in Chapter 44). Additional medications to support perfusion (inotropes, vasopressors) may also be indicated. Antifibrinolytics (aminocaproic acid at 3.5 mg/kg IV, conjugated estrogens at 25 to 50 mg/500 kg) are often administered to prevent breakdown of clots and help suppress continued hemorrhage.[35] Exploratory laparotomy may have both diagnostic and therapeutic indications because the source of bleeding may be identified and corrected.[34] Abdominal drainage and lavage is often not performed in these cases, unless severe abdominal distention precludes autotransfusion. To guard against development of septic peritonitis, antimicrobial administration is indicated if bacterial contamination is probably present.

The prognosis for horses presenting with hemoperitoneum is guarded; overall survival rates range from 39% to 74% and depend greatly on the severity of hemorrhage, ability to control hemorrhage, and underlying cause.[32-34] Nonsurvival is associated with respiratory rates higher than 30 bpm, diagnosis of neoplasia (odds ratio, 35.08), mesenteric vessel injury (odds ratio, 243.5), and uterine artery rupture (odds ratio, 13.72).[33] Idiopathic hemoperitoneum is associated with the best long-term survival outcomes.[34]

Gastrointestinal Ileus

Chris Sanchez • Guy D. Lester • Samuel L. Jones

A number of factors are responsible for movement of feed through the gastrointestinal tract, and disturbance in any of these can result in ineffective transit and signs of abdominal pain. Gastrointestinal motility involves an extremely complex interaction among the enteric nervous system, intestinal wall, and luminal contents. Other factors that potentially influence the transit of digesta include gravity, the volume and viscosity of intestinal contents, and pressure gradients created by simultaneous contraction and relaxation of adjacent bowel segments. The inhibition of propulsive bowel activity is usually referred to as *ileus.*

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Several equine diseases and syndromes that probably involve altered gastrointestinal motility include POI, cecal emptying defect, gastroduodenal ulcer disease, simple bowel distention, intraluminal and extraluminal obstructions, peritonitis, and IBDs. Ineffective intestinal motility can also be a feature of several neonatal disorders, including prematurity, systemic sepsis, and neonatal encephalopathy, and can be found in postparturient mares. Certain parasitic infections, electrolyte derangements, and endotoxemia can modify intestinal transit in horses of all ages. Intestinal motility is also disturbed by general anesthesia and sedation, especially with the α_2 receptor agonists.

■ Physiology of Intestinal Motility

The control of intestinal motility is complex and involves a combination of central innervation, autonomic innervation, and the enteric nervous system. Intestinal contractions are controlled primarily by the enteric nervous system and do not require extrinsic neural input. The inherent rhythmicity of electrical activity in the intestine is controlled by the interstitial cells of Cajal. These are highly specialized cells that are electrically coupled to the smooth muscle syncytium via gap junctions.[1] They are responsible not only for generation of slow waves (cyclical electrical activity) but also for coordination of pacemaker activity and propagation of slow waves along the intestine. Interstitial cells of Cajal appear to be critically involved in a range of motility disorders in human beings, including gastroparesis, pseudoobstruction, and chronic constipation.[1] In horses, a reduction in the density of interstitial cells of Cajal has been demonstrated with equine grass sickness and other large intestinal diseases.[2,3] The inherent “excitability” of smooth muscle cells in response to stimuli varies among regions of the gastrointestinal tract and among species. This variability in cell excitability is dependent on the magnitude of the membrane potential, which in turn is regulated by the number and subtype of potassium channels.[4]

The enteric nervous system plays an important role in control and coordination of intestinal contraction. Contractile events are influenced by central and autonomic innervation, but external neural input is not required for contraction. The parasympathetic supply to the gastrointestinal tract is via the vagus and pelvic nerves, and the sympathetic supply is through postganglionic fibers of the cranial and caudal mesenteric plexuses. A complex network of interneurons within each plexus integrates and amplifies neural input, and the intensity and frequency of resultant smooth muscle contractions are proportional

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to sympathetic and parasympathetic input. Additional binding sites for a number of other endogenous chemicals, including dopamine, motilin, and serotonin, can be found within the enteric nervous system and on smooth muscle cells.[5] Of importance is that mechanisms to slow progressive intestinal motility are also critical in order to retain feed for adequate digestion and absorption of nutrients. The terms *jejunal* and *ileal brake* have been used to describe the slowing of transit caused by mediators such as peptide YY, noradrenergic nerves, and opioid, serotonergic, and chemosensitive afferent neurons.[6]

Acetylcholine is the dominant excitatory neurotransmitter in the gastrointestinal tract and exerts its action through muscarinic type 2 (M_2) and and type 3 (M_3) receptors. Sympathetic fibers innervating the gastrointestinal tract are adrenergic, postganglionic fibers with cell bodies located in the prevertebral ganglia. Activation of α_2-adrenergic receptors on cholinergic neurons within enteric ganglia inhibits the release of acetylcholine and therefore reduces intestinal contraction. The β_1, β_2, and β-atypical receptors directly inhibit the activity of intestinal smooth muscle.[7] Inhibitory nonadrenergic, noncholinergic neurotransmitters include adenosine triphosphate (ATP), vasoactive intestinal peptide, and nitric oxide.[8,9] These neurotransmitters are critical for mediating descending inhibition during peristalsis and receptive relaxation. Substance P is a nonadrenergic, noncholinergic neurotransmitter that may be involved in contraction of the small intestine and large colon.[10-12] The rate and force of intestinal contractions along the small intestine and large colon of horses are key determinants of intestinal motility. Of even greater importance to the net propulsion of digesta are the cyclical patterns of contractile activity. These patterns are known as the small intestinal and colonic *migrating motility complexes* (MMC).[13] The colonic MMC usually originates in the right ventral portion of the colon and variably traverses the ascending and descending portions of the colon. Many of these complexes are temporally related to a specialized motility event of the ileum known as the *migrating action potential complex.*

■ Mediators of Gastrointestinal Ileus and Major Disease Categories

Inflammation within the intestinal muscularis layers and inhibitory neural events are important initiators of intestinal ileus.[14,15] Intestinal inflammation is

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important in primary inflammatory intestinal diseases in horses, such as DPJ and colitis, but it is also induced after simple intestinal handling during laparotomy. Experimental data from other species suggest that handling of the small or large intestine at the time of surgery induces an intense inflammatory response within the muscularis layers and a reduction in the intensity of smooth muscle contraction.[15-17] Furthermore, the inflamed intestine fails to contract normally in response to putative prokinetic agents. Additional studies have determined that this inflammatory response was not restricted to segments that were manipulated at the time of surgery but also involved other regions throughout the gastrointestinal tract.[14] Intestinal handling in experimental animals causes local overproduction of nitric oxide because of the upregulation of inducible nitric oxide synthase by resident macrophages.[18] Nitric oxide is a key inhibitory neurotransmitter of the nonadrenergic, noncholinergic system.[9] Consequently, nitric oxide synthase inhibition could be an important target for prevention of ileus.

The inhibition of motility associated with peritoneal inflammation may also be mediated through neural reflexes. The afferent segment is composed partly of capsaicin-sensitive visceral afferent C-fibers that terminate in the dorsal horn of the spinal cord, where they can activate inhibitory sympathetic fibers or, alternatively, synapse directly on the sympathetic ganglia. Consequently, the efferent limb of the neural pathway of the reflex expresses increased sympathetic outflow, mediated primarily through stimulation of α_2-adrenoreceptors, with subsequent inhibition of acetylcholine release. This provides the rationale for α_2 blockade in the treatment of ileus. Intraluminal infusion of capsaicin before abdominal surgery ameliorated the severity of POI in experimental rats.[19] This finding highlights the importance of visceral afferent fibers in the development of POI.

Ileus can also occur with intestinal obstruction or displacement. Mild to moderate distention of the bowel, such as that occurring in the early stages of an intraluminal obstruction, evokes an increase in local contractile activity.[20,21] Excessive distention results in inhibition of motility within the distended segment of bowel. Intestinal stasis is not always detrimental and, in certain conditions, may be protective.

Endotoxemia is a feature of many diseases of the equine gastrointestinal tract, and endotoxins can independently exert a negative effect on intestinal motility and transit.[22] Various mediators are probably involved, but activation of α_2-

adrenoreceptors and production of prostanoids appear to be important, as the inhibitory effects of experimental endotoxin infusion are ameliorated by pretreatment with yohimbine or NSAIDs (phenylbutazone or flunixin), respectively.[23,24] Endotoxin infusion induced an inflammatory response in the intestine of rats that mimicked that induced by handling during laparotomy.[25]

■ Cecal Emptying Defect (Cecal Impaction)

An important and specific motility problem involving the cecum occurs sporadically in adult horses and foals.[26-30] The pathophysiologic origin of cecal emptying defect is not known. This syndrome may best mimic POI in humans, which is generally considered a large intestinal disorder. An important difference in horses is that laparotomy is a rare predisposing factor, and most cases occur in horses undergoing routine extraabdominal surgical procedures. General anesthesia is a potent inhibitor of gastrointestinal motility in horses, but the effects are short-lived and reversible within hours of anesthetic withdrawal.[31] The return of normal motility in horses after experimental ileus was most delayed in the cecum, which suggests that this may be a common site of ileus in horses.[32]

Retrospective data regarding cecal impactions suggest that two subtypes exist, and retrospective studies highlight those differences. In a United Kingdom report of 20 horses undergoing surgery because of cecal impaction, the condition appeared after orthopedic (10 of the 20) or colic (5 of the 20) surgery in the majority of horses.[33] Short-term survival in that report was 65%, and all but 3 horses underwent cecal bypass. Alternatively, in a Texas report of 114 horses with cecal impaction, approximately half were treated medically and half surgically.[34] Of the horses allowed to recover from surgery, 95% survived to discharge, and typhlotomy alone was performed in 34 of 37 horses. Eighty-one percent of horses treated medically survived to discharge.[34] These reports appear to describe the two types of cecal impactions well, and the secondary (also called *type II*) impactions appeared to be associated with cecal emptying defect, and are therefore often categorized as a form of POI. In horses, postoperative cecal impaction was evident at a mean of 3.6 and 7.5 days after orthopedic and colic surgery, respectively.[33] The earliest detectable signs include lethargy and a reduction in appetite, fecal output, or both. Ineffective emptying results in overfilling of the cecum with moist contents, which is manifest by signs of mild to moderate colic. If the condition is recognized late or untreated, the cecum may

rupture, resulting in fatal peritonitis.

■ Postoperative Ileus

The most frequently reported form of ileus occurs after laparotomy and is termed *simple* or *uncomplicated postoperative ileus.* The condition in which intestinal motility is disturbed for longer periods after surgery, typically for more than 72 hours, is called *complicated* or *paralytic ileus.*[35] POI in horses is most commonly associated with surgery of the small intestine, particularly after resection and anastomosis. As stated previously, intestinal inflammation, particularly in the muscularis layers, is probably a key factor associated with the development of POI. The true incidence of POI in horses undergoing laparotomy for gastrointestinal disease is difficult to determine because of variation in definition, surgical skill, and anesthetic technique. POI was reported as a complication in only 10% of horses that underwent laparotomy for a small intestinal lesion at one referral practice[36] but in 27% in another.[37] In the latter study, horses with DPJ were included, but 30% of horses developed POI after small intestinal resection. In a multicenter study, 47 (19%) of 251 horses undergoing laparotomy for acute colic, including those with small and large intestinal disease, developed POI.[38] As stated previously, the retrospectively collected POI data are extremely hard to interpret, and many mechanical obstructions and surgical complications can mimic POI[39]; thus authors are encouraged to adopt uniform definitions of POI and make every attempt possible to distinguish POI from intestinal obstruction.[40]

POI can have a significant negative effect on short-term postoperative survival.[41-43] Motility dysfunction is probably present in all horses after laparotomy, but most cases are subclinical and necessitate minimal intervention. In symptomatic animals, clinical signs are typically observed within 24 hours of recovery; these signs include colic, tachycardia, dehydration, decreased borborygmi and fecal output, and sequestration of fluid within the stomach. Rectal examination and ultrasonography may reveal small intestinal distention with rare or no wall movement. The severity and duration of intestinal stasis is variable, lasting from minutes to days.

The development of small intestinal POI, but not cecal emptying dysfunction, is influenced by the duration of surgery.[27,38] Technique may have a weak influence on small intestinal POI after jejunojejunostomy. The duration of intestinal ileus was shorter in animals that received a side-to-side stapled

anastomosis than in those that had a hand-sewn end-to-end procedure.[41] The duration of ileus after stapled end-to-end anastomosis was no different from that after either of the other procedures.

Reported risk factors for the development of POI in horses include age (>10 years), small intestinal resection and anastomosis, breed, heart rate at admission, large volume (>8 L) reflux at admission, and duration of anesthesia and surgery.[37,38,43,44] Jejunocecostomy and side-to-side jejunojejunostomy have been associated with an increased risk of POI.[36,45] Pelvic flexure enterotomy and intraoperative and postoperative lidocaine infusion have been associated with a decreased incidence of POI.[38,43-45]

■ Miscellaneous Motility Disruptions

Other disruption of normal intestinal motility can occur in horses. Many, but not all, are associated with analgesic or sedative drug administration. The inhibitory effects of α_2-adrenergic agonists, such as xylazine and detomidine, on intestinal motility in horses are well described.[46-54] The activation of postganglionic cholinergic nerves in the myenteric plexus by this class of drugs results in reduced release of acetylcholine from autonomic and enteric nerves. Intravenous xylazine inhibits cecal and large colon motility for 20 to 30 minutes without seriously disrupting small intestinal myoelectric activity, and detomidine can reduce large intestinal myoelectric activity for up to 3 hours. The α_2-antagonist yohimbine has a weak but positive effect on cecal emptying in normal ponies, which suggests that normal motility is under constant α_2-adrenergic tone.[48]

Other analgesic medications can also decrease gastrointestinal motility. Opioids such as morphine have long been associated with decreased motility in humans.[55] Morphine has been shown to delay gastrointestinal transit and decrease gastrointestinal moisture content in horses.[56,57] Butorphanol administered alone appears to reset the antroduodenal MMC without substantial negative effects on motility, but it decreases duodenal motility when combined with xylazine more than does xylazine alone.[50,58] The roles of selective or preferential μ- and κ-receptor agonists vary different regions of the equine gastrointestinal tract: κ-Receptor agonists appear to have a more inhibitory effect in the jejunum, whereas μ-receptor agonists appear to inhibit the large colon more significantly.[59,60] Ketamine has also been shown to increase total gastrointestinal transit in healthy horses.[61]

Atropine is a postganglionic blocking agent that binds to muscarinic receptors. When administered at 0.04 mg/kg, individual small intestinal, cecal, and colonic contractions are inhibited for approximately 120 minutes, but small intestinal and colonic MMCs are suppressed for up to 8 hours.[62] The negative effect of atropine on gastrointestinal motility in horses can also be evident with topical ophthalmic administration of atropine.[63] This effect, in combination with pain and other management factors, probably relates to the high reported risk of colic in horses hospitalized for ocular disease.[64]

Gastric and small intestinal ileus, with no identifiable mechanical or physical disruption of motility, have also been identified as causes of acute colic in postparturient mares.[65] The origin of this condition has not been identified, but most mares responded well to decompression.

■ Diagnosis

The diagnosis of ileus is based on history and physical examination findings. Important tests include determination of pulse rate and rhythm, auscultation and percussion of the abdomen, rectal palpation, and passage of a nasogastric tube. CBC with fibrinogen estimation and cytologic analysis of peritoneal fluid may improve the accuracy of diagnosis. Affected animals may be colicky because of accumulation of fluid in the upper gastrointestinal tract (classical POI) or cecal contents (cecal emptying defect). Decompression of the stomach is important diagnostically and therapeutically in horses with POI after small intestinal surgery. The presence of intragastric fluid upon nasogastric intubation is a commonly applied diagnostic criterion, but little information is available to define the parameters that increase the predictive value of nasogastric reflux either alone or in combination with other clinical findings. Proposed criteria include gastric reflux of 4 L or more upon any single intubation or of more than 2 L/h on serial intubations; gastric fluid pH higher than 4.0; persistent tachycardia (>40 beats/min); signs of mild to severe abdominal discomfort; and rectal or ultrasonographic evidence of multiple loops of fluid-distended small bowel.[40] Failure to relieve pain with gastric decompression could indicate mechanical obstruction, severe inflammation of the intestine, or peritonitis. Most animals with ileus are depressed and have reduced fecal output and intestinal borborygmi. Intestinal sounds should, however, be interpreted with caution, because the presence of borborygmi does not always equate to progressive intestinal motility and may merely reflect local, nonpropagated contractions.

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Cecal distention with either firm or soft contents can be palpated rectally in horses with cecal dysfunction.

It is important to distinguish functional ileus from mechanical obstruction. This can be extremely difficult, but horses with mechanical obstruction typically have sustained high volumes of gastric reflux that vary little over time. Distinguishing mechanical obstruction from POI is especially important because horses with mechanical obstruction in the postoperative period may benefit from early repeat laparotomy.[39]

■ Treatment

Supportive Care.

The management of gastrointestinal ileus is dependent on the segment of gastrointestinal tract involved. Therapy for ileus of the proximal gastrointestinal tract typically involves a combination of gastric decompression, fluid and electrolyte therapy, and antiinflammatory drugs. Nasogastric decompression is the mainstay of management to prevent excessive distention of the stomach and small intestine. This often necessitates placement of an indwelling nasogastric tube, a procedure that some authors have speculated may in itself delay gastric emptying. In one study, the placement of an indwelling tube for 18 hours did not adversely affect the emptying of liquids, but in another study, a delay was noted when the tube was left in place for 72 hours.[66,67] Both studies used apparently healthy animals.

Electrolyte balance is important, particularly with regard to maintaining adequate extracellular concentrations of potassium, calcium, and magnesium. Calculation of appropriate fluid replacement volume should include maintenance requirements (40 to 60 mL/kg/day) and an estimate of losses, especially nutrients lost through gastric decompression. Overhydration should be avoided to prevent intestinal edema. Intravenous colloidal fluids may be useful in addition to crystalloid fluids to prevent overhydration. Whereas medical therapy with fluid replacement and antiinflammatory drugs may be helpful for horses with primary cecal impaction, surgical therapy is probably required for horses with secondary cecal emptying defect.[33,34,68] Surgical management may include typhlotomy alone, typhlotomy with a bypass procedure such as ileocolic or jejunocolic anastomosis, or a bypass without typhlotomy.[33,68] If affected horses survive postoperatively to discharge from the hospital, chances of long-term survival

appear good.[33]

Evidence in experimental models and in human medicine suggests that early refeeding after surgery helps prevent POI.[69] Early refeeding was found to be beneficial in equine surgical cases.[36] Many clinicians offer small (one or two handfuls) meals of good-quality roughage frequently to reduce the risk of POI. A significant clinical or economic benefit of parenteral nutrition in adult horses with gastrointestinal disease also has yet to be demonstrated.[70-72] Parenteral nutrition should be considered when feed has been withheld for more than 96 hours, particularly in horses with a surgical wound, increased metabolic demands, or risk of hyperlipidemia. Limited exercise, in the form of hand-walking, may provide some benefit to these animals, although there is no evidence that exercise has a direct effect on intestinal motility in either horses or humans with POI.[73]

The pivotal role of intestinal inflammation provides a strong rationale for the use of antiinflammatory drugs in affected animals. Flunixin meglumine is widely used in equine practice as an analgesic and antiinflammatory agent, and ameliorates many of the adverse systemic effects of endotoxin. A potential negative effect of NSAIDs on large intestinal contractility has been suggested on the basis of results of in vitro studies[74]; however, a similar response has not been reported in whole animal studies.[46,48,75] There is some concern that non–cyclooxygenase-selective drugs such as flunixin meglumine inhibit anastomotic site healing and mucosal repair. An alternative may be firocoxib, which is highly selective for COX-2 and is as effective as flunixin in controlling colic pain.[76] Lidocaine is also an alternative or adjunct analgesic and antiinflammatory drug. The use of lidocaine is discussed in more detail later in this chapter.

Broad-spectrum antimicrobial drugs are indicated when sepsis is suspected or if the immune system is compromised, as in cases of moderate to severe endotoxemia. Theoretic concerns have been raised regarding the use of aminoglycoside antibiotics in animals with ileus. Inhibition of intestinal contractions occurred when sections of intestine were exposed to high concentrations of aminoglycoside antimicrobial drugs, but this inhibitory effect is unlikely to occur at clinically relevant doses.[77] The administration of benzylpenicillin or ceftiofur was associated with an increased risk of colic in the week after anesthesia for diagnostic imaging or nonabdominal surgical procedures.[78] Potassium penicillin G appears to have a modest, positive effect on large intestinal motility and frequency of defecation in horses.[79]

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Motility Modification.

Motility-modifying drugs could play an important role in the prevention and treatment of gastrointestinal ileus. An effective prokinetic agent could shorten the length of hospitalization, thereby reducing the cost of treatment and the number of potential complications such as weight loss, thrombophlebitis, and laminitis. There is also evidence that the development of abdominal adhesions could be minimized with the use of an effective prokinetic drug.[80,81] A potential negative effect of prokinetic use in the postoperative period after anastomosis is increased predisposition to dehiscence.[82]

For most motility-modifying drugs to be effective, the intestinal wall must be healthy in order to enhance intestinal contraction. There are several examples in horses in which the expected contractile response to certain drugs is blunted in the presence of disease. It is reasonable to assume that many putative prokinetic drugs would be partially or totally ineffective in horses with abdominal disease. Such disease would include intestine that has undergone prolonged or excessive distention or that is in any inflammatory condition, such as after intestinal manipulation or in association with primary inflammatory diseases such as DPJ or *Salmonella* enteritis. Numerous drugs have been investigated in humans with POI, but no prokinetic agent has yet been found to be safe and effective.[83] The financial pressures associated with equine patient management often compel attending veterinarians to experiment with a range of putative prokinetic drugs.

Lidocaine, an aminoamide local anesthetic, appears to be the most commonly used putative prokinetic agent in the management and prevention of POI.[84] Intravenous administration of lidocaine increases gastrointestinal transit time in normal horses.[85] However, evidence regarding the efficacy of lidocaine in treating or preventing POI in horses is limited and conflicting (see below). Intravenous infusion of lidocaine may suppress primary afferent neurons, thereby limiting reflex efferent inhibition of motility. It is also possible that lidocaine may block the inhibitory effect of nonadrenergic, noncholinergic neurotransmitters on smooth muscle.[86] Lidocaine also has significant antiinflammatory properties, including amelioration of the cytokine response to endotoxemia, reduced neutrophil free radical production, impaired leukocyte phagocytic function, and inhibition of leukocyte migration through suppression of chemokines.[87,88] In addition, lidocaine has been shown to decrease clinical scores after experimental endotoxin administration in healthy horses, in comparison with untreated controls.[88] Lidocaine administration can also

ameliorate the inhibitory effects of flunixin meglumine on jejunal mucosal barrier recovery after ischemia.[89,90] Because systemic administration of lidocaine was shown to increase somatic thermal antinociceptive threshhold, but not visceral distention threshold, the beneficial effect of lidocaine in horses with gastrointestinal disease may not be associated with analgesia.[91]

A combination of intraoperative and postoperative lidocaine infusion is commonly used as a preventive strategy against POI on the basis of evidence suggesting that treatment with lidocaine during colic surgery improves postoperative prokinetic activity in ischemic intestine[92] and is associated with a decreased risk of POI.[38] Postanesthetic treatment typically involves a slow intravenous bolus of 2% lidocaine (1.3 mg/kg) followed by a constant infusion at 0.05 mg/kg/min for 24 hours, with a target serum concentration between 1 and 2 mg/dL. In a prospective study of horses undergoing laparotomy for colic, the authors failed to demonstrate any difference between lidocaine and saline infusion with regard to return of borborygmi, time to first feces, or gastric reflux.[93] The study was limited by a low incidence of small intestinal strangulating lesions and POI. A large prospective study in the United Kingdom did not demonstrate an effect of lidocaine treatment on the prevalence, volume, or duration of postoperative gastric reflux.[94] Lidocaine infusion was associated with a reduction in reflux duration, time to fecal passage, and hospital stay for survivors in a study of 32 horses with POI or DPJ.[86] In a larger retrospective study of 126 horses undergoing surgery for small intestinal colic, lidocaine administration was associated with a reduced incidence of POI and increased rate of short-term survival.[43]

The rate of lidocaine infusion requires close monitoring because infusion can be associated with reversible side effects that include muscle fasciculations, ataxia, and seizures. The drug is highly protein bound, so hypoproteinemic horses may be more susceptible to toxic effects.

Bethanechol is a methyl derivative of carbachol and is an acetylcholine receptor agonist. The drug acts both at the level of the myenteric plexus and directly on intestinal smooth cells through muscarinic receptors. The actions are primarily mediated through activation of M_3 receptors; M_2 receptors are also involved but to a lesser extent.[95] There is evidence in other species that activation of M_2 receptors not only facilitates intestinal contraction but also may lead to antinociception.[96] Bethanechol is not degraded by the enzyme anticholinesterase. As anticipated, the drug has a range of cholinergic side

effects, including abdominal discomfort, sweating, and salivation, although these are minimal when the drug is administered subcutaneously at 0.025 to 0.05 mg/kg of body weight.

Bethanechol is one of the most useful prokinetic agents in equine practice, inasmuch as it exerts effects throughout the gastrointestinal tract; however, it does not appear to be commonly used for that purpose.[84] It is most commonly used in the management of delayed gastric emptying and slowed small intestinal transit. The drug has been shown experimentally to significantly increase gastric contractility and hasten the emptying of liquid- and solid-phase markers from the stomachs of normal horses.[97] The drug has potent effects in the hindgut as well. Bethanechol increases both the relative strength and duration of wall contractions in the cecum and right ventral portion of the colon and consequently speeds up cecal emptying.[48] When given to ponies at a dose of 0.05 mg/kg SC, the drug increased electrical activity in the large colon for approximately 80 minutes.[75] Reported rates of bethanechol dosing have ranged widely; the doses most commonly recommended range from 0.025 to 0.05 mg/kg SC.

Neostigmine increases receptor levels of acetylcholine by inhibiting cholinesterase. The drug (0.022 to 0.025 mg/kg IV) promotes cecal and colonic contractile activity and enhances cecal emptying in normal ponies.[48] Neostigmine has been used in the management of small intestinal ileus but significantly delayed the emptying of 6-mm beads from the stomach of normal adult horses.[57] A survey of prokinetic use indicated that neostigmine was more commonly used in the management of large intestinal disease.[84]

Metoclopramide is a moderate partial 5-hydroxytryptamine 4 (5-HT_4) receptor agonist, a moderate 5-hydroxytryptamine 3 (5-HT_3) receptor antagonist, and an antagonist of both dopamine 1 and dopamine 2 receptors. It has been suggested that the 5-HT_4 receptor agonist properties are primarily responsible for the prokinetic effects of metoclopramide. Antagonism of prejunctional dopamine 2 receptors facilitates acetylcholine release and smooth muscle contraction. The effect on dopamine receptor antagonism is absent in newer benzamides. Metoclopramide crosses the blood-brain barrier, where its antagonist properties on central dopamine 2 receptors can result in extrapyramidal signs, including seizure. These signs were observed when the original reported dose of 0.25 mg/kg, given by intravenous infusion over 30 minutes, was used in practice,[98] and they were responsible for poor acceptance of the drug in equine practice. An experimental bolus of endotoxin caused a delay in gastric emptying, as assessed

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in the acetaminophen absorption test; this delay was partially ameliorated through pretreatment with metoclopramide (0.125 mg/kg in 1 L infused over 15 minutes), but, again, the investigators reported adverse side effects.[99] Most investigators have failed to demonstrate significant effects of metoclopramide in experimental animals, but constant intravenous infusion (0.04 mg/kg/h) in a population of horses after surgery significantly decreased the volume and duration of gastric reflux in comparison to control horses and horses receiving intermittent drug infusion.[100] Infusion was well tolerated and was superior to intermittent infusion and to no treatment at all.

Cisapride is a second-generation benzamide that is commonly reported to act as a primary 5-HT_4 receptor agonist and 5-HT_3 receptor antagonist. Furthermore, stimulation of 5-HT_4 receptors within the enteric nervous system enhances release of acetylcholine from the myenteric plexus, thereby promoting intestinal contraction. In vitro studies of equine jejunum concluded that the contractile actions of cisapride in the species were mediated primarily through 5-HT_2 and not 5-HT_4 receptors and that the response was noncholinergic.[101] Several reports suggested efficacy of cisapride in the management of intestinal disease in horses, including the resolution of persistent large colon impaction, treatment of equine grass sickness, and prevention of POI in horses after small intestinal surgery.[102-105] Cisapride has the potential to cause adverse cardiac effects, mediated through blockage of the rapid component of the delayed rectifier potassium current; those effects include lengthening of the QT interval and development of torsades de pointes, a potentially fatal arrhythmia. As a result, the drug has been withdrawn in the United States and in many other countries.

Another benzamide, mosapride, resulted in increased myoelectric activity of the small intestine and cecum of horses after oral administration. The authors reported that mosapride is a selective 5-HT_4 receptor agonist; consequently, the reported effects are surprising given that the actions of 5-HT on the equine jejunum were reported to be primarily mediated through activation of 5-HT_2 and 5-HT_3 receptors.[101] Further work has demonstrated increased gastric emptying, jejunal and cecal motility after mosapride administration (2 mg/kg PO) to healthy horses.[106] Mosapride (1.5 mg/kg PO) was also shown to increase electrointestinographic maximum amplitude within the small intestine, in comparison to untreated controls, after jejunocecostomy in normal horses.[107]

Tegaserod, a selective 5-HT_4 receptor agonist, is used in humans for the treatment of irritable bowel syndrome.[104,108] In horses, tegaserod has been shown to decrease total gastrointestinal transit time[109] and increase pelvic flexure contractile activity in vitro.[110,111] Tegaserod appears safe when administered orally to horses, and plasma concentrations considered therapeutic, according to in vitro work, were obtained after administration of a single dose orally at 0.27 mg/kg.[110]

Domperidone acts as a competitive antagonist at peripheral dopamine 2 receptors; these receptors are inhibitory. The drug has been used to manage gastroparesis in humans for many years.[112] The primary use in equine practice is in the management of mares grazing endophyte-infected tall fescue (1.1 mg/kg/day PO), principally because of drug-enhanced prolactin release from the anterior pituitary gland. The potential prokinetic effects of domperidone have not been studied extensively in horses, but modest efficacy of domperidone (0.2 mg/kg IV) was demonstrated in a model of experimental ileus in two ponies.[113]

Erythromycin is a direct motilin receptor agonist acting directly on smooth muscle cells, as well as within the enteric nervous system, to facilitate the release of acetylcholine and motilin. Erythromycin enhances gastric emptying in normal horses but, in contrast to most other species, has a more pronounced effect on the hindgut.[97,114] This is somewhat surprising because a higher density of motilin receptors was reported in the duodenum than in either the cecum or pelvic flexure of adult horses.[115] Erythromycin lactobionate (1 mg/kg IV) hastens cecal emptying in normal animals and induces propagating colonic MMC-like activity across the colon. Administration is often followed by defecation and abdominal discomfort. Several problems limit the use of erythromycin as a prokinetic agent in equine practice. Its principal use in human medicine has been restricted to management of acute exacerbations of diabetic gastroparesis, facilitation of feeding tube placement, and upper gastrointestinal endoscopy.[116] Although it has been shown to enhance emptying in normal horses, it was not as effective as bethanechol.[97] Because of its potent prokinetic effects in the cecum, erythromycin may help prevent cecal impaction in horses after anesthesia. However, its effectiveness on cecal motility appears to be markedly reduced in the immediate postoperative period.[32] High doses, constant infusion, or prolonged use of erythromycin also induces receptor tachyphylaxis, and its efficacy is thereby reduced. There is also evidence that intraluminal distention for as little as 2 hours leads to a reduction in the total number of

motilin receptors and in the amount of motilin receptor messenger RNA, although erythromycin binding to remaining motilin receptors is not affected.[117] Erythromycin can induce diarrhea in adult horses; therefore administration over many days should be avoided. The diarrhea induced by erythromycin is probably mediated by *C. difficile* overgrowth and toxin elaboration.[118]

Because opiates have an inhibitory effect on normal intestinal motility, opioid antagonists may have the potential for prokinetic activity. Naloxone (0.05 mg/kg IV) has been shown to induce contractile activity in the cecum and the left portion of the colon.[119] The administration of naloxone was often followed by defecation within 15 to 20 minutes. Naloxone has not been beneficial in preventing POI in human beings.[120] Peripherally acting opioid antagonists, such as *N*-methylnaltrexone, can improve gastrointestinal tract function in humans who require opioids for pain management. An in vitro study in horses demonstrated a direct contractile effect of *N*-methylnaltrexone on the circular muscle layer of the jejunum and large colon.[121] In healthy horses, *N*-methylnaltrexone therapy increased daily fecal weight and, when administered concurrently with morphine, partially prevented morphine-associated increases in intestinal transit time and decreases in fecal production.[122]

α_2-Adrenoreceptor antagonists, such as yohimbine and tolazoline, counteract increased sympathetic outflow in response to nociceptive stimulation. Yohimbine (75 µg/kg by slow intravenous infusion) hastens cecal motility and emptying in normal ponies and also attenuates the negative effects of endotoxin on motility.[23,48]

■ Prevention and Early Identification

Close monitoring is essential when horses have multiple risk factors for either POI or other forms of ileus, such as being on a regimen of opioid agonists, α_2-adrenergic agonists, or atropine, or combination of these. Monitoring fecal output closely can often help owners and practitioners identify horses developing impaction, thus allowing for early medical therapy. Similarly, close postoperative monitoring and gastric decompression are important for early detection of POI.

For horses at risk of cecal impaction or other miscellaneous motility disorders, limiting the number of drugs likely to inhibit motility and altering the diet to include increased water consumption and decreased bulk may be beneficial.

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Nonsteroidal Antiinflammatory Drug Toxicity

Samuel L. Jones

Use of NSAIDs is common in equine practice because of their antipyretic, analgesic, and anti-inflammatory properties. These drugs are used to treat horses with colic, sepsis/endotoxemia, musculoskeletal disorders, and other medical problems. In addition to these therapeutic properties, NSAIDs also produce unwanted toxic side effects. NSAIDs have a relatively narrow therapeutic range, and when they are administered at excessive doses, toxicosis can occur within a few days. Although they are generally safe when administered at recommended doses,[1] some horses may exhibit signs of toxicosis at these doses within days or weeks.[2,3] The risk of toxicity is exacerbated in animals that are dehydrated or septic (e.g., endotoxemic patients). Recommended doses for NSAIDs commonly administered to horses include the following:

- Phenylbutazone, 2.2 to 4.4 mg/kg IV or PO q12h
- Flunixin meglumine, 1.1 mg/kg q12h or 0.25 mg/kg IV or PO q8h
- Ketoprofen, 2.2 mg/kg IV q24h
- Naproxen, 5 to 10 mg/kg IV or PO q12-24h
- Aspirin, 12 to 25 mg/kg PO q12-48h
- Meloxicam, 0.6 mg/kg IV q24h
- Firocoxib, 0.1 mg/kg PO q24h or 0.09 mg/kg IV q24h

■ Pathophysiology and Predisposing Factors

The principal mechanism of the therapeutic and toxic effects of NSAIDs is related to their inhibition of prostaglandin synthesis by inhibition of the COX enzyme. Two isoforms of the COX enzyme, COX-1 and COX-2, have been identified.[4] COX-1 is generally expressed constitutively and is thought to play an important role in maintaining physiologic homeostasis; it is found in such tissues as the gastrointestinal mucosa and kidneys and in the endothelium and platelets. In contrast, COX-2 is primarily an inducible enzyme that has a critical

role in inflammation and is produced by a variety of cells, including monocytes, neutrophils, epithelial cells, fibroblasts, synoviocytes, and chondrocytes.

It has been postulated that drugs that nonselectively inhibit both COX-1 and COX-2 have greater toxic potential because they inhibit prostaglandins necessary for physiologic homeostasis, as well as prostaglandins that mediate inflammation and pain.[4] Both COX-1– and COX-2–dependent prostaglandins play an important role not only in maintaining the epithelial barrier in the gut but also in healing the epithelium when the mucosa is damaged (e.g., because of ischemic injury or infection). Most of the commonly used NSAIDs in horses are considered to be nonselective. Exceptions include meloxicam (3.8 to 10 times more selective for equine COX-2 versus COX-1[5,6]) and firocoxib (268 to 643 times more selective for COX-2 than for COX-1[7]). NSAIDs that are COX-2 selective are less ulcerogenic than those that are COX-1 selective in other species and may be so in horses. For example, COX-2 selectivity decreases the adverse effects of NSAIDs in a model of epithelial repair in horses.[8]

Although the COX-1 versus COX-2 scheme is currently considered valid, some evidence indicates that it may be overly simplistic. For example, COX-1 may play an important role in inflammation and is at least partly inducible.[9] In contrast, COX-2 can be induced physiologically in various organs and tissues and by stimuli other than inflammation.[4,10] In horses, gastric ulcerogenicity of even the nonselective NSAIDs varies (phenylbutazone is more ulcerogenic than flunixin meglumine, which is more ulcerogenic than ketoprofen).[11] This difference in toxicity among drugs may relate not only to the COX selectivity but also to other factors such as tissue distribution.

The gastrointestinal tract and the kidneys are the most common targets for NSAID toxicity. NSAID-induced injury can develop anywhere in the gastrointestinal tract (from the mouth to the rectum). Two well-recognized syndromes may be attributed, at least in part, to NSAID toxicity. The first is gastric ulceration: In the stomach, inhibition of COX can increase acid secretion, decrease output of mucus and bicarbonate, impair vasodilation, and diminish epithelial restitution, cell division, and angiogenesis.[12] Inhibition of COX also impairs the healing of existing ulcers. The second syndrome attributed to NSAID toxicity is right dorsal ulcerative colitis (RDUC). Although the right dorsal segment of the large intestine is most commonly affected, other segments may also be involved. Ulcerative lesions in the large intestine can be particularly troublesome because they can cause chronic debilitation, are difficult to

diagnose, and can be refractory to treatment. In the kidney, prostaglandin E_2 and prostacyclin (prostaglandin I_2) produce vasodilation in the autoregulatory response of renal blood flow to hypoperfusion; consequently, hypovolemia, hemorrhage, or renal disease increases the risk of renal NSAID toxicosis. Damage is greatest at the renal crest (papilla), and papillary crest necrosis may be associated with subsequent nephrolithiasis or ureterolithiasis and chronic renal failure.[13] In humans the most common side effect of NSAIDs is bleeding, caused in part by reduced function of platelets and in part by gastrointestinal hemorrhage.

Not all of the adverse effects of NSAIDs are attributable to COX inhibition. The NSAIDs also cause injury through a variety of mechanisms, including microvascular damage, increased intracellular concentration of reactive oxygen and other free radicals, direct local injury (particularly with ion trapping in the stomach), inhibition of cell division, and reduced hydrophobicity of the gastric mucous coat.[10,12] Inhibition of COX may cause arachidonic acid metabolism to be shunted toward the lipoxygenase pathway, thereby producing other biologically active eicosanoids. The clinical significance of this shunting is unclear, but it has the potential for deleterious effects.

Although the toxicity of NSAIDs is related to the dose and duration of administration, some horses develop toxicosis at recommended doses. Predisposing factors such as dehydration, renal disease, hepatic disease, or sepsis may contribute to the development of NSAID toxicity. Dehydration, renal disease, and hepatic disease predispose horses to NSAID toxicosis because of reduced tissue perfusion and reduced drug elimination. Sepsis may predispose horses to NSAID toxicosis because of secondary hypovolemia, decreased tissue perfusion, and direct and indirect effects of various mediators produced in response to sepsis (e.g., platelet-aggregating factor). In humans, risk of NSAID-induced ulceration is increased among those with various gastrointestinal disorders (e.g., IBDs). NSAIDs inhibit the ability of injured equine intestinal mucosa to repair, which may increase the risk of ulceration in horses with ischemic damage or intestinal infections. Body weight may be a predisposing factor in that NSAIDs are often administered to ponies, miniature horses, and small horses at doses higher than those recommended for their body weight. Inadvertent overdosing can occur regardless of body weight or size (e.g., administration of a 12-g tube of phenylbutazone paste when administration of an anthelmintic paste was intended).

Some horses may have an idiosyncratic predisposition for ulceration,

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particularly that of the right dorsal portion of the colon. In experimental conditions, arthritic laboratory animals were more susceptible to NSAID-induced gastropathy than were healthy animals.[14] This finding may have relevance to horses because NSAIDs are often administered to chronically lame horses. Two or more NSAIDs are used concurrently in some situations. It is important to recognize that the effects of combining NSAIDs are additive, so that administering two NSAIDs at each of their recommended doses is similar to giving twice the recommended dose of one NSAID. Combination of two NSAIDs prolongs their pharmacologic effect but increases the risk of toxicity.[15]

■ Clinical Signs

Clinical signs of NSAID toxicity are usually referable to the alimentary system and vary, depending on the segment involved. Oral or lingual ulceration may lead to difficulty in prehension and mastication. Esophageal ulceration may result in excessive salivation and apparent signs of pain (stretching of the neck, groaning) during swallowing. Gastric ulceration may result in slow consumption of feed, inappetence (particularly for grain in some horses), or anorexia. Horses that have gastric outflow obstruction associated with gastroduodenal ulceration may exhibit ptyalism, reflux esophagitis, and, in severe cases, spontaneous nasogastric reflux. Horses with ulceration anywhere in the gastrointestinal tract may exhibit signs of colic, which may be intermittent and may vary in severity. Horses with colonic ulceration may have soft stool or diarrhea and ventral edema secondary to enteric protein loss. Diarrhea can be severe, even fatal. Sepsis may result from intestinal mucosal damage caused by NSAIDs. Clinical signs of sepsis (e.g., tachycardia, altered appearance of mucous membranes, fever, and dehydration) may be seen in some horses with NSAID enteropathy. In some horses, hematuria may be seen.

Horses may have clinical signs days to weeks after NSAID therapy. Such horses are typically brought to medical attention because of recurring colic, weight loss, or loose manure. It is particularly important in these horses to determine any history of NSAID administration, even if it was several weeks before the time of presentation.

■ Diagnosis

Diagnosis is usually made on the basis of history of NSAID use, clinical signs, and clinicopathologic findings. The most consistent clinicopathologic

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abnormalities in horses with NSAID toxicosis are hypoproteinemia and hypoalbuminemia, presumably resulting from loss of protein through inflamed or ulcerated intestinal mucosa. These findings are more commonly observed with damage to the distal intestinal tract and are not reliable for diagnosis of NSAID gastropathy. Some horses have decreased serum concentration of calcium, presumably attributable to intestinal loss of protein-bound calcium. In horses with severe NSAID-induced diarrhea, hyponatremia, hypochloremia, hypokalemia, acidemia, and hypovolemia may be observed. In such cases, hypovolemia may make the serum protein concentration appear to be higher than its actual value would be if the horse were adequately hydrated.

In chronic cases, horses may be anemic from inflammation, intestinal loss of blood through ulceration, or reduced function of platelets. Occult blood may be found in the feces of horses with lesions in the more distal portions of the intestinal tract. Tests for occult blood often lack sensitivity, and false-positive results may be expected for up to 24 hours after rectal palpation.

The concentration of leukocytes is usually within the reference range, although leukocytosis and hyperfibrinogenemia, associated with inflammation, and leukopenia and neutropenia, presumably caused by sepsis, can occur in some horses with acute NSAID toxicosis that affects the distal intestine. In general, results of peritoneal fluid analysis are within reference ranges, but concentration of nucleated WBCs, total protein, and fibrinogen may increase in the presence of advanced intestinal damage or intestinal vascular infarction. When findings of cytologic examination of peritoneal fluid are abnormal, results are more consistent with nonseptic than septic inflammation; however, septic inflammation may be observed when severe intestinal ulceration leads to transmural lesions and septic peritonitis.

Several clinicopathologic changes may accompany NSAID-induced renal damage. The most consistent finding is a decrease in urine specific gravity, from 1.008 to 1.020. Inability to properly dilute urine can occur with acute NSAID toxicosis for years after the original insult. This results from preferential damage to areas of the kidney that contribute most to concentrating urine (medulla, papilla). In chronic cases, urine specific gravity typically ranges from 1.013 to 1.020. Some horses with NSAID toxicosis are azotemic. In acute cases azotemia can result from dehydration, NSAID-induced alterations in renal blood flow, and tubuloglomerular feedback mechanisms. Chronic azotemia, in which serum creatinine levels range from 2.1 to 3.5 mg/dL, results from tubuloglomerular feedback mechanisms that reduce glomerular filtration to compensate for

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reduced reclamation of solutes in the medullary collecting ducts. In acute NSAID toxicosis, affected animals may have overt hematuria. In other cases, urinalysis may reveal occult blood, increased renal cells, and increased WBCs. In chronic cases other than those involving decreased urine specific gravity, urinalysis results are typically normal.

Endoscopy can be useful for visualizing the location and extent of esophageal and gastric lesions. NSAID-induced gastric lesions are more common in the glandular epithelium, although nonglandular lesions can be observed. Contrast radiography or scintigraphy may be useful for documenting delayed gastric emptying in some horses. Lesions of the jejunum, ileum, cecum, and colon can be difficult to identify without celiotomy and enterotomy. Isotope-labeled WBC scintigraphic scans may identify colonic ulceration[16]; the sensitivity and availability of the procedure, however, are limited. Ultrasonography may reveal thickening of the right dorsal portion of the colon or other colonic segments, but the technique appears to lack sensitivity.[17] Horses with renal crest necrosis may exhibit increased ultrasonographic echogenicity of the renal crest and echogenic debris in the renal pelvis.

■ Management

Administration of NSAIDs should be discontinued if NSAID toxicosis is suspected. Gastric lavage and administration of 1 gallon of mineral oil per 450 kg of body weight via nasogastric tube may be of benefit in horses with acute NSAID overdose to reduce the absorption of the administered NSAID. Treatment for gastric ulceration with a proton-pump inhibitor (e.g., omeprazole, an H_2-receptor blocker such as ranitidine, or sucralfate, or a combination of these) should be implemented in horses with gastric ulceration. Sucralfate (10 to 20 mg/kg PO q8-12h) may also have a benefit in more distal segments of the equine intestine affected by NSAID toxicity. Sucralfate reduced ulceration in the stomach, small intestine, and colon and reduced protein loss in weanling-aged horses treated with an overdose of phenylbutazone.[18]

Regardless of the site of NSAID toxicity, administration of prostaglandin E analogs, or drugs that mimic their effects, may be of benefit. Administration of a synthetic analog of prostaglandin E_2 has been demonstrated to prevent phenylbutazone-induced gastrointestinal lesions in horses.[19] Misoprostol, a synthetic analog of prostaglandin E_1, ameliorated the effect of flunixin and promoted in vitro repair of equine intestinal mucosa damaged by ischemia.[20]

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The beneficial effects of misoprostol are probably due in part to the beneficial effects of prostaglandin E on the gastrointestinal mucosa (reducing injury and increasing repair) but may also be attributed to the antiinflammatory properties of misoprostol, particularly in the stomach, where misoprostol concentrations are high after oral administration.[21,22] Misoprostol can be administered orally starting at doses of 5 µg/kg q12h or 2 µg/kg q6h. Some horses develop signs of abdominal discomfort or diarrhea at these doses; another protocol is to start at 1.5 µg/kg q8h for 2 to 4 days and increase at increments of 0.5 µg/kg q8h every 2 to 4 days until a maintenance dosage of 2.5 to 3 µg/kg q8h is achieved. Because of the paucity of experimental and clinical data for this drug, dosage schedules should be individually tailored to a horse's illness and tolerance of the drug.

For horses with hypovolemia secondary to colitis, administration of crystalloid fluids is indicated. Infusion of plasma may benefit horses with NSAID-induced enteropathies and signs of sepsis. The aim of plasma transfusion in a hypoproteinemic horse with colitis need not be to increase the plasma concentration into the reference range, because this may be cost-prohibitive and infused protein may be lost rapidly via the intestinal tract. Smaller volumes of plasma (1 to 3 L in an average-size horse) may exert beneficial effects by increasing colloid oncotic pressure and perhaps by modulating the effects of sepsis. Alternative colloidal fluids may be beneficial as well. Hetastarch (5 to 10 mL/kg IV q48-72h) may maintain plasma colloid oncotic pressure in the acute stages of the NSAID toxicity. Administration of broad-spectrum antimicrobial drugs may be indicated when signs of sepsis are observed. Parenteral administration of antimicrobial drugs is preferable to oral administration in horses with colitis because of the presumed increased risk of antimicrobial-associated diarrhea with the oral route. Oral administration of metronidazole (10 to 15 mg/kg PO q8-12h) might be an exception to this guideline, because evidence indicates that metronidazole may exert an anti-inflammatory effect and enhance healing in NSAID-induced intestinal ulceration.[23]

For horses with RDUC, dietary management directed toward providing a low-bulk diet in the form of a pelleted concentrate and restricting or eliminating ingestion of roughage is recommended. The aims of this approach are to decrease the mechanical and physiologic load of the colon. A complete pelleted diet (i.e., a diet that contains both concentrate and adequate but relatively low dietary roughage) decreases intestinal fill in the colon. A diet lower in fiber

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should decrease the physiologic load of the colon because in horses the cecum and large colon are the primary sites of fiber digestion and exchange of fluid and electrolytes. Concentrate should be fed in smaller amounts and frequently (four to six feedings per day). Addition of corn oil may provide additional calories and may also aid in healing of the damaged intestinal mucosa by promoting prostaglandin E_2 production. Some horses will not eat complete pellets, and some horses that have roughage withheld will eat bedding or wood as a consequence. Such horses should be allowed to eat fresh grass in small amounts on a frequent basis (four to six times daily). The importance and optimal duration of restriction of roughage are unknown, but it probably requires months for the colon to heal. Horses should be changed from, and returned to, their usual diet over a period of several days to decrease the risk of inducing other digestive disorders.

Feeding psyllium mucilloid may promote colonic healing in horses with RDUC. In other animal species, psyllium mucilloid has been demonstrated to increase the concentration of short-chain fatty acids of the large bowel, and increased short-chain fatty acids can promote colonic mucosal repair.[24] The amount and duration of psyllium mucilloid administered orally that are necessary to alter the colonic concentration of short-chain fatty acids and the role of short-chain fatty acids in repair of RDUC in horses are unknown. Continuous feeding according to manufacturer's recommendations for 3 to 6 months is suggested, or feeding 1 to 2 oz of psyllium mucilloid once or twice daily for the same duration may be considered.

Horses with strictures of the pylorus, duodenum, jejunum, or colon may require surgical management. Bypass or resection of affected intestinal segments may be necessary.

Limiting the extent of predisposing factors, such as dehydration, should decrease the risk of NSAID toxicosis. Avoiding use of NSAIDs or limiting the dose and duration of treatment to the minimums necessary to control the primary problem is recommended to decrease the risk of NSAID toxicosis. Other approaches to analgesia, such as regional anesthesia (epidural or perineural nerve blocks of distal limbs) or administration of butorphanol or lidocaine via constant-rate infusion should be considered.

Fluid Therapy for Horses With Gastrointestinal Diseases

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Tiffany L. Hall

Most horses with acute gastrointestinal disturbances require fluid therapy to address decreased intake or excessive loss of fluids and to correct any alterations in acid-base and electrolyte balance. Conditions such as high-volume diarrhea and gastric reflux necessitate aggressive fluid therapy to correct hypovolemia, whereas other conditions (including intraluminal impactions) may necessitate a more conservative approach to maintain appropriate hydration. Assessment of hydration status and acid-base balance in horses presenting with gastrointestinal disease, as well as an understanding of the primary gastrointestinal condition, is critical for developing a fluid therapy plan. This section focuses on fluid therapy in horses with gastrointestinal disease. (For a more in-depth discussion of critical care and fluid therapy for horses, including selection of fluid types, monitoring and assessing fluid resuscitation, and complications associated with fluid therapy, see Fluid Therapy for Horses With Gastrointestinal Diseases section and Chapter 44.)

■ Identifying Patients Requiring Fluid Therapy

Clinical assessment begins with distinguishing hypovolemia from dehydration (Fig. 32.75). Hypovolemia is an emergency caused by an acute decrease in circulating blood volume that results in decreased tissue perfusion, anaerobic metabolism, organic acidosis, and ultimately shock. Clinical diagnosis of hypovolemia is based on altered perfusion parameters, including increased jugular refill time, prolonged capillary refill, tachycardia, poor peripheral pulse quality, decreased extremity temperature, decreased urine production, altered mentation, or a combination of these. Dehydration, on the other hand, is associated with a more insidious decrease in total body water and is reflected by clinical signs such as decreased skin turgor, decreased tear film, sunken eyes, and tacky mucous membranes.

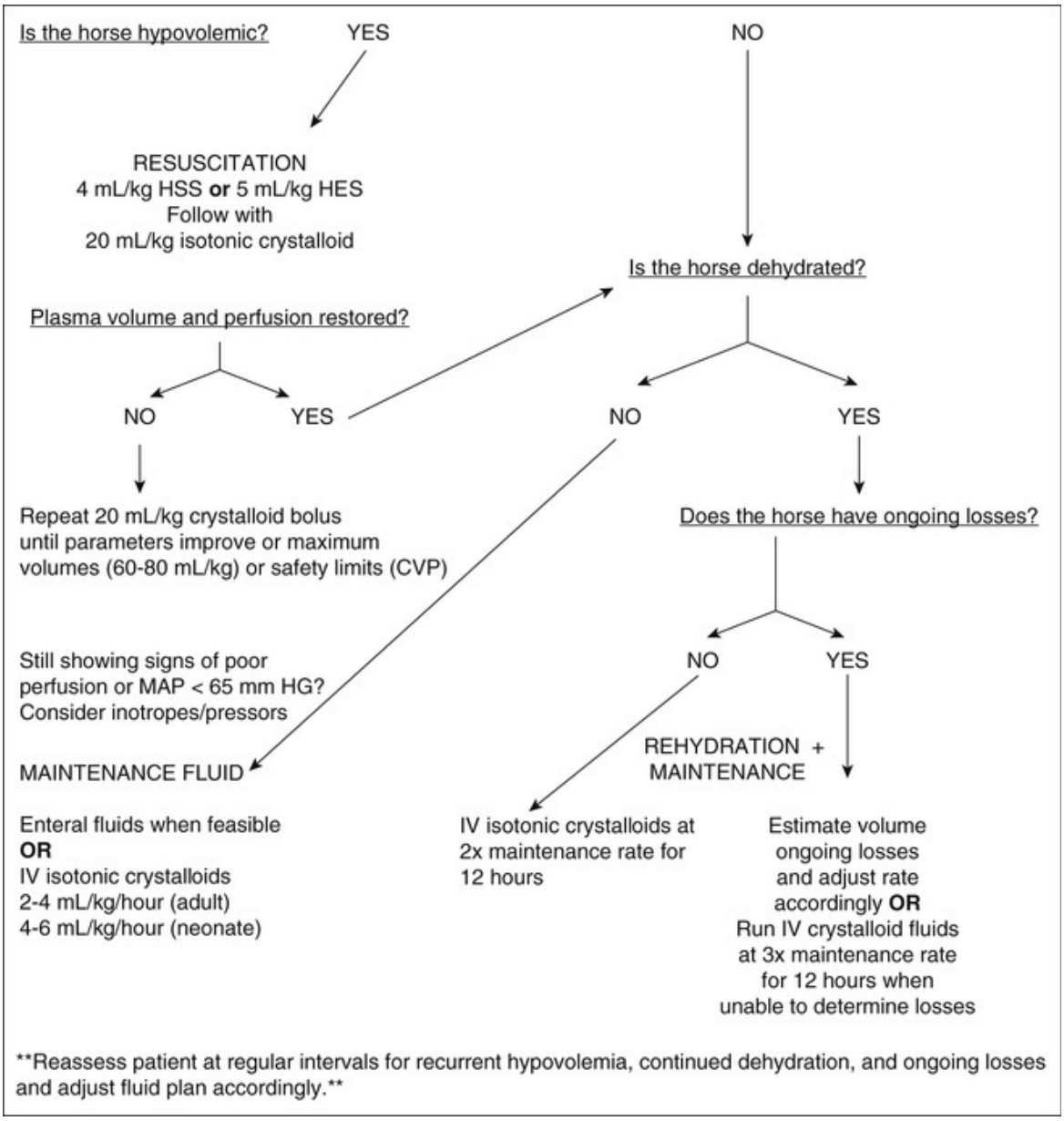


FIG. 32.75 Clinical assessment of perfusion parameters and hydration status. *CVP,* Central venous pressure; *HES,* hydroxyethyl starch solution; *HSS,* hypertonic saline solution; *MAP,* mean arterial pressure.

Laboratory parameters are beneficial for evaluating hydration status, developing a fluid plan, and monitoring response to therapy. PCV and measurement of plasma total solids are commonly used to assess hypovolemia; however, these are neither sensitive nor specific. Splenic contraction and protein loss are two conditions common in horses with acute abdomen that affect the clinical utility of PCV/total solid values alone in assessing hydration. PCV/total solid values are most useful when greatly increased or when measured serially to

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monitor the response to fluid therapy.

An increase in the concentration of blood lactate serves as an indicator of decreased tissue perfusion. The most common causes of increased lactate in horses with gastrointestinal disease are hypovolemia, sepsis, and intestinal ischemia secondary to strangulation. Lactate can be measured in the field on whole blood with handheld analyzers. Increased blood lactate concentrations were associated with worse outcomes in equine colic[1] and should be suspected in cases of metabolic acidosis (decreased pH, negative base excess) in the absence of hyperchloremia or hyponatremia.[2]

Plasma or serum creatinine concentrations are useful for assessing hydration status in the absence of renal dysfunction. Creatinine concentrations up to 3.5 mg/dL (310 µmol/L) are common with moderate to severe hypovolemia and can be as high as 5 mg/dL (450 µmol/L) with prolonged or marked hypovolemia. Even in severe hypovolemia, the creatinine concentration does not increase by much more than 2.3 mg/dL (200 µmol/L) per day.[3]

Urine specific gravity provides valuable information regarding renal function and hydration status. High urine specific gravity (>1.040) indicates probable dehydration and normal renal function. Isosthenuria (levels of 1.010 to 1.015) indicates possible renal damage or a recent high fluid load. Urine specific gravity is especially useful in monitoring hydration status of neonates, inasmuch as neonates are normally hyposthenuric (<1.010) when well hydrated, although this can be affected by the types of fluids administered (colloids versus replacement fluids cersus maintenance), medications, inappropriate antidiuretic hormone secretion, and glucosuria.

CVP is an indirect measure of the quantity of blood returning to the heart, or preload, and is often studied in the hospital setting to assess restoration of circulating volume, in the presence of normal cardiac function. The normal CVP of adult horses is 7 to 12 mm Hg. Assessment of CVP is one of the more accurate, readily available methods of evaluating response to fluid therapy; however, measurement is affected by a number of factors, including catheter placement, head position, and presence of distributive shock.[4]

Measurement of blood pressure, particularly MAP, is also important in determining efficacy of fluid resuscitation for improving tissue perfusion. Blood pressure in horses may be determined directly or indirectly with the use of oscillometric devices. When CVP is normalized, which indicates restoration of blood volume, but MAP is decreased (<60 to 65 mm Hg), inotropes and pressors

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are often used to improve vascular tone and restore normal tissue perfusion.[4]

■ Formulating a Fluid Therapy Plan

The goals of fluid therapy are to increase cardiac output, by increasing and then maintaining cardiac preload; improve oxygen delivery; and correct electrolyte and acid-base disturbances. The plan for fluid therapy consists of four overlapping phases: (1) resuscitation, (2) rehydration, (3) maintenance, and (4) ongoing loss replenishment. Frequent monitoring of the patient and adjustment of the fluid plan are also important to a successful outcome. The fluid plan should be based on the clinical status of the affected horse, an understanding of the primary disease process, and any laboratory information available.

Resuscitation.

Rapid fluid resuscitation is indicated in horses with clinical signs of hypovolemia. Reversal of hypovolemia is associated with improved outcome in human medicine and is shown to improve cardiovascular parameters in horses.[5-7] Balanced polyionic, isotonic crystalloid solutions are frequently used to restore circulating volume in hypovolemic equine patients; however, the use of colloids or hypertonic crystalloid solutions, or both, may provide more rapid results when available and indicated.

Small-volume resuscitation with hypertonic crystalloid or colloid solutions, or both, has been promoted to rapidly restore plasma volume in horses presenting with signs of hypovolemia.[8] The administration of hypertonic saline solution (HSS) was found to restore plasma volume and induce urination more rapidly than administration of an equal volume of isotonic crystalloids.[9] Hetastarch has been shown to increase circulating blood volume and improve tissue perfusion, as evidenced by decreases in heart rate and urine concentration after administration of hetastarch (10 mL/kg) with concurrent isotonic saline (10 mL/kg) to horses with colic.[10] Moreover, in horses undergoing exploratory laparotomy, cardiovascular indices were significantly improved after preoperative administration of 10% pentastarch (4 mL/kg), in comparison with 7.2% saline (4 mL/kg).[11] The administration of HSS is associated with development of an inorganic acidosis and hypokalemia, and the plasma expansion effects of small-volume resuscitation are short-lived; thus fluid therapy with hypertonic or colloid solutions should include concurrent administration or immediate follow-up with polyionic, isotonic crystalloid

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solutions.[8,9]

During resuscitation, isotonic crystalloid solutions are administered at doses of 20 to 40 mL/kg in adult horses (10 to 20 mL/kg in neonates) as rapid boluses. After each 20-mL/kg bolus, clinical evaluation of the patient, including evaluation of perfusion parameters, is performed in order to assess the need for repeat boluses. If perfusion parameters and blood pressure have not normalized on obtaining a normal CVP or at the completion of a total maximum "shock dose" of 60 to 80 mL/kg crystalloids, then inotropes and pressors are often incorporated in treatment, and the fluid rate is adjusted to maintenance rates. In horses and foals presenting for gastrointestinal disorders, alterations in vascular permeability and decreases in protein concentrations must be considered in determining the volume of crystalloid to be administered.

Rehydration.

In horses that do not present with signs of hypovolemia or in whom hypovolemia has been reversed, dehydration is corrected over the first 12 to 24 hours of hospitalization. To rehydrate patients, isotonic crystalloids are administered at rates in excess of ongoing losses plus maintenance requirements. Clinically, this is accomplished in most patients with gastrointestinal disease by administration of isotonic crystalloid fluids at two to three times the maintenance rate. Once dehydration is corrected, according to clinical parameters such as PCV/total solids and urine specific gravity, this rate is slowed to that needed to maintain hydration. Horses with urine specific gravities below 1.020, and foals with urine specific gravities below 1.010, are unlikely to be dehydrated.

Maintenance.

Depending on the gastrointestinal disease, free-choice feed and water may be withheld from horses with acute abdomen for a period of time, during which fluid requirements must be supplemented to maintain hydration. The mean daily water intake (including the water content of feed) of normal resting adult horses is 57 to 64 mL/kg/day at ambient temperatures of 5° C to 25° C (41° F to 77° F). Mares restricted to 40 mL/kg/day demonstrated significant dehydration.[12] Maintenance fluid rates for adult horses (2 to 4 mL/kg/h) and neonatal foals (4 to 6 mL/kg/h) can be met through enteral administration when appropriate for the diagnosis and when gastrointestinal function is normal. When enteral administration is contraindicated, polyionic, isotonic crystalloids are most frequently used in the parenteral administration of fluids.

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Electrolyte concentrations and hydration status should be monitored frequently as part of the maintenance fluid plan. Replacement crystalloid solutions higher in electrolyte concentrations are usually administered over maintenance crystalloid solutions according to the size of equine patients, the volume of fluids required, and availability. (See Chapter 44 for a comparison of commercially available fluid solutions.) Some patients, particularly neonates or those losing large volumes of fluid, are at risk for developing a free water deficit and subsequent inorganic acidosis when maintained on isotonic, replacement, crystalloid solutions. Monitoring of electrolytes, particularly sodium and chloride, helps identify such patients. In adult horses, physical examination and monitoring of body weight, PCV/total solids, creatinine concentrations, and urine specific gravity are useful in evaluating the efficacy of a fluid treatment plan. Overhydration in adults with normal renal function may be indicated by frequent urination, urine specific gravity lower than 1.013, and development of dependent edema. In neonates, body weight, urine production, urine specific gravity, and perfusion parameters are evaluated to monitor hydration status; detection of excessive fluid supplementation can be difficult because nursing neonates normally produce hyposthenuric urine. Development of preputial or stifle edema is an indication of overhydration in neonates. It is important that the volume of all intravenous solutions and enteral feedings be accounted for when fluid rates in neonates are calculated to prevent volume overload.

Ongoing Loss Replenishment.

Horses that present with gastrointestinal conditions that result in excessive fluid losses such as gastric reflux and diarrhea require supplementation in excess of maintenance fluid rates. Calculating the volume of fluid lost is the most accurate method of determining how much fluid will need to be replaced. Whereas the volume of nasogastric reflux can be tracked, determining the volume of fluid lost in adults and ambulatory foals with diarrhea is not possible; therefore frequent assessment of the patient by clinical examination and determination of relevant laboratory parameters are useful in evaluating the fluid plan to prevent continued dehydration or recurrence of hypovolemia.

■ Special Considerations in the Fluid Therapy Plan

The selection of fluids to be administered, rate and route of administration, parameters to be monitored, and frequency of monitoring are based on thorough individual case assessment. In addition to the various phases of fluid therapy,

special circumstances encountered in horses with gastrointestinal disease must also be considered in the fluid therapy plan. These include commonly observed electrolyte disturbances, acidemia, hypoproteinemia, and endotoxemia. Table 32.11 lists common fluid choices and additives for conditions observed in horses with gastrointestinal disease.

TABLE 32.11
Fluids and Additives for Electrolyte Disturbances in Horses

Metabolic Disturbance	Recommended Fluid	Dosage
Lactic acidosis	Polyionic crystalloids with or without small-volume resuscitation (HSS/HES)	Up to 60 mL/kg/h
Hyponatremia	Isotonic crystalloids	Sodium level should be corrected no faster than 1 mEq/L/h
• With hypochloremia	Polyionic crystalloids or sodium chloride	
• Without hypochloremia	Sodium bicarbonate	
Hypernatremia	5% Dextrose or 2.5% dextrose/0.45% sodium chloride	Sodium level should be corrected no faster than 0.5 mEq/L/h
Hypochloremia	Polyionic crystalloids or sodium chloride	0.9% or 7.5%, to effect
Hyperchloremia	Increased free water intake or administration	
• With hypernatremia	Polyionic maintenance crystalloid or 5% dextrose	Sodium level should be lowered no faster than 0.5 mEq/L/h
• Without hypernatremia	Sodium bicarbonate	5%, slowly, to effect
Hypokalemia	Potassium chloride	10 to 40 mEq/L or 0.5 mEq/kg/h Maximum, 1 mEq/kg/h
Hyperkalemia		
• With clinical signs	Calcium gluconate	1 mL/kg IV over 10 min 250 mL/1 L sodium chloride
• Potassium concentration >7 mEq/L	Sodium bicarbonate	1 to 2 mEq/L IV over 15 min
• Without clinical signs	5% Dextrose in polyionic crystalloids	2 mL/kg IV over 5 min
Hypocalcemia	Calcium gluconate	250 to 500 mL of 23% solution/5 L
Hypercalcemia	Polyionic crystalloids (without calcium)	4 to 16 mg/kg as an initial dose
	Magnesium sulfate	10 mL/5 L (maximum, 50 mg/kg)
Hypomagnesemia	Magnesium sulfate IV	4 to 16 mg/kg as an initial dose
Hypermagnesemia	Calcium gluconate	250 to 500 mL of 23% solution
Hypoalbuminemia	Fresh or fresh-frozen equine plasma	To effect, not to exceed 10 mL/kg
	HSS/HES	5 to 10 mL/kg to increase COP

All disturbances present must be taken into account before treatment begins.

COP, Colloid oncotic pressure; *HSS/HES,* hypertonic saline solution/hydroxyethyl starch solution (hetastarch); *IV,* intravenously; *PO,* by mouth.

■ Enteral Fluid Administration

Enteral fluid therapy may be sufficient to correct and maintain hydration in horses with gastrointestinal disease that have mild dehydration and normal small intestinal function.[13] In horses with gastrointestinal disease but no apparent dehydration, administration of an electrolyte paste and provision of fresh drinking water may be sufficient to supplement water and electrolytes.[14] However, enteral fluid therapy is contraindicated in horses with small intestinal obstruction or ileus and is not sufficient to treat hypovolemia.

Enteral fluids are often included in the treatment of impaction colic. Nasogastric administration of a balanced electrolyte solution (5.27 g NaCl + 0.37 g KCl + 3.78 g $NaHCO_3$ per L water) at 5 L/h is superior to enteral administration of magnesium sulfate, sodium sulfate, or magnesium sulfate with IV crystalloids in promoting hydration of colonic contents, and it does not alter plasma electrolyte concentrations.[15,16] An isotonic solution for enteral administration can be made without the use of weight scales by measuring salt crystals in the barrel of a syringe (15 mL of Lite salt and 15 mL of table salt added to 4 L of water).[17] In a prospective clinical trial, 8 to 10 L of enteral fluids administered every 2 hours was successful in the treatment of 99% of colonic impactions and 83% of left-sided colon displacements.[18] Because enteral fluids are significantly less costly than commercially available intravenous fluids, this is an ideal treatment in some gastrointestinal conditions.

■ Electrolyte Disturbances

In many horses with gastrointestinal disturbances, plasma electrolyte concentrations are altered, which may need to be addressed during fluid therapy. Portable equipment for measuring blood gases and electrolytes allows the field veterinarian to easily obtain information necessary to guide electrolyte supplementation and selection of appropriate fluids. Without case-specific determination of electrolyte concentrations, maintenance phase fluids in gastrointestinal disease should be limited to administration of isotonic, polyionic crystalloid fluids supplemented with 10 to 20 mEq/L of potassium chloride.

Generalized changes in electrolytes among horses with gastrointestinal disease are related to decreased feed intake, increased loss, and sequestration. Decreased sodium and chloride concentrations may be observed in cases of acute colitis, peritonitis, or intestinal torsion.[19] Hypochloremia without hyponatremia is also

observed in proximal enteritis and grass sickness associated with loss of hydrochloric acid in gastric reflux.[20] Hypokalemia is common in horses after colic surgery because of decreased feed intake, enhanced mineralocorticoid release, and kaliuresis associated with administration of sodium-containing fluids. Hypokalemia also occurs with colitis and metabolic alkalosis. Potassium is primarily an intracellular ion, and decreases in whole body potassium may not be detected through plasma measurements; therefore it is common to add supplemental potassium to maintenance fluids. Hypocalcemia is commonly observed in horses presenting with gastrointestinal disorders, including those with surgical colic, colitis, functional disorders of the small intestine, organic acidosis, and endotoxemia.[21] Plasma ionized calcium provides a better indicator of physiologic calcium status, inasmuch as hypoalbuminemia occurs in many gastrointestinal conditions. In one report, 44% of horses with gastrointestinal disease had low plasma magnesium concentrations.[22] Hypomagnesemia may be associated with refractory hypocalcemia and hypokalemia; thus supplemental magnesium may be beneficial in those situations. Hypophosphatemia has been reported in horses with strangulating intestinal lesions or intestinal ileus.

Acidosis.

Inorganic and organic metabolic acidoses occur frequently in horses with gastrointestinal disorders. Inorganic acidosis occurs with hyponatremia (colitis, peritonitis, intestinal torsion) and relative or absolute hyperchloremia (colitis, free water deficit). Many affected patients have a normal anion gap. Organic acidosis in horses with gastrointestinal disease is common, secondary to elevated lactate concentrations and associated with an increased anion gap. Increased blood or plasma lactate concentrations in these cases are usually a result of poor tissue perfusion or inappropriate anaerobic metabolism in endotoxemia.

Metabolic acidosis in horses with gastrointestinal disease usually resolves with correction of hypovolemia and restoration of tissue perfusion. In the case of inorganic acidosis, electrolyte abnormalities are occasionally severe enough to necessitate selection of a particular commercially available fluid. Administration of sodium bicarbonate to correct acidemia is reserved for cases in which the blood pH falls below 7.2 or for cases of severe hyponatremia with relative hyperchloremia, and only in patients with normal respiratory function.

Less frequently observed acid-base disorders in horses with gastrointestinal disorders include inorganic metabolic alkalosis (hypochloremia or hypoalbuminemia), respiratory alkalosis (hyperventilation associated with pain),

and respiratory acidosis (hypoventilation caused by extreme abdominal distention or respiratory center depression).[2]

■ Hypoproteinemia

Hypoalbuminemia occurs in horses with moderate to severe compromise of the colon, parasitism, intestinal malabsorption, or third spacing (peritonitis). Endotoxin exposure and ischemia-reperfusion injury induce capillary damage that allows plasma albumin to leak out into the interstitium. Clinical signs of hypoalbuminemia are peripheral, tissue, and organ edema, which lead to reduced oxygen uptake by cells and, in severe cases, organ failure. Albumin is a weak acid; thus severe hypoalbuminemia may contribute to metabolic alkalosis or mask concurrent metabolic acidosis.[2] Determination of the colloid oncotic pressure (COP) of the plasma is most useful in guiding colloidal fluid therapy, particularly when synthetic colloids have previously been administered.[23] COP and total protein concentrations were found to decrease over the course of anesthesia in horses undergoing colic surgery.[24]

Hypoalbuminemia and decreased COP should be treated when acute or if there are clinical signs. Options for colloidal support in horses include plasma transfusion and synthetic colloid solutions, such as hetastarch. Approximately 6 to 8 L of fresh-frozen plasma is necessary to effectively treat significant hypoproteinemia in adult horses, which makes plasma cost prohibitive in the treatment of decreased COP.[25] However, plasma has a role in treatment of SIRS by providing AT-III and other cofactors. The administration of 6% hetastarch at 8 to 10 mL/kg to conscious hypoproteinemic horses significantly improved COP for 6 hours after infusion and maintained an oncotic effect for 24 hours; however, administration of 2.5 mL/kg 6% hetastarch did not alleviate the decrease in COP observed in healthy horses receiving crystalloid during general anesthesia.[26,27] Hetastarch should be used with caution in patients with conditions of decreased renal perfusion, systemic inflammation/sepsis, or underlying renal insufficiency because it has been associated with development of acute kidney injury in humans.

■ Endotoxemia

Horses with gastrointestinal disorders, particularly ischemic lesions and conditions involving inflammation of the bowel, are at risk of exposure to endotoxin as damage to the intestinal mucosa allows intraluminal bacteria to

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gain systemic access. During endotoxemia, capillary damage leads to increased vascular permeability, altering fluid dynamics and contributing to tissue edema. HSS has been shown to reduce the capillary endothelial swelling associated with SIRS and to improve tissue microcirculation and oxygen delivery.[28]

Studies of the effects of HSS in horses with experimentally induced endotoxemia have yielded mixed results. One study in conscious horses found that administration of 5 mL/kg HSS after administration of a low dose of endotoxin (1.64 ± 0.22 µg/kg) improved cardiac output and decreased peripheral vascular resistance in comparison with isotonic saline.[29] These findings were not supported by those of another study in anesthetized horses that received higher doses of endotoxin. In that second study, administration of combined 5 mL/kg HSS and 10 mL/kg hetastarch to horses with hyperdynamic shock induced by administration of 50 µg/kg endotoxin did not improve cardiopulmonary parameters.[30] The combination of HSS and hetastarch may protect against hypocalcemia associated with endotoxemia without negatively affecting coagulation beyond that seen in control horses.[31]

■ Nutritional Support

Many horses with gastrointestinal disease are inappetant or are held off feed as part of their treatment for a variable amount of time. An enteral diet based on a horse's normal diet is the first choice for nutritional support; however, in adult horses are were held off enteral feeding for over 3 days because they have gastric reflux, ileus, esophageal obstruction, or anorexia should be supplemented parenterally.[32] In addition, horses with moderate obesity that are not eating may be at increased risk of developing hyperlipidemia and should receive supplementation earlier. Parenteral nutrition can range from the administration of 1% dextrose in intravenous fluids to the administration of a combination of dextrose, amino acids, and lipids that is based on the maintenance energy requirements for the individual patient. (See Chapter 50 for a complete discussion of nutritional support in horses.)

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▪ Ruminant Alimentary System

Gilles Fecteau, Consulting Editor

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Ruminant Alimentary Disease

Dental and Oral Diseases

Sylvain Nichols • Guy St. Jean

Digestion of forage, silage, and grains starts with proper mastication and rumination. To be efficient, ruminants depend on a properly functioning mouth, which includes teeth, bones (mandible, maxillary, palatine and hyoidal apparatus), synovial structures (temporomandibular joint), muscles (tongue, masseter) and salivary glands (parotid, mandibular, and buccal). Many arteries, veins and nerves are present to allow the normal function of all those structures for prehension, mastication, swallowing, and rumination. An insult to any one of those structures has a significant effect on digestive efficiency and overall performance of the animal.

Tooth Anatomy

To understand dental and periodontal diseases, it is mandatory to understand the anatomy of those structures (Fig. 32.76). The anatomy of the tooth varies from tooth to tooth, depending on the number of roots and infundibula.[1] Teeth are the strongest tissue in a living animal. They consist mainly of enamel, cement, and dentine. The enamel covers the labial, lingual, rostral, and caudal surfaces of the crown. On the occlusal surface of a tooth, the enamel forms ridges and crests. In the early life of a tooth, the ridges and the crests are connected. As dental wear occurs, the dentine becomes exposed between the ridges and the crests, which results in creation of the infundibulum. The center of the infundibulum is blackened cement. The neck is the connection between the crown and the root and is the junction between the enamel and the cement. The gum connects to the tooth at the point where the periodontal ligament attaches the cement to the alveolar bone (alveolar socket), which forms a shallow gingival sulcus. The inside of the tooth consists of dentine and the pulp cavity, where blood vessels and nerves are located. The nerves travel through the root canals.

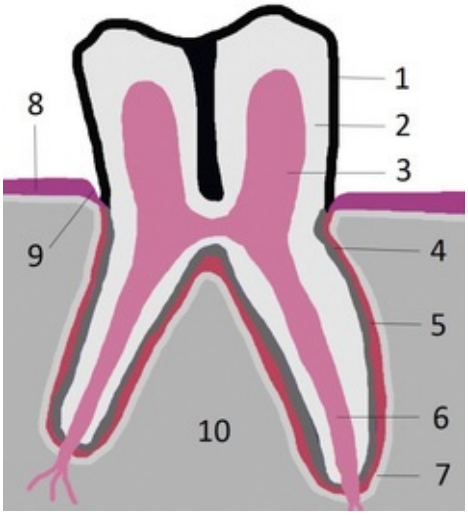


FIG. 32.76 Drawing of the normal anatomy of a mandibular molar. *1,* Enamel; *2,* dentin; *3,* pulp cavity; *4,* cement; *5,* periodontal ligament; *6,* root; *7,* alveolar socket; *8,* gingiva; *9,* gingival sulcus; *10,* mandibular bone. (Courtesy Sylvain Nichols, Université de Montréal.)

Eruption of Teeth

Determining an animal's age by examining the teeth is not an exact science because the appearance of the teeth can be affected by inherited factors, nutrition, and geographic location.[2,3] At birth or within 2 weeks, four deciduous incisors usually are present in ruminants. All eight deciduous incisors erupt within the first month.[4] The fourth incisor (corner) is a modified canine tooth. The incisors meet with the dental pad of the upper jaw for the purpose of gripping and cutting herbage. Usually, all three pairs of deciduous premolars have erupted at birth or shortly afterward.[2,3] In cattle, the formula for the deciduous teeth is as follows: 2(incisors 0/4, premolars 3/3) = 20.

The age at which permanent teeth erupt is often the best criterion for determining the animal's age if a registration certificate is not available. However, systemic illnesses and malnutrition can retard dental development and cause retention of the deciduous teeth.[5] The first molars erupt at 8 months of age and are fully exposed at 12 months. At 18 months, the second molar is fully exposed. The third molar erupts at 24 months and is fully exposed at 30 months. The permanent premolar teeth start to replace the deciduous at 24 months and are usually present at 3 years.[2,3] The first pair of permanent incisors (central incisors) erupt at 18 to 24 months of age. The second pair of incisors (medial incisors) appears at 24 to 30 months of age. At 3 years of age, the third pair of

incisors (lateral incisors) erupt. Between 3.5 and 4 years of age, the fourth pair of incisors (corner teeth) erupt.[4,5] Consequently, cattle have a complete set of permanent teeth at 4 years of age. Cattle have a shallow alveolar socket and associated tooth root. This may lead to dental attrition more readily than in horses. The formula for the permanent teeth in cattle is as follows: 2(incisors 0/4, premolars 3/3, molars 3/3) = 32.

The deciduous and permanent dental formulas of the sheep and goat are identical to those of cattle.[4] In sheep and goats, the periods of eruption are as follows: The incisors are present at birth or within the first 4 weeks. The premolars erupt 2 to 6 weeks after birth. The first pair of permanent central incisors replaces the deciduous pair at 12 to 18 months of age. The second pair erupts at 18 to 24 months of age; the third pair erupts at 30 to 36 months of age; and the fourth pair appears at 3.5 to 4 years of age. The three permanent premolars erupt at 18 and 24 months of age; the first molar, at 3 months of age; the second molar, at 9 to 12 months of age; and the last molar, at 18 to 24 months of age.[4]

Examination of Teeth

Dental disease in ruminants should be considered first on a flock or herd basis.[6,7] Determining dental health is particularly useful when unconventional feeds are incorporated into the herd nutritional program.[8,9] The clinical manifestations of dental diseases include inadequate food intake, inadequate calf development, weight loss, unthriftiness, low body condition score, quidding, low pregnancy rate in replacement heifers, decreased milk production, and mandibular or maxillary swellings or draining tracts.[4,7-10] Dental examination is especially of concern when animals are grazing on short grass. Examination of the herd should then be followed by dental examination of individual animals. For examination of the premolars and molars, the tongue should be withdrawn from the mouth and held at the commissure of the mouth opposite the teeth being examined. Use of a headlight or flashlight helps with performing a good oral examination. A small dose of xylazine (0.03 to 0.05 mg/kg IV) or a “ketamine stun” (butorphanol 0.05 mg/kg, xylazine 0.025 mg/kg, ketamine 0.1 mg/kg IV) and the use of a mouth gag allows for much a more thorough dental examination, including manual palpation in cattle (Fig. 32.77). A rigid endoscope is useful for evaluating the crown and the occlusal surfaces of the cheek teeth. Radiographic examination can also be important in certain cases.

Oblique views are mandatory to evaluate the roots of each cheek tooth completely.



FIG. 32.77 Photograph of a 2-year-old Holstein cow, with a Hau'Sman mouth gag in place to allow an oral examination. The cow was sedated with a “ketamine stun” (butorphanol, 0.05 mg/kg; xylazine, 0.025 mg/kg; ketamine, 0.1 mg/kg intramuscularly). The cow tolerated the gag and the examination well. (Courtesy Sylvain Nichols, Université de Montréal.)

The incisors have a sharp edge in front and are used for gripping and cutting herbage.[4,7] The incisors should be aligned closely with little space between them.[4,7] In sheep, the periodontium of the incisor allows a movement of up to 2 mm rostrocaudal to accommodate rotating or turning forces during grazing.[10] This makes the sheep incisor very prone to loss after periodontal damage. The length of the premolar and molar teeth and their firm placement in the alveolar bone means that they are lost less often than the incisors.[2,3,7]

Dental and Periodontal Diseases

Sylvain Nichols • Guy St. Jean

Dental Attrition and Erosion

Rapid wearing of teeth is most common in grazing sheep older than 5 years of

age. Many sheep and cattle grazing forage-deficient or sandy pastures and arid ranges in Africa, Australia, New Zealand, and the southwestern United States display accelerated tooth wear.[7,11] In Rhodesia, the incisors of Hereford cattle had an increased rate of wear because of softer enamel, in comparison with those of indigenous cattle.[12]

Examination of an animal with dental attrition reveals worn incisor or molar teeth (or both); often only short stumps are seen. The teeth also may be loose, fractured, or missing. Dental attrition from excessive wear must be differentiated from periodontal disease that causes tooth loss.[7,13,14] The pathogenesis of excessive tooth wear relates to tooth hardness and diet quality. Ingestion and mastication of soil and sand with forage abrades and wears the incisor and molar teeth. In New Zealand, dental attrition in sheep was attributed to acids and enzymes in the herbage consumed, which acted on the tooth dentine.[11] A calcium deficiency or calcium/phosphorus imbalance, causing softness of the tooth enamel and dentine, may accelerate the rate of wear.

In the United States feeding fermented sweet potato cannery waste to cattle resulted in substantial increases in incisor erosion.[8,9] Cattle producers feeding sweet potato cannery waste noticed poor growth rate, inadequate calf development, low pregnancy rates in heifers, and worn, mottled, discolored incisors.[8,9] Sweet potato cannery waste is highly acidic (pH, 3.2) and causes calcium loss and tooth erosion. Deciduous teeth are etched more rapidly, which places young cattle at higher risk for severe tooth wear and dental infection. In addition, the distance between the original enamel surface and the pulp chamber is less in deciduous teeth than in permanent teeth, which is, again, more significant in younger cattle.[8,9] Mixing 10% broiler litter with sweet potato cannery waste raised the pH to 4 and thus provided a palatable high-quality feed and prevented the severe dental problems associated with sweet potato cannery waste alone.[8] It is important to allow a withdrawal time of 21 days before slaughter of cattle fed broiler litter to avoid the presence, in the meat, of pharmaceutical residues used in the poultry industry.

A syndrome involving excessive wear of deciduous incisor teeth, maleruption of permanent incisors, and an increased prevalence of dentigerous cysts in sheep has been reported in New Zealand.[15] Excessive wear of the incisor teeth of cattle was also recorded on the same farms. Ingestion of soil during winter because of the inclement weather, overgrazing of pastures, and the presence of low copper levels in the blood of affected animals were the main causes for the syndrome.[15]

Dental attrition is prevented by providing supplemental feed to avoid overgrazing of pastures. The addition of 1% ground limestone to the feed in calcium-deficient areas is recommended.[16]

Periodontal Disease

Periodontal disease involves the supporting tissue that surrounds the teeth.[17,18] Periodontal disease of sheep is endemic in parts of New Zealand. A periodontal disease known as *cara inchada,* or "swollen face," has caused losses of cattle in Brazil.[19,20] Periodontal disease is characterized by protruding and loose incisors.[7,13] With time, incisors, premolars, and molars may be missing. Periodontal disease seems to be more prevalent in sheep than in cattle. However, an abattoir investigation in West Scotland revealed periodontal diseases in 12% of the heads evaluated. The disease was located mainly on masticatory teeth and was more frequent on beef cattle heads.[21] Periodontal disease results in pain during mastication, which leads to poor rumination and reduction in food digestibility.

Periodontal disease has been associated with bacterial plaque–induced gingivitis.[17,20,22,23] The acute gingivitis is replaced progressively by a chronic inflammation in the gingival sulcus. The periodontal ligament is destroyed by plaque-forming oral microorganisms and host enzymes. At this stage, periodontal pockets are formed, which cause loosening of teeth. This process may take months or years. Over time, the infection extends to the apical area. The gum margin begins to recede over the lesion, food accumulates within the pocket, and the entire alveolus becomes infected. At that point, the tooth becomes a sequestrum. The alveolar pyorrhea causes a periostitis of the external surface of the alveolar process, and swelling is observed. Once a tooth is lost from an affected alveolus, granulation tissue fills the alveolus and the alveolar bone undergoes remodeling.

Bacteria such as *Truperella pyogenes*, *Bacteroides* spp., *Actinomyces* spp., and spirochetes; metabolic or immune disorders in the host; and mechanical or chemical agents have been implicated in the pathogenesis of periodontal diseases in sheep.[7,22,24,25] Bacterial invasion in the gingival pockets has been associated with a defect of host immune competence.[26] Hypomagnesemia has been a common finding in sheep with periodontal disease, but this may be a secondary condition.[25] Gingival trauma may have a causal role.[27] Dissolution of the enamel at the attachment of the gingival epithelium by organic acids from

microorganisms of the soil may be a predisposing factor.[28] The serum values for calcium, albumin, ALP, and citrate were lower for sheep with periodontal disease than for sheep not affected by dental disease.[29]

A postmortem examination of Scottish-Hill sheep revealed that 60% of 478 aged sheep had either loose or missing teeth. Gingival pockets were present in 87% of the population and were correlated with tooth looseness.[30] In the United States, a 25% rate of mortality caused by dental disease in a herd of 300 ewes was reported.[31] The clinical signs were depression, anorexia, and emaciation.[31] Necropsy revealed dental disease of the mandibular teeth with plaque, plant fibers in periodontal pockets, and osteomyelitis of the mandibular bone. An initial trauma to the gingiva from cheatgrass awns in the hay field was implicated.[31]

A particular type of periodontal disease in cattle was reported in Brazil.[19,20] This condition involves an inflammatory process of the periodontium of calves and older Zebu cattle that results in alveolar periostitis of the maxilla or, less often, the mandible.[19,20] Examination reveals deep periodontal pockets and loss of or loosened teeth. Affected animals suffer from malnutrition, diarrhea, and loss of condition, and many die. *Bacteroides* and *Actinomyces* organisms often are found in the lesion and are suspected of causing the disease.[19] This disorder is seen only in certain areas of Brazil, and the cattle improve if moved to unaffected areas. In one trial, the development of periodontal disease in calves was avoided by administration of the antimicrobial drug spiramycin.[20]

The assumption that incisor condition is a good indicator of future productivity is not well founded. Little scientific evidence exists to support the culling of sheep affected by periodontal disease. Three farms with a high prevalence of periodontal disease were selected, and the body score and weight of affected sheep were compared with those of sheep with no signs of periodontal disease. A significant association between periodontal disease and body condition or weight was identified on only one farm. It was concluded that periodontal disease in sheep may impair productivity on some farms but not others.[32,33]

Treating periodontal disease on a flock basis often proves impractical. Dental treatment, drug therapy, and management change have been tried in sheep. One form of dental treatment, tooth grinding, consists of trimming the incisors to the level of the lower dental pad.[13] Two trials of the productivity effects of tooth grinding were conducted; neither showed any positive benefit from the

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procedure.[32] An attempt to influence the development of periodontal disease in sheep by long-term treatment with tetracycline and metronidazole was also found ineffective.[23] In commercial sheep, surgical treatments could improve conditions such as periapical and gingival abscesses, but these treatments are not economically feasible.

Sheep can live without incisors if they do not have to graze too closely. Supplementary feeding should provide a net gain to the owner. When premolar and molar teeth are involved, this approach is unlikely to be effective because of the inability to chew and ruminate efficiently.

Dentigerous Cysts

Dentigerous cysts have been described in ruminants, particularly sheep.[15,33] These are odontogenic cysts of unknown cause that manifest as localized, bony swellings. Radiographs demonstrate the cystic nature of the swelling and reveal one or more teeth in the cyst.[15,33] For valuable animals, treatment is surgical.

Developmental Anomalies and Retention of Deciduous Teeth

Developmental anomalies have been reported in cattle.[6] Occasionally, tooth buds fail to develop. The fourth pair of permanent incisors is the set most often absent. The mandibular premolar on one or both sides also occasionally fails to form. The permanent incisor teeth have been observed to be rotated up to 180 degrees in the alveolus. Rotation of a first permanent mandibular premolar was observed as well; the rotation was 90 degrees, and no precise cause was identified. Retention of a deciduous premolar is common in 12- to 18-month-old cattle. This results in difficulty in masticating food and excessive salivation. The treatment consists of removing the deciduous premolar with a molar-extracting forceps.

Overgrown or Loose Molar Teeth

Overgrown molar teeth are found most commonly in older ruminants. The opposite tooth is often missing. Food accumulates between the affected tooth and the cheek, causing obvious swelling of the face. Interference with mastication is often noted. The offending tooth should be rasped regularly or removed. A power tool to grind cheek teeth works well. Premolar or molar teeth

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can become loose in advanced cases of actinomycosis affecting the jaw. It may be difficult to determine whether the loose tooth is a cause or result of the bony abnormalities. One cow with maxillary lymphoma and loose teeth has been reported.[34]

Broken Teeth

Broken incisors are not common because of the loose alveolar attachment of these teeth. Broken premolars and molars are more common because these teeth are more solidly attached in their alveoli; breakage usually results from attempts to masticate hard objects. Most fractures usually involve only a portion of the tooth, do not involve the root, and are asymptomatic. A sagittal tooth fracture that includes the root causes pain and may result in reduced feed intake and loss of condition. (Treatment is described later in the Tooth Root Abscess section.)

Dental Caries

Dental caries, or decay, creates areas of decalcification of the tooth.[4] Dental caries is rare in ruminants,[4] but it sometimes occurs in both deciduous and permanent teeth and in both dentin and enamel.[6] Interference with prehension is rare. On oral examination, an orange or black pigment is seen in the defective enamel or exposed dentin; these areas should be probed with a fine dental pick or needle. Frequently, the caries fills with food material until it reaches the pulp cavity, which creates a tooth root abscess (Fig. 32.78). At that time, the productivity of the animal decreases, and a swelling on the mandibular or maxillary bone, or purulent discharge secondary to sinusitis appears. A head scan or oblique radiograph is useful for confirming the diagnosis (Fig. 32.79). The infected tooth should be removed. Because the infection is located at the apex of one or multiple roots, the periodontal ligament holds the tooth firmly in the alveolar socket, which makes oral extraction difficult. A surgical repulsion is often necessary. (See the Tooth Root Abscess section.)

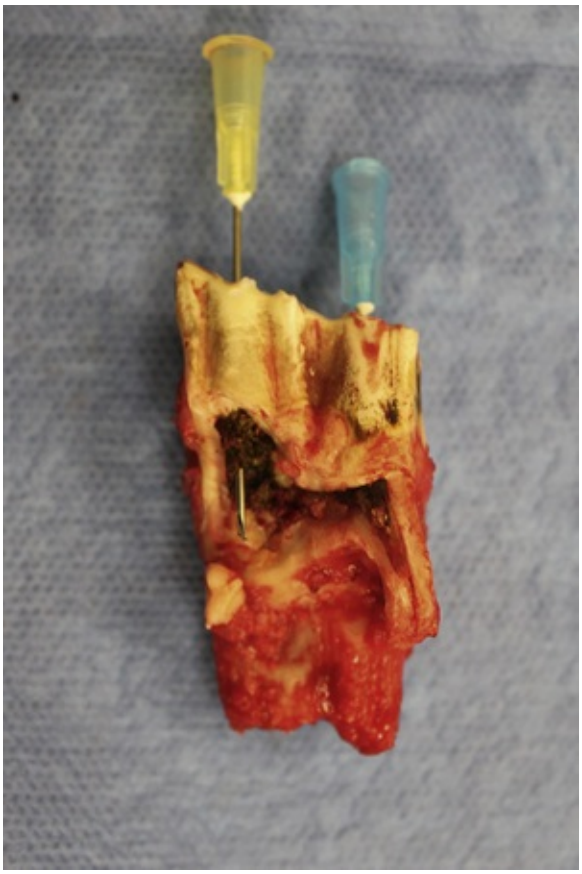


FIG. 32.78 Photograph of a third mandibular molar extracted surgically (the roots are missing). Two hypodermic needles are placed through infundibular caries. The pulp cavity is filled by food material that caused a root abscess. (Courtesy Caroline Constant, Université de Montréal.



FIG. 32.79 A right lateral oblique radiograph of the mandible of a 3-year-old Holstein cow shows a radiolucency center over the caudal root of the third molar. Lysis of the apex of the root is present. (Courtesy Université de Montréal.)

Osteodystrophia Fibrosis

Osteodystrophia fibrosa is caused by resorption of calcium from bone and its replacement by connective tissue.[35] It is most common in goats. Osteodystrophia fibrosa can result from calcium, phosphorus, or vitamin D deficiencies or from hyperparathyroidism. Usually a growing animal with osteodystrophia fibrosa has a bilateral, soft, nonpainful, and swelling of the maxilla or mandible or both jaws.[35] The diagnosis is based on radiographic evidence of poorly mineralized bone and inward rotation of the premolar and molar teeth. The treatment consists of supplementing the ration with adequate mineral levels while maintaining a 2 : 1 ratio of calcium to phosphorus.

Tooth Root Abscess

A tooth root abscess can be a complication of periodontal disease or dental caries. It can be diagnosed in aged cattle but seems more frequent in younger cattle. Periodontal disease at the time of permanent tooth eruption could explain the presence of this condition in young cattle. Early on, the repercussions on the health of the animal are minimal. Chewing behavior might change, and growth

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or milk production could be reduced. With time, a swelling appears around the infected tooth. Eventually, a draining tract becomes evident. If the molars or the caudal root of the fourth premolar is infected on the maxillary arcade, unilateral nasal discharge associated with halitosis appears because the roots of those teeth are located in the maxillary sinus. With time, the mandible or the maxilla becomes distorted from the severe periosteal reaction and the bony proliferation caused by the chronic infection. In some cases, the external appearance of the jaw resembles cases of osteomyelitis caused by *Actinomyces bovis* (actinomycosis). The oral examination may reveal periodontal disease (exposed roots), a fractured tooth, or caries. A rigid endoscope is useful for evaluating the caudal cheek teeth. The final diagnosis is confirmed by a head scan or oblique radiographs. Medical therapy fails to resolve the infection because the tooth has become a sequestrum; therefore the tooth should be removed. Oral extraction is possible in chronic cases or in cases secondary to periodontal disease. With the animal under sedation or general anesthesia, a mouth gag is used to open the jaw. The affected tooth is located, and the gingiva is elevated on the lingual and buccal side of the tooth. If the tooth is not already mobile, a molar spreader can be used to loosen the periodontal ligament. Molar-extracting forceps are placed on the crown, and the tooth is moved slowly from left to right until the periodontal ligament is completely broken. Finally, the tooth is removed by means of a fulcrum effect. The procedure is, in the author's opinion, difficult when caudal cheek teeth are involved. The limited mobility of the temporomandibular joint reduces the working space in the back of the oral cavity in cattle.

Dental repulsion is done, preferably with the animal under general anesthesia, with the affected tooth uppermost. Mandibular teeth are removed through a ventral or a lateral approach. With the ventral approach, a Galt trephine is used to remove the bone covering the roots of the infected tooth. Then a straight dental punch is placed over the roots before the tooth is hammered out. With the lateral approach, the lateral mandibular bone plate lateral to the infected tooth is removed with a pneumatic burr or with a bone rongeur and curette. The roots are freed from the bone, and a curved dental punch is used to hammer the infected tooth out. In the author's experience, the lateral approach works best to remove mandibular molars. The surgical approach is more challenging, and care must be taken to preserve the facial artery and vein that travel just over the third molar.

Maxillary premolars are removed through a dorsal approach by trephining the maxillary bone above the infected tooth. To remove maxillary molars, a

maxillary bone flap is made above the maxillary sinus. Straight or curved dental punches are used to hammer the tooth out. It is important to seat the punch perfectly on the tooth to prevent the punch from slipping and fracturing the hard palate or lacerating the palatal artery. Intraoperative imaging is essential to identify the proper position of the dental punch and to ensure that no tooth fragments are left behind.

The alveolus is packed with dental wax, gauze, or dental acrylic, such as Optosil (Heraeus Kulzer GmbH, Hanau, Germany).[8] On the mandible, the ventral aspect of the incision can be left open for drainage. If sinusitis is present at time of surgery, a Foley catheter is left in the sinus postoperatively to allow daily flushing. Antibiotics are administered for 1 to 2 weeks, according to culture antimicrobial sensitivity results. The dental plug is removed 3 to 4 weeks after surgery. Sedation and the use of a mouth gag may be necessary to remove the dental plug safely. The prognosis after oral or surgical extraction is good.

Dental Fluorosis

Dental fluorosis is associated with continuous ingestion of small but toxic amounts of fluorine in the diet or drinking water. Most reported occurrences of fluorosis are in cattle. Sheep are less susceptible. Developing teeth are very sensitive to the ingestion of excess fluorides. Fluorides inhibit the action of ameloblasts and odontoblasts during tooth formation, which results in failure of the tooth to incorporate minerals. Fluorosis causes striations or patches (yellow, brown, green, or black) in enamel. Some erosion of the permanent tooth can occur. Cattles are susceptible to dental fluorosis during enamel matrix formation from approximately 6 months to 3 years of age. Severe dental fluorosis results in dental wear, inability to graze properly, and difficulty with mastication and food intake because of tooth pain. In addition to clinical signs, the fluorine concentration in the blood and urine can be analyzed to confirm the diagnosis. Normal cattle have blood levels of up to 0.2 mg/dL of blood and 2 to 6 mg/kg in urine. Cattle with fluorine intakes sufficient to cause intoxication may have bloods levels of 0.6 mg/dL and urine levels of 16 to 68 mg/kg. Treatment usually entails removing the animals from the source of fluorine.

Rostral Mandibular Masses

Vascular gingival hamartomas are defined as disorganized and excessive proliferations of vascular tissue that are present at birth (Fig. 32.80).[36,37] They

are considered a developmental anomaly rather than a true neoplasm because of their limited growth. En bloc excision combined with rostral mandibulectomy is curative.[38]



FIG. 32.80 Photograph of a vascular gingival hamartoma in a 3-day-old calf. (Courtesy Sylvain Nichols, Université de Montréal.)

Odontogenic tumors are not common in cattle. They occur generally on the rostral mandible but can be found more caudally on the mandible and maxillary.[39] Ameloblastic tumors are the most frequent odontogenic tumor.[40] Depending on the tissue involved in the mass, they are called *ameloblastic fibroma* (dental epithelium), *fibrodentinoma* (dental epithelium and small island of dentine), or *fibroodontoma* (dental epithelium, dentine and enamel). They are benign tumors with continuous growth and are found in younger cattle. A mass of variable size covered with gingival mucosa with distorted deciduous and permanent incisors is present (Fig. 32.81). The mass has no effect on the health of the animal. Eventually, ulcerations appears from rubbing while eating. Rostral intraoral radiographs help determine the extent of the tumor in the mandible (Fig. 32.82). En bloc excision is curative. To obtain clean margins, a rostral mandibulectomy

is necessary.[41]



FIG. 32.81 Photograph of an ameloblastic fibroma in a 4-year-old Holstein cow. (Courtesy Sylvain Nichols, Université de Montréal.)



FIG. 32.82 An intraoral radiograph of the cow in Fig. 32.6. The tumor has changed the normal anatomy of the rostral mandible. (Courtesy Université de Montréal.)

Odontoma is a benign tumor composed of normal dental tissue that grows in an irregular way. It affects permanent teeth before eruption and is therefore found in younger cattle. It does not appear to be common in cattle, however.

Other masses affecting the rostral mandible are fibrosarcomas and osteosarcomas. Those malignant tumors occur in older cattle. Rostral mandibulectomy, if performed early, may be curative.

Rostral Mandibulectomy.

This procedure is best performed with the animal under general anesthesia in sternal recumbency. With a mouth gag in place, the gingiva is incised at the predetermined site of the mandibulectomy. A periosteal elevator is used to retract the gingiva attached to the periosteum rostrally and caudally. An oscillating saw or a Gigli wire is used to amputate the rostral mandible. The saved gingival mucosa is sutured to cover the bone. Bleeding is to be expected during the dissection of the gingival mucosa and from the mandibulectomy site. Bone wax helps control bleeding from the mandible. A pressure bandage may be needed postoperatively. It incorporates the lower lip and the remaining rostral mandible.

The surgery site heals rapidly without complications. Because cattle graze mainly with their tongue, no repercussions have been observed with regard to food intake after rostral mandibulectomy.

Salivary Gland Diseases

Sylvain Nichols • Guy St. Jean

The parotid, mandibular, and sublingual glands are the three largest salivary glands in ruminants.[1] In cattle, the mandibular gland is larger than the parotid gland. The parotid gland is located behind the caudal border of the masseter, from the zygomatic arch to the most ventral aspect of the mandible's vertical ramus. Its duct enters the gland at its most ventral location. It travels along the facial vein to enter the oral cavity abaxial to the second maxillary molar. The mandibular gland lies medial to the caudal portion of the mandible from the basihyoid bone to the paracondylar process. The duct exits the mandibular gland axially and travels rostrally between the deep mylohyoideus muscle and the sublingual gland. It enters the oral cavity rostral to the frenulum of the tongue. The sublingual gland has two parts: the monostomatic and the polystomatic portions. The monostomatic portion is 10 cm long, and its main opening is near the entrance of the mandibular gland's duct. The polystomatic portion has multiple microscopic ducts along the base of the tongue.[2]

A dairy cow in lactation produces 100 to 200 L of saliva in 24 hours. Saliva is secreted continuously, but the rate of secretion is increased by feeding, rumination, and the presence of coarse feed in the rumen.[1] The saliva provides a fluid medium for transport of ingesta during deglutition and regurgitation. It also maintains adequate phosphate for bacterial digestion of cellulose in the rumen and contains bicarbonate, which acts as a buffer to maintain ruminal pH above 5.5. Ruminant saliva contains approximately 90 to 140 mmol/L of bicarbonate. The normal pH is around 8.2.[3]

Excessive Salivation

Excessive salivation (ptyalism) is a sign of many pathologic conditions. The volume of saliva may be normal, but if it is not swallowed, salivation can appear excessive. As a precaution against exposure to rabies, gloves should be worn to examine the mouth of any animal that is salivating excessively. Excessive salivation may be seen with dental disease, stomatitis, foreign objects in the

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mouth or pharynx, or esophageal obstruction. It also has been seen with ruminal disorders, in cows that have eaten spoiled silage, and with impaction of the abomasum. Ptyalism may be a clinical sign in rabies, pseudorabies, meningoencephalitis, listeriosis, tetanus, and slaframine toxicity.[1,4] Mercury, iodine, lead, copper, and arsenic also can stimulate secretion by the salivary glands. Treatment depends on the underlying causes.

Salivary Duct Atresia or Agenesia

This condition is diagnosed in younger animals. A soft swelling is palpable along the normal location of the duct. Sialography may be performed to highlight the obstruction. If possible, creating an opening in the oral cavity allows the saliva to drain in the mouth. This procedure is performed with the animal under general anesthesia. A 1.5-cm opening is created by suturing the oral mucosa to the salivary duct mucosa.[5] This procedure is difficult to perform when the obstruction is located distally from the oral opening. Other therapeutic options include chemical débridement or surgical removal of the affected gland and duct (see Sialocele section, as follows).

Sialocele

A sialocele develops when saliva escapes from a duct or salivary gland and enters the surrounding tissue. The saliva contains enzymes that irritate the tissue. The accumulation of saliva is surrounded by inflamed tissue, which gives the lesion a cystic appearance. A soft, fluctuant swelling usually is seen. Pain may be observed during mastication. Trauma or a foreign body is usually the cause of a sialocele. The diagnosis is based on the history, palpation findings, ultrasound evaluation, fluid aspiration and cytologic evaluation, and sialography. Needle aspiration may yield yellow mucoid saliva. Two treatments have been described.[6,7] The first involves removal of both the involved glands and duct.[6] Surgical extirpation of the mandibular salivary gland in the caudal area of the mandibular spaces has been performed successfully in cows, sheep, goats, and buffaloes.[1] Exposure of the tissue by opening the capsule of the gland facilitates the process of extirpation and prevents trauma of the surrounding nerves and blood vessels.[6] In the second treatment option, the sialocele is opened, drained, and chemically débrided with a caustic agent such as iodine or copper sulfate.[7] Post-débridement analgesia is mandatory after chemical resection.

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Sialoadenitis

Inflammation of the salivary glands usually is caused by an ascending infection from a traumatized duct, by penetrating wounds or plant awns, or by a hematogenous embolization. Diffuse swelling of the salivary glands may be observed, and the swelling may be hot and painful on palpation. Abscess formation is a common complication. The pain may interfere with mastication and swallowing. Treatment consists of systemic antibiotics, antiinflammatory drugs, and analgesic drugs. Abscesses should be drained when they localize. Salivary fistulas can be sequelae to salivary abscesses. Surgical extirpation is also possible. However, because of the inflammation surrounding the gland, the dissection is more challenging, and the odds of traumatizing neurovascular structures are increased.[5]

Parotid Gland Carcinomas

In three cows at slaughter that had parotid gland carcinomas, the neoplastic cells appeared to originate from ductal and acinar epithelium.[8] Ocular squamous cell carcinoma may spread locally to the parotid or mandibular lymph nodes.[9]

Actinobacillosis (Woody Tongue, Wooden Tongue)

Bradford P. Smith

Definition and Etiology

Actinobacillus lignieresii, a Gram-negative rod, is a normal inhabitant of the rumen and mouth of cattle and sheep and probably goats. When the organism enters the soft tissues through a lesion, actinobacillosis results in a granulomatous abscessation. Ruminants of all ages can be affected, and the disease appears to have a worldwide distribution. The classic site of infection is the bovine tongue; because the condition causes a very hard, diffuse nodular swelling, it has been given the name “woody tongue” or “wooden tongue.” The prevalence of woody tongue in bovines at slaughter is 0.7% to 3.6%.[1] Atypical actinobacillosis lesions of cattle can occur in the lips, nose, or lymph nodes of the head or neck or at other sites. Although the lesions ordinarily occur sporadically, herd outbreaks with morbidity rates of up to 73% have been

reported.[1,2] Sheep are most commonly affected by hard swellings of the lips, often with fistulous tracts. Actinobacillosis has also been reported to cause tongue lesions in sheep and horses. These lesions appear to be rare in goats.

Clinical Signs and Differential Diagnosis

Actinobacillosis lesions usually involve soft tissues. When the tongue is affected, the major clinical signs are inability to prehend food normally, excessive salivation, and sometimes visible enlargement of the tongue, which protrudes from the mouth. The submandibular area often is enlarged and firm. On palpation the tongue is firm to very hard, painful, and nodular (Fig. 32.83). Nodular lesions are often slightly ulcerated. The base of the tongue is most frequently affected, but the shaft may also be involved. An ulceration filled with plant awns or stems often is seen in the sulcus lingualis at the junction of the base and shaft of the tongue. Because cattle use the tongue to prehend food, anorexia results when the tongue is painful and inflexible. Actinobacillosis must be differentiated from dental disease, oral foreign bodies, pharyngeal trauma, and other diseases that cause oral pain.

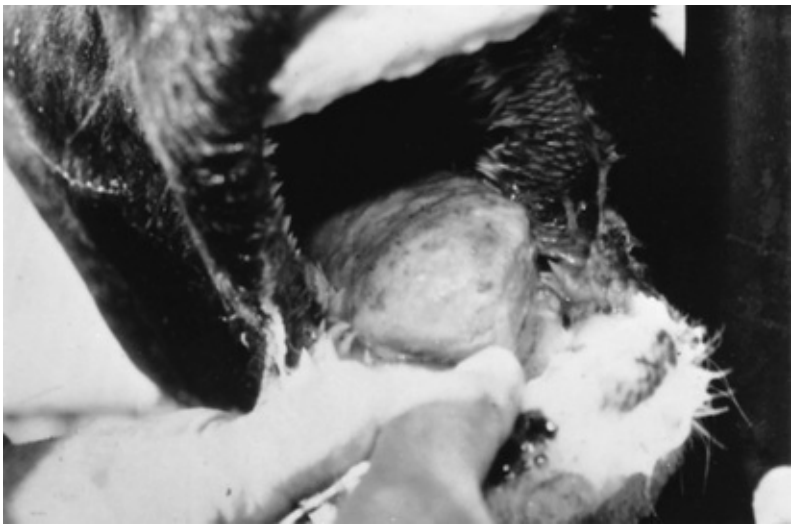


FIG. 32.83 Firm, enlarged bovine tongue typical of woody tongue caused by *Actinobacillus lignieresii.* Partly ulcerated areas of mucosa overlie hard nodules.

Atypical lesions in cattle involve sites other than the tongue.[3] Lymph nodes of the head and cranial cervical area are most frequently affected, but where any

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abrasion is present, granulomas or abscesses may develop, followed by licking or contact with pus draining from a lesion on another animal. Because plant awns and stems create entry sites for the organism in the mouth, most lesions are in the head. Granulomas in the nose and eyelids and needle puncture wounds over the left jugular vein have been reported. These granulomas may be confused with tumors, polyps, or cysts. Granulomas have been reported in the esophagus, pharynx, palate, flank, internal iliac lymph nodes, and testes; multiple subcutaneous lesions with regional lymph node involvement also have been reported. Three cases involving cutaneous lesions of the facial tissues were described as extensive swollen plaques under alopecic areas. Most granulomatous abscesses in a herd outbreak of actinobacillosis involved the tongue, muzzle, and lips and the submandibular, parotid, and cranial cervical areas. Generalized involvement or granuloma formation in internal organs may also occur.

Lesions in sheep typically involve the lips and face or parotid and submaxillary regions. The nasal cavity and internal organs are occasionally involved. Soft tissues of the head may be infected through fight wounds. Lesions of the lips must be differentiated from those of contagious ecthyma, and granulomatous abscesses in other sites must be differentiated from caseous lymphadenitis lesions. Lesions of the tongue in sheep, essentially identical to those found in cattle, have been reported as a cause of green staining of the lips and “cud-dropping” in sheep.

Clinical Pathology

Diagnosis of actinobacillosis requires biopsy and culture of the lesion. The pus usually is not malodorous. Pus crushed between two glass slides shows “sulfur granules,” “clublike rosettes,” or “club colonies.” Similar colonies may be found in actinomycosis and some staphylococcal infections. *A. lignieresii* organisms are small, Gram-negative rods. Definitive diagnosis relies on culture. No reliable serologic test is available for actinobacillosis, and the hematologic and biochemical findings may be normal or typical of a chronic infection.

Pathophysiology

A. lignieresii is a normal inhabitant of the mouth in ruminants and can be found in many plant awns. When mucosal lesions occur as a result of plant awns (e.g., foxtails), thistles, or particularly stemmy coarse feed, actinobacillosis may occur.

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Many affected cattle have a small ulcer in the sulcus lingualis at the junction of the base and shaft of the tongue. Plant fibers are sometimes found in the granulomatous lesions of actinobacillosis. Once inoculated into tissues, the organism may cause a local lesion, lesions in draining lymph nodes, or both. Lesions elsewhere on the body may be contaminated by saliva or by pus from other draining lesions or directly by plant awns on which *A. lignieresii* resides.

Epidemiology

Most cases of actinobacillosis are sporadic. Herd outbreaks may be associated with abrasive feedstuffs and crowded conditions in which the organism is spread rapidly to wounds on other animals by way of saliva. In one herd outbreak, 73% of a group of heifers (4 to 24 months of age) were affected 1 month after feeding of a coarse, stemmy haylage had begun.[2] Atypical lesions often are associated with a previous wound at the site, such as a nose lead wound, multiple needle punctures, or a head butting wound. Outbreaks of actinobacillosis in wounds of the head, neck, body, and limbs have been reported.

Necropsy and Biopsy Findings

Actinobacillosis lesions typically are firm, pale, gritty, granulomatous abscesses. On gross examination, they appear similar to exuberant granulation tissue and connective tissue, often appearing to have a yellowish granular (1- to 3-mm) surface. Masses contain multifocal necrotic foci, often filled with nonodorous, thick, yellow-white pus. Histological examination reveals that the lesion is a granulomatous abscess. An outer capsular region of connective and granulation tissue surrounds an area of leukocytes and rosettes (“club colonies”). Mononuclear cells, plasma cells, and eosinophils predominate. Many neutrophils are seen at the center of the lesion. Multinucleated giant cells or plant fibers, or both, may be present.

Treatment and Prognosis

Treatment usually is successful, and the condition has an excellent prognosis when only the tongue is involved. The prognosis may be only slightly less optimistic when internal organs and atypical sites are involved. Sodium iodide (70 mg/kg given IV as a 10% to 20% solution) is the treatment of choice. Intravenous treatment is given once and repeated at least one more time 7 to 10 days later. In refractory cases, intravenous therapy may be repeated more often

(2- to 3-day intervals). In severe cases, daily organic iodides can be administered orally at a rate of 60 mg/kg/day[4] in addition to the intravenous iodide. If signs of iodinism develop (excessive tearing, coughing, inappetence, diarrhea, or dandruff), iodine administration should be halted; the adverse signs normally disappear shortly thereafter.

The onset of therapeutic benefit of sodium iodide is remarkably rapid. Within 48 hours after treatment, the tongue is flexible enough to allow the animal to eat. Although the mode by which iodides exert their beneficial therapeutic effect in actinobacillosis is not well understood, they probably exert some antiinflammatory effect on the granulomatous inflammation. Iodides have little in vitro bacteriostatic or bactericidal effect at the concentrations given,[5] but the onset of action is very rapid. They probably act in some other way than by direct antimicrobial effect. The old belief that iodides cause abortion at the recommended dose has been cast into doubt by the author's clinical experience and by reports of others,[6] who gave 1.5 to 2 times the recommended intravenous dose without inducing abortion. Nevertheless, there are anecdotal reports of the association, and when products are labeled with a contraindication to their use in pregnant cattle, due caution should be exercised. Iodides should be given slowly and with caution to horses because of the possibility of severe generalized adverse reactions to intravenous sodium iodide.

Most strains of *A. lignieresii* are sensitive in vitro to a number of antimicrobial drugs, including ceftiofur, ampicillin, penicillin, florfenicol, sulfa drugs, certain approved aminoglycosides, and tetracyclines. Each isolate should be tested for antimicrobial sensitivity. Therapy with an antimicrobial drug to which the isolate is sensitive is recommended in severe, generalized, or refractory cases of actinobacillosis. Therapy should also include iodides.

Surgical debulking of lesions, particularly if they interfere with airflow, is also possible for atypical cases in which a large granulomatous mass is present and the mass has proved refractory to medical therapy. Hemostasis may be a problem after surgical debulking.

Prevention and Control

Prevention relies mainly on avoidance of coarse, stemmy, scabrous feeds and pastures full of hard, penetrating plant awns (e.g., foxtails) or thistles. If an outbreak occurs, immediate change to a softer feed is advised, and affected animals should be treated individually. Rapid resolution of the outbreak can be

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expected once these steps have been taken. If atypical lesions occur, a cause of skin wounds in the area should be sought and resolved.

Actinomycosis (Lumpy Jaw)

Bradford P. Smith

Definition and Etiology

Actinomycosis is caused by *A. bovis*, a Gram-positive, nonencapsulated, branching, filamentous bacterium that is a normal inhabitant of the ruminant mouth. The disease occurs mainly in cattle, but on rare occasions it affects sheep or goats, and one report of the disorder in a horse involving *Actinomyces viscosus* and *Actinomyces odontolyticus* has been published.[1] The bacterium enters the tissues and bone through oral abrasions, openings, and punctures associated with dental or gingival disease, hard plant awns (e.g., foxtails), thorns, stickers, or dry, coarse, stemmy feeds. Lesions may begin as cavities (caries) in the dentin or dental pulp.[2] They are sporadic and occur mainly in the mandible and less commonly in the maxilla. Because of the preponderance of mandibular lesions, with the development of periosteal new bone and fibrosis, the disease is commonly known as “lumpy jaw.” Lesions occasionally occur in soft tissues of the head, esophagus, forestomachs, and trachea. *A. bovis* occasionally causes granulomatous abscesses in other soft tissues. Most of the early reports of esophageal groove and forestomach involvement incriminate actinobacillosis rather than actinomycosis.

Clinical Signs and Differential Diagnosis

Bovine actinomycosis typically causes a hard, immovable, painless, bony mass on the mandible (Fig. 32.84). The lesion is most common on the horizontal ramus. Initially it is nondraining (has no fistulous tracts), but fistulous tracts may develop and involve tooth roots as the condition progresses (Figs. 32.85 and 32.86). When teeth become involved, the animal shows evidence of pain during chewing, and weight loss may result. A careful examination of the mouth is necessary to detect loose teeth, plant awns, or severe gingivitis and to rule out a pathologic fracture. If a fistula is present, the tract should be flushed with organic iodine and contrast radiographs obtained to determine whether it communicates with the mouth. The differential diagnosis includes tooth root

abscess, fracture, tumors, and osteomyelitis caused by other organisms. If a mandibular swelling continues to enlarge despite therapy, radiographs should be examined for evidence of a fracture or sequestrum. Atypical actinomycosis with lesions in soft tissue causes a variety of clinical signs, depending on the location.



FIG. 32.84 Hard swelling on the distal mandible of a cow infected by *Actinomyces bovis.* Loss of teeth and bone destruction, along with fibrosis and callus formation, are seen in this advanced case. The oral mucosa is secondarily ulcerated by trauma.



FIG. 32.85 Hard swelling and draining tract on the mandible of a cow, typical of *Actinomyces bovis* lesion.



FIG. 32.86 Radiograph of lesion in the cow in Fig. 32.86, showing cavitating central bone loss and peripheral bone density, typical of *Actinomyces bovis* lesion.

Clinical Pathology and Diagnosis

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Hematologic and clinical chemistry findings may be normal or may reflect a chronic infection. Radiographs of the lesion are helpful in determining dental involvement or a pathologic fracture. The radiographic lesion consists of multiple central radiolucent areas of osteomyelitis surrounded by periosteal new bone and fibrous tissue. If a fistulous tract is present, a contrast study performed while the tract is flushed may help determine the extent of the fistula. Before flushing, material from the core of the lesion should be aspirated or examined in biopsy. A Gram stain and culture of pus should be performed. The organism is Gram-positive, filamentous, and branching. “Sulfur granules” similar to those described for actinobacillosis may be seen. Many authors report that they were unsuccessful at culturing the organism.

Pathophysiology and Epidemiology

A. bovis appears to enter the bone through mucous membrane punctures caused by foreign bodies, plant awns, or coarse, stemmy feeds or through a diseased tooth or areas of gingivitis that allow oral bacteria access to the bone. Cases usually are sporadic.

Necropsy and Biopsy Findings

Actinomycosis causes a granulomatous abscess. Scattered through the mass of tissue are basophilic clumps of bacteria surrounded by eosinophilic clublike projections. The bacteria appear as long, filamentous, branching rods. Surrounding them is evidence of cellular reaction, composed of neutrophils, epithelioid cells, macrophages, and occasional multinucleated giant cells. In the outer fibrous tissue are plasma cells.

Treatment and Prognosis

Treatment of actinomycotic bone lesions usually results in arrest of the lesion, but seldom does the size of the hard mass regress significantly. The prognosis for arrest of the lesion with vigorous treatment is good. If the mass does not have any fistulous tracts and no affected teeth are loose, medical therapy alone may be sufficient. If the mass has fistulous tracts, it should also be vigorously curetted and flushed with povidone-iodine or other organic iodine. The lesion has a rich blood supply, and curettage can result in severe hemorrhage. If the cavity is large, it may be necessary to flush and pack with iodine-soaked gauze daily for several days and then less frequently as healing progresses. Three cases of

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actinomycosis were treated successfully with a repeated regimen of curettage followed by cryotherapy with liquid nitrogen poured into the lesion. The authors repeated the treatment on days 2, 9, and 16.[3] If there is an open fistula into the mouth (as judged by vigorous flushing) or if teeth are involved, the affected tooth or teeth should be carefully removed or repaired endodontically.[2] Care must be taken to prevent mandibular fracture, and the animal must be sedated or anesthetized to allow for proper intraoral manipulation. The empty alveolus should be carefully packed with gauze or a dental acrylic to which a wire or umbilical tape is attached and pulled through the fistula. The wire is tied externally to a small gauze roll to keep the alveolar packing firmly in place. The wire should be untied daily and the tract flushed thoroughly with povidone-iodine until the wound is completely granulated. Once granulation begins, it may not be necessary to check and flush the lesion more than once a week. The alveolus will take several weeks to close, pushing the gauze or acrylic out as it does so.

Medical treatment of actinomycosis involves the use of sodium iodide and penicillin or another antimicrobial drug to which the organism is sensitive. Sodium iodide is given IV at a dose of 70 mg/kg as a 10% to 20% solution. It can be given every 7 to 10 days or more often until signs of iodinism occur (i.e., lacrimation, cough, inappetence, diarrhea, and dandruff). If repeated intravenous treatments are difficult, oral organic iodides (total powder) can be given at the rate of 60 mg/kg/day for 3 weeks. As with actinobacillosis, the beneficial therapeutic effects of iodides appear to arise from their ability to reduce granulomatous inflammation rather than from direct antimicrobial effects. Iodides do not appear to cause abortion and can be safely given to pregnant cows,[4] although care should be used because there are anecdotal reports to the contrary, and products are labeled with a contraindication for pregnant cattle.

Isoniazid (10 mg/kg/day given PO for 1 month) is effective at arresting actinomycosis of the mandible in cattle.[5] It is inexpensive and readily consumed in a small amount of grain. A prolonged withdrawal period before slaughter for human consumption is required. The drug appears to be nontoxic at this dosage, but it may cause abortion and should not be used in pregnant cattle. The Food Animal Residue Avoidance Databank (FARAD; www.farad.org/vetgram/) should be checked before isoniazid is used.

Penicillin (22,000 U/kg IM twice daily) or another antimicrobial drug such as florfenicol or ampicillin can be added to the treatment regimen in cases involving valuable animals or when twice-daily treatment for 7 to 14 days is

possible. Streptomycin can be given twice daily, but because of the prolonged persistence of tissue residues, aminoglycosides generally are considered unacceptable in food animals.

Prevention and Control

A. bovis is a normal mouth inhabitant of ruminants; therefore the only possible means of prevention is to avoid feeding coarse, stemmy feeds; feeds with hard, penetrating plant awns; and feeds with other sharp materials. The recommendations in this regard are similar to those for actinobacillosis.

Pharyngeal Trauma and Abscess

Bradford P. Smith

Definition and Etiology

Pharyngeal trauma occurs relatively frequently in cattle, which results in cellulitis, abscessation, or hematoma formation. One case resulted in megaesophagus. Pharyngeal trauma is almost always associated with use of a balling gun, long dose syringe, speculum, paste wormer gun, rigid probe of calf esophageal feeder, or rigid stomach tube.[1] A foreign body such as a sharp stick or wire occasionally perforates the pharynx. Hematomas may result from unidentified blunt trauma. The puncture or laceration may be very small and usually is located in the area near the origin of the esophagus. The result is that feed and saliva enter the retropharyngeal area, and inflammation develops (also see Chapter 31, Retropharyngeal Lymph Node Abscessation section).

Clinical Signs and Differential Diagnosis

The clinical signs include anorexia, drooling of saliva, malodorous breath, extended head and neck, localized or diffuse pharyngeal pain, feed coming from the external nares, and forestomach stasis or bloat. Severe cases may involve obvious pharyngeal swelling, fever, easily elicited cough on laryngeal palpation, dyspnea, and aspiration pneumonia. Intraluminal submucosal pharyngeal abscesses with similar clinical signs have been reported. The differential diagnosis in cattle must include retropharyngeal abscesses (also see Chapter 31, Retropharyngeal Lymph Node Abscessation section), pharyngeal foreign body, actinobacillosis, megaesophagus, and lymphosarcoma or other tumors that

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involves the pharyngeal lymph nodes.

Careful digital palpation of the pharynx via the mouth often reveals the diagnosis, although restraint is difficult because the area is painful and swollen, causing dyspnea and struggling. A well-lubricated stomach tube should be gently passed to relieve bloat and ascertain that no esophageal obstruction is present. Pharyngeal trauma is rare in sheep and goats, and retropharyngeal abscesses caused by *Corynebacterium pseudotuberculosis* (caseous lymphadenitis) are the most common cause of pharyngeal swelling.

Clinical Pathology and Laboratory Aids

Endoscopy and radiography may be of great help in diagnosing the site of the lesion, the extent of cellulitis, and the presence of a foreign body. Endoscopy reveals a swollen, collapsed pharyngeal air space. The wound may be visible, and it may have exudate at its origin. Endoscopy can help rule out intraluminal masses and foreign bodies. Retropharyngeal cellulitis, abscess, or hematoma often can be visualized radiographically, and radiopaque foreign bodies can be seen (Fig. 32.87). Gas in the soft tissues or a discrete mass can be seen with cellulitis and abscess, respectively. Gas can often be seen in the lumen of the esophagus as well. Radiographs of the lungs and thorax may be helpful if aspiration pneumonia or mediastinitis is suspected. In some cases in which no appropriate treatment is instituted early or treatment fails, the infection can reach the mediastinum via the thoracic inlet, and the prognosis becomes more guarded. The results of hematologic analysis may reflect an infectious inflammatory process.

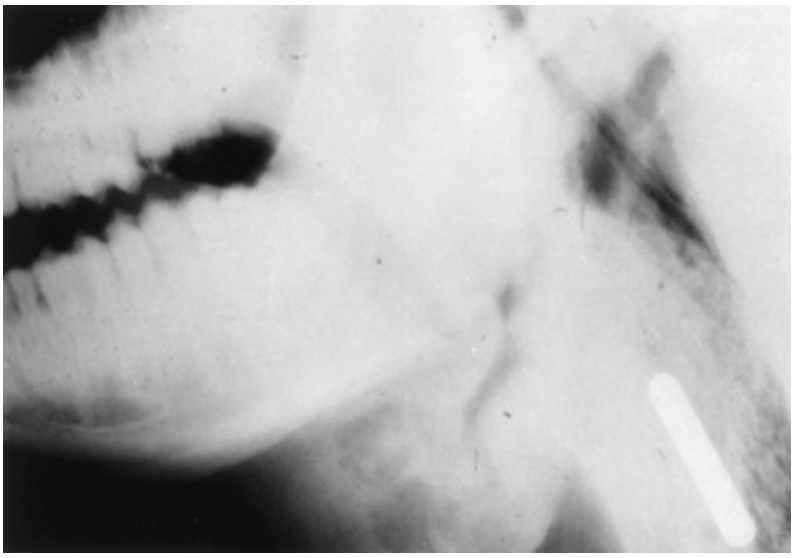


FIG. 32.87 Pharyngeal trauma in a 2-year-old bull caused by a magnet that was given forcefully with a balling gun 24 hours previously. The magnet is visible in the retropharyngeal tissues surrounded by cellulitis, with swelling and gas in the tissues. The area is swollen and painful.

Pathophysiology

Inflammation, swelling, and necrosis in the retropharyngeal tissues interfere with normal swallowing by causing pain when swallowing is attempted, by causing physical interference with passage of a bolus, and by causing neurologic involvement. The resultant dysphagia may predispose the animal to inhalation of feed and saliva.

If the retropharyngeal inflammation affects the pharyngeal branch of the vagus nerve on the dorsolateral surface of the pharynx, the esophageal and pharyngeal phases of swallowing and eructation are disturbed.[1] The resultant pharyngeal paresis may lead to reflux of feed through the nares. Involvement of the adjacent cranial laryngeal nerve makes the laryngeal mucosa less sensitive to foreign material and thus diminishes the cough reflex. Severe inflammation may involve the vagus nerve itself and cause forestomach stasis with bloat and laryngeal motor dysfunction.[1-3] Eructation also involves pharyngeal muscular activity, and the maneuver is likely to be quite painful when cellulitis is present in the area.

Treatment and Prognosis

In spite of the fact that affected animals often are completely anorexic and

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febrile and look very ill, most cases of pharyngeal puncture or laceration resolve successfully if the animal can be vigorously treated with broad-spectrum antimicrobial drugs for 7 to 14 days, if aspiration pneumonia can be controlled by limiting access to feed, and if adequate supportive care can be given. Tetracyclines, ampicillin, ceftiofur, trimethoprim-sulfonamide, and florfenicol have been used successfully. NSAIDs should be given for analgesia and for their ability to reduce inflammation. Oral administration of boluses should be avoided. FARAD must be checked before drugs are given off label (www.farad.org/vetgram/).

Affected animals should have access to water; if they cannot drink, and if passage of a tube is possible, a soft stomach tube should be used several times daily to gently administer a total of 30 to 50 L (8 to 13 gallons) of water plus electrolytes daily. If tolerated, it can be passed nasally and left in place securely sutured or taped in place to a halter. Alternatively, a rumen fistula may be surgically placed and used to water and feed the animal. The most important electrolyte to administer is potassium: 60 to 100 g of potassium chloride should be given daily with the water. Once the animal can drink without coughing or nasal reflux, soft green grass or a soft mash should be offered. If this is well tolerated, it should be continued for 2 weeks, after which green pasture or soft, green, leafy alfalfa hay or other equally palatable feed should be gradually and carefully introduced into the diet.

If a discrete retropharyngeal abscess forms, it is best first to attempt drainage into the pharynx through the original laceration by pushing a finger into the healing wound until pus escapes. If this fails, a surgical approach to the area may be necessary. Surgery is rarely required in cases of pharyngeal trauma or laceration with cellulitis.

Prevention and Control

Careful use of balling guns, paste wormer guns, and other equipment that can damage the pharynx is the best prevention. Adequate restraint of the head of any animal that is to be orally treated also helps prevent pharyngeal trauma. Care should also be taken to ensure that no wire, thorns, or sticks are incorporated in hay.

Contagious Ecthyma (Sore Mouth, Orf, Contagious Pustular Dermatitis, Scabby Mouth)*

Bradford P. Smith

Definition and Etiology

Contagious ecthyma (CE) (sore mouth, orf, contagious pustular dermatitis, scabby mouth) is a common disease of sheep and goats that is transmissible to humans and has a worldwide distribution. The disease has a short 2- to 14-day incubation period and tends to be more severe in goats; Boer and Boer crossbred goats are most likely to have severe generalized persistent infections with proliferative dermatitis, chronic pneumonia, arthritis, and lymphadenopathy.[1,2] A good review of human lesions was published in 2005.[3] The colloquial name *sore mouth* describes the most common presentation of the disease in sheep and goats; the name *orf* (possibly from the old Norse term *hrufa,* meaning a crust or scab) is more commonly used for the disease in all species in England and for human disease in the United States. The agent is a DNA poxvirus of the parapoxvirus subgroup, which includes several closely related parapoxviruses; these include pseudocowpox (another cause of orflike “milker's nodules” in humans), bovine papularstomatitis (BPS), parapoxvirus of red deer in New Zealand, squirrel parapoxvirus, and parapoxvirus of gray seals. Biological and genetic differences exist among strains of CE virus, and so cross-protection may be limited; vaccines must target the field strain. Wild ruminants (e.g., reindeer, musk ox) and camelids are also affected. A study demonstrated that the sheep orf virus does not cause lesions in camels, and the camel orf virus does not affect sheep, so it is likely that no infection is transmitted between camels and sheep or goats. Other species that can be affected include various wild ruminants, dogs, and cats.[4] The virus is epitheliotropic, usually creating proliferative lesions in the skin of the lips, nostrils, oral mucosa, teats, and occasionally the vulva.

Clinical Signs and Differential Diagnosis

The most common presentation is of a young animal with crusting, proliferative lesions of the mucocutaneous junctions of the mouth and nose (Fig. 32.88). Proliferative lesions may be seen on the gums (Fig. 32.89). Older immunologically naive animals may be affected, and lesions may occur at the coronary band, on the tongue, interdigitally, on the conjunctiva of the eye, on the external genitalia, or on the udder or teats, with the last site affected especially in does or ewes nursing affected kids or lambs. The disease progresses through papular, vesicular, and pustular stages, which are rarely seen, before the

characteristic presentation of proliferative, coalescing, scabbed lesions appears. In one report, the characteristic proliferative scabs appeared on the margins of healing burn wounds. Affected animals may be reluctant to nurse, eat, walk, or be nursed, depending on the location of lesions.



FIG. 32.88 Typical scabby lesions of contagious ecthyma (sore mouth, orf) on the lips of a young goat. Lesions tend to be proliferative rather than ulcerative.



FIG. 32.89 Typical proliferative lesions of contagious ecthyma (sore mouth, orf) on the gums of a young sheep.

Secondary bacterial infection or myiasis of affected parts may occur. The disease usually runs its course in 3 to 6 weeks, but chronic cases have been reported. Complete healing without scarring is the norm as scabs fall off. Severe infections may result in stunting of growth, particularly in goats. Overwhelming infection has been noted on rare occasions, with extension of lesions into the deeper respiratory or gastrointestinal tracts. Does and ewes with severe udder infection may develop mastitis from secondary bacterial infection. Sheeppox and goatpox occasionally produce lesions similar to those of CE, but they are virulent diseases with systemic signs, including conjunctivitis, pyrexia, anorexia, and rhinitis. One report from China documented an outbreak in goats consisting of mixed infections with goatpox, orf, and *Mycoplasma capricolum*, subspecies *capripneumoniae*, which together resulted in a 60% mortality rate.[5]

Animals with bluetongue may have a crusted mouth and nose and eye lesions in the convalescent phase, but bluetongue is a disease with more evidence of oral erosive rather than proliferative lesions and systemic signs, including pyrexia, reluctance to move, lesions on the tongue, and conjunctivitis. Bluetongue has a seasonal incidence (late summer, early fall) that coincides with the activity of its insect vector. CE may occur at any time but typically occurs in spring in the lamb or kid crop. Ulcerative dermatosis (lip and leg ulcer) is an uncommon disease caused by a virus similar to that of CE, but the lesions are crusted ulcers, to be distinguished from the crusted proliferations of CE. The author has observed a series of cases of what appeared to be mild CE of long duration (several years in one individual) in a family of Nubian goats; this was confirmed by an immunofluorescence assay. Smith and coworkers[6] reported on five sheep, 4 months to 3 years of age, that developed severe refractory distal limb lesions resembling warts. Two also had lesions on the head. The sheep were from three different flocks; one was a Hampshire and four were Suffolk. Lesions were confirmed as orf by electron microscopy and immunohistochemistry.[6] A report from Texas described severe multifocal persistent orf lesions in 16 Boer or Boer crossbred goat kids 2 to 5 months of age, from two different farms. Some of the kids had been vaccinated with live-virus vaccine at 1 day of age, others at 2 weeks of age. Lesions were found on lips, nose, ears, body, legs, and feet.[7]

Laboratory Diagnosis

The diagnosis usually is made in the field by recognition of the typical lesions in

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a naive flock or in a naive group (young lambs or kids) in a disease-endemic flock. Definitive diagnosis usually involves identifying the distinctive cross-hatched virus particles in typical early lesions with electron microscopy, PCR, immunohistochemistry, or inoculation into known protected or susceptible animals. Minced biopsy tissues have been used as a source of virus that is identified by fluorescent antibodies after it has been growing in embryonic ovine kidney cell cultures. Complement fixation tests to detect antibodies (with patient serum) or antigen (with vesicular fluid or a suspension of scabs) have also been used.

Pathophysiology

The disease follows a similar time course in animals and human beings: approximately 6 weeks. Six stages have been described,[8] which begin after an incubation period of 3 to 14 days. Each stage lasts approximately 1 week.

1. *Maculopapular stage:* An erythematous spot becomes elevated. Histological study of this stage reveals vacuolization of cells in the upper third of the epidermis with intracytoplasmic eosinophilic inclusions in the affected cells.
2. *Target stage:* A red halo of dilated blood vessels and inflammatory cell infiltrates surrounds a white ring of vacuolated epidermal cells with intracytoplasmic and intranuclear inclusions, which surrounds a red center of pyknotic epidermal cells.
3. *Acute stage:* The lesion is a red, weeping nodule. Microscopic study reveals reticular degeneration of the epidermis with vesicles. The dermis is infiltrated with macrophages and lymphocytes and is denuded of epidermis in places. The hair follicles are distended with pyknotic epidermal cells.
4. *Regenerative stage:* The nodule is now dry with small black dots (the pyknotic follicle cells, now extruded to the surface) in a thin yellow surface.
5. *Papillomatous stage:* The surface of the nodule is roughened with papillomas, which microscopic study proves to be fingerlike, downward projections of epidermis through a full thickness of dermis.
6. *Regressive stage:* The lesion decreases in size and elevation above the surface, the papillomas regress, and several crusts may come off.

Microscopic study reveals that the papillomas and infiltrates regress, leaving normal architecture.

Orf virus encodes for a protein that is apparently homologous to mammalian vascular endothelial growth factors. This family of molecules mediates vascular permeability, angiogenesis, and endothelial cell proliferation, which may account for the swollen, proliferative nature of orf lesions.[9] Transient fever and lymphadenopathy are occasionally seen in humans. Lesions in humans that are not excised and from which no biopsy sample is taken heal without a scar.

Orf virus encodes a range of immunomodulatory genes that interfere with host antivirus immune and inflammatory effector mechanisms, allowing time for virus replication in epidermal cells.

Epidemiology

The naturally occurring disease is primarily one of sheep, goats, and human beings, but it has also been reported in a variety of wild ruminants. Experimental transmission has been achieved in cattle, rabbits, horses, and monkeys. No naturally occurring clinical cases in these species have been reported. All ages and classes of sheep and goats are affected, and clinically normal sheep can infect naive individuals.[10] In herds and flocks in which the disease is endemic, it usually is seen in the lamb or kid crop and on the udders and teats of some of the nursing mothers. Animals that have had a bout of disease are solidly immune for 1 to several years, but the rate of morbidity is high (often 80%) among naive individuals. Humans are infected through contact with affected animals or fomites that have contacted affected animals (including one report of transmission by a pickup truck that had been used to haul sheep).[8] Effective disinfectants include hypochlorite, alkalis, glutaraldehyde, and Virkon. Virkon is a multi-purpose disinfectant containing oxone and inorganic buffers and has a wide spectrum of activity against viruses.

Human-to-human transmission can occur. The mortalityrate among animals is low except when young individuals are severely affected and quit nursing or when mothers have severe udder lesions. Overwhelming infections are rare except in Boer or Boer crossbred goats, but some outbreaks are more severe than others.

The virus is quite resistant to many environmental conditions and persists from year to year on infected premises. Dried scabs allow the virus to persist for

years, but wet conditions are less hospitable to it. Reports of PI sheep in wet climates point to another possible source of infection.

Treatment, Prevention, and Control

The infection usually is self-limiting and of minor consequence. Young individuals may need to be tube-fed if the lesions are severe enough to preclude suckling. Secondary infections, myiasis, or mastitis may be treated with topical disinfectants, antibiotics, or insecticides as appropriate. The hard crusts should not be removed because removal may delay healing and promote scarring. Also, humans should limit contact with affected animals and should wear gloves when handling them as necessary. Anecdotal reports, each consisting of one case, have claimed good results for treatment of human orf with intralesional corticosteroids, IFN, idoxuridine in DMSO, diethyl ether, or cryotherapy. An immunosuppressed human with a huge orf lesion on the finger was successfully treated with topical cidofovir antiviral cream. Similar good results were obtained in a group of 12 severely affected, bottle-fed lambs with painful intraoral lesions. The proliferative tissues were débrided and cauterized with a portable diathermy unit. The exposed submucosa was then frozen twice with liquid nitrogen spray. Healing occurred by second intention, and the lambs recovered rapidly.

The infection is prevented by keeping a herd or flock virus free by not introducing or contacting infected animals or humans. Lesions often are not apparent on carriers.[10] Once established, the disease persists on the premises because of virus in scabs. Vaccination should be undertaken only if the infection is persistent, because the vaccine consists of virulent live virus. Vaccination can also be achieved with dried scabs from the previous year's outbreak because there are distinct antigenic differences among orf viruses[11]; the scab material is rubbed into scarified skin in an inconspicuous location (inner thigh, under the tail, in the axilla). A localized inflammatory reaction at the site 1 week after vaccination indicates that inoculation was successful. Infected or vaccinated animals should not be allowed contact with unexposed animals until the lesions have healed. Lambs born to immunized ewes may not be protected by colostral antibodies even though their levels of antibody after suckling are high[12]; this points to the importance of cell-mediated immunity in protection from the disease. Lambs should be vaccinated at 6 to 8 weeks of age and are immune 3 weeks later. Yearly vaccination of the new lamb or kid crop and of new additions to the herd with farm-specific strains of orf should prevent devastating outbreaks

on infected farms. At a minimum, it appears that goat isolates should be used for kids and sheep isolates for lambs.[11-13]

Bovine Papular Stomatitis (BPS, Proliferative Stomatitis)

Bradford P. Smith

Bovine papular stomatitis (BPS) is a worldwide disease principally of young cattle caused by a parapoxvirus closely related to those of CE and pseudocowpox. BPS, CE, and pseudocowpox have many similarities, and they may represent a single virus adapted to different species.[1] There are as many antigenic differences among strains of BPS as among CE and pseudocowpox.[1] Local strains therefore are recommended for vaccination. Infection usually is asymptomatic, and one study of cattle in Virginia demonstrated that 31 of 45 samples from asymptomatic cattle were virus-positive.[2] In the same study no asymptomatic deer, goats, or sheep were found to be positive for parapoxvirus, which suggests that cattle are the reservoir host. Lesions consisting of raised papules may be noted on the muzzle, nose, oral mucosa (particularly the hard palate), or esophagus; the differential diagnosis includes *Vaccinia* virus[3] (an Orthopoxvirus found in cattle only in South America), vesicular stomatitis, foot-and-mouth disease (FMD), and bovine viral diarrhea (BVD). In young feedlot cattle, 2- to 10-mm lesions of BPS are common for the first 4 weeks after arrival.[4] The rate of morbidity may approach 100%. BPS also occurs as a chronic disease in young cattle.[5] It may be the same disease as proliferative stomatitis, muzzle disease, mycotic stomatitis, erosive stomatitis, ulcerative stomatitis, and necrotic stomatitis. In addition to cattle, water buffalo and wild ruminants can be affected.

Ulcerative esophagitis caused by BPS virus in a 5-month-old, unthrifty calf was associated with a 20% morbidity rate in a group of 25 calves.[6] Outbreaks of severe disease associated with BPS with a mortality rate over 50% have been reported. Weight loss and diarrhea accompanied by papular lesions are commonly associated with the severe syndrome. Many lesions are erosions or shallow ulcers with elevated borders, whereas others are obvious raised papules. Lesions are found in the mouth, esophagus, and rumen. There are no lesions on the feet. BPS is commonly seen in calves 1 to 12 months of age and is rare in adult cattle, but outbreaks of confirmed BPS in Brazil and Japan involved the

teats of dairy cows as well as the hands of milkers.[7,8] A confirmed case of severe esophageal lesions in an adult bull that died after 2 months has also been reported.[9] The disease is spread by animal contact and appears to be worldwide in distribution.

The first evidence of the disease is the appearance of 2- to 4-mm hyperemic foci, most commonly in the ventral margins of the nares. Similar lesions next appear in the mouth. Within 18 hours they become raised papules. Some lesions enlarge to form raised plaques over 1 cm in diameter. Lesions regress in 1 day to 3 weeks, leaving a yellow, red, or brown spot that persists for several weeks more.[10] Secondary lesions come and go; some calves are visibly infected for 4 months.[10] Most affected animals have no fever or obvious clinical signs, and they continue to eat normally. Leukopenia was not seen in experimentally infected calves.[10] Secondary lesions appear to be spread through the blood; intravenous inoculation results in similar upper alimentary tract lesions.[11]

Histologic lesions consist of hydropic degeneration of the epithelial cells of the oral mucosa, hyperplasia of the papillae of the lamina propria, and eosinophilic inclusions in the cytoplasm of the degenerating epithelial cells. Lesions reaching the ulcerative stage show secondary necrosis, bacterial invasion, and sloughing of epithelium. These are described in detail in the Contagious Ecthyma (Sore Mouth, Orf, Contagious Pustular Dermatitis, Scabby Mouth) section.

BPS has been associated with the “rat tail” syndrome of feedlot cattle.[12] Of 84 Texas feedlots, 36 reported the problem, with a morbidity rate of 1% to 10%. The syndrome consists of diarrhea, excessive salivation, poor weight gain, and loss of hair from the end of the tail. Sarcocystosis has also been mentioned in association with “rat tail” syndrome.

BPS is capable of causing painful proliferative lesions in human beings.[1] The lesions resemble those caused by CE or pseudocowpox, so they are often described as parapox virus infection. Most often the affected individual has a recent history of examining the mouths of cattle, often with cuts or abrasions on the hands. Lesions in humans apparently are limited to the primary site of inoculation on the hands.

Although ovine ecthyma vaccines are commercially available, no vaccine is marketed for protection against BPS. Local strains of parapoxviruses would be most likely to be more protective than commercial vaccine strains.

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Bluetongue

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Definition and Etiology

Bluetongue is an arthropod-transmitted viral disease of domestic and wild ruminants.[1,2] Clinical disease is largely restricted to sheep and certain wildlife (notably white-tailed deer, mule deer, pronghorn, bighorn sheep, American bison), but other ruminants, including cattle, may show disease in some circumstances. Cattle are considered to be especially common reservoir hosts of bluetongue virus (BTV).

BTV occurs throughout tropical and temperate regions of the world, where different constellations of BTV serotypes are transmitted by different species of *Culicoides* midge vectors in relatively distinct global "episystems."[3,4] Whereas infection often occurs year-round in tropical climates, it is distinctly seasonal in temperate areas, occurring only in the late summer and fall months. Bluetongue is usually manifested only in the temperate areas at the upper and lower limits of the global range of the virus. The global distribution of BTV has altered, perhaps as a consequence of the effect of climate change on the *Culicoides* midges that serve as biological vectors of the virus.[5-7] In particular, since 1998 multiple BTV serotypes spread throughout the Mediterranean Basin and, in 2006, additional virus serotypes invaded and spread throughout extensive portions of northern Europe to precipitate an economically devastating epidemic.[8] Coincident with this invasion of multiple serotypes of BTV into Europe, at least 10 novel BTV serotypes have also appeared in the southeastern United States.[2,9] BTV infection of sheep was detected for the first time in Ontario in 2015, which represents farther northward expansion of the range of BTV in North America.[10]

Although BTV has been isolated from ruminants or *Culicoides* midge vectors, or both, from all continents except Antarctica, the international movement of ruminants is highly regulated, and often severely restricted, for fear of importing BTV into bluetongue-free countries or regions.[11] The continuing occurrence of disease outbreaks globally, the wide host range, the potential for establishment of endemic infection (as has occurred in extensive portions of Europe that previously were free of the virus), and the similarity of some clinical signs of bluetongue to those of vesicular diseases have all made BTV infection the subject of intense regulatory interest worldwide. Import regulations promulgated

in reaction to the disease have been more of a threat than the disease itself to the livestock industries of some countries.[12]

BTV is the prototype virus in the genus *Orbivirus* within the family Reoviridae.[13] Other closely related viruses in this genus include epizootic hemorrhagic disease of deer and African horse sickness viruses. The genome of BTV includes 10 distinct segments of double-stranded RNA, each of which encodes at least one protein. The serologic classification of BTV into serotypes is based largely on the protein product of just one genomic segment (the *L2* gene that encodes the VP2 outer capsid protein), but virulence and other characteristics of individual virus strains may not be related to this protein.[14] There is marked genetic variation among field strains of BTV, even viruses of the same serotype and from the same region.[15] The genetic diversity and heterogeneity of field strains of BTV arises as a consequence of both genetic shift and drift. Specifically, genetic shift occurs by reassortment of the individual viral gene segments during infections of cells with more than one virus serotype or strain. Individual genes also evolve by genetic drift during alternating replication in the insect and animal hosts of the virus.[16]

The genetic determinants of BTV virulence are uncertain. At least 30 BTV serotypes are recognized worldwide, but virus strains of the same serotype may have markedly different virulence even to highly susceptible ruminants.[1,2,11,17,18] For example, BTV serotype 8 (BTV-8) is present in the Caribbean Basin, where it has not been associated with major outbreaks of disease, whereas the strain of BTV-8 that appeared in northern Europe in 2006 was highly pathogenic and caused significant production loss and mortality in a variety of livestock species, including cattle.[3,8,17] Some serotypes of BTV (BTV-25 to BTV-27) infect small ruminants but can have properties quite different from those of the “traditional” serotypes (BTV-1 to BTV-24), notably the capacity for truly persistent infections of ruminants and for contact transmission [19-21]

■ Clinical Signs and Differential Diagnosis

Clinical bluetongue disease is manifested in two ways: (1) as reproductive syndromes and (2) as bluetongue per se, a systemic hemorrhagic viral fever that affects multiple organs but especially the upper gastrointestinal tract, skin, and lungs.[1,2,17] Sheep most commonly are affected, particularly European fine-wool breeds such as the merino and crossbreeds thereof. Bluetongue also occurs in cattle, goats, and South American camelids, but less commonly than in sheep

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and only after infection with especially virulent virus strains.

In susceptible sheep, the first clinical signs of bluetongue appear after an incubation period of 3 to 7 days or sometimes longer. These signs include a transient fever (up to 41.1° C [106° F] or higher); edema of the face, lips, muzzle, and ears; excessive salivation; and hyperemia of the oral mucosa (Fig. 32.90). Affected sheep usually have a profuse serous nasal discharge that becomes mucopurulent after a few days, leaving crusts around the nostrils and muzzle. The tongue may be cyanotic (hence the name), although this is a relatively infrequent manifestation. The oral lesions progress to petechial hemorrhages, erosions, and ulcers, which are especially prominent on the dental pad and the commissures of the mouth. The oral lesions can be sufficiently painful that affected animals will not eat, and severely affected sheep will stand over water without drinking. Lameness and stiffness caused by coronitis and myopathy can be severe, and the coronary band characteristically shows petechial hemorrhages and hyperemia. Hemorrhages also may be evident in the subcutis of nonhaired skin such as the inguinal region. Lameness may progress to “knee walking” or recumbency. The hooves may slough, and breaks in the wool are common. Diarrhea, with or without blood, can occur. Many sheep become depressed, are unable to rise, and die, but some severely affected sheep make a full recovery. Pulmonary edema is often marked, especially in fatal cases, and some cases appear to livestock owners to be pneumonia. In fact, acute secondary bacterial bronchopneumonia is often superimposed on the characteristic pulmonary edema of bluetongue. Sudden death, presumably as a consequence of mediator-driven hypovolemic shock or cardiac necrosis and failure, may occur at any time, even in an animal that appears to be recovering. Although the lesions and signs of bluetongue are somewhat characteristic, as is the seasonal occurrence of disease in temperate regions such as much of the United States, the differential diagnosis for sheep showing some of these signs includes sore mouth (contagious ecthyma), FMD, peste des petits ruminants (PPR), and sheeppox.



FIG. 32.90 Face of a sheep with severe bluetongue; note submandibular edema and hyperemia and cyanosis of the lips and tongue (bluetongue).

The reproductive and teratogenic effects of BTV in sheep and cattle vary, depending on the virus strain, the host, and other factors. Reproductive effects, including abortions, stillbirths, and weak but live "dummy lamb" births, were profoundly evident when live attenuated vaccine was administered to pregnant ewes in California in the 1950s.[22,23] In South Africa, where BTV infection has been recognized as endemic since the first descriptions of the disease before 1900, teratogenic effects have not been commonly linked to the virus despite the use of polyvalent live attenuated vaccines and nearly continuous exposure to the virus.[1] However, fetal infections were documented in cattle after these same vaccines were more recently introduced into Europe. Furthermore, it was unquestionably established that these vaccine viruses also circulated naturally after they were introduced into Italy.[24] With the notable exception of circulation of live attenuated vaccine viruses, abortion and teratogenic defects are uncommonly associated with natural BTV infection of livestock in endemic areas.[25] However, major outbreaks of abortion have occurred after the introduction of virulent BTV into immunologically naive populations of sheep.[26-28] Moreover, the strain of BTV-8 that was responsible for the 2006 epidemic in northern Europe crossed the placenta in a substantial proportion of pregnant ruminants, including cattle.[8,17] Some authors have questioned whether this remarkable property of this northern European strain of BTV-8 might imply that it was, at some time in its history, propagated in cell culture, as live attenuated vaccine viruses.

Clinical disease is uncommon among cattle infected with most BTV strains, particularly in BTV-endemic areas.[1,2,11] However, as evidenced emphatically by the 2006 BTV-8 epidemic in northern Europe, disease certainly can occur in BTV-infected cattle. Severely affected cattle exhibit many of the same signs as do affected sheep. Excessive salivation may be the first clinical sign. Hyperemia and necrosis of the muzzle ("burnt muzzle") and a patchy dermatitis may also occur, along with necrosis of the skin of the teats. In cattle, depending on which signs are exhibited, the differential diagnosis should include mucosal disease (BVD), malignant catarrhal fever (MCF), vesicular diseases, rinderpest, photosensitization, BPS, and infectious bovine rhinotracheitis. Clinical disease in cattle can also be difficult to distinguish from FMD and vesicular stomatitis, and appropriate regulatory officials should be notified in such outbreaks. Outbreaks in the United States, North Africa, and the Middle East confirm that the related epizootic hemorrhagic disease virus can also cause a bluetongue-like disease syndrome in cattle that also mimics FMD.[29]

Ocular lesions occur in some BTV-infected ruminants. The syndrome was well characterized during the 2006 BTV-8 epidemic in northern Europe when calves infected transplacentally in late gestation developed transient corneal opacity (blue-eye) after ingestion of colostrum that contained BTV-8–specific antibody.[30] Similarly, non-African ungulates such as European bison at the Berlin Zoological Gardens developed similar ocular lesions after BTV-8 infection.[31] "White eye calf" syndrome was described in Oregon in the 1970s and associated with BTV or epizootic hemorrhagic disease virus infection.[32] It may be that the lesions result from deposition of immune complexes in the eye, analogous to the immune complex–mediated uveitis that follows immunization of dogs with certain canine adenovirus vaccines.

Laboratory Diagnosis and Immunology

BTV infection in livestock is routinely diagnosed serologically by competitive ELISA that detects antibodies to the core VP7 protein of BTV. The test is highly sensitive and specific and detects antibodies to most if not all BTV serotypes. These antibodies persist for long periods after natural infection, although it is not currently possible to distinguish animals that were naturally infected from those that were immunized with live attenuated vaccine. The presence of antibody indicates only prior exposure to BTV and implies nothing about disease causality. Serotype-specific antibody is currently assessed only with laborious

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and expensive virus-serum neutralization assays.

Identification of BTV infection in animals is most readily accomplished with a group-specific quantitative PCR assay. Such assays are routinely available in diagnostic laboratories and can identify all known serotypes of BTV. Furthermore, the amount of viral nucleic acid can be quantitated, which can be useful in determining the cause of disease. Acutely affected animals generally have large amounts of BTV nucleic acid in their blood and tissues, which is reflected by low cycle threshold values on the assay. Because ruminants remain positive for BTV nucleic acid for up to 6 months or longer after infection, the detection of either viral nucleic acid by quantitative PCR or of antibody to BTV by competitive ELISA is not proof of disease causality. Serotype-specific PCR assays can be used to serotype the virus present. The availability of these assays has largely obviated the need for virus isolation, which is cumbersome, laborious, and expensive and typically takes several weeks. Virus isolation also requires specialized laboratory facilities because some virus strains require initial propagation in embryonated chicken eggs before they will grow in cell culture systems. Advances in sequencing technologies have facilitated the characterization of the full BTV genome. Full-length sequencing approaches have helped identify novel serotypes (BTV 25-30), as well as characterize the genetic diversity of the virus. In developing a growing database of full-genome BTV sequences has facilitated the design of conventional and real-time PCR assays. [33]

The development of immune tolerance to BTV (in utero infection that results in antibody-negative, virus-positive individuals), as recognized in BVD infections, now is regarded as unimportant in the natural epidemiology of BTV infection, although some controversy persists.[17] Fetuses infected with BTV in late gestation are born viremic (virus positive) and, potentially, before they have had the time necessary to develop an immune response. The fact that these animals are born viremic and antibody-negative should not erroneously be interpreted as immunologically tolerant. However, it has been shown that BTV-25 causes persistent infection in goats, although these animals do develop immune responses to the infecting virus that are detected by standard serologic assays. [20]

■ Pathophysiology

Bluetongue is proposed to be a hemorrhagic viral fever analogous to viral

hemorrhagic fevers of humans such as Ebola.[17,34] Specifically, BTV replicates within the endothelium and mononuclear phagocytic cells of infected animals. Vascular injury, particularly to small vessels, is responsible for the manifestations of clinical sigms. Release of cytokine and vasoactive mediators from infected cells leads to capillary leakage and, subsequently, the edema and hemorrhage that are characteristic of fulminant cases. Direct virus-induced vascular injury leads to thrombosis and subsequent infarction of tissues, causing ulcers and manifestations such as the characteristic cyanotic (infarcted) tongue in some severely affected sheep. Teratogenic effects result from direct virus-mediated destruction of proliferating progenitor cells within the central nervous system of the developing fetus after transplacental transmission of the virus in pregnant ruminants. Teratogenic defects occur only when the fetus is infected at critical stages of organogenesis, which is before midgestation (approximately 150 days in cattle and 70 days in sheep). Transplacental infection soon after conception can lead to early embryonic death and cause infertility.[23]

Epidemiology

The development of clinical bluetongue disease is the product of a complex interaction among host, virus strain, vector, and environmental influences.[1,2,11] For example, many of the virus strains that circulate in endemic areas such as California are mildly pathogenic for livestock in the region. Epizootics typically occur when a new virus strain or new animals are introduced into a previously stable ecosystem. For example, the 2006 epidemic in northern Europe was the result of the introduction of a highly virulent strain of BTV-8.[8] In addition to sheep, this virus caused serious disease in cattle, South American camelids, goats, non-African wild ungulates such as yaks and European bison, and even some carnivore species.[31] Environmental alterations that favor the proliferation of midge vectors in a region also promote disease epidemics.

BTV infects wild and domestic animals primarily through the bite of the vector midge of the genus *Culicoides.* There are more than 1400 *Culicoides* species globally; however, only a few have been identified as BTV-competent vectors.[1-3,5,6,11,35] In temperate regions of the world, *Culicoides* midges are abundant in midsummer to early fall, and outbreaks of bluetongue in livestock occur during this time when temperatures support both midge activity and BTV replication within the vector. Other routes of virus transmission are possible even during the interseasonal period in temperate regions (winter, spring, and early

summer). For example, it has been shown that BTV can be spread to newborn ruminants via the ingestion of infective colostrum.[36,37] Lastly, although BTV can be transmitted sexually in infected semen and transplacentally from dam to offspring, the importance of these potential routes of virus transmission remains conjectural; they are unlikely to have a major role.[17] Specifically, animals infected in early gestation develop teratogenic brain defects and have cleared infectious virus by the time of birth. Fetuses infected in late gestation can certainly be born viremic and potentially contribute to virus amplification and circulation. Embryo transfer currently is not viewed as a significant risk of BTV transmission if the embryo is washed at least 10 times. In summary, dissemination of BTV by vector *Culicoides* midges is by far the most common method of transmission in endemic areas; however, some serotypes of BTV (notably BTV-26 and BTV-27, and probably BTV-25) can be spread by direct contact transmission without requirement for the insect vector. [19]

In much of North America, the prevalence of bluetongue closely mirrors the distribution and abundance of *Culicoides sonorensis,* with lower rates in northern climates that are less hospitable to the midge and higher prevalence in California and other warmer southern regions.[3,4] However, the vector species in the southeastern United States, where 10 additional serotypes of BTV have appeared, are less defined. Similarly, vector species other than *C. sonorensis* are important elsewhere in the Americas as they are in different regions of the world. In the absence of competent vector populations, animal-to-animal transmission appears to be incapable of maintaining endemic BTV infection; thus BTV-8 disappeared quickly from most of northern Europe.

It remains uncertain as to how BTV is maintained (overwintered) in temperate areas where infection is highly seasonal.[2,11] Although viremia can be prolonged in both cattle and sheep, BTV infection is not persistent in domestic ruminants and insufficient to sustain the virus through the several months of the overwintering period (approximately December through June in the northern hemisphere). Infection of vector midges is persistent and lifelong; however, the life span of midges is relatively short, and so it is unlikely that infected individuals could survive the entire overwintering period. Studies in California have confirmed the presence of BTV-infected parous female *Culicoides* midges in midwinter without concurrent infection of adjacent sentinel cattle, which suggests that long-lived vectors infected in the prior seasonal period of transmission sustain BTV throughout the overwintering period in seasonally

endemic areas. [38,39]

The severity of clinical signs in BTV-infected sheep varies by breed. Early in the history of the bluetongue investigation, it was noted that African breeds showed few if any signs of infection, whereas imported European breeds showed fulminant disease. [1,2] More recently, breed differences in immunologic response and susceptibility to disease expression after vaccination with live attenuated BTV vaccine have been reported.[40]

Necropsy Findings

The lesions of bluetongue are characteristic, particularly in sheep.[1,17,41] These include ulcers and hemorrhage throughout the oral cavity, including the dental pad and tongue. These lesions may extend from the esophagus into the forestomachs. Coronitis and subcutaneous hemorrhages and edema, along with edema between the fascial planes of the neck and abdominal musculature, are also common. Other typical findings are pulmonary edema, hemorrhages on the endocardial and epicardial surface of the heart and pulmonary artery, and necrosis of both skeletal and cardiac muscle. Especially characteristic lesions include gelatinous edema around the nuchal ligament (in addition to the other sites previously listed), subintimal hemorrhages in the pulmonary artery, and discrete focal areas of acute myocardial necrosis in the papillary muscle of the left ventricle. Microscopic study reveals cuffing of inflammatory cells around small vessels in the affected skin and gastrointestinal mucosa with pronounced hypertrophy of the endothelium lining affected vessels, acute and focally extensive necrosis within the musculature of the heart and some skeletal muscles, and pulmonary edema.

Treatment, Prevention, and Control

Treatment of bluetongue in affected ruminants is nonspecific and aimed at supportive and nursing care. Animals with severe oral lesions are reluctant to eat or drink. Valuable animals can be fed gruels of alfalfa pellets by stomach tube and can be encouraged to eat soft feeds or green grass. Muscle and coronary band pain may limit mobility; therefore water and shade must be close at hand. Sulfa drugs or other relatively broad-spectrum antimicrobial drugs can be administered in an attempt to prevent or treat secondary bacterial pneumonia. Antiinflammatory medications that include but are not limited to NSAIDs, aspirin, and flunixin are commonly given.

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Elimination of *C. sonorensis* (or other midge vectors) from the environment is usually not practical, but housing sheep indoors during the peak of activity (dusk, early evening) to minimize exposure to biting midges may be beneficial with regard to some vectors. Grazing wet areas such as irrigated pasture only during the heat of the day also may help, as most insects are not active in extreme temperatures. Midges that feed on ivermectin-treated cattle die, but the exchange of virus may occur before the insect's demise. *C. sonorensis* larvae develop in fine-grained mud with high organic matter content, such as those around farm reservoirs, overflowing watering troughs, and shallow septic systems. Elimination of these breeding grounds along with with larvicidal treatments may help in some situations. Especially valuable animals can be housed in insect-proof enclosures to prevent any contact with vector midges during outbreaks, or they may be treated with repellants to minimize the likelihood of vector attack.

Both inactivated and modified live BTV vaccines are available in some parts of the world, and these logically should be based on the local strains and serotypes.[1,2,42,43] Inactivated vaccines are inherently safer than live attenuated ones because the latter have the potential for transmission in nature, reversion to virulence, and the capacity to cross the placenta. There is little cross-protection between BTV serotypes, so animals need to be vaccinated against all serotypes of the virus circulating in a given region. A live attenuated vaccine is available in some western states of the United States for immunization of sheep, but there currently are no vaccines to other endemic serotypes such as BTV-2, BTV-3, BTV-11, BTV-13, and BTV-17.[37] Live attenuated vaccines should be given at least 2 weeks before breeding season to avoid teratogenic effects, and vaccination should be done before the seasonal period of virus transmission (late summer and fall) to avoid infection of vectors and so minimize the likelihood of recombination of vaccine and field viruses. Ewes may be vaccinated late in pregnancy, but there is some risk of inducing abortion. Vaccine should not be administered in early or midgestation because of potential teratogenic defects. Vaccinated breeding rams may have some risk of transiently decreased fertility. Vaccinated and naturally infected animals cannot readily be distinguished by current serologic diagnostic tests. New-generation BTV vaccines have been developed, including recombinant vector vaccines, and virus-like particle vaccines. In addition to being very safe, these vaccines also have the potential to allow vaccinated animals to be distinguished from infected animals (so-called DIVA).[44]

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Diseases Caused by Bovine Viral Diarrhea Virus (BVDV)

Paul Walz

Definition and Etiology

Infections with bovine viral diarrhea virus (BVDV) are endemic worldwide, and BVD is recognized as one of the most important infectious diseases of cattle. Not simply confined to causing disease in cattle and the alimentary system as the name would imply, BVDV is a pathogen capable of infecting other ruminants and pigs and affecting multiple physiologic systems, including the reproductive, respiratory, circulatory, immunologic, integumentary, musculoskeletal, and central nervous systems.[1] Reproductive losses and respiratory tract disease are the most consequential economically, and infection of the reproductive system is critical for maintenance and transmission of BVDV within and among cattle populations through the generation of persistently infected (PI) offspring.[2] Infection of pregnant cattle before day 125 of gestation can result in the birth of calves that are immunotolerant to and PI with BVDV.[3] PI calves are the most significant reservoir of BVDV and are at risk for the sporadic, usually fatal mucosal disease.

BVDV is the prototypic member of the genus *Pestivirus* within the Family Flaviviridae. The pestiviruses are enveloped, single-stranded, positive-sense RNA viruses. Historically, the genus *Pestivirus* contained four recognized species that include the two genotypes of BVDV (BVDV-1 and BVDV-2), classical swine fever virus and border disease virus. Genetically distinct pestiviruses that had not been designated as unique species included giraffe virus, Bungowannah virus, pronghorn virus, and HoBi-like viruses. The genus *Pestivirus* has undergone a change in nomenclature by the International Committee on Taxonomy of Viruses, with new species designations of *Pestivirus* A through *Pestivirus* K. The designations *Pestivirus* A through *Pestivirus* D correspond to the classic four species, BVDV-1, BVDV-2, classical swine fever virus, and border disease virus, respectively; the designations *Pestivirus* E through *Pestivirus* K correspond to pronghorn antelope pestivirus (E), Bungowannah virus (F), giraffe pestivirus (G), HoBi-like pestivirus (H), Aydin-like pestivirus (I), rat pestivirus (J), and atypical porcine pestivirus (K).[4] A part

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of the logic for this new classification scheme is the knowledge that not all BVDV strains are host restricted to cattle.

As in many RNA viruses, mutations can occur within BVDV genomes and lead to genetic, antigenic, and pathogenic variation. BVDV exists as quasi-species, which are different but closely related mutant viral genomes subjected to continuous competition and selection. Nucleotide sequence differences are the most reliable criteria for differentiation of BVDV species. Subgenotypes of BVDV are described within BVDV-1 and BVDV-2 species: 21 among BVDV-1 viruses (1a to 1u) and 4 among BVDV-2 viruses (2a to 2d).[5] Within the North American cattle population, there are three major subtypes, BVDV-1a, BVDV-1b, and BVDV-2a; the BVDV-1b subtype predominates in diagnostic laboratory submissions and prevalence studies of persistent infection.[6] Predominance of the BVDV-1b strains in North America is noteworthy because most vaccines licensed and marketed in the United States contain BVDV-1a and BVDV-2 strains.[7] Strains of BVDV can be also be further subdivided into cytopathic (CP) or noncytopathic (NCP) biotypes on the basis of their effect on cultured cells: CP strains cause vacuolation and death of cultured cells. The effect of the virus in cultured cells is not correlated with virulence, inasmuch as NCP BVDV are associated with cases of severe clinical disease, and only NCP strains of BVDV have been demonstrated, both naturally and experimentally, to induce persistent infection.[8] The NCP biotype predominates in the cattle population, accounting for approximately 65% to 90% of BVDV isolates.[9] The NCP biotype is often the source of CP strains, which arise by mutations and recombination in the NCP strain.

Epidemiology

Prevalence.

BVDV is distributed in cattle populations throughout the world as indicated be serologic surveys that test for the presence of neutralizing antibodies to the virus. Exposure to PI animals or vaccination against BVDV can cause seropositivity in an animal within a population. Prevalence of seropositive cattle varies among countries, with differences in seroprevalence rates largely dependent on management of cattle populations examined. Use of vaccines, open versus closed cattle production units, population densities, indoor versus pasture housing, communal grazing, and presence of PI animals greatly influence the

numbers of seropositive cattle. Surveys in North America have indicated high seropositive rates in cattle, approaching 90%.[10] In contrast, the number of PI cattle is much lower and is generally believed to account for fewer than 1% of all cattle. In randomly selected beef herds in five U.S. states, the prevalence rates of BVDV persistent infection in individual animals and in herds were 0.17% and 2.7%, respectively.[11] Other persistent infection prevalence studies in beef cow-calf operations within more geographically focused areas in the United States have demonstrated rates between 0.09% and 1.7%, respectively[12,13]; however, not all studies performed have involved randomly selected herds, which can affect prevalence rates considerably. Surveys conducted on United States dairy operations have demonstrated individual animal prevalence rates of 1.9%[14] and 0.13%.[15] PI cattle can be found in clusters within groups of cattle as a result of BVDV exposure in cows at similar times in pregnancy, and this can elevate the prevalence within a studied population. Although it is generally believed PI calves have poor survivability, they can survive to adulthood, become pregnant, and give birth to PI offspring. Of PI calves identified from randomly selected beef herds, 61% survived to weaning and thus were capable of providing a source of virus throughout the breeding season and early gestation.[11] The numbers of PI calves arriving at United States feedlots represent a prevalence rate between 0.1 and 0.4%.[16,17]

Host Range.

Cattle are considered the natural host of BVDV; however, BVDV is not strictly specific about hosts.[18] Historically, pestiviruses were assigned according to the species from which they were isolated; BVDV, classical swine fever virus, and border disease virus isolates were recovered from cattle, pigs, and sheep, respectively. Through serologic evidence, BVDV infections have been identified in more than 50 species within 7 of the 10 families of the mammalian order Artiodactyla. Species other than cattle that have been reported to be susceptible to BVDV infection include pigs, sheep, goats, bison, captive and wild cervids, and Old World and New World camelids.[18] Of the heterologous hosts, sheep and goats are considered to have high potential for BVDV infections because they are phylogenetically most closely related to cattle, and sheep and goats can have close contact with cattle under certain management conditions such as subsistence agriculture and hobby farming. Alpacas and white-tailed deer have received attention as heterologous hosts for BVDV infections because of the

identification of PI animals. PI alpacas can survive for several months, but low birth weights, failure to thrive, and chronic respiratory and gastrointestinal infections are described in such animals.[19] The BVDV-1b strain is most frequently isolated from PI alpacas and could be the result of introduction and intraspecific spread and maintenance of BVDV1b into North American alpaca populations; an alternative explanation is that unique BVDV1b subgenotypes are able to establish transplacental infections in alpacas.[20]

Infection of wildlife with BVDV has been demonstrated by several serosurveys and, less frequently, virus identification in individual animals. The livestock-wildlife interface is of great concern for a number of infectious diseases, including the related classical swine fever virus in wild boars. Wildlife may become infected with BVDV, but other factors, including shedding of the virus, intrapopulation maintenance, and amount of interspecific contact may influence the establishment of BVDV wildlife reservoirs. Persistent infections of white-tailed deer with BVDV have been demonstrated both by experimental and natural exposure.[21] As in cattle, the most dramatic effects of BVDV infections in white-tailed deer involve the reproductive system. Shedding of BVDV through nasal or rectal routes has been demonstrated in acutely infected and PI white-tailed deer, and shedding has resulted in transmission to other white-tailed deer.[22,23] Apparent prevalence rates of persistent infections in United States cervid populations were between 0.03 and 0.3% in tested populations.[24-26] Whether BVDV infection in these populations originated from contact with cattle or was the result of an endemic cycle is unknown.

Identification of heterologous PI hosts may have important implications for the epidemiologic behavior of BVDV; of most importance is that nonbovid PI animals may serve as reservoirs for BVDV. As reservoirs, nonbovid PI animals could threaten the health and well-being of other artiodactyls, including cattle, and adversely affect outcomes and ultimate success of organized BVDV control and eradication efforts.[27]

Transmission.

Methods of BVDV transmission can be classified as vertical and horizontal. With BVDV, horizontal and vertical transmissions are closely related, as horizontal transmission to a pregnant cow can result in vertical transmission to the developing fetus (Fig. 32.91). As stated previously, PI cattle can reach adulthood. Calves delivered from PI dams are themselves PI; however, the status

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of most PI offspring is the result of an acute infection, or horizontal transmission, in the dam.[11] BVDV can be horizontally transmitted continuously by PI animals and briefly by animals during an acute infection. As with other viral diseases, factors controlling BVDV transmission in a susceptible population are the infectiousness of the virus, the contact rate between infectious and susceptible animals, the duration of infectiousness, and the proportion of the population that is naive and susceptible.[28] Cattle PI with BVDV shed large amounts of virus their entire life and are the major source of BVDV transmission both within and among herds. They are capable of shedding virus from nasal secretions, urine, feces, milk and colostrum, uterine fluids, saliva, tears, and semen.[29] Direct contact with these body fluids from PI cattle is the most efficient method of horizontal BVDV transmission, inhalation and ingestion being the most common routes. Although heterologous PI hosts are capable of BVDV in nasal secretions in amounts equivalent to those shed by PI cattle,[21] they are assumed to play a reduced role in BVDV transmission because rates of contact rates between infectious heterologous hosts and susceptible cattle are lower.

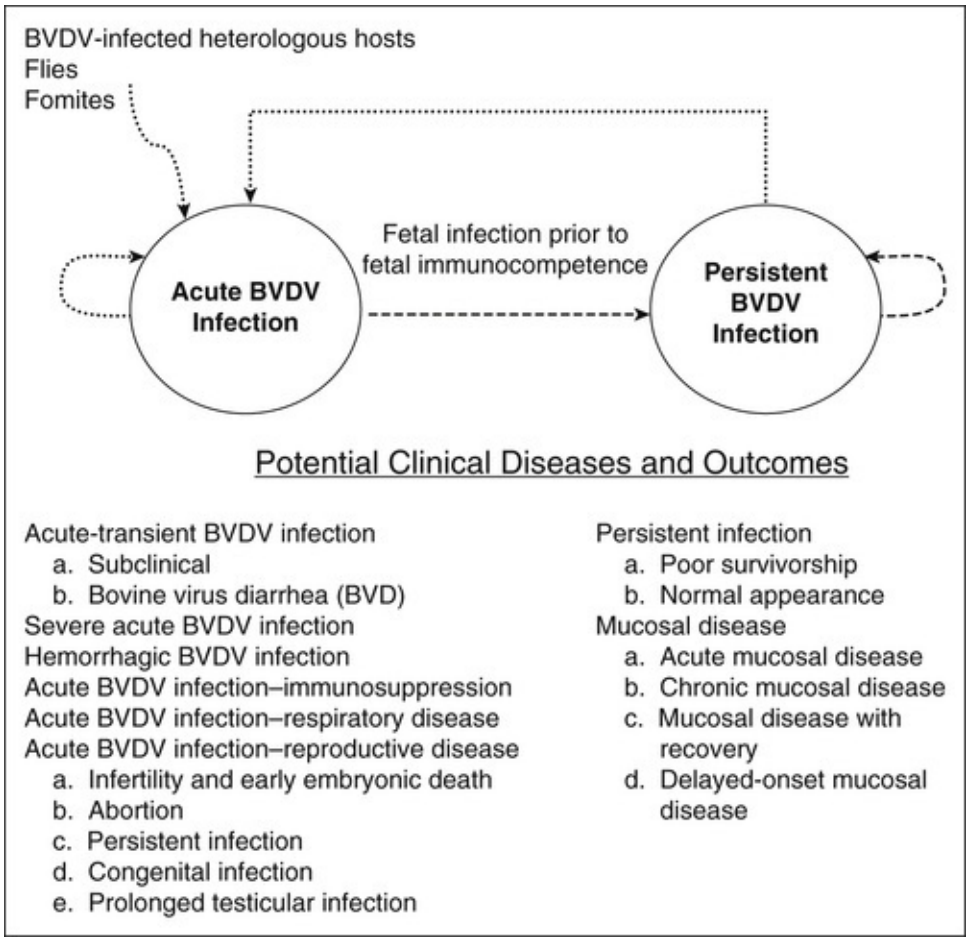


FIG. 32.91 Two forms of bovine virus diarrhea virus (BVDV) infection: acute and persistent. Routes of horizontal transmission are indicated by *dotted lines* (most consequential is from persistently infected [PI] cattle to naive cattle); routes of vertical transmission are indicated by *dashed lines* (most consequential is acute BVDV infection in pregnant cattle). Potential clinical diseases are not exclusive, and multiple clinical forms can be observed in the same population of cattle.

Acutely infected cattle also have a limited role in BVDV transmission because levels and duration of virus shed are considerably lower; however, potential for transmission of BVDV after acute infection can be greatly influenced by the virulence of the acutely infecting strain of BVDV, the proportion of naive animals being exposed, and the immune cross-protection acquired through either vaccination or exposure to field strains of virus. Calves acutely infected with a highly virulent strain of BVDV shed greater amounts of virus and for a longer duration,[30] and so they theoretically are a source of transmission. However, an experimental study demonstrated no spread of infection from acutely infected to susceptible animals even though they were in close contact, which further

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emphasizes the importance of virus and host characteristics during transmission.[31] After acute BVDV infection, virus can be found in nasal secretions usually for only a few days between 4 and 10 days after exposure.

Although contact with PI cattle is the most widespread cause of BVDV transmission, infections with BVDV in the absence of PI cattle have been described in seronegative herds.[32] Spread of BVDV can occur in the absence of PI cattle as a result of direct contact with acutely infected animals, contact with heterologous hosts, or indirect contact. Because BVDV is an enveloped virus, it is unstable at low or high pH and at high temperatures but can survive in a cool, protected environment for several weeks.[29] Temperature has a major influence on BVDV survival in manure slurry: The virus can remain infective for more than 6 weeks at 5° C but less than 2 weeks at 20° C.[33] According to research with the related classical swine fever virus, BVDV is probably susceptible to common disinfectants such as chlorhexidine, phenols, iodophors, aldehydes, and hypochlorites.[34] Indirect transmission through contaminated needles and equipment and through insect vectors has been demonstrated experimentally.[35,36] Insects such as stable flies, horse flies, and face flies can serve as potential sources of BVDV infection[35,37]; however, the horn fly, a common fly species affecting cattle, cannnot transmit BVDV between PI cattle and BVDV-naive cattle.[38]

Bulls acutely infected and PI with BVDV are capable of shedding virus in semen and have the potential for horizontal and vertical transmission.[39-41] The virus may survive cryopreservation and processing of semen for artificial insemination.[42] Although acutely infected bulls shed lower concentrations of BVDV in semen than do PI bulls, infection of artificially inseminated heifers may result from the use of semen from acutely infected bulls before seroconversion.[40] Prolonged, localized testicular infections have also been described after experimental BVDV infection of postpubertal bulls; however, their prevalence and epidemiologic significance are probably low.[43]

Herd-to herd transmission usually occurs through acquisition of PI cattle or pregnant cattle that are carrying PI fetuses. Introduction of pregnant adult females carrying PI fetuses, aptly named “Trojan dams,” have been recognized as an important source of infection transmission to BVDV-free herds.[44] Cattle operations that have purchased cattle within the past 5 years are at highest risk for having PI animals.[45] Purchase of new cattle incubating an acute infection or

exposure to other cattle through fence line contact, communal pastures, and animal exhibitions can also enable BVDV introduction into a herd.

Clinical Signs and Differential Diagnoses

BVDV infection in cattle may result in a complex spectrum of clinical manifestations ranging from subclinical to fatal disease. The virus is capable of infecting multiple organ systems, often concurrently. Clinical manifestations are dependent on the interplay of host factors, environmental stress levels, and viral factors.[46] Host factors influencing the outcome of viral infection include immune status, pregnancy status, gestational age of the fetus at the time of infection, and whether the host is immunotolerant or immunocompetent. Viral factors include biotypic variation, genotypic variation, and antigenic diversity. With regard to the clinical manifestations of BVDV infection in cattle, both BVDV-1 and BVDV-2 strains can be involved in the entire spectrum of clinical disease, including acute and persistent infections. Two states of infection (acute and persistent) are possible with BVDV infections in ruminants, and this is the basis for discussion of clinical signs and pathogenesis within this text (see Fig. 32.91).

Disease Associated With Acute BVDV Infection

The terms *acute, primary,* and *transient* have all been used to describe BVDV infection in postnatal cattle. Although postnatal cattle are able to respond immunologically to BVDV, immunosuppression induced the by virus is an important contribution to pathogenesis and clinical disease. For discussion of clinical disease states, acute BVDV infections can be further subdivided into six disease categories: acute-transient BVDV infection, severe acute BVDV infection, hemorrhagic BVDV infection, acute BVDV infection/immunosuppression, acute BVDV infection/respiratory disease, and acute BVDV infection/reproductive disease.

Acute-Transient BVDV Infection.

Acute-transient BVDV infection occurs in postnatal cattle. In most situations, the disease occurs in cattle considered BVDV naive, but disease could potentially occur in cattle seropositive for BVDV that become infected with a heterologous BVDV strain. Most acute BVDV infections occur without clinical manifestations; up to 90% of BVDV infections are estimated to occur without clinical signs.[46] If cattle are observed closely, however, mild fever, leukopenia,

and a decrease in milk production can be observed. Exposed cattle develop BVDV-specific neutralizing antibodies. If a pregnant animal has even subclinical BVDV infection, deleterious effects can be manifested in the fetus.

Bovine viral diarrhea is the term used to describe the clinical form of BVDV infection in immunocompetent cattle, and digestive tract disease manifested by severe diarrhea was part of the original description of BVD in 1946.[47] The incubation period for acute BVDV in naive cattle is 5 to 7 days. After oronasal uptake, BVDV initially replicates in nasal mucosa and tonsils. Viremia typically lasts for several days starting around day 3 after infection, but it can last for up to 15 days. During this period of viremia, spleen, thymus, lymph nodes, gastrointestinal epithelium, and the respiratory tract can become sites of further viral replication. Clinical signs of BVD include depression, oculonasal discharge, anorexia, fever, oral erosions and ulcerations, diarrhea, and, in lactating cows, decreased milk production. The respiratory rate may be rapid, which may be interpreted incorrectly as pneumonia. Clinical pathologic changes such as leukopenia are observed in calves acutely infected with BVDV.[46] The major decreases in the total leukocyte count have been in the numbers of neutrophils and lymphocytes.

One of the most important determinants for the outcome of acute BVDV infection in susceptible animals is the virulence of the infecting BVDV strain.[48] Experimental infections with BVDV strains of low and high virulence reveal similar initial infection and patterns of dissemination through the body but differences in the amount of virus in tissues and in speed of dissemination.[49] Virulent strains of BVDV result in widespread distribution of virus in tissues, and BVDV strains that induce high levels of viremia result in more severe clinical signs. Viral replication and antigen distribution can be detected in the thymus, lymph nodes, Peyer's patches, tonsils, and spleen with all strains of BVDV. In contrast to strains of BVDV with low virulence, in which antigen is found only outside of lymphoid tissues in the intestinal mucosa, antigen against high virulent strains can be found in bone marrow, intestinal mucosa, respiratory tract, endocrine tissues, and nervous system tissues after acute infection.[49] The HoBi-like viruses have received considerable attention because of their emergence and detection in South America, Europe, and Southeast Asia, and natural descriptions and experimental reproductions of infection with HoBi-like viruses have revealed very mild disease signs in cattle. Most description of HoBi-like virus infection in natural settings are related to either respiratory

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disease or reproductive disease, specifically abortion. During experimental reproduction of the disease, clinical signs associated with HoBi-like virus infection can be indistinguishable from those of BVDV infection with strains of low virulence.[50]

Disease associated with acute BVDV infection is often observed in seronegative cattle between the ages of 6 to 24 months. It is generally believed that maternally derived BVDV-specific antibodies have waned and acquired immunity is not yet formed, and thus calves as young as 4 to 6 months of age are susceptible. Maternally derived BVDV-specific colostral antibodies are thought to be protective unless sufficient antigenic diversity exists between the challenge strain and strain against which the maternally derived colostral antibodies were developed. Disease as a result of acute infection can be observed in preweaned calves.[51] Acute disease in neonatal or preweaned calves can result in signs of pneumonia or enteritis, often in association with failure of passive transfer. In studies of the duration of maternal colostrum-derived antibodies against BVDV-1 and BVDV-2, a major finding is the variability in duration between calves as a result of colostrum quality and consumption. Estimated mean time to reach seronegative status in dairy calves receiving maternal colostrum was 117.7 ± 37.7 days for BVDV-1 and 93.9 ± 61.9 days for BVDV-2.[52] In another study, the mean duration for colostrum-derived antibodies in beef calves was 185.6 ± 59.8 days for BVDV-1 and 157.8 ± 56.1 days for BVDV-2.[53]

Diarrheal diseases considered in the differential diagnosis for acute BVDV infection in adults include salmonellosis, winter dysentery, paratuberculosis, intestinal parasites, MCF, arsenic poisoning, and copper deficiency (molybdenosis). The differential diagnoses for acute BVDV infection for the neonatal period includes other causes of diarrhea in young calves, such as rotavirus or coronavirus infection, cryptosporidiosis, enterotoxigenic *E. coli* infection, salmonellosis, and coccidiosis. Other causes of calf pneumonia such as bovine respiratory syncytial virus, pasteurellosis, hemophilosis, or mycoplasma infection should also be considered.

Severe Acute BVDV Infection.

An atypical and significantly more severe form of BVDV infection was first described in cattle in the late 1980s.[54] The disease had a peracute course, caused morbidity in high rates, and resulted in substantial numbers of deaths in all age groups. In Quebec, mortality due to BVDV in veal operations was estimated at

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25% of 143,000 calves for 1993.[55] The outbreak in Ontario involved 150 dairy, 600 beef, and 100 veal herds. The severity of disease varied among herds; in some herds, mortality rates were 10 to 20% in all age groups of cattle. Clinical manifestations of severe, acute BVDV infections include diarrhea, pyrexia, decreased milk production, and, frequently in older cattle, oral ulcerations. Because of the presence of severe clinical disease in combination with oral ulcerations, mucosal disease was a primary part of the differential diagnosis in the late 1980s and early 1990s. Other diseases that cause oral lesions in cattle include MCF, vesicular stomatitis, papular stomatitis, FMD, and bluetongue. Abortions in cattle also were common. These outbreaks of severe clinical disease were reported to be associated with the introduction of cattle to the herd or history of inadequate vaccination programs.[54] BVDV isolates from outbreaks in Canada and the United States were analyzed, and NCP isolates were obtained from affected cattle. Nucleotide sequencing of the RNA genome of these isolates revealed a distinct group of BVDV, which were designated as BVDV-2,[56] which is now considered a separate species within the genus *Pestivirus*.

The outbreaks of severe BVDV infections clearly demonstrated that some BVDV strains can cause severe life-threatening disease in postnatal, immunocompetent cattle. Before 1993, it was believed that the majority of BVDV infections in immunocompetent, adult cattle resulted in subclinical or mild disease. Although BVDV-2 strains were associated with severe acute BVDV infections, not all BVDV-2 strains cause severe disease. Furthermore, it is likely that some BVDV-1 strains are capable of inducing severe clinical disease under unfortunate conditions involving host, agent, and environment factors.

Hemorrhagic BVDV Infection.

The hemorrhagic syndrome, which is characterized by thrombocytopenia, is an additional form of severe acute BVDV infection in immunocompetent cattle.[57] Hemorrhagic syndrome was first described in both calves and adult cattle naturally infected with BVDV; severe depressions in platelet counts and high case fatality rates were reported.[58] Clinical manifestations of the hemorrhagic syndrome are related primarily to thrombocytopenia and include bloody diarrhea, epistaxis, petechial hemorrhages, ecchymotic hemorrhages, hyphema, and bleeding from injection sites or insect bites. Fever, diarrhea, rumen stasis, and dehydration are also common. In addition to thrombocytopenia, leukopenia

characterized by severe neutropenia and lymphopenia are clinical pathologic abnormalities. Thrombocytopenic BVDV infections have been experimentally reproduced, almost exclusively with NCP BVDV-2 strains[57,59]; however, hemorrhagic syndrome has been reported after experimental inoculation of colostrum-deprived calves with a BVDV-1b strain.[60] Platelet dysfunction has also been described with experimental BVDV infection[61]; thus quantitative and qualitative platelet defects contribute to the hemorrhagic diathesis observed in infected cattle. Bone marrow infection, specifically BVDV infection in bone marrow megakaryocytes, may be important in the origin of BVDV-induced thrombocytopenia.[30,62] Diseases that can mimic hemorrhagic syndrome include septicemia with subsequent development of disseminated intravascular coagulation, sweet clover poisoning, and bracken fern poisoning.

Acute BVDV Infection/Immunosuppression.

Although the majority of BVDV infections in immunocompetent cattle are transient and self-limiting, it is apparent that when infection occurs in the presence of other microorganisms, BVDV can contribute to disease that becomes clinically evident. Numerous studies, under both natural and experimental conditions, have demonstrated the relationships between BVDV and other infectious agents. The virus has been reported to enhance the pathogenicity of bovine herpesvirus-1 (BoHV-1), actinomycosis, papular stomatitis, enteritis caused by *Salmonella* spp., colibacillosis, metritis, and mastitis. The role of BVDV in synergistic or mixed infections with other agents is probably to cause immunosuppression.[63] Mechanisms responsible for BVDV-induced immunosuppression are probably multifactorial; however, critical information on mechanisms of the suppression, the duration and extent of recovery, and the long-term effects are undetermined.[27] The ability of BVDV to induce quantitative and qualitative defects in leukocytes could provide some contribution to immunosuppression.

The defects involve immune system cells of both the innate and adaptive immune responses. A transient leukopenia occurs in most cattle acutely infected with BVDV that may be more severe with BVDV-2 than with BVDV-1. Decreases in helper ($CD4^+$), cytotoxic ($CD8^+$), and gamma/delta T-lymphocytes, as well as B-lymphocytes and neutrophils, have been reported and these decreases are often strain dependent.[64] The mechanism of leukopenia has been explained in several possible ways; these include immune system removal of

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BVDV-infected immune cells, destruction of immune cells by BVDV, and increased trafficking of immune cells into tissue sites of viral replication. During acute infection, various levels of lymphoid depletion are observed in the thymus, spleen, lymph nodes, and gut-associated lymphoid tissues (Peyer's patches).[65] The NCP BVDV strains are lymphotrophic, and lymphocyte apoptosis in lymphoid tissues results in cytolysis and lymphoid depletion.

Decreased functional responses in immune system cells have also been described during acute BVDV infection, and affected cells include lymphocytes, neutrophils, monocytes, and macrophages.[66,67] Dysfunction in both B and T cells has been demonstrated by poor culture response to phytohemagglutinin, pokeweed mitogen, and concanavalin A stimulation and by decreased production of interferon.[68] Infection of peripheral monocytes in vitro caused a significant decrease in the chemotactic responses to lymphokine.[69] Immunohistochemical and flow-cytometric studies have demonstrated that BVDV infects and replicates in antigen-presenting cells.[70] Infection of monocytes with BVDV has been shown to stimulate the synthesis of cytokines that may reduce their ability to stimulate T cell responses to specific antigens and mitogens. A decrease in the secretion of TNF-α from LPS- or *Salmonella*-stimulated bone marrow–derived macrophages that had been infected with BVDV has been reported.[71] These abnormalities, in combination with environmental or management stressors, or both, contributes to immunosuppression and concurrent infection with other pathogens. Increased susceptibility to other secondary infections is a consequence of BVDV-induced immunosuppression.

Acute BVDV Infection/Respiratory Disease.

Substantial data demonstrate that BVDV infection plays an important role in polymicrobial disease, and the bovine respiratory disease complex in feedlot animals and intensively housed calves is the best example of this type of disease process. In North American feedyards, bovine respiratory disease is the most frequently reported cause of morbidity and mortality. The role of BVDV in the bovine respiratory disease complex is debatable as to whether BVDV-induced immunosuppression or primary infection of the respiratory tract plays the major role, but BVDV can be isolated from pneumonic cattle more frequently than other viruses.[72] Certain BVDV strains may be pneumotrophic, as evidenced by some BVDV strains that cause interstitial pneumonia in experimentally inoculated calves.[73]

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BVDV may play a secondary role in bovine respiratory disease complex through immunosuppression. Although BVDV is frequently isolated from cattle with pneumonia, it is often isolated with the other infectious agents typically associated with bovine respiratory disease complex. Reports from disease outbreaks and experimental studies have supported a synergistic role of BVDV with BoHV-1 and bovine respiratory syncytial virus.[74,75] Calves experimentally inoculated with BVDV 7 days before inoculation with BoHV-1 developed more severe clinical disease, with dissemination of BoHV-1 into nonrespiratory tissues such as intestinal and ocular tissues, than did calves inoculated with BoHV-1 alone.[74] Initial BVDV infection may impair the ability of calves to clear BoHV-1 from the lungs and to contain BoHV-1 at the local infection site. Synergism between BVDV and bacterial pathogens, specifically *Mannheimia haemolytica* and *Mycoplasma bovis*, has also been described.[76,77] Viral-bacterial synergy in bovine respiratory disease complex probably is the result of BVDV compromise of the host defense mechanisms. Viral damage of nasal turbinate and tracheal epithelium alters mucociliary clearance of bacteria with subsequent bacterial attachment and colonization. The innate defenses of the lung are compromised with BVDV infections of macrophages and neutrophils, which results in depletion, destruction, or impairment in function. B and T cell–mediated immune responses can also be suppressed as a result of BVDV infection.[63]

Acute BVDV Infection/Reproductive Disease.

Reproductive tract infections have been described for male and female cattle. The importance of BVDV on the male reproductive tract has not received attention equivalent to the effects on female reproduction for a number of reasons, but from a transmission standpoint, acutely infected bulls and PI bulls are capable of shedding virus in semen.[39] Either acceptable or unacceptable semen quality may be observed in bulls acutely infected with BVDV. Although acute BVDV infections generally result in a transient viremia with subsequent clearance of the virus by the host immune system, a localized, prolonged infection of testicular tissue with NCP BVDV has been described in both natural and experimental conditions.[39,41] The original description of prolonged testicular infection with BVDV was identified in the testes of a seropositive, nonviremic bull at an artificial insemination center.[41] Despite absence of viremia, the bull continuously shed infectious BVDV in semen throughout his life, and the semen of this bull resulted in infection and subsequent seroconversion of an

inseminated seronegative heifer.[78] Furthermore, this bull displayed a consistently high concentration of circulating serum antibodies that neutralized the specific viral strain that was persistently shed in the semen. Since that original description, prolonged testicular infections with BVDV have been reproduced in post-pubertal bulls. Viral RNA has been detected in semen for 2.75 years after BVDV exposure, and infectious virus grown from testicular tissue has been detected up to 12.5 months after BVDV exposure.[39] Protection from a systemic immune response due to a blood-testes barrier is believed to be the mechanism for the localized, prolonged testicular infection.

Infection with BVDV can cause significant reproductive problems in nonimmune pregnant cattle, including fertilization failure, embryonic death, abortion, persistent infection, and congenital defects (Fig. 32.92). Transplacental infection is a common event in pregnant cattle exposed to BVDV, and in experimental studies, transplacental infection occurs with almost 100% efficiency.[79] As discussed previously, most acute BVDV infections are subclinical, but infection in pregnant cattle may result in significant disease. The economic damage caused by BVDV in susceptible herds is associated mainly with the outcomes of intrauterine infections. The outcome of fetal infection with BVDV is dependent on three main factors: (1) time of infection (i.e., gestational age of the fetus at the time of infection); (2) organ system involved in the infection; and (3) properties of the virus (i.e., biotype, virulence, and target cell range). Of importance is that BVDV-1 and BVDV-2, as well as CP and NCP strains, can result in reproductive disease, although only NCP strains are capable of resulting in PI cattle.

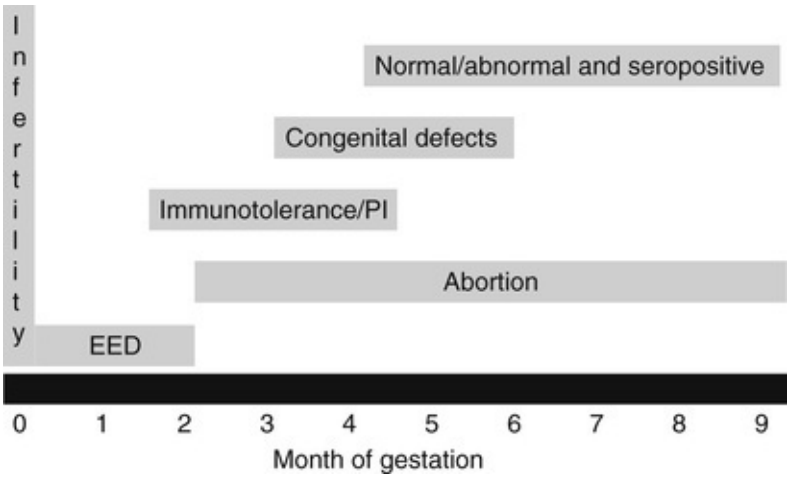


FIG. 32.92 Potential reproductive outcome after infection with bovine virus diarrhea virus during different stages of gestation. *EED,* early embryonic death; *PI,* persistent infection.

Infertility and Early Embryonic Death.

Infection of cattle before insemination can result in impaired conception rates.[80] This may be due in part to ovarian infection and dysfunction as a result of BVDV viremia. Viral antigen in macrophage-like cells and ovarian stromal cells and oophoritis have been described in cattle acutely infected with NCP BVDV[81] and in cattle vaccine with modified live-virus vaccines containing CP BVDV.[82] Of particular interest is that pathologic change and BVDV antigen were detected in some cattle up to 60 days after infection.[83] The first 45 days of gestation are the embryonic period, and conception and pregnancy rates are lower if cattle are exposed at the time of insemination and become viremic during the first 3 weeks of pregnancy.

Abortion.

BVDV infection can cause abortion at any time during gestation. Fetal resorption, mummification, or expulsion can occur after fetal death, depending on the gestational age of the fetus at the time of infection.[84] Although fetal death and abortion are most common during the first trimester, material from middle- and late-term abortions and stillbirths should be examined for BVDV. Diagnostic laboratory surveys indicate that BVDV isolation prevalence from aborted animal fetuses in the United States is quite variable; BVDV has been isolated in as few as 0.1% and as many as 27.2% of submitted fetuses.[85,86] After BVDV infection, expulsion of the fetus may occur shortly or may be delayed for several months after infection. As a result of delayed expulsion after fetal death, isolation of BVDV from aborted fetuses may not be successful. This has also been demonstrated experimentally, whereby abortion was observed 30 to 50 days after experimental infection at approximately days 100 to 120 of gestation.[87]

Persistent Infection in Offspring.

Gestational days 45 to 125 are the period of fetal development during which fetal immunocompetence for BVDV develops. The most outstanding outcome of infection during this period is the development of persistent infection. Immunocompetence for BVDV is not absolute at day 125 of gestation, and the

dams of most PI calves were exposed before gestational day 100. By definition, cattle that are PI with BVDV are immunotolerant to BVDV. Biotype plays an important role in infection during this period of gestation. Abortion can occur with infection with both CP and NCP strains of BVDV; however, only NCP strains are capable of causing persistent infection.[8] The PI animal's body cannot recognize the infecting NCP BVDV as foreign. Immunotolerance is specific to the infecting NCP strain of BVDV, and after birth, PI animals can respond immunologically to heterologous strains of BVDV. For this reason, PI animals may be seropositive for BVDV, and seropositive status cannot be utilized diagnostically to rule out persistent infection.

Congenital Defects.

Congenital malformations are associated with BVDV infection during the gestational period of organogenesis, which occurs approximately between days 100 and 150 of gestation.[79] Congenital malformations that have been reported in association with BVDV infection include cerebellar hypoplasia, hypomyelinogenesis, hydranencephaly, alopecia, cataracts, optic neuritis, brachygnathism, hydrocephalus, microencephaly, thymic aplasia, hypotrichosis, pulmonary hypoplasia, and growth retardation. Congenital malformations may be due to the direct result of viral infection on developing cells, or the host immune response in destroying virally infected cells. During a point-source of exposure of BVDV into a bred population of cattle, congenitally malformed calves will be born just before the birth of PI animals, and this information can be useful for determining sampling of calves for BVDV.

BVDV Infection During Later Stages of Pregnancy.

Fetal infections can occur in the last trimester, but at this stage of gestation, organogenesis is often complete and fetuses are considered immunocompetent to BVDV. Congenital infection during this period usually results in the birth of a calf that is seropositive on a precolostral blood sample. Detrimental effects of BVDV infection in late gestation seem to be less common; however, weak calves and abortions have been reported.[79] It has generally been accepted that infection in late gestation results in the birth of calves that are clinically normal; however, calves congenitally infected with BVDV may be at greater risk for increased morbidity and mortality postnatally.[88] The congenitally infected calves that are born with neutralizing antibody titers to BVDV have been shown to be

twice as likely to experience a severe illness during the first 10 months of life as are calves born free of BVDV antibody titers.[88] The prevalence and importance of congenital infections remains to be determined.

Disease Associated With Persistent BVDV Infection

PI cattle are the main reservoir for BVDV. Cattle PI with BVDV are characterized by a wide distribution of BVDV throughout their organs as a result of lacking an immune response to the persisting BVDV strain. In PI animals, the virus is present throughout all organs and tissues; therefore BVDV is shed in multiple body excreta, including nasal discharges, urine, semen, colostrum/milk, and feces. Some PI calves are born weak and stunted and die shortly after birth[46]; however, many PI calves are born without any observable abnormalities and can survive for at least several months. This is important for beef cattle herds because these animals can survive into the start of the subsequent breeding period and thus become an important source of horizontal transmissions. PI cattle can have decreased survival, as evidenced by reports documenting a mortality rate higher than 50% in the first year of life.[89] This mortality may be due in part to the fact that PI cattle may have an impaired immune response, which makes them more susceptible to opportunistic pathogens. The rate of vertical transmission is 100% as PI cows give birth to PI offspring.

PI cattle are at risk of developing mucosal disease. Mucosal disease is the most dramatic of BVDV-associated clinical disease because of the severity and characteristics of lesions. Mucosal disease occurs when cattle that are immunotolerant and PI with NCP BVDV become infected with a CP BVDV.[90] Because mucosal disease occurs only in PI cattle and PI cattle are less than 1% of the cattle population, it is characterized as a disease with low case attack rate and high case fatality rate. Although the origin of the CP BVDV can be external, such as after the use of modified live-virus vaccines, current theory holds that in the majority of cases of mucosal disease, the CP BVDV represents a mutation of the NCP BVDV (the persistently infecting biotype).[90] There are multiple clinical forms of mucosal disease; the variations are due to the antigenic relationship between the persistently infecting NCP strain and the superinfecting CP strain.[90] The multiple clinical forms of mucosal disease can be categorized as acute (fatal) mucosal disease, chronic mucosal disease, chronic mucosal disease with recovery, and delayed-onset mucosal disease.[90]

Acute Mucosal Disease.

Acute mucosal disease occurs when the superinfecting CP strain shares close antigenic homology to the PI NCP strain. The CP strain may arise de novo by a mutational event from the NCP strain in the PI animal. The mutational event affects the viral biotype but does not affect the viral antigenicity.[91] The clinical findings associated with acute mucosal disease include pyrexia, depression, anorexia, decreased milk production, profuse diarrhea, ptyalism, mucopurulent oculonasal discharge, and oral erosions.[46] Oral erosions are present on the lips, gingival margins, tongue, dental pad, and the hard palate. Experimental reproduction of acute mucosal disease indicates an incubation period of 7 to 14 days.[90] Acute mucosal disease is considered 100% fatal.

Chronic Mucosal Disease.

Chronic mucosal disease and mucosal disease with recovery are forms of mucosal disease in which the superinfecting CP strain is heterologous to the PI NCP strain. The likely source of the superinfecting CP strain is external, rather than a mutational event in the PI NCP strain. The clinical manifestations of chronic mucosal disease are anorexia, weight loss, diarrhea, chronic bloat, alopecia, erosive lesions on the mouth and skin, and lameness.[46] The lameness may develop as a result of laminitis, interdigital necrosis secondary to erosive lesions, and hoof deformities. In rare cases, a PI animal may mount an immune response to the superinfecting, heterologous CP strain and clear the superinfection; this situation has been referred to as *mucosal disease with recovery.*[90] Although recovery may be possible, a PI animal will always remain PI with the NCP strain.

Necropsy Findings

Pathologic lesions associated with BVDV infection can be quite diverse in types and degree and, like the clinical manifestations, are dependent on host and viral factors. Age of animal, immune status at the time of infection, and the presence of concurrent infections greatly influence the pathologic observations. Many lesions observed are not specific to BVDV infection; thus laboratory testing becomes an important component in the diagnostic process. Occasionally, only microscopic lesions are present, and unless histopathologic study is performed, a lesion can be unnoticed and infection undiagnosed.

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Acute BVDV Infection.

Animals that die of acute BVDV infection have less severe lesions. In addition, lesions, when present, can often be nonspecific and subtle. Edematous intestines, occasionally with ecchymotic hemorrhages and mild reaction in mesenteric lymph nodes, can be observed. Occasionally, linear erosions in the alimentary tract and proximal colon are present, along with atrophy of gut-associated lymphoid tissues (Peyer's patches). Secondary bacterial infections such as enteritis, pneumonia, or mastitis are present and have contributed to death. Animals that die of hemorrhagic syndrome can have evidence of hemorrhage in many organ systems, including the gastrointestinal, cardiovascular, respiratory, and urinary systems. Petechial or ecchymotic hemorrhages are often apparent on mucosal surfaces, and hemorrhage in the gastrointestinal submucosa and Peyer's patches may be significant. Lesions associated with cases of severe acute BVDV infection can be similar to lesions associated with mucosal disease. Because of this and the severe clinical signs observed, it is usually not possible to differentiate the two forms of disease without supporting laboratory testing.

Mucosal Disease.

Postmortem examination of cattle dying of mucosal disease usually reveals gross abnormalities most prominent in the alimentary system. Animals that die of mucosal disease usually have severe, necrotizing erosive or ulcerative lesions involving the mouth, tongue, esophagus, ruminal pillars, omasum, abomasum, intestines, and cecum.[92] Erosive lesions may extend onto the external nares and into the nasal cavity. Ulcers involving the esophagus typically are linearly elongated. Peyer's patches in the small intestine often are necrotic and hemorrhagic. Bowel contents are watery, hemorrhagic, and foul smelling. Pathologic gastrointestinal conditions may be absent or very mild in cattle with chronic mucosal disease, although histopathologic lesions usually are present with atrophy of Peyer's patches. Skin lesions are often found and include patchy hyperkeratosis around the neck, shoulder, and perineal areas. Erosive lesions involving the perineal area, the prepuce, and the interdigital cleft and coronary band of the hoof may be present. Skin lesions are most apparent in cattle suffering from chronic mucosal disease.

Abortions and Congenital Defects.

Pathological criteria for the diagnosis of BVDV as a cause of abortion are not established. Fetuses aborted as a result of in utero BVDV infection often are

autolytic when expelled. Lesions found in aborted fetuses and the accompanying placentas are nonspecific for BVDV. Under experimental conditions or when aborted fetuses are expelled soon after death, lesions observed include conjunctivitis, peribronchiolar and interalveolar pneumonia, and nonspecific myocarditis. A significant decrease in cerebellar mass may be evident in calves affected by cerebella hypoplasia as a result of in utero infection with BVDV during the second trimester of gestation. Other common congenital defects associated with BVDV infection that may be noted at necropsy include cataracts and thymic hypoplasia.

Diagnosis

Numerous methods are available for detecting BVDV infection. The choice of test depends on the clinical problem, the availability of tests by different diagnostic laboratories, and financial considerations (Table 32.12). Because the clinical manifestations of BVDV are diverse, accurate diagnosis of BVDV infection relies on laboratory testing. Sample selection and handling for BVDV testing is critical because the initial test material largely defines success or failure of the diagnostic test.[93] The introduction of PCR has transformed viral diagnostics, and real-time PCR technology has further improved the already significant benefits of traditional PCR. Real-time PCR has become the tool often used by diagnostic laboratories for the detection of BVDV.

TABLE 32.12

Diagnostic Testing for Bovine Virus Diarrhea Virus (BVDV)

Clinical Form	Diagnostic Test	Specimen	Comments
Acute-transient BVDV infection	Virus isolation PCR	Serum, whole blood or nasal swabs	Whole blood is preferred. Viremia may be too transient for successful virus detection.
	Virus isolation PCR	Nasal swabs	This is useful for establishing role of BVDV in bovine respiratory disease complex.
	Serum virus neutralization	Serum	Pair sera 3 to 4 weeks apart. Serologic testing for both types 1 and 2 BVDV should be performed.
	Fluorescent antibody immunohistochemistry virus isolation PCR	Postmortem tissues	Tissues of choice include ileum, mesenteric lymph nodes, spleen, thymus (calves), lung (pneumonia).
Infertility	Serum virus neutralization	Serum	Serum bank for at-risk animals may be needed as

			seroconversion is complete when reproductive problem is noticed, or titers of affected cattle should be compared with those of unaffected cattle. Serologic testing for both types 1 and 2 BVDV should be performed.
Abortion	Serum virus neutralization	Serum	Pair sera 3 to 4 weeks apart. Serologic testing for both types 1 and 2 BVDV should be performed.
	Serum virus neutralization	Fetal fluid	Presence of antibodies or BVDV is suggestive but not definitive for BVDV-induced abortion. Serologic testing for both types 1 and 2 BVDV should be performed.
	Fluorescent antibody immunohistochemistry virus isolation PCR	Fetal tissues	Tissues of choice include ileum, mesenteric lymph nodes, spleen, thymus, liver, and lung.
Persistent infection	Virus isolation (IPMA) Antigen capture ELISA PCR	Serum or whole blood	Testing should be repeated in 2 to 4 wk to confirm persistent infection. For virus isolation, buffy coats should be used in these studies for calves younger than 6 months of age.
	Antigen capture ELISA immunohistochemistry PCR	Skin biopsy	Blood samples should be retested in 3 to 4 wk to confirm persistent infection. Pools of skin or blood may be tested initially with PCR.
Mucosal disease	Virus isolation PCR	Serum or whole blood	Both CP and NCP BVDV must be isolated.
	Fluorescent antibody immunohistochemistry Virus isolation PCR	Postmortem tissues	
Herd screening	PCR	Bulk milk tank Skin biopsy	Milk test screens only lactating cows; 300 cows per milk pool can be tested.
	Serum virus neutralization	Serum from sentinel cattle	Unvaccinated cattle 6 to 12 months of age should be tested. Serologic testing for both types 1 and 2 BVDV should be performed

CP, Cytopathic; *ELISA,* enzyme-linked immunosorbent assay; *IPMA,* immunoperoxidase monolayer assay; *NCP,* noncytopathic; *PCR,* polymerase chain reaction.

Virus Isolation.

Virus isolation is a basic, reliable, and widely used method for diagnosis of BVDV infection, and remains the “gold standard” of BVDV diagnostic tests. The BVDV may be cultured and isolated from many samples, including serum, whole blood, semen, nasal swabs, and various types of tissues.[94] Although their use is time consuming and expensive, mononuclear cells in the buffy coat from

whole blood are an ideal sample for individual virus isolation when an acute BVDV infection is suspected because BVDV is highly cell associated and neutralizing antibodies to BVDV in serum do not interfere with the virus isolation.[94] Sample handling is very important for virus isolation with mononuclear cells because they need to be viable when inoculated in the cell culture.[93] The ideal tissue samples for virus isolation from deceased animals at postmortem examination include lymphoid organ–related tissues such as spleen, Peyer's patches, mesenteric lymph nodes, and thymus.[94] In addition, pooled tissues from the same animal can be applied to virus isolation. NCP BVDV strains are detected, and CP strains confirmed as BVDV, by immunofluorescence or immunoperoxidase staining techniques or reverse transcriptase PCR (RT-PCR).

BVDV Antigen Detection.

Direct antigen detection methods with blood and a variety of fresh, frozen, or fixed tissues have been described for BVDV. These methods include immunohistochemistry, antigen-capture ELISA (ACE), and immunofluorescence. Because of standardization of methods, ACE testing kits have largely replaced the use of immunohistochemistry in diagnostic laboratories. Viral antigens can be detected from BVDV infected tissue, whole blood, serum, milk, or nasal swab samples.[94] These tests are advantageous in that they allow rapid and inexpensive detection in comparison to virus isolation. In addition, amplification of antigen is not needed, so these tests are ideally suited for the detection of animals with considerable amounts of antigen: namely, PI carriers.

ACE methods on skin samples have become widely used to detect BVDV antigen and are applied for the detection of cattle PI with BVDV.[95] Skin biopsy samples may be obtained easily and inexpensively. A major advantage of testing by ACE on skin samples is that sampling can be performed on young PI calves, which could test negative by virus isolation, microplate virus isolation, and other serum or buffy coat testing because of inhibition by acquired colostral antibodies.[96] Both the immunohistochemistry and ACE tests are ideally suited for the detection of PI animals, and reports indicate these tests very rarely detect acute infection in cattle.[97,98,99] With immunohistochemistry testing, PI animals can be differentiated from acutely infected cattle on the basis of location of viral antigen in the skin.[100] In cattle vaccinated with modified live-virus vaccines,

immunohistochemistry or ACE methods do not yield positive results.[98,101]

Reverse Transcription Polymerase Chain Reaction.

Since sequences of BVDV isolates became available, molecular techniques have been developed for diagnosis of BVDV, and this method of BVDV diagnosis has gained widespread use as a routine diagnostic method.[95] An additional advantage of RT-PCR for diagnostics is that sequencing information can be readily and economically obtained, thus determining the BVDV species involved in the animal infection or herd problem. In comparison with traditional virus detection methods, PCR offers rapid results with high sensitivity and specificity. Development of commercial kits, with rapid and simple viral RNA extraction techniques, has made molecular techniques ideal for detection of viral genomic nucleic acids from many types of samples, including serum, whole blood, tissues, and bulk tank milk. The RT-PCR is more sensitive than virus isolation.[102] Because of the high sensitivity of RT-PCR, it is used for pooled testing, and pooling of whole blood, serum, or milk samples is an economical way to detect BVDV infection in herd screening assays. A U.S. Department of Agriculture (USDA)–licensed PCR testing protocol and kit are now available for the pooling of ear notch samples.

Serology.

Detection of antibodies to BVDV is another method of demonstrating virus infection; however, it is often difficult to distinguish antibodies produced in response to a natural infection, after vaccination, or as a result of transfer of maternal antibodies from dam to offspring. Interpretation of serologic results is difficult without important information about the herd being tested, such as the vaccination history. Serologic testing may be used to assess vaccine efficacy and vaccine protocol compliance, as well as to determine whether BVDV exposure has occurred in the herd.[94] The BVDV-specific antibodies can be divided into two groups: neutralizing and nonneutralizing antibodies. Although there are several applicable methods, serum utilization, more appropriately called *virus neutralization*, and ELISA have been most commonly used for serologic diagnosis of BVDV. Because of numerous technical and logistical challenges, the virus neutralization test is less useful than the ELISA.[103]

Treatment and Prognosis

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No specific treatment is available for animals showing clinical signs of BVDV infection. Owners should be informed that severely ill animals may have mucosal disease, which ordinarily is fatal. The goals of therapy for cattle suspected of having acute BVDV infection are supportive care and prevention of secondary bacterial infection. Broad-spectrum antimicrobial agents, fluids, electrolytes, and vitamins may be indicated.

Prevention and Control

Control of any infectious disease relies on eliminating the reservoirs of the pathogen and limiting transmission from infected individuals to susceptible animals. PI animals are the reservoirs, and eliminating the potential for the birth of PI calves is key to prevention and control. The goal of BVDV control is to ultimately reduce production losses associated with BVDV infection. Development and implementation of herd health programs that involve vaccination and biosecurity to limit exposure of pregnant cattle to PI cattle are important for success of control. Therefore for prevention and control of BVDV, three major actions should be instituted: (1) identification and elimination of PI animals, (2) enhancing immunity through vaccination, and (3) implementing strict biosecurity measures to prevent introduction of PI carrier animals into a population of susceptible cattle. Each of these three principles has been applied[104]; however, BVDV continues to be a major problem to the cattle industry worldwide. Some European countries have successfully eradicated BVDV,[105] and voluntary BVDV control programs have been implemented in the United States. Control and eventual eradication of BVDV can be possible in defined areas, even those with large and dense cattle populations.

Identification and Elimination of Persistent Infection in Cattle.

The primary source of BVDV is cattle PI with BVDV because PI animals have a high and persistent viremia and shed BVDV from nearly all secretions throughout their lifetime. PI animals ideally should by identified and removed from breeding herds. In beef cow-calf operations with a controlled breeding season, PI animals should be removed before entry of a bull into the breeding herd.[106] In this situation, all calves, replacement heifers, bulls, and nonpregnant dams without calves should be tested for BVDV PI status. Because PI cows always produce PI calves, a negative test result for a calf indicates a negative PI status of the dam.[107] For any calves that test positive, the dam must be tested for

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BVDV PI status. Most PI calves result from an acute infection in the dam, rather persistent infection in the dam. Dams with negative test results may reenter the breeding herd; they possess high natural immunity to BVDV. In beef herds with a controlled breeding season, the BVDV status of all animals can be determined if no animals are pregnant at the time of testing. If cattle are pregnant at the time of testing, those animals must be segregated, and their calves' test results must be negative before return to the breeding herd.

In dairy herds and beef herds without a controlled breeding season, young calves should be tested and removed as soon as possible to avoid possible transmission to the breeding herd. Screening young calves for PI status is best accomplished with ACE or RT-PCR methods on skin biopsy samples. The use of skin samples for testing young calves is advantageous over other methods in that it is relatively easy for laymen to collect the samples, samples may be taken from calves that possess circulating maternal antibodies, and a single positive test result usually indicates PI status. Because acutely infected animals can produce positive RT-PCR results and occasionally positive ACE results, valuable breeding stock should be retested 30 days later with virus isolation on blood samples or ACE or RT-PCR assays on blood or ear notches.[99]

Screening all individuals in a herd for BVDV is very costly, especially considering the low prevalence of PI animals among cattle herds. Instead of whole-herd testing, monitoring strategies may be initiated, and these include evaluation of production records, BVDV evaluation of aborted fetuses, use of sentinel animals, pooling strategies for RT-PCR testing, and BVDV testing on sick or deceased individuals within the herd.[106] Monitoring breeding records, calf morbidity and mortality rates, and weaning proportions are considered the minimal level of surveillance, and these involve the least expense, but this level of surveillance is not very sensitive for evaluating the presence of persistent infection with BVDV within a herd.[11,106] As an example of the difficulty in utilizing clinical suspicion as a reason to perform herd testing, BVDV was isolated from cattle in 53% of herds in which there was no suspicion of the infection,[108] and animals PI with BVDV were not identified in 81% of herds where veterinarians suspected BVDV was present.[11] On the other hand, identifying BVDV in sick or dead animals or in aborted fetuses provides the justification for further whole-herd testing for animals PI with BVDV.

Because of high sensitivity, RT-PCR assays with pooled samples have been developed and tested to screen populations of animals for BVDV persistent

infection.[102,109] Sample types that have been utilized in RT-PCR assays of pooled samples include serum, whole blood, bulk tank milk, and skin. With pooling whole blood samples, a single PI animal is detectable in pools of up to 250 negative samples. RT-PCR assays have also been developed and evaluated for testing pools of skin biopsy samples.[109] Pooled sample testing by RT-PCR is a rapid and cost-effective method for screening populations of cattle for animals PI with BVDV. Individuals within the positive pools may be tests subsequently with ACE, immunohistochemistry, virus isolation, or RT-PCR methods, depending on the class of animals being tested. When testing young beef calves, it is important to perform all testing before the breeding season to identify and eliminate animals PI with BVDV that pose a risk for bred cattle.

Enhancing Immunity Through Vaccination.

Many vaccines are commercially available for BVDV, and the majority of these USDA-licensed vaccines contain BVDV in combination with other bovine respiratory and reproductive pathogens, including BoHV-1, parainfluenza type 3, bovine respiratory syncytial virus, *Leptospira* spp., *Campylobacter* spp., *M. haemolytica*, *Histophilus somni*, and *Pasteurella multocida*. Because of antigenic diversity among BVDV 1 and BVDV 2 strains, modified live-virus and inactivated vaccines containing both species are now widely available. Advantages and disadvantages of BVDV modified live-virus vaccines and inactivated vaccines have been described.[110] One disadvantage of inactivated BVDV vaccines is that two doses are required for the initial immunization. A major problem with using inactivated vaccines is the widespread lack of compliance among producers.[111] Failure to give a booster during the primary series and failure to regularly administer annual boosters with inactivated vaccines are common.[111]

Vaccines are an important component to BVDV prevention and control, and their effectiveness has been to limit disease from BVDV infection. In discussing BVDV vaccination with owners and producers, it is important to discuss reasonable expectations after vaccination and to remember that *disease* and *infection* are not synonymous terms. Experimental and field data indicate vaccination with either inactivated or modified live BVDV vaccines are effective at reducing or obviating clinical disease.[54,112] In addition, modified live-virus vaccines containing BVDV 1 strains are effective at limiting or preventing clinical disease when vaccinated animals are subsequently challenged with a

virulent BVDV 2 strain.[113,114] Protection from clinical disease is important for stocker/backgrounder and feedlot operations, and immunity to BVDV has been demonstrated to be protective against bovine respiratory disease complex.[115] Preconditioning cattle by vaccination against BVDV before an expected exposure (commingling and shipping) reduces the effects of exposure of cattle to BVDV.

Protection against viremia is the true measure of BVDV vaccine efficacy. To be truly efficacious, vaccination against BVDV should protect against viremia to prevent dissemination of virus throughout the host, including preventing infection of target cells of the reproductive tract that result in fetal infection. Since 2005, the focus for vaccine efficacy has shifted from protection against clinical disease to protection against fetal disease or infection. Published studies indicate the protection against fetal infections after BVDV vaccination varies from 60 to 100%. This wide degree of variation depends on whether the vaccine is inactivated or modified live-virus, the timing of challenge, and the degree of homology between the vaccine strains and the challenge strains. Although both modified live-virus and inactivated BVDV vaccines have been demonstrated to provide fetal protection, modified live BVDV vaccines provide greater protection, according to a meta-analysis of clinical trials.[116] Fetal protection studies have been performed to evaluate commercial vaccines containing only BVDV 1 strains[117,118] and commercial vaccines containing both BVDV 1 and BVDV 2 strains.[119,120] From published studies, it appears that protection is superior when animals are challenged with strains from the same genotype.[114,121] An extremely important observation regarding these fetal protection studies is that although protection may not be 100% against all strains of BVDV, the level of protection is far superior to that observed when proper vaccination is not utilized, as evidenced by very high numbers of PI animals among unvaccinated cattle.[116]

Biosecurity.

Although BVDV prevention and control starts with identification and elimination of PI animals, strict biosecurity is essential to prevent reintroduction of the virus. Strict biosecurity is difficult for most cow/calf and dairy operations to achieve and is even more difficult or impossible for most stocker/backgrounder and feedlot operations to achieve. Biosecurity systems with isolation and testing of all incoming cattle are necessary to ensure that

BVDV does not enter the farm. All purchased cattle should be isolated and tested for persistent BVDV infection before entry into the herd. In addition, isolation of new additions for three weeks before entry into the resident breeding herd should prevent transmission of BVDV from acutely infected animals. Most lapses in herd biosecurity involve purchasing cattle that are PI with BVDV or purchasing pregnant cattle in which the BVDV status of the fetus is unknown. If pregnant cattle are purchased, these animals should be isolated and their offspring should be tested to ensure that they are free of BVDV. Semen should be used only from bulls that have test results negative for BVDV infection. For purebred herds marketing genetically valuable embryos and livestock, it is important to test embryo transplantation recipients to ensure that they are not PI with BVDV. Exposure of cattle to other cattle or small ruminants at exhibitions should be limited, and animals should be quarantined for 3 weeks before reentry into the breeding herd. Most biosecurity principles instituted for BVDV control have the added benefit of disease control with other pathogens of cattle.

Malignant Catarrhal Fever (Bovine Malignant Catarrh, Malignant Head Catarrh)

Robert J. Callan

■ Definition and Etiology

MCF is a severe lymphoproliferative disease caused by a group of herpesviruses collectively referred to as *malignant catarrhal fever viruses.*[1-6] The most recent taxonomic nomenclature places these viruses in the order Herpesvirales, family Herpesviridae, subfamily Gammaherpesvirinae, genus *Macavirus.*[7,8] Ten genetically and antigenically related viruses have been identified and constitute the group of MCF viruses. Six of these viruses are associated with clinical disease, and the remaining four viruses have not yet been associated with disease (Table 32.13).[5-9] Each virus has a reservoir host in which infection is typically asymptomatic. Clinical disease occurs in aberrant hosts and is characterized by acute onset of fever, inappetence, profuse ocular and nasal discharge, ocular signs such as corneal opacity and conjunctivitis, alimentary erosions, enteritis, and enlarged lymph nodes. The disease is typically progressive and often fatal.

TABLE 32.13

Ten Antigenically and Genetically Related Viruses in the Malignant Catarrhal Fever Virus Group and Their Respective Reservoir and Clinical Hosts[5-8]

Current Name	Previous Name	Primary Reservoir Host	Clinically Susceptible Hosts
Ovine gammaherpesvirus 2 (OHV-2)	Ovine herpesvirus type 2 (OvHV-2)	Domestic and wild sheep	Cattle, bison, deer and other cervids, swine, moose, alpaca, and other domestic and wild ruminants
Alcelaphine gammaherpesvirus 1 (AHV-1)	Alcelaphine herpesvirus type 1 (AlHV-1)	Wildebeest (*Connochaetes* spp.)	Cattle, deer, and other domestic and wild ruminants
Alcelaphine gammaherpsevirus 2 (AHV-2)	Alcelaphine herpesvirus type 2 (AlHV-2)[64,65]	Jackson hartebeest *(Alcelaphus buselaphus lelwel)*, topi *(Damaliscus lunatus)*	Barbary red deer *(Cervus elaphus barbarus)*, bison
Caprine gammaherpesvirus 2 (CHV-2)	Caprine herpesvirus type 2 (CpHV-2)[9,16,21,23,25,27]	Goat	White-tailed deer, sika deer, roe deer, moose, pudu, water buffalo, pronghorn
Unassigned	MCFV of white-tailed deer (MCFV-WTD)[19], Caprine herpesvirus 3	Goat	White-tailed deer, red brocket deer
Unassigned	Ibex-MCFV[66]	Ibex *(Capra nubiana)*	Bongo *(Tragelaphus eurycerus)*, anoa, pronghorn antelope
Hippotragine gammaherpesvirus 1 (HHV-2)	HiHV-1[67,68]	Roan antelope *(Hippotragus equinus)*, scimitar-horned oryx *(Oryx dammah)*	None identified
Unassigned	Oryx-MCFV[4,9], or Gemsbok MCFB	Gemsbok *(Oryx gazella)*	None identified
Unassigned	Muskox-MCFV[9]	Muskox *(Ovibos moschatus)*	None identified
Unassigned	Aoudad-MCFV[4]	Aoudad, Barbary sheep *(Ammotragus lervia)*	None identified

MCFV, Malignant catarrhal fever virus.

Clinical MCF is observed in cattle, deer, bison, buffalo, several other domestic and wild ruminants[5,6] (>33 species to date), pigs,[10-13] and alpaca.[14] It has worldwide distribution and can be a problem in zoos and game parks. There are two primary etiologic forms of MCF that are designated by the host reservoir of the virus. Wildebeest-associated MCF is caused by alcelaphine gammaherpesvirus 1 (AlHV-1). The principal reservoir of AlHV-1 is the blue wildebeest *(Connochaetes taurinus)* and the black wildebeest *(Connochaetes gnou).*[5,15] Wildebeest-associated MCF occurs primarily in Africa or in zoologic parks where other ruminants have contact with wildebeest. Sheep-associated MCF is caused by ovine gammaherpesvirus 2 (OHV-2). Domestic and wild sheep and goats are asymptomatic reservoirs of the virus. Sheep-associated MCF is the primary form of MCF that is observed outside of Africa and affects

primarily domestic and wild ruminants. MCF caused by OHV-2 has also been identified in pigs.[10-13] Goats are a reservoir for caprine gammaherpesvirus 2,[16] which has been isolated from cases of MCF in white-tailed deer,[17-20] sika deer,[21-24] roe deer,[25] moose,[25] pudu,[26] and water buffalo.[27] Both AlHV-1 and OHV-2 can be experimentally transmitted to rabbits and hamsters, in which infection causes an acute, fatal lymphoproliferative disorder similar to natural MCF.[28,29]

■ Clinical Signs and Differential Diagnosis

The clinical signs and pathologic process of MCF have been reviewed.[5,6] Cattle from 4 weeks of age to adulthood can be infected and develop clinical illness. After an incubation period of 2 to 30 weeks, the disease attacks vascular endothelium, causing a lymphocytic vasculitis. The incubation period can be prolonged; in at least one case, the incubation period was 200 days. High fever, alimentary erosions, diarrhea, dysentery, corneal opacity, anterior uveitis, conjunctivitis, mucopurulent nasal discharge, thickened cracking skin, encephalitis, lymphadenopathy, and hematuria may be present (Fig. 32.93). Oral and nasal erosions may be evident but are often too far back in the nasal or oral cavity to be observed externally. Ocular lesions are often present and consist of corneal opacity that originates in the periphery (centripetal) and progresses to the center. Corneal ulceration is generally not present, and there is no uptake of fluorescein dye. Affected animals exhibit generalized weakness and dyspnea. Ropy saliva may be dropped from the painful mouth, and scabs may develop on the muzzle. Swelling and hyperemia of the coronary bands may be observed, characteristic of coronitis. The hoof or horns may be shed, and lameness may be pronounced. Hematuria often is present and caused by a hemorrhagic cystitis. Nonsuppurative arthritis can also be observed. Neurologic signs include ataxia or altered mentation and are caused by a nonsuppurative encephalitis. Cutaneous lesions consist of multifocal coalescing alopecia with dermatitis and necrosis. When particular signs predominate, the condition may be labeled the alimentary form, the encephalitic form, the head and eye form, or the skin form. One strain of virus can cause all forms, and animals with most of these signs can be identified in a given outbreak. Clinical signs in any single animal may progress rapidly or over a course of weeks. Disease in Sitka deer (and perhaps other species) may consist primarily of dermatitis and alopecia.[21,23,24,30,31]



FIG. 32.93 A yearling steer with malignant catarrhal fever. Note the corneal opacity, lacrimation, and mucopurulent nasal discharge.

The course of the acute disease is usually 3 to 7 days; some animals survive longer. Disease is generally more severe and progresses more rapidly in bison than in cattle. The mortality rate is very high. Peracute deaths without any visible symptoms can also occur. A mild form, with transient fever and mild oral and nasal mucosal erosions followed by recovery, has been observed in experimentally infected cattle. Some animals survive clinical disease and, in a few cases, may return to normal productivity. The case mortality rate is generally high and may exceed 90%. However, chronic and recovered cases have been described, and in one report, recovery occurred in 50% of cases.[32]

MCF must be differentiated from BVD-related mucosal disease, rinderpest, bluetongue, vesicular stomatitis, and FMD. The last two diseases are not usually associated with diarrhea, and with vesicular stomatitis and FMD, morbidity rates tend to be high and mortality rates low. Clinical bluetongue is rare in cattle and not usually associated with dysentery. Arsenic toxicity and chlorinated naphthalene toxicity have some clinical similarities to the intestinal forms of MCF. Ocular signs, including corneal opacity, conjunctivitis, and discharges, must be differentiated from bovine keratoconjunctivitis (pinkeye), in which the lesion starts at the center of the cornea and corneal ulceration is present. In contrast, the corneal opacity of MCF starts at the limbus and is caused by edema secondary to the loss of the internal endothelial layer of the cornea.[33,34]

■ Clinical Pathology and Serology

Some affected animals show leukopenia caused by lymphopenia and neutropenia if tested early in the course of disease, but this is an inconsistent finding in natural outbreaks.[35] Joint fluid is cloudy and may contain increased protein and mononuclear cell numbers. Cerebrospinal fluid may have elevated protein concentrations and elevated WBC counts with mononuclear pleocytosis in animals displaying neurologic signs. Serologic tests include ELISA, indirect immunofluorescence, complement fixation, and virus neutralization.[1,5] Virus isolation can be attempted for cases of MCF caused by AlHV-1. Serologic tests identify antibodies directed to a conserved MCF virus glycoprotein and do not discriminate between the different MCF viruses. Serologic tests are best used to screen the infection status of reservoir animals or to identify asymptomatic infection in clinically susceptible hosts. Diagnostic PCR tests have been developed for AlHV-1 and OvHV-2.[1,5] PCR tests are best used to distinguish between AlHV-1 and OvHV-2 in animals with clinical MCF. PCR tests for the identification of other MCF viruses, including a multiplex PCR assay, are available from specific research laboratories.[1,5]

A presumptive diagnosis is based on a history of exposure, clinical signs, and evidence of infection supported by serologic or PCR results. A definitive diagnosis can be made only if characteristic histopathologic lesions, including lymphocytic vasculitis, are present, along with supportive diagnostic test results demonstrating infection.[1,5]

■ Pathophysiology

Natural infection occurs through inhalation of aerosolized virus or through direct or indirect contact with ocular or nasal secretions from reservoir hosts. The exposure dose plays a role in the likelihood of developing clinical MCF and the duration of the incubation period.[1,5,6,36-40] Experimental transmission studies in sheep and bison show initial replication of the virus in respiratory epithelium.[1,5,6,36,37,39,40] OvHV-2 DNA can be identified in the respiratory tract 9 to 12 days after infection in bison experimentally infected by intranasal inoculation.[41] OvHV-2 infection of lymphocytes is observed 14 to 21 days after infection. The incubation period for clinical MCF is highly variable and ranges from 14 to more than 200 days. MCF virus infection causes infiltration of lymphocytes, particularly T cells, into tissues.[2,5,6] This T cell proliferation is predominated by $CD8^+$ gamma-delta T cells and, to a lesser extent, $CD4^+$ T

cells.[5,42] There is also an increase in large granular lymphocyte cells that appear to have cytopathic activity. It is believed that the fundamental disease is caused by an autoimmune-like process involving dysregulation of cytotoxic T cells associated with expression of specific viral transcripts.[2,5,42,43]

■ Epidemiology

Wildebeest-associated MCF remains an important disease in cattle and other ruminants that encounter wildebeest.[5,6] AlHV-1, unlike OvHV-1, can be isolated in cell culture, and this has aided the ability to study the disease epidemiologic behavior and transmission. Wildebeest calves are generally infected with AlHV-1 in utero or soon after birth and shed the virus in ocular and nasal secretions until the age of 4 to 6 months.[5,15] Adult wildebeest become latently infected and transmit the virus to their offspring. Recrudescence and shedding of AlHV-1 in wildebeest can occur after treatment with corticosteroids. Cattle are infected with AlHV-1 when exposed to young, actively shedding wildebeest calves. The incubation period of wildebeest-associated MCF under natural exposure conditions in cattle can range from 2 weeks to 6 months and perhaps longer. In general, the incubation period of wildebeest-associated MCF is shorter than that of sheep-associated MCF. Some cattle that become infected with AlHV-1 do not develop clinical MCF. Diseased cattle do not shed free infectious virus and thus are not a risk to contact animals.[5]

Sheep-associated MCF is the predominant form of MCF outside of Africa. The prevalence rates of OvHV-2 infection determined by PCR or competitive inhibition ELISA in healthy adult North American domestic sheep is reported to be 99% and 94%, respectively.[44] Sheep serve as the primary reservoir of OvHV-2, although sheep do not show clinical signs of infection. Less than 5% of lambs are infected at birth.[5,45] The majority of lambs remain uninfected up to 2.5 months of age. After 3.5 months of age, the lambs develop infections through close contact with adult sheep; the prevalence rate approaches 100% by the age of 5.5 months. OvHV-2 is shed and transmitted through nasal and ocular secretions.[46,47] Seroconversion and detection of OvHV-2 DNA in nasal secretions lags behind the detection of viral DNA in blood by several months.[5,45] Lambs separated from adults at 2 months of age remain reliably OvHV-2 free.[5,48] These findings indicate that newborn lambs are not a major source of virus infection for cattle. Nasal viral shedding peaks at approximately 6 to 9

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months of age, and it is these infected adolescent lambs that pose the greatest transmission risk to other animals.[5,46]

Infected adult sheep continue to shed low numbers of virus throughout life.[5,46] Adult sheep may shed OvHV-1 in larger amounts during the periparturient period or while they feed in feedlots, which raises the risk for commingled cattle. OvHV-2 is readily transmitted between in-contact sheep; however, transmission by inoculation of whole blood or peripheral blood mononuclear cells is inconsistent.[49] This suggests that infectious virus is produced and shed primarily in nasal or ocular secretions and that infection of blood cells may be largely nonproductive.

Positive results of competitive inhibition ELISA tests have been identified in bison (2% to 23%), domestic goats (74%), elk (9%), mule deer (2%), white-tailed deer (3%), pronghorn antelope (25%), bighorn sheep (37%), muskox (40%), and mouflon sheep (62%). Black-tailed deer, llamas, and mountain goats have been tested and were not found to be seropositive for MCF.[50] However, it is not clear whether these species play any role as reservoir species.

Sheep-associated MCF can be acute or chronic, and infected animals may recover. Cattle and American bison *(Bison bison)* are the two primary species affected by sheep-associated MCF. The disease usually occurs sporadically, with only one or a few animals affected, but many large outbreaks have been reported.[5,6,51-55] Transmission probably occurs through direct contact, indirect contact, and aerosol of nasal secretions from sheep. In one report, exposure of bison to sheep for less than a day at an auction resulted in a high mortality rate.[55] There is evidence of transmission from sheep to cattle or bison extending over distances of 70 m up to 5.1 km.[53,56,57] In one example of natural infection of bison, the incidence rates of disease and mortality were inversely related to the distance of exposure.[53] The incubation period after experimental or natural exposure ranges from 14 to 220 days.[6,38,41,51,54,55] Cattle and bison are considered dead-end hosts and do not spread the infection to other animals.[2,5,55]

Bison are more susceptible to developing clinical MCF than are cattle by both experimental inoculation studies and natural exposure.[5,36,38,54] In bison, OvHV-2 infection and clinical MCF is observed with intranasal nebulization at doses as low as 10^3 DNA copies of OvHV-2.[5,36,37] Cattle become infected with doses as low as 10^6 OvHV-2 copies but require at least 10^8 copies to become infected with clinical MCF.[5,38] In contrast, the minimum infectious dose for sheep is

between 10^2 and 10^3 DNA copies, but sheep require a dose of 3×10^9 copies to develop nonfatal clinical signs of MCF.[5,39,40] Several studies have shown that both cattle and bison can be infected with OvHV-2 and not develop clinical MCF.[5,52,56,58] These studies show that infection, morbidity, and mortality are related to species susceptibility, inoculation dose, and probably other factors not yet determined. Both asymptomatic and clinically affected cattle and bison do not shed infectious virus and are considered dead-end hosts.[5]

■ Necropsy Findings

In an infected animal, the nasal mucosa is hyperemic and may have hemorrhagic superficial erosions. The oral mucosa has necrotic papillae and large areas of necrosis and ulceration. Multiple focal ulcerations are seen in the esophagus. Parts of the forestomachs and intestines are thickened, edematous, and occasionally ulcerated and hemorrhagic. The lymph nodes, tonsils, and Peyer's patches are enlarged, moist, and friable. Splenic lymphoid follicles are prominent, and the liver is swollen. The adrenal glands are hemorrhagic. The mucosal surface of the bladder has focal areas of hemorrhage. The eyes are hyperemic and show severe corneal edema. The brain may have intersulcal cloudiness and meningeal petechiation consistent with encephalitis. Joints may have swollen and reddened synovia with an increased quantity of cloudy fluid.[6,59]

Histologically, there is a marked lymphoid accumulation around blood vessels, as well as necrosis of the tunica media and intima in multiple tissues. Generalized lymphoid hyperplasia and lymphoid infiltrates are present in subepithelial and intraepithelial locations, in association with epithelial necrosis and sloughing. Similar changes occur in all epithelial tissues.[59] Chronic cases develop chronic obliterative arteriopathy.[32]

■ Treatment and Prognosis

There is no specific treatment for MCF beyond supportive care. Fluid therapy and nursing care may allow some animals to survive and recover from disease. Antimicrobial treatment to help prevent secondary bacterial pneumonia or septicemia may provide some benefit. Treatment with NSAIDs may provide comfort but could increase the degree of alimentary erosions or decrease their healing. Gastrointestinal protectants such as bismuth subsalicylate (Kaopectate) may provide support to the gastrointestinal tract and help maintain appetite.

Maintenance of appetite seems to be one of the key prognostic indicators in clinical cases of MCF. Although some animals that exhibit mild disease may survive, close to 100% of those with severe clinical signs die.

In one report, the severity and progression of ocular lesions associated with MCF in cattle were evaluated in relation to disease outcome.[33] The degree of corneal edema at presentation did not show prognostic value in predicting disease outcome (death versus survival). However, improvement of corneal edema over the course of the disease was associated with a better outcome. In addition, animals in which anterior uveitis worsened were more likely to die or be euthanized.

■ Prevention and Control

The primary method of control is to reduce the exposure of susceptible hosts to reservoir hosts.[5,6] Transmission is related to the distance between reservoir hosts and susceptible hosts, so these groups of animals should be physically separated. This can be particularly difficult because, as mentioned, transmission from sheep to bison over distances as far as 5 km have been reported.[53] Adult wildebeest and sheep pose a lesser risk of transmission than do neonatal wildebeest and adolescent sheep, which shed higher amounts of virus from nasal secretions than do the adults. These younger groups of reservoir animals should be kept at a greater distance from susceptible hosts. Feedlot sheep from 6 to 9 months of age pose a significant risk. Natural transmission of OvHV-2 between feedlot sheep and dairy cattle or bison has been reported and is probably related to the younger age of the feedlot sheep in comparison with adult breeding animals.[53,54,56]

Currently, no commercial vaccines are available for prevention of wildebeest-associated or sheep-associated MCF. Attenuated AlHV-1 vaccines have demonstrated some protection against virulent AlHV-1 challenge and natural infection in cattle.[60,61] Respiratory tract mucosal immunity appears to be critical in preventing initial infection and development of clinical MCF.[2,60,62,63] Further research identifying critical antigens and methods to induce strong, long-lasting mucosal immunity for both AlHV-1 and OvHV-2 are necessary for developing effective vaccines for bison and cattle.

Vesicular Stomatitis

Pamela J. Hullinger • Danelle A. Bickett-Weddle

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Definition and Etiology

Vesicular stomatitis virus (VSV) is a rhabdovirus in the genus *Vesiculovirus* that causes sporadic (cyclic) outbreaks in cattle, horses, donkeys, mules, and pigs. Clinical signs include vesicles, erosions, and ulcers. Although deaths are rare, these lesions can result in pain, anorexia, and secondary bacterial mastitis. Some animals may lose their hooves after developing laminitis.[1] Affected cattle younger than 1 year of age rarely show clinical signs. Affected sheep and goats rarely have clinical signs, and South American camelids are intermediate in susceptibility. Humans can become infected with VSV and develop a mild influenza-like disease.

Vesicular stomatitis viruses are endemic from southern Mexico to northern South America, but they regularly spread north and south from these regions, causing outbreaks and epidemics. Although these viruses are no longer endemic in the U.S., they are introduced periodically into the southwestern states and can sometimes spread further north.[1]

Four distinct viruses are now recognized: VS Indiana (formerly called *Indiana 1*), VS New Jersey, Alagoas virus (formerly called *Indiana 3*), and Cocal virus (formerly called *Indiana 2*). Indiana 1 and New Jersey occur in the United States.[1] Viral strains vary in virulence.

Historically, epizootic waves of vesicular stomatitis tended to occur at approximately 10-year intervals, usually in the summer or fall. However, outbreaks have become more frequent since the 2000s. An outbreak of vesicular stomatitis in the United States lasted from April 29, 2015, to March 4, 2016. A total of 823 premises were confirmed or suspected to have VSV infections (VS New Jersey serotype) in eight U.S. states: Arizona (36 premises in three counties), Colorado (441 premises in thirty-six counties), Nebraska (38 premises in ten counties), New Mexico (52 premises in thirteen counties), South Dakota (50 premises in seven counties), Texas (4 premises in four counties), Utah (56 premises in eight counties), and Wyoming (146 premises in ten counties).[2]

Although the VS New Jersey serotype has at least 14 distinct genotypes, only a few of these have been found in outbreaks in the United States. The VS New Jersey serotype should be considered a collection of serologically related but genetically variant viruses.

State and federal regulatory veterinarians should be contacted immediately when vesicular stomatitis is suspected so that quarantine and disease identification measures can quickly contain an outbreak.

Clinical Signs and Differential Diagnosis

The incubation period is usually 3 to 7 days but can be shorter or longer, depending on route of transmission and viral load. In the 1984 California outbreak, it was unusually long (9 days).[1] Vesicles occur in the mouth, on the teats, and in interdigital areas. Vesicles are only occasionally visible because the epithelium rapidly becomes necrotic and turns into painful ulcers. Lesions on the gums and tongue may coalesce to form large eroded areas that cause dysphagia and reluctance to eat, frothing at the mouth, drooling, and weight loss (Figs. 32.94 and 32.95). Milk production falls quickly. In dairy cattle, teat lesions are common and cause mastitis. Small ulcers in the interdigital area and on the coronary band are occasionally present and cause lameness. Recovery varies from 2 to 21 days, depending on the severity of the lesions and management factors such as the type of feed and milking sanitation.[3] Actual healing of the lesions may take 34 to 59 days.[4]



FIG. 32.94 Severe ulceration of the tongue of a dairy cow caused by vesicular stomatitis. A plaque of dying mucosa covered by fibrin is visible at the tip of the tongue, and excessive salivation is obvious. (Courtesy Dr. Mark Thurmond.)



FIG. 32.95 Tongue of horse with vesicular stomatitis, demonstrating severe lingual erosions. (Courtesy Dr. Skip Aaroe.)

In cattle, morbidity rates are generally high (5 and 60%)[3,4] and low mortality rates (1% to 5%). Although many exposed cattle do not show obvious clinical signs of disease, many more are found to have oral lesions if closely examined, and most animals in the herd seroconvert.

The major differential diagnostic consideration is FMD, which causes identical clinical signs, except that VSV can affect horses. Other diseases of cattle that result in oral lesions include BVD, BPS, bluetongue, and epizootic hemorrhagic disease. These usually appear, not as epidemics in herds, but rather in one or a few animals in the herd (although with BPS, morbidity rates may be high). Other causes of oral lesions such as bristle grass irritation and toxins should be ruled out.

Clinical Pathology and Laboratory Diagnosis

VSV can be found in vesicular fluid, swabs of ruptured vesicles, the epithelium of unruptured vesicles, and epithelial flaps from freshly ruptured vesicles.[1] Many cell lines and other methods can be used to isolate VSV from clinical samples. The identity of cultured virus can be accomplished by RT-PCR, immunofluorescence, complement fixation tests, or antigen-capture ELISA. Antigen-capture ELISA can also be used for serotyping.[1] Electron microscopy of tissue samples may be helpful in distinguishing VSV from some other viruses that cause vesicular lesions, such as the FMD virus. [1]

Vaccination with inactivated virus results in a rapid rise in titer, followed by a

gradual decline for a year.[5] Serum-neutralizing antibody titer rises rapidly after exposure and then gradually falls over the first year. Serum-neutralizing antibody titers that appear after natural exposure may persist for years. The presence of a serum-neutralizing antibody titer does not prevent reinfection or development of clinical signs. Hematologic and clinical chemistry findings generally reflect an acute to chronic inflammatory disease and are nonspecific.

Pathophysiology

After a short incubation period, fever occurs, and the virus invades the germinative layer of oral epithelial cells. Oral abrasions or trauma may increase susceptibility. Contact of virus with teats or feet can result in lesions in these areas, especially if the teats are chapped or cracked or the feet are traumatized. The lesions progress rapidly from blanched macules to vesicles and soon rupture, leaving sloughed epithelium and ulcerated areas. Healing occurs quite rapidly if feed is soft and does not cause oral trauma.

■ Epidemiology

Older, high-producing dairy cows that have been in milk longer are more susceptible to clinical disease caused by VSV than are younger herdmates.[5] Because the virus cannot penetrate intact mucosa, cattle fed coarse feeds or hard pellets that traumatize the oral mucosa are at higher risk. Cows with chapped or cracked teats and those on farms with poor milking hygiene are more likely to get teat lesions.[5] Cow-to-cow contact is a major mode of transmission in outbreaks, and increased interpen movement of cattle, as well as sharing of feed and water troughs (unless cleaned frequently), increase the risk of exposure to VSV. The virus can be transmitted by milking machines and human hands during outbreaks. In addition to being biological vectors, insects can also contribute to the mechanical spread of the disease.

The transmission of VSV is not completely understood, and transmission routes in individual outbreaks are unclear. Outbreaks can be associated with the movement of animals from another area, but disease epidemics unrelated to introduction of new animals do occur. The infection tends to be seasonal (occurring in the summer and fall in temperate areas and at the end of the rainy season in the tropics) and behaves like an arthropod-borne virus. Insect vectors are thought to introduce VSV into populations of domesticated animals. Sand flies (*Lutzomyia* sp.), black flies (family Simuliidae) and *Culicoides* midges can

act as biological vectors. Sand flies seem to be important vectors in endemic areas, but they have a limited flight range and are not thought to spread these viruses over long distances.[1] Black flies are believed to be particularly important vectors in parts of the western United States. It is still uncertain where the virus originates before entering livestock populations. Once animals develop lesions, however, insects may become infected by feeding on these lesions or contaminated secretions. Transovarial transmission has been demonstrated in sand flies and black flies in the laboratory and may be possible in *Culicoides* midges. It might contribute to virus overwintering in cold climates.[1] Both migratory western grasshoppers and the plants they eat can be infected with VSV,[6] which provides a means of livestock exposure. It is hypothesized that VSV may be a plant virus that strays into animals, in which it causes sporadic disease.

Other insects act as mechanical vectors. Antibodies have been found in a number of wild species of animals (deer, raccoons, bobcats, monkeys) that may serve as virus reservoirs. Active cases of vesicular stomatitis occur in Mexico between U.S. epidemics; it is possible that cattle from Mexico arriving in the United States may also be sources of VSV. Sheep and goats in contact often seroconvert, although clinical signs in these species are rare.

The virus survives several weeks in cool soils but is inactivated by sunlight and is very resistant to pH changes.

Necropsy Findings

Deaths from vesicular stomatitis are rare and usually attributed to secondary bacterial diseases, including environmental mastitis and pneumonia. Affected cattle become gaunt and weak as a result of dysphagia and anorexia. Erosive and ulcerative lesions are usually confined to the mouth. The teats are frequently involved in affected lactating cows, and lesions on the coronary band and interdigital area occasionally appear.

Histologically, intracellular and extracellular edema, ballooning and degeneration of epithelial cells, and vesicle formation accompanied by neutrophilic infiltration occur. There are no inclusion bodies. The characteristic bullet-shaped structure of the VSV can sometimes be seen with electron microscope examination of fresh lesions or vesicular fluid.

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Treatment and Prognosis

Mortality can be almost completely prevented if ill cattle are offered shade, fresh water, clean bedding, and soft feed. Offering soft feed hastens recovery and reduces the anorexic period. Judicious use of appropriate antibiotics to control secondary bacterial pneumonia may be warranted. Cattle with teat lesions are at high risk for developing mastitis and should be carefully milked last and monitored closely for mastitis. The prognosis for survival is very good, but agalactia and mastitis may necessitate the culling of animals.

Prevention and Control

The websites of World Organization for Animal Health (OIE)[7] and the USDA[2] provide the latest information on active vesicular stomatitis outbreaks. During an outbreak, regulatory officials implement a quarantine of the premises and require testing and isolation of sick animals. Leftover feed should be removed from feed bunks twice daily, and the bunks should be disinfected. Water troughs should be cleaned and disinfected daily. According to Spickler, "VSV is susceptible to numerous disinfectants including 1% sodium hypochlorite, 40-70% ethanol, 2-propanol, aldehydes (e.g., 0.5%-2% glutaraldehyde, formaldehyde), 1% cresylic acid, phenolic disinfectants and detergents. These viruses appear to be more susceptible to inactivation by acid (e.g., pH 2) than alkaline conditions. VSV are also susceptible to UV [ultraviot] light including sunlight, or heat (e.g., 4 minutes at 55°C, or one minute at 60°C)."[1]

Vaccination with killed[8] or live virus vaccines is rarely practiced preventively because the disease occurs as such rare epidemics in small areas and vaccination interferes with serologic testing and monitoring. Although VSV vaccine is available in some South American countries, it is not currently available in the U.S.

Foot-and-Mouth Disease (Aftosa, Aphthous Fever)

Pamela J. Hullinger • Danelle A. Bickett-Weddle

Definition and Etiology

FMD is an acute, highly contagious viral disease of cloven-hoofed livestock that

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is characterized by vesicular lesions, erosions, and ulcers in the mouth and interdigital areas and on the muzzle, teats, and coronary bands. Natural hosts include cattle, sheep, goats, swine, water buffalo, bison, deer, elk, antelope, wild ruminants, bears, llamas, camels, giraffes, elephants, rats, yaks, capybaras, and hedgehogs.[1] Of these, cattle and swine are generally the most susceptible, shed the most virus, and display the most severe clinical signs. Affected mature sheep and goats usually have mild clinical signs, and horses are not susceptible. Livestock of all ages are susceptible, and the mortality rate is higher in young animals because myocarditis can occur.[1]

FMD is caused by a picornavirus of the genus *Aphthovirus.* At least seven immunologically distinct types of FMD virus have been identified: A; O; C; SAT 1, 2, and 3; and Asia 1. Within the seven types, at least 60 subtypes have been recognized.[1] African buffalo can be a maintenance host of SAT serotypes in sub-Saharan Africa and may harbor the virus for at least 5 years. They have not been shown to play an epidemiological role outside of Africa or to transmit the virus naturally to domestic cattle.[2] Vaccination against one subtype generally does not protect adequately against another. This fact, together with the fact that immunity is generally short term, means that developing effective vaccination programs is challenging.

The virus is rapidly inactivated by pH above 9.0 or below 6.0 and by very high temperatures. For example, the OIE Terrestrial Animal Health Code recommends that deboned, defatted meat products be subjected to 70°C for a minimum of 30 minutes. Organic material and protection from sunlight promote virus survival. Sodium hypochlorite, citric acid, and a number of proprietary products are effective disinfectants.[3]

Clinical Signs and Differential Diagnosis

FMD is clinically indistinguishable from vesicular stomatitis except that the latter also affects horses. Clinical signs of FMD in cattle include fever, depression, anorexia, listlessness, occasional shivering, excess salivation, lip smacking, nasal discharge, and lameness. Milk production may be reduced. In addition to vesicular stomatitis, the differential diagnosis includes BPS, BVD, bluetongue, rinderpest, MCF, and severe cases of infectious bovine rhinotracheitis. Teat lesions can be confused with those caused by bovine herpes mammillitis or parapoxviruses.

Vesicular lesions (blisters) 0.5 to 5 cm in diameter rupture within 48 hours,

followed by a mucosal slough and large erosions. These lesions appear to be very painful, and affected animals are reluctant to eat or move. In general, the morbidity rate is high, but the mortality rate is low. Death may occur in young animals, mainly from myocardial necrosis and secondary bacterial pneumonia. Because of the response to the disease and its effect on trade, it is economically devastating, and its rapid spread and clinical signs (e.g., weight loss, mastitis, lameness) have significant effects on animal health and productivity. An outbreak of FMD in a country previously free of the disease can cost billions of dollars in trade loss over ensuing years.

Laboratory Diagnosis

FMD is clinically indistinguishable from vesicular stomatitis and other viral mucosal diseases. Therefore laboratory confirmation is obtained through demonstration of FMD viral antigen or nucleic acid in samples of tissue or vesicular fluid, either by RT-PCR or by virus isolation. Detection of virus-specific antibody can also be used for diagnosis, and the presence of antibodies to viral nonstructural proteins is an indicator of infection, irrespective of vaccination status. When vesicular stomatitis or FMD is suspected, state and federal authorities should be contacted immediately (see Chapter 47).

Pathophysiology

In cattle, the usual incubation period is 2 to 14 days. The primary sites of infection and replication by FMD virus are the pharyngeal and digestive mucosa and alveolar epithelium of the udder. The virus replicates in the cells of the stratum spinosum. It spreads locally and also enters the circulation and is carried to other susceptible tissues. The mucosal cell disruption results in separation of superficial epithelium from basal epithelium, which fills with tissue fluids. Within 2 to 21 days, a fever begins and some vesicles appear. Vesicles develop in the mouth, on ruminal pillars, and in coronary bands. When the epithelial layers slough, erosions are left behind that take days to weeks to heal, depending on their size.

Necropsy Findings

In addition to oral erosions and ulcerations, ulcers may be seen on the ruminal pillars. In young cattle, myocardial and skeletal muscle degeneration and necrosis may be noted. The vesicles are characterized histologically by

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ballooning, cellular degeneration, intracellular and extracellular edema, and separation of the basal epithelium. There are no inclusion bodies. Myocardial and skeletal muscle degeneration characterized by Zenker necrosis may occur in young cattle.

Epidemiology

Transmission occurs primarily through animal contact, inasmuch as the virus is shed in bodily fluids (saliva, feces, urine, milk, semen). Contaminated fomites such as clothing, footwear, tires, equipment, and bedding spread the virus, and aerosol transmission can occur in favorable environmental conditions. Recovered cattle usually stop shedding the virus within 2 weeks. Detection of virus for longer periods from the oropharynx of cattle has been documented, but such “carriers” have, to date, not been shown to transmit disease to other cattle in natural environments. African Cape buffaloes can be lifelong carriers, but outside of Africa, they have not been shown to play a role in the transmission of the disease.[2]

The virus exists in milk, and at low levels, it may survive high-temperature short-time pasteurization (72° C [161° F] for 15 seconds or more). Uncooked or partly cooked meat products or garbage scraps, hides, or other tissues contaminated with the FMD virus from an endemic area of the world may transmit the disease long distances. The virus can persist in frozen meat for years.

FMD is endemic in Asia, Africa, the Middle East, and small regions in South America and southern Europe (Turkey), where losses involve not only those caused by the disease itself but also the monetary losses resulting from loss of export markets. Noteworthy are some outbreaks in previously FMD-free regions, including Great Britain in 2001 and 2007, Uruguay in 2001, Japan in 2010, South Korea in 2011, and Bulgaria and Turkey in 2011. A 2012 outbreak involving an SAT 2 strain in the endemic regions of Egypt produced an unusually high rate of mortality in adult cattle.

Treatment and Prognosis

Where FMD is endemic, understanding the epidemiology of the disease can provide insights on how to reduce and possibly eliminate the disease through management, movement control, and targeted vaccination. Good nursing care and judicious use of systemic antimicrobial drugs to limit secondary bacterial

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pneumonia and mastitis can be beneficial. Soft feeds such as chopped green grass (or soaked hay) are much more palatable than dry hay to sore-mouthed animals. The prognosis for survival is good, although affected animals may lose weight, have reduced milk production, and experience mastitis secondary to viral teat lesions.

Prevention and Control

The OIE and USDA websites contain information about current global disease status, which changes frequently. In FMD-endemic areas, managed movement and vaccination can reduce disease incidence. In FMD-free areas (Great Britain, the United States, Canada, Mexico, Japan, New Zealand, and Australia), control programs are based on rapid detection and response, including quarantine, biosecurity, managed movement, depopulation, vaccination, or a combination of these.[4]

The current vaccination strategy used globally is to use a serotype-specific, killed FMD vaccine. Immunity, both vaccine induced and naturally occurring, is short-lived, and vaccination usually must be repeated two or three times a year.[1] Vaccine provides partial protection, and subsequent infections usually result in subclinical or mild disease. Calves nursing immune dams are likewise partially protected by passive antibody for up to 5 months. Molecular vaccines are currently under development globally and in 2012, an adenovirus-vectored FMD vaccine was approved for conditional license in the United States. This vaccine does not require live virus production and could be used in the event of an outbreak in the United States. The decision to use FMD vaccine to control an outbreak is complex, and strategies related to production, distribution, and animal identification require adequate resources for effective implementation.

Peste des Petits Ruminants (PPR, Sheep and Goat Plague) and Rinderpest (Cattle Plague)

Bradford P. Smith

Definition and Etiology

Peste des petits ruminants (PPR) and rinderpest are acute, highly contagious, and usually fatal viral diseases of ruminants. PPR is still active and threatens goats and sheep, but OIE and the Food and Agriculture Organization have the goal of

eradication by 2030.[1,2] Rinderpest was officially declared by the OIE to be globally eradicated in 2011, mainly through vaccination. It is the second disease after smallpox to be eliminated.[3] Cattle and water buffaloes were most frequently affected by rinderpest, but the disease also occurred in yaks, gaur, sheep, goats, pigs, and other cloven-hoofed animals, in which it is usually less severe. It was rarer in camelids. Many wild animals in Africa are susceptible, including buffalo, lesser kudu, eland, giraffe, warthog, and wildebeest.

The viruses causing PPR and rinderpest are closely related RNA viruses in the Paramyxoviridae family, genus *Morbillivirus.* The viruses can remain viable for at least 1 year in frozen tissue but are killed by direct sunlight in 2 hours. Other morbilliviruses pathogenic for animals include canine distemper and the Hendra virus, which caused disease in horses and humans in Australia in 1994.

PPR is a highly virulent virus of goats, sheep and occasionally camels. There is only one serotype. It occurs in Africa, the Near East, Middle East, and Asia; outbreaks have occurred in approximately 76 countries. In 2016 it reached the edge of Europe in Georgia.[1] There do not appear to be any carriers or reservoirs besides domestic goats and sheep.[1] PPR has important negative economic effects in agricultural societies. An effective single-dose vaccine that confers lifelong immunity is available. There are also accurate diagnostic assays. Thus it is hoped that massive vaccination programs in domestic animals can eradicate PPR by 2030.

PPR morbidity rates can reach 100%, and the mortality rate can be between 50% and 100% in goats and sheep. Cattle and pigs develop inapparent infections. The disease also occurs in wild species, including several gazelles, gemsbok, ibex, and wild sheep. In 2015, a massive outbreak occurred among Mongolian wild Saiga antelope, triggering a die-off due to PPR. The reader is referred to the OIE website[1] for current information.

Clinical Signs and Differential Diagnosis

Clinical signs of PPR in goats and sheep are similar to those of rinderpest in cattle. For both PPR and rinderpest, the incubation period is usually 3 to 10 days, which is followed by sudden onset of fever, depression, and anorexia. The nose is dry, and mucous membranes are congested. Within days oral erosions appear where necrotic foci have sloughed. Purulent occular and nasal discharge occurs. Diarrhea is severe and may be bloody. Interstitial pneumonia occurs, and secondary bacterial bronchopneumonia is common. Dehydration and starvation

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often lead to death.

In small ruminants with signs of PPR, bluetongue and Nairobi sheep disease must be ruled out.

In endemic areas, rinderpest is suspected in cattle when the signs described earlier occur in groups of animals. In nonendemic areas diseases that appear similar clinically are BVD-related mucosal diseases, MCF, arsenic poisoning, severe coccidiosis, and severe fulminating infectious bovine rhinotracheitis, as well as FMD and vesicular stomatitis.

Laboratory Diagnosis

A rapid strip test for PPR can be used in the field.[4] Laboratory confirmation of PPR or rinderpest virus can be accomplished by virus isolation; PCR; ELISA; detection of viral antigen by fluorescent antibody testing, virus neutralization, or agar gel immunodiffusion; counterimmunoelectropheresis; detection of rising antibody titer by ELISA or virus neutralization[5]; and histopathologic evaluation, including immunohistopathologic study. Virus isolation is most successful in the first days of infection (often before the onset of diarrhea). Blood should be taken in heparin. The lymph nodes and spleen are reliable sources of virus, as are tears and ocular discharges. Lymph node biopsy after day 3 of infection is the most reliable means of diagnosis in a living goat. Tissues should be shipped frozen on ice to the laboratory for virus isolation or detection of antigen. Detection of a rising antibody titer can help diagnose the disease retrospectively. Leukopenia may be noted in the acute early stages.

Pathophysiology

The virus usually enters through the respiratory mucosa. Lymphoid tissue and epithelial cells of the GI and respiratory systems are the primary targets of rinderpest virus. Lymphocytes are destroyed in the germinal centers of the lymph nodes, Peyer's patches, tonsils, splenic corpuscles, and cecal lymphoid tissue. Immunosuppression occurs as lymphoid tissue is destroyed. The virus also attacks the alimentary tract mucosa; Peyer patches are the most severely affected. As alimentary mucosa is lost, diarrhea and emaciation become severe, and secondary bronchopneumonia usually develops as the respiratory epithelium is destroyed.

Epidemiology

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PPR and rinderpest are highly contagious and spread mainly through airborne droplets, direct contact, feces, and contaminated fomites such as human beings. All secretions and feces of infected animals are contagious throughout the course of the disease. Wild ruminants with active disease may be a source of infection for livestock. Because the mortality rate is high, treatment is unrewarding and the prognosis is poor, although individual animals can be helped by good nursing, fluid therapy, and antimicrobials to control bronchopneumonia. Innate or specific resistance may protect individuals or herds from clinical signs after infection. Recovered animals do not appear to act as carriers for more than a few months.

Necropsy Findings

Lesions are found mainly in the alimentary tract, lymphoid tissues and lungs. Subendocardial hemorrhages may also be seen in animals that die of acute illness. Oral erosions, edema, and congestion of the abomasum are typical, and ulcers and hemorrhagic to necrotic Peyer's patches occasionally are present. The cecal and colonic mucosae are hemorrhagic, ulcerated, or necrotic. The lymph nodes are enlarged and have necrotic germinal centers. Severe interstitial pneumonia frequently occurs,[5] and secondary bronchopneumonia is common.

Prevention and Control

Because there is only one known strain of PPR and one of rinderpest virus, protection after infection or vaccination usually is lifelong. Vaccination of susceptible animals at 6 months of age and older in endemic areas with a live attenuated virus is an effective means of control.[1,6] The vaccine does not produce adverse reactions, has a long shelf life if refrigerated, and produces solid immunity. Its major disadvantages are that the lyophilized virus has to be kept cold, and once a vial has been reconstituted, it must be used quickly before the virus dies. Research is yielding more stable vaccine without a cold chain for up to 30 days. [7]

Control of epidemics in areas where the disease is not endemic involves quarantine and slaughter of infected and exposed animals, as well as other contact ruminants and swine. Disinfection of premises while they are under government quarantine is essential for controlling the disease. The virus is susceptible to most disinfectants and survives in the environment for only 2 to 3 days. A comprehensive review was published in 2014.[8]

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Choke and Esophageal Disorders

Bradford P. Smith • Charles L. Guard

Definition and Etiology

Choke is the term used for esophageal obstruction. In ruminants it is most common in cattle because of their eating habits, but it has even been reported in a goat that ate thread with a needle attached.[1] If the obstruction is complete, the condition is rapidly fatal (except in neonates) because of the inability to eliminate the gases of fermentation produced in the ruminoreticulum. Partial obstruction produces dysphagia or anorexia. Obstruction may be caused by the ingestion of foreign objects or large chunks of solid feedstuffs such as apples, potatoes, beet tops, corn cobs, or even a mango.[2] Dry grain, particularly in pellet form, may be consumed so rapidly that sufficient saliva is not produced to lubricate the passage of the feed boluses. This is more common in sheep than in other ruminants; with grain, spontaneous resolution usually occurs within minutes to hours. Obstruction also may be the result of space-occupying lesions in or near the esophagus. Choke must be differentiated from diseases that cause dysphagia by means of pharyngeal lesions and resultant neuromuscular dysfunction. Congenital or acquired lesions of the esophagus, such as aortic arch anomalies and diverticula, may cause signs similar to those of esophageal obstruction.

Clinical Signs and Differential Diagnosis

The earliest signs of complete esophageal obstruction from intraluminal objects are anxiety and ptyalorrhea (i.e., saliva dripping from the mouth because of an inability to swallow). The animal may violently swing the head from side to side and make repeated attempts to swallow. Staggering (which must be differentiated from ataxia caused by neurologic diseases) may be observed. Bloat develops soon after at a rate that depends on the nature of the ruminoreticular contents.

Intraluminal objects commonly causes obstruction in the cranial part of the cervical portion of the esophagus, at the thoracic inlet, or at the base of the heart. In a 2-week-old calf with a cloth foreign body obstructing the distal esophagus at the cardia, regurgitation after drinking milk was observed.[3] External palpation may localize the site of obstruction in the cervical portion of the esophagus. With

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more slowly developing and incomplete obstruction, anorexia and dysphagia may be observed. Bloat may occur repeatedly and resolve spontaneously or after passage of a stomach tube. The underlying cause may result in signs severe enough to mask the esophageal problem. Cellulitis along the cervical portion of the esophagus may result in a reluctance to lower the head or bend the neck laterally. Possible causes of cervical cellulitis include perivascular injection of irritating substances, abscesses, and reaction to *Hypoderma lineatum* larvae.

Esophageal stricture may follow a previous episode of esophageal obstruction or inflammation in adjacent tissues. If no site of obstruction is externally evident, careful attempts to pass a stomach tube usually reveal the site of the problem. Radiography with barium contrast material may help identify the site of strictures, perforations, and diverticula. Endoscopy of the esophagus may also aid in identifying the specific nature of functional or structural abnormalities. Megaesophagus has been observed after pharyngeal trauma, as a congenital disorder, and with hiatal hernia. An esophageal stricture or a diverticulum may cause reflux of boluses of feed mixed with saliva or regurgitation of liquid ruminal contents. Failure to gain weight or progressive weight loss accompanies the failure to swallow feed successfully. Signs may be seen only when forage is consumed, whereas water and grain are swallowed normally.

Systemic diseases may lead to esophageal dysfunction. Rabies must always be considered when dysphagia is present, and appropriate precautions must be taken. Botulism also leads to esophageal transport failure, although dysphagia and a weak tongue are more prominent in the affected animals that do not eat. Tetanus may be similar in appearance to esophageal obstruction because of the presence of bloat, dysphagia, and drooling. Several poisonous plants, including sneezeweed, larkspur, and milkweed, may cause excessive salivation, drooling, and bloat. Consumption of red clover infected with the fungus *R. leguminicola*, which produces the toxin slaframine, results in copious salivation. Pharyngeal trauma and subsequent cellulitis lead to dysphagia and drooling, but severe bloat does not occur unless the swelling is sufficient to occlude the esophagus. However, mild bloat frequently accompanies pharyngeal trauma caused by associated vagal nerve inflammation and dysfunction.

Clinical Pathology

Common features of long-standing choke are dehydration and metabolic acidosis resulting from continued loss of sodium bicarbonate and sodium phosphate in saliva. As sodium depletion develops, the composition of saliva shifts to include

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more potassium under the influence of aldosterone. Inflammatory diseases lead to predictable changes in the hemogram.

Necropsy Findings

Animals that die of acute esophageal obstruction are bloated and may have saliva and feedstuffs in the upper airway. Postmortem examination of animals with protracted esophageal dysfunction may reveal focal dilations or stenoses of the esophagus. Esophageal perforation may have occurred because of pressure around an intraluminal foreign body or necrosis caused by extension of an adjacent septic process.

Treatment and Prognosis

In cases of complete esophageal obstruction, relieving bloat is the first concern. Passage of a stomach tube may be attempted if the animal is not in respiratory distress. Trocharization of the rumen or installation of a temporary fistula may be required. Until the esophagus has been cleared, it is important to keep the muzzle level or pointed down to reduce the risk of aspiration of saliva. Sedative drugs such as acepromazine or xylazine may be useful for calming an animal and enabling careful examination. Suitable precautions should be taken if rabies is remotely possible. The history and an examination of the environment should enable the clinician to anticipate the nature of the obstructing object. Palpation of the neck along the left jugular furrow may reveal the site of obstruction in lean or thin-necked animals. A manual oral examination should precede probing attempts with a stomach tube. Gentle pressure on the stomach tube as it passes down the esophagus should allow localization of the obstruction. A small hand can reach into the cranial part of the esophagus and may retrieve some solid objects. If the object is solid (e.g., a potato), it may be possible to massage it into the pharynx by pressing in the jugular furrow on both sides of the neck. Specialized equipment, such as a probang, is available with a corkscrew-like or pincer-like end that can be used to grasp or engage a foreign body and expedite its retrieval. If a mass of grain is obstructing the esophagus, external massage, probing with the stomach tube, or pumping fluid against the mass through the tube may break it up.

If the choke is intrathoracic and probing with a stomach tube does not relieve the problem, several courses of action are possible. A small ruminal fistula can be inserted to prevent bloat, and the animal can simply be placed in a pen

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without bedding, feed, or water. Many masses consisting of grain or hay spontaneously pass within 24 hours, whereas solid objects rarely pass spontaneously. If the obstruction does not resolve in 24 hours, the animal can be heavily sedated, a cuffed endotracheal tube can be passed to prevent aspiration, and vigorous lavage with water through a stomach tube can be attempted. The head should be held lower than the body to minimize the risk of aspiration. If the obstruction still cannot be relieved or it is believed that the obstruction is a solid object, a rumenotomy can be performed. Access to the esophagus through the cardia should allow snaring of the object with a loop of stiff wire or breakup of a mass of grain.

The long-term prognosis after choke is good unless the esophageal mucosa has been damaged. Stricture formation may follow cellulitis or pressure necrosis at the site of the obstruction. Aftercare for the choked animal consists of a soft diet and antiinflammatory drugs to minimize tissue swelling. Well-soaked alfalfa cubes made into a mush may pass partly obstructed areas. Hay and grain should be moistened before feeding, and grain should be offered only in small amounts at each feeding. Broad-spectrum antibiotics should be given if mucosal damage is suspected. Maintenance of an indwelling nasogastric tube for feeding for up to 10 days after severe esophageal trauma may be helpful in preventing strictures during healing. Thick gruels made from soaked alfalfa cubes or pellets can be pumped into the rumen by a bilge pump designed for boats, or the animal can be fed and watered through a ruminal fistula. Surgical exploration may be required to determine the cause of esophageal obstruction from space-occupying lesions or strictures. Abscesses may be drained, and granulomatous lesions resected. Esophageal diverticula, aortic arch anomalies, and intrathoracic surgical problems are not easily treated.

Esophageal Dilation (Megaesophagus) and Hiatal Hernia

Bradford P. Smith

Megaesophagus rarely occurs in ruminants. It has been reported in association with pharyngeal trauma and resultant inflammatory involvement of the vagus[1] and with hiatal hernia (diaphragmatic hernia with herniation of the reticulum into the thorax) in which the megaesophagus was large (10 cm in diameter × 20 cm in length).[2] Vagotomy and hiatal hernia are recognized as causes of diminished esophageal pressure. A 4-month-old calf with megaesophagus lacked

esophageal muscle cells and ganglion cells, and many fat cells were present.[3] The esophagus of a 12-month-old ram with megaesophagus was found to be heavily infected with *Sarcocystis arieticanis*, and eosinophilic inflammation and degeneration of muscle fibers were noted.[4] However, *Sarcocystis* spp. have been found in the esophagus of many sheep without megaesophagus, which makes the diagnosis difficult. An 18-month-old heifer with megaesophagus also had eosinophilic submucosal infiltration, but no sarcocysts were seen.[5] Megaesophagus due to unknown causes in a goat was also reported.[6]

The principal clinical signs of megaesophagus are regurgitation and vomiting, usually shortly after eating. Mild, recurrent bloat and discomfort when a stomach tube is passed are also observed. In other cattle with a hiatal (diaphragmatic) hernia or an esophageal diverticulum, regurgitation or vomiting and bloat have also been reported. Contortion of the neck while eating, apparently caused by pain, was seen in one cow and is reported in human beings with hiatal hernia. In some cases of herniation of the reticulum into the thorax, bloat and regurgitation are not seen; in others, diaphragmatic hernia resulted in chronic bloat.[7] Diaphragmatic hernias may be either congenital or acquired. It appears that acquired diaphragmatic hernias are most common.

A stomach tube should be passed to the rumen to rule out choke or an intraluminal mass obstructing the esophagus as a cause. If a tube can be passed freely to the rumen, plain and contrast radiographs of the esophagus should be taken. If this is not possible, the abdomen should be explored surgically for a diaphragmatic hernia, and the cardia and terminal esophagus should be palpated digitally by means of rumenotomy.

Megaesophagus associated with pharyngeal trauma has a good prognosis,[1] whereas megaesophagus associated with hiatal hernia has a more guarded prognosis.[2] Supportive treatments and stomach tubing with fluids may be required for 1 to 2 weeks until the animal is able to drink unaided. Longer-term support can be given to a valuable animal by surgical creation of a ruminal fistula fitted with a rubber cannula through which feed and water can be given until normal deglutition returns.

Ultrasonography of the Ruminant Abdomen

Sébastien Buczinski

Medical indications of ultrasonography in cattle and small ruminants have

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expanded since the 1990s. This ancillary test can be performed at the patient's side and gives valuable information to confirm a clinical hypothesis. As for any diagnostic test, it is important for the clinician to know what he or she is looking for before performing the procedure. The cattle abdomen is vast, and a complete abdominal screening (including reticulum, spleen, abomasum, small and large intestines, bladder, kidneys, and uterus in females or inguinal area in males) can be time consuming and not practical in field situations. Practical questions that the clinicians can have in mind when planning abdominal ultrasonography are numerous. To this author's knowledge, in dairy practice, the most common questions to be answered by this test are as follows: (1) Does the affected cow have cranial peritonitis? (2) If so, what is the main presumptive diagnosis, depending on the localization of fluid and effect on reticular motility? (3) Is the right-sided ping truly caused by abomasal dilation, or is another organ the source? (4) Where is the pyloric part of the abomasum when left displaced abomasum is suspected but no typical ping is heard? (5) Does a cow with colic (e.g., evidence of intestinal obstruction) need immediate surgery? (6) Is the right kidney involved when left kidney pyelonephritis is suspected? (7) When peritonitis is suspected because of unsuccessful blind abdominal tap, can a better spot be chosen? All these questions can be answered rapidly (in less than 15 min) with a focused ultrasonographic examination

Units and Probes Required

The required characteristics of the ultrasound unit used for this examination depend on the size of the patient. For small calves (e.g., preweaned dairy calves weighing less than 100 kg [220 lb]) and small ruminants, a rectal linear probe (≥5 MHz) can generally be used for assessing abdominal structures and intraabdominal umbilical remnants. For larger animals, a lower frequency probe (<5 MHz) is needed to increase the penetration depth of the ultrasound beam (20 to 30 cm depth is obtained by a 2- to 3.5-MHz probe). The probe can be either linear, sectorial, or convex. Several portative ultrasound units are now available and produce good-quality images that can be used for medical diagnosis in ruminants.

Secondary characteristics of the ultrasound unit that may be suitable, especially in a teaching environment, are the ability to perform measurements (distance or area measurements), as well as the ability to store pictures and videos. These characteristics may help monitoring lesion progression and are very helpful if a second opinion is required and the examination has been

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performed on the farm.

Patient Preparation

The area of interest needs to be clipped or shaved. Then the skin can be rubbed with a moist towel before coupling gel that allows a good contact between the skin and the probe is applied. This standard preparation is the best way to obtain high-quality images. For a rapid screening, the author sometimes uses only direct spray application of 70° isopropyl alcohol on the skin (and only if hair is short and clean). The disadvantage of this preparation is premature wear of probe pad, which will eventually need to be replaced. In most situations, no specific containment other than head restraint (eg halter) is required, at least in dairy cattle, which are frequently manipulated for milking purpose. If the animal is not coooperative, another operator can be required to prevent injury or damage to the equipment.

General Comments About Ultrasonography Performance

Despite its more frequent use for medical purposes in cattle and small ruminants, there is a relative paucity of data concerning the accuracy of ultrasound examination (in terms of sensitivity and specificity). There are some reports as case-series or case-control studies from referral veterinary centers (eg university hospital). In many situations, ultrasonography is helpful for determining abnormal organ position, parenchymal anomalies or presence/extension of free abdominal fluid. The definitive diagnosis is generally reached by additional ancillary testing (e.g., clinical pathologic study, microbiological analysis, cytologic study, or biopsy). Ultrasonography is very helpful for selecting the best area to obtain these additional diagnostic samples.

Normal and Main Abnormal Ultrasonographic Aspects of Abdominal Organs in Calves and Cows

A thorough knowledge of the abdominal anatomy and normal ultrasonographic aspect of the abdominal organs is necessary to reach the confidence level necessary to perform this ancillary test. The major organs or structures that can be assessed with ultrasonography are the peritoneal space, reticulum, abomasum, small and large intestines, liver, kidneys, uterus, and ovaries. Other structures such as the omasum, rumen, pancreas, mesenteric lymph nodes, and abdominal vessels can also be assessed for specific purpose (Fig. 32.96) such as ruminitis,

pancreatitis, and lymphadenomegaly.

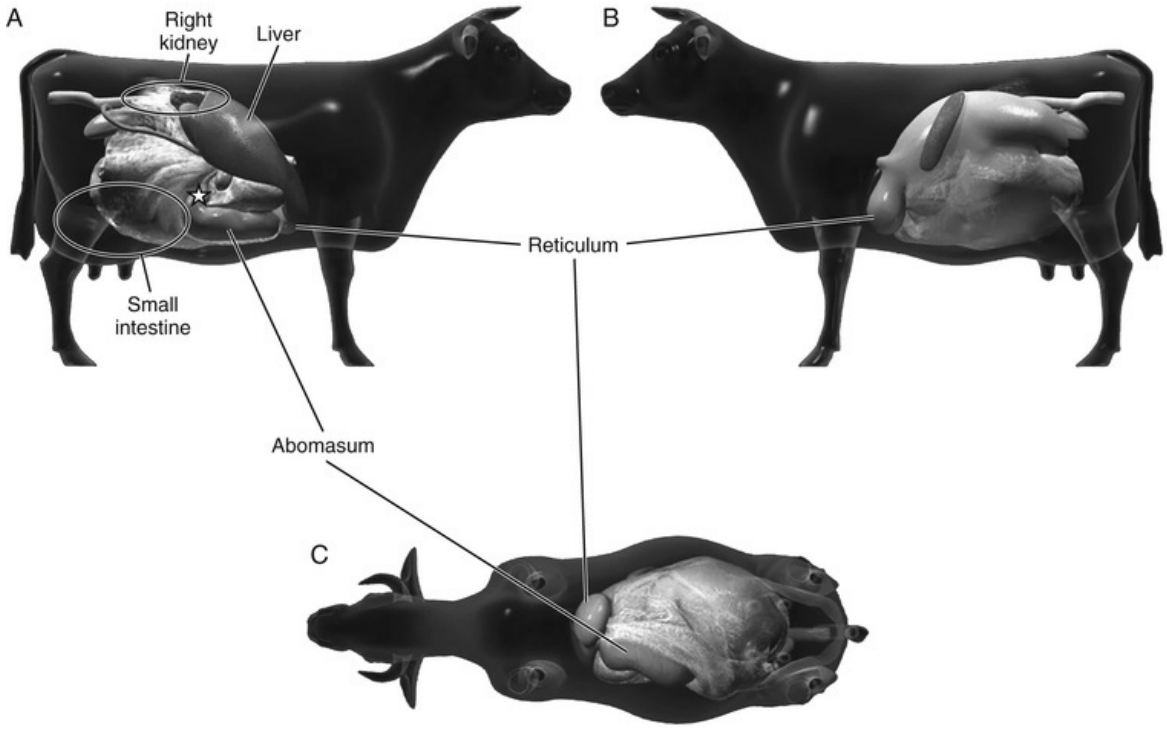


FIG. 32.96 **Practical anatomic landmarks for abdominal ultrasonography in a cow. The right (A), left (B), and ventral (C) views of the abdomen. The reticulum, abomasum (and pyloric part of the abomasum *[star]*), liver, small intestine, and right kidney area of interest are represented in the three different views. (Courtesy Dr. André Desrochers and Dr. Denis Harvey, from *Surgery of the abomasum in cattle, Version 2.0*, Université de Montréal.)**

The Peritoneal Cavity and Peritoneal Fluid Assessment.

Abdominal ultrasonography is a sensitive technique for detecting peritoneal fluid accumulation. The peritoneal fluid is generally present in small amount in the normal abdomen and serve as a lubricant. The peritoneal fluid quantity physiologically increases in late pregnancy because of hypervolemia and possible increased hydrostatic pressure on abdominal vessels secondary to mass effect of the fetus. Large quantities of free abdominal fluid can manifest as ascites (secondary to congestive heart failure or in the presence of caudal vena cava thrombosis; Fig. 32.97). Inflammation of the peritoneal cavity (peritonitis) is a common cause of focal or diffuse accumulation of free abdominal fluid. The typical findings in cases of peritonitis consist in the presence of heterogenic liquid content with various amounts of echoic to hyperchoic fibrin strands as

shown in Fig. 32.98. Depending on the condition chronicity and the bacteria involved, secondary abscessation and images associated with gas-producing bacteria can also be observed, as with a retroperitoneal abscess in Fig. 32.99. The retroperitoneal abscess can be distinguished from peritonitis because the accumulation occurs between the parietal part of the peritoneum layer and the transverse muscle.

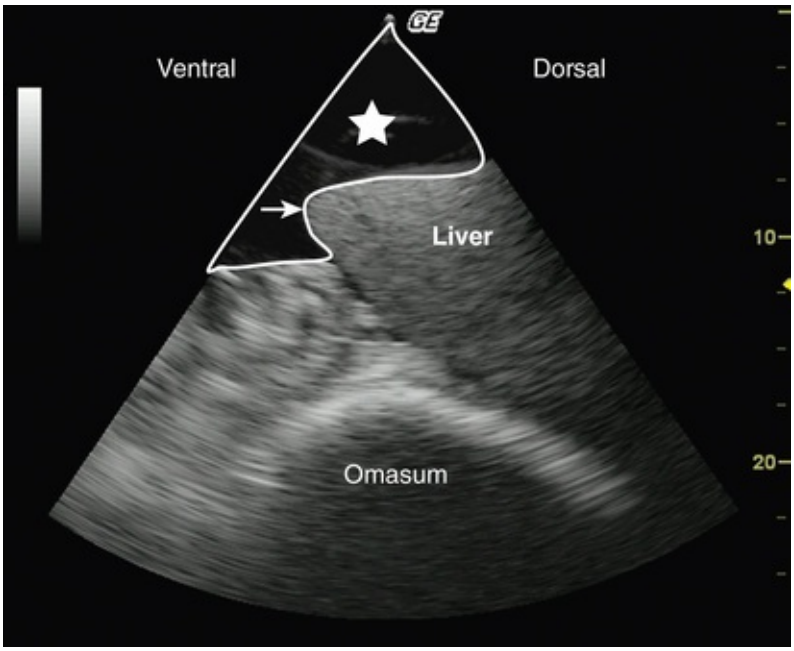


FIG. 32.97 **Ascites secondary to congestive heart failure in a dairy cow. Large amounts of anechoic fluid are observed on right flank ultrasonography *(star).* The ventral border of the liver is also observed. The liver ventral border is not as sharp as usual because of hepatomegaly *(arrow).* Image obtained with a phased-array 2.5-MHz probe (maximal depth, 27 cm).**

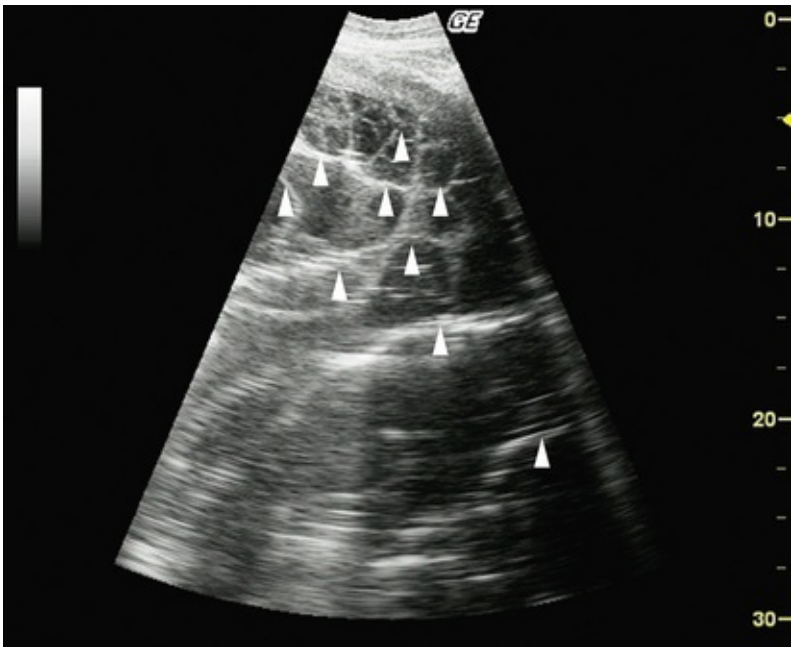


FIG. 32.98 **Sonogram of caudal peritonitis in a cow secondary to uterine laceration. A large amount of peritoneal fluid is observed. The "spider-web" appearance is due to the multiple echoic fibrin strands *(arrows).* Image obtained with a sectorial 3.2-MHz probe (maximal depth, 30 cm).**

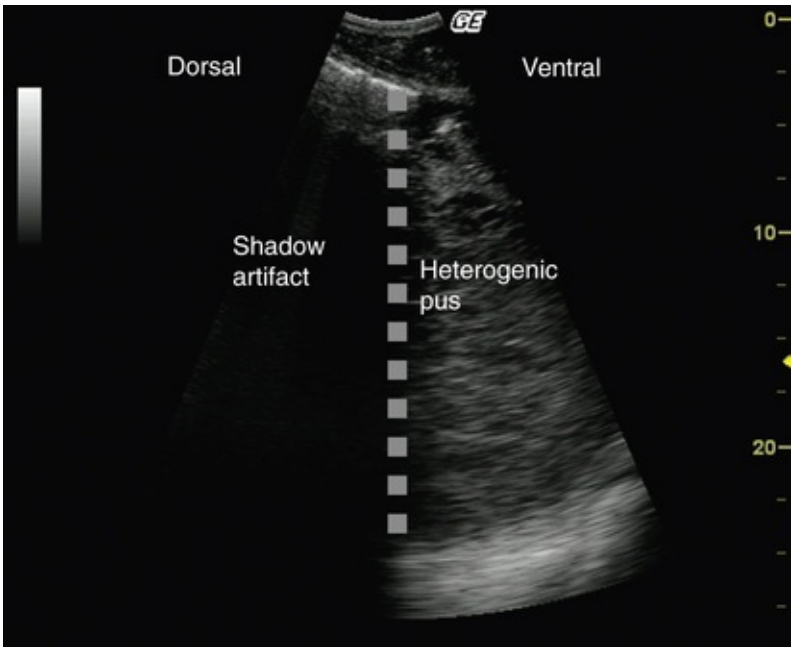


FIG. 32.99 **Gas-liquid interface seen in a cow with retroperitoneal abscess secondary to right flank laparotomy. The gas-tissue interface *(gray dotted line)* was caused by gas-producing bacteria present in the abscess. The shadow on the dorsal part of the flank is an artifact. Heterogenic pus is visible on the ventral part of the sonogram. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 28 cm).**

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Forestomachs.

The reticulum, rumen and omasum have the same ultrasonographic aspect. They have a thick hyperechoic wall. Their content cannot be imaged because of the presence of small gas bubbles in the rumen fluid (reverberation artifact). The topography of the scanning area for the main abdominal organs is represented in Fig. 32.96.

The reticulum can be imaged mainly in the left cranioventral abdomen in the area between the xyphoid process of the sternum and cranial to the left mammary vein (Fig. 32.100). The reticulum is recognized by its periodic biphasic movements (Video 32-1) during contractions preceding ruminal contractions. These biphasic contractions generally occur at the frequency of 1 per minute. Initially, a low-amplitude contraction (reticulum pushed from 5 to 10 cm deep in the abdominal cavity) is observed; then the reticulum returns to its relaxed state. Immediately after, a complete contraction (>17 to 18 cm) occurs.[1] The general ultrasonographic landmarks that can be used to identify the reticulum is the musculophrenic vein, which is an anechoic tubular structure between the abdominal wall and the diaphragm (Fig. 32.100). The reticulum wall is smooth and slides easily along the abdominal wall. The honeycomb structure of the wall is occasionally observed.

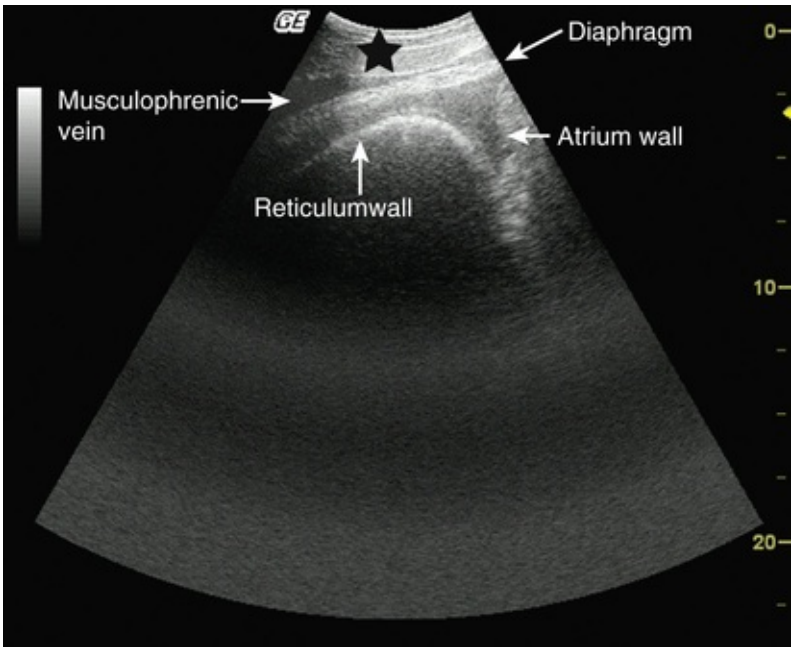


FIG. 32.100 **Sonogram of the reticulum at the beginning of its first contraction. The reticulum wall is characterized by its hyperechoic aspect. Because of gas content, no forestomach content can be seen. The musculophrenic vein allows distinguishing the diaphragm and abdominal wall *(black arrow).* The atrium wall is partially visible. At the beginning of the first contraction of the reticulum, the space between the reticulum and the diaphragm is slightly increased in comparison with the that between contractions. Better contrast enables easier reading of the sonogram. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 23 cm).**

The main abnormality seen during reticular assessment is associated with cranial peritonitis such as in hardware disease. In these cases, heterogenic fluid accumulation between the abdominal and reticular walls is generally observed (exudate with fibrin strands or clots; Fig. 32.101). In these cases, the motility of the reticulum is most often abnormal, with decreased frequency and amplitude of contractions due to pain and adherences. Other findings associated with hardware disease are deformation of the reticular wall Fig. 32.102, increased wall thickness due to fibrin deposit, and abscessation characterized by a cavitary lesion Fig. 32.103. The foreign body cannot be imaged in most cases. Therefore the definitive diagnosis is based on clinical findings, extension of the peritonitis findings (mainly left-sided), and other imaging tools such as abdominal radiographs.

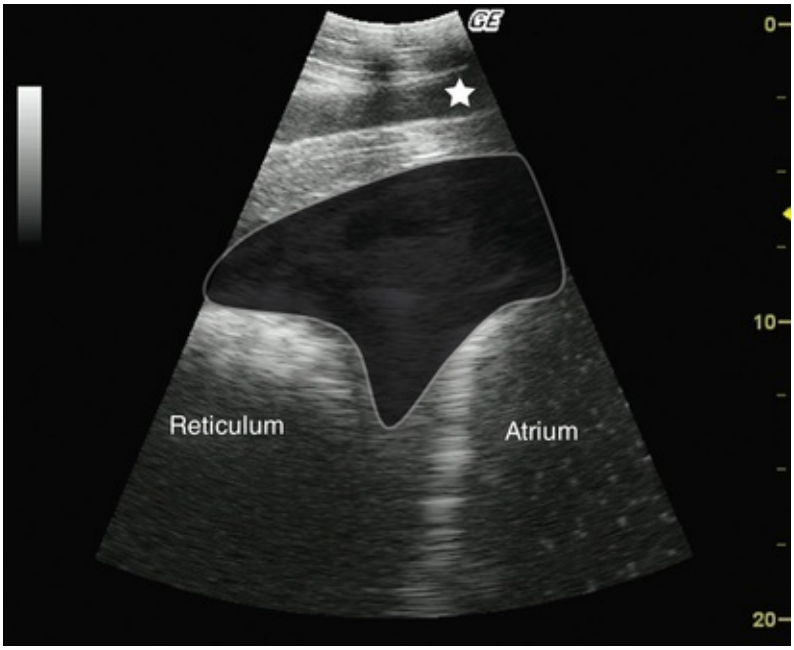


FIG. 32.101 **Typical aspect of traumatic reticuloperitonitis in a dairy cow. The heterogenic peritoneal content *(shaded area)* between the diaphragm, reticular wall (left), and rumen atrium wall (right) is observed. The diaphragm is surrounded by the musculophrenic vein *(star)* and peritoneal fluid. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 20 cm).**

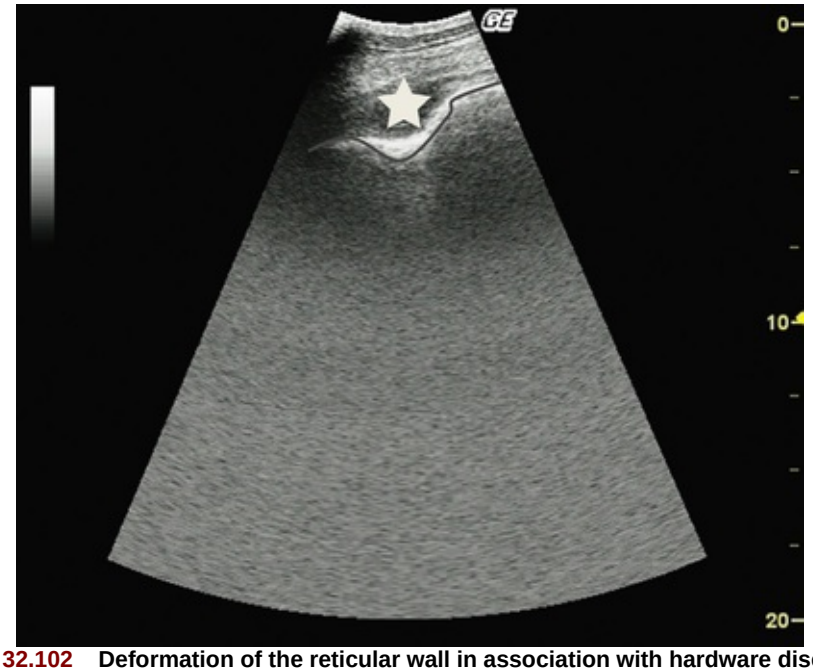


FIG. 32.102 **Deformation of the reticular wall in association with hardware disease. The reticular wall (highlighted in *gray*) is different from its traditional smooth appearance due to the presence of peritonitis *(star)* and focal increased pressure. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 20 cm)**

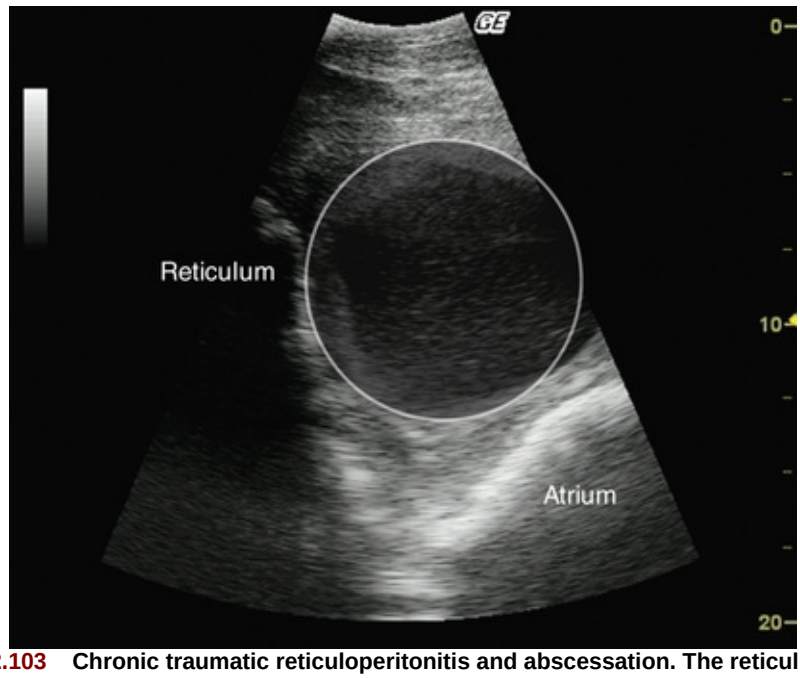


FIG. 32.103 **Chronic traumatic reticuloperitonitis and abscessation. The reticulum and**

atrium walls are visible. The atrium is pushed dorsally because of a cavitary lesion with an heterogenic content and thick wall (abscess). Image obtained with a sectorial 3.2-MHz probe (maximal depth, 20 cm).

The rumen and omasum are also seen as hyperechoic thick-walled viscera, but no content is visualized. The rumen occupies most of the left abdominal cavity, whereas the omasum is observed at the visceral border of the liver. The clinical value of specifically assessing these organs remains to be determined.

The abomasum has a distinct ultrasonographic appearance in comparison with others. The abomasal wall is thinner and can sometimes be difficult to identify specifically with a low-frequency probe. The normal abomasum position varies greatly throughout the production phase of a dairy cow. This organ is pushed cranial to the left in late pregnancy and then is slowly displaced toward the right ventral part of the abdomen. The pyloric part of the abomasum has specific characteristics used to localize the abomasum position. This portion has a thick multilayered wall and is most often observed as a crescent shape structure oral to the cranial part of the duodenum (Fig. 32.104**)**. The posterior (deeper) wall of the pyloric part is generally not observed because of shadow artifact associated with gas content of the viscus.

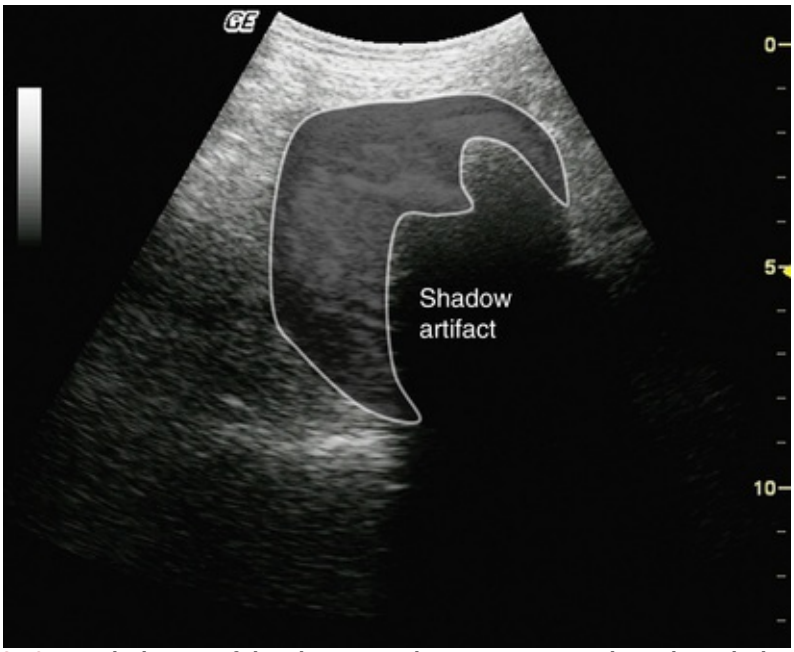


FIG. 32.104 Pyloric part of the abomasum in transverse section. The pyloric part of the abomasum has a thick layered wall. The characteristic crescent shape is visible because of residual gas within the abomasal lumen. A shadow artifact is therefore observed. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 13 cm).

Because of the difficulty in characterizing abomasal position, the pylorus position is a useful indicator of abomasal position when an abomasal displacement is suspected with no ping on auscultation or when right-sided ping indicates abomasal dilation. In these situations, the pylorus is not in its normal specific position, and secondary findings associated with abomasal dilation, such as the presence of a gas-liquid interface (on the left or right), can be observed (Fig. 32.105). When a "floating" displaced abomasum is suspected, the pylorus is generally found medial to the right mammary vein or close to the ventral midline. In these situations, ultrasonography may help in treatment decision. In case of abomasal dilation or volvulus of the abomasum, the distended abomasum precludes normal observation of the liver. The position of the pylorus is also interesting to distinguish abomasal dilation from volvulus because the pyloric part of the abomasum is observed more cranially in cases of volvulus. Infiltration of the abomasum by lymphomatous tissue can also be suspected when imaging the pyloric part of the abomasum (Fig. 32.106). In these conditions, transabdominal fine-needle aspiration or biopsy in the thickened wall may help determine the final diagnosis.[2]

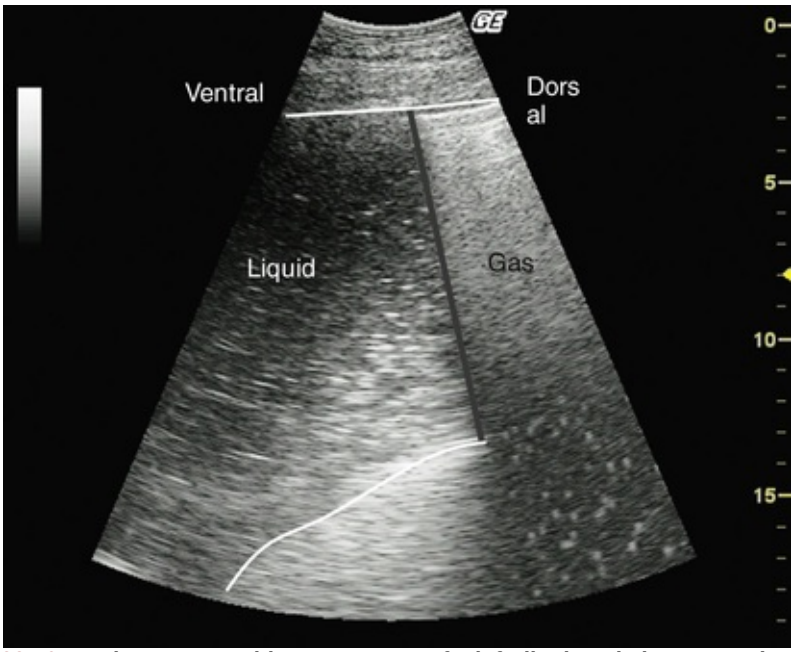


FIG. 32.105 **Ultrasonographic appearance of a left displaced abomasum (or right abomasal dilation/volvulus) A gas-liquid interface is observed *(gray dotted line).* The abomasal wall is indicated with *white lines.* The medial wall cannot be observed on the dorsal part because of the presence of gas within the distended abomasum. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 19 cm).**

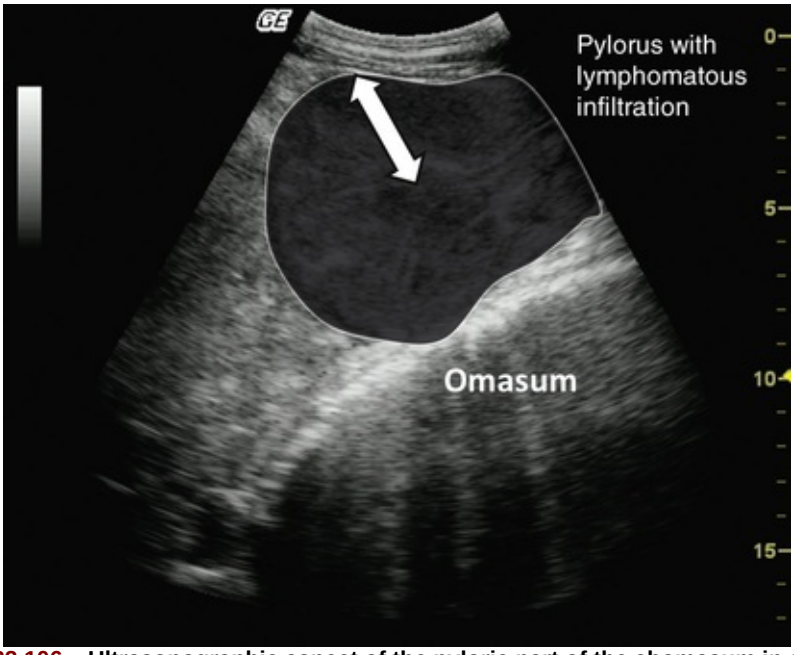


FIG. 32.106 **Ultrasonographic aspect of the pyloric part of the abomasum in a cow with abomasal infiltration by lymphomatous tissue. The wall of the pyloric part is thickened (3 to 5 cm; *arrows*), as is the cross-section of the pylorus *(gray shaded area).* The multilayered structure of the enlarged pylorus is also visible. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 17 cm).**

Abomasal ulcers cannot be observed with ultrasonography. Perforating ulcers can be suspected when finding images compatible with peritonitis are close to the abomasal projection area (Fig. 32.107). However, these findings are not specific and can be associated with any cause of peritonitis.[3]

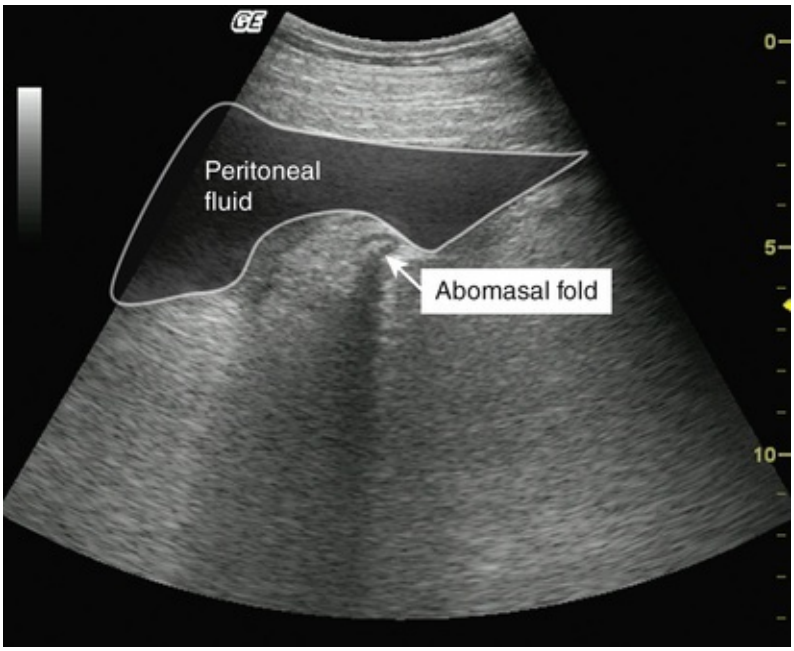


FIG. 32.107 **Cranial peritonitis associated with perforating abomasal ulcer. Hypoechoic peritoneal fluid accumulation is visible close to the abomasum. The abomasum is recognized by hypoechoic abomasal fold. Abomasal ulcer was suspected because of the localization of peritonitis close to the abomasum. However, it cannot be definitively diagnosed without other ancillary testing (e.g., laparotomy or necropsy). Image obtained with a sectorial 3.2-MHz probe (maximal depth, 14 cm).**

Small and Large Intestines.

Ultrasonography of the small and large intestines is generally straightforward. The small intestine is generally observed in the midventral part of the right flank. Multiples loops of small intestine are observed; constant movement indicates good peristalsis. The normal diameter of the small intestine is generally less than 4 cm, but its cross-sectional dimension varies constantly. The content of small intestine is generally visible as areas of variable echogenicity (Fig. 32.108, Video 32-2).

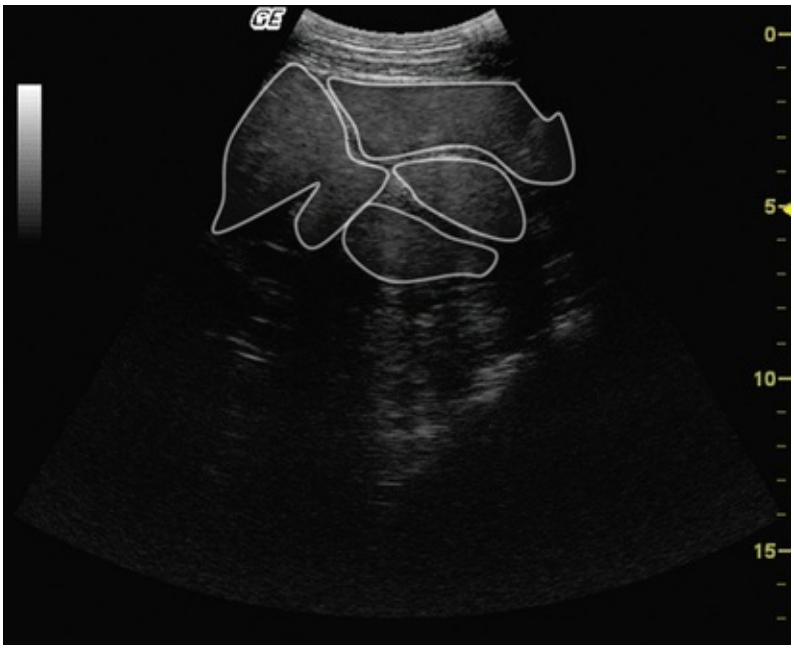


FIG. 32.108 **Sonogram of normal small intestine loops in an adult Holstein cow. The intestine loops are characterized by their various shapes, hypoechoic wall, and echoic content. Their wall is delimited by a *white line.* When imaging is done in real time, constant movement of the loops and their content is observed. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 17 cm).**

The most common abnormal findings during small intestine ultrasonography is ileus. In these situations (either paralytic or obstructive ileus), significant distention of the small intestine loops is observed with decreased motility (Fig. 32.109**,** Video 32.3). Secondary peritoneal effusion can be seen in association with impaired mesenteric blood flow and transudation. Edema of the intestinal wall can also be observed (e.g., wall thickness >2 to 3 mm)[3] (Fig. 32.110).

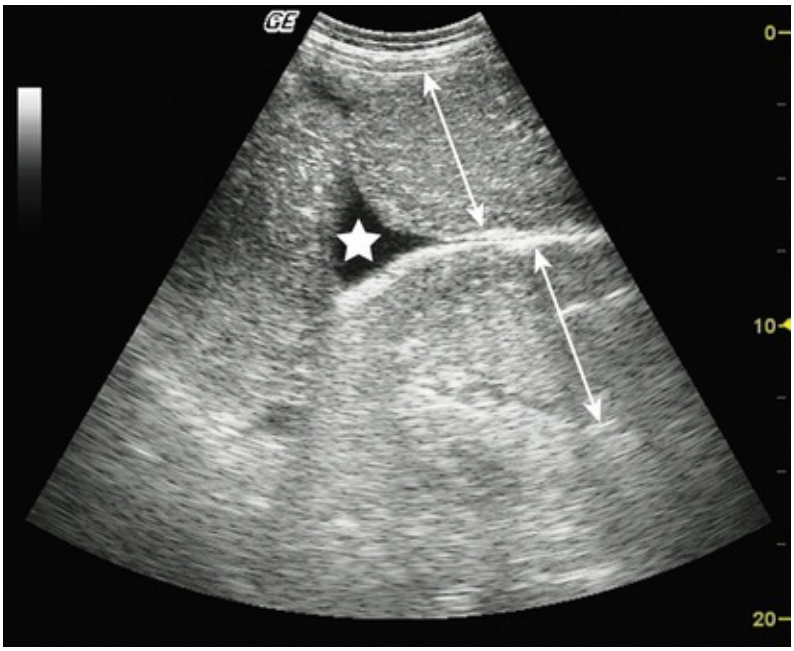


FIG. 32.109 **Sonogram of obstructive ileus associated with hemorrhagic bowel syndrome. An important distention of the small intestine loops is observed (>6 to 7 cm in diameter). Secondary anechoic peritoneal effusion is also observed *(star).* Image obtained with a sectorial 3.2-MHz probe (maximal depth, 20 cm).**

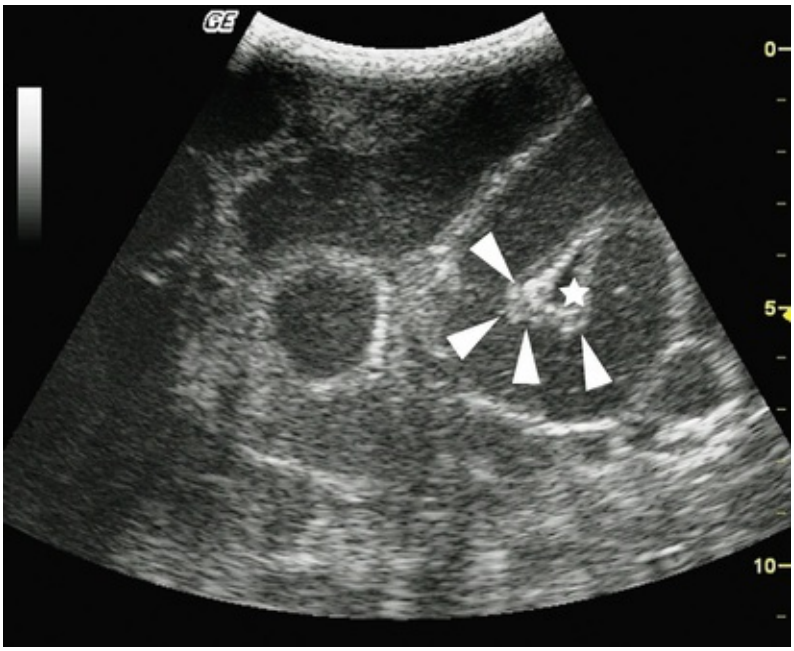


FIG. 32.110 **Sonogram of obstructive ileus secondary to atresia coli in a 3-day-old Holstein calf. Besides intestinal loops dilation and peritoneal fluid accumulation *(star),* thickening of the intestinal wall is also observed secondary to intestine wall edema *(arrowheads).* Image obtained with a sectorial 3.2-MHz probe (maximal depth, 12-cm).**

One of the main challenges during small intestine ultrasonography is to differentiate obstructive causes of ileus (i.e., necessitating surgical treatment) from medical causes. The exact cause of obstruction is rarely diagnosed on transabdominal ultrasonography because of the size of the bovine abdomen. However, identification of indirect consequences of obstructive ileus is an achievable goal that helps in the decision of medical or surgical treatment. In cases of obstruction, the visualization of distended (oral to the obstruction) and empty loops (aboral) of small intestine helps the clinician make the decision about whether surgery can be delayed.

The large intestine can be imaged by ultrasonography on the dorsal midright flank. However, limited information can be obtained. First, its content is full of gas and cannot be imaged. Second, it is difficult to identify each part of the large intestine. The thin large intestinal wall, which is close to the probe, can be observed. A shadow artifact hides deeper parts of the large intestine. The caecum can also be imaged with ultrasonography.[4] In general diagnosis of cecal problems relies on the transrectal examination findings. The general appearance of the caecum is the same as that of the large intestine (Fig. 32.111).

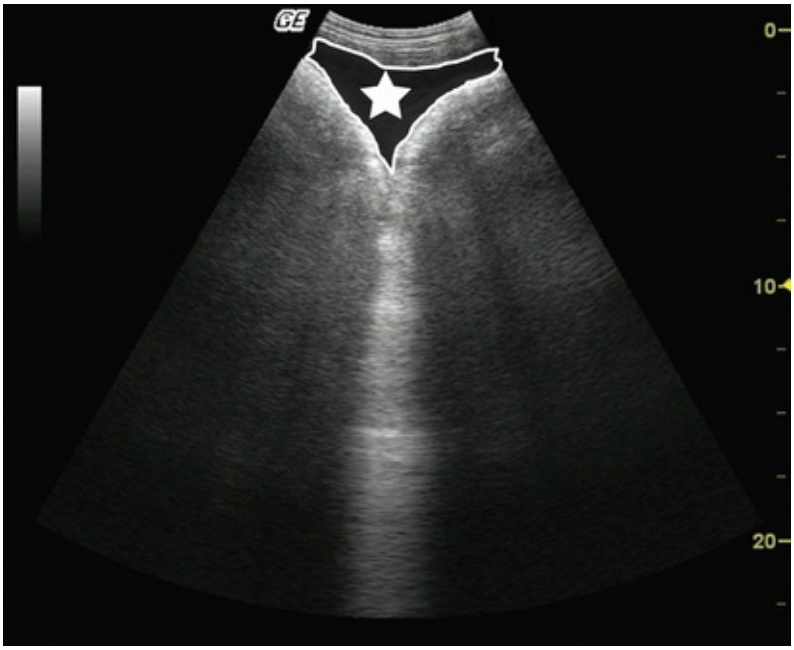


FIG. 32.111 **Right flank sonogram of large intestine in a Holstein heifer with cecal dilatation and torsion. The cecal/colonic wall is visible as a thin echoic wall. Because of the gas content, no ultrasound beam is transmitted beyond the superficial wall. Secondary findings associated with peritonitis (increased peritoneal fluid with small echoic fibrin strands) are outlined *(star).* Image obtained with a sectorial 3.2-MHz probe (maximal depth, 25 cm).**

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Liver Ultrasonography.

The liver can be imaged with transabdominal ultrasonography. A high-frequency probe can be used in calves, but a low-frequency probe is indicated for the assessment of the liver in adult cattle (especially if the caudal vena cava, which is located deep in the abdomen, is scanned). Prior knowledge of the liver anatomy is required, and the clinician must remember that an important part of liver parenchyma cannot be directly visualised because the diaphragmatic portion of the liver is surrounded by lung parenchyma. The screening area runs from the ventral fifth intercostal space to the last intercostal space.[5]

Different structures can be observed when the liver is scanned.[5,6] The liver parenchyma has a hypoechoic to echoic homogenous aspect. Small anechoic structures such as vessels or biliary ducts are visible within the parenchyma. The portal vein and major portal vessels, the caudal vena cava aspect (Fig. 32.112), and the gallbladder aspect (Fig. 32.113) are also observed during the ultrasonographic examination. Basic knowledge of the normal appearance of the liver and its structures is essential when ultrasonography is used on an animal with suspected liver disease. The right and caudate lobe of the liver can be observed, but a significant portion of the left lobe is not visible because of its relative position within the lung field. Pneumoperitoneum and abomasal right dilation/volvulus are also conditions that preclude a correct visualization of the liver parenchyma.

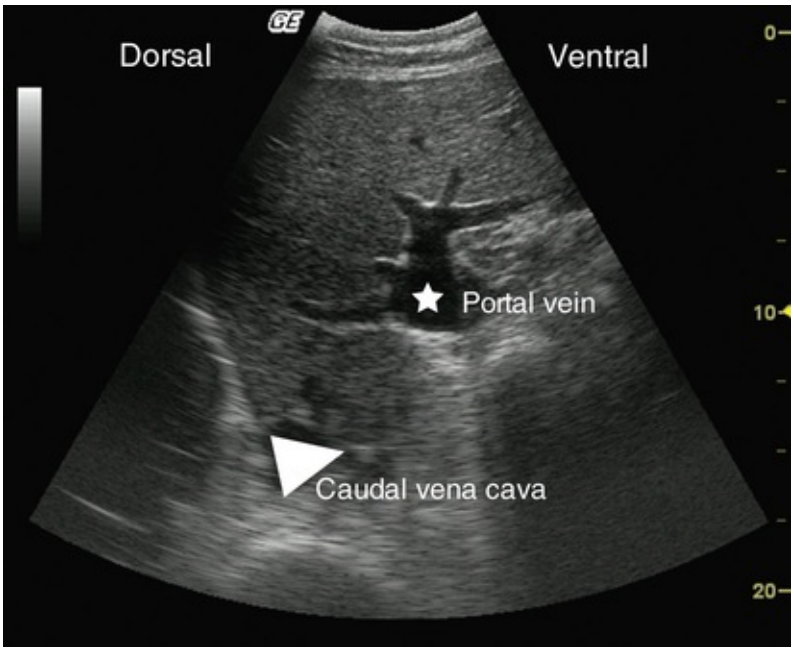


FIG. 32.112 **Ultrasonogram of the liver, showing the relative position of caudal vena cava and portal vein in a Holstein heifer. The liver parenchyma has an homogenous echogenic texture. The portal vessels and major portal vein are characterized by a hyperechoic wall *(star)* in the midvisceral part of the liver. The caudal vena cava is visible in the dorsal and deep part of the liver as a triangular shape. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 20 cm).**

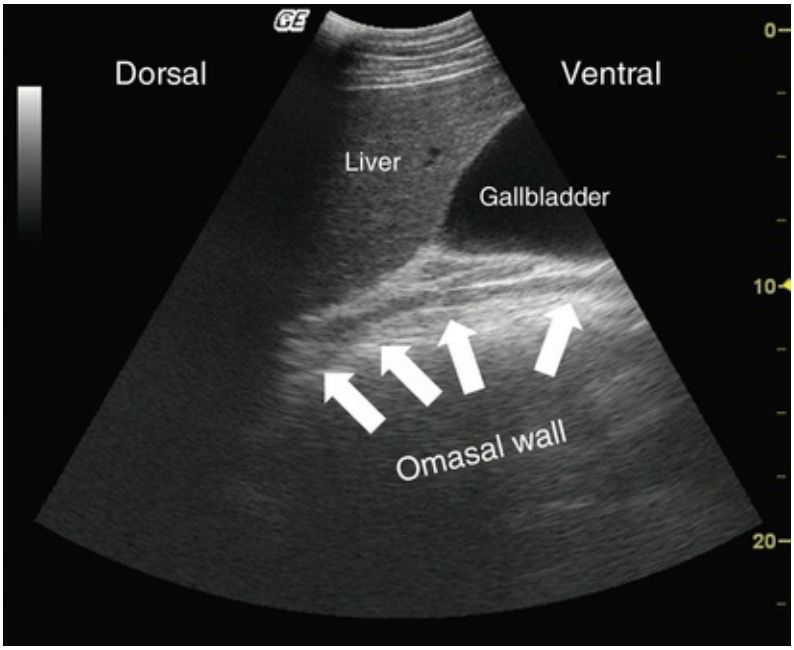


FIG. 32.113 **Normal aspect of the gallbladder. The gallbladder, as observed from the ninth to eleventh intercostal spaces, appears as a pear-shaped structure with anechoic content, originating from the ventral visceral surface of the liver. Image obtained with a sectorial 3.2-MHz probe at the ninth intercostal space (maximal depth, 22 cm).**

Liver ultrasonography is especially helpful for the diagnosis of liver abscesses, caudal vena cava thrombosis, and any focal or diffuse liver changes. Ultrasonography may help the clinician select the best area to perform liver biopsy or fine-needle aspiration for a definitive diagnosis.

Liver abscessation is a common hepatic condition in calves, dairy cows, and feedlot cattle.[7] The clinical signs are not specific, and liver ultrasonography is generally helpful if the affected site is not in the part of the organ beneath the lungs. Previous studies in feedlot calves have revealed the limited ability of ultrasonography to show lesions on the left hepatic lobe.[8] Cavitary lesions of various size and shape can generally be observed (Fig. 32.114). The abscess content can be homogenous to heterogenous. The definitive diagnosis is made through fine-needle aspiration to differentiate from liver neoplasm or cystic structures.[5] Liver neoplasms are uncommon in cattle, but the ultrasonographic aspect of hepatocellular adenoma, bile duct carcinoma, and adenocarcinoma have been reported.[9] The ultrasonographic changes are not pathognomonic and generally consisted in single to multiple circular structures. The definitive diagnosis necessitates biopsy or aspiration of the abnormal area. Liver metastasis secondary to the spread of a primary non hepatic tumor (e.g., lymphoma) has also been reported.[5]

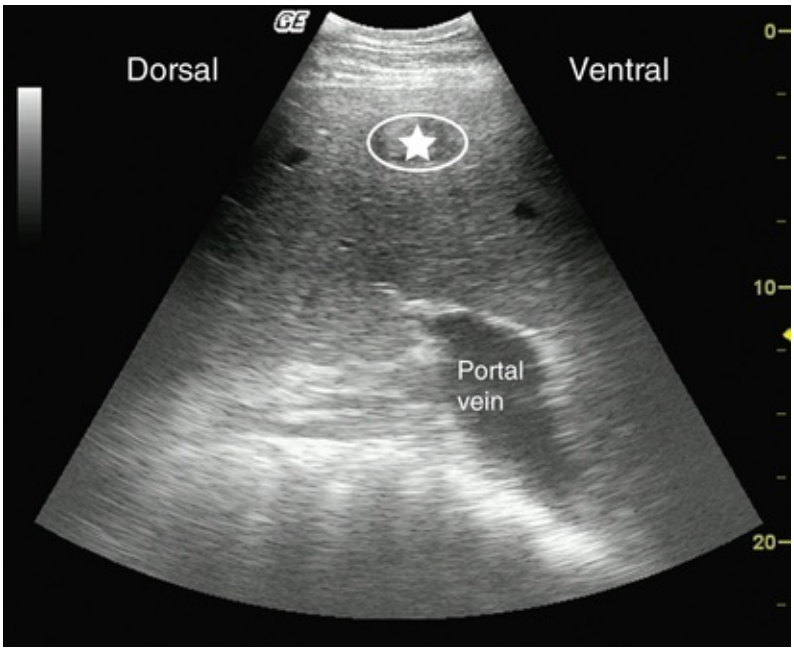


FIG. 32.114 Ultrasonographic aspect of liver abscess. The abscessation is represented by a cavitary lesion with heterogenic content *(star)* within liver parenchyma. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 22 cm).

Liver ultrasonography is helpful for the diagnosis of liver flukes and cholestastic disorders in cattle. In cases of chronic fasciolosis, calcified bile ducts are recognized by the acoustic shadowing below the mineralized duct.[10] Percutaneous puncture of the gallbladder to search for flukes' eggs is more a sensitive test than is fecal eggs testing for *Fasciola hepatica* and *Dicrocoelia dendriticum* infection.[11] Distention of the biliary tract is observed with any cholestatic disease. Establishing a differential diagnosis with liver vessels is not easy without color flow Doppler imaging. Distention of the gallbladder alone is not a specific sign of liver dysfunction because dilation may occur in anorexic cows without any primary liver disease.

Liver ultrasonography can also be performed for the diagnosis of fatty liver syndrome (hepatic lipidosis). This diffuse liver disease is characterized by fat accumulation within liver parenchyma. The excess of fat within the liver cells increases their impedance and therefore attenuates the ultrasonography beam more rapidly.[5] Contrast in the image is decreased, which renders the quality of imaging vascular structures poor (vascular blurring). The specific diagnosis of fatty liver is difficult without software for automatic texture analysis.[12,13] However, this type of digital analysis is not routinely performed in a clinical setting. The ultrasonographer is able to detect only severe liver infiltrations.

Anomalies of the liver vessels mainly consist of caudal vena cava thrombosis and liver congestion secondary to heart failure. In young calves, omphalophlebitis with or without liver abscessation is also commonly reported (Fig. 32.115).[14] Caudal vena cava thrombosis is a common vascular condition in which subacute ruminal acidosis is commonly observed (e.g., in feedlot calves and dairy cows). The thrombosed part of the caudal vena cava cannot be seen transabdominally because of interference with the lung field but can be imaged on intraabdominal ultrasonography during explorative laparotomy.[15] The main anomaly observed on transabdominal ultrasonography is associated with secondary changes of the caudal vena cava shape before the thrombosed area. The increased hydrostatic pressure is associated with a dilation and a shift in the shape of the caudal vena cava from triangular to round (Fig. 32.116). The reported range of the diameter of the caudal vena cava is 2 to 5 cm, depending on the intercostal space screened.[6] The portal vein normal diameter generally

varies from 1.7 to 5.3 cm. All liver vasculature can be distended secondary to right-sided heart failure (Fig. 32.117). Because of hepatomegaly caused by liver congestion, the liver borders are less sharp than usual (see Fig. 32.97). In these situations, the clinical presentation typically differs from caudal vena cava thrombosis.

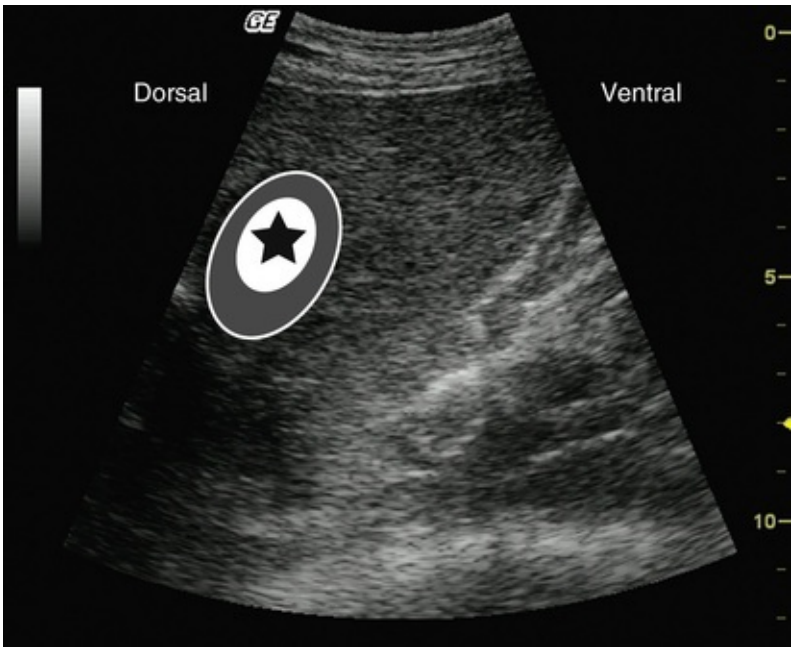


FIG. 32.115 **Liver abscess secondary to omphalophlebitis in a 2-week-old Holstein calf. The abscess is characterized by a thick hypoechoic capsule *(gray colored zone).* The pus appears with an hyperechoic aspect *(star).* Image obtained with a sectorial 3.2-MHz probe (maximal depth, 15 cm).**

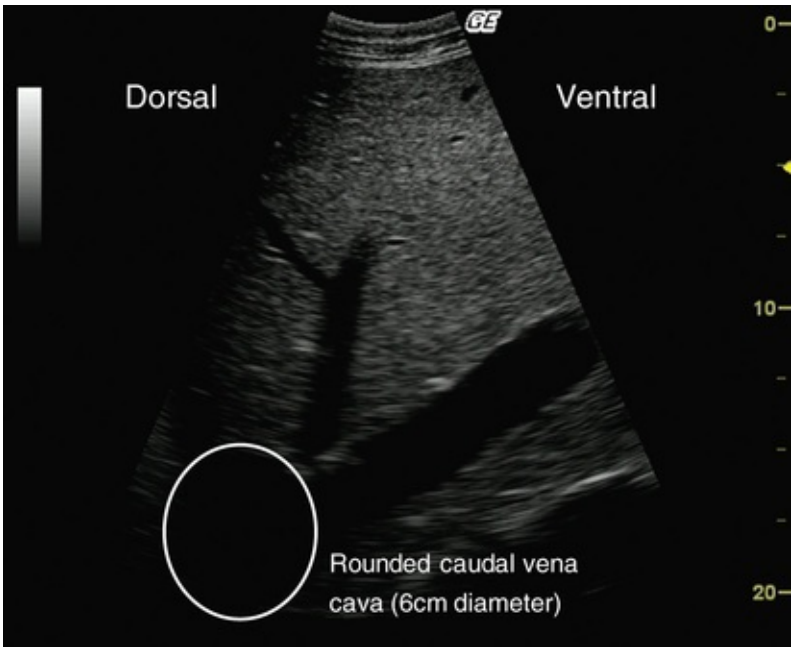


FIG. 32.116 **Ultrasonographic aspect of distension of the caudal vena cava in a Holstein cow with thrombosis of the caudal vena cava. Congestion of the caudal vena cava is characterized by distention (diameter, >4.5 to 5 cm) and change of shape from triangular to circular as a result of thrombosis of the vessel. The thrombus is generally not seen because it is masked by the lung field. Image obtained with a sectorial 3.2-MHz probe (maximal depth, 20 cm).**

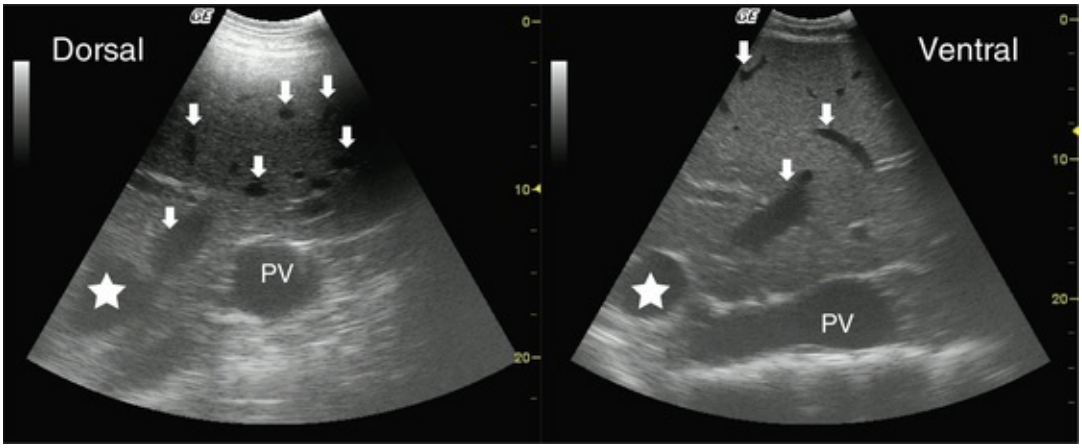


FIG. 32.117 **Liver changes secondary to right-sided heart failure. The main changes are related to liver vasculature. Dilation of the caudal vena cava *(star)* and the portal vein *(PV)* is visible, as is the general increase in the vessels' sizes, especially in the superficial part of the liver *(arrows).* Images obtained with a sectorial 3.2-MHz probe (maximal depth, 22 cm).**

The pancreas can also be observed on abdominal ultrasonography.[16] However, its visualization is difficult because of its poorly defined shape and structure.

Pancreatic diseases are uncommon in cattle, and little information about the use of ultrasonography to investigate pancreatic disease has been reported, except with regard to transabdominal biopsy[17] and induction of experimental pancreatitis by transabdominal chloroform injection.[18]

Kidneys and Urinary Tract.

The urinary tract can be imaged on transabdominal and transrectal ultrasonography.[19] Ultrasonography can be especially helpful in the detection of pyelonephritis, hydronephrosis, and distention/rupture of the bladder secondary to urolithiasis. Infection of the urachus and umbilical arteries can also be diagnosed in calves.[14]

During transabdominal examination with a low-frequency probe in an adult cow, the clinician can observe most of the right kidney and occasionally part of the left kidney. In young calves, the transabdominal approach can also be used with a high-frequency probe because of the superficial position of the kidneys. The caudal part of the left kidney is traditionally imaged through a transrectal approach with a high-frequency probe.

Most of the right kidney is observed on the dorsal part of the paralumbar fossa and the last intercostal space (extending from the thirteenth rib to the third lumbar vertebra). Other approaches such as placing the probe between the transverse processes of the lumbar vertebrae can also be done. Visualization of the left kidney by transabdominal approach is limited because of the presence of gas-filled superficial loops of large intestine.

The normal kidney is characterized by its lobulated aspect in cattle (Fig. 32.118), which is in contrast to the bean-shaped appearance in small ruminants (Fig. 32.119). The cortex is more echogenic than the medullary pyramids. In the central part of the kidney, the renal sinus is seen as a hyperechoic structure (because of fat content; see Fig. 32.119). It is difficult to differentiate vascular and ureteral structures.

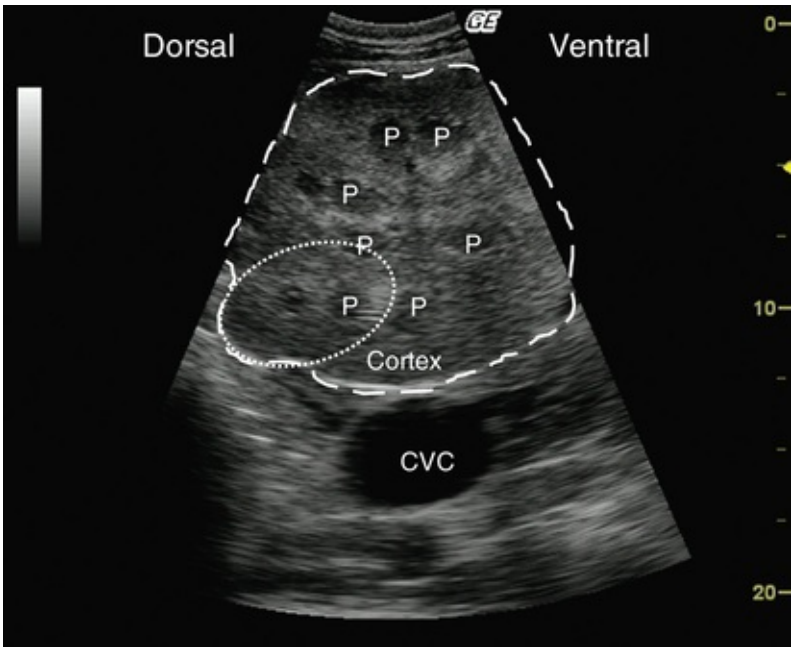


FIG. 32.118 **Transverse view of the right kidney in a cow with caudal vena cava thrombosis. The lobulation of the kidney is visible (example: *dotted circle*). The hypoechoic pyramids *(P)* can be distinguished from the more echoic cortex. The distended caudal vena cava *(CVC)* is also seen on that image. Image obtained at the dorsal right paralumbar fossa with a sectorial 3.2-MHz probe (maximal depth, 20 cm).**

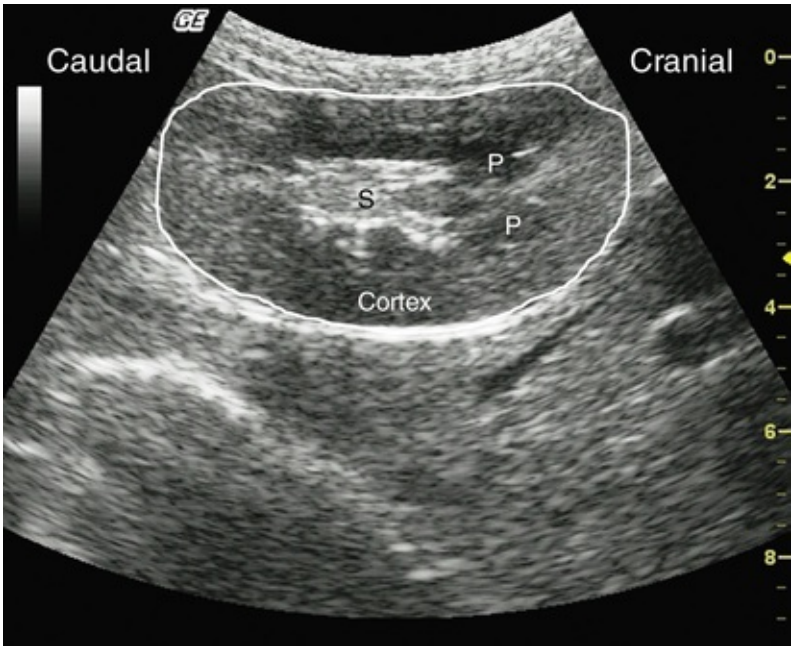
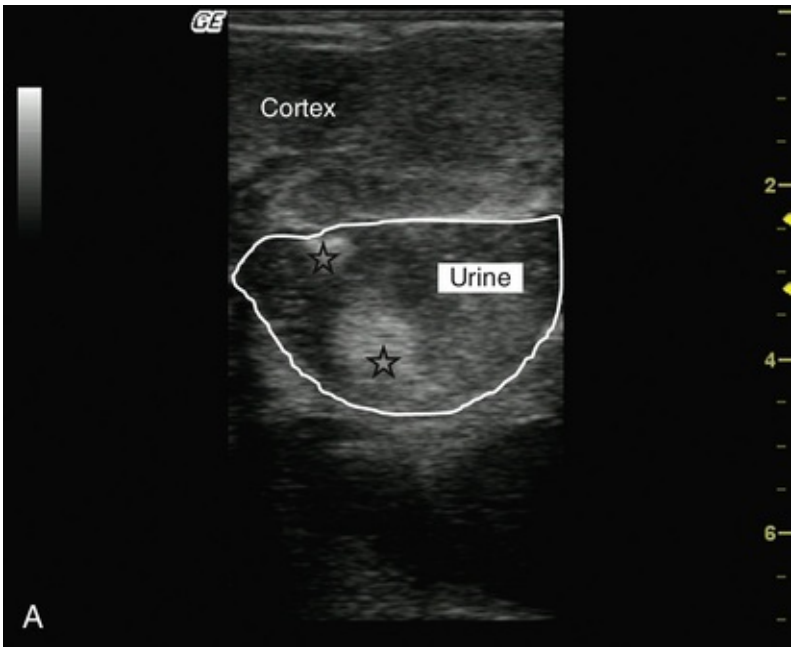


FIG. 32.119 **Longitudinal view of the left right kidney in an adult Boer buck. The bean shape of the kidney is observed. The hypoechoic pyramids (P) can be distinguished from the more echoic cortex. The hyperechoic renal sinus (S) is also observed. Image obtained at the dorsal right paralumbar fossa with a sectorial 3.2-MHz probe (maximal depth, 10 cm).**

Ultrasonography can detect kidney changes associated with pyelonephritis, which is a common urinary tract disease in dairy cows. The main changes are associated with abnormal deposits in the collecting structures of the kidney (Fig. 32.120). Distention of the urethra can be distinguished from renal vessels if color-flow Doppler imaging is available (Fig. 32.121). Hydronephrosis secondary to ureteral obstruction can be observed as a dilation of collecting structures and compression of both the pyramid and cortex (Fig. 32.122). Ultrasonography is of particular interest for distinguishing unilateral from bilateral renal diseases, which is of prognostic importance. Other less important renal anomalies (nephrolithiasis or cysts; Fig. 32.123) can also be observed during the examination.



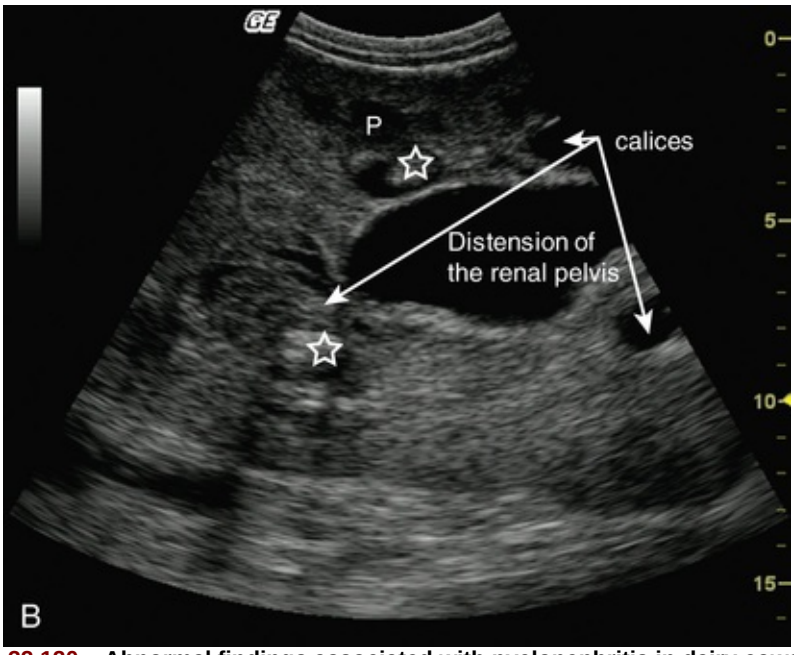


FIG. 32.120 **Abnormal findings associated with pyelonephritis in dairy cows. A, Distention of calices is observed with the presence of heterogenic urine secondary to infection. Hyperechoic purulent material *(star)* is also observed. Image obtained transrectally at the caudal part of the left kidney with a linear 8-MHz probe (maximal depth, 8 cm). B, Long-axis view of the right kidney in a dairy cow with pyelonephritis. The main anomalies are dilations of the renal calices and pelvis. Heterogenic material is seen within the distended calices and is compatible with pus or fibrin deposits. Some pyramids *(P)* are visibles within the renal cortex. Image obtained at the dorsal right paralumbar fossa with a sectorial 3.2-MHz probe (maximal depth, 16 cm).**

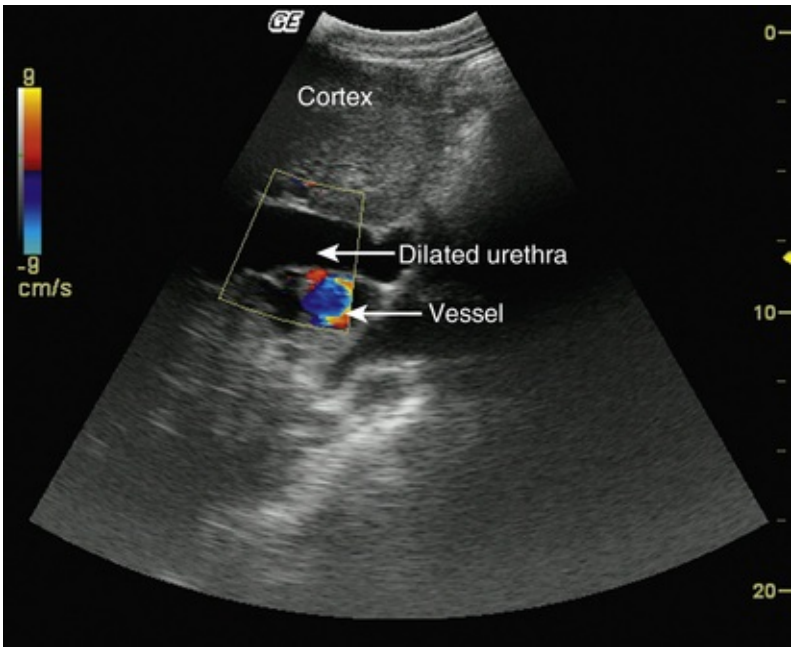


FIG. 32.121 **Distinction between vessels and collecting structures in the renal sinus**

with color-flow Doppler imaging. Transverse view shows color in anechoic tubular structures seen within the renal sinus in the left kidney. The positive Doppler signal allows distinction between vascular structures (where Doppler signal is positive) and dilated pelvis/urethra (where Doppler signal is negative). Image obtained at the dorsal right paralumbar fossa with a sectorial 3.2-MHz probe (maximal depth, 22 cm).

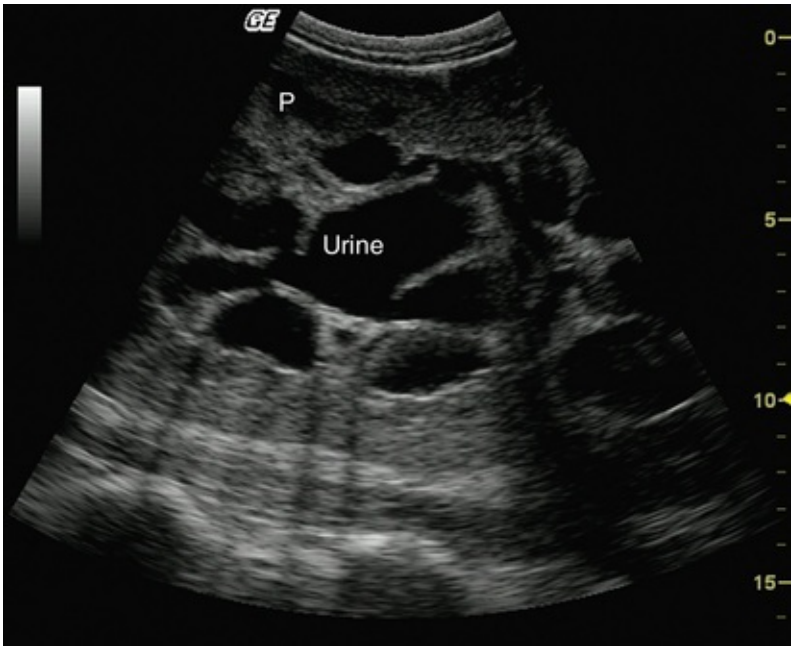


FIG. 32.122 Sonogram in a dairy cow with early-stage hydronephrosis secondary to pyelonephritis. Longitudinal section of the right kidney, showing significant dilation of collection structures (calices and pelvis), which are filled by anechoic urine. Several pyramids *(P)* are still visible. The renal parenchyma is compressed by urinary distention, which leads to irreversible renal failure. Images obtained at the dorsal right paralumbar fossa with a sectorial 3.2-MHz probe (maximal depth, 16 cm).

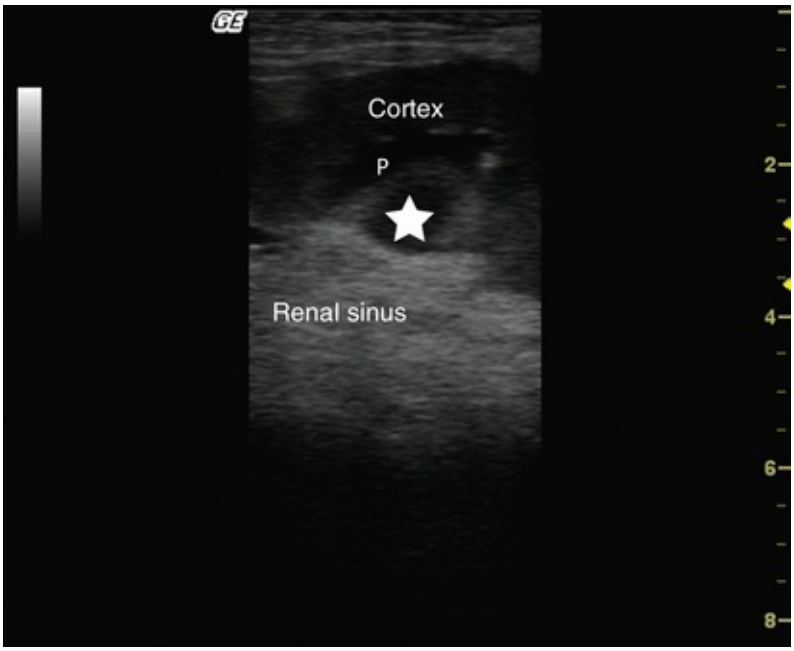


FIG. 32.123 **Transrectal sonogram of a left renal cyst in an Holstein dairy cow. This was an incidental finding. The cyst *(star)* is surrounded by the hyperechoic renal sinus and hypoechoic pyramid *(P).* Image obtained transrectally with a linear 8-MHz probe (maximal depth, 8 cm).**

The urinary bladder can be imaged transabdominally in small ruminants and calves (Fig. 32.124) and by transrectal examination in adult cattle. The more common anomalies of urinary bladder are associated with infection (cystitis), which leads to increased urine echogenicity and heterogenicity. Urolithiasis-associated changes are also an indication of performing urinary bladder ultrasonography to evaluate bladder wall integrity (rupture). Severe distention is observed (see Fig. 32.124) before rupture occurs. In case of ruptured urinary bladder, the ultrasonographic findings are very similar to those of ascites or diffuse peritonitis. Analysis of fluid obtained by abdominocentesis is helpful for reaching the final diagnosis.

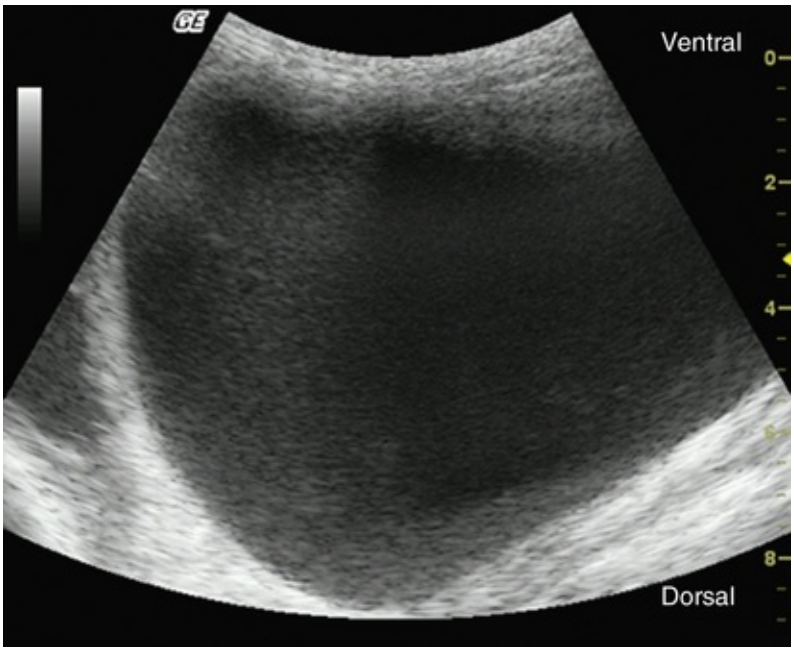


FIG. 32.124 **Distended urinary bladder in a 4-month-old Boer buck with urolithiasis. The distended urinary bladder is a circular structure with anechoic content. This finding is compatible with the absence of major rupture of the urinary bladder. Images obtained at the ventral part of the abdomen with a sectorial 3.2-MHz probe (maximal depth, 10 cm).**

Other Abdominal Structures.

The genital tract (male and female), abdominal lymph nodes, and spleen can also be imaged during the ultrasonography of the abdomen. The genital anomalies are beyond the scope of this chapter. The primary diseases of the spleen are uncommon and most of the time are caused by migration of a foreign body as a result of hardware disease. The mesenteric lymph nodes can also be observed during abdominal ultrasonography for various infectious and inflammatory conditions.

Acute Abdomen in Ruminants

David Francoz • Gilles Fecteau • André Desrochers • Sylvain Nichols

Abdominal emergencies in ruminants are both a therapeutic and a diagnostic challenge for veterinary practitioners. Some of them necessitate immediate surgical treatment, and others can be treated medically (Fig. 32.125). They are associated with numerous conditions that affect the abdominal cavity and can also be mimicked by diseases of extraabdominal origin (Fig. 32.126).

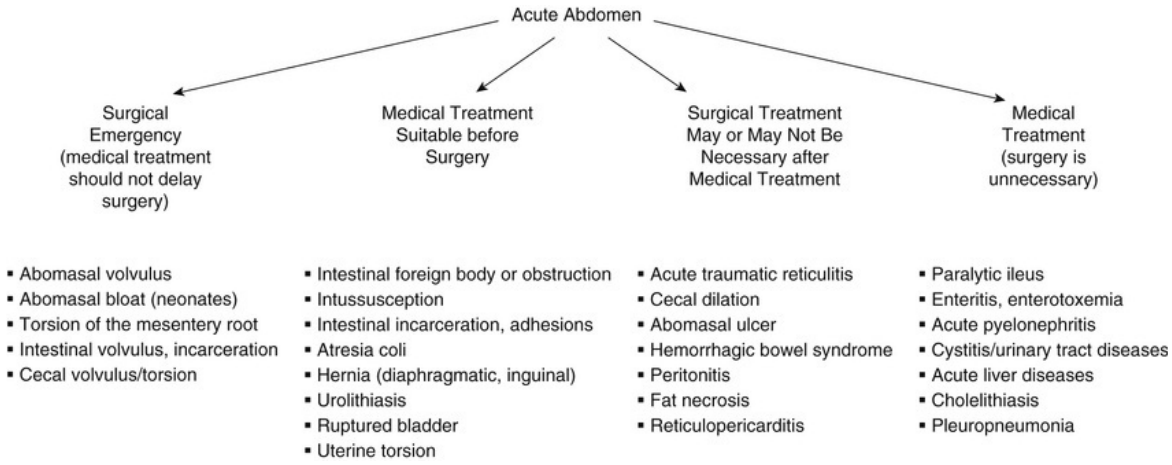


FIG. 32.125 Classification of abdominal causes of acute abdomen according to the need for surgical exploration or medical treatment.

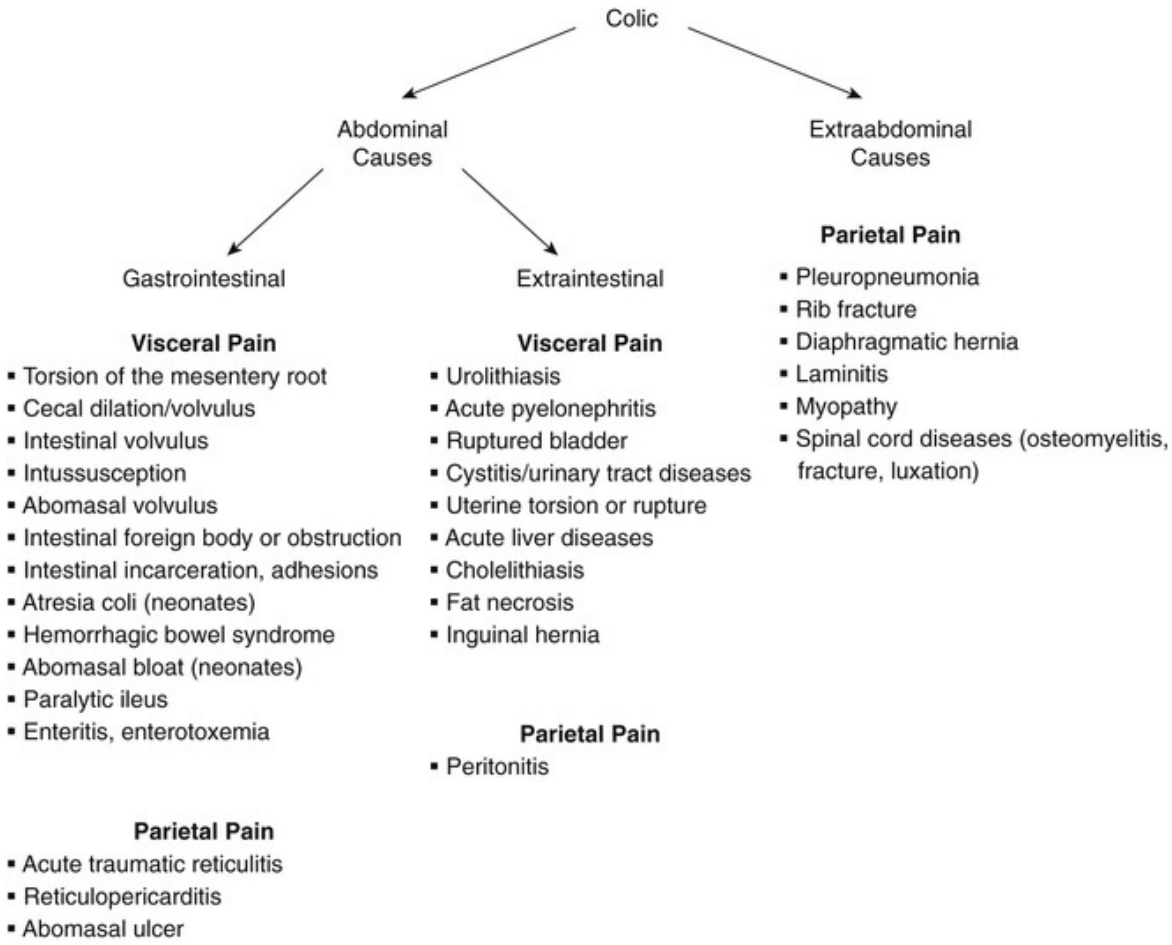


FIG. 32.126 Causes of colic (abdominal pain) in ruminants.

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Different questions should be addressed during management of an acute abdomen in ruminants: Where does the pain originate? Is it a medical or surgical problem? Is it an urgent or nonurgent problem? Is medical treatment indicated before surgery? What is the likelihood for survival and productivity? To answer these questions, the clinician should use a systematic approach that is based on adequate signalment and history, complete physical examination, and judicious choice of ancillary tests. Precise information is not yet available for accurately determining the prognosis about the outcome of an acute abdomen in ruminants. In most cases, prognosis should be based on past experiences of other clinicians as well as one's own experience.

Even though a precise diagnosis facilitates the institution of appropriate treatment and helps better predict outcome, emphasis should not be placed solely on the diagnosis. In addition, contrary to other species, the cost and risk associated with standing laparotomy are minor in cattle. Consequently, it could be more economical to directly perform a laparotomy and avoid additional diagnostic tests and procedures.

Abdominal Pain

Abdominal pain may be a consequence of excessive distention of a hollow viscus (excessive intestinal distention), spasms of intestinal smooth muscles, stretching of the mesenteric supporting structure, intestinal ischemia, or chemical irritation of the visceral or parietal peritoneum.[1] Abdominal pain is classified into two main categories: visceral pain (hollow viscera and solid organs) and parietal pain (parietal peritoneum, abdominal muscles, rib cage).

Pain sensation from the parietal peritoneum travels through the peripheral spinal nerves and usually localizes over the affected area.[1] Because parietal pain is exacerbated by pressure and tension modification, affected patients are reluctant to move and have tonic reflex contractions of the abdominal muscles.[2] No active clinical signs of colic are present. This scenario is typically observed in cases of peritonitis. In addition to being reluctant the move, the animal has a splinted abdomen, and external palpation produces specific responses,[3] such as a positive result of a xyphoid grunt test or not dipping the back when pinched over the withers.

Some pain fiber endings are located in the submucosa and muscle layers of hollow viscera (intestines, bladder) and in the capsule of solid organs (kidneys, liver). Consequently, distention, forceful contraction, or traction produces pain in

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a hollow viscus. Capsule stretching creates pain in solid organs. Visceral pain is typically recognized by active manifestations of colic: kicking at the abdomen; treading with the rear feet; lying down, standing, and stretching out and grinding the teeth. Affected goats may also vocalize. Affected animals are anxious and have an apprehensive attitude. Contrary to parietal pain, visceral pain is transmitted via sensory fibers in the autonomic nerves.[1] Visceral pain is often diffuse and difficult to localize.[1]

A Concise but Precise Evaluation of the Animal

An animal with acute abdomen may need immediate medical assistance. Therefore the clinician should identify life-threatening problems and take appropriate action rapidly. Acute abdominal emergencies are often associated with either hypovolemic or septic shock, which should be treated promptly. Hypovolemic shock is characterized by increased heart rate, pale mucous membranes, slow capillary refill time, and dehydration. Increased heart rate and dehydration are also observed in case of septic shock, but mucous membranes are hyperemic or bluish in color, and scleral vessels are congested and dark. Intensive fluid therapy is the treatment of choice for both hypovolemic and septic shock. Pain control may also be necessary to allow a more complete physical evaluation (see Medical and Supportive Treatment, Fluid Therapy, and Control of Pain and Inflammation sections). However, documentation of a complete history and meticulous physical examination should be performed before emergency medical therapy if the patient is stable.

History.

History documentation should be focused on the identification of risk factors of specific conditions, as well as the description of pain and associated clinical signs.

Signalment may identify an animal at higher risk of particular diseases. Age, sex, breed, and production stage are important parameters to consider in establishing the differential diagnosis. For example, abomasal volvulus develops more frequently in dairy cows than in beef cattle.[4,5] Similarly, uterine torsions are essentially observed at the time of parturition or in the last trimester. Colic in a wether or a buck goat should be considered a result of urolithiasis until proven otherwise. Specific nutrition programs and management systems have also been associated with specific conditions such as hemorrhagic bowel syndrome.[6]

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Paralytic ileus associated with hypocalcemia is reported to occur during estrus.[7] Previous history of surgery can be associated with the development of adhesions and colic. Recent calving and obstetric manipulations may cause a full-thickness uterine tear and subsequent peritonitis.

Description of the clinical signs observed by the owner and the chronologic sequence of events are of particular interest. Abdominal pain is an important criterion in deciding whether surgery is necessary. Severe colic is classically associated with surgical intestinal conditions,[3,8] although some animals with severe jejunal distention secondary to acute enteritis may have a similar clinical presentation.[9] Intussusception in cattle is characterized by an acute onset of anorexia, decreased fecal output (often with dark feces containing blood) and milk production, and colic. However, even though the abdominal pain eventually becomes less severe, the depression progresses.[3,10] Torsion of the mesenteric root has an acute onset with severe colic and rapid deterioration.[3,11,12] Previous treatments, especially those that can modify clinical signs or the interpretation of laboratory results, should also be noted. Administration of analgesics such as NSAIDs may partially control abdominal pain, attenuate signs of colic, and decrease the heart rate.

Identification of associated clinical signs may help identify not only digestive but also nondigestive causes of abdominal pain. Fecal output, consistency, and appearance are relevant information. Stranguria manifested by unsuccessful micturition efforts is associated with urolithiasis. Pleuritis, pleuropneumonia, or rib fractures may mimic abdominal pain.

Complete Physical Examination.

A thorough and complete physical examination is the most important step in evaluating an acute abdomen.

Evaluation of Vital Parameters.

Assessment of cardiovascular status (heart rate, mucous membranes, capillary refill time, and dehydration) is essential in the evaluation of an animal with an acute abdomen and is part of the rapid initial evaluation of the animal. Determination of rectal temperature, pulse or heart rate, and respiratory rate (TPR) should always be performed first because manipulations during the physical examination of an abdominal emergency can elicit pain and modify the heart rate.

The TPR and amount of pain exhibited may also be used to monitor the evolution of the condition and the response to the initiated treatments, as well as prognostic factors. Normal to moderately elevated heart rate and adequate hydration status are considered good prognostic indicators in abomasal volvulus.[13] Combination of heart rate and lactate measurements has been reported to improve the ability to predict negative outcome of right-sided abomasal disorders.[14]

Once vital parameters have been evaluated and the animal appears hemodynamically stable, a thorough complete physical examination of all body systems is performed.

Visual Examination.

The animal's abdominal profile or silhouette should be observed from the rear and both sides to detect and characterize abdominal distention. Bilateral ventral distention is associated with small intestine disorders, whereas distention in the right paralumbar fossa is associated with cecal and colon disorders. In cases of abomasal volvulus, the distended abomasum can be observed caudal to the last rib in the right paralumbar fossa. Gas in the rumen causes distention of the upper left abdomen, whereas some forms of chronic indigestion have a “papple” shape (pear on the right and apple on left). Lateral views of the abdomen help determine whether the distention arises primarily from the paralumbar fossa or extends cranially under the ribs. An affected animal may arch the back in cases of cranial abdominal pain, sole abscesses, or laminitis (sore feet).

Extraabdominal Examination.

Examination of the thorax (pleuropneumonia, rib fractures) and the musculoskeletal system (laminitis, myopathy) are important in ruling out diseases that mimic abdominal pain.

Abdominal Examination.

Abdominal examination is performed by auscultation, percussion, ballottement, and succussion of the abdomen. Pings are sounds of tympanic resonance caused by a gas-fluid interface in a distended organ and can be detected by simultaneous auscultation and percussion. Because rectal palpation may create an area of increased resonance on the right dorsal part of the abdomen, detection of pings should be performed before rectal palpation. On the right side of the abdomen, many organs may be responsible for pings. Determining the location, pitch

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characteristics, and variability of the ping is essential for establishing a differential and precise diagnosis. Pings localized from the thirteenth rib cranially to the ninth rib are typical of abomasal volvulus or rightward displacement of the abomasum.[3] Cecal dilation or volvulus causes a ping in the right paralumbar fossa and caudal quadrant,[3] often extending to the hip. Abomasal volvulus is more likely to cause a high-pitched ping, whereas animals with peritonitis may have a bilateral low-pitched ping in the upper paralumbar fossa. In normal animals, a monotone pinging area of 15 to 20 cm centered just under the last rib corresponds to gas in the spiral colon. Moving or constantly contracting viscera, such as gas in the descending duodenum or proximal colon, produce pings of changing pitch. For this particular reason, it is important to auscultate and percuss for a certain period of time to notice ping variation.

On the left side, pings are principally associated with left abomasal displacement, ruminal collapse, and pneumoperitoneum. Left abomasal displacement typically causes pings dorsally from the eighth to the thirteenth ribs. Pings associated with gas in the rumen, ruminal collapse, and pneumoperitoneum are localized dorsally in the left paralumbar fossa and extend cranially to the eleventh rib. Simultaneous auscultation and ballottement (succussion) of the abdomen may detect fluid-filled viscus with an interface of gas such as the rumen or the abomasum. The location of the fluid splashing sounds on auscultation-succussion may help confirm and differentiate among auscultation-percussion findings. Tense abdominal muscles, secondary to parietal peritoneum inflammation (parietal pain), may also be detected during succussion. Auscultation of ruminal contractions is also of importance. The number of rumen contractions should be counted and characterized over at least a 2-minute period. Three complete contractions per 2 minutes are considered normal. Incomplete and frequent contractions (>5 per 2 minutes) and complete absence of contraction for 2 minutes are abnormal. After initial treatment. the rumen auscultation should be repeated to evaluate the improvement.

Identification of Abdominal Pain.

Differentiation between visceral and parietal pain. as well as pain localization. should be attempted in order to investigate the cause. However, the task is often difficult in animals such as cattle whose behavior in response to pain is unpredictable.

Cranial peritonitis, secondary to traumatic reticuloperitonitis (TRP) or abomasal ulcers, is a common cause of parietal abdominal pain. Affected cattle

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are reluctant to move; they stand with the elbows abducted and an arched back.[3] During examination, bruxism (grinding of the teeth) may be present.[3] Pain can be elicited by pinching over the withers or applying forceful movement with the knee or upward pressure with a bar or pole over the xyphoid area or anterior abdomen. In response to pain, an animal may grunt or kick and be reluctant to dip the back when the withers is pinched.[3] Sensitivity of this test may be increased by simultaneous auscultation of the trachea to better hear the subtle grunt.

As mentioned previously, the visceral pain is more diffuse and associated with active manifestations of colic.

Rectal Palpation.

Rectal abdominal palpation of cattle is an essential part of the physical examination for acute abdomen. However, the size of the abdomen limits the systems or organs that can be palpated.

Cecal disorders are clearly diagnosed by rectal palpation. A firm mass palpated in multiple, dilated, turgid small intestine loops is a typical finding of intussusception[10] or hemorrhagic bowel syndrome.[6] Adhesions between the kidneys and the rumen, the intestinal convolutions, and decreased rectal mobility in the posterior abdomen are characteristics of a chronic peritonitis. Uterine wall integrity may be evaluated during rectal palpation, although examination per vagina may be necessary to confirm a full-thickness laceration in an early postpartum cow. In feedlot steers with urolithiasis, rectal palpation reveals a pulsatile pelvic urethra and a distended bladder. In cases of pyelonephritis, enlargement of one or both ureters may be palpated. Normally, only the left kidney can be palpated rectally: If infected, it will be painful to the touch and larger, and lobulation may become less obvious. Diseased right kidneys are exceptionally reached rectally especially if the animal is hydronephrotic. In small ruminants, urolithiasis is manifested by pulsations in the pelvic urethra that may be palpated by digital rectal examination. Bladder distention or kidney enlargement can be detected by deep abdominal palpation, and vocalization will be elicited during palpation of the distended bladder.

Fecal Output and Appearance.

Presence and macroscopic appearance of feces can be evaluated during rectal palpation. Decreased or absence of feces is principally associated with intestinal

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stasis or obstruction, which may occur secondary to a direct mechanical obstruction (necessitating surgical treatment) or to gastrointestinal ileus (necessitating only medical treatment). However, feces may be present in the first few days after an intestinal obstruction.

Ancillary Tests

Packed Cell Volume and Total Solids.

Shock, sepsis, and toxemia cause hemoconcentration and dehydration and are associated with an increase in total solids. On the other hand, increased PCV and decreased total solids are observed during the formation of a third compartment filled with a protein-rich fluid, as in generalized peritonitis.[15] In one study, total protein concentration was significantly lower in cows with septic peritonitis than in cows suffering from nonseptic peritonitis.[16]

Blood Gas Analysis and Electrolytes.

Blood gas analysis and electrolyte measurement results are helpful in the institution and monitoring of fluid therapy. Most adult ruminants with acute abdominal diseases suffer from metabolic alkalosis.[17] Metabolic alkalosis is often associated with abomasal volvulus, intussusception, cecal disorders, abomasal ulcers, peritonitis, renal diseases, and reticuloperitonitis.[17] Hypochloremia and hypokalemia are frequently combined with metabolic alkalosis.[18] Metabolic acidosis may be observed if urinary tract disease, small intestinal strangulation or obstruction, or enteritis with severe diarrhea is present.[17]

Some parameters could also be used as prognostic indicators. Serum chloride concentration, anion gap, and base excess have been proposed as preoperative prognostic indicators in dairy cattle suffering from abomasal volvulus. Poor short-term prognosis was associated with serum chloride concentrations lower than 79 mEq/L,[19] base excess values of −0.1 or less,[20] and anion gap values of more than 30 mEq/L.[21] However, a prospective study on the outcome of abomasal volvulus demonstrated that serum base excess and anion gap values did not differ between productive and nonproductive animals.[13] In that study, serum chloride concentration was significantly lower in nonproductive animals, but the prognostic test yielded numerous false-negative results.[13]

Blood Lactate Concentration.

Blood lactate concentration is frequently used to assess a compromised cardiovascular or respiratory system, to monitor the response to treatment, and to establish a prognosis for survival. Portable analyzers are available for the measurement of L-lactate, and so this diagnostic test is easily doable at the farm. In cattle, blood lactate concentrations have been reported as a predictor of uterine torsion[22] and abomasal disorders.[14,23-26] Blood L-lactate concentrations exceeding 6.5 mmol/L before correction of uterine torsion[22] or exceeding 6 mmol/L before surgery for right abomasal disorders[14] were associated with a poor prognosis. In the author's clinics, an early measurement (before any treatment) and a follow-up measurement after initial therapy (IV fluids, NSAIDs, or other) are performed. The author and colleagues have found that an increase in blood lactate or a very marginal reduction in blood lactate, despite aggressive therapy, indicates that surgery is needed or the prognosis is poor. However, in one study, short-term change (preoperative and postoperative values) in blood L-lactate concentrations did not appear to be a useful prognostic indicator.[23]

Serum Biochemistry Profile.

Evaluation of specific enzyme activity or markers (e.g., hepatic enzymes, BUN, and creatinine) along with physical examination and other ancillary tests may be useful in establishing a diagnosis and assessing progress.

Complete Blood Cell Count and Differential.

Hematologic findings are rarely specific to a condition and reflect the underlying inflammatory process. In most cases a minimal to moderate inflammatory process characterized by a neutrophilic leukocytosis is observed. Hematologic findings may also provide information about the acuteness of the disease and the severity of associated sepsis and toxemia. Severe sepsis is associated with neutropenia, degenerative left shift, toxic changes in neutrophil structure, and lymphopenia. Hematologic study is also an important ancillary test for monitoring the response to treatment.

Fibrinogen.

In ruminants, increased fibrinogen concentration is an early indicator of inflammation. Studies in cattle have demonstrated that fibrinogen concentration

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may increase within 1 to 2 days after induction of inflammatory conditions. Normal fibrinogen concentration despite severe visceral involvement should be observed only in peracute cases (within a few hours; e.g., torsion of the root of the mesentery). Moderate to marked increased fibrinogen concentration is also the signature of chronic active localized inflammatory conditions such as reticuloperitonitis, liver abscesses, and pyelonephritis.

Urinalysis.

Urinalysis is helpful in differentiating between colic of urogenital origin from gastrointestinal disorders. Urinalysis can be performed rapidly with a urinary dipstick (Chemstrip 9, Roche Diagnostics Corporation, Indianapolis, Ind.) and gross morphologic examination. Renal diseases are associated with proteinuria (>1+), glucosuria, and positive blood reaction. In cases of acute urethral obstruction, hematuria and proteinuria are consistently observed. Determination of urinary specific gravity before fluid replacement may help characterize azotemia.

Abdominocentesis.

Abdominocentesis is considered an essential ancillary test in the approach to acute abdomen in many species,[9,27] including cattle.[3] Because of the ability of cattle to wall off and localize infections in the abdomen, a four-quadrant method of abdominocentesis is suggested by some authors.[3] Ultrasonography can be used to find abnormal fluid location or quantity, which improves the precision of determining the abdominocentesis site. Fluid can be evaluated macroscopically for color, volume, odor, and turbidity. Normal and changes values are reported in the Peritonitis in Ruminants section of this chapter.

Different parameters may be evaluated in peritoneal fluid. Lactate, D-dimer, glucose, and ALP concentrations and pH of the peritoneal fluid have been reported to be indicators of intestinal ischemia and peritonitis in horses.[28,29] In one cattle study, decrease in glucose concentration in peritoneal fluid was a sensitive and specific marker of septic peritonitis.[16] D-Dimer level is also elevated in cases of ischemic and inflammatory abdominal conditions.[16,24] L-Lactate measurement could also be a useful diagnostic tool for the evaluation of various abdominal ischemic conditions in cattle.[24]

Diagnostic Imaging

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Ultrasonography.

Ultrasonography is a very helpful diagnostic tool for the management of acute abdomen. It helps in identifying the structures involved, the extension of the lesions, and the presence of abdominal fluid, as well as in the monitoring of the cases. With advances in multifrequency abdominal transducers, ultrasonography is used more frequently in ruminant medicine. More detailed information this type of imaging is available in the Ultrasonography of the Ruminant Abdomen section.

Radiography.

Radiographic images in adult cattle are obtained with powerful machines available only in referral centers. They are among the most helpful ancillary examinations for the diagnosis of reticuloperitonitis.[30,31,32] Abdominal radiographs have been used for the diagnosis of intestinal atresia and intussusception in calves.[3]

A lateral view of the abdomen of small ruminants may help for the diagnosis of urolithiasis because stones in the urethra or in the bladder may be detected.

Medical or Surgical Decision

A differential diagnosis and a decision for surgical or medical treatment should be established on the basis of clinical signs and ancillary tests results (see Fig. 32.126). If a definitive diagnosis is made, specific treatment can be instituted. When a definitive diagnosis cannot be established, attempts should be made to differentiate surgical and medical cases (see Fig. 32.125). Every animals with elevated heart rate, with organ distention found on rectal palpation, and that is producing little to no feces are surgical candidates even if a definitive diagnosis cannot be established. Intestinal obstructions necessitate immediate surgery. A mechanical obstruction may be suspected when there is a suspicion of intestinal or cecal torsion on rectal examination, pings indicating a right abomasal displacement or volvulus, peritoneal fluid indicating bowel devitalization, severe active colic, or rapid deterioration in the animal's condition.[8] If an intestinal mechanical obstruction is not suspected during the first examination, exploratory surgery may be delayed for up to 36 hours.[33] However, frequent monitoring should be performed and appropriate medical treatment provided to the animal.

Surgery.

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Most abdominal surgery in adult cattle is performed with the animal standing and with local or regional anesthesia. Sedation may be necessary in some cases, but the risk of lying down during surgery have to be considered. Cattle can tolerate intestinal resection and anastomosis standing if adequate local anesthesia and systemic analgesia are provided. However, some animals are reluctant to stand because of the primary condition or as a result of electrolyte imbalance. Any traction on the mesentery root is painful enough to make an animal go down during the procedure. Surgery should be performed with the animal in recumbency if it is in extreme pain or weak and likely to lie down. Because a right paralumbar fossa celiotomy provides the best exposure to the intestinal tract, left lateral or sternal recumbency should be favored. Other than the general status of the animal, the suspected affected organ, presence of aggressive behavior, surgeon preferences, and facilities should be considered in the choice of performing the surgery with the animal standing or in recumbency. If the animal is dehydrated or manifests signs of shock, preoperative fluid therapy and analgesics are recommended. For the prevention of surgical infection, appropriate preoperative antibiotic administration is also recommended.

Medical and Supportive Treatment.

The goal of therapy in an animal with acute abdomen is to initially correct the hemodynamic and metabolic imbalances associated with hypovolemic or septic shock, to control pain, and to correct or treat the primary cause of the disease, when identified. Consequently, medical treatment often includes fluid therapy, NSAIDs, and antimicrobial drugs.

Fluid Therapy.

Crystalloid solutions (0.9% NaCl, Ringer's solution) are indicated initially to replenish fluid loss and improve the circulating blood volume. To resuscitate critically ill neonatal patients, recommended intravenous fluid administration rates of isoosmotic crystalloid solution are 80 to 90 mL/kg of body weight per hour.[34] However, such rates are difficult to achieve through a catheter in adult ruminants. The maximal flow rate usually achieved through a catheter (14G catheter) in an adult cow is 15 to 20 mL/kg/h. Studies demonstrated that perfusion rates of 40 and 80 mL of an isoosmotic crystalloid solution per kilogram of body weight per hour can be used safely in adult ruminants and dehydrated calves, respectively.[35,36,37] If the animal is not critically ill, fluid and electrolyte deficits should be corrected over 2 to 8 hours.

Hypertonic solutions (7.2% or 7.5% NaCl) are also an alternative. Intravenous administration of hypertonic saline provides rapid resuscitation in dehydrated or endotoxemic ruminants.[38] A rate of 4 to 5 mL of hypertonic solution per kilogram should be administered IV through the jugular vein over 8 to 10 minutes. Animals should be provided with a supply of fresh water immediately after the treatment, or an intravenous infusion of an isotonic crystalloid solution should be instituted. Cattle not observed to drink within 5 minutes should have 20 L of water pumped into the rumen.[38] An administration rate for a hypertonic solution of over 1 mL/kg/min should be avoided because it induces a potentially fatal hypotension, coupled with a decrease in cardiac contractility.[38]

Correction of Acid-Base and Electrolyte Imbalances.

Correction of electrolyte imbalances should be based on laboratory results when available. Previous treatments should be considered (e.g., intravenous calcium, orally administered magnesium hydroxide) to initiate the most appropriate fluid therapy if no laboratory results are available. Most animals with acute abdominal diseases suffer from metabolic alkalosis, hypochloremia, and hypokalemia.

Calcium homeostasis is fragile in postpartum dairy cattle. Hypocalcemia is common in ruminants with gastrointestinal disorders or simply anorexia, particularly in lactating cows.[17,34] Moreover, metabolic alkalosis, frequently observed in cases of acute abdomen, is strongly associated with subclinical hypocalcemia.[7,39] Calcium ions are of particular importance in gastrointestinal motility. First, in the gastrointestinal smooth muscles, the channels responsible for generating action potentials are calcium-sodium channels.[40] Second, gastrointestinal smooth muscle contraction occurs in response to the entry of calcium into the muscle fiber.[40]

The Ringer's solution containing 8.6 g of NaCl per liter, 0.3 g of KCl per liter, and 0.3 g of $CaCl_2$ per liter, yielding 147 mEq/L Na, 155 mEq/L Cl, 4 mEq/L K, and 4 mEq/L Ca, is the commercially available solution of choice. At the author's veterinary teaching hospital, a homemade solution (7.5 g of NaCl per liter, 1.5 g of KCl per liter, and 5.75 g of Ca^{2+} per liter [25 mL of 23% calcium borogluconate per liter], yielding 128 mEq/L Na, 148 mEq/L Cl, 20 mEq/L K, and 26 mEq/L Ca) is used for adult cattle. The author and associates usually begin fluid therapy with rapid administration of a 0.9% NaCl solution (15 to 20 mL/kg/h) for rapid ressucitation and then administer the homemade solution at a rate of approximately 4 to 5 mL/kg/h.

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Control of Pain and Inflammation.

Pain and inflammation are important causes of gastrointestinal hypomotility. Gastrointestinal pain increases sympathetic tone, causing general inhibition of the gastrointestinal tract.[40,41] Numerous inflammatory mediators are released during disease of the gastrointestinal tract and alter intestinal motility.[42] Peritoneal inflammation or irritation and associated pain may initiate ileus in several species.[42] Release of proteinases, vasoactive substances, free oxygen radicals, and endorphins secondary to ischemia and reperfusion injury, or endotoxemia, impairs cardiovascular function and decreases gastrointestinal motility.[42] Release of inflammatory mediators leads to a pain response and modulates the intensity of noxious stimuli.[41] Consequently, analgesic and antiinflammatory drugs appear essential in the management of acute abdomen. These drugs must be used with caution; NSAIDs may induce abomasal ulcers, particularly in an anorexic patient, and analgesics may mask clinical signs (pain, fever) and thereby compromise adequate case management through a delay in surgery.

NSAIDs are the most commonly used drugs for gastrointestinal pain management in cattle. There has been no comparison of the efficacy of the different NSAIDs available in food animal medicine specifically in relation to their use in the management of acute abdomen. In some countries, meloxicam is approved for the reduction of pain associated with abdominal surgery. Preoperative and postoperative administration of flunixin, ketoprofen and meloxicam was demonstrated to have positive effects on animal recovery and pain control after left abomasal displacement surgery[43,44] or fistulation surgery.[45,46] However, no recommendation can be made about which one is most effective.[44,47] Ketoprofen and flunixin appear to have similar activities in endotoxic calves.[48] Meloxicam has been reported to decrease the severity of clinical signs and to reduce the production of thromboxane B_2 in calves with experimentally induced endotoxmia.[49] The choice of NSAID becomes a matter of previous experience, comparative medicine, legislation, and cost. In equine gastrointestinal pain, a poor or short-duration response to NSAIDs indicates a need for surgery.[41] This principle can be applied to cattle with caution because of their different behavior in response to pain.

α_2-Agonists that function as sedatives and analgesics, such as xylazine, detomidine, and medetomidine, could also be used to relieve pain in cases of

acute abdomen. All are considered strong analgesics that can alleviate most visceral pain, at least temporarily, in equine medicine.[41] There are few data on the use of α_2-agonists for the management of acute abdomen in cattle. In a cow with a large intestinal obstruction, signs of abdominal discomfort disappear immediately for at least 1 hour after the administration of a single dose of xylazine (0.05 mg/kg IV).[50] Different side effects must be considered before the administration of α_2-agonists. Xylazine is reported to have significant effects on the gastrointestinal tract in cattle, decreasing reticuloruminal and intestinal motility.[51] Because of the hemodynamic changes associated with the administration of α_2-agonists, these drugs must be used with caution in hypotensive patients and those suffering from shock.[52] α_2-Agonists can mask surgical pain and delay the decision for surgery. This is particularly critical with the use of detomidine.[41] Finally, dose and administration of α_2-agonists should be used with care if standing surgery is planned, as they may influence the animal to lie down.

Opioids, morphine or butorphanol can also be used alone or in combination to control abdominal pain. Information regarding their use in this situation in cattle is lacking. To the author's knowledge, opioid usage was studied in cattle in castration, dehorning, and preoperative analgesia but never for abdominal pain control. In the author's clinic, after the diagnosis of a nonsurgical process or correction of a surgical process, clinicians administer morphine (0.1 mg/kg, IM or SC), or butorphanol (0.05 to 0.1 mg/kg, IV, IM, or SC) or a continuous-rate infusion of a combination of ketamine (0.2 mg/kg/h) and butorphanol (0.02 mg/kg/h).

Finally, lidocaine may be used for its analgesic and anti-inflammatory effects, as well as its potential prokinetic effects. As described in horses, a continuous IV infusion of lidocaine at a rate of 3 mg/kg/h after an initial dose of 1 mg/kg (IV, over 15 min) can be administered. However, no data are actually available about its effect on the control of pain and inflammation and on the gastrointestinal motility in cattle.

Antimicrobial Drugs.

Bacterial translocation from the intestines can occur in cases of mechanical or functional ileus secondary to bacterial overgrowth, inflammation, and impairment of barrier function of the intestinal wall. A systemic broad-spectrum antibiotic treatment should be instituted when a septic process is suspected. This

initial antibiotic therapy should be effective against Gram-negative, Gram-positive, aerobic, and anaerobic pathogens. The choice of antibiotic should also take into consideration legal aspects and the cost of the treatment. β-Lactams, tetracyclines, and trimethoprim-sulfadoxine appear to be good choices. In ruminants, there is no accepted recommendation for the duration of treatment.

Other Medical Treatments.

The use of laxatives (magnesium hydroxide, mineral oil, liquid paraffin) in cases of suspected gastrointestinal obstruction or ileus in cattle has no therapeutic basis. Moreover, these treatments may exacerbate the condition. Because the intestines are already filled with gas and fluid, laxatives only impose additional distention. In human medicine, laxatives are frequently used for the treatment of POI; however, no study could demonstrate their actual benefit.[53] Braun and colleagues reported that the use of laxatives for the treatment of cecal disorders delayed the time to first defecation.[54] Moreover, magnesium hydroxide may be responsible for detrimental effects such as decreased potassium absorption, metabolic alkalosis,[55] sedation caused by hypermagnesemia,[55] increased ruminal pH,[56] and decreased ruminal microbial activity.[56]

Motility-modifying agents may be used in the management of gastrointestinal disorders. In most cases, intestinal motility is restored when pain is relieved and electrolytic imbalances are corrected. Steiner[51] and Constable and colleagues[57] reviewed the different prokinetics that can be used in ruminant medicine and their clinical implications. In cattle, according to their reviews, erythromycin (10 mg/kg, IM, bid for 2 days [Erythro-200[51]] or 8.8 to 10 mg/kg IM[57]) is the most effective drug for the treatment of abomasal hypomotility and can be used for the postoperative treatment of abomasal displacement or torsion. However, in a context of antimicrobial stewardship, the use of antimicrobial drugs for purpose other than antibacterial activity is controversial and should not be recommended. Bethanechol (0.07 mg/kg, SC, tid for 2 days, not approved for food animal use in the United States) alone or in combination with metoclopramide (0.1 mg/kg, SC or IM, tid for 2 days, not approved for food animal use in the United States), increased the contractility of abomasal smooth muscles, but no data on in vivo efficacy are available.[51,57] Metoclopramide alone is ineffective in cattle and sheep for the treatment of abomasal hypomotility.[51,57] Bethanechol (0.07 mg/kg SC tid for 2 days; not approved for food animal use in the United States) can be used for conservative or postoperative treatment of cecal disorders and treatment

of paralytic ileus.[51]

In contrast to cattle and sheep, in goats metoclopramide (0.5 mg/kg IM or IV; not approved in the United States) has been reported to significantly increase myoelectric activity of the duodenum.[51] Cisapride (0.5 mg/kg PO, not approved in the United States) was believed to be responsible for an increase in abomasal emptying rate in one study in calves.[58] However, in vitro, cisapride did not demonstrate any significant effect on the contractility of smooth muscle of cows from the pyloric antrum, proximal duodenum, and proximal colon.[59,60] Continuous infusion of neostigmine (87.5 mg in 10 L of sodium chloride-glucose infusion at 2 drops/sec per cow) was successfully used for the conservative and postoperative treatment of cecal disorders.[54] In that clinical report, this protocol was preferred to those previously reported (neostigmine SC every hour over 2 to 3 days in doses that gradually decreased from 12.5 mg to 2.5 mg).[54] Drug administration was easier and involved fewer disturbances for the animal.[54] However, no control group was included in this study. Also, neostigmine has been reported to have a pronounced effect on intestinal contractility, causing uncoordinated spikes to become more frequent, thereby compromising the potential beneficial effect.[60]

No prokinetic drug is reported to directly increase ruminal motility. In cases of prolonged anorexia or acute indigestion, ruminal flora can be disturbed and reduced. Transfaunation may help rapidly reconstitute the ruminal flora and hasten return to normal function of the rumen and the digestive tract. The technique for and beneficial effects of transfaunation (reduction of ketonuria, increased feed intake, and higher milk yield) have been reported in the postsurgical treatment of left abomasal displacement.[61]

Follow-Up.

When a definitive diagnosis cannot be made, close monitoring of the animal may be indicated (Fig. 32.127). Follow-up must also be performed after to surgery to ensure adequate response to surgical treatment and to allow possible adjustment of treatment. In a referral hospital, the animal should be reevaluated every 4 to 6 hours. In field practice, vital parameters, rectal palpation, presence and consistency of feces, and pain may be reevaluated every 6 to 12 hours. A significant reduction of heart rate was observed 4 and 6 hours after the initiation of treatment in cases of cecal dilation.[54] Feces are usually passed within 4 to 6 hours after surgery in cases of intestinal volvulus or cecal disorders. Failure to

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defecate for 24 hours or more is abnormal in cattle and therefore indicates persistence of intestinal obstruction and may adversely affect the prognosis. Deterioration or persistence of clinical signs despite the initiation of supportive treatment is also an indication for surgery. Surgical exploration is indicated if the following clinical signs are observed: persistence of colic, development of abdominal distention, heart rate exceeding 100 beats/min, scant feces, typical abomasal or cecal pings, or paracentesis results that indicate bowel devitalization.

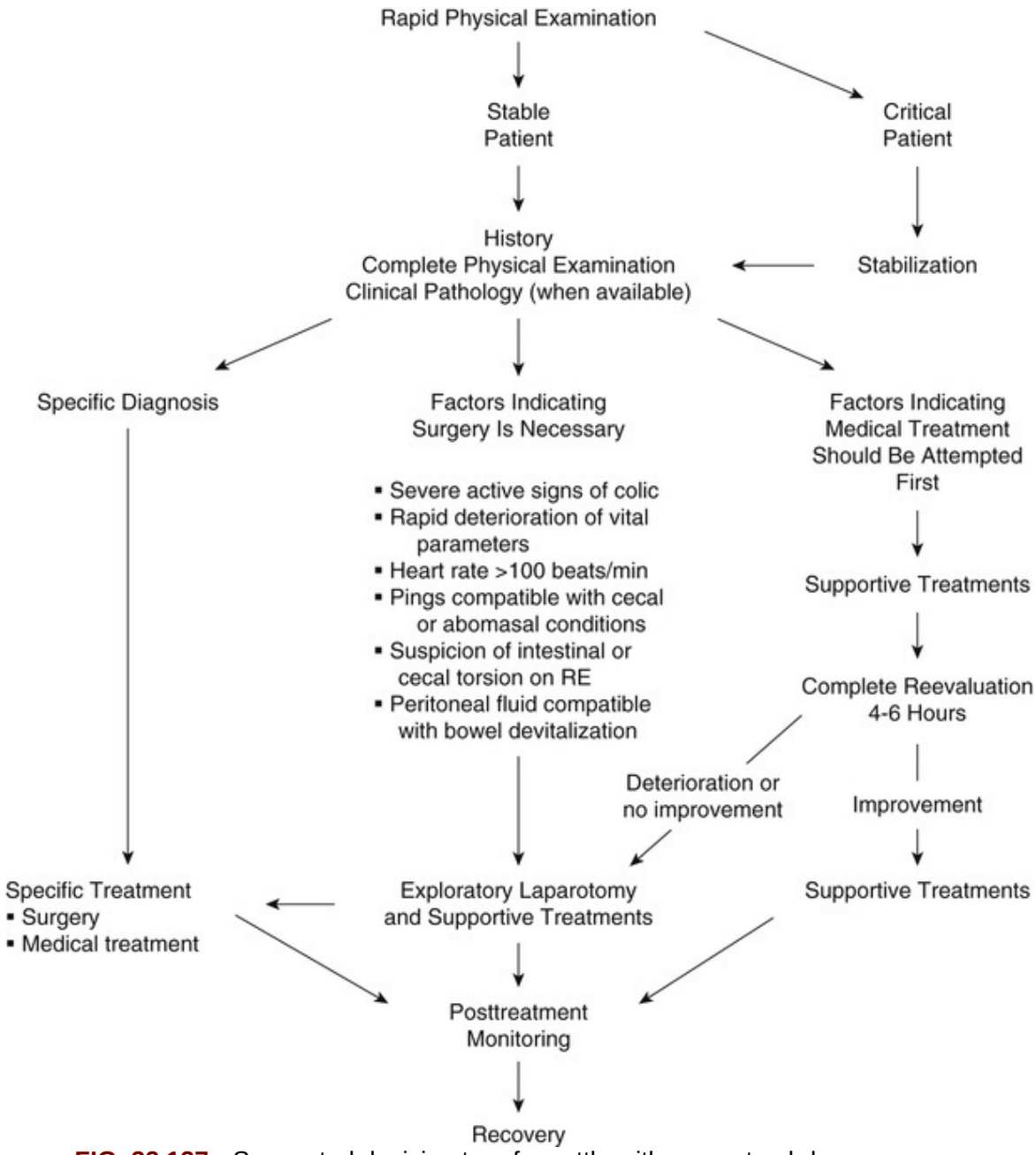


FIG. 32.127 Suggested decision tree for cattle with an acute abdomen. *RE,* Rectal examination.

The decision for surgery or medical treatment remains challenging in cases of acute abdomen in ruminants. Optimal management of acute abdomen prevents any unnecessary delay in cases requiring surgery and avoids unnecessary surgery. Knowledge of diseases associated with signs of acute abdominal pain is important, but no clinical signs are specific for a particular problem, and a specific diagnosis cannot be established postoperatively in many cases. On the

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basis of a systematic approach to clinical examination and a judicious use of ancillary tests, the clinician may be able to identify cases that necessitate immediate or delayed surgery, avoid unnecessary surgery, and establish a cost-effective management plan.

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Indigestion in Ruminants

Franklyn Garry • Craig McConnel

Definition and Etiology

Indigestion is a general term for a group of diseases characterized by dysfunction of the reticulorumen. Some texts have limited the use of the term to a single, poorly defined entity that includes inappetence, decreased reticuloruminal motility, and abnormal feces, with a nonspecific cause that involves intake of abnormal feed. The more generalized term applied here incorporates a pathophysiologic classification scheme of forestomach disturbances that was devised by workers in Germany.[43] An absolute division of the pathologic processes is impossible because the various forestomach functions are interdependent; that is, abnormal motor function affects microbial fermentation by altered mixing or passage of ruminal fluid out of the forestomach chambers, whereas abnormal fermentation products secondarily alter motor function. Nevertheless, this classification provides a clinically useful diagnostic framework by emphasizing the underlying pathophysiologic mechanisms of different forestomach disturbances.

The primary indigestions include diseases in which the reticulorumen is directly affected and responsible for the major clinical signs (Box 32.4). These problems can be divided into two categories:

Box 32.4

Classification of Ruminant Indigestion

Primary Indigestion

Reticuloruminal Motor Disorders or Diseases of the Rumen Wall

Traumatic reticuloperitonitis
Frothy bloat
Free gas bloat
Reticulitis/rumenitis

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Ruminal parakeratosis
Obstructive (vagal) indigestion (failure of omasal transport, failure of pyloric outflow, and free gas bloat)
Obstruction of the cardia
Obstruction of the reticuloomasal orifice
Diaphragmatic hernia

Reticuloruminal Fermentative (Microbial and Biochemical) Disorders

Inactivity of rumen microbial flora (caused by poor-quality roughage that leads to rumen impaction)
Simple indigestion
Acute ruminal lactic acidosis
Subacute ruminal acidosis
Rumen alkalosis
Putrefaction of rumen ingesta

Secondary Indigestion (Secondary to Systemic Illness)

Secondary reticuloruminal motor inactivity
Secondary reticuloruminal microflora inactivity
Abomasal reflux

1. Abnormal motor function of the reticulorumen, including disease of the reticuloruminal wall, its neuromuscular function, or impedance to the passage of ingesta
2. Abnormal contents of the reticulorumen, with dysfunction of microbial and biochemical fermentation

Secondary indigestions are the sequelae of systemic problems or disease in other organ systems. For example, problems such as endotoxemia, fever, or depression can produce anorexia, secondary ruminal hypomotility, and decreased microbial fermentative function. Primary abomasal disease can depress ruminal function, inhibit ruminal outflow, and cause reflux of abomasal contents back into the rumen.

With the exception of penetrating foreign bodies and sporadic infections of the

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forestomach wall (e.g., actinomycosis, mucormycosis), indigestions are due to abnormal physiologic function. In adult ruminants, one or more of the homeostatic processes of the fermentative environment are disturbed (e.g., an excessive carbohydrate intake generates an excessive amount of acid product; abnormal regulation of the ruminal motility pattern disturbs the mixing or aboral passage of ingesta). In young ruminants, the forestomachs are actively developing, and indigestions can result from disturbances of the developmental mechanisms. The forestomach diseases of young ruminants generally have received little attention, but they can be recognized and appropriately treated within a classification scheme similar to that for adult ruminants.[44]

Pathophysiology

Digestion of feedstuffs in the reticulorumen is accomplished by microbial fermentation. The mucosal epithelium absorbs and exchanges products of fermentation but performs essentially no secretory function. Appropriate forestomach fermentation depends on the coordination of processes that provide a fairly constant reticuloruminal environment. The requirements include addition of appropriate amounts and types of feed substrate and water by ingestion; buffering of substances from the saliva to counteract the acid nature of fermentation products; eructation of the gaseous products of fermentation; coordination of reticuloruminal motility to provide mixing; rumination and remastication; aborad passage of ingesta; temperature maintenance; and exchanges of electrolytes and VFAs across the ruminal wall. Because these functions are intimately interrelated, abnormalities in any one of them can lead to digestive disturbances.

Clinical Signs and Differential Diagnosis of Indigestion

General Signs.

A general physical examination allows the practitioner to recognize signs of reticuloruminal problems (Table 32.14) and to assess whether a disease is present that could induce reticuloruminal dysfunction as a secondary phenomenon. General signs common to all forms of indigestion include a reduction in or absence of appetite, dullness or depression, and decreased animal productivity. The most common clinical signs of ruminal dysfunction are a decrease, absence, or abnormality of ruminal contraction sounds in the left paralumbar fossa or an abnormal left-sided abdominal contour. The left

abdominal wall may show gauntness and decreased filling or display gross distention. It is often the failure to detect signs of another primary disease as the cause of ruminal dysfunction that directs attention to the forestomach as the possible primary site of disease. Indigestion in calves effectively produces a state of malnutrition, and additional signs in these growing animals include poor growth rate and long, rough hair coat. The acuteness of onset and the severity of these signs depend on the inciting cause of the indigestion. Specific abnormalities in the ruminal motility pattern are discussed in more detail, but most indigestions are marked by decreased or absent ruminations (regurgitation and cud chewing) and depressed ruminal contractions.[140] Only early cases of frothy bloat and some cases of obstructive (vagal) indigestion display increased ruminal motility.

TABLE 32.14

Clinical Signs Typically Associated With Primary Indigestion

Signs	Associated Problems
Fever	Traumatic reticuloperitonitis, reticuloruminitis
Decreased ruminal filling	Fermentative indigestion and secondary indigestion (especially with chronic anorexia) in which passage of material from the rumen is not impeded
Abdominal distention	See Fig. 32.119
Excessive fluid (or froth) in the rumen with loss of normal ingesta stratification	Acute ruminal acidosis, vagal indigestion, frothy bloat, anterior intestinal obstruction
Excessive firm, fibrous material in rumen	Ruminal inactivity caused by poor-quality roughage
	Prolonged ruminal stasis caused by chronic disease with anorexia
Firm, doughy ingesta in ventral rumen with decreased ruminal filling	Early cases of frothy bloat, some cases of vagal indigestion
	Traumatic reticuloperitonitis, abomasal ulceration, reticuloruminitis
	Traumatic reticuloperitonitis, omasal transport failure, ruminal inactivity with poor-quality roughage; also dental disease and some abomasal disease
Ruminal hypermotility	Acute or chronic ruminal acidosis
Abdominal pain, either present or can be elicited	Pyloric outflow failure, abomasal displacement
Abnormal feces	Acute ruminal acidosis
Decreased quantity, firm, dry, with increased fiber length	Fermentative indigestion, enteritis
	Anorexia (various causes), acute indigestion before later development of abnormalities
Feces with abnormal amounts of whole cereal grains	Ruminal overdistention with vagal indigestion, inflammation of reticulorumen, reticuloomasal orifice obstruction, diaphragmatic hernia, some intoxications (differentiate from esophageal disease)
Greasy consistency with very fine particle size	
Foamy, fluid, yellowish color, acidic odor	
Pasty to fluid consistency with foul odor	
Decreased quantity, dry, otherwise unremarkable	
Vomiting (rare)	

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Body temperature usually is within normal limits because the causes of indigestion are mainly physiologic abnormalities. Exceptions include TRP and occasional cases of rumenitis with significant inflammation. Disturbances of heart rate, respiratory rate, hematologic parameters, and body fluid vary tremendously among different forms of indigestion and different cases of any one form of indigestion. For example, an acute onset of severe ruminal bloat might produce a stress leukogram and severe disturbance of the cardiovascular and respiratory systems, whereas mild or chronic bloat may produce no remarkable change in these systems. Rapid accumulation of fluid in the forestomach chamber in severe ruminal acidosis with grain overload can induce severe dehydration with hemoconcentration, an inflammatory response, systemic acidosis, and increased heart and respiratory rates, whereas slow fluid sequestration in some cases of obstructive (vagal) indigestion may not induce marked changes in these parameters.

Most of the primary forestomach diseases do not induce remarkable changes in the serum biochemistry profile. In lactating or heavily pregnant animals, anorexia may induce a secondary form of ketosis, which is detected by the presence of urine or blood ketones. Affected animals must be carefully examined to differentiate ketosis with secondary anorexia and decreased ruminal activity from primary indigestion with secondary ketosis. Mild to moderate hypocalcemia and hypokalemia are commonly identified abnormalities in many cases of indigestion, especially when anorexia has been prolonged.

The history is important, especially with regard to the animal's feeding. Characteristics of the feed determine the type of fermentation pattern to be expected. Knowledge of the nutrient content thus allows an assessment of the biochemistry of microbial digestion. Consumption of a high-concentrate, low-fiber ration or legume pasture may lead to frothy bloat. A ration of poor-quality hay or straw may result in low microbial fermentative activity and accumulation of impacted indigestible roughage. Overeating of carbohydrates or sudden access to concentrate feeds without adequate adaptation time can induce chronic or acute ruminal acidosis. The feeding history should agree with the findings from inspection of the ruminal contents, or the history should be suspected to be inaccurate. The amount and consistency of the feces should also provide supportive evidence of the type and amount of feed intake.

Abdominal Contours and Animal Stance.

Visual inspection of the abdominal contours allows assessment of the degree of

forestomach filling (Fig. 32.128). Indigestions can be characterized by decreased, normal, or excessive filling of the reticulorumen. Most primary and secondary indigestions are associated with ruminal hypomotility and anorexia. Thus the rumen usually shows no obvious distention and may have less filling than normal, especially when the duration of the disease is prolonged. Forms of indigestion in which abnormal ingesta or abnormal ruminal motility prevents effective flow of ingesta (overfeeding of poor-quality roughage, obstructive indigestion) or in which fluid is actively sequestered in the reticulorumen (acute ruminal acidosis) typically cause some degree of forestomach distention (See Fig. 32.128).

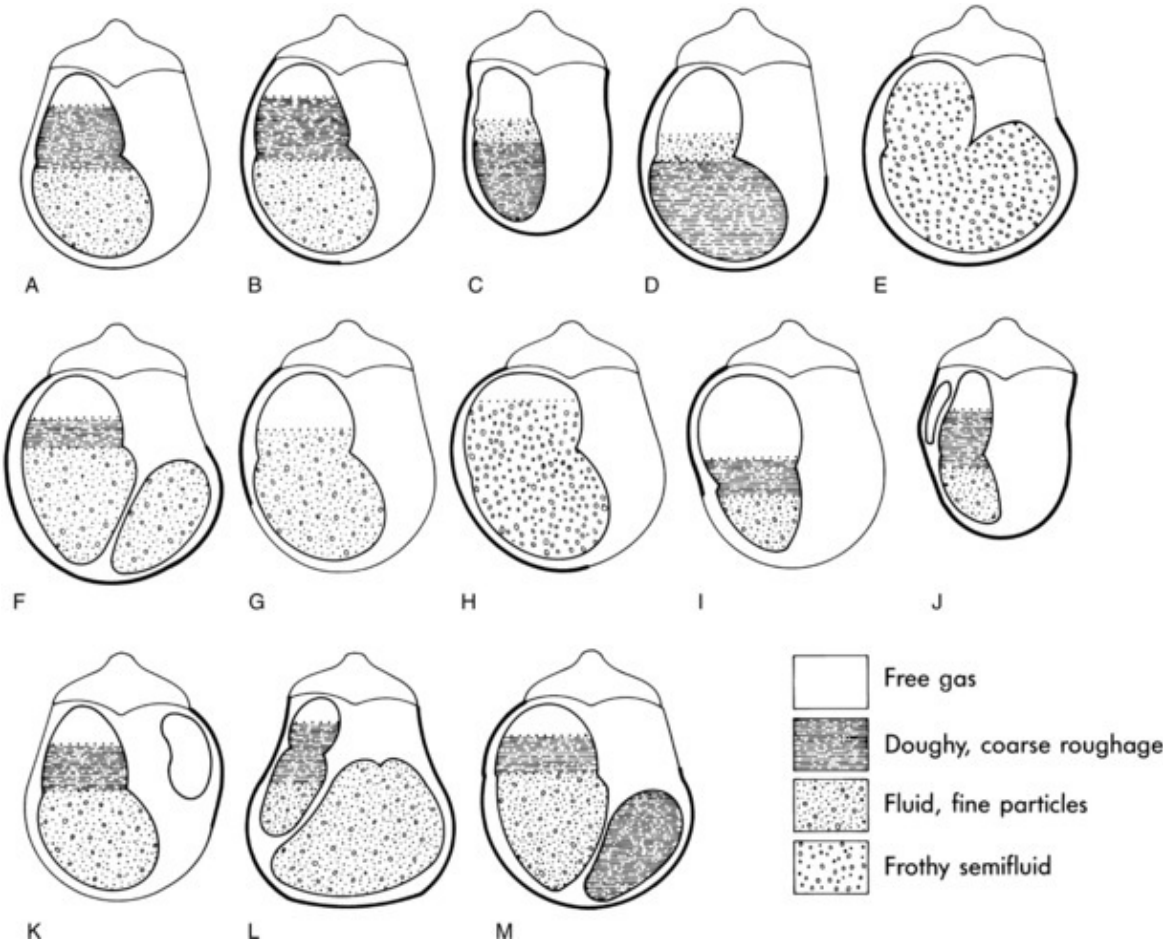


FIG. 32.128 Diagrams of abdominal contours (viewed from the rear) and abdominal palpation findings characteristic of cattle with various types of indigestion and other abdominal diseases. A *thin line* for the abdominal contour indicates the normal configuration. *Bold lines* indicate areas of the abdominal contour that typically deviate from normal in affected animals. **A,** Normal. **B,** Acute onset of rumen stasis with simple indigestion and

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traumatic reticuloperitonitis (findings: mild ruminal distention with normal layering of rumen content). **C,** Prolonged rumen stasis and anorexia: the most common results of subacute or chronic disorders such as microbial or fermentative indigestions, traumatic reticuloperitonitis, and secondary indigestions (findings: reduced rumen fill; “tucked-up abdomen”; firm, doughy contents that gravitate ventrally). **D,** Rumen inactivity with indigestible roughage (findings: rumen distended with firm, doughy contents that accumulate ventrally; recurrent free gas bloat often present). **E,** Omasal transport failure (findings: L-shaped rumen with gross accumulation of frothy ingesta; rumen hypermotility often present; free gas accumulation varies). **F,** Pyloric outflow failure (findings: fluid accumulation in abomasum; abomasal reflux to rumen common; doughy rumen content that usually accumulates dorsally until rumen stasis or anorexia is prolonged; abdominal contour similar to that for omasal transport failure). **G,** Acute rumen acidosis (findings: rumen distended with fluid; some free gas bloat common). **H,** Frothy bloat. **I,** Free gas bloat or chronic free gas bloat (findings: accumulation of gas in dorsal sac; layering or rumen contents usually normal; with chronicity, rumen fill often decreased; associated with some microbial or fermentative disorders and with esophageal and cardiac disorders). **J,** Left displaced abomasum (findings: gas-filled abomasum that often causes slight bulge of paralumbar fossa; rumen fill usually reduced). **K,** Right displaced abomasum, abomasal volvulus, cecal torsion (findings: distention of right flank with gas-filled viscus; rumen fill and consistency usually normal). **L,** Hydrops (findings: ventral abdomen distended with fluid-filled uterus: rumen fill usually decreased). **M,** Abomasal impaction (findings: abdominal contour similar to those in **E** and **F;** abomasum filled with firm ingesta).

A left-sided or bilateral ventral abdominal wall distention indicates ventral ruminal dilation, although advanced pregnancy and hydrops conditions must be considered. Distention of the dorsal left flank results from ruminal tympany with or without distention of the ventral rumen. Left abomasal displacement can produce mild distention of the dorsal left flank under the caudal ribs and extending into the paralumbar fossa, but the abdomen usually appears gaunt and empty when viewed from the side or the rear. Occasional cases of left displaced abomasum appear to inhibit eructation and produce gross ruminal tympany as the primary sign. Release of free ruminal gas through a stomach tube and reexamination for abdominal pings reveals this cause of secondary ruminal dysfunction. Frothy bloat in ruminants is discussed further in this chapter. Free gas accumulation is often secondary to the causes of ruminal motility inhibition and is an important sign of indigestion (Table 32.15). Right-sided abdominal distention suggests the various conditions of dilation, displacement, and obstruction or ileus of the intestines and abomasum. The diseases that cause obstruction and reflux of abomasal ingesta into the rumen may result in

reticuloruminal distention. Prolonged cases of gastrointestinal obstruction at any site and generalized peritonitis can produce gross bilateral dorsal and ventral distention of the abdomen.

TABLE 32.15

Differentiation of Types of Bloat Through Nasogastric Intubation

Results of Intubation	Probable Causes of Bloat
Tube does not pass.	Esophageal obstruction
Tube passes with resistance and releases ruminal gas.	Esophageal compression caused by thoracic inflammatory or neoplastic disease
Tube passes easily and releases ruminal gas.	Distortion of the cardia caused by inflammation, neoplasia, or abnormal anatomy such as abomasal displacement Ruminal stasis caused by reticuloruminal fermentative disorder, hypocalcemia Obstruction of cardia with ingesta (overfilling of rumen) or pedunculated mass Rumenitis (reticulitis) Weakened ruminal contraction caused by chronic overdistention with ingesta (vagal indigestion, indigestion with poorly digestible forage)
Tube passes easily but does not release gas or releases small amount of foamy ingesta.	Frothy bloat Frothy ruminal contents caused by abnormal motility in some forms of vagal indigestion

Affected animals should be studied for signs of pain. A pain-filled expression, reluctance to move, an abnormal stilted gait, an arched back with a tucked-up abdomen, and an extended neck are typical signs of anterior abdominal pain. These signs may indicate TRP, abomasal ulceration, or another source of pain. A similar stilted gait and reluctance to move are typical of laminitis, a common sequela of acute ruminal acidosis.

Palpable Findings.

Deep palpation of the left side of the abdomen is used to determine the consistency of the ruminal contents and thus the nature and volume of the ingesta (see Fig. 32.128). In normal animals the organized contraction sequence produces a layering effect.[155] A fluid consistency can be palpated ventrally, whereas the consistency is firm and doughy dorsally. The doughy layer consists of the fibrous portion of the feed. In general, an animal fed a high-roughage diet has a more prominent layer of doughy ingesta. The ruminal contents of an animal fed concentrate feed are softer. In sheep and goats, the normal dorsal rumen is softer than that of cattle no matter what the feed. In the normal

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condition, a small layer of free gas is present in the most dorsal region. Distention with gas or foamy feed produces a taut, elastic tension. With free gas bloat, the doughy layer can still be appreciated ventral to the gas accumulation, but in cases of frothy bloat, the doughy layer is much less prominent. Most cases of obstructive (vagal) indigestion and some cases of proximal intestinal obstruction cause gross dilation of the rumen with fluid or foamy contents that may fluctuate on ballottement.

Overfeeding of indigestible poor hay or straw with resultant inactivity of ruminal microbial fermentation leads to accumulation of more fibrous material than normal that barely yields to deep palpation. With prolonged or severe ruminal stasis, as may occur in TRP, the lack of ruminal motility leads to failure to maintain the normal layering of the contents. In some instances the ventral portion of the forestomach is firmer than the area above. During severe ruminal acidosis, fluid accumulates in the forestomach. This can lead to some degree of abdominal distention, and on palpation the ruminal contents are fluid and may even splash with ballottement.

The rumen should also be palpated rectally; a comparison of these findings with those obtained externally may be revealing. Moderate degrees of free gas accumulation are often more easily detectable on rectal palpation. Rectal palpation is also useful in distinguishing the presence of an L-shaped rumen, in which the ventral sac of the rumen is grossly distended and extends toward the right ventral quadrant. It is important to differentiate an L-shaped rumen from either abomasal distention or impaction, which can manifest in a similar external abdominal contour. It is also important to palpate for the size of the lymph nodes in the longitudinal groove of the rumen. These can enlarge to prominent size when rumenitis is present. The organs in the right half of the abdomen should be assessed as sources of abdominal problems.

Rectal examination is impossible in small ruminants and calves. External palpation with both hands can be valuable in these animals. In calves and goats, it is the best method for detecting bezoars or clotted clumps of milk in the rumen and for palpating intussusception, umbilical abscesses, or grossly abnormal kidneys.

Palpation of the left paralumbar fossa reveals the presence of ruminal contractions. In a normal animal, three contractions should occur over a 2-minute period. One of these contractions should be associated with an eructation of gas, which can be appreciated both visually and audibly. The rate of eructation increases or decreases in proportion to the fermentative production of gas. Most

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indigestions produce decreased ruminal motility or ruminal stasis. Early cases of frothy bloat and some forms of obstructive indigestion can result in prominent hypermotility. The motility pattern is characterized by changes in both frequency and strength, and weak contractions can also be detected by palpation. Some cases of secondary indigestion, in which the decrease in ruminal function is a result of inappetence rather than an inhibition of ruminal motility, manifest a normal contraction frequency but decreased contraction strength. The duration and strength of ruminal contractions are primarily determined by the nature of the forestomach contents, whereas the frequency relies on medullary gastric center control. Decreased ruminal fill, decreased fiber content of the ingesta, or overdistention of the ruminal wall musculature results in reduced strength and duration of the contraction sequence. These distinctions can be important in determining the cause of decreased ruminal motility.

Auscultable Findings.

Auscultation of abdominal sounds is performed over several sites in the left flank and rib areas. Initial auscultation is used to assess the nature, frequency, and strength of ruminal sounds. This information can be compared with the information about ruminal motility gathered on palpation. The sounds represent the friction of fibrous ingesta rubbing against the ruminal wall as the ruminal sacs contract and mix their contents. In healthy cattle on a roughage diet, the normal rustling sound is prominent and prolonged with each contraction cycle. The ruminal contents of animals fed a high-concentrate diet produce less sound because very low fiber rations induce weaker contractions, and less fibrous material is in contact with the ruminal wall.

As with palpation, both the frequency and the nature of the sounds yield information about reticuloruminal motility. The ruminal motility pattern is disrupted in obstructive (vagal) indigestion. Although contractions are present and may be more frequent than normal, their lack of normal coordination can lead to a churning of the ingesta without the usual progression of transport. This disrupts the normal stratification of the contents and produces abnormal sounds that are heard as a rumbling, bubbling, or splashing. When stratification is disrupted because of a hypoactive rumen and more fluid is present in the dorsal area of the rumen, contractions produce splashing sounds. The accumulation of gas under these circumstances may produce ringing tones as the fluid moves, similar to the pings found with a displaced abomasum.

Some circumstances necessitate a distinction between primary and secondary

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contraction cycles, and they can be differentiated by auscultating for reticular contractions. Holding the stethoscope at the seventh intercostal space at the level of the costochondral junction, the examiner can detect a tinkling fluid sound as the reticulum contracts. A hand held in the paralumbar fossa can detect the tensed bulging of the dorsal sac as it contracts, allowing the examiner to determine whether the ruminal contraction is associated with a reticular contraction. Reticular contraction and motility can also be assessed by transabdominal ultrasonography.[15,17,19] Hyperactivity of primary cycles associated with feeding or the immediate postprandial period is normal. Mechanical stimulation of buccal sensory receptors can lead to an approximate doubling of the primary cycle rate. Hypermotility that results from excessive secondary contractions, without the normal mixing and propulsion of primary contractions, is abnormal and represents ruminal dysfunction.

Ruminal features related to the size and stratification of ingesta, echogenicity and thickness of the wall, size of the dorsal gas cap, and ruminal height at different intercostal spaces can be achieved with ultrasonography.[23] Combining ultrasonography and auscultation with percussion or ballottement allows assessment of gas or fluid accumulations. The sounds heard in the left flank should be compared with those in the left rib area and right side of the abdomen. High-pitched pings and fluid tinkling sounds suggest a viscus filled with gas and fluid. In the left flank this may represent a displaced abomasum, gas-forming abscess, pneumoperitoneum, or static rumen. Careful comparison of the sounds heard at different sites, combined with the results of rectal palpation, should enable localization of the source. In general, the rumen can be ruled out as the source of pings if palpation reveals normal doughy ruminal contents, no ruminal tympany is palpated rectally, and sounds of normal ruminal contractions are heard in the paralumbar fossa. Prolonged anorexia associated with infectious or inflammatory diseases such as pneumonia or mastitis can result in a static, underfilled rumen, and occasionally a prominent ping can be auscultated in the left flank, where a filled rumen normally would be found. This condition has been called “ruminal collapse,” and careful evaluation is necessary to distinguish it from leftward displacement of the abomasum. Ballottement of the rumen may reveal splashing fluid sounds without a high pitch when the rumen has accumulated significant fluid. This occurs frequently in cases of severe ruminal acidosis. It may also occur in cases of marked inactivity of the ruminal flora with loss of the normal stratification of ruminal contents.

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Pain Elicitation.

Tests of pain sensitivity in the anterior abdomen (percussion, deep palpation, withers pinch, xyphoid pressure) are performed to detect localized peritonitis caused by TRP or abomasal ulceration. The same procedures, especially percussion or application of pressure to a localized area in the ventral portion of the abdomen, can be used to localize pain associated with rumenitis or ruminal abscessation or perforating abosomal ulceration.[25]

Fecal Abnormalities.

The rectal examination presents an opportunity to assess the volume and nature of the feces. The feces are abnormal in most cases of forestomach dysfunction. In adult cattle, passage of ingesta through the digestive tract requires 1½ to 4 days. Changes in the feces caused by acute diseases are thus often delayed by a day or longer beyond the first appearance of other clinical signs. Mature cattle typically pass a total of 30 to 50 kg of feces per day, divided into 10 to 24 defecations. The color and consistency of feces are influenced by the feed and should be assessed in view of the feeding history.

Diseases that reduce the flow of ingesta from the rumen to the lower gastrointestinal tract typically result in feces of reduced volume that are firm and dry. These findings are also present with reduced feed or water intake. If normal intestinal function is present, a decreased flow of ingesta from the forestomach allows longer retention in the bowel with greater resorption of water. In severe instances, the feces form into firm disks or balls with a dark, shiny mucus covering. These findings are typical of obstructive indigestion and forestomach diseases that produce ruminal stasis without a grossly abnormal fermentative pattern. Indigestions with abnormal fermentation may produce decreased quantities of dry feces initially but usually result in other fecal abnormalities as the abnormal ingesta passes into the lower tract. Intestinal obstructions also decrease fecal passage to the point of absence, but usually the material passed also has other gross abnormalities such as blood, melena, or discolored mucus.

The particle size of fecal material depends on the frequency and duration of rumination, the activity of the ruminal flora, and the function of the rumen in appropriately sorting out material for passage through the reticuloomasal orifice. Abnormalities of these digestive functions lead to passage of ingesta of inappropriate particle size. Plant fibers in normal bovine feces measure up to 0.5 cm. Particles with inadequate breakdown may measure 1 to 2 cm or longer. This

long particle size may be seen in the feces of cattle with TRP, some cases of obstructive indigestion, and poor-quality roughage with insufficient microfloral activity.[18,125] Similar findings occur with tooth disease and some cases of abomasitis or cellulitis at the cardia or esophageal groove, in which rumination or activity of the reticuloomasal orifice is inhibited. Whole cereal grains (especially whole corn) may pass in the feces of normal cattle, but excessive amounts of grain should raise suspicion of excessive intake and acute ruminal acidosis. Feces with an abnormally fine particle size and greasy-pasty texture are associated with delayed passage from the forestomach. These are common findings in most cases of obstructive indigestion and abomasal displacement.

The odor of bovine feces is relatively inoffensive in healthy individuals. Foul odors are the result of abnormal fermentation or decomposition. Thus abnormal odor typically occurs when the ruminal fermentation pattern is altered, as in simple indigestion caused by abnormal feed, ruminal acidosis, ruminal alkalosis, or ruminal content putrefaction. A repugnant odor is also typical of enteritis when blood products, inflammatory products, or tissues decompose in the intestinal tract (e.g., *Salmonella* enteritis). Foamy, fluid feces with a yellow-brown color and acidic smell are typical of ruminal lactic acidosis in adult cattle. Abnormal ruminal fermentation not only produces feces with abnormal odor but also typically leads to a pasty or fluid consistency as well. Exceptions occur in acute cases, when ruminal stasis or the delay in the passage of ingesta from the forestomach can result in normal or firm feces during initial stages of the disease.

Heart Rate.

Bradycardia of 40 to 60 beats/min is frequently associated with certain types of indigestion. This sign suggests reflex vagotonia to the heart and has been considered indicative of obstructive indigestion associated with vagal nerve damage. The bradycardia can be alleviated by subcutaneous administration of 30 mg of atropine, which differentiates increased vagal nerve tone from a primary cardiac conduction disturbance. The atropine test is not especially useful because only a minority of obstructive indigestion cases are caused by vagal nerve damage or show bradycardia.[18] Advanced cases with severe abdominal distention or fluid imbalances (or both) frequently manifest elevated heart rates (over 80 beats/min). In most cases the other physical signs are more reliable for establishing the diagnosis of obstructive indigestion. Moreover, bradycardia may be observed in other forms of indigestion when ruminal hypomotility is

prominent and no significant fluid or electrolyte imbalances are present. Even in normal cattle, postfasting heart rates may drop below 50 beats/min.[106] Therefore bradycardia in association with other signs of ruminal dysfunction is probably most useful as evidence that tachycardic stimuli, such as inflammatory, infectious, or fluid balance disturbances, are not prominent factors in the individual disease occurrence.

Vomiting.

Vomiting is uncommon in ruminants, but when it does occur, it generally reflects forestomach disease. Regurgitation from the abomasum frequently occurs with abomasal or intestinal disease. Abomasal reflux is not manifested externally and is discussed elsewhere because it is related to forestomach disease. Small volume regurgitation and remastication are routine and normal ruminant functions that do not result in expulsion of material from the mouth. Explosive vomiting of fluid ingesta in large quantity occurs when the reticulorumen is irritated and occasionally when it is overdistended. Vomiting may accompany diaphragmatic herniation of the reticulum, inflammation of the reticulorumen caused by actinobacillosis, obstructive indigestion, or obstruction of the reticuloomasal orifice. Animals are more prone than normal to vomiting around an orally passed stomach tube when they have almost any digestive disturbance. Vomiting also occurs with certain intoxications, most notably azalea, rhododendron, and sneezeweed toxicity and some organophosphate toxicities.

Disorders of Reticuloruminal Motor Function

Normal Motor Activity.

The two reticuloruminal contraction sequences function independently. The primary cycle of contraction occurs approximately once a minute but more often during feeding and rumination. It consists of a biphasic contraction of the reticulum followed by a contraction that runs caudally across first the dorsal and then the ventral ruminal sacs. At the height of the second reticular contraction, the omasal orifice relaxes and fluid, mostly composed of reticular ingesta, passes into the omasum. This reticuloruminal motility pattern directly influences ruminal fermentation by mechanically mixing the ingesta to provide contact with the microbes and to macerate the particulate matter. The mixing function prevents local accumulations of substrate or end products of fermentation, distributes the buffering saliva for neutralization of acids, and provides increased

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contact of the fluid with the ruminal wall to promote VFA absorption. The coordinated sequence of contraction of various parts of the ruminal wall maintains a stratification of fluid and particulate matter that selectively sorts the ingesta by particle size. The sorting function serves to retain large particles for further digestive breakdown while promoting passage of small particles (smaller than 6 mm) into the omasum and lower gastrointestinal tract.[19,32,155]

The secondary contraction cycle does not involve the reticulum. It begins in the caudal blind sacs, and a wave of contraction runs cranially across the dorsal rumen, pushing the gas cap into the cardia region. Eructation ensues, eliminating the gases generated by fermentation. Typically one secondary cycle contraction follows two primary cycles, so that three contractions occur every 2 minutes.[33] Two additional special contractions have been identified in sheep: primary-secondary contractions and prosecondary contractions.[9] These contractions appear when intraruminal pressure increases and allow ruminal gas to be evacuated. The primary-secondary and prosecondary contractions appear to help minimize free gas bloat when gas production is excessive.

Maintenance of the motility patterns requires well-coordinated neural control. The pathophysiologic mechanism of the first group of primary indigestions (i.e., diseases of the reticuloruminal motor function) involves disturbance of the mechanisms of normal ruminal motility, which secondarily affects ruminal fermentation.

The ruminal contraction sequences described rely almost completely on motor nerve activation arising from the medulla oblongata, in contrast to the intrinsic segmental and peristaltic movements of the intestine. Gastric centers in the medulla integrate sensory input and generate motor impulses, both of which are carried in the vagus nerves. The gastric centers have neither spontaneous activity nor an inherent rhythm. Generation of motor impulses relies on greater excitatory input than inhibitory input from the sensory nerves to determine the rate, magnitude, and duration of primary cycle contractions. During the quiescent period between the primary contractions, while the medulla collects the sensory information, there are no tonic vagal motor impulses.[94,153]

The splanchnic nerves also affect reticuloruminal motility by direct innervation and by neurohumoral effects of adrenal secretion. These nerves are not required for generation of normal contractions. The effect of splanchnic stimulation is inhibition of reticuloruminal motility. Splanchnic sensory nerves innervate sensory receptors in other areas of the gastrointestinal system, and some abnormalities such as intestinal distention or surgical manipulation

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produce reticuloruminal inhibition by means of reflex from splanchnic afferent activity.[153]

Primary Cycle Activity.

A decrease in or absence of normal primary cycle activity (i.e., ruminal hypomotility or stasis) implies either a decrease of vagal motor discharges originating from the gastric centers or an ineffective motor response after motor impulse, as in cases of hypocalcemia. Causes of decreased motor discharges include the following:

1. Decreased excitatory input to the gastric centers
2. Increased inhibitory input to the gastric centers
3. Depression of the gastric centers
4. Defective vagal transmission of motor impulses
5. Other factors

Decreased Excitory Input.

The three most important excitatory inputs to the gastric centers are from (1) low-threshold tension receptors in the reticulum, (2) buccal receptors in the mouth, and (3) acid receptors in the abomasum (Table 32.16). The tension receptors are located in the musculature of the medial wall of the reticulum. They are stimulated by mild distention during the resting phase and thereby influence contraction frequency. They are further stimulated by the tension generated during contraction and thus increase amplitude and duration of the primary cycle contraction. This mechanism is probably responsible for the increase in motility after feeding or during incipient bloat. Any cause of anorexia leading to decreased ruminal fill decreases this excitatory input, which results in ruminal hypomotility. Feeding mechanically stimulates buccal sensory receptors, providing a potent stimulus to both primary and secondary contraction cycles. This reflex can double the rate of primary contractions but is short-lived and declines as soon as chewing activity ceases. Thus anorexia effectively eliminates this potent excitatory input. Abomasal acidity increases as the abomasum empties, and this too provides excitatory input to the gastric centers. The resultant increased reticuloruminal motility leads to increased flow of ingesta to the abomasum, diluting the abomasal acid and maintaining normal filling of the abomasum. Certain types of abomasal disease such as abomasal distention

associated with abomasal displacement or abomasal impaction diminish this stimulus to forestomach motility.[94,96,153]

TABLE 32.16

Factors Influencing Vagal Motor Discharge From the Gastric Centers of the Medulla[a]

Input	Location	Stimulus
Excitation of the Gastric Centers (Causes Increased Rumen Motility)		
Low-threshold tension receptors	Reticulum, medial wall	Mild distention; tension generated during contractions
Buccal receptors	Mouth	Feeding (only during chewing)
Acid receptors	Abomasum	Increased acidity as abomasum empties
Tension receptors[b]	Medial wall of cranial rumen sac	Increased rumen gas pressure
Inhibition of the Gastric Centers (Causes Decreased Rumen Motility)		
High-threshold tension receptors	Reticulum and cranial rumen sac	Bloat or other severe ruminal distention
Tension receptors	Abomasum	Abomasal distention
Chemical receptors	Reticulum, rumen	Increased concentration of undissociated volatile fatty acid with rumen acidosis; also locally activated by some toxins
Pain receptors in body increase sympathetic tone and adrenal secretory activity	Anywhere in body; can act directly and through medullary gastric centers	Pain, especially abdominal
Gastric centers	Medulla	Anesthesia, depressant drugs, toxins, endotoxins, fever, acidosis
Hypocalcemia	Reticuloruminal smooth muscle	Hypocalcemia

[a]There is no inherent reticuloruminal motility such as that found in the intestines.

[b]Secondary cycle activity; independent of primary cycle activity.

Stimuli of reticuloruminal motility that are not as well defined include the physical and chemical characteristics of the ruminal ingesta. Fiber and water content, as well as the normal chemical products (i.e., VFAs) of fermentation, are important for normal ruminal contraction. The exact mechanisms through which these factors enhance ruminal motility have not yet been clearly defined,[81] but low levels of any of these ingesta characteristics impair normal function, causing decreases of both rumination and primary cycle activity. That these excitatory stimuli are decreased or absent in some feeding regimens and with some of the diseases attributable to abnormal fermentation may account for the impression of hypomotility observed clinically.[50]

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Increased Inhibitory Input.

Inhibitory inputs to the gastric center arise from (1) high-threshold tension receptors in the reticulum and cranial dorsal ruminal sac, (2) tension receptors in the abomasum, (3) epithelial receptors that detect high concentrations of nondissociated VFAs in the rumen, and (4) pain elicited at any site in the body (see Table 32.16). The high-threshold tension receptors are sensory nerve endings below the epithelial basement membrane of the reticulum and cranial dorsal ruminal sac. They respond to extreme distention of the wall and serve to modify the end stage of reticuloruminal contraction. With severe bloat or gross ruminal distention from other causes, such as overfilling with indigestible fibrous roughage, they can be continuously activated producing ruminal stasis. Abomasal distention can inhibit primary ruminal contraction cycles presumably through tension receptors in the abomasal wall.[78] In normal circumstances this activity serves to decrease the flow of ingesta to the abomasum when it is full. With abomasal displacement or impaction, this reflex may partly account for the observed ruminal hypomotility. Epithelial receptors in the reticulum and cranial dorsal ruminal sac are sensitive to increased concentrations of nondissociated VFAs. Inhibition of forestomach contractions occurs when conditions of excessive fermentation or acidosis increase the concentrations of these substances. Pain can reduce forestomach motility by increasing sympathetic nervous and adrenal secretory activity and by inhibiting the gastric centers. Although painful stimuli in the abdominal viscera are particularly potent, pain from anywhere in the body can inhibit or abolish reticuloruminal motility.[94,96,153]

Depression of the Gastric Centers.

Depression of the gastric centers reduces vagal motor activation of forestomach motility and can be induced by central nervous system depressant drugs and anesthetics such as barbiturates, inhalant anesthetics and xylazine. Endotoxemia, fever, and possibly blood pH and electrolyte abnormalities can induce ruminal hypomotility or stasis through central effects on the gastric centers. These factors may also inhibit ruminal motility by increasing sympathetic nervous activity. In addition, some toxins or other abnormal fermentation products reduce ruminal motility. These substances may act locally at the ruminal epithelial receptors to generate inhibitory impulses, as do increased VFA concentrations, or they may act centrally after absorption into the blood. For the most part, the nature of the substances capable of chemically suppressing ruminal function is unknown, but

abnormal fermentation end products are the likely cause of ruminal stasis in indigestion associated with abnormal ruminal contents.[50,94,95,155]

Defective Vagal Innervation.

Failure of vagal nerve transmission of motor impulses has been implicated as the cause of a reticuloruminal contraction abnormality that leads to failure of aborad flow of ingesta (hence the often-used name *vagal indigestion*). The left and right vagi in the thorax divide into dorsal and ventral branches that unite to form dorsal and ventral vagi as the nerves enter the abdomen. The ventral vagus innervates the cranial and medial parts of the reticulum, the omasum, and the abomasum. The dorsal vagus innervates the rumen and parts of the other segments of the ruminant stomach. Sectioning of more than 50% of the vagal nerve trunks leads to impaired motility function, but in most naturally occurring cases of obstructive (vagal) indigestion, it is not possible to demonstrate nerve involvement. The importance of vagal nerve lesions in the pathogenesis of forestomach disease has been a subject of considerable debate and is discussed later in this chapter.[94]

Other Factors That Affect the Primary Cycles.

Other influences on forestomach motility have been identified. Hypocalcemia inhibits motility by preventing contraction of the musculature after motor nerve discharge. This may explain the reduced ruminal motility seen in early cases of milk fever.[77] Low environmental temperatures[97,157] and milking[7] have been shown to increase ruminal motility mildly, whereas some drugs,[24,68,139] hyperglycemia,[149] and gastric hormones[66] are effective in decreasing reticuloruminal primary cycle contractions. These factors are not discussed further in this text.

Secondary Cycle Activity.

The secondary cycle activity responsible for eructation is elicited independently of the primary cycles. An increase in ruminal gas pressure stimulates tension receptors in the medial wall of the cranial dorsal ruminal sac. This triggers relaxation of the cardia and eructation of the gas accumulated in the cardia region by the secondary contraction cycle. Receptors that apparently distinguish gas from fluid or solid matter inhibit opening of the cardia if it is covered by material other than gas. This reflex inhibition of cardia opening is responsible

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for bloat in cases in which abnormal ingesta cover the area, (as in recumbent animals), in frothy bloat, and when abnormal motility or overfilling of the rumen precludes clearing of the cardia. Under such circumstances and when ruminal distention is not yet extreme, both primary and secondary cycle contractions may increase in frequency. In other forms of bloat, hypomotility is a prominent feature, and the gas accumulates as a result of the poor motility function. This is the most probable cause of bloat in some of the disturbances of fermentative function.

Gross overdistention of the ruminal wall may inhibit motility by stretching the musculature beyond its ability to contract forcefully. If the process leading to the distention develops slowly, the high-tension receptor inhibition of motility appears to adapt, and complete inhibition of motor impulses does not seem to occur. Rather, in these cases motility is present but weak and relatively ineffective. This motility disturbance is likely to occur when poorly digestible roughage accumulates in the forestomach. Patients with this condition often have mild to moderate chronic free gas bloat, which may result from poor ability of the weakened rumen to clear the cardia and dispel the gas.[43]

Reticulitis and Rumenitis.

The most important inflammatory problem is reticuloperitonitis caused by sharp foreign body punctures (TRP, hardware disease).[108] This disease is discussed elsewhere in this chapter. The localized infection established by reticuloruminal perforation causes inflammation of the forestomach wall and adjacent peritoneal cavity and pain in the anterior abdomen, inhibiting forestomach motility, appetite, and aborad flow of ingesta. Other causes of ruminal wall inflammation can cause acute or chronic forestomach dysfunction. Neutrophilia and hyperfibrinogenemia are routine findings of TRP or rumentis and can aid in differentiating them from other forestomach diseases that do not generally feature hematologic abnormalities.

Most infections of the ruminal wall follow primary mechanical or chemical damage to the mucosa. The secondary invaders colonize the damaged areas and may gain access to the circulation and invade other tissues as well. The ruminal wall may be the niche for some of these microorganisms, and isolates from the ruminal wall have been matched with those isolated from liver abscesses.[113] Probably the most common cause of the initial mucosal injury is acute ruminal acidosis produced by grain engorgement (discussed later). Chemical damage resulting in ruminal ulcers also occurs in oak or acorn toxicosis and with

ingestion of caustic chemicals. Common secondary ulcer invaders include *T. pyogenes, Fusobacterium necrophorum,* and several mycotic species.[113,151] Mycotic rumenitis can follow ruminal acidosis and septic diseases, especially after the use of oral antibiotics. It also can occur after feeding spoiled and moldy feeds and without apparent predisposing causes.[30,76] Diseases that cause anorexia and abomasal reflux of gastric acids may predispose an animal to mycotic rumenitis and omasitis. Mycotic rumenitis can be severe, with vascular thrombosis, infarction, mural necrosis and gangrene sufficient to cause death. Less frequently occurring, specific infections of the ruminal wall include atypical forms of actinobacillosis, actinomycosis, and tuberculosis. These infectious inflammatory diseases of the ruminal wall may be distributed widely throughout the forestomach, depending on the initial site of mucosal injury, but they tend to localize in the ventral regions of the reticulorumen. The granulomatous inflammatory lesions of actinobacillosis and actinomycosis are most commonly found in the cranial forestomach in the area of the esophageal groove.

Neoplastic growths in the rumen have also been identified. These uncommon lesions include papillomas, myxomas, fibromas, carcinomas, and lymphosarcoma.[62] These lesions are most commonly localized in the reticulum and cranial rumen near the cardia and esophageal groove.

The importance of these inflammatory reticuloruminal lesions depends on their extent and location. Acute and extensive lesions have been associated with signs similar to those of reticuloperitonitis caused by foreign body puncture, including pain, inappetence, impaired forestomach function, and in some cases death. The more chronic cases may cause forestomach motility disturbances and signs of obstructive indigestion. Pedunculated masses especially, but not exclusively, may obstruct the cardia or reticuloomasal orifice and lead to bloat or reticuloruminal outflow disturbance. Reticuloruminal inflammation can also result from certain generalized infections. These include BVD, FMD, MCF, and rinderpest. In these cases the forestomach problems are unlikely to be the most important clinical manifestation.

Diseases of the ruminal wall may be differentiated on the basis of the physical examination findings and results of a CBC, abdominocentesis, and ruminal fluid analysis. In many cases exploratory laparotomy is needed to confirm the diagnosis. Rumenitis or reticulitis may respond to antibiotic therapy, but the prognosis in these cases is guarded. Not only is the forestomach inflammation difficult to resolve, but also the hematogenous spread of infection to other organs

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often causes intractable disease in multiple organ systems.

Ruminal Parakeratosis.

In parakeratosis the papillae are darkly colored, enlarged, thickened, and clumped together. Histologic changes of the epithelial cells include a thickened, cornified layer with abnormal retention of nuclei in the cornified cells. These morphologic changes appear to represent a reaction to persistently high concentrations of VFAs. The changes occur predominantly in animals on pelleted or very finely ground rations, especially when the ration contains a high amount of energy. These rations tend to increase the proportions of propionate and butyrate, reduce the proportion of acetate generated by microbial fermentation, and lower ruminal fluid pH. The growth of the ruminal papillae is promoted by contact with the VFAs, especially butyrate, and secondarily propionate.[155] It appears that a disproportion of the concentrations of these VFAs may be the cause of an excessive change in the epithelium of the papillae.[55,147,160] Initial changes in the epithelium under these conditions appear to increase the absorption of the VFAs, but in severe cases the absorption decreases. This disease of the ruminal wall is not usually diagnosed as a primary problem. Although it may lead to impaired performance of the animal, the disease signs that lead to its discovery are usually those of chronic ruminal acidosis, a disease with which it often coexists. Parakeratosis can predispose to other injuries of the ruminal wall because the abnormal papillae are more easily traumatized, which leads to chronic inflammatory disease of the wall, as discussed previously. In calves the problem is also associated with the development of hairballs (trichobezoars) because of the propensity of calves fed rations associated with parakeratosis to lick their hair coat.[147]

Parakeratosis is best treated by correcting the causal feeding error (reducing the amount of concentrate and increasing the feeding of long-stemmed forage). The ruminal papillae can grow or regress in a period as short as 3 weeks when the feed is changed from low- to high-concentrate content or vice versa. Exactly how long it takes for parakeratotic papillae to return to normal remains uncertain, but it probably depends on the degree of change of the diet. The prognosis of this problem is good if inflammation of the ruminal wall is not present.

Obstructive (Vagal) Indigestion.

Obstructive indigestion syndrome (vagal indigestion, Hoflund's syndrome)

comprises a group of motor disturbances that hinder passage of ingesta out of the reticulorumen or abomasum or both. It is a syndrome, meaning a constellation of signs of disease, but with diverse potential causes. The disease signs are those that would occur if there were a physical obstruction of the reticuloomasal orifice or the pylorus. The author uses the term *obstructive indigestion* for this reason. Historically the term *vagal indigestion* has been used, but this has led to confusion because it implies that the vagal nerve is involved in the development of the syndrome, and this is true only in a minority of cases. Furthermore, damage to the vagal nerve can sometimes cause acute onset of free gas bloat as the most prominent disease sign, so some authors have felt obliged to develop a naming scheme for "vagal indigestion" that includes free gas bloat, even though this occurrence does not fit the syndrome that mimics obstruction of the reticuloomasal orifice or pylorus.

An animal with obstructive indigestion syndrome has progressive abdominal distention, characterized by distention both dorsally and ventrally in the left abdomen and ventrally in the right abdomen, and demonstrates overfilling and enlargement of the dorsal and ventral ruminal sacs with or without overfilling of the abomasum. Appetite gradually diminishes to complete anorexia. Body mass gradually decreases, and the animal may become weak and eventually unable to rise. Fecal output is scant, demonstrating little movement of ingesta through the gastrointestinal tract. In some cases free gas bloat occurs, adding to the abdominal distention. No single pathogenesis produces these signs of disease, and various investigations have yielded conflicting information.[18,20,42,72,124,125,129,146] It is the combination of all of these signs of disease that define the syndrome. Other disease conditions may cause some of these disease signs individually, but are distinguished from obstructive indigestion because the entire grouping of signs does not occur. For example, frothy bloat produces exactly the same abdominal distention, but it occurs rapidly, it does not lead to chronic loss of body condition, and feces are typically not scant. As an alternative example, free gas bloat can occur in a variety of circumstances but often is not accompanied by gross overfilling of the rumen and apparent obstruction of ingesta passage.

The term *vagal indigestion* was introduced by Hoflund, who hypothesized that the vagal nerve was damaged and experimentally produced motor defects and disease signs similar to those seen in clinical cases by transecting various branches of the abdominal vagal nerve.[72] On the basis of his experimental results, he defined the functional disturbance of stomach motor activity with

obstruction of ingesta flow at two sites:

1. *Omasal transport failure* (anterior or proximal functional stenosis, reticuloomasal stenosis), which impairs flow of ingesta through the reticuloomasal orifice and occurs with atony of the reticulorumen (often associated with chronic recurrent bloat), or normal to increased ruminal motility.
2. *Pyloric outflow failure* (posterior or distal functional stenosis, pyloric stenosis), which impairs flow through the pylorus and occurs continuously, or in an intermittent, recurrent pattern (incompletely).

Hoflund's description of the syndrome is convenient for explaining the observed functional defects, but its presumed pathogenesis is not supported by the findings of later investigators..[53,146] Later, a classification scheme of four types of vagal indigestion was proposed in which type 1 is associated with a failure of eructation. Animals with type 2 present with bilateral distention of the abdomen as the result of a failure of rumen outflow and fluid accumulation in the rumen. Type 3 manifests similarly to type 2, but the distention is due to a failure of abomasal motility and outflow. Type 4 is a syndrome of partial pyloric obstruction or generalized ileus, not as well defined as the other types.[52,53] Unfortunately, this classification scheme is also flawed. Types 2 and 3 in this scheme align well with Hoflund's description, but type 1 can be construed to include all forms of gaseous bloat. Failure of eructation can result from vagal nerve involvement in inflammatory processes in the thorax, but there are numerous other causes of free gas and frothy bloat, most of which are not chronic or associated with animal tissue wasting, characteristic of this syndrome. Type 4 in this scheme is not described in a way that clearly distinguishes it from type 3. Therefore in this text the terms *omasal transport failure* and *pyloric outflow failure* are used because they encompass the problems described here as obstructive indigestion.

Similar to the use of *vagal indigestion* as a descriptor is the use of the term *stenosis,* which has also led to some confusion, although it was appropriate in its original context. “Functional stenosis” suggested that the defect was a functional one that mimicked a stenosis at the site of outflow. This paralysis or muscular dysfunction can be appreciated in some experimental and clinical cases.

Failure of Omasal Transport.

Failure of omasal transport with hypermotility of the rumen is the most common naturally occurring form of the disease. Accumulation of ingesta in the reticulorumen leads to gradually progressive distention of the forestomachs, whereas the omasum and abomasum remain relatively empty. The animal's appetite diminishes as the rumen becomes overfilled, producing one of the most characteristic signs of the disease: inappetence with gross distention of the rumen in the left flank. Continued dilation of the rumen eventually leads to a marked and almost pathognomonic overfilling of the ventral ruminal sac. The rumen assumes an L shape because the ventral sac occupies both the right and left ventral quadrants of the abdomen. The resultant characteristic abdominal contour often is called a “papple” shape (see Fig. 32.128, *E*) because the left side of the abdomen is distended and assumes the appearance of an apple, whereas the right side assumes the contour of a pear. The reduced passage of ingesta results in low fecal volume. The normal ruminal process of selective retention of fibrous material is disturbed, which causes feces to have increased fiber length and a greasy or pasty consistency. In some cases, feces are firm with large particle size.[18,125] Affected animals often continue to drink water, but absorption from the rumen is poor, and the water accumulates in the forestomach while the animal becomes mildly dehydrated. Vigorous contractions of the rumen can be palpated in the left paralumbar fossa in most affected animals, although some display almost complete atony. The contraction pattern does not produce the typical stratification of material in the forestomach; rather, it churns the ruminal contents into a uniform frothy fluid.[124,125]

The signs just described, with abnormal flow of ingesta and normal or increased forestomach contractions, can be experimentally reproduced by sectioning of the ventral vagal trunk at the cardia and the dorsal trunk just distal to the branching of the ruminal nerves.[72] The forestomach distention, empty omasum and abomasum, and stasis of the forestomach with resultant free gas bloat can be reproduced by sectioning of both abdominal vagal trunks along the esophagus. The paralysis produced by vagal denervation can explain the failure of ingesta flow into the omasum by two mechanisms. First, the lower end of the esophageal groove is formed by two muscular lips. These overlap in a manner that allows a passive valve effect that blocks flow into the omasum when they are relaxed or paralyzed. Second, it appears that the flow of ingesta into the omasum is accomplished by an active pumping motion of the omasum that maintains a negative pressure gradient toward the omasum and draws fluid through the reticuloomasal orifice. Paralysis of the omasal musculature after

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denervation would eliminate the pressure gradient effect. Decreased reticular motility caused by paralysis may contribute to the changes in ruminal content and the alteration in particle passage.[124,125]

The most common predisposing cause of naturally occurring omasal transport failure is TRP. Other causes of omasal transport failure include abscesses, adhesions, and peritonitis around the reticulum (especially the right side of the reticulum) or reticuloomasal area without identification of an offending foreign body; hepatic abscesses; diffuse peritonitis; neoplasia of the ruminoreticular fold and esophageal groove; inflammatory disease of the reticular and ruminal walls; papilloma or other mass at the reticuloomasal orifice; herniation of the reticulum through a diaphragmatic defect; or chronic bronchopneumonia in calves. Foreign bodies that physically obstruct the reticuloomasal orifice cause this syndrome and can be identified in exploratory rumenotomy.[62] To reconcile the experimental findings with those from clinical cases, Hoflund hypothesized that the development of omasal transport failure resulted from involvement of the vagal trunks in the inflammatory process at the reticulum. Several findings make this an unlikely explanation in most clinical cases[94,146]:

1. Although sectioning the vagus nerves as described reproduces the syndrome, disturbance of only one of the two trunks still allows normal cyclic contractions in most cases. For a clinical lesion to produce disease development, the vagal nerves would have to be massively involved. In contrast, fewer than a third of examined cases reported show actual lesions in the nerve branches.
2. The ratio of sensory to motor nerve fibers in the abdominal vagi is approximately 9 : 1, which suggests the important sensory role of the nerve.
3. Inflammatory lesions of the reticuloruminal wall reported in clinical cases are predominantly in the area of important tension receptors that send afferent excitatory impulses to the gastric centers. Induration of the right (medial) wall of the reticulum and in the esophageal groove region may affect intramural nerves and ganglia and reduce the tension receptor activity and therefore the drive for primary cycle activity.

These considerations allow an explanation of some of the inconsistencies found in various cases. Omasal transport failure may occur with insufficient

vagal sensory excitation, which in turn reduces excitatory input to the gastric centers, diminishes primary cycle motor drive, and results in paralysis of the omasum and reticuloomasal orifice. Alternatively, substantial reticular adhesions that develop after TRP could prevent normal delivery of small particle ingesta, with fluid consistency, to the reticuloomasal orifice.[124] Because this reduces or abolishes flow into the omasum, both the omasum and abomasum would remain relatively empty, a common finding in these cases. The hypermotility observed in these cases may be the result of secondary rather than primary cycle contractions.[20] Distention of the cranial ruminal sac would still be able to induce the secondary contractions if this region is not involved in the induration. Without normal primary cycle activity, the typical stratification of the ingesta would be disturbed, as is usually observed in clinical cases. The existence of hypermotile secondary contractions with absence or severe reduction of primary contractions can be detected clinically. In occasional cases, damage to the thoracic or abdominal vagi by inflammatory or neoplastic lesions may lead to both omasal transport failure and atony of the forestomachs, with resultant free gas bloat. This would be similar to the experimental sectioning of both vagal trunks.

Pyloric Outflow Failure.

Failure of pyloric outflow (posterior or distal functional stenosis) causes accumulation of ingesta in the abomasum and omasum. Advanced stages of this form of the syndrome also display gross distention of the reticulorumen. In general, the motility of the forestomach is not markedly affected in the early stages, and normal stratification of ingesta is maintained. With severe distention, forestomach motility is reduced, and the ruminal contents become more fluid.[20]

Obstructive indigestion may cause no significant blood biochemical abnormalities or can result in severe disturbances of fluid and electrolyte homeostasis. Measurement of the serum electrolyte concentrations provides important clues about the site of obstruction of ingesta flow and is useful in adjusting fluid therapy. When the primary problem is a gradual failure of flow through the reticuloomasal orifice, the rumen fills and grossly distends with fluid but any dehydration tends to be mild, and significant abomasal reflux does not occur. The ruminal fluid maintains a normal chloride content, and affected patients generally show mild or no serum electrolyte abnormalities.[18,124] In contrast, overfilling of the forestomach as a result of pyloric outflow failure

(internal vomiting) with reflux of high-chloride abomasal ingesta may result in marked dehydration, elevated ruminal chloride concentrations (normal is less than 30 mEq/L), and associated hypochloremic, hypokalemic metabolic alkalosis. In some instances these abnormalities can be dramatic. Prolonged or severe hypochloremia and hypokalemia may also result in paradoxic aciduria associated with avid renal sodium resorption in the presence of low concentrations of chloride and potassium.

Failure of pyloric outflow can be experimentally reproduced by sectioning the ventral vagus trunk at the cardia and the continuation of the dorsal trunk as it crosses the omasum.[72] This mimics the usual clinical form of the disease, which is characterized by complete inhibition of flow from the abomasum. Combinations of more distal resections of the nerves produce the syndrome of recurrent atony of the abomasum as it occurs in natural clinical cases. Again, the term *stenosis* is a misnomer because a true stenosis or spasm of the pylorus is not identified. Rather, the experimental vagal nerve resection and the naturally occurring cases cause a flaccid paralysis, and ingesta accumulates as a result of failure of propulsive activity. The dilation of the abomasum is in the fundus and body and not in the pyloric part.[72]

A common predisposing cause of pyloric outflow failure syndrome is abomasal volvulus. Other abomasal disturbances, including right and left displacements of the abomasum and abomasal ulceration, can cause the disease as well. After surgical correction of a volvulus, the abomasum remains atonic, and the disease may develop within several days. Clinical signs compatible with obstructive indigestion may arise from gross distention and twisting of the abomasum and lesser omentum, which result in potentially coexisting but distinct injury to the vagal nerves or structural damage to the gastric wall, with or without peritonitis. Although focally extensive vagal nerve lesions have been associated with concomitant vascular damage, which indicates that even with nerve regeneration there may not be a return to normal function, the damage appears reparable in some cases as a return to normal function has been observed.[129]

Inflammation and adhesions involving the abomasal fundus and reticulum have been associated with pyloric outflow failure in some studies.[124] Inflammation of the reticular wall may account for the reticular atony reported in some cases. This form of obstructive indigestion may be more frequently associated with true vagal nerve impairment than appears to be the case in omasal transport failure. Alternatively, reticular adhesions may prevent normal

motility, alter the flow of ingesta to the omasum and abomasum, and lead to abnormal filling of the abomasum because of decreased fluidity of abomasal contents.[124]

Another predisposing cause of pyloric outflow failure is advanced pregnancy with a large fetus. An exact pathogenesis has not been clearly defined. Presumably the large, gravid uterus distorts the positioning of the abomasum or physically compresses and obstructs the anterior small bowel, preventing outflow of ingesta from the abomasum. In affected patients the gravid horn typically occupies most of the space in the omental sling. In support of these conclusions, the problem can be resolved by inducing delivery of the calf or performing a cesarean section. Supportive care may be required for severely affected cows, but the gastrointestinal system returns to normal function, which suggests that it was secondarily affected by the pregnancy. This problem is referred to as a form of obstructive indigestion because it appears as a pyloric outflow failure. Some patients have such severe obstruction of ingesta passage that they may be given the diagnosis of anterior bowel obstruction. This disease has been called *indigestion of late pregnancy*.

Animals affected with any form of obstructive indigestion for a prolonged time lose body condition because the failure to pass ingesta into the intestinal tract produces a state of malnutrion. The weight loss may be overlooked because of the impression of full body size produced by the abdominal distention, and in these instances a mild to moderate anemia may develop that may be attributable to micronutrient or macronutrient deficiencies.

Chronic Recurrent Bloat.

Chronic recurrent bloat is commonly identified with obstructive indigestion in any of its forms. It is mild to moderate in severity, commonly waxes and wanes, and adds to the visual impression of gross abdominal distention. The pathogenesis of this ruminal tympany varies. Experimental resection of both abdominal vagal trunks stops eructation by causing complete forestomach stasis. In naturally occurring cases in which lesions of the vagal nerve truly inhibit motor impulse transmission, bloat may arise from this mechanism. When vagal nerve damage does not appear to be involved, other mechanisms may explain the bloat (see Table 32.17). Overfilling of the reticulorumen with frothy ingesta, a common finding, can inhibit the cardia dilation reflex that is a prerequisite of eructation. Gross distention of the forestomach can also weaken the contractile ability of the rumen, so that the contractions are not strong enough to clear the

cardia before eructation.

TABLE 32.17
Causes of Rumen Tympany (Bloat)

Mechanism	Cause	Disease Examples
Obstruction of eructations	Esophageal obstruction	Choke, tetanus, thoracic inflammation or neoplasia with swollen mediastinal lymph nodes
	Cardia obstruction	Papilloma, fibroma, actinobacillosis
	Failure to clear cardia of fluid or ingesta	Lateral recumbency, reticulorumen overfilled with ingesta (as in vagal indigestion, ruminal microbial inactivity with poorly digestible roughage, obstruction of the reticuloomasal orifice)
Ruminal motor dysfunction	Gas trapped in stable foam	Frothy bloat
	Failure of smooth muscle contraction	Hypocalcemia
	Weakened muscle contraction	Chronic ruminal distention with indigestible roughage, outflow obstruction, or vagal indigestion; hypokalemia
Chemical inhibition	Abomasal distention	Displaced abomasum (especially in calves)
	Vagus nerve damage	Thoracic inflammation (especially in calves and with neoplasia)
	Ruminal stasis	Rumen acidosis, rumen alkalosis, abnormal fermentation products with simple indigestion

Bradycardia is often identified in association with obstructive indigestion but can also occur with other forestomach diseases. The origin of the vagotonia is unclear. When vagal nerve lesions are present distal to the cardiac innervation, reflex excitatory discharges may cause bradycardia. Naturally occurring obstructive indigestion shows bradycardia as a feature in only a third or fewer of the cases.[18] These variations may exist because the experimental and natural cases have different causes or because the disease varies in duration. Once the forestomach has become severely distended, the heart rate tends to be elevated, probably as a result of pain and discomfort and deterioration of hydration and cardiovascular parameters.

Obstruction of the Cardia or Reticuloomasal Orifice.

True mechanical obstruction of the forestomach is an uncommon occurrence. The obstruction can be either full or partial and occur at either the cardia or the reticuloomasal orifice. The inflammatory and neoplastic conditions described previously can appear to be obstructive indigestion when the tissues are

sufficiently distorted and lesions involve one of these orifices. Papillomas are most prone to causing an obstruction when they become pedunculated. A variety of foreign bodies create obstruction. In calves, trichobezoars are most commonly the cause, occurring predominantly in animals on a low-roughage diet that consequently lick their hair coats vigorously. In adult cows, ingestion of the placenta occasionally results in an obstruction. Curious ruminants, especially goats, sometimes consume plastic bags or discarded rectal palpation sleeves. These and other nondegradable materials can lead to obstruction even after considerable time has passed.

Cardia obstruction leads to the signs typical of esophageal obstruction, with free gas bloat as a prominent, perhaps life-threatening development. Obstruction of the reticuloomasal orifice produces the classic syndrome of obstructive indigestion. Failure of ingesta flow beyond the rumen results in accumulation of fluid material in the forestomach and diminished or no passage of ingesta through the intestines. The degree and duration of obstruction determine the severity of associated problems such as dehydration, depression, elevated heart rate, forestomach stasis, colic, and muscular weakness. Only rumenotomy can effectively differentiate these obstructive diseases from other problems with similar signs.[69] Removal of pedunculated masses or foreign bodies at the reticuloomasal orifice can promptly correct such problems.

Diaphragmatic Hernia.

Defects in the diaphragms of cattle are uncommon. Most cases involve a tear through which the reticulum can herniate. Other abdominal organs may also be involved if the rent is large. The diaphragmatic defect may be congenital or an acquired lesion caused by a local inflammatory process (TRP), sudden external trauma (fighting, hanging up on a fence), or internal pressure (parturition, acute tympany).[92] Entrapment of the reticulum may lead to acute changes in intrathoracic pressure and cause sudden dyspnea, tachycardia, and poor venous return to the heart. In general, however, this reticular problem causes the classical syndrome of obstructive indigestion with omasal transport failure.[43] Failure of flow through the reticuloomasal orifice may result from vagal nerve damage, or the anatomic distortion alone may explain the motility defect. Entrapment of the reticulum hinders normal reticular movements and distorts the esophageal groove and reticuloomasal orifice. Reticular ingesta can be heard moving inside the thorax, therefore complete reticular paralysis is unlikely to be the problem. Motility disturbance is reflected by hypermotility of the rumen,

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generation of frothy ingesta, persistent or recurrent moderate tympany, and overfilling of the rumen. Signs of pain may also be present, as in cases of TRP. Rumination usually is impaired, some affected animals develop a megaesophagus, and large volumes of ingesta may be vomited, especially after eating. Surgical correction of a diaphragmatic hernia involving the reticulum can be attempted but has usually proved unrewarding, especially if the lesion is chronic, involves a large defect, or is accompanied by inflammatory reaction.

Indigestion of Poor-Quality Roughage.

Ruminants fed roughage of extremely low quality, without supplemental nutrition, may develop prolonged inactivity of the rumen microbial flora. Many such animals simply fail to thrive and develop protein energy malnutrition, and some may develop specific nutrient deficiencies. This feeding pattern induces a form of indigestion, described later as one of the disorders of fermentative function. However, it is mentioned here because the extreme cases, seen as "Haybelly," appear as obstructive indigestions. When the fibrous feed that is not adequately fermented accumulates in the forestomachs at an excessive level, affected animals show the typical signs of obstructive indigestion syndrome, including gradually progressive gross abdominal distention, body tissue loss, reduced fecal passage of abnormal feces, and sometimes chronic recurrent free gas bloat. This condition can be differentiated from other cases of obstructive indigestion by ruminal palpation that reveals very firm and uniform rumen contents, history or observation of the feeding regimen, and rumen fluid analysis described later.

Treatment of and Prognosis for Obstructive Indigestion.

Obstructive indigestion is a chronic and insidious problem that generally warrants a guarded to poor prognosis. The syndrome of abdominal distention with an L-shaped rumen and possibly ruminal tympany has several different causes. Exploratory laparotomy and rumenotomy are essential for establishing an accurate assessment (see Fig. 32.128).[99] The two most common causes of obstructive indigestion syndrome are inflammatory lesions of the reticuloomasal region and abomasal diseases that involve gross distention, twisting, or vascular impairment of the organ. Obstructive indigestion caused by abomasal disease carries a poor prognosis, whereas the prognosis for cases with reticular involvement is more variable. Animals in either category may respond favorably with appropriate therapy[124,129] (Box 32.5). Surgical exploration not only allows

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an assessment of the cause of the problem but may also allow repair. When abscesses are identified at the reticulum or liver, surgical drainage may help resolve the forestomach motor disturbance.[124] Identification of adhesions and active inflammation indicates that broad-spectrum antibiotic therapy may be beneficial, and as a preventive practice, some clinicians have advocated aggessive antimicrobial therapy before and after the surgical correction of a right-sided abomasal displacement or volvulus.[129] Gross abomasal distention, which indicates pyloric outflow failure, usually worsens the prognosis, as does the presence of granulomatous or neoplastic processes or generalized peritonitis and adhesion formation.[124] When the presence of a large gravid uterus appears to be the inciting cause of outflow failure, parturition or cesarean section usually resolves the problem completely.

Box 32.5

Principles of Treatment of Obstructive (Vagal) Indigestion

1. Determine likely cause, often by means of exploratory laparotomy.
2. Administer specific therapy (e.g., give antibiotics or anti-inflammatory agents, remove foreign body or relief of obstruction, drain abscesses) for causative lesion.
3. Relieve forestomach distention; this often must be performed repetitively.
4. Limit feed and water intake; feed palatable, high-fiber rations.
5. Transfaunate.
6. Cannulate rumen if chronic bloat (free gas) is a problem.

The evaluation of animals with obstructive indigestion with a large fluid-filled rumen should include assessment of the fluid and electrolyte status. Abnormalities such as dehydration, hypocalcemia, hypochloremia, and hypokalemia should be addressed with supportive fluid therapy. Treatment should be administered parenterally because oral treatments are ineffective or deleterious. The forestomach should be emptied of the excessive ingesta accumulation either during surgery or with a large-bore stomach tube. This

procedure may have to be repeated if the recovery period is prolonged. Relief of persistent forestomach distention is crucial for the reestablishment of normal motility. Limited feed and water should be offered to prevent repeated accumulations in the reticulorumen, and intravenous fluid therapy should be continued until reticuloruminal motility is reestablished and oral fluid intake can be allowed at normal levels. Once the ruminal distention has been alleviated, several liters of ruminal fluid transfaunate from a healthy donor should be administered.[122] The limited diet must be palatable and should consist primarily of long-stemmed hay or green feed for maximum stimulation of the normal forestomach motility pattern. A temporary rumenostomy may be indicated if tympany is a prominent sign.[26]

Response to treatment of obstructive indigestion usually is a slow process and may take several weeks. Favorable signs include a return of the normal primary and secondary contraction patterns, improvement in appetite, maintenance of normal forestomach dimensions, weight gain, and increased fecal production. Repeated development of forestomach distention, continued scant fecal output, poor ruminal motility, and recurrent bloat are indications that the animal is not responding to treatment, and the prognosis is grave.

Free Gas Bloat.

Accumulation of free gas in the dorsal rumen should not be considered a primary disease entity but rather a sign of disease (see Table 32.17). However, because free gas bloat often is the most prominent sign and because it accompanies several different forms of indigestion, its pathogenesis is reviewed briefly here.

Ruminal microbial fermentation and neutralization of acids by salivary bicarbonate continually produce gas as an end product (primarily methane and carbon dioxide) in proportion to the rate of fermentation. Normally the ruminant can eructate volumes of gas that exceed the amount produced even at maximum rates of fermentation.[9] Thus an excessive production of gas is not the cause of bloat. Bloat develops either because the evacuation of gas is limited by a physical obstruction or because the mechanisms that expel the gas are inhibited.[28]

As in choke, physical obstruction of the esophagus by a foreign body can produce dramatic and peracute bloat. Other forms of esophageal occlusion (which may additionally involve inflammation of nerves or ruminal muscle malfunction) include muscular spasm (as in tetanus), swollen mediastinal lymph

nodes (as in chronic pneumonia or thymic lymphosarcoma), and tumorous or inflammatory swellings of the cardia region (as in papilloma or actinomycosis). These problems tend to show that bloat has a progressive or chronic nature, although the degree of bloat may be marked.

Bloat is a common feature of indigestions caused by microbial fermentative disorders. When ruminal hypomotility occurs, the fermentative rate may decline, but weak ruminal contractions may be inadequate to move the gas layer and to clear the cardia preparatory to eructation. Thus dietary, microbial, or metabolic factors that affect the excitability of the gastric centers or the reticulorumen can result in bloat. Ruminal stasis can result in bloat because eructation occurs only with ruminal contraction. Bloat also accompanies indigestions that produce gross distention of the reticulorumen with fluid or solid ingesta (i.e., obstructive indigestion, ruminal acidosis, and microfloral inactivity caused by indigestible roughage). The cause of bloat in these cases may be a combination of ruminal stasis, weakening of the ruminal wall caused by the gross distention, and failure to clear the cardia.

As is the case in adult cattle, it appears that free gas bloat in calves has numerous causes, including fermentative indigestions, ruminal wall disturbances, and esophageal involvement in an intrathoracic inflammatory process.[45,86] Chronic bloat in calves has also been attributated to a form of vagal nerve damage resulting from mediastinal inflammation, often caused by lymphadenopathy as a consequence of pneumonia. Distinguishing between vagal nerve impairment and esophageal compression or inflammation as the cause of free gas bloat requires a thorough assessment of ruminal motor function.

When ruminal tympany is a prominent sign, it necessitates very critical assessment. Frothy bloat and free gas bloat can be differentiated by a thorough physical examination and knowledge of the feeding history. Passage of a stomach tube to help in this differentiation is very important and may alleviate the acute problem if free gas is present (see Table 32.15). Evidence of respiratory or cardiovascular distress indicates that the bloat is an acute, life-threatening problem that necessitates emergency treatment. With the exception of cardia or esophageal obstruction, the free gas bloat associated with indigestive disturbances is mild to moderate in severity and chronic or recurrent in nature. It does not represent a major threat to the animal and can be handled by treating the primary forestomach disturbance. Chronic free gas bloat does not respond to the antifermentatives or surfactants commonly used for frothy bloat. Only the restoration of physiologically normal reticuloruminal function corrects this type

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of bloat.

Inhibition of eructation caused by lesions of the cardia region can usually be confirmed only by exploratory rumenotomy. This approach also determines whether the lesion is surgically correctable. Inflammatory lesions may respond to long-term administration of broad-spectrum antibiotics. This is also the treatment of choice when chronic pneumonia appears to be the cause of the bloat. Failure to respond within approximately 3 weeks suggests that the treatment is not effective, and slaughter should be recommended after an appropriate withdrawal time. Detection of abnormal forestomach ingesta should direct treatment to the primary fermentative or feeding disorder.

The various causes of chronic or recurrent bloat usually necessitate chronic treatment for correction. It follows that the bloat also does not completely resolve until the underlying disturbance is corrected. Repeated relief of the bloat may be accomplished by passage of a stomach tube during the treatment regimen. In many cases this proves too tedious or too traumatic for the animal, and the most viable alternative often is the establishment of a temporary rumenostomy.[26] Several devices are manufactured for this purpose, or the rumenostomy can be created by suturing the rumen to the skin. Release of the fermentative gas in this manner is important for the reestablishment of normal forestomach motility, which is inhibited if distention is extreme. When free gas bloat is the result of an obstruction of eructation or another gastrointestinal tract disease such as abomasal displacement, surgical treatment of the primary problem may be necessary. The tympany responds rapidly in these cases, and rumenostomy and cannulation are not required.

Signs such as ruminal tympany, ruminal hypomotility or stasis, and forestomach distention can all result from a number of causes. Ruminal hypomotility, for example, is commonly a physiologic response to problems such as abnormal ruminal contents, a ruminal wall lesion, pain, or overdistention. In many cases the ruminal motility disturbance serves as a protective role for the animal. Former treatments that were directed at stimulating ruminal motility without addressing the causative disturbance included rumenatorics (i.e., nux vomica, ginger, tartar emetic) or parasympathomimetics (i.e., neostigmine, carbamylcholine). Such agents are not indicated under these circumstances. Likewise the treatment of indigestions with alkalinizing agents such as magnesium hydroxide is indicated only when the pH of ruminal contents is low.

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Disorders of Reticuloruminal Fermentive Function

Forestomach Microbial Population.

The continuous culture system of the rumen involves an ongoing selection of microorganisms best adapted to grow in a variety of ecologic niches that are in a dynamic state. Numerous control mechanisms govern the environment and the resultant microbial population. Some of these mechanisms are related to the animal itself, such as salivation, mixing and rumination, removal of substances by absorption or diffusion, outflow through the reticuloomasal orifice, and eructation. Others are related to the diet, including nutrient quality of the substrate (feed), balance of required elements, solubility, particle size, presence of inhibitory substances, nutrient quantity, and rate of delivery to the rumen. Control of fermentation (see Box 32.4) also results from microbial interactions such as competition and symbiosis: cross-feeding between species, removal of inhibitory end products, and maintenance of the oxidation-reduction potential. The complexity of the system tends to promote an overall stability. Changes in the controlling factors create selective pressures that lead to population changes in the rumen.[100,155]

The rumen contains large numbers of bacteria, ciliated protozoa, anaerobic ruminal fungi, and bacteriophages.[100] Ruminal bacteria are predominantly anaerobes, with some coexisting facultative anaerobes. Although the facultative organisms are not important in normal ruminal function, they may be associated with some forms of ruminal dysfunction. Some microbes ferment the primary nutrients in the feed such as cellulose, hemicellulose, pectin, starch, and simple sugars. Other species ferment the products from the primary nutrient fermentation such as pentoses, glucose, lactate, succinate, and formate. Many species are very specialized and have numerous growth requirements that may be supplied by the general fermentation. Other microbes are important for their role in removing end products and cycling essential factors back to the other organisms.[71,101,155]

Effects of Feed Characteristics.

The concentrations and proportions of the microbial species vary with the composition of the diet (Table 32.18). An abundant supply of a certain substrate tends to favor a microbial population with a predilection or high capacity for

utilizing that material. The most important factors in the rate of digestion are the properties of the carbohydrates and protein in the feed. High-protein diets favor proteolytic organisms, whereas high-starch, low-fiber diets favor amylolytic bacteria.[111] Cellulolytic bacteria are prominent in a high-fiber diet, but their numbers also depend on the fiber size as this factor determines the rate of passage or retention in the forestomach. Cellulolytic species can be abundant with a high-concentrate diet if some long-stemmed roughage is included because the retention time of the fiber is prolonged. Diets with readily fermentable carbohydrates and low fiber favor species capable of rapid metabolism and tolerant of low pH. Acid production is rapid, and populations of microbes less tolerant of such changes decline.[85,101,144]

TABLE 32.18

Effects of Feed Characteristics on Ruminal Digestion and Health

Feed	Rumen Content	Effect on Health
Primary forage of high-quality, long fiber length, crude fiber > 18% of dry matter; with concentrate supplement at 20% to 50% of total intake, moderate protein level	pH, 5.5 to 7 VFA, 60 to 120 mmol/L Acetic acid level > propionic acid level > butyric acid level	Normal, healthy, productive
Excessive forage of low nutrient value (late cut) with little concentrate or protein supplementation	pH, 6.5 to 7 VFA, decreased Microbial activity, decreased	Poor production or growth, microfloral inactivity and rumen impaction, malnutrition caused by protein, energy, mineral, and vitamin deficiency
High level of concentrate feeding (>60%) with decreased forage or fiber length	pH, 5 to 6.5 VFA, increased Microbial activity, increased	High production, rapid growth; possible chronic rumen acidosis, milk fat depression, chronic laminitis, ketosis, ruminal parakeratosis, excessively fat condition
Extremely high level of concentrates (especially with sudden exposure to ration), low intake of forage	pH, 4 to 5.5 VFA, increased Lactic acid level, increased	Acute ruminal acidosis
Normal levels of forage intake, concentrate with very high protein or NPN supplementation	pH, 6.5 to 7.5 VFA, decreased	Ruminal alkalosis, possible urea toxicity

	Ammonia level, increased	

NPN, Nonprotein nitrogen; *VFA*, volatile fatty acid.

The microbial population is also influenced by the limits of supply of certain feed substrates.[154] High rates of fermentation and microbial growth on the abundant substrates depend on sufficient amounts of the more limited nutrients. Optimum carbohydrate use requires adequate sources of nitrogen, sulfur, and essential mineral nutrients.[46] When any essential nutrient is deficient, the rate of digestion and thus the digestibility of the feedstuff decrease. The presence of signs of nutrient deficiency or forestomach dysfunction with microbial and forestomach inactivity depends on the limiting nutrient and relative requirement of the host and bacteria for the nutrient. Substances and conditions that inhibit fermentation further reduce digestibility.

The feed material also affects ruminal fermentation by influencing the rate and extent of digestion and passage from the reticulorumen. Grains vary in average starch content; corn and sorghum contain the most starch (71 to 76%), followed by wheat (62 to 65%), barley (57 to 59%), and oats (44%).[117] Each grain also has unique features related to the protein matrix surrounding the starch, and the total quantity and rate at which starch molecules are converted to ruminal VFAs, lactate, and and gas are determined by the interaction of starch content, grain processing method, and degree of processing.[107] Fine grinding and pelleting of feed increase the rate of passage of the particulate matter from the reticulorumen. Very finely ground rations also reduce the stratification of fibrous material in the rumen. This affects the ability to sort material in the rumen selectively by particle size and density, so that larger particles less thoroughly fermented pass more readily into the lower bowel. Microbes associated with the feed particles are passed out of the rumen with the feed. Thus a faster rate of passage competes with the generation time of the organisms. Populations of slower growing microbes tend to be most influenced by changes in the retention or passage times. Slow-growing cellulolytic bacteria decline in numbers as the passage rate increases (retention time decreases). High passage rates usually produce faster digestion rates. Although these factors are primarily important to the feed efficiency of the animal, they also affect ruminal function and the adaptation of microbes to feeding changes.[155]

Adaptation of the microbial flora to dietary changes may require a week or longer.[51,65] The abruptness of a dietary change determines the degree of

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alteration of the ruminal microbial population and fermentation pattern and the potential for digestive disturbances. With abrupt and dramatic shifts to higher carbohydrate diets, the facultative species may overwhelm the more normal flora by producing excessive acid and lowering the pH. The importance of microbial adaptation to a particular diet is evidenced by the reduction in forestomach disturbances seen when the rumen is inoculated, before a feeding change, with fluid from animals already adapted to the new ration.[51,150]

The end products of microbial fermentation influence not only the microbial population but also ruminal function. High concentrations of nondissociated VFAs excite sensory epithelial receptors that reflexly inhibit ruminal motility. Ruminal stasis occurs if a sudden increase in concentrate feeding induces lactic acid fermentation. The ruminal pH suddenly declines, and a greater proportion of the VFAs shift to the nondissociated state with the degree of ionization governed by the rumen pH and the logarithmic acid dissociation constant (pKa) of each particular acid.[35,111] A consistently high level of concentrate feeding produces rapid fermentation, a high concentration of VFAs, and low pH, and the nondissociated VFA level may reach the threshold for stimulation of the inhibitory epithelial receptors. The ruminal stasis reduces the fermentation rate. Mild cases of ruminal acidosis may show spontaneous recovery of ruminal functions as the absorption of VFAs reduces the concentrations to a noninhibitory level. With more severe ruminal acidosis, the generation of acid continues despite the ruminal stasis, giving rise to more severe complications of the disease.

In some instances the effects of ruminal microbial metabolism and microbial end products extend beyond impacts on nutritional status and digestive system function. Several ruminant diseases are due to rumen-generated toxic effects. These have extremely variable manifestations and include toxicoses from ammonia, nitrate and nitrite, 3-methylindole, dimethylsulfide (*Brassica* spp., onion toxicity), and sulfur-associated polioencephalomalacia.[36,63,130,133]

In summary, excesses, deficiencies, or rapid changes of feed substrate can cause imbalance in the microbial population and the fluid milieu. The result can be bacterial overgrowth and overproduction of microbial end products or insufficient microbial growth and fermentation. The effects of these abnormalities on animals range from ruminal motility dysfunction to poor growth and performance and to outright toxicity and organic damage.

Inactivity of Ruminal Microbial Flora (Caused by Poor-Quality

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Roughage, Haybelly, or Ruminal Impaction).

When ruminal microbial flora inactivity occurs, the microbial populations and their metabolic and fermentative processes are diminished as a result of deficiencies of one or more nutrients. This occurs most commonly with poor-quality roughage deficient in protein and readily digestible carbohydrates (late cut, highly lignified hay or straw). Microfloral inactivity can also occur when specific mineral nutrients are deficient or when inhibitory substances such as antibiotics or some plant products are present in the feed.[155] Microfloral inactivity also occurs with prolonged anorexia, which abolishes the intake of all nutrients and is the primary pathogenesis of many cases of secondary indigestion.[21,41,79]

When microbial digestive processes decline, the breakdown of ingested feedstuffs is prolonged. Failure to reduce the particle size of the ingesta leads to a prolonged retention in the forestomach and gradual accumulation of the undigested feedstuff. Gradual distention of the reticulorumen is commonly observed (haybelly). In extreme cases, this produces the signs of obstructive indigestion. Forestomach distention can result in weak contractions and moderate recurrent tympany. Ruminal hypomotility alters the normal stratification of the ruminal contents, and the fibrous components are found mixed in the fluid or compacted ventrally on the ruminal floor. Abnormal passage of ingesta from the forestomach results in decreased fecal passage, and the feces usually are dried and contain undigested plant fibers. Other effects on animals are those of generalized or specific nutrient deficiencies (e.g., decreased growth or production, ketosis, emaciation, and a poor hair coat). When anorexia is the cause of the microbial inactivity, the ruminal fill decreases and the lack of normal distention also induces ruminal stasis.[43]

Acute Simple Indigestion.

Acute simple indigestion is the most common sequela of an abrupt change in the ration. Such feed changes present the ruminal microflora with nutrient substrates (1) to which they are not metabolically adapted, (2) to which they are adapted but in lesser quantities, or (3) that contain or produce substances that inhibit microbial growth and fermentation. The result is an imbalance in the microflora and its fermentation products. The difference between this problem and some of the other fermentation disorders is mostly a matter of degree. In general, this disease is relatively mild and self-limiting. Most affected animals show anorexia

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for 1 to 2 days, develop diarrhea in approximately 24 hours, and return to a normal appetite without treatment when the ruminal fermentation has stabilized and inhibitory substances have been eliminated. Ruminal motility is reduced but usually not absent, the filling of the rumen is not remarkably altered, and bloat, if it occurs, is mild. In some cases the ruminal fluid pH may change, but usually not dramatically. Mild acidosis or alkalosis of the ruminal fluid may develop, depending on the nature of the causative feedstuff and its resultant fermentative degradation. Signs of ruminal microfloral inactivity are common. Simple indigestion is an acute problem, in contrast to the microfloral inactivity discussed in the previous paragraphs, in which deficiencies produce microfloral inactivity over prolonged time.

Feeds commonly implicated as causes of simple indigestion include moldy or overheated feeds, frosted forages, and partly fermented, spoiled, or sour silages. This form of indigestion also occurs in animals fed high-quality feed, usually after an increase in the rate of feeding or after a change of one of the feed constituents. Thus these mild forms of indigestion can range from a mild acidosis to an excess of VFAs and to the generation of some bacterial inhibitory products. Because the rumen and its fermentative bacteria are very adaptable, the ways, if any, in which animals given a certain feed experience the problem vary considerably. It is not unusual to observe only one or several animals from a group on the ration may have signs.

Acute Ruminal Lactic Acidosis (Grain Overload, Toxic Indigestion).

The various forms of indigestion may be manifested as acute, subacute, or chronic illness. In general they do not appear as critical emergencies with fulminating systemic signs and life-threatening conditions. The exceptions to this are frothy bloat and acute ruminal lactic acidosis. Acute ruminal acidosis is the most dramatic of the forms of ruminal microbial fermentative disorders and in some cases is lethal in less than 24 hours. It has also received the most research attention; therefore the events in its pathogenesis are more clearly defined than those of the other forestomach disorders. The condition has been known as *lactic acidosis, acute ruminal impaction, ruminal overload, acid indigestion, toxic indigestion, grain engorgement, grain overload,* and *D-lactic acidosis*.

Cattle examined a few hours after engorgement of grain may yet be alert but anorexic with a mildly distended rumen, weak ruminal contractions, and mild signs of colic. If the acidosis is mild, affected cattle show the signs of indigestion

discussed previously and with or without treatment may recover their appetite within a few days. The severe form of this indigestion leads to severe systemic involvement, with depression, severe dehydration, weakness, recumbency, profuse diarrhea, and eventually death. The temperature usually is normal to subnormal. The heart rate elevates with the progression of dehydration and systemic acidosis; rates above 100 beats/min are usually associated with a poor prognosis. Respiration generally is increased (60 to 90 breaths/min) and shallow. The rumen accumulates fluid. Animals capable of rising may show a staggering gait and appear blind. The pupillary light reflex may be slower than normal. Recumbent animals usually lie quietly and may be stuporous. As the cardiovascular system becomes more severely affected with increasing dehydration and acidosis, the extremities become cool, and mucous membranes dry. Anuria may follow poor renal perfusion. Rapid progression of signs leading to recumbency bespeaks a poor prognosis, and affected animals may die within 24 to 72 hours. Therefore if the progression of signs is rapid, emergency therapeutic measures are mandatory.

Acute ruminal lactic acidosis is the result of excessive consumption of readily fermentable carbohydrates, which causes a rapid fermentation with production of lactic acid and a decrease in ruminal pH to physiologically inappropriate levels. This occurs when animals consume an excess of concentrate feeds (e.g., if animals are suddenly exposed to the feeds without prior adaptation; if animals already on such feeds suddenly consume an excessive quantity because of accidental access; or if animals that have been off feed return to feed and are offered unrestricted access to concentrates). The problem is more common when animals are grouped than when they are separate, probably because the psychological aspects of competition induce them to overconsume. In general the feeds involved include the cereal grains commonly used in high production rations and fruit and root crops (e.g., feed beets, sugar beets, potatoes) where they are available. Starch and soluble sugars promote an overgrowth of bacteria that produce glucose and organic acids. The acid end products increase ruminal acidity and osmolality, inhibit or destroy other ruminal microbes, and cause forestomach dysfunction and metabolic disturbances.[93,111,119,132]

Dramatic alterations of the blood biochemical characteristics may accompany severe ruminal acidosis. Usually the laboratory findings correlate with the degree of severity assessed on physical examination. Affected animals have metabolic acidosis with decreased blood pH and plasma bicarbonate. Blood lactate levels rise with the acidosis. The urine pH falls into the acidic range as

the kidneys excrete some of the excess acid, but eventually severe dehydration results in renal failure and anuria, eliminating this route of acid excretion. Decreased renal function is reflected by elevated serum creatinine and urea nitrogen concentrations. Other findings commonly include increased serum phosphate concentration, possibly caused by massive cellular destruction, and mildly decreased serum calcium concentration, presumably the result of decreased gut absorption. Other serum electrolyte abnormalities, such as changes in the sodium and chloride concentrations, may reflect fluid balance changes in response to ruminal fluid hyperosmolality (a third space phenomenon).[132] Concentrations of serum enzymes of muscle and liver origin rise when acidosis and dehydration produce cardiovascular impairment with poor tissue perfusion, increased recumbency, and cellular destruction. Portal bacteria and toxins from the damaged ruminal mucosa contribute significantly to the increased serum liver enzymes: aspartate aminotransferase, sorbitol dehydrogenase, (orthinine carbomyltransferase), and γ-glutamyl transferase.

Specific characteristics of the feedstuffs contribute to acidification of the ruminal fluid. Cereal grains inherently possess less buffering capacity than do the fibrous forages. Low structured fiber content and decreased forage particle size induce less salivation during ingestion and less rumination subsequently; therefore salivary buffering declines when concentrate feeds are consumed. Some silages contain both high carbohydrate and lactic acid and thus introduce more acid at both ingestion and fermentation.[55,88,119]

Feeding regimens that include significant fibrous roughage limit carbohydrate availability and rates of microbial fermentation and growth. Carbohydrate fermentation efficiency relative to the amount of ATP derived from each sugar provides competitive survival value. Slower growing cellulolytic bacteria use substrate most efficiently. When starch or sugar is available in excess, the faster growing species such as *S. bovis* metabolize carbohydrate faster and produce more ATP per unit time, even though they are less efficient in ATP production per carbohydrate molecule. Under these conditions they can overgrow, and lactic acid is their end product.[119]

The severity of ruminal acidosis and disease signs vary considerably, depending on the amount and type of carbohydrate-rich feed consumed and the degree of prior ruminal microbial adaptation to the carbohydrate substrate. The disease can range from a mild form of indigestion to an overwhelming toxemia that may be difficult to distinguish from other acute toxic conditions or various diseases with endotoxemia.

If consumption of fermentable carbohydrate is only mildly excessive, *S. bovis* proliferation decreases when the carbohydrate has been fermented, pH rises toward normal, and the efficient fermenters reestablish dominance. If the carbohydrate source is abundant and its supply is not exhausted, the acidosis becomes more severe. Continued production of lactate by *S. bovis* reduces the fluid pH to the range of 5 to 5.5, and the ruminal fluid osmolality rises concurrently. Both these factors inhibit or kill the ruminal protozoa, which normally use starch and small sugars and help limit increasing lactic acid levels. There are also numerous species of lactate-using bacteria, of which *Megasphaera elsdenii* and *Selenomonas ruminantium* are the primary examples. These bacteria, which increase in numbers when animals slowly adapt to a high-concentrate diet, are eliminated by abrupt changes and generation of excessive acid; therefore lactate use decreases when the acid is generated too quickly.[51,119]

The lactobacilli are the major group of lactic acid producers in the rumen. The increasing acidity of the fluid enhances the growth of these organisms. Because the lactate-using bacteria are killed off before the lactobacilli overgrow, their diverse end products are unavailable as substrate for other bacteria. The lactobacilli are left as the predominant organisms to use the available carbohydrates. Even the *S. bovis* organisms that began the lactic acid production are inhibited below a pH of 4.5, leaving the lactobacilli, as the most acid-resistant species, to generate more lactic acid.[111,156]

The acidification of the fluid milieu enhances the lactic acid production by altering microbial metabolism.[119] The loss of the fluid bicarbonate buffer and the increase in available hydrogen ions block the conversion of lactate to propionate even before the lactate users die off. Also, when the pH is above 5 but declining, ruminal fluid amylase activity increases and liberates more free glucose from starch. However, glucose use is reduced, and ruminal glucose accumulates. Apparently the lactate-using bacteria such as *S. ruminantium* degrade less lactate to acetate in the presence of increased glucose concentrations.[14,119,137] Thus not only does the microbial population change but also the characteristics of the fluid accelerate the lactic acid production when the available carbohydrate is excessive.[119]

The effects on the animal from the ruminal fluid changes are numerous and detrimental. In the early stages of the acidic fermentation, the VFAs are produced in abundance. Although VFA production decreases as the microbes are increasingly inhibited, VFA concentrations remain elevated in advanced

acidosis. The VFAs are much weaker acids than lactic acid; thus as pH drops, they accept hydrogen from lactic acid and serve as buffers in the fluid, so that a greater proportion of the VFAs exist in the nondissociated state. This form is more readily absorbable than free ions through the ruminal wall. During absorption some VFAs undergo metabolism by the ruminal wall epithelium, which results in the release of lactate and ketone bodies into the circulation. Excessive absorption of the VFAs leads to systemic acidosis, and circulating lactate and VFAs may also directly damage the liver. In addition, the high concentration of nondissociated VFAs at the ruminal epithelium provides a strong inhibitory effect on reticuloruminal motility and leads to ruminal stasis. This effect tends to protect the animal because it reduces the absorption of detrimental fermentation products from the rumen.[36,63,93,119,130,133]

The osmotic pressure of the ruminal fluid increases as lactic acidosis develops.[55,93,119] In a normal animal, ruminal osmolality remains relatively constant at approximately 280 mOsm/L, but osmolality may double in some cases of acute acidosis. Lactic acid accounts for a major fraction of the increase, but some of the components of this change remain unidentified. The increased osmolality inhibits and kills some of the microflora and draws fluid into the rumen, mostly from the extracellular compartment. This accounts for the increased ruminal fluid volume, ruminal distention, and severe dehydration observed clinically. The loss of circulating fluid volume leads to circulatory impairment, decreased renal blood flow and glomerular filtration, and in some cases leads to anuria. Poor peripheral circulation results in hypoxic metabolism and contributes to systemic acidosis.

Although it has been assumed that the systemic acidosis that develops with this disease is attributable to lactic acid absorption from the rumen, such absorption does not appear to occur readily.[119] Lactate is absorbed from the rumen at a much slower rate than are the VFAs because it is highly ionized at a pH near physiologic normal, which tends to inhibit absorption. At lower pH the rumen becomes static, thereby also inhibiting absorption. The hypertonicity of the ruminal fluid further limits absorption of lactate and other substances.[132] It appears that the peak entry of lactate into the circulation occurs in the early phases of the disease. Some lactate may be absorbed from the intestinal tract from fluid passed before the onset of complete stasis. Many experimental trials have not shown the development of severe systemic acidosis in the early phase of the disease. It may be that a large component of the later severe systemic acidosis is attributable to circulatory insufficiency rather than to absorption of

lactic acid.

Some absorption of the lactic acid does occur, however, as evidenced by the appearance of D-lactic acid in the circulation. Microbes produce both the levorotational (L) and dextrorotational (D) forms of lactic acid, whereas animal tissues produce only L-lactic acid.[111] The animals' pathways for metabolism of D-lactic acid are not as efficient as those for L-lactic acid; therefore absorption of both forms leads to an accumulation of predominantly D-lactate in the animals' system.[98] The lactate is eliminated by oxidation, gluconeogenesis, and renal excretion. An animal's hydration status, liver and muscle metabolism, and renal function determine how rapidly it can eliminate excess lactate. Animals that survive ruminal acidosis often have metabolic alkalosis after the acidotic phase, as a result of lactate metabolism and production of bicarbonate.

Lactic acid is a strong corrosive agent that can destroy the ruminal epithelium, giving rise to the name *toxic rumenitis*. The increased ruminal fluid osmolality also damages the epithelium as extracellular water influx across the epithelium occurs in response to osmotic pressure imbalance and disturbed Na transport.[132] The effects of epithelial destruction can be far-reaching because the damage persists after resolution of the acute acidosis.[55,91] Some yeast and fungi that are resistant to the high acidity readily colonize the damaged sites, invade the vasculature, and cause thrombosis or spread to the liver and other organs.[30] Ruminal acidosis is considered one of the primary causes of mycotic rumenitis (discussed earlier in the Reticulitis and Rumenitis section) and mycotic omasitis, although other predisposing causes have been identified.[30,76] Bacterial rumenitis can also result from the chemical damage and may lead to abscess formation, diffuse cellulitis, or perforation and peritonitis. If the animal survives the acute acidosis, it may succumb to secondary ruminal damage.[30] Alternatively, the rumen may heal uneventfully, leaving scars in the ruminal wall, but bacterial access to the circulation through these chemical lesions can result in hepatic abscessation, a common problem of animals fed high-concentrate rations.[110,112]

In addition to lactic acid, several toxic factors have been implicated in acute ruminal acidosis.[111,119] The altered metabolism of the ruminal microflora has been shown to generate increased quantities of histamine, ethanol, methanol, tyramine, and tryptamine. Although conlusive evidence is lacking, these may play a role in the pathogenesis of the disease. For example, histamine been implicated as an agent in the development of laminitis that sometimes accompanies ruminal acidosis.[56] Histamine-producing microbes such as

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Allisonella histaminiformans thrive at low pH, and histamine can be absorbed through the rumen wall when the epithelium is damaged, as occurs in acidosis.[8] In addition, the destruction of ruminal Gram-negative bacteria has been suggested to release large quantities of endotoxin for absorption through damaged epithelial surfaces. Endotoxin would contribute to most of the signs of the disease such as ruminal stasis, poor tissue perfusion with cardiovascular deterioration, weakness, and depression. Increased ruminal and blood concentrations of endotoxin and increased blood arachidonic acid metabolites have been found in cattle with experimentally induced ruminal acidosis, but their importance in naturally occurring disease remains uncertain.[1,4-6] With liver impairment and ruminal wall damage, toxin absorption and clearance are likely to be altered. Premature delivery and retained placenta may occur in pregnant animals after acute ruminal acidosis, possibly as a result of from the effects of these circulatory toxins and metabolites.[123]

Severe grain overload requires prompt and aggressive treatment. Animals showing severe depression, an unresponsive condition, apparent blindness, and gross ruminal distention warrant a grave prognosis. Immediate slaughter should be considered for animals with similar signs but still able to stand. Emergency rumenotomy and removal of the acidic ruminal contents may be life-saving if the procedure can be performed before significant amounts of ingesta have passed into the lower gastrointestinal tract.[99] An alternative treatment in less severe cases is repeated flushing of the rumen with warm water through a large-bore stomach tube. Administration of magnesium hydroxide into the rumen and sodium bicarbonate solution (5%) intravenously is necessary to counter the acidosis. Intravenous fluid therapy should be continued until the animal has recovered to provide support against hypovolemic shock.[138] Other treatments that may be considered include NSAIDs. Additional therapeutic measures such as transfaunation and dietary adjustment should be continued during the recovery phase.

Subacute Ruminal Acidosis.

Like acute ruminal acidosis, subacute ruminal acidosis (SARA) is caused by feeding of excessive quantities of concentrate or low levels of well-structured fibrous roughage. However, SARA results from continued ingestion of these feeds over a prolonged period rather than sudden exposure without adequate adaptation. Beef feedlot cattle may be chronically exposed to a ruminal pH

between 5.0 and 5.5 from the start of the intensive feeding period until slaughter. Dairy cattle are more probably limited to short periods of low ruminal pH, typically between calving and approximately 5 months post partum.[89,118] In early lactation, dairy cattle may be exposed to energy-dense rations too rapidly, whereas the high feed intake of cows in midlactation renders them particularly susceptible to sudden ration changes or faults in feed delivery or composition.[48] The ruminal microbial population adapts to a high grain ration, and large numbers of lactate-using and lactate-producing organisms are found. The proportion of cellulolytic bacteria decreases, whereas the starch- and glucose-fermenting species proliferate. The overall effect of the adaptation is development of a microbial population that rapidly ferments the ingested feedstuffs. Lactic acid does not accumulate because it is further metabolized by the bacteria. The increased rate of fermentation instead produces high concentrations of VFAs and results in moderately acidic ruminal fluid with pH values usually ranging from 5 to 5.5,[59] although pH values between 5.5 and 5.8 may suggest that cows are at risk for SARA.[48] Ruminal buffering of the increased acid load is impaired because the fine particle size of the high-energy rations induces less chewing and less saliva production.[40] As the name implies, the effects on the animal are chronic and insidious.

Along with the high concentration of VFAs and the low pH, a shift occurs in the proportions of the VFAs in the ruminal fluid. The proportions of butyric and propionic acids increase, and acetate decreases. Butyric and propionic acids stimulate dramatic structural changes and proliferation of the ruminal papillae epithelium within a few days of an acidotic insult. When this process is exaggerated it can progress to parakeratosis.[141] The ruminal papillae develop an excessively keratinized epithelium and clump. The parakeratotic changes are associated with decreased absorption of the VFAs and increased susceptibility to trauma and inflammation.[91] Epithelial damage and the acidic nature of the ingesta appear to be responsible for inflammation of the deeper tissues of the ruminal wall in some cases. The damage to the ruminal mucosa can lead to mycotic rumenitis or ruminal wall abscessation or can disseminate infection through the bloodstream to other organs, most notably the liver, which results in the formation of abscesses.[110] Liver abscesses usually have no pathognomonic signs. Affected animals tend to show poor productivity and may have signs of a chronic inflammatory response.[48,55,63,84,89,110]

The diagnosis of SARA is made on a herd level rather than on an individual

cow basis. Cattle afflicted with SARA may demonstrate numerous clinical signs, including reduced appetite and ruminal hypomotility.[118] High ruminal VFA concentrations can inhibit ruminal motility by stimulating the inhibitory receptors in the epithelium. The finely ground ingesta also induces less active ruminal motility because it lacks the physical bulk of high-roughage diets that stimulate strong and sustained contractions. Although the bacterial population is metabolically very active, the number of species of bacteria is reduced,[73] with losses to both ruminal and epimural bacterial community diversity.[61,158] Likewise, the protozoal population is inhibited when the pH remains in the lower end of this range. The microfloral environment is less stable when fewer species are present and is thus more susceptible to sudden changes in the diet.

A continual high acid load may also reduce metabolic efficiency and overall animal performance. Cows may produce less milk, increase milk fat percentage, and demonstrate a positive deviation in the milk fat-to-lactose ratio.[83] High-concentrate diets also have been associated with poor use of dietary protein.[101] Other pathologic conditions have been attributed to SARA, including acute or chronic laminitis[114,134] and cerebrocortical necrosis. These conditions may be induced by some of the toxic by-products of acidic ruminal fermentation, such as endotoxins and hydrogen sulfide.[1,4-6,36,63,84]

Frothy Bloat.

Frothy bloat results from the formation of stable foam in the rumen. Ruminal tympany is synonymous with bloat. The condition may be fatal if the distention is extreme enough to compromise ventilation by compressing the thoracic viscera. Cattle are more susceptible than sheep, but the disease does occur in small ruminants.

The degree of forestomach enlargement varies from that producing an even filling of the left paralumbar fossa to that causing a uniform, extreme abdominal enlargement when the animal is viewed from the rear. With intermediate degrees of distention, the left paralumbar fossa bulges beyond the contours of the last rib and the tuber coxae. Clinical signs of colic may be seen, including kicking at the abdomen, treading, frequent lying down and rising, and vocalizations. Some animals adopt a stretched stance with the rear feet placed far back. In sheep with heavy fleece, significant bloat may not be apparent because the changes in abdominal contour are not obvious. As the forestomach enlarges and compresses the diaphragm, breathing becomes more labored. Open-mouth breathing,

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cyanosis of mucous membranes, and collapse that leads to death may occur within a few minutes if the animal becomes frantic from the abdominal pain and respiratory distress. Other conditions to consider in the diagnosis of frothy bloat in ruminants include other causes of ruminal enlargement: free gas bloat and obstructive indigestion. Many systemic conditions influence the motility of the forestomach and thus may produce mild bloat coincidentally.

Clinical pathologic measurements are not necessary for the diagnosis and management of most cases of frothy bloat in ruminants. Evaluation of a sample of ruminal contents may provide useful information for prescribing treatment and prevention. The presence or absence of froth and the pH are critical features relating to the cause that influence the choice of therapy. The normal pH of the rumen varies with time after feeding but should be between 5.4 and 6.8.

Regardless of the cause of forestomach distention, the process may become self-perpetuating because of reflex inhibition of motility. Low-threshold stretch receptors in the ruminal wall augment cyclic forestomach contractions when stimulated. However, stimulation of high-threshold stretch receptors leads to inhibition of motility. Thus beyond a certain degree of stretching of the ruminal wall, further contractions that may relieve the distention through eructation are prevented.[126]

Frothy bloat is caused by the retention of gases of fermentation within the mass of ingesta that fail to rise and coalesce into a dorsal gaseous layer. This condition can arise from diets of lush legumes or winter wheat pasture or may be seen with high-concentrate finishing rations in the feedlot. In the case of legume-induced disease, bloat has occurred after grazing or feeding of fresh-cut forages or the feeding of alfalfa hay. The structure of stable froth in the affected ruminal contents is not true foam. The ingesta in the septa between adjacent bubbles form a complex structure that prevents coalescence. The viscosity of the fluid may prevent gravitational flow through the septa that would lead to the bubbles' rising and coalescing. Frothy ruminal fluid is higher in chloroplast membrane fragments, soluble protein, and very fine particles than is nonfrothy ruminal fluid.[74] The presence of the resulting frothy ingesta at neural receptors believed to be near the cardia prevents the reflex relaxation of the cardia during the secondary contractions of the forestomach that ordinarily lead to eructation.[67] In addition, the viscosity of the frothy ingesta is such that the cardia may become plugged during attempts to eructate.

Risk factors associated with the occurrence of frothy bloat can be categorized as animal risk factors, plant characteristics (species and maturity), and weather

conditions.[74] Individual cattle have been classified as having either high or low susceptibility to legume bloat. Highly susceptible cattle have been shown to have larger ruminal volumes and specific salivary proteins in consistently different proportions in comparison with bloat-resistant cattle. There is a relationship between plant factors associated with bloat and the rapidity with which leaf structure is disrupted after ingestion.[74] Bloat-inducing plants are more readily macerated, which provides quicker bacterial access to the inner leaf cells. Less bloat-predisposing cultivars of the main bloat-causing species, such as alfalfa *(Medicago sativa)*, red clover *(Trifolium pratense)*, and white clover *(Trifolium repens)*, have a thicker leaf cuticle, smaller stomata, and a more fibrous leaf structure. Ionophore antibiotics such as monensin inhibit ruminal protozoa that normally ingest chloroplasts, which leads to a reduction in the bloat potential of some forages.[13,80]

Grain bloat occurs in a manner similar to that caused by legumes; a stable froth is produced from high-concentrate rations. Particle size and the rate of fermentation are thought to be the determining factors in the froth production. A mucoprotein slime composed of bacterial by-products stabilizes the froth.[13,128] This material tends to be stable at a lower pH than is found in non–grain-fed ruminants, so grain feeding promotes slime accumulation by lowering ruminal pH. Animals (such as dairy cattle) that are fed grain and then legumes may be particularly susceptible to frothy bloat because all the factors that lead to froth production and accumulation are present. Both legume bloat and grain bloat may resolve spontaneously if the animal stops consuming the bloat-producing feed and microbial digestion eliminates the froth-stabilizing factors.

Acute distress, often appearing as abdominal discomfort, is caused by overdistention of the forestomach that stimulates pain receptors in the ruminal wall. As the abdominal distention increases, an affected animal's ability to achieve normal respiratory movements of the diaphragm and rib cage is impaired. This exacerbates the animal's anxiety and distress. Death from asphyxia ultimately results as the lungs are compressed by the cranially expanding diaphragm, and venous return via the posterior or caudal vena cava is compromised.

Frothy bloat often occurs as an epidemic. Pasture bloat may occur wherever alfalfa, red clover, or white clover is grazed. Environmental conditions that produce rapid, early growth lead to a higher incidence of bloat. Frothy bloat also occurs when stocker cattle are grazed on winter wheat pastures in the southern Great Plains of the United States. Death rates at pasture range from 0.5% to

2.5% of cattle at risk on an annual basis. The incidence of feedlot bloat has been estimated at approximately 1%, with death rates of approximately 0.1%.[74]

The finding of tenacious froth in the rumen, along with other evidence of bloat, is grounds for a presumptive diagnosis of frothy bloat. The challenge for the diagnostician is to determine whether the bloat occurred before death; this may not be possible if the animal was not observed before death. The increase in intraabdominal pressure prevents venous return from the hindquarters and may lead to obvious edema in the intermuscular areas. Unfortunately, this is not a consistent finding; other evidence of impaired circulation or a differential degree of edema between fore and hind parts must be used to make a diagnosis.

Passage of a stomach tube is indicated to determine the cause of the ruminal distention and possibly initiate treatment. A sample of the ruminal contents for pH measurement should be obtained at this time. Care must be taken to exclude saliva from the tube by blowing into the rumen, flushing water through the tube, or using a ruminal sampling device that carries the tip of the stomach tube down into the liquid ingesta. If no gas can be released with a stomach tube, the tube should be withdrawn after suction has been applied and should be examined for the presence of froth. If the animal is not in respiratory distress or extremely colicky, surface-active agents should be administered by means of a stomach tube. Poloxalene or mineral oil can be given.

Some cattle are in violent pain with bloat but not in respiratory distress. Sedation with xylazine may be necessary for further examination and treatment. Animals with extreme distention of the forestomach and in respiratory distress require immediate surgical intervention. A trocar introduced through the left paralumbar fossa after local anesthesia relieves bloat caused by free gas accumulation but may not be adequate for frothy bloat. An emergency rumenotomy may be necessary to evacuate frothy contents.

Prevention of frothy pasture bloat relies on the general principle of decreasing the rate of rumen fermentation. To significantly modify the rate of rumen fermentation, grazing management strategies and controlling pasture yields and quality remain the most common methods applied to a population. Cattle could be fed other feeds before being turned out and could be allowed limited access to the problem forages. Accurately predicting when forages are safe has not been reliable. Strip grazing, another option, allows cattle a reduced amount of new forage every few days. The choice of forages and the stage of growth are also to be considered. Agronomists are selecting cultivars of the bloat-producing forages for slower rates of initial fermentation. These are likely to become more

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widely used in the regions in which bloat is a regular occurrence. When grazing strategies and pasture management are not enough, then as an alternative, cattle at risk have been treated with supplemental surface-active agents such as poloxalene or mineral oil. In Australia and New Zealand, oils and tallows have been drenched daily, sprayed on fields, and smeared on the flanks to be later licked off, to prevent pasture bloat. Although poloxalene has proved effective, it is more expensive than oils. It can be fed in molasses blocks or individually administered. Ionophore antibiotics such as Rumensin (monensin; 1 mg/kg daily) greatly reduced the incidence of legume bloat. Beginning treatment before exposure to the bloat-inducing feed was more effective than waiting until bloat occurred. Providing adequate fiber in feedlot rations and slowly introducing higher proportions of concentrates, particularly corn, barley, and soybean meal, enable ruminal adaptation that helps prevent bloat.

Ruminal Alkalosis.

An alkaline ruminal fluid pH occurs most commonly when microbial fermentation is reduced while the animal continues to ingest saliva. A ruminal fluid pH between 7 and 7.5 is found with prolonged anorexia, microfloral inactivity caused by poorly digestible roughage, and some cases of simple indigestion. The low rate of fermentation does not generate enough acid to neutralize the alkaline pH of the saliva. In addition, the absorption of VFAs through the ruminal epithelium proceeds with the generation of bicarbonate in the ruminal fluid. Acetate absorption is associated with greater generation of bicarbonate than is absorption of the other VFAs, and acetate is the predominant VFA produced during fermentation of roughage. Although the fermentation rate is low, the VFA absorption contributes to the ruminal alkalinity. Ruminal alkalosis occurring with these diseases is not the primary problem; therefore these entities are discussed separately.

Ruminal alkalosis can occur with the generation of excessive ammonia. Ammonia concentrations rise when high-protein diets are fermented. The pH usually does not increase above neutral because these diets also contain sufficient readily fermentable carbohydrate to maintain a slightly acidic pH.

More dramatic elevations in the ammonia concentration, with a ruminal fluid pH above 7.5, occur with overfeeding of nonprotein nitrogen sources such as urea, biuret, and ammonium phosphate (see Chapter 54). Accidental ingestion of some common fertilizers that contain ammonium salts can produce the same results. For the purpose of this discussion, it is important to realize that some of

the signs of urea poisoning involve ruminal dysfunction. Severe cases of urea poisoning result in generalized signs such as muscle tremors, incoordination, weakness, tachypnea, and central nervous system excitation, and affected animals die quickly. Signs of forestomach dysfunction such as ruminal hypomotility, bloat, vomiting, and abdominal pain are also present. In milder cases, diminished appetite, ruminal hypomotility, recurrent tympany, and diarrhea may be the most prominent signs, along with muscular weakness and incoordination. Thus the disease may appear as a form of forestomach disease. The ruminal fluid shows an alkaline pH between 7.5 and 8.5 and has a strong odor of ammonia.[130]

Putrefaction of Ruminal Ingesta.

Putrefaction of ruminal ingesta infrequently results from overgrowth of a microflora that decomposes feed material in a putrefactive manner. A high ruminal fluid pH, as exists with high-protein feeds, and repeated inoculation with abnormal bacteria allow the development of the putrefactive decomposition. Fermented feeds undergoing spoilage, feed and water contaminated with feces, and spoiling, contaminated concentrates supply the offending microflora, which includes the coliform group and *Proteus* spp.[43] This type of abnormal decomposition is ordinarily inhibited by the existence of an active physiologic microflora. Thus most cattle are remarkably resistant to aberrant digestive patterns even when spoiled feeds are ingested. This form of indigestion typically follows a chronic course. Ruminal motility declines, appetite is poor, and recurrent tympany develops, sometimes with the generation of frothy ruminal contents. The ruminal fluid characteristically has a blackish green color, a foul, putrefactive odor, poor protozoal and bacterial activity, and a pH in the neutral to alkaline range of 7 to 8.5. The cause of the forestomach hypomotility may be inhibitory products generated by the abnormal fermentation. In cases of prolonged duration, animals lose weight and display a poor hair coat, probably as a result of dietary deficiencies in the abnormal fermentation products.

Rumen Fluid Analysis.

Evaluation of ruminal fluid characteristics is an essential procedure in establishing the cause of the indigestions of abnormal fermentation.[22,119] Several important determinations can be made at cowside in an ambulatory practice. Acquiring an appropriate sample is simplified with proper equipment. The

advantages of various collection techniques and devices have been discussed.[57,116] Needle puncture of the ventral ruminal sac (ruminocentesis) may yield a satisfactory fluid sample, and studies demonstrate that rumenocentesis samples provide the most reliable evaluation of ruminal fluid pH for field evaluation of subacute ruminal acidosis.[49,57,116] Oral or nasal passage of a collection tube produces more fluid volume with no risk of peritoneal contamination but with an increased risk of saliva contamination. The ideal site for collection of rumen fluid for pH evaluation is the ventral rumen sac, where saliva is minimal, whereas investigators examining analytes such as VFAs and ammonia have suggested that sampling in the central rumen is appropriate.[135]

An adequate tube for aspiration of a ruminal fluid sample should be at least 2.3 m long to reach the ventral ruminal sac and should have an internal diameter of 1 cm or larger to reduce the incidence of plugging with ingesta. To adapt a plastic stomach tube for use in passing orally or nasally, multiple holes can be cut into the ruminal end of the tube. A digital examination glove can be placed over the end during passage to limit saliva contamination of the sample and then is forcefully blown off before sampling. The sample can then be withdrawn by a dose syringe. This technique is successful when ruminal fluid is accessible in the dorsal rumen, but the flexibility of the tube is disadvantageous when a prominent layer of fibrous feed is present. Several instruments with a flexible steel outer tube are commercially available (Dirksen Rumen Fluid Tube, Allschwil, Switzerland; Geishauser probe, Hamburg, Germany; Select-Collector, Hamberg, Germany) and have the advantage of enough stiffness and weight to penetrate the overlying firm layer of ingesta for collection of fluid from the ventral rumen.[143]

Ruminal fluid samples collected in an expeditious manner yield the most useful results. When the animal strongly resists sampling and a prolonged time is required from introduction of the tube until the fluid is obtained, saliva contamination of the sample increases. This contamination alters the pH and consistency of the sample. The specially designed ruminal fluid collection tubes reduce this problem. If the sample must be collected with a standard nasogastric tube, passing the tube nasally avoids the presence of a device in the mouth. This reduces the amount of struggling (once the tube has passed the pharynx) and thus reduces excessive salivation.

The sample should be evaluated as soon as possible after collection to minimize the effects of cooling and air exposure on protozoal activity and pH. Some chemical tests such as chloride, and ammonia concentrations can be

delayed up to 9 hours on a room temperature sample and up to 24 hours on a refrigerated sample and still yield reliable results.[41] Ruminal fluid collected for therapeutic transfaunation also retains its beneficial activity for a similar duration.[109] Adding a 1-inch layer of mineral oil on the fluid may help preserve anaerobic microbial activity. The ruminal fluid parameters important in a clinical examination are listed in Table 32.19.

TABLE 32.19
Diagnostic Ruminal Fluid Analysis

Parameter	Normal
Color	Olive, brownish-green
Consistency	Slightly viscous
Odor	Aromatic, strong
pH	6 to 7 on roughage
	5. to 6.5 on grain diet
Sedimentation/flotation	4 to 8 min
Redox potential (methylene blue reduction time)	3 to 6 min
Protozoal activity	Multiple forms, active motion
Gram stain	Predominant Gram-negative bacterial population
Chloride concentration	<30 mEq/L

Color, Consistency, and Odor.

The color, consistency, and odor of aspirated fluid are assessed immediately after collection. Normal color varies, depending on the nature of the feed. Ruminal fluid produced by animals fed a hay ration is olive to brownish-green; that produced by animals feeding on grass is a deeper green; and that produced by cattle fed grain or silage is yellowish-brown. Fluid from cattle with acidosis tends toward a milky gray. Ruminal fluid from animals with prolonged stasis or decomposition of the ruminal ingesta (or both) is a darker greenish-black, and fluid from calves with milk sequestered in the rumen as a result of abomasal reflux or esophageal groove failure is gray and may contain clots of milk.

Normal ruminal fluid has a slightly viscous consistency. The fluid becomes more watery when the microflora is inactive. Saliva contamination causes greater viscosity; therefore the results from a highly viscous sample should be evaluated with care, and it may be best to discard such samples. Ruminal fluid has a typical odor that has been called “aromatic.” The odor is less prominent when the microflora are inactive. Abnormal odors include the acidic smell of lactic acidosis, the putrid, foul odor of protein decomposition or spoiled milk

with putrefaction of ruminal ingesta, or the ammonia smell of urea poisoning.

Ruminal Fluid pH.

The pH of ruminal fluid fluctuates within a broad range of normal values, varying considerably during the course of a day with shifts of 0.5 to 1.0 pH unit common during a 24 hour period.[89,115] The pH measured in a given fluid sample depends on the type of feed and fermentation pattern and the interval since the last feeding. Physiologic ruminal fluid pH typically ranges between 6 and 7 in animals on a mostly forage diet but is lower, at 5.5 to 6.5, in animals fed mostly grain.[57,89,93] The lower pH develops because the rate of amylolytic fermentation is faster than that of cellulolytic fermentation. Immediately after feeding, the pH tends toward the high end of normal with the addition of feedstuff and saliva, the production of which is determined by the duration an animal spends eating, ruminating, and resting.[102] Over a 2- to 4-hour period, the pH decreases to the lower range as the feed undergoes fermentation. With no further feed consumption, fermentation declines, and the pH rises with salivary buffering and acid end-product absorption. In animals held off feed, the ruminal pH rises above 7 within 12 hours after a hay meal and within 24 hours after a high-grain meal. Thus consideration of the most recent feed consumption is important in the interpretation of the ruminal fluid pH measurement.

Saliva contamination of the sample falsely elevates the measured pH value. Because it is impossible to exclude saliva completely from samples collected by tube, the pH is probably falsely elevated to a minor degree in all such examinations.[57] This elevation can be minimized by expedient collection of a large fluid volume (more than 100 to 200 mL). If the collected volume is small and the sample viscosity is high, the pH measurement will be inaccurate. Modest contamination (5% to 10%) raises the measured pH by approximately 0.1 to 0.2 pH units, whereas excessive contamination with approximately 50% saliva may increase pH by 1 pH unit. Ruminocentesis of the ventral ruminal sac below the left paralumbar fossa is preferred by some clinicians for preventing saliva contamination. This is particularly advantageous for samples collected to monitor ruminal pH for balancing rations and minimizing chronic ruminal acidosis. A sampling strategy that incorporates ruminocentesis and ruminal fluid pH measurement in groups of cows in a herd has been developed to optimally identify cow groups with feeding problems that lead to subacute ruminal acidosis.[57,116]

Ruminal pH values of 7 to 7.5 are common in animals with anorexia and in those that have ingested feed that is not suitable for fermentation (e.g., simple indigestion and inactivity of microflora caused by indigestible roughage). Even higher pH values may be measured with ruminal alkalosis caused by urea ingestion or putrefaction of ruminal ingesta. Low pH values result from engorgement with readily digestible carbohydrates and generation of ruminal lactic acidosis. In extreme cases, values occasionally decline to 4 to 4.5. Of importance is that prolonged anorexia and continued saliva ingestion result in rising pH values in these cases as well and that the ruminal pH of a cow with ruminal acidosis can be normal if a sufficient period of anorexia precedes the ruminal fluid analysis. Conversely, a ruminal pH of 5.5 to 6 is abnormal for a cow fed a roughage diet and may be indicative of unobserved access to grain and resultant lactic acidosis. Subacute or chronic ruminal acidosis usually is accompanied by a ruminal pH in the range of 5 to 5.5.[57,89,93,119] Abomasal reflux into the reticulorumen caused by abomasal disease, obstructive indigestion, or intestinal obstruction can cause mild decreases in ruminal pH because of the acidic nature of abomasal contents. However, ruminal pH measurement is a poor means of detecting abomasal reflux because the pH often remains within the wide range of normal values. Abomasal reflux is better assessed by measurement of reduced buffer capacity or the ruminal chloride concentration.

Sedimentation.

The sedimentation time, or sedimentation/flotation test, provides a quick evaluation of microfloral activity. It must be conducted promptly after collection of the sample. The aspirated fluid is allowed to sit in a tube, and the time for completion of sedimentation and flotation of the solid particles is measured. Normally the finer particles settle to the bottom and the coarser particles float, buoyed by the gas bubbles of fermentation. Some of the finer particles sink and then rise again when the fermentation is very active. The normal time for completion of this activity is 4 to 8 min. Grossly inactive fluid shows very rapid sedimentation, and none of the material may float. This occurs with ruminal acidosis, prolonged anorexia, and microflora rendered inactive by indigestible roughage. When the ingesta is particularly frothy, as in cases of frothy bloat or some cases of obstructive indigestion, there may be no appreciable sedimentation or flotation. This test provides a crude evaluation of microfloral activity but does not differentiate well among the different forms of indigestion.

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Redox Potential.

The redox (reduction-oxidation) potential of ruminal fluid is a biochemical characteristic that reflects the anaerobic fermentative metabolism of the bacterial population.[155] A clinician can determine the redox potential indirectly by measuring the time required by ruminal fluid to decolorize methylene blue dye. A mixture of 1 mL of 0.03% methylene blue with 20 mL of ruminal fluid at normal body temperature is observed in a tube and compared for color with another unaltered tube of the ruminal fluid. With highly active microflora from an animal fed a hay and grain diet, the initial dark blue color of the mixture decolorizes within 3 minutes, leaving a narrow ring of blue color at the top of the decolorized sample. Fluid from a diet of hay alone requires 3 to 6 minutes to decolorize, and that from a mostly grain ration requires as little as 1 min. Reduction times up to 15 min and longer occur with diets of indigestible roughage, in anorexia of several days' duration, and after ruminal acidosis.[22] Thus the methylene blue reduction time provides an assessment of the degree of bacterial fermentative activity.

Microscopic Examination.

Evaluation of the number and activity of protozoa in the ruminal fluid provides a sensitive indicator of the normality of the sample.[155] This is easily accomplished by microscopic examination of a drop of fresh, warm fluid. The examination requires only low magnification (×40 to ×100) and no special stains. In very active fluid samples, the largest protozoa can be seen with the naked eye. They are detectable in a tube as small gray specks of material in active motion in the fluid, and they tend to localize above the sedimented particulate matter. Both ciliate and flagellate forms of varying sizes and shapes can be observed microscopically, with ciliates usually outnumbering the flagellates. The protozoa are normal inhabitants of a healthy ruminant's ruminal fluid, although their specific function is not completely clear and their presence does not appear to be a prerequisite of normal digestive activity.[159] The importance of the protozoa from a clinical viewpoint is their sensitivity to abnormalities in the fluid milieu. Normal ruminal fluid should contain protozoa in a wide variety of sizes, in large numbers that are easy to see, and with active motility. Numbers of protozoa are reduced in inactive fluid samples. The larger species are more susceptible to abnormalities; thus a predominance of small protozoa would suggest a mild indigestive disturbance. All protozoa are killed off when the ruminal pH drops

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below 5. Thus a recent bout of acidosis results in lack of protozoal activity, even if the pH has subsequently risen back into the normal range. Fluid from such an animal should also show other abnormalities of color and consistency. Very recent disturbances of the fluid may result in the observation of a large number of dead protozoa.

Although elaborate isolation methods for evaluating ruminal bacterial growth are not clinically applicable, examination of an air-dried, Gram-stained smear of ruminal fluid can be useful in diagnosing ruminal acidosis. Normal ruminal fluid should contain a variety of morphologically distinguishable bacterial forms, with a predominance of Gram-negative organisms.[41] After the overconsumption of readily digestible carbohydrate (grain engorgement), a population of streptococci and lactobacilli proliferates as ruminal lactic acidosis develops. This shift in the bacterial population can be distinguished microscopically, and a predominance of Gram-positive cocci and rods are seen. The findings are best confirmed by comparing a smear from a herd mate.

Ruminal Fluid Chloride.

The chloride concentration in ruminal fluid can be determined from the supernate from a centrifuged sample through the use of standard chloride titration devices. A delay in measurement does not appreciably affect the value. Saliva contains concentrations of chloride similar to those of normal ruminal fluid, so that saliva contamination has minimal effect on the results. The normal ruminal fluid chloride concentration is less than 30 mEq/L, with elevated values demonstrating reflux of abomasal ingesta into the rumen or administration of chloride in the feed or as therapy. Accurate assessment of measured values requires information about possible previous oral administration of electrolytes. In the clinical evaluation of forestomach dysfunction, an elevated level of ruminal chloride suggests secondary indigestion caused by abomasal disease or obstruction of intestinal flow. This test can be very helpful in differentiating abomasal reflux from ruminal lactic acidosis as the cause of low ruminal pH and abnormal fluid accumulation in the reticulorumen. With obstructive indigestion a high level of ruminal chloride suggests that the failure of aborad flow is posterior at the pylorus rather than anterior at the reticuloomasal orifice.[124] In general, cattle with elevated levels of ruminal chloride also have hypochloremia and metabolic alkalosis as a result of the chloride sequestration in the forestomach, although very slow development of the sequestration may allow the animal to maintain normal plasma levels by altering other excretion rates.

Numerous other tests of the ruminal fluid have been described for the evaluation of digestive activity of the ruminal microflora. These include cellulose digestion, glucose fermentation, nitrite reduction, and measurements of titratable acidity, VFAs, lactic acid, and ammonia concentration.[41] These procedures can more clearly define the nature of the ruminal fluid but are not generally used in a clinical setting.

Treatment, Prognosis, and Prevention of Fermentative Disorders.

With the exception of severe acute ruminal acidosis, the disturbances of reticuloruminal fermentation generally are not fatal unless the disease is undiagnosed for a prolonged period, which leads to extreme debility. Treatment of fermentation disorders centers around restoring a normal ruminal fluid environment that allows normal microbial metabolism. Identification of ruminal fluid parameters (see Table 32.19) and the nature of the forestomach ingesta directs the appropriate treatment (Box 32.6).

Box 32.6

Principles of Treatment of Fermentative Indigestions

1. Determine and resolve initiating cause; adjust feed regimen.
2. Correct ruminal pH.
3. Correct systemic acid-base and electrolyte abnormalities through parenteral fluid therapy (especially Ca^{++} and K^{+}).
4. Remove grossly abnormal ruminal ingesta.
5. Correct ruminal fill (overdistention or emptiness).
6. Transfaunate repeatedly.
7. Resolve inspissation or impaction of ruminal contents that is present.
8. Provide oral and parenteral mineral and vitamin supplementation when indigestion or anorexia is chronic.

Feeding.

The first and most important step in treatment of nutritionally related

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indigestions is correction of the specific causal feeding error. Because the imbalance may have gone on for weeks, especially in cases of calf indigestion, correction of the problem may also take some time. The evolutionary development of the ruminant has adapted it to be a grassland grazer. Economic pressures in the animal industry have caused managers to institute feeding practices that diverge widely from a pasture setting. Fresh green grass, however, remains one of the best means of stimulating normal forestomach digestion and motility. The second best type of diet includes a balance of palatable and digestible sources of energy, protein, fiber, and mineral nutrients. Fiber requirements should be determined by considering both the physical effectiveness of fiber and the production of fermentation acids.[2] The content of structured roughage should not fall below 10% of the ration dry matter, and a crude fiber component above 17% is desirable for any ration.

Alteration of Ruminal Contents.

When the viability or activity of the ruminal microflora is in question, as in the primary fermentative disorders and most cases of secondary indigestion, ruminal transfaunation is indicated.[39,122] The material should be obtained from a healthy individual that preferably is adapted to a ration similar to the one the patient is expected to consume. The fluid can be obtained from an animal with the rumen cannulated, by removal with a stomach tube, or from a local abattoir. After the large particulate matter has been strained from the fluid (cheesecloth or large stockinette can be used), it can be administered through a stomach tube. The transfer from donor to recipient is best accomplished immediately, but fluid that contains active and healthy microflora remains viable for up to 9 hours at room temperature or 24 hours under refrigeration.[109] Some clinicians add mineral oil to the fluid, which rises to the top and minimizes exposure to air in order to maintain anaerobic conditions. In calves, inoculation with 1 L is appropriate to reestablish microbial populations, whereas 3 L is minimal in an adult cow, and 10 to 16 L is more desirable. Similarly, transfaunation of sheep or goats with 1 to 4 L of fresh rumen fluid can reestablish normal microbial populations.[39]

Many animals with indigestion exhibit decreased ruminal fill. As discussed, one of the primary stimuli for active ruminal contraction is mild forestomach distention. In addition to the administration of ruminal transfaunate, it is usually beneficial in these cases to administer enough oral fluid to produce mild ruminal distention. This can be accomplished with water warmed to body temperature,

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and 20 to 30 L of fluid administered through a tube may be needed to achieve the desired effect. The addition of salt (sodium and potassium chloride) in amounts sufficient to produce an isotonic solution (≈2 teaspoons per liter) supplements deficiencies and promotes rapid turnover of the fluid from the rumen to the lower tract. Cathartic agents such as magnesium sulfate have been used but do not serve to supplement the common electrolyte deficiencies.

Correction of pH abnormalities to the normal range of 6 to 7 is important when ruminal acidosis or alkalosis is detected. Alkalinizing agents such as magnesium hydroxide and sodium bicarbonate are indicated for treatment of acidosis at an initial dose of 1 g/kg. Magnesium hydroxide is commonly used by some as a routine treatment for any animals in which ruminal hypomotility has been identified. This practice is not justifiable in most cases of ruminal hypomotility because the fluid pH is commonly at or near neutral. The use of magnesium hydroxide in such settings may induce a mild systemic alkalosis, and the agent is better reserved for true cases of acidosis. Ruminal alkalosis can be corrected with the infusion of acetic acid (vinegar, initial dose of 2 mL/kg, up to 12 L). These agents are best administered in several liters of warm water to ensure good distribution throughout the ruminal fluid.

Overdistention of the ruminal wall may be a primary inhibitor of forestomach motility in some cases of indigestion caused by abnormal fermentation. Treatment of free gas bloat has been discussed. When the distention is caused by accumulation of abnormal ingesta, normal contractions do not return, and the ruminal tympany is not resolved until the distention is relieved. This situation is best exemplified by cases of microfloral inactivity caused by poor-quality roughage and is the underlying problem in calves with haybelly. One approach to this problem is to restrict the animal to small quantities of readily digestible feed given several times a day. Between meals the animal can be kept in an unbedded stall or muzzled. This process is continued until the accumulated ingesta has passed out of the forestomach. Repeated transfaunations during this time help reestablish a more normal microflora. This approach relies on motility and microbial activity sufficient to break down the ingesta and pass it to the lower tract.

An alternative approach is to remove the accumulated ingesta by means of rumenotomy, after which the animal is transfaunated and allowed access to moderate amounts of feed until normal motility is restored. Emptying the rumen surgically is the treatment of choice when spoiled milk, putrefactive ruminal ingesta, or severe ruminal acidosis is detected. Prolonged cases of microbial

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inactivity or anorexia (or both) with ruminal hypomotility can result in loss of the normal stratification of forestomach ingesta. The fibrous, floating layer sinks to the ventral ruminal sac in these cases, forming a dense, firm mass. Return of normal forestomach motility is delayed unless the accumulation of material can be eliminated. This can be accomplished during the process of microfloral reestablishment by massaging of the mass through the lateral and ventral body wall. Dissolution and passage of the material can be enhanced by the administration of mineral oil (4 L), or dioctyl sodium sulfosuccinate (4 to 6 ounces in 2 to 3 L of water). Because dioctyl sodium sulfosuccinate kills ruminal protozoa when given in amounts greater than necessary to saturate the fibrous matter, at least one ruminal transfaunate should be given 1 to 2 days after the last application of this agent.

Animals with prolonged anorexia caused by a depressant or febrile disease that produced secondary indigestion may not return to feed or have normal ruminal motility even after the ruminal contents has been restored to normal. Chewing activity is one of the strongest stimulants for ruminal motility, and these animals sometimes benefit if palatable hay or grass is placed forcefully into the mouth by hand. An alternative is to give such animals access to pasture. In fact, during a bout of SARA, cows have been shown to self-regulate their dietary preference for physically effective higher fiber and slower starch fermentability.[104] Both the ruminant and its ruminal microflora have trace mineral requirements that are often not met by the type of diets that may induce microfloral inactivity. The ruminal microflora is also responsible for supplying animals with their vitamin B requirements. The stunted, poor body condition of calves affected by chronic indigestion may reflect these deficiencies, as well as protein energy malnutrition (see Chapter 9). Oral supplementation of minerals and parenteral supplementation of the B vitamins may be helpful until normal ruminal digestive function is established. Adult cattle, especially lactating animals with high metabolic demands, may also benefit from B vitamin supplementation when ruminal function is impaired.

Feeding changes and ruminal transfaunation are effective in inhibiting undesirable microbial populations, and inoculating the desirable population. When spoiled milk, putrefactive ingesta, or extremely acidic ruminal contents are found on ruminal fluid analysis, the desirable treatment is rumenotomy, removal of the contents, and flushing of the rumen.

Supportive Treatments.

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Indigestion often is accompanied by varying degrees of dehydration and electrolyte imbalance. When these abnormalities are only mild or moderate, the animal's fluid homeostasis may correct itself as the normal digestive processes are restored. More rapid recovery is achieved if these problems are addressed during the initial treatment, and animals must be treated if the imbalance is severe. Restoration of normal fluid balance improves attitude, appetite, and gastrointestinal motility.

When laboratory facilities are available and the specific electrolyte imbalances can be assessed, fluid therapy can be tailored to the individual case. Empirical treatment with a balanced electrolyte solution administered intravenously is sufficient in most cases because extreme disturbances of the body fluid electrolytes are uncommon in most indigestions. Exceptions include severe ruminal acidosis and obstructive indigestion with pyloric outflow failure and sequestration of abomasal chloride. These problems should be identified during the examination.

Hypocalcemia and hypokalemia are routinely present in many cases of indigestion. Low serum concentrations of these elements can produce muscular weakness and impair gastrointestinal motility. Both calcium and potassium should be included in the administered fluids. As an alternative, calcium salts should be administered subcutaneously if intravenous fluid administration is not elected. Oral preparations of calcium salts are commercially available but seem less desirable as a means of treatment without normal rumen function. When anorexia has been prolonged, an additional oral dosage of potassium chloride (120 g/day) may be required even after adequate hydration has been achieved and fluid therapy has been discontinued.

Prevention.

Some of the sporadically occurring diseases of the forestomach wall such as granulomatous infections, neoplastic invasions, and diaphragmatic herniation cannot be foreseen or prevented. The most common cause of vagal indigestion is inflammation of the perireticular area caused by TRP. Prevention of this disease by keeping metallic foreign bodies out of the feed, removing them from the feed through the use of a metal retriever or magnet, or prophylactic administration of a ruminal magnet is highly effective.

The microbial-fermentative forestomach disorders are best prevented by proper feeding management. A well-balanced diet of palatable feeds with an adequate amount of well-structured roughage (not finely ground or pelleted)

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prevents most problems. Dietary changes should be introduced slowly (over 2 to 3 weeks) to allow adaptation of the microbial flora to the new substrate. Calves undergoing ruminal development and cattle fed high-production diets or changing between production groups are at risk of oversights in proper feeding management.

Feed-grade buffers are used widely in both dairy and beef cattle production, in which high-concentrate diets are fed to maximize production. Dietary buffering is largely explained by dietary cation-anion difference; diets high in sodium and potassium in relative to chlorine and sulfur demonstrate a higher dietary cation-anion difference and promote higher ruminal pH.[75] These buffers stabilize the ruminal pH and alter the mechanics of ruminal fluid outflow, thus decreasing the chances of overgrowth of the lactate-producing organisms. Commonly used "buffers" include sodium bicarbonate, sodium sesquicarbonate, sodium bentonite, magnesium oxide, and calcium-magnesium carbonate, of which only the sodium carbonates are truly buffering agents in the chemical sense. The other agents do tend to stabilize ruminal pH, however, and all of these have shown some benefit in reducing the disease problems associated with heavy grain feeding and diets that are low or marginal in effective fiber.

The ionophore antibiotics (e.g., laidlomycin, lasalocid, monensin) and some other antibiotics (e.g., the sulfur-containing peptide antibiotic thiopeptin) have also proved effective in reducing lactate production in animals fed high-grain diets. The effect of these agents is to suppress the lactate-producing organisms while not appreciably affecting the lactate users. The ionophores are in common use in feedlot cattle and dairy heifer rations because the selective effects of these agents on the ruminal microbes alter the ruminal metabolism in a manner that promotes increased animal weight gain.[107] In 2004 the U.S. Food and Drug Administration approved the use of the ionophore monensin for lactating cattle in the United States. Although approval was based on increases in milk production efficiency, ionophore use may also reduce the risk of ruminal acidosis and ketosis.[47,60]

A number of other feed additives have proven effective in preventing the overgrowth of high acid–producing ruminal microflora and reducing the risk of disorders related to reticuloruminal fermentive function.[3,10,29,38,105] Research has increased the understanding of the importance of ruminal microbial diversity and the functional capacity of rumen microbial ecosystems under different dietary environments.[87] Molecular biological advances have been used to profile

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microbial communities with the use of techniques such as terminal restriction fragment length polymorphism analysis, 16S ribosomal DNA libraries, and metagenomic approaches.[90] The application of these tools in the evaluation of manipulators of ruminal fermentation can provide added value in optimizing feedstuff and minimizing digestive disorders.[105]

Forestomach Diseases of Calves

Normal forestomach development and diseases of the forestomachs of calves have been reviewed.[11,37] The newborn ruminant has the same anatomic division of the stomach into four compartments as the adult ruminant. The abomasum is functional as a secretory digestive organ, like the stomach of monogastrics, and has a capacity approximately twice that of the other compartments. The remaining stomach compartments are small and do not perform digestive functions in the first days of life. The reticulorumen may not develop an adult-type function until the age of 4 months or later and does not completely develop proportional dimensions similar to those of the adult until the ages of 9 to 12 months.[37,43,44,54,155]

Traditionally, preruminant calves have been viewed as functionally monogastric animals, and little importance has been attached to diseases of the forestomachs. Under most management conditions, however, the forestomachs have begun to develop their digestive function within the first week or two after birth. During the development process, a calf's forestomach is susceptible to problems different from those of adults. After the rumen has developed a functional status similar to that of the adult, a calf is susceptible to the diseases discussed previously. Typically the feeding management of maturing young stock includes pasture or a mainly forage diet and does not predispose to digestive disturbance.

Esophageal (Reticular) Groove Function.

Liquid feed bypasses the reticulorumen in the young ruminant, flowing directly into the abomasum through the esophageal groove. The groove consists of two lips that extend from the cardia to the reticuloomasal orifice. These lips close together, forming a tube to shunt liquid material to the abomasum when the soluble proteins and salts of milk stimulate a reflex through specific receptors in the oropharynx. Other salt solutions and even water can stimulate the reflex in very young animals, but the reflex weakens with age, especially after weaning.

The response to stimuli varies among individuals, but generally milk produces the strongest response and plain water the weakest.[127,131,152] Both nipple and bucket feeding stimulate closure in very young calves, but beyond 12 weeks of age, closure is weak unless stimulated by nipple feeding. In older, weaned animals, the reflex can be stimulated weakly for short durations by orally administered strong solutions such as copper sulfate or sodium salts. Intravenous vasopressin can induce more profound closure of the groove and has been advocated to aid ruminal bypass of orally administered treatment.[131]

Milk replacers that contain nonmilk protein appear to stimulate a weaker closure of the esophageal groove than do whole milk or milk replacers containing real milk protein. Likewise, unpalatable fluids and spoiled milk do not seem to induce normal closure of the groove. Even in healthy calves that consume unspoiled whole milk, some overflow into the forestomach may occur. Failure of esophageal groove closure allows these fluids to pass into the rumen rather than bypassing it. Milk or other fluid administered through stomach tube or esophageal feeder does not contact the pharynx; therefore the reflex closure is not stimulated and the fluid deposits in the forestomachs. Under normal conditions fluid in the forestomach of neonatal calves younger than 2 weeks of age overflows into the abomasum when more than 400 mL has accumulated.[27]

Reticuloruminal Milk Accumulation (Ruminal Drinking Syndrome).

Milk can gain access to the reticulorumen by several means. Failure of esophageal groove closure, just discussed, is one possibility. In addition, if calves are maintained as preruminants for longer than 3 to 4 months, groove closure weakens and may allow greater escape of fluid to the reticulorumen. Fluid can also accumulate in the forestomach from abomasal reflux (Fig. 32.129). Overfeeding fluids beyond the capacity of the abomasum (≈2 L in the newborn, 35-kg calf) promotes backflow into the reticulorumen. Certain fluids affect abomasal motility and emptying times, prolonging their retention in the organ. These include acidic and hypertonic fluids and severely heat-treated skim milk powder. Nonmilk protein does not curd in the abomasum, as does casein, when it contacts the abomasal enzyme renin. Prolonged fluid retention and failure of curd formation in the abomasum may promote backflow into the rumen, especially when more fluid feed is consumed. Abomasal inflammation or ulceration may also inhibit normal emptying and promote abomasal reflux. In any case, ultrasonography may be useful for detecting milk in the reticulum and

rumen of calves with ruminal drinking syndrome.[16]

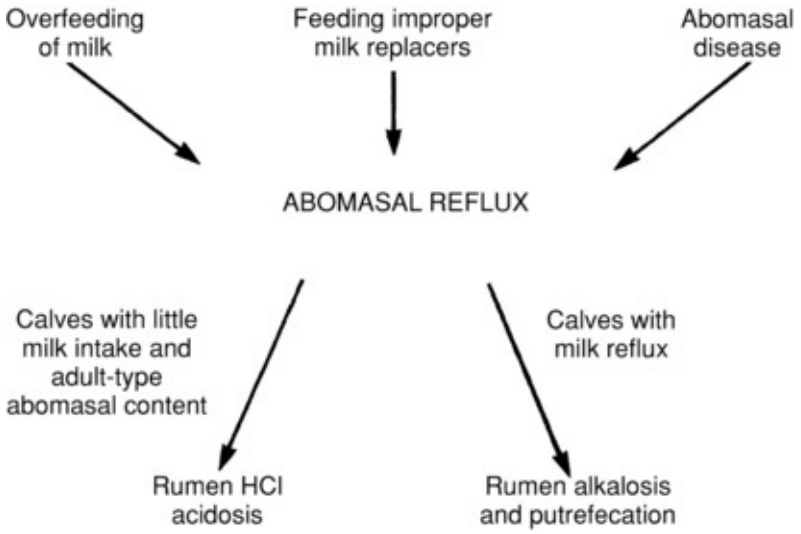


FIG. 32.129 Causes of abomasal reflux in calves. *HCl,* hydrochloride.

Some amount of milk reflux from the abomasum appears to be a physiologically normal occurrence. In fact, this route supplies some of the inoculum for ruminal microfloral development and strongly influences the species distribution of the microbial population. But prolonged, repeated, or excessive retention of milk in the forestomach can lead to the development of abnormal fermentation patterns. Although amounts of fluid greater than 400 mL do not normally accumulate in the forestomach of neonates, more fluid can accumulate when the abomasum is already filled and when ruminal size has increased during the development process. In some cases, milk flow into the rumen accumulates significantly over prolonged periods.

The predominant organisms that constitute the forestomach microflora of 1- to 4-week-old ruminants are the coliforms and lactobacilli. These lactose-fermenting, facultative anaerobes tend to maintain the ruminal pH in the acidic range before the adult-type, anaerobic, cellulolytic flora becomes established. The high fat and protein content of milk in the rumen can predispose to a flora that decomposes these constituents and produces spoiled and rancid ruminal ingesta. Problems associated with ruminal milk accumulation are compounded when the milk or other fluid ingested is already contaminated or spoiled. The abnormal microflora established under these circumstances does not supply the young animal with the necessary digestive end products, and signs of dietary

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insufficiency develop. Affected animals fail to grow normally, show a poor hair coat potentially with widespread alopecia, and may have a depraved appetite. The stimuli for normal forestomach development are also deficient; affected animals have a potbellied appearance, and the rumen is distended with fluid and clots of milk. Ruminal motility is poor, and recurrent bloat is a common sequela. The ruminal fluid pH may be alkaline as a result of the proteolytic formation of ammonia, but in most cases the ruminal pH is acidic (<6) because of an accumulation of VFAs and lactic acid from bacterial fermentation, and the fluid has a putrid, foul odor.[121] An enteric imbalance also seems to occur, and the feces are commonly pasty or fluid in consistency. Ruminal "drinking" appears to compound problems in calves with infectious enteritis and diarrhea, and affected calves frequently develop systemic acid-base and fluid balance disturbances.[58,145]

Problems in Ruminal Development.

The age at which a calf has reticuloruminal digestion depends largely on its diet. A plentiful supply of milk delays the time until the calf consumes significant quantities of dry feed. Neonatal ruminants maintained solely on milk during the first months of life show limited ruminal development with regard to rumen weight, capacity, papillary growth, keratinization, pigmentation, and musculature development.[11] The nervous reflexes that drive ruminal motility, eructation, and regurgitation are already functional before birth, awaiting only the drive of normal stimuli to begin operating. Dry feeds pass into the rumen, and bacterial inoculation from the environment or from abomasal reflux stimulates fermentation to begin. This process can be initiated as early as 1 week of age, when calves are encouraged to consume dry feeds.[34]

The increase in the size of the forestomach results from the ingestion of bulky, fibrous feeds.[70,82] Mild distention stimulates ruminal motility and the development of the muscular wall. Mucosal development is regulated through variable gene networks influenced by the presence of VFAs in the ruminal fluid that result from microbial fermentation.[31] Butyrate and propionate are most effective in this regard, whereas acetate is less stimulatory. The thickness of the mucosa increases with proliferation of the ruminal epithelium and elongation of the papillae.[160] These changes serve to increase the ability of the mucosa to absorb the VFAs. These metabolites act in concert with the resident microbiota and the microbes provided in feed to influence the gastrointestinal barrier

function.[12,142] Dietary excesses or deficiencies affect the developing rumen by altering the balance of these stimuli.

Calves fed concentrate diets to the exclusion of forages or mixed diets with the hay pelleted or finely ground may experience ruminal parakeratosis as a result of a lack of feed abrasion[64,148] and the excessive production of the stimulatory VFAs: butyrate and propionate.[160] These calves can have a form of chronic ruminal acidosis that results in a reduced growth rate and poor body condition. Ruminal contents in such calves are typically fluid with an acidic pH, ruminal hypomotility occurs, and recurrent free gas bloat is common. Affected calves often display a craving for fibrous materials. Hair coat licking is common in these calves, and hairball formation in the reticulorumen is a common sequela. The hairballs may not be deleterious, but occasionally they cause obstructive disease or abrade the parakeratotic papillae or the abomasal mucosa, predisposing the animals to ulcers and inflammatory lesions.[44] Acute ruminal acidosis is not typically recognized in young, developing ruminants, probably because feed consumption is limited and because the predisposing adult-type ruminal microflora have not yet developed.

An opposite extreme can occur when the young calf is fed dry forage to the exclusion of more readily digestible carbohydrates. Concentrates and grass contain soluble carbohydrates and are well digested by the developing ruminant. Hays contain much less soluble carbohydrate and an abundance of the structured, slowly digestible forms. These substances are not as well digested by calves because the appropriate cellulolytic microflora are not fully developed. With moderate hay intake and the supply of other sources of nutrition, problems are rarely encountered. When dry roughage is the only available feed, and particularly when the hay is of poor quality, adequate breakdown of the fiber is prolonged. The low availability of nutrient substrate that results from delayed digestion of the structured carbohydrates decreases microbial proliferation and fermentation. Inadequate fermentation of the feedstuff deprives animals of required nutrients as well and results in poor performance and growth. When the only available feed source is the hay ration, calves continues to consume while the long undigested fiber accumulates in the rumen. The rumen continues to expand as a result of the increased filling, eventually becoming grossly distended. Recurrent bloat is common in these animals because of the overfilling and poor ruminal contractility. This phenomenon is a frequent occurrence under some management conditions and has commonly been called “haybelly.” Affected animals display a typical abdominal contour, with gross distention of

the abdominal wall that is more prominent on the left side. The ruminal contents are very firm, the fluid has a pH around neutral and shows little microbial activity or odor, ruminal motility is poor, and, despite the full abdomen, the animal is thin. This form of microfloral inactivity is more common in calves than in adults because the young ruminant is less able to ferment fibrous roughage.[43,44]

Recurrent Bloat (Ruminal Tympany).

Moderate gas distention of the rumen is a common sign of disease in calves, usually as a result of free gas accumulation, whereas frothy fermentation is very uncommon in young ruminants. The pathogenesis of free gas bloat has been discussed, and the same principles hold for young ruminants. The differences between free gas bloat in adults and in young calves are more a matter of chronicity and frequency of occurrence than cause. Digestive disturbances of the adult rumen tend to develop more rapidly and are more readily identified than those of the calf rumen. Because of the involvement of ruminal developmental processes in the pathogenesis of calf indigestion, in young ruminants the diseases are often more chronic than acute in nature. In most cases the calf continues to consume feed, and the abnormal ruminal function and development may be easily overlooked.

Ruminal tympany seems to accompany indigestion in calves more often than in adult cattle and also assumes a more prominent appearance in calves than in adults. These factors may be reflections of the juvenile anatomy and the incomplete development of adult function. For instance, left-sided abomasal displacement, although uncommon in young calves, almost invariably is accompanied by marked ruminal tympany. In contrast, in adults the disease is common, but ruminal tympany is an infrequent sign of the disease.

Purulent lung infections appear to be a common cause of bloat in calves, probably as a result of intrathoracic compression or irritation of the esophagus or possibly the vagal nerves.[45] However, other causes of bloat that are associated with abnormal ruminal function are also common in calves with indigestion. They include overdistention of the rumen, insufficient clearing of the cardia, and inhibition of motility by abnormal fermentation products. Thus a thorough examination is necessary to determine the underlying cause of the individual case.

Abomasal dilation and tympany in calves (acute bloat syndrome) is often associated with forestomach distention as well. Although the exact pathogenesis

is unknown and appears multifactorial, large amounts of fermentable carbohydrate in the abomasum along with fermentative enzymes probably lead to gas production and bloat.[103,120,136] This syndrome is discussed in detail elsewhere (see Chapter 20). One presumed cause of bloat in calves that is not a cause of adult bloat is sudden filling of the abomasum by milk feeding during weaning. Calves not yet completely converted to a diet of solid feed still consume milk eagerly. In some cases, acute free gas bloat occurs immediately after the milk feeding. Because the esophageal groove directs the milk into the abomasum but the abomasum is already partly filled by ingesta from the developing rumen, acute overdistention of the organ can occur and reflexly inhibit forestomach motility. Feeding smaller milk meals or discontinuing the milk feeding resolves the problem in these cases, which is evidence of the presumed cause.

Peritonitis in Ruminants

Gilles Fecteau

Despite the frequency with which peritonitis is suspected, it remains a frustrating disease for all food animal clinicians. A presumptive diagnosis is often based on clinical signs and history and rarely confirmed by ancillary tests. If response to therapy is satisfactory, the clinician may never confirm the diagnosis or the precise cause.

Review of the Peritoneal Cavity

Histology.

The peritoneal cavity is lined by a serous membrane composed of two layers called the *peritoneum.* The deeper layer (subserosa) is composed of loose connective tissue containing collagen, fat and, reticular cells, and macrophages. Covering that layer is a single-surface layer of mesothelial squamous cells (serosa). On the surface of the diaphragm, special lymphatic collecting vessels are located under the mesothelial basement membrane. Small stomata are found between mesothelial cells. They act as channels for lymphatic drainage from the peritoneal cavity to the thoracic duct.

Normal Peritoneal Fluid.

The peritoneum acts as a bidirectional semipermeable barrier to the diffusion of

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water and low-molecular-weight solutes between the blood and the peritoneal fluid. Peritoneal dialysis is based on this principle. Normal peritoneal fluid provides lubrication for the movement of abdominal organs and apposed peritoneal surfaces. It is formed and resorbed constantly. Normal fluid movement is achieved by movement of the viscera and contraction of the diaphragm during respiration. A normal animal has no more than 1 mL of peritoneal fluid per kilogram of body weight.[1] In acute severe peritonitis, the inflammatory process may induce a net flow of liters of proteinaceous fluid (80 mL/kg/day in humans), which leads to hypoproteinemia, hypovolemic shock, or both.[2]

Several authors have described normal peritoneal fluid values.[3-10] Each study should be appraised for its strengths and weaknesses and conclusions drawn accordingly. Later, in the diagnostic section, the author shares his personal experience with interpretation of peritoneal fluid in cattle.

Pathophysiologic Mechanism of Diseases in the Peritoneal Cavity in Response to Injury

Healing.

Peritoneal regeneration and healing can occur by reperitonealization or creation of an adhesion with an adjacent nearby mesothelial surface. This adherent type of healing occurs more frequently if the inflammation is severe, with presence of bacteria, foreign material, or both.

Host Defenses Against Peritoneal Infection.

The first mechanism of defense is physical removal of the bacteria. The second mechanism relates to the response to noxious stimuli. This intense acute inflammatory response includes degranulation of peritoneal mast cells with release of vasoactive substances. This creates a net influx of fluid rich in complement and serum opsonins that can bind to the bacteria. Third, the omentum contributes to the defense mechanism by adhering to an area that is infected or damaged, or both, to wall off the problem site. Finally, the rapid movement of neutrophils and later, of macrophages is also an important mechanism of control of infection.

Adhesions.

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Adhesions are fibrinous or fibrous bands that create an abnormal attachment of two or more surfaces that should be moving freely against each other. Formation of adhesions is part of the healing process and should be interpreted as an effort to control an injury. The omentum is often involved in adhesions and acts as a natural sealing device to control the acute phase of inflammation. Whole blood potentiates adhesion formation by providing more fibrinogen. Adhesion may or may not be reversible, depending on the amount of organization that takes place in the process. Adhesions that are cut or broken usually rapidly re-form. As the fibrin deposition process is replaced by capillaries and fibroblasts, the adhesion becomes solid fibrous tissue. The three major elements responsible for dissolution of the fibrinous adhesions are (1) adequate oxygen and nutrient supply for the mesothelium, (2) liberation of plasminogen-activating substance by mesothelial and submesothelial cells, and (3) control of the inflammatory process.[2] Mechanical obstruction to the normal flow of ingesta and subsequent development of bowel obstruction are major undesirable side effects of adhesions.

■ Peritonitis

Definition and Etiology

Peritonitis is an inflammatory process involving the peritoneal cavity and its serosal surface, the peritoneum. Peritonitis is not truly synonymous with intraabdominal infection because the latter is defined as an inflammatory response of the peritoneum to microorganisms and their toxins that results in purulent exudates in the abdominal cavity. Peritonitis should be considered as the localized equivalent of SIRS, whereas intraabdominal infection is the localized equivalent of sepsis. Intraabdominal abscess is an intraabdominal infection confined within the abdominal cavity. Because most often in farm animals peritonitis is caused by bacteria, the two terms are often used as synonyms. The peritoneal inflammation may result from trauma, surgery, or vascular damage associated with an intestinal obstruction or an accident or from gastrointestinal ulceration (Box 32.7). Peritonitis is a serious and complex process that is often accompanied by various degrees of abdominal pain, changes in gastrointestinal motility, progressive signs of hypovolemia and septicemia, and endotoxemia.

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Box 32.7

Causes and Examples of Peritonitis in Approximate Order of Frequency

Traumatic Perforation

Traumatic reticuloperitonitis
Septic abdominal surgery
Vaginal perforation during coitus
Penetrating wound

Visceral Rupture

Perforation of abomasal ulcer
Perforation of ulcer in other part of gastrointestinal tract (oak toxicity of other cause)
Abomasal rupture after torsion
Small intestinal rupture after volvulus, strangulated hernia, or intussusception
Bladder rupture secondary to urolithiasis
Spontaneous uterine rupture during gestation or dystocia

Abscess Formation and Possible Intraabdominal Rupture

Reticuloperitonitis, localized
Liver
Umbilicus
Perimetritis
Pyelonephritis

Iatrogenic

Intraperitoneal injection of irritant solution or contaminated solution

Uterine rupture during dystocia
Perforation of the uterine wall with a pipette
Rectal tear secondary to palpation

Miscellaneous

Hematogenous with systemic infection: tuberculosis, septicemia
Fat necrosis

■ Classification

Peritonitis may be classified according to the clinical presentation, the cause, or both. Clinically relevant classifications include acute versus chronic, septic versus chemical, localized versus generalized, and primary versus secondary. Although classifying types of peritonitis is useful, it is imperative to recognize that it is a dynamic process. An apparently localized nonseptic peritonitis can evolve into a more diffuse septic process if the primary cause is not resolved.

■ Pathophysiology

After peritoneal injury or contamination, mesothelial cells initiate an inflammatory response, modifying the permeability of the peritoneum and its vascular supply. Then several blood constituents move into the peritoneal cavity. Macrophages and polymorphonuclear cells, humoral opsonins, natural antibodies, serum complement, and a protein-rich fluid are the most important. The inflamed peritoneum also becomes more permeable to toxins, allowing them to be absorbed into the bloodstream. Although this initial response is beneficial to the organism, it induces several systemic abnormalities that the clinician must recognize and treat adequately.

Hypovolemia, hypoproteinemia, bacteremia or septicemia, and toxemia are commonly observed in acute diffuse septic peritonitis. The major adverse effects of peritoneal contamination are (1) rapid clearance of bacteria, which leads to the development of endotoxemia, bacteremia, or both; (2) rapid influx of fluid rich in protein, which leads to hypovolemia and hypoproteinemia; (3) deposition of fibrin, which occludes lymphatic drainage and thus contributes to abdominal distention and enhances the chance of abscess formation; (4) ileus; and (5) adhesion formation, which may lead to obstruction.

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■ Clinical Signs and Diagnosis

Clinical signs are often nonspecific but suggestive of gastrointestinal dysfunction. Severity of clinical signs ranges from mild recurrent discomfort caused by a localized abscess to an acute severe onset of toxemia and hypovolemia that lead rapidly to death after the sudden rupture of a viscus. Cattle suffering from acute peritonitis tend to show more characteristic signs. As the condition becomes less acute, the ability of the bovine to seal the infection will attenuate the clinical signs. Chronic but active peritonitis remains to this day a very difficult diagnosis to make without ancillary tests. Abdominal rigidity and tenderness, abdominal distention, scleral injection, fever, anorexia, and sudden reduction in milk production are classic findings but not pathognomonic of acute peritonitis. In the acute stage, abdominal pain and the release of catecholamines often lead to a complete gastrointestinal stasis and ileus. The rumen is then completely atonic. Feces are abnormal in quantity and quality. In the acute stage, feces are present in small amounts and often dry. In more chronic cases, feces are present with a tendency to be diarrheic.

Pain, decreased plasma volume, and endotoxemia often result in persistent tachycardia. Anterior abdominal pain, evaluated by the withers pinch test, may be difficult to interpret. The withers pinch test is based on the normal reflex of the bovine to drop its back when the withers and back are pinched (ventroflexion). Cattle with anterior abdominal pain may be reluctant to ventroflex on withers pinch. The sensitivity of this test can be increased by simultaneous auscultation of the trachea during the manipulation. Production of an expiratory grunt during ventroflexion is considered a sign of pain. Cranial ventral pressure with the fist, knee, or some other external force (transverse pole under the abdomen) just behind the xyphoid process can help identify the presence of pain (expiratory grunt) and even localize it in some cases. The author believes that one of the most reliable clinical signs of abdominal discomfort in cattle is reluctance to move. Scleral injection, fever, tachycardia, gastrointestinal stasis, and distention are the clinical signs that should be monitored to evaluate peritonitis.

■ Ancillary Tests

Hematologic findings associated with peritonitis range from completely normal hemogram results to severe leukopenia with degenerative left shift and presence of toxic neutrophils, depending on the severity of the peritoneal contamination.

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In severe cases, variations observed reflect the degree of sepsis and toxemia. PCV tends to increase as plasma/proteins decrease. In less severe cases, neutrophilic leukocytosis and hyperfibrinogenemia are often present. Hematologic analysis has been a useful tool for monitoring response to therapy. Plasma fibrinogen concentration is also evaluated to monitor the progress of a particular case.

The blood chemistry profile is rarely altered by peritonitis in a way that is diagnostically useful. Chronic inflammation causes a marked increase in serum proteins, particularly the globulin portion. In acute severe cases, secondary findings may include increased serum urea nitrogen and creatinine levels, mildly increased liver enzyme levels, reduction in total CO_2, and strong ion difference and reduction in serum albumin level. Ileus and upper gastrointestinal stasis may result in marked hypochloremia and alkalosis.

In the author's experience, abdominocentesis followed by cytologic examination of the peritoneal fluid is a useful aid in making a definitive diagnosis of peritonitis. The technique is simple and safe. The right side just cranial to the udder is the preferred site (to avoid stomach and omentum; Fig. 32.130). A needle, a blunt teat canula, or a bitch catheter and scalpel blade may be used with success (Fig. 32.131). Because of bulls’ heavy fascia, a needle is preferable. Failure to secure fluid is common and should be interpreted with caution (because fibrinous peritonitis with fluid loculation is common). More than one site should be attempted if no fluid is secured on the first attempt.

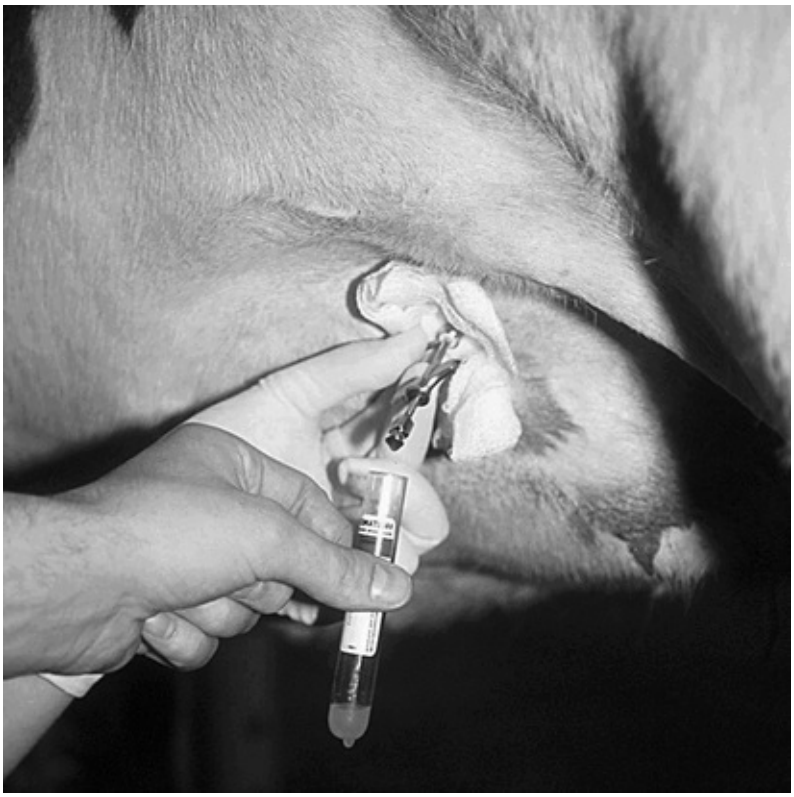


FIG. 32.130 Site of caudal abdominocentesis.

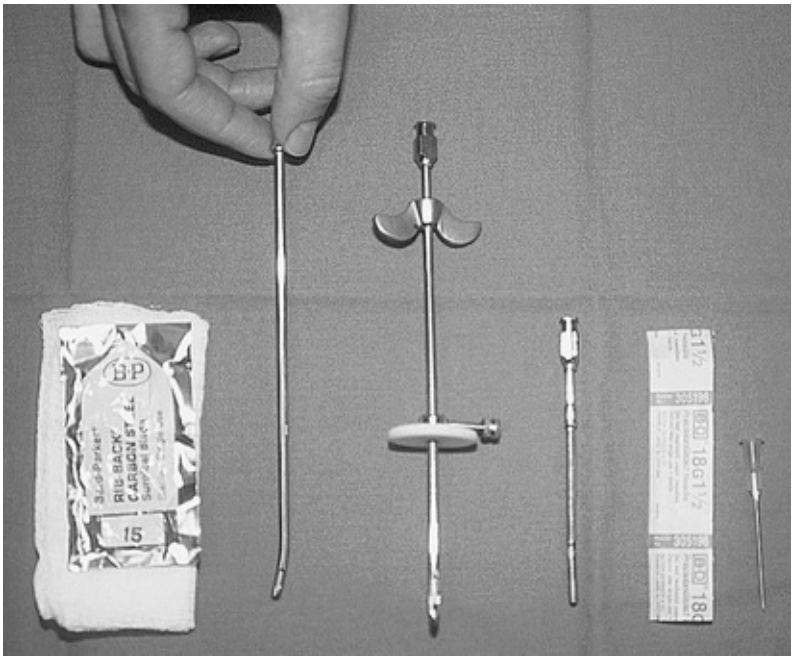


FIG. 32.131 Material used to perform abdominocentesis of bovines.

Interpretation of values and what is considered normal appears difficult when the entire literature is searched.[3-5,11] Some authors have tried to establish better reference values for cattle.[10] Unfortunately, the range seems extremely wide even in the normal cattle population. The authors have been using certain criteria over the years on the basis of some older literature and personal experience: Normal fluid is clear and often in small quantity. Ease in collecting a large amount of fluid should arouse suspicion. A sanguineous fluid leads to suspicion of a compromised bowel problem (e.g., intussusception). A cloudy fluid is more indicative of peritonitis. Any foul smell is enough to conclude that septic peritonitis is occurring. Cytologically, the total number of cells is not as important as the differential. More than 50% neutrophils is suggestive of a septic process. The protein concentration should be less than 30 g/L (publications have moved the cutoff value higher than this number). No bacteria should be visualized. After exploratory celiotomy and omentopexy on normal cattle, peritoneal fluid has increased specific gravity, total protein, and WBCs for at least 6 days, even without any peritonitis.[12] Because of the bovine's ability to deposit fibrin and seal areas of the peritoneal cavity, the interpretation of peritoneal fluid analysis applies only to the immediate area that was sampled. Results of a caudal tap can mislead the clinician into concluding that a nonseptic process is occurring, when in fact a septic process has already been sealed by the fibrin deposition in the cranial abdomen.

Abdominal radiographs obtained with a high-power unit are extremely useful in cases in which TRP is suspected. They have limited value in other causes of peritonitis. Ultrasound examination is useful for assessing the size and anatomic relationships of lesions, particularly when considering drainage, aspiration, or surgical exploration of a mass surrounding vital structures (see Ultrasonography of the Ruminant Abdomen section). Knowledge of the underlying anatomy is important to prevent misinterpretation. Recognition of free abdominal fluid is easily accomplished by ultrasound examination, and it is also useful for guiding a peritoneal tap. Areas that should be scanned include the caudal lower flank area (right and left), right perirenal area, liver, abomasum and pylorus, and right paramedian area. During exploratory surgery, ultrasonography can be used to image an internal mass or a viscera that appears abnormal. Intraoperative ultrasonography is performed by placing the probe in a sterile sleeve filled with ultrasound gel.

Surgical exploration is often used to confirm or rule out an intraabdominal problem. Information obtained from physical examination and laboratory data is

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often indicative of a diagnosis but does not provide a specific cause. Cattle are particularly amenable to exploratory surgery, as the procedure is performed when they are standing and is not often associated with complications. Advances in minimally invasive surgical technique in cattle are promising. Laparoscopy can be used to diagnose acute and chronic peritonitis, which is otherwise difficult to identify with ultrasonography or abdominocentesis. It is easier to evaluate the extent of the lesions with the organs in situ.

■ Treatment

The basic elements of therapy are support, antibiotics, and surgery.

Supportive Therapy.

Depending on the severity of the process, the patient may be in shock. Large volumes of isotonic intravenous fluids and correction of any acid-base deficit are indicated. Electrolyte abnormalities (hypokalemia and hypocalcemia) should be identified and corrected. If the animal is hypoproteinemic, plasma or whole blood transfusions may be beneficial. NSAIDs or steroidal antiinflammatory drugs, or both, may be of importance to prevent the synthesis of more inflammatory mediators. Pain control is also important. Transfaunation with normal rumen fluid may be beneficial in cases of prolonged anorexia.

Antibiotic Therapy.

Systemic antibiotic therapy should be instituted as soon as a decision to treat is made. Until results of culture and antimicrobial susceptibility become available, a broad-spectrum antibiotic should be used. The choice should take into consideration the following: cost of treatment, permitted use and withdrawal periods in food animals, spectrum of activity, and treatment regimen (frequency and route). Tetracycline or a β-lactam antibiotic (third-generation cephalosporin or a synthetic penicillin) appears to be a good choice. Diffusion into the peritoneal cavity is not a major limiting factor because the permeability of the peritoneum is always increased in peritonitis. However, when fibrin becomes organized and forms multiple small pockets of infected peritoneal fluid, diffusion becomes more problematic. Duration of therapy is empirical in bovines. The author and colleagues normally recommend at least 1 week of intravenous therapy, followed by another week of intramuscular therapy. Some clients elect to have their animals undergo the 2 weeks of therapy in the author's hospital, and the animals are maintained on intravenous antimicrobials.

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Surgical Therapy.

Surgical control of peritonitis includes peritoneal débridement, irrigation, and drainage. With ultrasound guidance, it is possible to safely establish drainage from the abdominal cavity. A thoracic chest trocar can be used temporarily until all fluid has been removed.

The concept of abdominal lavage during surgery was adopted by human surgeons at the beginning of the twentieth century, and it has been accepted as a part of the treatment of peritonitis since then with fluctuating support.[13] Although the principle of removal of any gross contamination is not in question, the level of aggression with which clinicians should institute abdominal lavage during surgery is still open to debate in human and veterinary literature. There is evidence of a negative effect of lavage on the mesothelial cells, the peritoneal defense mechanisms, and the risk of spreading the infection.[13] The solution used to irrigate is also under debate. There is no significant advantage to adding antibiotics to the lavage solution, and controversy exists regarding the possible advantages of adding an antiseptic.[13] In bovines, large amounts of fibrin may be deposited in a short period of time; in combination with the omentum, this makes drains plug and become rapidly ineffective.

■ Prognosis

The ultimate outcome of a bacterial peritonitis episode is determined by many factors, some of which are controlled by the clinician. The early decision on treatment (medical and surgical), correct choice of antimicrobials, and adequate supportive therapy contribute to the success or failure of a therapy. The owner's delay in seeking therapy, the primary cause of peritonitis, and the patient's age are important factors beyond the clinician's control. When aggressive therapy is economically possible, survival rates are good, but long-term sequelae may compromise a complete recovery.

Miscellaneous Peritoneal Conditions

Ascites.

Ascites is a collection of serous fluid in the peritoneal cavity. It must be considered a secondary sign rather than a primary diagnosis. In that regard the primary cause must be identified in order to treat the patient adequately. Common causes of ascites in ruminants include severe liver disease and

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congestive right-sided heart failure. Young cattle with mesothelioma have remarkable ascites. Ascites remains an uncommon condition that needs to be differentiated from septic causes of peritonitis and from urine accumulation with ruptured bladder.

Pneumoperitoneum.

Pneumoperitoneum is commonly observed postsurgically in the bovine. Presence of air in the abdomen can be recognized by simultaneous percussion and auscultation. A low-pitch resonance can be auscultated in the upper flank on both sides of the abdomen. Presence of pneumoperitoneum normally resolves in the week after surgery. No clinical signs seem associated with the presence of pneumoperitoneum, although some clinicians describe abdominal pain associated with no cause other than the presence of air in the peritoneal cavity. Pneumoperitoneum not associated with surgery is indicative of bacterial peritonitis and the presence of gas-producing bacteria (see Box 32.7).

Retroperitoneal Abscess.

Retroperitoneal abscess is a particular condition occurring in cattle after a flank laparotomy. It develops in many affected animals several days after surgery. They are mildly febrile, not performing adequately, and showing clinical signs compatible with peritonitis. The skin wound is often unremarkable, but some pain may be elicited while the flank area is palpated. A substantial mass may be palpated rectally, localized in the upper quadrant of the side of the previous surgical approach. The mass is firm, smooth, unmovable, and close to the previous flank incision and may have adhesions attached to it. Transabdominal or rectal ultrasound examination reveals a large amount of fluid located between the peritoneum and the rectus abdominis or the internal oblique of the abdomen. More superficial abscesses can also occur. A needle aspiration allows visual inspection of a thick, opaque, foul-smelling fluid. Treatment is aimed at establishing drainage and systemic antimicrobial therapy. A large volume of purulent and fibrinous material (up to 40 L) can be removed from the abscess. Rapid decompression may provoke hypovolemic shock, and intravenous fluids should be administered before a large abscess is drained. Prognosis is good, but the recovery phase is extremely long because of the large cavity left after drainage. Early closure of the drain is often observed, necessitating reopening. Some clinicians effectively use Penrose drains as they close a contaminated flank wound, to prevent serum accumulation in the wound, and stave off the

development of an abscess.

Traumatic Reticuloperitonitis (Hardware Disease, Traumatic Reticulitis)

David Francoz

Definition and Epidemiology

TRP, or hardware disease, is a frequent disease of cattle but it is rarely diagnosed in small ruminants. It is considered the most common cause of anterior abdominal pain in cattle. The ingestive behavior of cattle allows sharp nonfood items to be prehended and swallowed. Ingestion of such items by sheep or goats is rare. The disease affects confined cattle where mechanical processing of forages or construction activities increases the chances that piece of wire or nails will be included in the feed.

Few data available are on the frequency of TRP in cattle. In one study in Denmark, data were collected on 222,490 cows from 5979 herds. TRP was presumptively diagnosed by veterinarian in 1621 (0.7%) cows in the year before slaughter and in 1521 (0.7%) cows at slaughter. However, in only 48 of these 1521 cows had TRP been diagnosed by a veterinarian premortem.[1] Gröhn and Bruss[2] reported a similar prevalence (0.6%) of TRP veterinary diagnosis in live dairy cattle in 1990. Data from England and Wales indicated that 141 of 2709 adult cattle carcasses submitted to the Veterinary Laboratories Agency from January 2004 to May 2008 had a diagnosis of TRP.[3] In western Canada, TRP was the most frequent postmortem findings (8%) in beef cows and replacement heifers.[4] Most cases are sporadic, but outbreaks have occurred when such things as multistranded cable have been chopped up by a forage harvester and ensiled or when cattle have chewed nails containing charcoal from burned buildings.

Etiology and Pathophysiology

The ingestive behavior of cattle predisposes them to the accidental swallowing of metal foreign objects. Ingestion of a foreign body may also be associated with diseases that cause pica, such as phosphorus deficiency.[5] Foreign bodies of high specific gravity initially settle to the bottom of the ventral sac of the rumen. Subsequent contraction cycles of the forestomach move those objects from the rumen into the reticulum. Subsequently, depending on the presence of a magnet,

four things can happen to a sharp foreign body[6]: (1) It may attach to the magnet without any clinical disease; (2) it can penetrate the reticular wall only with intramural inflammation; (3) it can perforate the reticulum wall, penetrate into the peritoneal cavity, and create a localized septic peritonitis; or (4) it can migrate into the peritoneal and thoracic/pericardium cavities. The diaphragm, pericardium, and heart muscle are located just cranial to the reticulum, with the liver positioned medially and dorsally and the spleen laterally and dorsally. These organs are sometimes penetrated by foreign bodies and become involved in the inflammatory and infectious process. The pain and inflammation associated with the trauma and infection lead to decreased appetite and ruminal hypomotility or stasis. Agalactia is abrupt because of the acute anorexia and subsequent failure to absorb precursors for milk synthesis.

Rehage and colleagues[7] suggested that the motility disturbances of ingesta through the forestomachs and the abomasum in cows affected with TRP develop in three phases. The first one, characterized by poorly comminuted feces, occurs after reduce or arrest of the reticulum contractions caused by pain and inflammatory adhesions. With extension of the adhesions, additional impairment of reticulum motility develops. In this second phase, stratification of the food particles in the reticulorumen is lost, volume of these two forestomachs is increased, and ruminal outflow is reduced. In the third phase, the consistency of ruminal contents is changed and becomes pasty with high viscosity. Increase in viscosity of ruminal content leads to inhibition of the transpyloric outflow. Abomasal volume increases and internal vomiting occurs.

Clinical Signs and Differential Diagnosis

TRP in the most severe, acute form is characterized by fever, anorexia, decrease in or absence of ruminal contractions, and evidence of cranial abdominal pain. Pinching of the withers or upward pressure on the xyphoid region may elicit a grunt on expiration. Affected cattle may stand with an arched back and resist ventral flexion of the back when pinched over the withers (normal cattle flex ventrally). Some cattle grunt spontaneously when forced to move or when defecating or urinating. Lactating cows show a sudden decrease in milk production. Some cows regurgitate ruminal fluid, especially if the oropharynx is mechanically stimulated. Tachycardia, reluctance to move or lie down, mild bloat, constipation, or abducted elbows may also be observed. These typical signs often abate within the first day or two, making diagnosis more difficult as

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the disease progress. Sudden death has occurred as a result of the laceration of a coronary blood vessel or puncture of the heart by the foreign body.

Less severe or more long-standing cases show clinical signs that are more subtle and less specific. Cows in early lactation may have ketosis; however, a distinguishing feature of TRP is the abrupt onset of anorexia and hypogalactia. Fever may be absent or very mild. Weight loss, rough hair coat, diarrhea, or generalized lameness, along with cranial abdominal pain that is difficult to localize, may be the only clinical signs.

If the pericardial sac has been seeded with bacteria, pericarditis usually develops. Clinical signs of pericarditis are discussed in detail in Chapter 30. In addition to the clinical signs previously described for TRP (decreased appetite, fever, tachycardia, pain), muffled heart sounds, jugular vein distention, and edema of the submandibular region, brisket, and ventral abdomen are typically observed.[8]

The foreign body may penetrate the liver or spleen, which leads to abscess formation. These abscesses, as well as reticular adhesions, may be responsible for reticuloomasal outflow problems and may lead to chronic indigestion.[7] TRP is a leading cause of chronic indigestion, more specifically of type 2 chronic indigestion (i.e., failure of omasal transport).

Agreement between premortem and postmortem diagnosis of TRP has been reported to be low, which can be explained by the low specificity of the clinical signs associated with TRP.[1] TRP must be differentiated from other causes of cranial abdominal pain. They include localized peritonitis associated with abomasal ulcers or liver abscesses, pleuritis, and pericarditis. In one study, cows with a premortem diagnosis of TRP not confirmed during postmortem examination were more likely to have one of the previously listed diseases detected post mortem.[1] More information regarding the differential diagnosis of abdominal pain is presented in the section on acute abdomen in cattle. When thoracic structures are involved, TRP must be differentiated from pneumonia or pleuritis, diaphragmatic hernia, and heart diseases such as endocarditis, lymphosarcoma of the heart, and cor pulmonale. Finally, TRP must be differentiated from others causes of ruminal distention and chronic indigestion.

Ancillary Tests

Complete Blood Cell Count.

The WBC count and differential may indicate an acute or chronic inflammatory process depending on the stage of the TRP. Neutropenia and a left shift are expected in acute cases. However, in more chronic cases, changes are less pronounced, and both the WBC count and differential may return to normal,[6] but modification associated with chronic inflammatory diseases such as erythrocytopenia, thrombocytopenia, and hypohemoglobinemia may also be noted.[9,10] Gokce and colleagues[9] also reported longer activated partial thromboplastin time, prothrombin time, and thrombin time in cattle affected by TRP than in a control group of healthy cattle.

Plasma Proteins and Acute-Phase Proteins.

High total plasma proteins, primarily reflecting high globulin levels, are expected in chronic cases of TRP.[9,11] Higher concentrations of total plasma proteins has been observed in cases of TRP than in other abdominal disorders.[12,13] Plasma proteins concentration of 87 g/L[12] and 100 g/L[13] have been proposed for the differentiation between TRP and other abdominal disorders.

Elevated fibrinogen concentration may be observed in acute (2 to 3 days after the beginning of the disease) and chronic cases. A significant increase in fibrinogen concentration has been reported in comparison to healthy control cows.[14] In addition, studies in referral centers have demonstrated highest plasma fibrinogen concentration compared with other abdominal disorders.[12,13,15] Cutoff points have also been reported in these studies for the differentiation between TRP and other abdominal disorders. Jafarzadeh and colleagues[13] proposed a value of 6.91 g/L (with a sensitivity and specificity of 81% and 72%, respectively), whereas Nazifi and colleagues[15] suggested a value of 5.7 g/L (with a sensitivity and specificity of 32% and 100%, respectively).

Serum amyloid A and haptoglobin concentrations have also been reported to be elevated in case of TRP.[12,14-16] Cutoff points for the differentiation between TRP and other gastrointestinal disorders of 0.67 g/L[12] and 0.74 g/L[15] for haptoglobin and 68 µg/mL[15] for serum amyloid A have been reported. These two parameters seem to be more accurate than plasma fibrinogen or protein concentrations for the differentiation between TRP and other gastrointestinal disorders.[12,15] However, in one study, a nonsignificant increase of serum amyloid A was observed in cases of TRP in comparison to healthy control

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cows.[14] Of importance is that other inflammatory disorders can induce the same modifications, and absence of these abnormalities does not rule out TRP. Other diagnostic tests thus must be performed to confirm the diagnosis

Serum Biochemistry Profiles and Blood Gas Analysis.

Serum biochemistry profiles and findings of blood gas analysis are usually within normal range but may reflect anomalies associated with ileus and chronic indigestion, such as hypochloremic metabolic alkalosis, hypokalemia, and hypocalcemia.[10,11] Other abnormalities reported include increases in specific and nonspecific indicators of liver damage (such as aspartate aminotransferase, ALP, lactate dehydrogenase, and bilirubin),[6,9,10] and increases in specific and nonspecific indicators of skeletal or cardiac muscles (such as CK [CK-MB], lactate dehydrogenase, aspartate aminotransferase, and cardiac troponin).[9-11]

Diagnostic Imaging.

Ultrasonography and radiography are complementary methods that provide different and useful information for the diagnosis and management of TRP. Radiography of the reticulum is available only in centers where powerful equipment is available. Different techniques have been described for radiography of the reticulum. They can be performed on recumbent or standing animals; lateral radiographic views of the reticulum on standing animals are the recommended methods. Radiographs allow the detection of a metallic foreign body and the determination of its location in or outside the reticulum. They can also be useful in order to assess the success of magnet administration. Different parameters criteria may be evaluated on radiographs for the diagnosis of TPR. They include presence or absence of a foreign body, position of the foreign body, presence of focal gas shadows or gas-fluid interface near the reticulum, and the shape, size, and location of the reticulum (Fig. 32.132).[17-19] Of these parameters, location of the foreign body is the most reliable indicator for the diagnosis of TRP.[12,14]

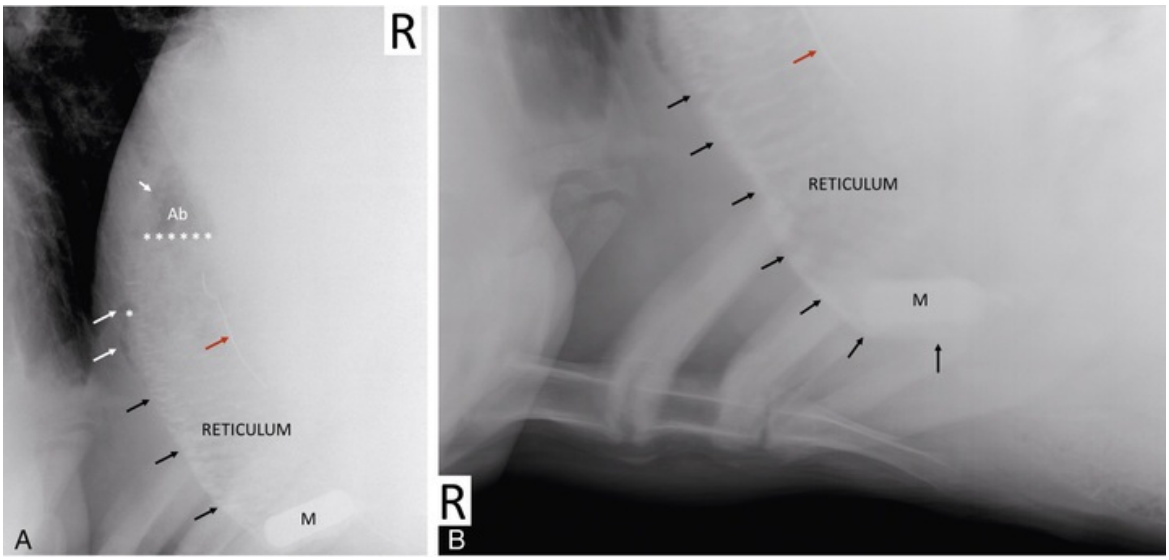


FIG. 32.132 Radiographs of the reticulum of a cow with traumatic reticuloperitonitis. Two lateral views were obtained: a craniodorsal view **(A)** and a caudoventral view **(B).** The reticulum is displaced dorsally and cranially. Its contour *(black arrows)* is irregular. Multiple gas bubbles *(white arrows)* are observed, and fluid lines *(white asterisks)* are also visible. Those observations are compatible with septic peritonitis and possible abscesses formation (*Ab,* large abscess). A linear foreign body *(red arrow)* is visible in the two views but most easily evaluated on the craniodorsal view. This foreign body is not attached to the magnet (M). (Courtesy Centre Hospitalier Universitaire Vétérinaire de l'Université de Montréal.)

Ultrasonography of the reticulum is presented elsewhere in the Diagnositic Imaging subsection of the Acute Abdomen section in this chapter. Ultrasonography provides information about the localization and extension of peritoneal effusion, the presence of perireticular abcesses, and the contraction of the reticulum.[20] Ultrasonography is also the most useful complementary examination for the diagnosis of pericardial effusion.[7]

Abdominocentesis.

Abdominocentesis and pericardiocentesis may be performed blindly or with ultrasound guidance. Abdominal fluid analysis and its limitations in cattle are discussed in the Peritonitis in Ruminants section. Pericardiocentesis may be performed at the level of the point of the elbow in the left fifth intercostal space. Aseptic preparation of the skin and local anesthesia of the region to be punctured are required; pulling the left forelimb forward may be helpful. A 5- to 10-cm spinal needle or intravenous catheter can be used; the length required depends on the size of the animal and the amount of subcutaneous fat. Previous

ultrasonographic examination is helpful for the choice of the needle. Caution is advised for advancing the needle to prevent laceration of the myocardium or of a coronary vessel. Ultrasonographic guidance helps prevent trauma to the myocardium. Visual inspection of the fluid obtained is usually adequate to confirm the diagnosis of pericarditis; in case of septic traumatic pericarditis it is cloudy and foul smelling. The fluid may be examined bacteriologically and cytologically.

Treatment

Conservative medical treatment is generally attempted first. It is based on the administration of a magnet for attachment of the foreign body, parenteral antibiotic therapy for the control of infection, administration of NSAIDs for the control of pain and inflammation, and the correction of dehydration and electrolytes imbalances when present. Different drugs have been used to enhance the chance of the magnet to enter the reticulum cavity. The effects of premedication with atropine, scopolamine, or xylazine and the practice of standing the cow with its forelimbs 30 cm lower than its hindlimbs on successful administration of a magnet (i.e., adequately located in the reticulum cavity) have been evaluated in healthy cows.[21] Adequate location of the magnet was controlled radiographically 1.5 hours after the administration of the magnet. None of the procedures increased the chance of the magnet's being successfully located in the reticulum. In all groups (treatment groups and control groups), only 57% of the magnets were adequately located in the reticulum.[21] In one study, Braun and coworkers evaluated radiographically the efficacy of magnet administration for the treatment of TRP.[22] They demonstrated that foreign bodies that have already penetrated the reticulum wall or that have clearly perforated the reticulum before magnet administration had approximately a 54% and 32% chance, respectively, of becoming attached to the magnet.

Treatment of peritonitis requires systemic antibiotic therapy and possibly drainage of the affected area; surgical correction of the inciting cause is discussed in the Peritonitis section in this chapter. Forestomach bacteria are involved the in acute phases, and *T. pyogenes* and anaerobic bacteria in chronic cases when perireticular abscesses are present. NSAIDs are the drugs of choice for the control of inflammation and pain. However, the risks associated with their side effects, abomasal ulcerations and renal toxicity, should be evaluated in case of anorexic and dehydrated animals. Multimodal approaches such as the

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combination of NSAIDs and opioids or continuous infusion of analgesics should also be considered for pain management.[23] Institution of fluid therapy is necessary in cases of diffuse peritonitis and associated hypovolemic shock, as well as for the correction of electrolytes imbalances associated with ileus or indigestion. Physiologic salines (0.9%) containing potassium and calcium are the solutions of choice.

Many cattle recover after such a course of medical therapy with resumption of forestomach motility and appetite within 1 to 3 days. Appetite and rumination activity monitoring is also useful for an objective assessment of the response to treatment. These parameters have been reported to normalize within 3 to 5 days after the initiation of medical treatment or rumenotomy.[24] Animals that have not significantly improved by the third day may require a rumenotomy to remove the foreign object. Ideally, radiography combined with ultrasonography is recommended at this time to verify the diagnosis and objectively assess the response to treatment,[22] but ultrasonography is more feasible in most practices. During rumenotomy, abscesses that adhere tightly to the reticulum may be drained into the lumen of the reticulum. In some instances, reticular abscesses may also be drained through an ultrasonography-guided transcutaneous incision,[25] ultrasonography-guided insertion of a chest trocar, or insertion of a trocar during ventral laparotomy.[6]

Prognosis

The prognosis of TRP depends mainly on the location of the foreign body and the other organs affected. The prognosis is fair to good when TRP is associated with localized peritonitis and when only the spleen or the liver is also affected. The prognosis is poor to guarded in TRP associated with pericarditis, pleuritis, or diffuse inflammatory adhesions in the abdomen.[6,7,26] In most cases, as inflammation diminishes, the reticular function can return to normal.[26] In a multicenter retrospective study on rumenotomy and rumenostomy, data on long-term outcome (5 months to 5 years after the procedure) were available for 23 bovines that underwent rumenotomy for TRP: Six bovines (26%) were still in the herd and productive, 9 (39%) were removed from the herd, and 8 (35%) died or were euthanized.[27]

Necropsy Findings

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Cattle that die peracutely may have a lacerated myocardium with resulting hemorrhage or cardiac tamponade. Diffuse peritonitis characterized by copious, foul-smelling peritoneal fluid with an obvious reticular defect may be present in acute cases. More chronically affected animals may have extensive pericardial effusion with a thick epicardial layer of fibrin if the pericardium was penetrated. Localized peritonitis with adhesions alone is unlikely to kill the animal. The penetrating foreign body generally is still present in the wall of the reticulum or pericardium.

Prevention and Control

Eliminating sources of sharp foreign objects in the feed supply prevents TRP. Installation of large magnets on feed handling equipment and prophylactic administration of forestomach magnets to all animals at 15 to 16 months of age prevent almost all cases caused by magnetizable objects.

Abomasal Displacement and Volvulus

Gilles Fecteau • Charles L. Guard

■ Etiology

Although the precise cause of displacement of the abomasum remains unknown, general agreement exists in veterinary literature that it is a multifactorial syndrome and that abomasal hypomotility is an absolute prerequisite. Abomasal motility can be decreased in many ways. Numerous common disorders of postpartum dairy cattle have been incriminated as possible triggering events to abomasal dilation and displacement. Among the most important, ketosis, low serum calcium levels, hyperinsulinemia, and reduced insulin sensitivity have been studied.

■ Prevalence and Incidence

Abomasal displacement occurs either to the right or to the left side of the abdomen when gas accumulates within this viscus. Left-displaced abomasum (LDA) is the more common, accounting for most of the cases. The incidence is highest by far in adult dairy cattle in the early postpartum period, but cases have been seen in all other classes of cattle. LDA is probably a worldwide problem. The prevalence among dairy herds is variable, depending on multiple factors

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such as geographic location, climate, management practices (confinement versus pasture), and feeding practices.

■ Pathophysiology

After abomasal atony, distention with gas produced by microbial fermentation occurs and probably precipitates the displacement. It has been hypothesized that the displacement is oriented (left or right) according to the size of the rumen. If the rumen is small and empty (as in the early postpartum period), the abomasum can move to the left, and LDA can occur (Fig. 32.133). If the rumen is large and filled, the left displacement is less likely, and the abomasum dilates and in some cases twists to the right (Figs. 32.134 and 32.135).

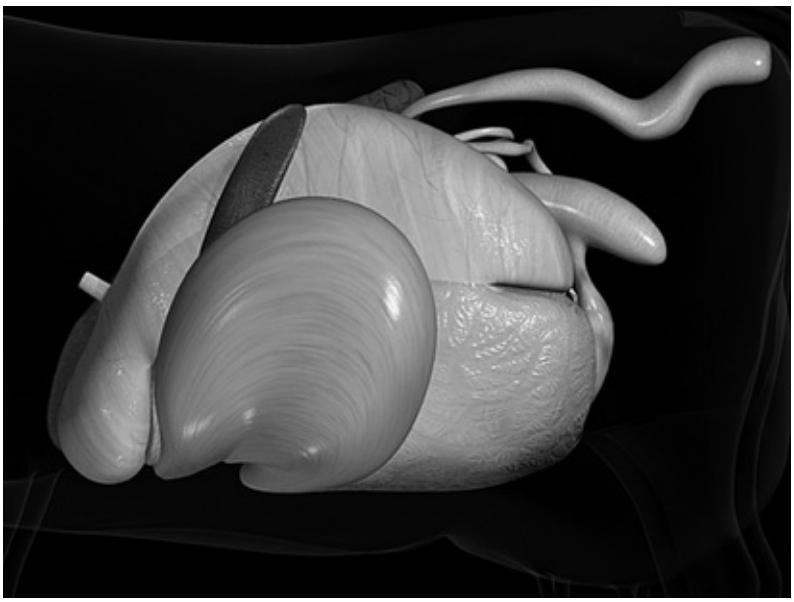


FIG. 32.133 Schematic view of a left-displaced abomasum. (Courtesy André Desrochers, from *Surgery of the abomasum in cattle, Version 2.0*, Université de Montréal.)

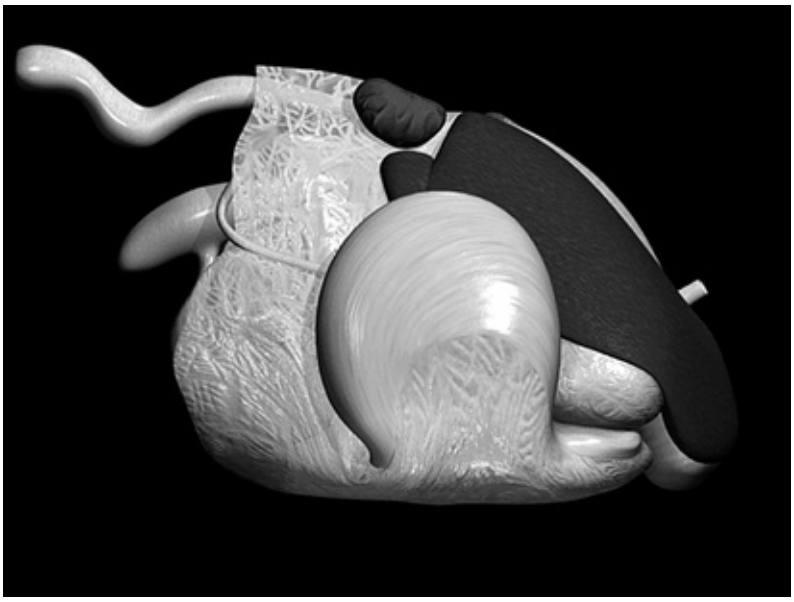


FIG. 32.134 Schematic view of a right-dilated abomasum. (Courtesy André Desrochers, from *Surgery of the abomasum in cattle, Version 2.0*, Université de Montréal.)

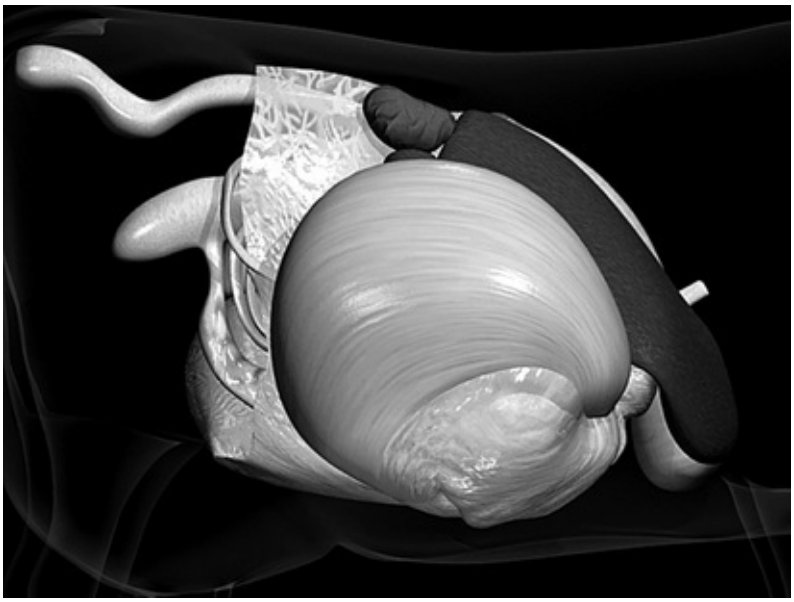


FIG. 32.135 Schematic view of an abomasal volvulus *(AV).* (Courtesy André Desrochers, from *Surgery of the abomasum in cattle, Version 2.0*, Université de Montréal.)

■ Surgical Therapy

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Numerous surgical techniques exist with advantages and disadvantages.[7] All techniques have a common objective to create a permanent attachment, usually by suturing either the abomasum or the greater omentum to the abdominal wall. This prevents recurrence. The techniques may be classified into three different broad categories: blind technique, surgical (open) technique, and laparoscopic technique. Another way to consider the different options is to classify the techniques as performed on an animal standing or in recumbency. Multiple factors influence the technique used or recommended for a particular case. Cost and preference of the surgeon are very important. Laparoscopic technique has also been described and studied.[8-11]

All techniques have been successful when performed adequately. The less invasive techniques have been studied to evaluate the possible advantages over the more invasive open techniques. The advantages are time to perform the surgery, less frequent use of antimicrobials, a shorter interval from calving to first service, and a faster abomasal emptying.[12-15] Understanding the limitations of each technique allows the clinician to best serve the patient and client in all situations. Success rates and possible economic advantages of having the procedure performed by herd personnel have been discussed in the literature.[16,17]

■ Left Displacement of the Abomasum

Clinical Signs and Differential Diagnosis

Cattle with simple LDA have a reduced appetite (complete anorexia, reduced consumption of concentrates, or alternating periods of normal appetite and anorexia). Milk production is reduced. Ketosis is usually present, either as a predisposing factor or as a consequence. Feces are often normal to softer than normal but reduced in volume. Rectal temperature is normal, unless a concurrent infectious problem is present (metritis, mastitis). Pulse and respiration rates are normal or slightly above normal, unless a concurrent or secondary problem is present. Ruminal contractions are decreased to absent and difficult to hear because the abomasum interferes with transmission of the sound. It is not unusual to observe the animal ruminating despite the displaced abomasum. The last one or two ribs on the left are sprung, but the abdomen is sunken in the paralumbar fossa. Gurgling or tinkling rather than normal scratching sounds may be heard on auscultation in the left paralumbar fossa. Simultaneous auscultation and percussion reveal a ping over the gas-filled portion of the abomasum. With

LDA the area of ping may be anywhere from the lower third of the abdomen in the eighth intercostal space to the paralumbar fossa (see Chapter 1, Physical Examination section). Attention should also be given to the cranial and lower aspect of the flank because in some cases the ping will be audible only in this area. On rare occasions, during rectal examination the clinician may be able to palpate the abomasum to the left of the caudodorsal blind sac of the rumen or at least perceive that the rumen is displaced medially.

Ruminal tympany, pneumoperitoneum, and collapsed rumen may all produce pings on the left side of the cow. Physometra (air in the uterus) and dilation and displacement of the cecum to the left of the rumen (which is rare) may also produce left-sided pings. Having an assistant blow on the stomach tube passed into the rumen while auscultating over the left side helps the clinician differentiate the rumen from other structures. Percutaneous needle aspiration of fluid or gas from the suspected abomasum aids in correct identification. A pH of less than 4.5 as determined with wide-range pH paper or the odor of abomasal gas (slightly acrid or of burned almonds) confirms the presence of LDA. Ultrasound examination could also be helpful in determining the position of the pylorus and to compare the position with the actual normal variation.[18]

■ Clinical Pathology

The most important abnormalities detected by clinical chemical evaluation usually involve the serum electrolyte levels, acid-base levels, and liver metabolism and integrity. Sequestration of the hydrochloric acid secreted into the abomasum or by means of reflux in the ruminoreticulum may occur and lead to metabolic alkalosis. The blood pH and bicarbonate concentration are slightly elevated, with a concomitant small decrease in the blood chloride concentration. Ketosis is common, and liver enzyme levels are often elevated, reflecting a degree of hepatic lipidosis.[6,19,20] The serum calcium level may be below normal as a result of decreased intake and absorption. Hypokalemia may develop as a consequence of both the metabolic alkalosis and reduced intake and absorption. Cattle with LDA tend to be hypophosphatemic.[21]

CBC analysis may reveal a mild dehydration and a stress leukogram. If LDA is combined with bleeding abomasal ulcers, it may produce severe anemia. The presence of a concurrent disease may lead to specific changes (e.g., left shift with acute coliform mastitis). The peritoneal fluid of cows with abomasal displacement reveals changes compatible with ischemia and inflammation.[22]

■ Epidemiology

Cows in early lactation (particularly the first month) are at greatest risk of developing LDA. The overall incidence is highly variable among herds and related to nutrition program and associated problems. Retained placenta, metritis, and increased serum concentration of β-hydroxybutyrate were associated with a greater risk for LDA.[3] Cows identified with subclinical ketosis early in lactation (3 to 5 days in milk) were 6.1 times more likely to develop an abomasal displacement than were cows affected later in lactation.[1] A serum β-hydroxybutyrate concentration above 1200 µmol/L in the first week after calving were associated with an increased risks of subsequent abomasal displacement (odds ratio, 2.6).[2] On a herd basis, in one study in Sweden, large herd size, high maximum daily milk yield, keeping dry cows in one group, and not cleaning the feeding platform daily appear to be risk factors associated with a high incidence of abomasal displacement or clinical ketosis.[23] The same research group also demonstrated that high-incidence herds have a lower metabolic index and a higher incidence of ketosis than do low-incidence herds.[5] The metabolic index used was the revised Quantitative Insulin Sensitivity Check Index (RQUICKI). Genetic factors may also play a role in the predisposition to LDA. Fox suggested that body depth had increased in dairy cattle since 1945 and that this may provide more room for the relatively empty abdominal viscera to move more freely at parturition.[24] More recently, cows selected for large body size had significantly greater health costs, related mostly to the greater incidence of LDA.[25] Also, the depth of the abdomen and the vertical distance between the ventral abdomen and the descending duodenum were greater in cows with a previous history of LDA than in the controls.[26] Some evidence exists to support a genetic basis for predisposition to LDA, and perhaps this is mediated through body size or conformation.

■ Treatment and Prognosis

Treatment of LDA involves returning the abomasum to its normal anatomic location and preventing recurrence (abomasopexy); treating the electrolyte and acid-base abnormalities and the energy metabolism problems (ketosis and hepatic lipidosis); and providing therapy for concurrent diseases. The prognosis for animals with LDA is good but is influenced by the severity of the concurrent disease. Cattle with severe hepatic lipidosis and LDA should be given a guarded

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prognosis because their recovery is often slow and incomplete. Also, some cattle develop LDA as a consequence of gastrointestinal malfunction. As an example, LDA could be diagnosed in an animal suffering chronic indigestion. The prognosis of this group of cattle is poor because the primary disease is often more serious than the LDA per se.

■ Prevention and Control

The incidence of LDA has been reduced in problem herds by dietary manipulation that reduces the likelihood of forestomach and abomasal atony caused by high-concentrate rations. This includes slow introduction of concentrates after calving, prepartum introduction of ensiled and concentrate feeds, and increase in the particle size of the forage. Maintaining serum calcium concentration at the time of parturition and reducing subclinical ketosis early in lactation are of particular importance. Dietary cation-anion difference is a reliable guideline for controlling hypocalcemia in dairy cows (see Chapter 41).

Right Displacement of the Abomasum

Simple right displacement of the abomasum (RDA) occurs at approximately 10% to 15% the frequency of LDA.

■ Clinical Signs and Differential Diagnosis

The general systemic state of cows with a simple RDA is the same as that of cows with LDA. On the other hand, as simple RDA evolves toward the volvulus, the systemic changes observed in cattle with abomasal volvulus progressively appear. An area of tympanitic resonance is heard on the right side with simultaneous auscultation and percussion. The ping usually is confined to an area under the last five ribs in the upper half of the abdomen. The condition must be differentiated from other causes of right-sided pings, such as cecal distention (with or without volvulus), gas in the spiral colon, pneumorectum after rectal examination, pneumoperitoneum, physometra (gas in the uterus), signoid flexure volvulus, and abomasal volvulus. Cecal and rectal pings usually are detectable in a linear pattern just below the transverse processes of the lumbar vertebrae extending to the tuber coxae (see Chapter 1, Physical Examination section). Rectal examination identifies the gas-filled structure. Pings heard with gas in the spiral colon typically have a variable pitch, depending on the location over the cranial paralumbar fossa and last three or four ribs. In general, the spiral colon

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may be palpated rectally as a laterally flattened, mildly distended viscus adjacent to the right body wall. Gas in the uterus can be detected on rectal palpation. Pneumoperitoneum creates a ping that is distributed all along the dorsal portion of the abdominal cavity and is usually heard on both sides.

Abomasal volvulus is the condition most difficult to differentiate from RDA. Determination of the difference by physical diagnosis in an early case of abomasal volvulus is probably impossible. With time affected cows become progressively more dehydrated and more severely ill with volvulus than is usual with RDA. Rapid heart rate (>100 beats/min), total absence of ruminal motility, and almost no fecal output are clinical signs in favor of a diagnosis of abomasal volvulus. Advanced cases of volvulus also produce a ping that reflects an arched dorsal border and a horizontal ventral border caused by the fluid level in the abomasum. This fluid is auscultable on succussion of the abomasum. Even with ultrasonography in one study to determine positions of the liver, omasum, and small and large intestines, the two conditions could not be distinguished from one another.[27]

■ Treatment and Prognosis

Surgical treatment is necessary to correct RDA. Because of the difficulty of differentiating RDA from early volvulus, intervention should be as prompt as possible. The prognosis for a successful recovery after surgery is comparable with that for LDA if no other concurrent disease is present.

Abomasal Volvulus

Abomasal volvulus, or right torsion of the abomasum, leads to complete obstruction of the flow of ingesta into the duodenum and is therefore a surgical emergency. The condition occurs in all classes of cattle. Although RDA is thought to precede its development, unknown factors lead to abomasal volvulus.

■ Clinical Signs and Differential Diagnosis

The systemic effects of the gastrointestinal obstruction that results from abomasal volvulus progress to a much more severe degree than in LDA or RDA. Sunken eyes and loss of skin turgor accompany the dehydration that develops. The heart rate increases above 100 beats/min, and the pulse is weak and thready. Abdominal distention is marked bilaterally. Complete ruminal stasis develops, which leads to bloat, and the abomasum greatly enlarges on the right. Despite the

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severe degree of gastric distention, colic rarely develops in cattle with abomasal volvulus; it is much more likely to occur with cecal distention. The skin is cool to the touch. Feces are absent or watery but scant. A large area of tympanitic resonance with uniform pitch throughout is detectable on the right, extending from the eighth rib to the middle of the paralumbar fossa. The ventral border of the ping is a horizontal line reflecting the fluid level in the greatly distended abomasum. Borborygmi is absent. Splashing fluid sounds can be heard when the abomasum is ballotted (succussed) behind the last rib.

Other causes of proximal intestinal obstruction and torsion of the intestinal mass around the root of the mesentery must be differentiated from abomasal volvulus. On rectal examination the abomasum can usually be palpated with abomasal volvulus. With intestinal obstruction or intestinal volvulus, distended loops of small intestine can be palpated. Pings caused by gas in the intestines have a variable pitch over the areas involved. Cecal distention with rotation can produce a similar degree of abdominal distention high on the right, but the abdomen usually is less filled cranioventrally on the right. A ping extends to the tuber coxae, and the cecum can be palpated rectally. Diffuse peritonitis leads to complete atony of the gastrointestinal tract, and the abdomen may become distended with gas in all parts of the tract; there is no discrete ping extending over a large area of the right side. As abomasal volvulus progresses, cattle become recumbent and depressed. Death occurs within hours in this stage, which occurs 1 to 3 days after the development of the volvulus.

■ Clinical Pathology

The serum biochemistry profile shows much more dramatic changes with abomasal volvulus than with RDA or LDA. Clinicopathologic consequences include hypovolemia, dehydration, hemoconcentration, metabolic alkalosis, hypochloremia, hypokalemia, and paradoxic aciduria. Hyperglycemia, hypocalcemia, and hyponatremia may also be observed. Later in the condition a superimposed metabolic acidosis is also present. Anion gap gradually increases with the severity of the disease. Systemic shock eventually causes fatality. Reduced fluid intake and sequestration of large quantities of chloride-rich fluid in the stomachs (third space problem) leads to dehydration and hypovolemia. Hyperphosphatemia was also observed, possibly as a consequence of decreased renal blood flow.[21]

Under the influence of carbonic anhydrase, hydrogen ions are normally pumped into the abomasal lumen. A chloride ion follows into the lumen,

whereas bicarbonate and sodium remain in the blood. Under normal circumstances, the hydrochloric acid leaves the pylorus, where the hydrogen ions are neutralized by pancreatic and intestinal secretions and the chloride is resorbed. When abomasal volvulus occurs, the hydrochloric acid is sequestered in the abomasum and regurgitated into the omasum and rumen (internal vomiting). Ruminal chlorides increase. The animal becomes alkalotic and hypochloremic. Because of shifts between intracellular and extracellular compartments, potassium moves intracellularly as hydrogen ions move extracellularly in response to the metabolic alkalosis. This, plus the total anorexia, leads to severe hypokalemia. The hallmarks of abomasal volvulus are metabolic alkalosis, hypochloremia, and hypokalemia.

Paradoxic aciduria occurs in the presence of metabolic alkalosis, when a cow should be retaining hydrogen ions. The overwhelming renal physiologic drive appears to be sodium retention. Dehydration and reduced cardiac output result in falling blood pressure. The animal must respond by volume expansion; thus sodium is resorbed in the renal tubules. Chloride is also resorbed. Because there is hypochloremia, the electrical gradient that must be corrected is high; if 140 mEq/L of sodium is resorbed and only 60 mEq/L of chloride is available, there is a net of 80 mEq/L (140 − 60) of cations that must be secreted back into the tubules. This is normally accomplished by secretion of potassium. Because hypokalemia is severe, hydrogen ions are paradoxically secreted to retain electrical neutrality so that blood pressure can be maintained by means of maximum sodium resorption.

Peritoneal fluid of cattle with abomasal volvulus has been studied.[22] In comparison with cows with a diagnosis of LDA, cows suffering from abomasal volvulus had significant changes in their peritoneal fluid parameters. Total protein, albumin, L-lactate, CPK, ALP, lactate dehydrogenase, and D-dimer levels were increased, whereas fibrinogen level was decreased. Also, a higher percentage of apoptotic and necrotic neutrophils was detected despite the fact that total leukocyte count was not significantly different. At least in one study, evidence of abnormal coagulation profile reflecting possible disseminated intravascular coagulation was present in a small proportion of cattle studied (3 of 10). Hemostatic dysfunction could be present in advanced stages of the disease.[28]

■ Pathophysiology

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At least some of the factors predisposing to LDA or RDA probably contribute to the development of abomasal volvulus. Whether true RDA precedes abomasal volvulus is not known. Dissection of naturally occurring cases of abomasal volvulus demonstrated that the structures involved in rotation can vary from the reticulum to the omasum at the orad end. The rotation probably occurs most frequently at the reticuloomasal junction. The duodenum is looped around the omasum, regardless of the degree of volvulus. The ensuing displacement leads to a counterclockwise rotation of the abomasum and omasum as viewed from the right side and the rear. The duodenum is pulled medial to the body of the omasum and wraps around the neck of the omasum in the final configuration. The continued hydrochloric acid secretion of the abomasum and the gas produced in the omasum and abomasum further stretch and occlude the duodenum. The abomasal blood vessels and the ventral vagal trunk are compromised near the site at which the duodenum wraps around the omasum in long-standing cases. Thrombosis of vessels may occur.

The acid-base and electrolyte abnormalities of early abomasal volvulus are the same as those of LDA. In cases of severe distention of the abomasum and omasum with vascular compromise, systemic cardiovascular insufficiency develops. Reduced perfusion of peripheral tissues may lead to metabolic acidosis terminally. Hemoconcentration develops, although bleeding into the abomasum may occur from devitalized mucosa, which lowers the hematocrit. These changes are compounded by the developing necrosis of the abomasum. The abomasum may physically leak contents through a weakened, overstretched wall. Endogenous inflammatory mediators and bacterial toxins may diffuse from the abomasum to viable surrounding tissues, where absorption occurs. In either case, the viability of the abomasum is lost, and death follows shortly. At least in a sheep model of abomasal volvulus, ischemia and reperfusion injury occur.[29]

■ Treatment

Immediate surgical intervention usually is necessary to save the animal's life. At the same time, fluid, electrolyte, and acid-base abnormalities must be corrected. For early cases of hypokalemic, hypochloremic alkalosis and dehydration, intravenous fluids consisting of 20 to 80 L of 0.9% sodium chloride with 25 to 100 mEq/L potassium chloride added are administered. Intravenous potassium should not be given at a rate greater than 1 mEq/kg/h to prevent cardiotoxicity. If the serum potassium level is unknown, it is best to stay with an IV rate of less than 0.5 mEq/kg/h. For advanced cases with metabolic acidosis, balanced

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electrolyte solutions such as Ringer's solution are indicated. Broad-spectrum antibiotics are appropriate if the integrity of the abomasal mucosa is questionable. NSAIDs are indicated to control pain, inflammation, and shock. Both standing right-sided and recumbent right paramedian approaches have been successful for correcting abomasal volvulus. There may be less cardiopulmonary compromise if the animal remains standing, especially if reperfusion injury is suspected.

■ Prognosis

Establishing an accurate prognosis before surgery would be optimal because at that time salvage remains a possibility and little expense has been incurred. It is not a simple task. A second critical time is shortly after surgery in cows suspected of not fully recovering. The decision will be whether to continue to treat (cost) or salvage, if that still is an option.

Preoperative assessment is difficult. In the author's experience, assessment cannot be based on a single clinical observation or serum biochemistry value. In the best published studies, investigators examined two different classifications of outcome: death versus survival and productivity versus nonproductivity. A logistic regression model of heart rate, base excess, and serum chloride level was developed as a preoperative predictor of death or survival.[30] Constable and colleagues found that four presurgical variables (hydration, heart rate, duration of inappetence, and pelvic alignment level) could be used to best predict cattle as productive or nonproductive after surgery.[31]

Assessment of outcome after surgery has been investigated. The overall success rate of surgery varies between 61.5% and 86.3%.[32-35] The number of forestomachs involved in the twist has been found to adversely affect survival and productivity. Wallace found only 20% success in cattle with reticuloomasal-abomasal volvulus.[35] Another study demonstrated success in 55% of cattle with omasal-abomasal volvulus and 87% success in cattle with only an abomasal volvulus.[31] Edema of the abomasum carries a guarded to poor prognosis.[35-37] Edema around the proximal duodenum was associated with a poor outcome in Pearson's study, but Fubini and coworkers found no association with outcome.[36,38] Purple discoloration of the abomasal serosa tends to bode poorly for long-term outcome, as does severe distention of this organ, abomasal necrosis, and thrombosis of the gastric veins.[30,35] The measurement of intraluminal pressures of greater than 16 cm Hg also carries a poor prognosis

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because of mucosal damage.[31] A logistic regression model of some of the surgical findings did not predict outcome any better than did the preoperative model.[30]

After surgical correction, cattle with abomasal volvulus often have diarrhea for 24 hours. Feces then firm up to normal consistency. Postoperative clinical signs associated with a poor prognosis include melena, anorexia, persistent tachycardia, and dehydration.[33,37,39] In the author's experience, even if appetite and general attitude are initially good (24 to 48 hours after surgery), persistence of a loose low-volume stool 72 hours after surgery may indicate complications.[40] Among animals in which clinical signs compatible with chronic indigestion develop, the survival rate is only 11.5% to 20%.[35,41] Prolonged treatment seems irrelevant. Prokinetics and their possible benefit in postoperative care have been studied and reviewed.[42,43] Erythromycin (10 mg/kg) IM given preoperatively improves abomasal motility in cattle suffering from abomasal volvulus.

■ Necropsy Findings

Cattle that die of abomasal volvulus are grossly dehydrated, and the abomasum is severly distended or ruptured. The omasum often is also distended when torsion occurs at the reticuloomasal junction. Affected cattle that die or are euthanized after developing postoperative complications have one or more of the following postmortem lesions: gastric compartment dilation, peritonitis, abomasal wall necrosis or ulcer, vascular thrombosis, or vagal nerve lesions.[40]

■ Prevention and Control

Because factors predisposing to atony of the forestomach and abomasum probably are important in the genesis of abomasal volvulus, prevention should be similar to that outlined for LDA.

Abomasal Ulcers

David Francoz • Charles L. Guard

■ Definition and Classification

Smith and colleagues[1] classified abomasal ulcers into four types: (1) nonperforating, (2) nonperforating with severe blood loss, (3) perforating with local peritonitis, and (4) perforating with diffuse peritonitis (Table 32.20). Braun and associates subdivided type 1 abomasal ulcers (nonperforating ulcers) into four subtype on the basis of their structure.[2] In some case, abomasal ulcers rupture into the bursa omentalis and lead to omental bursitis. This type of ulcer has been classified as type 5 abomasal ulcers.[3] These classifications are useful for describing the various clinical scenarios that may be observed in examination of an animal with abomasal ulceration.

TABLE 32.20
Abomasal Ulcers

Type	Lesions	Clinical Signs
1. Nonperforating	1a. Erosion with minimal mucosal defects sometimes distinguished from the surrounding tissue by mucosal discoloration (often reddish-violet or green-brown) 1b. Deeper erosions with focal mucosal hemorrhage, sharply demarcated with a depression in its center 1c. Craters with coating of detritus or fibrin, depression in its center, and bulging margins 1d. Radial wrinkles with a central point, affecting gastric folds only	Partial anorexia; decreased ruminal motility; positive fecal occult blood
2. Nonperforating with severe blood loss (bleeding)	Penetration of mucosa and submucosal blood vessel; hemorrhage into abomasum	Partial anorexia; decreased ruminal motility; anemia; pale mucous membranes; melena; tachycardia; cool extremities
3. Perforating with local peritonitis	Penetration from mucosa to serosa; leakage of abomasal contents; localized peritoneal reaction with adhesion formation	Total anorexia; low-grade fever; ruminal motility decreased or absent; localized abdominal pain; very similar to traumatic reticuloperitonitis
4. Perforating with diffuse peritonitis	Penetration from mucosa to serosa; widespread contamination of the peritoneal cavity with abomasal contents; significant exudate in peritoneal cavity; fibrin deposition of all serosal surfaces	Total anorexia; fever early, then hypothermia; ileus of entire gastrointestinal tract; tachycardia; shock; terminal recumbency with grunt on respiration

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■ Epidemiology

Abomasal ulceration occurs in cattle of all ages. Veal calves appear the most frequently affected. At slaughter, healthy veal calves are found to have clinically inapparent abomasal erosions and ulcers, with reported prevalence ranging from 67% to 87%.[4,5] In beef calves that died between the fourth day after birth and weaning, abomasal ulcers were observed in 3.9% on gross postmortem examination reported by a private veterinarians and in 18.9% on histologic examination or confirmation results by a veterinary pathologist.[6] In clinically affected calves, perforation with peritonitis (rather than hemorrhage) usually develops. In clinically normal cows, 20.5% had type 1 ulcers in a slaughter study.[2] In adult cattle with abomasal ulcers causing illness, approximately one third of clinical cases in a referral population had significant hemorrhage.[7] Of these, half had lymphosarcoma and, for the most part, were older than 6 years of age. The age of the cattle with nontumor-associated bleeding ulcers was generally younger. In the remaining two-thirds of the cattle, ulcers had perforated, with approximately half having diffused and half having localized peritonitis.[8] Most adult cattle with abomasal ulcer are in the first month of lactation after calving and have a concurrent disease. Several cows have been discovered to suffer of an abomasal ulcer during surgery to correct displaced abomasum. Metritis, mastitis, and ketosis are the other diseases commonly seen with abomasal ulcers.

Few data are available in small ruminants. However, the prevalence of abomasal ulcers at slaughter has been reported to be 61% among goats in one old slaughter study from Iran.[9] The incidence of abomasal ulcers was reported to be highest in goats severely affected with nematodes.[9] In two slaughter studies from the Middle East, the prevalence of abomasal ulcers in healthy sheep ranged from 18%[10] to 75%[11]; almost all of these abomasal ulcers were type 1 ulcers.

■ Etiology and Pathophysiology

The specific events leading to erosion and ulceration of the abomasal mucosal epithelium are unknown. Cytoprotective mechanisms include a mucous barrier, cloudy mucus containing bicarbonate ions to neutralize back-diffusing hydrogen ions, and high submucosal rates of blood flow to remove back-diffusing hydrogen ions. When these mechanisms are disturbed, gastric (abomasal) ulcers may occur.

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The exact cause of abomasal ulcers is still obscure and may be multifactorial. Hund and Wittek[12] reviewed the different suspected causes of abomasal ulcers in cattle and small ruminants. In calves, development of abomasal ulcers was proposed to be associated with mineral deficiencies (mainly copper), stressful management practices, feeding practices (type of milk and frequence of feeding), concomitant diseases, proliferation of microorganisms (*C. perfringens* type A or D, *Escherichia coli*, *Sarcina*-like spp., fungi, or others), and abrasion of the abomasal mucosa by roughage, geosediments, or trichobezoars. However, all explored hypotheses have failed to demonstrate involvement of any of these alone in the development of abomasal ulcers. In adult cattle, the disease is associated with stressful events such as recent parturition, peak milk production, presence of concurrent diseases (mainly those of the peripartum period), feeding practices such as diets high in starch, and presence of lymphosarcoma. Finally, abomasal ulcers are an adverse effect of antiinflammatory drug administration.

■ Clinical Signs and Differential Diagnosis

Loss of gastric epithelium may range from no clinical signs to hemorrhage and subsequent melena, to peritonitis if the erosive processes penetrate all layers of the abomasum (see Table 32.20).

The mildest form (type 1) is caused by nonperforating ulcers that do not result in extensive hemorrhage. Affected animals may have mild or no clinical sign. Mild abdominal pain, shown by partial anorexia, decreased ruminal motility, and mild ruminal tympany are the possible clinical signs if present. There is usually no fever. Feces may be normal or reduced in amount and stale because of prolonged transit. In some cases, abdominal pain may be evident on manual pressure on the right ventral abdomen. TRP or indigestion may be suspected. In one study, approximately two-thirds of affected cows produced a positive result of a fecal occult blood test measured with the use of an ortholidine-based tablet.[13]

In cattle with ulcers that erode into major gastric blood vessels (type 2), blood loss can be sufficient to cause signs of anemia and hemorrhagic shock. These animals have dark blood clots in their feces or tarry, black feces with the characteristic smell of partly digested blood. The mucous membranes may be pale, tachycardia and a pounding heart may be pronounced. Respiratory rate may be elevated. Total anorexia and rumen stasis usually are present. The rumen may have a fluid consistency, and if the animal is able to stand, abdominal pain

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sometimes is evident. There are other possible sources of proximal gastrointestinal hemorrhage in cattle, but abomasal ulcers are by far the most common cause. Among them, bleeding abomasal ulcers must be differentiated from melena sometimes seen with intussusception or hemorrhagic bowel syndrome (hemorrhagic bowel syndrome; see Diseases Caused by *Clostridium perfringens* Toxins [Yellow Lamb Disease, Lamb Dysentery, Necrotic Enteritis, Enterotoxemia] section). In these cases, feces are usually more the color of blackberry or strawberry jam. The PCV usually is increased with intussusception,[14] normal or increased in hemorrhagic bowel syndrome,[15-17] and decreased with a bleeding ulcer.[18]

Abomasal ulcers that perforate the serosal surface may lead to localized peritonitis (type 3) from contamination with abomasal contents. If the lesion is small or the local inflammatory reaction sufficiently swift, localized peritonitis results. This condition mimics the presentation of TRP. The animal may have a moderate fever and partly or totally anorexic. Milk production may decrease acutely. There is evidence of abdominal pain, usually localized to the right ventral quadrant (positive withers pinch test). Ruminal motility is reduced, and mild bloat may be present. As with TRP, the signs usually abate over the course of a few days if the infection is successfully contained. In some cases the infection is confined to the omental bursa, where extensive contaminated fluid (pus) may accumulate. The course of omental bursitis is much more prolonged than that of simple localized peritonitis and usually results in a guarded prognosis.

Major leakage from a perforating ulcer leads to acute diffuse peritonitis (type 4). The course of the disease usually is rapid, with signs of septic shock developing within 24 hours of the onset. Total anorexia and ruminal stasis are accompanied by tachycardia with a weak, thready pulse and a heart rate of more than 100 beats/min. Pain may be evidenced by grinding of the teeth or groaning. The extremities are cool, and affected animals usually become recumbent. Abdominal enlargement may be evident as a result of both ruminal tympany and the accumulation of peritoneal fluid. Dehydration is detectable by skin pinch or by observation of the position of the eye in the orbit. Septic shock from other causes may be difficult to distinguish. Diffuse peritonitis from uterine, cecal, or intestinal ruptures have the same final course. Abomasal volvulus of more than a day's duration has similar characteristics but can be differentiated by the right-sided ping and fluid in the abomasum.

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■ Ancillary Tests

Antemortem diagnosis of abomasal ulcers may be challenging, particularly in cases of nonperforating and nonseverely bleeding ulcers.

Complete Blood Cell Count.

If peritonitis is present, leukocytosis usually is present, with neutrophilia predominating in many cases. The plasma fibrinogen is increased (>700 mg/dL) in most cattle with peritonitis. The hematocrit is normal or elevated with peritonitis, but plasma protein levels may be decreased as a result of protein accumulation in the peritoneal cavity or increased if dehydration is severe. If blood loss is severe, the PCV is decreased.

Serum Biochemistry Profiles and Blood Gas Analysis.

Results of a serum biochemistry profile or blood gas analysis are nonspecific. In most cases, they reflect a digestive stasis (hypochloremic metabolic alkalosis), but in animals in shock a metabolic acidosis may be observed. BUN level may be increased. This can be a result of blood degradation in the intestine or hypovolemia and prerenal azotemia. The utility of BUN in the diagnosis of abomasal ulcers by identifying digestive hemorrhage remains to be determined.

Other Blood Tests.

Serum pepsinogen concentration has been reported to be increased in one study in cases of severe abomasal ulceration.[19] Because serum pepsinogen concentration can also be elevated in other abomasal diseases such as nematode infection, this finding is not specific.[19,20] Serum gastrin concentration has also been reported to be increased in cases of type 2 ulcers in comparison with healthy cows.[21] However, the sensitivity and specificity of this test are not known.

Cattle older than 5 years of age with a bleeding abomasal ulcer should be tested for bovine leukosis virus.

Abdominocentesis.

Abdominocentesis confirms diffuse peritonitis (a large quantity of abdominal fluid is obtainable); centesis fluid may contain leukocytes with phagocytosed or free bacteria and even feed particles. In localized peritonitis, the results of abdominocentesis may be normal (see Peritonitis in Ruminants section for more

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details).

Fecal Occult Blood Test.

Fecal occult blood tests may be helpful for detection of type 1 ulcers. The tests are inexpensive and can be performed during the physical examination. Testing multiple samples may increase its sensitivity.[22] However, these test did not provide any information about which part of the gastrointestinal tract is involved in the bleeding. One study have reported a sensitivity of 77% and a specificity of 97% for ulcers confirmed at surgery or necropsy.[13] However, the reagent used in this study is not commercially available anymore. Researchers have since evaluated a guaiac test and a urinary test strip for the diagnosis of type 1 ulcers. They reported low sensitivity, low specificity, or both and concluded that these tests are not suitable for the detection of type 1 ulcers.[23]

Diagnostic Imaging.

Because of forestomach anatomy, oral endoscopy of the abomasum is not possible in ruminants. Because ultrasonographic assessment of the abomasal mucosa integrity is difficult, ultrasonography is of limited value for the diagnosis of abomasal ulcers. However, images compatible with focal mucosal or omental edema and abdominal effusion associated with abomasal ulcers may be observed and lead to the suspicion of ulcers (Fig. 32.136). Ultrasonographic images of lymphomatous infiltration of the abomasal mucosa has been described in cows with lymphoma.[24] Abdominal ultrasonography is also useful for the diagnosis and the evaluation of peritonitis associated with type 3 and 4 abomasal ulcers (see Normal and and Main Abnormal Ultrasonographic Aspects of Abdominal Organs in Calves and Cows section). Braun and colleagues reported that percutaneous ultrasonography-guided abomasocentesis can be safely performed for the evaluation of abomasal fluid.[25] According to the investigators, the presence of blood or hemoglobin is principally associated with abomasal ulcers.

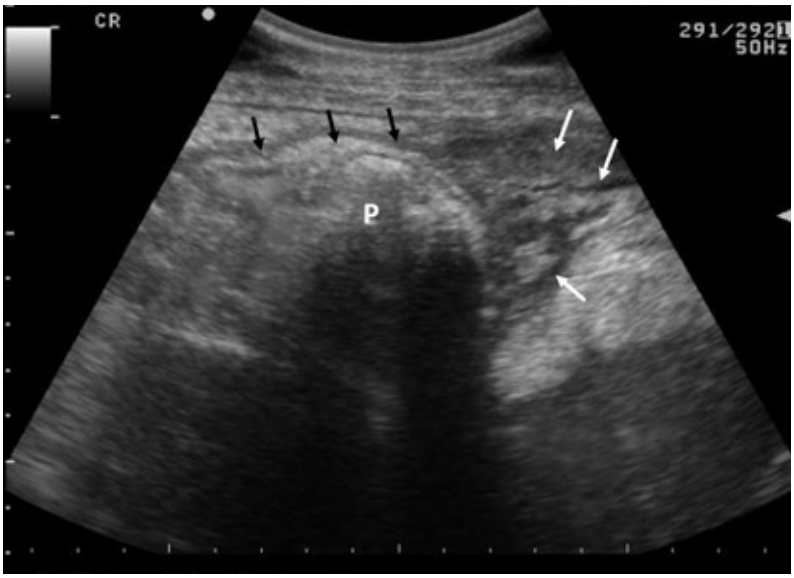


FIG. 32.136 Ultrasonography of the right cranial abdomen of a cow diagnosed with abomasal ulcers. The pylorus *(P)* is visualized *(black arrows).* The surrounding images are compatible with inflammatory changes (*white arrows,* indicating hypoechogenic pocket with structures of various echogenic appearance). (Courtesy Centre Hospitalier Universitaire Vétérinaire de l'Université de Montréal)

Exploratory Laparotomy.

Exploratory laparotomy may also be an alternative in the diagnosis abomasal ulcers by palpation of a thickening of the abomasal wall, roughing of the abomasum serosa, adhesion of the abomasum, or directly a perforation in the abomasal wall. However, potential aggravation after the exploratory procedures should be considered.

■ Treatment

Treatment is aimed at correcting dietary problems, reducing stress, treating concurrent diseases, and initiating specific therapy to address the consequence of the ulcers.

Supportive Treatments.

Removal of high-energy feedstuffs and replacement with good-quality hay combined to confinement in a stall are beneficial.[26] The buffer effect of food is very important in controlling the abomasal pH. Consequently, recovering a normal appetite is the main goal of the treatment of abomasal ulcers.[27]

Blood transfusions may be necessary for cattle that have lost enough blood to lower the hematocrit to 14% or below. Usually 4 to 6 L given once is adequate, but repeated transfusions may be necessary. Crossmatching is usually not necessary in cattle unless repeat transfusions are performed over more than 3 days.

Broad-spectrum antibiotics are administered when peritonitis is suspected. Principles and details regarding the treatment of peritonitis are described in the Peritonitis in Ruminants section. Intravenous or oral fluids may be necessary to treat dehydration and metabolic or acid-base disturbances. Animals with diffuse peritonitis must be given intravenous fluids with caution because of the risk of pulmonary edema associated with the low plasma oncotic pressure.

Drugs That Increase the Abomasal pH: Antiacids.

Numerous studies have been performed to evaluate the effect of different therapeutic agents on abomasal pH of healthy calves. Results of these studies have been summarized by Constable and colleagues.[27] The therapeutic agents studied in normal calves included oral administration of an antacid agent containing aluminum hydroxide and magnesium hydroxide (25 mL and 50 mL, tid), oral administration of specific H_2 antagonists (cimetidine, 100 mg/kg and 50 mg/kg, tid; and ranitidine, 10 mg/kg and 50 mg/kg, tid), and oral administration of the proton pump inhibitor omeprazole (4 mg/kg q24h). All these extralabel treatment regimens induce an increase in the mean 24-hour abomasal luminal pH. Oral administrations of aluminum hydroxide agent induced a dose-dependent increase in luminal pH and were more efficacious when administered postprandially. Because some deleterious effects (diarrhea, hypomagnesemia, metabolic alkalosis) were observed when this antacid was administered at the dose of 50 mL tid, this should be considered the maximal dosage in calves. Frequent (every 8h) oral administration of 25 mL of aluminum hydroxide is reported to be the most effective treatment.[27] Cimetidine (100 mg/kg tid) was the most effective. However, ranitidine (50 mg/kg tid) was the most cost-effective in these studies. Interestingly, the effect of omeprazole on abomasal pH decreased over time (reduced effect observed after five daily treatments).[28] Results of these studies may or may not apply to ill calves. In adults, oral administration of these therapeutic agents is of doubtful benefit because of dilution in the rumen and slow release into the abomasum. Oral medications administered after stimuli that induce esophageal groove closure

would be more likely to have the desired effect. Traditional stimuli have included copper sulfate solutions and 10% sodium bicarbonate solution. Vasopressin (0.25 IU/kg IV) was shown to induce reliable abomasal deposition of materials given by drench to adult goats.[29]

Intravenous administration of H_2 antagonists at lower doses may be efficacious, but their use by this route is cost-prohibitive ($100 to $200 per day) or reserved for valuable animals. In the authors' clinic, ranitidine 1 to 1.5 mg/kg IV tid is used; the clinical impression is that this is effective. Intravenous administration of ranitidine (1 and 2 mg/kg) in healthy sheep has shown an increase in the abomasal pH for up to 150 min, and authors conclude that administration of ranitidine at a dosage of 1 mg/kg tid or 2 mg/kg bid IV could be the most effective treatment protocols.[30] Intravenous administration of famotidine at 0.4 mg/kg once or tid has also been reported to increase abomasal outflow pH, but the effect decrease with time.[31] Injectable proton pump inhibitors (omeprazole, pantoprazole) are also available in some countries, but their efficacy in cattle and small ruminants is unknown.

Surgery.

Surgery may be an option in cases of perforated ulcers or when abomasal adhesion secondary to a localized peritonitis lead to abomasal dysfunction. Right paralumbar fossa, right paracostal, or right paramedian approaches can be used to access the abomasum (see abomasal impaction) and allow ulcer resection. However, prognosis associated with these surgeries is guard. In calves, 40% of 10 calves survived the corrected surgery in one study[32] whereas none survived in another (8 calves, one of which had a nonperforated ulcer).[33] In another study in cattle with concurrent abomasal displacement and perforating ulceration, the short- and long-term survival rates were 38% and 14%, respectively.[34]

■ Prognosis

The prognosis is good for ulcers that are neither bleeding nor perforated. For animals that stop bleeding and those with localized peritonitis, survival and eventual return to normal function are possible. Many dairy cattle stop lactating during the acute course of the illness and do not return to milk until the next lactation. Because abomasal ulcers generally occur within the first month after calving, most of these animals are used for slaughter. Most cattle with diffuse peritonitis (type 4 ulcers) die despite aggressive specific therapy. Cattle with

ulcers that occur secondary to lymphosarcoma should be euthanized.

■ Necropsy Findings

Cattle with bleeding abomasal ulcers resulting in death are very pale and may have blood or bloody fluid throughout the distal gastrointestinal tract. The lesion in the abomasum is typically small and involves an abomasal blood vessel in the submucosa. Most bleeding and perforating ulcers were found in the fundic portion of the abomasum in the region of the proper gastric glands. The most ventral portion of the abomasum in its normal position is frequently affected.[18] Most affected animals have a single bleeding ulcer, but approximately 60% have one or more additional ulcers or erosions.[18] Cattle with diffuse peritonitis have many liters of foul-smelling fluid in the peritoneal cavity. Fibrin usually covers the serosal surface of all abdominal organs. The defect in the serosal surface of the abomasum is usually nearly round and 3 to 6 cm in diameter. Abomasal fluid freely enters the peritoneal cavity. Omental bursitis may be present, with the omental recess filled with purulent to fibrinous fluid. In these cases, the remainder of the abdomen may not be grossly affected. Asymptomatic abomasal ulcers (often 50 to 200) may be found coincidentally in cattle that die of septic metritis or mastitis. These ulcers generally produce no signs of hemorrhage and go undetected until necropsy.

■ Prevention and Control

Because the exact cause of development of abomasal ulcers is unknown, prevention is difficult. Dietary management that reduces other abomasal diseases likewise reduces the incidence of abomasal ulcers. Avoiding abrupt changes in rations and including adequate fiber sources of sufficient particle size to facilitate normal ruminal function also promote normal abomasal function. Minimizing stress caused by overcrowding, excessive competition, and adverse environmental conditions and minimizing mastitis and metritis should also reduce problems with abomasal ulcers. Removal of animals infected with the bovine leukosis virus from the herd eliminates lymphosarcoma as a cause of abomasal ulcers. Judicious use of corticosteroids and NSAIDs is also important.

Abomasal Dilation and Emptying Defect of Suffolk Sheep

David Francoz

Definition and Epidemiology

Failure of abomasal transport and abomasal dilation has been described in adult sheep.[1] The disease has been reported mainly in Suffolk breed and has occurred mostly in winter months in association with lambing and feeding of concentrates. A similar syndrome has been described in two Hampshire,[2] one Dorset,[3] and one Texel sheep.[4] An abomasal emptying defect syndrome has also been reported in Toggenburg goats, which could suggest that this syndrome may therefore occur in goats.[5]

Animals described in reports from several teaching hospitals were adults of both sexes.[1,6] Most cases are sporadic, but at least two outbreaks have been reported.[1,6] The incidence in one report was 13 of 92 mature ewes affected in the flock during one winter.[6] In the other report, 5 ewes of a flock of 200 ewes were submitted for necropsy in the same day.[1] In both studies, pedigree analysis of affected sheep showed no hereditary pattern. One report from a diagnostic laboratory in England described abomasal impaction in a Texel ewe and in a Suffolk ram that were simultaneously diagnosed as having scrapie.[4] It remains to be seen whether any causative connection exists between the two diseases. In one study, six sheep were immunohistochemically tested for scrapie; five results were negative and one was positive, and the affected sheep had equivocal microscopic lesions.[1]

Pathophysiology

The mechanisms underlying the dilation of the abomasum and the failure to transport ingesta to the intestines are unknown. None of the problems commonly associated with abomasal impaction and dilation in cattle have been identified in affected Suffolk sheep. It has been advanced that abomasal emptying defect of Suffolk sheep may be an acquired form of dysautonomia.[1]

Clinical Signs and Differential Diagnosis

The disease is manifested primarily by anorexia and weight loss. Most patients eventually die. The following clinical signs have been reported in affected animals but are not always present: watery green diarrhea; ruminal tympany; pear-shaped abdominal distention; increase or decrease in or absence of ruminal

contractions; a palpable (by ballottement) firm mass in the right lower abdomen; mild abdominal pain; tachycardia; duration of observed signs from days to months; partial to total anorexia; dullness and depression; marked to undetectable weight loss; and ketonuria.

This syndrome should be differentiated from other wasting diseases of sheep such as malnutrition, parasitism, dental problems, Johne's disease, caseous lymphadenitis, other chronic infections, and neoplasia. Abomasal emptying defect is distinguishable by the palpable abomasum in advanced cases and the exclusion of other possible problems. Other causes of abomasal enlargement or impaction resembling those reported in cattle must also be considered. However, when a mature Suffolk sheep from a well-nourished flock shows weight loss and a palpable abomasum, this syndrome must be considered highly likely. Confirmation may require necropsy or exploratory surgery.

Ancillary Tests

Reports on cases diagnosed in North America have found CBC and systolic blood pressure to be of little benefit in the diagnosis.[6] The hypochloremic metabolic alkalosis common in cattle with abomasal problems may be present[2,7] but is not consistently observed in affected sheep.[3,6,8,9] Increased liver enzyme levels are frequently reported in affected sheep and goats and were associated with hepatic congestion and ischemia secondary to abomasal distention.[3,5,6,7] Mild hypocalcemia was observed in all cases in one report.[5] Because of internal vomiting, elevated ruminal chloride ion values (34 to 130 mEq/L; normal, 8 to 15 mEq/L) are also frequently reported in published reports.[2,3,6,7,9]

Treatment and Prognosis

Medical therapy alone with cathartics and laxatives has been of limited benefit. Mineral oil, dioctyl sodium sulfosuccinate, and magnesium sulfate have all been used. Neostigmine and calcium gluconate were not useful.[8] Abomasotomy has led to death from complications in many affected sheep,[6,8] but those that survived more than 2 days manifested recrudescence of clinical signs within 12 weeks.[8] Ewes treated with metoclopramide (dosage not reported) have shown varying degrees of recovery; some of them survived for 12 weeks but continued losing weight.[6] Experimental studies in cattle and sheep have failed to demonstrate any beneficial effect of metoclopramide on abomasal emptying.[10,11]

On the other hand, erythromycin has been shown to increase abomasal emptying rate in lambs.[12] However, in a context of judicious use of antimicrobial drugs, the administration of erythromycin for its prokinetic properties is questionable and is not recommended. Despite these successes, most affected sheep die of cachexia. Because of the expense, poor response, and risks associated with abomasotomy, this treatment is reserved for valuable breeding stock.

Necropsy Findings

The abomasum is greatly distended in sheep that die of this condition. The contents are either dry or liquid but most often have resembled normal ventral ruminal sac contents. Investigators always reported a patent pylorus. Normal ingesta have been observed throughout the remainder of the intestinal tract. Incidental findings have included aspiration of ruminal contents and subsequent pneumonia, abomasal ulcer with local peritonitis, passive congestion of the liver, megaesophagus, and esophageal ulcers. Reports of histopathologic findings include no lesions other than thinning of the abomasal muscle layers (presumably as a result of stretching),[6] mononuclear cell infiltration of the main muscle layers of the abomasum,[8] and, in one case, myxomatous changes in the abomasal branches of the vagus nerve.[9] Chromatolytic and necrotic neurons without signs of inflammation within the celiacomesenteric ganglia were found in all six affected sheep examined in one study.[1]

Prevention and Control

Until more is known about the pathogenesis of this specific defect in abomasal function in Suffolk sheep, no useful recommendations for prevention can be made.

Abomasal Impaction

David Francoz

Definition and Classification

Abomasal impaction is the accumulation of firm ingesta in the abomasum with failure of aboral transport associated with an increased volume of the abomasum. The impaction involves the body and the pyloric antrum of the abomasum. However, impaction of the pyloric antrum only is also described in dairy cattle.[1]

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Abomasal impaction can be classified as primary when no underlying cause can be identified and as secondary when impaction is secondary to another condition. *Dietary abomasal impaction* refers to abomasal impaction secondary to ingestion of abnormal diet.

Etiology and Pathophysiology

Primary abomasal impaction is considered idiopathic and has been described mainly in dairy cows in the early postpartum period.[1] Dietary abomasal impaction is the result of feeding poor-quality, coarse roughage as the sole feed. Abomasal impaction can also be secondary to consumption of nonfood material such as sand or gravel or secondary to abnormal alimentary behavior or ingestion of feed mixed with sand.[2-5] Secondary abomasal distention may also occur with normal diets after correction of abomasal volvulus, as a result of reticuloperitonitis, or as a result of the development of adhesions between the abomasum and the rumen or the abdomen wall (or both). Lymphoma involving the abomasum or other space-occupying lesions adjacent to the pylorus may lead to abomasal distention. These conditions are referred to as *chronic indigestion* and are discussed elsewhere in this chapter. Abomasal emptying defects of Suffolk sheep are addressed in the previous section.

The pathophysiologic mechanism of abomasal impaction is not known. In dietary abomasal impaction, animals fed roughage that is poorly digestible and incapable of meeting their energy requirements consume as much as the rumen will physically allow. The flow of ingesta from the forestomachs to the abomasum normally contains only small, finely digested particles of forage material. With chronic engorgement of highly lignified, poorly digestible forage, larger particles escape the forestomach and accumulate in the abomasum. Once a mass of fiber forms in the abomasum, further accumulation of particulate material is enhanced. Accumulation of dry materials modifies the abomasal content viscosity and consequently, the abomasal emptying rate decrease.[1] Additional ingesta distends the abomasum to several times normal size, which leads to a severe abomasal distention that prevents any return to normal motility. Also, abomasal secretion may be inhibited by the cachexia and chronic distention of the organ.

Clinical Signs and Differential Diagnosis

Adult dairy cows with primary abomasal impaction have a consistently

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decreased appetite, but other signs are inconsistent.[1] Primary abomasal impaction should be considered in the differential diagnosis of nonspecific clinical signs of decreased milk production and appetite in dairy cows.[1] Conditions that cause dehydration and bilateral abdominal distention with absence of feces must be considered in the differential diagnosis. In many of these cases, exploratory celiotomy is necessary to arrive at a definitive diagnosis.

Dietary abomasal impaction has mainly been described in beef cows, but dairy cows exposed to similar feeding and environmental conditions may also be affected. Several animals in a herd may be affected over a short period. Beef cows with abomasal impaction develop abomasal and ruminal distention over a period of days to weeks. Close monitoring of animals reveals reduced feed intake and a reduced volume of firmer than normal feces. The animal may have right ventral abdominal enlargement. Ruminal contractions are of normal or increased frequency but are often reduced in amplitude. In the later stages of the disease, ruminal motility is often absent. Cattle with advanced abomasal impaction may be recumbent and groan with each respiration. The consistency of the ruminal ingesta, as judged by ballottement, may be more fluid than expected on the basis of the coarse diet. Other animals have a uniformly firm and distended rumen. The pulse and respiration are usually normal until the animal is near death, at which time tachycardia develops. The abomasum may be palpable as a firm mass behind the right coastal arch. Rectal examination reveals a distended rumen; often the ventral sac extends to the right body wall (L-shaped rumen). The pyloric part of the distended abomasum may be palpable in the right ventral quadrant. Wintering beef cows usually are pregnant, and therefore the uterus may prevent palpation of the abomasum. Feces are absent or very scant and dry. Mucus may be all that clings to the clinician's sleeve after rectal examination. The body condition of affected animals is invariably poor because negative energy balance precedes and is amplified by the impaction. If the abomasum ruptures, signs of generalized peritonitis occur. Death usually follows within hours of rupture.

Ancillary Tests

The hypochloremic, metabolic alkalosis typical of upper gastrointestinal obstruction in ruminants does not always develop in abomasal impaction.[1] Initially some fluid ingesta may pass through the abomasum, preventing chloride sequestration. However, some cattle have metabolic alkalosis, with chloride

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accumulating in the rumen to a level greater than 30 mEq/L (internal vomiting). In terminal stages, a mixed acid-base imbalance with both a metabolic alkalosis and a metabolic acidosis can result in a normal overall pH. Anemia and leukopenia can accompany the cachexia of chronic abomasal impaction in poorly fed animals. If abomasal rupture has occurred, profound hemoconcentration and leukopenia are present. Abdominocentesis generally is not useful in diagnosing abomasal impaction because peritoneal fluid is abnormal only after abomasal rupture.

Treatment

Medical management includes correction of fluid and electrolyte abnormalities. Early cases may be resolved with easily digestible feeds, aggressive fluid therapy, and oral administration of laxatives such as mineral oil (4 L daily). The use of prokinetic drugs may be indicated in order to increase abomasal emptying rate and the passage of ingesta through the pylorus. However, no data on the efficacy of the administration of prokinetic drugs in the specific treatment of abomasal impaction are available. Constable and colleagues[3] published a comprehensive review on the data available for the recommendation of the use of prokinetic drugs in abomasal disorders. They concluded that (1) erythromycin (8.8 to 10 mg/kg IM bid) is the most effective drug to increase abomasal emptying rate; (2) according to in vitro studies, bethanechol (0.07 mg/kg SC tid) is potentially effective, but no controlled clinical trials have actually demonstrated its effectiveness; and (3) metoclopramide is ineffective in promoting abomasal emptying rate in cattle and cannot be recommended. However, prudent use guidelines from many countries indicate that the use of an antibiotic such as erythromycin for its prokinetic activities is controversial and should not be recommended. Pregnancy may be terminated by induction of parturition with corticosteroids or prostaglandin, or both, which improves comfort.

Different approaches have been proposed for a surgical treatment of abomasal impaction. Rumenotomy, followed by installation of a nasogastric tube inserted into the abomasum through the omasum, can be performed. Through the indwelling tube, laxatives and emulsifiers may be given during the postoperative days to aid in softening and removing the abomasal contents. Mineral oil (8 mL/kg/day), dioctyl sodium sulfosuccinate (50 mg/kg/day), magnesium hydroxide (1 g/kg/day), and magnesium sulfate (2.5 g/kg/day) have each been recommended. However, none of these treatments has been evaluated, and

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detrimental effects have been reported with some of them (see discussion of magnesium hydroxide in the Acute Abdomen in Ruminants section). Right paralumbar fossa, right paracostal, or right paramedial approaches can also be used to gain direct access to the abomasum. The authors prefer the right paracostal approach, with the animal in left lateral recumbency, for abomasotomy and removal of abomasum contents. However, even with this approach, complete exteriorization of the abomasum and exploration of the oral portion of the abomasum and omasum is often not possible, particularly in large animals. Even if the prognosis for restoring the abomasal function is poor, the authors have had some positive outcome, depending on the cause of impaction and the extent of abomasal lesions. External massage may help break up the contents of the abomasum. Intraluminal administration of 5% dioctyl sulfosuccinate solution or saline can also be performed during surgery.[1]

Prognosis

Because most cases of abomasal impaction are quite advanced when brought to the attention of the veterinarian, treatment is usually unrewarding. In dairy cows the short-term prognosis was reported to be good (93%) for impaction that affected only the pyloric antrum and guarded (50%) for impaction involving the entire abomasum.[1] The clinician must weigh the severity of the metabolic disturbances and the likelihood of recovery. Salvage by slaughter is often the most economic recommendation. If therapeutic measures do not resolve the impaction, death usually occurs within a few days of the onset of severe signs.

Necropsy Findings

Emaciation and a firm, grossly enlarged abomasum are consistent with primary or dietary abomasal impactions that involve the entire abomasum. The abomasal contents resemble normal, dry ruminal contents. The rumen is also enlarged but either filled with homogeneous, watery ingesta that lack normal stratification or impacted with dry ingesta, like the abomasum. Accumulation of sand or gravel is evident.

Prevention and Control

Prevention of dietary abomasal impaction requires proper dietary management of cattle in cold weather. Because animals outside without shelter have substantially increased maintenance energy requirements in cold, windy weather,

straw or corn stover (stalks) is not adequate as the sole feed. Concentrates and better-quality forage prevent abomasal impaction. Monitoring body condition during winter weather alerts the good manager that supplemental feed is needed before abomasal impaction occurs.

Obstructive Intestinal Diseases

David Francoz • Charles L. Guard

Definition and Etiology

Several conditions may lead to obstruction of the flow of ingesta through the intestinal tract. These conditions can be divided into functional or mechanical obstructions. Functional obstructions (pseudoobstruction or ileus) are the consequence of neuromuscular perturbations of the gastrointestinal tract. Mechanical obstructions are the consequence of a physical obstruction of the intestinal tract secondary to digestive tract lesions (intussusception, volvulus, or congenital lesions) or extradigestive lesions (mesenteric fat necrosis, fibrous adhesions, or hernia). Each of the specific diseases is discussed in the following paragraphs and summarized in Table 32.21.

TABLE 32.21

Causes of Intestinal Obstruction in Ruminants

Disease	Animals Most Commonly Affected	Signs
Intestinal atresia or stenosis	Neonates	No feces; abdominal distention
Intestinal volvulus around mesenteric root	All ruminants; more common in neonates	Colic; rapid abdominal distention; collapse; shock
Intussusception	All ruminants; large or small intestine of neonates; small intestine of adults	Colic early, then chronic low-grade pain; dehydration; mucus plus blood in dark red feces; slow abdominal distention; decreased fecal output; mass palpated rectally; distended loops of intestine palpated rectally
Cecal dilation and volvulus	Adult dairy cattle in early lactation	Mild to severe colic; distended abdomen, especially upper right; ping in right paralumbar fossa; distended cecum palpated rectally
Intestinal tumors	Sheep, rare in cattle	Progressive weight loss; in cattle, mass may be palpable rectally; in sheep, mass identified by celiotomy or necropsy
Mesenteric fat necrosis	Cattle, especially Channel Island breeds	Masses possibly discovered on routine examination; progressive weight loss; scant or no feces; dilated loops of bowel palpated rectally
Intestinal	All ruminants	Same as for intussusception

incarceration		
Ileus	All ruminants	Scant or no feces; right-sided ping; succussable fluid on right; often associated with peritonitis

Clinical Signs and Differential Diagnosis

Acute manifestations of obstructive diseases include a reduced amount of feces or failure to pass feces, progressive abdominal enlargement with areas of tympanic resonance on the right side of the abdomen, and sometimes colic. If pain is severe, forestomach atony may occur. Mechanical obstructions may lead to circulatory shock and collapse. Electrolyte abnormalities depend on the site of the obstruction; obstructions in the jejunum or near the duodenum or pylorus lead to sequestration of abomasal secretions and result in hypochloremic, hypokalemic metabolic alkalosis, whereas those in the cecum, colon, or rectum may lead to dehydration without alkalosis. If bowel necrosis or rupture occurs, acidosis may result from the circulatory collapse that accompanies peritonitis and the absorption of toxins.

Volvulus of the Duodenal Sigmoid Flexure

A syndrome affecting the duodenal sigmoid flexure was reported in Holstein cattle by Vogel and colleagues.[1] The etiologic and pathophysiologic features of this condition are not known, but the authors advanced a potential role of duodenal ulcers or previous omentopexy (years to months before development of volvulus of the duodenal flexure). Clinical presentation resembles abomasal volvulus with anorexia, decreased milk production, scant feces, tachycardia, moderate dehydration, tympanic resonance in the tenth to twelfth right intercostal spaces, and succussion of fluid in this area.[1] Serum biochemistry panels revealed a severe hypokalemic and hypochloremic metabolic alkalosis, as well as hyperbilirubinemia and increased liver enzyme levels. Interestingly, those modifications were more pronounced than those observed in cases of abomasal volvulus. Confirmation of the diagnosis is made by palpation of a counterclockwise duodenal sigmoid flexure volvulus during right flank exploratory laparotomy. Treatment consists of manual reduction of the volvulus, massage of the duodenum, and fluid therapy to correct electrolytic disorders. Prognosis of the condition is reported to be fair; 22 of 29 animals were treated successfully.

Intestinal Atresia or Stenosis

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Intestinal atresia or stenosis is a congenital anomaly reported in calves and lambs. Clinical signs usually become evident within a few days after birth. Animals with anal or distal rectal atresia usually have the slowest onset of signs, whereas proximal obstructions lead to more rapid onset of signs. Malformations of the anus and rectum are believed to be hereditary,[2] and breeding of surgically corrected survivors should be discouraged. Jejunal atresia in Jersey cows is reportedly inherited as an autosomal recessive trait. The etiopathogenesis of atresia coli in calves is not well understood, but autosomal recessive inheritance has been reported,[3] and Holstein calves seem to be predisposed to its development.[4] Rectal palpation of the amniotic vesicle for diagnosis in early pregnancy (<42 days of gestation) is also suggested to be a cofactor for the development of atresia coli.[4,5] If the anus or distal rectum is atretic, animals strain or pump their tails in an attempt to defecate. A fistulous connection may exist between the rectum and the urogenital tract (e.g., either the vagina or the pelvic urethra). Visual and digital exploration of the perineum reveals the absence of feces and may permit definition of the specific defect.

Stenosis or atresia of the intestinal tract may occur to any degree and can be differentiated in four types according to humans classification: narrowing, a membranous diaphragm with a perforation, or an imperforate membrane (type 1); a cordlike remnant of the intestine (type 2); a unique blind-ended dilation with complete separation of the intestine (type 3, the most frequent); and multiple sites of atresia (type 4).[6] All have been described in cattle. Affected neonates show depression and mild colic and progress to cardiovascular collapse after the intestine proximal to the obstruction becomes distended with fluid and gas. Tympany may be easily detected by percussion. If the anus and rectum are normal, a digital examination usually reveals only mucus or blood (or both). Because the rectal and descending colon walls are thin in cases of atresia coli, retrograde tubes or catheters should be used with extreme caution to prevent rupture of the bowel or should be avoided completely.[6] Complete intestinal volvulus must be considered in the differential diagnosis, but the histories in the two conditions are often different.

Surgical repair is indicated if the animal is of high value. However, the prognosis for normal and productive life is guarded. Many affected neonates develop severe complications in the immediate postoperative period. Pneumonia, sepsis, and peritonitis are among the most frequent complications, and the development of bowel stasis or ileus is common. A prognosis of a rate of 39 to

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44% short-term survival has been reported.[6-8] When registered animals are involved, a letter should be sent to the appropriate breed registry stating that the defect has been corrected.

Volvulus of the Large and Small Intestine Around the Mesenteric Root

Volvulus of the large and small intestines around the mesenteric root leads to severe colic and relatively rapid abdominal enlargement. Circulatory shock develops rapidly. Ruminants of any age are susceptible, but most cases are seen in preruminant neonates. Severe colic is seen, including kicking and vocalization. Affected animals rapidly become recumbent, and hypovolemic shock develops. The heart and respiratory rates increase drastically as shock develops. Variable-pitched resonant sounds may be heard bilaterally over the abdomen with the use of simultaneous percussion and auscultation. In affected adult cattle, the tympany is restricted to the right side. Succussion reveals splashing sounds, particularly on the right side. Rectal examination reveals distended loops of gut. Surgical correction is the only successful treatment option.[9] The prognosis depends on the degree of devitalization of bowel. Animals that undergo surgical correction during the early stages respond better.

Volvulus of smaller portions of the intestinal tract leads to signs similar to those of complete intestinal volvulus around the root of the mesentery, but often the onset is more progressive. Colic with accompanying tachycardia, ruminal stasis, and anorexia is present to varying degrees. The abdomen is moderately distended on the right, as viewed from the rear. Simultaneous auscultation and percussion on the right side reveal multiple-pitched, resonant pings from the gas accumulated proximal to the obstruction. Rectal examination may reveal scant feces, mucus, or blood. The affected bowel usually is palpable as grossly distended with gas and some fluid. Because of their relatively long mesentery, the spiral colon (or part of it), the distal jejunum, and the proximal ileum may develop an obstructive volvulus. Therapy requires correction of acid-base and electrolyte abnormalities and rapid surgical manipulation by means of celiotomy.

Intussusception

In the development of an intussusception, the oral portion of gut (intussusceptum) usually is engulfed and propelled distally by peristaltic action of the enveloping portion (intussuscipiens). Constable and colleagues reported

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that the prevalence is increased among calves younger than 2 months of age in comparison with adults and in Brown Swiss cows in comparison with Holstein cows.[10] The condition has also been reported in goats[11] and in sheep.[12,13] Intussusception may occur in either the large or the small intestine of calves but is much more frequent in the jejunum.[10] Clinical signs include colic caused by the tension on the mesentery on the invaginating portion of the intestine. With time, ischemia of this portion leads to pain and eventually loss of sensation. Distention of the intestine with fluid and gas proximal to the obstruction leads to abdominal pain. Therefore an affected cow may show violent behavior or kicking at the abdomen in the first few hours that is eventually succeeded by treading and repeated lying and standing. Over the course of several days, the intussusceptum may become totally devitalized and slough. This is accompanied by focal peritonitis, and in the event of bowel rupture, diffuse peritonitis and toxic shock develop. The exact cause of intussusception remains unknown. Intramural or luminal mass or lesions, viral enteritis, intestinal parasitism, abrupt dietary changes, administration of intestinal motility modifier drugs, and foreign body or prior surgery have all been reported to be potential predisposing factors, but in most cases, intussusception is idiopathic.[10]

Dehydration develops as gastrointestinal secretions accumulate in the gut lumen. In adults, hypochloremic, hypokalemic metabolic alkalosis develops gradually. The rumen becomes distended with fluid as its contents become more finely digested and abomasal reflux accumulates. The right side of the abdomen (or both sides) also enlarges as a result of the distention of the small intestine. Simultaneous auscultation and percussion of the right side of the abdomen reveal areas of variable-pitched resonance. Rectal examination reveals distended loops of small intestine. The intussusception may be palpable as a firm mass, painful when palpated. Feces may eventually be absent. The examiner may find mucus and blood in the descending colon. In long-standing cases the scant feces are very dark red and must be distinguished from the black feces (melena) associated with abomasal bleeding. Fluid obtained by abdominocentesis reveals an elevation in erythrocytes and leukocytes counts and an elevated protein concentration. If the condition is long-standing and bowel rupture has occurred, bacteria may be present. CBC may reveal neutrophilia and an elevated plasma fibrinogen level.

In neonates with enteritis, fecal output decreases and appetite is lost when the intussusception develops. A fever may develop as peritonitis occurs. Affected calves and other neonates may not exhibit obvious signs of colic. Percutaneous

abdominal palpation with both hands in an attempt to detect a mass is often successful in delineating an intussusception in a neonate. When neutrophilia, hyperfibrinogenemia, and loss of appetite develop after enteritis, intussusception should be suspected.

Findings compatible with an intestinal obstruction are seen on transabdominal ultrasonography (distended intestinal loops, decreased or absent peristalsis). In some cases, the affected intestinal segment may be visualized. At that time, ultrasonographic appearances described as “target-like” or “bull's eye” lesions or as multiple-layered, onion ring–type masses with a “sandwich configuration” are observed in transversal and longitudinal views of the intestine, respectively (Fig. 32.137).[14]

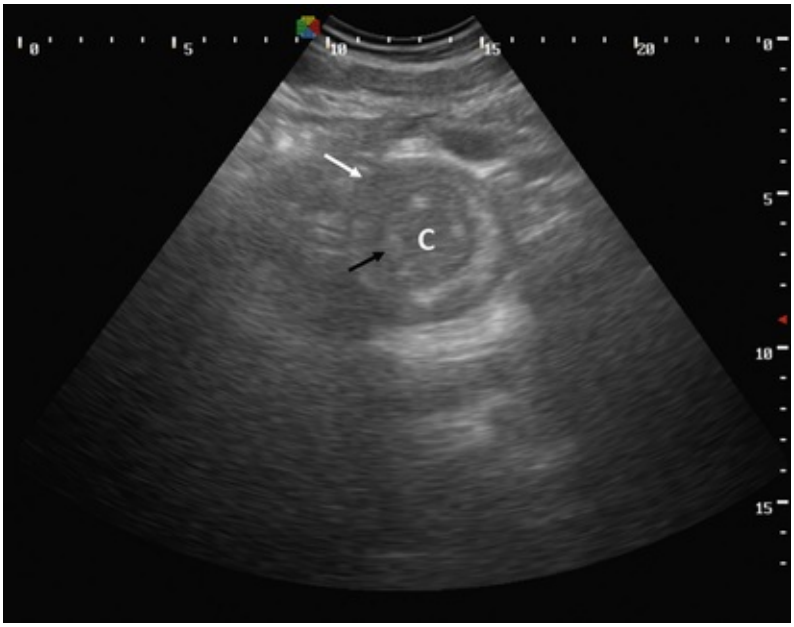


FIG. 32.137 Right abdominal ultrasonography of a cow with an intussusception: intussuscipiens *(white arrow),* intussusceptum *(black arrow),* and core *(C).* (Courtesy Centre Hospitalier Unversitaire Vétérinaire de l'Université de Montréal).

Treatment requires both surgical correction of the obstruction and parenteral restoration of fluid and electrolyte balance. Because of the losses of chloride and potassium and the development of alkalosis, 0.9% sodium chloride solution with 30 mEq/L or more of added potassium chloride is recommended. Intravenous potassium should not be given more rapidly than 1 mEq/kg/h (conservative rate is 0.5 mEq/kg/h). Once intestinal patency has been restored, oral fluid and

electrolyte supplementation usually allows the patient to achieve normal status.

The prognosis is usually good if surgery is performed early in the course of disease. Complications such as peritonitis can occur and need to be treated appropriately to maintain the chance of success. A retrospective study of 336 cases of intussusception demonstrated a postoperative survival rate of 43% and an overall survival rate of 35%.[10]

Intestinal Incarceration

Intestinal obstruction may occur in ruminants as a result of accidental entrapment of intestinal loops, usually of jejunum, around remnants of embryonic structures or through an acquired defects in mesentery, a ligaments or the abdominal wall. Remnants of the urachus, the omphalomesenteric duct, the left umbilical vein, and the ductus deferens have been described as responsible for incarceration of the jejunum. The authors of one report indicated that 26% of cows examined had a persistent round ligament of the liver and falciform ligament.[15] Thus tears in the falciform ligament that lead to intestinal entrapment may be among the most common causes of the relatively rare problem of intestinal incarceration in cattle. Duodenal obstruction caused by malposition of the gallbladder was also reported in a heifer.[16] Intestinal adhesions caused by intraperitoneal injections of irritating substances may also lead to intestinal obstruction. Initial signs of colic followed by depression, anorexia, progressive abdominal distention, and absence of feces usually develop. Distended loops of small intestine usually are palpable rectally. Treatment of intestinal incarceration requires surgical intervention.

Cecum Dislocation

Cecum distention may be classified in three ways: (1) In cecal dilation, the cecum is distended only by gas, and the apex of the cecum is displaced toward the rectum and may be palpable transrectally; (2) in cecal retroflexion (which can cause vascular damage and ischemia; i.e., volvulus,: the cecum is distended, displaced, and folded dorsally or ventrally, the apex of the cecum is consequently oriented cranially and is usually not palpable rectally; and (3) in cecal torsion, the cecum is distended and rotated along its long axis, and the apex of the cecum is displaced toward the rectum and can be palpated transrectally.[17] In a large study of 461 cases of cecal dilation, the preoperative clinical diagnoses based on rectal palpation were cecal dilation alone in 291 animals (63.2%), cecal

dilation and retroflexion in 94 animals (20.4%), and cecal dilation and torsion in 20 animals (4.3%); in the remaining 56 animals, no diagnosis of cecal dilation could be made preoperatively.[18] In adult cattle, cecal dilation generally is believed to precede retroflexion or torsion.

The etiologic and pathophysiologic features of cecal dilation and retroflexion or torsion remain unknown. Different feeding or management practices may predispose animals to cecal disease.[18] Increased luminal concentration of VFAs was classically believed to play a major role in the etiopathogenesis of cecal disorders. However, results of studies on the effect of VFAs on cecal motility have been contradictory. In one study, increased concentration of VFA had only minimal effect on large intestine motility and was unlikely to play an important role in the development of cecal disorders.[19] Factors that affect cecal motility, as described for displaced abomasum, are probably similar.

Cecal dilation produces a more gradual onset of illness than that noted with cecal retroflexion or torsion. The time required for dilation to develop into retroflexion or torsion is unknown. With simple dilation, feed intake and milk production decrease. Mild abdominal pain may be observed. Feces are usually still produced, but the consistency may be loose and the amount reduced. Rumen motility is decreased. Distention of the right paralumbar fossa without the ribs being sprung is frequently observed in the authors' clinic and has been mentioned in different reports. However, Braun and colleagues[18] reported that the abdominal shape was modified in only 51 animals of the 461 cattle affected with cecal dilation, retroflexion, or torsion. Of those animals, 22 had a slight distention of the right flank, 20 a bilateral abdominal distention, and 7 a pear-shaped abdomen. The most important clinical findings for the diagnosis of cecal dilation are (1) the presence of a large area of resonance (ping), auscultable from the tuber coxae to a variable distance cranially (see Chapter 1), which may or may not be associated with a positive succussion of the right flank[18]; and (2) the transrectal palpation in the pelvic canal or nearby of the apex of the gas-filled cecum. Cattle with cecal retroflexion or torsion have more severe clinical signs. They show an abrupt onset of anorexia, agalactia, and severe abdominal pain. Tachycardia and forestomach stasis are also present. Feces are scant or absent. The abdominal distention is usually more severe than in simple cecal dilation. The area of resonance in the right paralumbar fossa is larger, and fluid usually can be detected in the cecum and proximal colon by succussion. In cases of retroflexion, the apex of the cecum is usually not palpable rectally; rather, the

distended body of the cecum or proximal colon impinges on the pelvic canal because the apex is directed cranially. In cases of cecal torsion, the apex of the cecum can be palpated rectally as well as a tense ileocecocolic ligament that spirals around the cecum.[17] Distention of the small intestine may be palpated with either dilation or retroflexion or torsion.

Although some cows with simple dilation have no acid-base abnormalities, most cases of cecal retroflexion are accompanied by some degree of metabolic alkalosis with hypochloremia and hypokalemia. Hypocalcemia is reported to be observed in approximately 85% of cases of cecal dilation, retroflexion, or torsion.[18]

Medical management of cecal dilation is usually successful with fluid therapy to restore normal hydration status and correction of electrolyte abnormalities, including hypocalcemia. Administration of NSAIDs to control abdominal pain is also important. Laxatives have also been recommended for the medical treatment of cecal dilation. However, Braun and coworkers[20] reported that the use of laxatives (liquid paraffin) for the treatment of cecal disorders delayed the time to first defecation. Moreover, magnesium hydroxide may be responsible for detrimental effects such as metabolic alkalosis,[21] increased ruminal pH,[22] and decreased ruminal microbial activity.[22] Prokinetic drugs that can be used in the management of cecal disorders are presented in the section on the acute abdomen in cattle. Affected animals should be fed a high-fiber diet.

Braun and colleagues[18] reported that 122 of 461 animals with cecal dilation, retroflexion, or torsion were first managed medically. Of these 122 animals, 42 eventually required surgery. Considerations for medical versus surgical treatments are presented in the Acute Abdomen in Ruminants section. Cattle with cecal retroflexion or torsion require immediate surgical intervention, IV fluid, and pain management (NSAIDs). The prognosis for surgical patients depends on the degree of ischemic injury to the cecum and other structures involved in the obstruction. The recurrence rates after surgery range from 10% to 13.8% within a year of the first incident.[18] In cattle with recurrence of cecal dilation or with devitalized portion of the cecum wall, amputation of the cecum is recommended.

Intestinal Tumors

Intestinal tumors are rare in cattle. The most commonly reported intestinal tumors in cattle are adenocarcinomas. However, lymphosarcoma, adenoma,

adenomatous polyps, carcinoid, leiomyoma, leiomyosarcoma, and fibrosarcoma have also been described.[23] The incidence of adenocarcinoma in sheep is relatively high in some areas of the world, such as New Zealand.[24] The predisposing factors for adenocarcinomas are not known, but different environmental carcinogens have been suspected.[24,25] In sheep, no association with infectious agents (herpesviruses, *Helicobacter* spp., or *Mycobacterium avium* subsp. *paratuberculosis*) was found.[24] Genetic predisposition is suspected,[25] but no significant genetic defects were found in one study.[24]

Affected cattle or sheep may have a protracted course of weight loss with no other observable signs until near death. Alternatively, there are reports of acute gastrointestinal disturbances manifested by colic, abdominal distention, and auscultable right-sided pings.[26] Although these cases are rare, they must be differentiated from other causes of acute obstruction in cattle such as cecal volvulus, intussusception, or abomasal volvulus. In cattle in which rectal examination is possible, the lesion may be detected on routine examination as an intramural mass or annular constriction of the jejunum or ileum. In sheep, the diagnosis is usually made at necropsy. Clinical signs in affected animals might include diarrhea, abdominal distention caused by the accumulation of gas and ingesta proximal to the obstruction, or ascites. The well-characterized lesions in sheep involve local spread of the tumor through the lymphatic system and intraperitoneally. Ultimately, cellular deposits occur on all visceral and parietal peritoneal surfaces, severely impairing lymphatic drainage from the abdomen.

Mesenteric Fat Necrosis

Mesenteric fat necrosis affects cattle of all breeds, but more commonly Aberdeen Angus and Jersey cattle.[27] It has also been reported in a pigmy goat.[28] The cause remains unknown but dietary factors have been implicated, such as consumption of feed containing long-chain, saturated fatty acids; trace element deficiency; trauma; hormonal disturbance; and ingestion of endophyte-infected fescue.[27,28] The lesions develop as an inflammatory response around degenerating adipose cells. The triglycerides in these cells are thought to undergo hydrolysis to glycerol and fatty acids. Fatty acids with longer carbon skeleton have greater degree of saturation and are more resistant to removal by normal cellular mechanisms. Remaining clumps or crystals of fatty acids serve as inflammatory foci for the subsequent necrotic masses.[27] Affected cattle have subnormal serum levels of free cholesterol and elevated serum levels of free

fatty acids.[29] Cattle with fat necrosis may eventually develop an intestinal obstruction. The clinical signs resemble those of progressive intestinal obstruction from other causes. Weight loss, anorexia, diarrhea, bloody stool, abdominal enlargement, and right-sided ping are all possible signs. Fever, tachycardia, and signs of discomfort such as tenesmus, treading, and teeth grinding may be seen as the obstruction becomes more severe. Many affected cattle have no clinical signs, and the condition is discovered during rectal examination for other reasons. Rectal examination may be impossible because of stricture of the rectum, or dystocia may occur as a result of the necrotic fat masses in the pelvic canal. Fat necrosis usually affects mature cattle,[27] but there is a report of a 6-month course of illness attributed to fat necrosis in a 13-month-old Black Angus heifer.[30] Ultrasonographic appearance of abdominal fat necrosis has been described and appears to be a useful diagnostic tool, combined (or not) with ultrasonography-guided mass biopsy.[31]

Animals with fat necrosis that becomes clinical usually are not treated. Different treatments have been attempted over the years, but none was considered effective. Experimental therapy of subclinical fat necrosis with a compound that alters lipid metabolism in fungi was successful in one study.[29] The fungicide isoprothiolane was given at a dosage of 20 g/day PO for 8 weeks. Approximately half of the treated cows had a 50% reduction in necrotic masses by 12 weeks; at follow-up evaluation in 1 year, the masses were not detectable in half the surviving cows. Cows given such unapproved drugs should not be used for food.

Hemorrhagic Bowel Syndrome (Jejunal Hemorrhage Syndrome)

Hemorrhagic bowel syndrome, also called *jejunal hemorrhage syndrome*, is an acute enteric disease of cattle characterized by segmental intraluminal hemorrhage with subsequent obstruction of the small intestine. The disease seems to have been described for the first time in 1991[32] and is now reported in different countries. Hemorrhagic bowel syndrome affects mainly dairy cows, but it is also reported in beef cows and bulls.[33,34] It is principally a sporadic disease, but outbreaks in dairy herds have been reported.[35,36]

The pathogenesis, causes, and clinical presentation of hemorrhagic bowel syndrome is presented in the Diseases Caused by *Clostridium perfringens* Toxins (Yellow Lamb Disease, Lamb Dysentery, Necrotic Enteritis, Enterotoxemia)

section.

The prognosis for animals with hemorrhagic bowel syndrome is guarded. Mortality rates of 100%[33] and 77%[37] have been described. However, prognosis of 55% (20 of 36)[34] and 58% (18 of 31)[38] have been reported from two referral centers. In the first study, two animals of five that were treated medically and 18 animals of 30 treated surgically survived.[34] In the other study, all dairy cows underwent surgery; among the 18 animals that survived, 6 had a recurrence within the following 12 months and 13 were still alive after 12 months. In this study, short-term prognosis was reported to be significantly improved when the blood clot could be dislodged by massage.[38]

Functional Ileus (Pseudoobstruction)

Failure to pass feces usually is a sign of intestinal obstruction. However, in adult lactating dairy cattle, a condition of functional ileus (or pseudoobstruction) of the intestinal tract that mimics complete intestinal obstruction is commonly observed. The condition resolves with medical treatment (fluids, calcium, and pain management); in rare instances, surgical decompression of the affected bowel is required. Affected cows are most often in early lactation, and treatment is sought for partial anorexia. Colic sometimes is the presenting sign. Clinical examination reveals a normal temperature, a normal to elevated heart rate, and normal respiratory rate. Ruminal motility is decreased. Slight right-sided abdominal enlargement may be seen early and may progress to extreme distention of the abdomen on the right. No borborygmi is heard on the right side, but fluid tinkling sounds may be audible. Simultaneous auscultation and percussion reveal areas of variable-pitched resonance. Succussion produces sloshing sounds. On transrectal examination a distended spiral colon, cecum, or small intestine may be palpated. Early in the course of the disease, the distention is mild, and compression easily flattens the affected bowel. If abdominal distention is severe, introducing the arm into the abdominal cavity may be difficult because of the pressure of distended bowel at the pelvic inlet. No feces are passed, but the examiner's arm may be coated with sticky mucus and feces with a stale odor. Serum electrolytes and acid-base status are usually normal or toward a mild metabolica alkalosis. Serum calcium may be decreased. Differential diagnoses to consider include intussusception, intestinal incarceration, intestinal volvulus, and cecal dilation. There is no blood in the feces, and no masses are palpable rectally with functional ileus.

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Because most obstructive lesions of the intestine in cattle are not immediately life-threatening, symptomatic therapy combined with close observation may be elected for 24 hours. If surgery is necessary in the absence of an obstructive lesion, the bowel may be decompressed and drained. This is a laborious procedure that requires multiple punctures unless the distention is restricted to the cecum and spiral colon. Despite the lack of correction of a specific underlying defect, many affected cows pass feces soon after an exploratory celiotomy. Manipulation of the intestinal tract alone seems to have beneficial effects. This response is difficult to differentiate from the spontaneous recovery that may occur without surgery in cows. Moreover, medical treatment (IV fluids and pain control medication) is commonly provided during surgery, which makes it difficult to assess the effect of surgery alone. Relief of distention of portions of the intestinal tract may remove reflex inhibition of motility that can occur in response to extreme stretching of mural tension and pain receptors. The cause of functional ileus of the intestine is unknown, and little pathophysiologic information has been elucidated. Medical management is described in detail in the Acute Abdomen in Ruminants section. It mainly includes administration of fluids, calcium, and NSAIDs. Numerous practitioners also administer oral laxatives, but as mentioned earlier, the practice of using magnesium salts may be questionable and could have deleterious effects.

Diseases Caused by *Clostridium perfringens* Toxins (Yellow Lamb Disease, Lamb Dysentery, Necrotic Enteritis, Enterotoxemia)*

Francisco A. Uzal • Bradford P. Smith

Definition and Etiology

C. perfringens is a gram positive, toxin-producing, anaerobic, spore-forming rod that causes a variety of diseases in human beings and animals. Some biotypes are normal inhabitants of soil, and some are commensal intestinal organisms of humans and animals. Clinical isolates have historically been assigned to one of five types (A through E) on the basis of possession of the genes encoding four so-called major toxins (alpha-, beta-, epsilon-, and iota-toxins).This nomenclature has, however, been revised, and two additional toxinotypes, F and G, have been added on the basis of production of enterotoxin (that of *C.*

perfringens) and necrotic enteritis B–like toxin, respectively (Table 32.22).[1]

TABLE 32.22
New Toxinotyping System for *Clostridium perfringens*[1]

Type	Toxin Produced					
	Alpha	Beta	Epsilon	Iota	Enterotoxin	NetB
A	+	−	−	−	−	−
B	+	+	+	−	−	−
C	+	+	−	−	−/+	−
D	+	−	+	−	−/+	−
E	+	−	−	+	−/+	−
F	+	−	−	−	+	−
G	+	−	−	−	−	+

In addition to these six typing toxins, individual strains of *C. perfringens* may produce any of several other nontyped toxins, which may or may not contribute to the virulence of this microorganism, such as perfringolysin O and beta-2–toxin.[2]

C. perfringens enterotoxin is mainly responsible for the second most prevalent type of food poisoning in humans in the United States and also for a less prevalent antibiotic-associated diarrhea; its role in animal disease remains poorly determined.[2] Because the full name of this toxin is *C. perfringens* enterotoxin, the latter should be avoided to refer to other clostridial toxins produced in the intestine.

The different toxinotypes of *C. perfringens* cause diseases that are almost exclusively mediated by their powerful toxin arsenal.[2] Several diseases in many animal species have been ascribed to *C. perfringens*, but the ubiquitous nature of the organism and the fact that it rapidly overgrows into tissues after death makes the significance of its isolation questionable. This is particularly true for type A, which is the toxinotype most commonly found in the intestine of clinically healthy animals and in the environment.[3]

One additional potentially confusing bit of nomenclature concerns the term *enterotoxemia.* Although this term is widely applied to various diseases caused by *C. perfringens*, it is strictly appropriate only for diseases in which the major signs are caused by systemic spread of a toxin produced in the intestine through the blood. Whereas some *C. perfringens* diseases present as true enterotoxemias (e.g., type D enterotoxemia of sheep), others are characterized by the effects of the toxin only in the intestinal tract (e.g., colitis associated with the chronic form

of type D disease in goats) and a third group may show a combination of both forms (e.g., type C infection in multiple species).[4]

Diseases produced by the major types of *C. perfringens* in livestock are discussed in the following paragraphs. Type E is only occasionally isolated from livestock, and its role in animal disease has not been confirmed. Likewise, the newly defined types F and G are not considered to have a significant role in diseases of livestock.[1] These three types are therefore not discussed here.

General Considerations on Diagnosis of Disease Caused by *Clostridium perfringens*

Meaningful diagnosis of *C. perfringens* as the cause of death or disease in an animal requires an integrative, open-minded approach. Type A is routinely isolated from soil and intestine of clinically normal animals. Types C and D are only rarely isolated from soil but can occasionally be isolated from asymptomatic animals. The isolation of *C. perfringens* from a necropsy specimen is therefore not by itself sufficient basis for the diagnosis. However, if some of its toxin is also demonstrated in gut contents and the history and lesions are compatible, a diagnosis of death from *C. perfringens* intoxication can be made. This probably does not apply to alpha-toxin, as this toxin is produced by all types of *C. perfringens* and it is very frequently found in the intestine of clinically normal animals.[3]

Typing of *C. perfringens* is mostly achieved by a multiplex PCR technique that detects the genes for toxin production in a clinical isolate.[1,5] In addition, alpha-, beta-, and epsilon-toxins can be detected with commercially available assays. Meaningful samples for bacterial isolation come from freshly dead animals. Samples of gut contents should be collected into sterile containers and cooled or frozen. Whereas alpha- and epsilon-toxins are very robust and can be detected in samples of intestinal contents many hours or even days after a sample is collected, beta-toxin is very sensitive to the action of trypsin and other proteases and breaks down very soon after production, which causes results to be false negative; freezing or rapid submission of samples to the laboratory for beta-toxin investigation is paramount.[6]

Clostridium perfringens Type A (Yellow Lamb Disease)

C. perfringens type A can be found in many soils and is a normal inhabitant of the gut in many species. Although all seven types of *C. perfringens* produce

alpha-toxin, some type A strains may produce more than other types. The toxin is a phospholipase and causes lysis of RBCs, platelets, and leukocytes (equine and caprine RBCs are resistant to the hemolyzing effects of the toxin).[7]

The only type A disease on which there seems to be general agreement among several authors is the so-called yellow lamb disease (so named because of the icteric nature of necropsy specimens from such lambs). This is an uncommon disease characterized by widespread hemolysis, which leads to anemia, weakness, hemoglobinuria, and icterus. Affected animals have a high temperature and usually die within 6 to 12 hours of onset. Differential diagnoses for yellow lamb disease include other causes of hemolytic disease, such as leptospirosis and copper toxicosis. As with other type A infections, the diagnosis is always questionable because of the commensal nature of the organism and its rapid invasion after death. The finding of predominantly large Gram-positive rods in impression smears from intestinal mucosa and high counts (>10^6 colony-forming units/g) of *C. perfringens* type A, lend support to the diagnosis.[7]

Although type A isolates have been suggested to be implicated in enteritis, abomasitis and enterotoxemia of cattle,[8] definitive proof of the role *C. perfringens* in these syndromes is lacking.[2] Type A isolates were also thought to be associated with the so-called hemorrhagic bowel syndrome of cattle,[9] but this does not seem to be the case, and the cause of this syndrome remains undetermined.[3]

Clostridium perfringens Type B (Lamb Dysentery)

Definition and Etiology.

Lamb dysentery is a disease of young lambs that has been described in Britain, South Africa, and the Middle East. Type B disease has not been reported in the American continent. Its clinical course and presentation are similar to those of necrotic enteritis caused by *C. perfringens* type C.[4,10] *C. perfringens* type B has been postulated, although not proved, to be involved in the pathogenesis of multiple sclerosis in humans.[11,12]

Clinical Signs and Differential Diagnosis.

Affected lambs younger than 1 week of age become depressed and die. A yellowish diarrhea becomes brown from blood as the disease progresses. Morbidity rates may be high, and the mortality rate approaches 100%. The

disease must be differentiated from types C and D enterotoxemia in lambs.[10]

Pathophysiology.

The pathogenesis of type B infections is not fully understood. On the basis of experimental infections, it was postulated that intestinal lesions are produced by beta-toxin, whereas lesions in the brain are produced by epsilon-toxin.[13] Because epsilon-toxin requires trypsin for activation, whereas beta-toxin is degraded very quickly in the presence of trypsin and other proteases, it is thought that, depending on which of these toxins exerts its major action in a given case, clinical signs and lesions could be different.[13]

Gross and Microscopic Findings.

Necropsy findings include necrotizing enteritis and ulcers (rarely perforating) in the small intestines and dehydration of the carcass and tissues. Focal symmetrical encephalomalacia is occationally observed.[10]

Diagnosis.

A presumptive diagnosis of type B infection can be made on the basis of clinical signs and lesions, including diarrhea, neurological signs, necrotizing enteritis and, occasionally, focal symmetric encephalomalacia. Confirmation of the diagnosis should be based on detection of epsilon- and beta-toxins in the intestinal content. Isolation of *C. perfringens* type B from intestine adds certainty to the diagnosis, but it is not confirmatory as this type may be occasionally found in the intestine of clinically normal animals.[10]

Treatment, Prevention, and Control.

Sanitation and the use of type B vaccine aid in prevention and control. Types B, C, and D toxoids cross-protect because of the overlap in toxin types. Treatment is usually unsuccessful because of the acute nature of the disease.[10]

Clostridium perfringens Type C (Necrotic Enteritis, Neonatal Hemorrhagic Enterotoxemia, Struck)

Definition and Etiology.

C. perfringens type C elaborates the alpha-toxins, common to all types, and the beta-toxins. Beta-toxin is the main virulence of *C. perfringens* type C, and it is

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required for type C isolates to produce disease. The amount of this toxin produced varies greatly among isolates and determines the virulence of a type C strain.[14]

Necrotic enteritis is primarily a disease of neonates and occurs mainly in calves, lambs, foals, and piglets. A similar disease in adult sheep, known as *struck,* has a very limited geographic range in Great Britain.[15,16]

Clinical Signs and Differential Diagnosis.

Affected animals may die acutely without diarrhea, but this is rare. The diarrhea may be yellow or, in more hemorrhagic cases, brownish. Gray-red streaks of fibrin and blood which look much like necrotic mucosa may be present in the stools. Foals with type C disease at first show acute abdominal pain, then explosive yellow diarrhea that becomes brown and hemorrhagic. Affected animals become dehydrated, anemic, weak and moribund, despite intensive therapy. Neurologic signs due to epsilon-toxin may be observed in lambs, foals and calves with type C disease. Morbidity and mortality rates are high, but the disease is quite sporadic in occurrence. Salmonellosis and coccidiosis should be considered in the differential diagnosis of ruminants. In foals, the disease must be mainly differentiated from salmonellosis and enteritis produced by *C. difficile* infection.[15,16] Co-infection by *C. perfringens* type C and *C. difficile* may also occur in foals.[17]

Pathophysiology.

The causative beta-toxin is readily destroyed by proteolytic enzymes such as trypsin present in the intestine. Neonates are especially predisposed to beta-toxin attack by the trypsin inhibitor effect of the colostrum, the function of which is to prevent proteolytic degradation of immunoglobulins. The scattered cases of necrotic enteritis in adult animals may be the result of diets containing trypsin inhibitors such a soy bean (high content), beans, peas, peanuts, or sweet potatoes and others. Type C disease has been reproduced experimentally in lambs and goats by administration of type C cultures with soybean flour or other trypsin inhibitors.[18,14]

In humans, type C infection is known as *enteritis necroticans*, *darmbrand,* or *pigbel,* and it occurs sporadically in several Southeast Asian countries and occasionally in other parts of the world. Enteritis necroticans was highly prevalent in the 1960s in Papua New Guinea, where most cases were observed in

malnourished children thought to be trypsin deficient.[15,19,20,21]

Ingestion of a protein-rich diet into a protease deficient intestinal tract allows rapid growth of *C. perfringens* organisms, which produce large amounts of beta-toxin that is not destroyed by proteases. Beta-toxin results in necrosis and invasion of deeper intestinal layers. Death results from the direct effects of the severe diarrhea or may be caused by secondary bacteremia or toxemia from the compromised gut barrier.[16]

Epidemiology.

Neonates that ingest type C organisms during the first few days of colostrum feeding are at risk. They pick up the organism from an environment contaminated by a symptomatic or asymptomatic shedder, or from contaminated feed. Type C may be isolated from asymptomatic individuals on occasion but it is not usually considered a normal commensal as is type A. Once established on a premise, the disease may become endemic. In foals the disease is significantly associated with housing in a stall or dry-lot during the first few days of life, previous presence of livestock on the farm, low amounts of grass hay fed postpartum, being born on dirt, and having stock horse parentage (e.g., Quarter Horse, Paint).[22]

Gross and Microscopic Findings.

Necrosis of the mucosa of the small intestine, especially the jejunum, is the consistent finding in all species. The large intestine may be similarly affected in horses, whereas in other species it may be normal except for intraluminal blood. The peritoneal cavity often contains excessive fluid, which clots when exposed to air because of a high content in protein. The mesenteric lymph nodes may be hemorrhagic. Microscopic study of affected gut shows necrosis and hemorrhage throughout the mucosa and submucosa, as well as mucosal and submucosal thrombosis. The tips of the necrotic villi and the surface of the colonic mucosa are covered with numerous large Gram-positive rods.[15,16]

Diagnosis.

Although a presumptive diagnosis may be established on the basis of epidemiologic study and gross and microscopic pathologic study, coupled with isolation of *C. perfringens* type C from feces or intestinal content, confirmation of the diagnosis is based on demonstrating the beta-toxin in these specimens.

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Because this toxin is so sensitive to the action of proteases, failure to detect beta-toxin does not preclude a diagnosis of *C. perfringens* type C infection.[15,16]

Treatment, Prevention, and Control.

Once a case becomes clinically apparent, treatment generally is unsuccessful because of the fulminant nature of the disease. Foals can be treated with supportive intravenous broad-spectrum antibiotics (to cover Gram-negative and Gram-positive bacteremia caused by loss of gut integrity), oral metronidazole, fluids, plasma (intravenous and oral), withdrawal of milk for 24 hours, and intravenous *C. perfringens* type C antitoxin. Metronidazole (10 mg/kg PO or IV given twice daily) can be given to at-risk foals during an outbreak, beginning at 8 to 12 hours of age and continuing for 5 days. Toxoid has been administered to horses to control the disease on an apparently endemic property, with good results. Experimental oral treatment with trypsin has been used with apparent promising results. Vaccination is not routinely practiced, but it has proved to be effective in problem herds (J. Glenn Songer, personal communication). *C. perfringens* type C is a common component of multivalent vaccines. Because most cases of type C infection affect neonates, vaccination should be practiced on the dams. The primary vaccination series consists of two injections, approximately 1 month apart, with the final dose given roughly 2 weeks before parturition, and a yearly booster thereafter. Neonates should be vaccinated at 8 and 12 weeks of age on problem farms.[4] Also see Chapter 48, *Clostridium perfringens* toxoids.

Clostridium perfringens Type D (Enterotoxemia, Overeating Disease, Pulpy Kidney Disease)

Definition and Etiology.

Enterotoxemia caused by *C. perfringens* type D is a disease of major importance in sheep and goats, and of lesser importance in cattle. This type is not a common soil organism, as is type A, but it may be isolated from the feces of a relatively small percentage of apparently normal sheep and goats, and less often, cattle. Most clinical disease occurs in animals fed a highly nutritious diet, especially grain-fed livestock. The disease occurs most frequently in animals older than 2 weeks, but rare cases have been seen in lambs as young as 1 day of age.[2,3,4]

■ Clinical Signs and Epidemiology

Sheep.

The sudden death of a well-fed, rapidly growing animal is the most common presentation of the acute form of enterotoxemia. The disease may run its course in 30 to 90 minutes, with affected lambs showing ataxia, trembling, stiff limbs, opisthotonos, respiratory difficulty, convulsions, coma, and death. Diarrhea is rarely observed. At the onset of clinical signs, the animal may be hyperglycemic, and at death it may be glycosuric. The differential diagnoses should include other causes of neurologic signs such as listeriosis, enterotoxigenic *E. coli* infection, septicemia, polioencephalomalacia, acidosis, tetanus, and botulism, as well as causes of sudden death such as anthrax and black disease.[4]

Subacute and chronic cases may result in focal symmetric encephalomalacia (see Chapter 35) which causes affected lambs to be dull and unresponsive to normal environmental stimulation, and show respiratory difficulty. The major differential diagnosis is polioencephalomalacia.[4]

Morbidity rates are usually low, but the nature of the disease may be insidious with cases occurring over several days or weeks. Most affected animals die.[4]

Goats.

The disease in goats may be acute, subacute or chronic; the acute form is very similar to the acute form described in sheep, whereas the chronic form is confined to the intestinal tract, mainly the colon, diarrhea being the main clinical sign. The subacute form of type D enterotoxemia in goats includes a combination of the neurologic and respiratory signs observed in the acute form of the disease and the diarrhea characteristic of the chronic form.[4]

As in sheep, morbidity rates are usually low, although outbreaks affecting a significant number of dairy goats have been reported. Lethality rates are also close to 100%.[4]

Cattle.

Type D disease occurs rarely in cattle, and information about clinical signs and epidemiologic features in this species is scant. Experimental intravenous injection of type D epsilon-toxin and intraduodenal infusion of culture supernatant of *C. perfringens* type D in calves produced neurologic and respiratory signs similar to those described in the acute and subacute forms of

the disease in sheep and goats.[24,25,26]

Pathophysiology.

Some factor of overnutrition, often sudden access to heavy grain feeding or very rich pasture, provides substrate for rapid proliferation of the type D organism, which leads to elaboration of the epsilon-prototoxin. In vitro, production of epsilon-toxin by *C. perfringens* type D is enhanced in the absence of glucose. This seems similar to what occurs in vivo, when an animal is suddenly provided with excessive quantities of starch-rich food but adaptation of the ruminal flora is delayed. As a consequence of this, undigested starch reaches the intestine, and *C. perfringens* type D is likely to take advantage of it. The lack of digestion of starch would also be responsible for the absence of glucose in the small intestine, which enhances epsilon-toxin production.[27,4]

Other factors that alter the intestinal environment (i.e., heavy parasite infestation) may also predispose sheep to type D enterotoxemia.[27,4] Although it has long been assumed that the same factors also predispose goats to type D enterotoxemia, little information is available in this regard, and cases of enterotoxemia have been reported in goats fed hay diets for several months.[4]

In the intestine, cleavage of the relatively inactive epsilon-prototoxin by proteases yields the fully active toxin. Epsilon-toxin thus increases intestinal permeability, facilitating its own absorption into the blood. Once in circulation, epsilon-toxin causes vascular damage with increased vascular permeability, which leads to edema in a variety of organs, notably the lungs and brain, and fluid accumulation in body cavities.[28,29] When affected animals survive 24 hours or more, the edema in the brain leads to parenchymal necrosis, the so-called focal symmetric encephalomalacia.[30] Epsilon-toxin crosses the blood-brain barrier and has also a direct effect on neurons and oligodendrocytes.[29]

Gross and Microscopic Findings

Sheep.

In sheep that die of acute enterotoxemia, the carcass is usually in very good nutritional condition. Evidence of diarrhea around the rump may be observed, but this is rare. There is frequently an excess of yellowish pericardial, thoracic and abdominal fluid, which may contain fibrin strands; this fluid clots on exposure to air. Pulmonary congestion and edema and subserosal hemorrhages

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are evident. Usually there is no visible inflammation throughout the gastrointestinal tract, although the small and large intestine may be hyperemic and moderately distended with gas and liquid content. Softening of the renal parenchyma, so-called “pulpy kidney” may be present in a small number of cases, but it is of little, if any, diagnostic significance, inasmuch as it is probably consequence of accelerated autolysis and this change is never observed in freshly-dead carcasses.[27,3]

In the subacute and chronic cases, the gross lesions are similar to those in the acute form, but herniation of the cerebellar vermis or focal symmetrical encephalomalacia, or both, may be seen in the brain.[27,3]

Microscopic changes in the brain of sheep with type D enterotoxemia are observed in approximately 90% of acute and subacute cases and consist of intramural proteinaceous edema that is perivascular, vascular, or both. Microscopic lesions of focal symmetrical encephalomalacia can be observed in subacute and chronic cases.[27,3]

Goats.

Gross lesions in the acute form of the disease are similar to those in sheep, with the exception that brain lesions are very rare. In subacute cases, there is also mesocolonic edema and necrohemorrhagic colitis, which in some cases may extend to the small intestine. Chronic cases show colitis or enterocolitis with usually no involvement of organs outside the gastrointestinal tract.[27,3]

Microscopic changes are usually not seen in acute cases, except for very rare occasions in which perivascular edema of the brain similar to that described for sheep is seen. In the subacute and chronic forms, the main microscopic lesions consist of fibrinonecrotizing colitis, and, less frequently, enterocolitis.[27,3]

Cattle.

Type D enterotoxemia occurs very rarely in cattle, and the few cases documented share most clinical and pathological characteristics with the disease in sheep.[27,3]

Diagnosis.

In sheep, a presumptive diagnosis of type D enterotoxemia can be based on clinical history, including sudden access to a diet high in carbohydrates, clinical signs, and gross postmortem lesions. Hyperglycemia and glycosuria can be diagnostically useful when present, although this is neither pathognomonic nor

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consistent. In freshly dead animals, large numbers of Gram-positive rods found in smears of intestinal mucosa support a diagnosis of enterotoxemia. Isolation of *C. perfringens* type D from small or large intestinal content is also supportive of this diagnosis; however, because this microorganism can be found in a relatively small percentage of clinically normal animals, isolation alone is not diagnostic.Confirmation of the diagnosis should be based on one or more of the following: (1) perivascular or mural vascular edema in the brain; (2) focal symmetrical encephalomalacia; and (3) demonstration of epsilon-toxin in intestinal content.

In goats with acute and subacutely disease, the same criteria mentioned for sheep apply, although perivascular edema in the brain is rarely seen. Necrotizing colitis and, less frequently, enterocolitis seen in some acute and subacute cases supports but does not confirm a diagnosis. Confirmation of any of the forms of the disease should be based on detection of epsilon-toxin in intestinal content. In the rare cases in which perivascular edema is seen in the brain, this is considered a diagnostic finding. The diagnostic criteria for cattle have not been established, although it is usually assumed that they are probably similar to those reported for sheep.[27,3]

Treatment, Prevention, and Control.

If initiated at the first suspicion of overeating disease, type D antitoxin and oral antibiotics (sulfa) may have dramatic results.Vaccination is also recommended in an outbreak, but owners should be cautioned that antibody titers take between 12 and 14 days to appear, so deaths are expected to continue occurring for a while. The use of antitoxin provides passive immunity while active immunity from vaccination has time to occur.

The diet should be adjusted downward (more grass hay, less grain and legumes) in outbreaks to try to minimize the substrate, especially starch, that reaches the bacteria. Lambs on rich pasture should be moved to poorer pasture or corralled and fed hay until several days after they have been vaccinated twice.

Sheep and goats brought into a feedlot should be vaccinated before arrival, and should have the concentrate ration increased slowly to minimize microfloral disruptions.

Vaccination with type D toxoid is effective in preventing disease. Two doses should be given 4 to 6 weeks apart, to lambs and kids of approximately 2 to 3 months of age, which is when colostral antibody titers fall below protective levels. This should be followed with an annual booster to sheep and

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revaccination of goats every 3 to 4 months. The annual booster is recommended a week or two before heavy grain feeding or exposure to rich pasture begins or, in dams, 2 to 3 weeks before delivery. The aluminum hydroxide adjuvanted vaccines may cause raised subcutaneous lumps (most noticeable on goats) that may go on to abscess.[27,3]

Oak (Acorn) Toxicosis in Ruminants and Horses

Bradford P. Smith

Definition and Etiology

Toxic signs can appear in ruminants,[1,2] and occasionally in horses,[3] that ingest large quantities of oak buds, oak leaves (green or dried), or acorns. Most species of oak (*Quercus* spp.) cause similar signs when ingested, although there are marked differences in the amount of toxin among the 75 oak species.[4] The metabolites of oak tannins and volatile phenols present in the buds, leaves, twigs, and acorns are responsible for causing toxicosis. The mouth, esophagus, gastrointestinal tract, and kidneys (renal tubular nephrosis) are the organs most affected. Because they are less selective in what they ingest, cattle seem to be the most frequently affected species. Signs begin shortly after ingestion of 50% or more of the diet as oak, and young cattle (weighing less than 300 kg) often appear to be more severely affected than adult cattle. Acorns tend to be relatively low in crude protein (2% to 7%) but high in starch, with variable levels of tannins.[4]

Factors leading to toxicosis include the presence of large acorn crops when forage is scarce, wind or hail that causes large numbers of acorns to drop suddenly, or the sudden presentation of oak buds and young leaves to hungry cattle, as in spring windstorms or snowstorms that cover the grass and break branches. In the southwestern United States, range cattle regularly consume some oak species, which are apparently highly palatable and nutritious.[5] The condition has been described wherever oak grows, including most of the United States, France, Great Britain, Germany, Sweden, Australia, China, and South Africa.

Acorn calf syndrome is completely different from the oak toxicosis described in this section. Acorn calves are congenitally malformed calves born to dams that ingest large numbers of acorns under poor forage conditions during the

second trimester of pregnancy. The cause appears to be a combination of poor nutrition and exposure to acorns. The calves have very short leg bones and may have abnormal hoof development and a short or long narrow head (Fig. 32.138). In badly affected herds, as many as 15% of calves are affected. The disease has been reproduced experimentally. Supplementation of the herd with adequate protein and energy eliminates the disease.



FIG. 32.138 Acorn calf, a congenital defect from dam which consumed many acorns and low quality forage during gestation. The calf has short legs, abnormal head shape and deformed hooves. This syndrome is different from acute oak/acorn toxicity.

Clinical Signs and Differential Diagnosis

The course of oak toxicosis usually is 1 to 12 days, but some cattle have a protracted, debilitating disease.[1,2] In an outbreak in England, the first death from renal failure occurred 21 days after the animals had been removed from exposure and housed.[6] In the peracute stages, cattle are recumbent, weak, anorexic, and listless.[1] The rectal temperature is normal or below normal, and the heart and respiratory rates are elevated. Marked edema is present in the perineum and vulva (Fig. 32.139), and edema is obvious in the submandibular area, brisket, and ventral abdomen. Due to the edema, determination of hydration status is difficult, but anuria is present. Firm, dark, mucus-covered feces usually are produced. Evidence of hydrothorax, hydropericardium, and ascites may be noted

on physical examination. Some affected cattle may simply be found dead.



FIG. 32.139 Perirectal and vulvar edema in a 3-month-old calf with acute oak bud toxicity. Acute acorn or oak poisoning causes similar lesions.

A day or two after ingestion, affected animals appear anorexic and listless and have decreased ruminal motility. Many affected calves have hemorrhagic diarrhea or dark diarrhea that tests positive for fecal occult blood. The feces may have a smell of phenol. Dehydration occurs rapidly, but vital signs may be remarkably normal until hypovolemia develops. As uremia progresses, scleral vessels become dark and engorged, and the breath may take on the smell of ammonia. The major differential diagnoses are other causes of renal failure and other toxins and clostridial diseases; viral diseases that cause ulceration of the alimentary tract should also be considered. Protracted cases most often result from renal failure and uremia, although some animals have chronic oral, esophageal, or gastrointestinal ulceration or perforation with abscessation.

In horses, signs usually are peracute or acute; they include sudden death or colic, tenesmus, and hemorrhagic diarrhea.[3] Acorn husks and shells may be noted in the feces. As with most colics, tachycardia, hyperpnea, and injected oral mucous membranes are seen. Abdominal borborygmi often is increased, and hemoglobinuria may occur. Determination of serum or urinary phenolic (hydrolyzed tannin) content, on the basis of a gallic acid standard, may be used in acute cases.[3]

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Clinical Pathology

In cattle with peracute and acute signs, the serum urea nitrogen and creatinine levels are elevated, whereas other laboratory values may show considerable variation.[2,3] Initially, hyponatremia, hyperkalemia, hypochloremia, hyperphosphatemia, marked hypocalcemia (5.1 to 6.8 mg/dL) and a mild metabolic acidosis with a very high anion gap (29 to 32) are found.[1] Neutrophilia with mild hyperfibrinogenemia may be present. Although sorbitol dehydrogenase and GGT may be elevated, biopsy does not indicate that significant hepatic disease occurs with oak toxicosis. Affected animals may be anuric. If urine is being produced, often isosthenuria, proteinuria, and glucosuria occur. The urinary fractional excretion of sodium was elevated in one steer.[5]

In protracted cases, the major findings are elevated serum levels of urea nitrogen and creatinine and elevated anion gap, with variable hyponatremia, hypokalemia (as opposed to hyperkalemia in acute stages), hypochloremia, and hyperphosphatemia. A mild metabolic alkalosis may be present. Hyperfibrinogenemia and an increase in total plasma proteins also are variable. An elevated WBC count most often reflects chronic ulceration or abscessation (neutrophilia or monocytosis or both). Liver enzyme levels usually are normal in protracted cases. Urinalysis results are similar to those in acute cases; in addition, hematuria often is present. By 6 weeks after exposure, a normocytic, normochromic anemia may develop as a result of chronic inflammation and uremia, and hypoalbuminemia may result from chronic renal and gastrointestinal losses. By 8 weeks after exposure, surviving cattle have largely returned to normal renal function as determined by normal serum urea nitrogen and creatinine concentrations and by the ability to concentrate urine after a 24-hour water deprivation test.[1]

Laboratory findings in horses are similar to those in ruminants, except that during the acute stages, rapid hemoconcentration and marked increases in PCV occur.[3] Although protein, occult blood, and hemoglobin casts have been reported to be present in the urine, the urine specific gravity was 1.052.

Pathophysiology.

The toxicity of oak is attributed to its high concentration of tannins, which are hydrolyzed in the rumen to gallic acid, pyrogallol, and other compounds. The tannins themselves may contribute to oral, esophageal, and gastrointestinal damage by binding to proteins, including those in epithelial cells. This results in

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oral, esophageal, and ruminal ulcers or perforations. Protein-bound tannins are liberated in the acidic abomasum, making them available once again to damage intestinal epithelium. Some hydrolyzed tannins are absorbed and bound to plasma proteins and endothelial proteins, which results in hemorrhage and fluid loss from the vascular compartment into body cavities and tissues; this results in edema. The gallic acid and pyrogallols are extremely toxic to renal tubules, causing acute tubular necrosis, anuria, electrolyte abnormalities, and uremia. Ruminants are more susceptible than horses because of the hydrolysis of the gallotannins in the rumen.

Epidemiology.

Young cattle weighingh 100 to 300 kg seem to be particularly susceptible. In the southwestern United States, oak toxicosis accounts for considerable economic loss in cattle.[5] The disease is seen sporadically in other ruminants and in horses. Adult cattle fed 10 kg of fresh oak leaves preceded by feed restriction experienced a critical reduction in rumen fermentation along with acute oak toxicity. Adult cattle that were not feed restricted did not develop oak toxicity.[7] The morbidity rate in cattle varies considerably, with several to many calves in a pasture usually affected, and case fatality rates frequently exceed 80%.[2]

The disease is most often associated with ingestion of acorns in the fall and buds or young leaves in the spring. Cattle turned onto a pasture with oak trees under which acorns have accumulated may have toxicosis even when adequate forage is available.[2] In other cases windstorms have dropped numerous acorns or branches in a pasture to which cattle were already accustomed. In the early spring, a heavy, unseasonable snowstorm may cover the grass, bend young trees, and break branches so that oak buds and young leaves are accessible.[1] Young leaves and acorns are more palatable than older leaves and also contain more tannins (up to 10% dry matter in acorns). The seedlings, buds, and acorns of small scrub oak may be important forages for cattle in parts of the United States.[5]

Necropsy Findings

In peracute and acute cases, prominent edema is often the most striking lesion. Ascites, hydrothorax, hydropericardium, perirenal edema, and subcutaneous edema are found. The kidneys are normal in size with multiple diffuse hemorrhages on the surface and extending into the cortex. The liver is slightly

swollen and pale or mottled. Digestive tract lesions vary from congestion to hemorrhage and deep ulceration or perforation with necrotizing inflammation. Mucosal ulceration is found in the pharynx, esophagus, rumen, abomasum, small intestine, cecum, and colon. Free blood or melena may frequently be observed.

Diffuse renal tubular damage is present. The changes include coagulation necrosis of cortical tubular epithelium and dilated tubules devoid of epithelium but with intact basement membranes. Many medullary tubules contain hyaline, granular, or cellular casts. The principal renal lesion is necrosis of the proximal convoluted tubules, but glomerular degeneration and fluid in Bowman capsules are also seen.

By 3 to 6 weeks after exposure, the lesions include gastrointestinal ulceration, often with secondary infection; some healed ulcers; secondary bacterial bronchopneumonia; and slightly swollen, pale brown kidneys. Histologically, atrophy of the cortical tubular epithelium with a marked interstitial fibrosis and mononuclear infiltrate is seen. Evidence of tubular epithelial regeneration may be present. The liver appears normal.

Treatment and Prognosis

In acute stages, intravenous fluid therapy aimed at promoting diuresis and correcting acid-base and electrolyte abnormalities is indicated. Calcium, sodium, and chloride deficits should be replaced, and sodium bicarbonate should be given if needed to correct metabolic acidosis. In anuric animals, furosemide (1 mg/kg given IV) can be administered every 12 hours, along with adequate fluid therapy. Corticosteroids and NSAIDs are not likely to have a measurable effect on the course of the disease because they are unlikely to alter the direct toxic effects of the metabolites. The prognosis is guarded and must be considered poor in animals that remain anuric despite therapy. The case fatality rate undoubtedly depends more on the amount of toxic material ingested than on therapy. Antibiotics, given to prevent secondary pneumonia and abscessation, ruminal transfaunation, and readily accessible grass hay and water, are recommended components of nursing care.

If the animal survives the acute stage and begins to eat voluntarily, the prognosis for recovery is good unless secondary pneumonia or gastrointestinal abscessation after perforation occurs. Renal function can return to normal by 5 to 10 weeks, and weight gains as high as 1.76 kg/day have been recorded in recovered cattle.[1]

Colicky horses can be treated as usual for colic (intravenous fluids, analgesics,

oral laxatives). Particular attention should be paid to diuresis, acid-base balance, and maintenance of serum calcium levels.

Prevention and Control

No specific antidote exists for oak toxicosis, but supplementation with calcium hydroxide (hydrated lime) immediately before anticipated exposure to oak has been effective under experimental conditions.[8] Feed containing 10% or less calcium hydroxide is palatable. Consumption of 0.9 kg/head/day of cubed or pelleted supplement containing 10% hydrated lime is effective in preventing toxic manifestations.

Supplementation of cattle suddenly exposed to oak with any feed reduces death losses, apparently by allowing hungry cattle to consume the supplemental forage preferentially.[1,8] In an outbreak in California caused by spring snows in which 2700 cattle died of oak toxicosis, ranches where hay was immediately supplemented had fewer losses than did ranches where feed supplementation was not offered.[1]

Winter Dysentery in Cattle (Bovine Coronavirus)

Gilles Fecteau • Charles L. Guard

Definition and Etiology

Winter dysentery is an acute, contagious diarrheal disease of cattle (especially dairy) that occurs in epizootic manner in a herd, usually during the colder months of the year (November to April). It is usually recognized by the clinical syndrome that occurs in herds and by exclusion of other causes of contagious diarrhea.[1] In the United States the disease is more common in the northern states; it has also been reported in Australia, Sweden, the United Kingdom, Israel, France, Belgium, Japan, and Canada. The period of illness in an individual is brief (a few days to a week), and within a herd the outbreak usually lasts less than 2 weeks. Recovery is spontaneous in most individuals, but in some cases, supportive therapy is necessary. The morbidity rate is usually high (from 30% after a few days to almost 100% after 1 week to 10 days). Mortality, however, is usually rare.

The cause of winter dysentery is a bovine coronavirus that may be related (antigenic differences are reported) to the coronavirus that causes diarrhea in

neonatal calves.[2-7] By immune electron microscopy, antigenic cross-reaction has been demonstrated between the original Nebraska calf coronavirus diarrhea agent and coronavirus isolated from field outbreaks of winter dysentery.[4,6]

Clinical Signs and Differential Diagnosis

Winter dysentery is an explosive diarrheal disease accompanied by some degree of anorexia and depression. In lactating cows, milk production is severely reduced. If the diarrhea is severe or persists longer than one or 2 days, dehydration may develop. Loss of body condition is apparent. Rumen motility usually is reduced, but intestinal borborygmi may be increased. Thirst often is increased, and polydipsia follows the diarrhea. Rectal examination may reveal dilated intestinal loops. The feces vary from light tan to dark brown; bubbles commonly form in the puddles that are deposited several feet behind the cow. Blood may be present in the feces of several animals in a group, typically in the first-lactation cows. The amount of blood may range from just visible to large clots, or it may be uniformly mixed into the feces. Some animals may have thick mucus in the feces. The odor in a barn during an outbreak of winter dysentery has been described as musty, fetid, and sweet and nasty.[8]

Fever usually is not present during the diarrheal phase of the disease but has been reported to precede it[1] or have no consistent relationship.[9] Mild respiratory signs consisting of serous nasolacrimal discharge and a soft cough have been inconsistently observed before diarrhea. Diarrhea caused by BVDV, coccidiosis, and salmonellosis must be considered in the differential diagnosis of winter dysentery. With winter dysentery, no mucosal lesions are visible on physical examination. The absence of coccidial oocysts or parasite ova in the feces helps exclude these agents as responsible for the diarrhea. The rapid occurrence of multiple cases within a herd, and often within several herds in a locality, suggests winter dysentery. Fecal culture for *Salmonella* yields negative results in uncomplicated cases of winter dysentery.

Clinical Pathology

No consistent hematologic changes that would be of diagnostic benefit have been observed. If significant dysentery persists for longer than a day, signs of anemia may develop.

Pathophysiology

Epithelial cells of colonic crypts are destroyed by viral action, which leads to necrosis and hemorrhage. Even though histologic changes have been observed only in the colonic mucosa, blood was observed from the distal duodenum aborally in cattle that died of winter dysentery.[7] Loss of intestinal mucosal epithelium from colonic crypts leads to transudation of extracellular fluid and blood.

Epidemiology

The incubation period is thought to be 2 to 8 days. The most susceptible animals are first and most severely affected. In a small, housed herd, the typical incidence of diarrhea during an outbreak begins with the explosive appearance of signs in 10 to 15% of animals on the first day. The second day, another 20 to 40% are affected. On subsequent days, similar proportions become ill. By the end of a week, the first affected animals are completely recovered, and only a few new cases occur. Typically within 2 weeks of the onset of diarrhea, all animals have recovered. This period is marked by significant reduction in milk production. In large herds the outbreak may be prolonged for 6 to 8 weeks. This scenario is typical of a herd that had not experienced an epizootic of winter dysentery during the preceding few years. In some herds, milder outbreaks occur annually, with fewer animals showing diarrhea and with less severe clinical signs.

Treatment and Prognosis

Most animals with winter dysentery recover spontaneously in a few days without specific treatment. Many palliative treatments have been recommended and used over the years. On the basis of 30 years of observations, Roberts[10] considered none of these treatments to alter the course of the disease. Provision of adequate fresh water, palatable feed, and free-choice salt is the most useful nonspecific therapy. The occasional animal with prolonged or severe dysentery may need a transfusion of 4 to 8 L of whole blood.

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Salmonellosis in Ruminants

Bradford P. Smith

■ Definition and Etiology

Salmonellosis is one of the few diseases that appear to be increasing in prevalence, especially in dairy cattle. In addition, more than one million human cases of nontyphoidal salmonellosis occur yearly in the United States (90 million worldwide), and so this is an important public health concern. *Salmonella* serovar Dublin was isolated from the bloodstream of 60% of 228 human patients suffering from *Salmonella* serovar Dublin infection in the United States; 74.9% required hospitalization and 3.7% died, and so it is considered the most severe nontyphoidal *Salmonella* infection in humans. Twenty eight per cent of isolates were resistant to sulfas, tetracycline, ampicillin, chloramphenicol, amoxicillin-clavulanic acid, and ceftriaxone.[1]

Large dairy farms are more likely to be infected with *Salmonella* than are small dairy farms.[2] Milk yield decreased significantly in affected herds, and the reduction was detectable several months after the increase in bulk tank milk *Salmonella* antibodies. It took more than 1 year for milk yield to return to preinfection levels.[3] According to one study, 75% of dairies sampled in California had evidence of *Salmonella* infection.[4] A multistate study demonstrated that 56% of dairies sampled contained cows shedding *Salmonella* in feces.[5] *Salmonella* of concern for livestock belong mainly to one species, *Salmonella enterica* subsp. *enterica*, with numerous serovars or serotypes, such as *S. enterica* subsp. *enterica* serovar Typhimurium, with the words *serotypes* and *serovars* used interchangeably.[6] (In this text, the terms are shortened it to, for example, *Salmonella* Typhimurium by convention.) More than 2500 *Salmonella* serotypes (serovars) have been identified, and many are potential animal and human pathogens. Multidrug-resistant *Salmonella* Typhimurium DT104 (serogroup B) and *Salmonella* Newport (C2) are particularly virulent in animals and human beings. New variants occur; a variant of *Salmonella* Typhimurium designated I 4,[5],12:i:− lacking one H antigen has been a cause of clinical disease in cattle in the USA (Table 32.23; personal communication from Brenda R. Morningstar-Shaw, National Veterinary Services Laboratory, USDA, 2018). The presence of identical strains of *Salmonella* Newport among bovine

and human isolates indicates that zoonotic transmission is likely to occur.[7] Fortunately, only 10 serotypes of *Salmonella* in serogroups B, C, D, E, and K are responsible for most disease in cattle; therefore control programs can be aimed at these.

TABLE 32.23

Most Frequently Isolated *Salmonella* Serovars or Serotypes From Ill Cattle in the United States in 2016[a]

Order of Frequency	Serovar or Serotype (Serogroup)	Total	Percentage
1	Dublin (D1)	332	23.5%
2	Cerro (K)	275	19.5%
3	Typhimurium (B)	142	10%
4	Montevideo (C1)	110	8%
5	Heidelberg (B)	101	7%
6	Newport (C2)	67	5%
7	I 4,[5],12:i:-* (B)	54	4%
8	Anatum (E1)	33	2%
9	Kentucky (C3)	26	2%
10	Muenster/Meleagridis (E1)	22 each	1.5% each
All others		226	16%
Grand Total		1414	100%

[a]Variant of Typhimurium.

Data supplied by Brenda R. Morningstar-Shaw, National Veterinary Services Laboratories, United States Department of Agriculture, Ames, IA, 2018.

Table 32.23 lists the serotypes most commonly isolated from ill cattle in 2016 in the United States. Group K, not long ago considered an exotic serogroup, has become prevalent (number 2).[8] *Salmonella* organisms are Gram-negative enteric bacteria that are facultative intracellular parasites. Most serotypes are non–host-specific, but a few are host-adapted. *Salmonella* Dublin is host-adapted to cattle, *Salmonella abortus ovis* and *Salmonella* Arizonae to sheep, and *S. abortus equi* to horses. Host-adapted serotypes are found most often in their host species, where true long-term carriers exist.[9] In contrast, non–host-adapted serotypes rarely achieve carrier status and usually infect an animal for a period of 3 to 16 weeks before infection is cleared,[9] although one cow with multidrug-resistant *Salmonella* Newport excreted the organisms for 190 days.[7] Infection with either host-adapted or non–host-adapted serotypes can be symptomatic or asymptomatic, depending on the dose, the virulence of the serotype, and the host's immune status. There appears to be an association between an increased

incidence of *Salmonella* infections and intensive management practices such as large farms, crowded conditions, and high-protein diets. In the absence of carriers, chain infections and persistence of *Salmonella* in the environment are responsible for long-term persistence of a given strain on a given dairy.[7]

Salmonella are grouped into serogroups (A to Z and 51 to 65), depending on their cell wall antigens (somatic antigens that comprise specific oligosaccharides, often called *O antigens*, *LPSs*, or *endotoxin*). Thus for example, local and regional laboratories often report that an isolate is a group D *Salmonella*. The most common group D isolate of cattle is *Salmonella* Dublin, although nonmotile isolates that do not express flagella at that time also can be found. The author and colleagues found that these would express motility and be typed as *Salmonella* Dublin if the isolate were inoculated into semisolid media where it had to move to get nutrition (Smith BP, personal observation). Final confirmation that the *Salmonella* isolated is indeed *Salmonella* Dublin comes from the National Veterinary Services Laboratory in Ames, Iowa, or from some other laboratory in which antisera and facilities exist for identification of all 2500 serotypes on the basis of flagellar (H) antigens and somatic (O) antigens. Some serotypes also express capsular (Vi) antigens composed of mucopolysaccharide under some conditions. Identification of the serotype is important in planning control strategies. In addition to the serotypes listed, lambs may be infected with *Salmonella* Arizonae, which comes from several different serogroups. *Salmonella* organisms are relatively easy to culture from the feces or tissues of infected animals, with the use of common enteric agar such as Hektoen Enteric, XLT4 or brilliant green agar, with tetrathionate and selenite as selective enrichment media.

Clinical Signs and Differential Diagnosis

Salmonella infection can cause a variety of clinical signs. The most common signs are fever and diarrhea[10] after an incubation period of 1 to 4 days after exposure or a recrudescence from the carrier state. Ruminants of all ages may be affected, but serious illness is observed most frequently in very young animals and parturient dairy cattle.

The character of the diarrheic feces varies from watery to mucoid with fibrin and blood. Sheets of fibrin may look like sloughing mucosa. The feces often have a putrid, foul odor because of the presence of plasma proteins associated with severe inflammatory bowel disease. Salmonellosis causes an acute protein-

losing enteropathy. The systemic effects of endotoxins (and other toxic material) absorbed through the damaged bowel mucosa may be severe (fever, anorexia, depressed attitude, and shock).

Bacteremia may occur rapidly, especially in neonates infected with *Salmonella* Dublin, Typhimurium, or Newport. Peracute to acute septicemia in calves may produce lesions in many organ systems. Affected calves usually are younger than 2 months of age (the range is 1 day to 6 months). Dyspnea, respiratory symptoms, sudden death, and occasionally diarrhea are the principal signs of *Salmonella* Dublin infection, the incidence of which usually peaks in 6-week-old calves. Blood culture results frequently are positive. Pure cultures of *Salmonella* Dublin often can be grown from specimens from the lungs of 4- to 8-week-old calves with pneumonic (septicemic) salmonellosis. Calves infected with *Salmonella* Typhimurium are only 14 days of age on average (the range is 1 to 35 days) and have mainly enteric lesions, including enlarged mesenteric lymph nodes, abomasitis, fibrinonecrotic plaques in the ileum, and hemorrhage of Peyer's patches.[11]

Dry gangrene of the extremities may occur in calves after *Salmonella* infection, particularly with *Salmonella* Dublin. Legs, ears, and tails are most commonly affected, and cold agglutinins are suspected to be involved.[12]

A strain of *Salmonella* Saint Paul was implicated in an outbreak of encephalopathy (without encephalitis) in stressed Holstein calves.[13] Calves exhibited diarrhea, head tilt, ataxia, auditory hyper-responsiveness, and partial blindness. The β-lactam antibiotics ceftiofur and ampicillin protected against the neurological effects by increasing glutamate export from the brain despite resistance of the *Salmonella* St. Paul isolate to both drugs.[14]

In adult cattle, diarrhea or abortion may occur.[9] Abortion may occur by two mechanisms because both culture-positive and culture-negative fetuses and placentae may be found in an outbreak. In the former, bacteremia in the dam results in infection of the placenta or fetus, with resulting fetal death and expulsion. Bacteremia, endotoxemia, and fever associated with diarrhea and damaged gut mucosa in cattle may result in release of prostaglandin $F_{2\alpha}$ and subsequent lysis of the corpus luteum. Abortion follows in 2 to 3 days, and the fetus and placenta yield culture-negative findings. When the fetus has a culture-negative finding, many other causes of abortion must be considered. Many infectious agents that infect only the dam can act similarly to cause luteolysis and abortion.

Differential diagnoses for the enteric form of salmonellosis in neonates include all the common enteropathogens of neonates: *Escherichia coli*, rotaviruses and coronaviruses, clostridia, cryptosporidia, and other forms of coccidia. Concurrent infection with these agents is common. In older animals outbreaks should be differentiated from those caused by BVD, winter dysentery, and feed-induced indigestion. Pneumonic and bacteremic salmonellosis in 4- to 8-week-old calves must be differentiated by culture from pneumonic pasteurellosis; in goats, from mycoplasmal infection; and in lambs, from septicemic pasteurellosis.

Clinical Pathology

Salmonella enteritis often results in changes in the hemogram,[15] as effects of endotoxin manifest.[16] Plasma fibrinogen frequently is elevated because of the inflammatory nature of the disease, and either neutrophilia or neutropenia may be seen. In severe cases a left shift may be present. Initial dehydration may result in an elevated PCV and plasma protein level. The plasma protein level often drops over a period of days as protein is lost into the bowel lumen. Many other nonspecific abnormalities in clinical chemistry values are often seen, including elevated liver enzymes, decreased plasma calcium, and indications of prerenal azotemia if dehydration occurs.

Definitive diagnosis of salmonellosis requires culture of the organism from feces, blood, or tissues. PCR is also available. Culture was most sensitive and specific in comparison with ELISA and PCR.[17] Pooled fecal cultures from five cows provide a sensitivity of 62.5%, in comparison with individual samples from culled dairy cows.[18]

Pathophysiology

Salmonellae are invasive organisms that may penetrate ocular, nasal, oral, or intestinal mucous membranes. Once eaten, salmonellae attach to mucosal cells, probably by means of a nonfimbrial adhesion.[19] Attachment is increased if gastrointestinal stasis is present or the normal competitive flora has been disturbed or is not yet established, as in neonates. Salmonellae cause degeneration of nearby cells and penetrate both through microvilli and through tight junctions between cells.[20] The *Salmonella* type III secretion system translocates five *Salmonella* effector proteins (SipA, SopA, SopB, SopD, and SopE2) into enterocytes, and is required for induction of diarrhea by inducing

intestinal fluid secretion and recruiting neutrophils to the infection site. [21] The bacteria also pass through the enterocytes to the lamina propria, where they stimulate an inflammatory response and are engulfed by macrophages and neutrophils.[22] Intracellular bacteria reach regional mesenteric lymph nodes or beyond. The organism has a predilection for lymphoid tissues and is found in highest numbers in Peyer's patches and mesenteric lymph nodes.[23] This is one reson why culturing mesenteric, iliac and other lymph nodes is useful. Thrombi form in vessels, and tissue damage can be severe. Virulent salmonellae are capable of surviving in host tissues and multiplying, often as facultative intracellular parasites in macrophages and reticuloendothelial cells.[24] In the case of carrier animals, salmonellae survive in cells in the presence of high titers of specific extracellular serum immunoglobulins. This is the basis for using ELISA serologic testing to detect *Salmonella* Dublin carriers. Intracellular salmonellae can also avoid many antimicrobial drugs and complement. Stress may cause a latent infection to recrudesce, which results in fecal or mammary gland shedding or clinical disease.

The cell wall of all Gram-negative bacteria contains LPS as a component. LPSs are also called *endotoxins*, and they are extremely biologically active, setting off an immunologic cascade of events that can lead to leukopenia, fever, anorexia, and eventually shock and death.[16]

■ Epidemiology and Control

Salmonella infection is most often transmitted by fecal-oral contamination from livestock or rodents, or by feeding of contaminated protein source animal by-products (e.g., fish meal, meat meal, bone meal, or feather meal, many of which are contaminated) or contaminated forages or plant proteins such as soybean or cottonseed. Of cattle feed tested for *Salmonella* in 2010, approximately 6.1% was positive, according to U.S. Food and Drug Administration surveillance data. Even if small numbers of organisms are initially present, they multiply rapidly in moist warm conditions.

Salmonella Dublin is an endemic herd problem and is shed by lower numbers of animals compared with *Salmonella* Typhimurium, which tends to be epidemic and shed in higher numbers by many more animals at a time.[25] In 2009 in the northeast United States, in 11% of 831 herds with suspected clinical cases of salmonellosis, the leading isolates were *Salmonella* serovars Newport and Typhimurium.[26] A study of calves in California found that 18% of 1-day-old

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calves shed some serotype of *Salmonella*, but this percentage declined rapidly over the first 11 weeks of life. Perhaps even more alarming, a fetus may be infected with *Salmonella* in utero and thus vertical transmission occurs as well.[27] *Salmonella* Typhimurium, Muenchen, Cerro, and Kentucky were isolated from mesenteric, subiliac, and prescapular lymph nodes and calves at parturition.[27] Farms that received calves from other sources were 35 times more likely to have calves that were shedding *Salmonella* in feces than were closed herds.[28] *Salmonella* Dublin, Newport, and Typhimurium can also be tranmitted via colostrum and milk.[29]

Infection with host-adapted *Salmonella* serotypes may occur as a cyclic endemic disease, especially in calves when *Salmonella* Dublin is involved. *Salmonella* Dublin infections on a farm are maintained by carrier animals shedding *Salmonella* Dublin in the feces[9] or milk,[30] chain infections in infected calves and cows, rodents, and environmental contamination. *Salmonella* carriers infected with a host-adapted serotype such as *Salmonella* Dublin may shed constantly or intermittently. Cattle with the highest risk of becoming *Salmonella* Dublin carriers are heifers infected between 1 year of age and first calving and cows infected in the parturient period,[31] but calves surviving *Salmonella* Dublin infection and illness may also become carriers (BPS personal observation). Infected carriers that are not shedding are called latent carriers; stress may cause shedding in feces or milk to recrudesce. A single infected, asymptomatic fecal shedder may produce over one billion *Salmonella* Dublin organisms per day to contaminate the environment (one million organisms per gram of feces). Unlike most other serotypes, *Salmonella* Dublin may be carried as a chronic gut and mesenteric lymph node infection and passed in feces or carried as an intramammary infection and passed in contaminated milk.

Calving areas must be constantly cleaned and disinfected between calvings. Raw milk feeding to calves may be a source of *Salmonella* (100 to 100,000 organisms per milliliter of milk).[30] Raw milk must not be allowed to sit unchilled, as this allows *Salmonella* and other pathogens to multiply (numbers can double every 20 minutes at 100 F (37C). Acidification of milk to a pH lower than 4 for 2 hours can effectively eliminate most pathogens, including *Salmonella* spp. and *M. bovis* from milk; acceptance of taste by calves may be an issue with some acidification techniques.[32] Infected calves constantly amplify the number of organisms in the environment, causing exposure of other calves. Calves with clinical signs may shed billions of *Salmonella* into the environment

daily. See Chapters 19 and 20 for more on calves.

Environmental contamination can be difficult to eliminate because salmonellae survive for months in moist areas out of direct sunlight and in lagoons and drainage areas. Cows shed more *Salmonella* on a commercial dairy in hot weather by a factor of 4.5X for every 5C rise in ambient temperature.[33] *Salmonella* Dublin was recovered from feces dried for 41 months.[34] Freezing feces at −20° C (−4° F) kills 85% of salmonellae in 2 days and more than 95% by 1 month.[35] Direct sunlight and drying in hot weather are effective at eliminating salmonellae. Using composted manure for bedding can be effective: *Salmonella* Newport survived less than 24 hours in composted manure reaching 69° C (115° F) but survived for more than 4 months in the lagoon and more than 9 months in soil.[36]

Research has documented contaminated irrigation water as an important source of *Salmonella* organisms. In some cases municipal sewage treatment plant effluents had contaminated water.[37] On one dairy farm, river water used to sprinkler irrigate green chop contaminated the green chop, which was fed to cows.[38] On another farm, *Salmonella*-contaminated river water was used to irrigate cotton. When the cottonseed from that gin was used as feed, cattle became infected.[38] On a third dairy farm, contaminated irrigation water resulted in haylage containing *Salmonella* organisms.[38]

Feedlot cattle colonized by *Salmonella* organisms could pose a public health risk when meat is contaminated at slaughter. In a study by National Animal Health Monitoring System, 7.5% of cattle on feed the longest shed salmonellae, whereas 3.5% of cattle that had recently entered the feedlot were shedding salmonellae in the feces.[39] A study of 68 feedlots in 12 states found that 9.1% of 5050 fecal samples were positive for *Salmonella* and 64.7% of feedlots had at least 1 positive sample, and that fewer than 10% of isolates were resistant to antimicrobials other than sulfas and tetracyclines.[40] Contamination of the animals before entry can cause the entering cattle to have a higher rate of shedding than was found in cattle that had been in the feedlot for several months.[41] A major difference in the incidence of *Salmonella*-positive lymph nodes was found between two different feedlots and in time on feed, with cattle on feed more than 120 days having 94% (17/18) *Salmonella*-positive lymph nodes.[42] These lymph nodes are believed to be a major source of contamination for beef.

Standing water contaminated with feces is frequently highly contaminated

with *Salmonella;* culture of temporary shallow lakes (called *playas* in the southwestern United States) yielded numerous *Salmonella* serotypes.[43] An unusual outbreak of *Salmonella* Newport in cows and calves on a beef farm resulted in a cow mortality rate of 7.9% (32 of 407) and a calf mortality rate of 14.4% (52 of 361). BVD virus was also diagnosed in the group, and it was suspected of playing an immunosuppressive role.[44]

Control of *Salmonella* infection requires an integrated herd approach.[45,46] Pens of sick animals were found to be 7.4 times more likely to yield *Salmonella* than were pens of preweaned calves.[47] Management interventions that were found effective in helping control *Salmonella* on dairy farms include separation of sick and parturient cattle into hospital and maternity pens, respectively (considered the most important and effective intervention), switching from a phenolic disinfectant to a peroxygen biocide such as Virkon S (DuPont, Sudbury, U.K.) for equipment disinfection, use of separate footwear or footbaths for personnel in the hospital and maternity pen sections, strict protocols for disinfection of hands and equipment between handling each sick or periparturient cow, strict separation of feeds used in the hospital and maternity pens, and use of clean bedding in the hospital and maternity pens.[7] Having one person manage the calves, good colostrum management, and not purchasing cattle from an infected premise had beneficial effects in reducing infection.[48]

To detect herds infected with *Salmonella* Typhimurium or Dublin, a herd serologic profile based on ELISA can be used.[49] The commercial test available in the United States is the PrioCHECK *Salmonella* Ab bovine ELISA (Prionics, Switzerland). One laboratory that runs such tests on milk or serum is the Animal Health Diagnostic Center at the College of Veterinary Medicine, Cornell University. Rectal swab sampling and culture of culled dairy cows was found not to be a satisfactory method of detecting *Salmonella*-infected herds.[50] To control *Salmonella* Dublin, carrier cows and calves older than 6 months of age are identified by serologic testing (ELISA) for anti-*Salmonella* antibody.[30,51-53] Suspect animals are culled or tested further by serologic means or by multiple fecal cultures and milk cultures (five samples at weekly intervals). Strongly positive results of serum ELISA tests over an 8-month period are considered to indicate carrier status.[54] Animals with positive test results are culled. In infected herds, *Salmonella* Dublin carriers (fecal or mammary) usually make up 0.4% to 3% of a dairy herd. A Danish study[55] showed that only 14 of 31 persistently seropositive animals were culture positive for *Salmonella* Dublin at postmortem

examination, and one seronegative animal was culture positive. One study found that ELISA serologic testing had a good negative predictive value for cattle 100 to 300 days of age, whereas fecal culture had a poor predictive value.[56]

To control all non–host-adapted and host-adapted serotypes of *Salmonella*, calves and cows are promptly treated when signs of illness occur, and strict procedures to prevent the spread of infection are instituted. A study of 14 farms infected with *Salmonella* Typhimurium DT104 showed that clinical disease ceased by 4 months, but widespread infection and contamination continued. Over time the number of infected farms gradually declined, and vaccination correlated positively with a herd remaining free of clinical illness from DT104.[57] Control measures include the use of separate feeding utensils for each calf, washing of boots and hands by calf raisers between calves, isolation of ill calves to noncontact pens, and thorough disinfection of pens between calves. Decontamination of pens is most effectively accomplished if an all-in, all-out system is used. Pens are divided into four groups, with each group of pens used for calves born during a given week. When 3- to 4-week-old calves leave their pens as a group, these pens are cleaned and disinfected with a chlorine product such as bleach, a peroxygen product such as Virkon S, or a phenylphenolic disinfectant (also see Chapter 46 for more on disinfection). This helps prevent continuous recycling of bacteria to each group of new calves. Environmental monitoring by frequent swab cultures of pens is the best way to check the effectiveness of the sanitation and disinfection program.

Infection with *Salmonella* Typhimurium and other non–host-adapted serotypes most often occurs as an epidemic after the organisms enter the farm by means of feedstuffs, purchased cattle, rodents,[58] or rendering trucks. Even *Salmonella* Dublin may be maintained on a farm by mice.[59] A case control study of farms infected with *Salmonella* Typhimurium DT104 found that the most effective interventions included purchasing cattle directly rather than through a sales yard, quarantining purchased cattle for 4 weeks, housing sick cattle in dedicated isolation areas, and preventing wild bird access to feed storage areas.[60] Feeds may be contaminated by irrigation water,[38] in manufacturing when by-product ingredients contain *Salmonella* organisms, on the farm, or in shipment by birds or rodents or contaminated trucks. When an epidemic involving a common or exotic serotype occurs, feedstuffs should be examined as a likely source. Exotic serotypes are *Salmonella* from serogroups other than B, C, D1, E1, and K; that is, all those groups not listed in Table 32.23. High-protein supplements, rumen

bypass protein, or calcium-phosphorus supplements of animal origin are sources of epidemics of various *Salmonella* serotypes in livestock. Many animal by-product feedstuffs in the United States are contaminated with *Salmonella* organisms. Once a *Salmonella* serotype enters a herd, the bacteria are rapidly spread among livestock and into the environment, where they may cause a prolonged course of herd illness and can be difficult to eliminate. Such appeared to be the case with *Salmonella* Newport and *Salmonella* Montevideo in dairy cattle in California in the past (Table 32.24). These and other group C *Salmonella* spp. tend to become endemic and persist for years on a dairy farm once it has become infected. By 2016, *Salmonella* Montevideo was the fourth and *Salmonella* Newport the sixth most prevalent serotypes from ill cattle in the United States (see Table 32.23; National Veterinary Services Laboratory data). Culture of feeds before use on a farm currently is the only means of preventing the introduction of new *Salmonella* serotypes via feedstuffs because national and international feed quality controls currently appear to be inadequate.

TABLE 32.24

Changing Incidence of *Salmonella* Serotypes (Serogroup) From Ill Calves on California Dairy Farms, 1985 to 1988

Serotype	Percentage *(n)* of Farms From Which Each Serotype Was Isolated	
	1985–1986	1987–1988
Dublin (D1)	78 (29)	53 (49)
Newport (C2)	19 (7)	36 (33)
Typhimurium (B)	3 (1)	7.6 (7)
Montevideo (C1)	0	6.5 (6)
Infantis (C1)	0	2.2 (2)
Anatum (E1)	0	1.1 (1)
Muenster (E1)[a]	0	1.1 (1)

[a]Formerly called “S Arkansas.”

From Blanchard P, Anderson M. Unpublished data based on calves brought for necropsy to the laboratories of the University of California, Davis, Veterinary Medicine Teaching & Research Center and the California Animal Health & Food Safety (CAHFS), Tulare, Calif., from Tulare area farms, 1988.

Vaccination.

Control by vaccination of dams with killed bacterins may be somewhat beneficial in protecting neonates under 3 weeks of age through colostral and milk immunoglobulin. Because most dairy calves are taken from their dam and

fed milk replacer after day 1 to day 3 of age, the potential benefit of intraluminal milk antibody from the dam is lost. This may account in part for the fact that vaccination of cows by itself often is insufficient to protect dairy calves from salmonellosis. In neonates over 3 weeks of age, colostral immunity appears to play only a small role in protecting against salmonellosis. Because both humoral and cell-mediated immunity are important in protecting against salmonellosis,[60-62] active immunity is superior to passive. Modified live-virus, genetically altered vaccines that stimulate humoral and cell-mediated immunity offer better protection for calves than do killed whole cell vaccines.[62,63]

The role of increased nonspecific immunity to Gram-negative core antigens (through immunization with rough mutants of *E. coli* and salmonellae lacking complete cell walls) has been investigated. Some studies have been able to demonstrate an increased survival rate for salmonellosis after vaccination with a mutant strain of *E. coli* (J5),[64] designed to produce antibodies to the common core antigens of Gram-negative bacteria. Two such products available in 2012 are Enviracor J-5 (Zoetis, Florham Park, N.J.) and J-Vac (Merial, Duluth, Ga.). Endovac-bovi (Re mutant *Salmonella* Typhimurium bacterin-toxoid produced by Immvac Inc., Columbia, Mo.) is marketed with the same goal.

Available commercial *Salmonella* vaccines are killed whole-cell bacterins for use in cattle and a genetically altered modified live *Salmonella* Dublin vaccine for calves (EnterVene-D [Boehringer Ingelheim Vetmedica, St Joseph, MO]. Although the vaccine is to be given subcutanously, some practitioners report that they have used the live vaccine orally and found it to be effective but with fewer adverse reactions than when used parenterally. EnterVene-D was used in dry cows without any observed adverse reactions, and produced an increase in colostral antibody against *Salmonella* Dublin, but no natural or experimental challenge was given to assess its effectiveness.[65] The only products that are solely *Salmonella* vaccines contain (1) *Salmonella* Typhimurium, (2) *Salmonella* serovars Typhimurium and Dublin, (3) live *Salmonella* Dublin organisms, or (4) siderophore receptor protein (SRP) *Salmonella* Newport subunits (also see Chapter 48). Autogenous bacterins can be made for serotypes not commercially available when they are isolated from animals on a farm and believed to be the causative agent of disease. A subunit SRP vaccine called *Salmonella* Newport Bacterial Extract vaccine is being marketed by Zoetis for vaccination of cattle against *Salmonella* and other Gram-negative bacteria.

Siderophores (SRPs) are iron chelating proteins produced by all *Salmonella*,

so producing antibodies against SRPs from *Salmonella* Newport should theoretically be effective for all serotypes of *Salmonella*, and because they are a subunit, they should be less toxic. The initial vaccination requires 2 doses at 2- to 4-week intervals, followed by a yearly booster. The SRP vaccine did not decrease fecal shedding in feedlot cattle (which were mainly shedding *Salmonella* Montevideo [C1] and *Salmonella* Anatum [E1] and not *Salmonella* Newport [C2]).[66] To the author's knowledge, no peer reviewed controlled studies documenting the effectiveness of this SRP vaccine at controlling salmonellosis have been published as of early 2018. A major problem associated with *Salmonella* bacterins and modified live *Salmonella* vaccines is adverse reactions. Adverse reactions vary from fever, depression, and anorexia to collapse and death after vaccination. Affected animals may have severe reactions after the first, second, or third dose. The apparent cause of these severe reactions is a high degree of sensitivity to the presence of Gram-negative endotoxin, which results in a rapid immune cascade that leads to shock.[16] This sensitivity is genetically controlled, possibly accounting for the high frequency of adverse reactions in one herd and their absence in a neighboring herd. High ambient temperatures also increase sensitivity to the adverse effects of endotoxin. Adverse reactions usually can be averted or reversed with epinephrine (1 mL of 1 : 1000 [1 mg/mL] for every 50 kg of body weight given IM or IV) as soon as evidence of polypnea, dyspnea, or weakness appears.

Lack of efficacy of killed *Salmonella* bacterins in calves is evident in experimental studies. Commercial bacterin vaccines in aluminum hydroxide administered directly to calves at 2 and 4 weeks of age failed to protect the calves when they were orally challenged at 6 weeks of age.[64] Other research has demonstrated protection in older vaccinated calves that were challenged intravenously.[67] Calves younger than 12 weeks of age do not serologically respond with anti-LPS antibodies after vaccination with two or three doses of killed bacterins in aluminum hydroxide.[68] On the other hand, calves older than 12 weeks of age and cows do respond serologically to two doses of the same vaccine.[69] The ELISA titer in cows is short-lived (2 to 4 weeks); therefore the timing of vaccination before parturition is critical if the aim is to increase the anti-*Salmonella* colostral immunoglobulin G titer.[69] Under experimental conditions, calves fed colostrum from vaccinated dams were not protected against oral challenge at 3 weeks of age.[15] One report suggests that vaccination with killed *Salmonella* Typhimurium vaccine prevented reinfection and

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recrudescence of clinical signs after an outbreak of DT104 and helped in eliminating the organism from the farm.[59] As mentioned previously, these differences may in part be explained by whether a calf continues to receive milk from its dam and thus has or does not have intraluminal antibodies. Other live vaccines have been found effective in calves and capable of cross-protection against other serotypes, including a DNA adenine methylase–deficient *Salmonella* Typhimurium[70] and an avirulent live *Salmonella* Choleraesuis strain 54,[71] but neither was licensed for cattle in the United States as of 2018.

Necropsy Findings

Enteric Form.

Many affected calves are emaciated and have serous atrophy of fat. Especially with *Salmonella* Typhimurium, the ileal, cecal, or colonic mucosae may be thickened and hemorrhagic with adherent fibrinonecrotic plaques. Fibrin may be found in sheets, especially pronounced in the areas of Peyer patches. The abomasum, duodenum, and jejunum are often involved but less severely. The abomasum usually contains brown, fetid liquid. Bowel contents often are watery and may contain fibrin, blood, or both.[11] The mesenteric lymph nodes frequently are enlarged and dark. Chronically affected cows or calves may have discrete areas of necrosis in the cecum or colon that may involve the entire thickness of the wall.[11]

Septicemic Form.

Gross lesions of bacteremic *Salmonella* infection are acute and usually subtle. *Salmonella* Dublin is often septicemic in calves. Serosal and subcutaneous petechiae are widespread. The spleen usually is enlarged. The lungs are edematous and fail to collapse and have random foci of hemorrhage or congestion.[11] The wall of the gallbladder is thickened and may contain hemorrhages. The bile frequently is inspissated into a firm coagulum.[11] Less common lesions include jaundice, cystitis, meningitis, osteomyelitis, arthritis, and dry gangrene of ears, tail, or feet. Gastrointestinal lesions may or may not be present. Histopathologic study of *Salmonella* Dublin in calves younger than 6 months old demonstrates pulmonary alveolar capillary neutrophilia with or without hepatocellular necrosis and paratyphoid granulomas, splenitis and lymphadenitis.[72]

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Treatment

The keys to successful treatment of bacteremia caused by Gram-negative bacteria are (1) antimicrobial drugs, (2) fluids and electrolytes, and (3) NSAIDs. *Salmonella* Typhimurium antiserum is available commercially. Adverse reactions by cattle to horse serum are common; care should be taken.

Early in the course of disease in calves, appropriate antimicrobial therapy often increases the survival rate markedly because bacteremia frequently occurs. Appropriate antimicrobial therapy depends on culture and antimicrobial sensitivity patterns. Many of the most virulent *Salmonella* types are now multidrug-resistant, but isolates of relatively nonpathogenic *Salmonella* on dairies and feedlots found on surveys are usually sensitive to most antimicrobials, or resistant only to tetracyclines and sulfas.[28,73] In general, most pathogenic *Salmonella* isolates are sensitive to florphenicol, ceftiofur (and other third-generation cephalosporins), trimethoprim-sulfonamide, gentamicin, amikacin, and fluoroquinolones such as enrofloxacin.[24,28] Higher than label doses of ceftiofur used in calves with experimentally induced *Salmonella* Typhimurium infections did not alter mortality rates but did reduce fecal shedding and promote more rapid clearance.[74]

Sulfas and fluoroquinolones may not be used extralabel in food animals in the United States. Aminoglycosides such as neomycin, gentamicin, and amikacin produce long-term tissue residues and should be avoided in animals intended for use as food. Susceptibility to ampicillin, amoxicillin, sulfas, and tetracycline varies considerably, whereas resistance to penicillin, streptomycin, erythromycin, and tylosin is anticipated. Trimethoprim-sulfonamide combinations are relatively inexpensive, especially when given orally, but oral trimethoprim-sulfonamide should be used only in calves younger than 3 weeks of age. In calves older than 3 weeks of age, trimethoprim should be given intravenously because it is destroyed in the rumen and not absorbed. Antimicrobial drugs such as fluoroquinolones, florfenicol, or trimethoprim-sulfonamide that achieve good intracellular levels and have a large volume of distribution appear to be more effective than those that do not achieve good intracellular levels (e.g., gentamicin and amikacin). Florfenicol or cephalosporins such as ceftiofur may be good choices for therapy against many *Salmonella* isolates depending on susceptibility testing results. *Salmonella* strains resistant to fluoroquinolones and ceftiofur are also being discovered.[75] In a Minnesota study, researchers examined *Salmonella* from clinically ill cattle

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(2006 to 2015) and found that *Salmonella* Dublin, Montevideo, and Cerro became more frequent during those years, and none of the isolates were resistant to enrofloxicin or gentamicin, but 11% were resistant to trimethoprim-sulfonamide, 27% to neomycin, 37% to ceftiofur, 43% to florfenicol, 47% to ampicillin, 52% to oxytetracycline, and 83% to sulfadimethoxine.[76] A similar study in Wisconsin also demonstrated no isolates resistant to enrofloxacin.[77] Only 1 in 380 *Salmonella* organisms randomly collected from fecal floor samples in feedlots was resistant to fluoroquinolones despite the fact that a fluoroquinolone was used as the primary therapeutic antimicrobial to treat bovine respiratory disease in these feedlots.[78]

Antimicrobial drugs may not be effective at altering the clinical course of strictly enteric infections without bacteremia, but because bacteremia frequently accompanies salmonellosis, systemic antimicrobial therapy often is chosen. A very large precise genotyping and phylogenetic study comparing cattle and human isolates of *Salmonella* serovars Dublin and Typhimurium suggests that antimicrobial resistance genes are associated primarily with a particular host species with little overlap.[79] Another whole genome analysis concluded that the animal and human isolates of *Salmonella* Typhimurium DT104 were different, with only a small amount of spillover in each direction.[80]

In the United States, FARAD's VetGRAM must be consulted to ensure correct drug route, frequency, dose, withdrawal time, and legality.

The effects of endotoxins can be partially dampened or controlled by the judicious use of NSAIDs. The cascade of events caused by bacterial endotoxin (LPS from the cell wall) must be brought under control early and rapidly, by the use of drugs such as flunixin (Banamine) at a dose of 1.1 to 2.2 mg/kg IV every 12 hours. Once the animal is stabilized, NSAIDs should be discontinued, as continued administration can lead to adverse side effects such as abomasal ulceration.

Intravenous fluid therapy to maintain blood volume and pressure and correct acid-base or electrolyte abnormalities is important in any animal that is dehydrated or in shock (see Chapter 20, Neonatal Diarrhea section; this chapter, Fluid Therapy section, for adult equine; and Chapter 44, Critical Care section). Measurement of blood gases and electrolyte values assists in fluid therapy formulations. Balanced fluids containing sodium, with supplementation of glucose, should be administered intravenously as needed. Metabolic acidosis with mixed water and electrolyte losses is most often seen. Oral fluids and

electrolytes may also be effective supplements. The prognosis is good if animals are treated aggressively and early in the course of illness.

Control of Infectious Disease in a Veterinary Hospital

Veterinarians must also be aware of preventing the spread of *Salmonella* and other nosocomial diseases within an animal hospital and should have an effective written infectious disease control program in place.[81] See Chapter 46 for more details. In one study, 1.4% of cattle, mostly from dairy farms, shed salmonellae when in a veterinary clinic,[82] whereas the author has found an average of 7% of cattle (mainly dairy cows) ill with a variety of disorders in the author's large animal clinic were shedding *Salmonella.*

Clusters of cases occurred mainly in August and September in one northeast U.S. veterinary hospital, with 15 different serotypes involved; the most common were Typhimurium (33%), Newport (23%), and Agona (12%).[83]

Paratuberculosis (Johne's Disease)

Raymond W. Sweeney

Paratuberculosis is a chronic enteric disease of ruminants caused by infection with *Mycobacterium avium* subsp. *paratuberculosis (MAP).* Cattle, goats, sheep, deer, and camelids are most commonly affected, but the disease is also reported in wild ruminants and other species. In the United States, at least 68% of dairy herds have *MAP*-infected animals, with a much lower prevalence among beef herds (7.9% in one study).[1,2]

The causative organism, *MAP,* is a hearty organism that survives for prolonged periods in the environment, including soil and water. However, it has fastidious growth requirements in vitro, and culture on solid media may require 8 to 16 weeks. Results of studies indicate that *MAP* is also able to assume a spore-like bioform that is resistant to heat treatment in vitro, which may account for the organism's ability to survive pasteurization.[3] In vivo, the organism is an intracellular pathogen with the ability to survive within macrophages by preventing the maturation and acidification of the phagocytic vacuole. The term *Johne's disease* is often used to refer to the clinical syndrome of diarrhea and weight loss that results from *MAP* infection.

Transmission and Susceptibility

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Paratuberculosis is most commonly transmitted by the fecal-oral route. The organism is shed in the feces of infected animals (usually adults) and ingested by susceptible (usually young) animals. Critical points for potential exposure include maternity pen surfaces, cows' udders, contaminated feed or feeding implements, and calf housing areas. Small amounts of manure from heavy-shedding animals can result in vast contamination and exposure of susceptible young stock. Results of studies have also shown that *MAP* may be aerosolized and spread with dust barns with infected animals, which raises the possibility of exposure through inhalation, or oral ingestion of organisms where contaminated dust has settled on feeding utensils and other objects.[4,5] The organism can also be shed directly into colostrum and milk of infected cows, or these products can be contaminated by organisms on the skin, at the time of collection if insufficient sanitation is practiced. Transplacental transmission has been demonstrated and becomes more likely to occur (40% of fetuses from cows with clinical signs) as the infection progresses to advanced stages.[6,7]

Resistance to infection with *MAP* in calves increases with the age of the animal, with neonates considered particularly susceptible. Most studies indicate that calves older than 6 months of age are less susceptible, and by the age of 1 year, susceptibility is equivalent to that of an adult animal.[8,9] Although adult animals are more resistant to infection than juveniles, natural resistance in adult animals can be overcome by exposure to high doses of *MAP* organism. Furthermore, if infection with *MAP* occurs in an adult animal, the animal may be culled during the prolonged incubation period for other reasons before clinical manifestations of paratuberculosis are recognized. In addition to age, the exposure dose influences not only whether an animal becomes infected but also the rate of progression of the disease. Exposure to higher doses of *MAP* is thought to lead to more rapid progression of the infection and manifestation of clinical disease at a younger age.[9] Finally, there is growing evidence that genetic factors may play a role in susceptibility. Evidence gleaned from studies of breed differences, sire line differences, and DNA markers or candidate genes have indicated a clear genetic influence on susceptibility to *MAP*.[10] In the near future it may be possible to identify sires and dams with decreased susceptibility to *MAP* for breeding purposes.

Pathogenesis and Stages of Infection

Although tonsillar invasion by *MAP* after oral ingestion in calves has been

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demonstrated experimentally, most evidence suggests that the intestinal epithelium, particularly the ileum, is the usual portal of entry. The Peyer's patches are populated by specialized intestinal epithelial cells (M cells) that deliver the *MAP* organisms to macrophages in the submucosa of the intestine.[11] The progression of infection from this point is determined by a balance of the host's innate and adaptive immune response against the ability of the *MAP* organisms to evade destruction. In the early phases of infection, macrophages activated by T-helper type 1 (Th1) cytokines, such as interferon-gamma (IFN-γ), are able to limit proliferation of *MAP* and expansion of the infection.[12,13] Some animals might even eliminate the infection at this stage.[14] In those animals that do not clear the infection, the *MAP* infection is kept in check by the immune system, with limited slow progression initially. However, this comes at a cost to the host, and the persistent presence of *MAP* antigen in the intestinal and gut-associated lymphoid tissue incites a chronic inflammatory response. Inflammatory cells are recruited to the area, which results in granuloma formation with *MAP*-laden macrophages, epithelioid cells, lymphocytes, and multinucleate giant cells.[12] This period of insidious, slow proliferation is associated with a clinically silent “eclipse” phase, during which there is neither detectable fecal shedding of *MAP* nor detectable serum antibody production. Tests of specific cell-mediated immunity, such as detection of IFN-γ production in vitro after peripheral blood lymphocyte proliferation, might yield positive results during this eclipse phase, but are not available on a practical basis at this time.

Eventually, the host cell-mediated immune response is no longer able to contain the infection. The previously effective Th1-type response is replaced by development of a T-helper type 2 (Th2)–type response with elaboration of cytokines such as IL-4 and IL-10, which are associated with antibody production and waning of cell-mediated immunity.[16] Although there are no outward signs of clinical disease, and production is not yet affected, detectable fecal shedding (at a low level) begins at this stage, followed by development of detectable antibodies.[17,18] The asymptomatic fecal shedder has the potential to spread the disease within herds or between herds without arousing suspicion, as it appears clinically healthy.

As the infection progresses, *MAP* organisms begin to spread to extraintestinal sites, either via blood or through the lymphatic system. This can result in transplacental infection, and direct shedding in milk and colostrum, as noted

earlier. Fecal shedding of *MAP* also increases, so that high levels of fecal shedding may be detected before clinical signs are observed. In this subclinical phase of infection, effects on production parameters in dairy cattle are variably affected. A 16% reduction in milk production during the lactation preceding culling has been reported, with little (4%) or no reduction in the penultimate lactation.[19,20] Studies on the effect of *MAP* infection on parameters of reproduction efficiency (days open, pregnancy rates) and udder health (somatic cell count) have had conflicting results.[20,21] In one study, days open was greater in infected cows[21] yet another showed a greater number of days open in infected cows.[20] Results also vary depending on the diagnostic method used to identify cases. Most studies show no deleterious effect on somatic cell count.[20] Because the effect of *MAP* infection on these production parameters is usually not evident, producers are often reluctant to cull asymptomatic infected cows, as the animals remain apparently productive members of the herd.

Ultimately, the *MAP* infection, and accompanying inflammatory response, progressively leads to severe granulomatous infiltration of the bowel, causing thickening of the intestinal lining, with clubbing of villi and marked lymphangiectasia. The resulting maldigestion and protein-losing enteropathy result in the clinical syndrome recognized as Johne's disease.

Clinical Johne's Disease

The hallmark clinical sign of Johne's disease in cattle is watery (pipe-stream or projectile) dark green diarrhea. The diarrhea is not associated with tenesmus, blood or mucus is not typically present, and the animal does not exhibit fever, dehydration, or inappetance, but rather maintains a good appetite and possibly increased water consumption. Rapid weight loss usually accompanies the diarrhea, and edema due to hypoproteinemia develops in the submandibular and brisket areas (Figs. 32.140 and 32.141). Clinical laboratory tests will reveal hypoproteinemia, hypoalbuminemia, and possibly anemia of chronic disease. In this stage of the infection, *MAP* organisms are shed in the feces in massive quantities and these animals can serve as an important source of environmental contamination. Differential diagnosis might include severe parasitism, renal amyloidosis, or copper deficiency. If the animal is not culled at this point, progression to end-stage Johne's disease, with inappetance, cachexia, and death, ensues. Postmortem examination reveals grossly visible thickening and increased corrugation of the lining of the epithelium, and potentially enlargement

of the mesenteric lymph nodes in the ileocecal region. Histopathologic examination reveals the aforementioned granulomatous inflammation in gut and associated lymphoid tissue, with macrophages laden with acid-fast staining bacilli.



FIG. 32.140 A Guernsey cow exhibiting clinical signs of Johne's disease, including thin body condition and fecal staining on hind end. (Courtesy Dr. Robert H. Whitlock, Kennett Square, Pa.)



FIG. 32.141 Holstein cow exhibiting submandibular edema associated with clinical Johne's disease, hypoproteinemia, and protein-losing enteropathy. (Courtesy Dr. Robert H. Whitlock, Kennett Square, Pa.)

In sheep, goats, and camelids, diarrhea may not be a prominent feature of clinical Johne's disease as it is in cattle. Although watery feces may sometimes be found, more often, feces may be normal or lose their pelleted form and take the form of dog stool. Weight loss is prominent, and the hypoproteinemia with submandibular edema is a frequent finding. Goats, in particular, may become quite anemic, more than might typically be expected with anemia of chronic disease. Of course anemia, hypoproteinemia, and weight loss may be exacerbated by concurrent intestinal parasitism, which may initially obscure the diagnosis of Johne's disease. Johne's disease in farmed deer may differ in that there may be a shorter incubation period with rapid progression to clinical disease with diarrhea and emaciation. Also, postmortem examination of deer with Johne's disease may reveal caseation or calcification, or both, of mesenteric lymph nodes.[22]

Diagnosis

The available diagnostic tests are divided into two broad categories: (1) immune-based diagnostic tests that detect the host's antibody or cell-mediated immune response to *MAP* infection, and (2) organism detection tests that detect *MAP* organisms or *MAP* bacterial DNA in fecal or tissue samples.

Immune-Based Tests.

Tests of cell-mediated immunity include the intradermal Johnin test, which is similar to a tuberculin test, and in vitro lymphocyte stimulation with *MAP* antigens with detection of IFN-γ production. The intradermal Johnin test is generally regarded as unreliable because of both false-positive and false-negative reactions. Stimulation in vitro of peripheral blood lymphocytes with antigens of *MAP*, followed by detection of IFN-γ in cell culture supernatant, has shown the ability in a research setting to detect animals early in the course of *MAP* infection, in the eclipse phase before antibody production and fecal shedding are detectable. However, the tests are not available in a practical commercially available setting.

The most commonly applied immune tests are those that detect antibodies in serum or milk. These include the complement fixation test, the agar gel

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immunodiffusion test, and ELISA. The ELISAs have superior performance to the complement fixation or agar gel immunodiffusion tests when applied to serum from cattle, but some nations still list complement fixation or agar gel immunodiffusion testing as an import requirement. The ELISA is the most specific and sensitive of the commercially available antibody tests. It may be applied to serum or milk, and studies have shown comparable results when ELISA is applied to both matrices. The ELISAs are attractive because of their relatively low cost and amenability to automation, which makes testing of large numbers of samples practical and cost-effective. Many Dairy Herd Improvement Association services now offer the option to include Johne's ELISA testing on milk samples, adding to the convenience of testing. Preservatives added to Dairy Herd Improvement Association milk samples do not interfere with milk ELISA testing.

Antibody detection tests are hindered only by the natural biological features of the disease, in that infected cattle do not ordinarily produce detectable antibodies until after fecal shedding has begun. Thus the sensitivity to detect asymptomatic cattle that are “low fecal shedders” may be as low as 15%, whereas 90% of clinically affected, “heavy shedding” cattle are positive. The ELISAs generally have high specificity (98% to 100%).[23,24]

Organism Detection Tests.

Organism detection tests on fecal samples include both culture and PCR detection methods. They have the advantage over antibody-based tests in that they (1) generally allow detection earlier in the course of infection because fecal shedding usually precedes antibody detection; (2) allow quantification of the degree of fecal shedding to assess the biosecurity effect of individual animals; and (3) definitively identify *MAP* in a herd at the time of first diagnosis. They have the disadvantage of being more expensive than ELISA and, in the case of culture, requiring a long incubation period to obtain results. Cultures performed on solid Herrold's Egg Yolk Medium may require up to 16 weeks for incubation. Many laboratories now employ a liquid culture system that can shorten the culture time to 1 to 2 months. Commercially available real-time PCR tests for fecal samples also permit quantification of *MAP* shedding and have sensitivity comparable to or better than culture. The specificity of culture and PCR methods is generally regarded as 100%, but it should be remembered that when *MAP*-contaminated feed is consumed by uninfected cattle, the *MAP* organisms may pass through the gastrointestinal tract and cause a transient positive result on

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fecal PCR or culture. A list of USDA-approved or accredited laboratories for Johne's disease testing is available at the USDA Animal and Plant Inspection Service (USDA-APHIS) website (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/lab-info-services/sa_approved_labs/ct_approved_labs).

Testing Scenarios.

Diagnostic tests should be selected on a case-by-case basis, depending on the clinical scenario, the objectives of the producer, and the inherent advantages and disadvantages of each test. For example, to confirm the diagnosis of Johne's disease in an adult cow with weight loss and diarrhea, a clinician will not have the luxury of waiting for fecal culture results before making a culling or treatment decision. Thus a test with rapid turnaround time is indicated, and both ELISA and fecal PCR would provide rapid results with a high predictive value positive (or negative). If the case in question is the index case in a herd, then organism detection would be more appropriate than ELISA, to provide a definitive confirmation that *MAP* is the etiologic agent because the implications of a diagnosis for the herd may be great. Postmortem demonstration of typical lesions and identification of *MAP* by culture of mesenteric lymph node or ileum can also be used to confirm a diagnosis.

An alternative objective might be to identify infected asymptomatic cattle in a herd that is known to be infected with *MAP,* for purposes of culling in an eradication program, or segregation for calving pen or colostrum management. In higher prevalence herds, serum or milk ELISA can be used if the magnitude of the ELISA result is used to interpret the results (i.e., as opposed to just “positive” or “negative”). Animals with a negative ELISA result, even if infected, are probably not shedding *MAP* in feces, milk, or colostrum at a significant level. Animals with “low positive results” are more probably shedding *MAP* in feces and might remain in the herd if production is good, but their status should be kept in mind when managing calving pens and colostrum. “High positive” ELISA results suggest heavy fecal shedding and a potential significant source of farm contamination; affected cows should be culled as soon as possible. Although more expensive, fecal culture or PCR can similarly be used to identify asymptomatic infected cattle with greater sensitivity than ELISA. Where management/control is the objective, a low positive result will warrant appropriate calving pen and colostrum management but not necessarily culling, whereas a high positive result may warrant sooner culling. In an

aggressive eradication program, any fecal culture positive result might result in a decision to cull, either immediately or at the end of the lactation. Testing can be performed on an annual, whole-herd basis, or in some systems, cows can be tested at the time of drying off. With this method, if ELISA, fecal culture with liquid medium, or fecal PCR is employed, the results will be available before calving to guide management decisions.

A third scenario is to determine whether a herd has *MAP* infection or to document test-negative or low-prevalence status for certification programs. One of the more cost-effective methods for this purpose, on dairy farms, is to perform fecal culture or PCR on environmental fecal samples collected from areas with high cow traffic and from the manure pit or storage lagoon. Culturing from 5 to 6 such sites has been shown to detect at least 70% of herds with infected animals.[25]

The USDA-APHIS Uniform Program Standards for Voluntary Bovine Johne's Disease Control Programs (VJDCP) provide testing guidelines for establishing herd infection status. Although individual states' programs may vary, the current standard establishes six classification levels. Levels 1 to 3 identify herds with low test-positive prevalence, or herds with 1 year of all-negative test results, whereas levels 4 to 6 identify herds with 2 or more years of test-negative results, with level 6 having the highest certainty of infection-free status. Herds establish classification status by whole herd (or statistically determined subset for large herds) ELISA or organism detection testing (individual samples or pooled). The reader is referred to the VJDCP Program Standards for more information about more detailed testing requirements (https://www.aphis.usda.gov/animal_health/animal_diseases/johnes/downloads/jcups.pdf).

Finally, testing may be desired to screen animals purchased as herd replacements or for use as embryo transfer recipients. Unfortunately, currently available tests are not useful for detecting infection in these animals, which are often of a young age (<3 years) and in the "eclipse" phase of infection. Greater assurance of likelihood of infection-free status in young stock can be obtained through testing of adult animals in the herd of origin. Purchasing animals from herds that have achieved VJDCP classification level 4 or above will give the greatest assurance that the animals are not infected. If the seller does not participate in a VJDCP, results of comparable testing on adult cattle older than 3 years of age in the herd should be requested. If such results are not available, purchase is extremely risky and should be avoided. A potential but less desirable

recommendation is to screen potential replacements by ELISA and fecal PCR, recognizing that if the animal is in the eclipse phase, false-negative results are possible, and continued monitoring on an annual or semi-annual basis after addition to the herd is warranted.

Nonbovids.

In goats, serum ELISA and fecal culture and PCR have similar accuracy to that found in cattle. However, serum testing for antibodies in sheep is less reliable, and organism detection tests on feces are recommended. The sheep strain of *MAP* is more difficult to grow in vitro than the cattle strain that affects dairy cattle, beef cattle, goats, and camelids in the United States. Development of specialized liquid media for culture of *MAP* from sheep feces has improved sensitivity, but best results will probably be achieved by employing fecal PCR testing. In camelids, PCR and culture in liquid media have similar sensitivity to detect *MAP* in feces.

Treatment

In most production situations, treatment for *MAP* infection is not attempted. However, in some cases treatment may be desirable to allow for preservation of genetics (e.g., through embryo transfer or in vitro fertilization), or for sentimental reasons, especially those animals viewed as pets. Before undertaking treatment, the owner must be made aware that treatment may result in remission of clinical signs and reduction of fecal shedding, but the infection is rarely eliminated, and daily treatment will probably be required for the life of the animal, with relapse likely to occur when treatment is discontinued. Treatment of a clinically affected pregnant cow to salvage her fetus is not recommended because of the high likelihood of transplacental infection of the fetus. In addition, any chemotherapeutic program will involve extralabel use of antimicrobials, which in the United States must be performed in accordance with the regulations set forth in the Animal Medicinal Drug Use Clarification Act. As reliable withdrawal times are not established for many of the antimicrobials employed in treatment of Johne's disease, owners should be informed that once treatment begins, the animal or its products should never enter the human food supply chain.

The therapeutic agents most often employed include those used to treat mycobacterial infections in humans (isoniazid, rifampin, clofazimine), monensin, and aminoglycosides, and combination therapy is often

recommended, at least to induce remission.[26] Clofazimine, an antileprosy drug, has been used successfully by the author at a dose of 2 mg/kg q24h, alone or in combination with other agents. Improvement in fecal consistency and plasma total protein occurred within 7 to 14 days of starting treatment. However, this drug has not been available in the United States, prompting use of other combinations. Thus a typical currently employed treatment protocol, if clofazimine is not available, for cattle, goats, sheep, and camelids includes rifampin (10 mg/kg PO q24h) and isoniazid (10 to 20 mg/kg PO q24h). Again, because of its potential carcinogenicity, rifampin is not appropriate for extra-label use in animals intended for food and should thus only be used in pet animals or animals that will never enter the human food chain. Gentamicin (6.6 to 8.0 mg/kg IV q24h) for the first 5 to 10 days of treatment may hasten onset of remission, provided renal function is normal and can be monitored for signs of nephrotoxicosis. For cattle, monensin should also be recommended. Approved for its effect as a coccidiostat and for its effect on rumen microflora and digestion efficiency, momensin has also been shown to inhibit *MAP* growth in vitro and improve the signs and lesions of disease in experimentally and naturally infected cattle.[27,28] Use of monensin as a feed additive also has the potential to play a chemoprophylactic role in prevention of *MAP* infections in susceptible cattle. However, monensin as a feed additive cannot be used in an extra-label fashion in the United States, so the intended animal must have a label indication for use of monensin, not solely treatment of *MAP*.

Prevention and Control

For herds not currently infected with *MAP,* prevention relies primarily on establishing a closed herd. If herd replacements must be purchased, the herd of origin should be screened as indicated earlier, and ideally have achieved level 4 or higher status in the VJDCP.

For herds that are infected, clear objectives should be established. For large production herds with high turnover, no steps may be economically warranted. For other herds, management to reduce transmission and ameliorate the economic effect of the disease may be desirable, and in other herds eradication may be the goal. Regardless of the goal, a test-and-cull strategy employed without other management changes to reduce transmission will not be successful.

Whether the goal is eradication or managing the disease to minimize losses, a

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risk assessment should be performed to identify potential areas of *MAP* transmission, especially to susceptible young stock, and a management plan developed. A plan must be individually tailored to a specific facility, but in general key control points are calving pens, calf feeding (colostrum and milk) management, and calf housing, especially as they pertain to potential exposure of calves to feces of adult infected cows, or to fecal-contaminated surfaces. Handbooks for veterinarians to assist them in performing risk assessments and management plans for both dairy and beef cattle, designed by the Johne's Disease Committee of the U.S. Animal Health Association, are available at http://www.johnesdisease.org/. On most dairy farms, control strategies focus on calving pen hygiene, early removal of calves from the calving pen after birth, providing an uncontaminated source of colostrum and milk or colostrum replacer and milk replacer, and calf housing free of contamination by feces from adult cattle. Testing in some form to identify and remove or segregate highly infectious adult cattle is usually warranted. In beef cow-calf operations, preventing transmission to calves again must focus on manure contamination of calving areas, manure contamination of cows that are nursing calves, and other possible sources of calf exposure to feces from potentially infected adult cattle. Recommendations can be adapted as appropriate for use with small ruminants and camelids, again to focus on prevention of transmission to susceptible young stock.

Vaccination has been employed with mixed results in cattle and small ruminants. In the United States, vaccination of cattle is permitted in some states, on approval by the State Veterinarian. The only licensed vaccine (Mycopar [Boehringer Ingelheim Vetmedica, St. Joseph, Mo.]) is a killed oil suspension of *M. avium*. The vaccine is generally regarded to reduce the incidence of clinical disease, and in some instances also reduce the level of fecal shedding, yet in other studies prevalence of fecal shedding was not affected. Vaccination should be considered as a useful adjunct, particularly in herds of high prevalence with significant losses due to clinical Johne's disease. Vaccination alone, without implementation of management changes to reduce exposure of calves to *MAP*, is often unsuccessful as any resistance achieved by vaccination may be overcome by heavy *MAP* exposure.

Zoonotic Potential.

Traditionally, *MAP* was not regarded as a pathogen of humans. However, because of some similarities between Crohn's disease in humans and Johne's

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disease in ruminants, the possible connection between *MAP* and Crohn's disease has undergone further scrutiny. These studies, especially those that employ PCR methods to identify *MAP* in tissue samples from people with Crohn's disease, have definitively shown an association between presence of *MAP* in intestinal tissue and Crohn's disease.[29] However, what is more difficult to determine is whether this association is causal or secondary. Crohn's disease is thought to involve an overly florid immune response to antigens in the gastrointestinal tract. Proponents of the hypothesis that *MAP* causes Crohn's disease believe that *MAP* antigens are responsible for that response, whereas skeptics believe that *MAP* may be present secondarily to damaged mucosa with diminished resistance to *MAP* colonization. Improved clinical signs in patients with Crohn's disease in response to antimicrobial therapy directed against *MAP* might constitute further evidence for the role of *MAP* in the disease. However, results of clinical trials of antimycobacterial therapy have had mixed results with differences in opinion regarding their interpretation.[30] Undoubtedly, Crohn's disease is a multifactorial disease influenced by a complex interaction of genetics, environment, cigarette smoking, and potentially infectious agents. Human exposure to *MAP* occurs potentially via survival of *MAP* in pasteurized milk or drinking water contaminated by fecal runoff from infected farms. Increasingly, regulatory agencies around the world are treating paratuberculosis as a food safety issue. More recently, an association with immune-mediated disorders such as diabetes mellitus Type 1, multiple sclerosis, and thyroiditis through molecular mimicry and dysregulation of the immune system.[31] It may be difficult to scientifically establish an etiologic connection between *MAP* and Crohn's disease or these other disorders; however, in the author's opinion, even the potential for a role of *MAP* in Crohn's disease or other human conditions should motivate producers and veterinarians to control the disease in food-producing animals.

Copper Deficiency in Ruminants

John Maas • Bradford P. Smith

Definition and Etiology

Copper deficiency occurs when the diet contains an abnormally low amount of copper (primary copper deficiency) or when copper absorption or metabolism is adversely affected (secondary copper deficiency). If inadequate amounts of

copper are available to tissues in the form of essential metalloenzymes, the signs of copper deficiency (hypocuprosis) may occur. Clinical signs in ruminants can include diarrhea, decreased weight gain, unthrifty appearance, anemia, changes in coat color (achromotrichia) or wool quality, anemia, spontaneous fractures, lameness (epiphysitis), and demyelinization (enzootic ataxia of sheep and goats, or swayback). One of these syndromes usually predominates in a given herd. The reason or reasons that one or another syndrome predominates are unknown. For example, a report from New Zealand concluded that protein-calorie malnutrition with periods of copper deficiency resulted in spontaneous fractures in dairy heifers.[1]

The minimum recommended dietary copper concentration (dry matter basis) is 4 to 10 ppm (mg/kg) for cattle,[2,3] 5 ppm for sheep,[4] and 7 ppm for merino sheep.[4] Young animals and fetuses are more susceptible to copper deficiency than are mature animals, and cattle are more susceptible than are sheep. Secondary copper deficiency is associated with high dietary levels of molybdenum, sulfates, zinc, iron, or other compounds. Secondary copper deficiency often presents with clinical signs of diarrhea and weight loss or unthriftiness. It has been called *teart*, *peat scours*, *renguerra*, *pine*, and *salt lick disease*.[5] Salt sickness in Florida appears to be the result of combined copper and Co deficiencies. The cause of copper deficiency in clinical cases is often multifactorial and can be difficult to quantify. In addition, unknown factors cause clinical expression of copper deficiency in ruminants to be manifested as a variety of syndromes.

Clinical Syndromes and Differential Diagnosis

Profuse watery diarrhea with poor weight gains or weight loss is a common syndrome seen in ruminants with copper deficiency.[5] When it occurs on boggy pastures that contain high concentrations of molybdenum, it has been referred to as *teart*.[5] Decreased weight gains or weight loss as a herd problem can have many other causes, including parasitism, trace mineral deficiencies (selenium, cobalt), protein calorie malnutrition, and Johne's disease. A syndrome characterized by epiphyseal enlargement, stiffness, and unthriftiness is seen in young ruminants and is the result of copper deficiency[6] and is sometimes called *pine*.[5] Copper deficiency can cause spontaneous fractures in ruminants and can be associated with phosphorus deficiency or protein-calorie malnutrition.[1] Enzootic neonatal ataxia (swayback) of lambs and kids is characterized by

progressive incoordination and recumbency that begins with the hind limbs and progresses to the front-limbs. It has also been reported in deer and pigs. Inadequate keratinization of wool and achromotrichia is the result of imperfect oxidation of free thiol groups during hair growth and keratinization. Subsequently, the wool fibers do not crimp normally, and they appear to be "stringy" or "kinky." A copper-containing enzyme, tyrosinase (polyphenol oxidase), is needed to convert L-tyrosine to melanin. With copper deficiency, this conversion is slow and hair is lighter in color than normal (achromotrichia). Loss of wool crimp and pigmentation changes in sheep or cattle, respectively, occur late in the course of copper deficiency. In addition to the previously listed clinical syndromes that may occur alone or jointly, copper deficiency may be associated with anemia[7] (altered iron metabolism) or infertility.[8] Infertility probably has multifactorial causes and may not respond to an increase in copper intake alone. Copper deficiency also seems to result in decreased immune function in ruminants.[9,10]

Pathogenesis

A frank dietary deficiency of copper results in hypocuprosis and eventual clinical signs. Also, a variety of conditions can decrease copper absorption from the gastrointestinal tract (large intestine in sheep and small intestine in cattle). The interactions between dietary copper, molybdenum, and sulfates (or sulfur) are important (Fig. 32.142). Excess dietary molybdenum can lead to the formation of sparingly soluble cupric molybdates in the rumen that are not absorbed from the intestine. The addition of excess sulfur or sulfates in the diet or water can result in the formation of insoluble copper thiomolybdates in the rumen. The interactions among these three elements are complex.[11] The infertility seen with secondary copper deficiency may be caused by excess circulating oxythiomolybdates, which interfere with the release of luteinizing hormone.[12] However, the feeding of dried distillers grain, with a high sulfur content, at 0.75% body weight as fed did not result in differences in average daily gain, body weight, plasma copper, or plasma zinc concentrations in comparison to control cattle.[13] This study concluded that high sulfur, dried distillers grain fed at 0.75% body weight did not result in copper antagonism; however, liver copper concentrations were not measured.[13]

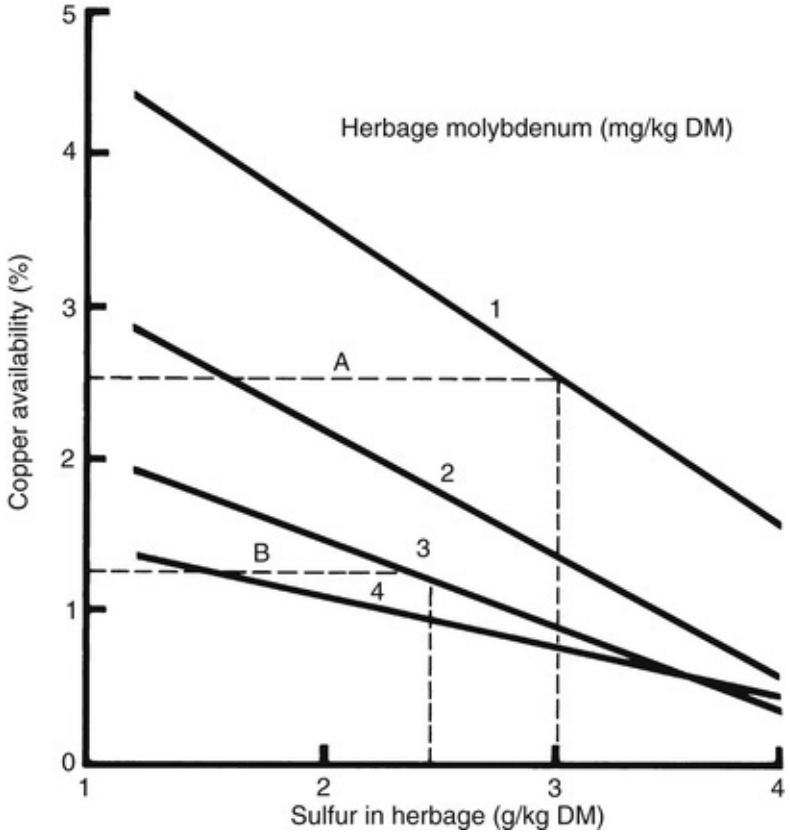


FIG. 32.142 Estimating the availability of copper in herbage from its molybdenum and sulfur concentrations: the difference of 3 mg of molybdenum and 0.5 g of sulfur per kilogram of dry matter *(DM)* between two pastures (*A* and *B*) is sufficient to reduce availability from 2.6% to 1.3%, thereby doubling a grazing animal's requirement of copper from the pasture. (From Suttle NF. 1986. Copper deficiency in ruminants: recent developments. *Vet Rec* 119:519.)

Of importance is that at low sulfur concentrations in the diet, excess molybdenum has a minimum effect on decreasing copper absorption. Even when no dietary molybdenum or sulfates are present, only approximately 5% of ingested copper is ordinarily absorbed. Excessive calcium in the diet, particularly in the form of limestone, decreases copper absorption. Excessive iron, 30 mg/kg of body weight or 1200 ppm in the diet of calves, reduces copper absorption.[14] Overgrazing, with the subsequent ingestion of excess soil, also decreases copper absorption. In addition, excess cadmium (3 to 7 ppm) or excess zinc (100 to 400 ppm) reduces hepatic copper concentration, probably through the combined effects of decreased absorption and competition with copper for hepatic metallothionein.[15,16] It had been suggested that excess dietary selenium might interfere with copper absorption, utilization, or both, but this has been

shown not to occur.[17] Copper is an essential component of a number of mammalian enzymes. Some of the medically important copper-containing enzymes are (1) the cytosol form of superoxide dismutase (copper and zinc), (2) cytochrome oxidase (c and aa_3), (3) lysyl oxidase, (4) ascorbic acid oxidase, and (5) ceruloplasmin.[18] In addition, normal copper nutrition appears essential for iron absorption and transportation of iron to the liver and reticuloendothelial system and is thus necessary for normal hemoglobin formation. The precise pathophysiologic mechanism of most of the copper deficiency syndromes is not known. However, the central role of copper in preventing cellular oxidative damage and its role in iron and sulfur metabolism are probably important.

Epidemiology

Copper deficiency can occur when diets are inadequate in copper or contain excess amounts of interfering substances, particularly molybdenum and sulfates. This occurs in many parts of North America. Forages and water can be sources of molybdenum, sulfur, and sulfate. To avoid primary copper deficiency, pasture (dry matter) should contain over 5 ppm of copper, with 3 to 5 ppm considered marginal and less than 3 ppm deficient. Soil copper concentrations are generally slightly lower than those of the harvested forage. Molybdenum adversely affects plant uptake of copper. Forage molybdenum concentrations greater than the copper concentrations often lead to secondary copper deficiency, even when forage copper is adequate. Because copper content in grasses and legumes can be different, forage samples must be selected to reflect dietary intake. Forage copper concentrations as high as 12 to 27 ppm have been associated with copper deficiency when molybdenum levels are high.[5] The critical ratio of copper to molybdenum in feeds is 2 : 1, with 5 : 1 recommended for sheep and 5 : 1 to 10 : 1 for grazing cattle.

Clinical Pathology and Diagnosis

The primary site of copper reserves is the liver and the copper concentration in the hepatic tissue is the best indicator of copper status (Fig. 32.143). The reference range for hepatic copper concentrations in cattle is approximately 90 to 200 µg/g (ppm) and in sheep 90 to 250 µg/g on a dry weight basis (dry matter basis [DMB]).[5,19,20] Hepatic copper concentrations as high as 250 µg/g DMB are not unusual in supplemented ruminants (even over 350 µg/g DMB in sheep). Blood (serum or plasma) copper concentrations can be maintained near normal

until hepatic copper concentration falls to 35 ppm DMB or less, at which time the serum copper concentration invariably begins to decrease.[21] When blood samples are used for copper level determination, serum or plasma are normally preferred. Plasma copper concentration is usually approximately 5% greater than an identical serum copper concentration.[22] Normal serum copper is 0.7 to 1.2 ppm (µg/mL).[5,18] Serum or plasma copper concentrations of 0.4 ppm or less are considered as evidence of frank deficiency. Values of 0.4 to 0.7 ppm are marginal and it is difficult to estimate the actual liver copper concentration on the basis of these serum copper concentration ranges. Approximately 50% to 90% of the copper in serum or plasma is present in ceruloplasmin. The remainder is bound to albumin or amino acids. The correlation between serum copper and serum ceruloplasmin was found to be weak (0.50)[22]; thus ceruloplasmin is not commonly used to aid in diagnosing copper deficiency. In addition, serum ceruloplasmin increases with inflammatory conditions and can result in falsely higher values. Hepatic copper concentration is the preferred diagnostic sample and is easily secured at necropsy. Hepatic copper values less than 35 ppm DMB are considered deficient.[5,19-21] However, surgical biopsy is necessary for live patients, and, because laboratories generally require 100 mg or more of tissue, a biopsy instrument with an internal diameter of 3 to 5 mm is necessary.[23] The biopsy procedure in cattle is performed by locating the tenth intercostal space on the right side of the animal along a line from the tuber coxae (point of the hip) to the point of the shoulder.[23] This site is surgically prepared and blocked with lidocaine (12 mL of 2% lidocaine) and a stab incision is made. The biopsy instrument is directed slightly ventrad and craniad and advanced through the intercostal space and the diaphragm to enter the liver where the biopsy sample is obtained.[23] The liver biopsy can place the patient at increased risk for black disease or bacillary hemoglobinuria in some areas. This risk should be decreased by prior vaccination and a single dose of procaine penicillin G (4 million IU SC) administered at the time of biopsy. This technique has been shown to be safe and effective.[23] The tissues of young animals (neonates) contain variable amounts of copper compared with adults of the same species. In sheep, serum and liver copper concentrations are the same for lambs (1 week of age) and adults.[24] The plasma copper levels in lambs are low at birth but rise to adult values by 1 to 7 days of age. Plasma copper levels in the bovine neonate are lower than in mature cattle.[25] In the bovine neonate hepatic copper concentration changes little from birth to maturity; however, copper distribution

in the liver is quite variable in neonates.[20,25] Because of these differences, interpretation of neonatal serum copper concentrations is difficult. Milk is a poor source of copper, containing only 0.2 to 0.6 ppm in normal ewes and 0.01 to 0.02 ppm in severely copper-deficient ewes or cows. Milk copper concentration in cattle is 0.05 to 0.2 ppm. To make matters worse, molybdenum is concentrated in milk.[26] Research has allowed for the estimation of true wet weight (fresh) or dry weight of hepatic samples by concurrently measuring potassium in the specimen.[27] This allows for much more accurate estimation of hepatic copper concentration in samples that have become dehydrated before reaching the diagnostic laboratory. This technique allows the laboratory to accurately estimate the original wet weight or to calculate the dry weight without time-consuming drying of the specimen.[27]

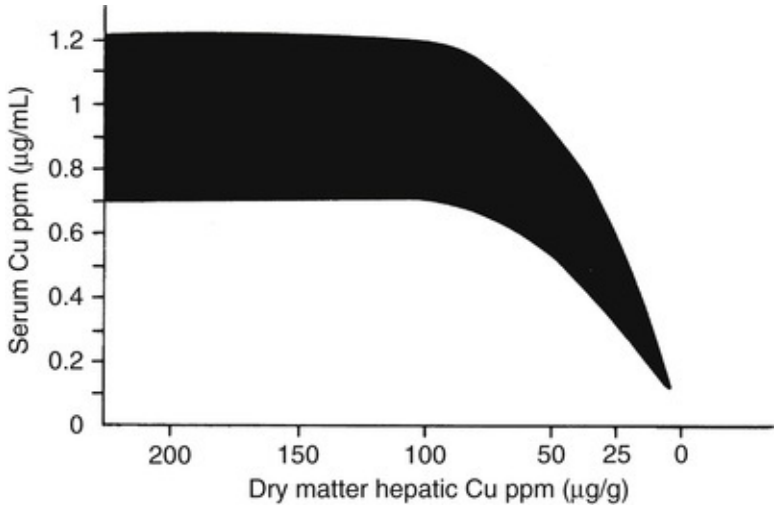


FIG. 32.143 Relationship between serum and hepatic copper concentration in ruminants.

Treatment and Control

Treatment of copper-deficient animals is usually possible, and the prognosis is guarded to good, depending on the severity of the deficiency and the associated syndrome or syndromes. When excess molybdenum, sulfate, and other factors leading to secondary deficiency are present, they can be overcome to some extent by increasing dietary copper or by injecting copper glycinate. Copper glycinate must be prescribed by the attending veterinarian and dispensed by a

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compounding pharmacy as no commercial over-the-counter products are currently available. There are currently very few compounding pharmacies manufacturing injectable copper glycinate. Injectable copper glycinate (30% copper by weight) is given to adult cattle at the rate of 400 mg (120 mg copper) subcutaneously. Calves are given 100 to 200 mg of copper glycinate (30 to 60 mg of copper), depending on their age. One injection may be effective as a treatment/supplement for up to 4 to 6 months in cases of primary copper deficiency. However, in cases of excess molybdenum, sulfates, or sulfur, repeat injections may be necessary. Injections of copper glycinate frequently result in large swellings, granulomas, or abscesses and may be cosmetic considerations for some cattle. These reactions can be minimized with sterile technique and the use of the subcutaneous tissue of the brisket as the injection site. Acute deaths can occur in calves after the use of copper glycinate injections. In some countries copper disodium edetate solutions are used as injectable copper supplements. The dosage of copper is usually the same as that recommended for copper glycinate solutions. Also, acute deaths can occur after copper disodium edetate use in cattle.[28] Copper can be supplemented to cattle in salt-mineral mixes in situations in which adequate consumption (1 to 2 oz [28 to 56 g]/cow/day) of the salt-mineral mix occurs. These mixes are usually 0.2 to 0.6% copper. Feed grade copper sulfate ($CuSO_4$-5 H_2O) is 25% copper on an as-fed basis (40% copper on dry matter basis). Feed-grade copper oxide is usually 50% copper as fed (80% copper on a 100% dry matter basis). To make a 0.4% copper salt mixture, 7.2 g of $CuSO_4$ or 3.6 g of CuO is added to each 454 g (1 pound) of salt. For large batches, 14.52 Kg (32 pounds) of $CuSO_4$ or 7.26 Kg (16 pounds) of CuO is added to each ton of salt. Salt mixtures for copper-deficient sheep should usually contain only 0.0625% to 0.13% copper (0.25% to 0.5% copper sulfate). Copper supplements can be added to a total mixed ration easily in the form of trace mineral–vitamin premixes or premix-containing pellets. Copper sulfate can be added to molasses or other sweet feed at 0.363 g/head/day for mature cattle and correspondingly less for calves. This would supply approximately 91 mg of copper to a 450-kg (1000-pound) cow per day or 10 ppm of the total diet (20 pounds [9.1 kg] of dry matter). The copper in $CuSO_4$ is more available than that in CuO.

Another method of copper supplementation involves the oral administration of copper oxide needles (fine rods, 1 to 10 mm long) placed in gelatin capsules that dissolve in the reticulorumen and liberate the CuO wires. These wires reside in

the reticulum and abomasum and slowly release copper for absorption. These boluses are currently available in the United States (Copasure, Animax, Bury St. Edmunds, Suffolk, U.K.]) and contain either 25 g or 12.5 g per bolus. The usual recommended dosage is 25 g per animal weighing 227 kg (500 pounds) or more. One 12.5-g bolus is recommended for calves and the usual dose is 2 to 4 g for ewes and does,[5,29,30] which is an extra label recommendation for sheep and goats. The copper oxide needles are thought to provide copper supplementation for 4 to 12 months. A rumen bolus containing a number of trace minerals (copper, iodine, manganese, selenium, zinc, and cobalt) has been made available in the United States (Reloader 250, Cargill, Minneapolis, Minn.). This bolus contains 6.0% copper and would release an average of 46 mg copper per day over a 250-day period. This would be a biologically significant percentage of the daily 40-100 mg of copper requirement for adult cattle. The report[31] of its efficacy detailed the measurement of plasma copper and found no differences between affected cattle and control animals; however, liver copper concentrations would have been the preferred measurement for copper status. Perhaps future studies will detail the practical pharmacodynamics of this device with regard to copper and other trace minerals. Sheep are particularly susceptible to copper toxicity, and appropriate care is necessary when supplementing them. Sheep can easily be intoxicated when consuming cattle supplements or feeds. Continued monitoring of hepatic copper concentration from slaughtered animals or via liver biopsy is an important tool in evaluating copper supplementation methods in cattle and sheep. Lambs can be given 35 mg of copper sulfate per head twice weekly to prevent swayback in endemic areas.

The usual recommendation by the National Research Council (NRC) is 10 ppm (10 mg/kg) of the total diet on a dry matter basis for cattle. However, diets of 20 ppm are commonly fed to lactating dairy cattle. The 2001 NRC recommendations for dairy cattle state that 40 mg/kg (ppm) of the diet on a dry matter basis is the maximum tolerable level, unless significant interference by molybdenum, sulfur, or other antagonists are present.[32] This is due to a number of copper toxicity episodes in the United States when the total diet contained 40 to 50 mg/kg copper or more in the total ration. In addition, the European Food Safety Authority (EFSA) has decreased the maximum concentration of copper in complete feeds to 15 ppm for pre-ruminant calves, 30 ppm for cattle, 15 ppm for sheep, and 35 ppm for goats.[33] Copper has the smallest margin of safety of all the trace minerals in ruminants. The most important goal of copper supplementation is to provide adequate dietary amounts without over-

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supplementing or risking toxicity.

Cobalt Deficiency in Ruminants

Robert Bascom Sager • John Maas

Definition and Etiology

A number of syndromes occur in ruminants as a result of a primary cobalt (Co) deficiency in their diet. These include ill thrift or enzootic marasmus and anemia. These conditions are characterized by decreased growth, weight loss, diarrhea, decreased feed efficiency, unthrifty appearance, anorexia, and anemia. A Co deficiency syndrome referred to as *ovine white liver disease* has been described in sheep.[1-3] This syndrome is also characterized by ill thrift, weight loss, serous ocular discharge, and occasionally photosensitization.[1-3] Histopathologic lesions of this syndrome included accumulation of lipid droplets and lipofuchsin particles, dissociation and necrosis of hepatocytes, and sparse infiltration by neutrophils, macrophages, and lymphocytes.[4] Co-deficient animals are more prone to parasitic infestation, particularly *Ostertagia ostertagi* in cattle.[1] Also, Co fed at levels above National Research Council (NRC) minimal recommendations has resulted in increased antibody production to a single antigen in weaned beef calves.[5]

Clinical Signs and Differential Diagnosis

Co deficiency in ruminants is associated with the nonspecific signs of decreased growth, weight loss, diarrhea, ill thrift, pica, emaciation, pale mucous membranes (anemia), and lacrimation. Clinical disease is more common in young, growing animals. Sheep are apparently more susceptible to Co deficiency than cattle. Primary differential diagnoses include helminthic parasitism; protein-calorie malnutrition; coccidiosis; Johne's disease; nutritional deficiencies of selenium, copper, or vitamin D; and other chronic diseases that may be associated with weight loss. Co-deficient ruminants are commonly anorexic and fail to thrive on lush pasture or high-quality feeds. Anemia with Co deficiency is characterized as normocytic normochromic and must be differentiated from other causes of anemia. Co-deficient cattle are more susceptible to infestation with *Ostertagia ostertagi* and to the effects of parasitism.[4] The primary differential diagnosis when considering Co deficiency is invariably internal

parasitism.

Clinical Pathology and Diagnosis

Because the role of Co in ruminant nutrition is tied to the formation, absorption, and use of vitamin B_{12}, the most significant biochemical role of Co is correlated with tissue vitamin B_{12} concentrations. However, the effects of starvation tend to increase vitamin B_{12} concentrations in the liver and kidneys.[6] If Co deficiency occurs with other conditions that cause anorexia, the tissue vitamin B_{12} concentrations may appear falsely elevated (normal). The appropriate analytic methods for serum B_{12} vary from humans to ruminants, so extrapolation of ruminant serum B_{12} concentrations analyzed in a human laboratory may not be possible. Serum or plasma vitamin B_{12} levels exhibit a marked diurnal variation.[7] In addition, serum vitamin B_{12} concentration more closely reflects short-term Co intake and can be decreased when adequate liver reserves of vitamin B_{12} remain. In normal, Co-sufficient ruminants' serum vitamin B_{12} values are usually 0.1 to 0.3 ng/mL (parts per billion [ppb]). When serum vitamin B_{12} values decrease, clinical signs of Co deficiency can become evident.[8,9] Because serum B_{12} values can give spurious results, the concentration of Co in hepatic tissue is probably the best current standard for determining Co status and making clinical decisions. The liver concentration of B_{12} for cattle and sheep considered to be adequate is 0.30 to 2.24 µg/mL (ppm) on a wet weight basis.[10,11] Table 32.25 contains reference ranges for cattle and sheep.

TABLE 32.25

Reference Values for Cobalt and Vitamin B_{12}

Analyte	Cattle	Sheep
Serum cobalt	0.1-0.3 ng/mL (ppb)[11,12]	0.1-0.3 ng/mL (ppb)[11,12]
Serum vitamin B_{12}	1-3 ng/mL (ppb)[10,11]	1-3.5 ng/mL (ppb)[11]
Liver cobalt	80-160 ng/g (ppb) wet weight[10-12]	80-160 ng/g (ppb) wet weight[10-12]
Liver vitamin B_{12}	0.3-2.24 µg/g (ppm) wet weight[10,11]	0.3-2.24 µg/g (ppm) wet weight[10,11]

Pathophysiology

Co deficiency in ruminants induces a deficiency of vitamin B_{12}

(cyanocobalamin). It is the lack of vitamin B_{12} that is thought to cause the majority of clinical signs and clinicopathologic abnormalities observed. Monogastric species need to ingest vitamin B_{12} preformed, whereas ruminants can manufacture adequate vitamin B_{12} if the rumen microorganisms are supplied with adequate Co in the diet. The rumen microorganisms incorporate Co into vitamin B_{12} and a number of physiologically inactive vitamin B_{12}–like compounds. The production of vitamin B_{12} from dietary Co was estimated to be approximately 15% in Co-deficient sheep and only approximately 3% in Co-sufficient sheep.[13] Approximately 50% of the vitamin B_{12} produced is absorbed in normal animals, but only 3% to 5% of vitamin B_{12} is estimated to be absorbed by Co-deficient sheep.[14] Although the absorption of vitamin B_{12} formed in the rumen is not particularly efficient, with normal dietary Co there are usually no clinical problems, and interference by other dietary components does not appear to be clinically important.

Ruminants use the VFAs acetate, propionate, and butyrate as their primary energy sources. Propionate produced in the rumen is the precursor of glucose for ruminant metabolism. The general metabolic steps for conversion of propionate to glucose are shown[15] in Fig. 32.144 use 32-134 from the 5th edition.

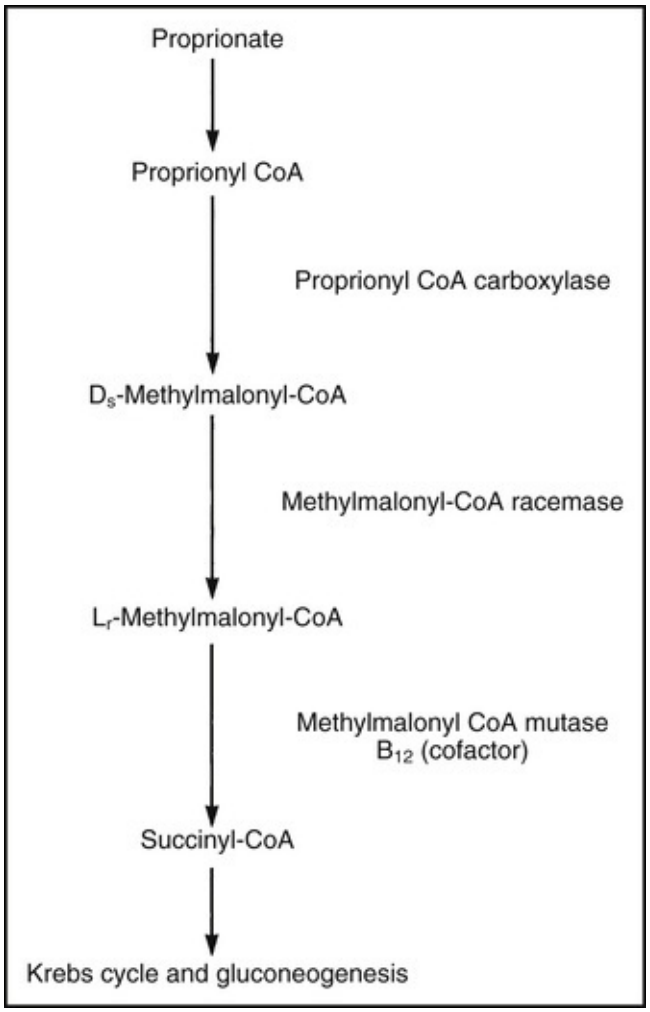


FIG. 32.144 Pathway for conversion of proprionyl coenzyme A (CoA) from proprionate to succinyl CoA.

A primary defect in Co-deficient ruminants is the inefficient metabolism of propionate at the point in the pathway at which methylmalonyl-CoA mutase, a vitamin B_{12}–requiring enzyme, catalyzes the conversion of methylmalonyl-CoA to succinyl-CoA.[16] As Co deficiency becomes severe, the rate of propionate clearance from the blood decreases, and the intermediate metabolite methylmalonyl-CoA accumulates. [17] With severe Co deficiency, the amount of methylmalonic acid excreted in the urine increases. As the half-time for propionate clearance increases, the voluntary feed intake of Co-deficient sheep decreases.[17] These changes correlate with the degree of anorexia and weight loss observed in severely Co-deficient sheep.

The decreased growth, weight loss, unthrifty appearance, and anorexia are closely correlated to the observed abnormalities of carbohydrate metabolism.

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The diarrhea commonly observed with Co deficiency is not well explained; however, an increase in susceptibility to parasitism[4] might explain a portion of this clinical observation.

The anemia that is associated with Co deficiency occurs late in the development of the syndrome and is characterized as normocytic normochromic.[18] Co deficiency results in the depression of the vitamin B_{12}–containing enzyme 5-methyltetrahydrofolate homocysteine methyltransferase.[19] This interference with the recycling of methionine has a marked influence on folate metabolism. In addition to potentially resulting in anemia through inefficient folate metabolism, the decreased activity of this methyltransferase could lead to a deficiency of methionine; this is a possible reason for nitrogen retention and the decreased body growth and wool growth observed.

■ Epidemiology and Cobalt Requirements

Co deficiency in ruminants occurs in selected regions throughout the world and in association with a variety of soil types. Clinically recognizable Co deficiency is reported in New Zealand, Australia, Brazil, United Kingdom, Ireland, Scandinavia, and North America. In the United States, Co deficiency is most commonly seen in Florida, in the Northeast, along the eastern seaboard, in the upper Midwest, and around the Great Lakes.[20] Although various soil types are associated with Co deficiency, heavy fertilization with limestone reduces the Co available to plants and animals.[21] The dietary requirement of Co by ruminants is generally recommended to be 0.1 mg/kg of dry matter (DM) of the complete ration.[22-24] The Co requirement of young, rapidly growing lambs is thought to be 0.2 mg/kg (ppm) of DM of the diet.[25] When pasture Co concentrations are less than 0.07 mg/kg of DM or 0.04 mg/kg of DM for sheep and cattle, respectively, signs of deficiency can be expected to develop. On a practical basis, diets with 0.1 mg/kg of DM are considered to be adequate. Legumes have relatively high Co concentrations. Rapidly growing grasses have much lower Co concentrations, and cereal grains are poor sources of Co.[22] Oilseed meals are generally good sources of Co. Co supplemented at levels above NRC recommendations (0.2 mg/kg versus 0.1 mg/kg) has been associated with increases in the immune response to one antigen in cattle.[5]

■ Treatment and Control

Treatment is best accomplished in the short term with vitamin B_{12} injections. Ruminants poorly absorb oral vitamin B_{12}; thus injections are the most efficient. Lambs receiving 100 µg of vitamin B_{12} per week or 150 µg B_{12} every other week show remission of clinical signs.[26] Sheep receiving injections of 300 µg of vitamin B_{12} weekly or cattle receiving 2000 to 3000 µg of vitamin B_{12} weekly would also be expected to regain normal status.

Rations with 0.1 to 0.2 mg/kg (ppm) of DM Co would be expected to prevent Co deficiency in ruminants. Salt-mineral mixes containing 0.1% Co also provide adequate supplementation. 0.1% Co in salt can be made by mixing Co carbonate (which is 46% Co) at the rate of 4.35 pounds/ton of salt, or 1 g of Co carbonate per pound of salt. A pound equals 453.59 grams.

Co sulfate as a top dressing for pastures (1.5 kg/hectare every 3 to 4 years or 0.3 kg/hectare every 1 to 2 years) has been used to increase Co concentration of pasture forage. Heavily limed pastures[21] and soils high in manganese oxide[27] decrease Co availability, and Co top dressing of the pastures or Co (B_{12}) supplementation to the animals should be considered.

A variety of rumen pellets containing Co are used to supplement grazing ruminants. These pellets have been successful in maintaining normal Co status in animals.[25-29] The pellets are not commercially available in the United States at this time.

The perennial grass, *Phalaris tuberosa*, can cause a syndrome in ruminants that is referred to as “phalaris staggers.” Co supplementation can aid in prevention of this syndrome because it inactivates or decreases absorption of the neurotoxin contained in *P. tuberosa, Phalaris minor* (canary grass), or *Phalaris* hybrids (ronpha).[29] The increased level of Co in the rumen is the important factor in preventing this condition; administration of oral or parenteral vitamin B_{12} is not effective.[26] Treatment of clinical phalaris staggers with Co is not effective, however.

Because Co is poorly absorbed, toxicity is an uncommon problem, and diets in excess of 30 mg/kg of DM are necessary for toxicosis to occur in most cases.[22-24]

A recommendation by the National Research Council of increased levels for Co (mg/kg DM) for beef cattle has been made since 2016. This increase has recommended increased Co levels of 20 mg / kg DM from the previous 10 mg/ kg DM. Research has reflected increased NRC Co levels improved performance (ADG) in Simmental bulls (Stangl, et al.). Increased NRC Co levels in feedlot

steers showed increased antibody titers of *M. haemolytica* leukotoxin ($P < 0.0565$), decreased BRD (bovine respiratory disease), and increased HCW (hot carcass weights of + 18.1 kg compared to controls; Sager, 2014). These results have demonstrated the need for increased Co in beef cattle for increased health and performance.

Rectal Prolapse in Ruminants and Horses

Spring K. Halland

■ Definition and Etiology

Rectal prolapse is the protrusion of the rectal mucous membranes through the anus. This evagination may be extensive and may include part of the small colon. Rectal prolapse occurs in all domestic animals, with the highest incidence in cattle, sheep, and swine. The age at which prolapse most commonly occurs is 6 to 12 months in sheep, 6 months to 2 years in cattle, and 6 to 12 weeks in swine.[1] Rectal prolapse is much less common in horses and occurs more often in mares than in males.[2]

Rectal prolapse generally is the result of an increase in the pressure gradient between the abdominal or pelvic cavity and the anus. Factors that cause the increased pressure gradient can be divided into four categories: (1) factors that result in increased abdominal fill (2) factors that cause tenesmus; (3) conditions that result in chronic or excessive coughing; and (4) miscellaneous conditions (e.g., short tail docking). One study strongly revealed that sheep with short docked tails (as close to the body as possible) had a 7.8% higher incidence of rectal prolapse when finished on a high-concentrate diet.[3] Certain toxicities such as from lead, fluoride, estrogen, and zinc have been implicated as playing a role in rectal prolapse.[4] Any combination of factors may precipitate a rectal prolapse. Identification of predisposing factors becomes important in management of the case.

■ Clinical Signs

Four categories have been used to described rectal prolapse (Fig. 32.145).[2] Types I and II are much more common and more amenable to correction. On physical examination, types I, II, and III are continuous with the mucocutaneous junction of the anus, whereas with type IV a protrusion with a palpable trench

inside the rectum is seen.[5] Chronic cases can be seen and usually are type I or II. Types III and IV often cause loss of vascular integrity to the rectum or small colon and necessitate more immediate intervention. Types III and IV may accompany dystocias in mares.[6]

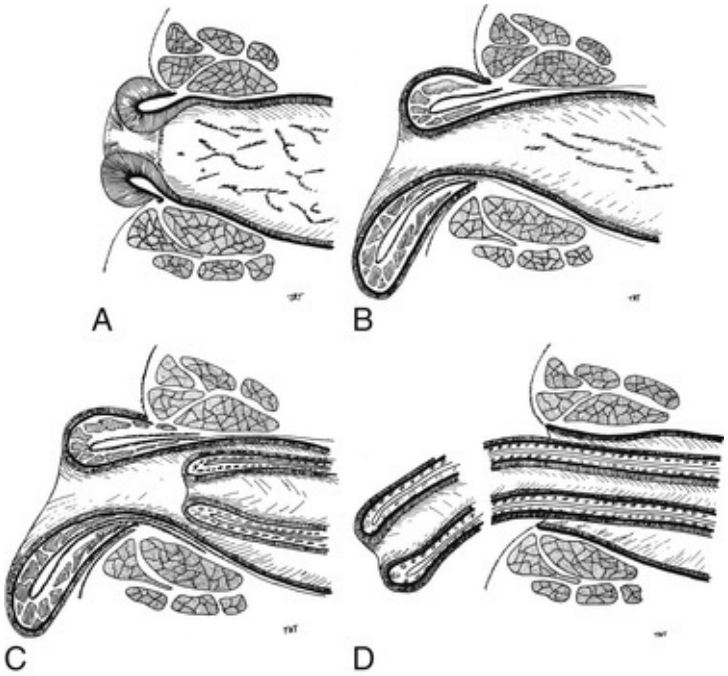


FIG. 32.145 **A,** Type I rectal prolapse: mucosal prolapse, involving only mucosa and submucosa of the rectum. **B,** Type II rectal prolapse: complete prolapse, involving full wall thickness of the rectum. **C,** Type III rectal prolapse: complete prolapse plus intussusception of peritoneal rectum or small colon. **D,** Type IV rectal prolapse: intussusception of the peritoneal rectum or small colon or both. (From Robinson NE [ed]. 1987. *Current therapy in equine medicine*, ed 2. Philadelphia: Saunders.)

■ Treatment and Prognosis

The first aim of therapy is identification and alleviation of the cause if possible. Early identification and correction of the prolapse is essential to saving tissues and the animal. The animal's value and intended use and the affected tissue's viability need to be considered when deciding on conservative or surgical options. The color of the membranes is a good parameter for determining if the tissue is salvageable. In general, the rectum is a forgiving structure, and attempts should be made to salvage the prolapsed tissue unless it is obviously cyanotic,

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necrosed, and devitalized. To prevent further damage, animals should remain standing and restrained in a small area until the prolapse can be corrected.

Types I and II usually are treated conservatively. A caudal epidural is used to reduce straining and facilitate correction of the prolapse. A range of 4 to 6 mL of 2% lidocaine is usually adequate for juvenile to adult cattle. The addition of a small amount of xylazine to the lidocaine epidural will extend the duration of the anesthetic. Sedation may also be necessary, depending on the individual animal. Effective conservative therapy includes thorough cleansing of the prolapse with warm water and mild soap to remove all debris. This allows evaluation for trauma, tears, necrosis, or sloughing. Edema can be removed by gentle kneading combined with topical application of glycerin or sugar. Generous lubrication and massage allow for reduction of the mass into the rectum. To ensure that the rectum is maintained in place, purse-string sutures with umbilical tape or other nonabsorbable suture are placed circumferentially around the anal sphincter, with care taken not to enter the rectum. The purse-string should not be so tight as to prohibit the passage of feces. If necessary, it should be loosened daily to expedite removal of accumulated fecal material. The purse-string should be removed in 3 to 4 days. Broad-spectrum antimicrobial drugs should be administered if tissue compromise is a factor. When indicated, stool softeners and enemas may be used to ease the passage of feces through the rectum.

Surgical intervention often is necessary if type I or type II prolapse cannot be reduced, if tissue necrosis is extensive, or if prolapse recurs after conservative therapy.[5] Submucosal resection, amputation, or the use of a prolapse ring are all accepted surgical options. Prolapses of types III and IV that cannot be manually reduced often necessitate a celiotomy for surgical reduction of the intussusception or resection or both. An important fact to remember is that even with manual reduction of a type IV prolapse, significant vascular compromise may have occurred, which results in bowel leakage and peritonitis. Vascular damage encountered by the colon may necessitate a colostomy.[6] Broad-spectrum antimicrobial drugs should be administered in these cases.

Unique problems are encountered when conservatively managing equine rectal prolapse, as opposed to ruminant prolapse. Equine patients may experience more hindlimb ataxia with caudal epidurals, which can be prevented with different combinations of xylazine, lidocaine, detomidine, morphine, and mepivacaine in the epidural. Placement of an epidural catheter can facilitate long-term therapy if needed. Another problem encountered is that horse feces often are too large and dry to readily pass through the purse-string in the anus.

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The use of enemas and stool softeners offers some assistance. The sutures tend to cause greater anal irritation than is seen in ruminants, causing horses to strain against them.

The common complications after rectal prolapse include prolapse recurrence, rectal strictures, obstipation, formation of a pararectal abscess, and peritonitis. The prognosis for all types of rectal prolapse depends on early identification and reduction of the prolapse. Prolapses of types I and II that can be managed conservatively have a favorable outcome. Surgical correction of types I and II also carries a good prognosis but with a higher incidence of postsurgical complications. Because of the cost of surgical repair, market animals often are slaughtered if conservative management fails. Rectal prolapses of types III and IV carry a fair to guarded prognosis, which depends on the extent of tissue involvement and viability, the surgeon's skill, and postsurgical complications.

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Contagious Ecthyma (Sore Mouth, Orf, Contagious

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Pustular Dermatitis, Scabby Mouth)

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(Enterotoxemia, Yellow Lamb Disease, Lamb Dysentery, Necrotic Enteritis, Enterotoxemia)

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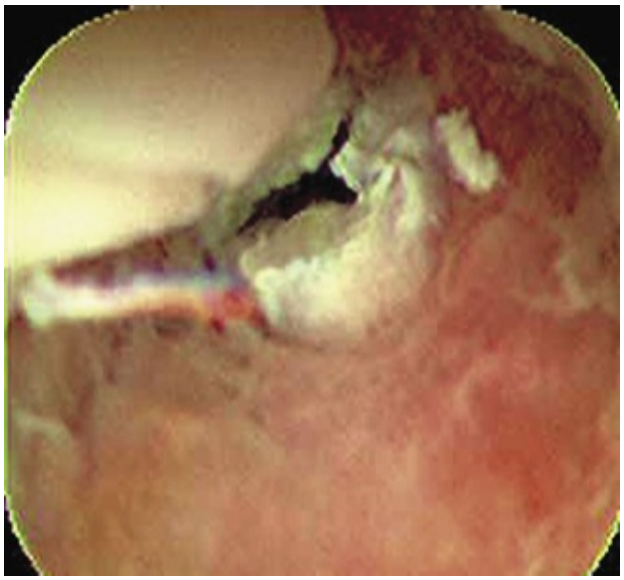
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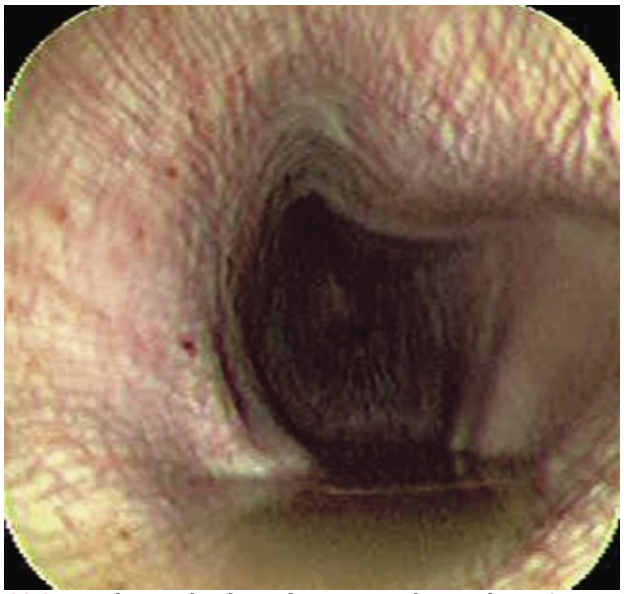
Color Plates



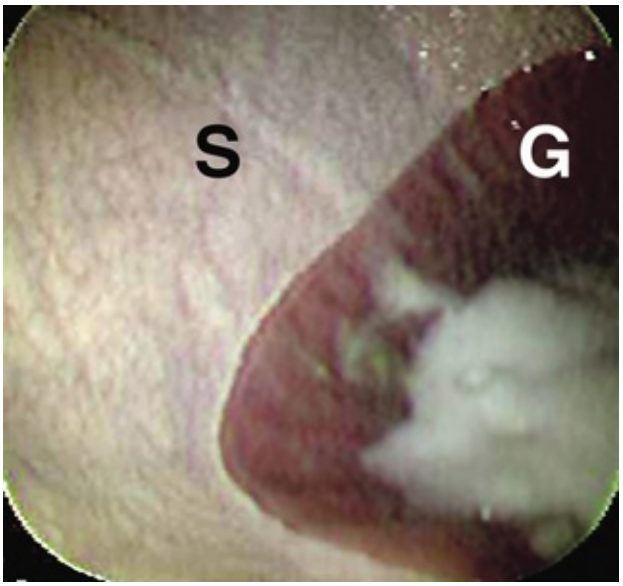
COLOR PLATE 32.1 **Endoscopic view of the esophagus of a 20-year-old gelding that presented with a 3-day history of esophageal obstruction. The horse had recently been rescued, and its previous history was unknown. After an obstruction consisting of grass was forcefully relieved by flushing water through a nasogastric tube, endoscopy revealed ulceration of the esophageal mucosa just orad to a stricture of the esophageal lumen. (Courtesy Dr. M.J. Murray.)**



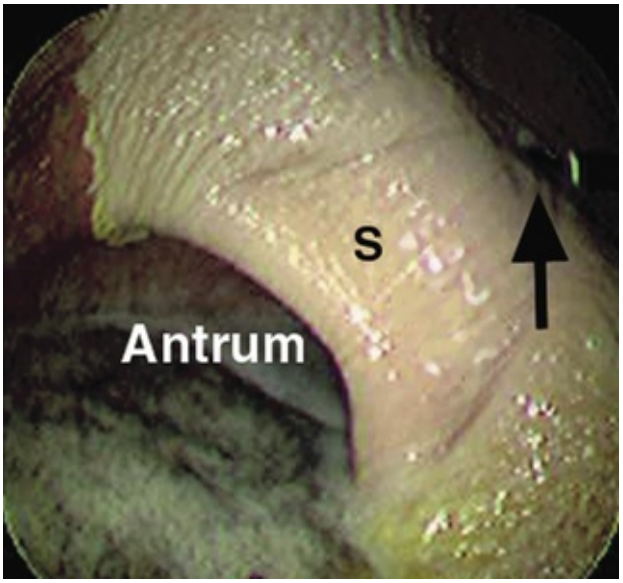
COLOR PLATE 32.2 Endoscopic view of the esophagus of the same horse as in Plate 32.1, 14 days after flushing. The mucosa adjacent to the stricture remained ulcerated, and the diameter of the esophageal lumen had progressively diminished. At this point, it was not possible to advance the 10-mm-diameter endoscope through the stricture. (Courtesy Dr. M.J. Murray.)



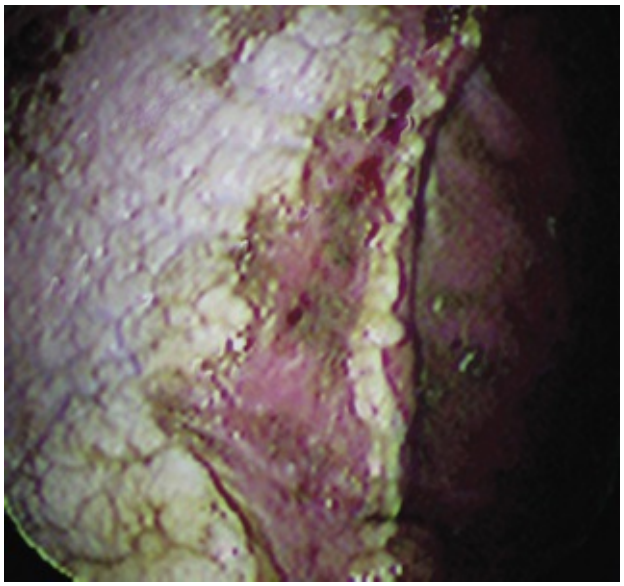
COLOR PLATE 32.3 Endoscopic view of megaesophagus in a 10-month-old foal (also shown in Fig. 32.45). The esophageal lumen is greatly distended, and the mucosa has multifocal erosion. (Courtesy Dr. M.J. Murray.)



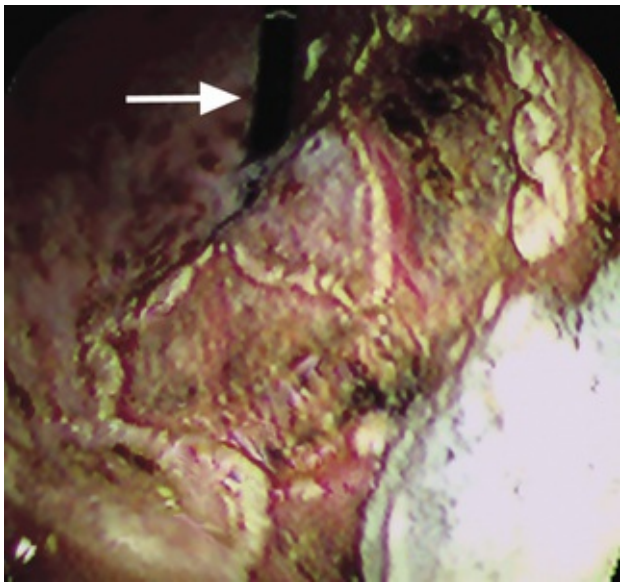
COLOR PLATE 32.4 **Endoscopic view of the right side of a normal stomach in a horse. Note the pale squamous mucosa *(S)* and the red glandular mucosa *(G)*.**



COLOR PLATE 32.5 **Endoscopic view of the lesser curvature of a normal stomach in a horse, showing the pale squamous mucosa *(S)*. The antrum lies ventral to a fold formed by the squamous mucosa along the lesser curvature, and the pylorus is immediately ventral to the cardia, through which the endoscope *(arrow)* can be seen entering the stomach.**



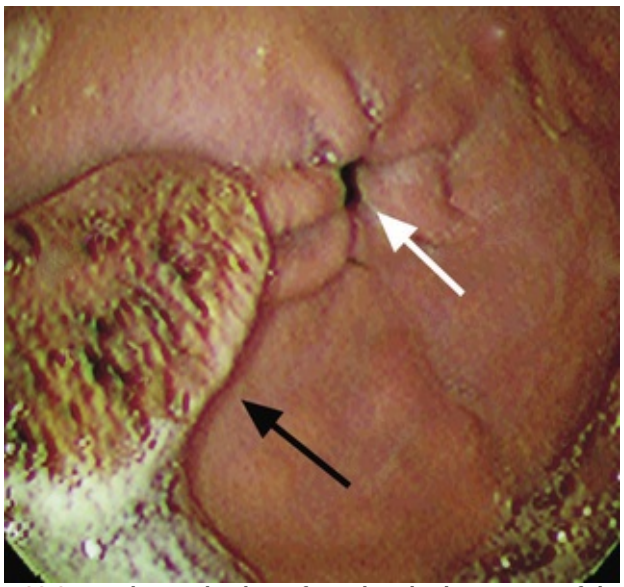
COLOR PLATE 32.6 Endoscopic view of a large area of ulceration of the squamous mucosa adjacent to the margo plicatus along the right side of the stomach in a horse.



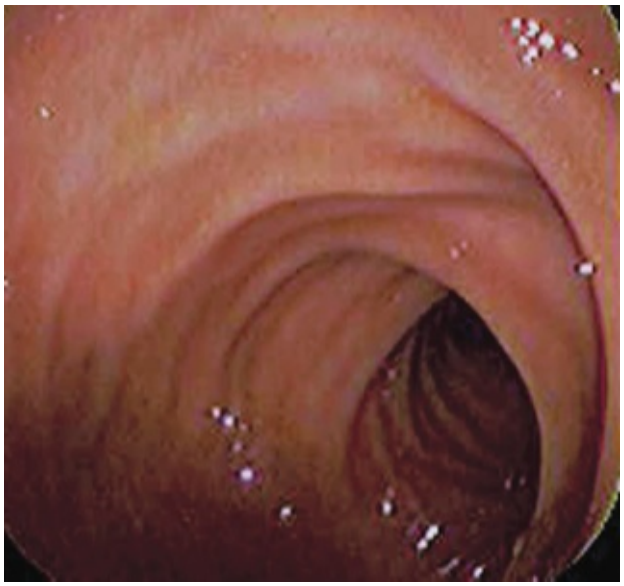
COLOR PLATE 32.7 **Endoscopic view of a large area of ulceration of the squamous mucosa along the lesser curvature of the stomach in a horse. The ulceration has a "butterfly" pattern, which is typical of ulcers at this site, and this pattern may reflect protection of the mucosa immediately ventral to the cardia by saliva entering the stomach from the esophagus. The endoscope *(arrow)* is entering the stomach through the cardia.**



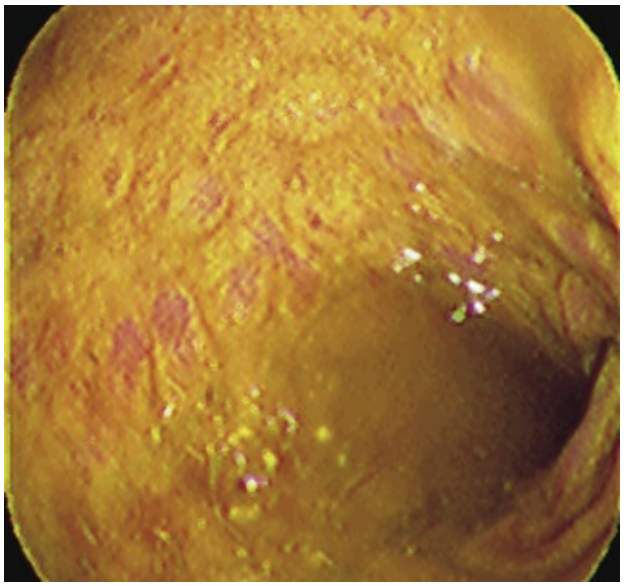
COLOR PLATE 32.8 Endoscopic view of an ulcer in the gastric glandular mucosa in a horse. The ulcer is in a rugal fold, which is a typical site of ulcers in the glandular portion of the stomach.



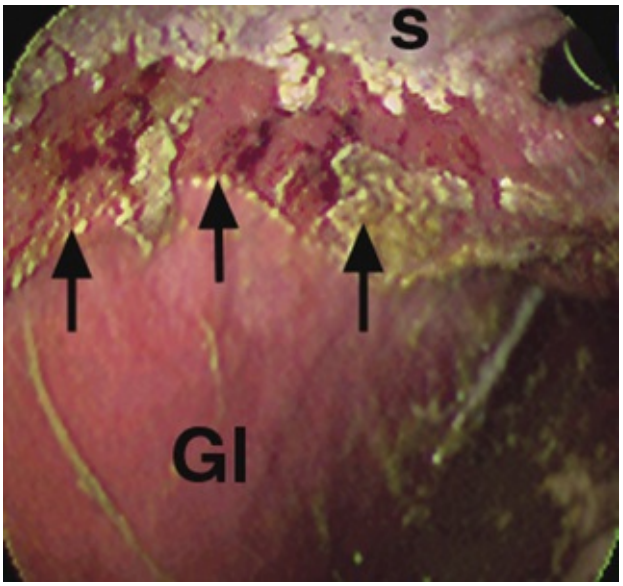
COLOR PLATE 32.9 Endoscopic view of an ulcer in the antrum of the stomach in a horse. The *white arrow* points at the pylorus. The *black arrow* points at an area of ulceration and thickening of a rugal fold leading to the pylorus. This is a severe example of a frequent finding in the stomach of adult horses: thickening of a rugal fold in the antrum in association with erosion or ulceration of the mucosa. The cause of these lesions is undetermined.



COLOR PLATE 32.10 Endoscopic view of normal duodenal mucosa in a horse. The endoscope has advanced aborad to the major duodenal papilla, which in most foals and horses is difficult and unusual to accomplish because of the anatomic configuration of duodenum in relation to the stomach.



COLOR PLATE 32.11 Duodenum of a foal that presented with fever, depression, leukocytosis, and hyperfibrinogenemia. This endoscopic view is orad to the major duodenal papilla. The mucosa is inflamed, and a yellow-orange fibrinous exudate adheres to the mucosal surface.



COLOR PLATE 32.12 **Endoscopic view of the stomach of the foal in Color Plate 32.11. Severe ulceration of the squamous mucosa *(S)* adjacent to the margo plicatus *(arrows)* was caused by delayed gastric emptying secondary to the severe duodenitis. Many foals with duodenitis present with classic gastric ulcer signs because of delayed stomach emptying, accumulation of acidic peptic secretions in the stomach, and, often, gastroesophageal reflux. *GI,* Glandular mucosa.**

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*Paul G.E. Michelsen contributed to writing this chapter in previous editions. His contribution to this section is acknowledged.

*The authors gratefully acknowledge contributions to this section in previous editions by Paul G.H. Michelsen.

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• CHAPTER 33

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Diseases of the Hepatobiliary System

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Diagnosis of Liver Disease*

Geoffrey W. Smith

In making a diagnosis, the veterinarian should first attempt to determine that the animal *has* liver disease and then move toward trying to identify a specific cause. Therefore this chapter discusses first the diagnosis of liver disease and then the individual conditions causing disease in horses and ruminants. The signs of liver disease are caused by the failure of some of the liver's many functions, but these signs are often not apparent early in the course of disease. Special tests may be necessary to detect early damage or minor impairment of function that has not yet produced clinical signs.

Liver Diseases Versus Liver Failure

As with many other organs like the heart and kidney, the liver can be diseased or damaged long before it fails to function. Early liver diseases are often inapparent to the owner or veterinarian through physical findings alone. Such cases are usually detected by finding elevated levels of liver enzymes in the serum. Pathologic changes in the liver may include biliary hyperplasia, death of hepatocytes, and fibrosis—all potentially occurring long before any signs of failure develop. Some functions may fail before others, and onset of liver failure varies with the species and disease process involved.

Liver Reserve and Regeneration

The liver has a large reserve capacity, and close to 80% of it can be removed before regeneration and recovery are no longer possible. Regeneration can occur in areas receiving portal blood, but most cell division takes place in Rappaport's zone 1 (the portal area), with cells being pushed to the central lobular area. The liver undergoes constant repair, and in humans it is estimated that hepatocytes are renewed every 50 to 75 days.[1]

Normal regeneration does not occur in some cases. For example, antimitotic agents such as pyrrolizidine alkaloid metabolites or antineoplastic drugs can prevent cell division. Regeneration may be restricted by connective tissue. Once fibrosis has bridged the various lobules, additional regeneration is impaired because the fibrosis itself perpetuates the condition. Loss of a stroma to build on

or lack of portal blood supply also reduces regeneration.

Signs of Liver Disease and Pathophysiology

Although ultrasound and biopsy may be more accurate indicators of disease, initial suspicion of liver problems in large animals usually arises from abnormal clinical signs or serum biochemistry abnormalities. Many signs can be present with liver disease, but no sign is pathognomonic or present in every case. Table 33.1 lists some of the signs that may be present and other possible causes of the same signs.

TABLE 33.1
Signs of Liver Disease or Failure

Sign	Pathogenesis	Other Causes
Icterus (E)	Failure of uptake, conjugation, or excretion of bilirubin	Massive hemolysis
		Bile blockage
		Fasting in the horse
Weight loss (E, B)	Energy demand greater than absorbed or metabolized	Poor nutrition, chronic inflammation, parasites, neoplasia, maldigestion, malabsorption
Ascites (B)	Portal hypertension and lymph leakage caused by cirrhosis or veno-occlusion	Cardiac failure
		Hypoproteinemia
		Cushing's syndrome
Change in liver size	Nodular hyperplasia, tumor, cirrhosis	Right-sided heart failure
	Fatty degeneration	Work hypertrophy
		Anemia
Diarrhea (B)	Bile deficit malabsorption	Gastrointestinal (GI) or systemic disease
	Intestinal edema, portal hypertension	
Pruritus	Retention of bile salts	Dermatologic or central nervous system (CNS) disorders
Dermatitis	Hepatogenic photosensitization	Primary phototoxic photosensitization
Unpigmented areas		
CNS signs	Hepatic encephalopathy (see text)	Brain diseases
Behavioral change, ataxia, dysmetria, circling, stupor, coma, tremors, bellowing		Metabolic diseases
		Toxic diseases
Tenesmus (B)	Hepatic encephalopathy	Rectal or colonic disease
		CNS disease
		Urogenital disease
Rectal prolapse (B)	Tenesmus	Rectal or colonic disease
Change in feces color	Bile pigment deficit	Diet
	Undigested fat	GI disease
Hemorrhage	Failure to synthesize clotting	Other clotting factor or platelet deficit,

	factors II, V, VII, IX, X	trauma, disseminated intravascular coagulation
Pain over liver, inflammation, swelling	Abscesses	Traumatic reticulitis
Inspiratory stertor (E)	Hepatic encephalopathy	Upper airway obstruction
Dyspnea		

B, Frequent sign in cattle; *E,* frequent sign in horses.

The clinical history is useful in some cases but not consistently. For example, liver flukes in cattle are generally restricted to certain geographic areas and occur more commonly when animals are grazing land infested with snails. Another example would be acute serum hepatitis in horses, which often occurs 4 to 8 weeks after administration of equine biologic products. In other cases, the lack of specific history information may not rule in or rule out specific causes of liver disease. For example, there may not be a history of animals consuming plants containing pyrrolizidine alkaloids because of the delay between consumption and the onset of clinical signs.

With the exception of change in liver size and pain over the liver elicited with pressure, most signs are related to failure of some function. Liver flukes may cause anemia and hypoproteinemia because of the effect of the parasite and its metabolites. Liver abscesses and other infections may produce signs like fever and anorexia owing to release of pyrogens and other inflammatory mediators (caused by the organism and not necessarily related to the liver itself).

Icterus is typically seen in acute liver disease in horses but is not seen in many cases of chronic liver disease, and it is seen less often in ruminants unless biliary blockage occurs. Icterus is due to failure of uptake, conjugation, or excretion of bilirubin. Excess production caused by hemolysis must also be considered when icterus is present. This is likely the most common cause of icterus in ruminants and occurs with several hemolytic diseases such as anaplasmosis and copper toxicity. Horses are frequently icteric (up to 6 mg/dL unconjugated bilirubin) from anorexia or fasting even when the liver is normal.

Weight loss is a common but nonspecific finding in some cases of chronic liver disease. It may be caused by anorexia or failure of metabolic functions of the liver and is probably not related to impaired fat absorption. Diarrhea is also seen, especially in cattle with chronic liver disease. It is thought to be related to portal hypertension and increased hydrostatic pressure, although the exact mechanisms are not completely understood. Diarrhea probably is not caused by fat malabsorption or steatorrhea because the normal herbivore diet contains less than 3% fat.

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Ascites can also occur in animals with liver failure. The ascites results from portal hypertension caused by venous blockage producing increased hydrostatic pressure and by protein leakage into the peritoneal cavity. Production of hepatic lymph high in protein (>3 g/dL) is increased. Because the liver sinusoids are permeable to plasma proteins, the protein-containing lymph leaks into the interstitial space and then into the peritoneal cavity.[2,3] Fluid moves into the abdominal cavity secondary to both osmotic and hydrostatic forces, according to the Starling equation. The abdominal fluid present with liver disease is a modified transudate, but the protein content may be relatively high (3 to 3.5 g/dL) owing to leakage of protein from the liver. Hypoalbuminemia can aggravate the ascites, but if it occurs alone, it usually will result in submandibular and brisket edema.

Hepatic photosensitization may lead to dermatitis of the white areas, wherein the skin of these areas first becomes erythematous, then thickened with keratin crusts, and finally necrotic. This is caused by the photodynamic agent phylloerythrin, which is formed in the gastrointestinal (GI) tract of large animals by bacterial degradation of chlorophyll. After absorption into the portal circulation, phylloerythrin should be conjugated by the liver and excreted into the bile. With cholestasis, phylloerythrin may be carried to the skin, where it acts as a photodynamic agent.[4] After bile duct ligation, the level of phylloerythrin steadily increases.[5] Although a small amount is removed by the kidneys, the rate is not fast enough to prevent accumulation in the plasma and skin. Phylloerythrin in the skin reacts to sunlight and emits energy that causes lesions of the white areas.[4]

Pruritus is seen in a few cases of liver disease in horses. In humans, pruritus is assumed to be due to bile acid accumulation in the skin when it is not excreted by the liver. This same process may occur in horses, but pruritus is not usually seen in large animals with liver disease.

A change in fecal color is not usually noted in either adult cattle or horses with liver disease because other pigments like chlorophyll contribute to the color. In young animals with simple digestive tracts, much of the fecal color is from stercobilin, a metabolite of bilirubin, so with cholestasis, feces may be somewhat lighter in color.

A few signs may be seen terminally in liver disease. Hemorrhage may occur when clotting factors are not synthesized in adequate amounts. Factors I, II, V, VII, IX, and X are all produced by the liver,[1,3] but the disease is usually

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advanced before a deficit develops.

Tenesmus, often followed by rectal prolapse, is seen in some cattle with liver disease. This may be associated with diarrhea, be part of hepatic encephalopathy, or be aggravated by edema of the bowel secondary to portal hypertension.

Pharyngeal or laryngeal collapse with loud stertorous inspiratory noises and dyspnea has developed in some cases of hepatic failure, especially in ponies. The exact mechanism for this is not known, but it may also be part of hepatic encephalopathy.[6] Horses sometimes develop a terminal hemolytic crisis caused by increased red blood cell (RBC) fragility. This has not been observed in ruminants.

Hepatic Encephalopathy

Hepatic encephalopathy is a neuropsychiatric syndrome caused by hepatic dysfunction or portosystemic shunting of the intestinal blood.[7] It is considered a potentially reversible metabolic or neurotransmitter disorder but is associated with characteristic (although nonspecific) lesions in the central nervous system (CNS), such as altered astrocytes.

Signs of hepatic encephalopathy are often subtle and nonspecific. Behavioral changes may be detected by the owner, who is more familiar with the patient's normal activity. Some docile animals become excitable and difficult to control, whereas other normally unruly animals may become passive. Depression and incoordination are frequent manifestations, and some animals may walk aimlessly or even head press (Fig. 33.1).[8] Apparent blindness is seen in some horses, and foot stomping was reported in 7 of 25 cases.[9] These animals eventually develop a stupor and may end up in hepatic coma. Yawning may be seen in horses, and ponies may have a stertorous respiratory noise. Ruminants show signs of tenesmus and sometimes vocalize excessively. In humans, hepatic encephalopathy is diagnosed by neuropsychological tests, which are not possible in animals.[10]

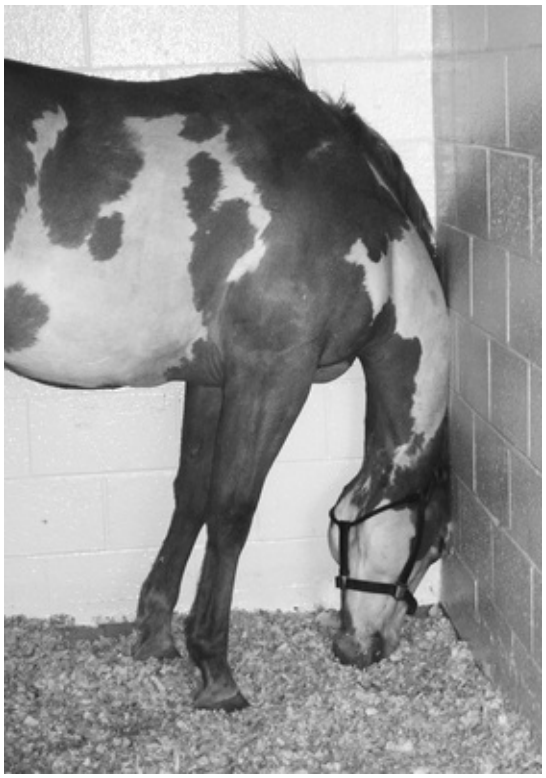


FIG. 33.1 Severe depression and head pressing in a horse with hepatic encephalopathy. Edema of the head developed secondary to the horse hanging its head.

The pathophysiology of hepatic encephalopathy remains undefined and is controversial.[8] It occurs when portal blood bypasses the liver, as with congenital shunts in dogs or with shunts secondary to portal hypertension induced by alcoholic cirrhosis in humans, or when the blood goes through an inadequately functioning liver. How neurologic function is altered has not been determined, but speculation abounds.

It seems possible to incriminate synergistic neurotoxins that bypass the liver. Most will agree that ammonia levels play a central role in pathogenesis. Blood ammonia is elevated in most cases of hepatic encephalopathy because the liver is not metabolizing ammonia to urea. Encephalopathy can be precipitated in cirrhotic patients by adding ammonia-generating substances, and there is an increase in cerebrospinal glutamine, the product to which ammonia is detoxified. Astrocytes contain the enzyme glutamine synthetase, which adds a molecule of glutamate to ammonia to form glutamine. The amount of glutamine formed in the brain correlates with the severity of hepatic encephalopathy.[11] However, much higher concentrations of ammonia are needed to induce coma in normal animals, and there is poor correlation between ammonia levels and degree of

encephalopathy.[9] Cases of hyperammonemia and encephalopathy without liver disease have been reported in horses.[12]

Magnetic resonance imaging (MRI) of human cirrhotic patients reveals increased image intensities from the globus pallidus region, probably caused by manganese deposits.[10] Serum manganese is increased in these patients, which correlates positively with the increased MRI intensities and negatively with neuropsychological tests. This indicates that manganese is another potential toxin that can enter the brain if not effectively removed from the blood by the liver.

There may be an imbalance of true inhibitory and excitatory neurotransmission. γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter. The increase in GABAergic tone was originally thought to result from an increase in GABA or its receptor sites. More recently, it has been proposed that neurosteroids with GABA-agonist properties could be involved.[13] Ammonia is believed to play a role in the metabolism of GABA in the brain and thus could act synergistically.[14] Also, receptor sites for benzodiazepine are increased in the brain of animals with hepatic encephalopathy.[15] Benzodiazepine augments the activity of GABA in stimulating the inhibitory neuron and causing sedation.

False neurotransmitters have been proposed to cause the abnormal nerve function. Increased amounts of tryptophan, phenylalanine, and tyrosine in the brain could cause more serotonin to accumulate in the brain. Plasma amino acid ratios are altered in horses with pyrrolizidine alkaloid–induced liver disease.[15] Concentrations of branched-chain amino acids (valine, isoleucine, leucine) are decreased, and concentrations of aromatic amino acids (tyrosine, phenylalanine, free tryptophan) are increased, partially because the liver is not adequately metabolizing aromatic amino acids. Amino acids are transported across the blood-brain barrier by a common transport system, so they compete for entry into the CNS. It has been suggested that higher levels of aromatic amino acids in the CNS would lead to formation of increased amounts of inhibitory neurotransmitters or to alteration of catecholamine or monoamine neurotransmitters like GABA or L-glutamate.

Laboratory Tests and Liver-Derived Serum Enzymes

A number of enzymes are compartmentalized in the hepatocyte or in bile duct epithelium. This compartmentalization is useful in holding insoluble molecules close to the enzymes for chemical reactions. Hepatocyte damage may result in release of the enzymes into the circulation, and cholestasis may cause increased release from bile epithelium. Serum levels of these enzymes may therefore be an indication of hepatocyte integrity or bile excretion. Table 33.2 lists frequently tested enzymes and their characteristics. Serum concentrations for some of these enzymes vary with the age of the animal and sometimes even with type or use. Table 33.3 lists some approximate upper limits of normal for animals of various ages. Normal values, especially for the enzymes, should be established by each laboratory.

TABLE 33.2
Liver-Derived Enzymes

Enzyme	Specificity	Problems
GGT	Liver	High in young animals from colostrum
	Kidney[a]	
	Pancreas	
ALP	Liver	Not specific
	Bone	
	Intestine	
	Macrophages	
	Placenta	
SDH	Liver	Not elevated in chronic disease; short life; not stable
GDH	Liver	Not elevated in chronic disease
AST (SGOT)	Liver	Not specific
	Muscle	
	Heart	
ALT (SGPT)	Liver	Low concentration in cattle and horses; not a good indicator in large herbivores
LDH	None unless isoenzymes	Not elevated in chronic disease; short life; not specific
OCT	Liver	Analysis not routinely available

[a]Elevated in urine, not blood.

ALP, Alkaline phosphatase; *ALT,* alanine aminotransferase (formerly *SGPT,* serum glutamic-pyruvic transaminase); *AST,* aspartate aminotransferase (formerly *SGOT,* serum glutamic-oxaloacetic transaminase); *GDH,* glutamate dehydrogenase; *GGT,* γ-glutamyltransferase; *LDH,* lactate dehydrogenase; *OCT,* ornithine carbamoyltransferase; *SDH,* sorbitol dehydrogenase.

TABLE 33.3

Upper Limits of Normal for Some Liver Function Tests (from Various Sources)

Test	Sheep				Cattle				Sheep	Goat
Age	<1 wk	1-4 wk	1-12 mo	Adult	<1 wk	1-4 wk	1-6 mo	Adult	Adult	Adult
Total bilirubin (mg/dL)	4.5	3.0	2.0	2.0	2.4	0.9	0.4	0.3	0.4	0.5
Direct bilirubin (mg/dL)	0.8	0.7	0.7	0.4	0.6	0.3	0.2	0.1	0.1	0.1
Total bile acids (µmol/L)	N/A	N/A	N/A	14	45	35	60	120	25?	N/A
BSP (half-life, $T_{1/2}$ min)	N/A	N/A	3.7	3.7	15	8	5	3	4.0	2.1
AST (IU/L)	600	540	700	270	60	60	60	60	110	80
GGT (IU/L)	170	170	40	30	4200	1300	N/A	24	55	50
ALT (IU/L)	2800	1200	840	194	1150	1000	N/A	81	188	386
SDH (IU/L)	8	8	N/A	5.8	N/A	N/A	N/A	15.3	28	23
GDH (IU/L)	N/A	N/A	N/A	11	24	22	19	19	N/A	N/A
LDH (IU/L)	N/A	N/A	N/A	412	1380	1280	N/A	1445	440	392

ALT, Alanine aminotransferase; *AST,* aspartate aminotransferase; *BSP,* bromsulphalein (sulfobromophthalein sodium); *GDH,* glutamate dehydrogenase; *GGT,* γ-glutamyltransferase; *LDH,* lactate dehydrogenase; *N/A,* not available; *SDH,* sorbitol dehydrogenase.

The cytosol of the hepatocyte contains high activities of the enzymes aspartate aminotransferase (AST, formerly serum glutamic-oxaloacetic transaminase [SGOT]), sorbitol dehydrogenase (SDH, sometimes called L-iditol 2-dehydrogenase), ornithine carbamoyltransferase (OCT), glutamate dehydrogenase (GDH), and lactate dehydrogenase (LDH). These are generally referred to as *leakage enzymes*, since with acute or chronic hepatocellular injury or necrosis the activity of these enzymes increases because they essentially "leak" out of hepatocytes into the serum.[16] Cholestasis increases production of other enzymes such as γ-glutamyltransferase (GGT) and alkaline phosphatase (ALP). Activity of these enzymes generally increases secondary to biliary obstruction caused by conditions like liver fluke infection or cholelithiasis. The cholestatic enzymes are more likely to have high serum concentrations in chronic hepatic disease than the leakage enzymes because of bile duct constriction or obstruction secondary to fibrosis.[16] GGT also is present in pancreas, mammary gland, lung, kidney tubules, and other duct epithelium, but serum levels usually are not elevated with renal disease because the enzyme is lost in the urine. Serum concentrations are normally higher in neonatal calves (sometimes >4000 IU/L after suckling)[17] because the enzyme is concentrated in colostrum.[18,19] GGT levels are also higher in foals than in adult horses, but the higher concentrations may partly be the result of increased production.[20] GGT is elevated in many horses with proximal enteritis or right dorsal displacement of

the large colon, possibly caused by transient extrahepatic bile duct obstruction.[21] Elevated GGT is the most sensitive indicator of liver disease in the horse, and levels will remain elevated for several weeks.[9,22]

ALP is often elevated in chronic liver disease of the horse but is variable in ruminants. ALP can come from other sources like bone, intestine, placenta, and macrophages, so it is not specific. Both ALP and GGT are elevated with cholestasis.[23] The dehydrogenases (e.g., SDH, LDH, GDH) are found in hepatocytes and elevated with acute hepatocyte damage, but serum concentrations may return to normal or below normal in chronic liver disease.

SDH is liver specific and extremely useful in detecting active hepatocellular necrosis, but it is not as stable as some of the other enzymes (levels drop significantly after 24 hours of refrigeration). Increased SDH activity can be seen in ruminants with infectious, inflammatory, toxic, or metabolic insults to the liver. In horses, any disease causing decreased perfusion of the tissues secondary to dehydration or hypoxia may result in rapid increases in SDH, with or without underlying liver disease. SDH should therefore always be interpreted in combination with other indicators of acute liver disease. In cases of chronic disease, however, the SDH concentration may be normal because either too few hepatocytes are damaged or the hepatocellular mass is substantially reduced.[24] AST and LDH are found in many tissues other than liver (especially muscle), so they are nonspecific unless isoenzymes are determined. Muscle injury or necrosis, especially in recumbent animals, will often result in marked increases in both AST and LDH. The clinician must evaluate AST and LDH concentrations in conjunction with muscle-specific enzymes like creatine kinase (CK). Elevations in these enzymes together with increased CK activity generally suggest muscle injury. However, AST elevations occurring with CK values that fall within the reference range give a strong suggestion of hepatic disease. AST and LDH are also found in erythrocytes, so if the serum is severely hemolyzed or allowed to remain on the clot for an extended period, falsely elevated values due to leakage from RBCs will result.

Ammonia is produced in the GI tract from the digestion of proteins and amino acids, absorbed by the intestine into blood, and carried to the liver in the portal circulation. Ammonia is converted to urea in the liver by the hepatic urea cycle. Ammonia is a useful test for assessing liver function, but it is generally not included in most serum biochemistry panels because it is highly volatile and requires special sample handling. Serum urea nitrogen (SUN) may also have some value as an indicator of hepatic disease in ruminants, since urea is

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produced in the liver. In severe cases of liver failure, SUN is usually low and ammonia is often high. However, since rumen bacteria synthesize protein from urea, ruminants that have been off feed have low SUN concentrations because all the urea is being used by rumen bacteria for protein production. Thus low SUN levels are not always specific for hepatic disease.

No single liver enzyme value can consistently confirm or rule out the presence of liver disease. A combination of tests, including serum enzymes, total bile acids, ultrasound, and liver biopsy, may be needed. Some blood constituents may be altered because of failure of certain metabolic functions of the liver, but none of these changes is specific for liver disease. Blood glucose is sometimes slightly lower in severe liver disease, especially in young animals, possibly because of decreased gluconeogenesis, but none of 28 adult cases in one study had low blood glucose concentrations, and in fact, 14 cases had hyperglycemia.[9] In some toxic liver diseases, blood ammonia levels can increase fourfold or more because the urease necessary to convert ammonia to urea is found only in the liver. For the same reason, SUN may decrease, especially in the terminal phases. In the later stages, blood-clotting factors may be diminished, with delayed partial thromboplastin time (PTT) and other clotting times.

Terminally, serum albumin concentration may decrease. Considerable protein synthesis takes place in the liver, which produces all the plasma proteins except γ-globulins. The amount of these proteins in the blood, however, depends not only on the rate of synthesis but also on the rate of removal. The albumin half-life in cattle is about 16.5 days; in the horse, 19.4 days; and in sheep, 14 days.[25] Therefore serum albumin is reduced mainly in chronic liver disease. With liver damage, the synthesis of α-globulins and β-globulins is increased, so total plasma protein concentration is invariably normal or elevated, but the albumin/globulin (A/G) ratio may be decreased. The healthy liver has a large reserve for protein synthesis, and lost protein can be replenished. In one study, 18% of the horses with chronic liver disease and 6% of those with acute liver disease had albumin concentrations below the reference value.[26] In a British study, only 6 of 37 cases of equine liver disease were hypoalbuminemic, and none of these were hypoproteinemic.[9] Therefore it is assumed that hypoalbuminemia is not a common feature in horses with liver disease and that hypoproteinemia is rare. Amino acid ratios are altered in liver disease; short branched-chain amino acids are decreased, whereas aromatic amino acids are increased.[27]

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Excretion Tests for Liver Function

Because the liver excretes a number of endogenous compounds and foreign substances injected into the animal, the rate of excretion or clearance of these substances can be used to test the excretory function of the liver. Bilirubin itself can be used and, if elevated above normal, would indicate liver failure, bile blockage, or excess production due to hemolysis. In the horse, bilirubin is also increased during fasting in animals without liver disease.[28] With liver damage in the horse or ruminant, most of the retained bilirubin is unconjugated (indirect reacting), and the direct-to-total ratio is usually less than 0.3. With bile blockage or intrahepatic cholestasis, the direct-to-total ratio may be greater than 0.3 in the horse or 0.5 in cattle.

Bilirubin is the main bile pigment and is produced from heme, 75% of which comes from RBCs. When the erythrocytes are broken down, heme is converted first to biliverdin and then to bilirubin in the macrophage system. This unconjugated bilirubin is insoluble and must be bound to albumin for transfer; the kidneys do not remove this bound bilirubin. Unconjugated bilirubin is taken up by the hepatocytes with cytosolic binding proteins within the hepatocyte. In the hepatocyte, some bilirubin is conjugated to diglucuronide, but in the horse, more than half the bilirubin in bile is conjugated with glucose. Conjugated (direct-reacting) bilirubin is water soluble, and some will enter the general circulation; if concentration is sufficiently high, the kidneys will filter it into the urine. Conjugated bilirubin is secreted into the bile canaliculi by an energy-dependent transport process. In most species, this is the rate-limiting step, but this may not be true in large herbivores. Conjugated bilirubin passes into the intestine through the bile ducts, and if they are blocked, both conjugated and unconjugated bilirubin will increase in the plasma. In the intestinal tract, bilirubin is converted to urobilinogen by anaerobic bacteria. Some urobilinogen is absorbed and reexcreted by the liver, but a small fraction will pass the normal liver and be excreted in the urine. With complete biliary blockage, there will be no urobilinogen in the urine, and with hemolysis, there may be increased urobilinogen in the urine. Urobilinogen is not very stable in the urine, so analysis must be done within 1 or 2 hours or the amount detected will be erroneously low.

Fasting decreases the efficiency of plasma bilirubin removal in all species, but the horse shows a greater rise in plasma bilirubin, often reaching a plateau two to three times the normal state. This increase is due to a decrease in removal of bilirubin by the hepatic transport and not by an increase in its production.[28,29] In

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normal ruminants, total bilirubin concentrations are low compared to other species, and the magnitude of increase is generally small and inconsistent even with severe liver damage.[2] Ruminants with cholestatic disease may have moderate increases in serum bilirubin, but this is not a consistent finding. Increases in direct bilirubin are usually the result of hemolysis.

Serum total bile acid concentration is a good test of liver function in horses. The concentration of bile acids in the serum will be increased if there is hepatocyte damage, blockage of bile flow, or shunting of portal blood to the systemic circulation, bypassing the liver. The liver synthesizes bile acids from cholesterol. Cholic and chenodeoxycholic acids are the primary bile acids conjugated with amino acids before excretion into the bile. Only conjugated bile acids are present in the intestine; they are soluble and form micelles with fat because of their detergent properties. Most bile acids excreted in bile are resorbed by an active transport system in the ileum and carried by the portal circulation back to the liver for reexcretion. In most species, more than 95% of the bile acids are resorbed and recirculated through the enterohepatic circulation.[30]

Many simple-stomached animals have a postprandial increase in serum bile acid because bile is released from the gallbladder during eating and subsequently resorbed by the ileum. This does not seem to be important in the horse, which has no gallbladder, or in cattle, in which no relationship to feeding could be found.[31] Table 33.3 lists the upper limits of normal for liver function tests in large animals of various ages. In cattle, there is an hour-to-hour fluctuation in bile acid concentration that could be as much as 60 µmol/L, along with considerable variation between individual cattle.[31,32] In dairy cattle, a significant decrease in serum bile acid concentrations occurs throughout the course of lactation.[33] In the horse, serum concentration above 14 µmol/L would indicate liver damage, bile blockage, or shunting.[33] Serum total bile acid concentration is likely a more sensitive indicator of liver disease in the horse than serum bilirubin; only 8 of 34 horses with liver disease had elevated bilirubin, but 31 of 37 had elevated bile acids.[9] In a more recent study, bile acids were also associated with prognosis in horses with hepatic disease, with values greater than 20 µmol/L relatively specific for nonsurvival.[34] In adult cattle, because of the hour-to-hour variations, bile acid concentration on a single sample would have to be above 126 µmol/L in beef cattle and 88 µmol/L in dairy cattle to be an indication of liver disease.[35,36] Although ruminants have a large normal range

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for bile acid concentrations, significant increases have been shown to be a specific indicator of hepatic disease.[36]

A number of dyes are excreted primarily by the liver; sulfobromophthalein (bromsulphalein [BSP]) is used most often. In large animals, BSP clearance (half-life) is used much more than the retention test. In the test, 500 to 1000 mg (≈2 mg/kg) of BSP is injected intravenously. Blood samples are taken before the injection and two to four times 5 to 12 minutes after the injection (i.e., at 5, 7, 9, and 11 minutes). These samples are analyzed for color produced by BSP, and a half-life is determined by plotting the points on semilog paper. Normal horses have a BSP half-life of less than 3.5 minutes, and for ruminants it is less than 5 minutes. This may be increased in very young animals (see Table 33.3) and in pregnant females. Other dyes, such as indocyanine green, have some advantage (less renal excretion than BSP) but at present are too costly for use in large animals.

Liver Biopsy

Liver biopsy can be very useful, not only in confirming the presence of liver disease but also in determining or ruling out some etiologies. It is a relatively safe and simple procedure but should be avoided when liver abscesses are suspected. A number of biopsy instruments are available, including aspiration punches, but the Tru-Cut biopsy needle or similar notch-cutting needles seem to work quite well. In all species the skin over the biopsy site should be clipped and prepared for aseptic insertion of the needle. A local infiltration of 2% lidocaine helps reduce the animal's reaction, but it may still flinch when the pleura and peritoneum are penetrated. A small stab wound through the skin at the site of insertion is made with a scalpel blade.

The site of skin puncture for liver biopsy in the horse is the right fourteenth intercostal space at the intersection of a line drawn from the tuber coxae to the point of the shoulder.[37] Some operators recommend more cranial insertion (twelfth or thirteenth space), but more lung is penetrated at points farther cranial. If a more cranial position is selected, it should also be more ventral. If the needle is directed slightly cranial and ventral, it is more likely to remain in the liver parenchyma and not penetrate larger vessels on the visceral surface or pass through into the right kidney, pancreas, or colon. Ultrasound guidance will increase the chances of obtaining liver specimens without penetrating other organs; in fact, recent research indicates that the practice of blind percutaneous

liver biopsy in horses should not be attempted due to the high risk of complications.[38]

Cattle must be suitably confined for liver biopsy. A biopsy can often be performed on quiet dairy cows in a stanchion while the tail is elevated ("tailed"). Although identification of the liver with ultrasound is preferable to a blind stick, the puncture site in cattle can be located by extending a horizontal line cranial from the middle of the paralumbar fossa. The needle is inserted where this line crosses the eleventh intercostal space on the right side. The lungs do not extend as far caudal as in the horse, so the liver is more exposed. The needle is directed slightly cranial and ventral, as in the horse.[2]

Liver biopsy in sheep and goats is slightly more difficult; additional sedation is usually required. A site at the ninth or tenth intercostal space at the level of the ventral end of the last rib has been recommended. The biopsy needle is advanced in a craniomedial direction until the liver is penetrated.

Diffuse or zonal lesions, as seen in most toxic, infectious, and metabolic liver diseases, can usually be diagnosed by liver biopsy. Focal lesions (e.g., abscesses, granulomas, neoplasias, as well as liver flukes) are easily missed by liver biopsy. If a liver abscess is suspected, biopsy is contraindicated because of the potential danger of rupturing an abscess. A scoring system has been developed for the prognostic evaluation of equine liver biopsies.[39] Examining liver biopsy tissue can confirm the presence of liver disease, help establish the type of disease, and aid prognosis.

Ultrasound Examination

Ultrasonographic examination of the liver is an extremely useful tool in diagnosing liver diseases (see ultrasound images in Chapter 32). Using ultrasound, the clinician can determine the size of the liver, where it is located, and the diameter of the primary hepatic vessels. Hepatic abscesses, cholelithiasis, neoplasia, and fibrosis can be diagnosed by ultrasound in the horse.[40] In cattle, diseases such as fascioliasis, liver abscesses, neoplasia, thrombosis of the caudal vena cava, and even hepatic lipidosis can often be detected using ultrasound.[41-45] Ultrasound of the liver can also facilitate collection of a biopsy sample, aspiration of an abscess, or even cholecystocentesis (aspiration of a bile sample for diagnosis of liver flukes). Parenchymal pattern of the liver is changed with diffuse fibrosis. The bovine liver is situated immediately underneath the right body wall, with the cranial

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portion hidden by the lung. Hepatic ultrasonography is performed on the right side of the standing animal. The examination is usually done from caudal to cranial, beginning at the last rib and moving forward past the tenth intercostal space using a 3.5- to 5-MHz linear probe.[41] In sheep, the examination is done on the right side in the seventh through twelfth intercostal spaces.[46] In horses, the ultrasonic examination is performed below and caudal to the lung in the right sixth to fourteenth intercostal spaces.[46] The liver can also be visualized on the left side of the horse in the lower intercostal spaces[47] or ventrally behind the xiphoid.

Prognosis

The severity of clinical signs may be the most useful noninvasive prognostic test in horses with liver disease.[48] Indicators of a poor prognosis in liver disease include an albumin concentration less than 2.5 g/dL in horses or an increased globulin level, a prothrombin time (PT) greater than 30% of normal, and greatly elevated GGT and ALP, especially if SDH or LDH is normal or decreased. Marked fibrosis that bridges the liver lobules on histopathologic examination suggests a poor prognosis. Severe pyrrolizidine alkaloid toxicosis carries a particularly grave prognosis because remaining hepatocytes are inhibited from regeneration by mitotic arrest. Terminal clinical signs include development of hemolytic crisis in the horse and marked hepatic encephalopathy in the patient with a fibrotic liver.

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Infectious, Toxic, and Parasitic Liver Disease

Acute Hepatitis in Horses

Joy E. Tomlinson

■ Etiology

Theiler's disease, also known as *idiopathic acute hepatic disease, serum hepatitis, postvaccinal hepatitis,* and *acute liver atrophy,* is the most common cause of acute hepatitis and hepatic failure in horses in North America.[1-5] The disease was first recognized by Sir Arnold Theiler in large numbers of horses in South Africa. Horses developed the disease following immunization against African horse sickness with simultaneous administration of live virus and hyperimmune equine serum.[6] Since then, Theiler's disease has been observed in two forms. First, it has been documented as a potential complication of any equine-origin biologic product used in horses, including plasma and serum products, and has most recently been suspected after allogenic stem cell treatment (unpublished). Theiler's disease has been most often associated with use of either tetanus antitoxin (TAT) or commercial equine plasma.[3,5,7-11] A recent outbreak was also associated with equine antiserum to botulinum toxin.[12] Second, Theiler's disease is occasionally seen without a history of recent equine-origin biologic product administration.[1,7,13] This is often seen as a herd outbreak and may have a seasonal nature, occurring most frequently in the summer and fall.[1,7,13] In addition, in outbreaks of biologic product–associated Theiler's disease, it is not uncommon for in-contact horses to also develop Theiler's disease, suggesting that an infectious agent may be involved.[1,6,7,13]

Theiler's disease is primarily a disease of adult horses.[1,5,7,10,11] There is no clear breed or sex predilection for Theiler's disease.[3,5,6,9-17] Postfoaling mares and postcastration geldings may be at increased risk due to frequent use of prophylactic tetanus antitoxin in those horses.

Little has been known about the etiology of Theiler's disease until recently. An investigation into an outbreak of Theiler's disease in a group of horses receiving prophylactic botulinum antiserum resulted in the discovery of a pegivirus that

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was named *Theiler's disease–associated virus* (TDAV).[12] Although this was initially suspected to be the cause of the outbreak, TDAV was not present in subsequent cases of Theiler's disease, and a new pathogen, *Equine parvovirus-hepatitis* (EqPV-H) was discovered.[18] EqPV-H was retrospectively found to also be present in the botulinum antiserum outbreak.[12,18] EqPV-H was present in sequential cases of non–biologic-associated cases of Theiler's disease, in biologic-associated cases, and in the biologic products implicated (unpublished). Experimental infection with EqPV-H in two adult horses resulted in acute necrotizing hepatitis.[18] However, not all horses that have EqPV-H-positive serum confirmed by polymerase chain reaction (PCR) testing have clinical or biochemical evidence of hepatitis, which may suggest that other host factors, immune-mediated hypersensitivity reactions, or co-infection with other etiologic agents may be necessary for disease.[12,18] Horses may become chronically infected with virus, with the majority remaining serum PCR positive for at least 1 year (unpublished).

■ Clinical Signs

The clinical effects of Theiler's disease are associated with signs of acute hepatic failure and typically occur 1 to 3 months after administration of blood products.[6,12,13] These signs include depression, jaundice, inappetence, pica, yawning, photoactive dermatitis, and hepatic encephalopathy.[2,3,7,9,14,15] Fever has been described as absent or rare in horses affected with Theiler's disease.[4] Intravascular hemolysis has been reported to lead to hemoglobinuria in some terminal cases of Theiler's disease.[2] Evidence exists for a subclinical component in some cases.[10,12,16] However, some horses that received tetanus antitoxin or botulinum antitoxin have clinicopathologic evidence of liver disease without developing clinical signs, indicating that disease severity may vary.[5,10,12,16]

■ Diagnosis

Diagnosis of Theiler's disease is based on the anamnesis, clinical signs, serum biochemical analysis, and hepatic biopsy or necropsy. High serum levels of unconjugated and total bilirubin and serum bile acids, coupled with high serum activity of GGT, SDH, AST, GDH, LDH, and ALP are indicative of hepatic necrosis in horses.[17] Additional findings with severe disease may include decreased blood urea nitrogen (BUN), hyperammonemia,[17] prolonged clotting

times (PT and activated partial thromboplastin time [APTT]), and decreased albumin. Theiler's disease may be confirmed by hepatic biopsy or postmortem examination of hepatic tissue. The liver is often small and has a characteristic "dishrag" appearance (Fig. 33.2). Typical histopathologic changes seen in specimens obtained by biopsy or at postmortem examination include widespread necrosis of hepatocytes that is most severe in the centrilobular and midzonal areas.[1,8] The few remaining living cells are confined to the periportal areas and commonly contain cytoplasmic vacuoles.[1,8] The normal architecture of the centrilobular and midzonal areas is replaced by a pale, eosinophilic granular mass in which ghost outlines of necrotic hepatocytes are present.[8] A mild inflammatory cell infiltrate is seen in the portal areas, as are a number of spindle-shaped fibroblastic cells.[8]



FIG. 33.2 Characteristic small, "dishrag" liver from a horse with Theiler's disease. (Photo courtesy Sam Jennings, North Carolina State University.)

Differential diagnoses include a variety of heavy metal and organic hepatotoxins (see the Pyrrolizidine Alkaloid Toxicity and Other Hepatotoxins sections later). Acute onset of chronic pyrrolizidine alkaloid toxicity can cause a

similar clinical and histopathologic presentation. Although EqPV-H is highly suspected to be a cause of Theiler's disease, the data remain associative and not definitive to date. PCR testing of serum or liver for EqPV-H is available.

■ Treatment

There is no specific treatment for Theiler's disease.[19] Treatment should be aimed at supporting liver function and controlling abnormal behavior. Dietary adjustments are important and should consist of reducing the quantity of protein in the diet while increasing carbohydrate intake.[2] Sorghum, milo, or beet pulp, which contains high levels of branched-chain amino acids, can be mixed with molasses to improve palatability and caloric content.[2] Diets high in branched-chain amino acids tend to lessen the degree of abnormal behavior associated with hepatic encephalopathy.[19] Oral (PO) neomycin, lactulose, and mineral oil may be administered to decrease ammonia production and absorption from the GI tract. Xylazine or detomidine may become necessary to sedate horses that display severe signs of hepatic encephalopathy,[19] but high doses that cause extreme lowering of the head should be avoided if possible. Benzodiazepines (diazepam or midazolam) should be avoided. Continuous intravenous (IV) administration of dextrose and balanced electrolyte solutions to reduce hepatic workload and maintain plasma volume are recommended.[16] If spontaneous bleeding occurs at injection sites or at sites of self-inflicted injury, plasma transfusions may be necessary to replace the deficient clotting factors.[2] The use of glucocorticoids for treating Theiler's disease is controversial but may be indicated based on some histopathologic evidence of an immune-mediated etiology.[14,17]

Currently, no preventive measures are available. However, since administration of TAT is associated with substantial risk for development of fatal Theiler's disease,[7,10,16] the routine practices of prophylactic administration of TAT to recently parturient mares or postcastration geldings should be strongly discouraged. TAT use should be restricted to clinical situations necessitating tetanus prophylaxis in which a history of active tetanus (toxoid) immunoprophylaxis is absent or unknown. The risk of postvaccinal Theiler's disease should be addressed with the owner before administration of TAT. Although the prevalence of serum hepatitis associated with administration of commercial plasma appears to be low in horses, it should be considered an

uncommon risk that can have a fatal outcome.[11]

Theiler's disease may be observed sporadically or affect a group of horses. Recognition of Theiler's disease in one horse should necessitate careful observation of horses on the same premises for either clinical or serum biochemical signs of Theiler's disease.[12,16] Based on recent case reports, it appears that not all cases of Theiler's disease are clinically apparent, and screening for its presence with routine serum biochemical analysis is useful in detecting subclinical cases.[10-12,16]

Black Disease

Geoffrey W. Smith

■ Etiology

Infectious necrotic hepatitis (black disease) is a peracute, highly fatal disease occurring worldwide. The disease most commonly affects sheep, particularly adults in good body condition, but cattle, horses, goats, and occasionally pigs may also be affected.[1,2] There has even been recent speculation that black disease is the cause of epidemic catarrh of sheep, a significant cause of mortality in Australian sheep dating back to the mid-1800s.[3] Black disease is caused by toxins produced by the bacterium *Clostridium novyi* type B, spores of which are commonly found in the soil and can also be present in the digestive tracts and livers of animals grazing affected pastures. Clostridial organisms require an anaerobic environment for growth, so black disease occurs only when there has been enough damage to the liver to provide the anaerobic environment required for growth of the organism and subsequent toxin production. In practice, the liver insult is almost always caused by larval migration of the common liver fluke, *Fasciola hepatica*. Therefore this is a seasonal disease related to the liver fluke cycle and occurring in animals typically infested by *F. hepatica.* Other liver parasites, such as *Fascioloides magna* or *Dicrocoelium dendriticum* (especially in France), are occasionally implicated, as is damage to the liver by biopsy or trauma severe enough to result in anaerobic conditions in the liver. Such a scenario should be considered when sudden deaths occur at times when flukes are not usually migrating or in families like Equidae that are not normal hosts for *F. hepatica.* Black disease occurs worldwide wherever liver flukes are present.

■ Pathophysiology

The *C. novyi* strains that cause black disease produce at least two potent exotoxins: alpha toxin and beta toxin. The alpha toxin enters cells by receptor-mediated endocytosis and inhibits ras and rho guanosine triphosphatases by glycosylation.[4] The beta toxin is a necrotizing and hemolytic phospholipase C (lecithinase). Other toxins may contribute to the pathophysiology as well.

C. novyi type B is widely distributed in soils, and its spores are continuously ingested and shed in feces of grazing animals. Some of these organisms cross the intestinal mucosa and become disseminated throughout the animal's macrophage system, including the Kupffer cells of the liver. When localized anaerobic conditions occur in the liver, as with migration of liver fluke larvae, these resident spores may germinate and enter a vegetative state. As they proliferate, they release their toxins and create enlarging zones of coagulative necrosis in the liver. The exotoxins produced will enter the circulation, where they cause damage to neurons, vascular endothelium, and other tissues, eventually causing sudden death of the animal.

■ Clinical Signs

Peracute death is the most common clinical presentation associated with black disease. When affected animals are recognized prior to death, clinical signs are relatively nonspecific. The animal will often be isolated from the herd and will appear depressed, anorexic, and possibly in respiratory distress. Temperature is elevated initially (40° to 41° C [104° to 106° F]) but declines before death. Sheep become sternally recumbent and generally die after a clinical course of only a few hours. Venous congestion darkens the skin, giving the disease its common name, *black disease*.[2] Unlike closely related bacillary hemoglobinuria, or “redwater” (see later discussion), affected animals do not show red urine or bleeding from the nose or rectum. Clinical signs in cattle are similar, but the disease course occurs over 1 to 2 days.

■ Diagnosis

Necropsy is often difficult because autolysis of the tissues after death is usually rapid. Fluid is often found in the pericardial sac and pleural and peritoneal cavities. Endocardial and epicardial hemorrhage is also a consistent finding. Urine is grossly normal. Tissues, especially solid organs like liver and kidney, appear to be in a much more advanced state of autolysis than time of death

would suggest. The liver is usually swollen and congested with small pale areas of coagulative necrosis, particularly along its diaphragmatic surface. The primary lesions of black disease are single or multiple areas (2 to 3 cm in diameter) of hepatic necrosis that appear yellow to white in color and are surrounded by a broad zone of hyperemia.[4]

Diagnosis of black disease is generally made by a combination of history, clinical presentation, necropsy findings, and isolation of *C. novyi* type B from the liver. A history of sudden death, particularly in endemic fluke areas, is highly suggestive of black disease, especially during warmer weather when fluke transmission is active. Flock or herd vaccination will be either overdue or absent. Time of death should be ascertained as closely as possible. The animal is usually presented in lateral recumbency without signs of struggle. It will be severely bloated even if death has occurred quite recently, giving the impression of a carcass in a more advanced state of decomposition than timing would suggest. Acute liver fluke infection in sheep can have a high mortality by itself, and postmortem findings may be similar to black disease. Other causes of sudden death (e.g., enterotoxemia, blackleg, anthrax) should also be ruled out.[2]

If necropsy does not confirm a diagnosis of black disease, or if additional documentation is necessary, a simple Gram stain of an impression smear taken from the margin of the liver lesion will typically reveal numerous gram-positive rods. Because clostridial organisms proliferate rapidly after death, such findings must always be interpreted carefully, with consideration of time elapsed between death and necropsy. Further diagnostic measures include anaerobic culture and isolation of *C. novyi* type B, identification of the specific toxins, and fluorescent antibody identification of the organism. Characteristic histopathologic changes may also be seen in fixed sections of liver associated with necrotic lesions. Impression smears obtained from the liver lesions are ideal for fluorescent antibody identification of *C. novyi* type B.

■ Treatment and Control

Treatment of black disease is rarely undertaken because of its peracute presentation; animals are usually found dead. Although *C. novyi* is highly sensitive to penicillin and the tetracyclines, toxin production is usually too far advanced for antibiotics to be of value. If used, they should be administered at high doses, intravenously if possible for most rapid onset (20,000 to 40,000 IU/kg sodium or potassium penicillin or 10 mg/kg oxytetracycline q12h),

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followed by intramuscular (IM) or IV doses at appropriate intervals. Supportive fluid therapy should be initiated to correct dehydration. Even with aggressive therapy the prognosis is poor and the chances for survival slim. In the event of an outbreak, vaccination should be initiated immediately, along with possible metaphylactic administration of penicillin or oxytetracycline.

A good prevention program involves both proper fluke control and the use of clostridial bacterins. Efforts to clear soils of the offending organism are unrewarding. However, it is recommended that carcasses of animals dying from black disease be burned, buried deeply, or removed from the premises. Commercial bacterin-toxoids against *C. novyi* are available in combination with other clostridial organisms. These products are generally safe and highly effective. Duration of protection is short, however, and should not be relied on for more than 5 to 6 months. Animals vaccinated when younger than 3 to 4 months old require revaccination at weaning. Local reactions at the site of subcutaneous vaccination are common but primarily of cosmetic concern. Intramuscular vaccination should be avoided because it frequently results in permanent damage to muscle tissue, with a negative impact on meat marketing. Timing of vaccination must be determined by the local climate and liver fluke season. In more severe climates where the fluke season is relatively short, a single annual injection before fluke transmission season may be sufficient. In more moderate climates with longer periods of fluke exposure, two vaccinations per year may be required.

Control of liver fluke infestation is also closely linked to prevention of black disease. Control measures include pasture or range management; control of water sources; strategic treatment of animals with appropriate anthelmintics; and limiting access to streams, canals, ponds, and marshes. This is a complex subject, and the reader should refer to the Liver Flukes in Ruminants section for more detail.

Bacillary Hemoglobinuria (“Redwater”)

Geoffrey W. Smith

■ Etiology

Bacillary hemoglobinuria (redwater, icteric hemoglobinuria) is a disease causing sudden death in cattle, small ruminants, and occasionally horses. The disease was first reported in California in 1916 and is caused by the toxins of

Clostridium haemolyticum (formerly *C. novyi* type D). Bacillary hemoglobinuria is quite similar to black disease, where clostridial infections of the liver occur under anaerobic conditions, presumably from liver fluke migration. However, in a recent study involving 20 cattle with naturally occurring bacillary hemoglobinuria, none had gross or histologic lesions indicative of liver flukes, suggesting that some other predisposing factor might be involved.[1] The major toxin in *C. haemolyticum* infection is the beta toxin, which is a phospholipase C that causes hepatocyte necrosis, hemolysis, and damage to capillary endothelium.[1,2] This results in hemoglobinuria and loss of fluids into tissues and cavities. The primary action of beta toxin is to induce localized hepatic necrosis and intravascular hemolysis. Like *C. novyi* type B, *C. haemolyticum* is also found in the soil. Spores are routinely present in the liver and can be passed in feces and urine of healthy animals grazing affected pastures. Disease occurs only when there is sufficient insult to the liver to provide the anaerobic conditions required for bacterial growth and toxin production. In many cases the liver insult is caused by migration of *F. hepatica* (common liver fluke) larvae.[3-5] As in black disease, *F. magna, D. dendriticum* (the lancet liver fluke), and *Cysticercus cellulosae* have also been occasionally implicated in the disease, as has liver biopsy or trauma severe enough to result in liver bruising.[6] Bacillary hemoglobinuria is, for the most part, a seasonal disease occurring at the time of larval fluke migration. In the United States, most cases are seen during summer and early fall. However, the disease is sometimes diagnosed in cattle in animals without liver flukes.[1,5]

Bacillary hemoglobinuria is a regionalized disease. It has been reported that *C. haemolyticum* is limited to alkaline soils, but the disease is also endemic in regions with acid soils. Outbreaks often follow flooding, which can bring spores into previously uninfected areas. The factors affecting distribution of the disease are not well understood. Even in areas where it is common, distribution is erratic, with some farms severely affected while others nearby are disease free.

■ Pathophysiology

Spores of *C. haemolyticum* are ingested by susceptible animals, cross the intestinal mucosa, and are transported to the liver and other organs, probably within the phagosomes of cells of the mononuclear macrophage series. The spores can persist in the liver within Kupffer cells for long periods. Any localized anaerobic area of the liver will allow these spores to germinate.

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Release of toxins from the bacteria further exacerbates the anaerobic environment, favoring accelerated bacterial proliferation, toxin production, and hepatic necrosis. Beta toxin leads to hepatocyte, erythrocyte, and endothelial cell disruption and thrombus formation. The progression of this lesion is likely responsible for the large necrotic foci observed in virtually all cases of the disease.[1] Absorption of toxins into the circulatory system rapidly leads to intravascular hemolysis, icterus, hemoglobinuria, and death.

■ Clinical Signs

Bacillary hemoglobinuria is most common in animals older than 1 year of age. Like black disease, sudden death without obvious clinical signs is common in animals that have peracute disease. In those rare cases where disease is recognized antemortem, signs include depression, anorexia, and fever of 40° to 41° C (104° to 106° F), declining as death approaches. Breathing may be rapid and shallow, and blood or blood-tinged froth may be present in the nostrils. Rectal bleeding or bloody feces may also be observed. Severe hemoglobinuria or passage of dark red, port wine–colored urine is often reported. Blood is thin and watery and coagulates slowly. Mucous membranes are pale and icteric. Severity of signs increases as the disease progresses. Postmortem, the animal is usually in lateral recumbency, severely bloated, and without signs of struggle. Blood is often present in the nostrils, mouth, rectum, or vagina. The carcass appears to be in an advanced state of decomposition even when it is actually quite fresh. A tentative diagnosis can be made on the basis of history and observation of the carcass.

At necropsy the mucous membranes and tissues can appear icteric. Skinning the animal reveals numerous subcutaneous petechial and ecchymotic hemorrhages, edema, and sometimes emphysema. There will be significant amounts of red-tinged abdominal and thoracic fluid. Hemorrhages are present on all serosal surfaces. Dark red urine is present in the bladder. Lymph nodes are congested and usually hemorrhagic. There may be hemorrhage into the bowel lumen. The spleen is enlarged. The lungs are usually filled with blood-tinged froth or foam. Pericardial fluid is blood tinged, and hemorrhages are present on both the epicardium and the endocardium. Solid organs such as liver and kidney appear to be in advanced stages of autolysis, even in fresh carcasses. The pathognomonic lesion is the so-called ischemic hepatic infarct, which has a zone of hyperemia at its interface with viable liver tissue. This area of coagulative necrosis, sometimes partially liquefied at its center, can reach up to a 30-cm

diameter and have a very irregular outline.[4] Unlike a classic infarct, the lesion in bacillary hemoglobinuria results from progressive enlargement of the focus of coagulative necrosis caused by the bacterial toxins. Any thrombosis seen in the lesion is secondary, with the vasculature being included in the necrotic process, along with other hepatic tissue.[6]

■ Diagnosis

Antemortem animals with bacillary hemoglobinuria will be anemic and have elevated hepatic enzymes such as AST and GGT.[7,9] Total bilirubin concentrations are also dramatically elevated.[7,9] If a urine sample can be collected, hemoglobinuria will be obvious. Postmortem, a Gram-stained impression smear from the liver will reveal numerous typical clostridial organisms. Smears may also be made from spleen, blood, or abdominal fluid, with the same outcome. Postmortem presence of clostridial organisms must be interpreted with caution because they are always present and proliferate rapidly after death. It is important to have an accurate estimate of time of death to determine the significance of these findings. Laboratory confirmation depends on identification of both the causative bacteria and the toxin. Fresh (refrigerated) and formalin-fixed liver lesions should be submitted. Fluorescent antibody tests on impression smears taken from a liver “infarct” will be positive for *C. haemolyticum* antigens. Extensive biochemical and toxin identification tests are confirmatory but seldom used if lesions and fluorescent antibody tests are compatible. A PCR assay that can detect *C. haemolyticum* in the blood of affected cattle has also been reported,[7] as have PCR assays to detect the beta toxin.[1]

■ Treatment and Prevention

Although successful treatment of cattle with bacillary hemoglobinuria has been described,[7,10] it is seldom undertaken because of the acute nature of the disease. If there is opportunity for treatment, penicillin at high dosages (at least 20,000 to 40,000 IU/kg IV or IM twice daily) is the antibiotic of choice, although tetracyclines (10 mg/kg IV twice daily) are acceptable. Fluids are given intravenously or intraruminally to correct dehydration. Because of severe hemolytic anemia, blood transfusion is recommended and should be repeated as necessary. In animals that recover, there will be a noticeable reduction in the

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severity of hemoglobinuria daily.[7]

An effective prevention program requires consideration of both the pathophysiology and immunology of the disease and the natural history of the liver fluke *(F. hepatica)* that is so intimately involved in expression of bacillary hemoglobinuria. Efforts to clear soils of the offending organism are unrewarding, but carcasses of animals dying from bacillary hemoglobinuria should be burned, buried deeply, or removed from the premises.

Commercial bacterin-toxoids against *C. haemolyticum* are available both in monovalent form and in combination with other clostridial vaccines. These products are generally safe and highly efficacious. Duration of protection is short, however, and should not be relied on for more than 5 to 6 months. Animals vaccinated when less than 3 to 4 months old require revaccination at weaning. Local reactions at the site of subcutaneous vaccination are common but primarily of cosmetic concern. Intramuscular vaccination should be avoided because it frequently results in permanent damage to muscle tissue, with a negative impact on beef marketing. Timing of vaccination must be determined by the local climate and liver fluke season. In more severe climates where the fluke season is relatively short, a single annual injection before fluke transmission season may be sufficient. In more moderate climates with longer periods of fluke exposure, two vaccinations per year may be required.

Control measures include pasture or range management, control of water sources, strategic treatment of animals with products effective against flukes, and limiting access to streams, canals, ponds, and marshes. This is a complex subject, and the reader should refer to the Liver Flukes in Ruminants section for more detail.

Liver Disease in Foals

Jennifer L. Davis

Liver disease in foals may be classified as primary or secondary and can be associated with infectious, parasitic, congenital, metabolic, or toxic causes. An initial diagnosis of hepatic disease is often made based on elevations in hepatic enzyme activities on biochemical analysis, but it is important to use age-specific reference ranges to interpret biochemical indicators of hepatic disease. Several hepatic enzymes can have increased activity even in healthy neonates.[1-3] Total bilirubin may be elevated as fetal hemoglobin converts to adult hemoglobin. Elevations may also result from a deficiency in liver binding and conjugating

enzymes.[1] ALP remains elevated for an extended time in young horses as a result of increased osteoblastic activity, with normal values as high as 3752 U/L reported.[4] Increased GGT activity may be present in foals for 2 to 4 weeks after birth, whereas only slight increases of SDH are expected during the same period.[1,3] Increased variability in ALP and GGT in healthy foals can make interpretation of hepatic function difficult. Serum bile acids (SBAs) are significantly greater in foals than adult horses for the first 6 weeks of life. According to one study, this is potentially due to upregulation of hepatic production, reduced excretion, differences in bile acid composition of the neonate, or enhanced intestinal or portal uptake.[3] An additional finding of that study was that SBAs were not significantly different between healthy and sick foals.[3] Another study noted that elevated liver enzymes were common in sick foals, and those foals with high liver enzymes were more likely to have sepsis than other diseases.[4]

Tyzzer's Disease

Tyzzer's disease is an acute hepatitis affecting foals 7 to 42 days of age, with no known breed or sex predeliction.[5-13] It has also been reported in calves, lambs, and other species.[14-16] The causative organism is *Clostridium piliforme* (formerly *Bacillus piliformis*), a gram-negative, flagellated, spore-forming intracellular obligate anaerobe.[17] Multiple strains can infect Equidae, and foals are susceptible to at least two distinct strains (isolate E and R1), with no evidence of cross-reactivity of antibodies between isolates.[17,18]

Although the exact pathogenesis is unknown, bacterial spores can be shed in the manure of carrier horses, suggesting a fecal-oral route of transmission with subsequent GI and hepatic colonization.[19] Farms with multiple cases per year have been documented to feed higher protein diets compared to farms without cases, suggesting that high-protein and nitrogenous diets fed to nursing mares may increase proliferation of *C. piliforme* in the gut of both mares and foals.[13] Several other risk factors, including time of year, age, resident status of the mare, and heavy rainfall in the spring, have been associated with development of disease.[13,20] Foals born between March and May were found to be more likely to develop disease in two different studies, and this was thought to be due to the increased number of animals present on the farm during that time. Foals from younger mares (<6 years of age) and those not from endemic farms were more

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likely to develop disease, possibly owing to lack of antibodies in the mare's colostrum or antibodies to different strains of *C. piliforme* being present. Early spring rainfall affects the growth of cool-season grasses, and those grasses may be rich in nitrogenous compounds.[13] Immunocompromised foals may also be at greater risk,[11,12] although disease often occurs in previously healthy, rapidly growing foals.[13]

Disease may occur sporadically or as an outbreak.[12,19,20] Clinical signs are acute to peracute, are nonspecific, and may be related to age. Younger foals are more likely to be found dead with no premonitory signs.[13] In older foals, signs observed may include severe depression, fever or hypothermia, colic and diarrhea progressing rapidly to seizures, blindness, coma, and death.[5-13] Icterus may or may not be present, depending on the acuteness of disease. Bloodwork abnormalities indicate overwhelming sepsis characterized by leukopenia, hyperfibrinogenemia, profound hypoglycemia, and severe acidosis, with concurrent elevations in bilirubin, bile acids, SDH, GGT, AST, ALP, and LDH-5.[9,11,20] Diagnosis is usually made at postmortem and is based on the presence of acute, widespread multifocal areas of necrosis and hepatitis, with intrahepatocellular filamentous bacteria present at the periphery of the lesion.[13,21] Silver stains (e.g., Warthin-Starry) and Giemsa stains may help facilitate diagnosis.The fastidious nature of the organism makes culture difficult. PCR techniques have been used for detection of *C. piliforme* in multiple species, including foals.[22] This test may aid in early diagnosis and treatment.

Treatment of Tyzzer's disease can be attempted, but the disease is highly fatal, with most foals dying within 2 to 48 hours (median survival is 30 hours) of showing clinical signs. Initial treatment with IV dextrose may cause an immediate but temporary improvement in clinical signs. There are reports of successful treatment of three suspected cases[20,23] and one confirmed case[22] in foals. When attempted, treatment should be early and aggressive and consist of antibiotics (including high-dose IV potassium penicillin or ampicillin), parenteral nutrition, correction of acidosis, and other supportive care.[22] Currently there are no preventive measures available for Tyzzer's disease in the foal.

Other Bacterial Causes

Leptospirosis was reported to cause jaundice and death in a 10-day-old foal.[24]

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Although *Leptospira interrogans* serotype Pomona is known to cause abortion and liver disease (giant cell hepatopathy) in the equine fetus, it is only a rare cause of neonatal liver disease. *Actinobacillus equuli* typically causes bacteremic embolic nephritis and acute death in very young (3-day-old) foals. It may also cause widespread multifocal hepatitis, similar in appearance to foals with equine herpesvirus 1 (EHV-1). *Streptococcus zooepidemicus* bacteremia may result in multifocal hepatic abscesses. *Listeria monocytogenes* has been reported as a cause of severe hepatitis with necrosis and fibrinonecrotic typhlitis and colitis.[25] Cholangiohepatitis and photosensitization vasculopathy with secondary pyoderma have been diagnosed as a result of *Bartonella henselae* infection in a 3.5-month-old Thoroughbred colt.[26]

Other bacteria and bacterial toxins may initiate an exaggerated response to sepsis (systemic inflammatory response syndrome [SIRS]), which may result in multiple organ dysfunction, including hepatic failure. Many vasoactive mediators are involved in this process; the hemodynamic system becomes ineffective, and certain organs (e.g., liver) may fail because of hypoxia. Diffuse hepatic necrosis and hepatocellular apoptosis are the characteristic lesions. The clinical signs may be identical to Tyzzer's disease, except the syndrome may affect a much wider age range. Prompt and aggressive treatment is often successful. Appropriate treatments include broad-spectrum antibiotics, fluids, oxygen, and antioxidants such as dimethyl sulfoxide (DMSO) and acetylcysteine.

Bacterial sepsis rarely may cause acute portal vein thrombosis. Variable degrees of hepatic hypoxemia and inflammation accompany the thrombosis. Hyperammonemic hepatic encephalopathy has been reported in foals with *Rhodococcus equi* abdominal lymphadenitis and subsequent portal vein thrombosis.[27,28] The thrombus may or may not be visualized with ultrasound examination. Diarrhea due to portal hypertension may occur in affected foals. Complete recovery requires appropriate long-term antimicrobial therapy. Hyperammonemia has also been associated with gastrointestinal disease in foals and may occur concurrently with cases of enteritis or enterocolitis.[29,30] A lack of elevated hepatic enzyme activity may help differentiate intestinal hyperammonemia from hepatic causes. Prognosis in these cases is good if the underlying disease process can be treated.[31]

Ascending infection of the umbilical vein can result in abscessation or inflammation of the liver with or without a concurrent elevation in hepatic

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enzyme activity. Bacteria associated with equine sepsis can frequently be cultured from the lesions. Diagnosis is dependent on ultrasonographic evidence of an enlarged umbilical vein extending into the hepatic parenchyma along with appropriate signalment and clinical signs. Treatment may be medical or surgical.

Equine Herpesvirus 1

Equine herpesvirus 1 (EHV-1) infection of a fetus late in gestation typically results in an aborted or stillborn fetus; however, it may occasionally result in the birth of a live foal with hepatic, respiratory, and/or GI disease.[32] Affected foals may have severe neutropenia and lymphopenia, and icterus is a common clinical sign. Secondary septicemia is likely to develop due to immunosuppression. Surprisingly, significant elevations in serum hepatic enzyme activities are not present even though a severe multifocal necrotizing hepatitis with inclusion bodies is present at necropsy.[33] Generally respiratory distress is progressive, and the animal's clinical condition rapidly declines within 5 days after birth despite aggressive and early treatment. Treatment with interferon and oral acyclovir (8 to 16 mg/kg q8h)[34] may improve survival rates.

Neonatal Isoerythrolysis

Foals with severe and prolonged neonatal isoerythrolysis (NI) may develop liver failure,[35] which results from a combination of chronic hepatic hypoxia and multiple blood transfusions. Foals receiving a total volume of blood products of 4 L or more were 19.5 times more likely to develop liver failure than foals receiving a lower volume.[36] Multiple blood transfusions are thought to result in iron overload and subsequent iron toxicity. Deferoxamine, an iron chelator, enhances urinary iron elimination and decreases hepatic iron accumulation after blood transfusion in healthy foals.[37] Administration of 1 g of deferoxamine subcutaneously (SC) q12h prior to blood administration may help prevent liver failure in those receiving multiple transfusions.

Kernicterus, or bilirubin encephalopathy, is another potential complication of NI in foals. Neurologic signs, including seizures, develop secondary to the neurotoxic effects of unconjugated bilirubin on the CNS.[36,38] Kernicterus is more likely to develop in foals with total bilirubin of 27 mg/dL or greater and is associated with a poor outcome.[36] The use of therapeutic plasma exchange techniques to lower plasma bilirubin concentrations and prevent or treat

kernicterus in foals has been performed in practice and holds promise as a successful treatment, if available.[39]

Drug-Induced Hepatotoxicity

Rarely, foals treated with macrolides, trimethoprim-sulfas, or histamine 2 (H_2) blockers for pneumonia or diarrhea develop an increase in serum hepatic enzymes despite clinical improvement. With changes in drug treatment, serum enzymes return to normal, suggesting that these cases may have drug-induced hepatotoxicity.[40] In one study of foals being treated for *R. equi* pneumonia, four of nine foals in the doxycycline-rifampin treatment group developed icterus and hemolytic anemia or increased liver enzymes, while no foals in the other treatment groups developed similar signs, including those receiving doxycycline alone.[41] Steroid-induced hepatic lipidosis has been observed in foals receiving both prolonged and high doses of corticosteroids.

Iron Toxicity

Iron toxicity is the best documented toxic cause of hepatopathy in foals and may occur following administration of nutritional supplements or iron formulations containing ferrous fumarate.[40,42] Toxicity manifests in newborn foals given iron prior to receiving colostrum; colostral-acquired glutathione or other substances may be protective against hepatotoxicity.[42] When iron is given at birth and before colostrum, clinical signs typically develop 2 to 5 days later, although in rare cases signs may develop in older foals. The initial clinical signs are associated with hepatic encephalopathy and include seizures, marked depression, ataxia, aimless wandering, head pressing, and abnormal behavior. Icterus is noted in most foals at the time neurologic signs are exhibited, although some foals die so rapidly that icterus does not have time to develop. Abnormally high ammonia, total bilirubin, GGT and ALP activity, and packed cell volumes were present, as was an abnormally high ratio of aromatic to branched-chain amino acids. PTT and PT were prolonged, and some foals had high SDH activity.[40] Affected foals had small livers with prominent bile duct proliferation, hepatic cell necrosis, and mild periportal fibrosis, and had histopathologic changes in the brain consistent with hepatic encephalopathy.[40-43]

Congenital or Inherited Diseases

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Congenital portosystemic shunts (CPSS) occur infrequently in the equine and bovine patient.[44] Clinical signs may not be noted until foals are 2 to 3 months old and begin ingesting large amounts of grain or grass. Encephalopathic signs and tenesmus are characteristic of the disease in calves. Waxing and waning signs of encephalopathy accompanied by elevated bile acids and ammonia levels and normal concentrations of hepatic-derived serum enzymes should arouse suspicion of CPSS in foals. Shunts may be single or multiple and may be intra- or extrahepatic. Diagnosis of CPSS can be made by computed tomography (CT) scan, positive-contrast portography, transrectal portoscintigraphy (in foals), or transabdominal ultrasound examination. Further corroborative evidence can be gained by ultrasound-guided percutaneous transsplenic injection of agitated saline with simultaneous echocardiography to look for contrast in the right atrium and ventricle.[45] Short-term medical management can be attempted with antimicrobials (minocycline, neomycin, metronidazole), anti-inflammatory drugs, enemas, lactulose, and IV fluids. Successful surgical ligation of CPSS has been described in a foal and a calf.[44-46]

A distinct syndrome of hepatic failure has been seen in Morgan foals.[47,48] Clinical signs (depression and weight loss) appear soon after weaning. Liver enzymes and ammonia are elevated, and variable degrees of portal and bridging fibrosis with bile duct hyperplasia, karyomegaly, and cytomegaly are often seen on microscopic examination. The disease is fatal and may end with a terminal hemolytic crisis. The cause is unknown but is thought to be an inherited defect in mitochondrial transporter proteins, such as ornithine, that are required for complete urea synthesis.[48]

Glycogen branching enzyme deficiency is a fatal autosomal recessive disease of Quarter Horses and Paint Horses caused by a mutation of the glycogen branching enzyme 1 *(GBE1)* gene that drastically decreases the amount of GBE protein in homozygotes.[49] Diseased foals cannot store and mobilize glycogen to maintain normal glucose homeostasis. Those that survive to parturition are often born weak, hypoglycemic, and hypothermic but improve with bottle feeding. Other clinical presentations include progressive muscle weakness, inability to rise, collapse, seizures, flexural limb deformities, respiratory failure, and sudden death. Common laboratory findings include leukopenia, intermittent hypoglycemia, and moderate elevations of serum CK, AST, and GGT activities. Genetic testing is available, but diagnosis can also be made based on liver and muscle biopsies from affected foals.There is no treatment, and all cases to date

have been fatal.

Chronic Active Hepatitis

Jennifer L. Davis

Chronic active hepatitis (CAH) is an idiopathic progressive hepatopathy with insidious onset. The etiology and pathogenesis are unknown but may be similar to human autoimmune or hypersensitivity conditions. Toxic and infectious etiologies have also been proposed, or it may be a manifestation of chronic cholangitis or cholangiohepatitis. In one retrospective report of 88 cases of liver disease in adult horses, CAH accounted for 9.9% of all cases reported.[1] Seven of nine cases in that report were in ponies, although a true breed predisposition has not been reported.

Clinical signs are those of progressive liver failure and include weight loss, depression, anorexia, colic, icterus, and fever.[2] These signs may be intermittent. Signs of concurrent intraabdominal diseases or other autoimmune diseases may also be present. In rare cases, a moist exfoliative coronary dermatitis may occur, which is thought to be an immune-mediated issue.[3] Concurrent elevations in hepatic enzymes, particularly GGT and ALP, will be present, with lesser elevations in SDH and AST as well as bile acids and direct bilirubin. The degree of elevation in liver enzymes cannot be used as an indicator of disease severity, since the liver may have significant fibrosis at the time of diagnosis. Other supportive clinicopathologic findings include an inflammatory leukogram, bilirubinuria, prolonged BSP clearance, and a polyclonal gammopathy. Ultrasonography may reveal a small liver with increased echogenicity indicative of hepatic fibrosis. Differential diagnosis includes pyrrolizidine alkaloid toxicity, bile stones, abdominal abscesses, and other chronic wasting diseases.

The final diagnosis of chronic active hepatitis is made histologically via biopsy of the liver or at necropsy. The principal features are localized primarily along the portal or periportal areas and include infiltration of inflammatory cells, biliary hyperplasia, and fibrosis or cirrhosis.[1] A mononuclear cell infiltrate (lymphocytes or plasmacytes) often predominates, but a neutrophilic component may be present with a primary or secondary infectious process. Bacteria, particularly gram-negative enteric bacteria, may be present in some lesions, and biliary hyperplasia may be marked if there is cholangiohepatitis. Grossly, the liver appears firm and is often pale brown to green in color, and the cut surface may have prominent irregular markings. An antinuclear antibody (ANA) titer

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and immunofluorescent staining of skin lesions (if present) may reveal evidence of an autoimmune reaction.

Treatment of CAH involves supportive care. Specific treatments can be determined based on biopsy results. If the predominant cell types are lymphocytes or plasma cells, corticosteroids may be beneficial. Dexamethasone (0.05 to 0.1 mg/kg/day IV or IM decreased over 2 to 3 weeks) or prednisolone (1 mg/kg/day PO for several weeks) is recommended. Antibiotics are indicated when a bacterial cholangiohepatitis is suspected on the basis of the histologic features of the liver, culture of the liver biopsy, and presence of a persistent intermittent fever. Other recommended therapies are aimed at resolving inflammation and preventing the progression of fibrosis. Flunixin (0.5 to 1 mg/kg PO q24h) or low-dose phenylbutazone (0.5 g/day PO q24h) can be used. Vitamin E (10,000 U PO q24h) is recommended to protect membrane phospholipids from oxidative damage and suppresses activation of inflammatory cells. Pentoxifylline (8 to 10 mg/kg PO q12h) has been used as a weak inhibitor of the inflammatory cytokines tumor necrosis factor (TNF)–α and interleukin 6 (IL-6), although results are variable, possibly owing to the low oral bioavailability in horses. Colchicine (0.03 mg/kg PO q24h) can be used to inhibit production of collagen and macrophage- or cytokine-induced inflammation.

The prognosis for CAH is variable and depends on the underlying cause and duration of disease prior to diagnosis. A retrospective study reported that five of nine horses with CAH survived, but they were 7.4 times more likely to die than those where a diagnosis of unclassified hepatopathy was made.[1] Liver biopsy and response to therapy are the best guides in formulating a prognosis. The prognosis for improvement and long-term survival is extremely poor in horses that have functional hepatic failure with widespread fibrosis and disruption of normal hepatic parenchyma. The prognosis is fair to good in patients with early (less severe) lesions, particularly those with a lymphocytic or plasmacytic cellular infiltrate that responds well to corticosteroids. The presence of cirrhosis in the biopsy sample warrants a grave prognosis.

Pyrrolizidine Alkaloid Toxicity

Geoffrey W. Smith

■ Etiology

Pyrrolizidine alkaloid (PA) toxicity is a chronic, progressive, often delayed

toxicity that results when animals consume plants containing PAs. Plants containing these alkaloids are found all over the world, and poisoning of horses, cattle, poultry, and even humans has occurred in many different countries. PA toxicity primarily manifests as liver failure.[1] More than 350 types of PAs have been identified in over 6000 plant species.[2,3] The primary plants of importance in the United States come from the *Senecio* and *Crotalaria* genera, but others exist. Table 33.4 lists the most common plants causing PA poisoning around the world.

TABLE 33.4

Common Plants Containing Pyrrolizidine Alkaloids (PAs)

Botanical Name (Genus and Species)	Common Name
Senecio jacobaea	Tansy ragwort or stinking willie
Senecio vulgaris	Common groundsel
Senecio douglasii var. *longilobus*	Threadleaf groundsel
Senecio riddellii	Riddell's groundsel
Senecio triangularis	Arrowleaf groundsel or tarweed
Senecio alpinus	Alpen-Kreuzkraut (Europe)
Amsinckia intermedia	Fiddleneck
Crotalaria spp.	Rattlebox
Echium plantagineum, Echium lycopsis	Patterson's curse, Salvation Jane, or viper's bugloss
Heliotropium europaeum	Common heliotrope
Symphytum officinale	Comfrey
Cynoglossum officinale	Houndstongue
Eupatorium maculatum	Joe Pye weed or Bruner's trumpet
Baccharis pteronioides	Yerba de pasmo
Borago officinalis	Borage or starflower
Erechtites spp.	
Trichodesma spp.	

PA toxicity is seen wherever plants containing the alkaloids are found. The plants are not very palatable and in most cases are not readily eaten, but animals may eat them when the growth of the toxic plant is so thick the animal cannot separate it from normal forage or when other forage is sparse. The plants are toxic in hay, including pelleted and cubed hay. PAs also survive ensilage. For example, oat silage contaminated with *Amsinckia* or other PA-containing plants has been responsible for disease in dairy cattle. Seeds of *Heliotropium* plants have also poisoned feedlot cattle.[4]

The approximate toxic dose of dried *Senecio* as a percentage of body weight for each species is horses, 5%; cattle, 2% to 5%; goats, 125% to 400%; and sheep, over 150%. Most tansy ragwort contains less than 0.2% PA by weight, but

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there are reports of much higher levels in some of the other plants. Horses were consistently poisoned by greater than 250 mg of total PA per kg body weight.[5] The PA in houndstongue *(Cynoglossum officinale)* is extremely toxic to horses.[6] The dose does not have to be eaten all at once, since the effects are cumulative. Because signs often are delayed, some animals may not become ill until a year or more after removal from feed sources containing the toxins.[7,8] Signs do not occur until hepatocyte loss and replacement by fibrous tissue have caused failure of liver function.

■ Pathophysiology

There are a number of PAs, and many of the poisonous plants contain four to six different alkaloids. About 50% of the alkaloids are toxic, and some are more toxic than others. The alkaloid concentrations vary slightly among plants from different areas, but there is greater variation in concentrations from different parts of the same plant.[9] PAs are not directly toxic but must be bioactivated to toxic alkaloids (pyrroles) in the liver. After absorption, the portal circulation carries the alkaloids to the liver, where they are metabolized by microsomal enzymes of the hepatocyte to more toxic pyrroles.[3,10] The pyrroles may crosslink double-strand DNA in a dose-dependent manner.[11] The degree of DNA crosslinkage depends on the concentration of the pyrrole but not on the base sequence of the oligonucleotide target.[12] The crosslinking of DNA produces an antimitotic effect.[13] The hepatocytes cannot divide and often become megalocytes as cytoplasm expands without nuclear division. As cells die, they are replaced by connective tissue rather than new hepatocytes. This antimitotic effect may explain why megalocytosis (large hepatocytes and large nuclei) is commonly seen with PA poisoning.

With progressive death of hepatocytes and subsequent fibrosis, liver function begins to fail. Blood supply through the hepatic lobule is disrupted by fibrosis, making regeneration impossible. This becomes a veno-occlusive disease, resulting in marked portal hypertension. The increased portal hydrostatic pressure leads to diarrhea and ascites in ruminants. It is unclear why diarrhea and ascites are seen infrequently in horses with PA toxicity.

■ Clinical Signs

The clinical signs of PA poisoning are basically those of liver failure. The most

common signs of PA toxicity in the horse are weight loss, slight to moderate icterus, and abnormal behavior (e.g., wandering, ataxia). Signs seen less frequently in horses include photosensitization of the white areas and, in rare cases, diarrhea. A few cases in ponies have shown loud, stertorous inspiratory noises, possibly caused by pharyngeal-laryngeal paralysis.[13,14] Abortion may occur from ingestion of sublethal doses.[15] Subtle signs such as poor performance (inability to race up to previous standards) may be seen in horses with pyrrolizidine-induced liver damage before the onset of liver failure. Secondary gastric impaction has been reported in ponies.[16] Cattle more frequently show diarrhea, weight loss, tenesmus, prolapsed rectum, and ascites. Calves are much more susceptible to PA toxicity than mature cattle. Behavioral changes or subtle neurologic signs may also be seen in cattle, but icterus is uncommon. Differential diagnosis includes other diseases causing liver failure (e.g., aflatoxicosis or liver flukes) and some chronic debilitating diseases such as GI parasites and Johne's disease.

Sheep and goats are more resistant to PA toxicosis but can be affected by certain alkaloids at doses 30 times or more than the dose that affects cattle and horses. A consortium of ruminal microbes from sheep degrades PAs found in *Senecio jacobaea* to less toxic metabolites.[17] Liver microsomal enzymes in sheep may also play a role in detoxifying PAs, but this alone does not seem to account for the differences in susceptibility.[18]

■ Diagnosis

Hepatic enzyme activities are generally elevated during periods of active hepatocyte destruction caused by PA poisoning. Although the dehydrogenases (e.g., SDH, GDH, LDH) are elevated initially, they may have returned to normal by the time the animal first shows clinical signs of functional failure. Because lesions are largely in the portal region, GGT and ALP tend to be consistently elevated.[7,19] In a study of sublethally poisoned horses, AST and the ratio of branched-chain to aromatic amino acids were persistently elevated.[15] Bile acid concentrations are increased, and levels above 50 µmol/L would be a poor prognostic indicator in the horse.[5] Serum protein concentration is usually normal, and only terminally does albumin decrease or blood clotting become altered. Bilirubin, both direct and indirect, tends to be increased in the horse at the later stages of the disease process.

Although liver biopsy can be very useful in the diagnosis of PA toxicity, other

causes of chronic hepatitis (e.g., aflatoxins) may produce a similar histologic appearance. The triad of fibrosis, bile duct proliferation, and megalocytosis is characteristic of PA poisoning. Modest changes in hepatocytes and biliary hyperplasia are reversible. Fibrosis bridging portal areas indicates an eventually fatal condition, as does the extensive fibrosis of an end-stage liver.

Cattle dying of PA poisoning have ascites and prolapsed rectums and are thin and emaciated. Horses are usually thin and may be icteric. In all species, the liver tends to be small, pale brown to yellow, and firm and may appear to be scarred. Hepatic megalocytosis is considered the hallmark of PA poisoning, but it has also been seen in aflatoxicosis and is not always apparent in the earliest stages of PA toxicity. Biliary hyperplasia may occur early in the disease. Nonspecific nuclear changes, such as invaginations of cytoplasm into the nucleus, have been seen.[7,9] Isolated hepatocyte necrosis is seen later, and finally portal or massive generalized fibrosis develops. Once bridging of connective tissue between the portal areas occurs, the disease is fatal.

■ Treatment

Liver failure may occur with either acute or chronic liver disease. The two must be differentiated for prognosis because end-stage fibrosis caused by PAs has virtually no chance for regeneration and recovery. No satisfactory treatment for PA poisoning exists. Once obvious clinical signs of liver failure develop, the animal usually dies within 5 to 10 days. Horses with mild clinical signs and reversible histologic lesions survived if they retained an appetite and were not exposed to any more PA-contaminated feed.[15] An accurate prognosis concerning mildly affected cases may best be obtained from a combination of consecutive liver biopsies and liver-derived serum enzyme activity, as well as from SBA concentrations.[5,15] Preventing further exposure to the toxic plants is indicated and may delay or stop the progression of the liver lesions, particularly if an uncontaminated feed source is provided before clinical signs develop.

Therapy of liver failure is inappropriate if severe fibrosis has occurred because regeneration is impossible. If the animal still has a reasonable appetite and only modest degrees of fibrosis histologically, treatment may be attempted by providing a low-protein, high-energy diet.

■ Prevention and Control

PA poisoning is prevented by keeping susceptible animals from pasture, hay,

cubed hay, or seeds that contain PA plants. Because most poisonings are attributed to contamination of forages or feed, careful inspection of feed is recommended. *Senecio vulgaris* tends to contaminate mainly first-cutting alfalfa, whereas *Amsinckia intermedia* is often found in planted fields of oat hay. *Senecio* can be controlled by cultivation because it is a biennial or by herbicide spraying in the early rosette stage. Species-specific herbicide regimens have been developed for most plants containing alkaloids and are widely available through state weed and extension services. Sheep are sometimes used to graze *Senecio*-infested pastures to control the weed, because they are less susceptible to PA poisoning.

Other Hepatotoxins

The liver is particularly vulnerable to toxic insults because it is the first organ to receive toxins absorbed from the GI tract. Enzymes in the hepatocyte may either activate a toxin or in some cases metabolize it before it can cause damage. Most hepatotoxic agents are described in more detail in Chapter 54. Some of the more common liver toxins are listed in Tables 33.5, 33.6, and 33.7, but these are not complete lists because many other plants and chemicals can damage the liver under the right conditions. Once a toxic liver disease has been diagnosed, possible sources of the toxin might be identified from these tables. A more detailed description of toxins affecting the liver can be found in Chapter 54.

TABLE 33.5
Hepatotoxic Plants

Common Name (Botanical Name)	Approximate Ld50 (%Bw)[a]	Geographic Distribution	Liver Lesion
For pyrrolizidine alkaloid–containing plants, see Table 33.4.			
Lantana *(Lantana camara)*	1	Northern North America	Necrosis, canalicular collapse
Littleleaf horsebrush *(Tetradymia glabrata)*	0.5	Dry desert	Necrosis
Sacahuista or bear grass *(Nolina texana)*	1.1	Southwestern U.S.	Fatty and centrilobular necrosis
Lechuguilla *(Agave lechuguilla)*	4-15	Southern U.S., Mexico	Necrosis, photosensitivity
Bindii or puncture vine *(Tribulus terrestris)*	?	Warmer regions	Biliary fibrosis, necrosis (big head)
Whitebrush *(Aloysia gratissima)*	?	Southern U.S., Mexico	Fatty degeneration
Panic grasses (*Panicum* spp.)	?	Texas-California, South	Biliary fibrosis, necrosis

		America	
Kleingrass *(Panicum coloratum)*	?	Southern U.S.	Necrosis, obstructed bile ducts
Scutch grass or Bermuda grass *(Cynodon dactylon)*	?	North America	?
Cocklebur *(Xanthium orientale)*	0.75-3	North America	Hemorrhagic centrilobular necrosis
Lupine (*Lupinus* spp.)	Varies	Western North America	Necrosis
Mycotoxin from *Phoronopsis inferior*			
Cottonseed (*Gossypium* spp.)	Varies; gossypol content	Southern U.S.	Necrosis
Gossypol pigment			Cardiac lesions
Poisonous mushrooms *(Amanita phalloides, Galerina venenata)*	Few mushrooms	North America	Necrosis, central nervous system signs
Blue-green algae *(Microcystis aeruginosa, Nodularia spumigena)*	? 0.001	Ponds, worldwide	Necrosis, dissociation
Alsike clover *(Trifolium hybridum)*	Varies	Cultivated	Portal fibrosis, biliary hyperplasia
Mexican fireweed *(Kochia scoparia)*	?	Southwest U.S.	?
Coffee senna *(Cassia occidentalis)*	0.05 (horse); 0.5-2 (cattle)	North and South America, Africa, Asia and Australia	Pericentrolobular vacuolar degeneration and necrosis
Cycad palm (*Cycas/Zamia* spp.)	?	South America, Australia	?
Yellow-wood or rosewood *(Terminalia oblongata)*	?	Australia, Africa	Centrilobular necrosis
Sneezeweed (*Helenium* spp.)	0.25	Northern U.S., Canada	?
Moldy alfalfa *(Medicago sativa)*	?	Wet areas	Biliary hyperplasia, necrosis
Bitterweed (*Hymenoxys* spp.)	1	Southwestern U.S.	?

[a]Lethal dose (as percentage of body weight).

?, Unknown; *Bw,* body weight; *Ld50,* median lethal dose; *U.S.,* United States.

TABLE 33.6
Hepatotoxic Chemicals

Chemical	Source	Approximate Lethal Dose[a]	Liver Lesion
Carbon tetrachloride (CC14)	Tremacide	10-40 mg/kg	Fatty degeneration, centrilobular necrosis, cirrhosis
	Fumigant		
	Solvent		
C1 hydrocarbons	Insecticides	Varies with species, chemical, and route	Necrosis
PCBP			
Solvents			
Pentachlorophenols	Wood preservative, herbicide, fungicide, molluscacide	100-200 mg/kg	Centrilobular fatty degeneration
Polybrominated	Fire retardant	100 mg/kg	Hemorrhagic necrosis, fatty

biphenyl (PBB)			degeneration
Carbon disulfide (CS_2)	Boticide	100 mg/kg	Necrosis
	Solvent		
	Fumigant		
Coal tar pitch	Clay pigeons	Swine 15 g/pig	Hemorrhagic necrosis
	Pipe sealer		
	Tar paper		
Phenol	Wood preservative	30 mg/kg	Hemorrhagic centrilobular necrosis
Iron	Iron supplements	>150 mg/kg young animals	Portal necrosis
		Older animals	
	Injectable iron		
Copper	Species-inappropriate supplements	Depends on species and molybdenum intake	Portal vacuolation and necrosis (hemolytic crisis)
	Fungicides, algicides		
	Molluscacide		
	Foot baths		
Phosphorus	Fertilizer	1-4 mg/kg	Portal necrosis and fatty degeneration
	Matches		
	Rodenticide		
Tannic acid	Oak	20 mg/kg	Centrilobular necrosis (also renal damage)
	Skin astringent		
Paraquat/diquat	Herbicide	4-10 mg/kg	Centrilobular necrosis (also lung damage)
Mycotoxins, aflatoxin B	Moldy feed	3 mg/kg	Centrilobular necrosis, biliary hyperplasia, megalocytosis
Rubratoxin B	Moldy feed	?	Necrosis
Sporidesmin	Moldy feed	?	Bile duct occlusion (big head)
Ochratoxin A	Moldy feed	?	Necrosis (also renal damage)
Phomopsin A	Lupine	?	Necrosis

[a]Lethal dose varies with individual, species, route of entry, rate or chronicity, enzyme induction, and many other factors.

?, Unknown.

TABLE 33.7

Drugs Used in Large Animals That Could Damage the Liver

Drug	Lesion[a]
Carbon tetrachloride	Centrilobular necrosis or fatty degeneration
Hexachloroethane	Centrilobular or massive necrosis
Carbon disulfide	Necrosis
Alcohol	Necrosis/cirrhosis
Tetracycline	Fatty degeneration (also renal damage)
Clindamycin	Cholestasis, icterus
Erythromycin	Cholestasis, icterus
Isoniazid	Active hepatitis → cirrhosis/massive necrosis

Rifampin	Cholestasis, icterus
Rifampin/doxycycline combinations	Hemolytic icterus, elevated liver enzymes
Nitrofurantoin	Active hepatitis → cirrhosis
Anabolic steroids	Cholestasis, icterus
Phenothiazine	Cholestasis, icterus tranquilizers
Halothane	Active hepatitis → cirrhosis/massive necrosis
Fluothane	Active hepatitis/massive necrosis
Isoflurane	Active hepatitis/massive necrosis
Some diuretics	Cholestasis, icterus
Diazepam	Cholestasis, icterus
Phenobarbital	Necrosis/cholestasis icterus
Aspirin	Active hepatitis → cirrhosis
Oil of pennyroyal	Centrilobular necrosis
Tannic acid	Centrilobular necrosis, fatty degeneration (renal damage)
Dantrolene	Active hepatitis → cirrhosis
Copper disodium edetate	Massive centrilobular necrosis
Iron (injectable)	Necrosis, portal, cirrhosis, hemosiderosis
Glucocorticoids	Hepatocellular vacuolization
Ionophores (salinomycin)	Hepatic lipidosis, necrosis

[a]May vary with dose and time.

Liver Flukes in Ruminants

John B. Malone

■ Etiology

The common liver fluke, *F. hepatica*, causes a disease of production in ruminants that mimics the production effects and clinical appearance of the GI nematode-parasite complex. The disease often has its maximum economic effect in late fall and winter when animals are most likely to be under seasonal nutritional stress. *F. hepatica* is unique among the common helminths of ruminants in that it has an asexual multiplication phase of the life cycle in snail intermediate hosts that is highly sensitive to environmental conditions. *F. hepatica* is well known for its exponential propagation of infective stages under favorable conditions, sometimes leading to explosive seasonal outbreaks of severe parasitism, especially in sheep. In addition, liver parenchyma migration forms leave necrotic tracts in their wake that are a primary predisposing factor in some areas for acute fatalities caused by *C. novyi* types B (black disease) and *haemolyticum* (bacillary hemoglobinuria), discussed earlier in the chapter.[1]

The geographic distribution of *F. hepatica* in the United States is limited mainly to areas in the south-central states and Florida and to the Pacific Northwest, where neutral well-buffered soils are found and local hydrologic

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conditions provide suitable habitats for lymnaeid snail intermediate hosts. The important vector species in temperate climates, recently renamed based on molecular evidence as *Galba* spp. or *Lymnaea* spp.,[2] are semiaquatic "mud" snails found in disturbed mud banks and hoofprints in shallow depressions in fields, drainage channels, and temporary water bodies in alluvial river basins, bottomlands, and coastal regions of the southeastern United States. Springs, small streams, seeps, and sloughs serve as habitats in areas of greater terrain relief in the western states. Most infections occur by grazing in and around water in fluctuating habitats that stay wet for more than half the year.

The life cycle development of both the snail host and the parasite in the snail occurs only when temperatures are above 10° C (50° F) and snail habitats are wet. This leads to a distinct seasonal transmission in the mild, wet winter and spring of the south-central states and Florida and a late spring to fall transmission in the cooler climates of the western states (Figs. 33.3 and 33.4). It takes a minimum of 42 days at 25° C (77° F) or the accumulation of approximately 600 growing-degree days to complete intramolluscan development, with release of cercariae that encyst as infective metacercariae on pasture vegetation (600 growing-degree days = 25° C minus the base temperature of 10° C = 15 growing-degree days × 42 days; an equivalent value for the life cycle is 15° C or 5 growing-degree days × 120 days). Using soil water budget analysis to indicate the length of time habitats are wet and the accumulated sum of growing-degree days over 600, a climate forecast index can be calculated for use in describing the pattern of seasonal transmission at a given site and to provide an indicator of the risk of economic losses in a given climate year. Two weeks of sustained summer heat and drought ends the transmission season by killing pasture metacercariae and forcing snail populations to estivate in soil or perish. In the cooler climates of the western United States, the season ends with drying of springs, seeps, sloughs, and other habitats or with the onset of sustained cold winter weather. Variation in the annual climate alone may lead to a hundredfold variation in fluke burdens in different climate years.[3]

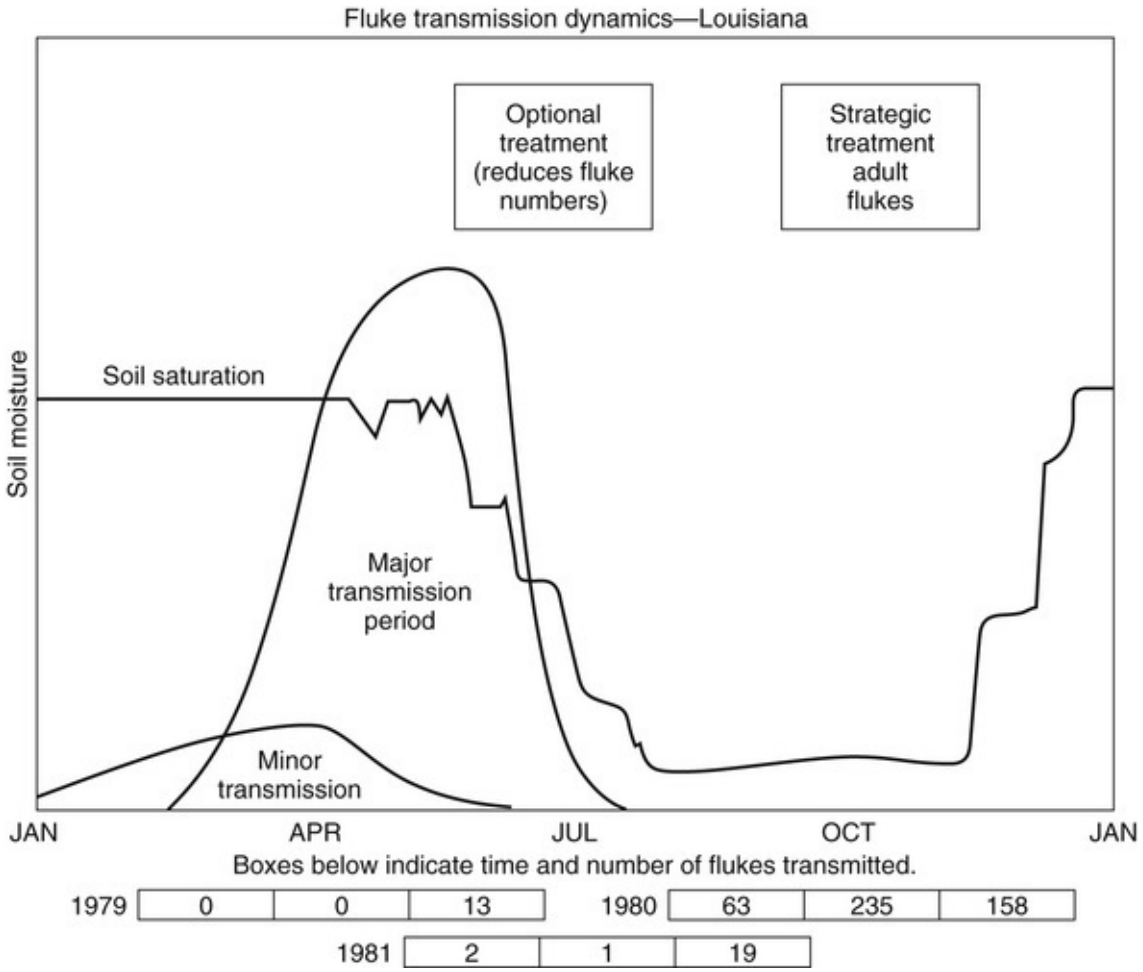


FIG. 33.3 Pattern of *Fasciola hepatica* transmission typical of the southern United States (based on 10 years of experimental data from Alexandria, Louisiana) and strategic treatment recommendations with adulticidal drugs. (From Malone JB, Loyacano AR, Hugh-Jones ME, et al.: A three-year study on seasonal transmission and control of Fasciola hepatica in cattle in Louisiana. Prev Vet Med 3:131, 1984.)

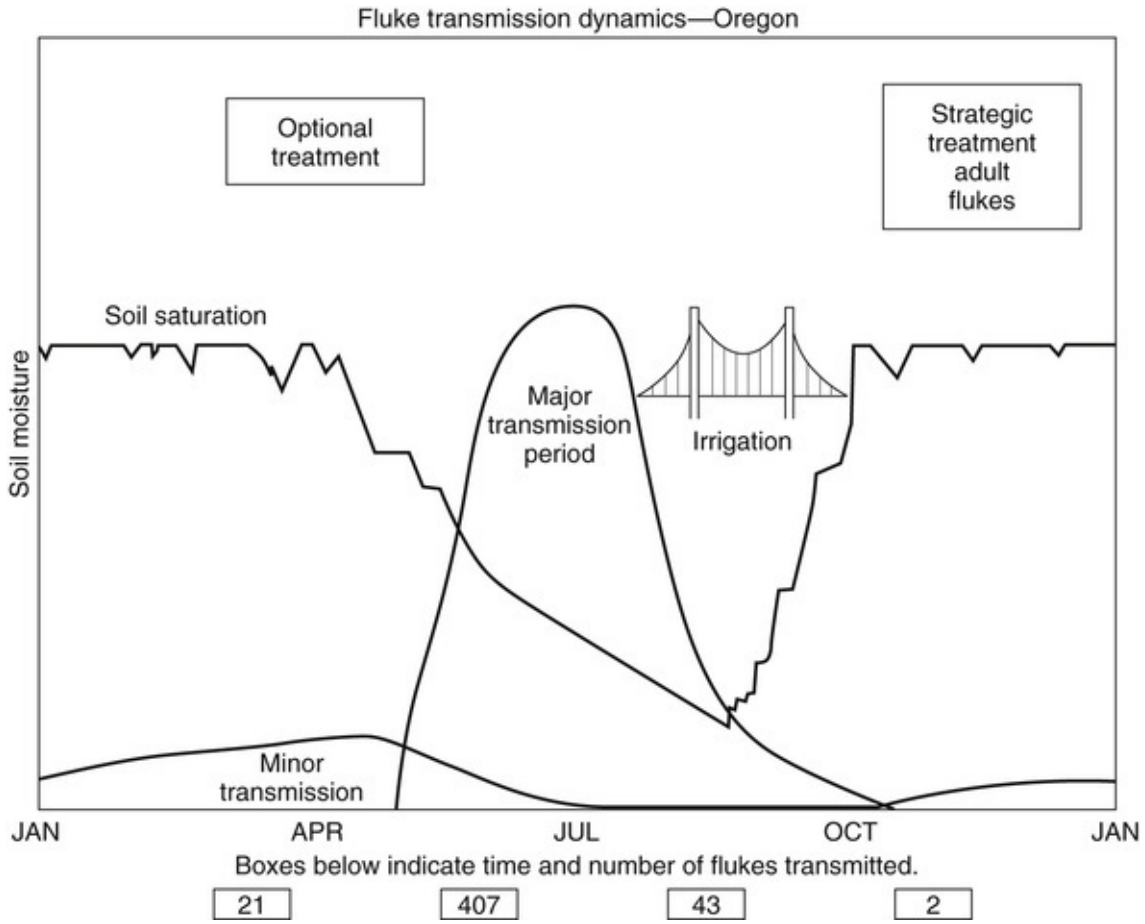


FIG. 33.4 Pattern of *Fasciola hepatica* transmission typical of the U.S. Pacific Northwest in natural rainfall and irrigated zones (based on experimental data from Langolis, Oregon) and strategic treatment recommendations with adulticidal drugs. (From Rickard LG, Zimmerman GL, Hoberg EP, et al.: Influence of ivermectin and clorsulon treatment on productivity of cow-calf herd on the Southern Oregon coast. Vet Parasitol 41:45, 1992.)

The amount of snail habitat present on individual farms related to pasture wetness conditions, such as premises with low-lying heavy clay soils with a high water table, is also an important consideration in evaluating the need for fluke control. This factor has also been shown to lead to a hundredfold variation in the risk of fluke losses in the same year on different premises in otherwise ecologically similar areas.[4] The snail habitat area on most enzootic livestock operations typically is only 1% to 5% of the total land area; operations with more than 5% habitat may be associated with a high risk of liver fluke losses.

■ Clinical Signs

Subclinical production effects of *F. hepatica* include reduced rate of gain and feed efficiency in growing stock. Economic effects have been experimentally demonstrated in calves on a marginal nutritional plane in the first 5 to 6 months after infection, resulting in an 8% loss in the rate of gain with a mean of 40 flukes and a 28% loss with 140 flukes. In cattle it is estimated that herd economic losses are “negligible” with a burden of less than 10 flukes per animal, “possible” at 10 to 40 flukes, and “probable” with more than 40 flukes. Clinical disease is seen with a burden of more than 200 flukes. In cow-calf operations, flukes often act in concert with periods of nutritional stress and concurrent heavy GI nematode infections, causing further reduction of body condition, poor milking ability, and slower return to estrus. This translates to reduced reproductive efficiency, prolonged calving interval, and lightweight calves at weaning.[5]

In cattle, flukes may lead to chronic disease or, in rare cases, subacute disease. When clinical signs occur, the typical population “overdispersion” (individual variation in parasite burdens) is manifested first in the 10% to 20% minority of the herd that harbor most of the parasite numbers. Signs may consist of weight loss, emaciation, depression, anorexia, rough hair coat, anemia, hypoproteinemia, submandibular edema, and in rare cases, mild icterus. The anemia associated with *F. hepatica* infections is more than can be accounted for by fluke blood feeding. Evidence indicates that depression, anemia, and biliary hyperplasia result from high levels of proline, a product of fluke metabolism.[6] Cattle are able to mount a protective immune response, with partial acquired resistance to *F. hepatica* beginning at 5 to 6 months after initial exposure.[7] This and the short life span of flukes in cattle typically lead to a linear reduction of fluke numbers, with few surviving by the end of 1 year. Sheep and goats are more susceptible, and fatal acute disease with ascites, abdominal hemorrhage, pallor, and icterus can occur in association with massive entry to the bile ducts at 6 to 10 weeks after infection by 1000 to 5000 or more migrating immature forms from the liver parenchyma. Subacute disease has been associated with a burden of more than 800 flukes acquired over time. Chronic clinical disease in sheep with submandibular edema, ascites, and emaciation has been associated with fluke burdens above 200.[8]

Liver flukes in horses are sometimes reported as an incidental finding during postmortem examination. In one study, prevalence was 9.5% in a population of horses from Ireland.[9] Horses with weight loss and diarrhea that respond to

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flukicide treatment provide anecdotal evidence that flukes may result in detectable clinical disease, although the association is unproven.

Necropsy findings attributable to migrating young flukes are caused by tortuous tunnels of coagulative necrosis that organize and fibrose, ultimately leading to a diffusely fibrotic liver parenchyma, especially in the ventral lobe, which in severe cases undergoes marked atrophy. Fibrous tags may result from fibrinohemorrhagic deposits left by large numbers of flukes at liver penetration 3 to 4 days after infection. Inflammatory events associated with penetration of the bile ducts at 6 to 8 weeks after infection are especially pathogenic. Once in the bile ducts, flukes grow rapidly from 1 mm to 2.5 cm or more and induce a proliferative cholangiohepatitis. The spines and suckers of flukes erode and denude the bile duct epithelium, leading to a fibrosed, thickened duct wall that is irregularly dilated and stenotic and begins to calcify in cattle (but not sheep) at about 20 weeks after infection. The bile becomes darkly discolored and laden with regurgitated fluke ingesta, plasma proteins, and inflammatory cells. The extent of pathologic change is generally proportional to the fluke burdens of current or recurring previous infections.[8]

■ Diagnosis

Fecal sedimentation methods are the standard means of diagnosing liver flukes, although classical methods are cumbersome. A reusable commercial “nematode counting chamber” (1-mL volume of sediment fluid) is available (Chalex, Wallowa, Ore.) and can be examined on a standard microscope stage. It reduces sample processing time by half and is suitable for use by practitioners for quantitative examination of individual animals or 10- to 15-animal herd composite samples. For herd or lot evaluations in cattle, egg counts of less than 1 egg per 2 g (EP2g) and 25% prevalence 2 to 4 months after the transmission season ends have a “low probability” of economic losses; 1 to 3 EP2g indicates “possible” economic loss; and 10 or more EP2g indicates “high probability” of heavy infections and economic loss. It is important to differentiate *F. hepatica* eggs from the eggs of *Paramphistomum* species, a nonpathogenic “rumen fluke” often found in the same herds in both the southern and the western enzootic areas. Flukecides used against *F. hepatica* are ineffective against rumen flukes, and egg counts thus persist after treatment. *Paramphistomum* eggs are gray (rather than amber), slightly smaller, and more pointed at the operculum end than *F. hepatica*. *Paramphistomum* egg counts can be used as a general indicator of the probable risk of *F. hepatica* in the absence of control in the southern states

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because *Paramphistomum* flukes are known to be transmitted by the same snail vector in that region.[5]

Diagnostic enzyme-linked immunosorbent assays (ELISAs) have been developed to detect serum antibodies or coproantigen in the feces of infected animals or in bulk milk samples.[10,11] These tests have not yet found wide use outside of research laboratories in the United States but are marketed in Europe.[11] ELISAs for the major *F. hepatica* excretory-secretory protein, CL1, have high specificity, but low sensitivity in horses, compared to ELISAs for the liver fluke 2.9-kDa antigen, which have high sensitivity and specificity in horse serum.[9] Blood and serum clinicopathologic results reflect the anemia, hypoproteinemia, and mild eosinophilia caused by *F. hepatica.* Pathologic changes in the liver bile ducts and parenchyma are reflected by an elevation in serum liver enzymes (e.g., GGT, GDH).

■ Treatment and Prevention

Prevention is the key to control in foundation herds and flocks because even low numbers of eggs shed can multiply asexually in snails and lead to significant infection rates during the following transmission season. A single routine fall or late fall–winter treatment after the end of the transmission season with a highly effective drug is recommended to remove adult flukes before winter stress and to prevent egg shedding and snail infection in the next season (see Figs. 33.3 and 33.4). Most of the pathogenic and economic effects of flukes in cattle are reported to occur within the first 5 to 6 months after the major exposure period and may be related to metabolic products associated with the rapid growth and heavy egg production phases of the life cycle. This, coupled with linear loss of heavy fluke burdens in cattle and the onset of effective immunity at 20 weeks after exposure, suggests the value of early flukecide treatment within 2 to 3 months after the transmission season ends. In some herds an optional curative treatment in spring may be needed in very high-risk years or on high-risk premises, or as a second treatment to remove flukes acquired during late, extended transmission on irrigation pastures or wet coastal areas in the west.

Flukecidal drugs available in the United States are effective against mature flukes in bile ducts (albendazole, 10 mg/kg; closulon, 2 mg/kg). Closulon at 7 mg/kg has added efficacy against juvenile flukes over 6 weeks old in the bile ducts. The optimum time to treat should be based on the estimated susceptibility of mature fluke populations (>12 weeks old after end of transmission season) but

early enough to remove flukes while they are most pathogenic (<6 months old). Triclabendazole, which is widely used in other countries, is reported to be more than 90% effective against migrating flukes over 2 weeks old and 99% effective against mature flukes and thus can be effectively given just after transmission ends. However, significant triclabendazole drug resistance issues have emerged.[11,12] Worldwide, a number of other drugs are available, including oxyclozanide, niclofolan, bithionol, and hexochlorophene (80% to 99% of adult flukes), nitroxanil, closantel (>90% adult and 50% to 90% juvenile bile duct flukes), rafoxanide (>50% late migratory flukes, >90% juvenile and adult bile duct flukes), and diamphenathide (>90% migratory flukes, 50% to 80% bile duct flukes).

The economic benefit of routine flukecide treatment of feedlot calves from enzootic areas in the United States has not been consistently demonstrated industry-wide because of the high variability of fluke burdens in animals from enzootic areas or because lots are often of mixed origin. Fluke-related losses would be expected to be mainly absorbed by stocker operations, where lightweight calves are typically placed on small grain pastures for extended periods before feedlot, a common practice in the south-central states. The economic return of treatment at feedlot should be evaluated on a case-by-case basis because significant losses may occur if the lot originates from the same premises and the history suggests a high risk of recent heavy infection rates, such as in favorable climate years or use of irrigated pastures in fluke areas. Fecal egg counts on 10 to 15 randomly selected animals may aid in herd evaluation. An example case of the explosiveness of the life cycle is the greatly reduced feedlot performance and 100% liver condemnations of a lot from a stocker operation in the Pacific Northwest. The animals originated from irrigated pastures where some habitats stayed wet year-round, and untreated calves from fluke areas were allowed to contaminate pastures with eggs, which translated to infection later in the grazing season and to the next stocker group rotated onto the premises.

Other Flukes

Fascioloides magna, the large American liver fluke, may infect cattle and sheep that graze common areas with deer, the natural host. The life cycle is similar to that of *F. hepatica,* but with a wider variety of lymnaeid snail hosts and a broader geographic distribution in the Gulf States, the Great Lakes area, and the Northwest. Cattle are abnormal dead-end hosts that react with an intense

encapsulation response, forming a closed cyst that does not allow escape of eggs and obviates diagnosis by fecal examination. The liver parenchyma and regional lymph nodes have a characteristic diffuse black pigmentation. The major economic effect of *F. magna* in cattle is condemnation of livers and other organs, such as lungs, in which aberrant migration sometimes occurs. In sheep and goats, however, *F. magna* does not encyst and migrates uninterrupted. One or two *F. magna* flukes kill sheep before the flukes have time to mature, and this parasite limits sheep production in some areas. Albendazole given at high dosage is moderately effective against *F. magna.*

In tropical regions, *F. hepatica* is replaced by *Fasciola gigantica,* a similar species that is somewhat larger, has a longer prepatent period (10 to 12 weeks), and is of somewhat greater pathogenicity. *D. dendriticum* occurs worldwide but in North America is an unimportant species, mainly limited to areas of central New York, with smaller foci in Pennsylvania, New England, Quebec, and British Columbia. Albendazole (20 mg/kg) and high doses of thiabendazole (150 to 300 mg/kg) are effective treatments.[1]

Hepatic Abscesses

T.G. Nagaraja

Hepatic abscesses occur sporadically in most animals but are most common in ruminants, particularly cattle fed high-grain diets. Hepatic abscesses occur at all ages and in all types of cattle but are most common and have the greatest economic impact in feedlot cattle. The incidence in feedlot cattle ranges from 1% to 2% to a high of 60% to 80% but averages 10% to 20% in most feedlots.[1] Because hepatic abscesses are generally a direct result of feeding practices, diet is an important factor influencing their incidence. Hepatic abscesses do occur in dairy cows, and in a survey of gross pathologic conditions in cull cows at slaughter, the incidence of liver abscesses was reported to be 32.1%.[2] In the United States, it has become increasingly common to raise Holstein bull calves in feedlot production systems for beef production. Liver abscess data collected at slaughter have shown that the incidence of liver abscesses in Holstein feedlot steers is greater than in crossbred beef cattle.[1,3] In addition, the proportion of more severe abscesses (one or more large or multiple small abscesses, often with adhesions to diaphragm and visceral organs) is greater in Holstein feedlot steers than in beef breeds (50% to 60% versus 30% to 40% of the total abscesses, respectively).

■ Etiology

Hepatic abscesses in cattle are generally polymicrobial infections, and in most cases the organisms are anaerobes.[4,5] *Fusobacterium necrophorum*, a gram-negative, pleomorphically rod-shaped anaerobe, is the primary etiologic agent.[3] The organism also is implicated as the primary pathogen in necrotic laryngitis (calf diphtheria), foot rot, and foot abscesses in cattle.[6,7] *F. necrophorum* is a normal inhabitant of the rumen, and its role in ruminal fermentation is mainly to use lactic acid to produce volatile fatty acids and also digest ruminal epithelial and feed proteins.[8] The organism is in higher concentration in grain-fed cattle than forage-fed cattle, possibly because of the increased availability of lactic acid from fermentation of starch in the grain. Several virulence factors have been implicated in the pathogenesis of *F. necrophorum* infections.[8,9] These include leukotoxin, endotoxic lipopolysaccharide (LPS), hemolysin, hemagglutinin, platelet aggregation factor, dermonecrotic toxin, adhesins (outer membrane proteins), and extracellular enzymes (e.g., proteases, deoxyribonucleases). Leukotoxin is believed to be the major virulence factor.[9] The leukotoxin is cytotoxic to polymorphonuclear neutrophil leukocytes (PMNs), macrophages, hepatocytes, and ruminal epithelial cells. Because of leukotoxin, the organism is able to survive, proliferate, and establish to set up infection of the ruminal wall and liver. There are two subspecies of *F. necrophorum*, subsp. *necrophorum* (formerly biotype A) and subsp. *funduliforme* (formerly biotype B). These two subspecies differ in cell morphology, colony characteristics, growth patterns in broth, and most importantly, in virulence factors. Subspecies *necrophorum* is more virulent (produces more leukotoxin) and thus more frequently encountered in liver abscesses than subsp. *funduliforme*, which tends to occur more often in mixed infections.[7,8]

In most situations, *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), a gram-positive rod-shaped organism, is the second most frequent pathogen isolated from liver abscesses.[10,11] The ruminal wall appears to be the niche for *T. pyogenes*, a facultative bacterium, because the wall provides an aerobic microenvironment in an otherwise anaerobic environment of the rumen.[12] The occurrence of *T. pyogenes* in liver abscesses is likely indicative of the ruminal damage that allows the entry of the organism into the portal circulation to reach the liver. In liver abscesses and other infections (foot rot in cattle, metritis in dairy cows), the organism acts in synergy with *F.*

necrophorum.[1] In recent years, *Salmonella enterica* has been found be associated with liver abscesses of cattle. In a study of bacteriology of liver abscesses of crossbred beef cattle and Holstein steers collected at slaughter, the prevalence of *S. enterica* was reported to be 25.3%.[13] A predominant serotype of *Salmonella* isolated from liver abscesses was Lubbock with the antigenic designation 6,7:g,m,s:e,n,z,15, a novel serotype closely related to Mbandaka. The Lubbock serotype has been isolated from lymph nodes of cattle at slaughter.[14] The contribution of *Salmonella* to the cause of abscesses is not known, but there are reports of *Salmonella* causing liver abscesses in humans.[15] A couple of features of *Salmonella* make its presence in liver abscesses not surprising. First, it is able to grow robustly in anaerobic conditions,[16] and second, it is a facultatively intracellular pathogen, hence able to reach the liver through phagocytic cells.[17]

A variety of other anaerobic and facultative bacteria, such as *Bacteroides* spp., *Clostridium* spp., *Escherichia coli*, *Klebsiella pneumoniae*, *Mobiluncus* spp., *Mitsuokella* spp., *Pasteurella* spp., *Peptostreptococcus* spp., *Porphyromonas* spp., *Prevotella* spp., *Propionibacterium* spp., *Pseudomonas aeruginosa*, *Staphylococcus* spp., *Streptococcus* spp., and many unidentified gram-positive and gram-negative bacteria are often isolated from liver abscesses of cattle.[3,5,10]

■ Pathophysiology

Abscesses in the liver result from entry and establishment of *F. necrophorum* either alone or with other bacteria. The routes by which bacteria can gain access to the liver include the portal vein, hepatic artery, umbilical vein (in newborns with omphalophlebitis), bile duct system, and direct extension. Entry through the hepatic artery (after an episode of septicemia) or the bile ducts (usually from obstruction, infection ascending from duodenum, or migration of flukes) is a rare occurrence. Direct extension of infection from adjacent tissues and organs, usually of traumatic origin (e.g., direct puncture of the liver by a foreign body lodged in the reticulum), is more likely to occur in dairy cows. Traumatic reticuloperitonitis caused by metallic objects lodged in the reticulum and perforating through the reticular wall, rarely involving the ruminal wall, is often a predisposing factor for liver abscesses in dairy cows. However, in both dairy cows and feedlot cattle, the most common route of entry of bacteria into the liver is the portal vein.

Liver abscesses are secondary to the primary foci of infection in the ruminal wall. Evidence to support this is the high correlation between ruminal wall

lesions (rumenitis) and liver abscesses, thus the term *rumenitis–liver abscess complex* (Fig. 33.5). In a recent study of the relationship between ruminal wall lesions and liver abscesses in beef cattle at slaughter, Rezac and colleagues[2] observed that 32% of cattle with mild or severe rumenitis had liver abscesses compared with 19% of cattle with healthy ruminal walls. However, not all studies have shown an association of liver abscesses with ruminal lesions.[18] More direct evidence for the pathogenesis of liver abscesses was obtained by restriction fragment length polymorphism analysis of rRNA genes (ribotyping) of *F. necrophorum* and *T. pyogenes* isolates from the rumen and liver abscesses of the same animal. The genetic similarity between the isolates from liver abscesses and ruminal walls supported the hypothesis that *F. necrophorum* and *T. pyogenes* isolates of liver abscesses originated from the rumen.[12,19] It is well accepted that ruminal lesions resulting from acidosis are the predisposing factors for hepatic abscesses. Acid-induced rumenitis and damage of the protective surface usually are associated with a sudden change to high-energy diets and other dietary indiscretions, such as a change in feeding patterns, letting cattle become overly hungry, feeding unpalatable diets, and feeding very little roughage. The ruminal damage often is aggravated by foreign objects in the feed, sharp feed particles, or hair.[20] The ruminal wall that is damaged from acidity or penetration of foreign objects becomes susceptible to invasion and colonization by *F. necrophorum.* Once colonization has occurred, *F. necrophorum* can gain entry to the blood or cause ruminal wall abscesses and subsequently shed bacterial emboli to the portal circulation. Bacteria from the portal circulation are filtered by the liver, leading to infection and abscess formation.

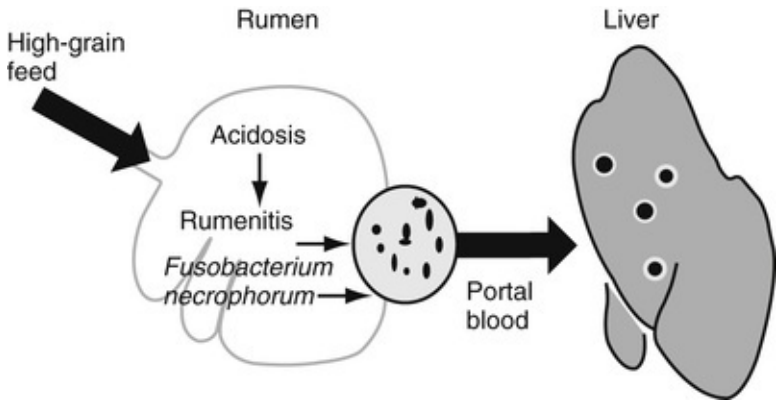


FIG. 33.5 Pathogenesis of liver abscesses in cattle fed high-grain diets.

(Modified from Nagaraja TJ, Chengappa MM: Liver abscesses in feedlot cattle: a review. J Anim Sci 76:287, 1998.)

The virulence factors of *F. necrophorum* play a critical role in the penetration and colonization of the ruminal epithelium and entry and establishment of infection in the liver.[8,9] The protease activity, dermonecrotic activity, and cytotoxic effect of leukotoxin on ruminal cells may aid in penetration and colonization of the ruminal wall. *F. necrophorum*, being an anaerobe, must overcome both high oxygen concentrations and phagocytic mechanisms to survive, proliferate, and initiate abscess formation. The leukotoxin may protect it from phagocytosis. Also, the release of cytolytic products such as lysosomal enzymes and oxygen metabolites, resulting from destruction of phagocytes, has a detrimental effect on the liver parenchyma. Synergism with facultative bacteria, intravascular coagulation induced by endotoxic LPS and platelet aggregation factor, formation of fibrin-encapsulated abscesses, and impairment of oxygen transport by damaged erythrocytes (action of hemolysin) all may contribute to the establishment of an anaerobic microenvironment conducive to the growth of anaerobic bacteria within the ruminal wall and liver.

■ Pathology

Abscesses found in the liver at slaughter or necropsy often are well encapsulated, possessing thick, fibrotic walls (Fig. 33.6). The earliest lesion is a microabscess induced by an embolus of *F. necrophorum* in the sinusoid, and the lesion then progresses to coagulative necrosis by involving adjacent hepatocytes. Subsequently, the lesion gradually changes into a pus-filled, encapsulated, true abscess. Histologically, a typical abscess is pyogranulomatous with a necrotic center, encapsulated, and often surrounded by an inflammatory zone.[11] Hepatic abscesses are pus filled, have capsules that vary in thickness, and range in size from a minute pinpoint to more than 15 cm (6 in) in diameter. The number of abscesses in the liver can vary from one to hundreds, and sizes range from less than 1 cm (0.4 in) to greater than 15 cm in diameter, often encircled by a hyperemic zone. The larger abscesses may result from small abscesses coalescing early in development. The distribution of abscesses in the liver shows no consistent pattern, with superficial and deep abscesses distributed almost evenly. Often small abscesses are scattered throughout the organ, whereas large abscesses are located close to the portal entry. Abscesses eventually become sterile and are replaced by fibrous scars, with eventual resorption.



FIG. 33.6 Liver from a feedlot steer demonstrating a large liver abscess.

■ Clinical Signs and Diagnosis

Liver abscesses are detected only at the time of slaughter. Cattle, even those that carry hundreds of small abscesses or several large abscesses, seldom show any clinical signs. Occasionally the rupture of a superficial abscess or erosion and perforation of the caudal vena cava could lead to extensive spread and massive infection of other organs and eventual death. Generally, hematology and liver function tests have not proved to be good indicators of liver abscesses.[21] In animals in which abscesses were induced by experimental inoculation of *F. necrophorum*, hepatic dysfunction was documented by elevated serum protein, bilirubin, and enzymes such as GGT and SDH concentrations.[22] In a group of Holstein dairy cattle where the presence of liver abscesses was diagnosed via ultrasound or exploratory laparotomy, the most common clinical sign was anorexia.[22]

Ultrasonography is a useful technique in the diagnosis of various hepatic diseases in cattle because of the location and tissue consistency of the liver (Fig. 33.7).[23] The technique has been shown to be useful for monitoring the onset and progression of experimentally induced abscesses where the site of injection is known.[22] The development of abscesses in feedlot calves has been recorded by ultrasonographic examination at regular intervals from weaning to slaughter.[21] However, its application to the diagnosis in feedlot cattle is limited because the

ultrasonographic scanning cannot visualize the whole liver, particularly the left side facing the internal organs, and parts of lobes are covered by other organs (e.g., lungs, kidneys).

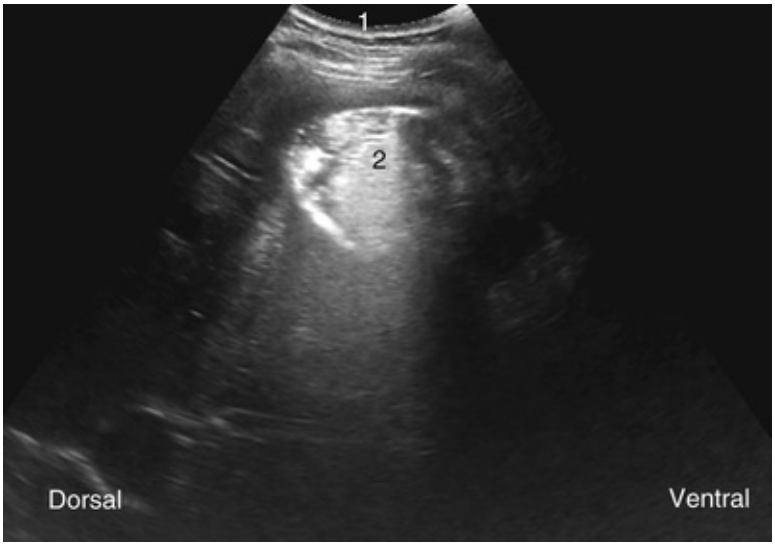


FIG. 33.7 Ultrasound image from the eleventh intercostal space of a cow. Abdominal wall *(1),* liver abscess *(2).*

■ Treatment and Prevention

Both *F. necrophorum* and *T. pyogenes,* but not *S. enterica*, are susceptible to penicillins and macrolides.[5,24] Although successful treatment of cattle with liver abscesses has been described,[25] antibiotic treatment is seldom practical in cattle because complete recovery is difficult to attain. Cattle with sequelae (e.g., caudal vena cava thrombosis syndrome) are generally culled for slaughter, for economic reasons. According to the U.S. Feed Additive Compendium, five antibiotics (bacitracin methylene disalicylate, chlortetracycline, oxytetracycline, tylosin, and virginiamycin) are approved for prevention of liver abscesses in feedlot cattle.[26] Of these, only chlortetracycline, oxytetracycline, and tylosin are used for prevention. Tylosin, a macrolide, is the most effective antibiotic and the most commonly used feed additive (8 to 10 g/ton or 60 to 90 mg/head/day) in the feedlot. Studies show that tylosin feeding reduces abscess incidence by about 40% to 70%. Although there is no evidence of resistance development in *F. necrophorum,*[5] the future of tylosin use as a feed additive in feedlot cattle is

uncertain. According to the Center for Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA), the judicious use of medically important antimicrobial drugs in food-producing animals should be based on two principles: (1) limit medically important antimicrobial drugs to uses in animals that are considered necessary for assuring animal health, and (2) limit medically important antimicrobial drugs to uses in animals that include veterinary oversight or consultation. Because tylosin is used to prevent liver abscesses and not intended for growth promotion, it could be categorized as use to assure animal health. As of January 2017, the use of tylosin in feedlot cattle for the prevention of liver abscesses is under veterinary oversight.[27] There is considerable interest in evaluating antibiotic alternatives, such as probiotics, essential oils, and vaccines, to control liver abscesses. In a feedlot study in cattle fed a finishing diet, inclusion of a product containing limonene, an essential oil, tended to reduce the incidence of liver abscesses compared to the control, but the difference was not significant.[28]

Because the pathogenicity and virulence factors of *F. necrophorum* have been studied widely, there has been considerable interest in and efforts to develop an effective vaccine.[1] The use of vaccines has dual benefits: control of liver abscesses and alleviation of public health concerns associated with the continuous use of medically important antimicrobials in the feed. A bacterin vaccine (Fusogard [Elanco Animal Health, Greenfield, Ind.]), injected subcutaneously in 2-mL doses 21 days apart, is commercially available and has been shown to be effective in reducing the incidence and severity of liver abscesses in feedlot cattle. In a randomized and blinded field trial, vaccination reduced prevalence of liver abscesses in cattle with a low prevalence (10%) but was not effective in cattle with a high (30%) prevalence of liver abscesses.[29] Two antigens of *F. necrophorum* that have been targeted as potential candidates for vaccine development are leukotoxin, a critical virulence factor for bacterial survival and establishment of infection,[30] and outer membrane proteins, which mediate adhesion of *F. necrophorum* to bovine cells.[31] Both proteins have been recombinantly expressed and efficacy has been demonstrated in vitro and in a mouse model.[31,32] However, the efficacy of the recombinant proteins in cattle has not been evaluated. Machado and colleagues[33] have reported a vaccine formulation containing different combinations of proteins of *E. coli*, *F. necrophorum*, and *T. pyogenes* to prevent puerperal metritis in dairy cows, leading to improved reproductive performance.

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In addition to inclusion of antimicrobial compounds in the feed or vaccination, prudent bunk management to minimize fluctuations in intake and ruminal acidosis is well accepted as a key factor for effective control of liver abscesses. Management recommendations include gradual adaptation to high-grain diets, avoiding either underfeeding or overfeeding, increasing feeding frequency to spread out intake, increasing roughage content of the feed, inclusion of grain by-products like distiller's grains, imposing quality control in mixing feeds, and providing adequate bunk space and fresh clean water.[34]

■ Sequelae

Septic cardiac and pulmonary emboli are also associated with liver abscesses in feedlot and dairy cattle. Occasionally, sudden death has been reported in cattle secondary to rupture of liver abscesses, with septic embolization in the right side of the heart. Generally, the condition starts as phlebitis caused by the extension of liver abscesses involving caudal vena cava. The phlebitis leads to thrombus formation anywhere between the liver and right atrium but most often at the point of entry of caudal vena cava into the diaphragm. The clinical syndrome and the extent of lesions observed depend on the degree of thrombosis and type of organisms involved. The syndrome can range from death caused by rupture of caudal vena cava to various degrees of pulmonary embolism, pneumonia, infarction, endocarditis, hemoptysis, and epistaxis. Collectively, these lesions are categorized under caudal vena cava thrombosis (CVCT) syndrome.[35,36]

■ Economic Importance

Liver abscesses are a major economic liability to the producer, the packer, and ultimately the consumer of beef. According to a National Beef Quality Audit report, 20.9% of livers were condemned at slaughter, and liver abscesses accounted for approximately two thirds of liver condemnations.[37] The greatest economic impact of hepatic abscesses is not from the condemnation of liver but from the reduced animal performance and reduction in carcass yield. Cattle with abscessed livers have reduced feed intake, reduced weight gain, decreased feed efficiency, and decreased carcass dressing percentage. These effects are evident only in cattle with the most severe abscesses (one or more large abscesses or multiple small abscesses).[38]

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Hepatic Abscesses in Horses

Hepatic abscesses occur sporadically in horses and are generally part of the intraabdominal abscess complex. In studies that have evaluated horses with intraabdominal abscesses, 12% (3 of 25)[39] and 5% (3 of 61)[40] of horses had abscesses in the liver. Hepatic abscesses in horses are usually associated with gastrointestinal diseases, including proximal enteritis, inflammatory bowel disease, or ileal diverticulitis, and may develop as a sequela to abdominal surgery or following intestinal perforation with foreign bodies.[41,42] A variety of bacterial species, particularly anaerobes, have been cultured from the pus. The most frequently isolated bacteria include *Streptococcus equi*, *E. coli*, *Bacteroides fragilis*, *Corynebacterium pseudotuberculosis*, *F. necrophorum*, and *Peptostreptococcus* species.[39-41]

Clinically, horses with hepatic abscesses cannot be differentiated from those with other intraabdominal abscesses. Generally, horses have a history of fever, loss of appetite, signs of colic, depression, and weight loss. Clinicopathologic changes are typical of chronic bacterial infection and include leukocytosis, thrombocytosis, hypoalbuminemia, and decreased A/G ratio.[39-41] The prognosis is generally poor because of failure to respond to antimicrobial treatment. Percutaneous or surgical drainage is an effective treatment in humans with hepatic abscesses and has been reported as a successful treatment in one horse.[43]

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Hepatic Lipidosis*

Vincent Dore

Fat Cow Syndrome and Lipid Mobilization Syndrome

Hepatic lipidosis (fat cow syndrome) is a multifactorial condition that occurs in dairy cows after parturition. The syndrome is characterized by progressive depression and failure to respond to treatment of other predisposing diseases. It is associated with excessive mobilization of fat to the liver in well-conditioned or overconditioned cows. This mobilization of fat is induced by the negative energy balance and hormonal changes that occur around the time of calving. This negative energy balance in most cases is aggravated by concurrent periparturient diseases that reduce feed intake and increase energy needs.[1-3]

Fat cow syndrome occurs sporadically in dairy cows but more frequently in cows that become overconditioned during late lactation and during the dry period.[2] The overconditioning may be caused by a poor breeding program associated with cows having very long lactations or extended dry periods and having excessive weight gain. Mortality can exceed 25%, with even higher rates occurring without intensive treatment and correction of concurrent diseases. Clinical disease in obese cows that enter the dry period can be minimized by carefully controlling their diets to meet National Research Council (NRC) requirements and preventing milk fever.

■ Clinical Signs

The clinical condition occurs in the postparturient period. Most affected cows are either obese or very well conditioned, with a large amount of omental and subcutaneous fat. Presenting signs usually include depression, anorexia, weight loss, and weakness that can lead to recumbency. Most have nonspecific signs like decreased rumen motility and decreased milk production. Other signs vary and are related to concurrent diseases. The concurrent diseases most frequently seen are metritis, retained fetal membranes, mastitis, parturient paresis, and displaced abomasum.[1] It is important to look for these other diseases; even if mild, they could be significant in these cases and must be treated.

■ Diagnosis

Most laboratory tests are poor indicators of hepatic lipidosis and are of little value in determining disease severity.[4] Liver-derived enzymes are usually elevated above the level in the dry cow but are often within normal ranges. Liver enzymes most consistently elevated in cases of hepatic lipidosis are OCT, total bilirubin, and AST.[5] Bile acid concentrations have not been shown to be significantly increased in most cows with fatty liver.[5] Many cows with hepatic lipidosis have leukopenia and a degenerative left shift, but this is not specific. As expected, non-esterified fatty acid (NEFA) levels will be increased, and triglycerides and cholesterol will be decreased. Most of the total cholesterol is in lipoproteins. The sulfobromophthalein dye excretion test may be useful prognostically because those with a half-life longer than 9 minutes have a more guarded prognosis.[6] Measurement of serum paraoxonase 1, an enzyme exclusively synthesized by the liver, was recently assessed for its ability to diagnose hepatic lipidosis and showed promising results.[7] Decreases in some amino acids, such as glycine and glutamine, can also be observed with increasing severity of hepatic lipidosis.[8]

Several recent studies have examined ultrasound as a tool to detect hepatic lipidosis in cattle. With increasing fat accumulation in the liver, an increased gray level (hyperechogenicity) is seen in the ultrasound image, and the liver appears brighter. Overall, hepatic vessels seem to be smaller. However, this is subjective and is also dependent on the settings of the machine. One study found that the liver increases in size and becomes rounded with increasing severity of lipidosis; however, measuring the thickness of the liver and angle of the ventral margin had limited diagnostic value.[9] Another study used digital analysis of hepatic ultrasound images via a computer-aided ultrasound system and found that imaging findings correlated well with liver triacylglycerol concentrations.[10] Digital analysis of B-mode liver images used a computer program to correct for abdominal wall effects and removal of artifacts. Although not commonly available at this point, the use of ultrasound and computer-aided correction has the potential to help determine the severity of hepatic lipidosis and to estimate with high accuracy the triacylglycerol content of the liver.[11]

Although clinical chemistry and ultrasound may be helpful in diagnosing hepatic lipidosis, a liver biopsy is the gold standard. Liver biopsy may confirm the fatty infiltration of the hepatocytes, but a moderate to high amount of fat is present in the liver of all postparturient, high-producing dairy cows, even those

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that remain healthy.[12] Fat is usually quantified using histologic methods by determining percentage of hepatocytes containing lipid vacuoles, measuring total hepatic fat on a wet-weight basis, or floating in copper sulfate solutions of various specific gravity (to estimate total fat on a wet-weight basis).[13] Classification schemes characterizing severity of hepatic lipidosis based on percentage of hepatocytes containing fat vacuoles have been presented (e.g., <50%, 50% to 75%, and >75% being equal to mild, moderate, and severe lipidosis, respectively).[4] More recent studies have advocated the use of triacylglycerol analysis on a wet-weight basis to differentiate degrees of hepatic lipidosis.[3] These studies categorized hepatic lipidosis as normal, mild, moderate, and severe by triacylglycerol concentrations of less than 1% (<30 mg/g), 1% to 5% (30 to 50 mg/g), 5% to 10% (50 to 100 mg/g), and greater than 10% (>100 mg/g), respectively.[3] At present, triacylglycerol analysis of hepatic tissue is not a routine procedure in veterinary diagnostic laboratories, so total hepatic fat concentrations remain the gold standard for laboratory diagnosis. A recent study evaluated the correlation between cytology of the liver biopsy and triglyceride concentration. The study showed that hepatic triglyceride concentration could be estimated with better accuracy by making touch imprint preparations of liver biopsy specimens than by measuring BHBA or NEFA.[14] Clinically, little correlation exists between the amount of hepatic fat and signs of disease until the fat is more than 34% wet weight, at which point the liver tissue will float in distilled water with a specific gravity of 1.000.

Generalized obesity is noted at necropsy unless the animal has been sick for more than 1 to 2 weeks. Changes in the liver are most striking; it is enlarged with swollen and rounded edges, is pale yellow in color, and may float in water. Histologically, there is fatty infiltration of the hepatocytes, especially in the centrilobular and intermediate areas. However, these liver tissues are sometimes not much different from those of healthy, high-producing dairy cows in early lactation.

■ Pathophysiology

Storage of excess energy as fat and the periodic mobilization of fat for use as energy by the body is crucial.[2,3] The liver plays a major role in lipid metabolism and must process the absorbed chylomicrons, the volatile fatty acids, and many of the fatty acids and much of the glycerol obtained by mobilization of fat from adipose tissue (Fig. 33.8). The liver of large herbivores has unique functions

because much of the dietary energy is absorbed as volatile fatty acids and not glucose. Glucose is still needed (in high amounts in lactating animals) and must be produced by gluconeogenesis, 85% of which takes place in the liver.[15]

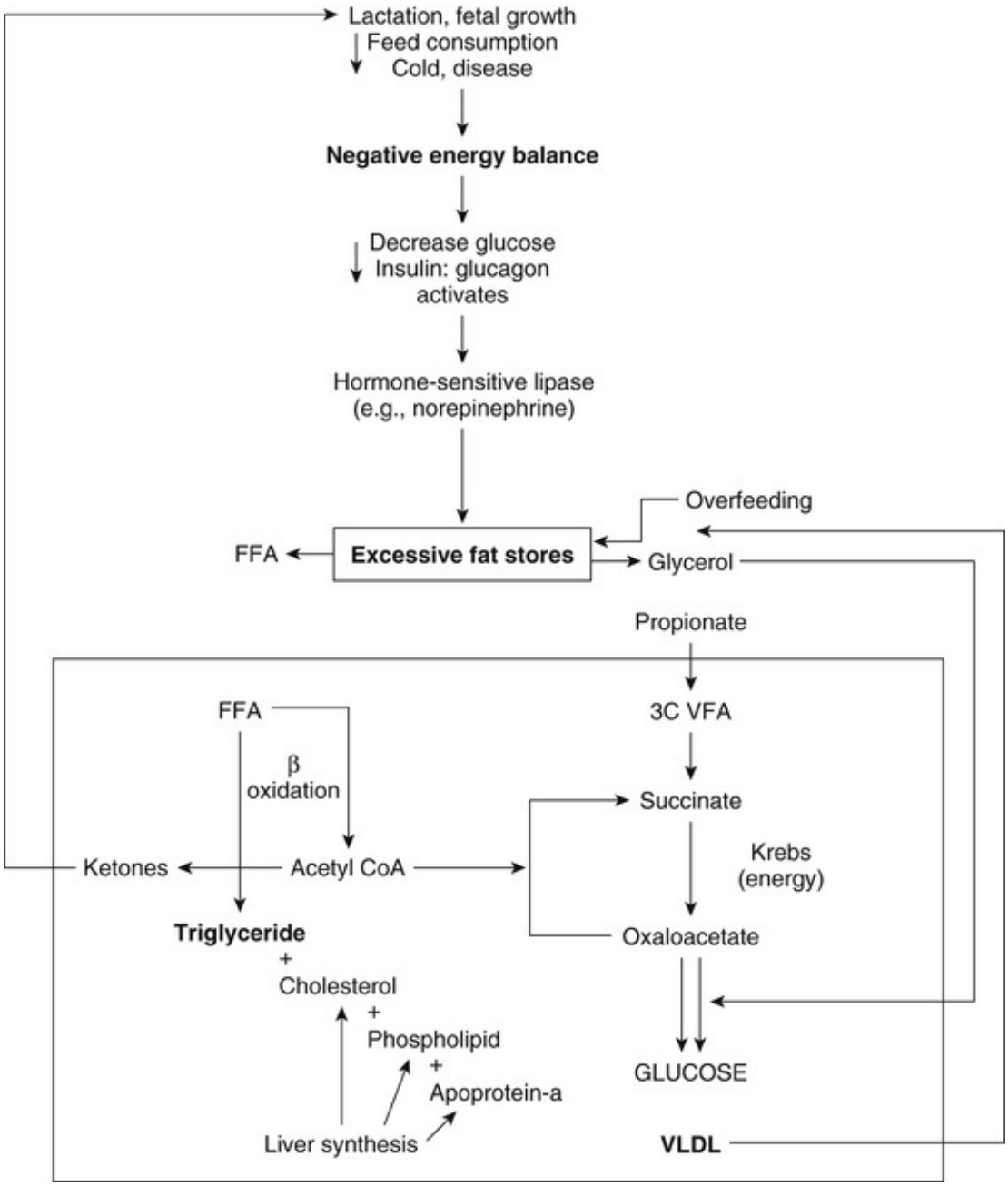


FIG. 33.8 Metabolism of fat in animals with hepatic lipidosis. *3C VFA,* Volatile fatty acid; *CoA,* coenzyme A; *FFA,* free fatty acid; *VLDL,* very low-density lipoprotein.

Negative energy balance is induced by lactation, fetal growth, exercise, decreased feed consumption, environmental chilling, and diseases (Fig. 33.9). During these periods of negative energy balance and before lactation, blood glucose may drop slightly, the insulin/glucagon ratio drops, and these and other hormones (e.g., catecholamines, growth hormone) activate hormone-sensitive lipases that convert tissue fat to free fatty acids (FFAs) or NEFAs and glycerol (Fig. 33.10). After a 4-day period of fasting in cattle, plasma insulin concentrations decreased and insulin-stimulated blood glucose reduction was decreased as compared to cows that were not fasted.[16] In this study, insulin response was negatively correlated with plasma NEFA and liver triglyceride concentrations, suggesting that decreased insulin response may be an important complication of negative energy balance. In the liver, the glycerol may be used to produce glucose or may be recombined with FFAs to make triglycerides (TGs). In addition to being recombined with glycerol to make TGs, the fatty acids may be degraded through β-oxidation, and the two carbon fatty acids converted to acetyl coenzyme A (CoA). The acetyl CoA combines with oxaloacetate to enter the tricarboxylic acid (Krebs) cycle for the production of energy. This pathway is in competition with the use of oxaloacetate for gluconeogenesis.[2] If there is not enough oxaloacetate available, the acetyl CoA is converted to ketone bodies, which in high concentrations can reduce feed consumption and perpetuate the negative energy balance.

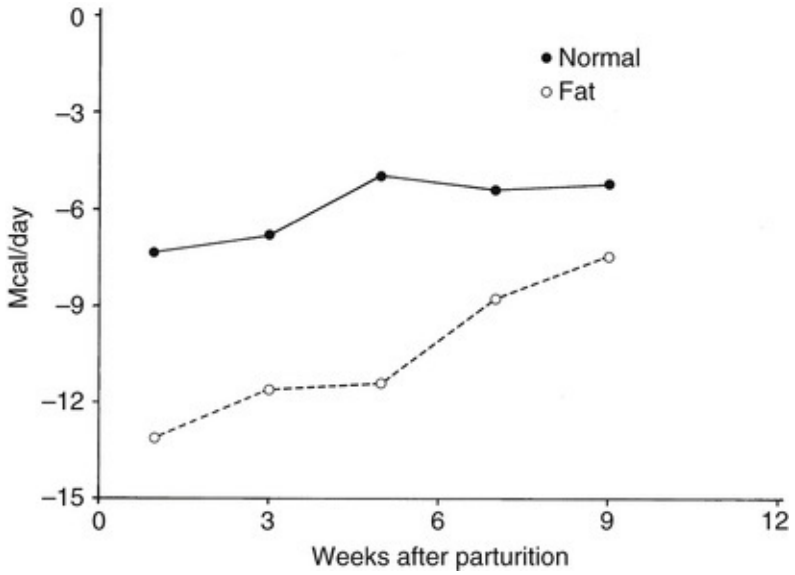


FIG. 33.9 Energy balance (megacalories per day) in normal-condition and

obese dairy cows after parturition. (From Perkins B: PhD thesis. Cornell University, Ithaca, NY, 1983.)

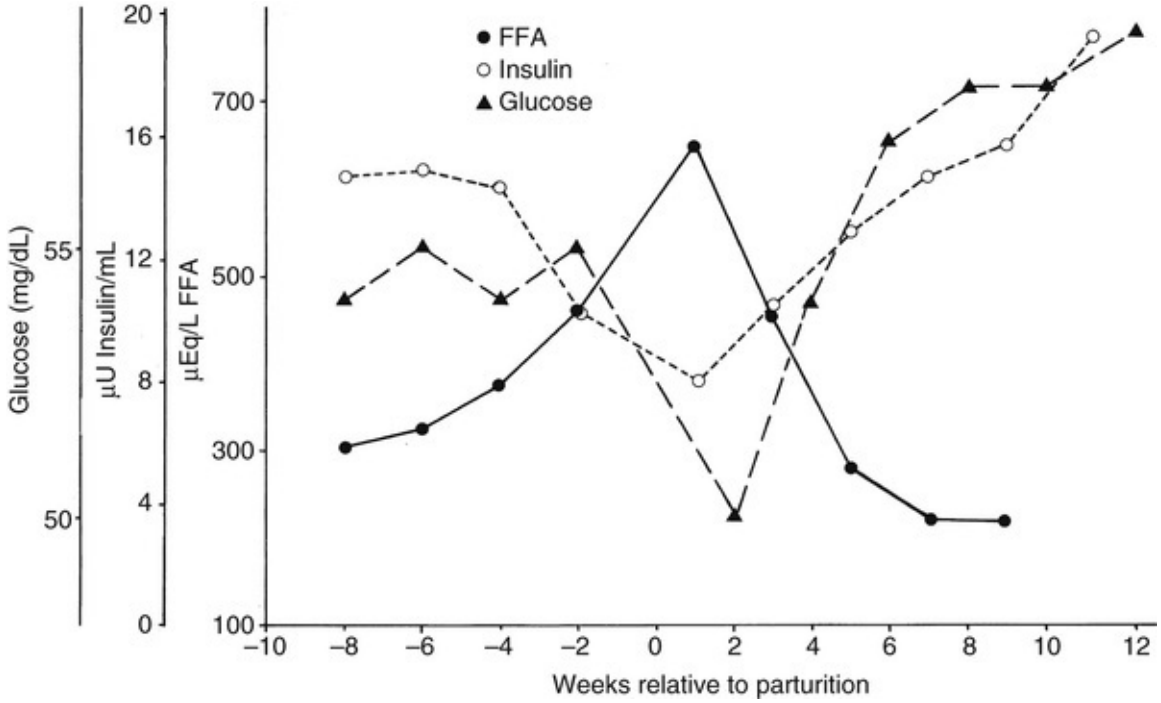


FIG. 33.10 Plasma levels of glucose, insulin, and free fatty acids *(FFA)* in dairy cows before and after parturition. (From Perkins B: PhD thesis. Cornell University, Ithaca, NY, 1983.)

When the liver is overwhelmed with mobilized NEFAs, greater amounts of TGs are deposited within the hepatocytes. These TGs eventually leave the liver as very low-density lipoproteins (VLDLs), which are plasma-soluble complexes of phospholipid, cholesterol, TG, and apolipoprotein A. Hepatic lipidosis results when the rate of hepatic triglyceride formation exceeds oxidation of fatty acids and the formation and release of VLDLs into the peripheral circulation. A number of factors have been incriminated in the inability of the liver to secrete adequate VLDLs to keep up with the deposition of TGs brought about by FFA mobilization from fat. Ruminants have a poor ability to export excess lipid from the liver as VLDLs. This is particularly true in bovine hepatic lipidosis[17,18] and is theorized to result from a shortage of apolipoprotein A. Hepatic lipidosis can be induced in cows by inhibiting the production of apolipoprotein,[19] and the lowest concentrations of lipoproteins occur in the serum of cows with the most

severe hepatic lipidosis.[18] Cows on low-protein diets in the dry period are more likely to develop hepatic lipidosis than those on higher protein diets, regardless of the energy content.[17] Depression in dry-matter intake in the final week before calving will increase the liver TG content after calving in dairy cows.[20] Hepatic lipidosis can be consistently reproduced experimentally in cattle by limit feeding or fasting overconditioned cows immediately after calving.[2] In the past, a lack of phospholipid or its precursor choline has been incriminated but never substantiated. However, in the face of an energy shortage, it seems redundant and a waste of energy to repackage fat and send it back to the tissues, even if the liver is being overwhelmed with fatty acids. Some of the same endocrine hormones that activate hormone-sensitive lipase and inhibit lipogenesis and glycogen synthesis may also inhibit production of VLDLs.

It has also been suggested that subclinical liver damage may inhibit the production of VLDLs, but experimental studies have indicated no significant elevation in liver-specific enzymes before lipid accumulation.[12] Function may eventually be impaired by the accumulation of fat, because fasted cows have a decrease in the surface area of rough endoplasmic reticulum and the number of mitochondria per unit volume.[21] Changes in the liver seem to be functional and not degenerative.[22] Hepatic lipidosis appears to be a reversible condition if the cause is removed and energy balance becomes positive (less negative). In cows fasted and then returned to full feed, all major liver functions returned to normal within 18 days of refeeding, and all lactating dairy cows with postparturient hepatic lipidosis had normal liver fat content (<15%) at 6 months after calving.[21]

All high-producing dairy cows have increased amounts of fat (15% to 32% by weight) in the liver before calving and during the first few weeks after parturition.[12,22] These fat accumulations in the liver begin before calving as the animal prepares for lactation, and the blood glucose concentration is actually lower before calving.[23] The amount of fat in the liver depends on the amount available and the extent of negative energy balance. Fatter cows tend to lose weight more rapidly and have more fat accumulation in the liver.[9]

■ Treatment

Treatment of mild to moderate fatty liver closely parallels that of traditional ketosis. With severe hepatic lipidosis, the most important principle of therapy is elimination of negative energy balance and the factors or diseases causing it.

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Continual IV glucose at a rate of approximately 100 to 200 mg/kg/h may provide continuing energy and induce an insulin/glucagon ratio that will decrease hormone-sensitive lipase mobilization of fatty acids and stimulate production of VLDLs. Insulin itself may be given to alter this ratio directly. In cattle, 200 IU of protamine zinc (NPH or Lente) insulin has been given every 12 hours per 1000 pounds of body weight, along with glucose. In cattle not on a continuous drip of glucose, the clinician must use insulin with caution because even low doses can result in profound hypoglycemia. Administration of glucagon at doses of 7.5 to 15 mg/day has been shown to increase glucose and insulin concentrations and decrease plasma NEFA and liver triacylglycerol concentrations,[24] but clinical use of glucagon is prohibitively expensive. Cows with severe ketosis are generally treated with glucocorticoid injections (10 to 30 mg of dexamethasone, 2 to 5 mg of flumethasone, or 100 to 200 mg of prednisolone) and with glucose precursors such as propylene glycol, glycerol, or other compounds that can be administered orally or parenterally.[3]

Precursors of lipoproteins such as choline, which is a component of phospholipid, have been advocated to increase the rate at which TGs leave the liver as phospholipids (VLDLs), but no controlled studies have proved their efficacy. Choline is degraded in the rumen,[25] but theoretically, choline chloride (25 g in 250 mL of sterile saline) given subcutaneously could have limited efficacy. Choline should *not* be given intravenously because it acts as a neuromuscular blocking agent. Rumen-protected choline fed (45 g/day to 75 g/day) from 21 days prepartum to 60 days postpartum has shown a decrease in liver capacity to accumulate NEFA and increased glycogen liver content. There were trends for increased milk yields, fat and 3.5% fat milk-correction, but no significant increase.[27] Addition of inositol both before and after birth did not reduce the incidence or severity of hepatic lipidosis.[26] Methionine at 40 to 50 g/day has also been used for the same purpose. Nicotinic acid (niacin) fed at 6 to 12 g/head/day may help reduce lipolysis at the tissue level and thus reduce the amount of fat presented to the liver.[28] Treatment of hepatic lipidosis with nicotinic acid is often associated with a rebound of clinical signs, and its use as a preventive measure is recommended.

Despite the treatments listed previously, it is imperative to get cows suspected of having fatty liver eating again. Everything possible should be done to encourage dry-matter intake. Appetite can sometimes be enhanced by transfaunating with rumen fluid from a normal cow. This may increase the

absorption of volatile fatty acids used for energy and for glucose precursors. Prognosis must be guarded unless the concurrent diseases can be treated successfully and the liver fat mobilized. It is most important to treat the primary disease. Reducing the negative energy balance and treating the hepatic lipidosis must be attacked vigorously.

■ Prevention

Prevention is based on preventing overconditioning during the late lactation period and dry period and treating periparturient diseases in a timely manner. Hepatic lipidosis and associated conditions are most common in dairy cattle. Preventing obesity in cows during late lactation is an important factor in controlling this disease. This process involves a successful breeding program (maintaining a 12- to 13-month calving interval), monitoring body condition (calving, breeding, mid-lactation, and dry periods), and closely matching energy in the ration to the level of milk production during late lactation. Once the cow reaches 7 months of pregnancy and the dry period, any dietary restriction below requirements for maintenance and pregnancy are certain to be counterproductive.

Prevention of hepatic lipidosis involves minimizing or eliminating the primary risk factors associated with disease both pre- and postpartum. The primary prepartum risk factors for fatty liver include obesity (body condition score ≥4.0), severe feed restriction, feeding excess energy, and long calving interval. Postpartum risk factors include other concurrent diseases, anorexia or fasting, feed restriction, and sudden feed changes.[3] Adequate protein in the dry period is essential.[15,19] It has been shown that cows fed higher protein diets during the dry period will perform better in the lactation that follows. Feeding good- to excellent-quality roughages (hay, silages) to meet most of these requirements is preferred. Additional grain 2 to 4 weeks before parturition is important to acclimate the ruminant to anticipated changes in the rations fed after calving. It must be stressed that high-quality dry cow rations be fed *but not overfed.* Dry-matter consumption should be limited to approximately 2% of body weight per day while meeting requirements. Other factors in the dry cow ration also must be considered to prevent periparturient diseases such as milk fever, displaced abomasum, mastitis, metritis, ketosis, ruminal lactic acidosis, and retained placenta. Rations should be adequately supplemented with cobalt, the precursor of vitamin B_{12} that is a cofactor in the rate-limiting step in conversion of propionate (the primary glucose precursor) to succinyl CoA. Nicotinic acid has

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been included in the dry cow ration at 6 g/head/day and in the early-lactating cow ration at 12 g/head/day to aid in the prevention of ketosis, which is a major risk factor for the development of hepatic lipidosis. The use of monensin in the dry cow ration and the early-lactation ration shows promise to aid in preventing ketosis and thus may be of some benefit in preventing hepatic lipidosis.[29,30] Other approaches such as sodium borate or administration of glucose precursors in the dry period have also been attempted.[3]

Immediately and aggressively treating cows (particularly obese cows) for other diseases that occur after calving is important in preventing fatty liver. This includes both infectious diseases (e.g., mastitis, metritis) and metabolic diseases like hypocalcemia. It is important to limit stress on fresh cows and provide adequate bunk space, good ventilation, and high-quality feed. Anything possible to encourage dry-matter intake is important. Several different therapies have been promoted to improve the metabolic state of cows during late gestation by supplying an extra source of glucose and decreasing the mobilization of NEFAs from fat. For example, subcutaneous injections of glucagon beginning 2 weeks prior to calving increased glucose and insulin concentrations and decreased plasma NEFA levels in a model of hepatic lipidosis.[31] Feeding an oral drenches of 1 L/day of propylene glycol for the last 10 days prior to calving also increased glucose and insulin level with decrease in NEFA and BHBA concentrations.[3,32] Slow-release doses of insulin (0.14 IU/kg) have also shown some efficacy in preventing triacylglycerol accumulation in the liver, but higher doses (0.29 IU/kg) can result in profound hypoglycemia.[33] Growth hormone had no beneficial effect.[34]

Protein-Energy Malnutrition and Pregnancy Toxemia of Beef Cows

Protein-energy malnutrition (PEM) and pregnancy toxemia of beef cows are conditions of pregnant beef cattle on marginal diets, usually occurring in the winter and characterized by weight loss, weakness, depression, and sometimes inability to rise. The condition is the result of the negative energy balance caused by decreased quality and quantity of feed when caloric requirements are increased by fetal development and cold weather. Growing, pregnant heifers are especially susceptible because energy requirements for growth are superimposed on the other caloric requirements. A number of other factors, such as unpalatable

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feed, snow cover, and diseases, may reduce caloric intake. Fatty infiltration of hepatocytes occurs transiently in early PEM, and at necropsy the liver is smaller than normal.

Animals are usually thin and have a long hair coat. In some cases, they are down and unable to rise but are still alert. The body temperature may be normal or subnormal. Occasionally the cows also develop diarrhea. Most animals die 7 to 14 days after becoming recumbent.[35] Differential diagnosis includes Johne's disease, lymphosarcoma, parasitism, chronic pulmonary disease, other deficiencies, and debilitating diseases.

■ Diagnosis

Diagnosis is usually based on demonstrating decreased caloric intake and ruling out other chronic diseases that could cause debility. Laboratory tests support but do not rule out the disease. Total serum calcium may be decreased. Packed cell volume also may be decreased, and serum insulin levels may be reduced. Ketonuria is not typical in PEM. At necropsy, muscle mass usually is decreased. Serous (brown) atrophy of fat is often present, especially in the coronary groove, bone marrow, and perirenal areas. Lesions of concurrent disease also may be found if PEM is acute, and a fatty yellow liver may be noted.

■ Treatment

Treatment is often unrewarding. Efforts to reverse an advanced catabolic state may fail. A 454-kg cow requires 13 Mcal of metabolizable energy daily, or approximately 6.5 L of 50% glucose solution by continuous drip. Alfalfa pellet gruels are helpful if force-fed, and approximately 11 kg/day of alfalfa is recommended. Propylene glycol (150 to 200 mL) orally twice daily can be helpful as a glucose precursor. Treatments include IV fluids, improving the energy balance, and treating any concurrent disease.

■ Prevention

Nutrient requirements increase greatly for beef cattle during the third trimester of pregnancy. As forage quality (digestibility) decreases, the time feed material stays in the rumen increases (increased rumen turnover time). Therefore as quality decreases, the maximum dry-matter intake (DMI) decreases, which greatly decreases the maximum nutrient (energy) intake. This compounding effect of poor-quality forage on maximum intake is particularly important for

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preventing hepatic lipidosis and the accompanying protein-calorie malnutrition (PCM) of pregnant beef cattle in the winter. The approximate maximum DMI of forage of poor quality (oat straw, corn stover), medium quality (meadow grass hay), and excellent quality (alfalfa hay [25% crude fiber], corn silage) is 1% to 1.5%, 2%, and 2.5%, respectively. Environmental temperature can increase energy needs for beef cattle on pasture or range; as the temperature falls from 20° C (68° F) to 10° C (50° F), roughly 10% more energy is necessary for maintenance, and at freezing temperatures, 0° C (32° F), 20% additional energy is required. The key to preventing PEM in pregnant beef cattle is adequate body condition (scores of 5 to 7) entering the third trimester and availability of good-quality to excellent-quality forage in adequate amounts.

Pregnancy Toxemia in Ewes and Does

Pregnancy toxemia, also known as *ketosis* or *twin lamb disease*, is a condition that occurs in ewes and does during the last 2 to 4 weeks of gestation. It is characterized by anorexia, weakness, and depression. Nearly 80% of the fetal growth occurs in the last 6 weeks of gestation, which can result in a negative energy balance occurring from the increased energy demands of rapid fetal growth in late gestation and insufficient feed intake. The incidence of pregnancy toxemia is greater in ewes with more than one fetus, during the last 2 to 4 weeks of gestation, and in does with three or more fetuses.[36] Poor-quality feed, cold weather, lack of exercise, and stress of movement during the period at risk also may increase the incidence. Overweight animals are also more likely to suffer from negative energy balance and develop the disease. Does seem to be more resistant to pregnancy toxemia than ewes, in that three or more fetuses are usually required to produce the condition. Prevalence in the herd varies from less than 5% to up than 20% in some herds, depending of the predisposing factors and nutritional state.

Initial clinical signs include partial to complete anorexia and separation from the rest of the flock or herd. The disease will progress to severe depression and recumbency. Neurologic signs such as tremors, star-gazing, incoordination, circling, blindness, and grinding the teeth may precede terminal depression. If untreated, animals will appear comatose in lateral recumbency and will die shortly after developing neurologic signs. Differential diagnosis includes other periparturient diseases, such as mastitis and hypocalcemia, as well as polioencephalomalacia, enterotoxemia type D, and toxicoses.

■ Diagnosis

Ketonuria is usually present and detected before ketonemia. Hypoglycemia is not a consistent finding but is sometimes present. Some authors associated sudden hyperglycemia in previously hypoglycemic goats suffering from pregnancy toxemia with death of the fetus.[37] Affected ewes and does often are generally acidotic and may have lowered serum calcium and potassium levels.[38] Blood urea nitrogen (BUN) and creatinine levels are elevated terminally in some cases. Fatty acid concentrations in the plasma are usually elevated above 500 µEq/L. Serum β-hydroxybutyrate (BHB) concentrations are elevated (>1 mmol/L) using electronic on-farm test in goat and sheep.[39-42] A nonspecific but marked neutrophilia may be found in some affected animals and is particularly dramatic in does, sometimes reaching 35,000 neutrophils/µL.

■ Treatment

Treatment of pregnancy toxemia is based on two principles: (1) administering exogenous energy sources (i.e., glucose) and (2) removing the factors increasing the energy demand on the animal (i.e., fetuses). Mortality is high unless treatment is started early and the fetuses are removed—the most important step—either by inducing parturition or by cesarean section. Parturition can be induced in ewes with 15 to 20 mg of dexamethasone; in does the dose is either 10 mg of dexamethasone or 10 µg of prostaglandin $F_{2\alpha}$.[42,43] A cesarean section may be performed if the animal's value warrants it and there does not seem to be enough time to induce parturition. Besides removing the fetuses, the ketotic condition should be treated with IV glucose (250 to 500 mL of 10% to 20% glucose as an IV bolus followed by a slow IV drip of 5% to 10% glucose). Acidosis and hypocalcemia must be corrected if present. Administration of oral propylene glycol as a glucose precursor has also been advocated. Although recommended doses vary, an initial treatment of two doses (150 to 200 mL) given at a 12-hour interval followed by 60 mL per dose thereafter for 3 to 6 additional days appears to work well.[43] Giving recombinant bovine somatotropin at a dose of 0.15 mg/kg of body weight also has shown some benefit.[44] The energy intake must be increased. If the ewe is down and unable to stand, removal of the fetuses should be performed by cesarian section as soon as possible. In such cases the prognosis is often poor, so euthanasia of the ewe or doe must be considered. Immediately after parturition or cesarian section, the animal should

be started on broad-spectrum antibiotics along with flunixin to prevent metritis.[43]

■ Prevention

Preventing pregnancy toxemia and the associated severe hepatic lipidosis in ewes and does requires measures similar to those outlined for PEM in beef cattle. Both overconditioned and thin ewes and does in the third trimester of pregnancy are at increased risk. Because of the common occurrence of twins and triplets, nutrient requirements for pregnant ewes greatly accelerate during this period. Good-quality to excellent-quality forage for feeding sheep is very important. An additional tool for diagnosing underfeeding in ewes and goats is measurement of plasma BHB during the last month of pregnancy.[45] This test greatly facilitates assessment of nutritional inadequacy in pregnant ewes. Plasma BHB concentrations of 0.8 mmol/L or higher are diagnostic of the need for increased energy consumption by pregnant ewes. Does have been shown to have a significant decrease in blood pH, bicarbonate concentration, and base excess values well in advance of the clinical signs associated with pregnancy toxemia.[38] Therefore these parameters could also be early indicators of disease in pregnant sheep or goats. Measures of the cardiac biomarker troponin I could also be used as a prognostic indicator in sick goats prior to cesarean section.[46]

Hyperlipemia and Hypertriglyceridemia in Ponies

Hyperlipemia is a life-threatening condition that occurs in horses, ponies, and occasionally donkeys.[47-49] It is characterized by a fatty liver and serum that is cloudy with accumulation of lipids. Triglycerides are usually much higher than 500 mg/dL.[47] The condition is caused by decreased caloric intake, which causes fat mobilization and fat accumulation in the liver and accumulation in the plasma. The decreased food intake may be secondary to other diseases. Suggested predisposing factors include hypophagia, pregnancy, or lactation, often in obese ponies, American Miniature horses, or donkeys.[48-50] The incidence of hyperlipemia is greater in ponies than in horses. It is seen more often in the winter, especially from February to May in animals receiving poor feed. Pregnant animals and those that are lactating are affected more frequently.

Equine hyperlipemia is characterized by production of an abnormal VLDL

fraction ($VLDL_1$) that has a reduced content of apolipoprotein B-100 and an increased content of apolipoprotein B-48.[51] The substitution of B-48 for B-100 is thought to allow greater TG content because B-48 is the apolipoprotein of importance in chylomicrons. The activities of lipoprotein lipase and hepatic lipase, the enzymes responsible for VLDL catabolism, were increased in hyperlipemic ponies.[51] It was concluded that overproduction of VLDL is the cause of hyperlipemia, possibly complicated by defective catabolism.

Hyperlipidemia is a mild condition of ponies and horses characterized by mildly elevated TG concentrations (100 to 500 mg/dL), clear plasma, and no evidence of hepatic dysfunction.[47] An increase in caloric intake is usually sufficient to reverse the condition. The more severe condition, hyperlipemia, is discussed further.

■ Clinical Signs

The clinical signs of hyperlipemia are nonspecific. Ponies usually are anorexic, depressed, weak, and uncoordinated. Diarrhea, colitis, cachexia, ventral edema, and abdominal pain are frequently seen in presenting cases.[52,53]

■ Diagnosis

Definitive diagnosis is based on an increased level of circulating TGs (>500 mg/dL). Gross examination of the blood and plasma to detect the white to yellow opacity caused by the presence of lipids is a fast method to evaluate the presence of lipemia. TG level and presence of gross lipemia and clinical disease are used to differentiate between the types of hyperlipidemias in horses. Those values are summarized in Table 33.8. Bilirubin usually is elevated, as in most horses that are fasted. Fatty acids are also increased. Bromosulfophthalein clearances are delayed and, terminally, a large base deficit may be caused by metabolic acidosis.[47]

TABLE 33.8

Types of Hyperlipidemias in Horses

Equine Hyperlipidemias	Serum Triglyceride Concentration	Presence of Gross Lipemia in Serum Sample	Fatty Infiltration of Organs	Clinical Disease	Breed Affected
Hypertriglyceridemia	>100 mg/dL	No	No	No	All
Hyperlipidemia	<500 mg/dL	No	No	No	All

Severe hypertriglyceridemia	>500 mg/dL	No	Rare	Rare	Large-breed horses
Hyperlipemia	>500 mg/dL	Yes	Yes	Yes	Predisposed: ponies, miniature horses, donkeys Rare: large-breed horses

Modified from McKenzie H: Equine hyperlipidemias. *Vet Clin Equine* 27:59-72, 2011.

Postmortem examination reveals fatty infiltration of the liver and kidneys, which are pale and swollen and have a greasy texture. In ponies the liver is sometimes ruptured, resulting in intraabdominal hemorrhage and death. Renal lesions may be seen histologically. There may be a primary disease that produces anorexia and secondarily has resulted in hyperlipemia.

■ Treatment

It is most important to treat any primary disease to alleviate the cause of anorexia and correct the negative energy balance. Resting energy requirements of a sick, hospitalized horse have been estimated at 22 to 23 kcal/kg/day.[53] Nutritional support is critical, in the form of either dextrose-supplemented fluids or partial parenteral nutrition. Oral supplementation using a 60-mL dose of corn syrup (4 kcal/mL) given orally every 2 hours will provide around 5 kcal/kg/day to a 500-kg horse and is usually well tolerated.[53] Heparin is also recommended in some cases and has been shown to decrease triglyceride concentrations in affected horses.[52] Regular insulin (0.2 IU/kg) IM every 3 to 6 hours can be used initially for severely lipemic animals; however, this is usually discontinued within 24 hours and a longer-acting product is used for maintenance. Protamine zinc insulin (PZI) has been used at an IM dose of 30 IU twice daily with 100 g of PO glucose for a 200-kg pony. This is continued on odd days; on even days, IM injections of 15 IU of PZI are given twice daily.[47] Ultralente insulin can be given at a dose of 0.4 IU/kg SC q24h.[52] The use of a continuous rate infusion at 0.07 IU/kg/h with concomitant IV drip of glucose to avoid hypoglycemia can also be used. If the hyperglycemia (>180 mg/dL) is not adequately controlled after 2 to 3 hours at the initial rate, increase the rate by 50%. Further increases can be made; however, it is important to allow the dose to equilibrate over a period of several hours before adjusting the dosage. Close monitoring of blood glucose levels is required while using insulin therapy. Slow IV drip of glucose for several days or until lipemia clears may be indicated. Heparin (100 to 250 IU/kg SC twice daily) has been used to alter the lipoprotein lipase activity and inhibit hormone-

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sensitive lipase of adipose tissue, but it may alter coagulation enough to cause hemorrhage.

The presence of hyperlipidemia is readily detected and easily solved by increasing caloric intake. Although therapy of hyperlipemic ponies and horses is often unrewarding, the diagnosis is relatively straightforward, and prevention depends on providing adequate feed of good quality and avoiding high-stress situations.

■ Prognosis

High mortality rates have been seen with hyperlipemia in ponies and donkeys. Previous studies reported mortality rates between 22% to 80% in hyperlipemic ponies.[54] A recent study from the United Kingdom revealed a mortality rate of 48.5% in donkeys due to hyperlipemia.[55] The donkeys were from a donkey sanctuary, and the disease prevalence was 10.7% over the study period. Development of hyperlipemia was highly associated with the presence of a concurrent disease (odds ratio [OR]: 76.98). Other risk factors associated with development of the disease were cardboard bedding, movement to the sanctuary in the previous 2 weeks, weight loss of more than 10 kg in the last month, dental disease, and concentrate feeding. Even if the prognosis is often grave, decreased mortality rates have been observed when adequate and aggressive treatment is performed.[49]

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Congenital Hyperbilirubinemia

Geoffrey W. Smith

Gilbert's Syndrome

Gilbert's syndrome is an unconjugated hyperbilirubinemia in the presence of normal erythrocyte life span. It occurs occasionally in humans and has been described in Southdown sheep.[1] Gilbert's syndrome involves a failure of unconjugated bilirubin to cross the liver cell membrane and be conjugated. This is most likely due to a defect in carrier proteins or the conjugating enzyme.[2] Hepatic bilirubin clearance is about 30% of normal when tested with a loading dose of radiolabeled bilirubin.[3]

Affected Southdown sheep may show icterus or at least elevated plasma bilirubin levels, both conjugated and unconjugated. Affected sheep also cannot excrete BSP into the bile. No histopathologic lesions are present, other than some pigment in the hepatocytes. The condition is inherited as an autosomal dominant trait in humans.[2] The bile acid levels are normal in humans, but one sheep exhibited defects in hepatic bile acid clearance.[4]

Dubin-Johnson Syndrome

Dubin-Johnson syndrome is a failure of conjugated bilirubin to enter the bile canaliculi. This has been diagnosed sporadically in humans and in Corriedale sheep.[5] There may be an impairment not only in bilirubin but also in excretion of other conjugated organic anions. Sheep affected by this syndrome may be jaundiced or have hyperbilirubinemia. Both conjugated and unconjugated bilirubin are increased, and BSP clearance is delayed. Bile acids are reported to be normal in humans, but delayed clearance was reported in three Corriedale sheep.[4] Histologically, the hepatocytes contain a black, melanin-like pigment.[5]

Persistent Hyperbilirubinemia in Thoroughbreds

A persistent hyperbilirubinemia has been reported in a Thoroughbred racehorse that had no evidence of liver damage, cholestasis, or hemolysis and was not

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fasting.[6] The horse was persistently icteric and had serum total bilirubin concentrations of 8.7 to 9.4 mg/dL; 90% or more of the plasma bilirubin was the unconjugated form. Serum bile acid concentration, along with the liver enzymes GGT, AST, and SDH, were within normal limits. The horse acted clinically normal, and the plasma fatty acid concentration was also within normal limits. The condition was similar to Crigler-Najjar syndrome type 2 in humans, which involves a deficiency in bilirubin uridine diphosphate glucuronyltransferase needed to conjugate bilirubin, but this was not verified.

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Miscellaneous Liver Diseases

Geoffrey W. Smith

Rift Valley Fever

Rift Valley fever, also known as *enzootic hepatitis*, is an acute febrile arthropod-borne disease of sheep, goats, cattle, and humans present in most countries of sub-Saharan Africa. With the current threat of bioterrorism, it could appear in other parts of the world.[1,2] Rift Valley fever is caused by a virus of the genus *Phlebovirus.* More than 20 species of mosquitoes have been implicated as possible vectors for the virus, including some North American mosquitoes that are competent laboratory vectors.[2] The disease causes abortion in pregnant females and a febrile condition with rapid death in lambs, kids, and calves. The mortality rate in young animals approaches 100% but it is much less (20% to 30%) in older animals.[2] Clinical signs may include fever, anorexia, weakness, salivation, diarrhea, and sometimes abdominal pain, and almost all pregnant animals will abort. The primary gross lesion is hepatomegaly and hemorrhage. Histologically, a focal hepatic necrosis is identified, and eosinophilic intranuclear inclusion bodies are present. Confirmation of the diagnosis is made in the laboratory by virus isolation or immune tests. If the disease is suspected, state and federal regulatory veterinarians should be contacted.

Telangiectasia

Hepatic telangiectasia, commonly known as “sawdust livers” in packing houses, is a focal degeneration in liver lobular circulation characterized by red-brown foci 1 to 5 mm in diameter. These lesions account for more than 10% of the bovine liver condemnations but do not result in any clinical signs.[3] Microscopically, hepatocytes are distorted and sinusoids congested.[4] Hypotheses proposed to explain the pathogenesis of the lesions include necrotizing hepatitis, ischemia induced by emboli or other vascular pathologies,[5] dilation of Disse spaces, reduced density of the reticulin framework, vitamin E–selenium deficiency, alteration of the sinusoidal barrier, and immune-mediated disease.[3] Some human pathogens have been isolated from these livers as well as normal

livers, but livers are condemned on the basis of aesthetics according to current U.S. Department of Agriculture (USDA) regulations.[3]

Ischemia, Hypoxia, and Congestion

Ischemia and hypoxia can lead to death of hepatocytes, but less severe insults cause fatty infiltration because lipoprotein synthesis depends on oxidative metabolism. This damage is more apparent in the centrilobular areas, which are the last to receive blood and oxygen. Chronic passive congestion causes the grossly visible “nutmeg liver” caused by distention of the sinusoids and central veins with blood. The liver may be enlarged in these cases, but other signs related to the liver are not usually present. More significant findings will be detected in the cardiovascular system.

Fetal Liver Damage

The liver of the fetus may be damaged by infectious and toxic agents, but the result is usually abortion or birth of a weak neonate with signs related to other systems. The lesions in the liver may be diagnostic of the disease. Equine herpesvirus infection of the fetus causes hepatocyte necrosis, with acidophilic intranuclear inclusion bodies in more than 50% of the hepatocytes. Aborted fetuses of cattle with infectious bovine rhinotracheitis may have some focal necrosis of the liver, but this is not enough to be diagnostic.

Failure of Drug Metabolism and Excretion

Jennifer L. Davis

Hepatic disease can affect drug metabolism in several ways. Ascites, if present, can alter drug distribution, and drug dosages should be adjusted based on lean body weight, estimating the amount of fluid present.[1] Also, since the liver is the primary organ involved in the metabolism of exogenously administered substances and represents an important method for excretion of drugs via the bile, liver disease can affect drug metabolism and clearance.

Factors influencing hepatic drug metabolism and clearance include hepatic blood flow, hepatic metabolism, and protein binding. Drugs are often classified as having high hepatic extraction ratios (flow-limited drugs) or low hepatic extraction ratios (capacity-limited drugs). Flow-limited drugs are quickly and

efficiently extracted by the liver, and their rate of elimination is limited only by hepatic blood flow. Chronic liver disease with decreased parenchymal blood flow or hepatic shunts can decrease blood flow in the liver and greatly compromise clearance of flow-limited drugs like morphine, verapamil, and lidocaine.[1] These drugs undergo a high first-pass metabolism following oral administration and, as such, are usually given at high oral doses. The dosage of these drugs may need to be decreased by up to 50% in patients with liver disease because bioavailability will be greatly increased and elimination decreased, possibly resulting in toxic levels of the drug.[1,2] The opposite may be true for drugs that require hepatic activation (prodrugs), and thus subtherapeutic levels may be present.[3]

Capacity-limited drugs are slowly extracted by the liver, and their elimination is independent of blood flow but highly dependent on hepatocellular uptake and metabolism. The effect of liver disease on drug metabolism in these cases is more variable, and drug clearance can be increased, as with atenolol, or decreased, as with diazepam and chloramphenicol.[1,2] The majority of phase I (oxidation-reduction) reactions and phase II (glucuronidation) reactions take place in the hepatocytes, and diseases that result in hepatocellular destruction can reduce the ability of the liver to metabolize drugs. The purpose of these reactions is to make compounds more water-soluble and prepare them for excretion via the kidney. Clearance of drugs eliminated by phase I reactions can be significantly decreased with hepatic disease, whereas phase II reactions are often not affected unless severe disease is present or certain types of glucuronidation are needed.[4,5] For example, ester glucuronidation will be decreased in patients with cirrhosis of the liver, and drugs cleared via this pathway will have lower clearance rates compared to drugs metabolized by ether glucuronidation.[4]

Humans with intrahepatic cholestasis showed a decreased activity of phase I cytochrome P450 enzymes and impaired microsomal drug metabolism in vitro, and this was well correlated with serum concentrations of total bilirubin and bile acids.[6] Making direct correlations between human drug metabolism and veterinary species is difficult, as there is a large interspecies variation in the types and activity of hepatic metabolizing enzyme among humans, horses, and cattle.[7,8] In addition, polymorphisms within some metabolizing enzymes (i.e., CYP2D50) have been demonstrated in horses, resulting in poor, extensive, and ultra-rapid metabolism of related drugs.[9] Further classification of the equine and

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bovine P450 enzymes and their roles in drug metabolism is needed.

Cholestatic diseases have been shown to decrease biliary excretion of a number of drugs in both animal models of disease and human patients with naturally occurring biliary obstruction. Increased plasma levels, prolonged mean residence times, increased area under the concentration-time curve, and decreased total body clearance have all been demonstrated.[10-12] In horses administered enrofloxacin intravenously, those animals with GGT activity greater than 200 U/L had a lower clearance and higher area under the curve than horses with GGT activity less than 200 U/L.[13] Renal clearance of some drugs may be increased as a compensatory response for the impaired biliary excretion, as is the case with cefpiramide in cholestatic human patients.[14] This decreased biliary clearance can be used to an advantage in certain instances when treating biliary tract infections in order to attain higher concentrations of the drug in the bile ducts, as long as the drug has a large therapeutic index.[14]

A deficiency in hepatic drug metabolism capacity may impair drug metabolism and elimination in young animals. This has been demonstrated in foals administered chloramphenicol, which is extensively metabolized in the liver via glucuronic acid conjugation and primarily excreted through the biliary system into the feces. Clearance was decreased and half-life prolonged in animals less than 1 week of age.[15] Nonsteroidal antiinflammatory drugs (NSAIDs) also show impaired metabolism in neonatal foals. Phenylbutazone, ketoprofen, and flunixin meglumine all have prolonged terminal half-lives over the first few weeks of life.[16-18] Neonatal foals also have a low capacity to metabolize enrofloxacin to ciprofloxacin. Ciprofloxacin was not detectable in foals, whereas in adult horses ciprofloxacin concentrations are about 17% of the enrofloxacin concentrations.[19] Drug metabolism also differs in neonatal calves and sheep, which may result in prolonged withdrawal times necessary for veal calves and lambs. Studies have shown that hepatic metabolic enzymes are similar to adult levels in sheep and calves by 7 days of age.[20,21] At this point, no quantitative research that specifically examines the development of metabolic pathways in the neonatal foal has been performed. It is likely these pathways are decreased in the early stages but rapidly develop and are within a range similar to adult horses within the first 1 to 4 weeks of life, as is seen in other veterinary species.

Neoplasia of the Liver

Geoffrey W. Smith

Primary neoplasia of the liver is uncommon in large domestic species. Only 0.011% of slaughterhouse animals seen in one study had liver tumors.[1] Metastatic tumors such as lymphoma are more common (Fig. 33.11), but the clinical signs of these are more likely to reflect changes at the primary site. Metastasis of lymphosarcoma in cattle is most common, but signs produced by growth in other organs (e.g., lymph nodes, abomasum, heart, uterus, spinal cord) are more predominant. In the horse, lymphosarcomas and carcinomas have metastasized from the digestive tract.[2]

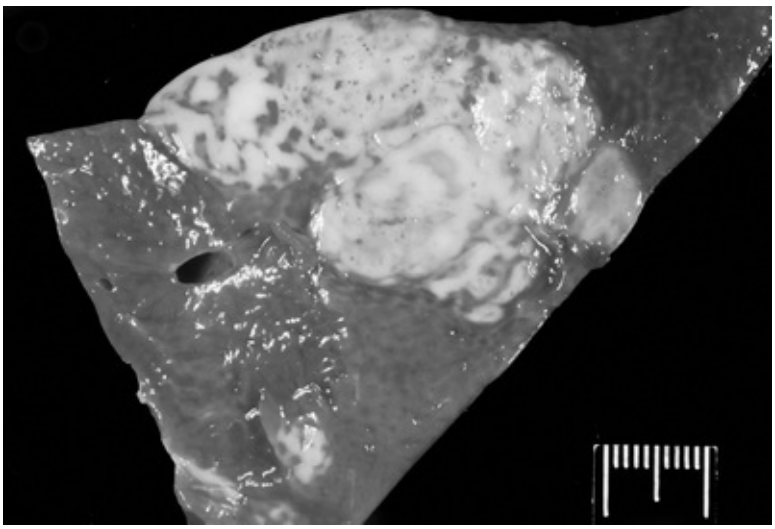


FIG. 33.11 Lymphoma in the liver of a horse. (Photo courtesy Luke Borst, North Carolina State University.)

Horses

Although uncommon, a number of different primary hepatic neoplasias have been reported in horses.[3,4] The nomenclature seems inconsistent throughout the years of reporting, and the signs are usually more consistent with neoplasia in general than with hepatic failure. Weight loss, weakness, anorexia, lethargy, and occasionally colic may be seen in these animals. Serum concentrations of liver-derived enzymes are elevated in many cases. The tumor can often be located by ultrasonography, but the definitive diagnosis of the type of tumor is based on

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histopathologic examination of biopsy tissue.

Hepatoblastoma has been reported in foals, young horses, and an equine fetus.[4,5] Young horses present with weight loss or failure to grow, lethargy, anorexia, and possibly icterus. Serum concentrations of several hepatic enzymes are increased. Ultrasonography reveals hepatomegaly and a heterogeneous appearance of the hepatic parenchyma. Erythrocytosis due to a paraneoplastic syndrome and increased production of erythropoietin is seen in some cases.

Hepatocellular carcinoma is seen in both old and young horses. These horses lose weight and are listless. Serum concentrations of LDH, GGT, and AST are often elevated. Erythrocytosis with a normal concentration of serum protein is seen in most cases as a result of paraneoplastic syndrome with elevated erythropoietin.[3,4,6]

Cholangiocarcinoma or cholangiocellular carcinoma arises from the intrahepatic bile duct epithelium and appears to be a disease of older horses.[4,7] Lethargy, fever, abdominal pain, anorexia, and ventral edema have been reported with this tumor. Hypoglycemia has been associated with hepatic cholangiocarcinoma as a suspected paraneoplastic syndrome.[8] Some of these animals have anemia rather than the erythrocytosis reported with hepatocellular tumors. GGT and ALP concentrations may be elevated, but SDH comes from hepatocytes and is usually within normal range.

Cattle

In addition to the lymphosarcomas, primary hepatocellular carcinomas have been described in cattle.[9] The most common presenting clinical signs are anorexia and weight loss of weeks to months in duration.[10] Liver-derived enzymes are generally elevated, and polycythemia (erythrocytosis) is a common laboratory finding in these cases.[10,11] Ultrasound of the liver may be helpful in diagnosing hepatic tumors in cattle.[10]

Hemochromatosis

Hemochromatosis is a disorder caused by deposition of hemosiderin in the parenchymal cells, resulting in tissue damage and dysfunction of the liver and other tissue. It is most frequently seen in humans and mynah birds, but hemochromatosis has been described as a new disease of Salers cattle[12] and has been reported in three horses.[13] In humans, the types include idiopathic

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hemochromatosis, an autosomal recessive familial condition associated with increased iron stores, cirrhosis, and saturation of the iron transport capacity.[14] Both horses and cattle show increased iron deposits in the liver; histopathology of liver biopsy specimens reveals brown pigment that stains for iron in the hepatocytes as well as Kupffer cells. An increased concentration of iron can be measured in the liver, and there is fibrosis and elevated liver-derived enzymes.

In Salers cattle the condition appears to be a homozygous recessive condition more like the human familial type. There is an inappropriate absorption of iron by the GI tract, with subsequent hepatic storage (iron overload) and eventual loss of hepatic function. It has been reproduced by experimental breeding in Salers cattle.[15] The primary clinical signs in cattle are decreased weight gain, poor body condition, dull hair coat, loss of incisor teeth, and sometimes diarrhea. Serum concentrations of liver enzymes are elevated, and there is marked hepatic fibrosis, in addition to the hemosiderin deposits in the liver. Total serum iron, total iron-binding capacity (TIBC), and saturation of transferrin (>60%) are increased, similar to the familial disease in humans. Liver iron concentration will be greater than 5000 µg/g (ppm) on a wet basis (normal herdmates of affected cattle, 84 to 100 ppm).

Horses with hemochromatosis present with evidence of liver disease. Serum concentrations of the liver enzymes ALP, GGT, and AST are elevated, and serum total bile acids are greater than 40 µM/L. In the cases reported, total serum iron was not elevated, and unlike the idiopathic human condition or the cattle cases, there was no saturation of the iron-binding capacity. Total liver iron has been as high as 6700 ppm (normal, 100 to 300 ppm).[13]

Hemochromatosis should be suspected in animals with emaciation or elevated liver enzymes and in Salers cattle with greater than 60% saturation of transferrin. It can be confirmed by histopathologic examination of the liver, with excessive iron accumulation in hepatocytes. Clinicians should differentiate hemochromatosis from hemosiderosis, in which iron accumulates in the reticuloendothelial system and not hepatocytes, and which can be caused by hemolysis and other conditions.

In humans, hemochromatosis is treated by reducing the iron stores through phlebotomies and blood removal. The one horse on which this was tried had advanced disease with severe cirrhosis, and it succumbed a few days after the blood removal. Removal of 160 L of blood over 12 months failed to reduce liver iron concentration in one heifer[12] but produced some improvement in other

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calves.[15] Deferoxamine is given to some human patients to induce a negative iron balance and reduce the rate at which iron accumulates.

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Gallbladder and Biliary Tract Disease

Jennifer L. Davis

Biliary tract disease in large animal medicine is rare and results from both intrahepatic and extrahepatic causes. Intrahepatic causes of cholestasis include cholangitis, cholecystitis, choledocholithiasis, and presence of a foreign body. Extrahepatic causes include abscess formation, obstructive or inflammatory intestinal disease, and neoplasia.

Choledocholithiasis, Cholelithiasis, and Hepatolithiasis*

By definition, *cholelithiasis* describes the presence of biliary calculi in either the bile ducts or the gallbladder, whereas *choledocholithiasis* describes stones found in the common bile duct. *Hepatolithiasis* indicates the presence of calculi in the intrahepatic bile ducts above the right and left hepatic ducts and is a variation of cholelithiasis. These conditions have been described in horses, cattle, sheep, and pigs, but they do not seem to be recognized as a clinical problem in sheep, and rarely in cattle.[1-15] Choledocholithiasis is the most common cause of biliary obstruction in large animals and occurs more frequently in horses.[1-9]

Biliary stone formation begins with precipitation or aggregation of normally soluble components of bile. Other mechanisms involved in the pathogenesis include ascariasis, ascending biliary infection or inflammation, biliary stasis, changes in bile composition, and presence of a foreign body.[14] Several pathogenic bacteria (*Salmonella* spp., *E. coli*, *Aeromonas* spp., *Citrobacter* spp., group D *Streptococcus* spp., *Clostridium perfringens*) have been cultured from the bile ducts of horses and cows with cholelithiasis.[2,6,9,16] Whether these bacteria were the cause or the result of the stone formation remains unclear. In most reports the chemical analysis has shown that choleliths have a mixed composition, containing bilirubin, bile pigments, cholesterol esters, esters of cholic and carboxylic acid, calcium phosphate, and sodium taurodeoxycholate.[6,8,9] In one study, 80% of the choleliths contained less than 10% cholesterol.[9]

Cholelithiasis should be suspected in horses when a triad of clinical signs exists: recurrent abdominal pain, intermittent pyrexia, and icterus.

Hyperammonemic hepatic encephalopathy, photosensitization, and weight loss are other, less common features of cholelithiasis.[3,5,6,14,16] A subclinical presentation due to partial obstruction of the biliary tree may be recognized only on postmortem examination.[11] A large cholelith was the cause of duodenal obstruction in a horse presented for colic.[12]

Elevations in the serum activity of ALP, AST, GGT, SDH, and total bilirubin are associated with cholelithiasis.[3,6,9,14,16] The rise in total bilirubin is due to an elevation in both direct and indirect bilirubin. Serum bile acid concentrations also increase when bile flow is obstructed. Other laboratory abnormalities that may be seen include hyperammonemia, increased urine bilirubin, and prolonged partial thromboplastin and thrombin times.[5,6,9] The most common alterations in the leukogram include a neutrophilic leukocytosis. Elevations in globulin and fibrinogen may also occur.[5]

Ultrasound examination of the liver is a safe, noninvasive tool for diagnosing cholelithiasis. Hepatomegaly and bile duct dilation are seen in horses with biliary calculi. The echogenicity of the hepatic parenchyma is increased compared with that of normal horses and may approach that of the spleen. The bile ducts are thick and distended. The *parallel channel sign* (dilation of interhepatic biliary radicals adjacent to the portal vein) may also be seen. Several choleliths are generally seen, but a single stone may be present (Fig. 33.12). Choleliths may be hyperechoic, casting acoustic shadows, or they may be sonolucent. Choleliths are most likely to be visualized in the cranioventral part of the right hepatic lobe, especially in the sixth to eighth intercostal spaces. Cholelithiasis can be diagnosed accurately by ultrasound in at least 75% of horses if an adequate scanning image of the liver is obtained and bile duct dilation and choleliths are visualized.[8]

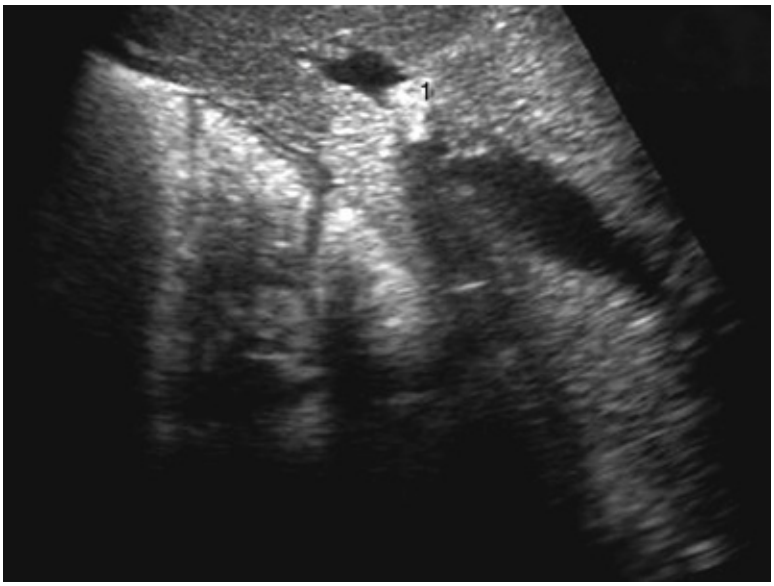


FIG. 33.12 Ultrasound image of a cholelith taken from the right side of a horse. Note the hyperechoic stone *(1)* visible inside a distended bile duct. Hyperechoic parenchyma is also noted beneath the stone, which may represent hepatic fibrosis.

The differential diagnosis for a horse with the clinical signs associated with cholelithiasis include other causes of liver disease and mild recurrent abdominal discomfort, including verminous arteritis, mesenteric abscesses, sand enteropathy, enterolithiasis, abdominal neoplasia, and urolithiasis.[3]

Hepatomegaly is usually noted at necropsy, although a shrunken liver may be observed. The liver is firmer than normal, has a consistent texture, and varies in color from red to green-brown. The hepatic ducts and common bile duct are generally dilated and may contain the calculi (Fig. 33.13). Histologically, periportal fibrosis is a common finding. Bile duct stasis and hyperplasia are usually noted; suppurative cholangitis is less common.[9,14,16]



FIG. 33.13 Multiple choleliths present with the bile ducts of a horse.

Treatment of cholelithiasis initially includes broad-spectrum IV antibiotics (penicillin plus gentamicin or enrofloxacin) and oral metronidazole. This is followed by long-term oral antibiotics, based on culture and sensitivity of a biopsy specimen, if available. If culture and sensitivity results are not available, treatment should be aimed at suspected gram-negative enteric bacteria or anaerobes. Potentiated sulfonamides or enrofloxacin plus metronidazole are good choices. Chloramphenicol has a good spectrum against most cultured bacteria, but since it is highly metabolized by the liver, it should not be used if hepatic function is severely compromised. Antibiotic treatment should continue for 6 weeks past the time when GGT values return to normal. DMSO (0.5 to 1 g/kg IV as <10% solution for 3 to 5 days) has also been recommended as a treatment to help dissolve intrabiliary sludge or small calcium bilirubinate stones. DMSO may cause hemolysis at higher concentrations, and horses with liver disease may already have fragile RBCs, so care should be taken with treatment. Fluid therapy may also help to thin secretions and promote bile flow. Anti-inflammatory drugs (low-dose NSAIDs) are also recommended. Choledocholithotomy and choledocholithotripsy, described in horses, have had limited success.[5-7] The prognosis is related to the degree of hepatic fibrosis,

severity of clinical signs, and number and location of the stones. Recent reports show a 75% to 80% survival rate with medical or medical plus surgical therapy.

Cholangitis and Cholangiohepatitis

Clinical disease of the bovine gallbladder is rare. Obstructive gallbladder disease has been associated with abdominal fat necrosis, choleliths, fascioliasis, foreign bodies, hepatic abscesses, neoplasia, and suppurative cholecystitis.[17,18] Adenomas and adenocarcinomas (most common tumors found in gallbladder), papillomas, and lymphosarcoma (rare) can cause obstruction.[17,19] Rupture of the gallbladder was found on necropsy of a cow in which icterus, anorexia, decreased milk production, and diarrhea had been present.[20]

Cholangitis and cholangiohepatitis may be primary or secondary and can result from cholelithiasis, duodenal inflammation, intestinal obstruction, neoplasia, parasitism, and certain toxins.[21] Sporidesmin, a fungal toxin from *Pithomyces chartarum*, causes cholangiohepatitis in cattle and sheep. Cholestasis and ascending infection resulting in cholangiohepatitis have been noted in horses with primary intestinal diseases such as proximal enteritis, right dorsal displacement of the large colon, and less frequently, left dorsal displacement of the large colon.[22-24] Duodenal strictures secondary to severe gastroduodenal ulceration have also been reported as a cause. Clinical signs associated with cholangitis and cholangiohepatitis in the horse may include anorexia, pyrexia, subtle behavioral changes, chronic weight loss, colic, and icterus. Septic peritonitis may occur as an extension of bacterial infection into the intraperitoneal space.[25] Alterations in hepatic enzyme activity may indicate hepatocellular damage, cholestasis, or both. Histopathologic examination and bacterial culture are indicated to further identify the causative agent. In cases of suspected bacterial etiology, long-term antibiotic therapy is indicated.[25] Antibiotic choice should be based on bacterial sensitivity, but in cases where no bacterial organism is identified, an antibiotic that is effective against enteric organisms and secreted or cleared in the bile is warranted.

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Therapy of Liver Failure

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Antibiotic Therapy

Antibiotic therapy is indicated in cases of cholelithiasis, cholangitis, and cholangiohepatitis, as well as liver dysfunction secondary to systemic diseases causing sepsis in horses. Initial treatment should include broad-spectrum IV antibiotics, such as potassium penicillin plus either gentamicin or enrofloxacin, and oral metronidazole to cover *B. fragilis*. This is followed by long-term oral antibiotics based on culture and sensitivity (if available).[1] If no culture is available, the clinician should suspect gram-negative enteric bacteria with or without concurrent anaerobic infection. Trimethoprim sulfonamide combinations or enrofloxacin plus metronidazole are good choices. Chloramphenicol has a good spectrum against most cultured bacteria, but since it is highly metabolized by the liver, it should not be used if hepatic function is severely compromised. High levels of IV penicillin and an aminoglycoside should be administered to foals with suspected Tyzzer's disease.[2]

Cattle with single or multiple liver abscesses often respond to penicillin therapy, but long-term therapy is required, and there is a significant rate of recurrence of clinical signs after therapy is withdrawn. Echolucent abscesses of small to medium size have the best prognosis. Abscesses with an echodense appearance are difficult to treat. Single large abscesses are best treated by surgical drainage, especially those interfering with vagal nerve function.

Treatment of Hepatic Encephalopathy

Treatment of hepatic encephalopathy (HE) involves treatment of the underlying hepatic disease combined with supportive and palliative care. This includes IV fluids, broad-spectrum antibiotics, and gastroprotectants. Padding and wraps should be provided to help prevent self-trauma. Sedation may be necessary to control behavior or aid in treatments, but many of these drugs are metabolized in the liver, so care should be taken during dosing. Small doses of α_2-adrenergic agonists like xylazine or detomidine are recommended. However, these drugs can cause respiratory depression at higher doses, and hypoventilation may

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aggravate signs of HE. Doses should also be low enough to cause sedation without resulting in prolonged lowering of the head below the level of the shoulder, which may result in worsening cerebral edema. Diazepam and other benzodiazepines should *not* be used; they may enhance the effects of GABA on inhibitory neurons, worsening HE.[3] Based on this, use of the benzodiazepine receptor antagonists has been recommended to lessen HE signs in humans.[4] The overall success of flumazenil in treating HE in humans and dogs has been low, and it has rarely been used in the horse. Sarmazenil, a partial inverse agonist at the benzodiazepine receptor, appears to be more promising for reversing signs of HE in dogs[5] and has been used for treating moxidectin intoxication in a foal.[6]

Dietary management of HE is very important. Liver failure results in increased serum glucagon, and muscle catabolism releases amino acids. At the same time, hepatic metabolism of aromatic amino acids (AAAs) is reduced and accumulation occurs, whereas muscle and adipose tissue can metabolize branched-chain amino acids (BCAAs), resulting in less accumulation. AAAs cross the blood-brain barrier and can act as false neurotransmitters, aggravating signs of HE, so a low-protein diet with a high BCAA/AAA ratio is recommended.[7,8] Low-protein, high-starch feeds include grass or oat hays, beet pulp, cracked corn, milo, sorghum, barley, and oats. Feed small amounts frequently (q2-4h). If affected horses are anorexic, forced enteral or partial parenteral nutrition may be used. Special formulations of amino acids that consist mainly of BCAAs should be used, and lipids should not be added if there is any possibility that lipidosis is present.

Other treatments for HE are designed to reduce intestinal ammonia absorption. Neomycin is an aminoglycoside antibiotic that suppresses enteric ammonia production. Because it is more nephrotoxic than gentamicin and can be irritating to intestinal mucosa (causing diarrhea), treatment duration is often limited to 3 days or less. Reported doses also vary widely, with some reports recommending higher and more frequent dosing (10 to 20 mg/kg PO q6-12h)[9] and others recommending lower doses to decrease the risk of adverse effects (4 to 8 mg/kg PO q8h day 1, followed by 2-4 mg/kg PO q12h for 2 additional days).[10] Oral metronidazole (10 to 15 mg/kg twice daily) may be used as an alternative in cases that do not tolerate neomycin. Metronidazole should be used with caution because it is metabolized by the liver, and signs of toxicity may mimic HE. Lactulose (0.2 to 0.5 mL/kg PO q6-8h; equivalent to up to 333 mg/kg) is poorly absorbed by the small intestine and therefore reaches the ileum

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and large intestine intact. Once in the distal GI tract, it is metabolized to organic acids, acidifying the intestinal contents causing a pH gradient to occur and ammonia to migrate from the blood into the colon, where it is trapped as ammonium and expelled. Acetic acid (vinegar, 0.5 mL/kg PO q12h), mineral oil, and magnesium sulfate administered by nasogastric tube have also been used to decrease ammonia absorption. However, induction of hemorrhage during the procedure may result in swallowing of blood and worsening of enteric ammonia production.

Treatments aimed at reducing cerebral edema may also be necessary. Drugs frequently used include furosemide (1 mg/kg IV/IM q8-12h), mannitol (0.5 to 1 g/kg as a 20% solution IV over 20 to 30 minutes q12-24h), and hypertonic saline (2 to 4 mL/kg IV). The prognosis for HE is poor unless the underlying disease can be treated quickly.

Fluid and Colloid Therapy

Dehydration should be corrected with a balanced electrolyte solution, preferably without lactate. Lactate is normally metabolized to bicarbonate in the liver and has an alkalizing effect. However, in horses with severe hepatic dysfunction, lactate may build up in the system and cause a worsening of acidosis. Acetate buffer solutions can be used as an alternative since acetate is mainly metabolized in the muscle. Sodium chloride (0.9%) with added calcium, dextrose (2.5% to 5%), and supplemental potassium (20 to 40 mEq/L) also can be used. Additional potassium can be given orally (5 to 20 g twice daily) to prevent or treat hypokalemia, since low potassium increases production and absorption of ammonia from the kidney.[11] Acidosis may be severe in many horses with hepatic failure, but attempts at correction must be made slowly.[12] Too rapid an increase in pH may exacerbate HE. Bicarbonate therapy should be carefully instituted only when the venous pH remains less than 7.1 after appropriate fluid therapy. The prognosis is poor in horses that remain persistently acidotic.

Glucose decreases ammonia concentration, reduces the reliance on catabolic gluconeogenesis, decreases protein catabolism, and spares hepatic energy consumed in hepatic gluconeogenesis, so it should be supplemented in cases of hepatic disease. The goal is to maintain blood glucose concentrations in the range of 90 to 120 mg/dL. In the case of hypertriglyceridemia with concurrent insulin resistance, supplemental insulin can be administered, as described in the Hepatic Lipidosis section earlier.

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Polycythemia may be relatively unresponsive in some cases of hepatic failure and should not be used as the primary guide for judging adequate fluid therapy. Fresh or fresh frozen plasma can be used to increase colloidal oncotic pressure, clotting-factor transport proteins, and antiproteases. Stored whole blood should not be used because ammonia levels may be high. Hetastarch should also not be used in hepatic failure, owing to its potential effects on coagulation.

Treatment of Inflammation and Fibrosis

Corticosteroids may be beneficial in treating lymphocytic and plasmacytic variants of chronic active hepatitis. Dexamethasone (0.05 to 0.1 mg/kg/day IM or IV decreased over 2 to 3 weeks) or prednisolone (1 mg/kg/day PO for several weeks) are recommended. Other recommended therapies for resolving inflammation and preventing progression of fibrosis include NSAIDs. Flunixin meglumine (0.5 to 1 mg/kg PO q12h to q24h) or low-dose phenylbutazone (0.5 g/day PO q24h) can be used for anti-inflammatory effects. Vitamin E (10,000 U PO q24h) is recommended as an antioxidant and anti-inflammatory agent. Pentoxifylline (8 to 10 mg/kg PO q12h) is a methylxanthine derivative and works as a nonselective phosphodiesterase inhibitor, resulting in weak inhibition of the inflammatory cytokines TNF-α and IL-6. It also acts to increase RBC deformability, perhaps preventing microthrombosis. In horses, results with pentoxifylline are variable, possibly because of the variable bioavailability with extended dosing.[13] Colchicine (0.03 mg/kg PO q24h) can be used to inhibit production of collagen and macrophage- or cytokine-induced inflammation, potentially resulting in decreased fibrosis. Numerous side effects are reported in humans, including nervous system, renal, and dermatologic problems; therefore its use in horses is not currently recommended.

Miscellaneous Treatments

Supplemental S-adenosylmethionine (SAMe) (20 mg/kg PO q24h) is used for treatment of liver diseases; endogenous production is reduced secondary to reductions in methionine adenosyltransferase.[14] Presumed beneficial effects of SAMe in liver disease include augmentation of glutathione synthase levels in the hepatocyte, stabilization of membrane function, modification of cytokine expression, and inhibition of apoptosis in normal cells. *N*-acetylcysteine (NAC; 70 mg/kg IV q6h × 8 treatments) is a cysteine donor thought to be

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cytoprotective. It may improve hepatic microcirculation and oxygen delivery, enhance hepatic metabolic functions by restoring glutathione levels, block TNF-α release, and act as a free radical scavenger.[14] DMSO (0.5 to 1 g/kg IV as <10% solution for 3 to 5 days) may act as an antioxidant as well as aid in dissolving intrabiliary sludge or small calcium bilirubinate stones. However, it may also precipitate a hemolytic crisis in animals with fragile RBCs secondary to end-stage liver disease. Ursodeoxycholic acid (also known as ursodiol) and silymarin/silibilin are often used for hepatic disease in small animals, and there are anecdotal reports of use in horses, but safety and efficacy have not been proven. Ursodiol at 15 mg/kg PO q24h has been reported to be beneficial, subjectively, when combined with antibiotics, fluids, DMSO, and pentoxifylline for treatment of cholangiohepatitis or choledilithiasis in horses.[10] Silibilin pharmacokinetics and pharmacodynamics have been studied in healthy horses.[15,16] Administration at doses up to 26 mg/kg PO q12h for 7 days resulted in no adverse effects. Despite a low oral bioavailability, an increased antioxidant capacity was noted, suggesting that treatment may be useful in horses with hepatic disease.

Treatment of concurrent diseases should also be considered. If the hyperlipemia is thought to be associated with a pituitary adenoma, treatment with pergolide (1 to 2 mg/day PO) is warranted. Hyperlipidemia associated with diarrhea and azotemia may also occur in horses in late pregnancy, and abortion may be advisable.[17,18] Hepatic failure in cattle associated with septic metritis or mastitis, as well as biliary obstruction due to hepatic abscesses, often can be treated successfully by force-feeding (e.g., alfalfa gruel, electrolytes) and systemic antibiotics.[19] Treatment of hepatic fascioliasis should be instituted as previously discussed.

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Pancreatic Disease

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Pancreatic disease is rare in both cattle and horses. In the horse, acute and chronic disease has been reported, whereas only chronic disease has been reported in cattle. One retrospective study of pancreatitis in horses noted a 0.4% incidence based on postmortem diagnosis.[1]

Recognized causes of pancreatitis include migrating parasites, bacterial and viral infections, immune-mediated damage, biliary or pancreatic duct inflammatory disease, vitamin D toxicity, and deficiencies of vitamin A or E, selenium, and methionine.[2-5] Drugs known to induce pancreatitis in humans that are used frequently in horses include furosemide, tetracycline, estrogen, and certain corticosteroids and sulfonamides.[2,4] One case report in a pony suggests an association with Cushing's syndrome.[6] The cause of acute pancreatitis in the horse is unknown, but it has been associated with grain overload and severe abdominal pain.[7] Three reports of acute pancreatitis in the foal suggest a possible relationship with sepsis, GI disease, vasculitis, and pancreatic lymphatic obstruction.[8,9] Pancreatitis was diagnosed postmortem secondary to severe gastroduodenal ulceration in a foal[10] following reproductive tract surgery in a mare.[11] In cattle, an association has been demonstrated between obesity and severity of pancreatic disorders, including fatty pancreas and pancreatitis.[12] The final common pathway may result from autodigestion by activated enzymes, but the exact mechanism remains speculative.

Clinical signs associated with acute pancreatitis are nonspecific and mimic those associated with an acute GI crisis. Characteristic clinical features are moderate to severe abdominal pain, gastric reflux, hypovolemic shock, and cardiovascular compromise.[2,5,13,14] Gastric distention accounts for the pain and gastric reflux associated with acute pancreatitis. Hypovolemic shock, occurring secondary to fluid losses into the peritoneal cavity and bowel lumen, results from release of vasoactive substances from the pancreas. Tachycardia, tachypnea, prolonged capillary refill, and congested mucous membranes result from hypovolemia and cardiovascular compromise. Pancreatitis should also be considered as a differential diagnosis in chronic or intermittent signs of colic, due to potential adhesion of bowel to the inflamed pancreas, or a mass-like effect

within the abdomen.[15,16] In foals, neurologic signs including dilated pupils, blindness, obtundation, and seizures have also been reported.[8] Hypoglycemia or pancreatic encephalopathy due to cerebral microthrombosis and infarction, as seen in humans, may be implicated.

Laboratory confirmation of pancreatic disease is difficult and not routinely attempted. The diagnosis is usually confirmed on histologic evaluation of the pancreas after necropsy. Laboratory tests that may be of value in the diagnosis of pancreatitis in the horse include measuring serum amylase and lipase activity, peritoneal fluid (PF) amylase concentrations, fractional excretion of amylase, and plasma trypsin levels.[5] Serum amylase values from normal horses range from 14 to 35 IU/L (mean, 21 ± 6), whereas PF values range from 0 to 14 IU/L (mean, 5 ± 4).[17] Serum lipase values from normal horses range from 23 to 87 IU/L (mean, 58 ± 19), whereas PF values range from 0 to 36 IU/L (mean, 14 ± 12).[17] Elevations of pancreatic enzyme activity are difficult to interpret because the enzymes may be elevated in horses with proximal enteritis, colic, primary renal failure, and damage to intestinal mucosal cells, as well as pancreatitis.[5,17,18] Amylase also originates from the salivary glands, and lipase can be released from the liver. Clinical cases documented at necropsy had serum amylase activity greater than 700 IU/L; this magnitude of elevation may be helpful in differentiating acute pancreatitis from other causes of elevated amylase. In acute pancreatitis, PF amylase levels are higher than serum levels.[18] Plasma trypsin levels increase in horses with suspected pancreatic damage and may be a better indicator of pancreatic disease.[19] Trypsin is specific to the pancreas and activates its own zymogen and those of all the other pancreatic enzymes. In one study of horses with acute abdominal disease in which pancreatic damage was suspected, trypsin activity was significantly higher than in healthy horses (196 ± 128.2 ng/mL versus 28.5 ± 19.2 ng/mL).[19] In cattle with experimentally induced pancreatitis, serum amylase and lipase concentrations increased rapidly but returned to normal within a few days, suggesting that this may not be a useful test for cases of chronic pancreatitis.[20] GGT does not appear to be a sensitive indicator of pancreatic disease in horses. In foals, an inflammatory peritoneal effusion with increased peritoneal protein and triglyceride concentrations, along with hypertriglyceridemia, has been documented.[8] Pancreatitis has not been successfully imaged with ultrasonography in the horse.[21] A technique for ultrasound examination of the

right lobe of the pancreas in healthy cattle has been described.[22] Using this technique, experimentally induced acute pancreatitis was monitored in cattle. Twenty-four hours after induction of pancreatitis, an increased echogenicity was noted, but within 3 days, hypoechogenicity was noted secondary to necrosis, hemorrhage, and inflammatory exudates, as confirmed at necropsy.[20]

Medical management of acute pancreatitis is symptomatic. Prevention of gastric rupture by continuous gastric decompression and control of abdominal pain are crucial in the treatment of pancreatitis.[4] Large volumes of balanced polyionic electrolyte solutions are necessary to maintain the circulating volume and prevent shock. Because hypocalcemia may be a problem, serum calcium concentration should be monitored. Broad-spectrum antibiotics are warranted because of the potential for secondary bacterial infection. NSAIDs and analgesics are used to control inflammation and pain.

Chronic interstitial pancreatitis (CIP) in horses and cattle seldom has clinical significance. In horses, *Strongylus equinus* and *Stronglyus edentatus* are most often identified as the etiologic agent of CIP; however, *Parascaris equorum* has been identified in one case report.[4,23,24] In cattle, CIP has been primarily associated with the trematodes *Eurytrema pancreaticum* and *Eurytrema coelomacticum*; these parasites have not been isolated in the United States.[18]

Pancreatic disease in adult cattle is related to endocrine dysfunction.[25-27] The most frequently reported disorder is type 1 diabetes mellitus, but the etiology in most cases is not determined.[25-27] Histopathologic examination generally reveals an absence of beta cells in the islet tissue. Foot-and-mouth disease virus has been associated with diabetes mellitus in cattle after convalescence.[18] Hypoplasia of the acinar pancreatic tissue has been described in calves.[18] Clinical signs include steatorrhea and diarrhea. Insulin-dependent diabetes mellitus with pancreatic beta cell dysfunction has been documented rarely in horses.[28,29] Transient type 1 diabetes has also been diagnosed in the foal,[30] and recent work shows that method of delivery (spontaneous versus induced foaling) may have a significant effect on pancreatic function.[31] Induced parturition was associated with two- to threefold higher cortisol levels and with differences in the absolute and age-related changes in basal concentrations of glucose, α-amino nitrogen, and insulin.[31] Adenocarcinoma of the exocrine pancreas is reported in rare equine cases and should be considered in horses exhibiting the clinical signs of pyrexia, depression, weight loss, and icterus.[3,32,33]

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Pancreatic calculi found in older cattle (>5 years) during necropsy are considered incidental findings.[18] The calculi are composed primarily of calcium carbonate and calcium phosphate. Their presence may be associated with grazing on silica-rich soil, vitamin A deficiency, or chronic inflammation of the pancreatic ducts.[18] In two reported cases of pancreatic calculi in cattle, the cause for euthaniasia was fracture of the lumbar vertebrae.[34,35] The correlation between pancreatic disease and bone pathology in cattle is unknown, but osteoporosis is a known consequence of chronic pancreatitis in humans.

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• CHAPTER 34

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Diseases of the Renal System

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▪ Equine Renal System

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Acute Renal Failure

Thomas J. Divers • Alexandra J. Burton

Acute renal failure (ARF) in the horse is usually due to exposure to nephrotoxins or vasomotor nephropathy (e.g., hypoperfusion or ischemia). The most common pathologic lesion with ARF is acute tubular necrosis (ATN).

Toxic Nephropathies

Aminoglycosides

Administration of aminoglycoside (AG) antibiotics (gentamicin or amikacin) is one of the most common causes of ATN in horses; however, irreversible ARF due to AGs is uncommon. Aminoglycosides exert their main toxic effect by accumulating within renal proximal tubular epithelial cells. After filtration through the glomerulus, the cationic charge of AGs causes them to bind to tubular epithelial cell phospholipid membranes.[1] Once within the cell, AGs disrupt a myriad of ultrastructural cellular elements causing cell swelling, death, and sloughing into the renal tubular lumen.[1] More recently, AGs have been found to also cause some glomerular damage and additionally, a decrease in renal blood flow, directly medicated by an AG-induced increase in vascular resistance.[2] The detailed molecular mechanisms of tubular cell necrosis, glomerular, and vascular effects caused by AGs are beyond the scope of this text, but in-depth reviews are available.[1,2]

Most cases of AG nephrotoxicity are not due to single-instance drug overdose. Horses with normal renal function can usually tolerate a single major overdose without detrimental effects. Thus, AG toxicity is almost always the cumulative effect of *repeated* administration (e.g., in order to induce a gentamicin nephrotoxicosis model in the healthy equine, doses of 20 mg/kg q8h several days are required; the standard equine dose is 6.6 mg/kg IV q24h).[3] Because AGs are water soluble and highly distributed in extracellular fluid (ECF), their clinical pharmacokinetics are influenced by variations in patient ECF volume owing to *disease state* or *age*, so different doses and dose intervals may be required to attain desired serum/plasma peak and trough concentrations depending on patient specifics.[4-10] Gentamicin is the most commonly used AG in horses. A retrospective study in hospitalized horses showed significant clinical variability

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in peak gentamicin concentration for a given dose and emphasized the importance for therapeutic drug monitoring (TDM) when using gentamicin to ensure adequate peak plasma concentrations, which is important for AG efficacy.[6] However, because renal cellular uptake of gentamicin is saturable, nephrotoxicity is associated with insufficiently low plasma trough (i.e., sampled just before the next IV dose), rather than excessively high peak concentrations.[1] The maximal trough concentration permissible to minimize the risk of nephrotoxicity is unknown in horses. In humans, gentamicin trough concentrations greater than 2 µg/mL have been associated with nephrotoxicity.[11,12] However, the optimal trough concentration of gentamicin to minimize nephrotoxicity in humans is still controversial, with recommendations ranging from attaining a trough less than 2 µg/mL once in 24 hours to maintaining a concentration of less than 0.5 µg/mL for at least 4 hours.[13-15] Recently in human medicine, there have been developments of gentamicin pharmacokinetic models to facilitate opportunistic TDM and to move away from daily trough concentration monitoring.[16,17] The rationale behind this is to avoid repeated daily timed venopuncture, especially in neonates and children, and allow AG concentrations to be evaluated within the model at times when blood would be taken anyway for other analyses.[16,17] Nephrotoxicity typically develops after several days of AG administration to horses with diarrhea or septicemia that are not adequately hydrated or because of other factors that may exacerbate a decrease in renal perfusion (e.g., concurrent treatment with nonsteroidal antiinflammatory drugs [NSAIDs]).[7-10] The shift to once-daily AG dosing in humans and horses, compared with previous dosing of AGs, which was two to three times daily, has become a standard practice that reduces the potential for nephrotoxicity (by ensuring a longer period of the day with sufficiently low serum trough concentrations) but still provides a similar therapeutic response.[18-21]

Prolonged administration of AGs without TDM or serum creatinine concentration monitoring is a common history with AG nephrotoxicity in the horse. Typically, AGs may be safely administered for longer than 10 days if the patient is adequately hydrated and appropriate serum AG trough and serum (or plasma) creatinine concentrations are maintained. However, with regard to using serum creatinine concentration to monitor AG toxicity, in one instance, experimental induction of gentamicin nephrotoxicity in ponies was reflected by a rather small increase (0.3 mg/dL) in creatinine concentration.[22] Thus, TDM and

measurement of the trend in urinary γ-glutamyltranspeptidase ($_U$GGT), which always increases rapidly with AG administration (even in the absence of nephrotoxicity), and trend in $_U$GGT:urinary creatinine ($_U$Cr) concentrations in at-risk patients will give a much earlier indication of impending nephrotoxicity than serum creatinine concentration alone.[23-25] Although it has not been proven, the neonatal equine kidney is likely more susceptible to AG toxicity than the adult kidney. This is probably reflective of the prolonged elimination half-life seen in foals.[4,26] Critically ill neonatal foals may be at greater risk for AG nephrotoxicity, although this may simply reflect an increased incidence of septicemia in neonates and longer courses of treatment with AGs.

When AGs are administered to high-risk patients (e.g., those with severe dehydration, sepsis or neonates), volume deficits must be continually replaced, and TDM and UGGT:UCr concentrations or, at the bare minimum, serum creatinine concentration monitored frequently.[27] In horses receiving appropriate fluid therapy, AG nephrotoxicity rarely develops. Increased urinary sodium (Na^+) excretion and fluid diuresis appear to have a protective effect on the kidney. In contrast, hypokalemia (or total body potassium (K^+) depletion) and low calcium (Ca^{2+}) intake may predispose horses to aminoglycoside nephrotoxicity by decreasing urine output.[25] Supplementation with oral electrolytes (e.g., 1 to 2 oz of NaCl and KCl daily) may be of benefit to horses being treated with AGs by increasing water intake and urine output and by replacing K^+ deficits in anorectic horses. Furosemide should not be administered prophylactically in an attempt to prevent AG nephrotoxicity as it is a potassium-wasting diuretic. In patients with prerenal azotemia that receive AGs, it is important to monitor serum creatinine closely (i.e., to make sure that it is decreasing in the face of AG therapy) and consider prolonging the administration interval, until volume deficits are corrected, or, if possible, select an alternative antimicrobial. However, because nephrotoxicity is a cumulative effect of repeated dosing, delaying administration of the initial dose of an AG in a critical septic patient pending rehydration is often unwarranted.

When ARF from AG use develops, it usually manifests as nonoliguric to polyuric renal failure. Outcome is generally favorable, so long as the duration of ARF is not prolonged and other underlying disease processes can be corrected; however, an elevated serum creatinine may take several days (and occasionally weeks) to return to within reference range. Nephrotoxicity should be considered in horses that become inexplicably depressed and inappetent while being treated

with AGs or within a few days after AG therapy is discontinued. Renal failure can develop even after the drug is withdrawn, so monitoring renal function for 2 to 4 days after discontinuing AG therapy is advised in high-risk patients. Polyuria may be observed before the onset of depression and anorexia, or, if the patient becomes oliguric, mild stranguria and repeated posturing to urinate may be observed. A tentative diagnosis of nephrotoxicity is based on history of AG use and supportive laboratory data. Abnormal laboratory findings associated with tubular damage that may be detected before onset of azotemia include enzymuria (e.g., GGT) and cylindruria (casts in urine).[22,23,27] Although these parameters can be monitored for early detection of tubular injury, enzymuria does not necessarily indicate nephrotoxicity per se, nor does it necessarily indicate if or when AGs should be discontinued or to what degree the interval of administration should be prolonged. A rising trend in serum creatinine concentration (even if within reference range) and TDM (e.g., gentamicin 24-hour trough >2 µg/mL) are often more useful indicators of a need to increase concurrent fluid therapy (diuresis), prolong AG dose interval, or discontinue AG therapy.

Pigment Nephropathy (Myoglobin and Hemoglobin)

Acute tubular necrosis (ATN) and ARF subsequent to a severe episode of rhabdomyolysis due to myoglobin from muscle necrosis, especially if the associated dehydration is prolonged.[28,29] Dehydration and administration of NSAIDs for analgesia may both increase the risk of ARF by decreasing renal blood flow. Pigment nephropathy can also occur secondary to any other cause of muscle necrosis (e.g., muscle trauma, prolonged recumbency). Rhabdomyolysis with ARF has been reported secondary to severe clenbuterol toxicosis in three Quarter Horse racehorses. Observation of grossly discolored urine is not a prerequisite for development of ARF in cases of myoglobin pigment nephropathy. Hemolysis (hemoglobin), which may be secondary to a variety of toxins and primary conditions, appears to be a less common cause of pigment nephropathy than myopathy. Horses with severe hemolysis and those suffering from disseminated intravascular coagulation (DIC) are at greater risk of developing hemoglobinuria and pigment nephropathy. In one study, 41% of 32 horses with red maple toxicosis and hemolysis had evidence of renal insufficiency, but it was not found to be an important risk factor for mortality.[31] Hemolysis with associated ARF is also a feature of acute severe cases of equine

piroplasmosis caused by either of the erythrocytic protozoa *Theileria equi* or *Babesia caballi*.[32] Pigment nephropathy should be suspected in horses that become anorectic and depressed during the week after an episode of tying up or during a hemolytic crisis. Measuring serum concentrations of creatine kinase (CK) and aspartate aminotransferase (AST) may help identify rhabdomyolysis, if no other etiologies of ARF are suspected. There is little preformed creatinine in muscle, so rhabdomyolysis alone does not produce an increase in serum creatinine concentration. Even if normal initially, it is also prudent to recheck serum creatinine 2 to 3 days after an episode of rhabdomyolysis.

Vitamin K_3

Vitamin K_3 was a common cause of ATN before its withdrawal from the North American market. Nephrotoxicity can occur rapidly after a single parenteral dose of the menadione sodium bisulfite form of vitamin K_3.[33,34] Development of ARF was thought to be idiosyncratic and likely involves direct tubular damage via oxidative stress and pigment nephropathy subsequent to hemoglobinuria.[33,34] Although horses are sensitive to its nephrotoxic effects, oral supplementation of vitamin K homologs with a view to enhancing bone strength has been investigated in horses in Japan, and no nephrotoxicity was reported.[35,36]

Nonsteroidal Antiinflammatory Drugs

Most horses do not experience appreciable adverse renal effects from NSAIDs as long as they are administered at the correct dose to euvolemic patients. However, NSAIDs may produce ARF in an occasional horse when excessive doses are administered, maximal recommended doses are administered chronically, and/or when dehydration is not corrected promptly or is ongoing.[37] A typical situation where this might occur is in a horse that has been on daily NSAIDs for several months/years and then is administered excessive additional NSAIDs for severe colic. The lesion produced by NSAID toxicity in horses is papillary necrosis in the renal medulla, also termed *medullary crest necrosis* (Fig. 34.1), which can be manifested by gross hematuria.[37-39] Unless severe, this lesion rarely causes overt clinical signs. One study suggested that ketoprofen was less nephrotoxic in comparison with flunixin and phenylbutazone (PBZ), but this study was short term (12 days) and used an atypically high-frequency dosing regimen of all three drugs, so extrapolation of this finding to inform clinical use is not clear.[39]

Occasionally, chronic interstitial nephritis (CIN) and nephrolithiasis may occur after prolonged administration (months to years) of NSAIDs at recommended doses.[40] The *renal medullary rim sign,* an ultrasonographic abnormality consisting of a hyperechoic band parallel to the corticomedullary junction, has been demonstrated in NSAID toxicity in adults and foals.[41,42] Presence of concurrent gastrointestinal (GI) ulceration (right dorsal colitis, nonglandular gastric and duodenal ulceration) and protein-losing enteropathy (hypoproteinemia) would further support NSAID toxicity. Interestingly, acute interstitial nephritis (rather than papillary necrosis) was the predominant renal histopathologic lesion recorded in clinically normal miniature donkeys administered NSAIDs (ketoprofen, flunixin, or PBZ) for 2 weeks.[43] In contrast to horses that may not show increases in serum creatinine while on fluid therapy or until severe renal compromise occurs, donkeys may show more acute increases in serum creatinine with NSAID toxicity.[43]



FIG. 34.1 Diffuse renal medullary necrosis *(yellow arrows)* in a 3-year-old gelding following a 21-day administration of phenylbutazone (2 g [approximately 4.4 mg/kg] q12h PO). This was aggravated by concurrent hypovolemia and hypoproteinemia due to hypoalbuminemia. (Courtesy Montague N. Saulez.)

The kidney is an important source of prostaglandins (PGs), particularly PGE_2, which plays a central role in control of renal blood flow.[44] The cyclooxygenase

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(COX) enzymes COX-1 and COX-2 are required from the production of PG (from arachidonic acid), and both isoforms (COX-1 and COX-2) are expressed by the kidney.[44] In humans, broadly speaking, COX-1 is expressed more in the renal medulla and COX-2 in the cortex, but there is considerable variation in expression site dependent on, for example, disease state, hydration, and even age.[44] During periods of renal hypoperfusion due to dehydration or hypovolemia, COX-2 expression is upregulated to increase PGE_2 and maintain renal blood flow.[44] Thus, it is not surprising that NSAIDs, which inhibit the COX enzymes, have increased nephrotoxicity in the dehydrated or hypovolemic patient. Indeed, an early study in horses demonstrated increased renal papillary necrosis when PBZ was administered after water deprivation.[45] There are no data concerning differential COX-2 versus COX-1 production in equine renal tissue. Further, there is not enough evidence in horses to conclude whether NSAIDs that more selectively inhibit COX-2 (e.g., meloxicam, firocoxib) are truly less nephrotoxic as opposed to NSAIDs that inhibit COX-1 and COX-2 (e.g., PBZ, flunixin). Indeed, a recent study comparing administration of PBZ with meloxicam to horses that had been administered furosemide or dobutamine found that both NSAIDs similarly reduced urine flow rate.[46] Interestingly, NSAIDs and COX-2 selective inhibitors, especially at low to moderate doses, have been shown to be protective in various animal models of acute kidney injury.[44]

Vitamin D

Although generally uncommon in horses, Vitamin D intoxication may result from ingestion of feed additives or plants (e.g., *Cestrum diurnum*) containing high amounts of vitamin D metabolites or parenteral administration of vitamin D.[47-49] Cholecalciferol (D_3) is thought to be more toxic than ergocalciferol (D_2) in the horse.[48] In general, horses do not need dietary supplementation with vitamin D if they are exposed to adequate sunlight and have access to green forages. The effect of vitamin D supplementation is cumulative, so signs of toxicity may not develop until several weeks after supplementation was started.

Clinical signs of vitamin D intoxication may be referable to mineralization of the musculoskeletal, cardiovascular, and urinary systems.[49] Abnormal laboratory findings with vitamin D intoxication include azotemia, isosthenuria, hypochloremia, and increased serum calcium and phosphorus concentrations.

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Hypercalcemia with hyperphosphatemia is unusual for any other disease in the horse, except for certain neoplasias. A definitive diagnosis of vitamin D toxicosis can be made by measuring serum concentrations of 25-OHD_3, 25-OHD_2, and 1,25-$(OH)_2D$. Treatment of vitamin D intoxication includes identification and removal of the inciting cause (feed or medication), fluid diuresis, and corticosteroid administration. Provision of feeds low in both calcium and phosphorus may be of benefit in less severely affected horses, but treatment is usually unrewarding once clinical signs due to tissue mineralization have developed.

Heavy Metals

Accidental ingestion of heavy metals may result in ATN and ARF in horses. Mercury, cadmium, zinc, arsenic, and lead are all nephrotoxic but are rare causes of ARF in clinical practice. Mercury has been used experimentally to induce ARF in horses, and there are reports of ARF in horses that have had legs "blistered" or "sweated" with products containing inorganic mercury.[50-53] Because inorganic mercury also causes severe damage to GI mucosa, signs of GI irritation (e.g., salivation, oral erosions, colic, hemorrhagic diarrhea) predominate with mercury intoxication. Further evaluation may reveal oliguria. Exposure to excessive amounts of zinc and cadmium can result in nephrocalcinosis and oliguric renal failure, but gait deficits (resulting from osseous effects, particularly in foals) and ill thrift are more likely presenting complaints.[53] Laboratory findings with heavy metal intoxication are characteristic for ATN: azotemia, hyposthenuria to isosthenuria or anuria (depending partly on concurrent hydration status), hyponatremia, and hypochloremia. In horses with ARF with concurrent GI disease, as with mercury toxicity, severe hypocalcemia may be present. A tentative diagnosis of mercury intoxication may be made from history of exposure, clinical signs of erosive GI disease, and oliguric renal failure. The diagnosis can be confirmed by measuring increased blood and tissue (kidney and liver) concentrations of the suspected metal. In addition to judicious fluid therapy, treatment of ARF induced by exposure to heavy metals should include parenteral dimercaprol and activated charcoal via nasogastric tube (see Chapter 54, Disorders Caused by Toxicants). Visceral analgesics and/or sedatives are often necessary to control abdominal pain.

Acorn Poisoning

Although less commonly seen in horses than cattle, acorn poisoning can result in equine ATN.[54,55] Death in horses is usually due to erosive, hemorrhagic GI disease, changes in vascular permeability, and resulting shock rather than a consequence of ARF. Immature leaves and green acorns are considered more toxic than mature acorns as they have a higher tannin content. Clinical signs may include diarrhea, edema, and body cavity effusion, and laboratory evaluation usually reveals azotemia, isosthenuria to hyposthenuria, hyponatremia, and hypochloremia. Detection of increased urinary excretion of phenols may be useful to confirm the diagnosis. There has recently been a suggestion that the prevalence of acorn poisoning in horses is increasing in the United Kingdom.[55]

Miscellaneous Drugs and Agents

Several other drugs and agents (oxytetracycline, polymyxin B, amphotericin B, imidocarb dipropionate, ethylene glycol, ochratoxins, pyrrolizidine, cantharidin toxicosis [blister beetle poisoning]; the nematode *Halicephalobus gingivalis;* and the apicomplexan parasite *Klossiela equi*) have been suspected of causing ARF in horses. When high doses of oxytetracycline (usually around 44 mg/kg IV diluted in saline) are administered to neonatal foals for correction of limb contracture, ARF is a potential complication, especially if the foal is dehydrated or has concurrent sepsis or hypoxic-ischemic encephalopathy.[56] Polymyxin B is sometimes used as an adjunct treatment for endotoxemia, and it is prudent to remember that it has nephrotoxic potential. However, studies in adult horses and foals with experimentally induced endotoxemia have demonstrated that the risk of polymyxin B nephrotoxicity is low, especially when it is conjugated with dextran 70.[57-59] Amphotericin B also has considerable nephrotoxic potential but is rarely administered systemically to horses. Imidocarb dipropionate, used in treating *Babesia equi* infections, has been shown to cause reduced renal function after multiple dosing.[60] Blister beetle poisoning (cantharidin toxicosis) may cause abdominal pain, shock, hematuria, diaphragmatic flutter, dysuria, and renal dysfunction in horses fed alfalfa hay grown in regions where the beetles are prevalent.[61] There are some reports of renal failure, as well as brain involvement, associated with granulomas caused by the nematode *Halicephalobus gingivalis*.[62,63] The coccidian parasite *K. equi* infects the kidneys of equids and can cause ATN and interstitial nephritis if infection is

heavy and/or the patient immunocompromised.[64] Many anecdotal reports exist of horses developing renal disease after administration of bisphosphonates for treatment of orthopedic disease, especially when administered frequently and in conjunction with NSAIDs. Renal disease is a reported complication in other species after bisphosphonate administration.[65]

Vasomotor Nephropathy

Any condition that causes sustained marked hypotension or release of endogenous pressor agents may initiate hemodynamically mediated (vasomotor) ARF. Although poorly documented, renal compromise due to a combination of vasomotor and nephrotoxic mechanisms probably occurs more frequently than clinically identified, especially in sick horses receiving drugs with nephrotoxic potential.[66] Hemorrhagic shock, severe intravascular volume deficit (e.g., enterocolitis), septic shock, and coagulopathy are important risk factors for vasomotor ARF in horses.[66] Another cause may be adverse drug reactions, including those accompanying IV administration of vitamin and mineral products or immunomodulators. The predominant lesion in vasomotor nephropathy is ATN, although diffuse renal cortical or renal medullary necrosis may also occur. Clinical signs of vasomotor ARF are nonspecific and more often referable to the primary disease (e.g., hemorrhage or diarrhea). Additional subtle signs (e.g., more marked depression and anorexia than would be expected with the primary disease), with or without signs of mild colic, should increase suspicion of ARF. Occasionally, horses with severe vasomotor ARF are markedly ataxic and/or manifest neurologic signs similar to hepatic encephalopathy. Oliguria, often seen as a lack of expected urination in response to fluid therapy, is an important early indicator of vasomotor ARF, and production of dilute urine (urine specific gravity [USG] <1.020) that may be discolored (hematuria or hemoglobinuria) can be observed when urine is eventually voided. If urine is grossly clear, microscopic hematuria is usually present, producing a positive result on a urine dipstick. Glucosuria, due to severe proximal tubular damage, may also be detected. Although the pathophysiologic relationship to ARF is not well defined, diarrhea and severe laminitis can develop in more serious cases of vasomotor ARF.

Acute Glomerulopathy

Subclinical glomerular damage likely accompanies several diseases affecting horses, especially immune-mediated disorders (e.g., purpura hemorrhagica), but acute glomerulonephritis (GN) causing ARF is rarely perceived to be a clinical problem.[67] However, a recent multicenter study identified glomerular disease in 34/142 (24%) diagnostic renal biopsies in horses, suggesting that glomerular disease may be clinically underrecognized.[68] A syndrome of arteriolar microangiopathy and intravascular hemolysis that caused distention of glomerular capillary loops with fibrin thrombi and accumulation of large amounts of proteinaceous debris in the Bowman capsule was described in two horses.[69] Affected horses presented with oliguric ARF accompanied by hematuria, proteinuria, and intravascular hemolysis; response to treatment was poor.[69] The cause of the syndrome in horses is not definitively known. Renal lesions resemble those found with hemolytic-uremic syndrome (HUS) in humans, which is caused by toxins of *Escherichia coli*.[69] In a case report of HUS with glomerular thrombotic microangiopathy in a postpartum mare, *E. coli* O103:H2 was isolated from the uterus and gastrointestinal tract.[70] Glomerulopathy with ARF caused by *Streptococcus mitis* has also been documented as a component of toxic shock in a horse.[71] Bacterial toxins, coagulopathy, immune complex deposition, vasoactive amines, and hemodynamic alterations may all be contributors to this syndrome in horses. Acute glomerulopathy should be considered in horses with severe ARF that do not have a predisposing primary disease leading to vasomotor ARF and that have not been exposed to nephrotoxins. Gross hematuria, proteinuria, and oliguria would support an acute glomerulopathy, and renal biopsy can be pursued to confirm the lesion.[68]

Acute Interstitial Nephritis

Acute interstitial nephritis (AIN) is a syndrome of ARF accompanied by rapid elevations in creatinine and clinical signs of uremia. In a recent multicenter study of equine renal biopsies, tubular interstitial disease/interstitial nephritis was the most common histopathologic finding, accounting for 63/142 (44%) of diagnostic biopsies.[68] With that said, not all of these cases may have presented as fulminant ARF and interstitial nephritis is the most common finding in horses with chronic renal failure (CRF). Lesions in AIN include interstitial edema with a mild inflammatory infiltrate. Adverse or idiosyncratic drug reactions may be a

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cause, but the main etiopathogenesis of this disease in horses is unknown. In humans, eosinophilic infiltrates in renal biopsy tissue are supportive of adverse drug reaction. Although there are no published reports of the syndrome in horses, one of the authors (TJD) has examined three horses with apparent AIN. However, experimentally, in miniature donkeys, interstitial nephritis (rather than medullary crest necrosis) was the predominant renal histopathologic lesion recorded following IV administration of NSAIDs twice daily for 2 weeks.[43]

Leptospirosis

Krista E. Estell

The bacteria *Leptospira* spp. is commonly found in the horse. It is predominantly a cause of uveitis and abortion but can also infect the equine kidney, causing renal disease in some instances. Several case reports document *L. interrogans* as a cause of interstitial nephritis in adults and foals.[72-75] Infection with *L. interrogans* should be considered in equine ARF when an underlying renal or vasomotor disease is not apparent and there has been no exposure to nephrotoxins. The most frequent clinical sign in both experimental and natural infection is fever, but anorexia and depression may also be present, and hematuria has also been observed.[74-76] Clinical pathologic abnormalities include azotemia and isosthenuria. Leptospiruria is not a consistent finding with ARF due to leptospirosis, making definitive diagnosis difficult. Diagnosis of *Leptospira* spp. can be achieved by urine polymerase chain reaction (PCR); administering furosemide and testing the second voided sample may increase sensitivity of this test. Serum titers performed by microscopic agglutination rise quickly after experimental infection.[76] Demonstration of a rising titer or a high baseline titer above 1 : 6400 indicates active infection. Treatment includes fluid and antimicrobial therapy (see section on Bovine Leptospirosis).

Diagnosis of Acute Renal Failure

ARF should be suspected in patients showing more marked depression and anorexia than would be expected with the perceived primary disease process and in those that fail to produce urine within 6 to 12 hours of initiating fluid therapy. Diagnosis of ARF is confirmed on the basis of history, potential exposure to nephrotoxins, clinical signs, and laboratory findings. Azotemia (elevated serum or plasma blood urea nitrogen [BUN] and creatinine concentrations) is present

with clinical ARF, but note that azotemia of purely renal origin only manifests when 65% to 75% of total functioning nephrons are lost. Relative to baselines, the increase in serum creatinine is often several-fold greater (e.g., up to 5 to 15 mg/dL) than BUN (e.g., up to 50 to 100 mg/dL), often resulting in a serum BUN–to–creatinine ratio less than 10 : 1. It is important to remember that serum creatinine concentration may be as high as 8 mg/dL with purely prerenal azotemia (e.g., due to dehydration). A BUN–to–creatinine ratio of greater than 20 : 1 is suggestive of prerenal azotemia. With ARF, hyponatremia, hypochloremia, and hypocalcemia are usually present. In more severe cases, with oliguric or anuric ARF, hyperkalemia, hyperphosphatemia, hypercalcemia, and metabolic acidosis may also be detected and indicate a guarded prognosis. Urinalysis and USG should be performed on all horses in which ARF is suspected. A low USG (<1.020) in the face of dehydration and gross or microscopic hematuria are common findings with ARF. It is important to remember that in many horses with ARF, prerenal azotemia is often present in conjunction with renal azotemia, due to dehydration/hypovolemia compounding acute kidney injury. In some cases (e.g., urinary tract obstruction or rupture) significant postrenal azotemia will also be present. Thus, assessment of renal function based on azotemia can sometimes only be made once factors contributing to prerenal and postrenal azotemia have been corrected, which may take several days. Azotemia may still take several days (and in rare cases, even weeks) to correct following severe ARF; therefore, a diagnosis of permanent renal damage (i.e., CRF) cannot be made immediately on the basis of the persistence of azotemia after symptomatic recovery.

In a few cases, rectal palpation in horses with ARF may reveal enlarged, painful kidneys. Enlargement can be confirmed by renal ultrasonography (US), which may also reveal perirenal edema, loss of detail of the corticomedullary junction, or dilation of renal pelves.[77,78] However, subtle changes in renal architecture can be difficult to detect via US, and sensitivity of this diagnostic modality largely depends on operator experience and image quality. Evidence of more substantial proximal tubular damage, including increased urinary enzyme activity and glucosuria, may be detected in some horses, dependent on etiology. Significant proteinuria (urine protein–to–creatinine ratio >2 : 1 [see Chronic Renal Failure section later]) suggests the presence of glomerular disease. Examination of urine sediment may reveal casts and increased numbers of erythrocytes and leukocytes, as well as a decreased amount of urine crystals. Increased fractional clearances of sodium and phosphorus are also common

findings with ARF. However, it is important to remember that administering IV fluids to healthy horses will also result in increased fractional clearances of sodium, chloride, and phosphorus.[79] Electrolyte clearances are ideally determined using the initial urine sample voided after admission or a sample collected by catheterization (i.e., before urine is substantially altered by fluid therapy).

The most accurate assessment of renal function is glomerular filtration rate (GFR), which can be measured by performing timed urine collections and measuring inulin and endogenous or exogenous creatinine clearances, or assessing plasma disappearance of several exogenous compounds including radiolabeled substances (see Diagnosis in Chronic Renal Failure section later).[80] Computed tomography (CT-GFR) has also been used to determine GFR in small animals and a foal with upper urinary tract disease.[81] In a clinical setting, measurement of GFR in cases of ARF is rarely pursued because multiple measurements are required to assess changes in GFR, and prognosis for recovery is more likely related to the duration of decreased GFR rather than to the magnitude of the decrease. Because of the inverse relationship between GFR and creatinine, changes in GFR can be more practically and economically assessed by *trend* in serum creatinine concentration measured q12-24h. Symmetric dimethylarginine (SDMA) is a renal biomarker specific to kidney function used in small animals, but it has not been investigated in horses.

Renal damage may be further confirmed by performing a renal biopsy.[68] However, biopsy is often not indicated in horses with ARF because the diagnosis is usually evident and response to initial therapy will serve as a better prognostic indicator. Immunofluorescent (IF) testing and electron microscopic (EM) examination are routinely performed on human renal biopsy samples to assess specific mechanisms of renal injury and extent of damage to glomerular and tubular basement membranes. If such detailed evaluation of renal biopsy tissue were routinely performed in horses with ARF, then more informed information regarding antemortem etiopathogenesis and prognosis could likely be obtained. At present, renal biopsy is most often indicated to evaluate horses with ARF when exposure to nephrotoxins or another underlying primary disease process is unapparent. Life-threatening hemorrhage is a potential complication of renal biopsy. A multicenter study of 151 horses that underwent renal biopsy found complications in 11.3%, generally associated with hemorrhage or signs of colic, and there was only one fatality.[68] Risk factors for complications included biopsy

of the left kidney, a diagnosis of neoplasia, and low USG.[68] Biopsy of the right kidney with US guidance, usually through the 17th intercostal space, is the preferred procedure.[82] Proper instrumentation (automatic or spring-loaded biopsy instruments) and adequate restraint (stocks and sedation) are important considerations. Renal tissue collected should be placed in formalin for histopathologic examination, plain tube and swabbed for culture if indicated, as well as frozen (or placed into additional media specified by the testing laboratory) for immunofluorescent (IF) and electron microscopy. Although biopsy of the right kidney alone is usually adequate for assessment of the disease process affecting both kidneys, samples of the left kidney can also be collected, by guiding the biopsy instrument through the spleen. When collecting a biopsy from the left kidney or when biopsy of a specific area of either kidney is desired, US guidance is vital.

General Principles of Treatment for Acute Renal Failure

Initial therapy should always focus on judicious IV fluid administration to replace volume deficits and to correct electrolyte and acid-base abnormalities. The magnitude of azotemia and serum concentrations of sodium, chloride, potassium, and bicarbonate should be monitored q12-24h. Horses with polyuric ARF require sodium chloride (NaCl) replacement, accomplished by administering IV 0.9% NaCl with or without supplementation of NaCl in grain feedings or as oral pastes. Some horses require an initial dose of hypertonic NaCl (2 mL/kg), but care should be taken not to correct hyponatremia too quickly if it is suspected to have been present for several days. Serum potassium concentration in horses with nonoliguric ARF is often normal, except in cases of postrenal problems (e.g., obstruction or rupture), where hyperkalemia is often present, therapy to lower serum potassium is usually unnecessary. Similarly, it is usually unnecessary to correct the mild hypocalcemia that can accompany ARF in horses.

After correcting volume deficits and electrolyte and acid-base abnormalities, an attempt should be made to determine whether the animal is oliguric or nonoliguric (polyuric); the prognosis for recovery appears to be more favorable with nonoliguric ARF. This often becomes apparent by simple observation: Oliguric horses fail to produce expected amounts of urine in the initial 12 to 24 hours of IV fluid therapy, and the bedding remains dry. Nonoliguric horses repeatedly void moderate volumes of dilute urine during the initial 6 to 12 hours

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of treatment. Fluid and sodium replacement in horses with oliguric or anuric renal failure must be monitored closely as overzealous fluid administration will result in rapid edema formation, often initially noticed in the conjunctiva. Other manifestations include generalized subcutaneous swelling of dependent areas, progressing to tachypnea and altered mental status if pulmonary and/or cerebral edema develop. In horses with prerenal azotemia (as opposed to intrinsic ARF), serum creatinine concentration should decrease by at least 30% to 50% within the initial 24 hours of fluid therapy. In contrast, creatinine concentration may remain unchanged or even increase in ARF.

During therapy for ARF, regular assessments of attitude, vital parameters, packed cell volume (PCV), and total plasma protein concentration are important. Monitoring should also include measurement of body weight q12-24h: Patients that are responding to treatment should *not* gain weight with continued fluid therapy after initial rehydration. An attempt should be made to compare fluid input (IV fluids) and intake (voluntary drinking) with urine output. Although there is no convenient method of collecting all urine voided by ambulatory foals or mares, urine output can be quantified in male horses by placing a urine collection bag, slung around the abdomen. When desired, monitoring urine output in critically ill foals and mares can be accomplished by use of an indwelling Foley catheter and urine collection bag (closed system), but ascending microbial infection is a serious risk.

In horses with severe ARF, especially those with vasomotor nephropathy, systemic blood pressure (BP) should be monitored to confirm that fluid therapy has been adequate to restore BP. Recent studies have demonstrated that indirect BP monitors have good precision and accuracy for measuring mean arterial pressure when corrected for height.[83,84] Some horses may remain hypotensive (systolic BP <80 mm Hg) despite administration of large volumes of IV fluids, owing to extravascular accumulation as edema or a third-space fluid. If systemic BP remains low, hypertonic saline, dobutamine, or other pressor agents may be required in an attempt to restore BP and GFR. Central venous pressure (CVP) can also be monitored as a more precise measurement of fluid balance in critical patients. It is measured with a manometer with the baseline at the level of the right atrium, attached to an IV catheter placed into the anterior vena cava via the jugular vein (normal CVP in horses, 7.1 to 9.4 cm H_2O)[85]; values as high as 12 cm H_2O have been reported in normal horses.[86]

In horses that remain oliguric after 12 to 24 hours of appropriate fluid and

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electrolyte replacement and restoration of systemic BP, furosemide at 1 to 2 mg/kg IV q2h up to four times should be administered (intermittent use [1 mg/kg IV q8h over 24h] in one study). A constant rate infusion (CRI) of furosemide at 0.12 mg/kg/h, preceded by a loading dose of 0.12 mg/kg IV, was considered superior to intermittent use in one study.[87] Unfortunately, furosemide treatment is often ineffective in increasing renal blood flow, GFR, and tubular flow in horses with ARF. It should be remembered that NSAIDs have been shown to attenuate the diuresis and increased GFR produced by furosemide and thus should be avoided.[46] If urine is not voided after the second dose of furosemide, a CRI of dopamine (3 to 7 µg/kg/min IV diluted in 5% dextrose) can be instituted. If dopamine does not increase urine production in 2 to 4 hours, it should be discontinued, but if it is successful, it may be continued for up to 48 hours if necessary. Dopamine administration should only be performed in a hospital setting where heart rate and BP can be monitored frequently and thus development of tachycardia and hypertension avoided; in the author's (TDJ) experience, the mean BP should not rise above 110 to 120 mm Hg. Dopamine use for selective renal vasodilatory and natriuretic actions has been called into question because most studies in humans have not demonstrated prevention of ARF in high-risk patients or improved outcome in those with established ARF, and in one study dopamine actually worsened renal perfusion in human patients with ARF.[88] Further, the drug may precipitate serious cardiovascular and metabolic complications in critically ill patients. As an alternative to dopamine, fenoldopam CRI (0.04 µg/kg/min IV) may be tried in foals. In oliguric patients with a normal CVP but low-normal BP, a dobutamine infusion (1 to 12 µg/kg/min IV, diluted in D_5W or 0.9% NaCl to a concentration of 500 µg/mL) or mannitol (0.5 to 1.0 g/kg IV) can be tried. Dobutamine should not be used concurrently with furosemide. Mannitol should not be used in anuric horses. If these treatments are successful in converting oliguria to polyuria (may require 24 to 72 hours), they should be discontinued, but maintenance of urine production must be monitored closely over the next few days. Fortunately, the majority of horses with ARF resulting from ATN are nonoliguric rather than oliguric, and thus furosemide, mannitol, dobutamine, or dopamine are unnecessary.

When this treatment approach to oliguria remains unsuccessful for more than 72 hours, the prognosis becomes grave. One study of horses with colic or colitis found that horses with persistent azotemia after 72 hours of fluid therapy were three times as likely to die or be euthanized as were horses without persistent

azotemia.[89] Dialysis therapy may be a further treatment option in selected patients. Hemodialysis has been successfully used to treat an adult horse with myoglobinuric ARF and a neonatal foal with oxytetracycline-induced ARF.[90,56] Continuous-flow peritoneal dialysis has been used to successfully treat ARF in an adult horse, and continuous flow (rather than intermittent peritoneal dialysis) helps avoid the problem of omentum blocking the peritoneal tubing.[91] Recently, renal replacement therapy (RRT), a blood purification modality, has been investigated in horses and a foal and appears to be a viable option, where finances permit and equipment is available.[92,93] Pleural dialysis is another option for which fluid exchange is less problematic but has not been investigated in horses. Hemodialysis or dialysis would likely be most effective in horses with nephrotoxic ARF rather than those with vasomotor ARF.

After volume deficits have been restored and polyuria achieved, patients usually need only continued fluid therapy (0.9% NaCl + 20 mEq/L KCl or another balanced electrolyte solution, at a rate of 40 to 80 mL/kg/day) to promote a continued diuresis and decrease in serum creatinine. Fluid therapy may have to be continued (20 to 40 mL/kg/day) for several days until serum creatinine returns to the normal range or a steady-state value and the horse is eating and drinking adequate amounts. Supplementation with oral electrolytes (1 to 2 ounces of NaCl twice daily) will also promote greater oral fluid intake and diuresis. Potassium supplementation (1 oz KCl PO twice daily) may also be required because diuresis results in kaliuresis. When horses remain anorectic during treatment, the addition of 50 to 100 g dextrose/L fluids can provide immediate calories in the short term. If anorexia persists for several days, caloric intake may have to be provided by nasogastric tube feeding or via total parenteral nutrition (TPN). Within the week after fluid therapy is discontinued, serum creatinine should be measured again to ensure it has not increased. Occasionally, creatinine may not decrease to below 2 to 3 mg/dL despite continued fluid therapy. As long as the horse is eating and drinking well, IV fluids can be discontinued. In some horses, further recovery will be seen as a return of creatinine to normal range within the next couple of months, whereas in other patients a persisting elevation in creatinine indicates permanent loss of renal function. In the author's experience, some normal Quarter Horses have a serum creatinine in the range of 2 to 2.5 mg/dL.

Serum Creatinine Elevations in Newborn Foals

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During the first 1 to 3 days of life, the serum creatinine concentration in foals is often 30% to 40% higher than in their dams.[94] The cause is unclear but likely related to an inability of creatinine to equilibrate rapidly across placental membranes. As supportive evidence, creatinine concentration of normal amniotic fluid (which contains fetal urine) at term is approximately 10 mg/dL (and may be >30 mg/dL in some mares).[95] The term "spurious hypercreatinemia" is used to describe the condition in foals that have truly increased serum creatinine levels but no other markers of renal injury (e.g., normal urinalysis, electrolyte and BUN concentrations). The increased creatinine is often related to placental dysfunction during gestation and can occasionally exceed 20 mg/dL in premature foals. In one study, 20/28 foals with spurious hypercreatinemia had a clinical diagnosis of neonatal encephalopathy (neonatal maladjustment syndrome).[96] The association between neonatal encephalopathy and hypercreatinemia is unclear. Surprisingly few foals were from mares with documented placental pathology in one study, but these foals often had evidence of periparturient stress including premature placental separation or dystocia.[96]

Therefore, when elevated creatinine is detected in an otherwise healthy foal (that has also been observed to urinate normally), there may be no cause for alarm, but if levels do not decline rapidly after birth (or remain >2.5 mg/dL on day 3 of life), peritoneal or retroperitoneal accumulation of urine, renal hypoplasia, or other causes of renal failure should be considered. Unlike creatinine, serum BUN values in foals are typically low (<10 mg/dL) after day 2 and remain low for the first several months of life.

Urinalysis results in normal neonatal foals are also different from those in adult horses. Specifically, for 1 to 2 days after birth, normal foals may have marked proteinuria resulting from filtration of small-molecular-weight proteins absorbed with colostrum. Fluid intake on a predominantly milk diet is high in foals (250 mL/kg/day, compared with 50 mL/kg/day of water intake by adults), so after day 2 of life, foal urine is hyposthenuric (USG = 1.002 to 1.006) and remains that way for several months. Urinary enzyme activity and sodium and chloride clearances may be greater than in adults, and urine pH is neutral to acidic in foals.[97] Fractional electrolyte clearance values are similar to those of adult horses.[98]

Electrolyte Abnormalities in Azotemic Foals

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Lisa E. Fultz

Urinary tract disorders and azotemia are primary causes for varying degrees of serum electrolyte abnormalities in foals. Severe hyponatremia (<122 mmol/L) occurred in 4% of Thoroughbred foals presenting to intensive care units and were most often related to urinary-tract related disorders (26.1% due to renal disease and 21.7% related to uroperitoneum).[99] Potential mechanisms include water retention due to reduced GFR, increased sodium loss with renal tubular damage, and interrupted aldosterone activity.[98-100] Hyponatremic encephaolopathy has been documented in azotemic neonatal foals; these foals commonly have seizure activity or central blindness, severe hyponatremia and hypochloremia in the absence of diarrhea, and variable (but typically mild) azotemia.[101] In one case series, 15.9% of foals with severe hyponatremia displayed signs of encephalopathy, likely related to cerebral edema and increased intracranial pressure.[99] Sodium-losing nephropathy with ARF has been confirmed in some cases.[101] In azotemic foals, hyponatremia due to ARF is often related to confirmed or suspected neonatal sepsis.[101] One study found no difference in the severity of hyponatremia and short-term survival rate (72.5%).[99] Azotemic foals experiencing hyponatraemic encephaolopathy typically respond well to IV fluid administration with gradual sodium replacement (0.5 mmol/h).[101]

Acute Renal Failure in Foals

Thomas J. Divers • Alexandra J. Burton • Lisa E. Fultz

Acute tubular necrosis (ATN) is the most common pathologic lesion causing ARF in neonatal foals. Many cases develop during or after episodes of diarrhea, likely caused by poor renal perfusion (vasomotor nephropathy) subsequent to varying degrees of dehydration. Surprisingly, the diarrheal disease in some affected foals does not appear to be serious, but the foals may still develop ARF. Similar to adult horses with ARF, the prominent clinical signs are depression and development of edema. Abnormal laboratory findings include azotemia, hyponatremia, hypochloremia, and hypocalcemia. In foals with ARF, both serum BUN and potassium in ARF tend to be significantly higher than in foals with spurious hypercreatinemia.[96] Foals are more likely to develop significant hyperkalemia and hyperphosphatemia than are adult horses with ARF. A USG of less than 1.018 and microscopic hematuria are also typical of foals with ARF.

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Urine output of sick neonates should be monitored closely because they may become oliguric to anuric 12 to 24 hours before significant depression or azotemia is recognized. In addition, fluid retention during incipient ARF is another cause of inappropriate weight gain (e.g., >2 kg in 24 hours), which can often be detected before obvious edema or other clinical signs develop.

Nephrotoxicity, most often due to aminoglycoside (AG), tetracycline, or NSAID administration, is a cause of ARF (usually nonoliguric) in neonatal foals, particularly those that are dehydrated. As in adult horses, the recent change to once-daily dosing appears to have decreased the incidence of AG-induced ARF in foals. Seriously ill and/or premature foals appear to be at even greater risk of nephrotoxicity than term foals, owing to reduced renal clearance.[102] Although there is a general impression that amikacin may be less nephrotoxic than gentamicin in foals, no data exist to support this notion. Regardless of which AG is selected, TDM (24-hour trough concentrations <2 µg/mL for gentamicin, <4 µg/mL for amikacin) is warranted to decrease the risk of AG toxicity in high-risk neonates. It should be noted that the actual optimal trough concentrations are unknown in horses and are based on those used in human medicine.[11,12] Dosage adjustment may be necessary in seriously ill neonates or premature foals because renal clearance may be decreased, necessitating an increased dosing interval to achieve low enough trough concentrations.[26] Judicious fluid therapy to correct dehydration and maintain BP is an important precaution. To complicate matters, foals also have a larger volume of distribution than adult horses and require an increased dose of AGs to attain therapeutic peak concentrations.[4,103] Volume of distribution may be increased even further in premature foals and with certain disease processes that increase extracellular fluid volume.[26]

Treatment principles for ARF in neonates are essentially the same as for adult horses (see earlier section General Principles of Treatment for Acute Renal Failure). However, even greater attention must be paid to monitoring responses to fluid therapy, including twice-daily measurement of body weight. Renal replacement therapy (RRT) is a viable option in foals and may have more potential to effectively treat foals with ARF due to their relatively small blood volume compared with adult horses. The hemodiafiltration process of RRT can allow for a slow and gradual clearance of toxins and metabolites and correct fluid volume overload.[92,93] In one case report, RRT was instituted in conjunction with a furosemide CRI in an anuric 3-day-old foal with postresuscitation ARF due to hypoxic injury.[93] Despite a 33% urea reduction ratio and establishment of

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urine production, the foal was euthanized after a single 6-hour session, so long-term follow-up has not been documented.[93] No long-term study has been performed examining the risk of developing CRF in the future following neonatal ARF.

Septic Renal Disease in Foals

Thomas J. Divers • Alexandra J. Burton • Lisa E. Fultz

Multifocal renal abscesses or infarcts may be a complication of neonatal septicemia and can lead to ARF. *Actinobacillus equili* is one of the most common pathogens isolated from renal abscesses, but affected foals often die or are euthanatized because of overwhelming sepsis before clinical signs of ARF develop. Foals 2 to 4 days of age appear to be at greatest risk of developing acute *Actinobacillus* septicemia; when this problem is suspected, aggressive IV fluid therapy with concurrent penicillin or ampicillin plus gentamicin or amikacin is recommended. Subsequent fibrin deposits in the kidney have also been identified in some foals with septicemia and ARF.[104] Unilateral nephrectomy has been attempted as therapy for severe renal abscesation in a foal.[105]

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Chronic Renal Failure

Thomas J. Divers • Theresa L. Ollivett • Erin McConachie Beasley

Chronic renal failure (CRF) in horses may be divided into two broad categories: primary glomerular disease and primary tubulointerstitial disease.[1,2] However, ongoing pathology in one portion of the nephron usually leads to altered function and eventual pathology in the entire nephron. Thus, CRF is an irreversible disease process characterized by a progressive decline in glomerular filtration rate (GFR). The rate of decline in GFR is variable among horses with CRF, making the short-term (i.e., months to ≈2 years) prognosis guarded to favorable, while the long-term prognosis remains poor. It is important to note that CRF with azotemia only develops after 65% to 75% of the total functioning nephrons are lost. This explains why a unilateral nephrectomy (e.g., for nephrolithiasis) can be performed in horses with a contralateral kidney that is nondiseased and functioning normally.

Primary *glomerular* diseases that can lead to CRF in horses include glomerular nephritis (GN), nonspecific glomerulopathy, glomerular hypoplasia, and amyloidosis. Primary *tubulointerstitial* diseases causing CRF include incomplete recovery from acute tubular necrosis (ATN), pyelonephritis, nephrolithiasis, hydronephrosis, renal dysplasia, and papillary necrosis. Collectively, the latter disorders produce pathology categorized as *chronic interstitial nephritis* (CIN). Unfortunately, because CRF is often advanced when horses are first presented for clinical evaluation, the initial inciting cause may be difficult to ascertain and end-stage kidney disease (ESKD) may be the pathologic diagnosis. The inciting cause may more likely be discerned from taking a detailed long-term history (e.g., chronic drug administration, possible toxin ingestion/exposure, episodes of myopathy, failure to thrive or attain expected adult size) rather than clinical findings at presentation, especially for primary tubulointerstitial diseases.

Causes of Chronic Renal Failure

Proliferative Glomerulonephritis

Proliferative GN, indicating increased cellularity of the glomerular tufts consequent to influx of inflammatory cells and proliferation of mesangium, is

the most common glomerular disease causing CRF in horses, and accounted for 53% of acquired causes of CRF in one retrospective study of 99 horses with CRF.[2] It is thought to result from deposition of circulating immune complexes along the glomerular capillaries or in situ formation of immune complexes along the glomerular basement membrane (GBM). Deposition of immune complexes causes activation of complement and vasculitis (type III hypersensitivity response). In one study, deposits of immunoglobulin (Ig)G and complement along the GBM were found through immunofluorescence (IF) staining in a large proportion (22/53) of horses at necropsy.[3] However, only 1/53 horses had developed CRF. Thus, although immune (antigen-antibody) complex deposition and subclinical GN may be common in horses, progression to CRF appears to be an infrequent occurrence. In this necropsy survey, the predominant IF staining pattern was granular (patchy deposits of immune complexes and complement along GBM), but linear deposits were found in two horses.[3] The latter finding was supportive of true autoimmune disease with more diffuse deposition of anti-GBM antibodies (type II hypersensitivity response) along the basement membrane.[3] Streptococcal antigens and purpura haemorrhagica have been suggested as an important trigger for development of proliferative GN.[4,5] In one report, a 12-year-old gelding developed CRF due to GN 3 months after a lower respiratory tract infection with *Streptococcus zooepidemicus*.[5] In this instance, group-C streptococcal antigens and IgG were confirmed to be present in diseased glomeruli at necropsy.[5] Equine infectious anemia (EIA) virus is the only other antigen that has been detected in glomeruli of horses with proliferative immune-mediated GN.[6] However, diffuse subclinical GN likely accompanies many other chronic infections in horses. It has also been suggested that equine GN may also be associated with either mixed or monoclonal cryoglobulins forming antibody-antibody and/or complement glomerular deposits resembling human cryoglobinemia.[7] In one horse, with no evidence of viral or bacterial infection, deposits consisting solely of IgM were identified within the GBM.[8]

Chronic Interstitial Nephritis

Chronic interstitial nephritis (CIN) and fibrosis are probably the most common causes of CRF in older horses. In one retrospective study of 99 horses with CRF, CIN accounted for 39% of acquired cases of CRF.[2] Interstitial nephritis

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(tubulointerstitial disease) usually develops as a long-term sequela to ATN caused by nephrotoxins or vasomotor nephropathy. Other causes of CIN include drug-induced interstitial nephritis, urinary obstruction, pyelonephritis, renal hypoplasia/dysplasia, and papillary necrosis. Although the majority of horses that develop ARF attributable to these causes recover with apparently normal renal function (they remain nonazotemic), a few may survive with significant loss of renal functional mass and subsequently (often years later) develop signs of CRF due to CIN.[9] In horses younger than 5 years of age that develop CRF unattributable to other causes, anomalies of development (e.g., renal hypoplasia, dysplasia, polycystic kidney disease [PCKD]) should be strongly suspected.[2,10-13]

Pyelonephritis

Bilateral septic pyelonephritis is a rare cause of CRF in horses.[14-16] Pyelonephritis is usually due to an ascending infection and is often accompanied by nephrolithiasis or ureterolithiasis. However, in septic neonatal foals, it may occur due to hematogenous bacterial seeding of the kidneys. Multiparous mares (especially those with a history of dystocia) and horses with bladder paralysis are at greater risk for lower urinary tract infection (UTI) and subsequent development of ascending upper UTI. Bladder paralysis with chronic distention compromises the integrity of the ureteral orifices and leads to vesiculoureteral reflux and pyelonephritis. If paralysis is long-standing, ureteral orifice(s) may appear wide open on cystoscopy and, occasionally, the scope can be advanced into the ureter with little resistance. With unilateral pyelonephritis, adequate renal function is usually maintained by the contralateral kidney. Gram-negative organisms appear to be the most common causative agents, although *Staphylococcus*, *Streptococcus,* or *Corynebacterium* spp. may be isolated and mixed bacterial infections are not uncommon (see the Urinary Tract Infections section later).

Miscellaneous Causes

Other reported causes of CRF in horses include amyloidosis, neoplasia, focal glomerulosclerosis−like disease, and chronic oxalate nephrosis.[17-20] One study described CRF secondary to PCKD in an aged pony with hematuria; the pony also had hepatic cysts.[21] Renal amyloidosis has only been reported in horses used for production of antiserum.[17] So-called oxalate nephropathy in horses is

likely a misnomer; the presence of oxalate crystals in renal tissue of horses with CRF is typically a consequence rather than the cause of CRF.[20]

Clinical Signs and Laboratory Findings

The most common presenting complaint in horses with CRF is weight loss.[2] A small plaque of ventral edema, usually between the forelimbs, is another frequent finding.[1,2,22] Moderate polyuria and polydipsia (PU/PD) are often present but may not be noticed except by the astute owner or trainer.[1,2] Rough hair coat, partial anorexia, and poor performance are also reported.[1,2] Dysuria is generally not reported unless CRF is due to pyelonephritis, which may be associated with bladder paralysis, urolithiasis, and lower UTI. Hematuria ± pyuria (gross or microscopic) may be present in some (but not all) horses with pyelonephritis, urinary calculi, renal hypertension, or neoplasia. Urine produced by horses with CRF is often light yellow and transparent because it is relatively devoid of crystals and mucus. Accumulation of dental tartar (especially on the incisors and canine teeth [Fig. 34.2]), melena, and oral ulcers may also be found in horses with CRF. Growth may be stunted in horses with renal hypoplasia, dysplasia, or PCKD. Colic signs are variable in horses with nephrolithiasis or urolithiasis producing obstruction of the upper urinary tract and may or may not be (intermittently) present.[9,23] Rarely, signs of uremic encephalopathy such as obtundation, anxiety, head pressing, and seizure may be present, but this is more common with severe, fulminant ARF.[24,25]



FIG. 34.2 Dental tartar caused by chronic azotemia in a 5-year-old

Standardbred with chronic renal failure.

Clinicopathologic findings in horses with CRF vary depending on appetite, diet, cause, and severity of renal damage. Most horses with clinical signs of CRF have moderate to severe azotemia (serum or plasma creatinine usually ≥5 mg/dL). The serum or plasma BUN–to–creatinine ratio may vary depending on protein intake, muscle mass, hydration, and degree of azotemia but is usually greater than 10 : 1.[2] Mild hyperkalemia, hyponatremia, and hypochloremia are typically found in horses with CRF. Hypercalcemia, with serum concentrations sometimes greater than 20 mg/dL, appears to be a laboratory finding with CRF that is unique to the equid. One study of horses evaluated at referral hospitals for renal failure reported 56% of 39 horses with CRF to be hypercalcemic, and a larger study of 99 horses with CRF found 67% to be hypercalcemic.[2,26] Hypercalcemia in horses with CRF is not due to hyperparathyroidism; its presence or absence appears to be more closely related to dietary intake than to the magnitude of azotemia.[27] For example, 4/4 bilaterally nephrectomized ponies fed alfalfa hay developed marked hypercalcemia, whereas serum calcium concentration remained within the normal range in 4/4 bilaterally nephrectomized ponies fed grass hay.[28,29] Similarly, hypercalcemia in horses with spontaneously occurring CRF can resolve within a few days of changing diet from alfalfa to grass hay. Serum phosphorus concentration in horses with CRF is usually normal to low, and hypophosphatemia is more often detected with concurrent hypercalcemia. Hypermagnesemia may also be detected in some horses with CRF. Acid-base balance usually remains normal until CRF becomes advanced, but metabolic acidosis is a common finding in horses with ESKD.

Many horses with CRF are moderately anemic secondary to decreased erythropoietin production by the diseased kidneys. Those with CRF resulting from GN frequently have hypoalbuminemia and hypoproteinemia. Horses with advanced CRF due to any cause may also have mild hypoproteinemia associated with GI ulceration. Hyperglobulinemia may be detected in horses with immune-mediated diseases or chronic pyelonephritis. Horses with CRF can also develop hypercholesterolemia and hypertriglyceridemia (hyperlipidemia), and with advanced CRF may occasionally have grossly lipemic plasma.[30]

Urinalysis varies depending on the cause of CRF but is usually relatively devoid of normal mucus and crystals and thus may appear more transparent than normal equine urine. Isosthenuria is typical (USG = 1.008 to 1.014), although heavy proteinuria in GN cases may produce USG values up to 1.020. Laboratory

quantification of urine protein concentration (rather than a dipstick) is required to accurately assess proteinuria. Urine protein concentration in normal horses is usually less than 100 mg/dL, and the urine protein ($_U$Pro)–to–creatinine ($_U$Cr) ratio is less than 1 : 1.[31,32] With significant proteinuria, the $_U$Pro:$_U$Cr ratio is usually greater than 2 : 1.[5] In the earlier stages of GN, excessive urine protein is primarily albumin, but with progression of glomerular pathology an increasing amount of globulin is also lost in the urine. Horses with CIN usually do not have significant proteinuria. Hematuria (gross or microscopic) can produce trace proteinuria, but the $_U$Pro:$_U$Cr ratio usually remains less than 2 : 1. Horses with septic pyelonephritis would be expected to have pyuria (>5 leukocytes/high-power field) and significant bacteriuria on sediment examination, but these findings are not consistently detected; a urine sample should be submitted for quantitative bacterial culture in all horses with CRF.

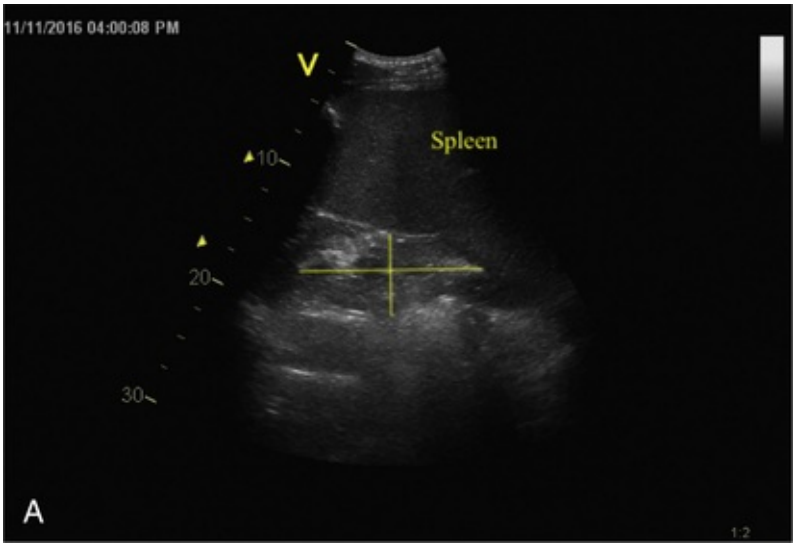
Diagnosis

A diagnosis of CRF is most often made in horses with azotemia and isosthenuria that present with a complaint of weight loss and/or decreased performance. Determining the inciting cause of CRF can be difficult because the disease has often advanced to ESKD when horses are initially presented for evaluation, although a detailed long-term history can help. Trends in serum creatinine and body condition score over weeks to months probably provide the most useful prognostic information in the horse with CRF. Urinalysis does not often reveal the cause of CRF except in some horses with pyelonephritis. Assessment of urine protein concentration and $_U$Pro:$_U$Cr ratio should be helpful in separating glomerular disease from tubulointerstitial disease, but in practice these laboratory measures have not consistently been elevated in horses with histopathologic evidence of GN. However, detection of moderate to heavy proteinuria ($_U$Pro:$_U$Cr ratio >2 : 1), *without* hematuria, provides support for glomerular disease.[29]

Rectal examination may be helpful as horses with pyelonephritis and/or ureteral calculi often have enlarged ureters that can be palpated dorsolaterally in the retroperitoneal space. Although kidneys of horses with CRF are often small with an irregular surface, these changes are not always apparent on palpation of the caudal pole of the left kidney *per rectum*. The right kidney cannot usually be palpated in the horse unless it is greatly enlarged or displaced caudally by the liver or a mass. US is useful for evaluating kidney size and echogenicity, and it

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may reveal fluid distention (indicating hydronephrosis, pyelonephritis, or PCKD) or presence of nephroliths.[33-35] Horses with significant renal parenchymal damage and fibrosis often have loss of detail of the corticomedullary junction, and echogenicity of renal tissue may be similar or even greater than that of the spleen (Fig. 34.3, *A*). The contralateral kidney may be normal or hypertrophic in cases with unilateral kidney disease (Fig. 34.3, *B*). Intravenous pyelography (IVP) provides little information in adult horses and is generally limited to foals less than 50 kg. When hematuria or dysuria accompanies CRF, cystoscopic examination can be helpful in determining from which kidney(s) hematuria is originating and allows assessment of ureteral orifice size and urine flow. A single case report of a stallion with hematuria due to unilateral nephritis described severe renal hypertension secondary to fibrotic constriction of the renal vein.[36] Nephrectomy of the affected kidney was curative in that stallion.



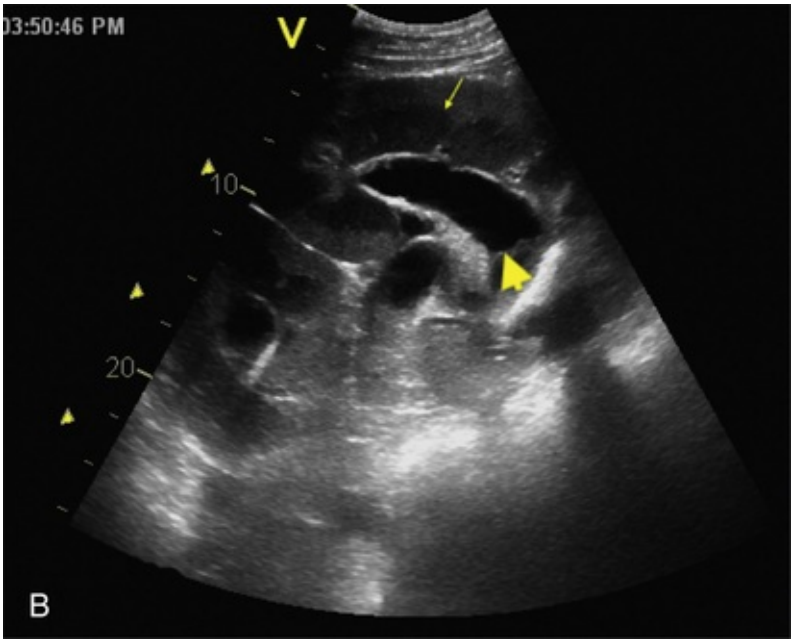


FIG. 34.3 **A,** Ultrasonographic image of the left kidney in a 4-year-old Quarter Horse gelding with chronic renal failure secondary to unilateral renal hypoplasia and exposure to nephrotoxic agents in the 6 months before onset of clinical signs (weight loss, polyuria, and polydipsia). The left kidney is measured in the 17th intercostal space (ICS) and is small (10.5 cm length × 5.8 cm width; reference range: 12.6 ± 2.2 cm length × 7.9 ± 1.1 cm width), hyperechoic relative to the spleen, and has a loss of corticomedullary distinction. **B,** Ultrasonographic image of the right kidney in the same horse measured in the 16th ICS is enlarged (23 cm length × 9 cm width; reference range: 16.0 ± 0.7 cm × 7.9 ± 1.0 cm width), with a distended renal pelvis *(wide arrow)* and distinct hyperechoic and widened renal cortex *(arrow)* (2.0 cm; reference range 1.3 to 1.6 cm). This kidney was suspected to be hyperplastic.

Measurement of GFR provides the most accurate assessment of renal function, and repeated measurements at monthly (or longer initially) intervals can be useful to monitor rate of progression of CRF and thus prognosis and remaining lifespan. It is also a useful measure to document a reduction in renal function in horses that are thought to have early CRF, before significant azotemia has developed. Measurement of GFR can be by several methods, including urinary clearance of endogenous or exogenous creatinine, inulin, or technetium-99m diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) (all require timed urine collections), and plasma disappearance of sodium sulfanilate, phenolsulfonphthalein, or radiolabeled compounds (e.g., ^{99m}Tc-DTPA).[13,37-40] Assessment of renal function by nuclear scintigraphic imaging of the kidneys has also been described, but in horses this technique appears to be better for

documenting decreased individual kidney function (i.e., with unilateral disease) than for quantitative assessment of GFR.[40,41] In most clinical settings, performing a 24-hour endogenous creatinine clearance is the most practical and economical method for measuring GFR. The major challenge is application of a urine collection device for collection of *all* urine produced, via a method that does not pose a risk of introducing ascending infection into the urinary tract. Once urine has been collected, a well-mixed sample is submitted to the laboratory, along with a sample of serum obtained during the collection period, and GFR is estimated by the following standard clearance formula:

$$\mathrm{GFR}(\mathrm{mL} \bullet \mathrm{kg}^{-1} \bullet \mathrm{min}^{-1}) = \{([\mathrm{Cr}_{\mathrm{urine}}]/[\mathrm{Cr}_{\mathrm{serum}}])\} \times \mathrm{UF}/\mathrm{bwt}$$

where *UF* is urine flow (mL min^{-1}) and *bwt* is body weight in kilograms.[38,39] In horses with normal renal function, GFR ranges from 1.5 to 3.0 mL/kg/min, and values <1.0 mL/kg/min are indicative of a decreased GFR. Repeated measurement of endogenous creatinine clearance provides useful information about the rate of decline in GFR in horses with CRF. However, it is much simpler and more economical to perform a physical examination, assess body condition, and measure serum creatinine concentration at monthly (or longer) intervals to evaluate the progression of CRF in affected horses.

Systemic blood pressure (BP) monitoring should be a component of a comprehensive database for horses with CRF. A recent case series describing hypertensive cardiomyopathy in horses revealed that the documented cardiac hypertrophy and systemic hypertension were associated with CRF or chronic laminitis.[42] The horses diagnosed with hypertensive cardiomyopathy were all euthanized due to the severity of their underlying disease, suggesting that CRF in these cases was at an end stage. Recent studies have demonstrated that indirect BP monitors have good precision and accuracy when measuring mean arterial pressure (MAP) in normotensive and hypertensive horses; these monitors allow trends to be followed in standing horses with hypertension.[43,44] Further diagnostic investigation, such as echocardiography, as well as consideration of antihypertensive medical therapy such as an angiotensin-converting enzyme (ACE) inhibitor, might be warranted if there is documentation of persistent systemic hypertension (uncorrected noninvasive BP MAP >116 mm Hg).[45]

The inciting cause of CRF can sometimes be confirmed by renal biopsy. Renal

biopsy should be approached somewhat cautiously and pursued only if findings are likely to change treatment or prognosis. However, a recent multicenter study on equine renal biopsies found that histopathologic diagnosis by biopsy had a 72% agreement with histopathology at necropsy.[46] This same study found a complication rate of 11.3%, generally associated with hemorrhage or signs of colic, and there was only one fatality.[46] Risk factors for complications included biopsy of the left kidney, a diagnosis of neoplasia, and low USG.[46]

Treatment

Treatment of horses with CRF is most likely to produce improved renal function if there is an acute reversible component exacerbating CRF (i.e., acute-on-chronic disease). Similar to ARF, sudden exacerbation can be caused by exposure to nephrotoxins or vasomotor nephropathy secondary to diseases producing hypovolemia (e.g., diarrhea). Ascending UTI or obstruction can also exacerbate CRF. If an acute component is detected, it should be corrected rapidly (as described for ARF) with the goal of minimizing further loss of functional nephrons. In addition, surgical removal or fragmentation of stones may be indicated in horses with calculi thought to be disrupting urine flow.

In horses with relatively stable CRF, management changes should be kept to a minimum and, when necessary, made gradually. Treatment of horses with stable CRF consists of supportive care: fluids, electrolytes, and nutritional support. Water should be available at all times, and salt can be provided freely so long as edema and/or hypertension are absent. If edema develops, salt should be restricted, even in the face of hyponatremia. In addition to serum creatinine, electrolyte concentrations and acid-base balance should be measured regularly (e.g., monthly or initially longer intervals). If serum sodium and chloride concentrations are decreased, 60 to 120 g (≈2 to 4 oz) of salt may be added to the feed, provided edema is not present. If metabolic acidosis is detected (e.g., blood pH <7.35 or serum bicarbonate concentration <20 mEq/L) and the patient is not edematous, sodium bicarbonate ($NaHCO_3$) powder (100 to 200 g/day) or a mix of $NaHCO_3$ and salt should be added to the diet. The goal of supplementation with salt and $NaHCO_3$ is to maintain serum electrolyte concentrations and acid-base balance within reference ranges. However, the effect of electrolyte supplementation on progression of CRF is unclear because high-salt diets may actually hasten the decline in GFR and exacerbate proteinuria in human patients with CRF.[47]

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Although no adverse effects of hypercalcemia in horses with CRF have been documented, decreasing calcium intake (e.g., replacing alfalfa or other legume hays with grass hay) may result in a return of serum calcium concentration to the normal range. The hypophosphatemia that usually accompanies hypercalcemia in horses with CRF may prevent mineralization of soft tissues. There appears to be no need for vitamin D supplementation in horses with CRF, but regular administration of vitamin B complex and anabolic steroids may be helpful to stimulate appetite. If the appetite remains good, anabolic steroids may further limit muscle wasting and may increase PCV. Attenuation of anemia in human and canine patients with CRF by administration of recombinant erythropoietin has been one of the most significant advances in the management of this disease; its application to equine CRF remains to be investigated.[48] In an occasional horse with advanced CRF, marked hyperlipemia may develop and administration of heparin (40 to 100 units/kg subcutaneously [SC] twice daily) may stimulate lipoprotein lipase and decrease plasma triglyceride concentration.[49] This treatment is not without risk, however, as it may cause a further decline in PCV and potentiate bleeding tendencies in a uremic patient. Corticosteroids and NSAIDs are best avoided in horses with CRF due to primary tubulointerstitial disease. If these drugs are essential for treatment of a complicating problem, they should be used judiciously. Management of CRF due to GN appears to be even less rewarding than that for CRF caused by tubulointerstitial disease. Immunosuppressive therapy has been of limited benefit in slowing the progression of the disease and may even hasten weight loss, although short-term improvement with dexamethasone therapy has been documented in one horse that had an immune-mediated (selective IgM) glomerulonephropathy.[8] For patients with significant edema, treatment with diuretics may result in transient improvement, and plasma transfusions may be of temporary benefit to horses with edema and hypoalbuminemia.

As CRF progresses, partial anorexia and lethargy lead to more rapid loss of body condition, so nutritional management aimed at maintaining body condition is probably the most important aspect of supportive care for these horses. Increasing carbohydrate (grain) feeds and adding fat to the diet are recommendations to increase caloric intake. Fat can be added by feeding corn oil (up to 16 oz/day) or a commercial fat supplement (often more palatable). Increased intake of omega-3 fatty acids (e.g., available in linseed oil or flaxseed oil) has been demonstrated to slow the progression of renal failure in experimental models, but potential benefits in spontaneously occurring CRF are

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less clear.[50,51] Restricting dietary protein intake by human and veterinary patients with CRF was once thought to have beneficial effects.[52] However, the current recommendations in humans with CRF are mixed and complex, with no clear benefit of restricting protein in metanalyses of multiple studies.[53] Rather, the literature supports individually tailored diets based on stage of disease, age, comorbidities, body condition, and the use of dialysis or not, and they may be high, moderate, or low protein depending on the individual patient.[53] In horses with CRF, appropriateness of dietary protein intake can be assessed by the serum BUN–to–creatinine ratio; values greater than 15 : 1 suggest excessive protein intake, and values less than 10 : 1 may indicate protein-calorie malnutrition. Finally, an important aspect of nutritional management of horses with CRF is provision of a highly palatable diet. Feeding smaller meals more frequently and varying the diet are helpful methods to increase food intake. It should be remembered that if the horse with CRF becomes anorectic or will eat very little, quality of life is an important factor to consider.

Additional treatments for CRF in human patients include antihypertensive agents, including diuretics, β-adrenergic blockers, and ACE inhibitors.[54] The ACE inhibitors may have an additional benefit of limiting proteinuria.[55] In dogs and cats, ACE inhibitors and/or angiotensin receptor blockers are considered standard of care for managing chronic kidney disease with proteinuria.[56] Little is known about the roles of systemic or intrarenal hypertension in progression of renal disease in horses. There are no research reports of potential benefits of use of antihypertensive medications in horses with CRF. Oral administration of the ACE inhibitor benazepril was evaluated in healthy horses following exogenous administration of angiotensin 1 and modestly attenuated a rise in systemic blood pressure at a dose of 1 mg/kg.[57] Future studies are needed to determine the optimal dose, frequency, safety, and efficacy for horses with CRF.[57]

Horses with end-stage CRF often develop oliguria and uncontrollable metabolic acidosis. At this stage, CRF can only be managed by hemodialysis or peritoneal/pleural dialysis. However, pursuit of either hemodialysis or peritoneal dialysis in horses with CRF is of questionable logic because even when successful, dialysis is likely to prolong the life of the horse for only a short time.

Prognosis

As soon as the diagnosis of CRF is made, the owner should be made aware that it is a terminal condition, so as to prepare him or her well in advance for making

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the decision to euthanize on humane grounds at the appropriate juncture, most likely within 2 years after the diagnosis of (stable) CRF. With patient-tailored management and monitoring, many horses with early CRF may be able to continue in performance or live as a “pasture pet” for months to a few years. In general, as long as creatinine remains less than 5.0 mg/dL and the BUN–to–creatinine ratio is less than 15 : 1, affected horses seem to maintain a reasonably good attitude, appetite, and body condition. Once creatinine is greater than 5.0 mg/dL, the rate of progression of CRF appears to accelerate and signs of uremia (e.g., anorexia, poor hair coat, loss of body condition) often become more apparent. Although this threshold for creatinine concentration is a useful figure for informing an initial prognosis for most horses, it is important to remember that progression of CRF is highly variable. Thus, each case must be handled on an individual basis, with the emphasis on maintenance of body condition until humane euthanasia becomes necessary.

Urinary Tract Infections

Thomas J. Divers • Dominic R. Dawson-Soto • Alexandra J. Burton

UTI can be anatomically divided into two categories: those affecting the upper urinary tract (kidneys and ureters) and those involving the lower urinary tract (bladder and urethra). Lower UTI usually results from anatomic or functional causes of abnormal urine flow, especially bladder paralysis (see Urinary Incontinence section later). Although recognized less frequently, upper UTI is often a more serious, potentially life-threatening problem. In horses, UTI is also frequently accompanied by urolithiasis and partial obstruction.[1]

Risk Factors and Causes

The most common risk factors for development of UTI are bladder paralysis, urolithiasis, and urethral damage (e.g., foaling trauma in mares, neoplasia or habronemiasis in males). However, in the case of urolithiasis, with the exception of single large cystoliths (which predispose horses to lower UTI), it is often difficult to determine whether concurrent nephroliths, ureteroliths, multiple small cystoliths, and/or urethroliths are a cause or consequence of UTI. The shorter urethra and its location near the anus can increase the risk of lower UTI in mares and fillies. One study in healthy horses showed that mares had significantly more colony-forming units (CFUs) of bacteria in their urine than males.[2] In humans, silent lower UTIs and pyelonephritis resulting from infection

with bacteria shed from the GI tract can develop in prepubertal girls and during pregnancy or after menopause in adult women.[3] In certain instances, this increased risk has been further attributed to a lack of estrogen, which appears to be important for production of glycosaminoglycans that cover uroepithelial surfaces and inhibit attachment of bacteria.[4] Whether fillies or pregnant mares are at increased risk for UTI has not been studied. Horses with bladder paralysis or decreased urethral sphincter tone are at greater risk of UTI. Immunosuppression should also be considered an important risk factor, especially in today's aging equine population (i.e., if uncontrolled pituitary pars intermedia dysfunction [PPID] is present). Finally, as bladder catheterization cannot be performed in a completely sterile manner due to normal bacterial flora in the vestibule and distal urethra, iatrogenic lower UTI is a risk of this procedure. However, UTI is an unlikely complication of bladder catheterization in otherwise healthy animals because host defense mechanisms, including urine flow, are highly effective in eliminating contaminating bacteria. When urethral or bladder mucosa has been damaged or urine stasis (e.g., bladder paralysis) is present, bladder catheterization has a greater risk of producing UTI.

Bacterial UTI is most common. In one study on urine from healthy male and female horses, multiple bacterial species were cultured, regardless of whether urine was obtained via midstream free catch or catheterization, with the predominant isolates being *Streptococcus* spp., *E. coli*, *Enterobacter* sp., *Bacillus* sp., *Staphylococcus* spp., *Diptheriods* sp., *Proteus* spp., and *Enterococcus* sp.[2] In one author's experience (TJD), *E. coli*, *Proteus mirabilis*, *Klebsiella* spp., and *Enterobacter* spp. are the most common pathogens isolated from individual horses with UTI. Historically in the literature, *E. coli*, *Staphylococcus* spp., *Corynebacterium* spp., *Streptococcus* spp., and *Pseudomonas aeruginosa* were the microbes isolated most frequently from horses with UTI.[5,6] A more recent study found *E. coli* (36%), *Streptococcus* spp. (20%), and *Enterococcus* spp. (20%) in urine cultures from equine clinical cases.[7] In a group of seven horses with pyelonephritis, *Pseudomonas aeruginosa*, *E. coli*, and *Streptococcus zooepidemicus* were cultured.[8] Individual case reports of cystitis in horses due to *Corynebacterium matruchotii* infection and a combined *E.coli* and *Enterococcus* spp. infection have also been described.[9,10] In horses with instrumentation of the urinary tract (e.g., indwelling bladder catheters, ureteral stents), UTI with nosocomial, antimicrobial-resistant pathogens should always be considered a risk. In septicemic foals, hematogenous infection of the kidney(s) with

Actinobacillus spp., *Rhodococcus equi*, and *Salmonella* spp. has occurred.[11-13] Lower UTI with yeast (*Candida* spp.) occurs in neonatal foals receiving broad-spectrum antibacterial therapy, especially if they are recumbent and/or have indwelling urinary catheters. The spirochete *Leptospira interrogans* can infect the equine kidney, occasionally causing acute interstitial nephritis, but it is more commonly implicated in uveitis and abortion.[14]

Equine parasitic UTIs do not commonly cause clinical disease. The coccidian parasite *Klossiella equi* infects the renal parenchyma of equids but has only been reported to cause disease (interstitial nephritis and tubular necrosis) in instances of heavy infection or host immunosupression.[14-18] The nematode *Halicephalobus gingivalis* is primarily a cause of equine neurologic disease (meningoencephalitis) but may also result in granulomatous nephritis via hematogenous spread.[14,19-21] Both *K. equi* sporozoites and *H. gingivalis* parasites can sometimes be found in the urine sediment of infected animals.[14,15,19,21] There is one report of two horses developing tubularinterstitial nephritis in association with productive, lytic equine polyomavirus infection.[22] The etiopathogenesis in these two horses was hypothesized to be similar to BK polyomavirus nephropathy of immunocompromised humans.[22,23] In horses without any obvious predisposing factor for UTI, primary immune dysfunction or other immunocompromise (e.g., uncontrolled PPID) should be considered, especially in cases where uncommon pathogens are identified as causative agents.[15,17,22] Sterile ulcerative cystitis due to phenylbutazone administration has been reported.[24] In addition, a newly described entity of equine sterile idiopathic hemorrhagic cystitis was recently documented in a cases series of 11 horses (see the Urinary Tract Neoplasia section later).[25]

Clinical Findings

Clinical signs of UTI usually reflect the location, severity, and duration of infection. Lower UTI seldom causes signs of systemic illness and infection and is typically characterized by disturbances in urine flow (dysuria, dysuria, stranguria, pollakiuria, and incontinence). An exception to this is in mares with subclinical cystitis/urethritis, where outward signs may not be present or recognized. Urine scalding of the perineum may develop with chronic UTI in mares but should not be confused with estrus or fecal crusting/scalding due to diarrhea or a sunken anus (poor conformation or as a result of low body

condition score). The sheath opening and dorsal aspects of the hindlimbs may be coated with urine crystals or blood in males with UTI. In an occasional horse, gross pyuria may also be observed as passage of mucopurulent debris in otherwise clear urine but should not be confused with the normal turbid appearance of equine urine (see Chapter 10, Fig. 10.2). Gross hematuria can be seen with urinary calculi, neoplasia, or if the bladder and/or urethral mucosa is eroded or very inflamed. Hematuria of bladder origin typically produces hematuria throughout urination, with gross discoloration of urine most obvious at the end of urination. Hematuria can also be caused by upper urinary tract hemorrhage. Renal hemorrhage was a major component of bacterial pyelonephritis reported in seven horses and has also been seen with clinical *K. equi* infection.[7,15] Horses with upper UTI are much more likely to have signs characteristic of a systemic infection, including fever, inappetence, lethargy, colic, and weight loss. However, because upper UTI is often accompanied by concurrent lower UTI, dysuria may also be present.

Diagnosis

A diagnosis of UTI is based on clinical signs, analysis of blood and urine samples, US, and cystoscopy. With lower UTI, the complete blood cell count (CBC) and serum biochemical profile are usually normal, whereas the CBC with upper UTI often supports a systemic inflammatory response. Detection of azotemia, low USG, and white blood cell (WBC) casts in urine sediment are indicative of upper UTI, especially when accompanied by signs of systemic illness. With chronic upper UTI, increased total protein and globulin concentrations are also often detected. In human medicine, pyuria (increased number of WBCs in the urine) is defined as the presence of greater than 10 WBCs per mm^3 urine or greater than or equal to three WBCs per microscopic high-power field (HPF).[26] In horses, to the author's (AJB) knowledge, there has been no peer-reviewed study specifically assessing the cellular content of urine in a large number of healthy adult horses. However, in horses, pyuria is generally considered to be the presence of greater than 10 WBCs per HPF of a midstream-voided or catheterized sample, with the urine of healthy horses generally said to have fewer than five WBCs per HPF.[27] That said, one study in healthy males and females found that no horse had a WBC count greater than one per HPF in midstream free catch sample.[2] This suggests that the generally accepted number of greater than 10 WBCs per HPF to diagnose pyuria may be too high for horses,

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and it should be diagnosed if greater than five WBCs per HPF are seen, providing collection is aseptic or midstream and there is clinical suspicion of urinary tract disease. When bacterial infection is the cause of pyuria, there are typically more than 20 organisms visible per HPF. Urine samples should be examined and processed for bacterial culture within 30 minutes after collection or be refrigerated because bacteria can continue to proliferate when urine is stored at room temperature. Culture results should be interpreted in light of the clinical picture, as not all organisms cultured may be causative and some may be innocuous contaminants.

Rectal examination and transrectal US may help confirm a predisposing cause of lower UTI (e.g., enlarged and atonic bladder, cystic calculi, bladder mass). Chronic cystitis also usually leads to bladder wall thickening, visible via US.[25] The ureters are not usually palpable during rectal examination of the normal horse, but in horses with upper UTI, careful palpation of the dorsolateral aspects of the caudal abdomen (retroperitoneal space) usually reveals enlarged ureters, and transrectal US can help confirm this finding. With pyelonephritis, rectal palpation may further reveal an enlarged, painful, or shrunken and misshapen left kidney, while the right kidney is usually not palpable. Transabdominal US of the kidneys is useful for detecting abnormal renal size, shape, or consistency in horses with upper UTI.[8,27-32] Horses with pyelonephritis may have a focus of septic infection with adjacent dilation of the renal pelvis (Fig. 34.4), which may be detected by US if it distorts renal architecture and echogenicity sufficiently.



FIG. 34.4 A transected kidney from a horse with pyelonephritis. Note the severely dilated renal pelvis adjacent to a septic purulent focus. (Courtesy The University of Pretoria, Faculty of Veterinary Science.)

Cystoscopic examination of the lower urinary tract is useful for evaluating the integrity of urethral and bladder mucosa, detecting small uroliths, and assessing urine flow from each ureteral orifice.[1,8,27,32] With long-standing cystitis, especially when bladder paralysis is the underlying cause, ureteral orifices may become dilated (and appear wide open), allowing for vesiculo-ureteral reflux and development of ascending pyelonephritis. When unilateral pyelonephritis is suspected on the basis of US findings, cystoscopy with catheterization and collection of urine samples individually from each ureter can be helpful to document unilateral disease. Ureters may be catheterized by passing sterile polyethylene tubing through the biopsy channel of the endoscope during cystoscopy or can be accomplished in mares by directing blunt-ended catheters (e.g., 8-Fr polypropylene) through the urethra into each ureteral orifice.[33]

Treatment

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Treatment of UTI consists of proper antimicrobial therapy and correction, if possible, of predisposing anatomic or functional causes. Selection of the appropriate antimicrobial agent is best determined by prior knowledge of susceptibility patterns of the causative pathogen(s), concentration of the antimicrobial in renal tissue and urine, activity of the antibiotic at different pH values, toxicity, compatibility with other antimicrobial drugs, ease of administration, and expense. In addition, with the increasing emergence of antimicrobial-resistant pathogens, especially within hospital settings, antimicrobial stewardship through rational antimicrobial therapy is vital (see Chapter 45). Resistance in vitro to a particular antibiotic may not preclude successful treatment with the drug, providing high enough concentrations are achieved in urine. Similarly, in vitro susceptibility does not always guarantee a successful response to treatment. Penicillin, ampicillin, cephalosporins, trimethoprim-sulphonamide (TMS), and gentamicin are all concentrated in urine. The antimicrobials of choice for horses with lower UTI are TMS or ceftiofur, or a broad-spectrum combination (i.e., penicillin or ampicillin or ceftiofur, plus gentamicin or amikacin).[34] Gentamicin and amikacin should be avoided in patients with severe azotemia or suspected renal failure, as these are potentially nephrotoxic. Fluconazole is the antifungal drug of choice for UTI involving *Candida* spp.[34] Treatment should be continued for 7 to 14 days and then urine recultured. For upper UTI (pyelonephritis), TMS, ceftiofur (or other third-generation cephalosporins), penicillin or ampicillin, or enrofloxacin are the antimicrobials of choice.[34] Therapy for upper UTI is usually required for 2 to 3 weeks and often longer.[34] Although less of a risk with newer preparations, horses with acidic urine, dehydration, or poor renal perfusion may develop hematuria and crystalluria with sulfonamides.[35] With presumed lower UTI, if the UTI recurs and the same organism is isolated, a focus of upper UTI should be suspected. In contrast, recurrence of UTI with a different pathogen suggests an anatomic or functional cause of abnormal urine flow as a predisposing cause of UTI.

Although unstudied in horses, the use of lactobacillus suppositories in women predisposed to UTI enhanced cure rates in some studies but showed no efficacy in others.[32,36,37] Preliminary research on vaccines against bacterial virulence factors to reduce the incidence of UTIs in predisposed populations of humans and mice appears promising.[38] There is no research into these alternative therapies in horses to date.

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Urinary Incontinence

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Risk Factors and Causes

Urinary incontinence in the horse can result from urolithiasis, congenital anomalies or defects of the lower urinary tract, trauma, neoplasia, neurologic diseases accompanied by bladder dysfunction, and decreased urethral tone. Bladder and urethral calculi frequently result in transient or intermittent incontinence secondary to sabulous cystitis or partial obstruction.[1-4] Ectopic ureter and other congenital malformations of the urinary tract generally produce incontinence from birth, although it may not be recognized until several weeks or months of age. Presentation of incontinence in adult horses due to congenital anomalies has also been described.[5-8] Trauma-induced incontinence may develop after breeding injury or dystocia in mares, or in both genders after sacral or spinal injury. Incontinence may also develop with severe long-standing lumbosacral or back problems if they make it difficult and/or painful for the horse to posture to urinate. In these instances, over time, *incomplete bladder emptying* allows the crystals normally present in equine urine to accumulate in the ventral aspect of the bladder. This crystalloid sediment becomes heavy (and in some cases quite firm), further preventing complete bladder emptying. This condition, which is termed *sabulous urolithiasis*, can accompany bladder paralysis of any cause but also may itself cause myogenic bladder dysfunction, in the absence of any underlying neurologic problem.[1,2] The weight of the sediment may induce chronic stretching of the bladder wall, contributing to myogenic dysfunction. Horses with lower urinary tract neoplasia can also present with incontinence, but other complaints (e.g., stranguria or hematuria) are usually reported as well.

Neurologic disorders that most commonly result in bladder paralysis and incontinence include equine herpesvirus-1 myeloencephalopathy (EHM), cauda equina neuritis syndrome, polyneuritis equi, sorghum toxicosis, and aberrant larval migrans *(Halicephalobus gingivalis)* and equine protozoal myeloencephalitis (EPM), dependent on parasite location within the nervous system.[9-14] These diseases, along with other problems affecting gray matter of the sacral segments, result in loss of lower motor neuron (LMN) function, whereas lesions of the lumbar or higher portions of the spinal cord result in loss of upper motor neuron (UMN) function. Loss of detrusor muscle function and

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overflow incontinence is seen with LMN damage, and a large, easily expressed bladder is found on rectal palpation. Initially, UMN disease is characterized by increased urethral resistance, which leads to increased intravesicular pressure before voiding can occur. Voiding may occur as short bursts of urine passage with incomplete bladder emptying, and rectal examination may reveal a turgid bladder that is variable in size. Although UMN signs are initially different from those of LMN disease, incontinence is not usually recognized until overflow incontinence develops as a result of sabulous urolithiasis and progressive loss of detrusor function. The latter progression can explain why bladder paralysis and incontinence may be found in horses with other neurologic diseases like cervical stenotic myelopathy (CVM), equine degenerative myelopathy (EDM), and even viral encephalomyelitis other than EHM. Presence of other signs associated with LMN dysfunction (e.g., loss of anal or tail tone) or UMN dysfunction (e.g., ataxia) may aid in differentiating the inciting cause of bladder paralysis. Despite many possible causes, the prognosis for recovery from incontinence resulting from bladder paralysis is generally poor because sabulous concretions and UTI rapidly complicate the problem. However, successful management of sabulous cystitis has been described in five horses for up to 3 years with medication in combination with bladder catheterization and lavage.[2] A syndrome of estrogen-responsive incontinence caused by decreased urethral sphincter tone has been reported in a few mares.[15,16]

Diagnosis

In addition to taking a complete history and performing physical and neurologic examinations, it is helpful to take time to observe the incontinence or any attempts to urinate. Clinical signs often include stranguria and urine scalding of the perineum and hind legs in females, sometimes with tissue thickening if the incontinence has been long-standing (Fig. 34.5). Rectal palpation, transrectal US of the bladder and upper urinary tract, transabdominal US of the kidneys, and cystoscopy are useful to rule out uroliths, neoplasia, cystitis, and congenital anomalies as causes of incontinence. If trauma or sacral bony abnormalities leading to incontinence are suspected, radiographs and pelvic ultrasound should be attempted. Nuclear scintigraphy may further help in identification of a traumatic lesion, especially in large patients where radiography is limited. CT or magnetic resonance imaging (MRI) should be considered in foals and small ponies.[17] Although most affected horses remain nonazotemic (unless significant

obstruction or bilateral pyelonephritis has developed), laboratory analyses of blood and urine, including a quantitative urine culture, should be performed in all horses with incontinence, because UTI is a common sequela. Urethral and bladder pressure profiles can be used to assess urinary sphincter and detrusor muscle function. Normal values for both mares and geldings have been reported.[18-20] Where an underlying neurologic problem is suspected, cerebrospinal fluid (CSF) collection and analysis may also be of value.



FIG. 34.5 Extensive thickening of the perineum and caudomedial thigh region due to chronic dribbling of urine (incontinence) in a 17-year-old mare with a large cystic calculus (see Fig. 34.10). (Image courtesy Montague N. Saulez.)

Treatment

Treatment for incontinence varies with the underlying cause. Removal of calculi and appropriate antimicrobial therapy are effective treatments for urolithiasis and UTI. Surgical correction is generally required for treatment of congenital anomalies, but owners should be discouraged from using affected animals for breeding. Incontinence due to EHM or EPM carries the most favorable prognosis for recovery, although in one author's (DRD) experience, with EHM, bladder paresis may persist for several weeks to months. To prevent continued distention and further damage to the detrusor function, removal of sabulous crystalloid material by bladder lavage with saline and temporary placement of an indwelling bladder catheter are indicated in cases of recent onset of bladder paresis. Debate exists in the human literature regarding the preference of intermittent versus continuous urinary catheterization. In animals, both methods carry potential risks—infection and/or trauma from repeated catheterization—and each case should be evaluated individually to choose the most appropriate method.[1,2,21] Antimicrobial treatment, ideally based on urine culture results, is also indicated in all horses with bacterial cystitis secondary to bladder paralysis.

Bethanechol (0.03 to 0.04 mg/kg SC or IV q6-8h, or 0.22 to 0.45 mg/kg PO q6-8h [poorly absorbed]), a parasympathomimetic agent that has a somewhat selective effect on smooth muscle of the gastrointestinal tract and bladder, has been recommended for improving detrusor tone and strength of contraction in horses with bladder paralysis. However, response to treatment is often disappointing, perhaps because of long-standing paralysis before incontinence is recognized, although bethanecol-responsive bladder atony has been reported in a foal.[22] Use of phenoxybenzamine (0.4 mg/kg PO q6h), an α-adrenergic blocker that decreases urethral sphincter tone, has also been recommended in combination with bethanechol in cases with UMN bladder dysfunction. In horses with evidence of urethral sphincter hypotonia, the sympathomimetic agent phenylpropanolamine (0.5 to 2 mg/kg PO q8-12h) has also been used. Dosing regimens for these autonomic drugs have been extrapolated from other species because no pharmacokinetic data are available for the equine species.

In general, treatment with these autonomic drugs has largely been ineffective in controlling incontinence due to bladder paralysis, and overall the long-term prognosis for recovery is usually poor. On a more positive note, treatment of a few mares with urethral sphincter hypotonia with estradiol cypionate or benzoate (5 to 12 µg/kg IM every day for 3 days, then every other day) has been effective

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at resolving incontinence as long as detrusor function is normal. Historically in the literature, estrogen-responsive incontinence has been reported in a total of three mares.[15,16] Estrogen may modulate the effect of norepinephrine on α-receptor activity in the urethral sphincter, thereby improving urethral sphincter tone. There is also a report of successful surgical repair of an incompetent (damaged during removal of a cystic urolith) urethral sphincter in a mare.[23]

Ectopic Ureter

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Although rare, ectopic ureter is the most frequently reported developmental anomaly of the equine urinary tract and there are many case reports and series.[1-13] This abnormality is the result of an error in embryologic development causing one or both ureters to empty into the urethra, uterus, or vagina instead of attaching normally to the dorsal wall of the urinary bladder.[1] Of the cases reported, almost all have been fillies, and the primary complaints were urinary incontinence and perineal dermatitis (urine scalding).[1-13] However, this gender distribution may reflect easier recognition of partial urinary incontinence in females rather than a true gender predilection. In the male, intermittent urine dripping from the end of the penis is less easily recognized; further, urine entering the pelvic urethra may pass retrograde into the bladder.

Diagnosis

Ectopic ureter should be suspected in young horses with incontinence observed shortly after birth. Renal function is usually normal, but the affected ureter may be extremely dilated. In young foals (e.g., <50 to 75 kg), an excretory urogram (after IV administration of contrast agent) or pyelography (after percutaneous injection of contrast agent into renal pelvis via ultrasonographic guidance) may aid in diagnosis of ectopic ureter.[3-6,8] Unfortunately, most patients are not presented until they are too large for this procedure to be performed. Ultrasonographic examination may reveal mild dilation of the renal pelvis on the affected side(s).[3,5] Vaginoscopic and cystoscopic examinations should also be pursued in older foals to determine whether the problem is unilateral or bilateral and, when unilateral, to determine which ureter is ectopic. In the latter case, cystoscopic examination should reveal urine entering the bladder from only one normal ureteral opening, located at either 2 or 10 o'clock in the bladder neck.

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Urine can be seen squirting from normal ureteral openings approximately every 20 to 30 seconds. Observation of normal bouts of voiding, in addition to incontinence, further supports a unilateral problem. To determine the location of the opening of the ectopic ureter, visual examination of the vestibule and vagina (using a blade speculum) should be performed initially to look for intermittent urine flow from the area of the urethral papilla. Ectopic ureteral openings are usually not apparent unless urine flow is seen. Intravenous (IV) administration of dyes including sodium fluorescein (11 mg/kg IV; yellow-green color), indigotindisulfonate (indigo carmine, 0.25 mg/kg IV; blue-purple color), azosulfamide (1.9 mg/kg IV; red color), or phenolsulfonphthalein (0.01 mg/kg IV; red color) to discolor the urine may help locate ectopic ureteral openings.[1,4] Nuclear scintigraphy has been employed to assess renal function and anatomy of involved urinary tract structures before correction.[11] CT has also been used to diagnose ectopic ureter in a filly.[7] Magnetic resonance (MR) urography is the diagnostic tool of choice in children with ectopic ureter and thus may have utility for diagnosis in young foals if size and cost permit.[14]

Treatment

If the ectopic ureter is unilateral, ultrasonographic examination of the opposite kidney appears normal, and azotemia is not present, the preferred treatment may be surgical removal of the kidney on the affected side and ligation of the ureter.[6,9,12,13] Nephrectomy may produce an increase in creatinine (0.5 to 1.0 mg/dL) for a few days, but creatinine usually returns to the prenephrectomy concentration within a week. If both ureters are ectopic, which is not unusual, implantation of the distal ureters into the bladder neck should be attempted. Several surgical techniques have been described.[1,4,6,8,10-12] Complications can include ascending infection, resulting from dilated ureters, and development of adhesions, but successful repairs have also been reported.[1,4,6,8,10-12]

Urinary Tract Neoplasia

Thomas J. Divers • Stephanie A. Brault • Alexandra J. Burton

Neoplasia of the urinary tract has generally been considered rare in horses. That said, two recent retrospective post mortem studies identified a higher proportions of urinary tract neoplasia than expected.[1,2] A study in Germany, prompted by an observed increase in cases of equine kidney tumors, identified

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renal neoplasia in 20/1069 horses necropsied.[1] Another study in Indiana, specifically looking at horses 15 years of age and older submitted for necropsy, found that 12 of the 241 horses had squamous cell carcinoma, and the most common site for it to be found was the urinary bladder (5/12).[2] These recent findings likely reflect today's aging horse population, supported by the fact that the majority of horses with renal or urinary tract neoplasia in both studies were older than 20 years of age.[1,2] This assumption is further supported by another recent study comparing idiopathic hemorrhagic cystitis with bladder neoplasia: The median age of horses with bladder tumors was 24 years (range 16 to 30 years of age).[3]

Primary kidney neoplasms include renal cell carcinoma (Fig. 34.6, *A*), adenoma, and nephroblastoma, with carcinoma and then adenoma being the most common.[1,4-14] Renal cell carcinoma (or adenocarcinoma) and adenoma occur more frequently in older horses, older than 10 years of age and most often older than 20 years old. Nephroblastomas may be detected in young horses.[15] Lymphosarcoma (Fig. 34.6, *B*), hemangiosarcoma, multiple myeloma, and melanoma may also involve the kidneys and, on rare occasions, the bladder.[13] Squamous cell carcinoma is the most common bladder tumor, but horses may also develop transitional cell carcinoma, adenocarcinoma, and undifferentiated carcinomas of the bladder.[3,4,19] Fibromatous bladder polyps may occur in younger horses and a poorly differentiated aggressive leiomyosarcoma of the urogenital tract with extensive bladder involvement has been described in a 2-year-old filly.[4,19,20]

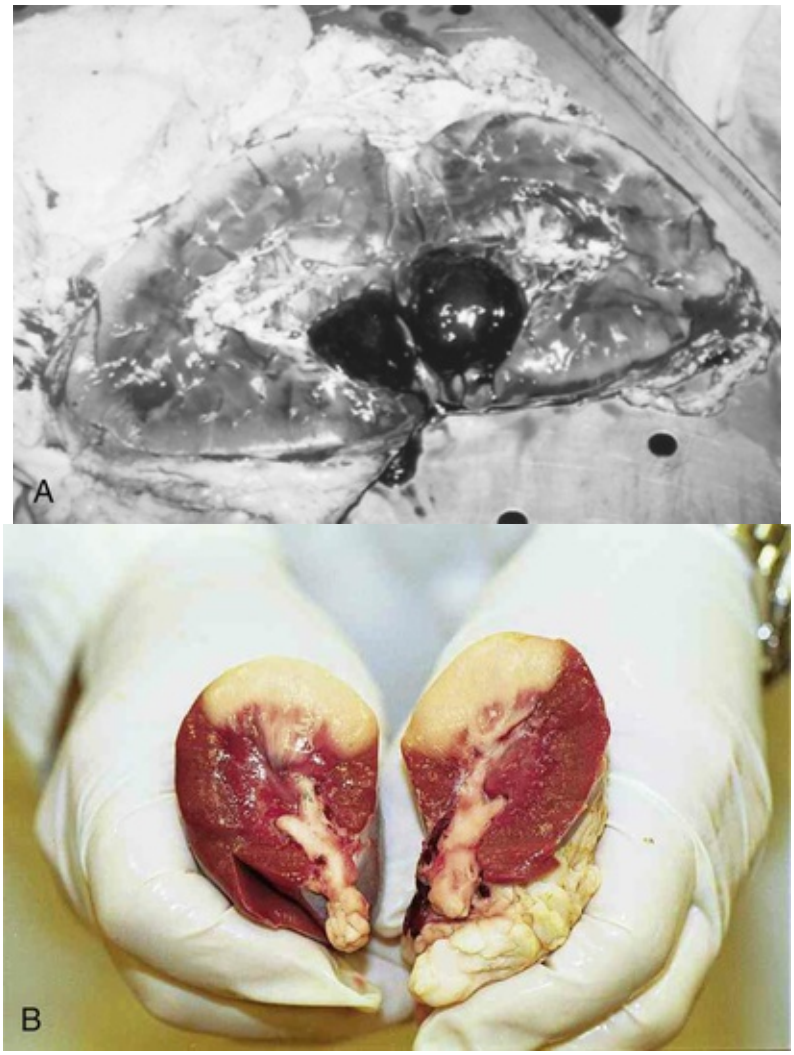


FIG. 34.6 **A,** Cut section of the left kidney from a 25-year-old horse with chronic weight loss, hematuria, and severe anemia. The kidney appeared normal except for a small 4 × 5 cm carcinoma with surrounding hemorrhage. **B,** Cut section of an equine kidney with metastatic lymphoma infiltration (pale tissue). (A, Courtesy Thomas J. Divers. B, Courtesy Montague N. Saulez.)

Clinical Signs and Diagnosis

Clinical signs in horses with renal neoplasia include hematuria, weight loss, and recurrent colic. Sudden death may occur if the neoplasm hemorrhages into the abdomen or thorax. Renal tumors may result in marked enlargement of the kidneys such that both left and right kidneys may be found on rectal palpation. In other cases, tumors may be circumscribed lesions within a kidney that disrupt the renal architecture but cannot be felt during rectal palpation. Ultrasonography

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may be invaluable for detecting such tumors, however, if very small, renal tumors may still be difficult to detect. Affected horses are usually not azotemic, but anemia may be detected when gross hematuria is observed. Although neoplastic cells are unlikely to be found in urine, cytologic examination of urine sediment is still warranted. Renal biopsy has been found to be associated with a low rate of serious complications and provided a histopathologic diagnosis in agreement with necropsy in 72% of cases.[21] Although horses with a diagnosis of renal neoplasia had a greater risk of complications than those with any other histopathologic diagnosis, only 4/151 horses in the study had neoplasia.[21] Nephroblastoma usually remains limited to the kidney; renal cell carcinomas typically metastasize. The liver and lungs are the most common sites of metastasis, but tumors can also spread to unusual sites, leading to variable adjunct clinical signs such as lameness or an ulcerated mass on the premaxilla.[7-10,14] Multiple myeloma involving the kidney resulted in hypercalcemia and a high serum parathyroid hormone–related protein concentration.[17] Hypoglycemia was the chief clinical sign in a 6-year-old horse with renal cell carcinoma producing insulin-like growth factors.[12]

Bladder tumors most commonly present with hematuria, weight loss, pollakiuria, and stranguria. A mass can usually be palpated on rectal examination, but it should not be confused with a cystolith or accumulation of sabulous concretions in the ventral aspect of the bladder.[3] There may be mild to moderate anemia and sometimes hypoproteinemia (hypoalbuminemia). Other than hematuria and associated proteinuria, urinalysis results are often unremarkable, but with bladder tumors, cytologic examination of urine sediment is more likely to reveal neoplastic cells than with renal tumors.[18,19] A diagnosis of bladder neoplasia may be confirmed by cystoscopic examination (Fig. 34.7) and biopsy. A recently described new syndrome of *idiopathic hemorrhagic cystitis* in horses closely resembles bladder neoplasia in clinical pathologic presentation.[3] Unfortunately, biopsy and histopathology were not helpful in discriminating between bladder neoplasia and idiopathic hemorrhagic cystitis in this study.[3]

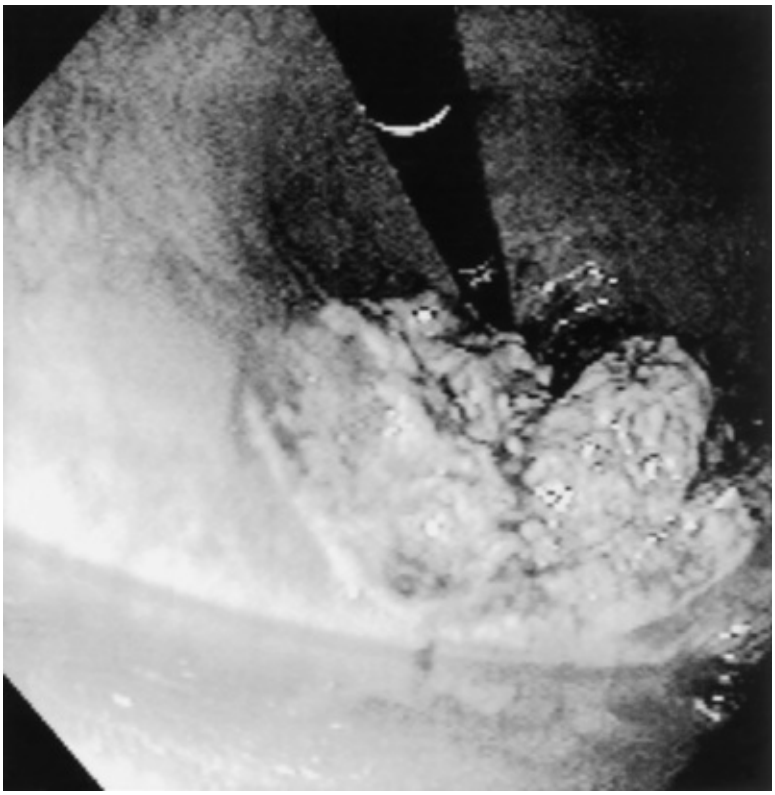


FIG. 34.7 Cystoscopic image of a squamous cell carcinoma of the bladder causing intermittent hematuria in a 14-year-old warmblood mare. The endoscope has been passed beyond the tumor and retroflexed to provide a view directed caudally; a pool of urine is in the foreground, and the tumor can be seen in the ventral aspect of the bladder neck.

Treatment

The treatment of choice for unilateral renal neoplasia is nephrectomy.[7,13] Unfortunately, most cases of renal cell carcinoma have metastasized by the time the diagnosis is made, and surgical intervention is of little benefit to horses with disseminated disease. In addition, many horses with renal neoplasia will be aged. Thus, careful evaluation for metastatic disease, assessment of comorbidities (e.g., PPID, poor dentition), and consideration of age should be undertaken before contemplating a nephrectomy. Survival following diagnosis of renal carcinoma ± nephrectomy has been reported to be very poor (median 11 days, range 0 to 365 days).[7] However, of interest, there is one report of a renal tubular cell carcinoma (confirmed by renal biopsy) considered too large to be operable, in a 15-year-old mare. No treatment was implemented, and the mare was reported to still be stable and in foal 1 year later.[22] Treatment of confirmed

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bladder tumors includes surgical excision, and/or topical chemotherapy using either 5-fluorouracil or triethylenethiophosphoramide and systemic doxorubicin has also been used but prognosis is guarded to poor.[19,20] Again, as affected horses are likely to be aged (often >20 years old), careful consideration of comorbidities and quality of life is important before under taking treatment.

Equine Idiopathic Hemorrhagic Cystitis.

Idiopathic hemorrhagic cystitis in horses is a newly described syndrome in horses presenting with stranguria and hematuria.[3] In a case series of 11 horses from California with this condition, pyuria was present but not bacteria, and no bacterial growth on urine culture (aside from one horse, which was deemed a contaminant).[3] Other than bacterial cystitis, which is often precipitated by urolithiasis and/or bladder dysfunction, sterile ulcerative cystitis in horses has been described in two horses in association with long-term phenylbutazone administration.[23] Of note, idiopathic hemorrhagic cystitis was almost indistinguishable from bladder neoplasia in terms of clinicopathologic presentation, even by histopathology following mucosal bladder biopsy.[3] However, horses with idiopathic hemorrhagic cystitis made rapid (within approximately 8 weeks), full recoveries, with antimicrobial ± nonsteroidal antiinflammatory treatment. Horses with idiopathic hemorrhagic cystitis were significantly younger (median age = 16, range, 9 to 30 years) compared with those with neoplasia (median age = 24, range, 16 to 30 years), and much more likely to be male—10/11 horses were male, whereas all horses with neoplasia (*n* = 7) were mares.[3] Finally, although gross cystoscopic findings were not different, horses with bladder neoplasia were more likely to have a mass visible on transrectal US.[3] Thus, in a horse with clinicopathologic signs that could be attributable to either neoplasia or idiopathic cystitis, it may be worth treating conservatively as described earlier and waiting a few weeks to see if the signs and lesions resolve, rather than immediately employing chemotherapy or euthanizing the patient.

Urolithiasis and Obstructive Disease

Montague N. Saulez

While the prevalence of obstructive disorders affecting the equine urinary tract is low, morbidity is high and the consequences thereof can be permanent

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and fatal. Obstructions may occur throughout the urinary tract and clinical symptoms are dependent on the location and degree of obstruction. Partial obstructions may not initially be recognized and can lead to intermittent dysuria, stranguria, hematuria, incontinence, and variable signs of pain. Horses with complete obstruction exhibit severe abdominal pain (colic) leading to bladder or urethral rupture followed by depression and metabolic deterioration. Unfortunately, reoccurrence is frequent irrespective of treatment modality followed or the elimination of potential risk factors.

Renal and Ureteral Calculi

Following renal tissue damage, calcium carbonate and calcium oxalate crystals can tightly adhere to the renal parenchyma, forming a nidus that allows repeated crystal precipitation and enlargement of the calculus.[1] Underlying renal disease should always be suspected in horses with nephrolithiasis.[2,3] It is thought that in horses, a risk factor for nephrolithiasis is prolonged use of nonsteroidal antiinflammatory drugs (NSAIDs), which can cause renal medullary necrosis (Fig. 34.1), thereby increasing the risk of nephrolith formation in the renal pelvis and terminal recess.

Clinical symptoms are dependent on the degree of luminal obstruction and include anorexia, dullness, and weight loss. This may progress to severe colic, hematuria, and stranguria. Bilateral nephrolithiasis may lead to chronic renal failure (CRF).[2,3] Horses can also remain clinically asymptomatic with the presence of renal calculi incidentally discovered at necropsy[4] (Fig. 34.8, *A* and Fig. 34.8, *B*). Diagnosis of renal or ureteral calculi is made by rectal examination revealing an enlarged kidney, ureter, or bladder. Ureters are not normally palpable but can be detected if enlarged, and the entire ureter should be carefully palpated as calculi may easily be missed. Transabdominal or transrectal ultrasonography should be used to confirm the presence and location of ureteral calculi, which most commonly occur near the entrance to the bladder (Fig. 34.9). In horses affected by a nephrolith and/or ureterolith, typical ultrasonographic findings include hydronephrosis, hydroureter, and a hyperechoic structure with acoustic shadowing in either/both the renal pelvis or ureter.[5-8] Horses affected by hydronephrosis typically have marked distention of the renal pelvis, thinning of the renal cortex, as well as fibrosis within the kidneys. Serum biochemistry analysis may reveal azotemia in horses with bilateral disease and subsequent CRF, but not in those affected by unilateral disease. Further examination of the

urine may reveal isosthenuria, pigmenturia, and microscopic hematuria. Culture of the urine and calculus/calculi is worthwhile, especially in the presence of pyuria, bacteriuria, and in horses with systemic indications of infection (e.g., pyrexia, alterations in the complete blood count and inflammatory markers). Calculi should also be analyzed, and the mineral composition determined.



FIG. 34.8 **A,** Multiple nephroliths in the left kidney of a 12-year-old Thoroughbred that presented with a complaint of intermittent hematuria. The right kidney appeared normal on ultrasound examination, and renal function was normal. **B,** A single nephrolith in the kidney of a 10-year-old mare discovered incidentally at necropsy. (**A,** Courtesy Thomas J. Divers.)

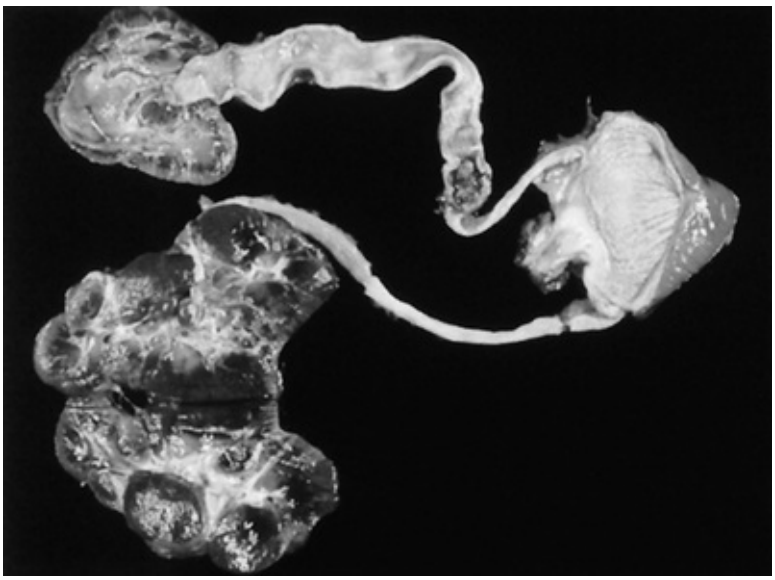


FIG. 34.9 Urinary tract removed from a 5-year-old Standardbred with chronic renal failure caused by intermittent or persistent obstruction by renal and ureteral stones. Note the location of the ureteral obstruction near the bladder. This is the most common site for the obstruction to occur. (Courtesy Thomas J. Divers.)

Nephrectomy should be considered in horses affected solely by unilateral nephrolithiasis without the presence of renal azotemia and concurrent damage to the contralateral kidney.[9,10] The advantages of a nephrectomy include prevention of calculus reoccurrence and elimination of any unilateral upper UTI. A nephrostomy or ureterotomy can be performed to manage ureteroliths.[11,12] Transendoscopic laser or electrohydraulic lithotripsy may be considered for noninvasive fragmentation of ureteral stones; however, this technique is time-consuming and often causes tissue trauma.

Cystic Calculi

Cystolithiasis is most commonly observed in geldings.[13] Typically, cystic calculi present as single, large, spiculated stones composed of $CaCO_3$ crystals (Fig. 34.10).[1] Less often, calculi consisting of both $CaCO_3$ and $CaPO_4$ crystals may be found; these tend to be smooth and are resistant to fragmentation.[13,14] Although the precise etiology is unknown, contributing factors may include neurologic disease causing bladder dysfunction, renal injury, incomplete bladder emptying, underlying cystitis, anatomic defects, bladder trauma or surgery, and neoplasia. Although equine urine is normally supersaturated with $CaCO_3$ crystals, in the healthy horse, the secretion of mucus produced by glands in the renal pelvis and

proximal ureter serves as a lubricant to prevent crystal adherence to the uroepithelium.



FIG. 34.10 A large cystic calculus composed of calcium carbonate crystals retrieved from a 17-year-old mare through manual distention of the urethra. Note the easily recognizable spiculated surface that caused chronic cystitis. The mare had urinary incontinence with perineal and hindlimb scalding (see Fig. 34.5).

Clinical symptoms in horses affected by cystic calculi include intermittent hematuria, stranguria, polyuria, dysuria, oliguria, and incontinence. If chronic, then weight loss; urine scalding of the ventral abdomen, preputium, perineum, and hind limbs (see Fig. 34.5); and intermittent colic may occur. The presence of cystic calculi can be confirmed by palpation of the bladder per rectum following bladder catheterization to remove urine. Advanced diagnostics such as US and cystoscopy should be employed. Due to the possibility of calculi present in multiple locations, US of the entire urinary tract should be performed.[1] Cystoscopy allows improved planning for extraction of the calculus or calculi (size vs. shape and quantity), determines the degree of luminal obstruction and mucosal damage, and allows for visualization of urine production from both ureteral openings. Due to urine volume, mucoprotein secretion, and normal sediment, the bladder may require lavage and suction before a complete cystoscopic examination can be performed. It is important to be able to differentiate between sediment and the presence of calculi in the bladder.

Sabulous urolithiasis is the accumulation of urine sediment in the ventral aspect of the bladder and often occurs with a concurrent encrusted cystitis and infection (Fig. 34.11).[15-17] In turn, over time, sabulous urolithiasis itself leads to a degree of bladder paralysis (myogenic dysfunction), thereby creating a vicious cycle of incomplete voiding, which further predisposes the patient to urolithiasis. Long-standing sabulous cystitis with inherent bladder paralysis may lead to sabulous urolithiasis in the form of an inspissated sphere.[16] Care must be taken to avoid confusing inspissated sabulous urolithiasis with the presence of discrete cystoliths. Hematology and serum biochemistry are usually normal with cystolithiasis, but elevation of inflammatory markers should raise suspicion for concurrent upper UTI, and azotemia should prompt careful investigation for concurrent upper urinary tract disease and CRF. In addition, cytology and culture of an aseptically collected urine sample and culture of a bladder mucosal biopsy may expand the minimum database and help initiate appropriate antimicrobial therapy.

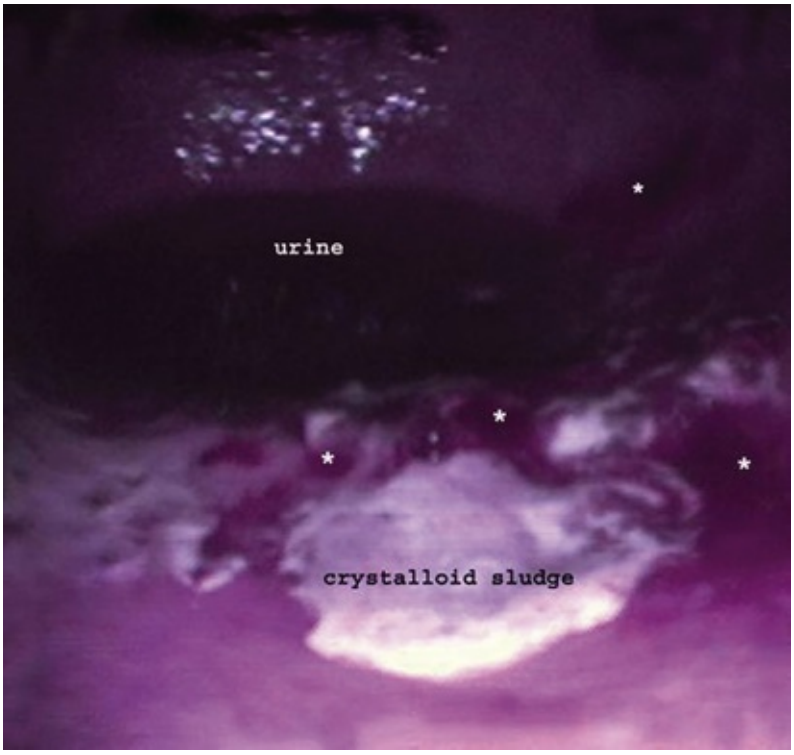


FIG. 34.11 Encrusted cystitis and sabulous urolithiasis due to infection with *Corynebacterium matruchotii* in a 17-year-old Quarter Horse × Thoroughbred gelding. Note the accumulation of crystalloid sludge and ulceration of the bladder mucosa. (Reprinted with permission from the

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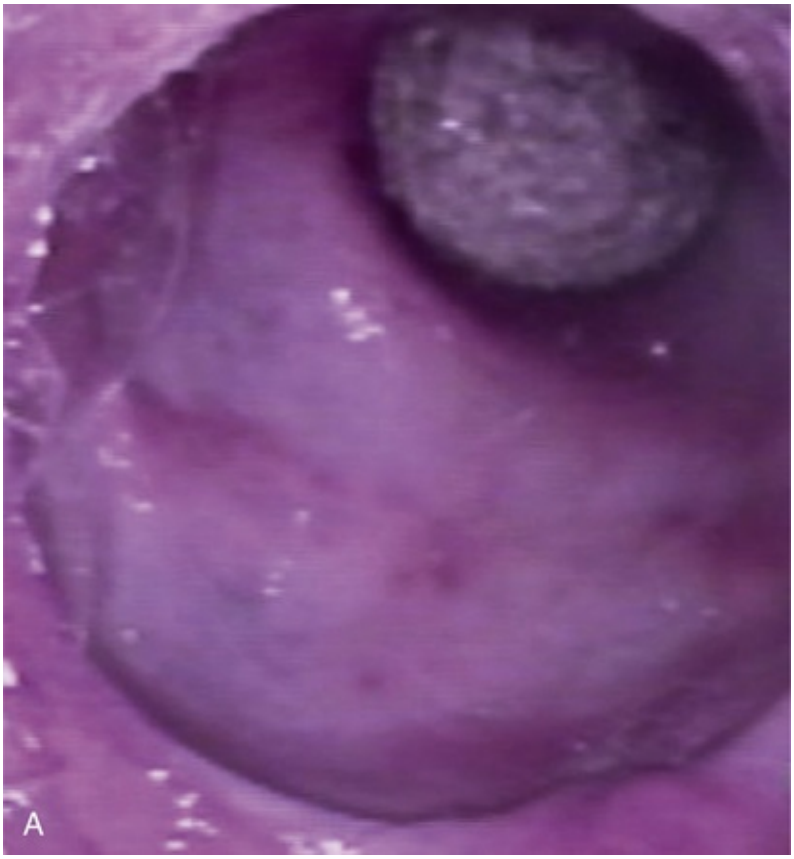
Using sedation and caudal epidural anesthesia, small fragmented calculi may be manually removed using a perineal urethrotomy in male horses.[13] Care must be taken to avoid further soft tissue trauma and damage to the pelvic urethra, bladder, and rectum. Larger calculi may need to be removed by laparocystotomy through a paramedian, ventral midline incision or with laparoscopic guidance under general anesthetic.[18-20] It is the author's (MNS) opinion that the most superior surgical technique is laparocystotomy under general anesthetic, as this allows complete removal of the calculus without fragmentation, thereby reducing the chance of reoccurrence and urethral obstruction, as well as postoperative cystitis and urethritis. Most recently, successful laparoscopic removal of cystic calculi has been described in standing sedated horses, which has the advantage of avoiding general anesthesia.[21,22] Gokel's cystotomy, using a perirectal incision, can also be used to remove intact, cystic calculi in the standing horse.[23] In mares, following caudal epidural anesthesia and manual distention of the urethra, calculi may be easily retrieved intact. Laser (Ho:YAG or pulsed dye laser) or shock wave lithotripsy in the standing horse is also an attractive, noninvasive treatment option for fragmenting large stones.[24] Electrohydraulic lithotripsy can be used transendoscopically or via a perineal urethrotomy to fragment large calculi using electrical energy; however, this technique is time-consuming and results in many fragments, which can cause obstruction.[25] It is important to submit retrieved stones for analysis and mineral composition. Management of sabulous cystitis has been described in five horses for up to 3 years with medication in combination with bladder catheterization and lavage.[17]

Unfortunately, calculi may frequently reoccur regardless of treatment modality. Horses with perineal urethrostomy tend to have greater incidence of reoccurrence than horses with cystotomy most likely due to remaining fragments of calculi. As the precise etiopathogenesis is unknown, preventative measures are difficult to prescribe. Recommendations include urinary acidification with ammonium chloride (50 to 200 mg/kg q24h PO) or ammonium sulfate (200 to 300 mg/kg q24h PO) and changing from a diet of legumes to grass hay to help decrease urinary calcium excretion.[26,27] Lastly, the addition of 25 to 50 g NaCl in the feed daily may help promote diuresis by stimulating increased water intake.

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Urethral Obstruction

Urethral obstruction is typically caused by urethroliths located over the ischial arch where the urethra is narrowest. These stones may move further distally and cause luminal obstruction (see Fig. 34.12, *A* and *B*). Mares seldom develop urethral obstruction due to a much shorter, nontortuous, and more distensible urethra. Patency of the urethra may also be affected by neoplasia, congenital disorders, edema, inflammation, and trauma. Should complete urethral obstruction persist, bladder rupture is likely to develop and can be confirmed by abdominal ultrasonography and paracentesis of urine in the abdomen.



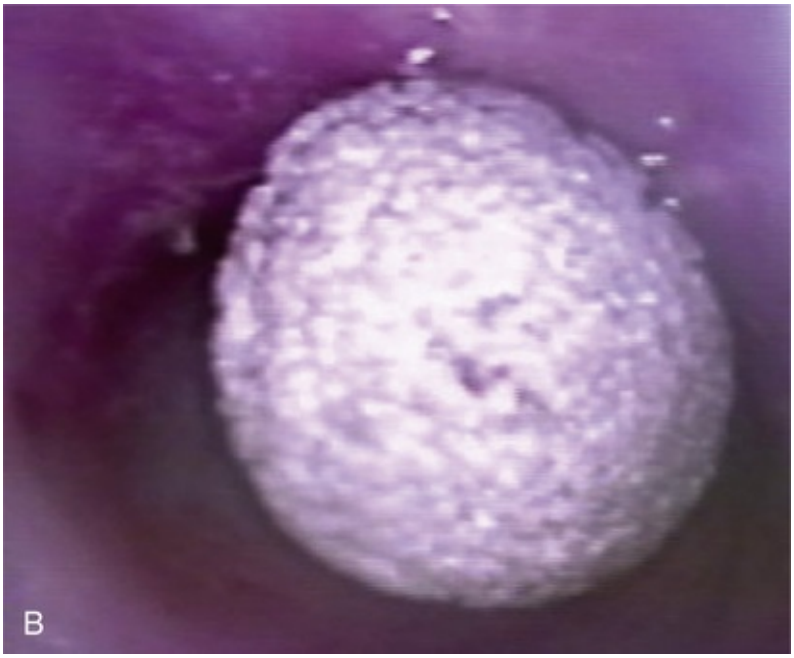


FIG. 34.12 **A,** Urethroscopic image of a calculus causing intermittent hematuria and stranguria in a 12-year-old gelding. The spiculated calculus caused severe mucosal irritation and damage. **B,** Urethroscopic image of an impacted stone in a 15-year-old gelding with intermittent colic and hematuria.

Urethral obstruction is best diagnosed by careful urethroscopy. Therapeutic urethroscopy may be used for direct retrieval of stones, thereby minimizing potential trauma, mucosal irritation, and stricture formation. Retrieval of urethroliths that are large and immovable may be performed by a perineal urethrostomy or a distal urethrotomy. However, this may lead to urethral stricture formation and urine fistulization. Urethroscopic lithotripsy can be considered if instrumentation is available. Radial extracorporeal shockwave therapy may be also considered for urethrolith fragmentation in the male horse.[28] In horses with urothelial tumors, ureteroscopy will allow improved visualization and treatment by resection using a Nd:Yag laser. Larger obstructive tumors such as squamous cell carcinoma affecting both the penis and prepuce may be treated by surgical resection with topical application of 5-fluorouracil.

Idiopathic Renal Hematuria

Harold C. Schott II • Alexandra J. Burton

Idiopathic renal hematuria (IRH) is a syndrome characterized by sudden onset of gross, often life-threatening hematuria.[1] Hemorrhage arises from one or both

kidneys and is manifested by passage of large blood clots in urine. Endoscopic examination of the urethra and bladder usually reveals no abnormalities of these structures, but blood clots may be seen exiting one or both ureteral orifices. Although a definitive cause of renal hemorrhage may be established in some horses (e.g., renal adenocarcinoma, arteriovenous or arterioureteral fistula, renal pseudoaneurysm), the disorder is termed *idiopathic* when a primary disease process cannot be found.[2-5] Both genders, a wide age range, and several breeds of horses (including donkeys and a mule) have been affected. However, more than 50% of animals with IRH have been Arabians.

Use of the term *idiopathic renal hematuria* to describe this syndrome of horses was adopted from its use in human patients and dogs with severe renal hemorrhage.[6-10] *Benign essential hematuria* and *benign primary hematuria* are other terms that have been used to describe less severe hematuria that is not associated with trauma or other obvious causes of hematuria.[6-10] In humans and dogs, hematuria is more often a unilateral than a bilateral problem, similar to what has been observed in the few affected horses. The pathophysiology remains poorly understood, but macroscopic hematuria has been associated with immune-mediated glomerular damage (e.g., acute postinfectious glomerulonephritis [GN], membranoproliferative GN, IgA nephropathy, or Berger disease), thin basement membrane nephropathy, and the loin pain–hematuria syndrome in human patients. One of the authors (AJB) has seen a case of IRH in a donkey in conjunction with simultaneous onset of severe laminitis. The donkey recovered over the course of 6 weeks with extensive supportive care.

Hematuria and pigmenturia can accompany several systemic diseases in horses.[11] However, patients affected with IRH appear to have spontaneous severe hematuria, in the absence of any other signs of disease. Although one report suggested that severe renal hemorrhage was caused by pyelonephritis, supportive data were lacking.[12] In cases managed by the author (HCS), neither UTI nor urolithiasis were detected, and the magnitude of hematuria often resulted in the need for repeated blood transfusions. As with hemorrhage associated with guttural pouch mycosis, the syndrome may produce episodic hemorrhage. Initially, hemorrhage is noted by finding a large amount of clotted blood in stall bedding or in the pasture. However, other client complaints (e.g., depression, anorexia, weight loss) are typically absent. Examination may reveal dried blood at the end of the penis or in the sheath of males or on the vulvar lips

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and between the hindlimbs of mares. In both genders, neoplasia of the external genitalia or urinary tract is an important differential diagnosis, and in mares, varicosities in the area of the vestibulovaginal sphincter also must be considered, especially in multiparous mares. When blood is not detected in the sheath or vulvar areas, further evaluation may be unrewarding because the renal bleeding may cease spontaneously. In the absence of positive urine culture results, bleeding has anecdotally been attributed to cystitis and pyelonephritis, because hemorrhage stops during a course of antimicrobial therapy. More likely, spontaneous resolution has occurred. The magnitude of hematuria is considerably greater with IRH than most UTIs, pyuria is absent, and urine culture results are negative. In the author's (HCS) experience, one or two initial episodes of hemorrhage are followed by a more severe hemorrhagic crisis within months to 2 years after observation of the initial bleeding episode. Signs of colic have been notably absent in the history of affected horses.

Diagnosis

A diagnosis of IRH is made by exclusion of systemic disease, other causes of hematuria, and alterations in hemostasis. Physical examination may reveal tachycardia, tachypnea, and pale membranes, consistent with acute blood loss. Rectal palpation may reveal an enlarged, irregular bladder resulting from the presence of blood clots. Azotemia is uncommon. Endoscopic examination is important to document that hematuria is originating from the upper urinary tract and to determine whether hemorrhage is unilateral or bilateral (Fig. 34.13). Repeated examinations may be required to answer the latter question. Ultrasonographic imaging is necessary to rule out nephrolithiasis or ureterolithiasis and may occasionally reveal a distended vascular space or renal vascular anomaly as the cause of hematuria. Renal scintigraphy can be a useful technique in affected horses, providing semiquantitative information about renal function when a nephrectomy is being considered. Renal biopsy and immunofluorescence (IF) staining may assist in documenting immune-mediated glomerular injury, but the significance of such results is not well understood at this time.

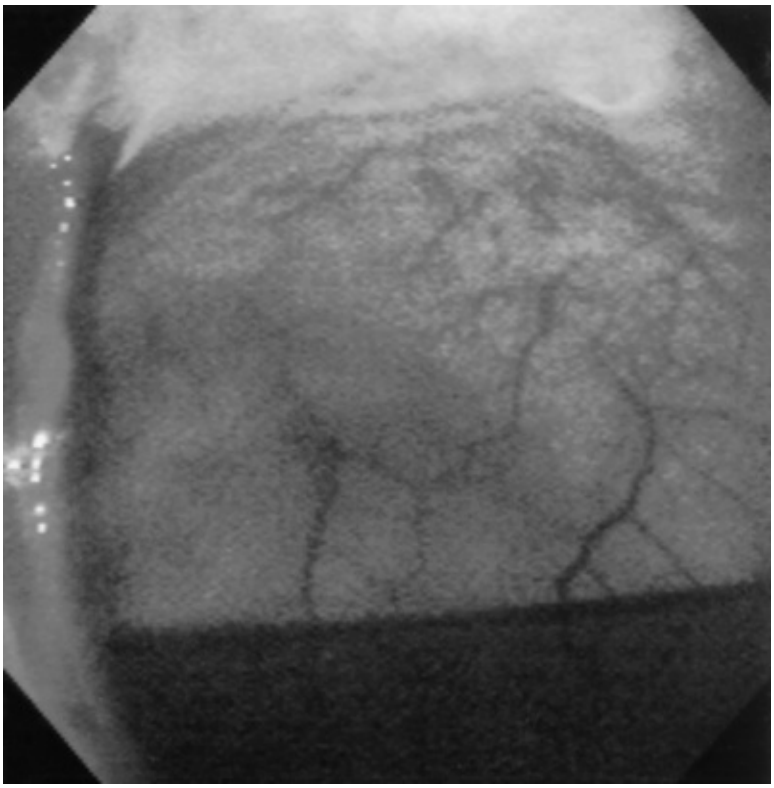


FIG. 34.13 Cystoscopic image of a 19-year-old Arabian mare with idiopathic renal hematuria. A large blood clot can be seen exiting the left ureter, whereas the right ureteral opening appears normal.

Treatment

Treatment for IRH consists of supportive care for acute blood loss, including blood transfusions. Medications intended to promote hemostasis (e.g., α-aminocaproic acid, formalin) have also been administered, but their efficacy has not been validated. Because the condition may be self-limiting in some patients, supportive care is warranted. With severe and recurrent hematuria of unilateral renal origin, a nephrectomy may be indicated, but owners should be warned of the risk of hematuria developing in the contralateral kidney. In the author's (HCS) experience, risk of contralateral renal bleeding appears to be greater in the Arabian breed. Recently, topical sclerotherapy of the renal pelvis using 5% povidone iodine ± silver nitrate via ureteral stents has been reported as a treatment for IRH in dogs.[13,14] This therapy shows some promise, as it was successful in the short term, but longer-term follow-up and a larger case cohort are needed to fully evaluate this technique.[13,14]

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Urethral Hemorrhage

Harold C. Schott II • Alexandra J. Burton

Although a recognized cause of hemospermia in stallions, defects or tears of the proximal urethra at the level of the ischial arch are a more recently described cause of hematuria in geldings.[1-4] Urethral defects typically result in hematuria at the end of urination, in association with urethral contraction. Affected horses generally void a normal volume of urine that is not discolored. At the end of urination, a series of urethral contractions results in squirts of bright red blood. Occasionally, a smaller amount of darker blood may be passed at the start of urination. In most cases, the condition does not appear painful or result in pollakiuria. Interestingly, the majority of affected stallions with hemospermia and geldings with hematuria have been Quarter Horses or Quarter Horse crosses that have been free of other complaints. Treatment with antibiotics for a suspected cystitis or urethritis has been routinely unsuccessful, although hematuria appears to resolve spontaneously in about 50% of affected horses. Because the defects are difficult to detect without use of high-resolution videoendoscopic equipment, previous reports of urethral bleeding have been attributed to urethritis or hemorrhage from “varicosities” of the urethral vasculature. However, vasculature underlying the urethral mucosa becomes quite prominent when the urethra is distended with air during endoscopic examination, especially in the proximal urethra (to the point that blood can be seen flowing in the submucosal vasculature). Thus, it would be logical to suspect that hemorrhage could arise from an apparent urethritis or urethral varicosity, although these problems are poorly documented in horses.

Examination of affected horses is often unremarkable, and laboratory analysis of blood reveals normal renal function, although mild anemia can be an occasional finding. Urine samples collected midstream or by bladder catheterization appear grossly normal. Urinalysis may have normal results, or an increased number of red blood cells may be found on sediment examination, a finding that would also result in a positive reagent strip result for blood. Bacterial culture of urine yields negative results. The diagnosis is made with endoscopic examination of the urethra, during which a lesion is typically seen along the dorsocaudal aspect of the urethra at the level of the ischial arch. External palpation of the urethra in this area is usually unremarkable but can assist in localizing the lesion, because external digital palpation can be seen through the endoscope. With hematuria of several weeks’ duration, there is little

evidence of inflammation; rather, the lesion appears as a fistula communicating with the vasculature of the corpus spongiosum penis (Fig. 34.14).

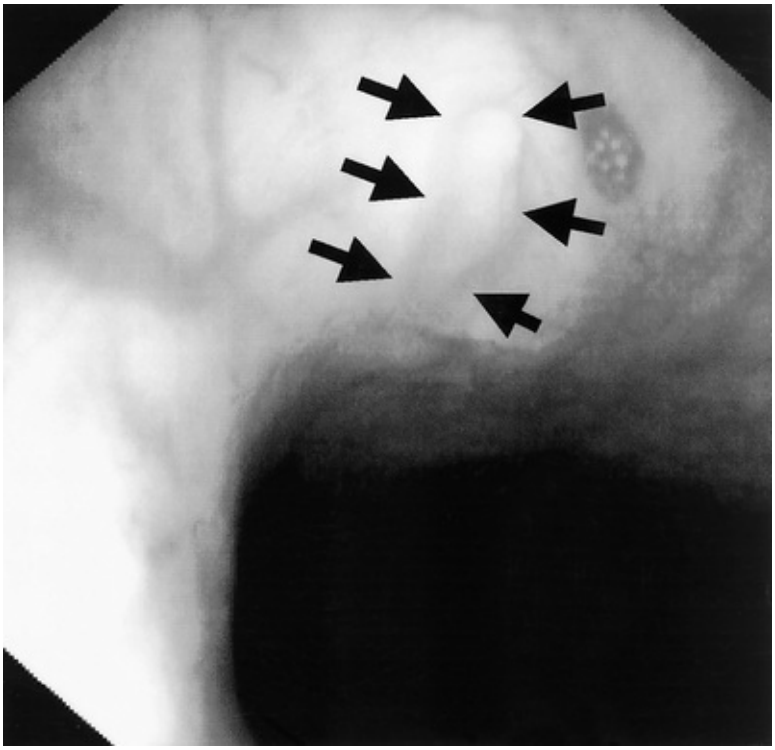


FIG. 34.14 Endoscopic image of the proximal urethra of a gelding with hematuria at the end of urination. A urethral defect can be seen between the *arrows* along the caudal aspect of the urethra as it passes dorsocranially over the pelvic brim.

Although the pathophysiology of this condition remains unclear, it has been speculated that the defect is the result of a “blowout” of the corpus spongiosum penis (cavernous vascular tissue surrounding the urethra) into the urethral lumen.[3] Contraction of the bulbospongiosus muscle during ejaculation causes a dramatic increase in pressure in the corpus spongiosum penis, which is essentially a closed vascular space during ejaculation. The bulbospongiosus muscle also undergoes a series of contractions to empty the urethra of urine at the end of urination, so the defect into the urethra may develop by a similar mechanism in geldings. Once the lesion has been created, it is maintained by bleeding at the end of each urination, and the surrounding mucosa heals by formation of a fistula into the vascular tissue. An explanation for the consistent location along the dorsocaudal aspect of the urethra at the level of the ischial

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arch has not been documented but may be related to the anatomy of the musculature supporting the base of the penis and an enlargement of the corpus spongiosum penis in this area. Narrowing of the lumen at the distal extent of the ampullar portion of the urethra may also contribute to the location of the defects. An anatomic predisposition in Quarter Horses has not been documented but could be speculated on the basis of an apparent increased risk in this breed.

Because hematuria may resolve spontaneously, no treatment may be initially required. Resting of breeding stallions for several months may facilitate healing of the rent and cessation of recurrent bleeding. If hematuria persists for more than a month or if significant anemia develops, surgical intervention is indicated. Surgical approaches are aimed at reducing decreasing pressure within the corpus spongiosum, with the goal of reducing tension on the urethral rent site and thus allowing it to heal.[3] A temporary subischial "incomplete" urethrotomy has been successful in some affected geldings. After sedation and epidural or local anesthesia, a catheter is placed in the urethra and a vertical incision is made into the corpus spongiosum penis but not the urethral lumen. The surgical wound requires several weeks to heal, and moderate hemorrhage from the corpus spongiosum penis is apparent for the first few days after surgery. Hematuria should resolve within a week after this procedure. Additional treatment consists of local wound care and prophylactic antibiotic treatment (typically a trimethoprim-sulfonamide combination) for 7 to 10 days. Most recently, a case series (1989 to 2013) of 33 male horses (stallions and geldings) with urethral rents treated with perineal urethrotomy (PU) or corpus spongiotomy (CS) has been described.[4] Both PU and CS were successful in the long term for resolving hematuria in horses with urethral rents but did not always resolve hemospermia in stallions.[4] Repair of a urethral defect using subischial urethrotomy and a buccal mucosal urethroplasty has been described as a successful treatment for recurrent hemospermia in one stallion.[5]

Polyuria and Polydipsia

Harold C. Schott II • Theresa L. Ollivett • Alexandra J. Burton

Polyuria and *polydipsia* (PU/PD) are defined as urine output in excess of 50 mL/kg/day (PU) and fluid intake of more than 100 mL/kg/day (PD).[1,2] These values equate to production of 25 L of urine and consumption of 50 L of water for a 500-kg horse. It is important to remember that urine production and water consumption vary hugely with age, diet, workload, environmental temperature,

prolonged periods of water deprivation, and gastrointestinal water absorption.[2-4] For example, urine production increases by 50% to 100% when the diet is changed from a grass to legume hay.[5] Similarly, horses in heavy exercise, hot climates, or with chronic diarrhea may have water intake in excess of 100 L/day yet produce normal volumes of urine. Young foals urinate much more frequently than adult horses due to a predominantly fluid (milk) diet. The major causes of PU/PD in horses include chronic renal failure, PPID, and primary or "psychogenic" polydipsia. Less common causes include excessive salt consumption, central and nephrogenic diabetes insipidus (DI), diabetes mellitus (DM), sepsis/systemic inflammatory response syndrome (SIRS), and iatrogenic causes (e.g., α_2-agonists, corticosteroids, diuretics).[2]

Polyuria/Polydipsia With Pituitary Pars Intermedia Dysfunction

Adenoma of the pituitary pars intermedia results in PPID (formerly termed equine Cushing's disease), with elevated adrenocorticotrophic hormone (ACTH) and hyperadrenocorticism. The syndrome has been well recognized and clinically characterized in equids for more than 40 years and is common in older horses (see Chapter 41).[6,7] Generally, the most consistently reported clinical signs in horses are delayed shedding, hirsutism, and muscle wasting. Although a degree of PU/PD is nearly always present in horses with uncontrolled PPID, it may not be readily noted or reported by the owner/trainer. This is because PU/PD associated with PPID is generally of lesser volume than that observed with psychogenic PD or DI and also because if the horse is out with others in a pasture, PU/PD is difficult to assess.

Several mechanisms may lead to PU/PD in horses with PPID. Firstly, PU may be the result of an osmotic diuresis. The renal threshold for glucose in horses (≈150 to 175 mg/dL) appears to be lower than in small animals.[8] When plasma glucose concentration exceeds the renal threshold, the resultant glucosuria can lead to an osmotic diuresis. Although often implicated as the cause of PU/PD in horses with PPID, hyperglycemia and glucosuria are not always present with the disease and are often only found in more advanced cases or those with concurrent equine metabolic syndrome (EMS). A second mechanism implicated in the development of PU with PPID is antagonism of the action of antidiuretic hormone (ADH) on the collecting ducts by excess cortisol. Vasopressin, arginine vasopressin (AVP), and argipressin are all other names for ADH. Although

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frequently cited as the mechanism of PU in canine hyperadrenocorticism, experimental evidence to support this mechanism is lacking in both dogs and horses. There is considerable species heterogeneity in the effects of corticoids on ADH activity, and in some species, a primary dipsogenic (thirst-stimulating) effect may be more important. Growth of the adenoma (as PPID becomes more advanced) may lead to impingement on the posterior pituitary and hypothalamic nuclei (located immediately dorsal to the pituitary gland), the sites of ADH storage and production, respectively. Decreased ADH production and release would result in central DI as a third mechanism for PU. Finally, if not body clipped, horses with hirsutism will become excessively hot and sweaty in warm climates or during exercise and thus PD may develop as a normal physiologic response to fluid loss in sweat. Therefore, PU/PD seen in horses with PPID is likely the combined result of several mechanisms.

Primary Psychogenic Polydipsia

Primary, or "psychogenic," PD is rare but probably the most common cause of PU/PD in adult horses for which clients will have a primary complaint of excessive urination.[2,4,9] This is because the magnitude of their PU/PD is typically dramatic, with owners reporting that horses drink two to three times more water than other horses on the premises, and stalls can be flooded with urine. Horses with this problem are generally in good body condition and not azotemic but will be hyposthenuric with a USG <1.005.[2] In some horses, primary PD appears to be a stable vice that reflects boredom, whereas in others it may develop after a change in environmental conditions, stabling, diet, or medication administration. Anecdotally, it has been reported to be more common in southern states of the United States during periods of high temperature and humidity.

The diagnosis of primary PD is made by exclusion of renal failure, PPID, diabetes insipidus (DI), and chronic, persistent hyperglycemia. Other factors (e.g., salt supplementation, medication) must also be excluded. Exclusion of DI is achieved by demonstrating urinary-concentrating ability after water deprivation.[10,11] After water deprivation of sufficient duration (12 to 24 hours) to produce a 5% loss of body weight, USG should exceed 1.025 in normal horses. In horses with long-standing PU, the osmotic gradient between the lumen of the collecting tubule and the medullary interstitium may be diminished (medullary washout). In these horses, insensitivity to ADH activity may fail to increase USG over 1.020. Consequently, in horses with primary PD of several weeks'

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duration that fail to concentrate their urine (>1.020 USG) after 24 hours of water deprivation, a modified water deprivation test may be tried. During the modified water deprivation test, water intake is restricted to about 40 mL/kg/day, for 3 to 4 days. By the end of this period, USG should exceed 1.025 in a horse that has had medullary washout. If USG remains in the isosthenuric range (1.008 to 1.014), the polyuric horse should be further evaluated for early chronic renal failure, in which the ability to concentrate urine may be compromised before the onset of azotemia. In theory, this could only occur when 65% to 75% of functional nephrons have been lost. Subtle signs of decreased performance and mild weight loss would also support early renal failure.

Management of horses with primary PD is empirical. Because primary PD is a diagnosis of exclusion, once it has been established that the horse does not have significant renal disease, it is safe to continue restricting water intake to meet maintenance, work, and environmental requirements of the horse. In addition, steps should be taken to improve the attitude of the horse by reducing boredom or any other potential stress trigger factors. Increasing the amount of exercise and turning the horse out to pasture are possible options, along with providing a companion or diversions in the stall. Increasing the frequency of feedings or amount of roughage in the diet may increase time spent eating and thereby reduce the habitual drinking. That said, the more roughage a horse eats, the more it needs to drink; thus, slow hay feeders or nibble nets might be preferable to free-choice loose hay.

An occasional case of primary PD may be attributed to “psychogenic salt eating” (excessive salt consumption) and is manifested by an increased fractional sodium clearance.[3,4] However, salt intake may have to exceed 5% to 10% of dry matter intake before significant PU/PD develops.[12,13] Successful management consists of limiting water intake and preventing or limiting access to excess salt. However, this must be balanced against any salt loss via sweat due to very high ambient temperatures and exercise. In these situations the horse may need to be allowed some (regulated) salt and mineral lick consumption to replace high losses in sweat. In addition, in one author's experience (AJB) removal of a salt block/lick from a psychogenic salt eater can lead to consumption of excessive amounts of soil/dirt instead, as salt is a natural component of soil. This could potentially lead to sand colic, dependent on the soil composition.

Diabetes Insipidus

Diabetes insipidus (DI) is generally rare in horses. It may be divided into two types: inadequate secretion of ADH (neurogenic [central] DI) or decreased sensitivity of the renal epithelial cells of the collecting ducts to circulating ADH or loss of ADH receptors on these cells (nephrogenic DI).[1,2,14] With both forms of DI, dramatic PU/PD may be reported and affected animals fail to concentrate urine in the face of water deprivation.

In human patients, neurogenic DI is the more common form of DI, with both hereditary and acquired forms described.[15] In two well-documented cases of neurogenic DI diagnosed in adult horses, neither horse could concentrate urine in response to water deprivation, but administration of exogenous ADH resulted in an increase in USG and a decrease in urine volume.[16,17] In a Welsh pony in which the condition was considered idiopathic, the absence of an increase in plasma ADH concentration after water deprivation further supported a diagnosis of neurogenic DI.[16] Acquired neurogenic DI secondary to encephalitis was confirmed histologically in the other horse.[17] Presumed congenital neurogenic DI has also been described in a 10-day-old Friesian colt with tachypnea and polyuria, documented by a modified fluid deprivation test and a rise in plasma ADH (vasopressin) after treatment with exogenous synthetic ADH (desmopressin).[18] Neurogenic DI has also been reported in a 20-year-old gelding with PPID and PU/PD that was normoglycemic, did not respond to a water deprivation test, but did respond to desmopressin administration.[19]

Nephrogenic DI is most often a familial disorder in humans, with an X-linked semirecessive mode of inheritance.[15] Therefore, the disorder is carried by females and expressed in male offspring. Nephrogenic DI has been described in two full sibling Thoroughbred colts, suggesting that an inherited form may also occur in horses.[20] These two colts could not increase USG in response to water deprivation, although they did show appropriate increases in plasma ADH concentration. Nephrogenic DI has also been reported in a 14-year-old gelding with PU/PD and urinary incontinence.[21] In all three cases, a lack of response to exogenous ADH administration confirmed resistance of the renal collecting ducts to ADH. Nephrogenic DI can also develop in association with drug therapy (e.g., lithium or tetracyclines in humans) or a variety of metabolic, infectious, or mechanical (postobstruction) disorders. Anomalous or neoplastic disorders resulting in structural deformation of the kidneys are other potential causes of nephrogenic DI.[15]

After determining that an equine patient with PU/PD is not azotemic, the

initial diagnostic test to differentiate DI from primary PD is a water deprivation test.[2,14] However, horses with suspected DI should be monitored closely during water deprivation because horses that do have DI will continue to excrete excess water in the face of water deprivation. As a result, they may become substantially dehydrated (10% to 15%) within the first 12 hours of water deprivation. When a patient fails to concentrate urine during water deprivation, neurogenic DI can be differentiated from nephrogenic DI by measuring plasma ADH (AVP) concentration or by administration of synthetic ADH (aqueous synthetic vasopressin or 1-desamino-8-d-arginine vasopressin [DDAVP or desmopressin] may be used).[2,14] After administration of exogenous ADH, if USG rises in response, then this indicates neurogenic DI, whereas a lack of urine concentration indicates nephrogenic DI.[2,14,16-21]

Treatment of DI is directed at managing PU/PD. With neurogenic DI, hormone replacement therapy with desmopressin (DDAVP), a potent ADH analog administered as a nasal spray or orodispersible tablet (humans), eyedrops (dogs) or orally (cats), has been a successful treatment for neurogenic DI.[22,23] There is a report of a 10-day-old Friesian colt with suspected neurogenic DI being successfully temporarily treated using human desmopressin acetatehydrate nasal drops administered as eye drops.[18] With nephrogenic DI, hormone replacement therapy is ineffective, and the only practical form of treatment for many years has been to restrict sodium and water intake and administer thiazide diuretics. The latter treatment may reduce PU by 50% in human and canine patients.[15,24] Thiazide diuretics inhibit sodium reabsorption in the distal tubule (the diluting segment of nephron) and increase solute delivery to the collecting duct, but the mechanism by which such therapy benefits patients with nephrogenic DI is not well understood. Administration of prostaglandin inhibitors (e.g., NSAIDs) or amiloride may also decrease PU in patients with nephrogenic DI. Interestingly, in humans, NSAIDs reduce urine volume further if used in combination with thiazide diruretics and probably work by decreasing renal blood flow and glomerular filtration rate. Amiloride is a sodium channel blocker and is thought to act similarly to the thiazide diuretics. No reports have documented the use of these treatments for nephrogenic DI in horses.

Diabetes Mellitus

Diabetes mellitus (DM) is a state of chronic hyperglycemia usually accompanied by glucosuria. The resultant osmotic diuresis by glucose causes PU/PD. In one

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horse, DM resulted in water intake in excess of 80 L/day.[25] Although generally rare in horses, there are several reports of type I and type II (more common) DM.[25-29] Lately, equine DM has received more attention, probably due to increasing recognition and understanding of the equine endocrinopathies equine metabolic syndrome (EMS) and PPID, both of which may result in persistent chronic hyperglycemia in a subset of severe cases. In EMS, peripheral insulin resistance and subsequent hyperinsulinemia are classic features. Occasionally, the pancreas becomes “exhausted” with pancreatic ß cell dysfunction (inadequate insulin production), with the result being persistent hyperglycemia and DM.[29,30] Blood glucose concentrations are often mildly to moderately elevated in horses with PPID due to elevated ACTH and cortisol, but these horses do not usually develop chronic persistent hyperglycemia that exceeds renal threshold until PPID is quite advanced. However, if the horse has prior and/or concurrent EMS, then significant, persistent hyperglycemia is much more likely to occur and DM to develop. As discussed previously, PPID may also lead to PU/PD by a variety of other mechanisms.

Iatrogenic Polyuria

The most obvious iatrogenic cause is fluid therapy, for which PU is a desired response. Diuretics such as furosemide also cause intentional PU in horses. Polyuria has also been observed with exogenous corticosteroid administration, although the mechanism remains unclear. Humans and dogs appear to experience a potent thirst response to exogenous corticosteroids, so PD may be an important cause of the PU observed. Further, in horses receiving chronic dexamethasone treatment for immune-mediated disorders, profound glucosuria (2 to 3 g/dL) may be observed and could lead to an osmotic diuresis. A transient diuresis or PU accompanies sedation with the α_2-agonists xylazine and detomidine, even when water has been withheld for 24 hours previously.[31,32] Although these agents also cause transient hyperglycemia and occasional glucosuria, a more likely mechanism for PU is existence of α_2-adrenoreceptors on collecting duct epithelial cells. Activation of these receptors is another mechanism by which the action of ADH can be antagonized.[33]

Renal Tubular Acidosis

Luis G. Arroyo • Krista E. Estell • Monica Aleman

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Renal tubular acidosis (RTA) occurs due to improper functioning of the renal tubules and is characterized by hyperchloremic metabolic acidosis with a normal anion gap. It can occur primarily, from genetic or idiopathic causes, or secondarily, from underlying disease processes or as a complication of drug administration. Drug-induced RTA has been well documented in human patients following administration of certain antimicrobials that are also used in horses, including amphotericin B, trimethoprim-sulfamethoxazole, tetracyclines, gentamicin, cephalosporins, carbonic anhydrase inhibitors, lithium carbonate, and other organic compounds. Carbonic anhydrase deficiency was documented in a Friesian stallion, but the inciting cause in most affected horses has not been determined.[1] Other predisposing causes suggested in horses include pyelonephritis, hyperparathyroidism, and hypervitaminosis D.[2]

Two types of RTA have been reported in dogs, cats, and horses, and both types result in a hyperchloremic metabolic acidosis with a normal anion gap.[3-6] Type I develops when *distal* tubular excretion of hydrogen ions (H^+) is compromised, and affected patients are unable to produce acidic urine. Type II results from decreased *proximal* tubular bicarbonate resorption and subsequent urinary loss of bicarbonate. Normally, H^+ is excreted when bicarbonate is reabsorbed in the proximal tubules. Thus, acidosis with both type I and type II RTA results from decreased H^+ excretion. Hyperchloremia develops as a result of an increased renal absorption of chloride ions subsequent to bicarbonate loss. Type I RTA results in more severe acidosis and electrolyte abnormalities, since the distal tubule is responsible for maximal acidification of the urine. In the absence of H^+ excretion, potassium ions (K^+) are excreted in exchange to maintain electroneutrality, which can result in severe hypokalemia. Mixed type I and II RTA has been documented in horses and is notably refractory to treatment, likely because of widespread tubule dysfunction.[7] Type II RTA is often a self-limiting problem but may be accompanied by more widespread proximal tubular dysfunction known as *Fanconi syndrome,* which is characterized by defective resorption of glucose, amino acids, phosphate, potassium, sodium, calcium, magnesium, uric acid, and other organic acids. As with RTA, Fanconi syndrome may be a primary (inherited) disorder or can develop secondary to renal, metabolic, and autoimmune diseases or drug administration.[4-6] A transient Fanconi syndrome has been reported in two unrelated adult Quarter Horses.[8]

Equine RTA has been sporadically reported, mostly in North America and Europe. Across the literature, there is no obvious sex predilection. Quarter

Horses (QHs) (*n* = 11), QH-crosses (*n* = 4), Friesians (*n* = 6), and Arabians (*n* = 5) accounted for approximately 70% of RTA cases.[1,2,7,9-18] Affected horses range in age from 2 months to 27 years. Several genetic mutations in ion transport genes have been associated with heritable forms of RTA in humans, but there is no documented evidence of an inherited form in horses.

Typical presenting complaints and clinical signs include dullness, anorexia or poor appetite, weight loss, poor performance, weakness, decreased borborygmi and fecal output, and mild colic signs of variable duration. Vital parameters are generally within normal ranges, and horses do not appear clinically dehydrated. Hematologic and clinical chemistry abnormalities are usually mild or within reference ranges, with the exception of electrolyte concentrations and acid-base balance. Electrolyte concentrations and acid-base balance abnormalities can be profoundly abnormal but are variable between cases. A severe metabolic acidosis (venous blood pH range 6.98 to 7.25), low plasma bicarbonate concentration (<13 mEq/L), and hyperchloremia (serum chloride concentration of 105 to 124 mEq/L) are characteristic for horses with RTA. A compensatory decrease in carbon dioxide partial pressure (P_{CO_2}) is also observed in most horses. Hypokalemia (and total body potassium depletion) due to the combined effects of anorexia and ongoing loss of potassium in urine may occur in horses, particularly with type I RTA.

Mild to moderate azotemia—persistent in some cases—may be detected in horses with RTA, particularly those dehydrated at presentation or with renal damage. Affected horses may also have evidence of renal tubular damage detected on urinalysis (e.g., pigmenturia, glucosuria), and USG may be low. Despite profound metabolic acidosis, urine pH is generally neutral to alkaline. Ultrasonographic examination has shown hyperechoic kidneys in some cases, and several histopathologic abnormalities in renal biopsy samples have been found, generally showing tubulointerstitial disease.

Differentiation of type I from type II RTA in human and canine patients is most easily accomplished by assessing urine pH; it remains neutral to alkaline with type I and should be neutral to acidic with type II.[4-6] Most horses with RTA have had neutral to alkaline urine, but because herbivores normally have alkaline urine, this distinction may not be useful. A few reports have described horses with acidic urine, supporting type II RTA, but urine pH values near neutral are difficult to interpret.[12-14] Assessment of all laboratory abnormalities (Table 34.1), along with additional testing (e.g., ammonium chloride challenge, urinary ammonium concentration, administration of thiazide diuretics), may allow

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further discrimination between type I and type II RTA.[9,13,19] Regardless of RTA type, however, the treatment approach and the prognosis are similar for both in horses.

TABLE 34.1

Classification of Type I and Type II Renal Tubular Acidosis

	Distal or Type I	Proximal or Type II
Acidosis	Severe	Self-limiting
Hypokalemia	Severe	Mild to moderate
Serum phosphate	Normal	Low
Urine pH	Neutral to alkaline	Neutral to acidic

Treatment consists primarily of intravenous (IV) and oral administration of sodium bicarbonate ($NaHCO_3$). For initial correction of acidosis, IV $NaHCO_3$ must be administered aggressively, and large amounts (3000 to 9000 mEq) are often required to return plasma bicarbonate concentration to values above 20 mEq/L. Half the estimated bicarbonate deficit is generally replaced with IV $NaHCO_3$ over 6 to 12 hours, and the remaining deficit is replaced with a combination of IV and oral $NaHCO_3$ (initial oral dose: 100 to 150 g twice daily; 1 g contains 12 mEq $NaHCO_3$). Close monitoring of serum electrolyte concentrations and acid-base balance is required to adjust the rate of IV $NaHCO_3$ replacement. Marked improvement in attitude and appetite usually accompanies correction of the acidosis, but relapse after discontinuation of IV therapy can occur. Continued oral administration of $NaHCO_3$ for months to years may be required for maintenance of a normal acid-base status. Because potassium excretion is proportional to bicarbonate delivery to the distal tubule, initial correction of acidosis with $NaHCO_3$ promotes kaliuresis and may exacerbate potassium depletion. Therefore, concurrent supplementation with IV or oral potassium chloride (KCl) is advisable during initial correction of the acidosis. Complications associated with rapid correction of acidosis have not been described, but transient diarrhea ± mild colic may develop if large quantities of $NaHCO_3$ (>200 g) are given by nasogastric tube to horses that are completely anorectic.

Recurrence of metabolic acidosis also can occur when oral $NaHCO_3$ is discontinued, especially in horses that have evidence of renal damage. Relapses can be immediate or delayed for weeks to months. Reinstitution of $NaHCO_3$

supplementation usually corrects the metabolic abnormalities and accompanying depression and anorexia. The short-term prognosis for horses with RTA is good, with some horses reported to recover and compete successfully, but the long-term prognosis is still largely undocumented.[2,9,10,20]

Bladder Rupture in Adult Horses

Thomas J. Divers • Dominic R. Dawson-Soto • Alexandra J. Burton

Although more common in foals, on rare occasions, bladder rupture can also occur in adult horses. The problem can develop in association with urolithiasis, foaling, prolonged recumbency, or trauma.[1-11] Two cases of ureteral tears have also been reported in adult horses.[12,13] Bladder rupture in mares occurs most commonly due to foaling trauma.[1-5] In male horses, urolithiasis is the most common cause of bladder rupture.[7-9] Bladder rupture has also been reported as a complication following endoscopic electrohydraulic shockwave lithotripsy for treatment of urolithiasis.[10] There is one report of bladder rupture in a 2-year-old horse that had previously had a bladder rupture repair as a foal, the bladder retorn at the same site (old surgical scar) after recovery from routine cryptorchid castration.[11]

Following bladder rupture, azotemia develops and affected horses become depressed and inappetent. Clinical signs may not be apparent for several days, depending on how large the tear is and how fast urine leaks into the abdomen. Stranguria may be observed depending on the cause of the rupture. If severe, uroabdomen may produce signs of abdominal discomfort, tachycardia, and abdominal distention. Abdominal distention may not be as apparent in adult horses as in foals. The diagnosis is based on history, rectal examination findings, laboratory results, and findings on urinary US or cystoscopic examination. Postrenal azotemia develops within 24 hours after rupture and is accompanied by hyponatremia and hypochloremia. Unlike uroperitoneum in neonates, hyperkalemia is not a consistent finding. Transabdominal US examination of the abdomen reveals a large amount of free peritoneal fluid. Abdominocentesis yields a peritoneal fluid with a creatinine concentration that is twofold or greater than that of serum; this finding confirms a diagnosis of uroabdomen. Detection of calcium carbonate crystals on cytologic examination of peritoneal fluid is also diagnostic for uroperitoneum. Endoscopic examination of the bladder should allow determination of the location and extent of the bladder tear. Rarely,

uroperitoneum may also develop in some horses without full-thickness disruption of the bladder wall, and it is difficult to establish definitively the cause of uroperitoneum in these cases.[9]

Surgical repair is indicated in horses with large tears in the ventral half of the bladder. In mares, standing surgical repair may be feasible.[3-5] In patients with small dorsal tears or incomplete tears, use of an indwelling bladder catheter (closed system) to keep the bladder small may allow the tear to heal without surgery.[7,9] A temporary ureteral stent may be used to allow healing of ureteral tears.[12] Before surgery, IV fluids (0.9% NaCl) should be administered to correct dehydration, and if severe hyperkalemia is present, $NaHCO_3$ and/or 5% dextrose administered IV to drive potassium intracellularly. Broad-spectrum antibiotics should be administered as prophylaxis against sepsis. If the abdomen is distended, urine accumulated in the abdomen should be removed (e.g., by placement of chest tube or other large catheter through the ventral abdominal wall) before general anesthesia is induced to avoid further compromising respiration.

Urinary System Disorders in the Foal

Thomas J. Divers • Dominic R. Dawson-Soto • Lisa E. Fultz

Umbilical disorders of the neonatal foal, including patent urachus, urachal infections, and omphalitis, are discussed in detail in Chapter 17.

Uroperitoneum

Bladder Rupture.

The most common bladder disorder in otherwise healthy newborn foals is bladder rupture.[1-3] Foals aged less than 1 week are the most commonly affected, with an incidence of 0.2% to 2.5%.[4] There may be an increased incidence in colts, but some reports fail to support this.[4,5] In septic foals, bladder necrosis leading to leakage of urine may occur, possibly secondary to hematogenous spread of bacteria.[6] *E. coli* was the most common bacteria isolated from both peripheral blood and tissue sample in septic foals with ruptured bladders.[4] Focal necrotizing cystitis leading to tiny focal bladder perforations, uroperitoneum, and peritonitis has been reported in association with septic omphalitis in a 15-day-old foal, and *Clostridium perfringens* urachal infection was identified as a

cause of uroperitoneum in two neonatal foals.[7,8] Clinical signs include stranguria and repeated posturing to urinate during the first few days of life. Urine accumulates in the abdomen, typically leading to depression and abdominal distention between days 2 to 4 of life. Repeated posturing and stranguria can easily be misinterpreted as tenesmus associated with meconium impaction. Further, affected foals may continue to void small volumes of urine, so establishing a diagnosis of ruptured bladder can initially be challenging until more obvious signs of uroperitoneum (e.g., decreased nursing, abdominal distention) develop.

Laboratory findings in foals with uroperitoneum include hyponatremia, hypochloremia, hyperkalemia, and azotemia.[1-3,9,10] Foals receiving continuous fluid therapy before the diagnosis may not exhibit typical electrolyte changes, and instead suspicion of uroperitoneum should be raised with other signs such as decreased urinary output, abdominal distention, weakness, or other changes in clinical condition. Occasionally, a foal may also develop intermittent fine muscle tremors or a cardiac arrhythmia resulting from these electrolyte alterations, especially hyperkalemia.[10] Transabdominal ultrasonographic examination usually reveals a large quantity of free fluid in the abdominal cavity, but occasionally the bladder can still appear fluid filled, depending on the size of the leak (Fig. 34.15, *A* and *B*). A peritoneal fluid creatinine−to−serum creatinine ratio >2 : 1 or the presence of calcium carbonate crystals in the abdominal fluid confirms uroperitoneum.[1-3,9]

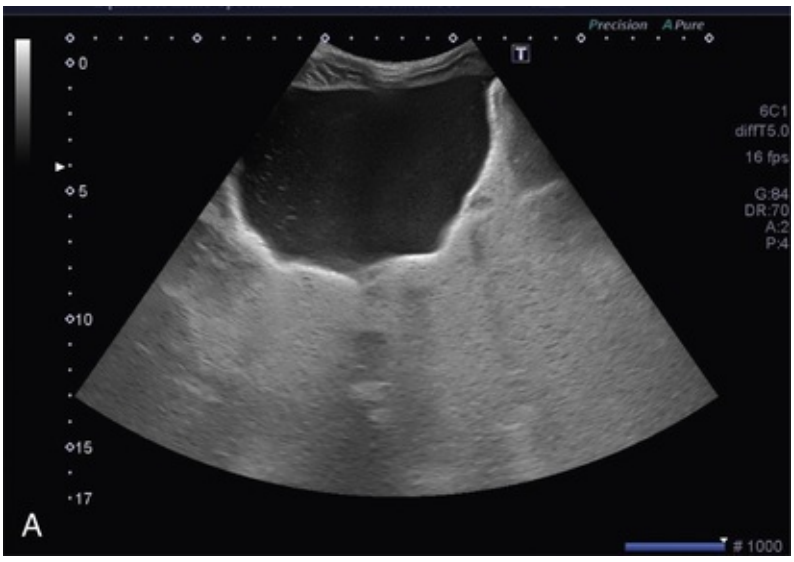




FIG. 34.15 **A,** Ultrasonographic appearance of a normal bladder in a foal. **B,** Ultrasonographic image of a ruptured bladder in a foal. The increased free peritoneal fluid is outlining the bladder and a loop of small intestine. The creatinine within the fluid was greater than twice that of the serum, consistent with uroabdomen.

Treatment of bladder rupture includes surgical closure of the defect, supportive care, and broad-spectrum prophylactic antibiotics for 3 to 7 days postoperatively.[1,2,6,11] An emergency surgical procedure is usually not required, and in most cases, postponement of surgery for several hours until electrolyte abnormalities are partially corrected (most notably correction of hyperkalemia to a serum concentration <6.0 mEq/L) is recommended. This can usually be accomplished by IV administration of 1 to 3 L of a 0.9% NaCl/5% glucose solution. Treatment with insulin should be avoided unless hyperkalemia is causing significant electrocardiographic (ECG) abnormalities and response to initial fluid therapy is poor. With marked hyperkalemia or abdominal distention causing respiratory embarrassment, slow drainage of urine from the abdomen (e.g., by chest tube or 10- to 14-gauge IV catheter) may be necessary before induction of anesthesia; IV fluid support should be provided during drainage. Despite significant azotemia in some affected foals, use of aminoglycoside antibiotics is generally safe because the azotemia is postrenal rather than

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reflecting intrinsic renal disease. In most cases, placement of a urinary catheter to maintain an empty bladder for the initial 2 postoperative days is unnecessary, but careful monitoring of urine output along with serial abdominal ultrasonography is recommended if a catheter is not placed. Postoperative bladder atony requiring bethanechol and an indwelling urinary catheter has been reported.[12] Uroperitoneum may recur after surgery in an occasional foal as a result of ongoing leakage from the bladder tear. When this complication occurs, it can usually be managed conservatively by placement of an indwelling bladder catheter (closed system) for 3 to 5 days. Rarely, a second celiotomy may be required. Nonsurgical management using an indwelling catheter and closed urinary-collection system has been successfully used in a critically ill foal, in which the bladder defect was sealed within 5 days.[13]

Urachal Urine Leakage.

Uroperitoneum may also develop in foals with urachal infection or ischemia. Affected foals are often septicemic or hospitalized for treatment of prematurity, hypoxic-ischemic encephalopathy, or botulism, and uroperitoneum is recognized later (e.g., after 5 to 10 days of treatment).[4,11] Prolonged recumbency and bladder distention are likely risk factors. The urachus of many affected neonates appears normal during the first 2 days of life, but in some cases, particularly with septicemia, may subsequently become patent. Urine leakage through the umbilicus may or may not be accompanied by leakage into the abdominal cavity or subcutaneous tissues of the abdominal wall. In other affected foals the umbilicus remains normal, and all urine leakage accumulates into the abdominal cavity. When monitored, inappropriate weight gain (e.g., >2 kg in 24 hours) is another common finding in hospitalized neonates that develop uroperitoneum, along with decreased urinary output. Transabdominal ultrasonography can be useful in detecting inappropriate urachal patency and communication with the bladder (Fig. 34.16, *A* and *B*).

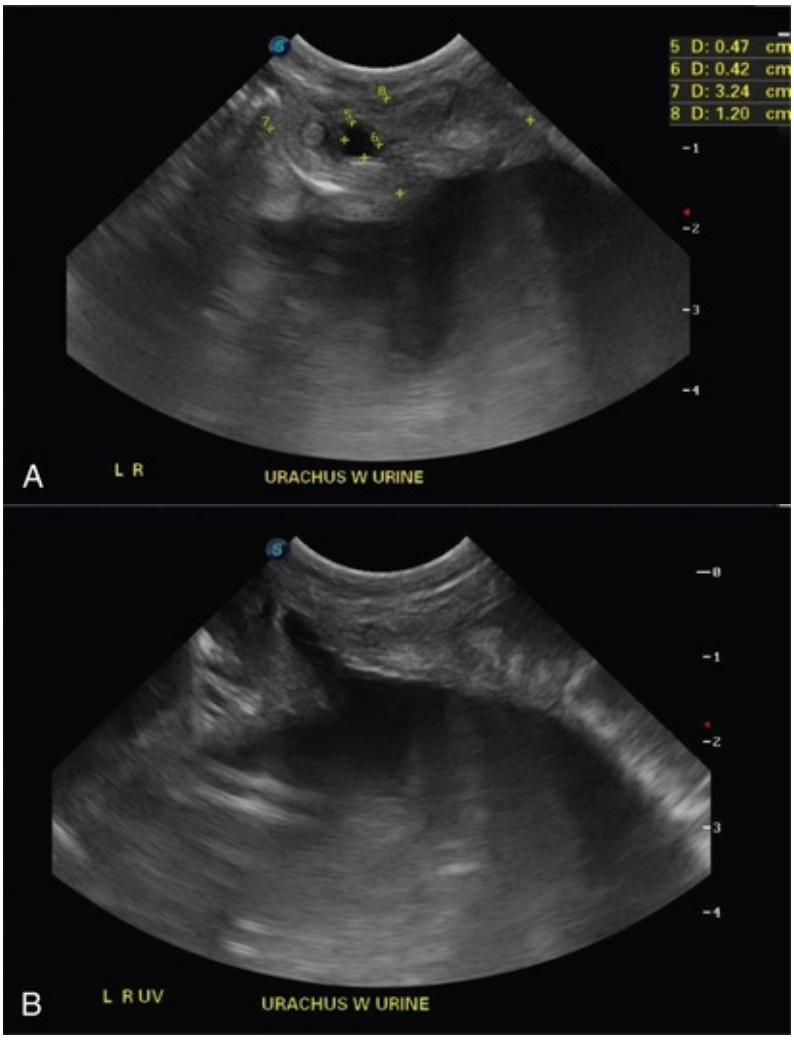


FIG. 34.16 **A,** Ultrasonographic image of hypoechoic fluid within a foal's urachal remnant, consistent with patent urachus. **B,** Ultrasonographic image of communication between the urachus and bladder in a foal, diagnostic of patent urachus.

Laboratory abnormalities typical for uroperitoneum may be found in affected foals but are not consistently abnormal, because these patients are often being treated with IV fluids. Correction of the problem includes surgical removal of the diseased urachus, closure of the bladder apex, and continued supportive care for the primary disease. The prognosis for a successful outcome for these foals is not as favorable as for bladder rupture because they often have a degree of peritonitis (increasing risk for adhesions), and uroperitoneum is often only one of several complications of the underlying disease.[4,11]

In an occasional foal, the urachus may also rupture more distally than usual and lead to subcutaneous accumulation of urine, ventral abdominal swelling,

stranguria, signs of colic, and distress.[14] The swelling may be differentiated clinically from a hematoma or septic omphalitis because it may enlarge quickly and often becomes cold. Ultrasonographic examination and/or local aspiration of fluid and measurement of creatinine (twofold or greater than in serum) confirm the diagnosis. Prompt surgical removal of the leaking urachus is indicated.

Ureteral Defects.

Ureteral defect(s) or disruption may also lead to development of uroperitoneum in both male and female foals.[1] Although rare in comparison with bladder rupture in foals, numerous case reports do exist, encompassing both traumatic and congenital ureteral abnormalities.[15-23] Stranguria is usually absent, and urine initially accumulates in the retroperitoneal space, but with time the retroperitoneal tissue ruptures, causing uroperitoneum. Affected foals may not be presented until 5 to 10 days of age or even older because urine accumulation is slower than with a ruptured bladder. Clinical signs include decreased nursing, depression, and mild colic, and in fillies an external bulging of the vagina may be observed. Laboratory findings are typical for uroperitoneum, and with significant hyperkalemia, intermittent muscle fasciculations may also be noted.

If urine accumulation remains localized to the retroperitoneal space, ultrasonographic examination of the lower abdomen may be normal, but a large amount of retroperitoneal fluid will be detected around the kidney and upper flank (within retroperitoneal space) on the affected side(s). In addition, the renal pelvis may be mildly dilated.[24] If the peritoneal membrane is ruptured, physical and ultrasonographic examination findings are similar to those seen with a ruptured bladder, but careful ultrasonographic examination may also reveal a full bladder or concurrent retroperitoneal fluid accumulation. As with a ruptured bladder, the ratio of retroperitoneal or peritoneal fluid creatinine–to–serum creatinine is >2 : 1. In small foals (e.g., <50 to 75 kg), excretory urography (after IV administration of contrast agent) or pyelography (after percutaneous injection of contrast agent into renal pelvis with ultrasonographic guidance) may be useful for localizing the ureteral defect(s).[20] Computed tomography can also be useful in the diagnosis of ureteral abnormalities in foals.[21,22]

One or both ureters may be involved, and during surgical exploration, one or more defects can usually be found in the proximal half of the ureter, often near the renal pelvis. During surgery the defect(s) can be localized by catheterizing the ureter through a cystotomy and then injecting dye (e.g., Evans blue,

methylene blue). Successful correction of unilateral and bilateral defects can be accomplished by placing a stent in the affected ureter(s) for 7 to 26 days.[15,16,23] Surgical reimplantation of a ureter into the bladder (ureteroneocystostomy) has also been used to successfully correct a stenotic ureter in a 2-day-old foal.[23]

A report describing bilateral ureteral defects adjacent to the renal pelves provided histopathologic evidence that the lesions were traumatic in origin rather than developmental anomalies.[18] The foal in that report had previously been kicked by its dam. One of the authors (TJD) has seen three foals with similar ureteral defects, all of which also had multiple rib fractures. Ureteropelvic junction injuries and proximal ureteral tears are a recognized complication after blunt abdominal trauma in human patients.[25] These observations suggest that many ureteral defects in foals may more likely be traumatically induced at foaling rather than being developmental anomalies. However, there are several case reports of nontraumatic congenital ureteral defects in foals.[17,20,21,23]

Cystitis

Cystitis can develop in septic, recumbent, premature, or neonatal foals being treated with broad-spectrum antibiotics. Evidence indicates that bacterial infection of the urinary tract, whether primary or due to hematogenous spread, may contribute to the development of uroperitoneum.[5,6] When cystitis is suspected, the bladder should be catheterized and a urine sample submitted for urinalysis and quantitative culture. Urinary tract infections with *Candida* spp. are fairly common in recumbent neonates on broad-spectrum antibacterials. Specific antimicrobial therapy is not usually necessary for *Candida* cystitis as long as systemic antibiotics can be discontinued. However, fluconazole is an option for treatment because if antibiotic therapy continues, dissemination of the *Candida* infection can sometimes spread to other sites (e.g., joints).

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▪ Ruminant Renal System

Emily A. Barrell

Ulcerative Posthitis and Vulvitis

Stacey R. Byers

Ulcerative posthitis and vulvitis (enzootic balanoposthitis, pizzle rot, sheath rot) is an ulcerative bacterial infection of the mucous membrane and surrounding skin of the prepuce and vulva. It is most commonly observed in small ruminants but has been reported in dromedary camels.[1]

Clinical Signs and Differential Diagnoses

In male small ruminants, the infection begins as a moist ulcer, usually at or near the mucocutaneous junction of the prepuce. A thin, loose, brown to red, malodorous scab (Fig. 34.17) covers the ulcer. If the scabs are removed, little or no hemorrhage occurs. Focal swelling is often noticeable at the cranial aspect of the prepuce, and the area is painful on palpation.



FIG. 34.17 Ulcerative posthitis in a Suffolk ram.

If untreated, the infection spreads along the mucosal surface inside the prepuce, creating the more serious internal form of ulcerative posthitis. In such cases the entire prepuce may be swollen and elongated. Affected animals often show dysuria, and goats may vocalize during voiding. As the local inflammation progresses, ulceration may result in fibrous adhesions between the penis and

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prepuce. Severe inflammation of the glans penis can cause stricture of the urethral process (pizzle) and restrict urine egress, resulting in signs similar to those of obstructive urolithiasis. Impairment of breeding soundness may result from pain, blood or exudate in the ejaculate, penile adhesions, scarring of the preputial orifice, or suppurative urethritis. Weight loss may occur in chronic cases. Phimosis has been reported in affected camels.[1]

Ulcerative lesions of similar appearance can develop on the vulva and perineum of affected females. Gross vulvar enlargement may be noticed from a distance. Dysuria may result from involvement of the urethral orifice. The fibrosis and contracture that develop in chronic, severe cases may distort normal vulvar conformation to the point of impairing copulation or parturition.

Ulcerative dermatosis (lip and leg ulcer) in sheep is dermatitis caused by poxvirus related to the contagious ecthyma virus. Infection with this agent may manifest as balanoposthitis and vulvitis, and the crusted ulcers that develop closely resemble those induced by infection with *Corynebacterium renale.* Ulcerative dermatosis can be differentiated from ulcerative posthitis because lesions are also present on the face and legs with the former condition. The lesions readily bleed and often contain a nonodorous, purulent discharge.

Contagious ecthyma (orf) occasionally affects the genitalia and perineum, although lesions are more frequently found on the lips, face, and udder. These lesions are raised, appear proliferative, and are covered with a thick, durable scab. Secondary bacterial infections and necrosis can occur with concurrent *Fusobacterium necrophorum* infection.[2]

Urolithiasis must be strongly considered in the differential diagnosis of any dysuric male small ruminant. Preputial trauma, particularly if resulting from entrapped grass awns, can cause preputial swelling, pain, and exudation within the preputial cavity. External ulcerative lesions would not be expected in such cases.

Caprine herpesvirus 1 (CHV-1) and ovine herpesvirus 2 (OHV-2) infections have been documented to cause preputial, penile, vulva, and vaginal lesions in goats and sheep, respectively. Ulcers tested positive by PCR for the herpesviruses.[3-6]

Corynebacterium pilosum, Corynebacterium cystitidis, Mycoplasma mycoides subsp. *mycoides* large colony type, *Actinobacillus seminis, Ureaplasma* spp., *Mycoplasma ovine-caprine* serogroup 11, and *Mycoplasma capricolum* subsp. *capricolum* have been implicated in posthitis and vulvitis in sheep.[7-9] A possible synergism between *Mycoplasma mycoides* subsp. *mycoides* large lolony type and

Trueperella pyogenes has been demonstrated in Dorper sheep in South Africa.[8]

Pathophysiology

C. renale is the bacterium most commonly implicated in ulcerative posthitis. These are aerobic, gram-positive, pleomorphic, club-shaped bacteria that are normal inhabitants of the skin and external genitalia of small ruminants. The bacteria contain the enzyme urease. A high-protein diet results in increased ammonia production in the rumen, which is converted to urea in the liver. The urea is eliminated through the renal system. *C. renale* proliferates, and the urease hydrolyzes the urea back to ammonia, causing chemical irritation and ulceration of the prepuce and surrounding skin.

Epidemiology

The condition appears to be more common in males than females. Risk factors are associated with increased or excessive dietary protein concentration (usually >16%), such as alfalfa hay or lush legume or legume-grass pastures. However, diets with protein levels as low as 12% have been implicated.[7] Rams, pet wethers, club or show lambs or kids, wool and fiber production animals, and feedlot lambs are most predisposed to the disease. Increasing the plane of nutrition in intact males before breeding predisposes to development of this disease, and multiple animals can be affected simultaneously.[10,11] Breeds with dense wool or hair, such as Merino sheep and Angora goats, are also at risk owing to urine soaking the coat near the preputial orifice. Blowfly myiasis appears to increase the risk of ulcerative posthitis.[11]

Disease can occur in individual or multiple animals, since the organism can persist in wool, hair, and scabs for as long as 6 months and can survive freezing in scabs and exudative material. Venereal transmission of the disease has been documented; several months may pass between exposure of ewes to infected rams and development of vulvitis in the ewes. Production losses result from debilitation caused by pain, incapacitation of breeding animals, loss of breeding soundness, and deformation of external genitalia.

Treatment and Prognosis

Reduction of protein and nonprotein nitrogen intake is crucial for successful

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treatment of affected animals and prevention of additional cases. Dietary changes alone may result in satisfactory cure if the lesions are early in development. Incorporation of grass hay feeding into a program of legume pasture grazing may help limit protein intake.

Affected animals should be isolated to limit venereal or contact transmission. Fly control should be implemented. Wool or hair should be removed from the skin surrounding the prepuce or vulva, and a topical antibiotic may be applied. Caustic antiseptic solutions should not be used. Treatment with systemic antimicrobials is indicated for advanced cases or for outbreaks, in which handling of several animals for topical therapy is not feasible. *C. renale* is sensitive to penicillin, ampicillin, cephalosporins, and oxytetracycline. Treatment should continue until the lesions have dried and acute inflammation has subsided. Topical therapy of the preputial or vulvar mucosa includes application of mastitis treatment tubes, triple antibiotic ointment, or “petercillin.” Petercillin is prepared by mixing 240 g anhydrous lanolin, 20 mL of procaine penicillin G (300,000 IU/mL), and 200 mg aqueous prednisolone. A small amount can be warmed up and injected into the prepuce using an AI infusion pipette or small feeding catheter. Oral or injectable NSAIDs can be used to decrease the inflammation and pain associated with the infection.

Surgical treatment of advanced cases is recommended for severe strictures. The ventral preputial tissue can be resected to allow for normal urine flow or be incised along part of its length.

Response to treatment is optimal early in the infection, before deformation of the prepuce or vulva secondary to fibrosis occurs. The chances for full recovery without recrudescence are poor if dietary protein intake is not reduced. Complete recovery of breeding soundness is unlikely in animals with internal ulcerative posthitis. In breeding males, the presence of ulcerative posthitis does not directly influence semen motility or morphology, but since pain is likely to suppress libido, proper treatment and documentation of lesion resolution are recommended in affected males before the breeding season.[12]

Prevention

Prevention primarily involves limiting both protein and nonprotein nitrogen intake. Breeding males should be body condition scored early enough before the breeding season so that any necessary weight gains can be made slowly rather than as a sudden onset immediately before the breeding season. Whenever

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possibly, weight gain should be induced by feedstuffs with a protein concentration of less than 12% on a dry matter basis. Separation of affected males will help decrease spread through contact with exudative materials. Shearing, especially at the time of highest protein intake, may be efficacious in reducing disease incidence.

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Urolithiasis

Stacey R. Byers

Definition and Etiology

Urolithiasis is a common metabolic disease in all livestock species, but castrated small ruminants are particularly at risk. Uroliths cause disease through trauma to the urinary tract and obstruction of urinary outflow. Urolithiasis can occur in outbreaks, as an endemic problem in group-housed animals, or as an individual disorder.

The clinical signs of urolithiasis vary and are based on duration, extent (complete vs. partial), and location of the obstruction. Early clinical signs can be remarkably subtle and may include anorexia, depression, and mild bloat. A history of colic and straining to urinate or defecate may be provided, and novice owners often mistake stranguria for constipation or tenesmus. If investigating a sick, intact, or castrated male small ruminant, urolithiasis should be high on the differential list, regardless of the clinical signs.

Four common disorders can result from urolithiasis: acute urethral obstruction, chronic urethral obstruction, urethral rupture, and urinary bladder rupture. Less commonly seen are ureterolithiasis and hydronephritis.

Clinical Signs and Differential Diagnoses

Acute Urethral Obstruction

Impacted calculi lead to urethral trauma and progressive bladder distention, resulting in stranguria and abdominal pain. Affected animals may be restless, tread, swish their tails, and grind their teeth. Goats and camelids may vocalize. Tachycardia, tachypnea, and mild bloat secondary to ruminal stasis are common findings. Stranguria is manifested as repetitive bouts of stretching and contraction of the abdominal muscles. Straining may induce secondary rectal prolapse, so urethral obstruction should be investigated as the primary disease in cases of rectal prolapse. Rarely, affected calves develop a visible dilation of the urethra at the midline of the perineum proximal to the obstruction.[1] Anuria occurs if urethral obstruction is complete, whereas urine may dribble in cases of

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partial obstruction. Crystals or blood may be found on the hairs of the preputial tuft; in cases of anuria the hairs are dry. If a urine sample can be collected for dipstick analysis, proteinuria and occult hematuria are frequently detected.

Rectal palpation (digital rectal palpation in small ruminants and camelids) often reveals pulsation of the pelvic urethra. In cattle, bladder distention is palpable per rectum, although if bladder or urethral rupture has occurred, the bladder is typically not palpably enlarged.

Abdominal palpation may be useful in affected small ruminants, small camelids, and pot-bellied pigs. The examiner should place the fingertips of each hand into the ventral flank on each side of the abdomen. While slowly pressing the fingertips toward midline in the caudal abdomen, the examiner may encounter an orange- to grapefruit-sized, firm, spherical structure, which is the distended bladder. Severe bladder distention will not be palpated in cases of incomplete urethral obstruction or bladder rupture.

Common sites for urolith obstruction include the distal aspect of the sigmoid flexure, near the insertion of the retractor penis muscles in cattle, and the urethral process in sheep and goats. However, uroliths can be found along any length of the urethra.

Owing to the frequent lack of specific clinical signs, acute urethral obstruction can resemble a variety of diseases. Tachycardia, colic, bloat, and anorexia are characteristic of GI obstruction, but auscultation and percussion of the abdomen, abdominal succussion, rectal palpation, and transabdominal or transrectal ultrasonographic examination should differentiate this condition from acute urethral obstruction. Encephalopathies, salmonellosis, coccidiosis, and proctitis from rectal prolapse or trauma frequently cause tenesmus. Additional signs of primary neurologic or GI dysfunction should be evident with these diseases.

Although rare in male ruminants, primary UTIs may result in dysuria and pollakiuria. Bladder distention is uncommon with UTI, and large numbers of WBCs and bacteria are present in the urine sediment.

Occasionally, an animal with urolithiasis successfully voids the obstructing urolith(s). The resultant traumatic urethritis might cause dysuria, but the rate and ease of urination typically improve over time and with anti-inflammatory treatment.

Juvenile male camelids have been observed straining or posturing to urinate. On cystotomy, no uroliths have been discovered. Etiology has not been conclusively determined, but transrectal ultrasound has identified prostatitis in some individuals. It is suspected that hormonal influences or ascending UTIs

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may be contributing to prostatic or urethral inflammation.

In younger animals, it is important to consider congenital abnormalities (e.g., ectopic ureter(s), pelvic displacement of the urinary bladder, urethral duplication). Congenital abnormalities may manifest at birth or not until later, depending on the level of observation and whether the defect results in obstruction, partial obstruction, or constant urine dribbling.

Chronic Urethral Obstruction

Uncommonly, partial urethral obstruction causes chronic dysuria and stranguria if calculi impair but do not completely obstruct urine outflow.[2] If a chronic partial obstruction is present, the affected animal has a characteristic slow or intermittent urine flow during voiding. Lethargy, reduced appetite, and thin body condition are evident if renal failure has developed. On rectal palpation, the bladder may be small, and thickening of the bladder wall may be palpable.[2]

Urine dribbling may also occur in animals with neurologic disease, previous urethral trauma (stricture formation), congenital anomalies of the urogenital tract, infection, or neoplasia. Contrast urethrography may be used to identify the presence of strictures or anomalous structures. Small ruminants with the internal form of ulcerative posthitis may dribble urine. In such cases, characteristic preputial lesions are present. Tumors of the urinary tract, although rare compared with urolithiasis, may cause gradual obstruction in cattle, small ruminants, and camelids.

If there is a complete urethral obstruction for approximately 36 hours or more, the animal is at risk of developing bilateral hydroureter and hydronephrosis, and imaging studies of the kidneys and ureters are warranted.

Urethral Rupture

Urethral rupture is a common complication of urethral obstruction in ruminants and camelids. The wall of the obstructed urethra undergoes pressure necrosis, causing leakage of urine into the subcutaneous tissue of the perineum and ventral abdomen. Sequelae include cellulitis, penile adhesions (possibly creating phimosis), urethral fistula formation, and urethral stricture. Erection failure secondary to vascular obstruction of the corpus cavernosum of the penis has been reported as a sequela to urethral obstruction and rupture in a goat.[3]

Affected animals are frequently depressed and inappetent and have bilaterally symmetric, pitting edema in the ventral perineum, inguinal region, prepuce, and

ventral abdomen (Fig. 34.18). Swelling of the abdominal wall may extend as far forward as the axillae. The affected areas are initially warm and painful on palpation. As necrosis progresses, the tissues become cool, dark, nonpainful, and potentially gangrenous. A fistula may develop to allow urine to escape. Fever may occur if tissue necrosis and sloughing are extensive. Transrectal palpation or ultrasound reveals a small bladder.



FIG. 34.18 Urethral rupture in a Holstein steer. Tissue swelling from urine accumulation may extend to the sternum and axillae.

Ventral abdominal swelling is also found with umbilical or scrotal hernias and omphalophlebitis. These conditions can be differentiated from urethral rupture by careful palpation of affected tissues, aspiration of any fluid pockets for cytologic examination, and ultrasonography. In bulls, penile hematomas may cause localized swelling of the prepuce in the prescrotal region and caudal sheath, but the swelling does not involve the ventral abdominal wall. Aspiration of a suspected penile hematoma is not recommended because of the risk of iatrogenic infection.

Urinary Bladder Rupture

In all ruminants and camelids, prolonged bladder distention secondary to urethral obstruction may result in pinpoint perforations, tears, or necrosis of large areas of the bladder wall. In cows, bladder rupture may also occur as a rare complication of dystocia.[4] Rupture of an urachal remnant may also result in

uroperitoneum.[5] The dorsum of the bladder fundus is the most common site for rupture, but bladder rupture can occur at any site.

Relief of bladder distention causes cessation of stranguria. Bilateral distention of the ventral abdomen develops within 1 to 2 days after rupture and is accompanied by worsening clinical signs of depression, anorexia, weakness, dehydration, and shock. Ballottement of the abdomen may elicit a fluid wave. Rectal temperature may be normal, but shock may result in hypothermia. The animal's breath may smell like ammonia. On transrectal or transabdominal palpation, the bladder is small or not palpable. Transabdominal ultrasonography reveals a large volume of free fluid and a collapsed or partially filled bladder. Abdominocentesis yields a large volume of blood-tinged fluid; the fluid may smell like urine when heated, although this is quite subjective. On occasion, urine will translocate into the thoracic cavity or scrotum through the inguinal canals. Uremia and dehydration result in debilitation and eventual death if medical and surgical treatments are not provided.

Seepage of urine across the bladder wall and into the abdominal cavity may occur in cases of severe bladder distention; in such cases, rupture is often imminent.

Differential diagnoses for bladder rupture include diffuse peritonitis, ileus, enteritis, vagal indigestion, ascites, caudal vena caval thrombosis, and hypoproteinemia. Marked peritoneal cavity effusion may be found in cases of mesothelioma or lymphoma. These conditions are differentiated from bladder rupture through transrectal palpation, ultrasonography, cytologic and chemical analysis of peritoneal fluid, evaluation of serum chemistry, and abdominal exploratory surgery.

Ureterolithiasis and Nephrolithiasis

Animals with acute ureteral obstruction may show severe colic with stretching, kyphosis, treading, collapse, and vocalization. Signs of distress may be less severe or even absent if obstruction is intermittent or incomplete.[6] Enlargement of the blocked ureter may be palpated transrectally, and if the left ureter is obstructed, enlargement of the left kidney may be appreciated. Transabdominal or transrectal ultrasound may aid in the diagnosis in small ruminants and camelids. Pyelonephritis can be the inciting cause of ureteral obstruction or renal calculosis. With ureteral or renal rupture, uroperitoneum or retroperitoneal accumulation of urine may occur.

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Similar signs of abdominal pain or colic can result from GI or urinary tract obstruction in ruminants and camelids. Auscultation and percussion of the abdomen, rectal palpation findings, ultrasonography, or radiography may allow for differentiation of GI obstruction from ureteral or renal obstruction. Cases of ureteral or renal calculosis without colic may show nonspecific signs of illness, and serum chemistry, urinalysis, and ultrasound examination are needed for definitive diagnosis.

Ancillary Diagnostic Tests

Examination of the Urethral Process in Small Ruminants

Sedation or general anesthesia facilitates extrusion of the penis for examination. Because of its diuretic effect, xylazine may exacerbate bladder distention and is not recommended. Diazepam (0.1 to 0.2 mg/kg IV) and acepromazine (0.05 to 0.1 mg/kg IV or IM) have been used successfully, either as sole agents or in combination with butorphanol (0.05 to 0.1 mg/kg IV). Alternatively, isoflurane by mask can be used.

An adjunct or alternative to sedation is administration of epidural anesthesia, which provides greater patient comfort and eliminates muscular resistance to penile extrusion. One milliliter of 2% lidocaine per 15 kg (33 lb) of body weight is injected into the epidural space at the lumbosacral junction. Lower dosages may provide sufficient anesthesia. The total dose should not exceed 15 mL of 2% lidocaine in any small ruminant, regardless of size. If CSF is obtained, half of the epidural lidocaine dosage can be administered as a true spinal block. Hindlimb motor blockade is expected with either epidural or true spinal anesthesia at this site; the effects typically last 1 to 2 hours.

To exteriorize the penis, the sheep or goat is propped up on its rump and the hind legs are pulled up alongside the trunk. For larger sheep or goats, this can be aided by a person sitting (e.g., in a chair or on a bale of straw), with the animal propped up between his or her legs. It is critical that the animal be positioned such that its spine is perpendicular to the floor. Addition of lidocaine jelly or several milliliters of 2% lidocaine added to a water-based lubricant and squirted into the prepuce may decrease discomfort for exteriorizing the penis. The examiner can then exteriorize the penis by pushing the sigmoid flexure cranially from the base of the scrotum while pulling the sheath caudally. In some animals and overconditioned males, the preputial mucosa must be carefully grasped with small forceps or Allis tissue forceps to aid in extruding. The penis can then be

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grasped with a piece of gauze to keep it exteriorized. The urethral process can then be inspected and palpated for the presence of discrete uroliths or sandlike grit within the lumen. If the urethral process is obstructed, it can be amputated with a scalpel blade (see Surgical Treatment section later).

Ultrasonography and Radiography.

A presumptive diagnosis of urolithiasis can usually be made through historical and physical examination findings. Ultrasonographic and radiographic evaluation of the urinary tract is useful for confirming the diagnosis, locating obstruction sites, and aiding in determining prognosis.[7-11] In cases of prolonged urethral obstruction (≥48 hours) or urethral obstruction with severe azotemia, it is prudent to perform ultrasonographic examination of the kidneys before considering surgical treatment. Detection of severe hydronephrosis warrants a poor prognosis for recovery.

Ultrasonographic evaluation of the bladder of pot-bellied pigs, small ruminants, and camelids is most easily accomplished through transabdominal scanning directed caudodorsally from the inguinal area. Both kidneys of small ruminants and camelids and the bovine right kidney can be examined from the right paralumbar fossa. In cattle, transrectal examination of the pelvic urethra, bladder, ureters, and left kidney can be performed. Marked distention of the bladder, thickening of the bladder wall, and echogenic material within the bladder lumen may be seen with acute urethral obstruction. A large volume of free fluid in the abdomen is characteristic of uroperitoneum and is suggestive of existing or impending rupture.

Radiographic examination of the urinary tract is limited to pot-bellied pigs, camelids, small ruminants, and young cattle. Lateral views of the abdomen can be used to detect and locate radiopaque calculi in the bladder and urethra.[9] This is accomplished most easily with the animal in lateral recumbency with the hindlimbs pulled caudally. It is also essential to image the entire urethra to determine the presence and location of additional stones.

Intravenous, normograde or retrograde contrast urethrography can assist in the detection of radiolucent urethral calculi, urethral strictures, or urethral rupture. A contrast urethrogram can be performed in adult bucks and rams and some older castrated males by placing a catheter approximately 5 cm into the penile urethra and injecting 10 to 30 mL of water-soluble contrast media. The catheter should be completely filled with contrast material before insertion into the urethra to

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avoid accidental introduction of bubbles into the catheter. Injection should be performed slowly with minimal pressure to avoid iatrogenic urethral rupture. The technique may not be possible in juveniles and wethers as the penile frenulum limits exteriorization of the penis. Following tube cystostomy, contrast urethrography can be performed by injecting the contrast material into the bladder through the catheter. The catheter can then be clamped shut temporarily to detect stones, strictures, or urethral rupture.

Clinical Pathology

Acute and Chronic Urethral Obstruction.

Hematologic and serum chemistry findings may be unremarkable in ruminants with acute urethral obstruction uncomplicated by urethral or bladder rupture. Hyperglycemia and a stress leukogram may be present. With time, hemoconcentration and azotemia develop secondary to reduced water intake. Hematuria and proteinuria are consistent abnormalities, whereas crystalluria is a variable finding. With chronic urethral obstruction, hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, and severe azotemia with isosthenuria suggest extensive nephron damage caused by hydronephrosis. Pyuria is present with traumatic urethritis, cystitis, or secondary bacterial infection.

Bladder Rupture.

Bladder rupture and accumulation of urine in the abdomen result in hematologic and serum biochemical parameter alterations that worsen over time. Urine osmolality is normally two to three times that of extracellular fluid (ECF), and urine contains higher concentrations of urea, creatinine, and potassium but lower concentrations of sodium and chloride than ECF. Therefore, movement of water, urea, and electrolytes occurs along diffusion gradients, resulting in hyponatremia, hypochloremia, hyperphosphatemia, uremia, and hemoconcentration.

Serum potassium concentration in ruminants with bladder rupture is more variable, depending on appetite and time before diagnosis. Although animals with uroperitoneum are at risk of hyperkalemia, serum potassium concentration tends to be normal or low in ruminants with bladder rupture, even if uroperitoneum exists for several days. Anorexia may contribute to hypokalemia

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or normokalemia in these cases, and aldosterone release secondary to volume depletion results in dramatic increases in salivary potassium excretion, providing an alternative route of potassium excretion in affected animals. Once in the GI tract, potassium absorption may be diminished by ileus and preferential absorption of sodium over potassium. Alkalosis, which occurs secondary to hypochloremia, may also serve to reduce ECF potassium concentration by encouraging movement of potassium intracellularly.

Although only a small fraction (<10%) of phosphorus excretion in the ruminant is via urine, hyperphosphatemia may occur secondary to uroabdomen. Potential mechanisms for hyperphosphatemia include phosphorus diffusion from the urine into the ECF, reduced glomerular filtration, and tissue hypoxia causing breakdown of organic phosphate compounds in cells. In addition, reduced salivary flow from anorexia may limit phosphorus excretion in the saliva, contributing to phosphorus retention. Anorexia, ileus, and a competitive effect of hyperphosphatemia may contribute to reduction in serum calcium concentration in cases of uroabdomen.

Measurement of creatinine in the peritoneal fluid can be used to confirm a diagnosis of uroperitoneum. Creatinine is a relatively large polar molecule that does not readily diffuse from the abdominal cavity into the ECF space. Therefore, peritoneal fluid creatinine can be compared to serum creatinine concentration, with a peritoneal fluid–to–serum creatinine ratio of greater than 2 : 1 indicative of uroperitoneum.

Uroperitoneum may induce a mild chemical peritonitis. WBC count and blood fibrinogen levels may increase in cases of ruptured bladder. There is a risk of coagulopathies due to azotemia and uremia affecting platelet aggregation and coagulation factor function.

Urethral Rupture.

Leakage of urine into the subcutaneous space following urethral rupture produces hematologic and serum biochemical alterations that are similar but typically less severe than those seen with bladder rupture. Tissue necrosis and secondary infection may result in neutrophilia, leukocytosis, and hyperfibrinogenemia.

Ureterolithiasis and Nephrolithiasis

Azotemia and secondary hydronephrosis are most severe if the obstruction is

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bilateral. With chronic ureteral obstruction, hyponatremia, hypochloremia, hypocalcemia, hyperphosphatemia, and severe azotemia with isosthenuria suggest extensive nephron damage caused by hydronephrosis. Pyuria is present with traumatic urethritis, cystitis, or secondary bacterial infection.

Pathophysiology

Multiple factors influence the development of urinary calculi, but of primary importance is the development of high urinary concentrations of soluble ionized minerals (crystalloids) that aggregate to form insoluble crystals. Supersaturation of urine with a calculus-forming crystalloid is a prerequisite for urolith development, but supersaturation alone is not solely responsible for urolith initiation because normal urine is typically supersaturated with a variety of calculogenic ions.[12] Urine contains variable concentrations of mucopolysaccharides, ions, and organic acids that act as intrinsic inhibitors of crystallization. Through physical and electrochemical interactions, these compounds maintain calculogenic minerals in a colloidal suspension. Calculus formation is initiated if supersaturation of urine with appropriate crystalloids exceeds the protective capabilities of the crystallization inhibitors. The crystalloids are rendered insoluble and precipitate out of the aqueous phase of urine. Calculi enlarge as further mineral precipitation takes place on the crystal surfaces. Dietary, environmental, and management influences interact to determine the degree of supersaturation of urine with calculogenic minerals. Dehydration, with resultant concentration of urinary minerals, would appear to be a potential contributing factor in the development of all types of uroliths.

The solubility of some calculogenic crystalloids is influenced by urinary pH. Struvite (magnesium ammonium phosphate), calcium phosphate, and calcium carbonate uroliths are less soluble in alkaline urine, whereas calcium oxalate solubility is not affected by changes in urine pH within the physiologic range. The effect of urinary pH on silica calculi is debatable, but there is a trend toward reduction in formation under conditions of mild aciduria.[13]

Primary UTIs are considered an uncommon cause of ruminant urolithiasis. Purulent debris within the urinary tract may serve as a nidus for crystal development, and bacterial ureases may increase urinary pH, thereby reducing the solubility of certain crystalloids. Vitamin A deficiency has been incriminated as a contributory factor for urolith development by leading to metaplasia of urinary tract epithelium.[12] This may create nidi for calculogenesis through

desquamation of cells or altered cell surface characteristics.

Feeding patterns may influence the risk for calculogenesis. Meal feeding exerts an osmotic draw of fluid into the rumen from the ECF. This leads to a release of antidiuretic hormone that results in a transient decline in urine output and an increase in urine concentration. These changes in urine composition can be limited through ad libitum feeding.[14]

The influence of water hardness (dissolved mineral content), in particular in magnesium concentrations, has been implicated in the pathogenesis of this disease in ruminants.[15]

Phosphatic Calculi.

Ruminants consuming rations high in phosphorus (grain-based rations) typically develop struvite (magnesium ammonium phosphate hexahydrate) or apatite (calcium phosphate) calculi.[12,16] Rations where the calcium/phosphorus ratio is less than 2 : 1 are particularly prone to cause outbreaks of urolithiasis.[12] However, the role of phosphorus in urolith formation is not clearly defined, and struvite urolith formation appears to be primarily affected by the magnesium and, to a lesser extent, other minerals in the diet.[12,17,18] Magnesium absorbed from the gut is excreted through the kidneys. High potassium in the diet alters the dietary cation-anion difference (DCAD) and increases the risk of urolith formation (see more about DCAD in Prevention section later).[19]

Ruminant saliva is rich in phosphorus, and the GI tract is the primary route of phosphorus excretion in ruminants. In theory, ruminants consuming pelleted rations produce less saliva, which would reduce GI phosphate losses and increase urinary phosphate excretion. Struvite uroliths are typically white or gray, usually smooth, radiopaque, and easily broken.[12] They can be found as a single stone or sandlike debris, which is more commonly seen in ruminants.

Silica Calculi.

Silica urolithiasis is primarily a problem of ruminants grazing native rangeland grasses of western North America. A fraction of dietary silica, as unpolymerized silicic acid, is dissolved in the ruminal fluid of the grazing animal, absorbed, and excreted in the urine.[12] Water intake is usually intermittent in ruminants on rangeland. During periods of water deprivation, water and sodium resorption by the kidneys results in the formation of highly concentrated urine. Calculi can

develop as the silicic acid concentrates and polymerizes to the less soluble form, polysilicic acid.

The incidence of silica urolithiasis can be increased by feeding sheep rations that have a high calcium–to–phosphorus ratio (≥ 2.8 : 1) and induce more alkaline urine.[13,20] It is important to note that a high calcium-to-phosphorus ratio in the diet can help to prevent one type of urolith (struvite) but may be a contributory factor for another (silica). This underscores the importance of both ration and urolith mineral analyses in the formulation of preventive measures for this disease.

Silica uroliths in ruminants are hard, smooth, white to brown, radiopaque, and often layered.[12] The uroliths are usually composed of about 20% mucoprotein, 75% silicon dioxide, and variable amounts of calcium oxalate and calcium carbonate.[12]

Calcium-Based Calculi.

The two main types of calcium-based uroliths are calcium carbonate and calcium oxalate. Calcium carbonate uroliths are common in small ruminants grazing lush, rapidly growing clover pastures or being fed alfalfa hay.[21] Forages like these are rich in calcium and low in phosphorus and magnesium and have high oxalate content. In the gut, oxalate avidly binds calcium and makes it unavailable for absorption. With gradual introduction of oxalate-rich diets, ruminal bacteria efficiently metabolize oxalate to bicarbonate, so metabolism of oxalate in the rumen may increase the availability of dietary calcium. These factors may combine to increase urinary calcium excretion and alkalinize urine, thereby promoting calcium carbonate calculogenesis.

Oxalates in the diet, as well as low calcium and decreased water intake, may increase the risk of forming calcium oxalate stones. Given its low solubility, calcium oxalate crystals are often present in normal urine and may be incorporated into other uroliths as a trace component.[22]

Calcium carbonate uroliths have a characteristic round, smooth shape and copper color and are often present as multiple uroliths scattered throughout the lower urinary tract. Calcium oxalate uroliths are typically dense, hard, white to yellow, and either smooth or jagged.[12]

Epidemiology

Gender.

Obstructive urolithiasis in ruminants and camelids is almost exclusively a disease of males and castrated males. Urinary calculi appear to develop to a similar degree in female ruminants, but most calculi can pass through the relatively short, distensible urethra of the female, making urethral obstruction uncommon. The urethra of the male is long and surrounded by the less distensible corpus spongiosum and tunica albuginea.

Research indicates calculi form to a similar extent in the urinary tracts of intact and castrated male ruminants. The increased predisposition for urethral obstruction in steers and wethers may be due to the loss of testosterone on urethral diameter.[23,24] However, because many castrated small ruminants are kept as pets, factors such as diet, environment, and age are likely to differ compared with intact males. Specific gender risks in camelids and pot-bellied pigs are not well described; in commercial pigs, urolithiasis is generally associated with husbandry problems such as improper calcium/phosphorus ratio in the ration and inadequate water availability.[25]

Season.

The incidence of urolithiasis increases in hot, arid months in warm climates and in late fall and winter in North America. Seasonal effects are likely due to limited water availability and decreased consumption with colder weather.

Age.

All ages of ruminants are at risk for developing obstructive urolithiasis. The tendency for this disease to be seen in younger ruminants may be the result of dietary influences because younger animals are more often fed concentrates for weight gain and eventual slaughter than are mature males kept for breeding. Because relatively fewer mature males are kept for breeding, the apparently increased prevalence of urolithiasis in younger animals may simply reflect the greater numbers of younger males and castrated males at risk.

Other.

Inherent differences in an individual animal's mineral metabolism or urinary tract health may also play a role; some animals can ingest a calculogenic diet and remain unaffected, while others develop uroliths rapidly. Animals prone to develop uroliths may have ineffective protective capabilities within the urinary

tract, such as a lack of crystallization inhibitors.

Certain breeds of ruminants appear to be predisposed to urolithiasis; for example, African pygmy and Nigerian dwarf goats appear to be prone to developing this disease. Again, because these goats are often kept as pets, it is possible they may be fed or managed in ways that increase their disease risk; further, they may be more likely to be seen by a veterinarian compared with ruminants intended for food or kept out on rangeland.

Necropsy Findings

When the entire length of urethra is opened along the sagittal plane, hemorrhage and necrosis of the urethral mucosa are evident at the site of obstruction. Attention should be paid to examination of the distal urethra in camelids, the urethral process in sheep and goats, and the sigmoid flexure in cattle. Calculi may be relatively large, discrete mineral aggregates or very fine and sandlike. Calculus material should be collected for analysis of mineral composition (Box 34.1). Occasionally, no calculi can be found in the urinary tract, but mucosal trauma and necrosis of the bladder or urethra persist.

Box 34.1

Urolith Analysis Laboratories

Minnesota Urolith Center
University of Minnesota
College of Veterinary Medicine
1352 Boyd Avenue, B325
St. Paul, MN 55108
Phone: 612-625-4221
www.urolithcenter.org

G.V. Ling Urinary Stone Analysis Laboratory
2108 Tupper Hall
University of California Davis
School of Veterinary Medicine
Davis CA 95616
Phone: 530-752-3228
http://www.vetmed.ucdavis.edu/usal/

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Canadian Veterinary Urolith Centre
University of Guelph, Laboratory Services Division
95 Stone Rd. W.
Guelph, ON N1H 8J7
Phone: 519-823-1268 ext. 57454
www.uoguelph.ca/ahl/sites/uoguelph.ca.ahl/files/EnglishCVUCForm2017.pdf

Urethral rupture is characterized by the subcutaneous accumulation of urine in the inguinal area, prepuce, and ventral abdomen and hemorrhage at the site of the urethral defect.

In cases of bladder rupture, the abdominal cavity is filled with a large volume of blood-tinged fluid. Defects in the bladder wall vary in size and location, and necrosis of large areas of bladder wall may be present. In rare cases, the bladder wall is intact but obvious uroabdomen exists, suggesting transmural seepage of urine.

Hydronephrosis, hydroureter, and bladder wall hypertrophy may be present in animals with chronic urethral obstruction.[2]

Treatment and Prognosis

Salvage.

Steers and feeder lambs may be sent for immediate slaughter if urethral obstruction is diagnosed before development of azotemia or urinary tract rupture.

Medical Treatment.

Medical treatment of urolithiasis is aimed at relief of the obstruction and correction of any fluid and electrolyte abnormalities. The antispasmodic effect of certain tranquilizers may facilitate passage of a urethral obstruction. These drugs may also aid in relaxation of the retractor penis muscle, which results in straightening of the sigmoid flexure to facilitate passage of calculi. In small ruminants, medical treatment with IV fluids, NSAIDs, or tranquilizers alone is usually unsuccessful, resulting in surgical intervention or euthanasia.

While stabilizing a patient before surgery or as an adjunct to medical treatment, the bladder can be drained with a percutaneous catheter inserted in the lower flank or ventral abdomen. Long IV catheters or a suprapubic catheter can

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be inserted, using ultrasonography as a guide, and temporarily left in place. Percutaneous infusion using Walpole solution has been used following cystocentesis in goats.[26] Urine was removed, and the solution infused into the bladder one to three times to decrease the urine pH to 4 to 5. This process was thought to promote chemical dissolution of uroliths in the bladder and urethra.

Ruminants and camelids with urinary tract obstruction, particularly those with uroperitoneum, often require preoperative stabilization of hypovolemia and correction of electrolyte abnormalities, especially if surgery is to be performed under general anesthesia or with the animal restrained in recumbency. Fluid therapy should be guided by analysis of serum electrolyte concentrations. An initial bolus of hypertonic (7%) saline followed by physiologic (0.9%) saline solution can be used to correct intravascular volume deficits, hyponatremia, and hypochloremia. Calcium salts can be added to the fluids if indicated.

Empirical supplementation of IV fluids with potassium should be avoided because the potential for hyperkalemia always exists. Hyperkalemia can induce bradycardia and fatal cardiac dysrhythmias, and this effect is augmented by concurrent hyponatremia. Administration of dextrose, sodium bicarbonate, and/or insulin (regular insulin at 0.25 to 0.4 U/kg) reduces serum potassium concentration by promoting movement of potassium from the extracellular to the intracellular space. Blood glucose should be closely monitored when insulin is administered. Uremic animals undergoing IV fluid therapy may develop pulmonary edema, so attention must be paid to respiratory rate, auscultatory findings, and respiratory effort during fluid therapy.

Slow drainage of urine from the abdominal cavity reduces pressure on the diaphragm and slows progression of metabolic derangements caused by uroperitoneum. This can be difficult to achieve as the omentum is prone to occluding the cannula. In long-standing cases of uroabdomen, urine may also be present in the thorax, further warranting close observation of respiratory function during anesthesia. Thoracocentesis to remove thoracic urine is indicated if respiratory function is compromised; otherwise, abdominal drainage usually induces resolution of thoracic urine accumulation.

Although bacterial infection is not considered to be a common primary cause of urolithiasis, secondary UTIs may develop after surgical intervention. Loss of the flushing effect of urination, urinary mucosal damage, impaired host cellular defenses secondary to uremia, and indwelling urinary catheter placement may contribute to the development of ascending UTI. Perioperative antibiotic therapy is therefore prudent, with due consideration of withdrawal times in animals

intended for slaughter.

Surgical Treatment.

There are multiple surgical options for urolithiasis, which are dictated by economic considerations, intended use of the animal, available facilities and equipment, types of stones, and status of the patient.[27] Removal or bypass of the obstruction and restoration of urine output are the goals of surgical treatment. The prognosis for both short- and long-term survival will vary according to the patient's status and the surgical procedure chosen. Acute renal failure is an occasional sequela to urinary tract obstruction and should be considered in the prognosis. Regardless of the surgical technique used, the client should be forewarned about the future risk of reobstruction.

Urethral catheterization and retrograde flushing may dislodge urethral calculi and restore urine flow, but successful clearance of the urethra is rarely achieved and retrograde flushing under pressure may result in urethral rupture or may simply flush stones back into the urethral diverticulum rather than the bladder. Retrograde passage of a catheter may allow for localization of the urethral obstruction, potentially guiding further surgical treatment. Passage of a catheter into the bladder of ruminants and camelids is exceedingly difficult as the catheter typically becomes lodged in the urethral diverticulum near the ischial arch.

Surgical options range from standing procedures in a field setting to surgery under general anesthesia in a hospital. All of the factors mentioned earlier contribute to the wide range of procedures that have been developed, and surgeon preference, case selection, and owner compliance are critical to the success of a technique.

In sheep and goats, *amputation of an obstructed urethral process* is a simple procedure that may at least temporarily restore urethral patency. The urethral process can be removed without detrimental effects on breeding soundness. Recurrence of urethral obstruction is extremely common, and urethral patency is often maintained for only hours to days before reobstruction occurs.[28] This may provide enough time to allow feeder lambs and kids to survive until slaughter.

Penectomy is an option for animals intended for slaughter and is similar to the perineal urethrostomy for risk of stricture formation. *Prepubic urethrostomy, perineal urethrostomy,* and *modified proximal perineal urethrostomy* are surgical options for ruminants not intended to be used for breeding.[29,30] In small

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ruminants, postoperative stricture of the stoma or recurrent obstruction with additional calculi is a long-term risk with urethrostomy procedures. *Ischial urethrostomy* with placement of a Foley catheter into the bladder has been used as a treatment for urolithiasis in heavy feedlot steers and bulls.[31] If urethral damage is not severe, this procedure allows the breeding ability of bulls to be maintained.[31]

Urethrotomy can be used to remove the obstructing calculi followed by primary closure of urethra; however, there is a risk of urethral stricture, adhesions resulting in phimosis in breeding males, and reobstruction with additional calculi.

A *vesicopreputial anastomosis* procedure has recently been described in a small number of goats as an option for management of recurrent obstructions.[32]

Cystotomy can be used to remove calculi from the bladder and maintain breeding soundness. In small ruminants and camelids, bidirectional (normograde and retrograde) flushing is used to restore urethral patency.[28] Even if the urethra is successfully cleared of calculi, traumatic urethritis may cause significant postoperative dysuria in these animals. Therefore, some surgeons prefer to also perform a tube cystostomy to allow for rest and healing of the irritated urethra.

Tube cystostomy (surgical or percutaneous placement) allows urine to exit the bladder through a temporary Foley or other type of suprapubic catheter, which is anchored in the bladder lumen and exits the ventral abdomen.[33-35] Urethral patency is restored when calculi are spontaneously expelled from the urethra, dissolved, refluxed into the bladder, or removed via urethrotomy. Spontaneous resolution of urethral obstruction after tube cystostomy may take several weeks or longer, and urethral rupture at the site of obstruction due to pressure necrosis can occur. To judge when removal of the catheter is appropriate, the catheter can be clamped shut and the animal observed for urination through the urethra. Fewer complications of tube cystostomy have been reported with surgically placed tube cystostomies versus percutaneously placed cystic catheters.[33,35] The primary complication is a dislodged catheter, followed by tears of the bladder, leakage of urine into the abdomen, adhesions of the bladder to intestine or body wall, and obstruction of the catheter.

In cases of urethral rupture where patency of the entire urethra is the preferred outcome, tube cystostomy is often the sole feasible option. Primary repair of the urethral defect is rarely successful because of swelling and maceration of the damaged mucosa and risk of stricture formation. Contrast medium can be

introduced into the bladder through the catheter to monitor urethral patency, locate urethral obstruction, or identify urethral rupture. The catheter can also be used to lavage the bladder to facilitate dissolution of calculi using Walpole solution or a commercially available urinary lavage product (Renacidin, Guardian Laboratories, Hauppauge, N.Y.).[35]

In cases of bladder rupture, the urine should be drained from the abdominal cavity and a surgical procedure should be performed to divert urine to the exterior. If primary repair of the bladder defect is desired, a laparotomy and cystotomy or tube cystostomy can be performed. Primary repair of the bladder defect is not always necessary, however, because spontaneous sealing of the bladder with fibrin or omentum can occur. Daily or continuous abdominal drainage may have to be performed until spontaneous sealing occurs. Tears are more likely to seal spontaneously if they are located on the dorsal aspect of the bladder.

In *bladder marsupialization* the apex of the bladder is exteriorized using a small paramedian incision, and the seromuscular layer of the bladder is circumferentially secured to the abdominal wall. A cystotomy is performed, and the bladder mucosa is secured to the skin, creating a permanent opening for urine drainage from the bladder to the exterior.[36] Advantages of bladder marsupialization include decreased hospitalization time and expense for the owner. However, complications include chronic urine scalding, ascending bacterial infection, stricture formation, reobstruction, and bladder prolapse.

Ureteral calculi may be removed by *ureterotomy.*[37] *Nephrectomy* may be performed in unilateral cases of obstructive nephrolithiasis.[38] If unilateral nephrectomy is under consideration, measurement of BUN, serum creatinine, and USG should be performed, and US and renal biopsy can be used to evaluate the remaining kidney.

Postoperative Considerations.

Continued assessment of hydration status, urine output, serum creatinine, and serum electrolyte concentrations is indicated after surgery. Postobstruction diuresis may result from tubular damage, accumulation of urea or natriuretic factors, or preoperative fluid therapy. Induction of modest diuresis through fluid therapy after surgery may help to reduce azotemia and accumulation of blood clots and bacteria in the urethra.

Antimicrobial therapy with an antibiotic that achieves high urine

concentrations is warranted. Duration of antimicrobial therapy depends on the surgical procedure chosen, residue withholding considerations, legal restrictions on use of certain products, and whether or not UTI exists at surgery. For tube cystostomy, antimicrobial therapy is recommended by some while the tube is in place and for at least 1 week after the tube is removed. A study examining indwelling Foley catheters identified *Aerococcus* and *Enterococcus* most frequently, and 42% of cultures were resistant to two or more antibiotics.[39] Therefore, it is recommended to submit urine samples for culture and sensitivity testing.

Prevention

A preventive approach to urolithiasis begins with a search for risk factors associated with the diet, management, and environment. Whenever possible, ration analysis and mineral analysis of the urolith(s) should be performed to accurately identify causative dietary factors. Consult Box 34.1 for urolith analysis laboratories. If uroliths are not obtained, ration analysis and a thorough dietary history may provide a strong suggestion of the urolith type. Considering the central role of urinary supersaturation in calculogenesis, the ultimate aim of preventive measures should be reduction of urinary concentration of calculogenic mineral ions. The urine should be diluted to such an extent that the calculogenic ions are less prone to precipitate. Dilution of urine is achieved through increased salt and water intake.

Dietary Management.

Prevention of urinary calculi can be difficult because of the conflicting dietary effects of minerals, pH, individual animal susceptibility, and feed availability. General guidelines for prevention of phosphatic calculi require adjustment of the dietary calcium–to–phosphorus ratio to a level of greater than 2 : 1, which can be performed by reducing the amount of grain or other high-phosphorus dietary components and/or increasing calcium in the diet with forages like alfalfa or other legumes. Use of a 0 mEq/kg DCAD diet using ammonium chloride has been shown to help reduce urinary pH to between 6.0 and 6.5 without significantly decreasing blood pH.[18] Increasing the quantity of long-stem forage in the ration may increase salivary flow and fecal phosphate excretion.

Because restriction of dietary silica intake in ruminants grazing native grasses is not feasible, dietary management is limited to salt (sodium chloride or

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ammonium chloride) supplementation to increase water consumption and thereby produce a diuretic effect to reduce urinary calculogenic compounds. Loose salt or lick salt is unlikely to be ingested in sufficient quantities to affect water intake. Gradually increasing quantities of sodium chloride or ammonium chloride in creep feed can help reduce silica urolith development in calves and lambs.[13,19] The feeders should be located near a reliable source of palatable water. In one study, reduction of the dietary calcium–to–phosphorus ratio from 2 : 1 to almost 1 : 1 resulted in a trend toward reduced silica calculi formation.[19] Prevention of calcium carbonate uroliths in pet small ruminants can be reduced by feeding or supplementing with grass hay rather than feeding alfalfa alone. Salting the grass hay with increasing concentrations of salt may increase water consumption to help maintain a dilute urine. Use of ammonium chloride can aid in urine acidification and increase water consumption.

Ammonium chloride supplementation fed at a level of 0.5% to 1.5% of ration dry matter was found to reduce urine pH to 6 to 6.5 in a group of goats.[18] Urine pH in this range should increase the solubility of struvite and apatite crystals. However, the pH of the urine is also influenced by the relative concentrations of strong cations (sodium and potassium) and strong anions (chloride and sulfate) of the entire ration, so the efficacy of ammonium chloride in reducing urinary pH may vary among different livestock operations, because the concentration of these cations and anions will vary among rations.[18,40] Long-term or excessive supplementation with ammonium chloride has been reported to result in chronic metabolic acidosis with a corresponding decrease in bone density and excessively low urine pH.[18,40] Ammonium chloride is not palatable, so mixing the salt with a more palatable low-potassium product (e.g., sucrose) is typically necessary. Some animals appear to have a renal physiologic adaptation resulting in gradually increasing urine pH with long-term feeding of ammonium chloride. Owners can monitor for changing urine pH with urine pH strips used on a weekly basis. Pulsed feeding of ammonium chloride can be attempted if the urine pH begins to increase.

Water Management.

Maximizing water intake is an important aspect of urolithiasis prevention, regardless of the urolith type involved. Cleaning water containers should be a regular practice. White water containers allow owners to see contamination of the water with dirt and feed; this may prompt more frequent cleaning. Water

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palatability may also be improved by providing shade for water containers during the summer and heaters in the fall and winter. Automatic waterers should be checked regularly for proper function. Shallow containers capable of rapid refilling provide higher rates of water turnover, resulting in less stagnation.

In operations involving multiple animals or large pastures, placement of multiple watering sites might allow for more frequent intake. This is especially true for sheep, whose banding instinct usually prevents individuals from traveling alone to distant watering sites.

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Urachal Disorders

Stacey R. Byers

Definition and Etiology

Abnormalities of the umbilicus and umbilical remnants, including the urachus, are frequently encountered disease conditions of neonatal calves and, to a lesser extent, in other neonatal ruminant species.[1] Infections of the urachus are often associated with omphalophlebitis, which commonly arises from environmental contamination of the umbilicus at birth. Cloned calves appear to be predisposed to having a patent urachus.[2] The association of umbilical abnormalities with calfhood morbidity and mortality is well known. However, chronic conditions of the urachal remnant are observed in older neonates and mature ruminants, with complications including internal abscessation, adhesions, sepsis, peritonitis, uroperitoneum, cystitis, and intestinal strangulation.[3-6] Urachal fistulas or acquired patent urachus are infrequently observed in ruminants. Chapter 20 provides more information on these disorders.

Clinical Signs and Differential Diagnoses

Calves with internal urachal abscesses, adhesions, and other sequelae are usually older than 4 weeks of age. A history of umbilical infection during the neonatal period may or may not exist, and external umbilical abnormalities may not be present. Clinical signs may be nonspecific and include fever, lethargy, poor body condition, rough hair coat, and poor growth or productivity. Dysuria, pollakiuria, stranguria, and colic may be evident on examination or in the medical history. When an infection extends into the bladder lumen, hematuria and pyuria are expected. Transabdominal palpation of the umbilicus and abdomen in smaller neonates may reveal painful and enlarged umbilical remnants. Complications from associated septicemia (e.g., lameness and joint distention, pneumonia, hypopyon, meningitis) can occur.

If the urachus fails to regress completely, a persistent communication between the bladder apex and the pouchlike urachal remnant occurs. The volume of urine retained in the urachal remnant is variable. Animals with this problem may dribble urine from the urachus during micturition or remain asymptomatic. Urine

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retention can predispose the animal to UTIs.

Rupture of the infected urachal stalk may result in the acute onset of peritonitis. If the urachal remnant communicates with the bladder lumen, rupture of the urachus results in uroabdomen. Rupture may occur spontaneously or after abdominal trauma or parturition in older animals. A report found a possible inheritance link with abnormal involution in a group of Brown Swiss-Braunvieh cross cattle.[7]

A detailed ultrasonographic examination of the interior of the umbilical remnant and caudoventral abdomen is warranted in cases of suspected urachal or umbilical abnormalities, but adhesions may not be visualized.[7-9] The bladder and other viscera may assume abnormal shape or position as a result of urachal adhesions. The luminal contents of the urachal remnant and bladder may appear flocculent in cases with concurrent cystitis. Uroabdomen is characterized by accumulation of echolucent fluid in the abdominal cavity, with variable amounts of fibrin deposition evident.

Laparoscopic examination can allow a more thorough evaluation of the abdomen and has identified adhesions and focal umbilical artery and urachal enlargements not identified by ultrasonographic examination.[9]

Because of the variable nature of urachal problems, the differential diagnoses will vary according to the organ(s) involved. Urachal adhesions to the intestine or uterus may result in colic, signs of intestinal obstruction, and postpartum peritonitis or uroabdomen. Concurrent signs involving the lower urinary system might indicate the potential for primary ascending infections, such as cystitis or pyelonephritis. In cases of uroabdomen in males, obstructive urolithiasis is an important differential. Urolithiasis, urethritis, or neurologic disease may be included in differential diagnoses of dysuric animals. Nephritis of hematogenous origin or pyelonephritis should be considered in animals showing ill-thrift, colic, kyphosis, or abnormal urine.

Clinical Pathology

Laboratory findings may be variable, but an inflammatory leukogram, hyperfibrinogenemia, and hyperglobulinemia are expected. Urinalysis may be normal or indicative of cystitis if the urinary bladder is involved. Abdominocentesis findings are variable and depend on the presence and extent of peritonitis associated with the urachal lesion. Voluminous blood-tinged abdominal fluid suggests uroperitoneum, and analysis of the fluid and serum

creatinine concentration is indicated (see Urolithiasis section earlier).

Pathogenesis

Following bacterial infection of the urachus, the inflammatory response within the abdomen precipitates development of fibrinous adhesions between the urachus and surrounding viscera, including the rumen, intestine, uterus, bladder, or ovaries. Abscesses may form in single or multiple locations in the urachal stalk and, if involving the apex of the urinary bladder, can result in concurrent cystitis. Urachal fibrosis and adhesions may cause mechanical interference of bladder emptying. Infrequently, the urachal abscess perforates, with subsequent peritonitis, sepsis, or uroperitoneum.[3,4] Most urachal infections involve *Trueperella pyogenes*, *E. coli*, *Staphylococcus* spp., or *Streptococcus* spp., but other organisms may be present.[1,5,8,10]

Treatment and Prognosis

For early and uncomplicated or congenital persistent urachal disorders, medical management using chemical cautery and antibiotic therapy has been reported.[1] Chemical cautery of the urachus with sedation and analgesia has been performed using silver nitrate sticks, iodine, or phenol. There is a risk of incomplete resolution or other complications, so animals should be monitored to determine if additional surgical management is warranted.

Surgical management is recommended for complicated cases, infected urachal remnants, where medical management has failed, or when complete evaluation of the abdominal cavity is needed. Ventral midline celiotomy, paramedian celiotomy, or laparoscopy under general anesthesia is recommended to enable complete evaluation of the abdominal cavity.[7,11,12] Complete resolution may require resection of the urachal remnants and the bladder apex if the urachus incorporates or communicates with the bladder. Perioperative and postoperative antibiotic therapy is essential, and appropriate antibiotic selection should be based on culture and sensitivity of the abscess(es) or urine.

Outcomes following surgical management are often satisfactory, but development of adhesions should always be considered a potential risk. A guarded to poor prognosis is warranted for severe peritonitis or extensive adhesions.

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Urinary Bladder Eversion and Prolapse

Stacey R. Byers

Definition and Etiology

Urinary bladder eversion and prolapse are uncommon events that occur during or shortly after parturition.[1] With eversion, forceful straining moves the bladder fundus caudally, eventually turning the bladder inside out. The bladder is then forced out of the urethral orifice. Prolapse of the bladder is more frequently associated with dystocia. In this condition a full-thickness tear of the vaginal wall occurs during delivery, allowing the bladder (and possibly other viscera) to be displaced from the abdominal cavity into the vagina.

Clinical Signs and Differential Diagnosis

Females with either eversion or prolapse of the bladder have a smooth, spherical mass within the vagina, usually protruding from the vulva. The female may be alert and ambulatory, but if concurrent hypocalcemia, exhaustion, or peritonitis exists, the animal may be recumbent and depressed. Careful vaginal examination is required to differentiate these two conditions from each other and from vaginal prolapse, vaginal polyps, fat protrusion from a vaginal tear, vaginal neoplasia, fetal membranes, and uterine prolapse.[1] Epidural anesthesia is necessary to prevent straining to reduce fecal contamination while cleaning the perineum and vestibule and to reduce the risk of viscera herniation through the urethra (bladder eversion) or through the vaginal tear (bladder prolapse).

With urinary bladder eversion, the mucosal surface of the bladder is exposed. The ureteral openings may be visible on its dorsal aspect, although these may be occluded and difficult to see if the wall of the bladder is edematous. Vaginal palpation reveals that the protruding tissue originates from the urethral orifice. With time, constriction of the everted bladder by the narrow urethra may cause venous congestion, edema, thrombosis, and eventual necrosis. Palpation and ultrasonographic examination are required for detection of herniation of other viscera through the urethral orifice and into the interior of the everted bladder. Careful fine-needle aspiration of the interior of the eversion has been used to differentiate eversion from prolapse of the bladder. With bladder eversion,

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aspiration may yield peritoneal fluid, but laceration of herniated bowel is a concern.

In contrast, the serosal surface of the bladder is exposed with urinary bladder prolapse. Careful palpation of the vagina reveals that the bladder protrudes from a full-thickness tear in the floor or lateral wall of the vagina. Other viscera may be present in the vagina, as well. Fine-needle aspiration yields urine from the bladder lumen.

Treatment and Prognosis

Manual reduction of an everted bladder may not be possible if it is edematous or if other viscera have herniated into its interior. The dorsal aspect of the urethra may be incised to widen the route through which the bladder is to be replaced.[1] Viability of the involved structures is of primary concern for prognosis, and laparotomy is required for assessment of the viability of herniated bowel. Bladder paralysis and rupture are potential sequelae to ischemic damage that develops during eversion. Cystitis and pyelonephritis may develop, and antibiotic therapy is warranted if repair is attempted. Animals with chronic conditions may develop hydroureter, hydronephrosis, and renal failure.[2]

A bladder prolapse can be resolved by first passing a flexible catheter into the urethra to remove urine from the bladder. This also confirms the diagnosis and facilitates bladder replacement. After catheterization and removal of urine, the bladder can be replaced into the abdominal cavity, and the vaginal tear can be sutured. Severe contamination of the peritoneal cavity may render attempts at treatment unjustified. Antibiotic therapy is indicated for surgical candidates.

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Pelvic Entrapment of the Bladder

Stacey R. Byers

Definition and Etiology

In pelvic entrapment of the bladder, the apex and fundus of the bladder are displaced caudodorsally into the pelvic cavity, resulting in impaired urine outflow. It has been reported in cattle, sheep, and an alpaca cria. Occurrence has been associated with postpartum straining, perineal hernia, vaginal prolapse, and suspected vaginal irritation or secondary bladder displacement from trauma.[1-3]

Clinical Signs and Differential Diagnoses

Bladder emptying is impaired, and the presence of the bladder in the pelvic inlet induces straining. An affected animal may show tenesmus, pollakiuria, and stranguria. On rectal palpation a soft, fluctuant mass may be detected beside the vagina. Radiography with contrast can be used to demonstrate the pelvic position of the bladder.[1,2] Ultrasonographic examination can be used in larger animals.[3]

Differential diagnoses include proctitis, vaginitis, retained placenta, bladder paralysis, cystitis, and perivaginal abscess. Needle aspiration of the bladder per vaginam has been used to make a definitive diagnosis, although the danger of uterine puncture should be considered.

Treatment and Prognosis

Draining the bladder through catheterization or needle aspiration facilitates replacement of the bladder by manipulation per vaginam. However, fibrinous adhesions between the bladder and vagina may make laparotomy necessary to replace the bladder. Ventral midline laparotomy with replacement and fixation was successfully performed in an alpaca cria.[2]

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Enzootic Hematuria

Stacey R. Byers

Definition and Etiology

Enzootic hematuria is a disease of chronic or intermittent hematuria that occurs in a wide variety of ruminants and is most commonly associated with chronic ingestion of bracken fern (*Pteridium* spp.). However, research has identified other fern species (*Pteris* spp., *Cheilanthes sieberi, Onchyium contiguum)* associated with enzootic hematuria.[1-3] Enzootic hematuria occurs after ingestion of large quantities of the responsible ferns (approximating the animal's body weight), usually over a period of 1 to 3 months, and is different from acute bracken poisoning. Acute bracken poisoning manifests as acute coagulopathy or fulminant septicemic crisis associated with severe bone marrow suppression (see Chapter 54).

Clinical Signs and Differential Diagnoses

Protracted, possibly intermittent, hematuria is the first clinical sign detected in most animals. Blood clots may be voided and can cause urethral obstruction. Chronic blood loss eventually results in tachycardia, tachypnea, exercise intolerance, pale mucous membranes, and a decline in productivity and body condition. A thickened bladder wall and bladder tumors may be palpated per rectum. Proliferative changes or overt neoplasia of the bladder may cause dysuria, pollakiuria, and, rarely, obstruction of the bladder trigone. Depending on the magnitude and duration of fern ingestion, hematuria may last for months to years before severe debilitation or death occurs.

Examination of serum for evidence of hemolysis and analysis of sediment from a freshly voided urine sample for intact RBCs allow for differentiation of hematuria from the hemoglobinuria found in hemolytic diseases. Icterus, also characteristic of ruminant hemolytic disorders, is not found in cases of enzootic hematuria. Hematuria may be evident in a UTI, but pyuria and bacteriuria are marked, and anemia, if present, is usually mild. Simultaneous involvement of several animals is common with enzootic hematuria. Hematuria may also be evident in cattle affected by malignant catarrhal fever. Protracted, severe

hematuria is rare in cases of urolithiasis, and anemia is also not expected.

Ultrasonography or cystoscopy examination of the urinary bladder may help with antemortem diagnosis.[4-6] Diagnosis is often made on necropsy.

Clinical Pathology

Severe, regenerative anemia is often seen with enzootic hematuria. However, evidence of a regenerative response may not be present if bone marrow suppression exists or chronic blood loss induces iron deficiency. The platelet, segmented neutrophil, and lymphocyte counts may be reduced. Clotting profiles show increased antithrombin III and protein S activities.[4] Urinalysis reveals hematuria, proteinuria, and variable pyuria.

Pathophysiology

All parts of the ferns are toxic to ruminants. The ferns contain multiple compounds that have irritant, mutagenic, carcinogenic, and immunosuppressive activities and cause a variety of medical conditions in addition to enzootic hematuria. The carcinogenic compound, ptaquiloside, appears to be the primary compound that leads to the bladder tumors. A synergistic interaction between ptaquiloside and bovine papilloma virus type 2 is thought to induce many of the bladder tumors.[1,3,7,8] Ptaquiloside is also found in the milk and meat of animals grazing the ferns and has been found to increase the risk of esophageal and gastric tumors in humans.[3,9]

Bladder carcinomas from cows with enzootic hematuria have been shown to express both cyclooxygenase-1 (COX-1) and COX-2 at a high level relative to normal controls when evaluated by immunohistochemical methods.[10] The efficacy of COX-2 inhibitor drugs on cancer prevention or treatment in cattle at risk for bladder tumors has yet to be investigated.

Epidemiology

Enzootic hematuria has a worldwide geographic distribution as the plants are found almost everywhere. The ferns are often invasive and opportunistic but do not grow in extreme temperatures or low-humidity conditions.[3] Ruminants are poisoned by grazing the plant or consuming contaminated hay over an extended period of time. Cattle grazing infested pastures may develop hematuria by 2 to 3

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years of age. Papillomas of the bladder have occurred as early as 1 year after feeding begins, with invasive carcinomas arising 2 to 6 years later. Within endemic areas, up to 90% of adult cattle may be affected.[11]

Necropsy Findings

Tissue pallor from anemia is often appreciated. The bladder wall is thickened, and the mucosa hemorrhagic and ulcerated. Microscopic examination of the bladder wall reveals capillary engorgement, intramural hemorrhage, and metaplasia of the bladder epithelium. Several types of bladder tumors and mixed-origin neoplasms may be present. Metastasis of epithelial neoplasms to the regional lymph nodes or other organs can occur.[11]

Treatment and Prevention

Treatment of enzootic hematuria is limited to reduction or elimination of the responsible ferns from the diet. Forage improvement may help limit incorporation of the plant into hay. A program of early culling may help prevent low productivity from anemia and neoplasia. Hematuria will cease if bracken feeding is discontinued before the onset of tumor formation.

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Urinary Tract Infection

Brandon J. Dominguez

UTI in ruminants typically present as cystitis, ureteritis, and pyelonephritis from ascending infection with *C. renale* or *E. coli*.[1] Other coliform species[2] and close relatives of *C. renale* may be involved with lesser frequency.[3] Less commonly, *Salmonella* spp., *T. pyogenes, P. aeruginosa, Proteus* spp., *Streptococcus* spp., and *Staphylococcus* spp., among others, have been implicated in renal infections of hematogenous origin (suppurative embolic nephritis).[4-7] In small ruminants, *Corynebacterium pseudotuberculosis* has also been cultured from renal infections.[8]

Clinical Signs

Cystitis is suggested clinically by dysuria and pollakiuria; hematuria and pyuria may not be grossly apparent. Affected animals may dribble urine, tread their feet, swish their tail, or retain an arched stance after voiding. Occasionally, blood, purulent debris, or urinary crystals may be found on the preputial tuft or ventral commissure of the vulva.[1] The bladder may be thickened and painful on rectal palpation, and on cystoscopy, catarrhal, hemorrhagic, fibrinous-purulent, and fibrinous-hemorrhagic lesions may be observed.[9] Generalized signs of malaise are not seen if infection is limited to the bladder.[1]

Acute cases of pyelonephritis often present with a history of sudden reductions in feed intake and milk production. Fever, tachycardia, tachypnea, decreased skin turgor, enophthalmos, ruminal stasis, scleral injection, and occasional episodes of mild colic may be noticed in addition to signs of cystitis.[1] When the left kidney is involved, renal enlargement, pain, and loss of the normal lobulation may be noted on rectal palpation. Affected animals may dribble urine, resulting in phosphate calculi present on the vulvar or preputial hairs. This may be accompanied by wet hair on the perineum and hind legs, progressing to excoriations due to urine scald.

Evaluation of the right kidney in cattle can be accomplished via ultrasound with a 5.0-MHz or lower frequency transducer in the 12th intercostal space and right paralumbar fossa.[10-12] In small or thin cattle, the left kidney may be visible in the left paralumbar fossa on transcutaneous ultrasound. Alternatively, the left

kidney can be assessed transrectally with a 5-MHz or higher transducer. In small ruminants and camelids, both kidneys are often visible via transabdominal ultrasound from the right paralumbar fossa. Renal enlargement, abnormal kidney shape, dilated renal calyces, and flocculent echogenic material in the renal pelvis and ureter are suggestive of pyelonephritis.[10-12] The ureters may be palpated per vaginam in cattle, with the examiner using their fingers to detect one or both enlarged, painful ureters adjacent to the ventral vaginal wall.[1]

Chronic pyelonephritis presents with vague signs.[1] Weight loss, muscle wasting, poor growth, anorexia, diarrhea, and reduced milk production may be evident from history. No abnormal behavior or posturing during urination may be noted. Pale mucous membranes (due to anemia) may be noted during physical examination. A loss of lobulation on the left kidney may be evident on rectal palpation in cattle; pain and enlargement may not be noted.[1] Cystic lesions may be noted ultrasonographically in chronic renal disease.[12]

Differential Diagnosis

Mild colic may be a symptom of numerous GI or intraabdominal disorders, and urinalysis findings will be normal. Dysuria may be the result of vaginitis, perivaginal abscess, pelvic entrapment of the bladder, vulvar trauma, or postparturient swelling of the vagina and vulva. Urolithiasis can cause dysuria and hematuria, but males are typically affected, whereas females are predisposed to UTI. On rectal palpation in cattle, bladder distention will be evident in cases of urolithiasis, a finding not expected with UTI. A careful neurologic examination will help determine whether there is underlying bladder paresis or incomplete voiding from neurologic diseases. Hematuria may be due to bleeding from parturition, papillomas in the urinary tract, postparturient hemoglobinuria, or enzootic hematuria. In cases of enzootic hematuria, multiple animals are typically affected and the presence of bracken fern can be demonstrated. In addition, a profound anemia is expected with enzootic hematuria, and if pyuria or bacteriuria is present, it will be mild. Papilloma of the bladder may be ruled out with cystoscopy.

Clinical Pathology

A neutrophilic leukocytosis with hyperfibrinogenemia is expected in cases of pyelonephritis. If the duration of the infection has been several days,

hyperglobulinemia will develop. Continued, severe proteinuria, resulting in hypoalbuminemia, can lead to diarrhea because of decreased plasma oncotic pressure. As the chronicity of the disease lengthens, anemia may develop. This may be due in part to the decreased production of erythropoietin in the affected renal tissue and from blood loss through urination.[1] Measurement of serum BUN and creatinine is critical for prognosis in cases of pyelonephritis.[9,13] When azotemia and isosthenuria are combined in cases of pyelonephritis, bilateral kidney involvement is indicated and the prognosis for successful treatment is poor.[1] Prerenal causes should be considered when evaluating the severity of azotemia.

Urinalysis is necessary for definitive diagnosis of UTI. A midstream or endstream caught sample should provide the most accurate results as contaminants in the distal urogenital tract are purged. Concomitant metritis, vaginitis, or prostatitis may contaminate urine with blood, bacteria, and inflammatory cells. Hematuria, proteinuria, and bacteria should be present in the urine of a UTI-afflicted animal. Specific gravity may be in the range of 1.005 to 1.020.[12] A Gram stain of the urine may yield preliminary identification of the causative organism.

Pathophysiology

Initiation of an ascending infection is dependent on the amount and virulence of bacteria introduced into the urinary tract. Urogenital trauma during parturition or obstetric manipulation, abnormal vulvar confirmation, conditions leading to urine retention, and bladder catheterization may provide routes of introduction for pathogens. Impaired bladder emptying due to bladder adhesions, urachal remnant infection, or diseases of the spinal cord may create an environment for the establishment of cystitis and ascending infection. Urethral trauma from catheterization, urolithiasis, breeding, or urogenital papilloma may be adequate to initiate infection.[14] Vesiculoureteral reflux due to decreased bladder contractility or ectopic ureters may occur, aiding in the extension of infection up the urinary tract. Ureteral and renal obstruction due to inflammatory debris, hemorrhage, and fibrin deposition may lead to episodic signs of colic. After pyelonephritis is established, necrosis of papillary and tubular epithelium leads to an accumulation of necrotic debris in the renal pelvis, loss of functional nephrons, abscessation, fibrosis, and distortion of the renal shape. Struvite uroliths and other renal calculi may develop when necrotic debris serve as foci

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of crystal deposition in the alkaline microenvironment created by bacterial urease activity.[4]

C. renale is a large, pleomorphic, nonmotile, gram-positive bacillus.[3] It is grouped with and closely related to two other *Corynebacterium* that may cause pyelonephritis: *C. cystitidis* and *C. pilosum*.[5] *C. renale* pyelonephritis has been documented in a sheep[14] and induced experimentally in goats.[15] Evidence suggests that *C. renale* may be maintained in the environment for several weeks.[3] The bacterium may be transmitted by direct vulvar contact between females or by splashing of urine from infected animals. Iatrogenic transmission may occur via contaminated obstetrical instruments or urinary catheters. Males may spread *C. cystitidis* and *C. renale* through sexual contact.[16] *C. renale* adhere to the urinary tract epithelium via pH-mediated pili.[17] Adherence is enhanced in alkaline conditions and reduced in acidic conditions.[18] This pH influence may explain the improvement in clinical signs realized after the feeding of urine-acidifying salts. The organism uses ureolysis and ammonium production to maintain urine alkalinity and promote colonization of the epithelium. A serum antibody response will develop after renal infection. This humoral response is rarely curative, nor does it provide resistance to reinfection.[1]

E. coli, among other coliforms, is frequently implicated in ruminant UTI.[1] The serotype(s) and virulence factors of *E. coli* specifically involved in bovine pyelonephritis are unknown at this time. Because of the ubiquitous nature of this gram-negative coliform, it is thought that infection originates from fecal contamination or a loss of natural defenses in the urogenital tract.

Epidemiology

On-farm prevalence of pyelonephritis in cattle varied from 0.3% to 2.7% in an Israeli study.[13] An Iranian abattoir study found a 13% prevalence of urine infected with pathogenic organisms.[6] Female animals have a greater potential for infection owing to a shorter urethra in addition to potential contamination and trauma during parturition and breeding. A majority of pyelonephritis cases in cows develop within 90 days post calving, which suggests that the postpartum period is a significant risk period in the development of infection.[4] Reproductive tract abnormalities such as pneumovagina, metritis, and poor perineal conformation were identified in 7 out of 15 cows diagnosed with

pyelonephritis.[1]

C. renale has typically been regarded as the most common pathogen in bovine pyelonephritis.[2,12] In some studies, *E. coli* has been found as the more prevalent bacteria in pyelonephritis cases.[4,5,19] *C. renale* and *C. pilosum* have been found in healthy cows, whereas *C. cystitidis* is considered the most virulent pathogen in the *C. renale* group.[5] Once established, *C. renale* can be difficult to eradicate on a herd level.

Necropsy Findings

The bladder will have evidence of hemorrhage, ulceration, and fibrin deposition on the epithelial surface, which may extend through the urethra. Polypoid growths may develop with chronic infection. As these resemble tumors, histopathologic examination is necessary for definitive diagnosis.[2] Ureters may be noticeably enlarged on one or both sides and contain purulent debris. Acute to subacute pyelonephritis cases may show gross enlargement of the affected kidney(s). A viscous gray, odorless exudate may be found in the renal pelvis and extend into the medulla and cortex, especially on sagittal section. A Gram stain of the exudate is helpful for differentiation of the cause. Chronic cases of pyelonephritis may have gross distortion of renal size and shape (Fig. 34.19).



FIG. 34.19 Postmortem specimen of unilateral pyelonephritis and ureteritis in a cow. The affected kidney and ureter are greatly enlarged.

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Treatment and Prognosis

Aggressive and long-term antibiotics are required for successful treatment of UTI. Diuresis with oral or parenteral fluid therapy is beneficial in facilitating the removal of necrotic debris and bacteria from the urinary tract.[1] Nephrectomy in cases of unilateral pyelonephritis that are unresponsive to medical therapy is an option.[12] Studies have indicated that there is no apparent limitation on growth and production following unilateral nephrectomy if the remaining kidney is normal and healthy.[20]

Penicillin is typically the first-choice treatment of *C. renale* and *E. coli* infection. Twice-daily IM administration of procaine penicillin G (22,000 to 44,000 units/kg) or ampicillin trihydrate (11 mg/kg) is effective.[1] Higher serum and urinary concentrations may be attained with IV administration of sodium or potassium penicillin (22,000 to 44,000 IU/kg q6h) or sodium ampicillin (10 to 50 mg/kg q8h). Animals with coliform UTI should be continually monitored for appetite, attitude, pyrexia, and reagent-strip urinalysis. If there is no improvement within 96 hours of treatment, therapy should be modified.[1] Gentamicin (2.2 mg/kg IM bid),[1] trimethoprim-sulfadiazine (15 mg/kg IV once daily),[2] and ceftiofur (3 mg/kg IV bid)[21] have been used to treat refractory coliform UTI (check on whether permitted in the United States). However, the nephrotoxicity of gentamicin is an important consideration,[1] and at present the American Association of Bovine Practitioners has implemented a voluntary ban on aminoglycoside use in cattle due to prolonged withdrawal times. Furthermore, current U.S. regulations limit the use of sulfa antibiotics in lactating dairy cattle to approved formulations only, and ceftiofur use in major food-producing species (cattle, swine, turkeys, chickens) is limited to the label dosage, route, duration, and frequency.[22] Meat and milk withdrawal times must be extended appropriately after prolonged and extralabel dosages of any antibiotic. Urinalysis and urine culture should be assessed 1 week after therapy is discontinued to confirm resolution.

Treatment is more likely to be successful the earlier it is initiated in the course of disease. Case fatality and nonvoluntary cull rates due to pyelonephritis in dairy cattle have been reported between 18%[1] and 47%[4] for treated cases. Recrudescence rates have been reported at 9.4%.[13] Cystitis alone yields a better prognosis than concurrent ureteritis or pyelonephritis, especially if bilateral disease is evident. Cows with marked azotemia noted by a BUN above 100

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mg/dL and/or a creatinine above 1.5 mg/dL and pyelonephritis were at much greater risk of culling than nonazotemic cows with pyelonephritis.[13] Recent studies indicate that acute-phase proteins, particularly haptoglobin, serum amyloid A, and α_1-acid glycoprotein, reflect response to treatment and may serve as prognostic indicators.[23]

Prevention and Control

Isolation of diseased animals, particularly with *C. renale*, is recommended to limit the spread of the organism. Cleaning and disinfection of contaminated areas are advisable. Aseptic technique during urogenital and obstetric procedures can limit iatrogenic transmission. Venereal transmission is difficult to control in herds with natural service and subclinically infected males. Artificial insemination or mass treatment programs could be introduced in herds with increased problems due to UTI.

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Amyloidosis

David C. Van Metre

Amyloidosis is caused by extracellular deposition of insoluble, fibrillar protein in tissues.[1] Amyloid arises from various precursor proteins that become abnormally folded. Normally, misfolded proteins are degraded by macrophages in the extracellular space. Amyloid, however, forms beta-pleated sheets that are highly resistant to degradation. Aggregates of amyloid collect in various organs, resulting in dysfunction.

Clinical Signs

Although subclinical deposition of amyloid can occur in a variety of tissues,[2] in cattle, the kidneys are most commonly affected in clinical disease.[3,4] The most common clinical signs of bovine amyloidosis include chronic diarrhea, weight loss, generalized edema, and poor productivity in mature animals.[3-5] Enlargement of the left kidney may be palpated rectally.[5] The enlarged kidney is not painful and maintains its normal lobulation. Because amyloidosis may develop secondary to an underlying inflammatory disease, such as metritis or traumatic reticuloperitonitis, signs of the primary disease process may be superimposed.

Clinical Pathology

Marked proteinuria and hypoalbuminemia are hallmarks of disease.[3-5] Hyperfibrinogenemia, hyperglobulinemia, and an inflammatory leukogram may reflect the underlying inflammatory disease. Renal azotemia may exist. Urinalysis reveals persistent, heavy proteinuria. Importantly, a positive reaction for protein on urine dipstick is expected when the urine is alkaline (as is common in cattle); therefore, more specific tests for protein, such as the sulfosalicylic acid precipitation test, should be used to confirm proteinuria. Polarized light microscopy and electron microscopy have been used to detect amyloid protein in urine sediment.[6] There is no pyuria or hematuria.

Differential Diagnosis

Amyloidosis must be differentiated from other diseases causing chronic diarrhea, hypoproteinemia, weight loss, and poor productivity. Diseases to consider include Johne's disease, copper deficiency, salmonellosis, bovine viral diarrhea, GI parasitism, liver fluke infestation, peritonitis, bovine leukosis virus infection, and glomerulonephritis. Glomerulonephritis is the only other differential diagnosis wherein persistent proteinuria is an expected feature. Renal biopsy can differentiate these two conditions.

Pathophysiology

Light-chain (AL) amyloidosis is a rare disorder associated with immune cell dyscrasias, such as multiple myeloma. In AL amyloidosis, the amyloid forms from abnormally folded immunoglobulin light chain.[1] In contrast, bovine amyloidosis is classified as the reactive (AA) type, which is frequently associated with chronic inflammatory disease in domestic animals and humans.[1-5] Most, but not all, cattle with AA amyloidosis have concurrent inflammatory disease, such as traumatic reticuloperitonitis, pneumonia, mastitis, footrot, or metritis. Serum amyloid A protein (SAA) is an acute-phase protein that is synthesized in the liver and is a precursor of amyloid A (AA) fibril in tissues.[1] SAA concentrations increase in cattle with inflammatory disease.[3] Some of these cattle may subsequently develop amyloid deposits in organs because of abnormal catabolism, misfolding, and deposition of SAA.[1] Once embedded in tissue, smaller AA fibrils may serve as a nidus for further AA accretion and enlargement of the amyloid deposit.[7] Accumulation of amyloid in the glomerulus alters glomerular filtration and enables sustained albuminuria and a gradual loss of plasma oncotic pressure. Diarrhea develops as a result of gut wall edema, fluid loss into the gut lumen from the hypooncotic plasma space, and amyloid deposition in the GI tract.[5]

Necropsy Findings

Renal enlargement with yellow-tan to white discoloration is frequently present. A waxy quality of the renal parenchyma may be appreciated on cut surface of the kidney.[3-5] Generalized edema is apparent. Primary inflammatory disease may be found in other sites. Histologic examination of the kidney reveals amyloid deposition in the glomerulus, interstitium, and tubule lumen.

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Prognosis

The prognosis for affected cattle is poor. The resilient nature of the amyloid protein generally results in its persistence in tissues, even if the underlying inflammatory disease is treated. Specific treatment for amyloidosis has not been reported in cattle. The potential for cross-species transmission of amyloidosis is an area of active research.[8]

Amyloidosis in Other Ruminants

AA amyloidosis has also been reported in domestic sheep and goats, as well as a variety of nondomesticated ruminants.[9-11] It appears to be a consequence of chronic suppurative diseases such as pneumonia,[9] caseous lymphadenitis,[10] and in lambs, polyarthritis caused by *Erysipelothrix rhusiopathiae*.[11] As for cattle, amyloid deposition can be detected histologically in multiple tissues of affected animals, with gross and histologic lesions primarily involving the kidneys. The clinical course of AA amyloidosis in small ruminants is poorly described but is speculated to be a protein-losing glomerulopathy, akin to the disease in cattle.[10]

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Glomerulonephritis

David C. Van Metre

Glomerulonephritis (GN) is a rare kidney disorder of ruminants that may result from deposition of antigen-antibody complexes and/or complement in the glomerulus, or from binding of antibody to intrinsic or foreign antigens localized to the glomerulus. Glomerular injury occurs subsequent to targeting of glomerular tissues by the immune system. Clinical signs reflect sustained albumin loss in the urine and the resultant loss of plasma oncotic pressure.

Clinical Signs

Cattle with GN may have a history of lethargy, weight loss, mucous membrane pallor, poor productivity, and chronic diarrhea,[1,2] although the course of disease may be acute in some cases.[3] Generalized edema is often apparent, typically involving the brisket and submandibular space. An enlarged but nonpainful left kidney may be felt on rectal palpation.[2] GN can occur in cattle with liver fluke infestation,[4] metritis,[5] or those acutely[6] or persistently[7,8] infected with bovine viral diarrhea (BVD) virus. As is expected for persistent BVD infection, the appearance of affected cattle can range from unthrifty[7] to clinically normal.[8] GN can also occur without a detectable concurrent disease.[2,3] Further, a heritable proliferative glomerulopathy (defined as hyperplasia of cells within the glomeruli without a marked inflammatory infiltrate) has been described in Gelbvieh calves; clinical signs in affected animals reflect a concurrent peripheral neuropathy that manifests as paraparesis, hind limb ataxia, and recumbency.[9]

In small ruminants, the clinical course of GN is less well described than for cattle, but thin condition, pale mucous membranes, and generalized edema are expected.[10] Subclinical GN has also been detected at necropsy in sheep with caseous lymphadenitis,[11] Maedi-Visna virus infection,[12] and in sheep experimentally implanted with long-term, indwelling vascular catheters.[13] Finnish Landrace lambs may develop GN early in life as a result of a heritable defect in the C3 component of complement.[14] Clinical signs of this disease begin within hours after birth to 3 months of age. Affected lambs may be dull and ataxic and appear blind. Fine muscle tremors, colic, and convulsions may also be

seen.

Differential Diagnosis

The differential diagnosis for ruminants with GN is similar to that for amyloidosis (see preceding section).

Clinical Pathology

Heavy proteinuria, mild anemia, hypoalbuminemia, and azotemia have been reported in ruminants with GN.[1-5,7,10] Variable amounts of granular or hyaline casts, red blood cells, and leukocytes may be found in the urine sediment. GN in Finnish Landrace lambs is characterized by uremia, hypoalbuminemia, proteinuria, hypocalcemia, and hyperphosphatemia.[14]

Pathophysiology

In humans and animals, GN may result from a variety of infectious, toxic, or autoimmune disorders, all of which induce eventual immunologic injury to the glomerulus.[15,16] Antibodies may be directed against the host's own antigens or antigens of infectious agents that become “planted” in the vascular endothelium, mesangial cells, or basement membrane. In many cases, circulating immune complexes develop under conditions of sustained antigenemia produced by chronic infections. These immune complexes deposit in the glomeruli and adjacent capillary walls. The ultimate consequences are activation of complement and chemotaxis of leukocytes, both of which result in glomerular injury and increased glomerular permeability.[15,16] Immunohistochemical data suggest involvement of these immune-mediated mechanisms in spontaneous GN,[1-3] as well as GN associated with infection with BVD,[6-8] Maedi-Visna virus,[12] and indwelling vascular catheters.[13] Notably, glomerular lesions may be found in animals with septicemia, as septic emboli may embed in the glomeruli or surrounding capillary beds, resulting in multifocal glomerulitis.[14-16]

Passage of plasma albumin through the damaged glomerulus results in chronic albuminuria, eventually leading to reduced plasma oncotic pressure and generalized edema. Affected animals may develop nephrotic syndrome, characterized by hypoalbuminemia, generalized edema, unrelenting proteinuria,

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and hypercholesterolemia[1-3,10]; however, because serum cholesterol is not commonly measured in ruminant biochemistry analysis, the frequency of hypercholesterolemia in affected ruminants is unknown.

Treatment and Prognosis

In other species, treatment aimed at removal of the source of antigen in the bloodstream may reduce immune complex deposition and slow or reverse the progression of disease. Treatment of GN in ruminants has not been described. Because most clinically overt cases of GN are advanced at the time of diagnosis in ruminants, the prognosis can be assumed to be poor.

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Congenital Defects

David C. Van Metre

Most severe congenital defects of the urinary tract of ruminants manifest at an early age, although occasionally defects remain clinically occult until adulthood and some are incidental findings at necropsy or slaughter. Congenital defects of the urinary system should be considered in the differential diagnoses for a young animal with renal disease or abnormal urination. However, tubular necrosis caused by severe volume depletion, nephrotoxins, and infectious diseases are much more common. If a congenital defect of the urinary tract is identified, a careful examination of other body systems should be performed; 73% of lambs with urogenital defects were found to have one or more defects in other organ systems.[1]

Renal Defects

Common renal defects in cattle include fused kidney, polycystic kidney, unilateral renal agenesis, and renal oxalosis.[2] A single report exists of ectopic fused kidneys and hermaphroditism in a cross-bred calf.[3] In sheep, common defects include renal lobulation, fused kidney, hydronephrosis and hydroureter, polycystic kidney, and unilateral or bilateral renal agenesis.[1,2] Unilateral renal agenesis and polycystic disease involving the liver, pancreas, and kidney have been reported in goats.[2,4] A retroperitoneal, perirenal *pseudocyst* (a fluid sac lacking an epithelial layer) was described in a ram with acute abdominal pain.[5] Pseudocysts typically develop as outpocketings of the renal capsule and can develop as a result of renal trauma, urinary tract obstruction, or vascular or lymphatic anomalies.

Renal oxalosis is a metabolic disease that is suspected to have an inherited basis[6]; a severe form has been reported in Beefmaster calves.[7] Affected calves show weakness, lethargy, and anorexia within days to several weeks of age. Dehydration, diarrhea, and alopecia may develop. Evidence of renal failure is found on serum chemistry analysis. An inherited abnormality of glycine or glyoxalate metabolism may generate high levels of endogenous oxalate, which readily complexes with calcium. Subsequently, calcium oxalate crystals accumulate in the renal tubules, obstructing tubular outflow. Exposure to

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oxalate-containing plants and ethylene glycol must be ruled out in all cases of renal oxalosis.

Ectopic Ureter

Ectopic ureter is a rare congenital defect in which one or both ureters terminate in an abnormal location. An ectopic ureter may terminate in the urethra, vagina, or cervix or caudal to the bladder trigone in females. In males, the ectopic ureter usually terminates in the urethra, vas deferens, or seminal vesicles. Urinary incontinence is the most common presenting complaint for affected animals.[8] Urine dribbling results in scalding of the perineum and medial surfaces of the hindlimbs in heifers, and scalding in males is usually located on the prepuce and ventral abdomen. Occasional episodes of normal micturition may be seen. UTI, polycystic kidney(s), and hydronephrosis may exist concurrent to ectopic ureter(s). Diagnosis and treatment of this condition in ruminants are similar to horses (see the previous section in this chapter). The use of affected animals for breeding should be discouraged.

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Neoplasia

David C. Van Metre

Other than those associated with ingestion of bracken fern, primary neoplasms of the urinary tract of ruminants are rare. In a North American abbatoir survey, primary tumors of the bladder were detected in 0.05% of more than 21,000 cattle examined, with cases of papillomas, adenomas, and transitional cell carcinomas identified in the sample population.[1] Tumors of the genitalia, typically fibropapillomas and squamous cell carcinomas, may impinge upon urine egress from the urethra. Urinary tract involvement may be seen in occasional cases of lymphosarcoma in ruminants.[3]

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Hemolytic Uremic Syndrome

David G. Renter • Charles C. Dodd

Hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy (TM) disorder of multiple etiologies. Although primarily a disease of humans, there are reports of HUS in multiple species including horses and cattle. Clinically, HUS manifests as microangiopathic hemolytic anemia, thrombocytopenia, and, in many cases, renal failure. HUS is characterized morphologically by thrombotic lesions in capillaries and arterioles in tissues including those of the kidney.[1] The presence of schistocytes (fragmented red cells) in peripheral blood is considered an important diagnostic indicator of TM,[1] but an apparent lack of schistocytes in peripheral blood has been reported in both human[2] and equine[3] cases of HUS. Unlike DIC, TM disorders are generally associated with normal coagulation times and normal to slightly elevated fibrin split products.[1] TM disorders can be classified as typical HUS, atypical HUS, and thrombotic thrombocytopenic purpura.[1]

The typical form of HUS in humans is associated with consumption of food or water contaminated with Shiga toxin–producing bacteria, whereas atypical HUS is associated with inherited mutations of complement-regulatory proteins and diverse causes of endothelial injury including antiphospholipid antibodies, complications of pregnancy and contraceptives, vascular renal diseases like systemic sclerosis and malignant hypertension, use of chemotherapeutic and immunosuppressive drugs, and radiation.[1,4,5] Typical HUS is a major cause of ARF in young children and infants, and the majority of the cases occur after intestinal infection with Shiga toxin–producing enterohemorrhagic *E. coli* (EHEC).[1,6] *E. coli* O157:H7 is the most commonly reported serotype of EHEC in human cases of HUS, but many other EHEC serotypes have caused the syndrome.[6] Infection with neuraminidase-producing *Streptococcus pneumoniae* has also been reported to cause typical HUS in humans.[7,8] Although literature on HUS in large animals is limited, case reports on four horses[3,9,10] and two cows[11,12] have demonstrated clinical syndromes and pathologic lesions consistent with HUS in humans.

Clinical Findings

Horses with clinical signs indicative of HUS exhibited fever, lethargy, diarrhea, hematuria, hemoglobinuria, azotemia, oliguria, and ventral edema.[3,9,10] Hematologic findings in three cases included leukocytosis, anemia, and evidence of hemolysis.[9,10] The blood smear of one of the four equine cases of apparent HUS revealed the presence of poikilocytes and schistocytes.[3,9,10] All four horses with evidence suggestive of HUS were euthanatized following unsuccessful treatment with fluid therapy and diuretics.[3,9,10]

In a postparturient mare ultimately diagnosed with HUS, there was initial clinical and laboratory evidence of endotoxemia and endometritis.[3] However, after clinical signs of endotoxemia subsided, stranguria, hematuria, hemoglobinuria, tubular casts, thrombocytopenia, hyperfibrinogenemia, azotemia, and a left shift in the leukogram were noted.[3] Her foal was apparently healthy at birth but subsequently developed progressive CNS signs culminating in refractory seizures.[3] Although a direct causal relationship was not established, *E. coli* O103:H2 was recovered from the GI contents of both the mare and foal, as well as from the mare's uterus. In humans, serotype O103:H2 is one of the more common non-O157 EHECs.[6]

A reported fatal postparturient HUS case in a heifer was characterized by severe, progressive, anuric renal failure, acute hemolytic anemia, and consumptive thrombocytopenia.[12] A 6-year-old cow that had evidence of metritis 1 month after parturition was a suspected HUS case based on clinical and laboratory findings including anemia, hemolysis, thrombocytopenia, azotemia, and hemorrhagic diathesis.[11]

In humans, HUS can present suddenly as generalized hemorrhagic diathesis (especially hematemesis and melena), pallor, severe oligoanuria, hematuria, edema, microangiopathic hemolytic anemia, and, on occasion, seizures or other prominent neurologic changes.[1,12] In prodromal human cases, HUS develops an average of 1 week after the onset of diarrhea.[12] The classic clinical presentation of typical HUS in people includes the triad of ARF, thrombocytopenia, and hemolytic anemia.[1] Treatment in this acute phase of HUS primarily involves supportive care; there is limited evidence for more specific therapies, and some treatments may be detrimental.[4,13-15] At this writing, conflicting data exist in the published literature regarding the efficacy or potential for harm imparted by certain antimicrobials used to treat HUS. For example, in vitro research indicates that fluoroquinolone administration may result in increased Shiga toxin

production by certain strains of causative bacteria,[15] so avoiding use of this drug in cases of suspected HUS is likely prudent. New therapeutic strategies, including those aimed at binding or neutralizing Shiga toxins, have shown promising results in animal models for human disease.[15] Supportive therapy that includes fluid and electrolyte replacement, plasma therapy, and dialysis can be critically important in the acute stage of HUS. Approximately one third of those surviving the acute phase are at risk for chronic sequelae.[14] Although diabetes, intestinal strictures, myocardial infarction, and motor, sensory, or intellectual deficits and other sequelae can occur, chronic renal lesions leading to end-stage renal disease are more common.[14]

Pathophysiology and Necropsy Findings

Two processes appear to dominate the pathogenesis of TM and ultimately cause vascular obstruction and vasoconstriction resulting in organ ischemia: (1) endothelial injury and activation, leading to intravascular thrombosis, and (2) platelet aggregation.[1] In humans, endothelial injury appears to be the primary cause of HUS, and HUS is the most common life-threatening complication of hemorrhagic colitis from EHEC infection.[1,6] EHEC produces exotoxins Shiga toxin 1 and Shiga toxin 2, also referred to as *verotoxin 1* and *verotoxin 2*. Shiga toxins are considered a necessary but insufficient cause of typical HUS because other bacterial and host factors are important for disease progression.[6,16] Many serotypes of *E. coli* (as well as *Shigella* and other Enterobacteriaceae) can carry Shiga toxin genes and are capable of causing disease, yet certain EHEC serotypes (e.g., O157:H7) are more common human pathogens.[6] EHECs are considered noninvasive but attach to the intestinal mucosa and produce characteristic attaching and effacing lesions seen histologically.[1,6,16] Microvascular endothelium is the major target of Shiga toxins, which are released from the bacteria in the intestine and absorbed across the gut epithelium, where they access the systemic circulation and are transported to small vessel endothelial cells.[6,16] The toxins bind to specific glycolipid receptors on the surface of vascular endothelial cells, are internalized by endocytosis, and may injure the cell through inhibition of protein synthesis, stimulation of prothrombotic messages, or induction of apoptosis.[6,16] Exposure of subendothelial collagen followed by activation of the coagulation cascade may result in thrombosis of small vessels in the kidney and other organs. Acute

oliguric or anuric renal failure can result from fibrin/platelet thrombi in renal vessels and glomeruli, fibrinoid necrosis of vessel walls, congestion of glomeruli, and tubular ischemia.[1,16]

Cattle feces are considered to be a major source of EHEC, but these bacteria have been isolated from the feces of many other species including other livestock and humans.[16,17] Although EHECs do not generally cause illness in cattle, they do colonize the large intestine.[17] It is generally believed that the lack of specific glycolipid receptors for Shiga toxins is the reason cattle typically do not develop severe colitis or HUS, despite the common presence of EHEC in their gastrointestinal tracts.[17] Humans are generally infected with EHEC via consumption of food and water contaminated by feces. However, the small infectious dose makes direct contact with EHEC-positive animals (e.g., at petting zoos) and person-to-person transmission also a concern.[16,17]

In four of the large animal cases reported with HUS, the inciting cause was unknown and isolation of EHEC or other Shiga toxin–producing organisms was not attempted.[9,10,12] One heifer had a necrotizing endometritis, but during postmortem examination of three horses, no focus of infection was identified.[9,10,12] Renomegaly, renal infarcts, and scattered petechial and ecchymotic hemorrhages within the renal parenchyma were apparent on gross necropsy. Acute tubular necrosis and fibrin thrombi within the glomerular capillaries were evident on histologic examination.[9,10,12]

In another equine case report, an EHEC serotype O103:H2 carrying a Shiga toxin gene was recovered from both the mare and foal, but direct Shiga toxin assays were not performed.[6] While the causal significance of this finding is unclear, the unusual and concurrent disease progression in both animals may suggest a common etiology. Except for lack of evidence of microangiopathic hemolysis on a blood smear, the mare had clinical and postmortem signs consistent with HUS.[6] Significant renal pathology included evidence for plasma protein and hemoglobin in both cortical and medullary tubules, with occasional epithelial necrosis. In addition, renal capillary lumina were apparently obscured by fibrin, and only remnants of glomerular capillary endothelial cell cytoplasm were evident. Evidence of numerous platelets within the glomerular capillaries and their adherence to exposed basement membranes was apparent, as were other pathologic changes.[6] The foal's brain had evidence of widened perivascular spaces, with apparent perivascular plasma protein accumulations in the corpus striatum and thalamus.[6]

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Although the etiology is often undetermined in large animal cases of apparent HUS, the clinical signs and pathologic lesions reported are compatible with a diagnosis of HUS. It may be notable that three of six reported cases occurred postpartum. On the basis of HUS reports in large animals, it appears there may be features comparable with the disease syndrome in humans.

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Tubular Necrosis

Meredyth L. Jones

Tubular necrosis (TN) is a term referring to intrinsic acute renal failure (ARF) caused by hemodynamic, nephrotoxic, glomerular, or interstitial disorders. Tubular damage may be a primary clinical entity or a secondary effect of another systemic illness. The kidneys receive a large proportion of circulating blood volume, resulting in a high rate of toxin exposure, as well as increased vulnerability to ischemia and reperfusion injury with diseases causing changes in nutrient blood flow. Acute renal failure, characterized by a sudden decrease in glomerular filtration rate, nitrogenous waste accumulation, and loss of the ability to manage sodium, electrolytes, protein, acid-base and water balance, develops over hours to days. Depending on the nature and duration of the primary insult, widespread dysfunction or necrosis of tubular epithelial cells may produce reversible renal injury, ARF, or chronic renal failure (CRF).

Potential causes of TN and ARF are included in Table 34.2.

TABLE 34.2

Differential Diagnoses for Acute Renal Failure in Ruminants

Inorganic Compounds	Organic Compounds	Therapeutics	Endogenous Compounds	Hemodynamic Causes	Infectious Agents	Plants
Arsenic	Cantharidin	Aminoglycosides	Calcium oxalate	Blood loss	Malignant catarrhal fever	Castor bean *(Ricin)*
Bismuth	Carbamate fungicides	Gentamicin, neomycin, amikacin	Hemoglobin	Endotoxic shock	*Coxiella burnetii*	Beets *(Beta*
Boric acid	Carbon tetrachloride	Amphotericin B	Myoglobin	Disseminated intravascular coagulation	*Leptospira* spp.	Bristle gras *(Setaria)*
Cadmium	Cholecalciferol-based rodenticides	Bacitracin		Renal vein thrombosis	*Mycobacterium* spp.	Cocklebur *(Xanthium)*
Calcium	Diquat	Cephalosporins		Heat-related injury	Rift Valley fever	Crocus *(Colchicum*
Chromium	Ethylene glycol	Doxycycline			Septicemia	Curlydock *(Rumex)*
Copper	Mycotoxins	Ionophores			-*Mycoplasma agalactiae*	Daisy *(Nolletia)*
Lead	Natural gas condensate	NSAIDs			-*Salmonella enterica*	Greasewoo *(Sarcobatus*

Mercury	Ochratoxin, citrinin, fumonisin	Oxytetracycline			-Others	Halogeton *(Halogeton)*
Molybdenum	Oxalic acid	Polymyxin B				Hybrid sudan or Sudan grass *(S*orghum)
Phosphorus	Pentachlorophenol	Sulfonamides				Inkweed *(Phytolacca*
Sodium fluoride	Phenolics	Vitamin C				Jessamine *(Cestrum)*
Uranium	Stillage liquid from ethanol production	Vitamin D, particularly D3				Kleingrass *(Panicum)*
Zinc		Vitamin K3				*Kochia scoparia*

NSAIDs, Nonsteroidal antiinflammatory drugs.

Clinical Signs

The clinical signs of ARF in ruminants are nonspecific and usually not indicative of overt urinary tract dysfunction. Depending on the inciting cause, anuria, oliguria, or polyuria may exist. Cattle with ARF frequently are presented for evaluation of poor appetite, diarrhea, or epistaxis.[1] Depression, nasal discharge, ileus, melena, and mild free-gas bloat may also be present. If a concurrent septic condition exists, fever, tachycardia, and scleral injection may be present. The saliva may have a strong ammonia smell. Muscular weakness, even recumbency, may result from the acid-base and electrolyte imbalances and intravascular volume depletion that occur with severe, acute TN. Rectal palpation findings are usually unremarkable, although renal enlargement and perirenal edema may be found in occasional cases. If untreated, CRF may ensue, usually producing weight loss in addition to the signs listed. In such cases, a reduction in size of the left kidney may be appreciated on rectal palpation.

Renal (uremic) encephalopathy is a syndrome of brain dysfunction associated with renal disease. It is characterized by signs of intracranial disease, such as altered behavior or sensorium, weakness, motor dysfunction, and convulsions, which may resolve on restoration of normal renal function or improvement of clinical parameters of renal disease. The pathogenesis of renal encephalopathy is complex and incompletely understood, but neurologic function appears to be impaired by alterations in the extracellular fluid content of acids, phosphorus, amino acids, or certain hormones. Alteration in neurotransmitter balance or release within the central nervous system (CNS) may also be involved. Renal

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encephalopathy appears to be a rare complication of renal failure in ruminants, as reported in two cows and a goat, where the lesions included myelin vacuolation.[2-4]

Differential Diagnosis

Formulation of a differential diagnosis list for a ruminant with TN may be difficult because of the nonspecific nature of clinical signs and variety of primary disease conditions that may predispose an animal to TN. Generic systemic illness differential diagnoses are similar to those of renal origin. Diseases causing signs of acute, severe illness in ruminants include pneumonia, pleuritis, mastitis, metritis, peritonitis, endocarditis, and metabolic derangements.

Pathologic Studies

The complete blood count and serum biochemistry can provide important evidence for the presence of renal disease and clues as to its etiology. Inflammatory diseases are common in ruminants, and the leukogram may reflect those primarily affecting the upper urinary tract. Acute inflammation affecting renal tubules may result in neutropenia or a left shift to immature (band) neutrophils. Renal enzymes and electrolytes evaluated in the serum biochemistry are useful indicators of renal function. Blood or serum urea nitrogen (BUN) is interpreted as a measure of glomerular filtration rate (GFR), reflecting function and perfusion of the kidneys. BUN is influenced by the protein level in the diet and the ability of the rumen to recycle urea. Creatinine is produced and eliminated in constant amounts in the body and is not influenced by rumen physiology, making it superior for evaluation of renal perfusion and function in ruminants, although it may be elevated above reference ranges in heavily muscled bulls with adequate renal function. Azotemia may result from prerenal, renal, or postrenal causes, with renal causes indicated by persistent isosthenuria or hyposthenuria in the absence of iatrogenic causes. Overinterpretation of a single, dilute urine sample should be avoided.

Fractional excretion of (FE) electrolytes can further delineate the nature of renal azotemia. Fractional clearance of sodium has been used to help document renal failure in cattle, with values of 0% to 4% described in normal cattle.[5] Age, ration, and metabolic status may affect FE values.[5] When applying this test, it is

prudent to compare the patient's FE value for sodium to that of an age-matched herdmate in a similar physiologic state and on a similar ration. The normal values for several urinary diagnostic indices in healthy calves have been reported.[6]

Hyponatremia, hypochloremia, and metabolic alkalosis may also be present with ARF, with variable potassium levels.[1,7] Because the kidney is the primary organ controlling magnesium excretion in ruminants, hypermagnesemia may occur in TN, particularly under conditions of high magnesium intake.[1,8] Hyperphosphatemia results from reduced phosphorus excretion in saliva during anorexia, reduced urinary phosphorus excretion, and tissue hypoxia.[9,10] Hypocalcemia is also common in TN in ruminants because of reduced calcium intake, gastrointestinal stasis, urinary losses, and the competitive effect of hyperphosphatemia.[1] Metabolic acidosis may develop in juvenile ruminants with TN and concurrent diarrhea.[5,10]

A urinalysis should be performed on all animals with suspected renal disease. Proteinuria, hematuria, and granular casts may be found in cases of tubular necrosis.

Table 34.3 lists additional clinical and clinicopathologic criteria that may facilitate diagnosis of TN caused by nephrotoxins.

TABLE 34.3

Clinical Characteristics of Acute Toxic Nephrosis Caused by Common Nephrotoxins

Nephrotoxin	Clinical Findings[a]
Aminoglycosides	Usually nonoliguric, ototoxicosis possible; hematuria, glucosuria, proteinuria, increased serum trough concentration of drug
Tetracycline	Hematuria, glucosuria, proteinuria; possible hepatocellular enzyme elevation
Ionophores	Diarrhea, dark urine, dyspnea, cardiac dysrhythmias; elevated CK, AST, and indirect bilirubin
Ethylene glycol	Anuria or oliguria, tachypnea, ataxia, weakness; hemolysis, increased anion gap, increased serum osmolality, increased osmolar gap, acidosis, calcium oxalate crystalluria
Oxalate-containing plants, vitamin C	Hindlimb ataxia or paresis, apprehension, salivation; hypocalcemia, calcium oxalate crystalluria, aciduria, increased renal cortical echogenicity on ultrasonogram
Oak, acorns	Hemorrhagic diarrhea, ascites, hydrothorax, subcutaneous and perirenal edema; hyperfibrinogenemia, increased hepatic enzymes
Myoglobin	Muscle stiffness and weakness, dark urine; elevated serum CK and AST, positive reactions for blood and protein on urine chemistry strip, hemolyzed serum not present
Hemoglobin/methemoglobin	Icteric to pale mucous membranes, tachycardia, tachypnea, red or brown urine; positive blood and protein reactions on urine chemistry strip, anemia, elevated serum total protein, hemolyzed serum (hemoglobin only)

Arsenic	Colic, hemorrhagic diarrhea, ataxia; elevated blood and liver arsenic levels

[a]Many general clinical characteristics of acute tubular necrosis are also present. See Clinical Signs and Clinical Pathology.

AST, Aspartate aminotransferase; *CK,* creatine kinase.

Pathophysiology

The mechanisms of TN include hemodynamic changes within the kidney, as well as ischemic and toxic damage to tubular cells. Reduced blood flow to the kidneys most often occurs during generalized loss of vascular volume, as seen with marked blood loss, septicemia, endotoxemia, or severe dehydration. In ruminants, the most common primary conditions resulting in these changes include mastitis, metritis, enteritis, rumen acidosis, and intestinal accidents. These conditions may also cause infarction of the renal cortex and renal vein thrombosis.[1] Acute, severe renal tubular necrosis has been reported in lambs as heat stress-related injury, similar to ischemic, heat-induced injury in humans.[11] Prolonged, severe ischemia may destroy the tubular basement membrane, thereby preventing tubular epithelial cell regeneration.[12] Rumen acidosis or other conditions resulting in severe rumen distension may additionally result in mechanical obstruction of renal vasculature, impairing renal perfusion.[1]

Bilateral bacterial infection of the kidneys may result in ARF or CRF as a result of destruction of nephrons by bacterial toxins and host inflammatory response. Renal infection may be established by ascending urinary tract infection or via hematogenous infection of the kidneys.

Pigment nephrosis is an endogenous toxicity from the presentation of large amounts of hemoglobin or myoglobin to the kidneys as a result of hemolytic disease or myopathies. These pigments result in renal vasoconstriction and tubular obstruction from protein coagulation.

A variety of toxins may result in significant damage to the kidneys by a variety of mechanisms that result in ARF. The high metabolic demands of renal tubular epithelial cells render them susceptible to toxins that disrupt cellular enzymes. The injury caused by most nephrotoxins is compounded by dehydration, which concentrates the toxin in the tubular filtrate, slows toxin clearance, and if severe, reduces renal perfusion. Because some nephrotoxins are therapeutic agents, it is vital that the veterinarian monitor appetite, body weight, water intake, urine output, routine urine chemistry, serum drug concentration, and serum creatinine concentration during administration of these agents. Young

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or elderly patients, patients with preexisting renal insufficiency or sepsis, those receiving other potentially nephrotoxic drugs, and patients on prolonged or high-dose therapy with these agents warrant the closest attention.[13] Nonsteroidal antiinflammatory drugs block the effects of prostaglandins, which are important for maintenance of renal blood flow, and may cause medullary crest necrosis when used in pediatric, geriatric, and inadequately hydrated patients or for a prolonged dosing regimen.[14] Some sulfonamide antimicrobials have been associated with deposition of insoluble precipitates in the renal tubules and blocking excretion of creatinine.[15] Aminoglycoside antimicrobials, particularly gentamicin, have cumulative effects on the renal tubules and may cause cell death through mitochondrial oxidation and other mechanisms.[13,16]

Ethylene glycol, the primary ingredient in many antifreeze products, is converted by the liver into nephrotoxic metabolites, mainly glycolic acid. Additionally, calcium oxalate crystals form and are deposited in the renal tubules, causing further compromise.[17] Lethal doses for ethylene glycol are 5 to 10 mL/kg in mature cattle and 2 mL/kg in preruminating calves.[18,19] Insoluble oxalate crystal deposition in the renal tubules is also a common pathologic mechanism for some nephrotoxic plant poisonings including halogeton, greaseweed, pigweed, sorrel, dock, and Russian thistle. Several nephrotoxic plants also exhibit effects on other body systems including the respiratory, gastrointestinal, cardiac, and hepatic systems, with additional symptoms observed. Many of the nephrotoxic plants, particularly those causing oxalate toxicity, are also nitrate accumulators.

Treatment and Prognosis

Treatment of ARF should include binding and removing any offending toxin or source, promoting diuresis through intravenous (IV) fluid administration and diuretic medications, correcting acid-base and electrolyte derangements, and close monitoring for positive or adverse responses to treatment. Rumenotomy, with removal of toxic material, is most beneficial if performed soon (within 24 hours) after the animal has ingested a nephrotoxin. Activated charcoal (2 to 4 g/kg PO) may bind the agent in the gut lumen. The use of magnesium sulfate or other magnesium-containing laxatives should be avoided in such cases because severe hypermagnesemia may result in animals with concurrent compromise of renal function.[8] Drugs that directly target known nephrotoxins, such as heavy

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metal chelators, may be initiated. Prophylactic diuresis should be instituted as soon as an animal has suspected exposure to a potentially harmful quantity of a nephrotoxin. Delaying treatment until azotemia is present allows for a significant (>75%) loss of nephron function before medical intervention.

The cornerstone of treatment of TN is restoration of adequate renal perfusion and urine production. This is most effectively achieved through IV administration of isotonic, sodium-containing fluids, with calcium and potassium supplementation as indicated. Normal (0.9%) saline or 0.45% saline + 2.5% dextrose serve as reasonable base fluids. Additional IV potassium can be substituted if indicated after initial therapy, being cautious to remain below the generally recommended toxicity rate of 0.5 mEq/kg/h. Diuresis should continue until the patient is producing sufficient volumes of urine. If cost or facilities make IV fluid therapy impractical, repeated administration of water and electrolytes by orogastric or nasogastric tube is an option. A small-bore tube can be passed through the nasal cavity into the rumen and secured to the animal's halter to allow one person to administer fluids repeatedly without the need for repeated tube passage. Placement of a small rumenostomy also would allow one person to administer fluids repeatedly with relative ease. Administration of IV or oral fluids at 1.5 to 2 times the adult maintenance level of 60 mL/kg/day may be adequate to induce diuresis. The patient should be monitored for chemosis, ventral or peripheral edema, or labored or rapid respiration, which may be indicative of overhydration. Fluid therapy should be continued until azotemia resolves, at which time the patient's voluntary fluid intake can be assessed. Oral supplementation of potassium and calcium salts may be necessary in some cases because it is often not possible to include adequate yet safe levels of these salts to IV fluids in cases of refractory hypokalemia and hypocalcemia, respectively.

Restoration of urine production is necessary in anuric or oliguric animals. If fluid therapy does not promote diuresis, furosemide (1 mg/kg IV or IM) may be administered. Repeated administration (every 1 to 2 hours) may be necessary to induce urine production. With repeated use of furosemide, the patient's serum sodium and potassium concentrations must be monitored. Mannitol (0.25 to 1 g/kg IV bolus) can be used to provide osmotic diuresis.

Vasopressors and inotropes may assist with renal perfusion but must be administered using fluid pumps as constant rate infusions. These have wide and controversial ranges of therapeutic efficacy. Drugs and dosages used anecdotally in ruminants include intravenous dopamine (2 to 5 µg/kg/min), dobutamine (5 to 10 µg/kg/min), and combination norepinephrine (0.4 µg/kg/min) + dobutamine

(5 µg/kg/min) based on available information.[20] It should be noted that the use of dopamine alone in cases of ARF may not be as beneficial as once thought and adverse effects have been discovered.[21]

Additional supportive therapy may include broad-spectrum antimicrobials against susceptible infectious agents, plasma transfusion to treat hypoproteinemia, and nutritional support through parenteral nutrition or rumen transfaunation. Antiinflammatory agents may prove useful but should be used cautiously where renal damage exists and only when the kidneys are being therapeutically well perfused. Urinalysis and FE of electrolytes can be measured in conjunction with serum monitoring parameters during intensively managed cases.

Lesions that occlude tubular blood flow (renal vein thrombosis, DIC) warrant a poor prognosis, whereas renal failure resulting from toxic causes carries a more favorable prognosis with early diagnosis and aggressive therapy. Return of appetite and progressive reduction in BUN and serum creatinine levels are positive prognostic indicators.[7] Prolonged supportive treatment (2 to 3 weeks) may be necessary to allow for regeneration of tubular epithelium in cases of acute TN.

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Leptospirosis

Robert J. Callan

Leptospirosis is a complex disease of both animals and humans caused by pathogenic species of *Leptospira*.[1-9] Pathogenic *Leptospira* species persist as chronic infections of the renal tubules of the maintenance host species, often causing little or no disease. Transmission to incidental hosts results from direct contact with urine from an infected maintenance host or through environmental or feed contamination with infected urine. Infection in the incidental host can cause acute disease in multiple organ systems (e.g., kidney, liver, CNS) and result in abortion or reproductive failure. This discussion focuses on *Leptospira* infection and disease of the urogenital system of ruminants.

Leptospira is a diverse genus of motile, gram-negative, obligate aerobic, tightly coiled spirochetes approximately 0.1 to 0.3 µm in diameter and 6 to 20 µm in length.[1,2,5,8,9] The bacteria can survive in the environment for up to 6 months.[2,5,10] *Leptospira* spp. prefer a warm, moist environment with a pH of 7.2 to 8.0. Survival is short under dry conditions or at temperatures below 10° C.[2] *Leptospira* does not survive freezing in the environment.[11]

Before 1989, *Leptospira* was divided into the pathogenic species *L. interrogans* and nonpathogenic saprophytic species *Leptospira biflexa*. The current taxonomy and classification of *Leptospira* use a complex system of both genetic and serologic characteristics.[1,5,9,12] The *Leptospira* species is determined by DNA sequence similarity.[1,5,9] Twenty-two genomospecies have been identified on the basis of DNA sequence heterogeneity (e.g., *Leptospira borgpetersenii*).[9,12] Further classification by serovar is based on antigenic grouping of the lipopolysaccharide (LPS) and other outer surface antigens using the cross-agglutinin adsorption test (CAAT).[12] More than 250 serovars are characterized for pathogenic strains of *Leptospira* (e.g., *L. borgpetersenii* serovar *hardjo*). Serovars may be further divided into serogroups (e.g., *L. borgpetersenii* serovar *hardjo* type hardjobovis). Serogroups represent antigenically related serovars and are determined by the microagglutination test (MAT). There are currently 24 serogroups described for pathogenic strains of *Leptospira*.[12] Because serovars of a given serogroup can be distributed across multiple *Leptospira* species, the serogroup classification does not represent taxonomic

relatedness.

Epidemiology

Leptospirosis is predominantly observed under conditions where livestock come in direct or indirect contact with urine from an infected maintenance host (Table 34.4).[1,2,5,10] The prevalence of infection within a maintenance host population tends to be high (30% to 50%); in such populations, infection is often spread between animals by direct contact.[2] Transmission to incidental hosts is generally by contact with the environment, feed, or water that is contaminated with urine from an infected maintenance host. Transmission can also occur from contact with an infected fetus or uterine discharge. Survival of the bacteria in the environment and the incidence of infection in animals are increased in warm, humid climates. The seasonal incidence is higher during the summer or fall in temperate regions and during the rainy season in warm-climate regions.[5] Environmental conditions that contribute to moist surroundings and foot abrasions may contribute to *Leptospira* transmission, particularly in housed dairy cattle.

TABLE 34.4

Current Nomenclature, Maintenance Host, and Incidental Hosts for Common *Leptospira* Isolates in Ruminants

Genomospecies	Serovar	Maintenance Host	Incidental Hosts
Leptospira interrogans	*Canicola*	Dogs	Cattle
L. interrogans	*Pomona*	Swine, opossums, skunks, raccoons	Horses, cattle, sheep, goats, dogs
L. interrogans	*Icterohaemorrhagiae*	Rats	Dogs, cattle, swine
L. interrogans	*Bratislava*	Pigs, mice, horses	Dogs, cattle, horses
L. interrogans	*Hardjo type hardjoprajitno*	Cattle	Sheep, goats
Leptospira borgpetersenii	*Hardjo type hardjobovis*	Cattle	Sheep, goats
L. borgpetersenii	*Ballum*	Mice	—
Leptospira kirschneri	*Grippotyphosa*	Raccoons, muskrats, squirrels	Cattle, sheep, horses, dogs

Cattle are the primary maintenance host reservoir of *L. interrogans* serovar *hardjo* type hardjopragitno and *L. borgpetersenii* serovar *hardjo* type hardjobovis. *L. interrogans* serovar *hardjo* type hardjopragitno is isolated primarily from cattle in the United Kingdom, and *L. borgpetersenii* serovar

hardjo type hardjobovis is observed worldwide. Sheep and goats may also serve as maintenance hosts for *L. borgpetersenii serovar hardjo* type hardjobovis.[13-15] Cattle can serve as maintenance or incidental hosts for *L. interrogans* serovar *pomona* and *L. interrogans* serovar *grippotyphosa*.

Serovars *hardjo*, *pomona*, and *grippotyphosa* are most often implicated in renal infection of cattle.[16] Although data are scarce, renal disease caused by leptospirosis in small ruminants appears to be uncommon.[11,17] Detection of *Leptospira* spp. from vaginal fluid and semen of sheep and goats has been reported and suggests the possibility of venereal transmission in those species.[13,18] Sheep may serve as subclinical carriers of serovars *hardjo*, *hardjobovis*, and *pomona*.[3,13,19,20] Some serovars of *Leptospira* have zoonotic potential, and humans are always considered an incidental host.[1,2,4,5]

An abattoir study of more than 5000 cattle in the United States identified approximately 2% renal carriers of *L. interrogans*.[16] Serovar *hardjo* was the most common renal isolate, followed by serovars *pomona* and *grippotyphosa*. A study of Texas slaughterhouse cattle detected *Leptospira* spp. in 36% of urine samples by PCR. The seroprevalence for serovars *pomona* and *hardjo* was 22% and 15%, respectively.[21] A national survey showed 49% seroprevalence for *L. interrogans* serovars in cattle, with the highest seroprevalence found in cattle from southeastern, south-central, and Pacific Coast states.[22] Because contact with urine from infected animals is a means of transmission within cattle populations, high stocking density or confinement may increase the rate of infection in a herd.

In general, infection of cattle with the host-adapted serovar *hardjo* rarely results in acute, severe disease. If present, signs of disease are usually mild in acutely infected cattle and may simply present as cases of undifferentiated fever. Persistent, latent urogenital infection usually follows acute infection of host-adapted serovars in cattle, with most overt losses attributable to adverse effects on reproduction.[4,23-25]

Acute, severe renal disease is more characteristic of incidental (also termed *accidental*) infection of cattle, particularly calves, with a non–host-adapted serovar of *Leptospira*. However, exceptions to this generalization do occur because host immunity and virulence of the organism are variable.[3,4]

Clinical Findings

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Serovar *hardjo* is host adapted to cattle, and many infections are asymptomatic or result in nonspecific reproductive failure or abortion. *Leptospira* serovar *hardjo* infection of cattle may produce chronic interstitial nephritis of variable severity, but overt renal dysfunction is rarely observed.[26] Chronic infection of the genital tract of cows and bulls is common.[7,27] Protracted shedding of the organism in the urine often occurs, possibly lasting for the life of the animal.[26,27] Infertility, stillbirth, abortion, and birth of weak calves are typical clinical manifestations of infection with serovar *hardjo* in cows.[7,24,28,29] The fetus can be infected in utero, and if it survives the acute infection, it may be born persistently infected.[2] Fever, agalactia, and mastitis may occasionally occur, and the resulting syndrome has been termed the *milk-drop syndrome*[3] or *flabby udder*[4] in lactating cows. The udder is uniformly soft, and the milk may be yellow or red tinged and thick.

In contrast, infection with non–host-adapted serovars can result in severe systemic disease, hemolytic anemia, hepatitis, interstitial nephritis, and tubular nephrosis in calves and less often in adult cattle.[7,26] Meningitis is a rare manifestation.[17] Agalactia and mastitis often occur in lactating cows, and pregnant cows may abort. Urine shedding of non–host-adapted serovars by infected cattle can persist for weeks to months.[4,7,29] Renal lesions result from direct damage to the vascular endothelium during leptospiremia, hypoxia from endothelial damage and hemolysis, tubular epithelial damage from hemoglobin, and interstitial nephritis.[2,5,26] Some *Leptospira* serovars, particularly *pomona*, produce hemolysins that can cause acute intravascular hemolysis and anemia in cattle.

Clinical signs associated with acute infection may include fever, anorexia, lethargy, decreased milk production, petechiation, hemolytic anemia, icterus, and hemoglobinuria. Oliguria may be seen with interstitial nephritis or hemoglobinuric nephrosis. Elevated creatinine concentration caused by prerenal or renal causes may be observed on serum chemistry analysis. Examination of the urine may show proteinuria, pyuria, and cellular or granular casts in cases of nephritis. Hemoglobinemia and hemoglobinuria may be observed in patients with leptospire-induced hemolysis and can occasionally result in hemoglobinuric nephrosis (pigment nephropathy).

Pathophysiology

Contaminated feed and surface water, wildlife, rodents, and domestic animals are potential sources of pathogenic serovars for cattle.[2-5] Leptospires penetrate external mucosal surfaces and scarified or macerated skin. The bacteria multiply locally during an incubation period that can last 2 to 20 days.[2,5] After the incubation phase, the organism enters the bloodstream through the lymphatics or by direct penetration into the blood vessel. Leptospiremia results in dissemination throughout the body and infection of multiple organs. This bacteremic phase lasts 4 to 7 days. Fever and other systemic signs are often present in clinically affected animals. Humoral antibodies can be detected at the end of the bacteremic phase. Opsonizing antibodies are generated and aid in clearing infection from most tissues in the host.

During the convalescent phase, leptospires may become localized in the mammary gland, kidney, or genital tract, where they appear to be protected from the immune response.[2,30] Depending on the virulence of the serovar involved, chronic renal infection may create few histologic changes, mild interstitial nephritis, or diffuse, severe, lymphocytic interstitial nephritis with fibrosis.[17] Nephritis may persist long after the host immune response has cleared the organism. Chronic infection of the kidney or reproductive tract allows for transmission of the organism in urine, uterine and vaginal secretions, placenta, fetal tissues, and semen.[3,7,27,31] Shedding in the urine may last for weeks to months with non–host-adapted infections. Renal shedding of host-adapted serovars can persist for months to years. The bacteria reside in the lumen of the renal proximal tubules, where they are protected from phagocytes and humoral antibodies. The bacteria do not stimulate a systemic immune response while localized in the proximal tubule lumen, so serum antibody titers can decline and become negative even though the kidney is infected and urinary shedding of bacteria continues.

Multiple potential virulence factors may contribute to leptospirosis.[1,5,8,32] Virulence mechanisms include the toxin effect of lipopolysaccharide, adhesion to cells and extracellular matrix, bacterial motility, hemolysins, and iron sequestration. Leptospiral LPS and outer membrane proteins are believed to contribute to the development of interstitial nephritis. Motility is an important pathogenic mechanism and contributes to invasion and dissemination of the bacteria. As many as 50 genes are related to leptospiral motility.[1] Adherence to cells is in part conferred by fibronectin-binding protein present on the surface of pathogenic strains but not on nonpathogenic strains. Leptospiral

immunoglobulin-like protein A, B, and C (LigA, LigB, LigC) may also be involved in attachment and invasion. Additional proteins that may contribute to virulence include hemolysins, sphingomyelinase C, sphingomyelinase H, and hemolysis-associated protein 1 (HAP-1).[1,5,8,32] There appears to be significant redundancy in proteins associated with virulence mechanisms, making it difficult to isolate individual virulence factors using single gene knockout mutations.

Diagnosis

Diagnosis of *Leptospira* spp. infections is challenging due to the imperfect nature of currently available tests.[33] The microscopic agglutination test (MAT) is the most widely used serologic test for the diagnosis of leptospirosis in cattle. The MAT detects antibodies to specific serovars, but cross-reactivity occurs between related serovars, particularly within the same serogroup. Thus, an infection with one strain may result in increased MAT titer to multiple serovars. Serum antibody enzyme-linked immunosorbent assay (ELISA) tests have been developed for research but have not yet been adopted in the routine clinical diagnostic setting for animals.[34-37]

An elevated serum antibody titer is observed after the bacteremic phase and is suggestive of *Leptospira* infection when associated with concurrent clinical signs, but interpretation of a single titer is problematic in vaccinated animals or when endemic exposure is suspected.[7,8,30] A fourfold increase in MAT titer between acute and convalescent serum samples, or conversion from a negative titer to a titer of 100 or greater, supports a diagnosis for both host-adapted and non–host-adapted serovars. However, vaccinated animals may have a diminished serologic response after challenge and renal colonization with *L. borgpetersenii* serovar *hardjo*.[38] Serologic detection of persistent infection with serovar *hardjo* can be difficult because paired serum titers may be increasing, static, decreasing, or undetectable at the time of clinical examination (e.g., at abortion).[7,30] Serology is unsuitable for screening individual animals for carrier status because many animals that are chronically infected and shedding may have negative serologic status.[39,40] Considering the serovar with the highest titer as being the infecting strain is generally recommended. However, serologic antibody titers may not accurately predict the infecting strain.[40,41]

Leptospira shedding in urine and semen can be detected by multiple tests, including urine culture, phase-contrast microscopy, darkfield microscopy,

fluorescent antibody (FA), PCR, nucleic acid hybridization, and immunoblot.[8,16,30,31,42-44] Urine cultures are often unrewarding because of the fastidious nature of the organism, and conclusive results may not be obtained for up to 6 months.[8,31] Darkfield microscopy, FA, and PCR assays are typically used by veterinary diagnostic laboratories to identify *Leptospira* species from urine samples. None of these tests will determine the infecting serovar. The sensitivity of detecting *Leptospira* shedding can be improved by performing two tests on a single sample.[31,44] Evaluation of serovar-specific antibody titers from positive animals may aid in identification of the infecting serovar.

Second-voiding urine samples collected after administration of IV furosemide are recommended for urine testing.[11,45] Furosemide is administered at 0.5 to 1.0 mg/kg IV or IM, and the first-voided urine is discarded. A second urine sample is then collected after cleaning the vulva of gross debris. Approximately 10 mL of urine should be collected and stored on ice (not frozen) for transport to the diagnostic laboratory. Urine from 10 to 15 adult animals should be tested when evaluating a herd for endemic *Leptospira* serovar *hardjo* infection.

Biopsy or necropsy samples of renal tissue may be treated with Warthin-Starry or Levaditi silver stains for microscopic examination.[17] Immunoperoxidase staining was shown to be more sensitive for identifying *Leptospira* species in kidney and liver of naturally infected cattle than Levaditi silver stain.[46]

Treatment and Prognosis

Treatment of acute leptospirosis caused by non–host-adapted serovars should focus on eliminating the bacteria, systemic support, and diuresis if renal involvement is observed. In vitro susceptibility has been demonstrated for several antibiotics that could be used in food-producing ruminants, including ampicillin, amoxicillin, penicillin G, erythromycin, tetracycline, tylosin, and tilmicosin.[29,47-49] Daily oxytetracycline (100 mg/mL, 10 mg/kg IV or IM once daily for 5 to 7 days) or long-acting oxytetracycline (20 mg/kg IM or SC every other day for two to four treatments) are considered clinically effective, but controlled clinical studies reporting efficacy in acute leptospirosis have not been reported. Penicillin G procaine (25,000 IU/kg IM twice daily) and sodium ampicillin (20 mg/kg IM twice daily) have been suggested for treatment, but the efficacy of these regimens in cattle remains unproven.[11] In humans, doxycycline (100 mg q12h for 7 days) has been shown to reduce the duration and severity of

illness.[5] Consideration of other antibiotics for treating acute leptospirosis should be based on their efficacy in clearing renal infections with host-adapted *L. borgpetersenii* serovar *hardjo* (see later).

IV or oral fluids may be indicated for systemic support. In animals with severe hemolysis, blood transfusion may be considered. Diuresis should be established in animals with hemoglobinuria or evidence of ARF from hemoglobinuric nephrosis or interstitial nephritis. The prognosis for renal disease caused by leptospirosis is influenced by the virulence of the serovar involved, host immunity, and extent of renal lesions. Cases with renal azotemia warrant a guarded prognosis because more than 75% of nephrons are affected in such cases, and chronic interstitial nephritis and fibrosis may occur after treatment of the acute disease.

Several antibiotics have been shown effective in clearing *Leptospira* spp. renal colonization and shedding in cattle. Long-acting oxytetracycline (20 mg/kg IM or SC, two doses 10 days apart) has been recommended to treat chronic leptospiral infections or reduce the risk of introduction of infected animals into a herd.[3] Oxytetracycline (20 mg/kg IM once), ceftiofur sodium (2.2 mg/kg IM q24h for five treatments), ceftiofur crystalline free acid (6.6 mg/kg SC at the base of the ear once), tilmicosin (10 mg/kg SC once), and tulathromycin (2.5 mg/kg SC once) have been shown effective in clearing renal shedding of *L. borgpetersenii* serovar *hardjo* type hardjobovis from experimentally infected cattle.[50,51] The efficacy of these antibiotic treatments has not been demonstrated in acute infections with other species and serovars of *Leptospira,* but their use could be considered relative to the lack of clinical data showing specific antimicrobial efficacy for treating acute leptospirosis in ruminants and swine.

Prevention

Draining or fencing off standing water may reduce transmission. Maintaining a dry, clean environment may also help reduce exposure and infection. Limiting rodent and wildlife contact with cattle and their feed and water is often difficult to accomplish but reduces the potential for transmission of non–host-adapted leptospires.[7] For host-adapted *Leptospira* serovar *hardjo*, preventing or eliminating the renal carrier state in infected cattle is necessary to reduce transmission.

Vaccination is regarded as an effective means of preventing losses from leptospirosis. Conventional pentavalent (*L. canicola, grippotyphosa, hardjo,*

icterohaemorrhagiae, and *pomona*), whole-cell, inactivated leptospiral vaccines are recommended in calves and adult cattle as an aid to prevent clinical disease caused by *Leptospira* spp. However, these conventional pentavalent vaccines may not consistently prevent renal colonization and shedding after challenge with host-adapted *L. borgpetersenii* serovar *hardjo* type hardjobovis.[52,53]

A monovalent *L. borgpetersenii* serovar *hardjo* type hardjobovis vaccine (Spirovac, Pfizer Animal Health, New York, N.Y.) is licensed for preventing *Leptospira* serovar *hardjo* infection, including reproductive and renal tract colonization and urinary shedding for up to 12 months. This vaccine stimulates an immune response characterized by IgG1 and IgG2 agglutinating antibodies, as well as antigen-specific T-cell production of interferon (IFN)-γ.[38,54-56] The strong IFN-γ response is consistent with induction of a type 1 immune response and may be responsible for antibody class switching to IgG2, which is a more potent opsonin than IgG1.[54] A multivalent vaccine containing *L. borgpetersenii* serovar *hardjo* (Vira Shield 6+VL5HB, Novartis Animal Health, Larchwood, Iowa) has also been shown to prevent renal and reproductive system colonization and decrease shedding in cattle.[57]

Because *Leptospira* species are largely extracellular pathogens, the relevant protective immune response appears to be antibody-mediated neutralization and opsonization during leptospiremia.[1,5] There is no indication that cytotoxic immunity is a relevant immune response for protection or resolution of *Leptospira* infection. However, the exact immunologic mechanism responsible for protection from colonization and shedding of *L. borgpetersenii* serovar *hardjo* type hardjobovis in cattle is not fully understood. Although vaccines help prevent colonization and shedding of *Leptospira* serovar *hardjo* from the kidney, they are not effective in resolving current renal infection and elimination of the carrier state. Thus, vaccination at an early age followed by annual boosters is recommended to prevent initial renal colonization. Renal shedding in previously infected animals can be resolved by antibiotic treatment, and vaccination can be used to prevent future colonization. The efficacy of combined antibiotic and vaccination programs in controlling *L. borgpetersenii serovar hardjo* type hardjobovis infection and reproductive losses at the herd level is not fully established. Combination treatment with oxytetracycline and vaccination with a monovalent *L. borgpetersenii serovar hardjo* type hardjobovis vaccine (Spirovac, Pfizer Animal Health, New York, N.Y.) did result in decreased detection of leptospires in urine and kidney samples from dairy cattle.[58]

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However, one study in beef cattle and one in dairy cattle did not show improvement in herd reproductive performance following similar intervention.[59,60]

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Equine Renal System

Acute Renal Failure

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• CHAPTER 35

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Diseases of the Nervous System

Robert J. Mackay, John R. Middleton, Consulting Editors, Monica Aleman

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Cerebrospinal Fluid

Mary O. Smith • Lisle W. George • John R. Middleton

Cerebrospinal fluid (CSF) is partly derived from and in equilibrium with the extracellular fluid that bathes the brain and spinal cord parenchyma.[1-4] The composition is an indicator of the state of the intrathecal contents. CSF is produced by a combination of ultrafiltration of plasma and active secretion.[5] The sites of CSF production are the choroid plexuses of the lateral, third, and fourth ventricles; the ependymal lining of the ventricular system; the pia arachnoid; and the meningeal blood vessels. The CSF in the ventricular system flows caudally and diffuses out of the lateral apertures in the fourth ventricle. It then circulates around the brain and spinal cord. Circulation of CSF is achieved through regional pressure changes caused by spinal motion and pulsations of blood vessels. CSF is resorbed from both the cranial cavity (75%) and the spinal canal (25%).[6] Some resorption of brain CSF occurs at the arachnoid villi that are near large veins and sinuses, but most resorption occurs at the cribriform plate, into nasal lymphatics.[7,8] Spinal CSF is resorbed into the lymphatic vessels near spinal nerves.

The predominant direction of CSF flow in the spinal canal is cranial to caudal. CSF specimens can be collected from the cisterna magna when the site of interest is the brain, whereas it should be collected from the lumbar subarachnoid space when the lesion is in the spinal cord. In large animals, however, the risks associated with the general anesthesia required for cisterna magna tap are considerable, and so lumbar puncture is usually the most suitable technique for CSF collection in these species, regardless of the site of the lesion.[9,10]

Collection of Cerebrospinal Fluid

Lumbosacral Spinal Tap

For collection of CSF by lumbosacral puncture, the animal is lightly sedated, and the skin of the dorsal midline over the junction of the sixth lumbar (L6) and first sacral (S1) vertebrae is surgically prepared (Fig. 35.1). A variety of standard sedative protocols are suitable; xylazine has been shown to reduce CSF

pressure.[11] Correct placement of the spinal needle is more easily achieved when the animal is standing. The proper anatomic site for insertion of the spinal needle is between the dorsal spinous process of L6 cranially and S1 caudally and the two tuber sacrales laterally. The overlying skin forms a depression that can be revealed by palpation, although this may be difficult in well-muscled animals. The correct site for needle placement can also be determined by locating (1) the dorsal midline at the highest point of the quarters or (2) the point where an imaginary line drawn between the caudal aspects of the two tuber coxae intersects the midline.

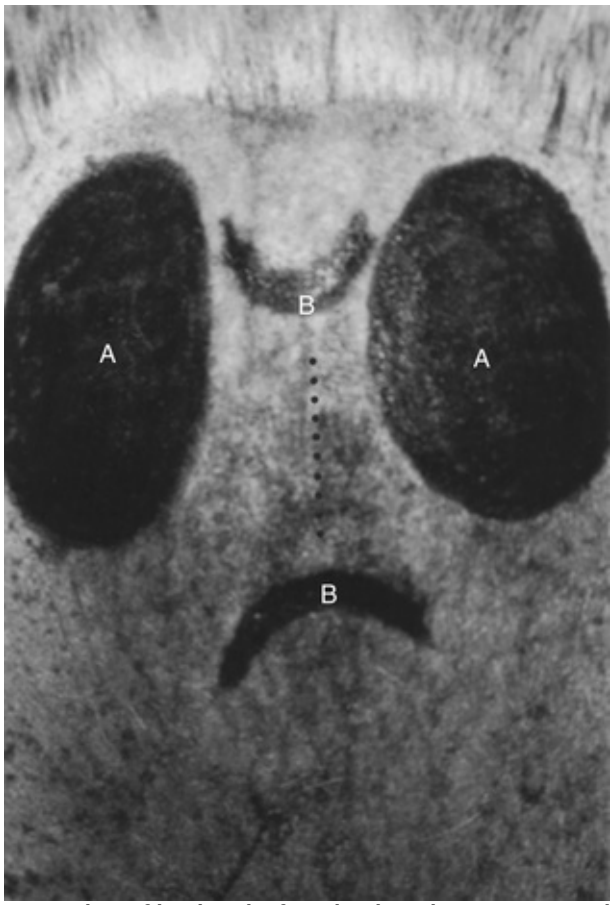


FIG. 35.1 **Close-up view of landmarks for a lumbar cistern puncture in a horse. The large dark ovals *(A)* represent the position of the two tubers sacrale. The smaller curved lines *(B)* represent the respective caudal and cranial aspects of the L6 and S1 dorsal spinal processes. The *dotted line* represents the optimum area for placement of a skin stab.**

The skin is anesthetized with 2% lidocaine, and a 1-cm incision is made with a No. 15 scalpel blade. Alternatively, the skin can be punctured with a 14-gauge

needle and the needle removed or left in place as a guide through which the spinal needle is passed. In adult horses and cattle, a 6- to 9-inch, 18- to 20-gauge spinal needle is inserted perpendicularly through the incision (or 14-gauge needle) and advanced, usually with the stylet seated, until the tip punctures the lumbosacral cistern. For small ruminants, foals, and calves, a 3.5-inch needle can be used. Use of hypodermic needles for CSF collection is discouraged because they have a cutting surface on the end; such a surface is absent on spinal needles. A “snapping” sensation is sometimes felt as the needle passes through the interarcuate ligament. The patient may reflexively contract the tail, anus, and gluteal muscles. Some patients, particularly horses, may respond with violent motor activity. Therefore a lumbosacral spinal tap performed on a conscious horse should be done only when the animal is restrained in stocks. The average depth of insertion is 17.64 cm (7 inches) in adult horses, 8.26 cm (3.3 inches) in ponies,[10] and approximately 7.5 to 10 cm (3 to 4 inches) in adult cattle.

The spinal needle is advanced gently to the floor of the spinal canal. Passage of the needle through the terminal spinal cord or the cauda equina does not cause subsequent neurologic abnormalities. When the needle is seated in the spinal canal, the stylet is removed, and fluid is allowed to drip from the hub into a sterile tube, or gentle negative pressure can be applied to withdraw spinal fluid into a series of 3-mL syringes. If frank blood is obtained, the tip of the needle is probably in one of the ventral vertebral sinuses. The needle should be withdrawn a few millimeters, and a clean syringe should be attached to the hub. Compression of the jugular vein causes engorgement of the ventral vertebral plexus, which increases CSF pressure in the lumbosacral cistern.

Cisterna Magna Tap

General anesthesia is required for a cisterna magna tap. After the patient has been anesthetized, the dorsal area of the neck overlying the atlanto-occipital joint is surgically prepared. The patient's head is held flexed at a right angle to the neck, with the sagittal plane of the head parallel to the floor or table on which the patient is lying. The head must not be allowed to move while the needle is inserted. The needle is inserted 1 to 2 cm caudal to a point, usually 6 to 9 cm (2.5 to 3.5 inches) from the poll (Fig. 35.2), that corresponds to the intersection of the dorsal midline, and a line is drawn between the cranial aspects of the wings of the atlas. A 3.5-inch, 18-gauge spinal needle is inserted perpendicular to the skin and aimed toward the nose. The needle is advanced slowly with the stylet seated. After the needle has been advanced a few millimeters, the stylet is

removed, and the hub of the needle is examined for CSF flow. The stylet is replaced if it is dry and CSF is not spontaneously dripping from the hub, and the needle is advanced another few millimeters and checked again for CSF flow. Entry of the tip of the needle into the cisterna magna may be accompanied by the sensation of “popping” through a tissue plane or by a sudden decrease in resistance to the advancement of the needle. In other cases, no such sensation is perceived; thus CSF flow must be checked every time the needle is advanced a few millimeters.



FIG. 35.2 **View of the ideal area for a cisterna magna cerebrospinal fluid tap in a cow. The two lines *(a)* represent the wings of the atlas. The large spot in the center *(b)* is the optimum area for needle insertion. Use of anesthesia and restraint is essential to prevent head movement.**

In most adult large animals, the needle is seated at approximately 5 to 8.75 cm (2 to 3.5 inches). While the needle is advanced, the heel of the hand should be held firmly against the patient's neck to minimize the possibility of spinal cord injury. The mean depth of insertion is 6.5 cm (2.5 inches) in adult horses[10] and 5 cm (2.25 inches) in adult cattle. In a cisterna magna tap, the needle entry site is close to the cervical spinal cord and brainstem. To minimize the danger of central nervous system (CNS) damage during a cisterna magna tap, the patient should be adequately anesthetized and ventilated because an increase in the partial pressure of carbon dioxide (P_{CO_2}) results in an elevation in intracranial pressure.[12] Removal of fluid from the cisterna magna is contraindicated in a patient with increased intracranial pressure because the brain may herniate

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through the foramen magnum, which could be fatal. Signs of increased CSF pressure include a moderate to marked decrease in mentation, mydriatic pupils, opisthotonos, extensor rigidity, ventrolateral strabismus, and papilledema.

Ultrasonography can be used as an aid to needle placement for collection of CSF from both the atlanto-occipital cistern and the lumbosacral subarachnoid space.[13,14]

Myelography

Contrast material for myelography is injected into the cisterna magna in large animal patients. Withdrawal of CSF before injecting the contrast medium is unnecessary, as is reinjection of CSF after it has been withdrawn. The turnover of CSF is rapid and under strict homeostatic control; therefore withdrawal of CSF through a spinal tap does not have deleterious effects that necessitate its replacement.[15-17]

Analysis of Cerebrospinal Fluid

The color of the CSF should be noted as it flows from the hub of the spinal needle. Blood can originate from the tapping procedure (iatrogenic hemorrhage) or from a traumatic CNS lesion. Iatrogenic hemorrhage is usually unevenly mixed in the CSF and disappears as the fluid drips from the needle. Fluid collected immediately after placement of the spinal needle tends to be mildly contaminated with blood even when this is not apparent grossly. Subsequent aliquots are usually less contaminated, and so the later aliquots are most suitable for cellular and protein analysis.[18] Blood from CNS hemorrhage is evenly mixed with CSF even after a large amount has been removed. Hemorrhage that occurred days earlier may have a brownish rather than red discoloration. Prior hemorrhage also results in *xanthochromia*, a yellow discoloration of the CSF. Xanthochromia can be observed in the CSF for at least 10 days after the introduction of blood. Xanthochromic samples do not contain bilirubin.

The normal values for CSF are presented in Table 35.1. Cell counts should be determined in a noncentrifuged specimen as soon as the sample is collected, with the use of a hemocytometer. Automated methods for counting cells are not suitable for CSF because the low numbers of cells in CSF in comparison with blood result in erroneous counts. Morphologic examination of cells from CSF is most suitable on cytospin preparations in an appropriately equipped laboratory.

Normal CSF from large animals contains fewer than six white blood cells (WBCs) per deciliter; however, WBC counts greater than 40 cells/dL have occasionally been documented in the CSF of normal horses.[19] Although various "correction factors" have been suggested to correct for the effects of iatrogenic blood contamination, they are inaccurate and should not be used.[18,20]

TABLE 35.1

Normal Range of Values in Cerebrospinal Fluid for Large Animals[1,4,5]

Component	Unit	Equine	Bovine	Ovine	Caprine
Specific gravity	1.004-1.008	1.004-1.008	NA	NA	NA
Refractive index	1.3343-1.3349	1.3343-1.3349	NA	NA	NA
Protein	mg/dL	5-100	20-40	8-70	24-40
White blood cells (WBCs)	WBCs/dL	0-6	0-3	0-5	0-7
Glucose	mg/dL	30-70	35-70	48-109	45-87
Sodium	mEq/L	140-150[a]	132-144[a]	145-157[a]	NA
Potassium	mEq/L	2.5-3.5	2.7-3.2	3-3.3	3
Creatine kinase	IU/L	0-8	2-48	NA	NA
Magnesium	mEq/L	NA	1.7-2.7	NA	NA

[a]Cerebrospinal fluid (CSF) sodium level is the same as serum or plasma sodium level when measured with ion-specific electrodes. When other measurements are used, the level of sodium in CSF is usually higher than that in plasma.

NA, Result not available.

The refractive index of normal CSF is less than 1.335. The protein concentration of CSF is less than 50 mg/dL in normal adult ruminants and less than 100 mg/dL in normal horses, although reference values vary with the techniques used for protein measurement. Reference values should be established for each laboratory.[21]

Studies of the specific and relative quantities of albumin and immunoglobulins, particularly immunoglobulins G and M (IgG and IgM), have been stimulated by the increasing importance of immunologic testing of CSF for diseases such as equine protozoal encephalomyelitis. Reference values for a number of parameters have been established.[22] The most important of these parameters are *albumin quotient,* a measure of blood-brain barrier permeability,[23] and *IgG index,* a measure of intrathecal production of IgG.[24] The formulae for these parameters are as follows:

$$\text{Albumin quotient} = (\text{CSF albumin}/\text{Serum albumin}) \times 100$$

$$\text{IgG index} = (\text{CSF IgG}/\text{Serum IgG}) \times (\text{Serum albumin}/\text{CSF albumin})$$

Reference values must be established for each species. An elevated albumin quotient indicates blood-brain barrier leakage or contamination of CSF with blood, with possible introduction of immunoglobulins from serum. An elevated IgG index indicates intrathecal production of IgG and may support a diagnosis of infectious disease of the CNS. The usefulness of these parameters is influenced by a number of other variables, including the immunoreactivity of blood.[24] Therefore clinical interpretations must be made with great caution. The composition of protein from the CSF of horses and cattle has been established.[3-5,10]

The concentrations of glucose and protein in the CSF of newborn foals are almost twice those found in the CSF of adults, but they approximate adult normal values by the age of 2 weeks.[25] In contrast, calves between 1 and 2 months have lower protein concentration and higher leukocyte numbers in CSF than do adult cattle.[26]

Neural tissue contains the BB isoenzyme of creatine kinase (CK-BB), which increases after damage to the nerve cells.[27-29] The molecule does not cross the blood-brain barrier, and so CK in the CSF originates from neural tissue. Contamination of CSF with dura or fat, however, falsely elevates the CK concentration. Some have suggested that CK is an accurate marker and a prognostic indicator of CNS disease, but other studies have not supported this conclusion, and measurement of CK, although interesting, has limited clinical utility.[27,29,30]

The normal concentration of glucose in CSF is approximately 80% of that in blood. A decline in the ratio of CSF to serum glucose occurs in animals with bacterial meningitis because of increased use of glucose by inflammatory cells.

Measuring sodium concentration of the CSF may be helpful for diagnosing salt poisoning in cattle. In animals that do not have salt poisoning, the sodium concentration is less than 160 mmol/L; in animals with salt poisoning, the concentration is usually greater than 160 mmol/L.

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Electrodiagnostic Testing

Monica Aleman, *Consulting Editor*

Neuroelectrodiagnostic medicine is considered an extension of the neurologic examination and comprises several diagnostic techniques for the evaluation of the various components of the nervous, neuromuscular, and muscular systems.[1] Electrodiagnostic testing might assist in the identification, and determination of localization and severity of lesions in certain challenging cases.[1] Although electrodiagnostics might not provide a definitive diagnosis in every case, it aids in the approach, direction, or support of a clinical diagnosis.[2] Depending on the electrodiagnostic technique performed and patient cooperation, some techniques can be done with the patient under intravenous (IV) sedation or general anesthesia. Examples of techniques that can be performed with the patient under IV sedation include electroencephalography, brainstem auditory evoked response (BAER) testing, visual evoked response (VEP) testing (helpful for the study of central blindness), blink reflex testing, electroretinography (ERG; helpful for the study of blindness due to retinal disease), and electromyography (EMG). Techniques that can be performed with the patient under general anesthesia include sensory and motor nerve conduction studies and repetitive nerve stimulation (RNS).[2-10] It is preferable for single-fiber EMG (SF-EMG) to be done with the patient under general anesthesia for more accurate performance and interpretation of results.[2] However, this technique has been performed in awake horses.

Electroencephalography

Electroencephalography is the recording of spontaneous electrical activity (field potentials) of the cerebral cortex. It is the graphic representation of the voltage difference between two locations within the cerebral cortex plotted over time. This primarily represents synaptic activity: excitatory post-synaptic potentials (EPSP) and inhibitory post-synaptic potentials (IPSP) in cortical neurons, mainly pyramidal cells. It has been estimated that approximately a minimum of 108 neurons are needed to produce a detectable change in voltage on the electroencephalogram (EEG). However, electrical activity might be modified by deeper structures such as the brainstem, reticular activating system, and

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thalamus. Thalamic oscillations are transmitted to the cerebral cortex via projection neurons and are thought to be responsible for the slow waves and spindles associated with slow-wave sleep. With regards to electrical activity, ion excitation or inhibition occurs between the intracellular and extracellular spaces when sodium or chloride, respectively, moves intracellularly. The extracellular current is what gives rise to the surface recorded EEG.

Electroencephalography is valuable diagnostic technique for the study of paroxysmal activity (e.g., epileptic discharges), sleep and sleep disorders, alterations in behavior, and detecting abnormal activity such as seizure-like episodes, tremors, and myoclonic activity other than seizures.[11-14] Along with clinical observations, electroencephalography aids in the refinement of epileptic disorders (e.g., localization and classification of paroxysmal discharges within the cerebral cortex).[11] A normal EEG does not rule out the presence of an epileptic disorder; it means only that at the time of recording, abnormal electrical activity was not observed. Alteration in mentation and behavior might be associated with paroxysmal activity, but this is not possible to define unless electroencephalography is performed.[15] The effects of antiseizure medication in the patient can also be evaluated through evaluation of the EEG. Similarly, sleep and sleep disorders can be further investigated and classified on the basis of clinical observations, along with evaluation of the EEG.[16,17] Sleep deprivation is not a sleep disorder; it is simply lack of sleep, whose various causes include sleep disorders.[16,17] Other reports about the use of electroencephalography include the assessment of nociception during surgical procedures and studying the effects of various sedatives and anesthetics on the EEG.[3,18-25] Electroencephalography has also been used in slaughter facilities to monitor brain activity during captive bolt stunning in cattle.[26] The author has used electroencephalography in patient monitoring at the intensive care unit (e.g., for traumatic brain injury, status epilepticus, comatose patients) and euthanasia (i.e., through overdose of intravenous [IV] barbiturates or intrathecal lidocaine during general anesthesia).[27,28] Depth of anesthesia has also been studied with EEG power spectrum analysis in horses.[19,29]

Depending on patient cooperation, goals of the study, and disease process, the EEG can be obtained with the patient in standing sedation or general anesthesia. However, it is recommended that electroencephalography in a horse be performed when the horse is not anesthetized because of the effects of drugs and anesthetics on EEGs.[17] Examples of alterations in the EEG include suppression

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of electroencephalographic activity by anesthetics, transient paroxysmal discharges, and the lack of observation of all states of vigilance. The major disadvantage of performing electroencephalography in a sedated horse is movement artifacts. However, interpretable recordings are possible. Furthermore, the states of vigilance can be evaluated only in a nonanesthetized animal. States of vigilance in the horse as determined through electroencephalography consist of wakefulness, drowsiness, slow-wave sleep, and rapid eye movement (REM) sleep.[17] Automated quantification of electroencephalographic activity in animals have been used. However, a disadvantage of quantitative electroencephalography is that artifacts might be included in the analysis of data, which results in misleading clinical interpretation.

While the EEG is recorded, electro-oculography, electrocardiography, and respiratory monitoring are concurrently performed to distinguish electrical activity by other structures or movement.[17] Furthermore, concurrent performance of electroencephalography, electrocardiography, and respiratory monitoring could be very useful and in some cases diagnostic for the investigation of causes of collapse (e.g., distinguishing syncope from seizures). The author also performs concurrent video recording to further investigate the effects of movement on the EEG in the standing sedated horse.[3,17] Electrode nomenclature and placement are based on a modified human 10-20 system and described in horses previously.[17,30] Two EEG montages have been described in the literature: bipolar and referential.[17] Electrode placement can be rostral to caudal or transverse in a bipolar montage (Fig. 35.3). Needle or surface electrodes are commonly used in veterinary medicine. If surface electrodes are used, the skin in the area of the recording has to be shaved and cleaned for better contact. In contrast, needle electrodes can be placed subcutaneously in the scalp without additional preparation.[17] The author's institution has a protocol for EEG recording, and areas to record include the prefrontal (two electrodes), frontal (three), central (three), parietal (three) and occipital (two) regions (see Fig. 35.3). Concurrently, electro-oculography (two subcutaneous electrodes per eye, one each in the upper and lower eyelids), electromyography (two subcutaneous electrodes in the splenius muscle), and electrocardiography (one subcutaneous electrode in the region of the left-sided heart base and one at the left-sided heart apex) are also performed.[17,30] An additional electrode needs to be placed as the ground (between the two prefrontal electrodes). The author usually records for

30 minutes to 1 hour, except in sleep studies, in which case the electrodes are glued to the scalp and recording lasts several hours.

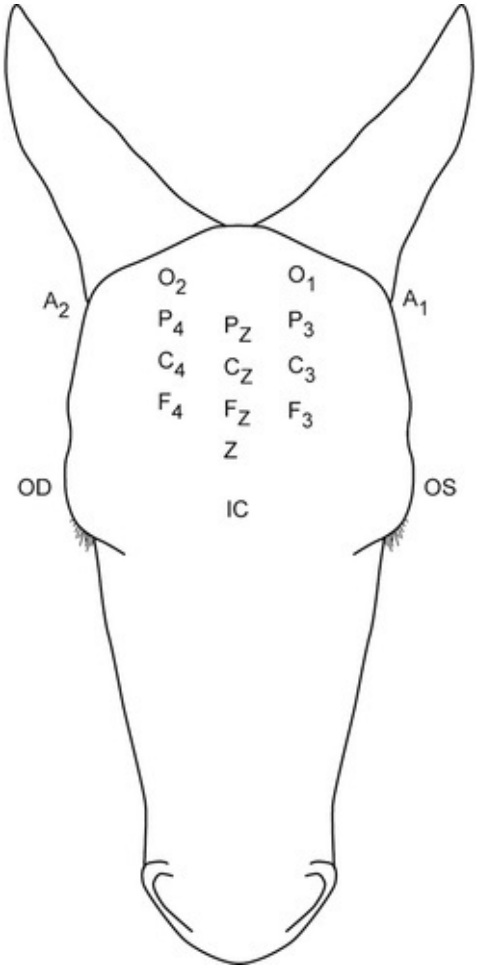


FIG. 35.3 Electrode placement in electroencephalography. *Even numbers* represent the right side; *odd numbers* represent the left side; *A,* aural; *C,* central; *F,* frontal; *FP,* frontopolar; *IC,* intercanthus; *O,* occipital; *OD,* right eye; *OS,* left eye; *P,* parietal; *Z,* ground; subscript *z,* midline. From Aleman M, Gray LC, Williams DC, et al. Juvenile idiopathic epilepsy in Egyptian Arabian foals: 22 cases (1985-2005). *J Vet Intern Med* 2006;20:1443–1449.

The recorded frequencies are confined to a relatively low range (0.5 to 50 Hz), most being below 30 Hz. Waveform frequencies are 0 to less than 4 Hz (delta waves), 4 to less than 8 Hz (theta waves), 8 to less than 13 Hz (alpha waves), 13 to less than 30 Hz (beta waves), and 30 Hz or more (gamma waves; Fig. 35.4). Electroencephalography produces a low-voltage signal: The recorded amplitude

varies from a few to several hundred microvolts, usually less than 100 μV. In contrast, the electrocardiogram is recorded in millivolts (Fig. 35.5). Epileptic discharges are depicted as distinct paroxysmal EEG waveforms that are strongly associated with seizures. Common types include spikes (<70 ms), sharp waves (70 to 200 ms), and spike-and-wave discharges (>200 ms; Fig. 35.6). These discharges can be observed as single or multiple discharges.

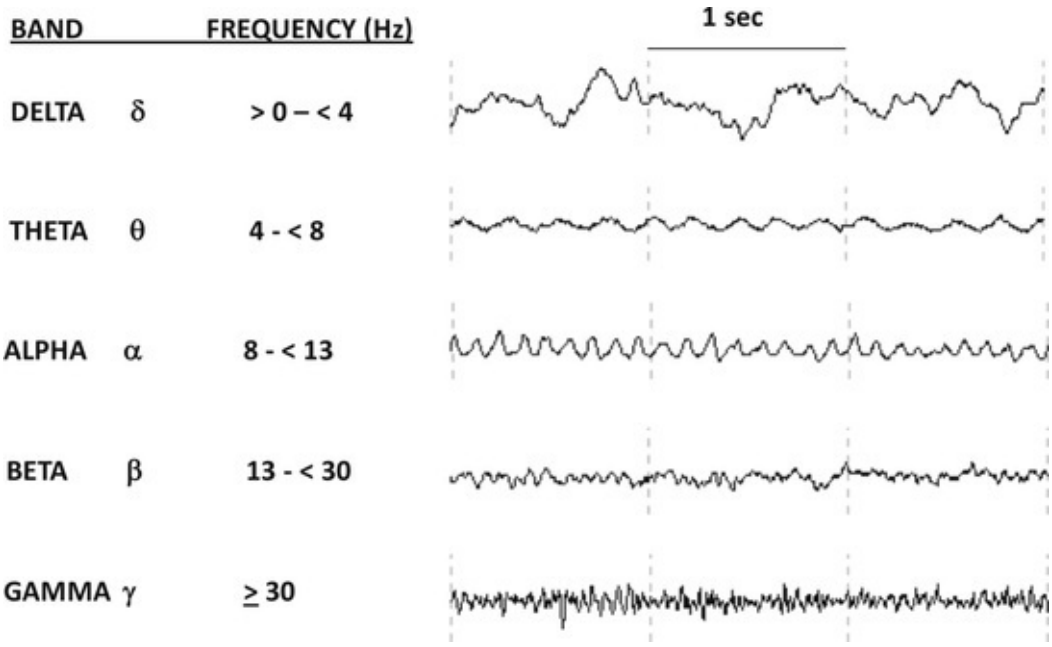


FIG. 35.4 Frequency band definitions and waveforms. (Figure belongs to the Clinical Neuroelectrophysiology Laboratory at the University of California, Davis.)

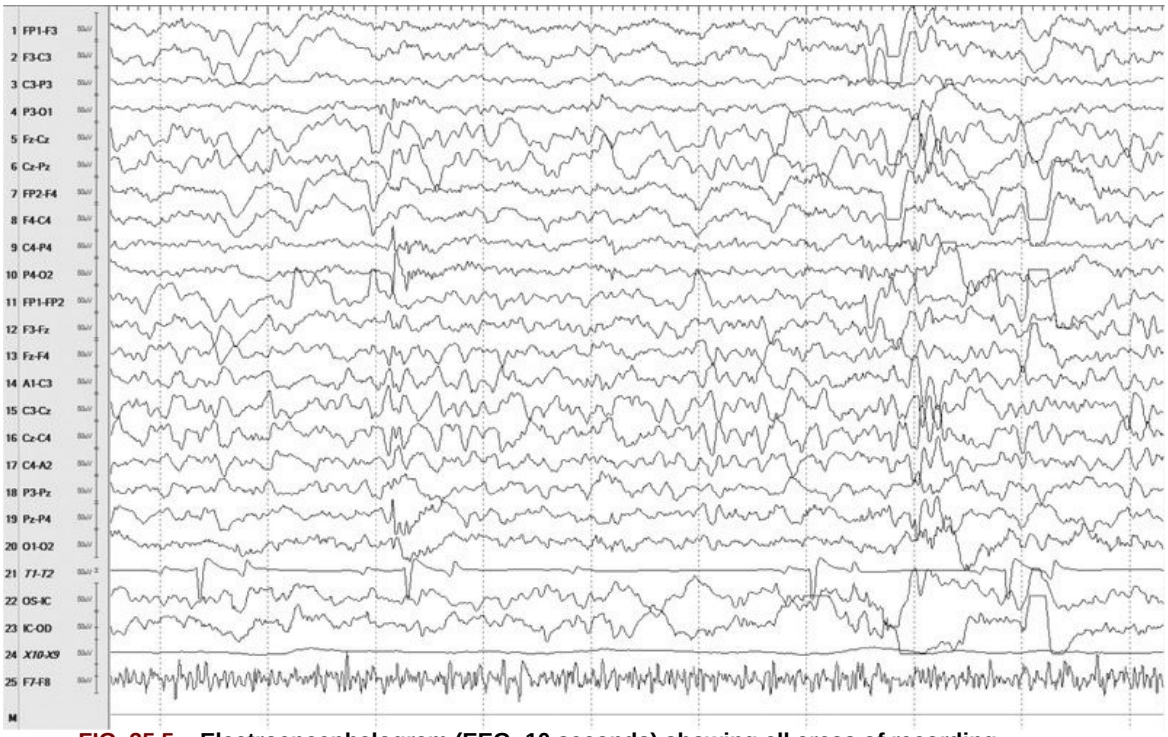


FIG. 35.5 **Electroencephalogram (EEG; 10 seconds) showing all areas of recording. For this figure, channels T1 and T2 recorded the electrocardiogram (ECG), X10 to X9 recorded respirations, and F7 to F8 recorded the electromyogram. Each *horizontal line* represents 1 second, *even numbers* represent the right side, *odd numbers* represent the left side, and subscript *z* represents the midline. Note scale on left in microvolts and difference between the EEG and ECG. Also note atrioventricular block in a horse in slow-wave sleep. *A,* Aural; *C,* central; *F,* frontal; *FP,* frontopolar; *IC,* intercanthus; *O,* occipital; *OD,* right eye; *OS,* left eye; *P,* parietal; *Z,* ground.**

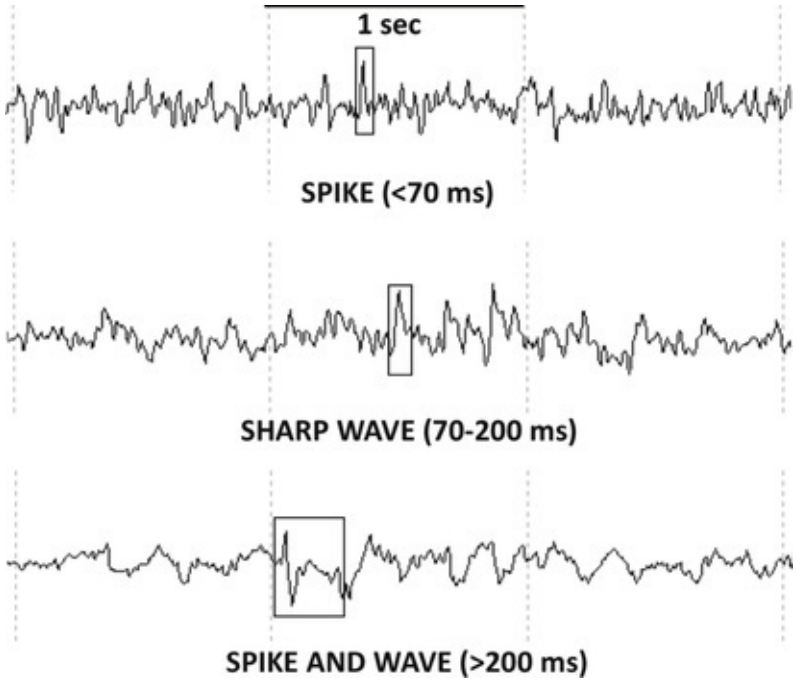


FIG. 35.6 Paroxysmal electrical activity: spike, sharp wave, and spike and wave patterns.

Study of sleep in animals has been based mainly on observation. However, to further understand normal sleep and its variants, as well as abnormal sleep, EEG recording for several hours a day is important.[16] A few indoor studies in some species (e.g., horses) have allowed the staging of phases of vigilance.[16] However, those stages might not represent natural sleep. In wakefulness, fast electroencephalographic activity is observed; however, the transition from wakefulness to drowsiness is not as defined as in humans. In the transition stage, intermittent rhythmic 4-Hz background activity is observed on the EEG.[17] During this period, horses are usually standing. Variants of sleep can occur during this period. Other normal transient events (sleep spindles and K complexes) have been recorded on EEGs from horses and can be used to identify sleep (equivalent to light sleep in humans).[17] The gradual appearance of high-amplitude delta activity, signifying a deeper plane of sleep (human slow-wave sleep [stages 3 and 4]), is similar between species. In horses, the equivalents to stages 2 to 4 of humans can be collectively referred to as slow-wave sleep. Slow-wave sleep can occur while the horse is standing or recumbent. REM sleep in horses has a pattern similar to that in other species: low voltage and mixed frequencies with episodic fast eye movements and loss of EMG activity.[17] This stage of sleep constitutes approximately 15% of the total sleep time in horses.

This stage cannot occur in the standing horse, otherwise the horse would collapse from lack of muscle tone.[16] Horses lie down in lateral recumbency or, if in sternal recumbency, theysupport their heads on the ground or an object.

Auditory Evoked Responses

These consist of the study of early latencies (0 to 10 ms) such as BAER, middle latency (10 to 80 ms), late latency (80 to 250 ms), and long latency (>250 ms).

Brainstem Auditory Evoked Response

BAER testing is performed to evaluate the integrity of the auditory pathway from its peripheral (cochlear nerve) to central (brainstem) components.[31] It is useful in the detection of complete, partial, unilateral or bilateral auditory loss and in the differentiation between conductive and sensorineural auditory loss.[31] In animal species, five distinct waveforms are recognized and represent specific areas in the auditory pathway: the cochlear nerve (wave I), the cochlear nucleus in the medulla (wave II), the olivary nucleus in the medulla (wave III), the lateral lemniscus at the pons (wave IV), and the caudal colliculus in the midbrain (wave V). To better identify the different waveforms, two different derivations have been used in veterinary medicine: vertex to mastoid for large and small animals, vertex to C2 in large animals, and vertex to T1 in small animals.[32,33]

BAER interpretation consists of the evaluation of wave configuration, symmetry (right and left ears), latency, and interval. Clinically relevant amplitude difference includes the ratio of waves V and I (V/I amplitude ratio), whereby a ratio of less than 2 is strongly suggestive of brainstem disease. Reference ranges for the interpretation of BAER have been published for various species and ages.[4,33-35] It is important to note differences in methods such as transducer and derivations (vertex to mastoid versus vertex to C2) used.[33] For example, the use of insert earphones, with stimulus delivery by tubing 25 cm in length, adds an additional 0.9 ms to the recorded latencies of each peak in comparison with headphones with no additional tubing.[4,33] In BAER testing with the horse in standing sedation or general anesthesia, minor latency differences in BAER waves are not significant and therefore not clinically relevant.[4,32,36] Excessive debris or wax can obstruct the conduction of sound during BAER testing, which results in false results of auditory loss.

BAER can vary with age, gender, breed, head size, and skull

thickness.Differences in body temperature can also alter BAER.[31] Evolutionary biological differences between prey and predator species also play a role in how early full hearing develops. For instance, neonatal foals are born with fully developed hearing and wave latencies comparable to those of adult horses, whereas in puppies, it might take a few weeks before a BAER study can be performed with reliable results.[33,37] Table 35.2 lists some causes of wave prolongation.

TABLE 35.2

Brainstem Auditory Evoked Responses (BAER): Possible Causes of Wave Prolongation

Prolonged Wave	Possible Causes
I	External ear disease
	Middle ear disease
	Cochlear disease
	Temporohyoid osteoarthropathy
	Aminoglycosides
I–V Interval	Brainstem disease
I–III Interval	Caudal brainstem disease
III–V Interval	Rostral brainstem disease
V/I Ratio	If <2.5, strongly suggestive of brainstem disease

Causes of hearing loss in adult horses include temporohyoid osteoarthropathy (THO), congenital sensorineural deafness in Paint horses, multifocal brain disease, and otitis media/interna.[31-43] Causes of hearing loss in neonatal foals include congenital sensorineural hearing loss, congenital anomalies (skull deformation), sepsis, neonatal encephalopathy, neonatal isoerythrolysis, and prematurity.[44,45] BAER testing can be used for the investigation of brainstem disease (inflammatory, infectious, vascular), traumatic brain injury, and other brain disorders. BAER testing has also been used to confirm brain death during euthanasia.[27,28]

Electromyography

Electromyography is the study of the electrical activity of the muscle.[38] The distribution of electromyographic abnormalities might aid in the localization of lesions in spinal cord segments (lower motor neurons), nerve plexus, and nerves (Table 35.3).[7,39,40] Quantitative EMG can further assist in classifying disorders

as myopathic, neurogenic, or both.[7,8,41-44] EMG usually does not provide a definitive diagnosis, but the findings might support or refute a clinical diagnosis. For example, myotonic discharges are a hallmark feature of myotonic disorders but do not indicate a specific myotonic disorder (e.g., myotonia congenita versus myotonia dystrophica).[45] Other EMG alterations such as complex repetitive discharges are identified in horses with hyperkalemic periodic paralysis.[46] However, these discharges can be observed in other disorders.

TABLE 35.3

Electrodiagnostic Techniques for the Investigation of Neurogenic, Neuromuscular, and Muscle Disorders

Electrodiagnostics	Disorders
Electromyography (EMG)	
Insertion	
Absent	Advanced or end-stage disease of nonmuscle tissue (fat, fibrous)
Prolonged	Denervated muscle, polymyositis
Spontaneous Activity	
Fibrillation potentials (FP)	Neurogenic, neuromuscular, muscle disease
Positive sharp waves (PSW)	Neurogenic, neuromuscular, muscle disease
Complex repetitive discharges (CRD)	Neurogenic: motor neuron disease; muscle: HYPP, others
Myotonic discharges (MD)	Myotonic disorders: myotonia congenita/dystrophica
Nerve Conduction Velocity (NCV)	
Motor	Various causes: lead toxicity, delayed OP toxicity
Sensory	Various causes: most toxic neuropathies
Repetitive Nerve Stimulation (RNS)	
Decremental CMAP	Myasthenia gravis (humans, small animals)
Decreased baseline CMAP	Botulism
Incremental CMAP (amplitude, AUC)	Botulism, hypermagnesemia (facilitation)
Incremental CMAP (amplitude only)	Nonpathologic (pseudofacilitation)
Mixed/multiple patterns	Organophosphate toxicity
Single-Fiber Electromyography (SF-EMG)	
Increased jitter	Junctionopathies

AUC, Area under the curve; *CMAP,* compound muscle action potential; *HYPP,* hyperkalemic periodic paralysis; *OP,* organophosphate poisoning.

Modified from Aleman M. Neurologic or Neuromuscular Disorders in Horses. Modified from: *Vet Clin N Am Equine* 2011;27:481-506.[2]

Patient preparation for the procedure is better performed in stocks for safety reasons; the restraint provided limits excessive movement. Electromyography can be performed in a standing horse without sedation in some cases. In the author's experience, horses usually react more when distal limb muscles are tested, and sedation may be required. The procedure can also be performed with

the patient under general anesthesia. The author prefers performing the study with the patient under IV sedation.

The study in a standing horse can be diagnostic and provides information about the electrical activity of contracting muscle (electromyography during activity) provoked by the examiner (e.g., making the horse move its limbs or neck, bear more weight on one limb) or of voluntary movement, and possible risks of anesthesia are avoided. The study during controlled or sustained voluntary muscle contraction is routinely performed in awake human patients but not possible in veterinary medicine.[47] Depending on the muscles tested and duration of the study, the examiner may use short- or long-acting sedatives (xylazine hydrochloride, 0.3 to 0.4 mg/kg IV, or detomidine hydrochloride, 0.005 to 0.01 mg/kg IV, respectively).[2] It is important that the area of the muscles to be studied is clean because a needle will be inserted into the muscle and redirected multiple times. The area should be cleaned or washed if necessary. If the area appears clean, the author usually wipes the area with alcohol gauzes until no dirt is visible. Risks associated with electromyography are uncommon or rare and might include infection at the needle insertion site and inadvertent probing of a nerve or nerve terminal. Mild local discomfort might be experienced at the insertion site.

Both insertional and spontaneous EMG activity can be recorded. Insertional activity is the activity related to mechanical stimulation of muscle fibers upon insertion of the electrode into the muscle being tested. This activity should not last more than 1 to 2 seconds in normal animals.[39] Insertional activities that are absent, decreased (low amplitude), increased (high amplitude), or prolonged (long duration) are abnormal. Normal spontaneous activity may be found at the end plate or motor unit region.[39] Spontaneous normal activity includes miniature end plate potentials, end plate spikes, and motor unit action potential (MUAP).[38] The morphologic features (phases, peaks, turns), duration, and amplitude of each MUAP are important for determining abnormality and whether it might be myopathic or neurogenic; for example, giant MUAPs are observed in neurogenic disease.[38,48] Spontaneous activity with neuromuscular disease includes fibrillation potentials, positive sharp waves, complex repetitive discharges, myotonic discharges, and neuromyotonic discharges.[7,40,46,49-51] In acute neuropathic disorders, abnormalities might not be evident on the EMG immediately.[39] It might take approximately 2 weeks to detect alterations in the EMG.[47]

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Nerve Conduction Velocity Studies

Nerve conduction velocity (NCV) studies are performed to evaluate multiple parameters (e.g., amplitude, latency, velocity) of motor and sensory evoked responses to stimulation of nerves (see Table 35.3).[52] To study motor nerve conduction, a nerve must be stimulated during recording from a muscle innervated by that nerve.[2] To study sensory nerve conduction a mixed nerve must be stimulated during recording from a cutaneous nerve.[52] NCV studies aid in the localization of nerve, neuromuscular junction, and muscle disease. Furthermore, they help distinguish between axonal degeneration and demyelination.[52] NCV studies of the facial, radial, median, ulnar, lateral and medial palmar and plantar, sural, and superficial and deep peroneal nerves have been reported in horses and ponies.[6,53-61] These studies should be performed with the animal under general anesthesia for safety reasons, for patient cooperation, to prevent pain in the patient, and to obtain interpretable recordings. Most toxic neuropathies have symmetric clinical manifestations and are predominantly sensory.[62] Acute lead poisoning can cause motor neuropathy, and chronic lead poisoning can cause both sensory and motor neuropathy.[62]

Repetitive Nerve Stimulation

Repetitive nerve stimulation (RNS) is one of the most useful diagnostic techniques for the study of neuromuscular disease (see Table 35.3).[63] A compound muscle action potential (CMAP) or M wave reflects the number of muscle fibers activated by a train of stimuli (repetitive stimulation) applied to a single nerve. The test result is considered abnormal if the number muscle fibers activated during repetitive stimulation (usually 10 consecutive stimuli) decreases.[63] This is called a *decremental response* and is observed in cases of myasthenia gravis.[64] The opposite, an incremental response of the M waves in its amplitude and area under the curve (more muscle fibers activated), is observed in cases of botulism.[5]

Single-Fiber Electromyography

This is a selective EMG study for the study of junctionopathies by allowing the measurement of neuromuscular transmission of single end plates (see Table

35.3).[65] The MUAPs from a single motor unit are recorded over a small area with a concentric EMG electrode. Variations in myofiber end plate potential amplitude and firing threshold result in variations in latency of subsequent action potentials during nerve stimulation.[64] This phenomenon, termed *neuromuscular jitter,* is increased in diseases in which neuromuscular transmission is disturbed.[63,64] This technique has been scarcely used in veterinary medicine.[66-68]

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Diseases Manifesting Principally With Forebrain Dysfunction or Multiple-Level Brain Dysfunction

Alphaviruses

Robert J. MacKay

The causative agents of eastern, western, and Venezuelan equine encephalomyelitis (EEE, WEE, and VEE) are New World arboviruses belonging to the genus *Alphavirus* of the family Togaviridae.[1] Ross River virus is an Old World alphavirus in Australia that was implicated in more than 100 cases of neurologic disease in horses during an outbreak of arboviral encephalitis in 2011 and previously was suspected of causing a syndrome of lethargy, muscle soreness, and ataxia in horses in Victoria and South Australia.[2,3]

EEE, WEE, and VEE affect all common domestic equid species, including horses, mules, and donkeys. Each of the viruses was first isolated during epizootics in the 1930s.[4-6] Alphaviruses are nonsegmented, single-stranded, positive-sense RNA viruses..[7] Each of the three equine alphaviral encephalitides is among the 13 equine infectious diseases that must be reported to the World Organization for Animal Health (Office International des Epizooties [OIE]). Data on the occurrence of these diseases in the United States are collected by veterinarians, diagnostic laboratories, and state animal health officials and are reported to the National Animal Health Reporting System.

At least three strains of the WEE virus antigenic complex have been identified. Two of these are found in both North and South America, which suggests that circulation of WEE viruses between the New World continents is common.[7,8] There is a distinct North American lineage and three South American lineages of the EEE virus antigenic complex.[7] South American strains are now classified as a distinct species, *Madariaga* virus.[9] In contrast to the situation with the WEE virus, there is no evidence of movement of EEE virus between North and South America.

The VEE antigenic complex contains six subtypes, eight varieties, and seven species, most of which are maintained continuously in enzootic life cycles in northern South America.[7,10] Until the 1990s, when a subtype IE variant caused

two outbreaks in Mexico, all equine epizootics had been caused by subtypes IAB and IC.[11]

■ History

Western Equine Encephalomyelitis.

What was almost certainly the first recorded outbreak of WEE in horses occurred in the Great Plains of the United States in 1912, when at least 35,000 horses died of the disease.[5,12] Epizootics in California and other western states in 1930 to 1932 resulted in the deaths of an estimated 9200 horses and mules (≈50% of those affected).[5,13] In 1938, WEE was recognized in every state west of the Mississippi River and affected more than 184,000 horses in that year alone.[1] WEE virus was also implicated in outbreaks of fatal equine disease in the early 20th century in Canada and Argentina, and epizootics have since been reported in western Canada, Mexico, Central America, and South America.[14] Between 1972 and 1981, an annual average of 267 cases of WEE in horses was reported by the National Veterinary Services Laboratory in Ames, Iowa[14,15]; in 1993, there were 15 cases in 10 states, and since 2005, no case has been reported in the United States. There have been isolated cases of encephalomyelitis in Florida horses associated with the Highlands J virus, an eastern member of the WEE virus complex with epidemiologic characteristics similar to those of EEE virus.[16]

Eastern Equine Encephalomyelitis.

An outbreak of what was probably EEE was recorded in 1831 in Massachusetts.[17] Approximately 100 horses were affected, and 75 died. Over the subsequent century, there were at least five other outbreaks characteristic of EEE.[18] An epizootic in 1933 involved a least 1000 horses in the coastal regions of the mid-Atlantic states.[4] Epizootics of EEE in North America have since occurred periodically in the coastal areas of the Atlantic, the southeastern United States, and Texas. In the largest recorded outbreak, in 1947 in southern Louisiana and Texas, 14,344 cases of EEE were recorded and resulted in 11,722 deaths (mortality rate of 82%).[19] Focal outbreaks and sporadic cases have also occurred regularly in Michigan and are occasionally reported from other locations in the eastern half of the United States and Canada. A single case of

EEE in a stallion in California was reported in 2002.[20] Although the origin of the infection in this horse was not determined with certainty, incompletely activated EEE vaccine was suspected. Despite the availability of effective vaccines since the late 1930s, cases of EEE still occur every year in Florida and other southeastern states. The annual incidence of EEE in horses in the United States since 2003 has ranged from 60 (in 2011) to 712 (in 2003).

Epizootics of a mild form of EEE have been widespread in Central and South America, extending southward from Panama to Argentina.[18] More recently, outbreaks with high rates of mortality have occurred in Brazil.[21] The disease has also caused serious losses in the Caribbean.[17]

Venezuelan Equine Encephalitis.

The disease in equids was first recognized and described in Venezuela and Colombia in 1938.[6] At intervals of approximately 10 years, there were large subtype IAB or IC epizootics in northern South America that usually involved tens of thousands of horses. Some of these outbreaks may have been caused by incompletely inactivated vaccine. One epizootic in central Colombia during 1962 to 1964 was estimated to have killed 100,000 horses.[22] An outbreak of VEE caused by subtype IAB began in Peru in the winter of 1969, jumped to Central America in June 1969, and then entered Mexico in 1970. The outbreak spread north to the U.S. border in the spring of 1971, and the first case of VEE in a U.S. horse was confirmed on June 30.[23] By the time of the last case on November 7, 1971, more than 1500 horses had died in the southern counties of Texas. No further epizootic activity was reported until 1992, when a series of epizootics of VEE subtype IC began. Subtype IE has been associated with fatal VEE in Mexico, beginning with small outbreaks in 1993 and 1996.[24]

Epidemiology

Eastern Equine Encephalomyelitis and Western Equine Encephalomyelitis.

In North America, the WEE and EEE viruses are maintained between epizootics by low-level cycling between New World passerine birds (i.e., songbirds) and ornithophilic mosquitoes in freshwater, forested swamp habitats.[1] Snakes may also be an overwintering host for North American EEE virus.[25] Infected mosquitoes can be found throughout the year in Florida and other southeastern

states. Under favorable environmental conditions, the viruses periodically spread outward from focal reservoirs to infect the general wild bird population, through which they are spread and amplified by rapid bird–mosquito–bird transmission. The mosquito vectors involved in maintenance and amplification of WEE and EEE viruses are usually *Culex tarsalis* and *Culiseta melanura,* respectively. Many avian species, including migratory passerine birds (e.g., starlings and northern cardinals) and wading birds, become infected and develop high-order viremia and high serum titers of EEE virus or WEE virus but usually do not become ill. Among some introduced species, including pigeons, house sparrows, Chukar partridges, and Chinese pheasants, infection with EEE virus may cause high rates of morbidity and mortality.

Cases of encephalitis usually begin in susceptible horses 2 to 3 weeks after the virus spreads into birds. Human cases may occur several weeks later. *C. tarsalis* transfers WEE virus from bird to horse (and human). Although *C. melanura* may also function in some locations as a bridge vector for EEE virus, mosquitoes of a variety of other species usually transfer the virus from bird to horse.[7,18] Viremia in horses is low titer, so mosquitoes feeding on horses with either EEE or WEE virus are unlikely to be infected further, and horses are considered “dead-end” hosts. Both EEE and WEE viruses have been associated with neurologic disease in calves, and EEE virus has caused fatal infections in New World camelids, deer, ratite birds, cats, dogs, mice, foxes, sheep, and pigs.[7,26-28]

Epizootics of EEE and WEE usually last 1 to 3 months and occur in summer and early fall when warmth and humidity favor breeding, longevity, and mobility of mosquito populations.[29] Outbreaks in Massachusetts and Michigan probably occurred during the second consecutive year in which rainfall exceeded the annual mean by more than 20 cm; however, unusually high temperatures did not appear to be a risk factor.[29,30] The month in which disease onset peaks varies from June in Florida to August or September in northern and western states.[5,26,31,32] In Florida and some other southeastern states, isolated cases of EEE can occur at any time of year.[31] Standing surface water for mosquito larval development, bush cover for wild hosts, and the immune status of the various hosts also affect the timing and magnitude of equine epizootics.

Many of these physical factors are significantly affected by the cultivation, clearing, and irrigation of land and by drainage of swamps. The proximity and size of plantations of trees were risk factors for EEE for horses in Florida.[33] The equine epizootic usually declines with the onset of cool or dry weather

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unsuitable for mosquito or bird activity, as well as with the depletion of susceptible equine hosts by death or development of immunity among survivors.

The epidemiologic features of EEE and WEE viruses in South America are poorly understood. Small mammals play a greater role in sylvatic cycles of viral transmission in South America than in North America. *Culex (Melanoconion)* subspecies and *Aedes albifasciatus* appear to be involved in transmission of EEE virus and WEE virus, respectively.[8,34]

Venezuelan Equine Encephalomyelitis.

Enzootic VEE viruses are maintained by cycling between mosquitoes and small rodents. The Everglades virus, a subtype II found in the Everglades region of Florida, is of this type, cycling between *Culex (Melanoconion)* subspecies mosquitoes and wild rodents.[10] The epizootic varieties IAB and IC have probably arisen on at least four separate occasions by mutation of enzootic subtype ID strains.[11,35] Because of the high-order viremia that develops in infected animals, the defining characteristic of epizootic VEE virus varieties is that equids serve as amplification hosts. Domestic rabbits, goats, dogs, and sheep also suffer fatal disease during VEE outbreaks.[10] There does not appear to be any single “epizootic” vector mosquito species; during outbreaks, the virus may be isolated from mosquitoes of many different species.[10] Epizootics terminate when susceptible horses are no longer available. The leapfrog-type spread characteristic of VEE is usually attributed to transport of horses incubating the virus. Movement of infected bats may also contribute to discontinuous spread of virus. In contrast to the situation with WEE and EEE viruses, birds do not have an important role in amplification and spread of epizootic VEE virus. It is not yet clear whether neurovirulent subtype IE virus is amplified in horses. Evidence from experimental infections suggests that viral titers in blood of infected horses may be insufficient to infect feeding mosquitoes.[36] The interepizootic reservoir of epizootic varieties, if any, is not known.

■ Clinical Findings

Clinical signs of infection with each of the viruses are similar, although signs of EEE are typically more severe and progress more rapidly than those of VEE and WEE.[4,5,19,20,29,37,38] Infected horses respond in any or even all of the following ways after experimental infections:

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1. Inapparent infection with a very-low-grade viremia and fever approximately 2 days after inoculation. This manifestation corresponds to the initial viremia after viral proliferation in regional lymph nodes and probably occurs commonly during outbreaks without progression to subsequent stages.
2. Generalized febrile illness (up to 41.7° C), with anorexia, depression, tachycardia, and diarrhea. This stage is associated with viral proliferation in various body organs after spread from regional lymph nodes.
3. Clinical encephalomyelitis, which is the classic form of the disease.[39]

Young horses (especially yearlings) are most susceptible: Approximately 90% of 95 horses with EEE admitted to the University of Florida (UF) College of Veterinary Medicine Large Animal Hospital were younger than 5 years of age. The onset of neurologic signs, associated with the second febrile crisis, typically occurs approximately 5 days after infection (range 2 days to 2 weeks), and most deaths occur 2 to 3 days later.[38,39] Almost all horses with EEE are febrile at the onset of neurologic signs (mean of 40.3° C in horses admitted to the UF Large Animal Hospital), although the temperature declines thereafter. The onset of severe neurologic signs is peracute to acute, and progression is rapid. Horses may not be found to be affected until they are recumbent and comatose or dead. If they are observed while alive, initial CNS signs are quite variable and referable to diffuse or multifocal forebrain disease; evidence of brainstem and spinal cord involvement quickly becomes obvious as the illness progresses (Fig. 35.7). Obtundation is the most common initial clinical sign, although owners also report suspected colic as part of the initial presentation.



FIG. 35.7 **Eastern equine encephalomyelitis in an 18-month-old Paint filly. At presentation, the filly was febrile (39.9° C [103.8° F]), stuporous, and cortically blind and had a marked head tilt and body lean to the left, indicative of asymmetric central vestibular dysfunction. Vaccination history was unknown. With nursing care, this filly completely recovered over several weeks.**

Affected horses often stand apart from pasturemates, have no interest in food, or fail to respond to an owner's call. Further signs of dementia may follow, including head pressing, odontoprisis, hyperesthesia, irritability, aggression (rarely), leaning against a wall or fence, or compulsive walking, often in a circle (especially around the inside of a stall or small paddock). Several observers have noted a “peculiar looseness of the lips” as a characteristic early sign.[5,40] Blindness and lack of a menace response may also be noted at this stage. Signs of cranial nerve disease, including abnormal pupillary light reflexes, head tilt, nystagmus, tight circling, facial and tongue paralysis, and inability to swallow often develop as the disease advances. Abnormal signs usually manifest asymmetrically, at least initially. Ataxia and paresis of the trunk and limbs cause gait to become progressively unsteadier. Tremors occur in the antigravity muscles of the limbs. Once recumbent, affected horses seldom regain their footing and are often noted to make galloping or swimming movements in lateral recumbency.[5] Seizures occur in approximately one third of horses with EEE and may happen at any stage. Mucopurulent nasal and ocular discharges and

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abrasions/lacerations of the face and limbs are the most common nonneurologic findings; the latter occurs secondary to trauma from falling, seizures, or running into objects.

Mortality rates are 75% to 95% for EEE, 19% to 50% for WEE, and 19% to 83% for VEE.[5,7,19,34,41] Vaccination within the preceding year was reported to be associated with lower risk of death in horses with EEE.[29,31] Death is usually preceded by a period of recumbency during which the horse may be semicomatose and convulsing. Surviving horses gradually recover over a period of weeks. Many horses with WEE apparently recover completely, but it is estimated that two thirds of horses that survive EEE have residual signs of CNS damage, such as central blindness, dullness, and diminished learning capacity or signs of cranial nerve dysfunction such as facial paralysis and head tilt.[18] Such horses are often referred to as “dummies.”

■ Laboratory Findings

Abnormalities on hemograms and in plasma chemistry panels of horses with alphaviral encephalomyelitis are minor and nonspecific. Horses with EEE may have abnormal WBC counts and high fibrinogen concentration. In 73 horses with EEE admitted to the UF Large Animal Hospital, the following hematologic abnormalities were noted: leukocytosis (56%), neutrophilia (60%), hyperfibrinogenemia (57%), monocytosis (36%), lymphopenia (13%), leukopenia (7%), neutropenia (4%), and lymphocytosis (3%). Mild to moderate elevations in plasma enzyme activities of affected horses either reflect direct organ damage or are secondary to anorexia, fever, stress, recumbency, and seizures. Hyperammonemia is found in some horses with EEE; its significance in horses is unknown but may reflect intestinal or hepatic injury by EEE virus.

The results of CSF analysis for horses with EEE are quite distinctive. More than 95% of horses with EEE admitted to the UF Large Animal Hospital had abnormal CSF cytologic findings. Among patients at the UF Large Animal Hospital, 88% of samples had high protein concentrations (mean of all samples, 139 mg/dL; range, 38 to 526 mg/dL; normal is <60 mg/dL). Nucleated cell counts (normal range, 0 to 6/µL) were high in 87% of samples (mean, 248/µL; range, 0 to 3100/µL); pleocytosis is characterized by high neutrophil concentrations (mean, 46%; range, 0% to 97%). Neutrophils are typically nondegenerate. Protein concentrations and nucleated cell counts are typically higher in samples obtained from the atlantooccipital site than they are in samples

from lumbosacral taps. In the WEE outbreaks of 1930 to 1932, CSF nucleated cell counts were typically 12 to 30/µL, and most cells were lymphocytes.[13]

■ Diagnosis

A clinical diagnosis is usually presumptive, especially in areas where these diseases are prevalent during the mosquito season. The finding in a CSF sample of moderate neutrophilic or lymphocytic pleocytosis further supports a diagnosis of alphaviral encephalomyelitis. Hemagglutination-inhibition, complement fixation, fluorescent antibody, and virus neutralization tests have traditionally been used for serologic diagnosis.[18] IgM antibody capture–ELISA is the method of choice for use in horses with viral encephalomyelitis because titers of greater than 1 : 400 can distinguish vaccination-induced (IgG only) from viral infection–induced (IgM and IgG) antibody responses.[36,42] These assays are available at many state diagnostic laboratories and also at the National Veterinary Services Laboratories (NVSL) in Ames, Iowa. In surviving horses, demonstration of a fourfold or greater rise in hemagglutination-inhibition or plaque-reduction neutralizing titer between acute and convalescent samples provides additional diagnostic support. Positive results of these tests could simply reflect *subclinical* infection with either virus. Virus can be isolated from fresh or frozen (with low efficiency) cultured brain tissue or mice and can be detected in histologic sections with immunohistochemistry or polymerase chain reaction (PCR) techniques.[43]

Differential diagnoses include hepatoencephalopathy; gastrointestinal (GI) hyperammonemia; heavy metal or other toxicosis; rabies; other viral encephalomyelitis (West Nile encephalitis, Borna disease, equine herpesvirus myeloencephalopathy, Aujeszky disease, louping ill); equine protozoal myeloencephalitis (EPM); trypanosomal (South America), verminous, or bacterial meningoencephalomyelitis; space-occupying lesion within the calvaria (e.g., cholesterol granuloma, neoplasia, brain abscess); brain infarction; brain trauma; and leukoencephalomalacia.

■ Treatment

Treatment is largely supportive and, in the case of EEE, usually ineffective. Any adult horse with presumptive EEE that is unable to stand should be euthanized. Such horses should not be subjected to slinging. Hyperthermia is known to exacerbate brain injury and must be treated vigorously with cold water or

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alcohol baths until rectal temperature is less than 102° F. Convulsions can be controlled with diazepam, xylazine, or barbiturates (pentobarbital or phenobarbital).

In addition to receiving excellent general nursing care, all affected horses should be treated for brain edema and inflammation, although only horses with a predominance of forebrain signs are likely to respond. Drugs used for this purpose include dimethyl sulfoxide (DMSO), 1 g/kg as a 10% solution intravenously (IV) or intragastrically; flunixin meglumine (or equivalent nonsteroidal antiinflammatory drug [NSAID]) 1.1 mg/kg q12h for 3 days IV, or orally (PO); dexamethasone (or equivalent corticosteroid), 0.05 to 0.1 mg/kg daily for 3 days IM or IV and then tapered; and mannitol (0.25 to 1 g/kg as a 20% solution IV) or hypertonic saline (e.g., 7.2% saline 2 mL/kg 4 to 6 times IV during the first day). Anecdotal evidence suggests that a lengthy course of dexamethasone is an important determinant of neurologic recovery in surviving cases. Treatment should be titrated to minimize neurologic signs but generally must be tapered over several weeks. Complete recovery, if it occurs, may take several months.

Treatment with serum from horses hyperimmunized against WEE virus was thought to reduce mortality rates modestly during the outbreak in 1930 to 1932; however, these claims were not tested scientifically.[5] Furthermore, administration of large quantities of hyperimmune serum to experimentally infected horses by investigators at Lederle Laboratories was reported to have no beneficial effect.[44]

Adjuvant antiviral therapy with interferon α or β has salutary effects in some experimental models of alphaviral encephalitis and could be tried in valuable horses.[45] A reasonable protocol is described in the section on West Nile encephalitis.

■ Public Health Significance

All three viruses infect humans, causing subclinical, febrile, or neurologic disease.[7] Since 1964, 640 cases of human WEE have been reported in the United States, with annual average of 27 cases in the period up to 1987. Since 1988, however, only five cases of WEE have been reported. In contrast, the 268 cases of EEE in humans reported in the United States since 1964 have occurred at a fairly steady rate of 6 cases per year. Epidemics of VEE are closely associated with equine epizootics; thus during the 1962 to 1964 epizootic in central

Colombia, which killed approximately 100,000 horses, 200,000 humans were infected, of whom 1000 (0.5%) died. The enzootic Everglades subtype II strain, which is nonpathogenic for horses, has caused human encephalitis in Florida. No cases of human disease were recorded during the VEE subtype IE equine epizootics in Mexico in 1993 and 1996, but South American strains of EEE virus have been reported to cause encephalitis in humans. Rates of short-term mortality from EEE, WEE, and VEE in humans are 74%, 4%, and less than 1%, respectively. Most human survivors of EEE suffer long-term neurologic impairment.

■ Postmortem Findings

Most organs exhibit congestion, and the brain and spinal cord have a slate-gray discoloration, often with petechial hemorrhage, obvious especially on sections of formalin-fixed tissue.[43,46,47] Brain swelling and evidence of occipital subtentorial herniation are common, with brainstem compression. Histologic study reveals evidence of acute to subacute and multifocal to diffuse meningoencephalomyelitis. Gray matter is predominantly involved, with diffuse neuronal degeneration, gliosis, perivascular and neuroparenchymal infiltrates, and meningitis. Neutrophils or, on occasion, eosinophils are prominent in acute EEE, whereas lymphocytes predominate in older lesions.[46] Treatment with corticosteroids may suppress the inflammatory cell infiltrates, which then appear mild.

Bronchopneumonia is found in approximately 20% of fatal cases of EEE, probably secondary to pharyngeal paresis and aspiration of particulate material. Up to 10% of horses with EEE have histologic evidence of myocardial necrosis, probably a sign of brain–heart syndrome.[47]

Because high infection rates in humans have been documented after exposure to aerosols from infected laboratory animals or as a result of laboratory accidents (or possibly exposure to equine carcasses), necropsies of horses with suspected VEE should be performed only by personnel who possess demonstrable immunity in the form of neutralizing antibody.[48] All laboratory manipulations must be carried out within certified biological safety cabinets in accordance with physical containment level 3 procedures.

■ Control

Active immunization through use of formalinized vaccines began in 1934 and is

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still the only commercial method of immunization of horses against EEE and WEE viruses. These inactivated vaccines are also used routinely to protect ratites from EEE and WEE and South American camelids from EEE.[49] The attenuated tissue culture–origin vaccine, TC-83, derived from a Trinidad VEE virus isolate, which was originally developed to protect military personnel, provides durable immunity against VEE virus and was effective in minimizing the incursion of VEE into the United States in 1971[23] and in limiting the 1993 and 1996 outbreaks in Mexico. Although TC-83 is no longer licensed for use in horses in the United States, a formalin-inactivated vaccine containing the TC-83 vaccine strain is available and is often included with EEE virus and WEE virus in trivalent products.[50] For any of the formalin-inactivated alphavirus vaccines, adult horses should be given an initial two inoculations 4 to 6 weeks apart at least a month before the anticipated risk period or before the onset of vector mosquito activity and then revaccinated at intervals when the risk is likely to be higher. Vaccination should begin in January or February in Florida and in May or June in parts of Canada and the northern United States. Clinical evidence suggests that vaccination against EEE virus or WEE virus provides less than 6 months of protection, and so revaccination at least once during the mosquito season is necessary in areas with warm climates and long mosquito seasons. Vaccinated mares should receive a booster dose 4 to 6 weeks before foaling to provide colostral antibody for newborn foals.

Foals should be given an initial inoculation at 4 to 6 months (if the dam has been vaccinated) or 3 to 4 months (if either the dam is unvaccinated or the vaccination history is unknown) and then a second inoculation 4 to 6 weeks later and a booster at 10 to 12 months of age. The American Association of Equine Practitioners (AAEP) recommends that foals of vaccinated dams in high-risk areas be given a primary series of four doses beginning at 2 to 3 months of age. Two additional inoculations are then given at approximately 4-week intervals and a booster at 10 to 12 months of age, before the onset of mosquito season.

Routine surveillance of the virus pool by serum antibody testing of sentinel chickens and virus detection in trapped mosquitoes by health authorities often reveals early warning of an impending outbreak and allows time for vaccination of susceptible horses. General mosquito control (removal of standing water, spraying by local authorities) will reduce risk of EEE and VEE in horses.[29] Because of the role of horses in amplification and transmission of VEE virus, quarantine of infected and exposed horses with area-wide and international restrictions on horse movement is an integral part of the management of VEE

epizootics.[51]

Miscellaneous and Foreign Emerging Viruses Causing Neurologic Signs

Robert J. MacKay

Since the encroachment of West Nile virus (WNV) in 1999 into North America, the potential for emerging foreign disease with widespread effect has been realized. Given the opportunity, many other viral infections could become established in previously unaffected countries as a result of the globalization of the horse industries and effects of global climate change.

Getah/Ross River Viruses

The Semliki Forest complex of the Togaviridae is widespread throughout its geographic range, either in the Orient (Getah virus) or South Pacific (Ross River virus). Although closely related, these viruses have little geographic overlap. Like the North American alphaviruses, these viruses are transmitted by mosquitoes. The reservoir for Getah virus is not known, although swine appear important in its transmission to mosquitoes.[1] Important reservoirs for Ross River virus are marsupials.[2] Getah virus infection may be transmitted by horses, but this is unlikely to occur with Ross River virus. Seroprevalence in horses varies from less than 10% to more than 90%.[3-5] Ross River virus infection is endemic in horses and widespread; seroprevalence among Australian horses ranges from 50% to 80%.[6,7]

Clinical signs of Getah virus infection include fever, edema of the limbs, and urticaria over a course of 7 to 10 days.[3,5] Horses infected with Ross River virus may develop fever, lameness, swollen joints, inappetence, generalized stiffness, and even colic.[8] Of the horses in which viral encephalitis cases were diagnosed during the 2011 Australian outbreak, more than 100 were seropositive for Ross River virus; however, detailed description of these cases has not yet been published.[7] Getah virus and Ross River virus infections are diagnosed serologically or by reverse transcription polymerase chain reaction (RT-PCR) testing of blood samples. Treatment is supportive. A vaccine for Getah virus is available in Japan. An inactivated vaccine against Ross River virus for humans is being tested in Australia, but no equine vaccine is available.[9]

Borna Disease

Classical Borna disease is a viral encephalitis principally of horses and sheep that was first recognized in southwestern Germany in the eighteenth century but is associated with the village of Borna in the Kingdom of Saxony, where the disease emerged in the late nineteenth century. It is estimated that approximately 16,000 horses in Saxony died of this disease annually from 1896 to 1940.[10] These numbers declined rapidly in the 1960s in parallel with declining horse numbers, and only 1216 horses died of classical Borna disease in Saxony from 1958 to 1991.[10] Outbreaks of classical Borna disease have been restricted to central Europe in the upper Rhine valley in Switzerland, Austria, and Liechtenstein. Borna disease virus–associated encephalitis has also been reported in humans, cattle, an alpaca, deer, zoo herbivores, cats, rabbits, and dogs.[11] Since the 1990s, evidence of Borna disease virus infection—including antibodies, antigen, RNA, or the virus itself—has been reported in many countries and in numerous mammalian species, including humans. There is serologic evidence of Borna disease virus infection in horses in the United States.[12,13] Some of these reports are questionable because of problems with contamination of samples by laboratory Borna disease virus strains and poorly validated immunoassays; however, there have been enough well-documented infections to confirm that Borna disease virus or Borna disease virus–like viruses are widespread.[14] It is possible that Borna disease virus is involved in several human neuropsychiatric diseases, but evidence is lacking.

Borna disease virus 1 (BoDV-1), the etiologic agent of classical Borna disease, is a nonsegmented, negative-sense, single-stranded RNA virus of the order Mononegavirales, family Bornaviridae. For many years BoDV-1 was the only known member of Bornaviridae, but since 2005, at least five additional species have been identified, and endogenized BoDV-1 sequences are common in the genomes of mammals.[11] The significance of this last intriguing finding is unknown.

Most outbreaks in horses and sheep occur during the spring and early summer. Although horse-to-horse transmission is theoretically possible, it is unimportant in the evolution of an outbreak.[14] The virus is probably maintained in small mammals with geographic ranges approximating the endemic Borna disease area. The bicolored white-toothed shrew is an important reservoir host in endemic areas.[15] BoDV-1 is shed through nasal and lacrimal secretions and in the urine of infected animals.[14,16] BoDV-1 is resistant to drying and other

adverse environmental conditions. It is assumed that BoDV-1 enters the horse though intranasal infection and migrates to the brain transaxonally.[17] Direct replication occurs in neurons and glial cells, with centrifugal spread to peripheral nerves and retina. BoDV-1 infection of the retina may contribute to the blindness that characterizes acute Borna disease in horses.[18] Subclinical BoDV-1 infection is common; in endemic areas, seroprevalence among horses ranges from 10% to 20%, and it is as high as 50% among stablemates of horses with Borna disease. In subclinically infected horses and in horses that recover from Borna disease, the virus becomes quiescent and largely undetected by the immune system.

The clinical signs of Borna disease in large animals are similar to those of the other equine encephalitides. The incubation period is 4 weeks to 3 months. There is a predominance of forebrain signs initially, followed by signs of brainstem and spinal cord involvement. In moderate to severe cases, horse die 1 to 4 weeks after onset of signs. In mild cases, horses can recover, but abnormalities and exacerbations commonly persist. The prodrome is characterized by fever, inappetence, colic, and vague behavioral changes. The onset of neurologic signs is marked by changes in mentation with alternating hyperresponsiveness and stupor; compulsive walking, often in circles; odontoprisis; and aggression. Other signs of brain disease include trismus, pupil constriction, nystagmus, head tilt, and blindness. With progression, ataxia and weakness of the limbs and trunk occur, and areas of cutaneous desensitization or hyperesthesia develop. Collapse into recumbency and seizures constitutes the final stage. The mortality rates are approximately 80% among affected horses and 50% among affected sheep. Up to 10% of affected horses develop a chronic relapsing form of the disease and may become persistently infected carriers.

For antemortem diagnosis, antibodies to the agent may be found in the serum and CSF of most infected animals by ELISA, indirect fluorescent antibody test (IFAT), and Western blot.[15] CSF analysis often reveals mononuclear pleocytosis and high protein concentration. RT-PCR techniques have demonstrated virus in the CSF and peripheral mononuclear cells.[19] The criteria for diagnosis in a horse with neurologic abnormalities include positivity for BoDV-1 antibodies in serum or CSF and characteristic histopathologic changes.

Pathologic abnormalities resemble those of a viral encephalomyelitis, and the diagnosis is confirmed by immunohistochemistry, virus isolation, and detection of viral nucleic acids.[14,15,20-24] The characteristic microscopic lesion of Borna disease is Joest-Degen inclusion bodies in the neuronal nucleus, but these are not

always observed. Virus is detectable easily with monoclonal or polyclonal antibody tests. Histopathologic changes are those of a typical polioencephalomyelitis, with a particular loss of neurons in the hippocampus. The gray matter of the olfactory bulb, basal cortex, caudate nucleus, thalamus, hippocampus, and medulla oblongata is involved.

No antiviral agents are available for the treatment of BoDV-1 infection, and use of amantadine sulfate (developed for treatment of influenza infection) is controversial but common.[25,26] Likewise, vaccination as a protective strategy is controversial. It is widely assumed that a modified live vaccine would offer more protection; however, the live vaccine available until the early 1990s in East Germany was removed from the market because of questionable efficacy.

Henipavirus

Hendra virus (HeV) is one of two *Henipavirus* species. HeV infection of horses was first recognized in 1994 during simultaneous outbreaks of severe respiratory disease in Queensland, Australia: one in the Hendra suburb of Brisbane and the other near the town of Mackay. Of 22 affected horses, 14 died, and each outbreak was associated with transmission to humans, one of whom died.[27] As of 2015, there had been almost 50 outbreaks of HeV infection in horses, all but one in coastal Queensland and New South Wales. Five outbreaks also involved seven human cases, of which four were fatal. Although horses in the original outbreaks showed signs of fulminant febrile respiratory disease, neurologic signs dominated the clinical presentation in five horses in an unusual outbreak at an equine referral practice in the Redlands suburb of Brisbane in 2008. The illness was characterized by severe obtundation, dementia, head tilt, and progressive ataxia. More recently, the respiratory syndrome has been the typical presentation of horses with HeV infection; neurologic signs are observed only occasionally.

HeV replicates initially in the respiratory epithelium before spreading hematogenously to multiple organs, including the CNS, to cause widespread vasculitis, endothelial syncytia, vascular thrombosis and hemorrhage, and cellular necrosis.

Nipah virus (NiV), the other species of *Henipavirus*, emerged as the cause of porcine respiratory and encephalitis syndrome in Malaya in 1998.[28-30] Signs were predominantly respiratory, and most affected pigs recovered. NiV also caused severe febrile encephalitic illness among workers in contact with infected pigs; of 265 affected people, 105 died. NiV or Nipah-like virus has also been

implicated in an outbreak of fatal encephalitis in a group of horses in the Philippines.[31] Deaths also occurred in humans, dogs, and cats that consumed meat from the dead animals.

HeV and NiV are closely related viruses; the genus, *Henipavirus,* belongs to the family Paramyxoviridae. They are enveloped, single-stranded, negative-sense RNA viruses. The henipaviruses are highly pathogenic for a wide range of mammals, including horses, pigs, and humans. The natural reservoirs throughout the geographic range (Northern Australia, Malaysia, and Bangladesh) are fruit bats from the genus *Pteropus* (also known as *flying foxes*).[32] In each spillover event, the virus is probably transmitted to horses through contact with the urine or reproductive fluids of infected bats. During the incubation period in horses, HeV is infectious to other horses and to humans for at least 48 hours before the onset of clinical signs, and at least two outbreaks in stables were caused by introduction of horses that were incubating the virus before manifesting the disease. Virus is secreted in all body fluids and feces of infected horses, and appropriate precautions must be taken to prevent transmission to other horses and humans.

The disease is diagnosed both serologically by ELISA or neutralization test and by detection of RNA by RT-PCR in blood, other body fluids, or tissues taken at necropsy.[30,33]

Infected horses are euthanized as a matter of public health. Ribavirin has been used with partial success to treat NiV and HeV infections of humans, and a monoclonal antibody (m102.4) has been shown to be protective in experimental animals if given before clinical signs are manifested and has been used in several exposed humans.[34] An HeV subunit vaccine (HeV-sG) has been tested successfully in multiple species, including horses, against both HeV and NiV challenge and was launched commercially in Australia in 2013 for vaccination of horses in endemic areas (EquiVac HeV, Pfizer Animal Health).[34]

Bunyaviridae

The Bunyaviridae are mostly arboviruses and are found worldwide. These viruses are usually maintained in mosquito–vertebrate host–mosquito cycles, whereby midges act as the arthropod hosts for a few viruses.[35] Twelve serotypes, known collectively as the *California serogroup,* have been isolated in North America, South America, Africa, Europe, and Asia. In rare cases, these viruses can cause acute encephalitis in horses. Snowshoe hare, Main Drain, and

Bunyamwera viruses have been associated with encephalitis in horses,[36-38] and serologic evidence of subclinical infections with Jamestown Canyon virus and Cache Valley virus have been found in horses in the United States.[39,40] Clinical signs in a horse from which Main Drain virus was isolated included ataxia, weakness, stiff neck, head pressing, dysphagia, tachycardia, and fever.[37]

Equine Encephalosis

Equine encephalosis is an arthropod-borne viral infection, affecting all species of equids, and is characterized usually by mild or subclinical infection but occasionally by severe clinical disease.[41] The causal agent, equine encephalosis virus (EEV), is transmitted through the bites of certain *Culicoides* spp. biting midges. EEV is an orbivirus, as are African horse sickness virus and bluetongue virus. All equids (horses, donkeys, zebras) are susceptible to EEV, although donkeys and zebras are thought to be resistant to the clinical disease. The infection is endemic in southern Africa, where seven EEV serotypes have been identified.[42] An outbreak of febrile disease due to EEV in Israel in 2008 and 2009 involved 60 horses, and serologic evidence of the infection has since been found in several other areas outside southern Africa.[43,44]

The virus was originally named for isolation from a horse with typical signs of encephalitis, including mild to severe ataxia, reluctance to walk, stiffness, dementia, and seizures.[41] In its current forms, infections are either subclinical or associated with an influenza-like syndrome of fever, edema, tachycardia, tachypnea, and congested mucosae. An African horse sickness–like syndrome of respiratory distress and cardiac failure has been described, and pregnant horses may abort. A competitive ELISA for detection of group-specific antibody to EEV has been described for use in diagnosis.[45] There is no recognized treatment for EEV infection or method of prevention.

West Nile and Other Flavivirus Encephalitis

Robert J. MacKay

The causative agent of West Nile encephalitis (WNE) is a small, positive-sense, single-stranded, enveloped RNA virus,[1] West Nile virus (WNV), which is a member of the Japanese B encephalitis antigenic complex of neuroinvasive arboviruses within the genus *Flavivirus,* family Togaviridae.[1] In addition to WNE virus, Kunjin, Japanese B encephalitis, and Murray Valley encephalitis

viruses are members of the Japanese B encephalitis antigenic complex that have caused encephalomyelitis in horses outside the United States. WNV has seven genetic lineages; two of these, lineages 1 and 2, have caused neuroinvasive equine (and human) infections.[2] Outbreaks of neuroinvasive disease in horses and humans have traditionally been associated with lineage 1 isolates that circulate among the Mediterranean basin, West African, and northern European countries. A virus of this lineage is responsible for the North American epizootic. Lineage 2 isolates are widespread in sub-Saharan Africa and commonly have infected horses without apparent clinical effect. Since 2005, the number of cases has been increasing, and several outbreaks of neurovirulent equine and human disease have been caused by lineage 2 WNV in Africa and Europe.[2,3]

The Kunjin virus is a lineage 1 WNE virus that traditionally has caused mostly subclinical or febrile nonneurologic disease in horses and humans in northwestern Australia and Papua New Guinea. A neurovirulent strain of Kunjin virus emerged in New South Wales in Australia in the late summer and fall of 2011 and caused encephalitis in at least 1000 horses in southeastern Australian states, with mortality rates of 10% to 15%.[4,5] This unprecedented epizootic of Kunjin encephalitis (and also of encephalitis due to the arboviruses Ross River virus and Murray Valley encephalitis virus) followed unusually heavy spring rainfalls in southeastern Australia.[4] There is evidence that the 2011 outbreak probably resulted from a complex interplay among novel genetic virulence determinants and unusual ecologic and epidemiologic conditions.[5] Since the Murray Valley encephalitis epizootic in 1974, cases had been reported only sporadically.[6] Japanese B encephalitis virus is endemic in east Asia and southeast Asia and has made incursions into the northern tip of Australia.[7] It is maintained in cycles among porcine and avian reservoirs through mosquito hosts. Humans and horses are dead-end hosts. Cases of encephalitis in horses occur sporadically throughout the virus's range, and effective vaccines are available. Although the geographic ranges of WNV and Japanese B encephalitis overlap minimally, diagnostic serologic testing may yield confusing results in areas where both diseases (and vaccinations) do occur. Louping ill, Powassan, and tick-borne encepahlitis viruses are tick-borne flaviviruses that have the potential to cause encephalitis in horses.[1]

■ History and Distribution

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WNV was originally isolated from the blood of a febrile woman in the West Nile region of Uganda in 1937. Cases of WNE in humans were first recorded in Israel in the 1950s, and cases in horses were recorded in Egypt and France between 1960 and 1965.[8,9] Since 1996, cases have been sporadic, and outbreaks of equine WNE have been small and localized in numerous countries in the Mediterranean basin and northern Europe. These incursions of lineage 1 and, more recently, lineage 2 WNV continue to expand in number and geographic range.[10] It is now clear that WNV has become enzootic in several locations in Europe.

In August 1999, the first case of WNE in humans was reported in Queens, New York. Characterization of the virus from this outbreak showed it was highly homologous with Israel 1998 (Is98), a strain of WNV that had originally been isolated from a goose.[11] Ultimately, 62 cases occurred in humans in 1999, with 7 mortalities. From August to October 1999, 25 horses on Long Island were diagnosed with WNE; 9 of these horses died.[12] Deaths occurred in numerous native bird species, particularly in corvids (crows, ravens, jays) and in exotic species housed at the Bronx zoo. In 2001 the disease became a national epizootic; cases occurred for the first time in Florida, Kentucky, Louisiana, Georgia, Alabama, Illinois, Indiana, Mississippi, New Hampshire, North Carolina, Tennessee, and Virginia.[13] There were 738 cases reported nationally, of which 33.2% died or were euthanized. Despite the availability of an effective vaccine from August 2001 onward, there was a dramatic westward spread of WNE in 2002, with 15,257 horses affected in 40 states. The national incidence of the disease in horses declined in 2003 to 5181 cases in 44 states. By 2006, equine cases had been reported from all 48 contiguous states. Total annual cases dropped below 1000 in 2007, and only 79 were reported in 2011. In 2012 there was an upswing in WNE in all parts of the country with a total of 627 cases, of which 120 were in Texas. This upswing was attributed to unusual climatic conditions and not to the emergence of a more virulent strain of WNV. From 2013 to 2016, equine WNE cases in the United States averaged 280 annually.

Equine or human WNE or both have been reported in multiple Canadian provinces, and there is serologic evidence of WNV in the Caribbean and Latin America.[1]

■ Natural History

WNV cycles between ornithophilic mosquito vectors and avian reservoir hosts. In temperate climates, the virus overwinters by long-term infection of

hibernating vector mosquitoes, followed by vertical (transovarial) transmission and possibly by latent infection of avian hosts.[14] *Culex* spp. are the most important vectors for the North American epizootic in birds. Different species transmit the virus in different parts of the country. Major vector species include *Culex pipiens* in the northeast and central United States, *C. tarsalis* from the far western United States to the panhandle of Texas, and *Culex quinquefasciatus* in the southeastern United States from Texas to Florida. Although birds of more than 300 species have been reported to be WNV-positive, passerine (true perching bird) and charadriiform (shorebird) species are considered the most competent reservoir hosts for WNV in the United States. Corvid species such as crows and blue jays are efficient hosts, but their mortality rates were high during the North American epizootic. The house sparrow (an Old World passerine species) also develops high-titer viremia after WNV infection but is relatively resistant to the adverse effects of the virus. Various domestic mammals, including sheep, alpacas, and dogs, suffered fatal WNE during the North American epizootic.[1,15] Horses, humans, and other mammals are "dead-end" hosts and do not amplify the virus in quantities sufficient to infect mosquitoes. In contrast, alligators exhibit high-titer viremia and may be important reservoirs for infection in the southeastern states.

"Bridge vector" species of mosquito transmit the virus from birds to mammals, including horses. The mosquito species important for bird–horse transmission are not known with certainty but may include members of *C. pipiens* complex, *C. tarsalis,* and *Culex salinarus.*

The occurrence of WNE reflects vector mosquito activity, which is seasonal in temperate zones and year-round in tropical and subtropical regions. Significant viral activity begins in July, and the incidence peaks in September and October. The epizootic usually declines rapidly after the first frost.

■ Clinical Signs

Experimental infections in horses result in viremia 3 to 5 days after viral inoculation into the CSF, and clinical signs begin at 7 to 10 days.[14] Experience during clinical outbreaks indicates a similar 1- to 2-week incubation period before signs of WNE are manifested.

Clinical signs have been extremely varied; however, surveys of cases published across the United States and from Europe have revealed some consistent combinations of signs.[8,12,16-20] Approximately 25% of affected horses

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have had mild to moderate fever at the time of initial examination, although it is likely that most were febrile before examination. Consensus neurologic signs in 726 cases from the northeastern United States, Florida, Indiana, Nebraska, and Colorado[8,12,16-20] have included limb ataxia (71%), limb weakness (58%), muzzle twitching (45%), obtundation (43%), recumbency (31%), lip droop (22%), hyperresponsiveness/hyperesthesia (18%), odontoprisis (12%), dog-sitting posture (10%), thoracic limb collapse (7%), compulsive walking (7%), muscle atrophy (6%), seizure (4%), blindness (4%), circling (4%), and head pressing (3%). Clinical signs reflect the reported predominance of lesions in the gray matter of the hindbrain and spinal cord of horses with WNE, with lesser involvement of the rostral brainstem and forebrain.[21]

The observation of coarse twitching of the muzzle (and, to a lesser extent, the eyelids) is a particularly distinctive finding in acute cases of WNE. Less frequent are fine fasciculations of the cutaneous muscles of the torso and neck. Horses acutely affected may be frantic, fearful, and hyperresponsive to stimuli. This stage is transient (usually <1 day in duration) and typically is the only behavioral change observed. Mild obtundation is common at initial presentation and progresses to stupor with narcoleptic episodes in horses with severe midbrain or hindbrain involvement. In addition, such horses often have facial or tongue paralysis, or both, or vestibular signs of head tilt and body lean. Ataxia and weakness of the trunk and limbs occur with or without signs of brain disease and may manifest asymmetrically. Such manifestations are clinically indistinguishable from those of horses with EPM. Because of the predilection of WNV for gray matter in thoracic spinal cord segments, horses may present with the unusual combination of acute-onset bilateral thoracic limb weakness/collapse and normal pelvic limb strength (Fig. 35.8). Severely affected horses are often unable to roll from lateral to sternal recumbency and tend to lie quietly without much voluntary activity. Comparable presentations in human patients with paralytic forms of WNE are described as “polio-like.”[22] With time, muscles of the thoracic girdle can become severely atrophied, and such horses are rendered permanently unable to move from lateral to sternal recumbency even though they may be able to walk once assisted to stand. The convalescent stage of WNE is described later in the Treatment section.



FIG. 35.8 **West Nile encephalomyelitis in a 3-year-old Thoroughbred gelding with involvement of the gray matter of the spinal cord supplying the thoracic limbs. During the first 5 days after onset, the gelding's thoracic limbs frequently buckled, and he collapsed into this position for several minutes before regaining his feet. Pelvic limb strength was normal.**

Published mortality rates during the U.S. epizootic ranged from 22% to 44%. Among 2326 reported cases from across the United States, including national statistics for the years 1999 to 2001, the overall mortality rate was 31%. Surprisingly, death rates were relatively high (43%) among the 1050 cases reported from California during 2004 to 2006. A history of no or incomplete vaccination, persistent recumbency or difficulty standing, paresis of pelvic limbs, and facial or tongue paralysis was associated with poor outcome, and mortality rose with increasing age after the age of 5 years.[17,18,20] In one study, affected females were 2.9 times more likely to die than were affected males.[18]

■ Laboratory Findings

Abnormalities found in hemograms and serum/plasma chemistry results are usually mild and nonspecific. Of 46 horses with acute WNE admitted to the UF Large Animal Hospital, the most common abnormalities were lymphopenia (23%), hyperbilirubinemia (72%), and high plasma creatinine concentration (8%).[17] Hypokalemia, hyponatremia, and hypochloremia were also common, as were high muscle enzyme activities secondary to trauma and prolonged recumbency.

Most affected horses have CSF pleocytosis. Of 30 samples collected in the UF Large Animal Hospital series, 22 (73%) had abnormally high nucleated cell counts or protein concentrations.[23] Mild xanthochromia was also common. Mononuclear pleocytosis was found in 16 samples (53%), and high protein

concentrations with normal nucleated cell counts were found in the other 6. Nucleated cell counts in abnormal samples ranged from 0 to 882 cells/µL (median, 14 cells/µL), and protein concentrations ranged from 64 to 316 mg/dL (median, 100 mg/dL). Cells were predominantly lymphocytes or macrophages with occasional neutrophils. Of 14 samples exhibiting pleocytosis (nucleated cell count, >6 cells/µL) without significant red blood cell (RBC) contamination, neutrophil proportions ranged from 0% to 8% (median, 2.5%; H. L. Wamsley, personal communication, 2007). Of interest is that nucleated cell counts and protein concentrations were significantly higher in lumbosacral samples than in atlantooccipital samples.[23] The CSF findings have not been strongly correlated with the severity of the clinical presentation.

■ Diagnosis

A presumptive diagnosis is often based on clinical signs, especially in areas where the disease or virus is currently active and the horse has not been vaccinated against WNV within the previous 12 months. Diagnostic confidence is increased by the observation of muzzle twitching. The finding in a CSF sample of mild to moderate mononuclear pleocytosis with low numbers of neutrophils further supports a diagnosis of WNE. In a horse with signs of encephalomyelitis, presumptive diagnosis requires a positive result of a serum IgM antibody capture–ELISA and negative or unsupportive results of tests for other possible diagnoses, including alphaviral encephalitis, equine herpesvirus myeloencephalopathy, EPM, and hepatoencephalopathy. Single-point assays of anti-WNV IgG, such as the plaque-reduction neutralization test, are not particularly useful because titers can be affected by prior vaccination; however, demonstration of a fourfold or greater rise in titer between acute and convalescent samples supports the diagnosis in unvaccinated horses. It must be emphasized that serum antibody tests are diagnostic only of WNV infection, not WNE per se. For every case of WNE, approximately nine horses have nonneurologic or subclinical WNV infections.[14] The finding of WNV-specific IgM in CSF increases the specificity for WNE.

At necropsy, PCR (nested or quantitative), immunohistochemical, and viral isolation methods are used to demonstrate the presence of viral components in the CNS,[14] although immunohistochemistry tests are much less sensitive for WNV than for EEE.

Differential diagnoses for WNE in horses include alphaviral

encephalomyelitis (EEE, WEE), rabies, verminous or bacterial meningoencephalomyelitis, EPM, brain or spinal cord trauma, cervical stenotic vertebral myelopathy, hepatic encephalopathy, or compressive mass in the calvaria or vertebral canal.

■ Treatment

No antiviral treatment for horses with WNE is readily available. Type I interferons (i.e., interferon α or β) or interferon inducers stimulate nonselective cellular resistance to viral infection and are used for prevention or treatment of viral diseases. The limited data so far reported for the use of interferon in humans with WNE do not suggest any positive effect on outcome, although some anecdotal evidence supports this approach in horses. A reasonable dosage is 3×10^6 to 15×10^6 international units (IU) of interferon $\beta_{1\alpha}$ IM or IV (Avonex [Biogen, Cambridge, Mass.], 30 μg) three times weekly. The concept of therapy with WNV-specific globulin is supported by findings in a guinea pig model of WNE, although no controlled studies of its use in horses have been reported. In a limited series of cases, horses given a hyperimmune globulin product showed a trend for less recumbency, but the product had no significant effect on severity of clinical signs or mortality.[14] Several commercial products of this type are available for horses in the United States. These products are given slowly IV according to label instructions.

Supportive care is of paramount importance. Secure footing, deep dry bedding, protective covering of distal limbs and bony prominences, climate control, and provision of ample food and water are important in all cases. Recumbent horses must be repositioned from one side to the other regularly, and decubital injuries must be addressed. Early and systematic use of slinging is helpful in some otherwise recumbent horses. The Anderson sling, which transfers some of the horse's weight onto the upper limbs, is probably more effective in horses with WNE than are slings that rely entirely on torso support. In one series of 12 horses with prolonged recumbency that were treated by slinging, 2 were able to stand unassisted after slinging was used to help them rise, and 2 were able to stand after slinging was discontinued.[18] In horses that have long-term difficulty in rising to the standing position, semipermanent mobile slinging systems have been devised and marketed. These slings are stocklike frames that have wheels on each corner and webbing that rides under and supports the horse's torso.

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NSAIDS and other antiinflammatory drugs are typically used empirically in horses with WNE to control local pain, inflammation, and fever. Drugs commonly used for this purpose are flunixin, 1.1 mg/kg IV or PO (bid in U.S., sid in Europe); DMSO, 0.25 to 1 g/kg in a 10% solution IV or intragastrically bid; vitamin E, 20 IU/kg PO q24h; and pentoxifylline, 10 mg/kg PO bid. The use of corticosteroids is controversial. Because recrudescence of WNV infection and clinical relapse in recovering immunosuppressed horses are at least theoretical concerns, corticosteroids should be used only in horses that are recumbent or in imminent danger of becoming so. A typical dosage regimen is dexamethasone, 0.05 to 0.1 mg/kg IV or 0.1 to 0.2 mg/kg PO, once or twice daily for 1 to 3 days. Affected horses are often treated for presumptive EPM with antiprotozoal drugs (e.g., ponazuril, 5 mg/kg PO q24h) until IgM antibody capture–ELISA results become available.

Recovery, when it occurs, takes from 1 day to several months (mean, 22.3 days for 271 horses recovered from WNE in Nebraska and Colorado[18] and 10.7 days for 569 horses in North Dakota[20]) and is not always complete. Of 125 predominantly pleasure horses in Minnesota that survived WNE, 22 (17.6%) were classified by their owners as incompletely recovered 6 months after diagnosis.[24] Gait abnormalities, behavioral changes, muscle atrophy, and lethargy were among the residual abnormalities reported by the horses' owners. An additional 29 horses (23.2%) were considered fully recovered with residual deficits. A surprisingly high 9% of horses suffered some form of relapse of clinical signs 2 weeks to 5 months after diagnosis.

■ Necropsy Findings

Gross abnormalities of the CNS in horses with WNE are limited to meningeal congestion and hemorrhagic foci in the brain and spinal cord. Histologic study reveals mild to severe multifocal lymphocytic polioencephalomyelitis with a predilection for the ventral and lateral horns of the thoracolumbar spinal cord. The brain exhibits lymphocytic perivascular cuffing and microgliosis in the medulla oblongata and pons and, to a lesser extent, in the basal nuclei, thalamus, and mesencephalon. In severe cases, there is evidence of neuronal degeneration characterized by central chromatolysis, cytoplasmic swelling, or cell shrinkage. The cerebral and cerebellar cortices usually are relatively free of lesions.

■ Control

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General mosquito control is important at the individual operation level. Local authorities may undertake area-wide mosquito abatement when sentinel chicken serologic tests or viral isolations from wild birds suggest high local WNV activity.

A killed whole virus vaccine has been available since August 1, 2001, and has had full U.S. Food and Drug Administration approval since 2003. This vaccine is effective beginning approximately 2 weeks after the second dose of the initial series, but antibody levels drop substantially by 4 months after vaccination. Two additional vaccine types became available afterwards: a recombinant subunit vaccine in a pigeon poxvirus vector and a live chimera virus vaccine based on an attenuated yellow fever virus backbone. WNV vaccines are available in combinations with alphaviral encephalitis and tetanus vaccines, although there is evidence that simultaneous multiple vaccines can diminish the antibody response to WNV vaccination.[25] The live chimera vaccine was withdrawn in 2010 for safety reasons, and an inactivated version is now offered. For all products, the primary series or booster vaccination is completed at least 1 month before anticipated WNV activity, and boosters are given once or more annually, depending on the length of the vector season. Various challenge models have been used for each of these vaccines (except the killed version of the chimera vaccine) to demonstrate early protection against encephalitis and continuing protection against infection 12 months after a primary vaccination series. Foals of vaccinated mares should begin vaccination at 4 to 6 months of age and should have been given three inoculations by 12 months of age. Boosters should be given at least annually and more often in high-risk areas. Vaccine failures are more common in old horses. A DNA vaccine against WNV was approved by the U.S. Department of Agriculture in July 2005 but has since been discontinued.

Trauma to the Brain and Cranial Nerves

Robert J. MacKay

Because of their flighty temperaments, fast gaits, and relatively thin calvaria, horses suffer head trauma more often than do other livestock and have a higher rate of neurologic sequelae of such trauma (i.e., traumatic brain injury). Head injuries to horses occur from blows to the frontal-parietal area from running into stationary objects or being kicked by other horses, as well as from impact to the occipital protuberance (poll) or temporal areas after flipping over backward during handling or restraint accidents.[1] Specific cranial nerves may also be

injured on the outside of the skull by focal trauma. In the special case of THO, fractures of the petrosal bone can occur suddenly without any external trauma. THO is covered in a separate section. Penetration by missiles, most often bullets, is also a cause of neurotrauma in horses. Missile head injury is not be covered in this section, but a review of the subject is available elsewhere.[2]

Frontal/Parietal Trauma

Blows to the front of the head over the dome of the calvaria directly injure the cerebral cortex adjacent to the point of impact.[3] Brain injuries are most severe when the overlying bone is fractured and pushed inward or if hemorrhage occurs around or within the brain. Because of the violent distortions and movements of the cerebral hemispheres in relation to the impact, additional cortical injuries may occur diametrically opposite the point of collision (contrecoup) and caudally adjacent to the tentorium cerebelli. With the development of the secondary phase of cerebral injury and edema, the enlarging cerebral hemispheres herniate under the falx cerebri (asymmetric injury) or tentorium cerebelli, or both, to compress other parts of the brain. Horses may recover from the acute effects of calvarial fracture only to suffer recurrent seizures later. Horses that collide at speed with fixed objects are at risk for both head trauma and spinal cord injury.[4]

Impact to the Poll and Temporal Areas

When a horse flips over backward, the point of contact is either the poll or the side of the skull.[5-14] Of 34 horses with neurologic signs due to head trauma, 15 were injured by flipping over backwards.[15] Nine of these horses were younger than 1 year. The force of impact is absorbed by the poll, the zygomatic arch, or both and transmitted around the skull to the petrosal bones. Presumably because of the asymmetry of impact, only one side is usually injured. This may be either the upper or lower (i.e., impacted) side. There is hemorrhage into the middle and inner ear with or without fracture through the petrosal bone. The vestibulocochlear end organs in the inner ear are vulnerable to injury by both hemorrhage and the lacerating effects of fracture. In the latter case, the facial nerve may be damaged as it courses through the facial canal within the petrosal bone. When the point of impact is centered on the poll, the basilar bones under the brainstem are subject to fracture and separation (Fig. 35.9). The basioccipital and basisphenoidal bones are pulled apart at their synchondrosis connection, at

least in part by the strong distracting force of the rectus capitis ventralis muscles. Fragments of bone from the basisphenoid may be displaced ventrally and caudally by muscular attachments.[14] Because the synchondrosis is beneath the midbrain and flanked on each side by the foramina lacera and guttural pouches, basilar fractures are clinically serious. There may be life-threatening arterial hemorrhage between or into the guttural pouches; injury to cranial nerves IX (glossopharyngeal), X (vagus), XI (accessory), and the mandibular branch of V (trigeminal) as they pass through the foramen lacerum; direct laceration and contusion of the midbrain and adjacent parts of the brainstem; or a combination of these. Because the connection between the basilar bones ossifies and fuses by 2 to 5 years of age, this type of injury is probably more likely to occur in young horses. In the most serious cases, fracture lines extend laterally and dorsally through the squamous temporal and occipital bones or rostrally through the sphenoidal bones (see next section).

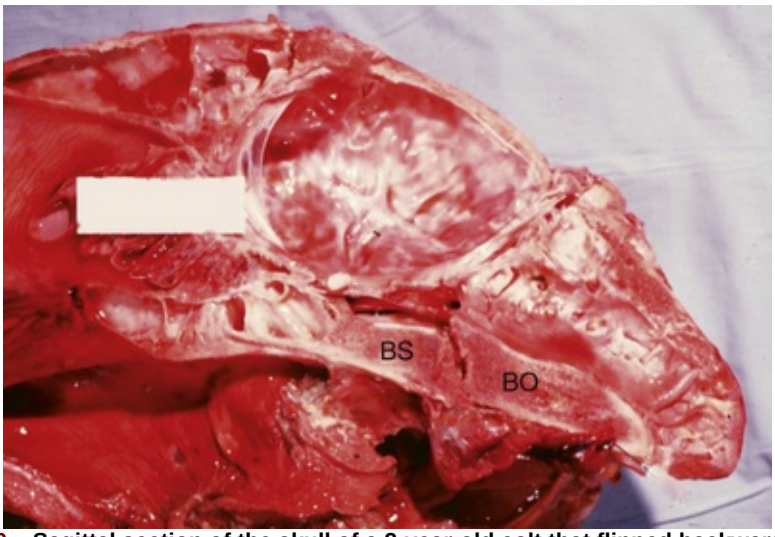


FIG. 35.9 **Sagittal section of the skull of a 2-year-old colt that flipped backward during handling and suffered multiple skull fractures. Note separation/fracture in the region of the synchondrosis between the basioccipital *(BO)* and basisphenoid *(BS)* bones and hemorrhage in the region of the attachment of rectus capitis ventralis major.**

Other Cranial Nerve Injuries

The optic nerve of one or both eyes can be stretched and damaged within the optic canals by the violent to-and-fro gyrations of the brain after impact to the head[12,16] and by fractures through the optic canals. Sphenoidal bone fractures

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also may involve cranial nerves III (oculomotor), IV (trochlear), and VI (abducens) or the ophthalmic and maxillary branches of cranial nerve V as they pass to the orbital foramen and foramen rotundum. Injury to the facial nerve proximal to the vertical ramus of the mandible causes full facial paresis. Proximal facial nerve trauma is usually caused by fractures of the petrosal bone, vertical ramus of the mandible, or stylohyoid bone or by fracture of the paracondylar process related to pulling back in a tied horse.[17] Distal facial nerve damage is usually due to direct injury from a blow, lateral recumbency, or strangulation by a tight-fitting halter. Cattle whose heads are clamped in the head-catch on stanchions may present with “stanchion head” or ptosis and drooping ears caused by bilateral neurapraxia of the auriculopalpebral branches of the facial nerves. The nerve or its branches are often damaged as they cross the mandible or zygomatic arch. Facial paresis after recumbency during general anesthesia is common and usually involves only the nose, lips, or both. When a horse pitches headfirst into the ground while traveling at speed, it is possible for components of a fractured atlas to be driven rostrally around the occipital condyles, where they may traumatize cranial nerve XII (hypoglossal) as it exits the hypoglossal foramen.

Skull fractures occur in cattle from blows to the top of the calvaria.[18] Most skull fractures are located in the center of the frontal bones, where the internal and external plates of the frontal sinus are fused into a single-layer dorsal wall of the cranial vault. This position can be located on the skull as the imaginary cross formed by intersecting lines drawn between the medial canthus of the eye and the horn of the opposite side. Injuries in this area compress the frontal and parietal lobes of the cerebral cortex. The pressure changes result in loss of sensorium, sensory deficits, blindness contralaterally, or convulsions.

In young goats and horned sheep younger than 4 to 6 months of age, the calvaria can be inadvertently opened by removal of excessive bone during disbudding or dehorning. In goats, cerebrocortical burns can occur from overapplication of a hot iron or caustic dehorning paste. Cortical necrosis caused by bacterial infections after dehorning of calves has also been described.

■ Clinical Signs

Epistaxis is common after a blow to the head of severity sufficient to cause neurologic signs.[5,9] After frontal/parietal or poll trauma, blood may flow from either or both nostrils and is typically dark (venous) and of low to moderate

volume. With poll trauma, epistaxis may be bilateral, copious, and occasionally bright red, and may also issue from the mouth.[14] In such cases, the hemorrhage is from one (usually) or both guttural pouches and originates from adjacent veins or arteries.[19] If the tympanum is perforated, blood may flow in addition from the external ear. Profuse hemorrhage into the retropharyngeal area may cause obvious swelling behind the vertical ramus of the mandible and inspiratory dyspnea, which can be life-threatening. Respiratory distress may also be associated with a poorly understood syndrome of noncardiogenic pulmonary edema that is reported to occur after serious head injury. Head trauma in humans is often complicated by systemic arterial hypotension. The cause is not completely understood but may be explained in part by *brain–heart syndrome,* in which myocardial damage is inflicted by the reflex actions of sympathetic nerves.

Immediately after impact to the frontal/parietal area, there is often a period of apparent concussion that may last minutes to hours. The most severely affected animals transiently lose all reflexes and are sometimes thought to be dead. Even after recovery of consciousness, such horses are typically obtunded for up to several hours. Altered behavior (i.e., dementia) is another characteristic of forebrain injury: A suckling foal may lose affinity for its dam; the horse may fail to respond to training cues; and the horse may exhibit yawning, head pressing, compulsive walking (often in circles around the inside of an enclosure, usually toward the side of the injury), or, in rare cases, hyperexcitability or aggression. Because of damage to the visual centers in the occipital cortex, vision and the *menace response* may be impaired in the eye contralateral to the lesion; however, pupillary light reflexes are usually intact. Injury to the somesthetic centers of the parietal cortex interferes with awareness of (and thus response to) touch on the opposite side of the head in a manner analogous to the way in which trauma can cause cortical blindness and an abnormal menace response. This perception of touch is best evaluated by comparing the horse's reactions to tapping the nasal septal mucosa on either side. Seizures, which occurred in 7 of 34 cases of head trauma in one equine series,[15] are likely to be generalized, with loss of consciousness and uncontrolled autonomic activity (e.g., salivation, urination, defecation, pupillary dilatation, chewing movements) and abnormal motor function (e.g., muscular rigidity, followed by running and paddling movements of the limbs). In comatose horses with cerebral injury, the breathing pattern may be irregular, with periods of either Cheyne-Stokes breathing or hyperventilation.

Midbrain injury is a relatively uncommon but serious complication of head

trauma of any type. It may occur immediately after the injury or be secondary to subtentorial herniation of forebrain components, rostral herniation of the cerebellum, or intraparenchymal bleeding. Because of involvement of the ascending reticular activating system, affected horses are usually obtunded and may be comatose. Weakness of limbs is observed bilaterally or on the side opposite an asymmetric midbrain lesion. In recumbent horses with severe midbrain injury, the neck, back, and limbs may be rigidly extended in a decorticate posture. If the nucleus of cranial nerve III (oculomotor) is involved, the horse exhibits strabismus and a dilated, unresponsive pupil. With severe diffuse injury, bilateral pupillary miosis may occur initially, followed by gradual progression to fixed, dilated pupils. Vision is normal unless there is involvement of other parts of the brain.

Vestibular dysfunction is common in horses after poll trauma or THO. Clinical signs may arise because of injury centrally or, more commonly, because of involvement of the vestibular apparatus or vestibulocochlear nerve (cranial nerve VIII). Peripheral vestibular disease is characterized by head tilt, neck turn, body lean, and staggering in tight incomplete circles, all toward the side of the lesion. These signs can be revealed or exacerbated by blindfolding. With acute severe vestibular dysfunction secondary to THO, recumbency may occur suddenly, with flailing and thrashing movements. These signs of vestibular disease can easily be mistaken for seizures. The ipsilateral eye is usually rotated ventrally and laterally, especially when the horse's nose is elevated, and horizontal or rotatory nystagmus may occur, with the fast phase away from the side of the lesion. Facial paralysis is attributable to damage to cranial nerve VII as it passes close to the middle/inner ear. With central vestibular disease, signs are similar to those observed when the injury is peripheral; however, additional signs suggestive of brainstem damage may also be present, including spontaneous vertical nystagmus, signs of other cranial nerve dysfunctions, obtundation, and limb ataxia and weakness. In horses, central lesions quite commonly result in a *paradoxical vestibular syndrome* in which the lesion (usually in the caudal cerebellar peduncle or the flocculonodular lobe of the cerebellum) is located on the side opposite that expected from the clinical signs. An important clue to the presence of this syndrome is the finding of other signs of cranial nerve dysfunction (e.g., facial paralysis) on the side opposite the direction of circling.

In horses with traumatic damage to the pons and medulla of the hindbrain, there is evidence of dysfunction of multiple cranial nerves in association with obtundation and limb ataxia/weakness. An affected horse may exhibit reduced

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jaw tone or deviation of the jaw (cranial nerveV [motor]), reduced facial sensation (V [sensory]), facial paralysis (VII), vestibular signs (VIII), dysphagia and respiratory stridor (IX and X), or tongue paralysis (XII). The gait may appear hypometric (spastic), like that in horses with compression of the cervical spinal cord. With severe hindbrain lesions, rapid deep breathing or other abnormal respiratory patterns can be observed.

Signs of cerebellar injury are rare and are usually a result of poll trauma. Coarse head tremors are the most consistent sign; these are especially obvious during attempts to eat or suckle (intention tremor). Horses with cerebellar injury typically have a broad-based swaying stance, and limb movements may be hypermetric or spastic, clumsy, faltering, and jerky. Infrequent signs of cerebellar trauma include absence of the menace response with normal vision and paradoxical vestibular syndrome (see earlier description).

With traumatic optic neuropathy (usually after poll trauma), vision and pupillary light reflexes are impaired or absent and pupils are dilated immediately after the injury. Because the secondary phase of nerve injury continues for many hours after the initial trauma, visual function may progressively deteriorate during at least the first 24 hours after trauma. The signs of facial nerve injury depend on the site of damage. Evidence of complete unilateral facial paralysis includes deviation of the nose toward the normal side, reduced flaring of the ipsilateral nostril during inspiration, and ipsilateral drooping of the lip, eyelid, and ear. Reflexes involving cranial nerve VII, such as the lip, eyelid, and ear reflexes, and the menace response are reduced or absent. Inability to close the eyelid causes minimal corneal problems in a horse with normal mentation unless there is also damage to the secretomotor fibers of the facial nerve along its greater petrosal branch or proximal to the geniculate ganglion, in which case interference with lacrimation causes corneal drying (keratitis sicca). Typically, a deep horizontal corneal ulcer develops within hours of the injury. The tongue protrudes out of the paralyzed side of the mouth, which is often misinterpreted as a problem with lingual function. Buccinator (cheek) paralysis causes a form of dysphagia, evidenced by dropping of and accumulation of feed between the teeth and cheeks (quidding). The peripheral parts of other cranial nerves are infrequently damaged with head trauma. The key to distinguishing central from peripheral causes of neurologic deficits is that the former usually involve multiple cranial nerves and are accompanied by obtundation, ataxia, and weakness, which are not found with peripheral lesions.

■ Pathophysiology

Impact to the brain causes immediate damage to intracranial vasculature, neuronal cell bodies, axons, and glia.[2,20,21] Neuronal depolarization initiated at the site of impact may spread centrifugally throughout the cortex and cause the transient coma characteristic of severe concussion. In axons, a dramatic rise in intracellular calcium concentration activates processes that cause interruption of axoplasmic flow and result over hours to days in death of the distal axon. Diffuse axonal injury is thought to account for many of the permanent neurologic sequelae of head trauma. These early events constitute *primary brain injury.* Subsequent damage occurring during the response phase is termed *secondary injury.*

The surface and parenchyma of the brain may be lacerated by fracture fragments pushed inward from the calvaria. Significant bleeding at any site compresses the brain against the skull, thereby raising intracranial pressure (ICP). Extravasated blood also elicits inflammatory responses in glial and other cells, initiating many of the autodestructive cascades that characterize the secondary phase of traumatic brain injury. Bleeding, ischemia, and mechanical damage to tissues result in liberation and production of vasoactive and other mediators.[20,22] The production and action of damaging mediators is much affected by brain temperature: Adverse effects are muted in the presence of hypothermia and are exacerbated by increased temperature.

Hemorrhage, increased permeability of damaged vasculature, and inflammatory edema all increase extravascular volume at the expense of brain volume. Exuberant swelling of the relatively mobile cerebral hemispheres may force portions under the falx cerebri (if asymmetric) or tentorium cerebelli.[20,21] In extreme cases, the pressure of subtentorial herniation in turn pushes the caudal cerebellum through the foramen magnum. The effects of reduced systemic blood pressure and increased ICP combine to choke off oxygen and glucose supply to cells and prevent removal of cellular metabolites such as lactic acid.[22] The consequent tissue hypoxia is more severe if blood oxygen content is also reduced, as may occur after traumatic blood loss that results in anemia or hypoxemia.

In the hypoxic environment of the traumatized brain, neuronal adenosine triphosphate (ATP) is depleted rapidly, and energy-dependent homeostatic systems of membranes collapse.[22] Calcium and sodium ions flow into cells in response to changes in membrane ion channel function associated with energy

depletion, damage by reactive oxygen species, and the actions of glutamate/aspartate. Brain damage that occurs during the primary traumatic event is irreversible; however, there is a window of minutes to days in which equally important secondary injuries theoretically can be prevented or treated.

■ Diagnosis

Changes in routine hemograms and chemistry profiles are nonspecific. Collection of CSF from the atlantooccipital cistern is generally contraindicated in head trauma because of concern about inducing cerebellar herniation, but CSF can be collected via the lumbosacral space. Characteristic changes include xanthochromia, high RBC count, and high protein levels with normal nucleated cell counts.

Conventional diagnostic radiography is the best and most practical method for initial evaluation of skull trauma; on radiographs, however, the extent of bony and soft tissue abnormality is significantly underrepresented. Because the brain is not visible in plain radiographs, degrees of brain injury must be inferred from secondary changes in the skull. Fractures are visible as radiolucent lines within the calvaria; however, such lines may be characteristic of normal suture lines. A step defect is visible when the fracture fragments are misaligned. Lateral views are most useful for detecting parietal/frontal and basilar fractures and for finding bone fragments originating from the basisphenoid or nuchal crest. On dorsoventral images, a thickened stylohyoid or radiodense osseous bulla is most easily appreciated. Increased opacity of the affected bulla may reflect hemorrhage into the middle ear in association with petrosal bone injury, or it may reflect reactive thickening of the ventral bulla wall in cases of THO. Intracranial or spinal intrathecal gas shadows may be visiable if a communication exists between the subarachnoid space and the skin surface, nasal cavity, paranasal sinuses, or middle ear. Bleeding into the paranasal sinuses, guttural pouches, or retropharyngeal area may be radiographically evident. In cases of frontal/parietal impact, it is also prudent to obtain radiographs of the cervical spine so as to detect fractures/dislocations caused by the axial compressive force of the original impact.

On computed tomography (CT), characteristics of brain trauma include change in ventricular size, shape, or position; deviation of the falx cerebri (falx shift); and focal change in brain opacity.[23] Extrdural, subdural, and subarachnoid hemorrhages may each be appreciated as discrete lines between the cortical surface and skull. Administration of iodinated contrast medium intravenously

causes focal enhancement of areas of brain injury or hemorrhage. CT is particularly useful for identifying fractures of the bones that surround the caudal fossa; such fractures are often not well depicted by conventional radiography.[24] They include fractures of the petrosal bone, basilar and sphenoid bones, occipital condyles, and squamous temporal bone.[16] Blood in the middle ears, paranasal sinuses, guttural pouches, or retropharyngeal tissues and changes associated with THO are also easily observed. The principal disadvantage of CT in North America, apart from high cost and limited availability of necessary equipment, is the need for general anesthesia. In Europe, and increasingly in North America, CT of the skull can be performed in standing, unanethsetized animals.

The main advantages of magnetic resonance imaging (MRI) over CT include lack of beam-hardening artifacts, ability to acquire images in any plane, and higher sensitivity for detection of early infarcts and edema. CT is more sensitive than MRI for detection of bony abnormalities, acute brain hemorrhage, and intracranial gas. The brain is not accessible to ultrasound imaging; however, the technique is sometimes useful for assessing fractures of the skull.

Clinical findings and historical information may form the sole bases for diagnosis in many cases.

■ Treatment

Relevant treatments for brain injury can be classified in two levels according to evidence-based support for their use. All applicable level 1 treatments should be used in every case of clinically apparent brain injury, whereas level 2 treatments are less clearly indicated and can be considered optional.

Level 1

Treat Other Injuries or Diseases.

The normal principles of critical care medicine apply to the brain-injured patient: Establish an airway, obtain vascular access, clean and dress wounds, stanch the bleeding, sedate the horse if necessary, and move the horse to a cool, well-padded area. If necessary, a padded helmet can be used to minimize additional head trauma. A regimen of broad-spectrum antibiotics should be begun if the horse has an open wound or fracture.

Treat Hyperthermia.

Hyperthermia after head trauma results from either a resetting of the

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hypothalamic temperature set point (fever) or excessive heat production in horses with normal set points. High brain temperature accelerates all of the destructive forces unleashed during the secondary phase of brain injury, and so it must be detected and treated vigorously. Rectal temperature should be checked frequently, and efforts at cooling should begin when the rectal temperature exceeds 38° C (101° F). In brief, ambient temperature can be reduced, the hair can be clipped, ice water or isopropyl alcohol can be repeatedly applied to and removed from the skin (including the head), and overhead or box fans can be placed close by. Antipyretic medication (e.g., flunixin meglumine, 1.1 mg/kg IV bid or sid) is particularly useful when the horse has a fever but should be tried in all cases of hyperthermia. NSAIDs have the additional advantages of analgesic and antiinflammatory action.

Prevent or Treat Hypotension.

Blood pressure must be normal or close to normal to sustain adequate cerebral perfusion. The old notion that patients with head trauma should be "kept a little dry" is no longer viable. Blood pressure should be monitored frequently, and heart base–adjusted systolic blood pressure should be maintained above 110 mm Hg.[25] Blood volume should be maintained or expanded by IV infusion of isotonic (Normosol-R; Plasma-Lyte A; lactated Ringers solution) or hypertonic (hypersaline) crystalloid or colloid (plasma, hetastarch) solutions. Plasma may have additional useful effects, including antioxidant and protease-inhibiting activities. In the case of significant blood loss, cross-matched whole blood is the fluid of choice. If volume resuscitation alone is inadequate to restore normal pressure, pressor/inotropic drugs may be used (e.g., dopamine, dobutamine, norepinephrine).[25] The effects of these drugs on cerebral vascular tone, however, are difficult to predict.

Optimize Oxygen Content of Blood.

Oxygen is carried in blood either bound to hemoglobin (predominantly) or as free gas. Thus it is important that both hemoglobin concentration and partial pressure of arterial oxygen (Pa_{O_2}) are at least in the normal range. Hypoxemia (arterial oxygen saturation, <94% in this setting)[25] should be treated by establishing airway patency, treating underlying pulmonary disease (e.g., head trauma–associated noncardiogenic pulmonary edema), and beginning nasal or tracheal insufflation with oxygen. Foals may be intubated and manually or

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mechanically ventilated. At several equine hospitals, there are hyperbaric oxygen chambers that theoretically could be used to dramatically increase blood oxygen content in horses with brain injury; however, the efficacy and safety of this approach have not been established. Hemoglobin concentration must be kept above at least 7 g/dL (packed cell volume of 21%) and probably above 11 g/dL. Anemia can be treated with whole blood (preferable in the case of blood loss anemia) or packed RBCs.

Ensure Adequate Pulmonary Ventilation.

High P_{CO_2} has the potential to exacerbate CNS acidosis and cerebral edema. In foals, hypercapnia can be addressed by mechanical ventilation of the lungs. In all horses with head trauma, pulmonary ventilation must be optimized by ensuring a patent airway and treating lung disease. For example, acute pulmonary edema may be treated with furosemide (0.5 to 1 mg/kg IV q8h or continuous rate infusion). Ventilation-induced hypocapnia has been advocated as a way to lower ICP[26]; however, low P_{CO_2} may cause reflex cerebral vasoconstriction and probably should not be used in foals with brain injury.

Control Pain.

Alleviating pain in brain-injured horses not only is humane but also may reduce ICP.[27] An NSAID (e.g., flunixin meglumine, 1.1 mg/kg IV or PO bid) or opioid (e.g., morphine, 0.1 to 0.3 mg/kg IV or IM qid) can be used for this purpose. Useful analgesic effects have also been achieved with constant-rate infusion of butorphanol or lidocaine.

Regulate Blood Glucose and Maintain Nutrition.

Experimental studies have shown that at least 140% of maintenance energy is expended by animals with severe brain injury.[28] Even during the first 24 hours after injury, nutrition (enteral or parenteral) probably should be provided to anorexic horses with head trauma. Blood glucose concentration ought to be kept greater than 80 mg/dL in order to provide adequate substrate for brain cells and less than 180 mg/dL so as to prevent hyperglycemia-induced exacerbation of CNS acidosis and apoptosis of brain cells. Dextrose and regular insulin can be infused IV as needed to maintain normal blood glucose concentration.

Prevent or Treat Brain Swelling.

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If possible, the neck should be free of constrictive wraps and only one jugular vein should be punctured or catheterized in order to prevent obstruction of venous flow from the head. Likewise, any recumbent horse should have its head elevated at least 10 degrees in order to facilitate blood flow. If the horse is significantly depressed (i.e., at least stuporous) or has signs of worsening brain function, a hyperosmolar infusion should be given to try to reduce the extravascular volume of the brain. The solution of choice is hypertonic saline (e.g., 1232 mmol Na/L), which is given as a continuous IV infusion of 1 mL (1.2 mmol)/kg/h for 6 hours and then 0.2 mL/kg for another 12 hours. Alternatively, boluses of 2 mL/kg can be given q4h in five infusions. Further treatment with hypertonic saline should be based on reassessment of clinical signs and plasma sodium concentration (keep <150 mmol/L). Hypertonic saline has additional salutary actions, including plasma volume expansion, antiinflammatory effect, and reduction of microvascular permeability. Mannitol (20% solution) can also be used for this purpose as a series of bolus infusions of 0.25 to 1 g/kg q4-6h. Craniectomy is not used yet for this purpose in horses, although the necessary surgical approaches have been described.[29]

Treat Seizures.

There is no justification for prophylactic anticonvulsant medication. Seizures should, however, be treated vigorously when they occur. They may be treated with diazepam, phenobarbital or pentobarbital. Once a horse has a seizure for the first time, anticonvulsant medication (usually phenobarbital) should be continued for at least a week. If delirious thrashing or recurrent seizures remain a problem, the horse can be immobilized by continuous infusion of propofol or pentobarbital for up to 24 hours.

Perform Emergency Skull Surgery.

After the patient is initially stabilized and general anesthesia induced, techniques described in standard texts may be used to carefully elevate and reduce depressed fractures of the frontal/parietal area that impinge on the cerebral cortex.[30-32] No surgical approach to basilar fractures has been described for the horse; such an approach would be extremely difficult and risky.

Level 2.

Such treatments are supported by either strong anecdotal data from equine practice or convincing experimental data in other species. However, they do not

meet the standard of evidence-based medicine.

Treat With Antioxidants.

Oxidant damage is known to be an important part of the secondary phase of brain injury, but clinical evidence supporting the therapeutic use of antioxidants is scant. DMSO is widely used by equine practitioners for treatment of CNS trauma and other disorders. The potential advantages of this drug's antioxidant and diuretic actions are obvious; however, there is virtually no evidence of effectiveness in the setting of brain injury. Common use suggests a protocol of 1 g/kg as a 10% solution in isotonic solution, given IV or by nasogastric tube q12h. Vitamin E (α-tocopherol; 50 IU/kg PO daily), vitamin C (ascorbic acid, 20 mg/kg PO daily), mannitol (see earlier), and allopurinol (5 mg/kg PO q12h) are all antioxidant therapies that can be used in the horse and can be rationalized as part of the overall approach to brain trauma.

Give Conventional Doses of Corticosteroids.

High-dose steroids are harmful to humans with brain trauma[33] and should not be used in horses. Traditional antiinflammatory doses of dexamethasone (0.05 to 0.1 mg/kg IV or 0.1 to 0.2 mg/kg PO q12-24h) or prednisolone (1 to 4 mg/kg PO bid) probably inhibit production and action of injurious mediators in the brain and may be of some value.

Give Magnesium Sulfate.

Magnesium sulfate has the potential to inhibit several aspects of the secondary injury cascade, including glutamate release, activity of the *N*-methyl-D-aspartate and calcium channels, and lipid peroxidation.[34] In view of these findings and its demonstrated safety in horses, it seems reasonable to give a single 50-mg/kg IV infusion of $MgSO_4$. This dose (25 g in a 500-kg horse) can be conveniently administered with the first 5 to 10 L of IV fluids.

■ Prognosis

In one series, horses that had basilar fractures were 7.5 times more likely to die than were those that did not have such fractures.[15] Nevertheless, one horse with a basilar fracture returned to racing, and of 34 horses with basilar fractures, 21 survived to discharge. Most surviving horses recover completely, although residual vestibular and facial nerve signs sometimes remain.

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Facial nerve dysfunction due to neurapraxia usually resolves over days to weeks. If morbid axonal injury (axonotmesis) has occurred, the facial nerve may regrow via axonal sprouting along existing nerve sheaths. Regrowth of nerves occurs at a rate of approximately 1 cm per week, and reinnervation may continue for at least a year.

Traumatic Optic Nerve Blindness of Horses

Robert J. MacKay

Severe blunt trauma to the skull in horses may result in a rapid caudal displacement of the brain and avulsion or stretching of the peripheral optic nerves within the bony optic canals. Typical settings for such injuries are blows to the poll from flipping over backward and trauma to the frontal-parietal area from running into stationary objects such as posts or trees. The clinical signs include sudden blindness, loss of pupillary reflexes, and pupillary dilation. Ophthalmoscopic changes in the retina occur after 2 to 4 weeks and include pallor of the optic disk, reduction in the number and caliber of the retinal vessels, and linear peripapillary pigment disruptions (Fig. 35.10). The condition can be partial or complete, asymmetric or symmetric, and generally does not respond to treatment.[1-3] Because traumatic optic nerve injury probably progresses for many hours after the initial injury, robust antiinflammatory treatment during the first 3 days after injury is a rational action. Treatment should include an NSAID such as flunixin meglumine at a dosage of 1.1 mg/kg IV or PO q12-24h and a corticosteroid such as dexamethasone, 0.05 to 1 mg/kg IV or IM sid or bid. The iron chelator deferroxamine has been described as treatment for traumatic optic neuropathy.[3]

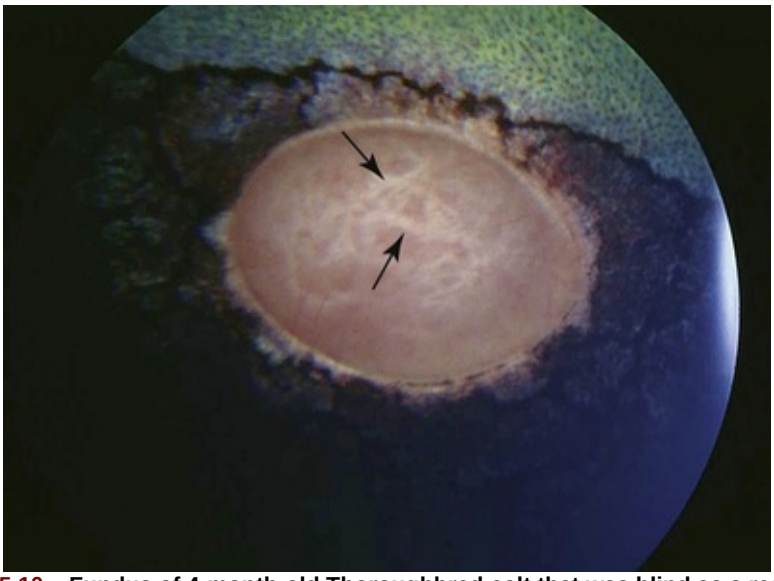


FIG. 35.10 **Fundus of 4-month-old Thoroughbred colt that was blind as a result of severe bilateral nerve injury that occurred as a result of poll trauma 2 months earlier. Note absence of fundic blood vessels and exposure of the lattice-like lamina cribrosa *(arrows),* which indicates demyelination.**

Thiamine Deficiency of Horses

Mary O. Smith

Horses may develop thiamine deficiency when fed diets that contain thiaminases. Potential sources of thiaminases are bracken fern *(Pteridium aquilinum),* horsetails *(Equisetum arvense),* and toxic doses of amprolium (e.g., 400 to 800 mg/kg/day). The clinical signs of thiamine deficiency are ataxia, conscious proprioceptive deficits, heart block, bradycardia, blindness, weight loss, dysuria, hypothermia of the extremities, and periodic muscular fasciculations. In affected horses, convulsions are a terminal development. Electrolyte changes include hyperkalemia, hyperphosphatemia, hyperglycemia, and decreased glucose tolerance. Parenteral thiamine is an effective treatment.[1,2]

Equine Leukoencephalomalacia

Robert J. MacKay

Equine leukoencephalomalacia (ELEM) is a fatal CNS intoxication of horses caused by ingestion of fumonisin toxins on corn or corn by-products.[1-3] Fumonisin toxins (B_1, B_2, and B_3), produced by the fungi *Fusarium verticillioides* and *Fusarium proliferatum* (previously known together as

Fusarium moniliforme), interfere with sphingolipid metabolism, disrupting endothelial cell walls and basement membranes.[4] Although all three are toxic, B_1 is the most common and most thoroughly studied. See Chapter 54 for more details.

■ Clinical Signs

The onset of ELEM is usually sudden. In previously healthy animals, the first indication may be death, but most affected horses show abnormal neurologic signs for hours to days before death.[5,6] These include obtundation to the point of stupor and dementia manifested as compulsive walking in large circles, head pressing, and hyperesthesia. Blindness and lack of menace response, as well as reduced reaction to touch around the face, may be present. Movements of the muzzle, lips, and tongue may be weak and ineffectual. Signs are typically asymmetric. Muscle fasciculations occur over the neck and withers and in antigravity muscles, and limb ataxia and weakness are prominent in the terminal phase. Seizures are common after affected horses become recumbent, and many affected horses die while convulsing. The few horses that survive ELEM usually have permanent neurologic dysfunction. Hepatic involvement occurs in many cases, as evidenced by high serum levels of liver enzymes, although hepatic failure is uncommon.[4,7] Signs of liver disease include icterus, petechiation on mucous membranes, and swelling of the muzzle or lips. Fatal outbreaks of liver disease without brain involvement have been reported.[4] Cardiovascular abnormalities are also described in horses with experimental ELEM and include decreases in cardiac contractility, heart rate, and arterial pulse pressure and increases in systemic vascular resistance.[8]

Fumonisin toxins cause a variety of clinical syndromes in other species, including pulmonary edema in swine, but horses appear to be the most susceptible domestic animal species and can show signs when exposed to toxin concentrations as low as 5 to 10 ppm.[4] Regulatory guidance issued by the U.S. Food and Drug Administration calls for fumonisin (B_1, B_2, and B_3) concentrations of no more than 5 ppm in horse feeds.

■ Clinical Pathology and Diagnosis

No findings on routine bloodwork are unique to ELEM. Serum levels of liver enzymes (i.e., aspartate transaminase, γ-glutamyltransferase, and sorbitol

dehydrogenase) and bilirubin are often high. Anemia, leukocytosis, and leukopenia all have been reported, but none is a consistent finding. Markedly high protein concentration (i.e., >100 mg/dL) with normal nucleated cell count is a typical CSF finding in affected horses.[9] High serum sphinganine level, sphingosine level, and sphinganine-to-sphingosine ratio suggest acute fumonisin toxicosis,[8] but the assays for these substances are available only at research laboratories. In practice, antemortem diagnosis relies on recognition and demonstration of fumonisin (B_1, B_2, and B_3) concentrations greater than 10 ppm in feed. Fumonisin assays are widely available through diagnostic laboratories, and turnaround should be rapid.

Differential diagnoses include traumatic brain injury, the arboviral encephalitides, hepatic encephalopathy, EPM, and botulism.

■ Epidemiology

Leukoencephalomalacia occurs worldwide. Corn becomes contaminated during growth rather than in storage, and climatic factors that stress the plants, such as drought followed by high rainfall, increase the likelihood of mold development. The fungus is introduced into the growing corn by insects such as the western flower thrip, which enters the ear and damages the kernel as it feeds.[10] Cereal grains and baled hay similarly may be contaminated.[11] Most cases of related equine disease occur during the winter and early spring.[1] Repeated exposure to the toxin, rather than a single large dose, seems to be associated with the development of clinical signs.[12] Experimental studies with infected corn demonstrated an onset of clinical signs on the ninth day after the beginning of the feeding period, but the reported delay between exposure and signs in outbreaks has ranged between 4 and 180 days. Older animals develop clinical signs of ELEM more rapidly than do younger animals and thus appear to be more susceptible to the effects of the mycotoxin.

The rates of disease in exposed horses vary widely, from 14% to 100% in some reports; the rate of lethality is close to 100%.

■ Pathology

The major pathologic features in the CNS result from the vascular damage caused by fumonisin toxins, including liquefactive necrosis and degeneration or malacia of the white matter of one or both cerebral hemispheres.[5,13] The lesions

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may vary from grossly inapparent in peracute cases to complete subcortical cerebral necrosis. Flattening of the cortical gyri, enlargement of the cerebral cortex, vascular congestion, cortical softening, yellowish discoloration of the white matter, hemorrhage, and cavitation of the cerebral cortex may be present.[1] A gelatinous fluid can be observed in many of the cavitary lesions. Hemorrhage in the CNS has also been reported. Lesions in the visceral organs, including hepatic congestion, centrilobular hepatic necrosis, hemorrhagic enteritis, and cystitis, are found in some affected horses. The relationship between these lesions in the CNS and those in the liver, urinary bladder, and GI tract is unknown.

■ Treatment

Specific treatment is not available, and early euthanasia is usually the most humane option. Because of cerebral edema, it is rational to administer IV antiedema drugs, including corticosteroids (e.g., dexamethasone 0.1 mg/kg daily), DMSO (1 g/kg as a 10% solution), hypertonic saline (4 mL/kg of 7.2% NaCl every 4 hours), or mannitol (1 g/kg as a 20% solution). Nonsteroidal antiinflammatory drugs (e.g., flunixin meglumine 1.1 mg/kg PO or IV bid), once or twice daily antioxidants (DMSO, α-tocopherol, 20 IU/kg PO), ascorbic acid (25 mg/kg in IV fluids), and thiamine (5 mg/kg, slowly IV) can all be tried to limit secondary brain injury, but none of these treatments is likely to be effective.

Intracarotid Drug Injection

Robert J. MacKay • Mary O. Smith

Intracarotid drug injection is common in horses because the jugular vein and the common carotid artery are closely apposed in the caudal third of the neck. The condition is rare in cattle because the omohyoid muscle lies between the carotid artery and the jugular vein in the posterior part of the neck.[1] Hypertonic or caustic drugs (including phenothiazine tranquilizers, chloramphenicol, chloral hydrate, barbiturate anesthetics, phenylbutazone, calcium gluconate, and sodium iodide) cause cortical necrosis when injected into the carotid artery.[2-5]

The common carotid artery provides blood supply to the circle of Willis via the internal carotid artery and thence to the thalamus and rostral and middle cerebrum. The internal carotid artery also provides arterial supply to the eyeball via the ophthalmic artery. In contrast, the blood supply to the caudal cerebrum,

midbrain, pons, medulla, cerebellum, and inner ear is via the vertebrobasilar arteries and originates in the vertebral branches of the subclavian arteries. Thus the carotid artery injectate travels principally to the ipsilateral thalamus, cerebrum, and eye but relatively spares the rest of the brain. The effect of the arrival in the forebrain of a bolus of irritant material is akin to a cerebral stroke of variable severity. Intense vasospasm occurs, as does physical endothelial damage with endothelial swelling, increased vascular permeability, mural necrosis, hemorrhage, intercellular edema, and thrombosis. As a result of ischemia, glucose, oxygen, and energy starvation occur, progressing to calcium ion influx, anaerobic metabolism, and eventually loss of function and accumulation of excitotoxic amino acids, free radicals, and eicosanoids. At necropsy, ipsilateral brain swelling and hemorrhage are grossly evident.

When the drug is injected into the carotid artery, the animal recoils backward and falls over. Some horses strike or rear violently or run wildly, often in circles toward the injected side, without regard to obstacles. After falling, many horses convulse violently, whereas others become comatose without showing excessive motor activity. Some severely affected animals die after a variable period, but others regain their footing and recover completely. Milder and residual neurologic signs include contralateral (thalamic) or ipsilateral (retinal) blindness (or both), contralateral facial hypalgesia, circling (toward the side of the injection), and contralateral conscious proprioceptive deficit.

If it can be done safely, convulsing horses should be given IV anticonvulsant medications (diazepam, 0.1 to 0.4 mg/kg; pentobarbital, 2 to 10 mg/kg; or xylazine, 0.2 to 1.1 mg/kg), which can be repeated as needed to control seizures. If possible, horses should be placed in a padded stall and treated with antiinflammatories, including dexamethasone (0.05 to 1 mg/kg IV or IM sid), flunixin (1.1 mg/kg PO or IV bid) or equivalent, and DMSO (1 g/kg IV as a 10% solution bid). The use of hypertonic antiedema drugs in this setting is controversial because of the possibility of active bleeding in the CNS and loss of the blood-brain barrier.

Intracarotid injection of drugs is best prevented by the use of large-bore needles or catheters for intravenous injections. In the horse, venipunctures should be performed in the anterior one third of the jugular furrow because the artery and vein are separated by the omohyoid muscle in this area. The inexperienced phlebotomist may prefer to place the needle into the vessel without a syringe attached to confirm that the blood is dark and drips from the hub, which indicates proper placement into the jugular vein. Conversely,

intracarotid placement of the needle results in forceful, often pulsatile ejection of bright red arterial blood from the hub.

Brain Tumors

Mary O. Smith • Lisle W. George

Nervous system tumors of ruminants include medulloblastoma, ependymoblastoma, neurofibrosarcoma, angioblastoma, meningioma, meningeal hemangioma, neurofibroma, schwannoma, choroid plexus papilloma, pituitary adenocarcinoma, primitive neurectodermal tumor, and reticulosis.[1-5] CNS tumors of horses include pituitary adenomas, microgliomas, medulloepithelioma, choroid plexus papilloma, ependymoma, neurofibroma, meningioma, meningeal carcinoma, and reticulosis.[1,6-10] Secondary tumors that invade the CNS include melanoma, lymphosarcoma, adenocarcinoma, squamous cell carcinoma, hemangiosarcoma, and osteoma.[1,10-15] Of these, lymphosarcoma is most common.[16,17] Metastatic invasion to the CNS occurs either by vascular routes or by extension along the peripheral nerve rootlets.[18] Local extension from adjacent tissue, such as the paranasal sinuses, can also occur.[11]

Clinical signs of brain tumors vary with the location and include abnormalities of gait (ataxia, paresis, hypometria/hypermetria); seizures; altered mentation (especially dullness); facial paresis or paralysis; facial anesthesia or analgesia; dysphagia; head tilt; strabismus; nystagmus; and loss of the menace reflex.[11,18-20] Migration of facial tumors (squamous cell carcinomas) into the cranial vault through the cranial nerve foramina may also result in facial swelling, exophthalmos, Horner syndrome, or asymmetric airflow through the nares.[17] Pituitary adenomas of aged horses (see Chapter 41) rarely cause neurologic disease, but they secrete melanocyte-stimulating hormone, which stimulates the adrenal cortex and causes Cushing disease. Some tumors are discovered incidentally at necropsy.

Antemortem diagnostic tests include radiographs of the skull (for tumors that spread locally and some metastatic tumors), and electroencephalography to elucidate brain dysfunction.[11] Where available, CT or MRI can greatly facilitate diagnosis, but limited availability and considerations of cost restrict their use in most cases.[18,20-22]

Treatment of brain tumors in horses and livestock is generally not feasible because of limitations of cost, nursing care challenges after craniotomy, lack of

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access to radiation therapy for large animals, and considerations of safety for personnel who handle animals with significant neurologic deficits. Palliative treatment such as corticosteroids may reduce clinical signs temporarily in some animals. Euthanasia is the choice for most large animals with brain tumors.

Cholinesteric Granuloma Encephalopathy

Robert J. MacKay • Mary O. Smith

Cholinesteric granulomas (CGs) develop in association with the choroid plexuses of the fourth ventricles and lateral ventricles. Up to 20% of older horses have CGs in one or both lateral ventricles, usually without adverse effect.[1] CGs are thought to develop as a chronic inflammatory reaction to cholesterol released from extravasated degenerating RBCs within the choroid plexus. Syndromes of neurologic dysfunction in association with CGs have been described in horses aged 7 to 23 years.[2-5] The onset of signs is ascribed to combinations of attenuation and edema of cerebral tissue overlying a large CG, hydrocephalus secondary to obstruction by a CG of CSF efflux from the lateral ventricle through the foramen of Monro, and ependymitis/meningitis in response to proinflammatory substances released from CG.[2-5] Some affected horses have a history of months to years of intermittent neurologic episodes, presumably related to waxing and waning hydrocephalus, intermittent inflammation, or both.

Signs can develop insidiously or appear suddenly and are usually referable to forebrain dysfunction.[2,4] Affected horses may exhibit dementia, manifested as irritability, aggression, yawning, head pressing, compulsive walking, drifting to one side when walking, circling, abnormal body posture, loss of learned skills, syncope-like attacks, seizures, blindness and lack of menace response with normal pupillary light reflexes, and reduced response to tactile stimulation of the face.[2-5] With presumed CG-associated cerebral edema, signs suggestive of brainstem compression also have been described, including stupor, limb weakness and ataxia, anisocoria, head tilt, stiffness in gait, and facial paresis. Signs are typically asymmetric or unilateral, reflecting asymmetric involvement of the lateral ventricles.

CG should be suspected in any mature horse showing signs referable to waxing and waning forebrain dysfunction. Results of CSF analysis may be normal, may show high protein concentration with normal cell count, or may show mild pleocytosis notable for the presence of nondegenerate neutrophils.

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The diagnosis is strongly supported by advanced imaging. CT in the standing[5] or anesthetized horse[2,3] is the diagnostic method of choice, but MRI has also been used.[4] The finding on CT of heterodense, hyperattenuating, poorly contrast-enhancing masses in the lateral ventricles is tantamount to the diagnosis of CG. A technique for CG biopsy has been described and can be used to exclude the possibility of other choroid plexus tumors, including papillomas and ependymomas.[3] At necropsy of clinically affected horses, CGs are found as brownish ellipsoid masses at least 3 cm in diameter attached to the choroid plexuses of one or both lateral ventricles. Histologically, these masses contain abundant cholesterol crystals interspersed with empty clefts, hemosiderin, and heavy infiltrations of macrophages and giant cells.

Traditionally, CGs in horses have been considered terminal and untreatable. It is clear, however, that all of the components of the pathophysiology of CG encephalopathy—namely, enlarging granulomas, hydrocephalus, and ependymal inflammation—are potentially treatable with antiinflammatory drugs. In horses with CG encephalopathy, antiinflammatory drugs, including dexamethasone, prednisolone, and phenylbutazone, have induced clinical remissions lasting from months to indefinitely. A reasonable treatment protocol includes seizure control as needed and induction of remission from clinical signs with dexamethasone (0.05 mg/kg IV or 0.1 mg/kg PO, once daily for 7 to 14 days), followed, if successful, by prednisolone (1 mg/kg PO bid), to be given indefinitely except for intermittent trials designed to test the effect of tapering the dose. Hyperosmolar IV solutions (mannitol, 0.5 to 2.0 g/kg as a 20% solution; 7.2% saline, 2 to 4 mL/kg) can be given in the acute phase to address cerebral edema and repeated as needed every 4 to 6 hours for the first 24 hours. More aggressive interventions, including direct drainage of CSF from enlarged lateral ventricles and surgical removal of CG by techniques adapted from human brain surgery, are also possible but have not been described. The prognosis for short- to medium-term (i.e., up to a year) maintenance of remission from clinical signs of CG encephalopathy is considered fair.

Epilepsy

Robert J. MacKay

According to guidelines put forth in 2015 by the International Veterinary Epilepsy Task Force, epilepsy is defined as a *disease of the brain* characterized by a persistent predisposition to generate epileptic seizures.[1] In practice, this

usually means at least two unprovoked epileptic seizures more than 30 days apart. A systemic condition or chemical/drug may cause a normal brain to generate *reactive* seizures; however, these are not classified as epilepsy. Epilepsy may be idiopathic or structural. *Idiopathic* epilepsy connotes either genetic predisposition (known or suspected) or epilepsy of unknown cause in which there is no indication of a structural cause. Genetic epilepsies are rare in large animals, but a few heritable epilepsy syndromes have been described in horses, such as juvenile idiopathic epilepsy of Arabian foals of Egyptian lineage,[2] Arabian lavender foal syndrome,[3] and suspected familial epilepsy in cattle of various breeds.[4,5] *Structural* epilepsy occurs as a result of known or suspected intracranial/cerebral disorders, including vascular, inflammatory/infectious, traumatic, anomalous/developmental, neoplastic, or degenerative diseases. Polioencephalomalacia is the most commonly reported diagnosis in ruminants with seizures caused by structural brain disease: In one report, 14 of 19 sheep and goats and 8 of 13 cattle with structural-origin seizures had polioencephalomalacia.[6,7] In 42 horses older than 3 weeks with structural-origin seizures, the causes listed were skull fractures, cerebral hemorrhage, cerebral edema, neoplasia, cholesterinic granuloma, vasculitis, meningoencephalitis, abscesses, intracranial vascular events, leukoencephalomalacia, congenital abnormalities, and EPM.[8]

Epileptic seizures result from abnormal, synchronous, electrical discharges in the neurons of the forebrain that spread to the somatic and visceral motor areas to initiate spontaneous, paroxysmal, involuntary movements that may begin and end spontaneously.[1] Each seizure (ictus) may be *generalized*, involving neural networks of both cerebral hemispheres and resulting in generalized bilateral motor activity over the whole body, or *focal*, involving one side of the forebrain and lateralized motor signs or sensations. Generalized seizures usually begin with tonic muscle contractions of the muscles of the neck and limbs but progress to rhythmic clonic limb thrashing, often accompanied by abnormal eye positions and movements. Affected animals often fall and display various autonomic signs, such as salivation, urination, and defecation. The oroalimentary form of generalized seizures occurs particularly in neonatal foals and is characterized by lip smacking, lip pursing, chewing, licking, odontoprisis, or swallowing.[1] Focal seizures begin as involuntary tonic or clonic contractions of groups of facial, jaw, or body muscles. These signs may stop spontaneously without progression, but more typically they spread from the initial focus to involve the whole body.

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In rare cases, seizures may be preceded by a prodrome of up to several hours' duration, usually characterized by signs of restlessness or disorientation, and are usually followed by a period of stupor, restlessness, and central blindness that is usually short-lived but can last several days in foals.

In large animals, the best characterized genetic epilepsy syndrome is *juvenile idiopathic epilepsy* in Arabian horses of Egyptian lineage.[2] Seizures usually begin in affected foals by 2 months of age (range, 2 days to 6 months), but onset as late as 18 months has been described. Seizures are usually symmetric and generalized, often with no prodrome. After a brief period of whole-body myotonus and collapse into lateral recumbency, the animal exhibits clonic ("galloping") limb movements, opisthotonos, sweating, retracted lips, and staring, unblinking eyes. Each seizure can last up to 5 minutes but typically is less than a minute. Postictal signs are usually profound and persistent and are often the first abnormality detected by the owner: obtundation, cortical blindness, loss of maternal bond and interest in suckling, and other variable behavioral signs. Blindness, the last sign to resolve, typically lasts several days (range, hours to 2 weeks). Injuries, especially to the skull, may occur during seizures or as a result of collisions during the period of blindness. Juvenile idiopathic epilepsy responds well to anticonvulsant therapy and does not usually recur (see Treatment section). Untreated foals also may grow out of the condition by a year of age but are subject to cumulative seizure-associated injury, and there are anecdotal reports of permanent behavioral abnormalities in untreated horses.

A diagnosis of epilepsy is supported by the finding of epileptiform discharges on interictal EEG, although this test does not appear to be highly sensitive.[9] Epileptiform discharges were identified on EEG of only 9 of 13 foals with juvenile idiopathic epilepsy.[2] Artifacts induced by patient movement or sedative drugs limit the usefulness of traditional electroencephalography in large animals. Ambulatory electroencephalographic recording, as is routinely used in human neurology, may be a more sensitive and reliable method for investigating suspected seizures in large animal patients.[9]

Specific protocols for antiepileptic drugs have not been established for most large animal species. However, most seizures are controlled in the acute phase with diazepam (0.05 to 0.2 mg/kg IV) and over the long term with oral or IV phenobarbital. A simple approach to treatment of epileptic horses has been described and can be followed in other species[10]: oral phenobarbital, 5 mg/kg

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twice daily, begun without a loading dose. Treatment at this dosage is continued for at least 2 weeks. If signs are insufficiently controlled, the dosage is increased by 1 mg/kg and continued for another 2 weeks. This cycle of incremental dosage increase is continued until adequate control is achieved or side effects prevent further increase. Potassium bromide (90 mg/kg once daily PO, which may be preceded by an optional loading course of 120 mg/kg/day for 1 week) can be added to phenobarbital in these cases to provide additional anticonvulsant effect.

The therapeutic trough concentration of phenobarbital is 15 to 40 µg/mL. After 6 months of seizure-free therapy, the dosage of phenobarbital can be tapered over several weeks. If the horse remains free of seizures for 6 months after anticonvulsants have been discontinued, the horse is considered by some authorities to be no longer epileptic; however, it is prudent to continue to advise owners that such horses should never be ridden or used for sporting purposes. Foals with juvenile idiopathic epilepsy are usually treated for 3 months with phenobarbital, which is then tapered. Basic pharmacokinetic studies have been used to rationalize antiepileptic dosages of phenytoin (10 to 15 mg/kg PO once daily) and levetiracetam (32 mg/kg), although these drugs have not been field tested for efficacy.[11] All ruminants experiencing seizures should also immediately be treated with thiamine (10 to 20 mg/kg IV, IM, or subcutaneously [SC]).

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Narcolepsy–Cataplexy

Robert J. MacKay

■ Definition and Etiology

Narcolepsy is a spectrum of CNS disorders characterized by episodes of excessive sleepiness or muscular weakness, or both, and REM-onset sleep. The disorder actually comprises two separate pathologic phenomena: *narcolepsy,* a tendency for abrupt transitions from wakefulness into non-REM sleep, and *cataplexy,* the pathologic intrusion of REM sleep into wakefulness or at the onset of sleep.[1] Attacks of narcolepsy and cataplexy are considered a paradoxic form of sleep because the EEG is characteristic of an alert, awake animal, but the REM is characteristic of deep sleep.

Sleep–wakefulness regulation is normally achieved through reciprocal interplay of consciousness-arousing and consciousness-depressing regions of the brain.[1] Included in the arousal system are cholinergic and monoaminergic (histaminergic, serotonergic, dopaminergic, and noradrenergic) neurons located in the caudal hypothalamus/brainstem regions that diffusely project to the forebrain to upregulate cortical function. Conversely, gamma-aminobutyric acid (GABA)–ergic neurons of the rostral hypothalamus play a critical role in sleep by inhibiting neurons of the arousal system. Two closely related neuropeptides, *orexins A* and *B* (also known as *hypocretins 1* and *2*), produced exclusively by neurons in the lateral hypothalamus, are neurotransmitters critically involved in the neuronal circuitry regulating sleep and wakefulness states. Via numerous afferent connections, orexin-positive neurons sense the body's external and internal environments and regulate wakefulness accordingly, mostly by stimulating consciousness-arousing monoaminergic neurons. Multiple lines of evidence suggest that sporadic narcolepsy in humans is caused by a dysfunctional orexin system, usually as a result of degeneration of orexin neurons. Some familial cases are associated with nonfunctional orexin receptors. With removal of orexin neuronal function, monoaminergic and GABA-ergic neurons set up a poorly regulated mutually inhibitory circuit, which results in unwanted and abrupt transitions between wakefulness and sleep recognizable clinically as narcolepsy and cataplexy.[1]

Narcolepsy has been reported in numerous horse and pony breeds, a Suffolk

lamb, Spanish fighting bulls, a Guernsey bull, and a Brahman bull.[2-11] Most cases appear to be sporadic, but early-onset, probably familial occurrence has been reported in American Miniature Horse, Lipizzaner, Suffolk, Shetland pony, and Fell pony foals[2,12] and has been observed by the author in a family of Morgan horses. The collapse syndrome associated with squeezing neonatal foals traditionally has been viewed as a transient form of cataplexy; however, one study demonstrated that the associated EEG patterns were slow waves consistent with abrupt transition to non-REM sleep and thus were more characteristic of narcolepsy than of cataplexy.[13]

■ Clinical Signs

The clinical signs of narcolepsy include staggering, lowered head and neck, buckling of the thoracic limbs, kneeling posture, flaccidity of the lips, closure of the eyes, loss of the menace reflex, stertorous breathing, and ataxia. During severe narcoleptic attacks (narcolepsy–cataplexy), the animal collapses into lateral recumbency and appears comatose. Only rarely is REM sleep observed after collapse. The sensorium returns to normal after seconds to minutes. In the periods between attacks, the animal appears normal, although repeated attacks result in trauma to the dorsal aspects of the fetlocks and the knees and to the face.[12,14] Cataplexy, which may occur with or without narcolepsy, is a sudden episode of paralysis of the voluntary muscles, often induced by strong emotions (usually positive) in the patient and can range from atonic, areflexic paralysis of all skeletal muscles, except those of the diaphragm and eyes, to slight transient buckling of the limbs without collapse into recumbency. Episodes of cataplexy last seconds to minutes.

Environmental factors that can stimulate cataplectic attacks include active restraint, suckling, feeding, changing of the stall environment, grooming, or cross-tie–related activities of horses such as saddling, removal of tack, and washing. Despite this association, narcolepsy in adult horses usually occurs while horses are in stalls or at pasture without any obvious prior stimulation.[14] Most cases of narcolepsy in humans are associated with cataplexy, but sleep attacks without cataplexy and cataplexy without sleep attacks also occur. Mild cataplexy and attacks of excessive sleepiness can be difficult to distinguish in adult large animals in that both may cause blank facial expression, hanging of the head and neck, and buckling of the limbs with or without collapse into recumbency.[14] Sudden arousal associated with the stimulation of collapse and

ground impact also could terminate either type of episode. In view of diagnostic ambiguities based on observations of mild sleep attacks, cataplexy that persists after collapse is the most frequently recognized manifestation of sleep disorders in large animals.

Signs are generally stable and lifelong. The cataplexy component of juvenile cases usually improves as the animal gets older but rarely resolves completely.

■ Diagnosis

Strict electroencephalographic criteria, including the early onset of waveforms typical of REM sleep at the beginning instead of in the middle of a sleep cycle, are in place for confirming the diagnosis and for distinguishing narcolepsy from narcolepsy without cataplexy. The electroencephalographic changes of narcolepsy and cataplexy have been reported in a Brahman bull.[3] In horses, electroencephalographic waveforms may be normal or may reveal fast waves typical of REM activity.[14] Orexin concentrations in CSF are typically low in humans and dogs with sporadic or familial narcolepsy but normal in familial forms associated with mutations in the genes for orexin receptors.[15,16] In CSF samples from a narcoleptic Icelandic foal and three related narcoleptic Lipizzaner fillies, immunoreactive orexin concentrations were comparable with those from normal horses.[2,17] It is important to evaluate this diagnostic finding in both juvenile and adult-onset forms of the disease in large animals.

Cataplexy can be induced by IV administration of the centrally acting cholinesterase inhibitor physostigmine salicylate (0.05 to 0.1 mg/kg),[4] but attacks cannot be evoked in all animals. In one series of 3 narcoleptic horses challenged, 2 responded positively to the challenge[2]; in another report, only 1 of 10 affected horses had a positive response.[9] Signs of cataplexy can be reversed for at least 24 hours by one dose of atropine sulfate (0.02 to 0.1 mg/kg IV).[9,17] Diagnostic drugs must be administered with caution because of the possibility of inducing colic, especially in horses.

Syncope and seizures are included in the differential diagnosis of narcolepsy. In general, syncope is characterized by acute collapse without warning and, unlike narcolepsy, is not preceded by a gradual lowering of the head and drowsiness. Increased focal or generalized tonic–clonic muscle activity and postictal depression are typical with seizures but not with narcolepsy. In addition, excessive sleepiness can be observed in horses that have an underlying painful physical condition, environment, or social position that prevents them

from lying down to sleep.[18] Therefore a complete history and thorough physical examination are essential.

■ Treatment and Prevention

The tricyclic antidepressant imipramine (0.5 to 1 mg/kg PO bid to qid) can be used to treat cataplexy but is ineffective in treatment of the sleepiness component of narcolepsy. This drug must be administered with caution, and oral dosages in horses should not exceed 2 mg/kg.[6] Results of oral imipramine therapy are inconsistent; duration of effect is approximately 5 hours. Anecdotal reports indicate that tyrosine has been of benefit in some, but not all, narcoleptic horses. Its presumed mode of action is to increase dopamine neurotransmitter concentrations.[14]

Selective serotonin reuptake inhibitors are also used in humans for treatment of cataplexy but have not been evaluated in large animals for this purpose.[19] Sodium oxybate (the sodium salt of gamma hydroxybutyrate) is widely used as a wakefulness-promoting drug in narcoleptic humans and may apply to the treatment of veterinary patients.[19]

Headshaking in Horses

Robert J. MacKay

Headshaking renders an otherwise normal horse unsuitable for riding or driving. There is no obvious predilection for age, breed, or gender. In the United Kingdom, owner-reported prevalence of headshaking of horses in 2017 was 4.2%.[1] Surveys have usually demonstrated that more than 50% of headshakers are geldings, and mean ages reported in published series are 7.3 to 12.8 years (range, 1 to 28 years).[2,3] Headshaking develops mostly in horses used for pleasure riding, dressage, or show jumping, but horses of any breed or discipline can be affected.[4,5] Signs of headshaking usually first occur while the horse is being ridden or driven (i.e., with the horse in a bit and bridle) and become more pronounced over time, both in severity and duration.[2] The condition usually renders a horse unsafe or at least unsatisfactory for riding and in severe cases may cause inhumane suffering to the affected horse. Once established, the condition occurs during any form of exercise, and approximately 60% of affected horses eventually also exhibit headshaking at rest.[2,4] Additional trigger factors that exacerbate or provoke headshaking have been identified: bright light,

sun, heat, cold, stress, wind or rain, eating hay, extreme neck flexion, riding on narrow roads, hearing people's voices, and riding near trees or water.[6,7] On average, approximately half of cases from multiple series are either partially or completely seasonal; signs begin suddenly or get worse in spring and end or become milder in the late summer or fall.[2,6,8] A few cases begin in the fall and end in late winter. Signs may stop for weeks, only to recur for no apparent reason.

Headshaking is classified as either *symptomatic* or *idiopathic*. Symptomatic headshaking has an identifiable physical cause that, if removed, permanently resolves the problem. Idiopathic cases either have no discernable basis or continue after removal of a putative cause. Reported or postulated symptomatic causes have included skull lesions, allergic rhinitis, vasomotor rhinitis, otitis externa or media/interna, *Trombicula autumnalis* (harvest mite) infection, fungal sinusitis, THO, temporomandibular degenerative joint disease, mites or ticks in the external ear canals, guttural pouch mycosis, *Onchocerca* dermatitis, dental problems, sinus surgery, cervical arthritis, and ocular lesions, such as cystic corpora nigricans, “floaters” in the anterior chamber, allergic conjunctivitis, and blocked lacrimal ducts.[9-12] Because horses are normally programmed for headshaking as, for example, for fly avoidance,[13] almost any unpleasant condition around the head (or possibly elsewhere on the body) seems to have the potential to amplify the behavior to abnormal levels. Despite the seemingly impressive (and incomplete) number of potential causes just listed, no physical basis for headshaking was found in 89 of a series of 100 reported cases.[2] Headshaking does not appear to be associated with latent equine herpesvirus 1 infection.[14]

Headshaking may be defined as involuntary sudden violent repetitive movements of the head, either dorsally and ventrally in the median plane (most common), horizontally, and/or in a rotatory manner. Other signs, particularly in horses with idiopathic headshaking, have included snorting, sneezing, snoring breath sounds, rubbing the face on stationary objects, keeping the head low while trotting or even rubbing the nose along the ground, acting as if a bee has flown up the nose, excessive nasal and lacrimal discharge, hyperesthesia/hyperresponsiveness around the face, anxiety and agitation, hopping off the ground in one or both thoracic limbs, head pressing, shade seeking, muscle fasciculations, sweating, and striking at the nose. Many of these signs seem directed by the horse toward noxious sensations coming from the

nose or face. In one study, anesthesia of the infraorbital nerves at the infraorbital foramina prevented headshaking in 3 of 19 horses,[15] whereas in another, 24 of 27 horses stopped headshaking when the caudal nasal nerves were blocked.[16] The latter technique probably blocks the maxillary nerve in addition to branches such as the caudal nasal nerve and infraorbital nerve.[17] These results indicate that idiopathic headshaking is triggered in the caudal parts of the nasal passages in most horses.

Sensory nerve conduction studies have been used to show that the threshold for activation of the infraorbital nerve of headshakers is lower than that for normal horses.[7] Idiopathic headshaking that can be relieved by sensory nerve blocks is termed *trigeminal-mediated headshaking.* Some cases of headshaking are almost entirely induced by bright light and appear to represent summation of stimuli arriving via both the optic and trigeminal nerves.[3] It is not yet known how these clear-cut cases of *photic* headshaking are related to the much more numerous cases in which light is not directly involved or is only a weak trigger. It may be that photoperiod (i.e., the proportion of the day that is light) is more important than light intensity in such horses and may explain the role of season in many cases.[3] Whatever the inciting cause, idiopathic headshaking appears to be a nasal/facial pain syndrome associated with hyperexcitability of trigeminal pain pathways.[7] In humans, trigeminal neuralgia is often caused by vascular impingement on the trigeminal ganglion or nerve root adjacent to the brainstem. Trigeminal nerve root demyelination, a characteristic finding in humans with trigeminal neuralgia, has not been found in headshakers.[18]

Horses with headshaking should undergo a complete physical examination; ophthalmic, otoscopic, neurologic, and dental examinations; endoscopic examination of nasal passages, pharynx, and guttural pouches; radiography of the skull; and a complete blood cell count and chemistry panel. When available, CT is the preferred imaging technique. No abnormalities are usually noted in these examinations.

■ Treatment

Physical.

Mild cases of headshaking that occur during exercise can often be partially suppressed by the use of muzzle nets or devices that dangle over the face and nostrils. Approximately 30% of horses managed with muzzle nets showed at

least 70% improvement, although the durability of any salutary effect has not been established.[19] There was no difference between the effectiveness of full face nets and that of nasal nets. A number of organizations and jurisdictions now allow horses to be shown wearing a muzzle net. A few horses respond to a heavy hair net or a dangling device that makes contact with the nose area or upper forehead. This type of contact may prevent the nerve from firing, in a manner similar to blocking a sneeze by placing a finger under the nose and applying pressure.[20] Facemasks and contact lenses that substantially reduce ambient light are available and are very effective in preventing photic headshaking.[3] Some researchers have argued that bitless bridles may be helpful if the action of the bit triggers headshaking.[21] These devices have been used widely.[6]

Surgical.

Surgical approaches to headshaking are controversial because considerable morbidity and even severe suffering are frequent side effects of the procedures.[6] Notwithstanding these problems, surgery does appear to achieve a permanent cure in some horses.[15-17,22] The objective of surgery is interruption of pain pathways in the trigeminal nerve or its branches. Two approaches have been used: infraorbital neurectomy and caudal infraorbital nerve compression. In the first procedure, a 2-cm section of nerve is removed just rostral to the infraorbital foramen.[15,22] To effect nerve compression, up to eight platinum embolization coils are introduced via the infraorbital foramen and packed around the infraorbital nerve within the caudal aspect of the infraorbital canal.[16,17] Five of 26 horses (19%)[15,22] and 26 of 57 (46%)[16] horses had long-term elimination of headshaking after infraorbital neurectomy and caudal compression, respectively. Temporary remission of headshaking was achieved in other horses but was followed by relapse weeks to months after surgery. Further long-term remissions were achieved when the procedure was repeated in some of the horses that suffered relapse.[16,22] Exacerbation of headshaking and self-inflicted trauma around the muzzle and lips were problems in most horses after these procedures. These complications typically resolved within weeks but were persistent in some; four of these horses were euthanized because of the severity of signs. The results of nerve blocks was not completely predictive of response to surgeries; however, two of three horses that responded to infraorbital blocks achieved complete remission with infraorbital neurectomy.[15] Tracheostomy has been shown to be effective as a salvage procedure, presumably by bypassing the

passage of air through the nasal passages.[6]

Medical.

It is unlikely that complete and permanent remission can be achieved medically. Cyproheptadine, 0.3 mg/kg PO twice daily, has been used with some success for photic headshaking[3] and with limited success in other cases of idiopathic headshaking.[4,15,23] Mild lethargy and colic are occasional side effects. Headshaking can be suppressed for variable periods by the potent analgesic antiseizure drugs carbamazepine and gabapentin, but effects are often not complete, and signs return within several weeks after treatment begins.[6,24] Cyproheptadine may potentiate the analgesic actions of carbamazepine. In one horse, persistent 95% remission was obtained by the CT-guided injection of glycerol into the trigeminal ganglia.[25] Individual horses are reported to have responded to corticosteroids or antihistamines, which perhaps indicates a role for allergic rhinitis in those few cases, but intermittent treatment with high-dose dexamethasone or NSAIDs is ineffective.[2,15,26] Melatonin is advocated as a way to suppress the neurologic responses to increasing photoperiod (i.e., seasonal effect), so it should be started before the anticipated seasonal onset of headshaking.[3] This has reportedly been effective in a few cases. Various other supplements and traditional or alternative products have anecdotal or conceptual support with (as yet) no evidence. Most of them are inexpensive and nontoxic at recommended doses. There are protocols for chiropractic therapy and acupuncture for headshaking. These have not been successful in the author's experience.

Electrical Nerve Stimulation.

Percutaneous electrical nerve stimulation (PENS) of the infraorbital nerves is a promising technique for the management of trigeminal-mediated headshaking. Nerves are stimulated by subcutaneously positioned portable PENS probes.[27] After three treatments with a neurostimulation device, five of seven horses had durable positive responses, returning to work at the same level as before the onset of headshaking. Median remission time was 15.5 weeks (range, 0 to 24 weeks). PENS treatments need to be repeated when clinical signs return. The procedure has now been used in more than 130 horses, of which approximately 50% have returned to their previous level of activity.[28] The logical next step would be the development of programmable implantable nerve stimulators that

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could conveniently be used for long-term control of trigeminal-mediated headshaking.

Small Ruminant Lentivirus Infections

Mary O. Smith • Lisle W. George • John R. Middleton

Maedi-visna virus and caprine arthritis–encephalitis (CAE) virus are retroviruses in the subfamily Lentivirinae that constitute a single virus group, termed the *small ruminant lentiviruses,* which can cross between small ruminant species.[1-3] These agents are enveloped RNA viruses.[4]

■ Definition and Etiology

Maedi-Visna Virus Infection (Ovine Progressive Pneumonia Virus Infection; Zwoegerziekte)

Maedi-visna virus causes a chronic disease of sheep.[1-4] Visna virus, which affects the brain, is closely related to the many lentiviruses that cause immunodeficiency and neurologic disease in other species; these viruses include equine arteritis virus, CAE virus, and simian, feline, and human immunodeficiency viruses.[5] The respiratory aspects of the viral infection (maedi virus) are discussed in Chapter 31.

■ Epidemiology

Maedi-visna virus is spread through ingestion of infected milk by neonates, through in utero transmission, and horizontally within a herd.

■ Pathogenesis

After exposure to the virus, sheep develop an asymptomatic infection for as long as 6 weeks. Replication of the virus occurs in circulating cells during this stage of the infection.[6] Once the disease has been recognized, affected sheep should be slaughtered. Control measures are discussed in Chapter 31.

The lesions of maedi-visna virus infection are partly induced by the host's inflammatory response. Experimental immunosuppression of infected sheep ameliorates the severity of the clinical signs and reduces the CNS lesions without altering the amount of viral shedding.[7,8] The maedi-visna virus is in

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itself immunosuppressive, and infections may lead to a variety of secondary bacterial infections.[9] Chronic viremia is typical.

■ Clinical Signs

Neurologic disease caused by maedi-visna virus is relatively rare. Adult sheep and lambs as young as 4 months of age can be affected.[10] Nervous system signs may be characteristic of a diffuse encephalitis and include ataxia, twitching of the facial muscles, conscious proprioceptive deficits, circling, and blindness; gait along a straight path is normal, but the animal staggers or stumbles when turned or when forced to perform a complex maneuver. Coma, convulsions, and hyperexcitability may occur in the terminal stages. Other sheep have gradually progressive limb weakness and ataxia, often worse in the rear limbs; neurologic dysfunction localized to the spinal cord may be the sole clinical manifestation of maedi-visna virus infection.[11] Some sheep merely show emaciation without neurologic signs. Others may show nonsuppurative, progressive arthritis of one or more joints or symmetric enlargement of the mammary gland. The time between the onset of clinical signs and death is highly variable but can be as long as 2 years. The presence of antibody in the serum is considered evidence of active infection.[12,13]

■ Clinical Pathology

The CSF of affected animals is characterized by pleocytosis, with the cell counts ranging from 1012/dL to 1478/dL in animals infected for 1 month and 4 years, respectively.[14] The protein concentrations of CSF can range from 50 to 100 mg/dL for 30 days after infection. Antiviral antibody and virus can be detected in CSF specimens.

■ Pathology

Gross lesions of visna infection are rare when inflammation and malacia are extensive. In such cases, areas of yellowish tan discoloration are present in white matter.[15] The microscopic lesions of visna are predominantly those of a diffuse, nonsuppurative, perivascular inflammation throughout the neuraxis; white matter is affected more severely than gray matter. Lesions include demyelination, gliosis, lymphocytic choriomeningitis, and focal necrotic areas that are infiltrated by macrophages.[16,17]

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■ Diagnosis

The diagnosis of visna infection starts with recognition of the clinical neurologic disease in groups of animals in which the pulmonary, joint, or mammary form of the disease is also present. Agar gel immunodiffusion (AGID) testing has been superseded by more accurate ELISA and PCR tests.[18] The diagnosis and epidemiologic features of maedi-visna virus infection are discussed in detail in Chapter 31.

■ Treatment and Control

No effective treatment for maedi-visna virus infection is available. Prevention is based on herd hygiene and culling of affected animals, as described in Chapter 31.

■ Definition and Etiology

Caprine Arthritis–Encephalitis Virus Infection (Infectious Leukoencephalomyelitis)

CAE is caused by a small ruminant lentivirus that is closely related to the virus that causes maedi-visna virus infection in sheep.[1]

■ Epidemiology

The disease is distributed worldwide but tends to be more common in regions with intensive goat-rearing operations.

■ Pathogenesis

When inoculated into goats, the virus causes a chronic infection characterized by demyelinating encephalomyelitis, arthritis, and interstitial pneumonia. The pathologic changes resemble those of an autoimmune process and are probably caused by interactions among the host's immunologic responses, denatured myelin, and the virus.[2]

■ Clinical Signs

The systemic manifestations of the disease are thoroughly discussed in Chapter 38. The leukoencephalomyelitis form of CAE occurs predominantly in goats

younger than 1 year of age; occasional cases occur in older goats.[3] The clinical signs of leukoencephalomyelitis are highly variable but typically involve the spinal cord. Signs include progressive ataxia, paraparesis, paraplegia, tetraparesis, tetraplegia, hemiparesis, and hemiplegia. Goats with lesions in the cervical spinal cord (L1 to L4 levels) are recumbent and unable to raise their heads from the ground. They may show resistance to passive neck flexion. Spinal reflexes range from hypertonia and hyperreflexia to hypotonia and hyporeflexia. Intracranial signs may also develop; these include head tilt, nystagmus, tremors, torticollis, salivation, depression, coma, and opisthotonos.[4-10] Vision and pupillary light reflexes may be diminished. The neurologic deficits may be either symmetric or asymmetric. This diversity of signs is related to the variable location of lesions in the CNS.

Other signs that may be associated with CAE infection include fever (although the occurrence of this, too, is highly variable), enlarged joints, mammary gland enlargement (usually symmetric), vague and shifting leg lameness, weight loss, and tachypnea without significant auscultatory abnormalities.

The major differential diagnostic considerations for the neurologic form of CAE include head or spinal trauma, listeriosis, cerebrospinal nematodiasis (verminous meningoencephalomyelitis caused by *Parelaphostrongylus tenuis*, the meningeal worm of the white-tailed deer), and multisystemic infections with *Mycoplasma* spp. The CAE virus causes neurologic lesions in numerous regions of the CNS, whereas the lesions of listeriosis are generally restricted to the brainstem. Mycoplasmal infections typically affect kids 1 to 6 months of age, and affected animals are systemically ill and often display septic polyarthritis and polyserositis. *Mycoplasma* infections of goats are described further in Chapter 38. Verminous meningoencephalomyelitis and CAE virus can be presumptively distinguished by serologic or PCR testing for CAE virus and CSF analysis, season, and geographic distribution of the white-tailed deer host for meningeal worm. However, the neurologic forms of these diseases cannot be definitively diagnosed by these means.

■ Clinical Pathology

The results of hematologic and blood chemistry analyses are generally normal; however, in one study of affected goats, total plasma protein levels were increased and hypergammaglobulinemia was common.[4] The changes in the CSF

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are characteristic of a chronic granulomatous inflammation. Specific changes include an increased protein concentration and pleocytosis.[11] Cell counts in the CSF of affected goats range from 5/dL to 1800/dL, and the protein concentration ranges from 0 to 700 mg/dL.[3]

■ Pathology

Gross pathologic changes in the CNS of naturally infected goats include cloudiness of the meninges and tan discoloration of the white matter.[3] Microscopic changes include disseminated perivascular accumulations of mononuclear cells, demyelination originating in the subependymal region, astrocytosis, and mononuclear leptomeningitis.[2,4,8,12,13] Spinal cord lesions are most frequently observed in the thoracolumbar segments.[3]

■ Diagnosis

Previously, an AGID test was used for the diagnosis of CAE, but this has been superseded by ELISA and PCR tests.[12,14] The virus may also be cultured from infected tissue.[15]

■ Treatment and Control

No treatment is available for goats with leukoencephalomyelitis. Control measures are discussed in Chapter 38.

Border Disease (Hairy Shaker Lambs; Hypomyelogenesis Congenita)

■ Definition and Etiology

Border disease is a congenital infection of sheep and goats caused by a noncytopathic togavirus (genus *Pestivirus*).[1] The border disease agent is antigenically similar to the viruses that cause bovine viral diarrhea (BVD) and hog cholera (classical swine fever). Once introduced into a flock, the border disease virus causes abortion, infertility, and deformities in lambs. In a naive ewe, viral infection during pregnancy results in a variety of complications, including early embryonic death, abortion, and stillbirth, and lambs that survive are small and malformed. It is important to note that lambs infected in utero become immunotolerant and remain viremic for life, similar to calves

persistently infected with BVD virus.[2] Adult sheep that become infected with the border disease virus develop an inapparent, short-lived viremia and become immune to reinfection.

■ Epidemiology

Border disease is transmitted both vertically and horizontally.[3,4] As with BVD in cattle, the major reservoir in infected herds is the congenitally infected, seronegative animal that shows no symptoms.[2,5] Such animals may shed the virus through the placenta, infected offspring, saliva, respiratory secretions, urine, or feces.[3,6] In one seroepidemiologic study of infected ewes in the western United States, lambs were more often seropositive than were ewes.[2] A large percentage of the seropositive lambs were born to seronegative ewes, which indicated the presence of a large amount of virus cycling from carriers that have no symptoms. Strain-related differences in viral pathogenicity appear to exist.[7]

■ Pathogenesis

Hypomyelination is probably caused by a combination of virus-induced degeneration of the oligodendroglial cells (dysmyelinogenesis), persistent viral infection, and diminished secretion of the thyroid hormones.[8] The diminished production of thyroid hormones is thought to be related to direct inhibition of the thyroid gland, because the pituitary activity of affected lambs appears to be normal. In lambs infected in utero, white and gray matter is decreased in the spinal cord as a result of the decreased myelin content.[9] Depressed blastogenic activity of lymphocytes, a decrease in T-helper cell function, and an increase in T-suppressor cell function have been demonstrated in affected lambs between 4 and 7 months of age and indicate viral immunosuppression.[3,10,11] Such lambs may succumb to common diseases such as parasitism, diarrhea, and bronchopneumonia.

■ Clinical Signs

The severity of clinical signs in affected lambs varies. Changes are most marked in newborn lambs infected in early gestation (before 50 days). The CNS, skin, and skeleton are the most seriously affected. The hairs of congenitally affected lambs are coarse, straight, and elongated and stand out from the body like a halo.[12] The coat is abnormally pigmented and may have a dark-gray appearance

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or hyperpigmented spots that are especially prominent over the top of the neck.[13] Animals that survive shed the abnormal hairs at 9 to 12 weeks of age and replace them with normal hair fibers. Affected lambs also have a short, thickened body, shortened legs, smaller orbital size, and doming of the frontal bone.[14,15]

Arthrogryposis occasionally occurs. Some infected lambs show neurologic symptoms such as ataxia and uncontrollable tremors; the latter sign, combined with the characteristic hair coat, accounts for the common term “hairy shakers.” The tremors are coarse, involve the trunk and head, and disappear when the animal is asleep.[16,17] Affected lambs are often alert and appetent but initially need assistance to stand and nurse. Some animals walk normally but hop on the rear limbs when forced to run. The CNS signs usually disappear by 20 weeks of age, but the animals appear stunted. Affected animals have far lesser viability than do uninfected herdmates and may die unexpectedly. Aside from neonatal death losses, economic burdens imposed by the viral infection include low birth weights, diminished weaning weights, lowered carcass quality, and infertility.[15,18]

Abortions occurred 9 to 106 days after inoculation in 30% of experimentally infected sheep.[6,13,14] In field outbreaks, the average gestational age of the aborted fetus is 63 days. Teratogenic effects are most often observed when lambs are infected at 50 to 90 days of gestation.[19] Fetal mummification occasionally occurs.

The border disease virus is also pathogenic in goats.[20] As in sheep, inoculation of pregnant does results in fetal mummification and abortion. The spinal cords of infected kids are hypomyelinated, but the haircoat is normal.

The border disease virus has low pathogenicity in cattle. Abortions can be induced in cows inoculated with the virus at approximately 50 days of gestation, and affected calves have cerebral cavitations.[21] When cattle comingle with infected sheep, cattle can be naturally infected.[22]

■ Pathology

The macroscopic changes associated with border disease virus infection are hydranencephaly, porencephaly, microcephaly, cerebellar hypoplasia, abnormal curvature of the ribs, brachygnathia, doming of the frontal bones of the skull, narrowing of the distance between the orbits, a decrease in orbital size, shortening of the crown-to-rump and diaphyseal lengths, retention of secondary hair fibers, and abnormal skin pigmentation.

Microscopic changes in lambs with congenital infection include hypomyelinogenesis and hypercellularity of the white matter with abnormal-appearing glial cells.[16,17,19] The CNS shows dysmyelinogenesis, secondary demyelination, and periarteritis. Viral antigen can be demonstrated in CNS arterioles.[23]

■ Diagnosis

Identification of the viral antigens in tissues with fluorescent antibody tests is the most accurate method of diagnosing border disease. Tissues that most consistently contain viral antigens are those of the abomasum, pancreas, kidneys, thyroid, and testicles.[24,25] Serodiagnostic methods such as serum neutralization, AGID, and complement fixation tests have been developed.[26] In most cases, the BVD virus has been used as the indicator antigen. Serodiagnosis of infected lambs is difficult because the lambs tend to be immunotolerant and therefore do not develop strong serologic responses. The presence of viral antibodies in the CSF suggests border disease virus infection.

The differential diagnosis for border disease virus infections in sheep and goats includes other causes of infectious abortion, copper deficiency (swayback), and other viral diseases that may result in hydranencephaly, such as those caused by the Cache Valley, bluetongue, and Schmallenberg viruses.

■ Treatment and Control

There are no specific treatments. Control measures are centered on disease monitoring and biosecurity. In herd situations, virus isolation from whole blood or examination of skin biopsy samples by fluorescent antibody tests can help identify carriers.[24] Serologic testing is not a reliable indicator of infection because congenitally, persistently infected animals may be immunotolerant of the virus. Noninfected pregnant sheep should be separated from other members of the flock for the first 60 days of gestation to ensure that in utero infections do not occur.

Encephalitic Bovine Herpesvirus Infection

■ Definition and Etiology

Two herpesviruses, bovine herpesvirus type 1 (BoHV-1) and type 5 (BoHV-5),

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have in rare cases been associated with encephalitis in cattle.[1-4] BoHV-1 infection typically results in infectious bovine rhinotracheitis (IBR), an acute upper respiratory tract disease characterized by fibrinonecrotic white plaques of the nasal, pharyngeal, and tracheal mucosa and by abortions (see Chapter 31). Other clinical conditions associated with bovine herpesvirus infections include epizootic conjunctivitis (Chapter 39) and infectious balanoposthitis or vulvovaginitis (Chapter 43).

■ Epidemiology

Bovine herpesviruses cause disease in cattle worldwide. Epidemiologic factors that appear to favor dissemination of herpesviruses among cattle include a high stocking rate, repeated introduction of animals from diverse backgrounds, and mass weaning of calves at a time when the passively acquired anti-IBR antibodies are waning.[2] BoHV-1 may survive in the environment for up to a month; cooler ambient temperatures and higher humidity promote virus survival.[5] Calves younger than 6 weeks are most susceptible, but infection and resultant neurologic disease also have been described in adult cattle.[1,3,4,6-9] Animals that survive the disease become persistently infected; virus survives in the nasal and tracheal mucosa and the trigeminal ganglion.[9] Reactivation and virus shedding may occur during periods of stress.[4,5,9] Although clinical disease caused by reactivation of latent virus is usually mild and may go unnoticed, shedding of virus during such episodes can cause infection of in-contact animals. The viruses replicate in the nasal and pharyngeal mucosa. Brain involvement results from centripetal spread along the sensory neurons of the trigeminal and olfactory nerves.[9]

■ Pathogenesis

Encephalitic IBR infections cause a nonsuppurative meningoencephalitis that is widely distributed in the gray matter of the brain, primarily in the cerebrum and thalamus. The virus can usually be isolated from affected calves.[10] Signs of respiratory disease may precede or occur coincidentally with neurologic disease.[10]

■ Clinical Signs

The clinical signs of encephalitis include depression, mild nasal and ocular

discharge, conscious proprioceptive deficits, head pressing, aimless circling, bellowing, salivation, bruxism, paralysis of the tongue, head tilt, nystagmus, convulsions, blindness, coma, and death.[2,3] Seizure activity is characterized by a tonic-clonic convulsion with violent spasms or tremors of the head, with all four legs flexed and the head in opisthotonos. Rectal temperatures of 41° C and 42° C (108° F) have been reported.[6] Encephalitic herpesvirus infection is frequently fatal, although asymptomatic cases have been induced experimentally.[10] In experimental infection, signs develop 1 to 2 weeks after infection.

■ Clinical Pathology and Pathology

Mononuclear pleocytosis is found on analysis of CSF.[10] Extensive lymphocytic meningoencephalitis is evident on histologic examination. Intranuclear inclusion bodies are rarely observed in bovine herpesvirus encephalitis. Encephalitis may be evident on histopathologic examination of fetuses from cows that abort as a result of BoHV-1.[11]

■ Diagnosis

Accompanying respiratory disease raises the index of suspicion for herpesvirus encephalitis in animals with neurologic clinical signs. A rising serum titer of neutralizing antibody in surviving animals can be used to confirm infection, although this does not distinguish between BoHV-1 and BoHV-5. Specific diagnosis is usually made at necropsy through a number of modalities, including virus isolation, immunohistochemistry, and PCR.[12-14] Many of these tests do not distinguish between BoHV-1 and BoHV-5; more specific PCR tests can differentiate between these two virus types.[15]

Differential diagnoses for encephalitic herpesvirus infections in cattle include almost all encephalitic, encephalopathic, and neurotoxic diseases of cattle, including rabies, polioencephalomalacia, salt poisoning, and lead toxicity.

■ Treatment and Control

No specific therapy exists for the encephalitic form of BoHV-1 infection. Treatment is palliative and supportive and should include oral or intravenous fluid support, NSAIDs, antibiotics in animals with secondary bacterial pneumonia, and nursing care. Benzodiazepines or phenobarbital may be used for seizure control when necessary (Table 35.4). Animals with severe clinical signs

may be euthanized for humane reasons.

TABLE 35.4

Recommended Drug Dosages for Treatment of Cerebrocortical Disease

	Dosage	Route	Frequency
Anticonvulsant Drugs			
Diazepam or midazolam[a]	0.01-0.4 mg/kg	IV or IM	Twice daily or as needed
Pentobarbital sodium[b]	2-10 mg/kg	IV	Three times daily
Phenobarbital[a]	Loading dose, 20 mg/kg	IV	One time
	Maintenance dosage, 1-4 mg/kg	IV, PO, or IM	Divided twice daily
Antiinflammatory or Antiedema Drugs			
Methylprednisolone[a]	1-30 mg/kg	IV	One time
Dexamethasone[c]	1-4 mg/kg	IV or IM	Twice daily
Mannitol[a]	0.25-0.5 g/kg 20% solution	IV	Twice daily
Furosemide[d]	1 mg/kg	IV, IM, or SC	Twice daily
Flunixin meglumine[e,f]	1 mg/kg	IV or IM	Twice daily
Phenylbutazone[a,g]	2-4 mg/kg	IV or PO	Twice daily
Dimethyl sulfoxide (DMSO)[a]	1-2 g/kg	IV	Twice daily
Acetylsalicylic acid (aspirin)[a]	7-10 g/500 kg	PO	Twice daily

[a]Diazepam, phenobarbital, methylprednisolone, mannitol, phenylbutazone, dimethyl sulfoxide (DMSO), and aspirin are not FDA-approved for use in food-producing animals in the United States.

[b]Pentobarbital is approved at dosages of 0.44-1.1 mg/kg as a general anesthetic and 0.11-0.275 mg/kg as a sedative-relaxant in beef and dairy cattle.

[c]Dexamethasone is approved as an antiinflammatory for use in calves and in beef and dairy cattle administered IV or IM at a dose of 5-20 mg per animal or as an oral bolus or powder at 5-10 mg/animal on day 1 and 5 mg/day thereafter as required.

[d]Furosemide is approved at a dosage of 500 mg/animal once daily or 250 mg/animal IV or IM twice daily for no more than 48 hours after parturition for treatment of parturient mammary edema in beef and dairy cattle.

[e]Flunixin meglumine is approved at 1.1-2.2 mg/kg IV as a single dose or divided evenly into two doses administered 12 hours apart for up to 3 days for the control of inflammation associated with endotoxemia. It is also approved as a transdermal pour-on material for use in beef and dairy cattle for the control of pyrexia associated with bovine respiratory disease complex or pain associated with foot rot.

[f]Monitor for signs of gastric or abomasal bleeding (fecal occult blood).

[g]An initial oral loading dose of 10 to 20 mg/kg, followed by 2.5 to 5 mg/kg PO daily or 10 mg/kg PO every 48 hours thereafter, has been recommended for cattle. Because of the prolonged plasma half-life in ruminants, serial administration of the drug should be accompanied by careful monitoring of renal function and gastrointestinal bleeding. Use of phenylbutazone in dairy cattle

over 20 months of age is prohibited in the United States by the FDA. Other use in food-producing animals in the U.S. would be off-label, in which case the guidelines set forth in the Animal Medicinal Drug Use Clarification Act should be followed.

Many of the drugs and dosages listed below are not approved by the U.S. Food and Drug Administration (FDA) for use in food-producing animals for the treatment of cerebrocortical disease (lettered superscripts are explained in the table footnotes). Off-label use of drugs in food-producing animals should follow specific guidelines in the jurisdiction where the drugs are being administered.

Additional notes on use of these drugs in food-producing animal in the Umited States:

IM, Intramuscular; *IV,* intravenous; *PO,* oral; *SC,* subcutaneous.

Vaccines that protect against BoHV-1 have traditionally been considered potentially useful in the prevention of BoHV-5 infection because of the close antigenic relationship between the two viruses.[7,16] However, more recent trials have shown that certain BoHV-1 vaccines may not confer protection on cattle challenged with BoHV-5.[17,18]

In some European countries, eradication programs that employ testing and culling of infected animals have been successful in eliminating BoHV-1. Bovine herpesviruses can be spread through fomites and by aerosol transmission for up to 4 miles (6.4 km).[5] Strict biosecurity procedures are therefore essential for developing and maintaining virus-free herds.

Bovine Spongiform Encephalopathy ("Mad Cow" Disease)

Christine F. Berthelin-Baker • John R. Middleton

■ Definition and Etiology

Bovine spongiform encephalopathy (BSE) is a transmissible spongiform encephalopathy (TSE) of cattle that was first recognized in 1986 in Great Britain.[1] The TSEs are a group of slowly progressing, invariably fatal, neurodegenerative diseases that can affect humans and animals. They are also called *prion diseases* because of the accumulation of abnormal prion protein in the CNS. Since the prion hypothesis was first formulated in 1982, prions have been widely accepted as the etiologic infectious agents of the TSEs.[2] The prion is an altered conformation (PrP-BSE) of the normal prion protein (PrP), a host-encoded membrane protein that does not carry any nucleic acid. PrP-BSE replicates by inducing a post-translational conformational change in the normal

protein PrP to form the abnormal prion PrP-BSE.[2-4] After a characteristically prolonged incubation period, the abnormal isoform of the protein aggregates and accumulates in the CNS of affected animals, creating progressive neurologic dysfunction.

■ Epidemiology

Current evidence indicates that BSE resulted from a single agent.[5-10] BSE may have originated from feedstuffs containing rendered carcasses of scrapie-infected sheep, or it might have been a preexisting sporadic and rare disease unrecognized in the bovine population. The BSE epidemic was traced to the recycling of BSE-infected carcasses into cattle feed, which occurred mostly in the 1980s in the United Kingdom.[6] Cattle in other countries were affected as a result of the importation of infected feedstuffs or cattle, followed by later recycling the agent in their own rendered ruminant feedstuffs. At the time of writing, the OIE reported that BSE had been detected in 28 countries, including the United States.[11] Since 1986, more than 181,000 cases of BSE have been confirmed in Great Britain.[11] These cases were distributed among 37,170 farms.[12] The incidence of BSE was highest among the cattle cohorts born between 1986 and 1989, and the outbreak peaked in 1992, when 36,680 cases were detected by screening suspected clinical cases (passive surveillance) in Great Britain. Active surveillance has revealed a sustained and sharp decrease in the number of cases since 2001.[12] The decline in the Great Britain epidemic is directly related to the successive bans on the feeding of ruminant-derived meat and bone meal to cattle. The initial 1988 ban took effect in 1989 in the United Kingdom and has been tightened and refined since then. Similar feed bans have been adopted by many countries around the world. A list of countries that have reported home-born or imported cases of BSE and the number of cases reported each year is available and regularly updated on the website of the OIE.[11]

BSE has affected predominantly dairy cattle because of their longer life span and feeding practices, which in Great Britain included feeding animal-derived protein to youngstock. No clear genetic predisposition to BSE has been demonstrated in cattle, in contrast to scrapie in sheep, although offspring of affected cattle seem to be at increased risk for the disease. The epidemic (classical) form of the disease is considered to be a foodborne disease of cattle, associated with the ingestion of meat and bone meal contaminated with the BSE prion. This is substantiated by the steady decline in the incidence rate of BSE in

endemic countries since the enactment of bans on feeding ruminant protein to ruminants.[11]

Rigorous, active surveillance programs have been initiated in many countries to screen cattle and beef products for the BSE agent. As a result of this large-scale testing, two extremely rare prions were discovered on the basis of protease resistance patterns and glycopatterns.[13-16] These novel agents have been termed *H-BSE* and *L-BSE*, and animals from which these agents have been identified are said to have *atypical BSE*.[5] These cases have been detected in multiple countries by rapid prion detection tests conducted on aged (>8 years) cattle that were tested either during slaughter surveillance or through targeted surveillance of downer cattle. Investigations regarding the origin and pathogenesis of atypical BSE are ongoing. Owing to the advanced age of affected cattle and the low known prevalence of atypical BSE, it has been speculated that atypical BSE may arise spontaneously.[5]

■ Pathogenesis

The exact function of the normal prion protein is unknown, as are the mechanisms of abnormal prion protein (e.g., PrP-BSE) induced neurodegeneration and CNS dysfunction in TSEs. On the basis of research in transgenic mice expressing bovine PrP, the PrP-BSE is thought to undergo limited propagation in the distal ileum before spreading to the CNS, probably by moving through the gut-associated lymphoid tissue into the peripheral nerves.[17,18] Studies of naturally infected cattle, combined with experimental oral challenge studies in cattle, have revealed that BSE infectivity may exist in the brain; spinal cord; retinal tissue; optic nerve; cervical, thoracic, and trigeminal ganglia; facial and sciatic nerves; and the distal ileum. The skeletal muscles, spleen, and lymphatic tissues did not demonstrate infectivity.[19,20] Intracerebral inoculation of cattle has also been demonstrated to result in infectivity of the tonsillar tissue.[21] After a prolonged incubation period, accumulation of PrP-BSE in the CNS creates progressive and irreversible neurologic dysfunction.

■ Clinical Signs

As with all TSEs, BSE has a long incubation phase. It occurs mostly in 4- to 6-year-old cattle (age range, 20 months to 18 years), although the atypical forms tend to occur in cattle older than 8 years. The clinical signs of BSE usually have

an insidious onset.[22,23]

The detection of clinical signs of BSE and the array of clinical signs reported are influenced by how closely the cattle are being observed and the handler's awareness of the insidious and nonspecific nature of the clinical signs. Subtle early behavioral changes are unlikely to be observed in large herds. Affected cattle may become apprehensive, stay apart from their herdmates, and become fearful of their handlers. As the disease progresses, cattle often become extremely excitable, especially when restrained or placed in confined quarters or an unfamiliar environment. Cattle with BSE may refuse to move through previously familiar doorways and become impossible to restrain. Unprovoked aggression is less frequent. Hyperesthesia is most marked around the head and neck. A light touch on the hindlimbs may induce violent and often repetitive kicking, which may also be observed during milking. Animals may overreact in response to sudden visual, tactile, or auditory stimuli. The startle reaction may be gauged by a hand test (punching fist abruptly toward the animal's head without touching it), flashlight test, a hand clap, or a loud metallic “bang.” Normal animals rarely startle in response to such stimuli, or they may startle once or twice when the stimulus is repeated. Cattle with BSE frequently startle violently and repeatedly, with no habituation to a repeated stimulus. In some cases, the response may escalate to an extreme aberrant startle, with headshaking and seizure-like head bobbing, which may be followed by violent turning, running around, and falling.

Other possible clinical signs of BSE include ptyalism, increased head rubbing, muscle fasciculations, and excessive vocalization. Other behaviors observed in animals with BSE may include frequent and repetitive head tossing, licking of the nostrils, yawning, flehmen response, head butting, and restlessness.[24] Because of the hyperexcited state of these animals, tachycardia is expected; however, relative bradycardia (60 beats/min) may be observed. Affected animals often lose weight and have reduced milk output. Ataxia and tremors occur in more advanced cases. Tremors most often involve the head and neck and may become generalized, especially with exercise. Ataxia is most marked on turns, when the animal goes over steps, or on uneven terrain; it may also be accentuated with exercise. Animals with BSE may become recumbent and unable to feed if the disease is left to run its course. Recumbency may also be triggered by an intercurrent illness or an injury during a fall. The clinical signs of BSE may be more difficult to recognize in animals that have become recumbent than in less advanced cases,[25] and systematic targeted surveillance of downer

cattle (fallen stock) have allowed for the detection of previously unsuspected cases of BSE in various countries.[26]

■ Diagnosis

No in vivo test is approved for the diagnosis of BSE. The diagnosis can be confirmed only by postmortem examination and is based on microscopic brain examination or tests that identify the abnormal prion in brain or spinal cord tissue.[1,27] Rapid prion tests include Western blot, paraffin-embedded tissue (PET) blot, and ELISA.[28-31] Rapid tests have enabled the detection of BSE through surveillance in targeted at-risk populations such as fallen (downer) cattle.

Histopathologically, BSE is characterized by neuronal degeneration and intraneuronal vacuolation in specific brain areas. The vacuolation is accompanied by or preceded by the accumulation of PrP-BSE.[6,7,32] The obex of the medulla is currently considered to be the tissue of choice for detection of the BSE agent.[33]

Nervous system diseases that could be confused with BSE include viral encephalopathies (pseudorabies, rabies, Borna encephalitis, bovine immunodeficiency virus encephalitis), listeriosis, polioencephalomalacia, lead poisoning, CNS parasitic migration, brain tumors and abscesses, and vitamin A deficiency. Hepatic encephalopathy and other metabolic imbalances may also be confused with BSE. Because of the insidious nature of BSE, affected cattle may appear to recover coincidentally with blanket therapy for suspected metabolic imbalances and later exhibit relapse. This must be kept in mind whenever therapy for metabolic imbalances initially appears to be successful but is followed by one or more relapses.

■ Treatment and Control

BSE is always fatal, and no treatment is available.

Various measures have been taken to protect public health by removing potentially infected animals and tissues from the food chain. The disposal of BSE-infected tissues and the sourcing of bovine tissues and body fluids for the preparation of medicinal products must take into account the extreme resistance of TSE agents. All TSE agents remain infectious after exposure to a wide range of inactivating treatments and environmental changes such as autoclaving, rendering, storage for months to years, exposure to ultraviolet light, freezing,

thawing, prolonged boiling, and incubation with formalin.[34-36] Because of the public health risk, the carcasses of animals suspected of having BSE should be disposed of in an alkaline-hydrolysis tissue digester designed to inactivate TSE agents.[37]

In countries that have had an outbreak of BSE, the complete exclusion of ruminant tissues from ruminant feed has aided progress toward eradication of BSE, as previously noted. In the United Kingdom the initial feed ban of 1988 was found to be insufficient and was reinforced by successive measures. The 1996 ban on feeding mammalian meat and bone meal to all farmed animals was introduced to prevent contamination of ruminant feed at feed mills and down the supply chain to the farm. Because of the long incubation period of BSE, the implementation of feed control measures did not reduce the incidence of this disease immediately.

■ Public Health Consideration and BSE in Other Nonbovine Hosts

Since the onset of BSE epidemics, new TSEs have been identified in animals other than cattle. Strain typing in mice showed that these new TSEs were caused by the BSE agent,[38,39] which has proved to be a relatively promiscuous TSE agent, capable of experimentally infecting mice, sheep, goats, pigs, cats, mink, and primates.[5] The disease in humans, termed *new-variant Creutzfeldt-Jakob disease* (vCJD), was first identified in 1996 in the United Kingdom, where it had affected 178 people as of April 2018.[40] Other countries have detected vCJD cases in people who had lived in the United Kingdom between 1980 and 1996, as well as in citizens who never traveled to the United Kingdom. The emergence of vCJD has put worldwide emphasis on the prevention and detection of TSEs in animals. The route of infection of people by BSE has not been clearly traced, but a case-control study demonstrated that the consumption of food that included infected cattle nervous tissue was associated with increased risk of vCJD.[41] This and other evidence has led to successive “Specified Risk Materials” bans in many countries, aimed at preventing contamination of human food with nervous system or other specified high-risk tissues from ruminant animals.

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Scrapie

■ Definition and Etiology

Scrapie is a TSE that naturally affects sheep, goats, and mouflons. It is the oldest known TSE, described more than two centuries ago. The causative agent is considered to be an abnormal prion (PrP-Sc) distinct from that of BSE.[1] At least three distinct types of the scrapie agent have been identified in the natural hosts.[1] Although sheep are susceptible to experimental challenge with the BSE agent, natural BSE has not been reported in sheep.[1]

■ Epidemiology

Scrapie occurs endemically in sheep flocks worldwide, with the exception of Australia and New Zealand.[1] Sheep are the natural host of scrapie, but the infection can be maintained in goats that have no direct contact with sheep, which indicates that transmission in goats is both lateral and vertical.[2-4] Scrapie cases occur sporadically in infected flocks. Only one or a few animals are affected at any given time. Outbreaks may occur if scrapie is introduced into a genetically susceptible flock.

Although no breed is known to have a predisposition to scrapie, the genetic makeup of the host controls differences in susceptibility and resistance to scrapie in various breeds.[1,5,6] The molecular basis of this resistance is largely controlled by the PrP gene.[7] Polymorphisms at three codons of this gene (136, 154, and 171) appear to be the main determinants of the susceptibility of sheep to scrapie.[1] According to current evidence, the genotype $VV_{136}RR_{154}QQ_{171}$ (or $AA_{136}RR_{154}QQ_{171}$ in some breeds) is most susceptible, and the genotype $AA_{136}RR_{154}RR_{171}$ is highly, but not completely, resistant.[1] Susceptibility is most clearly linked with variation at codons 136 and 171 in breeds studied to date; the genotype of a particular animal is often referred to as *RR, QR,* or *QQ* to designate the alleles at site 171. Pedigree, phenotypic expression of the disease, or genetic testing may be used to identify sheep with “resistant” PrP genotypes. Genetic polymorphisms or the PrP gene may also influence susceptibility to scrapie, the incubation period for scrapie, or both in goats.[8]

■ Pathogenesis

In contrast to BSE, which is restricted to the gut-associated lymphoid tissue and nervous tissue, the scrapie agent can be identified in infected sheep in various nonneural tissues such as those of the lymphoreticular system, kidney, and placenta.[9,10] This difference has facilitated the development of lymphoid tissue biopsy techniques to detect scrapie (described later). Most transmission of scrapie appears to take place during the birthing season.[1] The scrapie agent is probably spread by the placentas and birthing fluids of infected animals,[11,12] and oral uptake is considered the probable route of entry.[11-13] Transport of PrP-Sc to the CNS probably occurs along the vagus nerve from the GI tract,[14] and in most cases the agent can be demonstrated in the vagal nucleus of the brainstem early in the stage of neuroinvasion.[15] It then spreads into higher brain centers. Dysfunction of the CNS appears to correlate approximately with accumulation of PrP-Sc in the brain; however, subtle dysfunction can occur with little or no characteristic histologic changes. The exact mechanism that causes neurologic dysfunction remains to be fully defined.[9]

■ Clinical Signs

Most animals with scrapie are 1 to 5 years old. The clinical course varies but is typically slow and may last several months. Early behavioral changes are often accompanied by weight loss. Animals with scrapie may stay apart from the flock and become nervous and restless.[16] Pruritus of increasing intensity is a common feature; affected sheep may rub on fixed objects, scratch with their horns or hooves, and bite or lick themselves excessively. The head, withers, flanks, back, rump, base of the tail, and lower limbs are typically affected, showing secondary wool loss, dermatitis, and skin infections or excoriations.[2,16] Head and face rubbing and shaking may also cause ocular lesions or aural hematomas. When scratching the pruritic areas (mostly the back and rump), the animal may display a “scratch reflex” (or “nibble reflex”), which may include reflex nibbling, lip licking, and rhythmic head movements. This reflex is often, but not always, present in scrapie cases. This response may also be observed in other CNS diseases and in pruritic skin diseases, particularly ectoparasitism, so it should not be considered specific for scrapie.

Other clinical signs of scrapie include bruxism, ptyalism, and regurgitation. Tremors may start with the head and generalize to the whole body. Apathy, exercise intolerance, hypermetria, and ataxia may develop. Animals with the most severe and advanced cases show stupor, episodic collapse, and convulsions.

Death may occur during a convulsion or as a result of starvation. The clinical signs of scrapie in goats are broadly similar to those in sheep.[2,3,17-19] Scrapie has been identified in fallen (down) sheep as well.

■ Diagnosis

Because the scrapie agent can disseminate in lymphoid tissue before the development of clinical disease, immunohistochemistry studies may show PrP-Sc in biopsy samples containing lymphoid tissue from the tonsils,[20] nictitating membranes,[21] retropharyngeal lymph nodes,[22] or rectoanal junction.[23,24] However, these tests have limited sensitivity, primarily because of variable lymphoid involvement among infected sheep, a phenomenon that may be associated with the host's genetic makeup.[25] Microscopic examination of the brain and spinal cord is the classic diagnostic method for scrapie. The scrapie agent is possible to identify only when tissues are collected soon after death, before autolytic changes take place. Neuronal vacuolation and PrP-Sc deposits are found in specific brain nuclei.[26-31] Collection of brainstem tissue (particularly the obex), tonsillar tissue, and medial retropharyngeal lymph nodes is currently recommended for testing suspect sheep in the United States.[32] In autolyzed tissues, PrP-Sc can be identified by immunohistochemistry testing, Western blot tests, or ELISA.[33-36] As with BSE, heightened active surveillance for scrapie has revealed at least one atypical strain of scrapie (termed *atypical scrapie*).[37]

Nervous system diseases that could be confused with scrapie include pseudorabies, rabies, Borna encephalitis, listeriosis, polioencephalomalacia, lead poisoning, cerebrospinal nematodiasis, gid (coenurosis), brain tumors, brain abscess, maedi-visna virus infection, vitamin A deficiency, pregnancy toxemia, and other metabolic imbalances. When pruritus is the only clinical sign, skin diseases such as psoroptic and sarcoptic mange, ringworm, myiasis, pediculosis, and atopy may be considered in the differential diagnosis. Because of the insidious nature of the illness, animals with early scrapie may initially appear to respond to a variety of treatments. This must be kept in mind whenever specific therapy for another suspected illness appears initially to be successful but is followed by relapse. When therapy of an alternative condition fails, the final diagnosis must rely on detailed examination of postmortem samples, as discussed previously.

■ Treatment and Control

Scrapie is a fatal and irreversible disease for which there is no known treatment.

Because there is no effective treatment for scrapie, control measures designed to prevent the spread of the disease are especially important. Scrapie is a reportable disease. Eradication measures vary from country to country. Animals suspected of having scrapie are destroyed. Contaminated pastures or paddocks may be left empty of livestock, but the scrapie agent is unlikely to be inactivated in the environment. Contaminated stalls, corrals, and sheds should be disinfected with sodium hypochlorite diluted at 4% available chlorine. In the United States and Canada, scrapie-affected and related animals are destroyed, and their flocks are quarantined. Lines of sheep genetically resistant to the development of clinical scrapie have been developed,[38,39] and genotype testing is currently used to select for resistance to the disease.[1]

■ Public Health Considerations

Although scrapie has been endemic in various areas of the world for more than two centuries, epidemiologic studies have not shown any correlation between the incidence of Creutzfeldt-Jakob disease in humans and that of classical scrapie in sheep; the zoonotic potential of atypical scrapie remains under investigation.[1] It is nevertheless prudent to take precautions to minimize the potential for human exposure to scrapie because of the high fatality rate characteristic of TSEs and the potential for emergence of novel strains of prions with unknown host ranges.[1]

Pseudorabies (Aujeszky's Disease, Mad Itch, Bulbar Paralysis)

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■ Definition and Etiology

Pseudorabies is an acute, severe, and usually fatal encephalitis caused by an encapsulated DNA virus, Suid herpesvirus type 1, a member of the genus *Varicellovirus*, subfamily Alphaherpesvirinae, family Herpesviridae.[1,2] This virus can infect the CNS and other organs (e.g., respiratory tract) of virtually all mammals except humans and most primates. Domestic and feral swine are the

natural hosts and may become latent carriers. The virus can also infect cattle, sheep, cats, dogs, goats, wildlife (e.g., raccoons, opossums, skunks, rodents), and, in rare cases, horses.[3,4]

■ Epidemiology

Pseudorabies has a worldwide distribution and, although cases occur only sporadically, is an economically important disease because of the regulatory quarantine and other restrictions imposed on animals from affected herds. This disease was endemic in the United States, but it has been successfully eradicated in domesticated swine. In the United States, all states are currently classified as free of pseudorabies in domesticated swine (OIE status V), although pseudorabies virus remains present in feral pigs in parts of the country.

The viral infection in cattle is perpetuated partly by the occurrence of latent infections in pigs, which can be recrudesced by stressful conditions.[5] The virus is occasionally transmitted from swine into ruminants because of the proximity of the two species in many livestock operations.[6,7] The natural routes of transmission include nose-to-nose, fecal–oral, and venereal.[2,8] Indirect transmission usually occurs by inhalation of aerosolized virus. The virus may travel via aerosols up to 2 km (1.2 miles) in certain weather conditions and may survive up to 4 days in straw bedding. It is inactivated by drying, sunlight, and high temperatures (≥37° C). Dead-end hosts such as dogs, cats, and wildlife can transmit the virus between farms, but aside from feral swine, these animals survive only 2 to 3 days after becoming infected.

Latency of the viral infection in ruminants is not an important mechanism for perpetuation of an outbreak because most affected animals die within 48 hours of disease onset. In the few that survive longer, shedding in saliva occurs for up to 6 days after infection. The virus is unlikely to be transmitted directly from infected and uninfected cattle.[7] Wild mammals such as raccoons may play a role in pseudorabies survival and transmission;[9] rats, however, develop transient infections and do not appear to transmit or perpetuate the virus.[10] The pseudorabies virus may survive in contaminated meat products for up to 7 weeks. The role of this prolonged survival in perpetuating outbreaks in ruminants is unknown.

■ Pathogenesis

Ruminants are susceptible to pseudorabies infection after intradermal,

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subcutaneous, intranasal, or oral exposure to the virus. After subcutaneous, oral, or nasal infection, the virus spreads centripetally to the CNS by axonoplasmic transport. During the acute infection, the virus may be present in the nasal mucosa, secretions, and saliva.

■ Clinical Signs

The incubation period ranges from 90 to 156 hours, and the illness may last 8 to 72 hours, although some affected animals have been found dead without having exhibited any clinical signs.[6,11] The initial clinical sign in ruminants is usually acute and severe pruritus that induces self-trauma, dermal abrasions, swelling, and alopecia.[11] Other signs may include fever, bellowing, bloat, feet stamping, excessive salivation, twitching, chewing of the tongue, ataxia, circling, nystagmus, and strabismus.[12,13] Some affected animals exhibit aggression, but most become depressed. As the disease progresses, affected animals may exhibit hyperesthesia, tenesmus, excessive licking of the nostrils, continuous mastication, vocalization, coma, convulsions, and opisthotonos. Most cases are fatal. The clinical signs of pseudorabies in cattle closely resemble those of rabies, polioencephalomalacia, salt poisoning, meningitis, lead poisoning, hypomagnesemia, and enterotoxemia.

■ Clinical Pathology

The pseudorabies virus can be isolated from the pharyngeal or nasal secretions of affected animals and can be easily cultured from infected nervous tissues. Strains of pseudorabies virus are antigenically distinct from other herpesviruses but share common antigens with the IBR virus. Heterospecific antibodies to the IBR virus may cross-neutralize the pseudorabies virus and confound serologic tests. For virus culture, tissues should be collected from sensory ganglia or the dorsal horn of the spinal cord. Segments serving the pruritic sites should be collected preferentially because these areas contain the highest concentration of virus.

■ Pathology

Gross findings include excoriation, alopecia, edema, and hemorrhage at the pruritic site. The neuropathologic changes include nonsuppurative encephalitis, neuronal degeneration, and eosinophilic intranuclear (Cowdry type A) inclusion bodies. The lesions are most pronounced in the dorsal nerve rootlets and the

dorsal horn.[11]

■ Treatment and Control

There is no treatment for pseudorabies, which is usually fatal in livestock, but rare recoveries have been reported.[13]

The most effective method of preventing pseudorabies virus infection in ruminants is eliminating their exposure to swine. Contaminated pens can be disinfected with 10% sodium hypochlorite solution, quaternary ammonium compounds, tamed iodine, or phenolic compounds.[14] At least 5 minutes of contact time should be allowed before the disinfectant is rinsed from the contaminated surfaces. Fumigation with formaldehyde for 6 hours effectively kills the virus, as does 360 minutes of contact with ultraviolet light.

Ovine Encephalomyelitis (Louping Ill)

■ Definition and Etiology

Louping ill is an acute, fatal encephalomyelitis of sheep that occasionally infects humans, wild ruminants, horses, and cattle.[1-3] The disease has been reported in England, Scotland, Ireland, Norway, Turkey, and Bulgaria.[4-6] The etiologic agent of louping ill is a neurotropic, single-stranded RNA virus (flavivirus) that is transmitted primarily by the tick *Ixodes ricinus,* as well as by *Rhipicephalus appendiculatus, Ixodes persulcatus,* and *Haemaphysalis anatolicum.* Most outbreaks occur in swampy areas with dense populations of infected ticks and wild animals. Infection through blood contamination of hypodermic needles, other fomites, and blood products has been reported.[7] Minor genetic variations of the viruses exist in different geographic areas, constituting four subtypes.[8]

■ Epidemiology

Louping ill affects principally yearling sheep in the spring, although lambs and adults can be affected. Maternal immunity wanes when lambs are approximately 3 months old. Infection develops weeks to months after sheep have been placed on pastures inhabited by infected ticks. In an outbreak, the prevalence of clinical louping ill is low, but the seroprevalence of antibodies in adult sheep in endemic areas is high, which indicates a continuous, low-level exposure to the virus, and many animals are affected without showing symptoms. Factors such as climate,

tick population, and immune status of the flock all play a role in the severity of an outbreak.[7] The attack rate may reach 60% of the population, but the mortality rate rarely exceeds 15%. Adults tend to be more heavily parasitized by the host ticks and thus play a major role in virus survival and transmission.[9] Pigs, goats, cattle, horses, and red deer also become infected with the virus and can develop similar clinical disease.

In sylvatic cycles of virus transmission, viral amplification takes place through certain wild mammals and red grouse.[1,10,11] The hare serves as an important source of virus for the red grouse.[12,13] The red grouse is infected by ingesting, rather than by being bitten by, the infected tick.[14]

The high incidence of louping ill in the spring and summer months probably corresponds to the peak activity of ticks. The virus may persist for long periods in the arthropod vector, but it is unclear if transovarial transmission of the agent occurs. *I. ricinus* is a three-host tick with a life cycle of 3 years. These ticks do not walk, and so dissemination requires animal transport. After a blood meal, the tick molts and then rests on vegetation until the next meal, approximately 12 months later. The activity of the ticks tends to increase greatly in the spring whenever the ambient temperatures are above 7° C (43° F).

■ Pathogenesis

Ticks become infected when feeding on a viremic host. The virus survives in the salivary glands of the tick and can overwinter there, being transmitted to a new host when the tick becomes active the following year.[7] After inoculation into susceptible sheep, the louping ill virus migrates into the regional lymph nodes and spleen and then replicates. Viremia occurs 6 to 20 days after invasion into the lymphatic tissues.[2] Viral replication in the brain causes nonsupportive inflammation and neuronal degeneration. Rapid antibody production is associated with recovery.[15] Concomitant infection of sheep with the agent of tick-borne fever *(Anaplasma phagocytophilum)* results in a greater level of viremia and increased mortality from the louping ill virus.[16] The virus is transmissible in unpasteurized milk from sheep and goats.[17]

■ Clinical Signs

In sheep, the initial clinical signs of louping ill include fever, anorexia, depression, constipation, and generalized muscular tremors. The ensuing signs

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are characteristic of CNS disease and include ataxia, conscious proprioceptive deficits, head tremors, hypermetria, and hyperexcitability. The hypermetria results in a characteristic “bunny-hopping gait,” which gives the disease its name (“loup” in vernacular Scottish means *leap*). Further progression of clinical signs is associated with cerebrocortical dysfunction; these signs include head pressing, hyperesthesia, recumbency, convulsions, coma, and death. Survivors have residual neurologic deficits. The duration of the illness is approximately 12 days.

■ Clinical Pathology

Both hemagglutination inhibition and complement fixation tests can be used to detect virus in infected animals.[7] High levels of virus-specific IgG and IgM can be detected in the CSF of affected animals.[18] Viremia peaks at approximately 3 days after inoculation and disappears by 7 days. Because animals are usually not viremic at the time the nervous system lesions develop, virus samples are collected most efficiently from the brain or spinal cord.

■ Pathology

Gross lesions are absent at necropsy. The histologic lesions of louping ill reflect meningeal inflammation with mononuclear cells.[19,20] Microscopic lesions are most severe in the Purkinje cells, motor nuclei, and ventral horn cells. The forebrain is spared.[21] Virus in tissue can be detected by virus isolation, immunohistochemistry, and RT-PCR.[7,22,23]

■ Treatment and Control

There is no treatment for louping ill encephalitis, but supportive care should be provided.

A formalin-inactivated vaccine given to pregnant animals in the last trimester has been recommended for preventing louping ill encephalitis.[24] A single dose of the vaccine provides responses that are protective for at least 2 years. Other methods of preventing the disease include frequent acaricidal dipping of sheep and clearing of pastures to reduce the population of infected intermediate hosts.

Louping ill has not been detected in the United States, but it is a reportable disease. Any suspicion of this disease should be reported to state and federal authorities.

■ Public Health Considerations

The disease has zoonotic potential; infection of humans is rare but can occur through tick bites, unpasteurized infected sheep or goat milk, or fomites. Mild occupational infections have been noted in shepherds, veterinarians, and laboratory workers who cultivate the virus.

Rabies

Christine F. Berthelin-Baker • Lisle W. George

■ Definition and Etiology

Infection with rabies virus results in severe and usually fatal neurologic disease. Most mammals are susceptible and are infected through bites from other animals during or near the clinical phase of illness. The rabies virus and other highly neurotropic rabies-related viruses belong to the genus *Lyssavirus*, family Rhabdoviridae (bullet-shaped RNA viruses). Wildlife provides a natural reservoir for rabies, and each rabies strain is maintained in one or more particular reservoir hosts. Although they can readily cause rabies in other species, wildlife-adapted strains of rabies usually die out when passed into species to which they are not adapted. Other "rabies-related" lyssaviruses can cause a neurologic disease identical to rabies. They include the Lagos and Duvenhage viruses of bats in parts of Africa, the Mokola virus of rodents and shrews in Africa, and the lyssaviruses of European and Australian bats.[1-3]

■ Epidemiology

Rabies is a reportable zoonosis that has been detected worldwide, with some exceptions (primarily islands). It currently does not occur in Sweden, Norway, the United Kingdom, Ireland, Australia, New Zealand, or Iceland.[1] The disease is endemic in other parts of the world, including the United States, Canada, and Europe but remains epizootic in Central and South America, Africa, and parts of Asia, especially where a tropical climate and a high population of infected feral mammals enable viral propagation and transmission.[2,4] The rabies virus is shed in the saliva and does not survive when dried or exposed to ultraviolet light. The most common method of viral transmission to domestic animals is through the bite of an infected feral or wild mammal. Humans and laboratory animals have also developed fatal infections after respiratory exposure to viral aerosols. Low

levels of rabies virus are also shed in the milk of infected animals and occasionally infect offspring nursing from infected dams.[5,6] Laboratory animals, foxes, and skunks can also be infected experimentally by ingestion of infected tissues from animals with rabies.[5,6] In the United States, survival of the virus in the wild may depend on cycling of infections in skunks, bats, raccoons, and foxes, which are also common sources of livestock infections.[7,8]

Certain strains of rabies virus have low virulence in skunks and bats; as a result, these animals are symptomless carriers serving as reservoirs. The rabies virus is also transmitted directly among bats through aerosols in caves. The bats may die off from rabies during periods of high viral contamination. In the United States the most common wild reservoirs are foxes in Alaska and along the border of Mexico, raccoons in the East, and skunks in the central and western regions.[4] Mandatory vaccination of dogs has virtually eradicated canine rabies from industrialized countries, where rabies transmission from domestic dogs to livestock is rare.[1,9] Island nations have remained free of rabies by imposing a 6-month quarantine on imported dogs and cats. In South America, rabies outbreaks in cattle often result from vampire bat bites, causing up to 50,000 cattle deaths annually. Human rabies cases may result from bites inflicted by infected pets, feral dogs and cats, bats, or wildlife. Cases resulting from contact with infected cattle or horses are rare.[4,9,10]

■ Pathogenesis

After subcutaneous or intradermal inoculation, the rabies virus replicates locally. Subsequently, it binds to the acetylcholine (and other) receptors of the peripheral nerves and then migrates to the CNS through peripheral nerves, spinal rootlets, and the spinal cord. After entry into the nerve cell rootlets, the virus travels to the brain along nerve tracts and into CSF. From there it spreads centrifugally along the rootlets of the cranial nerves to the salivary glands and the nasal epithelium. While inside cells, the rabies virus evades the immune system by blocking certain signaling proteins necessary for those cells to respond to interferons.[11] The virus must replicate in the brain before it can reach the salivary and nasal secretions. Therefore whenever an animal bites a person, the attacking animal can always be euthanized and tested for the potential of rabies virus transmission, and it not necessary to wait for disease progression before testing an animal for rabies, as historically recommended when histologic examination for Negri bodies was the main diagnostic test for rabies. Negri

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bodies are aggregates of viral proteins and nucleic acids, most commonly observed on histologic examination of the hippocampus of rabies-infected animals. In humans, most cases become apparent within 1 to 3 months of infection, but a small proportion of cases have had incubation periods in excess of 6 months, extending to several years in rare cases.[1] The rabies virus replicates in the cell bodies (gray matter) of the CNS. Dysfunction of these neurons results in behavioral changes and variable abnormalities of the cranial and the peripheral nerves, with multifocal loss of lower motor neuron and autonomic function. Death results from cardiorespiratory paralysis as the virus infects the medullary centers of the brainstem.

■ Clinical Signs

Livestock cases of rabies have been reported mostly in cattle and occasionally in horses, sheep, and goats.[3,4] Rabies should be included in the differential diagnosis of any unexplained acute, rapidly progressive intracranial disease, especially in the presence of autonomic instability, dysphagia, hydrophobia, paresis, or paresthesia.[3,12] The incubation period ranges from a few days to 6 months, depending on the pathogenicity of the inoculum and the distance from the site of inoculation to the brain. The incubation periods are shortest in animals bitten on the head, whereas the longest incubations have been reported after bites on the extremities of the pelvic limbs.

The disease is usually fatal after a clinical course of 1 to 8 days. Occasionally, an affected animal is found dead without having exhibited any clinical signs previously. Early clinical signs of rabies in livestock may be nonspecific sensory and behavioral changes, including anorexia, restlessness, depression, separation from the herd, and mild ataxia. In ruminants, rumination may cease. Many affected horses appear colicky. Affected animals may show regional paresthesia with pruritus, creating excoriation and hair loss. As the disease progresses, affected animals may become hyperexcitable, fearful, or enraged *(furious rabies)* or mentally depressed *(dumb rabies).* Cattle rabies frequently manifests as dumb rabies with flaccid paraparesis, tetraparesis, and tetraplegia *(paralytic rabies)* as it progresses. Therefore the examiner should consider appropriate personal protective equipment (coveralls, boots, gloves, mask, and eye protection) when examining downer cattle in rabies-endemic areas.

In an experimental study, all cattle and sheep infected with the rabies virus exhibited excessive salivation and behavioral changes, and the majority also

displayed tremors, bellowing, aggression, hyperesthesia, and pharyngeal paresis/paralysis.[3] Tetraplegic animals may bellow and show frantic motor activity of the legs when stimulated. Animals with dumb rabies are depressed, inappetent, and often febrile (>39.4° C [103° F]), and they may exhibite head and neck drooping, ptosis, flaccid facial musculature, profuse salivation, and yawning. They may also demonstrate repeated nibbling motions with the lips. Other signs include tenesmus, paraphimosis, priapism, odontoprisis, head pressing, circling, basewide stance, difficulty rising, and falling episodes. Flaccidity of the tongue, tail, anus, and urinary bladder may also be evident, as may blindness, strabismus, and nystagmus.

The first clinical sign of paralytic rabies in horses may be an unexplained ataxia or shifting leg lameness, soon followed by paraparesis or paraplegia.[13] Spinal reflexes and tone in the affected limbs may be decreased or absent. Most affected animals become recumbent in 3 to 5 days. Initially, the recumbent animal may be able to eat and drink with help, but it soon becomes anorectic and develops encephalopathic signs, followed by generalized seizures and coma[14,15] (Fig. 35.11).



FIG. 35.11 **Ten-month-old mixed-breed calf with terminal rabies virus encephalitis. The calf is comatose and showing opisthotonos.**

Regardless of the clinical manifestations, rabies is a rapidly progressive and fatal disease leading to cardiorespiratory failure, and death usually occurs within 10 days. In all disease forms in livestock, the clinical signs rapidly worsen over 1 to 3 days, ending in recumbency and coma. A pharyngeal–laryngeal paralysis

may develop, resulting in stertorous breath sounds, inability to drink (hence the common name of *hydrophobia*), and accumulation of frothy saliva at the commissures of the lips.[16]

One summary of 21 cases of rabies in horses enumerated the frequency of particular clinical signs observed as the presenting complaint (Table 35.5). Rabies can be differentiated from other encephalitic disorders only by specific postmortem tests or virus isolation, which is usually not possible before death occurs. In horses, the clinical signs of rabies are often indistinguishable from other encephalopathies such as hepatoencephalopathy, leukoencephalomalacia, togaviral encephalitis, equine herpesvirus 1 (EHV-1), protozoal and other meningoencephalomyelitides, and space-occupying masses. In ruminants, rabies may resemble pseudorabies, herpesvirus encephalitis, infectious thromboembolic meningoencephalitis, nervous ketosis, grass tetany, hypocalcemia, polioencephalomalacia, nervous coccidiosis, or even focal spinal cord or peripheral nerve diseases. Most horses with fatal encephalopathy die within 5 days of the onset of signs, but cases lasting as long as 14 days have occasionally been observed.[17]

TABLE 35.5

Clinical Signs of Rabies in Horses

Clinical Signs	Frequency of Occurrence
Ataxia, paraplegia	11/21
Lameness	5/21
Pharyngeal paralysis	2/21
Recumbency	21/21
Colic	2/21
Hyperesthesia	17/21
Tail and anal paralysis	12/21
Fever	11/21

From Green S, Smith LL, Vernau W, et al. 1992. Rabies in horses: 21 cases. *J Am Vet Med Assoc* 200:1133.

■ Clinical Pathology

There is no valid antemortem test to diagnose rabies in livestock. Rabies usually remains immunologically and serologically silent throughout the incubation and clinical phase of the illness. Clinicopathologic tests are not specific for rabies but may help rule out other, more common diseases. The CSF may be normal or may

show moderate mononuclear pleocytosis (5 to 30 cells/µL) and increased protein levels (60 to 200 mg/dL), occasionally with neutrophils, eosinophils, or xanthochromia. Laboratory personnel should be warned that rabies is part of the differential diagnosis when CSF is submitted for analysis.

■ Pathology

Rabies causes a nonsuppurative meningoencephalomyelitis. Microscopic changes include edema, meningeal congestion, focal areas of hemorrhage, perivascular cuffing, gliosis, neuronophagia, and neuronal degeneration. These changes are most severe in the dorsal root ganglia and can be observed in most CNS regions.

A definitive diagnosis of rabies may be based on the finding of Negri bodies on histologic examination of brain tissue (of note, these are not always present, especially in animals euthanized early in the disease course) or through a positive direct or indirect fluorescent antibody test conducted on fresh smears of CNS tissues (thalamus, hippocampus, brainstem, pons, medulla, and cerebellum).[18-20] If results of these tests are negative or inconclusive and humans have been exposed, additional testing can be performed with intracerebral inoculation of mice with CNS tissue from the suspected case. The direct fluorescent antibody test on brain tissue has become the standard against which the value of other rabies tests is evaluated.[18] In cases of human exposure, public health authorities should always be contacted before sample collection and submission. Most diagnostic pathologists accept the refrigerated head (or even whole body, for small animals and bats) or refrigerated brainstem and cerebellum collected through the foramen magnum in mature cattle and horses. Care should be taken to prevent any human exposure to body fluids and CNS tissue of any animal with rabies on the list of differential diagnoses, especially in areas where rabies is known to be present in any domestic or wildlife species; open wounds or small healing sores may be portals of entry for the rabies virus.

■ Treatment and Control

There are no specific treatments for rabies, and once an animal is infected, the disease is usually fatal. Although widespread rabies vaccination of livestock may not be economically justified in low-incidence areas, vaccination of valuable livestock or animals that travel or are in regular contact with humans (e.g., at petting zoos or in animal shows) should be considered, particularly in or near

rabies epizootic areas. A list of licensed rabies vaccines for the protection of animals against rabies is regularly updated by state veterinary authorities.[21] Strict adherence to label directions for use of these vaccines is mandatory. In some jurisdictions, immunization of large animals is considered by regulatory authorities to be valid only if the vaccine is administered by a licensed veterinarian.

The disposal of livestock that have been bitten by rabid animals depends on the bitten animal's vaccination history, local and national regulations, and the animal's value. In the United States and Canada, the disease must be reported to the state or province/territory public health department. Management of exposed livestock must be coordinated with public health officials. Any livestock bitten by a wild animal should be considered to have been exposed to rabies, regardless of the availability of the biting animal for testing. If a bitten horse had been vaccinated before the bite, it should be revaccinated immediately and kept under observation for 90 days. Other exposed, unvaccinated animals with low economic value should be euthanized; if the animal is valuable, the bite wound may be washed with copious amounts of water and iodine or quaternary ammonium disinfectants, after which the animal should be quarantined for at least 6 months, and the brain should be examined if it dies.[21] The prolonged quarantine period is based on case reports of prolonged incubation periods in certain species.[1]

Initial vaccination of animals shortly after rabies virus exposure is not recommended because it is less effective than prophylactic vaccination, and idiopathic responses to the vaccine may complicate interpretation of the animal's disease status after exposure.[1] When human exposure to rabies virus is suspected, the biting animal must be euthanized and its brain examined for evidence of infection. A vaccinated or valuable animal may be quarantined for 6 weeks under veterinary supervision, and the animal must be euthanized and its brain examined if it develops clinical signs suggestive of rabies during that period. The World Health Organization (WHO) publishes and regularly reviews its recommendations for vaccination and prophylaxis in humans after actual or suspected exposure to the rabies virus.[2]

Control of rabies by immunization of susceptible wildlife through the use of baits containing modified live vaccines has been successful in certain cases.[1,4,22,23] Such approaches may provide a means for large-scale immunization of wildlife or feral animal populations for eventual eradication of

the disease.

Sporadic Bovine Encephalomyelitis (Buss Disease; Polyserositis; *Chlamydophila pecorum* Infection)

■ Definition and Etiology

Sporadic bovine encephalomyelitis (SBE) is caused by *Chlamydophila pecorum* biotype 2, an organism previously named *Chlamydia psittaci* and *Chlamydia pecorum*.[1] The disease was first reported in the United States in 1940.[2] A similar but not identical viral disease occurs in cattle in Australia and has been named *bovine ephemeral fever*.[3-5]

■ Epidemiology

Infected cattle shed the organism in urine, feces, nasal secretions, and milk. It can also be found in the feces of calves that are exposed to clinically affected herdmates but show no symptoms. The agent tends to remain endemic on a single farm, and sporadic outbreaks of disease may occur only on those premises. Outbreaks of SBE are rare, but the attack rate in an epizootic ranges from 5% among adults to 25% among calves. The mortality rate is highest in calves and approximates 30% for all age groups.[6] The pattern of these outbreaks varies: from a few cases annually to acute, recurrent epizootics with high case-attack rates that subside after 3 to 4 weeks.

■ Pathogenesis

The mode of transmission and the genesis of pathologic lesions are unknown in natural cases, but postmortem lesions indicate the role of hematogenous dissemination of the organism to the CNS and other tissues. The extracellular form, termed an *elementary body,* is metabolically inert and can be shed in the feces and urogenital secretions of multiple animal species.[1] The pathogenesis of infection and invasion into the host's bloodstream is not well understood.

■ Clinical Signs

Affected animals show signs of a multisystemic disease. The initial clinical signs in cattle are fever (39° C to 41.5° C [102.1° F to 106.7° F]), diarrhea, anorexia,

depression, and stiffness. Animals in the early stages may show signs of a respiratory disease characterized by nasal discharge, dyspnea, and cough. These animals occasionally have a pain response to percussion of the hoof, as well as swelling of the coronary band or polyarthritis and tenosynovitis.[2] Auscultatory abnormalities may include high-pitched wheezes and crackles over the lung fields or pleural and pericardial friction rubs. Because of the fibrinous peritonitis and pleuritis, the clinical signs in some affected animals may resemble those of hardware disease. These animals may grunt or groan when sudden pressure is applied to the xiphoid region. Progression of the disease is related to development of the meningoencephalitis and is characterized by ataxia and conscious proprioceptive deficits, circling, head tilt, opisthotonos, hyperesthesia, stiff neck, convulsions, and coma. Affected animals may die after 4 to 10 days.

■ Clinical Pathology and Diagnosis

The detection of reticulate bodies in the exudate cells of pleural and peritoneal effusions is highly suggestive of SBE. The agent can be most readily detected in clinical samples by PCR, although inoculation of laboratory animals may also be used.[1] Serologic testing is difficult to interpret because antibodies to *C. pecorum* may cross-react with other *Chlamydophila* spp. on certain serologic tests.[1]

■ Pathology

Growth of the organism in the arteriolar endothelium causes vasculitis, hemorrhage, edema, and accumulation of fluid in the body cavities. Diffuse fibrinous pleuritis, peritonitis, and meningitis are also present. Microscopic changes include perivascular mononuclear cell infiltration and neuronal degeneration.

■ Treatment and Control

Early cases of SBE can be treated with oxytetracycline (20 mg/kg/day IV, SC, or IM for a minimum of 7 days). Efficacy is indicated by a reduction of fever within the first 24 hours of treatment.

There are no known effective control measures for the prevention of SBE. The chlamydial agent is susceptible to a number of disinfectants, including 2% sodium hydroxide (NaOH), 5% cresol, and 0.3% quaternary ammonium compounds.

Meningitis (Suppurative Meningitis; Bacterial Meningitis)

■ Definition, Etiology, and Epidemiology

Bacterial meningitis is defined as inflammation of the meninges surrounding the brain or spinal cord, or both, that results from bacterial invasion of these tissues.[1] If the infectious process extends into brain tissue, the condition is termed *meningoencephalitis;* if it extends into the ventricles of the brain, it is termed *meningoventriculitis*. Differentiation of meningitis from the other two conditions almost always necessitates advanced imaging techniques or histologic examination, but the conditions result in similar clinical signs.[2] It is relatively rare in large animals. It is most often the result of hematogenous infection in neonates, as a consequence of septicemia with partial or complete failure of passive transfer of colostral antibodies or of septicemia resulting from translocation of invasive bacteria from the GI tract, respiratory tract, or umbilicus.[2,3] Hematogenous infection of the meninges, brain, or both also occurs sporadically in adults; such events may be associated with septicemia from a primary focus of infection such as the udder, uterus, or GI tract. As with neonates, underlying immunodeficiency may predispose adult animals to this disease.[4,5]

Bacterial meningitis can also result from direct extension of infectious agents into the calvaria, such as extension of pyogenic infections into the calvaria from infected skull fractures,[6,7] osteomyelitis from sinusitis or otitis media/interna,[8] or osteonecrosis caused by thermal cauterization during dehorning (particularly in goat kids).[9] Improper placement of trephination holes, cribriform plate fractures, and extension from infected coccygeal vertebrae are additional routes of meningeal infection. In horses, septic meningitis is a potential sequela to surgical removal of progressive ethmoidal hematomas and has also been reported as a consequence of local spread of infections of the paranasal sinuses, nasal cavity, periocular tissues, and submandibular lymph nodes.[10]

Many different bacteria have been isolated from the blood, meninges, brain, and spinal cord of affected large animals. In neonatal calves and foals, Gram-negative enteric bacteria such as *Escherichia coli*, *Salmonella* spp., and *Klebsiella* spp. are considered common isolates.[1,2] *Mycoplasma* spp. may be isolated in goat kids. *Histophilus somni* is a potential cause of meningitis in juvenile cattle in feedlots and is reviewed later in this chapter, as are CNS

infections caused by *Listeria monocytogenes*. A variety of Gram-positive and Gram-negative bacteria may be involved in adults, a fact that underscores the importance of cytologic examination, Gram staining, and aerobic and anaerobic culture of CSF samples obtained early in the clinical course of disease.[1,2,11]

■ Pathogenesis

Bacterial turnover leads to liberation of exotoxins and endotoxin, which, in concert with various inflammatory mediators, including cytokines, damage the neural parenchyma. Vascular sequelae to infection may include thrombotic or hemorrhagic infarctions. After several days, inflammation of the arachnoid trabeculae and choroid plexus can result in decreased CSF absorption and hypertensive hydrocephalus.[1,3]

■ Clinical Signs

The earliest clinical signs of meningitis are often nonspecific and may reflect the signs induced by a primary infection site (e.g., diarrhea in neonates with invasive bacterial enterocolitis). Fever is common, as is anorexia and loss of a coordinated suckle in a neonate.[3] Reluctance to lift or bend the neck may be evident, and manipulations by the examiner may induce responses suggestive of hyperesthesia.[2,3,12] Slight tactile stimulation of the skin may result in strong spasmodic extension of the limbs, fasciculations of the underlying musculature, or even generalized frantic motor activity. The patient's behavior may vary from extreme depression to hyperexcitability. A subtle intentional head tremor is often observed in affected foals. Dysfunction of one or more cranial nerves may result in facial muscular tremors, nystagmus, facial palsy, blindness, anisocoria, or strabismus. Progression of the clinical signs is associated with a decreased sensorium, propulsive walking, coma, seizures, and status epilepticus. Sequelae to septicemia, such as septic arthritis or polyarthritis, uveitis, panophthalmitis, hypopyon, cardiac murmurs secondary to valvular endocarditis, and pyuria/proteinuria, may be detected as well.

The clinical signs of bacterial meningitis closely resemble those of viral encephalomyelitis caused by such agents as rabies, West Nile, and togavirus encephalomyelopathies (EEE, VEE, and WEE, described earlier in this chapter). Metabolic encephalopathies may also mimic bacterial meningitis including hypomagnesemia, hypocalcemia, hypoglycemia (which may occur simultaneously with septic meningitis in neonates), hepatic encephalopathy,

renal encephalopathy, and encephalomalacias (e.g., salt poisoning, polioencephalomalacia). Congenital neurologic disorders of neonates may be considered; however, these disorders do not typically induce fever, inflammatory leukogram patterns, or inflammatory changes in the CSF.

■ Clinical Pathology

Meningitis is diagnosed on the basis of examination of the CSF (for normal values, see Table 35.1). The CSF of animals with meningitis may be turbid and white to amber in color, may foam when shaken, and may clot. Xanthochromia may be observed in some specimens. The WBC counts in CSF of calves with purulent meningitis are typically greater than 100 neutrophils/µL, and protein concentrations range from 20 to 270 mg/dL.[3] The differential cell counts in the CSF are either predominantly neutrophilic or mononuclear. Because of bacterial consumption of glucose in the CSF, the concentration of glucose in the CSF is often less than 50% of the corresponding concentration in the serum. Gram staining of CSF should be conducted in all cases. Abnormalities in the blood are inconsistent and reflect secondary conditions such as septicemia, diarrhea, or concurrent fluid therapy. These changes could include leukopenia or leukocytosis, left shift, toxic changes in the neutrophils, hyperkalemia, respiratory acidosis, hypoglycemia, and hyponatremia or hypernatremia.

The numerous differential diagnoses discussed previously are distinguished from bacterial meningitis by compilation of data obtained from physical examination, serum immunoglobulin measurement, serum biochemistry analysis, complete blood cell count, and, of most importance, cytologic examination, Gram stain, and culture of CSF.

PCR assays of CSF may be used to identify specific suspected organisms, as was done for diagnosis of meningitis caused by *Borrelia burgdorferi* in a horse.[5]

■ Pathology

Gross lesions of primary infection in other organs or lesions suggestive of generalized sepsis may be apparent. When meningitis is secondary to trauma, the site of organism entry may be detectable. The meningeal vessels appear to be congested, and the meninges are swollen, opalescent, and petechiated. The CSF is cloudy or amber and may contain fibrin clots. Microscopic changes of CNS tissues include infiltration by neutrophils and lymphocytes, inflammation of the meningeal vessels, scattered hemorrhages, and bacterial colonies around the

blood vessels of the meninges and the brain parenchyma.

■ Treatment and Control

Early clinical suspicion of bacterial meningitis and rapid administration of appropriate antimicrobials are necessary to improve chances of survival and to minimize long-term neurologic impairment.[1,2,11] In a human study of pneumococcal meningitis, a delay of antimicrobial treatment of more than 3 hours after hospital arrival was associated with a higher rate of morbidity 3 months after admission.[13] Therefore it may be prudent to initiate appropriate antimicrobial therapy if the animal shows signs compatible with bacterial meningitis and then, if that diagnosis is subsequently refuted by ancillary diagnostic data, withdraw or modify antimicrobial therapy.

Treatment of bacterial meningitis is difficult, and the mortality rate is high, so treatment should be initiated only after owners are appropriately counseled. Antimicrobial sensitivity tests performed on isolates from CSF may provide valuable information on ideal drugs; however, drug selection must account for whether the drug will reach therapeutic concentrations in the CSF (discussed further later). Because prompt treatment of meningitis is critical, antibiotic therapy can initially be based on the Gram-staining characteristics of bacteria in CSF, when available, and on the initial 24-hour culture results, when possible. When expert laboratory cytologists are not immediately available, CSF can be placed into two microhematocrit tubes and centrifuged for 10 to 15 minutes. The tubes can then be scored with a file and broken at the interface of the fluid with the clay sealant, and the cell-rich fluid from the two ends of the broken tubes can be smeared for cytologic examination and Gram stain. In rabies-endemic areas, clinicians should take appropriate precautions when handling CSF.

Domestic animals have a well-defined blood-CSF barrier, and antibiotics that reach high plasma concentrations may not necessarily reach bactericidal concentrations in the brain. However, under conditions of local inflammation, this barrier becomes considerably more permeable by certain antimicrobials.[1,11] As a general rule, in order to maximize distribution of antimicrobials across this barrier into infected meningeal or neural tissue, the highest dosage of antimicrobial established for the species in question should be used.[1,11] Toxicity potential or excretory organ dysfunction may limit dose escalation of certain classes of drugs such as aminoglycosides. Intravenous administration is preferred in order to obtain peak blood concentrations and spur greater diffusion

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of drugs across this barrier. Because normal neural tissue lacks endogenous immune capacity, bactericidal antimicrobials have been considered superior to bacteriostatic drugs, although successful use of bacteriostatic drugs has been reported.[1,11] The primary factors influencing CSF penetration of drugs in the healthy state are the lipid solubility (increased penetration with more lipid solubility) and molecular size (increased penetration with smaller size). However, the penetration capacity of a given antibiotic is not the sole determinant of appropriate antimicrobial selection because the blood-CSF barrier is made more permeable in bacterial meningitis. In fact, high-dose therapy with certain β-lactams, some with limited lipid solubility, either as monotherapy or in combination with antimicrobials of other classes, is currently recommended for many bacterial agents that cause meningitis.[11]

At present, use of all antimicrobial agents in treatment of bacterial meningitis in food animals and horses represents off-label use, and legal restrictions on use should be considered in all cases. Furthermore, the paucity of clinical reports and the variety of treatments used in those reports complicates the goal of making evidence-based decisions for treatment of this disease in horses and food animals. Therefore guidelines from published reviews of treatment in horses,[1] cattle,[3] and human medicine[11] are presented here.

When possible, meningitis caused by Gram-negative enteric bacteria should be treated with specific third-generation (ceftazidime, ceftizoxime, ceftriaxone, cefoperazone, cefotaxime) or fourth-generation (cefepime) cephalosporins. For horses, ceftriaxone (50 mg/kg IV q6h) or cefotaxime (40 mg/kg IV q6h)[1] have been used. Because of its high degree of protein binding in serum, ceftiofur (at 2 mg/kg IM) does not appear to spread into the CSF of normal horses.[1] Its performance in penetration of the inflamed blood-CSF barrier remains to be determined. In the United States, off-label use of third-generation cephalosporins in food-producing animals is prohibited except under very specific circumstances, and thus current drug use guidelines within a given jurisdiction should be followed.

As an alternative, penicillin G sodium or potassium (20,000 to 40,000 IU/kg IV q6h) or sodium ampicillin (20 mg/kg IV q8h) may be used; success is considered to be highly dependent on the susceptibility of the causative organism, a parameter that is often unknown in the initial treatment decision process. If enteric organisms are suspected in a neonate, and if third- or fourth-generation cephalosporins are not available or are too costly for use, ampicillin

is recommended; its Gram-negative spectrum is considered superior to that of penicillin G. Coadministration of an aminoglycoside can be considered for such neonates, with due consideration of nephrotoxicosis potential and, in animals intended for food, withdrawal time.[1,11] Although aminoglycoside antimicrobials are highly effective against Gram-negative bacteria and are bactericidal, their efficacy in the treatment of purulent meningitis is diminished by their polar characteristics and low attainable CSF concentrations. Nonetheless, combination therapy consisting of a β-lactam and an aminoglycoside may provide effective broad-spectrum coverage[11]; the latter drug may at the very least reduce the circulating burden of Gram-negative bacteria in the bloodstream and elsewhere. Intrathecal administration of preservative-free aminoglycosides, although still used on occasion, has not been shown to produce tangible clinical benefit in comparison with intravenous use.[11]

Alternative treatments for meningitis caused by Gram-negative enteric bacteria, according to anecdotal data in horses only, include enrofloxacin (5 mg/kg, with due consideration of potential cartilage damage and reduction of seizure threshold,[1] IV q12h), or trimethoprim-sulfonamide (5 mg/kg according to trimethoprim component, IV q12h).[3] In horses, chloramphenicol (25 to 50 mg/kg PO q6h) may be considered for use.[1] If β-lactam–resistant organisms are suspected, imipenem (10 to 20 mg/kg IV q6h) may be used, but its efficacy in treating meningitis in foals remains undetermined,[1] and it carries the potential to lower the patient's seizure threshold.[11] In the United States, off-label use of fluoroquinolones (e.g., enrofloxacin) and use of chloramphenicol in food-producing animals, as well as use of off-label use of sulfonamides in dairy cattle older than 20 months, are all prohibited by the Food and Drug Administration.

Meningitis caused by Gram-positive bacteria may be treated with high doses of intravenous penicillin, ampicillin, or the trimethoprim-sulfonamide combinations described earlier in accordance with the same provisos for food-producing animals. Third- and fourth-generation cephalosporins can be considered because these retain activity against certain Gram-positive organisms.[1] For humans, moxifloxacin penetrates the blood-CSF barrier and has greater Gram-positive activity than earlier fluoroquinolones.[11] Other antimicrobials showing promise against specific Gram-positive agents in human medicine include daptomycin and linezolid.[11]

Anaerobic infections are uncommon and probably result from penetrating or necrotizing wounds of the skull bones. Such infections in horses should be

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treated with metronidazole (15 to 25 mg/kg PO q6h)[1]; penicillin or ampicillin would be appropriate therapy in food-producing animals. Treatment of meningitis caused by *Chlamydophila* or *Mycoplasma* spp. has not been critically investigated in large animals, but the decision to treat with oxytetracycline, doxycycline, fluoroquinolones, or florfenicol depends on the animal class being treated. In general, treatment for 2 weeks is considered to be an empirical standard[3]; however, if aminoglycosides are included in the treatment regimen, the patient should be monitored carefully for nephrotoxicosis.

Adjunct therapy for bacterial meningitis includes analgesics, antiinflammatories, and antipyretic agents; fluid therapy; anticonvulsant therapy for seizures; protection against self-induced trauma (including corneal trauma); and nutritional support. Maintenance of euvolemia and euglycemia is considered vital for treatment success.[11] Hypoxemia and hypercapnia are deleterious and should be prevented whenever possible; mechanical ventilation of severely affected patients may be necessary. Osmotic diuretics such as mannitol or glycerol should be administered if CSF pressure, neurologic examination findings, or fundic examination findings are suggestive of cerebral edema. Use of narcotic agents for analgesia should be weighed against their potential to increase cerebral blood flow and therefore intracranial pressure. Although outcomes vary according to the causative organism, concurrent administration of dexamethasone may improve clinical outcome, although this remains controversial.[11] NSAIDs may be a preferred choice if dexamethasone-related complications (e.g., laminitis in horses) must be prevented. Lmited food intake and the pain associated with this condition increase the potential for gastric ulceration, and prophylactic antiulcer medication should be considered in horses.

Treatments for seizures, cerebral edema, and inflammation are listed in Table 35.4.[14-18] The maximum desirable trough concentration of phenobarbital is 40 µg/mL, and the minimum therapeutic level is 15 µg/mL.[15,16] After initial sedation, long-term control of convulsions in horses can be maintained by oral phenytoin (2.8 to 16 mg/kg three times daily) or IV phenobarbital (11 mg/kg once daily).[16-18] The trough plasma concentration of diphenylhydantoin should also be measured repeatedly during continuous drug therapy; the maximum desirable trough level is 10 to 20 µg/mL,[17] and the optimum plasma concentration is 5 to 10 µg/kg. In critical care settings, constant-rate infusions of selected anticonvulsive drugs and drug combinations can be considered. The concentration of plasma immunoglobulins should be measured in neonatal

patients with bacterial meningitis, and plasma should be administered if those values are subnormal for the species.

A guarded prognosis at best is warranted for most cases of bacterial meningitis. In a retrospective study of 32 calves with septic meningitis, only 5 (16%) survived until discharge, and all 5 subsequently died or had to be euthanized.[2] In a case series in Spain, only 2 of 7 treated foals survived to discharge.[19] The survival rate among adult horses may be higher.[10] Early detection is considered pivotal for successful treatment; therefore a poor prognosis is warranted for animals with severe neurologic impairment. However, because concurrent metabolic derangements (e.g., hypoglycemia) may cloud the clinical picture, aggressive antimicrobial treatment—including achievement of euvolemia, euglycemia, and control of convulsions (if present) and normalization of acid-base, blood gas, and electrolyte status—may be attempted for valuable animals, with the prognosis refined on the basis of response to therapy.

Because cases of bacterial meningitis are usually secondary to other infections as discussed previously, prevention is centered on early detection and intervention for the primary disease. Ensuring adequate passive transfer of immunoglobulins in neonates is also important for reducing the risk of bacterial infection, septicemia, and meningitis.

Pituitary Abscesses

Pituitary abscesses occur sporadically in ruminants and are rare in horses. *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*) is the bacterium most frequently isolated, but *Corynebacterium pseudotuberculosis*, as well as *Streptococcus* spp., *Staphylococcus* spp., *Actinomyces* spp., *Bacteroides* spp., *Fusobacterium* spp., *Acinetobacter* spp., *Pasteurella* spp., *Pseudomonas* spp., and *Actinobacillus* spp. have occasionally been isolated.[1]

The clinical signs of pituitary abscess occur suddenly and progress for 7 to 10 days before the affected animal dies.[1] The initial signs are ataxia, head-neck extension, basewide stance, inappetence, depression, head pressing, and recumbency.[1-3] Most affected animals have asymmetric deficits of one or more cranial nerves, which result in dysphagia, blindness, anisocoria, absence of pupillary light reflexes, mydriasis, flaccid tongue, or a combination of these. Nystagmus, facial paralysis, facial hypalgesia, ventrolateral strabismus, or head

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tilt may also be observed.[1,4] Approximately half of the affected animals have bradycardia (pulse rate, <60 beats/min).

The CSF protein concentration in affected cattle ranges from 70 to 502 mg/dL, and nucleated cell counts range from 6 to 12,640/µL (6% to 84% neutrophils).[1] The antemortem diagnosis is based on the observation of bradycardia, blindness, and nonresponsive pupils in conjunction with evidence of pyogenic inflammation in the CSF.

Some authors have postulated that the infectious agent gains entry to the sella turcica hematogenously and then localizes in the rete mirabile, which is the complex of blood vessels encircling the pituitary gland.[1] A direct relationship exists between the complexity of the rete mirabile and the incidence of pituitary abscessation in different mammals. Horses and dogs lack a well-defined rete and correspondingly have a low risk for developing a pituitary abscess, whereas the opposite situation is true in cattle. In one study, 55% of cattle with a pituitary abscess had pyogenic foci in other organ systems or in the sinuses, teeth, or soft tissues of the face,[1] which indicates that the abscesses may result from a retrograde bacterial embolization through branches of the facial veins.

Ataxia is caused by interruption of extrapyramidal motor nuclei in the brainstem by the expanding abscess. Extension of the abscess into the communicating retroorbital rete may result in exophthalmos. Extradural extension of the abscess along the brainstem causes loss of the cranial nerve function. Bradycardia may be caused by interference with diencephalic cardioacceleratory centers.

Animals aged 9 months to 12 years have been affected, but most cases occur between the ages of 2 and 5 years.[5] Pituitary abscess appears to have a slightly increased prevalence among castrated and intact males.[1] Pituitary abscess has been related to infections that develop in bulls after insertion of a nose ring.[3] Prophylactic administration of penicillin and attention to aseptic procedure during insertion of the ring can reduce disease incidence. Because of the high mortality rate associated with pituitary abscesses, treatment is not usually attempted.

Brain Abscesses

Streptococcus equi is the most common cause of brain abscesses in horses, probably because the occurrence of strangles in this species.[1] *T. pyogenes*

(formerly *A. pyogenes*) is a common cause of brain abscesses in cattle by means of extension of a sinus infection through the calvaria. Brain infections of cattle with *Bacteroides* spp. have also been reported.[2] The neurologic dysfunction caused by brain abscesses typically has a slower onset and is more commonly asymmetric than that caused by meningitis. However, onset of signs can also be acute.[1] Forebrain abscesses compress the cerebral cortex, causing a caudal displacement of the brain and functional loss of one or both occipital lobes, which may result in cortical blindness in one or both eyes. Because of the high proportion of crossed fibers in the optic nerve decussation, unilateral cortical abscesses may result in vision loss in the contralateral eye. Increased CNS compression by the mass may induce ipsilateral mydriasis caused by interference with the oculomotor nerve. Further increases in the size of the lesion cause more generalized cortical signs, including blindness, propulsive walking, circling, head tilt (toward the lesion side), depression, coma, head pressing, or sudden unexplained mania (Figs. 35.12 and 35.13). Abscesses at the base of the brain may cause additional abnormalities of cranial nerve function, including vestibular disease. Ophthalmoscopic examination may reveal papilledema in the ipsilateral eye.[2] Advanced imaging studies such as CT and MRI, if available, may be helpful for antemortem diagnosis.[3-5]



FIG. 35.12 Head pressing in a pony caused an abscess in the right cerebral hemisphere. (Courtesy Dr. R.H. Whitlock.)

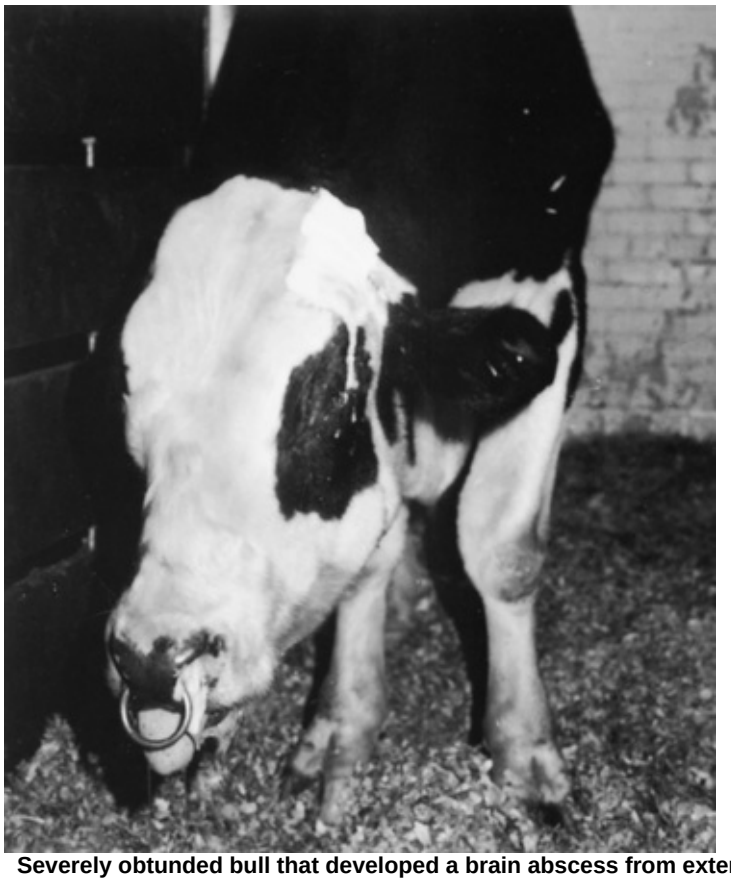


FIG. 35.13 **Severely obtunded bull that developed a brain abscess from extension of a frontal sinusitis. The abscess extended to the base of the brainstem and affected cranial nerves V and XII, which resulted in dropped jaw and tongue paralysis. The bull was also severely depressed, blind, and ataxic and had facial analgesia.**

In later stages of the illness, animals may assume lateral recumbency and display a decerebrate posture characterized by hypertonicity, hyperreflexia, opisthotonos, coma, and convulsions. At this stage the disease is difficult to differentiate from septic meningitis. CSF findings in animals with brain abscesses are variable, ranging from normal to very abnormal, with high protein concentration and marked pleocytosis.[1,5,6] Treatment of brain abscess includes antibiotics and supportive care (see Meningitis section). In one clinical report, a brain abscess in a horse was localized with CT scanning and successfully drained through a craniotomy.[7]

Nervous Coccidiosis

■ Definition and Etiology

Nervous coccidiosis is a neurologic syndrome of calves and yearling cattle, sheep, and goats that is associated with enteric infections by *Eimeria* spp. The

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condition is most often observed in western Canada and the northwestern United States and is particularly prevalent in feedlots. The incidence of nervous coccidiosis is highest in the winter months. In contrast to that of enteric coccidiosis, the rate of mortality from nervous coccidiosis is relatively high (≈70%).[1] The pathogenesis of the encephalopathy may be related to the elaboration of a labile neurotoxin by the parasite.[2] The clinical signs and history of nervous coccidiosis are similar to those of other neurologic diseases that affect the function of the cerebral cortex.

■ Epidemiology

Nervous coccidiosis occurs most frequently in feeder cattle, but dairy and pastured beef calves, lambs, and kids are also be affected on occasion. In one survey, 0.3% of the calves were affected with the intestinal form of nervous coccidiosis. Nevertheless, outbreaks with a large percentage of calves developing CNS disease have been reported.[3] In western Canada, CNS signs have been reported in 21% of cases in herd outbreaks of intestinal coccidiosis.[4] Most cases occur in middle to late winter.

■ Pathogenesis

The pathogenesis of the encephalopathy is unknown. The nervous form of coccidiosis cannot be transmitted to mice by injection of CSF from infected calves; however, a heat-labile neurotoxin has been identified in the serum of calves with nervous coccidiosis.[2] The coccidia do not directly invade the CNS.

■ Clinical Signs

The onset of the nervous system signs is usually preceded by diarrhea, tenesmus, and hematochezia. Some calves with severe diarrhea develop prolapsed rectums. Initial signs of CNS dysfunction include depression, incoordination, twitching, and hyperesthesia. As the clinical signs worsen, the animal becomes recumbent and develops numerous cerebrocortical signs, including opisthotonos, periodic tremors, horizontal nystagmus, frothing at the mouth, bellowing, snapping eyelids, and muscular fasciculations.[3,5-7] Blindness is rare. Stimulation of the patient may precipitate a tonic-clonic seizure.[3,5-7] Affected animals may die after 1 to 5 days of encephalopathy. Convulsive calves may regain consciousness but relapse days later.[8]

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■ Clinical Pathology

Fecal flotations from the patient and herdmates show a large burden of coccidial oocysts. Fecal egg counts of affected animals may range from 5000 to 4 million per gram of feces. To exclude the possibility of other neurologic diseases with similar clinical manifestations, blood should be collected for measurement of electrolytes (calcium, magnesium, potassium). The acid-base status, plasma glucose, and blood lead concentrations should be measured. Acute meningitis and salt poisoning may be ruled out by CSF analysis. The plasma vitamin A concentration should be measured in any animal that has not had exposure to green forage. Polioencephalomalacia, ethylene glycol poisoning, lead poisoning, rabies, pseudorabies, petroleum distillate poisoning, and clostridial enterotoxemia should be considered in the differential diagnosis.

■ Pathology

No macroscopic lesions are observed in the CNS of calves with nervous coccidiosis. The microscopic lesions of the brain are mild and nonspecific and include edema, congestion, and occasional shrunken neurons. Parasitic invasion of the ileum, cecum, and colon results in lesions in these organs.

■ Treatment and Control

Treatment should include supportive fluid, macromineral, and electrolyte therapy. The coccidial infection should be treated with sulfadimethoxine (55 mg/kg PO or IV, followed by 27.5 mg/kg PO or IV q24h). Alternatively, sulfamethazine (110 mg/kg PO q24h for 5 days, or 1 lb/100 gallons of drinking water) or amprolium (50 mg/kg/day PO for 7 days) can be administered. Treatment administered via drinking water will be effective only if animals are willing and able to drink. Diazepam, sodium pentobarbital, or phenobarbital may be used to control tonic-clonic convulsions (see Table 35.4). Response to treatment is poor, and the case fatality rate can be high in calves that develop tonic-clonic seizures. Specific chemotherapeutic regimens and methods of preventing intestinal coccidiosis are described in Chapter 49.

Sporozoan Infections of Ruminants (*Sarcocystis* Infection)

■ Definition and Etiology

The three recognized species of *Sarcocystis* that infect cattle—*Sarcocystis cruzi*, *Sarcocystis hominis*, and *Sarcocystis hirsuta*—are sporozoan parasites with definitive hosts of dogs, primates, and cats, respectively.[1,2] For three other *Sarcocystis* species—*Sarcocystis capricanus*, *Sarcocystis ovicanus*, and *Sarcocystis tenella*—dogs are the definitive host, and secondary hosts include goats and sheep.[3]

When a carnivore ingests flesh from infected cattle, *Sarcocystis* spp. cysts in muscle are broken down by digestive enzymes, and motile bradyzoites are released. The bradyzoites infect intestinal mucosal cells and differentiate into sexual stages. The gametes fuse to form an oocyst, which is shed onto pastures as sporocysts. When eaten by a ruminant, the sporocysts hatch in the proximal small bowel and penetrate into the medium-sized mesenteric arteries, where they enter endothelial cells and form sporozoites. The sporozoites then mature in three successive waves. Each wave of development spreads downstream. The third-generation merozoites enter the soft tissues and encyst as sarcocysts. The total period of development in the ruminant requires 10 weeks. The life cycle is completed when a carnivore ingests uncooked meat containing viable sarcocysts. Disease may develop in cattle during the maturation of the cyst in the muscles, at approximately 9 to 11 weeks after infection.

■ Epidemiology

Estimates of infection rates range from 70% to 98% in cattle in the United States.[1] When infected flesh is eaten by carnivores, the encysted sporozoites complete their life cycle.[1] The prepatent period of the parasite in the carnivore (primary host) ranges from 9 to 45 days. The primary host may shed the sporulated oocysts in the stool for as long as 2 months after a single infection. The oocysts withstand freezing but are rapidly killed by sunlight and drying.[1] Reexposure of previously infected canids results in a large fecal output of sporocysts. Ingestion of approximately 250 g of infested meat by a dog can result in an output of 100 to 6000 sporocysts per gram of feces. Wild canids are even more susceptible than domestic dogs and may serve as a major mechanism for propagation of *Sarcocystis* spp. in range cattle in the western United States.

■ Pathogenesis

The pathogenesis of *Sarcocystis* is poorly understood. Pathologic changes in the skin and muscle and in serum chemistry profile are speculated to result from a

combination of parasite-directed immunologic responses and diffuse vasculitis. Abortions probably occur because of luteolysis that results from the increased concentrations of prostaglandin $F_{2\alpha}$, caused by vascular infection by the parasite.[4]

■ Clinical Signs

Most cases of *Sarcocystis* spp. infestation are asymptomatic in both definitive and secondary hosts. However, if a large number of sporocysts are ingested by a nonimmune ruminant, clinical illness may develop. Clinical signs include fever (>39.5° C [103.5° F]), anorexia, weight loss, symmetric lameness, and diarrhea. Neurologic signs include ataxia, muscular weakness, tremors, hyperexcitability, hypersalivation, recumbency, tonic-clonic seizures, leg biting, blindness, opisthotonos, and nystagmus.[5,6] Cattle may lose the hair of the tail switch ("rat tail"). Sheep may show wool break.[1-3,5,6] Animals with chronic infections may develop edema of the limbs, poor weight gain, muscular atrophy, and pallor.[1-3,5,6] Second-trimester abortions may occur in cattle and small ruminants beginning 28 days after ingestion of infectious sporocysts.[7] The fetuses may appear either normal or autolyzed.

■ Clinical Pathology

Serum activity of liver enzymes is increased. The packed cell volume and the serum protein concentration are often decreased. In the early stages of infection, there is a marked normocytic, normochromic anemia. The anemia is thought to be caused by extravascular hemolysis.[8]

Antibodies to solubilized freeze-dried *Sarcocystis* spp. antigens have been detected by indirect hemagglutination, ELISA, and an AGID test.[9-11] IgM responses first occur by 3 to 4 weeks after infection and peak by 11 to 15 weeks.[9-11] The concentrations of *Sarcocystis*-specific IgG begin to rise by 5 to 6 weeks after infection. Background titers of normal cattle range from 1 : 54 to 1 : 486, and titers of infected cattle often exceed 1 : 10,000.

■ Pathology

The pathologic lesions in the CNS are similar for all species of sporozoans; they include granulomatous meningoencephalomyelitis, focal malacia, perivascular cuffing, neuronal degeneration, and gliosis. The changes are generally most

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severe in the cerebellum and midbrain but can occur anywhere in the CNS, including the spinal cord. The pathologic diagnosis is based on the finding of meronts and merozoites in the affected sections of neural tissue.[12,13]

Pathologic lesions elsewhere include hemorrhages on the sclera, serous surfaces, and muscles; fluid in the body cavities; and lymphadenopathy. The muscles have alternating light and dark stripes. Macroscopic changes may not be evident in animals with chronic sarcocystosis. If changes are not evident, postmortem diagnosis is based on the finding of intravascular schizonts or intramuscular hemorrhages without significant inflammation. Ultrastructural examination of affected areas of CNS reveals an intracellular colony with rosette orientation of agents in the cytoplasm of infected astrocytes.

■ Treatment and Control

Treatment of infected sheep with salinomycin (1 to 2 mg/kg) has also been recommended.[14] Amprolium (100 mg/kg once daily for 30 days) may reduce the severity of *Sarcocystis* spp. infection[15] but may not completely eliminate the clinical disease.

The best method of controlling *Sarcocystis* spp. infection is to protect the food supply of ruminants. Scavenging of carcasses by carnivores should also be prevented by deep burial or incineration. Feed bunks should be kept clean and raised approximately 1 to 3 feet (30 to 90 cm) off the ground. All carnivorous pets that have access to the feed or pastures should be fed cooked meat or processed dry food. In range pasture situations, prophylactic feeding of monensin or elimination of predatory or scavenging carnivores may be necessary.

Neospora Infection of Cattle (Protozoal Abortion)

Neospora caninum is a protozoal parasite that causes disease primarily in dogs and cattle.[1] The predominant clinical sign of *Neospora caninum* infection is a midterm to late-term abortion (3 to 8 months of gestation). Fetal lesions consist of focal nonsuppurative necrotizing encephalitis, nonsuppurative myocarditis and myositis, and mononuclear cell infiltrates disseminated in other tissues.[2,3] Occasionally, stillborn calves are mummified. (See Chapter 43 for more on abortion.)

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Nonfatal infection in the fetus results in neurologic dysfunction of the newborn. The clinical signs of neurologic disease vary because of the random and widespread distribution of the parasite within the CNS. Affected calves are often unable to stand and suckle and have abnormal spinal reflexes. Flexural contractions of the forelimbs, domed skull, and torticollis have also been reported in spontaneously occurring cases.[4,5] Calves born alive are usually born with the CNS signs, which initially are mild but then worsen after birth. Pathologic lesions associated with the fetal infection include focal areas of brain discoloration, focal cavitation with cyst formation, and reduction of gray matter. Microscopic changes in the CNS of affected calves include nonsuppurative inflammation of the gray and white matter, focal lymphocytic meningitis, and neuronal necrosis. Changes in other tissues include nonsuppurative myocarditis, myositis, and hepatitis. Protozoa can be observed in microscopic sections of the stained tissues.

Neospora organisms have been isolated in pure form in cultured cells.[6] Antibodies have been produced by intubation of laboratory animals, and the agent can be identified microscopically through immunoperoxidase staining on the fixed tissues. The CSF changes in affected calves range from normal to mild pleocytosis.[7] Similar conditions have been described in sheep[8,9] and goats.[10,11]

Babesia Encephalitis (Babesiosis; Piroplasmosis; Texas Cattle Fever; Tick Fever; Redwater)

Parasitemia of cattle caused by the protozoans *Babesia bovis, Babesia argentina,* and *Babesia* is usually subclinical, but results in devastating economic losses worldwide.[1] The disease is transmitted to cattle by the cattle fever ticks *Rhipicephalus* (*Boophilus) annulatus, Rhipicephalus microplus,* and *Rhipicephalus decoloratus.* Babesiosis occurs in the Americas, Europe, Africa, Asia, and Australia. Ticks acquire *Babesia* infection from an infected animal and then pass the agent to their offspring through the ovaries. The protozoan is passed to susceptible cattle by adult ticks and nymphs. Most infections result in intravascular and extravascular hemolysis and in kidney and liver failure. See Chapter 37 for more detail.

A small proportion of *Babesia* infections cause acute encephalitis.[2,3] CNS signs begin suddenly and include fever (41.7° C [107° F]), anorexia, depression,

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ataxia, conscious proprioceptive deficits, mania, convulsions, and coma. Sudden death is occasionally observed. The nervous system signs are accompanied by engorgement of the scleral vessels, icterus, proteinuria, and hemoglobinuria. Encephalopathic diseases that closely resemble babesiosis include rabies, nervous coccidiosis, polioencephalomalacia, lead poisoning, bovine herpesvirus encephalitis, theileriasis, heartwater disease, salt poisoning, and chlorinated hydrocarbon toxicity.

The pathogenesis of the CNS signs is unclear; however, possible causes include capillary thrombosis and infarction, disseminated intravascular coagulation, anoxic encephalopathy, and direct invasion of the CNS by the parasite. Thrombi are disseminated throughout the CNS. Expression of parasite proteins on the surface of infected RBCs facilitates binding of RBCs to capillary endothelial cells.[4] The proclivity of *Babesia*-infected RBCs for binding to brain capillaries, particularly those in the cerebellum, is supported by the high incidence of parasite-positive RBCs found in the brains of infected cattle.[5] These findings and the observation of increased prothrombin and partial thromboplastin times, thrombocytopenia, and decreased fibrinogen concentrations suggest that disseminated intravascular coagulation may play a role in the pathogenesis of the CNS disease.[6-8] Vascular blockage in the CNS, caused by severe sludging of RBCs within brain capillaries, appears to be central to the pathogenesis of neurologic disease in infected animals.[9] Studies of *Babesia ovis* in sheep, in which neurologic disease did not occur, failed to demonstrate RBC blockage of brain capillaries.[10] This further supports the belief that CNS vascular pathology is key to the development of neurologic signs in bovine babesiosis.

Babesia encephalitis is a reportable disease in the United States. Suspected cases should be referred to the appropriate state and federal authorities.

Ehrlichia (Cowdria, Rickettsia) ruminantium Infection (Heartwater Disease)

■ Definition, Etiology, and Epidemiology

Ehrlichia ruminantium is a rickettsial parasite that causes a fatal encephalitis in goats, sheep, and cattle.[1] The disease originated in sub-Saharan Africa and has spread to cattle in the West Indies (Guadeloupe, Antigua, and Marie Galante).[2]

E. ruminantium is transmitted by *Amblyomma* ticks.[3,4] Although a number of *Amblyomma* species have been implicated in the transmission of heartwater disease, the ones that cause most cases are *Amblyomma variegatum* and *Amblyomma hebraeum.* The intermittent feeding behavior of the tick makes it particularly difficult to control. *Amblyomma* ticks require three separate blood meals to complete their life cycle. The gravid females fall from the host and lay the eggs in rotting vegetation, particularly in areas where the hosts are bedded for the evening. Recently hatched larvae crawl onto foliage and await a host. After their first feed the larvae detach, molt into nymphs, and await a second host. After refeeding, the nymphs detach and molt into adults. The adults remain under rotting vegetation until they are activated by carbon dioxide exhaled by a large mammal. They are further attracted to the host by pheromones from male ticks that remain permanently attached to the host. Animals that do not have male tick infestations are poor attractants for nongravid females. Once attached to the proper host, the females seek the male, breed, feed, and fall from the host when it lies down for the evening. Ticks that feed from *Ehrlichia*-infected hosts develop ovarian infections and transmit the agent to their offspring. This serves to perpetuate the agent over successive seasons.[5]

Many species of vertebrates, including snakes, iguanas, lizards, and birds, are reservoirs for *E. ruminantium* because these animals may serve as the first two hosts for the *Amblyomma* tick.[6] A vector-wildlife cycle facilitates the survival of *E. ruminantium* even when domestic livestock are absent from the environment.[7]

■ Pathogenesis

After inoculation into a ruminant, the rickettsial agent infects reticuloendothelial cells and proliferates by binary fission within membrane-bound vacuoles.[8,9] Release of the parasite from degenerating macrophages and neutrophils causes successive waves of parasitemia that infect endothelial cells and cause vasculitis.[9,10] Nervous system lesions may be caused by permeability changes in the cerebral capillaries. Changes in the other soft tissues include hydropericardium, hydrothorax, and subcutaneous edema.[1]

Except for Angora goats, which are highly susceptible to *Ehrlichia* infection, animals reared in indigenous areas usually have a high level of immunity and do not succumb to the infection.[11] Animals that survive the initial infection no longer show symptoms but remain rickettsemic for as long as 223 days (sheep), 246 days (cattle), and 8 days (goats). Calves younger than 3 weeks of age, lambs

younger than 8 days of age, and kids younger than 6 weeks of age are inherently resistant to *E. ruminantium* infection, regardless of the amount of colostral protection they have received.[12,13]

■ Clinical Signs

Animals with the peracute form of *E. ruminantium* infection die suddenly without premonitory signs. The acute form of the disease is characterized initially by fever, anorexia, depression, and respiratory distress. Cyanosis may also be noted. Nervous system signs, which may appear within a few days, include hyperesthesia, snapping closure of the eyelids, rapid extension of the tongue, behavioral changes, muscular fasciculations, hypermetria, ataxia, conscious proprioceptive deficits, and head pressing. As the disease progresses, the animals become recumbent and comatose. Convulsions may occur in the terminal phase. These episodes are characterized by opisthotonos, nystagmus, chewing movements, and frothing at the mouth. Mild forms of the disease are characterized by transient diarrhea, malaise, and fever, with no CNS involvement. The mortality rate in sheep ranges from 6% to 80%. Animals that recover are immune to reinfection for at least 58 months.[14] Losses may reach 60% of susceptible cattle and 40% of goats. The mortality rate among Angora goats may exceed 90%. Enterotoxemia caused by *Clostridium perfringens* type D is important in the differential diagnosis in small ruminants.

■ Pathology

Pathologic changes of heartwater disease include hydropericardium, hydroperitoneum, hydrothorax, pulmonary edema, perirenal edema, hemorrhages in the pleura and peritoneum, and hemorrhagic enteritis. Microscopic changes include microgliosis, necrotizing vasculitis in the brain, hemorrhage, edema of the neuropil, microcavitation, and focal necrosis of the granular layer of the cerebellum. In clinical cases, the parasite can be definitively diagnosed only through biopsy of the cerebral cortex or by collection of the cortical tissues at postmortem examination.[15] Simple techniques for collection of such biopsy specimens have been described.[16-18] Squash preparations of the biopsy sample should be stained with either methyl green pyronine or Giemsa stain before microscopic examination of the tissues.[19,20]

Diagnostic tests developed to identify infected livestock include an IFAT in which infected bovine aortic endothelial cells serve as indicators, several

ELISAs, and tests involving PCR methodology.[21-24] Of these, PCR is the most accurate.

■ Treatment and Control

The administration of oxytetracycline (6 to 10 mg/kg IV twice daily for 3 or 4 days) may be beneficial for treatment of the early stages of the disease. The long-acting formulation of oxytetracycline is also effective, but for best results it should be administered as soon as the animal becomes febrile. Treatment is usually futile if the first dose of oxytetracycline is administered after the onset of neurologic signs.[25] Despite the depository nature of the long-acting formulation, two or more doses 48 hours apart are necessary to achieve a good clinical response. Cattle should be re-treated if they develop a fever after the first dose has been administered.[26] Many animals with CNS signs die despite intensive antibiotic therapy. Angora goats are highly susceptible to heartwater disease. In South Africa, Angora producers routinely treat all animals every 14 days during the summer with oxytetracycline. Animals that remain essentially tick free never develop adequate immunity to the *Ehrlichia* organism.

A small degree of tick infestation and exposure of the animals to low numbers of the agent, combined with judicious oxytetracycline therapy, appears to favor the development of immunity over time.[27] One method of immunization is to use a controlled infection of a virulent strain (Onderstepoort Ball 3 strain) of the *Ehrlichia* organism and treatment with long-acting oxytetracycline (800 mg per adult goat) at the beginning of clinical disease and 10 days later.[28] Vaccination with this isolate produces immunity against exposure to homologous, but not heterologous, strains of *Ehrlichia.*[29-31] More recent strategies have included vaccination with inactivated organisms, live attenuated organisms, and fragments of *E. ruminantium* nucleic acid, but none has produced great success.[32-36]

Control of ticks on pastures is the most desirable means of controlling heartwater disease. Complete eradication of the ticks in most regions of sub-Saharan Africa is neither possible nor desirable. Cattle that are reared in areas where *Ehrlichia* infection is endemic acquire immunity over time. In these areas, the ticks should be sufficiently abundant to enable a low level of heartwater infections in most cattle but not so populous as to introduce severe, overwhelming infections. Integrated methods for tick control have been recommended. These include exclusion of wildlife from paddocks, artificial induction of host resistance to ticks, application of insecticidal ear tags, and

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conventional acaricide application. Application of insecticides as the sole method of tick control has not proved highly effective. Resistance to the acaricides may develop with prolonged use.

Heartwater is a reportable disease in the United States. Suspected cases should be referred to the appropriate state and federal authorities.

Cerebral Theileriasis (Turning Sickness; Draaisiekte; East Coast Fever; Corridor Disease; January Disease; Tropical Fever)

■ Definition, Etiology, and Epidemiology

Cerebral theileriasis is an encephalitic disease of cattle caused by the piroplasma parasites *Theileria annulata* and *Theileria parva*.[1,2] Theileriasis occurs mainly in Africa (Kenya and Tanganyika) and India, where it is characterized by a high mortality rate and is known as East Coast Fever. *Theileria sergenti* is found in Korea and Japan. *Theileria mutans*, a parasite of cattle in the southwestern United States, is relatively nonpathogenic.[3] A mild form of theileriasis, locally called "January disease," occurs in cattle in Mozambique. This condition is caused by the subspecies *T. parva bovis.* Corridor disease is caused by *T. parva lawrencei,* and *T. annulata* is the cause of Mediterranean Coast fever or tropical theileriasis.

European breeds of cattle *(Bos taurus)* develop a more severe disease than do comparably infected Indian breeds *(Bos indicus).* Both types of cattle appear to be equally susceptible to infection but differ in their ability to control the course of disease.[4] *Theileria* organisms are transmitted to susceptible cattle by the ticks *Hyalomma anatolicum*, *Hyalomma lusitanicum*, and *A. hebraeum.*[5]

■ Pathogenesis

Trypanosoma spp. manipulate the immune system both to evade destruction and to promulgate infection. Organisms escape the host immune response by altering immune system activation so that infected cells avoid recognition and destruction.[6-8] Clonal expansion of infected lymphocytes is promoted, and these cells disseminate throughout the body.[9]

■ Clinical Signs

The clinical signs of *Theileria* infections include lymphadenopathy, nasal discharge, lacrimation, tachycardia, fever, subcutaneous edema of the face, gangrenous dermatitis, sloughing of facial skin, dyspnea, pallor, CNS disease, and emaciation.[10] The neurologic syndrome is characterized by ataxia, hypermetria, conscious proprioceptive deficits, depression, head pressing,

hyperesthesia, blindness, nystagmus, circling, and aggressiveness. In the terminal stage, the animals become recumbent and develop opisthotonos, tonic-clonic seizures, and coma. In rare cases the parasite may localize in the spinal cord. The CNS signs result from vasculitis and lymphocytic inflammation of the brain.[11-13] Clinically recovered animals remain persistently infected.

■ Pathology

The postmortem lesions of theileriasis include capillary engorgement, scattered punctate hemorrhages on the surface of the brain, thrombosis of the meningeal vessels, hemorrhage in the cerebral ventricles, pulmonary edema, peripheral lymphadenopathy, and infarctions of the kidney and spleen. The brain of an affected animals appears to yellowish.[13] On microscopy, blue cytoplasmic inclusion bodies (Koch blue bodies) are observed in the lymphocytes adjacent to the hemorrhagic areas.

The nervous form of theileriasis is difficult to diagnose definitively because the parasite is only sporadically visible in sections of nervous tissue from the infected animals. Parasitemia is occasionally detected in microscopic examination of blood smears from infected calves. Reliable blood tests are not currently available. Biopsy of the cerebral cortex has been recommended as a confirmatory test for the disease. The CSF of affected animals is normal or has an increased protein concentration ranging from 1400 to 12,452 mg/dL, with normal numbers of WBCs.[12]

■ Treatment and Control

Parvaquone (10 to 20 mg/kg IM in two injections 48 hours apart) and buparvaquone (at a single dose of 2.5 mg/kg) are approximately 90% effective for the treatment of theileriasis.[14] Some studies have shown buparvaquone to be the most effective treatment.[15,16] Parvaquone can be combined with furosemide, which improves survival of cattle that develop pulmonary edema, a common consequence of theileriasis.[17] Menoctone (10 mg/kg IV or IM) is also curative. Single doses were effective in one study, but repeating the treatment daily for 5 days eliminated posttherapeutic recrudescence.[18]

Prevention of *Theileria* infection has been based largely on the use of live attenuated vaccines, which produce a solid, cell-mediated immunity.[19] These vaccines are used in an “infection and treatment” manner, whereby vaccination

must be combined with administration of long-acting tetracyclines.[20] Recent efforts at vaccine development have focused on the creation of subunit vaccines involving a variety of *Theileria* antigens.

The naphthoquinones are the preferred chemotherapeutic agents in vaccinated animals and include parvaquone, halofunginone lactate, and buparvaquone.

Tick control is vital for prevention. Weekly spraying with coumaphos and insertion of ear tags impregnated with cypermethrin have been effective for controlling ticks and preventing *Theileria* infections in calves in Tanzania. If the tags are removed, the calves become infected with *T. parva* within 3 months. Woodford[21] suggested that intensive tick control could minimize the incidence of theileriasis until the calves can be successfully vaccinated. However, inadequate or incorrect application of products and tick resistance to chemicals present challenges to effective tick control. The disease is exotic to North America.

Cerebral Trypanosomiasis (Sleeping Sickness)

■ Definition, Etiology, and Epidemiology

Trypanosomiasis is a hemoprotozoan disease of African cattle that also infects the CNS. The disease is transmitted to cattle by the bite of the tsetse fly (*Glossina* spp.). The agents that infect cattle include *Trypanosoma vivax*, *Trypanosoma congolense*, and *Trypanosoma brucei*. An especially severe neurologic form of the disease has been caused by the inoculation of cattle with *T. congolense*, followed 1 year later by infection with *T. brucei*, or by simultaneous inoculation with the two agents.[1]

■ Clinical Signs

Encephalitic signs of the disease develop 2.5 to 5 months after infection and include ataxia, conscious proprioceptive deficits, knuckling (partial collapse of a joint into a flexed position), depression, circling, and head pressing. Some animals may show signs of behavioral change, lose the herd instinct, and develop hyperesthesia and constant repetitive movements. Other signs associated with progression of trypanosomiasis are semicoma, coma, recumbency, opisthotonos, and intermittent tonic-clonic convulsions, which occur 2 to 3 days before death. Affected animals are emaciated, anemic, and icteric at death.[2]

Experimental infection with trypanosomes causes a marked fever (as high as

40.5° C [105° F]). Other common nonneurologic signs include anemia, petechiation of the mucous membranes, occult fecal blood, melena, and epistaxis. Some affected animals exhibit chronic weight loss without other clinical signs.

■ Clinical Pathology

Hematologic abnormalities include anemia, hypoalbuminemia, hyperbilirubinemia, and increased plasma concentrations of aspartate transaminase and urea nitrogen.

Acutely infected animals may develop thrombocytopenia and prolongation of the prothrombin and partial thromboplastin times, which indicates that disseminated intravascular coagulation may be responsible for the vascular changes that occur before death. The anemia is characterized by increases in mean corpuscular volume and mean corpuscular hemoglobin, with increases in serum iron concentrations early in the infection.[3,4] In one study, changes in the concentration of WBCs or protein in the CSF did not occur in animals with the encephalitic form of trypanosomiasis.[1] However, in another study, these parameters were significantly altered in cattle infected with *T. brucei*.[5] The alterations included an increase in total protein (range, 37 to 44 mg/dL) and pleocytosis (range, 0 to 3060 mononuclear cells per microliter). The abnormalities in the CSF may be present in infected cattle not currently displaying clinical neurologic signs. Antitrypanosomal antibody may be found in the CSF of affected cattle with the use of IFAT.

■ Pathology

The pathologic lesions of trypanosomiasis are a nonsuppurative encephalomyelitis, serosanguinous pericardial fluid, serosal hemorrhages, pulmonary edema, centrilobular coagulative necrosis, splenomegaly, necrotizing myocarditis, and glomerulonephritis.[6] Macroscopic lesions of the CNS include subtle thickening and grayish discoloration of the meninges. The meningeal vessels are congested. Microscopic lesions of the CNS reflect moderate diffuse meningoencephalitis. The pathogenesis of the encephalitis is not understood.

Trypanosomes may be cultured from the blood and CSF of infected cattle. The number of hematogenous parasites is highest in animals with a dual infection by *T. congolense* and *T. brucei*. The clinical diagnosis of trypanosomiasis may be confirmed by inoculating blood or CSF specimens into laboratory mice and

observing the recipients for parasitemia with direct darkfield examination of the patient's blood. Identification of motile trypanosomes in the buffy coat zone of a microhematocrit capillary tube with darkfield illumination is apparently the most accurate of all diagnostic methods. Trypanosomes can be differentiated by their morphologic features, manner of attachment to erythrocytes, and type of motility.[7] Infected cattle develop acquired resistance to homologous, but not heterologous, isolates of trypanosomes.

■ Treatment and Control

Of the drugs available for the treatment of trypanosomiasis, isometamidium chloride is most often used. The recommended dose ranges from 0.25 to 1 mg/kg IM; a single dose of 1 mg/kg exerts a protective effect for up to 6 months.[8] The higher dose (1 mg/kg) is necessary to increase weight gain and prevent recurrent infection. The treatment was particularly effective when combined with weekly surveillance, followed by treatment of animals confirmed to be infected.[9] Side effects of isometamidium include tachycardia, salivation, lacrimation, pollakiuria, muscle fasciculations, convulsions, diarrhea, and, in rare cases, death. The drug apparently does not cause abortion in pregnant cows or otherwise affect the calf.[10]

Other drugs used include suramin sodium, diminazene aceturate (7 mg/kg), quinapyramine sulfate, and homidium chloride (1 mg/kg). These drugs provide residual protection from reinfection for approximately 2 months; however, recurrent infection and resistance, especially to diminazene, have been reported.[11-14] Combinations of these drugs (e.g., diminazene followed by isometamidium) reduce the number of resistance-related therapeutic failures. Relapses also occur, undoubtedly because many of the chemoprophylactic drugs are unable to penetrate the blood-brain barrier in sufficient concentrations to eliminate the parasite in the CNS tissues.

Because of the variable responses to treatment and the ability of *Trypanosoma* organisms to develop drug resistance, all control programs must include methods of controlling the tsetse fly.[13] Because the tsetse fly prefers to feed from the ventral torso or the legs, insecticide-impregnated ear tags have been ineffective for preventing infection; other means of application of insecticide are necessary.[15] Other fly control methods include aerial spraying with endosulfan, ground-based spraying with 4% dichlorodiphenyltrichloroethane (DDT), or use of scented insecticidal traps.[14] However, cost and environmental concerns have

limited the usefulness of these techniques.

Selection of resistant lines of cattle is possible. The taurine N'Dama and West African shorthorn breeds have innate resistance to trypanosomiasis and are the sole breeds of cattle in areas of tsetse fly range.[16] Resistant breeds of small ruminants include the Djallonke, Red Maasai, Blackhead Persian, and East African sheep and goats.[17] Imported breeds of livestock usually cannot be maintained, even in areas of low tsetse fly risk, without intensive drug therapy.[18]

Polioencephalomalacia (Cerebrocortical Necrosis)

Christopher Cebra • Guy H. Loneragan • Daniel H. Gould • John R. Middleton

■ Definition and Etiology

Polioencephalomalacia (PEM) is a common and important neurologic disease of ruminants[1,2] with a worldwide distribution. An animal with clinical manifestations of PEM is often referred to as having “polio” or being a “sleeper” or “brainer.”

Polioencephalomalacia is a descriptive term for histologic lesions[1,3] that may arise from a variety of etiologies. Literally, the name means softening or necrosis (malacia) of regions of the gray matter (“polio-”) of the brain (“encephalo-”). Thus a definitive diagnosis of PEM requires histologic examination of brain tissue. The possible causes of PEM include, but are not limited to, excessive sulfur consumption (manifested by elevated ruminal sulfide production),[4-8] altered thiamine metabolism,[9] salt poisoning or water deprivation,[10] amprolium administration,[11-13] rations composed of molasses and urea,[14] and lead intoxication.[15] Of cases in which a cause can be determined, most involve altered thiamine metabolism, excessive sulfur consumption, or both.

■ Epidemiology

PEM has a worldwide distribution. The condition occurs both in individuals and as herd outbreaks. In one instance, approximately 2000 of 2200 sheep grazing were clinically affected with PEM.[4] No predilection by gender or breed is observed. The condition affects cattle, sheep, goats, deer, camels, and

camelids.[5,11,16-19] Although PEM occurs predominantly in animals that eat a high-concentrate supplement, the condition can also occur in unsupplemented animals on pasture.

The age ranges for susceptibility to PEM have been reported as 3 weeks to 5 years in sheep, 3 weeks to 8 years in cattle, and 2 months to 2.5 years in goats. The occurrence peaks at the age of 18 months or younger in cattle and sheep but depends on the production system.[1,8,20] The incidence of PEM has been reported as high as 90% in some sheep flocks, with mortality rates ranging from 1% to 10%.[4] In one report, the incidence of PEM was reported to be high in sheep exported by sea from Australia to the Middle East, where the underlying cause was postulated to be thiamine deficiency caused by alterations in rumen synthesis secondary to the shipboard feeding conditions.[21]

■ Pathogenesis

The fundamental lesion with PEM appears to be neuronal edema with necrosis. In most cases, the edema is thought to result from ATP depletion and decreased activity of the sodium-potassium pump in cortical cells. The bony calvaria limits tissue expansion, and neuronal swelling leads to pressure necrosis.

The brain is susceptible to PEM because of its high energy and oxygen requirements. Brain tissue makes up only approximately 2% of body weight but accounts for 20% to 30% of body glucose utilization and 20% of oxygen utilization in adults.[22] The brain relies heavily on glucose as an energy substrate, and the blood-brain barrier limits the ability to utilize alternative energy substrates. In comparison with liver or muscle, the brain has relatively small glycogen stores—only approximately a 10-minute supply—and it is entirely dependent on circulating oxygen. Under normal conditions, the extracellular fluid contains approximately 100 times as much glucose as the oxygen required for complete aerobic glycolysis. Thus oxygen delivery or utilization limits the rate of ATP production under most circumstances much more than does glucose availability,[23] and factors that inhibit oxygen utilization (e.g., hydrogen sulfide, lead) affect neuronal ATP production.

Much of the early work on PEM focused on the importance of thiamine (also known as vitamin B_1, thiamin, and aneurin). In adult ruminants, thiamine is produced by rumen microbes at a rate that is marginally faster than the rate of consumption; very little is stored.[24] Preruminants depend on dietary thiamine. Thiamine compounds play several important roles in the glycolytic pathways.

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Thiamine pyrophosphate (thiamine diphosphate) is an important coenzyme for transketolase, the rate-limiting enzyme in the hexose monophosphate pathway (pentose phosphate shunt) of glycolysis, and for the α-ketoacid dehydrogenases of the Krebs cycle. The role of thiamine in the hexose monophosphate pathway was long thought to be key in the development of PEM, but this pathway actually accounts for less than 3% of cerebral glycolysis.[25] Hence, it is unlikely that impairment of this pathway alone could lead to such severe disease. However, decreased function of the Krebs acid cycle through inactivity of the α-ketoacid dehydrogenases could cause the necessary reduction in ATP production. Thiamine triphosphate may also play a role in neuronal function independent of its enzymatic function.

The dependence of ruminants on microbial thiamine production led to investigation of factors that might decrease production, absorption, or function. Proposed mechanisms include ruminal production of bacterial thiaminases, production or ingestion of inactive thiamine analogs, ingestion of preformed plant thiaminases, decreased intake of preformed thiamine by preruminants, impaired absorption or phosphorylation of thiamine by rumen bacteria, increased fecal excretion of thiamine, and decreased ruminal production of thiamine diphosphate. The inactive thiamine analog most frequently reported is amprolium.[11-13]

Two types of bacterial thiaminases have been described. Thiaminase I, produced by *Bacillus thiaminolyticus* or *Clostridium sporogenes,*[26] catalyzes the cleavage of thiamine at the methylene bridge between the pyrimidinyl and the thiazole ring. A basic cosubstrate is necessary to combine with the pyrimidinyl derivative to form a new compound[27], and many common medications, including benzimidazoles, levamisole, and promazines, appear to be able to serve as this cosubstrate. Several plants also apparently make a thiaminase similar to thiaminase I. These include bracken fern *(Pteridium aquilinum),*[28,29] horsetail *(E. arvense),*[29] and Nardoo fern *(Marsilea drummondii).*[30] Of these, only the Australian Nardoo fern has been strongly linked to outbreaks of PEM. Thiaminase II is produced by *Bacillus aneurinolyticus,* which proliferates in response to excessive grain intake.[31] Thiaminase II catalyzes the hydrolysis of the methylene bridge between the two ring structures of the thiamine molecule. The specific relationship of this thiaminase to the clinical syndrome of PEM as observed in the field is unclear.

Complete correlation has not been established among production of ruminal

and fecal thiaminase, tissue and plasma concentration of thiamine, and development of clinical encephalopathy.[32,33] Some affected animals may show normal amounts of thiamine in the plasma but have greatly decreased levels in the erythrocytes and other tissues, which is evidence of the diversity of causes of PEM.[34]

Dietary sulfur and sulfates are an important factor in the development of many cases of ruminant PEM. Beef cattle require 0.15% to 0.20% of dietary sulfur on a dry matter basis.[35] Sources of sulfur include elemental sulfur,[4] feed additives such as gypsum and ammonium sulfate,[5,36] feedstuffs such as corn by-products,[35] cruciferous crops,[37,38] molasses,[14] and fertilizers. Water is an important contributor to sulfur intake, usually in the form of sulfates.[7,39,40]

There are two primary metabolic pathways of sulfur in the rumen.[40-45] The *assimilatory pathway* involves reduction of sulfate to sulfides and incorporation into sulfur-containing organic compounds such as cysteine and methionine.[43] These are ultimately incorporated into microbial crude protein. The *dissimilatory pathway* is an energy-producing pathway in which microorganisms use sulfate as a terminal electron acceptor, in a manner similar to how mammals use oxygen.[46] The end product is liberated sulfide ion. At a ruminal pH of 5.2, 97.2% of sulfide ions are in the form of hydrogen sulfide and move freely to the rumen gas cap.[42,47] Hydrogen sulfide is readily absorbed and transported to the liver and oxidized to sulfate.[47,48] Some hydrogen sulfide may be lost through eructation,[48,49] but the significance of this route has been questioned.[50] Excess sulfur is excreted in the urine and large intestine[51,52] or recycled to the rumen.[53,54] A period of adaptation is required for maximum production of hydrogen sulfide after exposure to sulfur.[44,51,54-56]

Because sulfur and sulfate demonstrate low cellular toxicity, it is unlikely that sulfur-associated PEM results from sulfate or sulfur toxicity. However, sulfides are highly toxic.[57-59] The chances of sulfur-associated PEM are higher after sulfide toxicity.[6,8,49] It has been proposed that the pathogenesis of sulfur-induced PEM involves inhibition of cytochrome *c* oxidase, an enzyme in the electron transport chain; this chain is important for regenerating the intermediaries of aerobic glycolysis and the final round of ATP production. Because oxygen availability already limits aerobic glycolysis in the brain, inhibition of the electron transport chain could profoundly alter neuronal ATP production.

For highly toxic sulfide to reach the brain, it must escape hepatic oxidation.

This is achieved by two mechanisms. A surge in ruminal sulfide generation usually follows a period of adaptation to high-sulfur diets. This surge may overwhelm the hepatic detoxification capacity. Because cattle inhale the majority of eructated ruminal gas,[60] it has been proposed that eructated hydrogen sulfide may be inhaled and absorbed via the pulmonary tree, bypassing hepatic circulation and leading to neurotoxicity in the brain; however, this concept has been questioned.[61]

In feedlot cattle, a summer peak in PEM cases was associated with consumption of water containing 2500 mg/L of sulfate.[7] The total sulfur intake of these steers was estimated to be 0.6% on a dry matter basis during the hottest days of the year. Most PEM cases occurred between 15 and 35 days after arrival in this feedlot. In another investigation, 11% of weaned calves consuming a diet containing 0.9% sulfur on a dry matter basis developed clinical manifestations of PEM.[8] Lesions were confirmed in one steer that died. Addition of gypsum (calcium sulfate) to feeder cattle rations at a final concentration exceeding 2% organic sulfate resulted in a significantly greater risk of developing PEM. The addition of sodium sulfate (0.6% to 0.8%) to diets may induce PEM within 11 days.[49,55,62,63] An outbreak of PEM in Canada was traced to high sulfur concentrations in well water in combination with accumulation in forage.[8] One survey described an outbreak of cerebrocortical necrosis in cattle eating diets containing 7200 mg/kg of sodium sulfate.[40]

The recommended maximum tolerance level of sulfur is 0.4% of dry matter intake.[35] Other effects of excessive sulfur intake are decreases in feed intake and weight gain. Accurate diagnosis of sulfur toxicity requires measurement of sulfur in all food and water sources. Sulfur from water must be included when total sulfur intake is calculated. One third of the molecular weight of sulfate is sulfur. Accordingly, if an animal drinks 30 L of water a day containing 2000 mg/L of sulfate, this contributes 60,000 mg of sulfate, or 20 g of sulfur. Furthermore, if this animal consumes an average of 10 kg of dry matter daily at 0.15% sulfur, the feed or forage contributes 15 g of sulfur, and thus the total sulfur intake is 35 g, or 0.35% on a dry matter basis. This scenario illustrates that water may be a substantial contributor to total daily sulfur intake.

Some authors have suggested that sulfides result in thiamine destruction, thereby directly implicating a thiamine deficiency in the pathogenesis of sulfur-associated PEM. Rumen thiamine production was slightly reduced by the inclusion of excessive sulfur in the ration.[64] However, the authors deemed the

measured reduction to be clinically insignificant; they suggest that sulfur-associated PEM occurs independent of thiamine metabolism. One study suggested that the reductions in activities of pyruvate dehydrogenase, α-ketogluterate dehydrogenase, and cytochrome *c* oxidase in the cerebral cortex is associated with the pathogenesis of sulfur-induced PEM.[65]

PEM induced by feeding of molasses and urea is thought to be related to the high sulfur content of the molasses and to the depletion of propionate and other glucogenic precursors[14]; it is not considered to be caused by thiamine destruction. The tissue thiamine concentrations of animals with molasses-related PEM are normal,[66] and signs are preventable by concomitant feeding of glycerol, which is converted to glucose in the rumen. Outbreaks of PEM in range cattle have been associated with ingestion of the plant *Kochia scoparia*.[67,68] The pathogenesis of this condition is unknown; however, some authors have suggested that the plant has the capacity to accumulate sulfur.[40]

Some cases of PEM cannot be linked either to problems with thiamine or to sulfur toxicity. Other compounds, such as lead, affect electron transport in a manner similar to that of sulfides and therefore also impair ATP production. Water intoxication creates a similar histologic lesion, but the pathogenesis of edema is related more to the generation of osmotic compounds and fluid shifts with rapid fluctuations in blood and neuronal osmolality (see Salt Poisoning [With or Without Concurrent Water Deprivation] section).

■ Clinical Signs

PEM appears to manifest both subacutely and acutely.[1,8] In the subacute form, signs may develop within hours or over several days. In the early stages of the disease, the affected animals detach from the herd or flock, become anorectic, and stagger. Neurologic signs are symmetric. Affected animals are blind, walk with the head held erect, and demonstrate a slight hypermetric gait. Progression of the condition is associated with bilateral cortical blindness, head pressing, opisthotonos, bilateral dorsomedial strabismus, miosis, repetitive chewing, profuse ptyalism, and odontoprisis.[1,5,69-71] Despite the defective menace response, the animals usually have normal palpebral reflexes. Affected animals may also develop a variable nystagmus. The rectal temperature is normal unless excessive muscular fasciculations have developed. The pulse and respiratory rates are usually increased. An odor of hydrogen sulfide may be detected on the breath if the PEM is associated with excessive sulfur consumption.

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Although most of these animals respond favorably to aggressive therapeutic intervention, clinical signs may progress to recumbency, tonic-clonic convulsions, and death. In facilities with certain types of fencing, such as cables, affected animals may push or press on their airway with such force that they die of asphyxiation.

In the acute form of PEM, animals are found recumbent and comatose.[1,8] These animals often exhibit episodic tonic-clonic convulsions, and they remain recumbent and hypertonic between seizures. The prognosis is poor for acutely affected animals and those with advanced subacute manifestations. Survivors may remain irreversibly decorticated and are culled because of poor performance, chronic anorexia and ataxia, or blindness. However, mildly affected animals may remain productive members of the herd.

Because the clinical manifestations of PEM may be subtle and nonspecific, they can be confused with other disorders. PEM is often confused with lactic acidosis that develops after consumption of excessive amounts of readily fermentable carbohydrates. Animals with lactic acidosis may appear ataxic and obtunded, in addition to having a foul-smelling, watery stool and a distended, fluid-filled rumen. PEM can occur concurrently with carbohydrate engorgement but may go undiagnosed, or PEM may be confused with lactic acidosis or primary ruminal tympany in acutely affected animals that have remained laterally recumbent for some time.

The major differential diagnoses for PEM include enterotoxemia type D (focal symmetric encephalomalacia in small ruminants), salt poisoning/water deprivation, head trauma, bacterial meningoencephalitis, coccidiosis with nervous system involvement, vitamin A deficiency, ethylene glycol poisoning, locoism, rabies, and IBR encephalitis.

■ Clinical Pathology

Although a definitive diagnosis requires histologic examination of brain tissue, a presumptive diagnosis before death may be based on the history and clinical signs or response to therapy. If PEM is diagnosed, the investigation should proceed at the animal, herd, and environmental level to identify evidence supportive of sulfide toxicity, thiamine deficiency, lead toxicity, or water deprivation/salt toxicosis.

Sulfide concentrations in the ruminal fluid and gas cap in experimentally induced sulfur-associated PEM have been shown to be high.[49,72] However,

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unpublished data supported a finding of a decrease in gas cap sulfide concentrations in naturally developing PEM associated with increased sulfur consumption.[73] This is probably caused by the rapid metabolism of sulfate to sulfide in the rumen and resultant absorption or eructation of hydrogen sulfide. Animals with naturally developing PEM are likely to have been anorectic for some time, which results in a decrease in oxidized and reduced forms of ruminal sulfur.

In clinically healthy penmates of affected cattle, the concentration of hydrogen sulfide in the rumen gas cap can be estimated; this is an effective chute-side diagnostic procedure whose results can indicate excessive sulfur consumption.[8] This method provides real-time results that may aid direction of further animal and environmental investigations. In short, an area in the left paralumbar fossa is prepared for ruminocentesis. An 18-gauge, 3.5-inch spinal needle is inserted through the body wall and into the rumen gas cap. A modified gas sampler is attached to the spinal needle by means of an extension set, and a known amount of gas is drawn through a hydrogen sulfide detector tube.[72] It is important to adjust the values to account for any dead space of the sampling instrument, such as the extension set and other modifications. Hydrogen sulfide concentrations greater than 1000 ppm are indicative of excessive sulfur consumption.[74]

Blood samples may be analyzed for lead concentration and possibly estimation of thiamine status. Thiamine status is generally evaluated with one of several available methods, including determining the total blood thiamine concentration through a thiamine-dependent *Lactobacillus* bioassay.[75] The erythrocyte thiamine pyrophosphate concentration may be measured by high-performance liquid chromatography.[76]

Another method of evaluating thiamine status is to determine erythrocyte transketolase activity.[77] In this test, the specific activity in the active (holoenzyme) and inactive (apoenzyme) forms is compared with the activity of the two forms after addition of thiamine to the homogenates. A large increase in specific transketolase activity after addition of the thiamine pyrophosphate suggests thiamine deficiency. Theoretically, in animals with thiamine-associated PEM, the concentration of holoenzyme is decreased and that of the apoenzyme is increased. If thiamine deficiency is identified in an affected animal, caution should be used in interpreting the results, because a period of anorexia may result in a decrease in ruminal de novo synthesis.[78,79]

Changes in CSF of affected animals are usually vague. They include mild

pleocytosis (5 to 50 WBCs/dL) with vacuolation and increased protein concentrations (>50 mg/dL).[9,80] Electrophysiologic studies of affected animals show a normal latency and decreased amplitude of the late peaks of the visual evoked potentials. These changes reflect decreased numbers of neurons capable of responding to the photic stimulation.[81]

Environmental investigations should include evaluation of all feed and water sources for sulfur concentrations or the possibility of lead contamination. The diet should also be checked for molasses, salt, and urea content.

■ Pathology

In cases of sulfur-associated PEM, rumen contents may have an odor of hydrogen sulfide. In other cases, there may be evidence of grain overload, coccidiosis, or respiratory disease. Some of these lesions are related to management conditions, but they may also be related directly or indirectly to PEM. The macroscopic pathologic brain lesions of PEM include cortical swelling and softening, flattening, and yellowish discoloration of the gyri. Necrotic areas of the cerebral cortex demonstrate autofluorescence under ultraviolet light (365 nm).[82,83] In severe cases, the cerebellum herniates through the foramen magnum or the occipital cortex under the tentorium cerebelli. Necropsy months after recovery may reveal cerebral atrophy and submeningeal cortical cysts. The major microscopic lesion is a diffuse laminar necrosis. Other changes include intracellular and intercellular edema, neuronal necrosis, and neuronophagia.[3,70]

■ Treatment and Prognosis

Regardless of the underlying cause, animals with the subacute form of PEM often respond favorably to parenteral administration of thiamine hydrochloride. These animals may remain blind and may have depressed sensorium for weeks or months.[84] Thiamine should be administered at 10 to 20 mg/kg IM or SC three times daily. In severe cases, IV administration of the first dose might be warranted. If given intravenously, thiamine should be administered slowly to avoid adverse reactions. If no improvement occurs initially, the treatment should be continued for at least 3 days. In some patients, recovery may take as long as 7 days, but most patients show improvement within 24 hours. A single administration of sodium dexamethasone (0.1 to 0.2 mg/kg IM or IV) or mannitol (1 g/kg of mannitol in a 20% solution IV) may help reduce cerebral

edema. Anecdotal reports indicate that feedlot animals that have recovered from PEM are at increased risk for respiratory disease; therefore prophylactic antimicrobial administration may be indicated. Convulsions may be controlled with phenobarbital, pentobarbital, or diazepam (see Table 35.4). Animals with the acute form of PEM usually have more severe cortical and deep gray matter lesions than do animals with the subacute form.[8] Animals with the acute form generally do not respond to therapeutic regimens. Ruminants with PEM secondary to the molasses-urea diet do not appear to respond to treatment with thiamine. They may respond more favorably to parenteral administration of glucose or enteral or parenteral administration of a glucose precursor.

■ Prevention and Control

Ultimately, the best way to prevent outbreaks is to manage the dietary intakes of susceptible animals appropriately. Ruminants should be allowed an adequate period of adaptation to high-concentrate rations. All feedstuffs and water sources should be carefully analyzed on a routine basis to estimate total sulfur intake. If excess sulfur consumption is a factor, steps should be taken to remove sources such as high-sulfur hay, ammonium sulfate, and molasses. If the excess sulfur intake is unavoidable, steps can be taken to limit its effects. Older members of the cow herd could be used to graze the high-sulfur pastures, and younger, more susceptible animals could be kept in lower-sulfur pastures or given hay supplementation. Personnel should be trained to identify PEM early and treat it appropriately.

Thiamine may be given as supplementation (3 to 10 mg/kg of feed) in rations in which the concentrate/fiber ratio is high, but this has little or no effect in preventing PEM. Other recommendations for preventing PEM include addition of brewer's yeast to the ration and gradual adaptation of ruminants (at least 2 weeks) to high-concentrate diets. Gypsum, if present as a feed-limiting additive, should be removed from the diet. Elimination of supplementation and rotation of pastures have been sufficient for controlling some outbreaks.[20] Supplementation with cobalt in trace-mineral salt mixes may be necessary in deficient areas.

Salt (Sodium) Poisoning (With or Without Concurrent Water Deprivation)

Lisle W. George • John R. Middleton

■ Definition and Etiology

Salt (sodium) poisoning is a common CNS disease of livestock. Ingestion of sodium-rich solutions over time can cause production-related losses and even death. Ingestion of water containing more than 7000 mg/L of total dissolved salts is likely to result in acute salt poisoning.[1,2] Water that contains less than 3000 mg/L of total dissolved salts is considered safe for consumption. Salt poisoning can be associated with water deprivation.[1,3,4] If access to free water is constantly available, animals may tolerate up to 13% dietary NaCl intake.[5]

The acute toxic doses of oral NaCl have been reported as approximately 2.2 g/kg body weight for cattle and horses and approximately 6 g/kg for sheep.[5] With water restriction, the toxic dose is considerably lower, and poisoning has resulted from ingestion of 0.9% NaCl in water-restricted cattle.[6] Chronic toxicity can occur at lower dietary NaCl levels than can acute toxicity. Ingestion of water with NaCl concentrations above 1% uniformly results in toxicosis if no other source of ion-free water is provided.[7,8]

Ingestion of water containing 0.7% NaCl impairs the fertility of females,[8] and water containing 0.25% NaCl suppresses milk production in cattle.[9] Dairy calves have been poisoned by daily feeding of 4 L of milk replacer containing 2.6% NaCl.[10] Animals are most susceptible to salt poisoning during the summer because of the increased insensitive loss of water at that time. Salt poisoning in ruminants is most frequently a syndrome of concurrent “water intoxication”: a period of restricted access to water, followed by unrestricted access to water.[1,3,4] In such cases, the dietary intake of sodium can be relatively modest, but disease occurs once water enters the extracellular fluid and moves into the brain tissue.

■ Epidemiology

Animals are tolerant of high dietary sodium levels if they have concomitant access to fresh drinking water. Feedstuffs that are common sources of excessive sodium include whey, saline-preserved fish or fish meals, bakery by-products, and certain milk replacers.[11] Confined calves may be poisoned by improperly formulated milk replacers or oral electrolyte solutions.[11,12] Brine is used extensively as a flush during the drilling of oil wells, and cattle eagerly ingest large amounts of oil well sludge in the western and southwestern United States.[13-15] Effluents from drilling rigs may contain as much as 100,000 ppm NaCl. Drilling effluent is also contaminated by heavy metals and magnesium

salts, which complicate the clinical syndrome of salt poisoning.

Concurrent neurologic disease may predispose animals to reduced water intake, as occurred in a group of goats with locoweed (*Oxytropis* spp.) poisoning who became water deprived because of reluctance to move to a water source. They developed clinical and pathologic evidence of sodium poisoning when moved subsequently to an area where water was easily available.[3] Sodium poisoning caused by water restriction may result either from freezing of water sources in northern climates or from intentional water restriction of veal calves.[12] Ingestion of brackish or tidal water is a cause of sodium poisoning in cattle pastured in the coastal regions of the world.

■ Pathogenesis

In salt poisoning, disease can occur acutely after ingestion of a large quantity of NaCl or chronically after long periods of reduced water consumption with low to moderate sodium intake. Thus hypernatremia results from an imbalance in sodium and water regulation. Increases in plasma sodium concentration cause movement of intracellular water into the extracellular fluid causing cellular dehydration. Cerebral dehydration is transient but is probably the cause of clinical signs in acute sodium overload. Intracellular hyperosmolality can reduce energy-dependent sodium transport mechanisms and glycolysis.[16] These mechanisms normally provide energy by which the sodium ion is removed from the cell cytoplasm.[17]

Within a few hours, osmotic adaptation begins to occur, whereby there is a net flow of fluid from the CSF into the brain interstitium as a result of a reduction in hydraulic pressure caused by the initial cerebral dehydration, and cellular uptake of Na, K, Cl, and organic solutes *(osmolytes)* increases intracellular osmolality, pulling water into cells and restoring cell volume.[18] Hence, with chronic hypernatremia, the animal may not manifest symptoms in the presence of high plasma sodium concentrations because of osmotic adaptation in the brain. In such cases, however, rapidly reducing plasma sodium concentrations and thus plasma osmolality during treatment or when the animal drinks large volumes of ion-free water can result in movement of free water into the brain; this causes edema and neurologic deterioration because loss of the accumulated osmolytes occurs more slowly than the relatively rapid loss of excess Na and K ions taken up during osmotic adaptation.

GI signs may also occur when animals ingest large quantities of salt over short

periods of time. The hyperosmolality in the intestinal lumen results in saline catharsis and osmotic diarrhea.

■ Clinical Signs

Acute ingestion of large amounts of salt causes GI and neurologic signs.[7,10,19,20] These include mucohemorrhagic diarrhea and colic, head-neck extension ("stargazing"), blindness, aggressiveness, hyperexcitability, psychomotor seizures (characterized by paddling and loss of consciousness), vocalization, ataxia, proprioceptive deficits, head pressing, constant chewing movements, nystagmus, muscle twitching, and coma. Death occurs as a result of respiratory failure. Before the onset of neurologic signs, cattle with chronic salt toxicosis may appear to be depressed and dehydrated.

Excessive salt intake may also interfere with productivity in the absence of acute neurologic signs. In one study, cattle were given either tap water (196 ppm of dissolved salts) or saline (2500 ppm NaCl), and their milk production was measured.[9] Cows given tap water had greater fluid intake and significantly greater lactational persistence and daily milk production than did cows given saline, despite the fact that the latter group showed normonatremia and normokalemia. This study illustrates the importance of provision of high-quality water for optimization of milk production.

■ Clinical Pathology and Diagnosis

The clinical diagnosis of salt poisoning depends on the demonstration of exposure to toxic concentrations (>7000 ppm or 0.7% of sodium), the presence of water deprivation, or the determination of serum or CSF sodium concentrations greater than 160 mEq/L (occasionally exceeding 200 mEq/L).[12] Ratios of CSF sodium to serum sodium that exceed 1 : 1 also suggest salt poisoning. The plasma sodium concentration may vary, depending on whether the patient had recently been given ion-free water before measurement. Some animals with acute neurologic lesions may be normonatremic if they have recently drunk to repletion with ion-free water, whereas others that have not had ion-free water may be hypernatremic.

Ruminal sodium concentrations above 0.36% to 0.5% or brain sodium concentrations above 150 mEq/g or 1800 ppm[21] also suggest salt poisoning in cattle.[12,19,22] Rapid intake of low-sodium water during the rehydration phase of the disease may cause intravascular hemolysis with resultant hemoglobinuria;

such findings raise the index of suspicion of salt poisoning.[2]

■ Pathology

The pathologic changes of salt poisoning include cerebral edema and softening and flattening of the cortical gyri. Microscopic lesions include laminar cortical necrosis, poliomalacia, and, on occasion, meningeal or perivascular infiltration of eosinophils, mononuclear cells, or both.

■ Treatment and Control

Treatment of animals affected by salt poisoning is difficult. Many animals die even after intensive medical treatment. Prognosis depends on severity of clinical signs at the start of treatment: Animals that already have significant cerebral edema have a guarded prognosis. Therapy should be aimed at limiting the ingestion of nonionic water and attempting to remove intracellular solutes slowly from the brain while simultaneously controlling cerebral edema and attendant CNS signs. To prevent brain swelling and herniation of the brain through the foramen magnum or the tentorium cerebelli, slow reduction of the CSF and plasma sodium is imperative. Slowly lowering plasma Na concentrations over time by means of intravenous fluids is recommended.

Slight underestimation of fluids is preferable to excess fluid administration. Serum sodium should be monitored regularly and correction effected over 24 hours or longer. Oral fluids can be introduced gradually toward the end of the first day of treatment; salt should initially be added to oral fluids to make them isotonic to blood. When IV replacement is not feasible, isotonic to hypertonic oral fluids should be administered at a maintenance level, divided into four to six feedings daily. Access to low-salt water is gradually allowed after 3 to 4 days. Any worsening of clinical signs is an indication to increase the salt level in fluids, and IV mannitol (0.5 to 2.0 g/kg as a 20% solution) or oral glycerin (1 mL/kg diluted 50 : 50 with water) may be necessary to reduce cerebral edema.[2]

High-sodium crystalloid solutions (HSCS) have been used for individual treatment of severe hypernatremia, which might develop in salt poisoning.[23] Sodium (as dry salt or, if metabolic acidosis is present, as sodium bicarbonate) is added to normal (0.9%) saline to create a final sodium concentration in the HSCS that is 10 to 15 mEq/L lower than the patient's serum sodium concentration. Dry table salt (17 mEq NaCl/g) can also be added to 0.9% saline to achieve the desired sodium concentration in the HSCS. The HSCS is

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administered at 1 to 3 mL/kg/h while the patient's neurologic status and serum sodium concentration are monitored carefully over the first day or two of treatment; reduction of serum sodium concentration by 0.5 to 1 mEq/L/h is considered optimal.[24] Small volumes of water are subsequently offered to aid in gradual reduction of the sodium concentration in extracellular fluid; this gradual decline is thought to prevent development of an abrupt osmolar gradient that favors water entry into brain cells.

The use of solutions containing 5% glucose is contraindicated because this represents ion-free extracellular fluid, which can exacerbate brain edema. Administration of corticosteroids (dexamethasone, 0.04 to 0.08 mg/kg by slow IV injection twice daily for 2 to 3 days) may be helpful in animals with acute cerebral edema. If the neurologic signs diminish and the plasma sodium level returns to normal, the animal may be given fresh drinking water. Thiamine (10 mg/kg SC) may be a useful adjunctive therapy.

Control measures are centered on ensuring appropriate dietary sodium intake and *ad libitum* availability of ion-free drinking water. Cattle should be fenced away from polluted ponds and oil wells. Cattle on coastal pastures should have access to fresh ion-free well water. The total daily dietary salt intake should not exceed 4% of dry matter intake. Drinking water must contain less than 7000 ppm of sodium unless the dietary sodium load is reduced correspondingly. Oral rehydrating fluids and milk replacers for calves should be mixed with ion-free water in strict accordance with the manufacturer's recommendations. Assessment of water cleanliness and availability should be a component of a daily animal husbandry plan.

Vitamin A Deficiency

■ Definition and Etiology

Vitamin A (retinol) is found in green plants and can be synthesized from plant carotenoid precursors in the liver and intestinal mucosa. Precursors of vitamin A are usually fed in cattle rations as β-carotene or as retinoids. Vitamin A deficiency occurs primarily in growing ruminants in feedlots. Deficiency develops under these conditions because the growing animal has a higher requirement for the vitamin, and feedlot-reared animals may have limited access to succulent plants. Exposure to ultraviolet light inactivates vitamin A in stored feedstuffs. Diets that are naturally low in vitamin A include cereal grains, beet pulp, and cottonseed hulls. Conditions in which the immune system is

challenged, as when exposure to pathogens is high, also increase the requirement for vitamin A. Other scenarios conducive to vitamin A deficiency include prolonged grazing on dry pastures or cereal grains other than corn, exclusive feeding of cereal grains that have been stored at high temperature and humidity, or prolonged feeding of mineral oil as a preventive for frothy bloat.

■ Epidemiology

The vitamin A requirement for common livestock species ranges from 40 to 110 IU/kg daily.[1-3] The minimum recommended daily dose of vitamin A for growing calves up to 1 year of age, for pregnant sheep, and for growing horses is 40 IU/kg. Pregnant cattle and pregnant and lactating horses require 40 to 50 IU (13.76 to 17.2 µg/kg) of vitamin A daily.[2] Lactating cattle require 80 IU (27.5 µg/kg) of vitamin A daily. Horses are susceptible to vitamin A deficiency, but the condition is rare; this situation is thought to be the result of differing conditions of management rather than an inherent resistance to the deficiency. The daily dietary requirement for carotene in cattle, sheep, and swine is 0.12 mg/kg.[2] Pasture forage, silage, and properly cured hay (<1 year old) contain large amounts of carotene. Common constituents that have low concentrations of vitamin A are sorghum, brewer's grain, and wheat straw.

Livestock are protected from short-term deprivation of vitamin A by their ability to accumulate the vitamin in the liver; however, it is estimated that the dietary intake required to initiate storage is at least three times the minimum daily intake requirement.[2] Vitamin A–replete cattle fed a diet devoid of vitamin A begin to show clinical signs of deficiency after approximately 180 days. Cattle grow and fatten normally and show no adverse effects until hepatic stores are depleted, but offspring born to these animals may show severe deficiencies. Papilledema and blindness develop rapidly after the hepatic stores are depleted.[2]

Vitamin A deficiency is categorized as a primary or secondary condition. Primary deficiencies of vitamin A develop in cattle confined in dry lot corrals, those pastured on dry grass forage for prolonged periods, and those kept indoors and fed unsupplemented, vitamin-depleted cereals and dry forage in which the activity of carotene has been depleted. Vitamin activity in feedstuffs can vary by season; for example, cattle grazing on green pastures are consistently replete with the vitamin, whereas those grazing on dry pastures at the end of summer may become marginally deficient. Approximately 80% of the vitamin A activity in hay is lost during field curing.[4]

Destruction of carotene is hastened by many environmental and physical factors, including heat, sunlight, trace mineral supplements, and humidity.[5] Other factors that affect the stability of vitamin A in feedstuffs include pelleting and exposure to rancid fat in the feed.

Secondary deficiencies of vitamin A result from interference with vitamin absorption, inhibition of the conversion of β-carotene to retinol (vitamin A) in the small intestine, or an increased requirement in the presence of limited vitamin intake. The conversion of carotene to retinol is impaired in vitamin A–deficient patients.[6] Sheep may be more resistant to vitamin A deficiency because they convert β-carotene more efficiently than do cattle.[6] Fever, lactation, high ambient temperatures, and inadequate dietary energy may increase the daily requirement for vitamin A.[5] Other factors that can affect availability of vitamin A or the requirement for the vitamin include diets with low forage content, high proportion of corn silage to hay in the diet, increased exposure of animals to pathogens, and periods in which immunocompetence is reduced (e.g., the peripartum period).[3] Secondary deficiencies in vitamin A may be caused by impaired vitamin absorption, which may result from long-term feeding of mineral oil.

■ Pathogenesis

Vitamin A is responsible for the regeneration of rhodopsin in the retina and in normal function of osteoblasts and osteoclasts, epithelial tissues, the choroid plexus, and reproductive tissues. Vitamin A deficiency causes a thickening of the dura mater, which results in diminished CSF absorption from the arachnoid granulations and the nerve rootlets. Narrowing of all the bony foramina of the skull occurs in immature animals, although bone remodeling does not occur in adults. The combined effects cause an increase in CSF pressure.[7] Closure of the optic foramen may lead to transection of the optic nerve. The high CSF pressure is transmitted into the optic nerves and results in papilledema.

Three causes of blindness have been associated with vitamin A deficiency. Nyctalopia (night blindness) is presumably caused by the decreased formation of vitamin A aldehyde in the regeneration of the visual pigment rhodopsin; this type of blindness is usually reversible. Second, degenerative changes in the outer retinal layers also cause blindness; this is reversible if treated in the early stages. The third cause is associated with stenosis of the optic foramen and compression of the optic nerve; this condition is irreversible.[8]

■ Clinical Signs

Signs in deficient calves include anorexia, ill-thrift, blindness, diarrhea, and pneumonia. The syndrome in adults is characterized by “stargazing” posture, blindness, diarrhea, anasarca, nystagmus, strabismus, exophthalmos, loss of pupillary light reflexes, and intermittent tonic-clonic convulsions. The seizures may last for only a few minutes and can be followed by partial recovery.[9-11] Animals may die during seizures. Stimulation of the animals frequently precipitates seizures.[12,13] Death is often preceded by hyperesthesia and coma.[6,9,10] Inadequate vitamin A supplementation of calves is associated with unthriftiness, intermittent fevers, and a higher incidence of diarrhea.[14] Vitamin A–deficient adults appear to be in good body condition unless parasitism or some other nutritional deficiency is superimposed on the low vitamin A intake.[1,7] Secondary factors that can influence the appearance of the animals include concomitant nutritional deficiencies, parasitism, and pneumonia.

The ocular changes of vitamin A deficiency are characteristic. The pupils become dilated and unresponsive. As papilledema develops, the optic disk becomes pale, and its borders become indistinct, particularly in the upper quadrants,[9,11,15] which gives it the appearance of an inverted heart. The swollen disk may cast a shadow on the adjacent retina. The color of the disk fades. In advanced cases, the disk may become atrophic and appear dull, gray, flattened, and smaller than normal.[16] The retinal blood vessels become tortuous or appear to be occluded as they course over the disk. Retinal detachment and subretinal hemorrhages are possible.[9]

Reproductive disturbances can occur, including fetal malformations, abortions, loss of libido, testicular degeneration, and decreased sperm counts. Calves born to vitamin A–deficient dams are blind, have domed foreheads and thickened carpal joints, and are weak at birth.[17]

Vitamin A deficiency can be clinically differentiated from PEM and salt poisoning by comparing the menace response with the pupillary light reflex. Calves with lead poisoning and PEM generally have intact pupillary light reflexes because of normal function of the mesencephalon and optic nerves, whereas vitamin A–deficient cattle have no pupillary light responses because of retinal degeneration and constriction of cranial nerve II at the level of the optic foramen.

■ Clinical Pathology

Assay of vitamin A and β-carotene concentrations in the plasma and feed is the most direct method of diagnosing the dietary deficiency. The concentrations of plasma vitamin A and β-carotene in normal animals range from 25 to 85 µg/dL and 150 and 397 µg/dL, respectively.[10] Plasma concentrations in vitamin A–deficient and β-carotene–deficient animals usually are lower than 7 and 70 µg/dL, respectively. The hepatic concentrations of vitamin A and β-carotene in normal calves range from 60 to 200 µg/g and from 4 to 800 µg/g of tissue, respectively. In deficient calves the hepatic concentrations of vitamin A and β-carotene range from 2 to 14 µg/g and from 0.5 to 32 µg/g, respectively.[7] There are no consistent changes in the blood chemistry analysis or the hemogram of deficient animals. Changes in the CSF of vitamin A–deficient animals include mononuclear cell pleocytosis (40 to 50 nucleated cells/dL) and increased protein concentration (140 mg/dL).[18] CSF pressure may also be increased (>200 mm Hg).[19]

■ Pathology

The major pathologic changes in the fundus of vitamin A–deficient calves include papilledema, small flame-shaped hemorrhages around the optic disk, venous congestion in the area of the swollen optic disk, degeneration of the retinal ganglion cells, focal retinal thinning, and fusion of parts of the retina to the choroid plexus.[15] Other changes associated with vitamin A deficiency include doming of the frontal bones, enlargement of the carpi, cerebellar and cerebral compression, partial transtentorial herniation of the cerebellum, cystic dilation of the hypophyseal cleft, focal ruminal hyperkeratosis, and increased keratinization of the squamous epithelium of the penile and the preputial mucous membrane. Corneal ulceration and clouding have been observed in the eyes of calves with naturally occurring deficiencies.[18] Vitamin A deficiency also can cause anasarca, squamous metaplasia of the salivary ducts, degeneration of the germinal testicular epithelium, degenerative changes in the intestinal epithelium in lambs, and reduction in intramuscular fat in cattle.[20-22]

Microscopic changes in the CNS include attenuation of the optic nerve with necrosis and demyelination. Focal accumulations of phagocytic cells containing lipofuscin and hemosiderin are present in the necrotic area. The optic nerve is attenuated along its entire length. The meninges are thickened by fibrosis and

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mononuclear cell inflammation. The microscopic changes in the bones include wider-than-normal spacing of the central canals and reduction of osteoclastic lacunae.

■ Treatment and Control

Cattle with severe blindness caused by damage to the retina or optic nerves do not regain their vision when treated with vitamin A; however, cattle with acute encephalopathy and simple papilledema may respond favorably after a short period of vitamin supplementation.[2] Affected cattle should receive 440 IU/kg of vitamin A parenterally and then 6000 IU/kg parenterally every 50 to 60 days until the diet has been enriched. High-dose oral therapy is important because carotene and oil suspensions of vitamin A are not efficiently utilized when administered by parenteral injection.[23] Administration of large doses orally is important because conversion of β-carotene to vitamin A is inhibited in deficient calves. The recommended concentration of vitamin A in milk replacers for preruminant calves is 11,000 IU/kg dry matter.[14]

Prophylactic dietary supplementation of vitamin A should be considered in all cattle that lack access to green feed. Dietary supplements could include leafy, freshly cured hay, green pasture, or alfalfa meal. Concentrate feeds formulated with exogenous, stabilized vitamin A are commercially available. Recommended concentrations (per kilogram of dry matter) of vitamin A in feed are 2200 IU for feedlot cattle, 2800 IU for pregnant cows, and 3900 IU for lactating cows.[4]

Hydrocephalus and Hydranencephaly of Ruminants

■ Definition and Etiology

Hydrocephalus/hydranencephaly is an apparently common abnormality of the CNS in large ruminants. It is probably underdiagnosed because many of the affected animals die of complications, and the primary condition is overlooked during clinical and pathologic examinations. One study reported that 97 of 155 calves with CNS lesions had hydrocephalus.[1] Hydrocephalus may be classified as hypertensive or normotensive.[2]

Normotensive Hydrocephalus (Hydranencephaly)

Normotensive hydrocephalus that develops as a result of a failure of cell growth or cellular necrosis is called *hydranencephaly.*[2] Most cases of hydranencephaly in domestic livestock are caused by in utero infection of the fetus by viral pathogens such as bluetongue, BVD, Akabane, Cache Valley, Aino, border disease, and Schmallenberg viruses.[1,3-13] The pathogenesis and epizootiology of bluetongue and BVD are discussed in detail in Chapter 32. The neurologic effects of border disease virus infection are discussed earlier in this chapter.

The loss of fetal neurons in utero results in flexural contractions of the limbs (arthrogryposis), which may manifest as dystocia. Affected neonates may be stillborn or born alive but weak, blind, unable to stand, and unable to nurse. They may exhibit a dysphonia, which resembles a bark. Neonates that are unable to nurse fail to ingest colostrum and often die from septicemia.

Akabane Virus Infection.

The Akabane virus is a member of the Simbu serogroup of the *Orthobunyavirus* genus in the *Peribunyaviridae* family.[3] It has been isolated from cattle in Africa, Japan, Israel, Korea, and Australia.[4-9] Hosts of Akabane virus include sheep, cattle, and goats. Infection of pregnant, nonimmune dams results in hydranencephaly or arthrogryposis of the fetus.[14] The disease is thought to be transmitted to the cow by various *Culicoides* spp. Experimentally infected calves develop porencephaly and encephalitis when exposed to the Akabane virus between gestational days 62 and 96.[15] Studies in naturally infected cattle showed that infection of calves between days 76 and 104 of gestation resulted in hydranencephaly or porencephaly, whereas infection between days 103 and 174 of gestation resulted in arthrogryposis.[16] Lambs are susceptible when exposed to the virus between gestational days 30 and 36.[9] The CNS lesions are apparently the result of a direct necrotizing effect of the virus on the developing neurons. The pathologic changes in the CNS of experimentally infected calves and lambs are similar to those of naturally acquired infections.[6,9] Adults occasionally abort when infected by the virus but do not develop clinical disease.

A syndrome of arthrogryposis, facial deformities, kyphoscoliosis, hydranencephaly, and hypoplasia of multiple regions of the brain and spinal cord has been described in Corriedale sheep in Australia. Although it resembles the disorder caused by congenital Akabane virus infection, results of breeding trials indicated autosomal recessive inheritance for the disease.[17]

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Aino Virus Infection.

The Aino virus causes stillbirths, premature calving, and congenital malformations, including arthrogryposis, cerebellar hypoplasia, and hydranencephaly, in calves of Japan and Australia.[18-20] Aino virus is antigenically and biologically distinct from Akabane virus, but the clinical syndromes of fetal infection by the two viruses are indistinguishable.

Chuzan Virus Infection.

Hydrocephalus, hydranencephaly, and cerebellar hypoplasia have been attributed to infection of pregnant cattle with the Chuzan virus.[21-23] This virus is a relative of the Akabane and Aino viruses and is a member of the Palyam subgroup of the genus *Orbivirus.* The virus has been isolated from *Culicoides oxystoma,* which may serve as the major vector. The clinical signs are characteristic of hydrocephalus.

Cache Valley Virus Infection.

A flock outbreak of arthrogryposis, myositis, hydranencephaly, and a variety of other brain malformations (microcephaly, cerebellar hypoplasia, porencephaly) in newborn lambs in the southwestern United States was attributed to in utero infection with the Cache Valley virus (family *Peribunyaviridae*).[24,25] Cache Valley virus was first isolated from mosquitoes from Utah and has since been isolated from caribou, horses, sheep, and cattle elsewhere. Antibodies have been found in white-tailed deer in the southwestern United States, but the role of deer in the survival of the virus and the transmission of the disease to livestock is unknown.[26] In one survey of sheep in the western United States, the seroprevalence for the Cache Valley virus was 19.1%.[24] Vectors for the virus include *Anopheles, Aedes, Culex,* and *Coquellettidia* mosquitoes.[27] Infection before 30 days of gestation may cause embryonic death, and infection between days 30 and 52 causes fetal malformations.[27]

Bluetongue Virus Infection.

Hydranencephaly, arthrogryposis, or both may occur in ruminants when the dam is infected at specific times during gestation; abortions or fetal resorption can also occur. Serotypes 11 and 17 are the serotypes most frequently isolated from neonatal calves and lambs in field epizootics.[28,29] Bluetongue virus serotype 8 has caused devastating disease in ruminants in Central and Northern Europe; of

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importances is that neonates infected in utero may be born viremic, thereby providing *Culicoides* spp. with more abundant viremic hosts during the subsequent spring.[30] Calves, lambs, and kids infected in utero may be born normal or manifest one or more associated birth defects, including hydranencephaly, arthrogryposis, brachygnathia, prognathia, and excessive gingival tissue (see Chapter 32 for additional information).

Bovine Viral Diarrhea Virus Infection.

Hydranencephaly, hydrocephalus, and cerebellar hypoplasia have been associated with fetal infection of cattle with the BVD virus.[31-34] Precolostral serum antibody titers for the virus in affected calves vary; some titers range from 1 : 32 to 1 : 256, but other calves may have persistent viremias without demonstrable antibody.

Schmallenberg Virus Infection.

The Schmallenberg virus is an enveloped RNA virus belonging to the genus *Orthobunyavirus*.[10] The Schmallenberg virus is a member of the Simbu serogroup, which includes the well-known teratogenic Akabane virus. It is named after a town in west-central Germany where, in the autumn of 2011, signs of this viral disease first emerged in local cattle. Diagnosticians at the Friedrich-Loeffler Institute (the Federal Research Institute for Animal Health) subsequently identified this virus as a cause of transient fever, depression, reduced milk production, and occasional diarrhea in cattle. The virus was subsequently detected in several countries in continental Europe, the British Isles, the Mediterranean Basin, and Turkey.[12] During the fall of 2011, infections in small ruminants in the region were predominantly asymptomatic; however, once ruminant birthing commenced in late 2011 and early 2012, it became apparent that the virus had induced significant fetal morbidity and mortality, primarily in sheep but in goats and cattle as well.

Fetal infection with Schmallenberg virus may result in abortion or stillbirth; newborns may be weak, may have significant neurologic deficits, or may be normal and healthy. On the basis of the pathophysiologic features of Akabane viral infections, the outcome of fetal infection with Schmallenberg virus is considered to probably depend on the timing of viral infection in relation to the stage of fetal development.[10,11] Infection early in gestation, within the first trimester, appears to result in the most significant fetal deformities, with

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arthrogryposis of one or more limbs, torticollis, spinal malformations (scoliosis, kyphosis, lordosis, or a combination of these), brachygnathia inferior, and a multitude of CNS malformations.[10,11] Hydranencephaly, porencephaly, and hydrocephalus are among the more common neurologic malformations. According to the OIE, the clinical disease in ruminants can best be categorized as an *arthrogryposis/hydranencephaly syndrome*.[12] Fetal limb, neck, and spinal skeletal anomalies can result in dystocia. To date, there have been no reports of Schmallenberg virus causing human infections, and the virus is not currently considered to be a zoonotic threat.

As is the case with other members of the *Orthobunyavirus* genus, Schmallenberg virus is an arthropod-borne virus, and *Culicoides* spp. midges (e.g., *Culicoides obsoletus*) are currently considered the vector in Europe.[13] Other vectors, however, may also be involved. Vertical transmission of the virus from infected ruminant dam to ruminant fetus is considered to be the primary means of spread within animals. Horizontal transmission is a possible but less likely means of transmission.

Other Infectious Agents.

A single case of hydrocephalus in a calf aborted at 7 months of gestation was associated with necrotizing encephalitis caused by *Neospora caninum*.[35]

Hypertensive Hydrocephalus

An increase in CSF volume that results from compressive or obstructive lesions in the ventricular system or from decreased CSF absorption is called *hypertensive hydrocephalus*.[2] Obstructive lesions of the ventricular system trap the CSF in the ventricles, causing an increase in CSF volume and pressure. Ischemia and CNS degeneration result from the high CSF pressure. The sites of obstruction are most often the lateral apertures, mesencephalic aqueduct, lateral ventricles, interventricular foramina, and fourth ventricle. The obstructions may be either congenital or acquired. Causes of acquired obstructive hydrocephalus include cerebral abscess, cholesteatoma (in equines), equine infectious anemia, *Coenurus cerebralis* infestation, meningitis, and lymphosarcoma. Hypertensive hydrocephalus may also be caused by acute inflammatory disease such as meningitis and vitamin A deficiency. In these diseases the increased pressure is the result of impaired CSF resorption.

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Congenital Hypertensive Hydrocephalus

Congenital hypertensive hydrocephalus is a hereditary condition in Hereford, Charolais, Ayrshire, Dexter, Holstein, and Jersey calves.[36-38] The condition has also been recognized in Arabian foals.[39]

■ Clinical Signs

Hydrocephalic animals are often born dead or are weak and die shortly after birth. The most obvious signs in animals that survive include failure to bond to the dam, depression, diminished learning ability, partial failure of suckling, droopy head and ears, muscular fasciculations, head tremor, conscious proprioceptive deficits, blindness, ventrolateral strabismus, nystagmus, dysphonia, tongue flaccidity or paralysis, retention of food material in the cheeks and lips, limb spasticity, hyperreflexia, psychomotor seizures, recumbency, and coma. Occasionally, doming of the calvaria or protrusion of fluid-filled cystic structures through an open fontanelle is observed. Affected neonates often do not ingest sufficient amounts of colostrum and frequently die of septicemia.

In virally induced cases of hydranencephaly, associated skeletal deformities such as abnormally curved ribs, kyphoscoliosis, flexural deformities of the limbs, domed skulls, and brachygnathia may be observed. Patients with hydrocephalus caused by compressive lesions around the ventricular system may show unilateral or bilateral signs of increased intracranial pressure. The clinical signs of unilateral lesions include head tilt (toward the lesion side), ipsilateral mydriasis, and contralateral deficit of the menace response. Signs of hydrocephalus in foals are similar to those in calves. The cause of the condition in horses is unknown.

Antemortem diagnosis of brain malformations has been facilitated by CT and MRI. However, these techniques are rarely warranted or available for use in large animal species. A more practical technique involving ultrasonography, transorbital echoencephalography, has proved effective for the diagnosis of hydrocephalus and hydranencephaly in calves younger than 3 months of age.[40]

■ Clinical Pathology

The diagnosis of hydrocephalus in calves and lambs is typically based on the presence of characteristic clinical signs and a domed skull. Whenever hydranencephaly is suspected, blood should be collected for virus isolation, serologic testing, and quantitative immunoglobulin determination. Presuckle

serum samples from neonates that have been infected by the Akabane or bluetongue virus in the latter part of gestation may be seropositive.[26]

■ Pathology

The pathologic lesions of hydranencephaly are similar regardless of the etiologic agent. They include microcephaly, cerebellar hypoplasia, hydrocephalus, hydranencephaly, and porencephaly of the cerebral and the cerebellar cortex. Microscopic lesions of hydranencephaly include segmental loss of dorsolateral ventricular ependyma, thinning of the periventricular white matter, porencephalic cysts, and nonsuppurative meningoencephalitis. Lesions in other parts of the CNS may include loss of ventral horn cells in the spinal cord and demyelination in the spinal cord. Nonsuppurative inflammatory changes may occur in cases caused by viral infections. Polymyositis has been described in affected calves; however, it is unclear whether these lesions are caused by viral infection or occur secondary to the denervation. The skeletal deformities associated with virally induced hydranencephalies include rigid extension or contraction of one or more limbs (arthrogryposis), abnormally curved ribs, domed skull, thickening of the calvaria, kyphoscoliosis, and brachygnathia.

Obstructive or compressive lesions may be observed with congenital or acquired hypertensive hydrocephalus.

■ Treatment

Except for one report of successful surgical intervention in a calf with a meningocele, no satisfactory therapy is available for the treatment of hydrocephalus or hydranencephaly in large animals.

Ammoniated Forage Toxicosis (Cow Bonkers)

Application of anhydrous ammonia to poor-quality forage improves the nutritional density of the material and reduces certain toxic fungal metabolites, specifically the prolactin-like toxins of the endophytic fungus *Acremonium coenophialum* in fescue hay.[1] Ammoniation increases dry matter intake, enhances digestibility, and increases the relative value of the protein content of the feed. However, overammoniation of the forage, at a rate exceeding 3% of the forage on a dry matter basis, may result in toxicosis. Studies now suggest that several dialkylimidazoles may be responsible for the neurotoxic effects of

ammoniated feedstuffs, superseding previous theories that 4-methylimidazole is the primary neurotoxin.[2,3] Ammoniated feedstuffs containing high levels of molasses are more toxic than similarly treated grass hay. The toxin may be concentrated in milk; consequently, calves suckling from normal-appearing dams may show clinical signs of intoxication.

Affected animals are hyperesthetic and ataxic. At rest they assume a sawhorse stance, but when excited, they become hyperactive, appear to be blind, and circle propulsively. Other clinical signs include vocalization, dysphonia, and walking or running into objects. The periods of frenzy may result in recumbency and convulsions. The spasmodic episodes last for 15 to 20 minutes. Afterward, the affected animals rest quietly with occasional muscle tremors. Recurrences of the mania may be precipitated by loud noises or other startling stimuli. The concentrations of ammonia in the blood and CSF may be increased. Although specific treatments have not been identified, one report indicated that affected calves benefited from acepromazine (0.045 mg/kg IV) and thiamine (1.14 mg/kg IM). Thiamine dosages higher than described in this report[4] (such as 10 to 20 mg/kg SC q12h) have been used for treatment of other neurologic diseases and may be considered for use in this disease.

Lead Poisoning

■ Definition and Etiology

Lead poisoning in ruminants is characterized by an acute encephalopathy. In contrast, lead poisoning in horses is characterized by chronic polyneuritis. Blindness, ataxia, and depressed sensorium are significant clinical signs in cattle, sheep, and goats, whereas in horses the poisoning is associated with weight loss, dysphagia, and secondary aspiration pneumonia. Cattle are most often poisoned because of their tendency to lick or chew on foreign objects, their access to lead-containing materials, and their propensity to drink contaminated petroleum distillates.[1]

■ Epidemiology

Sources of lead are numerous and include lead arsenate defoliants, lead acid batteries, used motor oil, linoleum, roofing felt, paint, machinery grease, caulking compounds, improperly compounded mineral supplements, and foliage near lead smelters and battery-recycling plants.[2-10] High lead levels have been

reported in grasses growing near busy roadways, but the clinical significance of these findings is unclear.[7,11,12] Factors that can increase the likelihood of ingestion of lead-contaminated feedstuffs include lack of alternative feed, hunger, and phosphorus deficiency.[13] The acute lethal dose of lead for cattle is estimated to range from 220 to 600 mg/kg in calves, 600 to 800 mg/kg in adult cattle, and 400 mg/kg in goats.[13,14] Lead poisoning has been reported in cattle exposed naturally to 6 to 7 mg/kg/day of lead on foliage and in calves given oral lead acetate at 2.7 to 20 mg/kg/day.[15] The interval for development of clinical signs ranges from 5 to 20 days and is related to the dose and ionic form of lead administered.[15] Ensiling of contaminated forage results in percolation and concentration of lead at the bottom of the silo.[16]

The toxicity of ingested lead is apparently influenced by dietary factors. Calves on a milk diet are more susceptible to lead poisoning than are calves fed hay and grain.[17] There appears to be a direct correlation between high levels of vitamin D and enhanced lead absorption, which may explain the greater occurrence of poisoning during the summer. Elevated copper concentrations in forage, such as may be found in pastures fertilized with pig slurry, may potentiate accumulation of lead in animals consuming it.[18]

The estimated cumulative toxic dose of lead for horses is 2.9 mg/kg/day.[19] Poisonings have been reported in horses grazing on pastures contaminated with 320 to 440 ppm of lead from a metal smelter; this amounted to a daily intake of 2 g (≈6.4 mg/kg). Metallic lead and “galena” (insoluble sulfide salt) are less toxic than acetate and carbonate lead salts.[20]

■ Pathogenesis

Lead enters the body through the GI tract or, less often, through the respiratory tract. Metallic lead and the sulfide form are less well absorbed than the acetate, phosphate, carbonate oxide, and hydroxide salts. Metallic lead is poorly absorbed and causes toxicity only when a lead foreign body becomes entrapped in the stomach for prolonged periods. Interaction between lead and other minerals may occur. For example, high levels of dietary calcium reduce the GI absorption of lead. Concomitant exposure to lead and cadmium results in a worsening of the clinical signs of lead poisoning.[21]

Although intestinal absorption of lead is relatively inefficient, significant amounts can cross into the blood if sufficient quantities are ingested.

Approximately 1% to 2% of the total oral dose of lead is absorbed within 24 hours.[22] Most of the lead absorbed from the digestive tract (90%) is bound to erythrocyte proteins, which results in a low lead concentration in the plasma, but higher concentrations in whole-blood specimens.[23] At the end of the erythrocyte's life span, the cell-bound lead is metabolized from the erythrocyte proteins and deposited in the bone as the triphosphate salt. The half-life of blood lead in adult cattle is extremely variable and unpredictable, ranging from 48 to 2507 days in one study.[24] Phenotypic or genotypic factors may affect metabolism and storage of lead. The variable time for clearance of lead has an obvious implication for public health because all carcasses of animals suspected or known to be exposed to lead must be tested before being cleared for human consumption.[25]

Lead also crosses the placental barrier and accumulates in fetal bone, liver, and kidneys but does not substantially accumulate in milk. However, cattle with higher blood lead levels may have greater concentrations in milk.[26]

The toxic effects of lead include inhibition of free sulfhydryl groups found in many enzymes, interference with zinc-containing metalloproteins, and steric inhibition of enzyme activity.[27] Enzymes of heme synthesis are particularly susceptible to injury. These include δ-aminolevulinic acid dehydratase and ferrochelatase. Interference with ferrochelatase inhibits the formation of heme from protoporphyrin, which results in a buildup of unmetabolized porphyrins.

Because of the interference with heme metabolism and the altered function of other erythrocyte proteins, the erythrocyte half-life is shortened, which may result in a normochromic, normocytic anemia in a small proportion of chronically poisoned animals.[28] Iron is not adequately used and is stored in sideroblasts in the bone marrow.[29] Lead also interferes with the activity of pyrimidine-specific 5′-nucleotidase, which results in basophilic stippling of red blood cells.[30]

After absorption, lead rapidly enters the brain at a dose-dependent rate. The lead deposition in the CNS results in acute cerebellar hemorrhage and edema from capillary dysfunction.[23] The pathogenesis of lead encephalopathy is multifactorial. Encephalitic signs probably originate from a combination of microvascular damage, cellular necrosis, brain swelling, neurotransmitter dysfunction, and decreased glucose uptake by the brain.[28]

Ingestion of lead also results in competitive inhibition of selenium uptake, thereby diminishing the absorption of selenium by up to 26%.[31] If selenium

intake is marginal, lead toxicosis could manifest as overt selenium deficiency.

■ Clinical Signs

The signs of lead poisoning in ruminants are characteristic of CNS derangement. During the first stages of lead poisoning, affected cattle stand alone and are depressed.[2] They may show hyperesthesia, muscular fasciculations, and rapid, spastic twitching of the eyelids or other facial muscles. Progression of the disease is associated with ataxia, conscious proprioceptive deficits, cortical blindness, head pressing, odontoprisis, coma, and convulsions.[22,32] Some affected animals display episodic running, hyperesthesia, and bellowing. Others die suddenly without premonitory signs. The more acute and severe the toxicity, the more acute, severe, and excitatory are the clinical signs.[13] Affected cattle may accumulate frothy saliva at the commissures of the lips. GI signs such as bloat, diarrhea, rumen atony, and colic occur in approximately 60% of lead-poisoned cattle; the presence of such signs is more indicative of lead toxicity than of other causes of cerebral dysfunction.[33] Infertility, abortions, and fetal malformations may result from exposure to lead.[13]

The clinical signs of lead poisoning in horses include weight loss, lack of coordination, laryngeal or pharyngeal paralysis, dysphonia, roaring, conscious proprioceptive deficits, loss of anal tone, facial paralysis, and difficulty with mastication.[34] Aspiration of pharyngeal debris caused by dysphagia may result in pneumonia. Fine muscular tremors occur intermittently. The poisoned animals die in psychomotor seizures. Horses that die of lead poisoning are emaciated.[3]

■ Clinical Pathology

Diagnosis of lead poisoning is based on measurement of increased blood and tissue concentrations of lead. Tissue levels of lead in naturally poisoned cattle can reach 20 to 100 ppm in the liver, 30 ppm in the kidneys, and 5000 ppm in bone. When interpreting the results of a lead measurement, the reference ranges obtained with similar methods must be considered. Heparin is the anticoagulant of choice for collecting blood for lead measurement because it does not chelate the lead. The lead concentration of ruminal fluid from acutely poisoned cattle ranges from 0 to 11,875 ppm.[22]

In livestock that are chronically poisoned with low concentrations of lead, the lead concentration may be normal in blood but high in bone. In these cases the

poisoning can be diagnosed by administration of calcium disodium ethylenediamine tetraacetic acid (EDTA), which solubilizes the bone lead stores and increases the concentration of lead in the plasma. The soluble lead-EDTA complexes are excreted in the urine. The urinary lead concentration may rise by 40-fold over pretreatment levels within a few hours. In cases of chronic lead poisoning, radiographs of the abdomens of smaller patients may reveal lead-containing radiodense foreign material in the GI tract.[35] "Lead lines"—radiopaque transverse bands at the metaphyses—may also be visible on radiographs of the long bones of young animals chronically exposed to lead.

When blood lead concentrations are normal in chronically poisoned animals, measurement of free erythrocyte porphyrins and erythrocyte concentrations of δ-aminolevulinic acid are the preferred methods of diagnoses. The concentration of porphyrins is increased in the blood, urine, and feces of animals with lead poisoning. The reference range of blood porphyrin concentrations in normal calves is 21.6 ± 11.6 to 45.6 ± 10.3 µg/dL for whole blood and 113 and 142.8 ± 32.4 µg/dL for erythrocytes.[29,32,36] In chronically exposed cattle without symptoms, the free erythrocyte porphyrin concentrations are frequently greater than 2000 µg/dL.

Reference ranges for aminolevulinic acid dehydrase are 45.8 ± 20.6 U, whereas activities ranging from 28 to 33 U have been reported in naturally exposed calves.[3] The urinary concentration of δ-aminolevulinic acid exceeds 500 µg/mL.[4,37] Measurement of aminolevulinic acid in the erythrocytes is more reliable than measurement in urine.[38]

Environmental sources of lead can be detected by direct measurement of the lead concentration of the soil or pasture forage. Forage from toxic pastures contains more than 30 ppm of lead, and in some cases the level may exceed 300 ppm.[4,39]

The hematologic abnormalities of lead poisoning are subtle. Most poisoned livestock have a normal hemogram. Lead-related changes, if present, are characteristic of hemolytic anemia with an inappropriately robust regenerative response. The morphologic abnormalities of erythrocytes include anisocytosis, poikilocytosis, polychromasia, hypochromia, Howell-Jolly bodies, metarubricytes, and basophilic stippling.[22,27] The shape changes begin within hours after ingestion of the lead and peak by 100 days.[22,27] Blood changes do not occur in all cases of the disease and are not necessarily specific indicators of lead poisoning in cattle, in which blood lead levels may be elevated without

hematologic abnormalities.[40] However, hematologic abnormalities tend to be more consistent in chronic lead toxicity and in lead-poisoned horses.

Lead toxicity has a variety of effects on endocrine function in cattle. Elevated levels of serum triiodothyronine, thyroxine, estradiol, and cortisol have been demonstrated in cattle with elevated blood lead levels.[41] Parameters of liver function are also affected; serum alanine and aspartate transaminase (AST) levels are increased, whereas serum lipids, total protein, and albumin levels are decreased.

In poisoned animals, the concentrations of protein and WBCs in CSF are increased, ranging from 50 to 100 mg/µL and from 5 to 50 mononuclear cells/mL, respectively. Such changes are relatively nonspecific and found with other causes of cerebral cortical necrosis.

■ Pathology

The macroscopic brain lesions of lead poisoning are mild and include brain edema, congestion of vessels of the cerebral cortex, and yellowish discoloration and flattening of the cortical gyri. Lesions tend to be most severe in the occipital lobes. Microscopic changes in the brain include capillary prominence, endothelial cell swelling, edema of the Purkinje cell layer of the cerebral cortex, laminar cortical neuronal necrosis, and edema of the white matter.[42]

■ Treatment and Control

Therapy for lead poisoning includes removal of the lead from the digestive tract, chelation therapy with calcium disodium EDTA, and fluid and nutritional support of the patient. Treatment with calcium disodium EDTA (calcium versenate) has been shown to be superior to treatment with penicillamine or dimercaprol. The EDTA chelates osseous lead but not soft tissue–bound lead. After chelation, the unsaturated bone stores reequilibrate, with the lead remaining in the soft tissues. In cases of acute lead poisoning, several days are required before reequilibration results in a decreased blood lead concentration. The dose of calcium disodium EDTA is 66 mg/kg/day, divided into several doses daily for 3 to 5 days.[43] After five daily treatments, a 2-day nontreatment period is recommended to reequilibrate the soft tissue and bone lead. After the 2-day rest, daily treatments are given for another 5 days. The decision to continue therapy with EDTA should be based on the results of posttreatment blood lead analyses and renal function tests. Another recommendation is for administration

of two IV injections of calcium disodium EDTA (110 mg/kg per dose) given 12 hours apart for 2 days.[44] Therapy is then withheld for 2 days, after which the EDTA treatments are reinstituted for 2 more days. The comparative efficacy of this regimen is unknown.

The EDTA also chelates other divalent cations. Consequently, prolonged administration of the drug results in trace mineral deficiencies, especially of zinc. For this reason, after prolonged EDTA therapy, oral supplementation with zinc should be considered so as to prevent the development of parakeratosis.

Reports have indicated that thiamine therapy is an effective adjunctive treatment with EDTA in cases of acute lead poisoning of cattle.[14,45,46] Administration of thiamine (2 mg/kg daily) was more effective than treatment with disodium EDTA (62 mg/kg twice daily for 4 days) or thiamine plus disodium EDTA in inducing remission of clinical signs of experimentally induced lead poisoning.[47] For clinical treatment of lead poisoning, thiamine dosages of 500 mg for small ruminants and 1 g for cattle weighing 300 kg have been recommended[45]; an alternative dosage is 10 to 20 mg/kg SC q12h. Administration of daily doses of thiamine (100 mg/day or 5 mg/kg) has protected experimentally exposed calves from clinical signs of lead poisoning and reduced lead deposition in the soft tissues.[46,48,49] The nature of the protective effects of thiamine is unclear. Apparently, either lead interferes with thiamine synthesis or the tissue distribution and deposition of lead are reduced by the formation of rapidly excreted lead-thiamine complexes.

In ruminants, ingested lead is best removed from the digestive tract by means of a rumenotomy.[14] Magnesium sulfate laxatives are administered concomitantly to form insoluble lead sulfides. Patients that respond slowly to chelation and thiamine therapy should be given supportive care. These measures should include provision of 40 to 80 mL free water/kg/day for maintenance, oral hyperalimentation, and administration of diazepam or phenobarbital for convulsions (as discussed in the Meningitis section).

Toxic pastures can be made safe by removal of contaminated forage. This is best done by cutting, baling, and burying native grasses and then burning the stubble. The source of the lead should be established, and the affected animals should be carefully documented. In the United States, insurance liability responsibilities may be covered under homeowner or farm insurance.

Helichrysum argyrophyllum (Golden Guinea

Everlasting, Vaal Sewejaartjie) Poisoning

Both naturally occurring and experimental poisoning of sheep and cattle in South Africa by plants of the genus *Helichrysum* results in blindness and a variety of CNS signs.[1,2] The clinical signs of intoxication include progressive tetraparesis, depression, nystagmus, mydriasis, blindness, intentional head tremor, and stargazing attitude. Older sheep may develop lens cataracts 2 to 3 months after eating the plants. The case-attack rate ranges from 1% to 29%. Plants are toxic only in the flowering stage. *Helichrysum* spp. have been shown to contain substances that bind at the GABA–benzodiazepine receptor, which is suggestive of a mechanism for toxic effects on the nervous system.[3]

Pathologic findings include widespread status spongiosus of brain white matter, particularly in subependymal areas and in the cerebellar peduncles and brainstem.[2] Myelin edema is present in some cases. Edematous swelling of the optic nerve causes compression of the nerve in the optic canal, with secondary damage to nerve axons and myelin. The toxic principle in *Helichrysum* plants also causes a primary retinopathy in some animals.

Flatpea *(Lathyrus sylvestris, Lathyrus collis)* Poisoning

Ingestion of flatpea results in a CNS disorder. The condition may manifest within 5 days after consumption of a diet of which 50% is flatpea vines. Toxicosis has been induced in sheep ingesting forage of 35% flatpea vines.[1] Livestock can develop a tolerance for the plant through rumen microbial detoxification. Nevertheless, acclimatized animals can be rendered susceptible by treatment with monensin or by a change in rumen microflora.[2]

The toxic constituent of the plant, 2,4-diaminobutyric acid, is known to inhibit ornithine transcarbamylase, an enzyme responsible for urea detoxification. Consequently, the blood ammonia concentration in clinically affected animals is increased.

The clinical signs of flatpea intoxication are depression, muscular tremors, and spasmodic torticollis. Affected animals become recumbent and are reluctant to rise. When stimulated to move, they display circling, head pressing, and odontoprisis. The urine may appear dark brown. The clinical disorder often culminates fatally in a seizure. During the interictal periods, affected animals

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may rest, rise, and resume normal behavior and gait. Treatment is empirical and supportive and could include 1 to 2 L of vinegar PO, diazepam (0.1 mg/kg IV) or midazolam (0.1 mg/kg IV or IM) every 4 to 6 hrs as needed and removal from the offending forage.

Lathyrus sylvestris is a leguminous plant with a high protein content that might be an adequate substitute for alfalfa in areas where the latter grows poorly.[3] *L. sylvestris* harvested in the vegetative state has been fed to lambs in combination with alfalfa and as a sole diet without ill effect.[4] Similarly, when fed as part of a mixed silage in which the concentration of diaminobutyric acid was approximately 1%, *L. sylvestris* produced an acceptable weight gain in cattle without signs of toxicity.[5]

Nitrofurazone Toxicosis

Nitrofurazone is an antimicrobial that has been fed to cattle for the treatment and control of respiratory or GI diseases. Treatment of food-producing animals with the nitrofurans is now prohibited by the U.S. Food and Drug Administration. Nervous system signs of nitrofurazone toxicosis occur after 1 to 3 weeks of continuous feeding at dosages exceeding 15 to 30 mg/kg.[1,2] Lower dosages (7.1 mg/kg) reduce feed intake but do not result in neurologic signs. Nitrofurazone inhibits enzymes of the oxidative glycolytic pathways and is thought to interfere with brain metabolism of carbohydrates.

Clinical signs of nitrofurazone toxicosis include hyperirritability, propulsive running, muscular tremors, blindness, convulsions, and death. With lower doses, the convulsions may appear intermittently, but as the condition progresses, the signs become continuous.

Coenurosis (Sheep Gid; *Coenurus cerebralis* Infestation; *Taenia multiceps* Infestation)

■ Definition, Etiology, and Epidemiology

Coenurosis is caused by invasion of the CNS by *C. cerebralis*, the larval stage of the tapeworm *Taenia multiceps.* The adult worms live in the intestine of domestic dogs and some wild carnivores, where they shed eggs into the feces. Ruminants eat the eggs from contaminated pastures. The eggs hatch in the small intestine of the ruminant, and the larval stages travel through the blood to the

CNS, where they mature into *C. cerebralis*. The life cycle is completed when the ruminant dies and the brain is eaten by a scavenging carnivore. *Coenurus* cysts then develop into sexually mature adults in the bowel of the carnivore host.

Many animals including sheep, goats, cattle, horses, wild ruminants, and humans are susceptible to *C. cerebralis* infestation.[1-3] Outbreaks of coenurosis may occur in previously uninfected sheep that are suddenly exposed to contaminated fecal matter from carnivores. Cases initially occur as early as 2 weeks after the sheep are exposed and continue for as long as 4 months.

■ Pathogenesis

Lesions in the CNS may result from three separate pathogenic mechanisms: encephalitis from invasion of the CNS by large numbers of larvae, hypertensive hydrocephalus resulting from interference with CSF drainage, and development of large cerebral cysts that increase intracranial pressure.

■ Clinical Signs

Clinical signs can occur acutely, during the migratory phase of the larval stage in the intermediate host (e.g., the ruminant). Lambs 6 to 8 weeks old are most often affected by this form and develop fever, dullness, and mild neurologic deficits.[4] Acute encephalitis occasionally occurs, leading to sudden onset of severe neurologic signs and death within a few days. More frequently, the clinical presentation of coenurosis is that of a space-occupying brain lesion; signs include depression, anorexia, ataxia, unilateral or asymmetric loss of vision, facial hemiplegia, head tilt, circling, high-stepping forelimb gait, and hyperesthesia. When the spinal cord is the site of cyst development, hindlimb ataxia and paresis or paralysis are the main clinical signs.[5] As the disease progresses, the sheep assume lateral recumbency and become comatose.[6,7] In advanced cases, the calvaria directly over the parasite enlarges and softens.[3]

■ Pathology

In the acute form of coenurosis, the main finding is coagulation necrosis and inflammation associated with the larval migration path through the CNS.[8] This may be visible grossly as yellow to red tracks in the brain parenchyma. Coagulation necrosis and surrounding inflammatory cells such as degenerate granulocytes, macrophages, and histiocytes are found microscopically. The

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mature cysts, up to 7 cm in diameter, are thin walled and contain clear fluid or, occasionally, purulent fluid. Protoscolices, up to many hundreds, can be visualized microscopically within the cysts, which are surrounded by severe and mainly nonsuppurative inflammation. The cysts deform and compress the underlying brain tissue.

■ Diagnosis

The combination of a characteristic clinical syndrome and location in an endemic area supports a presumptive diagnosis. Radiographs in the lateral and posteroanterior planes may reveal radiolucent areas in the calvaria. The optimum diagnostic views in the posteroanterior projection occur whenever the base of the nose is level with the upper margin of the orbit. CT, if available, effectively demonstrates the presence of cysts.[9]

■ Treatment and Control

Praziquantel (50 to 100 mg/kg PO q24h for 3 to 5 days) is effective in the treatment of coenurosis in sheep that do not yet have neurologic signs.[5,10] Concomitant administration of an NSAID or dexamethasone may enhance the posttreatment survival rate. The cyst can also be removed surgically by craniotomy.[11-15]

In endemic areas, the carcasses of affected animals should not be fed to dogs, and dogs in endemic areas should be treated repeatedly with a vermifuge to minimize the possibility of pasture contamination. Appropriate management practices have virtually eliminated this disease from North American sheep flocks.

Ceroid Lipofuscinosis

Ceroid lipofuscinosis is a lysosomal storage disease that has been reported in South Hampshire, Swedish Landrace, and Rambouillet sheep; Nubian goats; Devon cattle; and horses.[1-5] The disease is known to be inherited as an autosomal recessive trait in many cases[6] and is believed to be so in others.[7] It is characterized by the intracellular accumulation of abnormal autofluorescent lipopigments in lysosomes of neurons and other cells throughout the body. The storage material has been shown to consist predominantly of the subunit *c* of mitochondrial *c* synthase.[8,9] Affected animals display progressive ataxia and

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postural abnormalities, blindness due to retinal involvement in many cases, sensory depression, and, in the terminal stage, coma. Lesions seen on CT scans include enlargement of the lateral ventricles and reduced thickness of the cerebral cortex.[10]

Gross pathologic lesions in the CNS may include moderate enlargement of the lateral ventricles, flattening of cerebral gyri, and a yellow to brown discoloration of the brain parenchyma. Accumulation of protein storage material in neuronal lysosomes is evident on microscopic examination and is accompanied by neuronal necrosis and astrocytosis, which may be severe. The lesions sometimes have a lamellar appearance.[11] The disease is ultimately fatal, and no practical method of treatment is currently available.

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Diseases Manifesting Principally With Brainstem and Cranial Nerve Dysfunction

Peripheral Vestibular Disease of Horses

Robert J. MacKay

■ Definition and Etiology

Vestibular disease of horses is an acute, usually asymmetric, condition with several major causes: bacterial or mycotic infection of the middle/inner ear, polyneuritis equi, viral/idiopathic labyrinthitis, remodeling or fractures (or both) of the petrous temporal bone in association with THO, and external trauma to the skull with or without fracture of the petrous temporal bone.[1] Idiopathic labyrinthitis is probably an acute viral inflammation of the vestibular system that is severe, but complete recovery is common. Lightning strike is also an uncommon cause of vestibular signs in horses.[2,3] *Staphylococcus, streptococcus, Actinobacillus, Aspergillus, Enterobacter, Pseudomonas,* and *Salmonella* spp. and *C. pseudotuberculosis* have been isolated from cases of otitis media/interna in horses.[4] Some authors have speculated that THO results from extension of chronic low-grade bacterial otitis media to the adjacent temporohyoid joint[5]; however, remodeling and fusion of the temporohyoid joint are probably the result of repeated trauma, chronic degenerative processes, or both.[6,7] Primary otitis media/interna in horses is probably rare and, in contrast to this disease in ruminants, young age does not appear to be a risk factor. It is presumed that the middle ear is infected via the eustachian tube or hematogenously. With the exception of viral/idiopathic labyrinthitis, the proximity of the facial canal to the vestibular system means that the facial nerve (VII) is frequently involved in conditions causing vestibular signs. Because the first three cervical nerves contribute proprioceptive information to the caudal vestibular nuclei, upper cervical injury also can cause signs of vestibular ataxia.[8]

■ Clinical Signs

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Affected horses exhibit rotation of the poll (i.e., head tilt) toward the affected side, abnormal physiologic nystagmus, spontaneous horizontal or rotatory nystagmus with the fast phase away from the affected side, and vestibular strabismus with downward rotation (infraduction) of the eye ipsilateral to the lesion that can be exaggerated by elevation of the horse's chin. The gait is usually staggering and dysmetric, with a tendency, because of increased extension of the contralateral limbs, to lean or circle toward the affected side. Horses with any acute peripheral vestibular disease sometimes fall or even roll to the side of the lesion and may panic and thrash wildly in an effort to stand. Bilateral vestibular disease causes severe dysmetria and ataxia and complete absence of normal physiologic nystagmus. The horse may have wide swinging movements of the head.

Signs of vestibular disease are markedly exacerbated by blindfolding. Deafness is also apparent with bilateral involvement of the cochlear division of cranial nerve VIII. With unilateral vestibular disease, visual accommodation often occurs over a period of weeks, and affected animals may even return to racing. Signs of vestibular disease may still be elicited by blindfolding, however.

Concomitant ipsilateral facial paralysis is manifested by deviation of the nose toward the normal side, reduced flaring of the ipsilateral nostril during inspiration, and ipsilateral drooping of the lip, eyelids, and ears. Reflexes involving cranial nerve VII such as those of the lip and eyelids, the menace response, and ear reflexes are reduced or absent. Inability to close the eyelid causes exposure keratitis, which is particularly severe and usually involves deep horizontal corneal ulceration when there is damage to the secretomotor fibers of the facial nerve. With chronic facial paralysis, there is visible atrophy of the parotidoauricularis caudal to the vertical ramus of the mandible.

Horses with bacterial otitis media/interna may have other sites of infection, including the paranasal sinuses, guttural pouches, and lower respiratory tract. Extension of infection along a fracture defect or from otitis media/interna into the meninges is associated with development of additional neurologic signs, including obtundation, limb ataxia and weakness, and cranial nerve deficits, along with systemic signs of sepsis such as fever, tachycardia, and tachypnea.

■ Diagnosis and Treatment

A complete blood cell count usually reveals leukocytosis and increased fibrinogen and serum amyloid A concentrations in cases of chronic otitis media/interna, whereas neutrophilic pleocytosis in CSF samples is evidence of

secondary meningitis. Diagnostic procedures for horses with peripheral vestibular disease include skull radiography, CT, and endoscopic examination of the external ear canal and guttural pouch.[9] General anesthesia is required for diagnostic transtympanic centesis of the middle ear, although this procedure can rarely be justified.[5,10] The rate of tear secretion, which may be tested with a Schirmer tear test strip, usually exceeds 17 mm/min. BAER testing may help establish the location of vestibular system disease as peripheral or central.[11]

Antibiotic treatment of peripheral vestibular disease due to otitis media/interna should, if possible, be guided by antimicrobial susceptibility testing of bacteria cultured from the middle ear or from related disease processes such as sinusitis, guttural pouch empyema, or pneumonia. In the absence of such information, coverage should be provided against Gram-positive bacteria by penicillin G (22,000 U/kg IM bid as procaine penicillin or IV qid as potassium penicillin) or ceftiofur sodium (2.2 to 5 mg/kg IM sid to bid). Additional coverage (which includes staphylococci) can be provided by the addition of enrofloxacin (5.5 mg/kg IV or 8 mg/kg PO sid). Oral continuation of treatment can be conveniently provided by trimethoprim-sulfonamide drugs (30 mg/kg PO bid) or chloramphenicol (50 mg/kg PO qid). Treatment should continue for at least 30 days and ideally should be guided by results of repeated imaging of the affected petrous temporal bone. For cases refractory to antibiotic treatment, a procedure has been described for opening the affected osseous bulla by transendoscopic neodymium-doped yttrium aluminum garnet (Nd:YAG) laser surgery.[12]

Affected horses should be kept in a quiet, heavily bedded stall with good footing. Exposure keratitis may be treated or prevented under a partial tarsorrhaphy.

Equine Nigropallidal Encephalomalacia (Star Thistle Poisoning, Knapweed Poisoning)

Robert J. MacKay

Nigropallidal encephalomalacia (NPE) is a disease of adult horses characterized by facial and lingual dystonia and variable obtundation, behavioral signs, and ataxia. NPE is caused by ingestion of large quantities of the plants *Centaurea solstitialis* (yellow star thistle) or *Rhaponticum repens* (Russian knapweed; synonyms: *Acroptilon repens, Centaurea repens*).[1-4]

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■ Clinical Signs

The signs appear suddenly but always after long-term ingestion of large quantities of the plants. Characteristic signs of NPE include weight loss, mild to moderate obtundation, ataxia, yawning, lowered head, protruding tongue, tremor of the tongue and lips, and facial grimacing when feed is offered. The facial hypertonicity causes a retraction of the lips, which results in a fixed grimace with the mouth and lips held half open. Although affected horses can grasp food between the incisors, prehension, chewing, and swallowing of food are uncoordinated and inefficient. There may be constant chewing movements and food retained in the mouth, and cheek pouches may protrude from the commissures of the lips. Affected animals may attempt to drink by immersing their muzzles deeply into the bucket to force the water into the back of the pharynx. There also may be a transient tendency to walk compulsively, often in circles. Occasionally, horses with NPE are hyperexcitable.

After several days of progression, signs stabilize and do not then progress. Affected animals usually do not recover and are euthanized or die of starvation or dehydration.

■ Diagnosis

The CSF of affected horses may have high nucleated cell counts.[3] There are no characteristic changes in complete blood cell count or serum chemistry profiles. MRI was used to make an antemortem diagnosis in one horse with NPE.[5]

■ Pathophysiology

The toxic principle in yellow star thistle and Russian knapweed is not known with certainty, but there is some evidence for *repin*, a sesquiterpene lactone with high affinity for neural tissue.[6-8] Studies in rats suggest that repin exerts its neurotoxic effects by inhibiting dopamine release.[8] A role for neurotoxic amino acids, including aspartic and glutamic acids, has been proposed, but researchers could not confirm their presence in yellow star thistle.[9] Immunohistochemical staining of affected brains show that NPE is similar to environmentally acquired toxic parkinsonism of humans, whereby clinical findings are attributable to lesions in the globus pallidus and substantia nigra pars reticulata rather than to destruction of dopaminergic neurons.[10]

■ Necropsy Findings

At necropsy, sharply demarcated areas of yellowish malacia are visible grossly in the substantia nigra and globus pallidus (extrapyramidal system). Lesions are symmetric in most but not all cases. Lesions in other brainstem nuclei are found in a small number of animals.[2,9] Microscopic lesions include neuronal necrosis, vacuolation with gliosis, liquefactive necrosis, and cavitation in well-developed lesions.[11]

■ Epidemiology

NPE has been reported in horses of the United States, Australia, and South America. Yellow star thistle is a common plant in unirrigated pastures in the arid regions of the western United States. The plant is resistant to the effects of saline or alkaline soil conditions and requires minimal moisture. Russian knapweed belongs to the sunflower family and grows predominantly on flood plains, where it can extract deep subterranean moisture. In the United States, the plants tend to remain green during the dry months, so most poisonings occur during the summer or late autumn. Most horses are reluctant to eat *Centaurea* and *Rhaponticum* plants unless other vegetation is unavailable, but some develop a craving and selectively seek it out. Horses that develop NPE are usually being fed a poor-quality, high-roughage diet. Affected horses range from 4 months to 10 years of age (median, 2 years).[11] The case-attack rates of yellow star thistle poisoning range from 3% to 31% of horses on infested pastures.[11] Feeding studies have demonstrated that as much as 59% to 200% of the body weight of yellow star thistle and 59% to 63% of Russian knapweed must be eaten over 3 to 11 weeks to cause clinical disease.[2,11] Continuous protracted exposure to the weeds seems to be important for expression of clinical disease. The plants retain their toxicity when dried.

■ Treatment and Prevention

There is no known treatment. Prevention is best aimed at correcting the nutritional problem by daily supplementation with good-quality forage and by not pasturing horses in areas where either of the responsible plants grows.

Temporohyoid Osteoarthropathy

Robert J. MacKay • Lisle W. George

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THO is a progressive syndrome of horses involving periosteal reaction and enlargement and sclerosis of the stylohyoid bone, tympanic bulla, and petrous portion of the temporal bone (Fig. 35.14).[1] Ultimately, there is fusion between the skull and hyoid apparatus, stricture of the external ear canal, and obliteration of the lumen of the tympanic bulla. These changes are thought to represent a primary degenerative process in the temporohyoid joint (THJ), although some cases may be secondary to chronic otitis media.[1-3] The tympanic membranes of horses with this condition are usually not inflamed, and ruptures and associated discharges from the external ear are uncommon.[1] Horses aged 6 months to older than 20 years have been affected; the mean or median age reported in all studies is 10 to 12 years.[1,4-8] Quarter Horse and Quarter Horse–type breeds accounted for more than 50% of cases in several but not all series.[4-7] Both joints are affected, albeit asymmetrically, in most horses with clinical THO, and some cases are accompanied by associated bilateral clinical signs, including deafness.[4-6,9] Fusion of the THJ causes interference with the interdependent coordinated movements of the tongue, hyoid apparatus, and larynx. Particular stress is placed on the fused joint or joints during chewing, swallowing, vocalizing, and combined head and neck movements. Veterinary procedures such as dental work and passage of a nasogastric tube also put unaccustomed pressure on the THJ. Any of these mechanical forces applied to the immobilized THJ may result in fractures through the petrous temporal bone or proximal stylohyoid bone. THO is also probably a risk factor for fracture of the petrous temporal bone during head trauma, especially in horses that flip over backward and strike the poll. The facial nerve (cranial nerve VII) and vestibulocochlear nerve (VIII) and apparatus are within the petrous temporal bone and can be impinged on by bony proliferation or lacerated by fracture. After fracture of the petrous temporal bone, there may also be extension of middle/inner ear infection around the brainstem with signs of meningitis or extradural abscess.



FIG. 35.14 **Rostral view of left *(right)* and right *(left)* stylohyoid bones from a horse with left-sided temporohyoid osteoarthropathy. Note fusion of the temporohyoid joint on the affected side and the extensive remodeling and enlargement of the stylohyoid.**

■ Clinical Signs

Two sets of clinical signs are associated with the evolution of this disease process.[1] Early in the syndrome, including the period before ankylosis of the temporohyoid joint, affected horses may show reluctance to chew, dysphagia, headshaking, ear rubbing, sensitivity to pressure at the base of the ear, facial hyperesthesia, wild tossing of the head and neck under tack, reluctance to take a bit, dropping of feed, or even weight loss; most THOs, however, are probably subclinical until development of neurologic signs. Fracture of the proximal stylohyoid bone increases the likelihood of pain-associated clinical signs. Because of bony proliferation around the ear canal, the external ear may be unusually narrow and difficult to examine by endoscope.

After fusion of the THJ, the disease may manifest as sudden onset of asymmetric signs of cranial nerve VII or VIII dysfunction, or both. Almost all affected horses have degrees of facial paresis, with drooping of the ear, upper eyelid, and lower lip on the affected side and deviation of the muzzle to the contralateral side.[1,6,7] Buccinator weakness results in “quidding” (retention of

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feed material in the denervated cheek) and dropping of feed. Facial denervation may be evident as fine fasciculations of facial muscles and, after 2 weeks, obvious atrophy of the parotidoauricularis muscle behind the vertical ramus of the mandible. Facial paralysis is occasionally bilateral.[5] Schirmer tear tests commonly reveal reduced tear production (i.e., values of 5 to 19 mm; normal, ≥20 mm),[5] indicative of injury to the parasympathetic lacrimal (great petrosal) branch of the facial nerve. By the time of presentation, most such horses already have a deep horizontal corneal ulcer with corneal edema and miosis. Because of facial weakness, affected horses cannot mount the typical response to corneal ulceration—namely, blepharospasm and epiphora—and so ulcers often go undetected by horse owners. Signs of vestibular dysfunction accompany facial paresis in the majority of cases. Of 29 horses with THO that had involvement of VII, 23 (almost 80%) had vestibular signs.[6] Typically, affected horses exhibit sudden onset of head tilt, neck turn, body lean, and tight circling, all toward the affected side, and a staggering ataxic gait with preservation of limb strength. These signs may be revealed or exacerbated by blindfolding of the horse. In the acute stages, horizontal nystagmus may be present, with the fast phase away from the side of the lesion. In a study of 24 horses with THO and neurologic signs, all had electrodiagnostic evidence of partial to complete hearing loss on the affected side; 12 also had partial hearing loss on the contralateral side.[10] Vestibular signs can occur without concurrent involvement of the facial nerve, although this is unusual.[10] Of interest is that 12/19 (61%) of horses with THO had concurrent left laryngeal hemiparesis.[10] Horses may also have difficulty eating and swallowing because of either pain (e.g., from acute stylohyoid fracture) or involvement of cranial nerves IX and X. A few horses have seizure-like convulsions at the onset of neurologic signs. Bacterial abscess adjacent to the brainstem or meningitis may be sequels to fracture of the petrous temporal bone and result in the death of the horse.

■ Diagnosis

Endoscopic examination of the inside of the guttural pouches is the diagnostic imaging test of choice because of its convenience in standing horses and its high sensitivity for detection of THO.[6] Evaluation of the external contour of the THJ from within the guttural pouch can reveal asymmetric enlargement and discoloration of the stylohyoid bone and THJ and, in some cases, hyperemia, edema, or hemorrhage in the guttural pouch lining surrounding the joint.

Previously healed fractures of the stylohyoid bone may be evident as angulation and distortion of the bone close to the THJ. CT of the THJ allows appreciation of changes not always evident on endoscopy (or plain radiographs), including involvement of both sides, enlargement of the ceratohyoid bone, fractures of the petrous temporal and stylohyoid bones, and the presence of fluid in the tympanic bullae.[4,11] A system has been developed to quantify the remodeling changes found in horses with THO.[4] The main disadvantage of CT is the expense and requirement for general anesthesia. Where standing CT units are available, this is less of a concern, although adequate positioning can be difficult in horses with severe vestibular dysfunction.[8] Radiographic examination of the skull with ventrodorsal, lateral, and lateral oblique views reveals cases in which the bony proliferation has progressed to cause osteitis and fusion of the temporohyoid joint. Optimal images are obtained with the horse under general anesthesia and in dorsal recumbency; however, adequate views can be obtained with the use of a dorsoventral projection while the horse is standing but heavily sedated. Sensitivity for detection of THO by plain radiography in one series was 20/24 (83%).[6] MRI and nuclear scintigraphy have also been used successfully for THO diagnosis but have not been widely applied.[6,8,12]

BAER testing of vestibulocochlear nerve function has been described for horses with THO and is the only way of evaluating auditory function in these horses.[5] It is also a sensitive method for detecting involvement of the contralateral side.

In horses with neurologic signs other than dysfunction of CNN VII and VIII, CSF tap, analysis, and possible culture are recommended. Two of four horses tested in one report had increased nucleated cell counts or protein concentrations suggestive of septic or nonseptic meningitis.[6] Xanthochromia and increased RBC counts are also expected in acute cases.[3]

■ Treatment and Prognosis

Medical and surgical approaches to THO have been described.[1,3,13] Conservative medical therapy involves prolonged rest and treatment with an NSAID (e.g., 2 mg/kg phenylbutazone PO bid, or 1.1 mg/kg flunixin IV or PO bid for 3 days, then once daily for 1 to 2 weeks more) and broad-spectrum antibiotics (e.g., trimethoprim-sulfamethoxazole, 30 mg/kg PO twice daily for 30 days). The lever action of the hyoid apparatus on the petrous temporal bone can be resected surgically by complete removal (ostectomy) of the ipsilateral ceratohyoid bone

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or removal of a 1- to 2-cm section from the middle of the stylohyoid bone.[3,13,14] Because midbody partial stylohyoid ostectomies tend to heal,[14] the ceratohyoid procedure is now favored. If necessary, this surgery can be performed bilaterally when the horse is standing and sedated. With facial nerve paralysis and keratitis sicca, corneal ulcers are a medical emergency and must be treated or prevented with topical antibiotics, artificial tears, and, preferably, a multifocal partial split-thickness tarsorrhaphy.[3] For this purpose, shallow 3- to 5-mm-long incisions are made in the tensed lid margins of each eyelid immediately posterior to the line of tarsal gland openings. With 5-0 absorbable suture, a bite is taken in each eyelid deep in the incision, in the plane of the eyelid, and then the suture is carefully tied so that margins evert away from the corneal surface.[3] One or two shallow horizontal mattress sutures are then placed in the everted lid margin. The eyelids are joined in this manner at two or more sites, leaving open the nasal third of the palpebral fissure. The tarsorrhaphy is maintained permanently or until resumption of lacrimal and eyelid function, which may take up to 18 months.

Both medical and surgical approaches reportedly have returned most treated horses to athletic activity after a period of weeks to months, and so evidence to support the need for surgery in all cases is not yet clear.[1,6,7] On theoretical grounds, however, it is clear that a horse with THO will remain at risk for catastrophic relapse of neurologic signs as long as the hyoid apparatus and skull remain connected through a fused THJ. Relapse is particularly likely to occur if the temporal bone is fractured. In a series of horses with THO, 13 of 20 (65%), 1 of 25 (4%) and 1 of 8 (12.5%) horses treated by medical therapy, ceratohyoid ostectomy, and partial stylohyoid ostectomy, respectively, died as a consequence of THO.[9] In comparison with surgical therapy, medical therapy was significantly associated with nonsurvival.

If possible, the management of convalescent horses should be adjusted to minimize stress on any remaining THJ. Cribbing collars can be tried for crib biting, bitless bridles can be used for riding, and dental work and other professional procedures can be minimized and performed cautiously.

Horner Syndrome

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■ Definition and Etiology

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Horner syndrome results from interruption of ocular sympathetic pathways. Sympathetic pathways to the head originate as first-order neurons (upper motor neurons) in the tectum of the midbrain. Axons descend to the first to third thoracic segments (T1 to T3) of the spinal cord, where they enter the gray matter of the dorsal horn, synapse on second-order (preganglionic) sympathetic motor neurons, and exit in the ventral spinal nerve roots. From there the nerves pass through the cervicothoracic and middle cervical ganglia (combined as the stellate ganglion) and ascend in the cervical sympathetic trunk (part of the vagosympathetic trunk) to the cranial cervical ganglion (CCG), where they synapse on the third-order (postganglionic) sympathetic nerve. In the horse, the CCG is part of a neurovascular bundle in the caudodorsal aspect of the guttural pouch; in ruminants, the CCG is located under the petrous temporal bone. The third-order fibers are distributed with the blood supply via canals through the petrous temporal bone to the sweat glands of the head, ciliary muscles, and periorbital smooth muscles, including an eyelid levator (superior tarsal muscle) and periarteriolar musculature. The sympathetic nerve supply of the head thus can be damaged within the brainstem or spinal cord (first order); in the cranial thoracic nerve roots, spinal nerves, or cervical sympathetic trunk (second order); or in the CCG, in the skull, or behind the eye (third order).

Specific causes of Horner syndrome include mycotic guttural pouch infections; traumatic lesions of the basisphenoid area; otitis media; cervical trauma; abscesses, tumors, or space-occupying lesions in the anterior aspect of the thorax; periorbital abscesses or tumors; parotid duct obstruction and inflammation; esophageal rupture; and complications associated with surgical ligation of the carotid artery.[1-7] Lesions involving first-order sympathetic neurons in the ipsilateral brainstem are rare but have been reported as a consequence of metastatic neoplasia or with EPM in horses.[8,9] Horner syndrome has also occurred after intravenous injection of certain drugs, including xylazine, vitamin E or selenium, and phenylbutazone.[10-12] The sympathetic nerve supply to the eye is rare cases involved in the inflammatory polyneuropathy characterizing horses with polyneuritis equi (cauda equina neuritis) syndrome.[13,14] Tumors that have resulted in Horner syndrome include sclerosing respiratory epithelial carcinoma, squamous cell carcinoma, lymphoma, mesothelioma, and melanoma.[2,4-6,10,15,16]

■ Clinical Signs

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The clinical signs of Horner syndrome in horses vary but include miosis, ptosis, regional hyperthermia, excessive sweating on the ipsilateral side of the face, congested mucous membranes, inspiratory stridor, and dermatitis caused by chronic sweating. Although enophthalmos is reported to be a reliable sign of equine Horner syndrome, many (possibly most) affected horses do not exhibit prolapse of the nictitans and thus are probably not enophthalmic. The presence of this sign is apparently variable among species: Enophthalmos is part of Horner syndrome in cats and dogs[9] but not in humans and ruminants.[15,17] Ptosis is caused by the combined effects of loss of the eyelid levator function of the superior tarsal muscle and of variable enophthalmos. It is most reliably detected by comparison of the eyelash angles on each side. On the affected side, the eyelashes slope at a relatively downward angle. The palpebral reflex and the menace response are normal. If the vertebral nerve or its cervical sympathetic branches are damaged concomitantly, sweating may also be observed on the skin of the neck. Regional hyperthermia results from cutaneous and mucosal vasodilation, which in turn results from removal of sympathetic vasomotor tone. Sweating is thought to be caused by vasodilation and increased delivery of epinephrine to sweat glands. Facial sweating may begin to decrease 6 to 14 days after sympathectomy.[10,18,19]

In cattle, there is *dryness* of the ipsilateral planum nasale. This can be explained by the mediation of normal sweat gland secretion by postganglionic sympathetic fibers and α-adrenergic receptors in cattle.[19] The other signs in cattle are similar to those in horses. The clinical signs of experimentally induced Horner syndrome in sheep and goats are limited to mild ptosis.[19] Retrobulbar tumors may cause both exophthalmos and Horner syndrome.[15] On cold days, while exhaled breath from the external nares of cattle normally contains a mist of condensed water vapor, breath from the relatively warm nostril on the affected side may be mist free.[9]

■ Diagnosis

The level of sympathetic interruption can be determined by pharmacologic testing.[9] Hydroxyamphetamine (1% solution) instilled into the eye will result in release of norepinephrine from intact postganglionic sympathetic neurons, causing pupillary dilation, but in no response when the postganglionic neurons are damaged. A positive response to this test indicates a preganglionic sympathetic lesion, and a lack of response indicates a postganglionic lesion. In

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animals with a postganglionic lesion, topical administration of 0.1 mL of 1 mg/mL epinephrine solution directly activates the iris musculature and produces mydriasis within 20 minutes, whereas the onset of dilation occurs in approximately 40 minutes in animals with preganglionic lesions. Similarly, topical administration of 2.5% to 10% phenylephrine solution will produce pupillary dilation in an eye with a postganglionic sympathetic lesion but not in a normal eye. The sensitivity to these direct-acting sympathomimetics in animals with postganglionic sympathetic lesions is increased as a result of the phenomenon of denervation hypersensitivity, in which numbers and sensitivity of norepinephrine receptors in the iris muscle increase for days to weeks after postganglionic nerve injury. A positive response therefore is not observed until several days after the injury. Parenteral administration of 1 mL of 1 mg/mL epinephrine solution causes affected horses to sweat profusely over the affected side of the face.[10] However, this test does not differentiate between preganglionic and postganglionic lesions.

The guttural pouches of horses and the pharynx of all patients should be examined endoscopically to exclude the possibility of pharyngeal or laryngeal paralysis or guttural pouch disease. The jugular furrows should be palpated for swellings. Insertion of a nasogastric tube during palpation may be helpful for detecting subtle lesions on the left side of the neck. The thorax should be examined with auscultation, ultrasonography and, if indicated, radiography. Cranial ribs can be evaluated for lesions by scintigraphy.[20] A neurologic examination should be performed to evaluate the function of the spinal cord. The skin temperature may be measured with thermography[1,6,21]; on the affected side, it is 1° C to 3.5° C higher than normal.

■ Treatment

The treatment for Horner syndrome depends on the underlying cause of the denervation. Except for Horner syndrome related to IV injection of xylazine, the signs are often irreversible, even if the primary cause of the condition has been eliminated. With xylazine-associated Horner syndrome, the condition disappears spontaneously. The necrotizing effects of perivascular drug injections can be minimized by immediate dilution or irrigation, or both, with large volumes of saline infiltrated into the perivascular tissues. Antiinflammatory doses of flunixin and dexamethasone can be given systemically. Abscesses should be drained, and fungal infections of the guttural pouch should be treated as

described in Chapter 31.

Guttural Pouch Mycosis

Robert J. MacKay

■ Definition and Etiology

The clinical signs occur because fungi invade vital vascular and neural structures in the roof of one, or occasionally both, guttural pouches. There is no apparent age, sex, breed, or geographic predisposition to this disease.[1] Foals as young as 3 months of age have been affected.[2] *Aspergillus fumigatus* and *Emericella nidulans* (the sexual form of *Aspergillus nidulans*) are the fungi most commonly identified in pure or mixed culture.[3,4] Lesions are typically diphtheritic membranes of variable size, composed of necrotic tissue, cell debris, a variety of bacteria, and fungal mycelium (Fig. 35.15).[1]

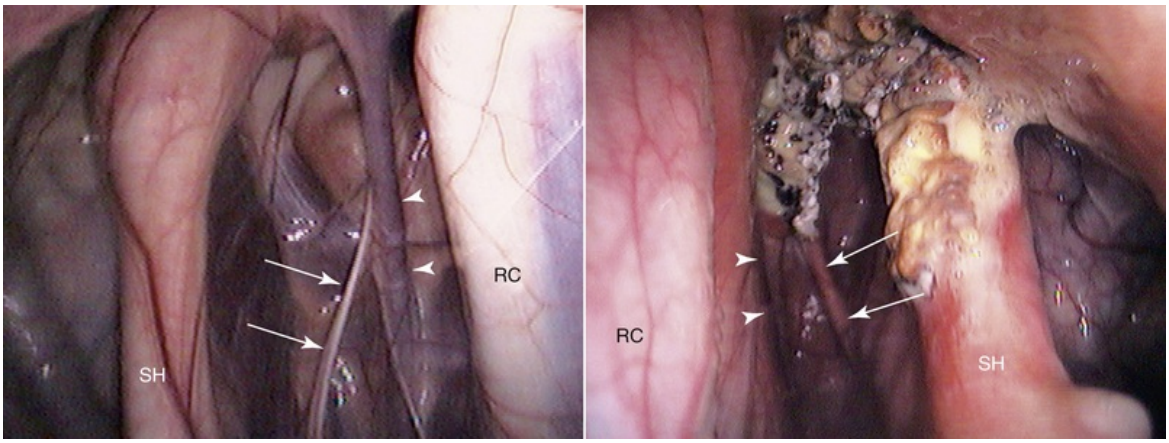


FIG. 35.15 **Endoscopic views of the caudal aspects of the left guttural pouch with a mycotic plaque over the neurovascular structures of the medial compartment of left guttural pouch *(right)* and normal right guttural pouch *(left).* There is also thickening of the left stylohyoid bone secondary to temporohyoid osteoarthropathy. *Arrows* point to the glossopharyngeal nerves, and *arrowheads* point to the internal carotid arteries. *RC,* Rectus capitis ventralis major muscle; *SH,* stylohyoid bone.**

The guttural pouch is partially separated into two compartments by the stylohyoid bone and occipitohyoideus muscle. Cranial nerves IX through XII, the cranial cervical ganglion and postganglionic sympathetic nerve, and the internal carotid artery are located in a fold that traverses the dorsomedial aspect of the medial compartment. For unknown reasons, this site is susceptible to

colonization and destruction by invasive mycotic infections.[5] In approximately one third of cases, the fungal lesion is located in the lateral compartment, sometimes after extension from a primary site in the medial compartment.[1] At this location, the fungal mycelium may invade the wall of the external carotid artery or any of its branches and affect the facial nerve (VII). Facial nerve paralysis has also been observed as a result of direct invasion by a fungal guttural pouch infection into the overlying parotid lymph node and salivary gland.[6] Fungal plaques may also spread from one guttural pouch to the other by eroding through the apposed medial walls of the pouches.

■ Clinical Signs

Initial signs are headshaking and unilateral nasal discharge. There is a tendency to hold the head in extension or lower to the ground than normal. Additional clinical signs are nasal discharge, dysphagia with nasal return of feed-stained saliva, head shyness, stridor, dysphonia, protrusion of the tongue from the mouth, and epistaxis.[6,7] Epistaxis may be bright red, high volume, and life-threatening. Other clinical signs include sensitivity to pressure over the parotid salivary gland, Horner syndrome (sweating, miosis, and ptosis on the side of the lesion), paralysis of the tongue on the affected side, and facial paralysis.[6-10] Atrophy of the brachiocephalicus and trapezius muscles secondary to denervation of the spinal accessory nerve (XI) has been described in a few cases. Horner syndrome is a development secondary to damage of the cranial cervical ganglion and postganglionic fibers. The sensorium is intact unless aspiration pneumonia develops or the fungus spreads into the brain.[11,12] Affected horses may die peracutely as a result of exsanguination from ruptured internal or external carotid arteries or their branches. Endoscopic examination of the larynx of affected horses may reveal dorsal displacement of the soft palate, inability to swallow, and laryngeal hemiplegia. Mycotic guttural pouch infection can be diagnosed definitively endoscopically by identifying the characteristic fungal mass in the caudodorsal aspect, usually of the medial compartment. Radiographic examination of the pouches shows a poorly defined border of the pouch in the abnormal area.

■ Treatment

Before the onset of neurologic signs, the affected artery or arteries may be occluded on each side of the lesion by ligation/balloon-tipped catheter,

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embolization coils, or nitinol plugs.[1] Occlusion of the ipsilateral common carotid artery alone does not prevent fatal hemorrhage.[13] Complete arterial occlusion prevents fatal epistaxis, but it is not clear whether it affects fungal growth. Some studies have shown excellent, albeit delayed, rates of resolution of mycotic lesions in horses that underwent the procedure with or without additional antifungal therapy,[14,15] but in other animals the lesion may progress despite complete arterial occlusion.[8] Because some such lesions resolve spontaneously over time, the role of surgery in their resolution remains controversial.[1] Optic neuropathy and blindness of the ipsilateral eye are occasional sequelae of occlusion of the external carotid artery and its branches.[1] Lesions may be treated topically through an endoscope with povidone-iodine or triazole antifungal agents such as enilconazole, voriconazole, and itraconazole. Itraconazole is also affordable and safe when administered systemically. Nystatin, natamycin, miconazole, and fluconazole have little activity against *Aspergillus/Emericella* spp. Amphotericin B is effective, although systemic treatment is limited by its toxicity. Topical treatment may be repeated daily (or as frequently as is practicable) for up to several weeks. As the fungal mass degenerates, pieces can be carefully removed endoscopically with biopsy forceps in horses that have previously undergone arterial occlusion. Dysphagic horses may be fed via an indwelling esophagostomy tube while lesions are being treated.[16] Neurologic signs may be permanent, although improvement or recovery over many months has been reported in some horses.[15] Affected horses are often euthanized for humane reasons. (See Chapter 31 for more on treatment of guttural pouch mycosis.)

Listeriosis (Circling Disease; Silage Disease; *Listeria monocytogenes* Infection)

Lisle W. George

■ Definition and Etiology

Listeriosis is an acute meningoencephalitis caused by the Gram-positive bacterium *L. monocytogenes.* The disease has a worldwide distribution, but occurs most often in temperate climates. Listeriosis typically affects ruminants, fowl, and humans but is rare in horses. The prevalence of listerial

meningoencephalitis in infected herds does not usually exceed 1% of the adult animals at risk.[1]

Clinical manifestations of listeriosis include septicemia of neonates, abortion, neonatal death, ophthalmitis, uveitis, septicemia and diarrhea in ewes, and neurologic disease.[2] Neurologic listeriosis may manifest as a multifocal brainstem disorder, diffuse meningoencephalitis, or myelitis. The condition usually affects individual animals but occasionally affects several members of a herd.[3] Asymptomatic intramammary infections apparently occur and may be responsible for outbreaks of listeriosis in humans. Repeated intramammary inoculation of 10^6 to 10^7 colony-forming units of *L. monocytogenes* into cattle resulted in 500 to 50,000 colony-forming units of the organism in the milk for as long as 12 months.[4]

■ Epidemiology

Among untreated cases, the fatality rate is almost 100%.[5] The survival rate is considerably higher among treated animals than among untreated patients. The disease in sheep and goats tends to be more acute and results in a higher case fatality rate than in cattle. Occasional outbreaks of listeriosis may occur in sheep without access to silage.[5,6] In these cases, the source may be the feces of carrier animals or rotting vegetation on the pastures or feed bunks. During an outbreak of listeriosis, the bacterium can be isolated from the feces of a large percentage of normal animals.[7] It is unclear whether this high rate of asymptomatic carriage represents a true carrier state or is simply the result of a high environmental contamination by nonpathogenic isolates.[7] The agent infects the udder but rarely causes clinical mastitis. In sheep, excretion of the bacterium in the milk is greatest during the immediate postlambing period.[8,9]

L. monocytogenes can survive for long periods in the environment and in carriers with no symptoms. The bacterium can multiply at low environmental temperatures and is resistant to environmental influences. *L. monocytogenes* is shed in the feces of carriers with no symptoms, especially at the end of pregnancy and at lambing. Once in the environment, the bacterium can survive for 2 years in dry soil. It is resistant to freezing and thawing in the soil, but it does not survive for more than 1 to 2 weeks in properly preserved silage. The bacterium proliferates in rotting vegetation in which aerobic conditions exist and the pH is above 5.4.[10-12] Common sources of contamination in forage include

spoiled silage at the ends of trench silos, decaying forage at the bottom of feed bunks, or rotting hay at the periphery of hay stacks.[10,13] The incidence of listeriosis may be increasing because of the greater use of trench silos and bulk handling methods, in which the amount of spoilage is greater than in conventional upright silos. Although *L. monocytogenes* can be isolated from silage with a pH below 4, fewer bacteria are found in well-preserved forage.[14]

A selective enrichment medium has been developed for identifying and enumerating the *Listeria* organisms in silage. This medium enables semiquantitative enumeration of *Listeria* bacteria in 10 g of silage. Hemolysin production is measured by overlaying the colonies with bovine blood agar and reincubating the plates. With this method, outbreaks of listeriosis have been correlated with silage containing 1 million *Listeria* organisms and more than 1 million enterobacteria per gram of silage. The pH of such silage characteristically exceeds 7.8.[15]

There is a significant public health concern about *Listeria* contamination of milk products. The 4b serotype of *L. monocytogenes* is most often responsible for infections in humans.[16] Outbreaks have been traced to ingestion of unpasteurized milk, cole slaw, and soft, ripened cheese. Foodborne listeriosis outbreaks have also been linked to contaminated fruit and vegetables.

■ Pathogenesis

Listeria organisms produce a hemolysin, listeriolysin-O, which is a thiol-activated toxin (molecular weight, 58 kD) that, in certain amounts, produces disease. The molecular role of the toxin in dissemination of the infection and in cell death is not known.

It is unclear whether infection of the brain by *L. monocytogenes* occurs hematogenously or by ascent from the cranial nerve rootlets.[17] Morphologic studies of naturally occurring cases of encephalitic listeriosis have demonstrated the bacterium in the axons of the trigeminal nerve rootlets, which indicates possible centripetal migration.[17,18] Similar findings have been reported in animals infected experimentally.[19] Younger animals may be susceptible because eruption of the permanent teeth may expose trigeminal nerve rootlets. Lsteriosis has been experimentally induced by inoculation of the bacterium into the pulp cavity of sheep.[20] Infection of the CNS without bacteremia has been detected, which also indicates that centripetal migration of the bacterium is possible.[21] Some investigators consider axonal migration as an unlikely mode of

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pathogenesis because *L. monocytogenes* is not nutritionally dependent on nervous tissue and because of the ready ability to produce multifocal brain microabscesses by intravenous inoculation of the bacteria into susceptible hosts.[17,22]

■ Clinical Signs

The neurologic signs of listeriosis in adults reflect dysfunction of the caudal brainstem, cerebellar peduncles, or spinal cord.[5] Fever may be present early in the clinical course, and poor appetite and depression are common. CNS signs are usually asymmetric and include conscious proprioceptive deficits, head pressing, and cranial nerve deficits. Depressed consciousness is the result of lesions of the reticular activating system. Conscious proprioceptive deficits are caused by interference with the descending motor pathways and the ascending proprioceptive fibers in the brainstem and may precede or accompany cranial nerve dysfunction. Head pressing and propulsive walking or compulsive circling are caused by lesions of the basal ganglia. Severely affected animals may be recumbent and may display torticollis, head tilt, or other unilateral vestibular signs.

Cranial nerves V through XII are usually dysfunctional in listeric animals. Patients with loss of the trigeminal nerve (cranial nerve V) show dropped jaw or asymmetric jaw closure and facial analgesia or anesthesia. Facial analgesia is best detected by stimulation of the nasal septum with a pencil or piece of straw. Animals with lesions of cranial nerve VI exhibit a medial strabismus on the ipsilateral side of the lesion. Animals with lesions of cranial nerve VII have ptosis, loss of menace response, no palpebral reflex, drooped ear, loss of levator nasolabialis muscle function, and decreased lip tone (Fig. 35.16). Small ruminants with cranial nerve VII loss have a deviated philtrum. The paralysis of the orbicularis oculi muscle results in exposure keratitis.[23] The loss of levator nasolabialis function is best detected by observation of the muscular contraction on the dorsum of the nose during inspiration. Loss of lip and cheek muscle tone is best detected by observation of drooling from the ipsilateral side of the mouth and by palpation of the lips and nostrils.



FIG. 35.16 **Clinical appearance of the neurologic form of listeriosis in a Charolais bull. Note the drooped right eye and ear and the drooling from the right side of the mouth. (Courtesy Dr. W.D. Wilson.)**

Animals with cranial nerve VIII lesions display nystagmus that changes as the position of the head is altered. Other signs include a head tilt toward the side of the lesion and a tendency to circle or fall to the lesion side. The nystagmus may be horizontal, vertical, or rotatory and is usually inconstant. If the spinal reflexes can be tested, the affected animals show a mild to moderate hypertonia and hyperreflexia in the limbs opposite the side of the lesion. Animals with acute loss of cranial nerves IX, X, and XII develop stertorous breathing and dysphagia. Animals with dysfunctional cranial nerve XII have paresis or paralysis of the tongue. With unilateral lesions, the tongue protrudes from the side of the mouth ipsilateral to the lesion. Progression of listeriosis is associated with decreased consciousness, coma, and convulsions.

Lambs may selectively develop spinal myelitis without brainstem disease. This condition results in flaccid paraparesis or hemiparesis without attendant signs of brainstem dysfunction.[24] The clinical signs of myelitis include tetraparesis, tetraplegia, paraparesis, paraplegia, conscious proprioceptive deficits, and recumbency. The sensorium and appetite are normal in some

affected animals and greatly depressed in others.[25] Primary ocular disease caused by *L. monocytogenes*, manifesting as keratitis, conjunctivitis, or uveitis, may occur in cattle or horses with no signs of neurologic disease.[26]

■ Clinical Pathology

Examination of the CSF usually helps confirm a diagnosis of listeriosis, but the cell and protein concentrations of the specimens are not necessarily correlated with the severity of the clinical signs or prognosis. The protein concentration in the CSF may exceed 40 µg/dL, and WBC counts in the CSF may exceed 12 cells/µL with mononuclear pleocytosis.[1,27,28] Many cattle with advanced signs of listeriosis develop metabolic acidosis as a result of salivary bicarbonate loss.

■ Pathology

Pathologic confirmation of listeriosis is based on identification of multifocal microabscesses in the brainstem and isolation of *L. monocytogenes* from infected brain tissue. The agent is only rarely isolated from CSF and is best recovered from refrigerated nervous tissues. Enrichment of the *Listeria* organisms may be accomplished by refrigerating slices of brain at 4° C (39.1° F) for 3 months while the tissues are cultured weekly. In contrast to septicemic listeriosis of monogastric animals, peripheral monocytosis is not observed in infected ruminants.

■ Pathology

The lesions of listerial meningoencephalitis are most common in the pons and trapezoid bodies, but they can be located anywhere in the brainstem. Neurologic structures most often affected include the reticular formation and cranial nerves V and VII to X. Macroscopic lesions are limited to mild meningeal congestion and clouding of the CSF. Microscopic lesions include perivascular cuffing with mononuclear cells, multifocal asymmetric brainstem microabscesses, and mononuclear cell meningoencephalitis.[16] The microabscesses are composed predominantly of neutrophils. Other microscopic changes include degeneration of the neuropil and neuronophagia.

■ Treatment and Control

The recovery rate is best if treatment is administered early in the disease course.

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Animals that are recumbent, comatose, or convulsive rarely survive despite intensive antibiotic and supportive therapy. In most cases, treatment must be administered for a prolonged period because recovery may take as long as 1 month. *L. monocytogenes* is susceptible to most of the common antimicrobial drugs. Recommended treatment is either oxytetracycline, 10 mg/kg IV twice daily, or therapy with penicillin G.[23] Specific recommendations for penicillin therapy include an initial dosage of 40,000 IU/kg (potassium penicillin G) IV three or four times daily for 7 days and then 22,000 IU/kg (procaine penicillin) IM once daily for 14 to 21 additional days.[23]

The plasma concentrations of bicarbonate and potassium should be measured, and specific corrective fluid therapy should be administered as indicated by acid-base and electrolyte assays. Good footing and nursing care are also beneficial.

Serologic responses to flagellin and listeriolysin-O develop after oral administration of virulent *L. monocytogenes* and confer protection against listerial bacteremia.[21] Vaccines of attenuated or killed bacteria have been used successfully to protect sheep and goats. Although these vaccines reduce the incidence of listeriosis in vaccinated flocks, they are not commercially available in the United States.

Although the case attack rate of listeriosis is low, occasional epizootics may occur in cattle, sheep, or goat herds, invariably in association with high rates of environmental contamination. In such cases, the hay and silage should be cultured for *L. monocytogenes.* Rotten vegetation should be discarded, and cattle should be fenced from contaminated areas.

Thromboembolic Meningoencephalitis (*Histophilus somni* Infection; Sleeper Calves)

■ Definition and Etiology

Thromboembolic meningoencephalitis (TEME) is a fulminant neurologic disease of cattle that arises from septicemia caused by the pleomorphic, nonencapsulated, Gram-negative bacterium *H. somni* (formerly *Haemophilus somnus*).[1] Because it can disseminate via the bloodstream, this organism can incite infection in multiple organs. In addition to TEME, *H. somni* can cause pleuropneumonia, myocarditis, laryngeal abscesses, polyarthritis, polyserositis, and infections of the ear, eye, udder and urogenital tract.[1-6]

■ Epidemiology

Although TEME occurs most frequently in feedlot cattle,[7] outbreaks in the western United States and Canada have been reported in both pasture and dry lot environments.[8,9] In a serologic study of feedlot cattle, seroconversion to *H. somni* occurred early in the feeding period (soon after placement).[10] This may be reflective of the role of stressors (e.g., comingling of animals from different sources, transport, or changes in feed) in the pathogenesis of this disease. Chapter 31 includes further details on the epidemiology of *H. somni* infections in cattle.

■ Pathogenesis

Infection of cattle by *H. somni* probably occurs through the respiratory tract. Bacterial proliferation in the lungs and other soft tissues by serum-resistant isolates results in bacteremia. *Histophilus* possesses multiple virulence factors including the capability to induce apoptosis of endothelial cells.[6] Exposure of subendothelial collagen occurs subsequently, which results in microthrombus formation and organ damage through hypoxia and inflammation. The sites of the body most affected by the thrombosis are the brainstem, spinal cord, synovial membranes, pleura, and lungs. Although the name *thromboembolic meningoencephalitis* implies the passage of solid material in the vasculature to a downstream occlusion site (embolism), thrombus formation probably occurs directly at the site of the vascular lesion.

■ Clinical Signs

Only the neurologic syndrome (TEME) is discussed here. Descriptions of other clinical syndromes of *H. somni* infection are discussed in Chapters 31, 39, and 43. The initial signs of TEME are fever (40° C to 41.6° C [104° F to 107° F]), anorexia, depression, and ataxia.[7,8,11,] In addition to depression, affected animals show a number of conscious proprioceptive deficits, including knuckling, circumduction, crossing over, and interference. Affected animals may fall while attempting to walk. Signs specifically associated with lesions of the cerebellum and caudal brainstem include head tilt, nystagmus, strabismus, blindness, muscular tremors, opisthotonos, coma, and convulsions.[12] Signs of infection in other organ systems (e.g., pneumonia, arthritis) may be present in the affected animal or in cohorts. Death may occur within 36 hours after the onset of

neurologic signs.

■ Clinical Pathology

Examination of CSF may be helpful in substantiating a clinical diagnosis of TEME. Specific CSF changes characteristic of hemorrhage include high erythrocyte counts, xanthochromia, and increased concentrations of protein (>100 mg/dL) and neutrophils (>500 WBCs/μL). In untreated cases of TEME, the bacterium may be isolated from the brain, kidneys, pleural fluid, lung sections, aspirated tracheal exudate, urine, blood, and preputial washings. Standard transport swabs containing Amies medium are appropriate for culturing of clinical samples. Isolation of *H. somnus* from joint fluid and CSF is usually unsuccessful.[13] The kidneys and brain should be collected for postmortem examination because these tissues contain the highest concentrations of *H. somni*.[13]

Initial changes in the peripheral WBC count include neutropenia, left shift, and toxic changes in the neutrophils. In cattle that develop acute TEME, agglutinating antibody titers are invariably greater than 1 : 400 and increase fourfold by 2 to 4 days after infection.[14] Serum agglutination titers are greater than 1 : 1024 in convalescent cattle; they may be lower with inapparent infection or vaccination.[15]

■ Pathology

Macroscopic pathologic lesions of the CNS include disseminated multifocal hemorrhages and infarctions in the spinal cord, brainstem, and cerebral cortex. Bacterial colonies are frequently observed in thrombosed blood vessels and the surrounding infarcted tissues. Ocular lesions are characterized by conjunctivitis, multifocal retinal hemorrhages, and areas of retinal edema. The CSF is cloudy and xanthochromic. A focal fibrinous meningitis is observed, and suppurative otitis may occur in some cases.

The earliest microscopic lesion of TEME is vasculitis that progresses to septic infarction and abscess formation. The lesions are usually found in the CNS, but in severe cases they may be disseminated throughout the body.

Nonneurologic lesions of *H. somni* infection include suppurative arthritis, synovitis, myocarditis, suppurative pleuritis, urogenital infections, and bronchopneumonia. Changes associated with the bronchopneumonia include infarction, cranioventral pulmonary consolidation, and hemorrhagic interstitial

pneumonia. Other lesions include ecchymotic to petechial hemorrhages over the serous surfaces, purulent exudate in the joints, and ulceration of the laryngeal and tracheal mucosa with diphtheritic membrane formation.[16]

■ Treatment and Control

During an outbreak, cattle must be examined frequently and should be treated when the neurologic signs first appear. *H. somni* is susceptible to many antibiotics and antimicrobial drugs. Drugs that have been reported to be effective for the treatment of TEME include tetracyclines, penicillin, aminoglycosides, and ampicillin. Parenteral oxytetracycline is regarded as the most cost-effective treatment for infected commercial cattle; the dosage is 10 mg/kg of a conventional formulation given IV twice daily for 3 days or 20 mg/kg of a long-acting formulation given SC. Some authors advocate the addition of chlortetracycline (2.2 mg/kg) to the feed for 10 successive days.[17] This, however, would constitute off-label drug use in feed and is currently prohibited by the U.S. Food and Drug Administration. Chlortetracycline is approved as an oral drench for the treatment of *H. somni* pneumonia in beef, non-lactating dairy cattle, and calves in the United States at a dosage of 22 mg/kg for 5 days.

Antibody responses protective against respiratory challenge have been generated by vaccination with anionic, heat-stable proteins derived from the bacterial cell wall.[18] Vaccination of cattle with commercial products affords substantial protection from experimentally induced *H. somni* septicemia and neurologic disease for more than 3 months[18-20] (See Chapter 48 for more information about vaccines). Mass prophylactic treatment of affected cattle with a parenterally administered, long-acting oxytetracycline formulation may be efficacious in preventing TEME in cattle at high risk for the disease.[21]

Otitis Media/Interna of Ruminants

■ Definition, Etiology, Epidemiology, and Pathogenesis

Otitis media/interna is a common bacterial disease of cattle and sheep; it is less commonly observed in goats. The condition usually occurs as a sequela to upper or lower respiratory infections caused by *Mannheimia haemolytica*, *Pasteurella multocida*, *C. pseudotuberculosis*, *H. somni*, or *Mycoplasma* spp.[1-5] Subclinical otitis media/interna is common in feedlot-reared animals, particularly early in the feeding period.[1,3] Although viral infections are the cause of a large

proportion of otitis media/interna cases in children,[5] the role of viral infections in ruminant otitis media/interna remains speculative; it is possible that viruses play a role in facilitating otitis media interna similar to that in facilitating lower respiratory tract disease. Because *Mycoplasma* spp. have been detected in clusters or outbreaks of otitis media/interna on dairy farms, contaminated milk is considered an important potential source of this organism in young stock.[4,6] Chapter 31 includes more detailed discussion on the role of *Mycoplasma* spp. in the bovine respiratory disease complex.

Otitis media/interna is considered to most commonly result from ascending infection of the middle ear from the nasopharynx via the eustachian (auditory) tube.[5] Infection that progresses from the external ear into the middle ear is less common but may occur secondary to aural infestation by ectoparasites. Once infection is established in the middle ear, it may extend into the inner ear as a result of erosion of bone or extension of the infection through the round or oval windows, or both. The constellation of clinical signs of otitis media/interna results from damage to the peripheral vestibular apparatus residing in the tympanic bulla and petrous temporal bone. In chronic cases, the peripheral vestibular apparatus can be damaged beyond repair, and neurologic deficits may be permanent. In rare cases, infection can extend into the CNS, which results in subdural abscess formation, meningoencephalitis, or brain abscess formation.[5] The vast majority of cases shows clinical signs of unilateral peripheral vestibular disease; however, subclinical inflammatory lesions may be present in the contralateral, clinically normal side. Bilateral, clinically apparent peripheral vestibular disease is rare. Additional signs of multisystemic disease caused by *Mycoplasma bovis, Pasteurella multocida*, or *H. somni* may be present (e.g., pneumonia, polyarthritis).

■ Clinical Signs and Diagnosis

Headshaking (possibly producing an aural hematoma), an ear droop, and reduction in appetite may precede the clinical vestibular signs. Fever is inconsistent.[6] Patients with vestibular signs display unilateral head tilt (toward the side of the lesion), continuous horizontal nystagmus (fast phase away from the side of the lesion), and imbalance, manifested as a tendency to stumble, fall, or walk in a tight circle toward the side of the lesion. If the tympanic membrane ruptures, or in the rare case of otitis externa as a preceding condition, purulent exudate may be evident in one or both ears.

Affected animals may become recumbent and lie with the lesion side toward the ground; if turned, they return to the same position. Many animals with otitis media also develop ipsilateral facial nerve dysfunction, which results in ptosis, drooped ear, and flaccid lips and nostrils. In small ruminants, facial nerve paralysis results in deviation of the philtrum toward the normal side. Deviation of the philtrum does not occur in cattle because of the large amount of connective tissue surrounding the planum nasale. On occasion, affected animals develop subtle or pronounced signs of cortical or brainstem disease as a result of extension of infection from the middle ear into the meninges. CSF analysis may reveal increased leukocyte counts in such cases.[6]

Although the clinical signs of peripheral vestibular disease are characteristic, it is important to differentiate this condition from that of central vestibular disturbance. Animals with peripheral vestibular disease are usually appetent, alert, and aware of their surroundings and do not have a significant deficit of postural placement. The nystagmus of these animals is constantly horizontal. In comparison, animals with central vestibular disturbances are depressed, have a nystagmus that varies in direction, and show marked conscious proprioceptive abnormalities.

Diagnostic imaging, including radiography, CT, and ultrasonography of the tympanic bulla, may be useful in confirming a diagnosis of otitis media/interna.[7]

■ Treatment and Control

Treatment of bacterial otitis with procaine penicillin (44,000 IU/kg IM or SC daily) may be effective. Because bacteria that do not have a cell wall (*Mycoplasma* spp.) may be involved, however, initial treatment with an antibiotic other than a member of the β-lactam class might be warranted (e.g., tetracyclines, florfenicol, macrolides, and, where legal, fluoroquinolones), unless bacterial culture and sensitivity results or clinical response indicates treatment with a β-lactam class antimicrobial drug.[6] Relapses may occur, which warrants prolonged treatment (3 to 6 weeks). Treatment is effective in obtaining a complete cure of acute otitis but is less so in treating the chronic form. In chronic cases, infection may irreversibly damage middle or inner ear tissues, causing neurologic deficits that can persist despite resolution of infection with antimicrobial therapy. Osteomyelitis of the petrous temporal bone, abscess formation in the tympanic bulla, or a noninfectious cause (e.g., neoplasia) are other considerations for affected animals that do not respond to antimicrobial

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therapy.

Management practices aimed at reducing the risk for upper respiratory tract infection may aid in reducing the incidence of disease. In dairy herds with a history of otitis media/interna caused by *Mycoplasma* spp. in calves, pasteurization of waste milk fed to calves or feeding milk replacer instead of waste milk may be warranted.

Ear Mite Infestations of Ruminants

The ear mite of cattle is *Raillietia auris*, and that of small ruminants is *Psoroptes cuniculi.* Severe infestations perforate the tympanum and result in vestibular disease, facial paralysis, and ataxia.[1-4] Infestation can be recognized by observation of ulceration and purulent debris in the auditory canal next to the tympanum. Mites may or may not be visible during otoscopic examination. Malodorous discharge on the side of the face under the ear canal may be observed in some affected animals.

The accumulation of purulent debris and the swelling of auricular tissues block the transmission of sound to the tympanum.

Ear mite infestations in cattle are common and in some herds may affect most of the adults. The biologic importance of the infestation may be related to changes in the herding or mothering behavior of range cattle. The economic significance of the infestation is unknown.

Ear mite infestations have been successfully treated in goats with eardrops containing rotenone once daily for 5 to 10 days. Good clinical responses can be obtained in cattle with the same treatment. Fenthion drops have also been used successfully. In cases of parasitic otitis in which the discharge has been inspissated, lateral resection of the ear canal should be considered to establish adequate ventral drainage.[5] A single subcutaneous injection of ivermectin at 0.2 mg/kg has been shown to be an effective treatment for *P. cuniculi* otitis in both sheep and goats.[6,7]

The life cycle of the mite involves two free-living stages, the protonymph and deutonymph stages. These forms molt in the vegetation and reinfest cattle as they graze or bed during the evening.[8] Therefore tilling the soil of the infested pastures or re-treating cattle every 14 to 21 days with insecticide should be considered as part of an eradication scheme.

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Diseases Producing Tremors and Ataxia; Cerebellar Diseases

Cerebellar Abiotrophy

Robert J. Mackay

The term *abiotrophy* refers to spontaneous premature degeneration resulting from an inborn error of development.[1] Syndromes of cerebellar abiotrophy have been described for Arabian,[2] Gotland Pony,[3] and Eriskay Pony foals.[4] In Arabian foals with cerebellar abiotrophy, degeneration begins only after formation of the cerebellum and is characterized by apoptosis of Purkinje cells.[5] The likely genetic basis for cerebellar abiotrophy in Arabian foals is a single-nucleotide polymorphism upstream of the *mutY* homolog gene *(MUTYH),* in a region involved in transcriptional upregulation of the gene.[6] *MUTYH* encodes for a DNA glycosylase involved in repair of oxidative damage to genomic DNA during organogenesis and mitochondrial DNA during postnatal life. This gene is expressed abundantly in the cerebellums of normal horses; expression is significantly lesser in foals with cerebellar abiotrophy.[6]

The mode of inheritance of cerebellar abiotrophy is simple autosomal recessive.[2,6,7] The cerebellar abiotrophy allele was found in 19.7% of approximately 4200 Arabian horses and is well represented in Egyptian, Spanish, and Polish lineages.[6,7] Among tested horses, 1.4% were homozygous for the allele. Nine of these were clinically normal, which, together with the observed range of ages at onset, is evidence for variable expression of the cerebellar abiotrophy trait. The allele was also present at low frequency among Bahkir Curly Horses, a breed for which Arabian horses were foundation stock, and in Welsh Ponies and Trakehners, breeds that allow out-crossing with Arabian horses.[8]

Signs of cerebellar abiotrophy typically begin in foals between 6 weeks and 4 months of age; however, affected foals may show signs at or shortly after birth. Among 18 confirmed or suspected cases, signs were present at birth in 4 (22%) and began at the age of 3 months or younger in 10 (56%), at ages 3 to 6 months in 2 (11%), and after age 6 months in 2 (11%).[9-12] The first signs noticed are incoordination, basewide posturing in the thoracic limbs, and head tremors. The head tremor is usually a coarse bobbing in either the horizontal or vertical plane. When the head is extended (e.g., toward the dam's udder or toward offered

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food), the head tremor becomes more pronounced. Although foals with cerebellar abiotrophy can see normally, the menace response cannot be elicited in most cases. Affected foals walk with a swaying, lurching gait and may even wobble side to side or back and forth while standing still. Thoracic limbs may appear stiff, or there may be exaggerated flexion ("paddling") during the protraction phase. Gait abnormalities are most obvious when movement is initiated and during turns. Normal strength is preserved even in severely ataxic foals, and blindfolding does not exacerbate clinical signs. All clinical signs are exaggerated by stimulation of affected foals. Such hyperresponsiveness means foals with cerebellar abiotrophy are difficult to halter-train and lead; even normal handling often causes an affected foal to pull away or even flip over backward. Severely affected foals that fall often panic and struggle for some time before standing.

The diagnosis in an Arabian foal with compatible clinical signs is strongly supported by demonstration of homozygosity for the cerebellar abiotrophy allele. This test requires submission of 20 to 30 hairs with roots to the Veterinary Genetics Laboratory at the University of California, Davis (http://www.vgl.ucdavis.edu/services/horse.php). Hematologic and serum chemistry findings are usually normal. Some foals have high CSF protein concentration and creatine kinase activity, which are consistent with active neurodegeneration at the time of CSF collection.[11] MRI, and possibly CT, of affected foals reveals atrophy of the cerebellum in foals with cerebellar abiotrophy.[13]

Signs may be stable after onset or get worse for up to several months. It is rare, however, for foals with cerebellar abiotrophy to become persistently recumbent. Modest improvement has been noted in some mildly affected horses once they become adults.[9] Foals with cerebellar abiotrophy seldom succumb to direct effects of the condition, but most are euthanized because of severe clinical signs and poor prognosis.

Gross appearance of the affected brain is usually described as normal; however, the ratio of cerebellar to whole brain weight is usually less than 8%, whereas normal ratios are 8% or higher. The characteristic histologic lesion is thinning of the cerebellar cortex, affecting both granular and molecular layers.[2,9-12] There is marked reduction in the number of Purkinje cells in the granular layer, and some of those remaining show degenerative changes (swelling, shrinkage, and hyperchromasia of the perikaryon). There is relative sparing of

the Purkinje cells of the nodulus and flocculi.[11] Vacuolation may be noted in the olivary nuclei, and mineralized neuronal cell bodies may be found in the thalamus adjacent to the third ventricle.[10]

Cerebellar Hypoplasia Caused by Congenital Bovine Viral Diarrhea Virus Infection

Lisle W. George

A complete discussion of bovine viral diarrhea–mucosal disease (BVD-MD) can be found in Chapter 32. BVD virus infection of susceptible cows from 90 to 170 days of pregnancy results in abortion or stillbirth, hydranencephaly, or cerebellar hypoplasia in the fetus.[1,2] The BVD virus infects the developing germinal cells of the cerebellum and kills Purkinje cells in the granular layer, which results in necrosis and inflammation.[3] The microscopic lesions include necrosis of the external germinal cells, focal parenchymal hemorrhages, and folial edema.

The signs of cerebellar dysfunction are usually present at birth and include truncal ataxia, falling backward, opisthotonos, basewide stance, coarse intentional head tremors, hypermetria, hyperreflexia, and nystagmus or strabismus (Fig. 35.17).[4,5] If severely affected, the animal may be unable to stand or lie in sternal recumbency. Excitatory stimuli in these animals precipitate wild oscillations and side-to-side movements of the head, which can be mistaken for convulsions. The affected calves may have a deficient menace response and appear to be blind, especially with concomitant hydranencephaly or microphthalmia. The neurologic condition rarely improves after birth. Other fetal changes that may be induced by the BVD virus include thymic atrophy, retinal degeneration, corneal opacity, and failure to grow.[1,4] The diagnosis of cerebellar hypoplasia is based on identification of the specific clinical signs and the recognition of BVD antibodies in precolostral blood specimens. The virus may be cultured from the blood of some affected calves, but this appears to be dependent on whether an immune response to the virus has developed in the affected calf.



FIG. 35.17 Characteristic head position and basewide stance of a calf with cerebellar hypoplasia.

Storage Diseases and Inborn Errors in Metabolism

Robert J. MacKay

Inherited Myoclonus of Peruvian Paso Foals

Inherited myoclonus was described in two Peruvian Paso foals that demonstrated myoclonic contractions of the musculature in response to auditory or tactile stimuli.[1] These contractions were sustained with repeated stimulation. One foal could not stand without assistance, and the other had a “bunny-hopping” gait in the pelvic limbs. Analeptic drugs and tranquilizers were ineffective for controlling this condition. Inherited myoclonus was associated with a specific deficiency of spinal glycine receptors, which are responsible for synaptic inhibition in the CNS. Glycine is a major inhibitory transmitter providing reciprocal inhibition via type Ia afferent fibers and interneurons, as well as recurrent inhibition on motor neurons via Renshaw cells.

Congenital Encephalomyelopathy in Quarter Horses

Congenital encephalomyelopathy has been described in Quarter Horse foals.[2] The condition occurred in three foals born to two different mares and three unrelated stallions. Signs were present at birth and included recumbency and coarse tremors of the pelvic limbs. When the foals were assisted to stand, the hindquarters bounced off the ground. Thoracic limb function appeared normal; however, patellar reflexes were exaggerated. The affected foals were bright, alert, and responsive and had intact pain perception. They had no gross CNS lesions. Microscopic lesions included spongiform degeneration and axonal swelling of the spinocerebellar spinothalamic tracts within the medulla and spinal cord.

Lavender Foal Disease (Coat Color Dilution Lethal)

Lavender foal syndrome is an autosomal recessive disorder of Arabian foals that has been recognized for many years but reported only as recently as the mid-2000s.[3,4] Lavender foal syndrome is characterized by a dilute coat color, episodes of opisthotonos, hyperresponsiveness to touch, limb paddling, and rapid, uncontrolled eye movements. Affected foals are unable to assume sternal recumbency or stand. Despite the incapacitating neurologic signs, animals with lavender foal syndrome are able to vocalize and usually have a strong suckle response. The important feature of this condition that distinguishes it from neonatal encephalopathy and other causes of neonatal neurologic dysfunction is the dilute hair color. In a few cases, the color is the striking iridescent silver to pale lavender hue, as suggested by the name. *Coat color dilution lethal* may be a more appropriate name, however, because many affected foals exhibit other dilute coat colors, including pewter (pale slate gray) and pale chestnut (pink), and because complications from neurologic abnormalities invariably lead to death or necessitate euthanasia by approximately 72 hours. Abnormal findings at necropsy are nonspecific and minimal. A single base pair deletion in the *MYO5A* gene is responsible for lavender foal syndrome.[5,6] This deletion results in a frame shift and truncation of the protein at a premature stop codon 12 amino acids beyond the deletion. Loss of *MYO5A* disrupts melanosome trafficking and endoplasmic reticulum transport in cerebellar Purkinje cells, thus leading to the clinical signs of cerebellar seizures. Reported allelic frequencies are 5.2% among Egyptian Arabian horses in the United States,[6] 1.62% among European Arabian horses, and 0% among European Thoroughbred and Standardbred horses.

Testing for the *MYO5A* gene mutation is available commercially and is performed on plucked mane and tail hairs.

Overo Lethal White Syndrome

Overo lethal white syndrome is an inherited syndrome of American Paint foals from parents with the frame overo coat pattern.[7,8] Affected foals are totally or almost totally white and die within days from complications of intestinal aganglionosis.[7] Aganglionosis is characterized by a complete lack of submucosal and myenteric ganglia from the distal small to large intestine. Foals with vero lethal white syndrome are homozygous (designated OO) for a dinucleotide mutation, which causes an isoleucine-to-lysine substitution at codon 118 in the gene for endothelin receptor B.[9,10] Although heterozygotes for the lys118 mutation (nO) are mostly frame overos, the mutation is also found at lower frequency in other white patterned horses, including tobianos and solid pattern breeding stock.[11] The mutation is not usually found in breeds without white pattern variants, although overo lethal white syndrome was reported in the offspring of a registered Quarter Horse. Genetic testing is the only reliable method for detecting carriers. Plucked mane or tail hairs are submitted to commercial laboratories for testing.

■ Definition and Etiology

Robert J. MacKay • Lisle W. George

Locoism (Swainsonine Toxicity)

Chronic ingestion of various plants worldwide can result in an acquired neurovisceral storage disease. Plants incriminated so far include members of *Astragalus* and *Oxytropis* genera (locoweeds) in the western United States, Canada, Africa, Asia, and Australia; *Ipomoea carnea* in Mozambique; the darling pea in Australia (*Swainsona* spp.); and *Ipomoea* spp., *Turbina cordata,* and *Sida acuta* (also known as *S. carpinifolia*) in Brazil.[1-8] The disease was also diagnosed in a horse in Belgium; however, the causative plant was not identified.[9] Horses are most susceptible, but cattle, sheep, goats, and deer can also be affected.[10]

Conditions that promote locoweed poisoning are hot, dry weather and a scarcity of alternative forage. Horses may be more prone to graze on locoweed

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than are cattle, particularly when other green forage is scarce, and may increase their consumption over a single season.[10] Chronically exposed livestock become addicted to locoweeds and feed selectively on the plant over successive grazing seasons.[11]

Locoweeds represent only a small proportion of the species in the *Astragalus* or *Oxytropis* genera; many *Astragalus* spp. contain nitrotoxins or are selenium accumulators, and many other members of both genera are nontoxic. The indolizidine alkaloid *swainsonine* (also known as *locoine*) has been identified as the cause of locoism. Swainsonine acts by potent inhibition of mammalian α-D-mannosidase and of Golgi mannosidase II.[5,12] Swainsonine synthesis in *Astragalus* and *Oxytropis* plants is dependent on the fungal endophyte *Undifilum oxytropis* or closely related *Undifilum* spp.[13,14] Swainsonine, along with slaframine (slobber toxin), is also produced by *Rhizoctonia leguminicola*, a fungus that causes black patch disease of red clover.[15] Whether plants other than *Astragalus* and *Oxytropis* spp. are also colonized by swainsonine-producing fungi has not yet been clarified. Other toxins identified in locoweeds have included β-galactosidase and β-glucosidase; aminonitrile, a toxin that causes abortion and teratogenesis; and miserotoxin, a cause of respiratory disease.

Oxytropis and *Astragalus* plants are legumes that have herbaceous stems and alternate pinnately compound leaves.[16] The fruits are characteristic leguminous pods that contain kidney-shaped seeds with pods marked by characteristic longitudinal grooves. The plant is eaten because it is the first vegetation available in the spring. Neurologic signs do not usually develop in cattle until 3 weeks after the animals first begin grazing on the plant and may not occur until long after ingestion of the plant has stopped. In parallel with changes in the concentration of endophyte in locoweeds, toxicity may vary from year to year and even within one season.[17]

■ Clinical Signs

Experimentally and naturally poisoned horses show clinical signs by 2 to 3 weeks after continuous ingestion of locoweed.[2,10] The clinical signs include ataxia and obtundation alternating with periods of frenzied or manic activity.[7] Some affected horses demonstrate a high-stepping gait suggestive of cerebellar dysfunction.[7] At rest, there is intention tremor of the head; flaccidity of the nose and lips; repetitive, dystonic movements of the lips and tongue; and dysphagia.

The clinical signs worsen when affected horses are handled or transported. Signs in goats are similar, including ataxia, hypermetria, hyperesthesia, and muscle tremors.[1,2] When the chin is raised for 30 seconds and then suddenly released, even mildly affected goats fall into recumbency with additional signs of nystagmus, opisthotonos, tetanic spasms, and seizures. Sedation is usually ineffective for controlling the hyperexcitability of locoism. Horses that survive locoweed poisoning retain altered behavior and an irregular gait. Abortions, stillbirths, and neonatal deaths can occur in all species exposed to these toxic plants, regardless of whether the dams have clinical signs of neurologic disease.[2,3,18]

Neurologic signs in adult cattle include ataxia, limb hypermetria and weakness, obtundation, dull staring eyes, and loss of herding instinct. Heavy losses from abortions or malformed calves have also been described. The indolizidine alkaloids are secreted in the milk and may cause unthriftiness and weak suckling behavior in calves. Calves that have been exposed to the toxin in utero are weak and fail to thrive. Some may have flexural contractions of the limbs and lateral rotation of the carpus.[8,19,20] Ingestion of locoweed by certain cattle at high altitudes may result in the development of cor pulmonale.[21] Many cattle with mild signs of locoweed poisoning recover completely by 60 days after removal from the involved pastures. Poisoned sheep have a stargazing attitude and appear to be blind, nervous, and stiff. The normal flocking behavior is absent.[12] Affected sheep may salivate excessively. Testicular atrophy has been reported in affected rams.[22] The immunosuppressive actions of swainsonine predispose affected animals to pyogenic infections such as pneumonia, keratoconjunctivitis, and foot rot.

■ Clinical Pathology

Microscopic examination of stained blood smears may reveal cytoplasmic vacuolation of lymphocytes. These changes are found in the majority of lysosomal storage disorders but might be considered diagnostic of locoweed poisoning in animals with characteristic clinical signs and historical evidence of exposure. Serum activities of alkaline phosphatase and AST are high; elevated concentrations reflect liver dysfunction in association with prominent vacuolation of hepatocytes.[23] Definitive diagnosis can be established by assays of blood from affected animals for α-D-mannosidase activity and swainsonine concentration. The half-life of swainsonine in the serum is 16 to 20 hours.[24] This

means that an animal suspected of locoweed poisoning must have a blood sample taken within 2 days of eating locoweed for swainsonine to be detected.

■ Pathology

The microscopic abnormalities of the soft tissues of acutely poisoned animals are similar to those of the inherited lysosomal storage diseases of cattle, including cytoplasmic vacuolation of neurons, particularly cerebellar Purkinje cells, and cells in various other tissues.[2,7] Paraffin-embedded tissues can be examined with lectin photochemistry testing to characterize the stored material within the vacuoles.[25] Vacuolation of renal tubular epithelial cells may occur as early as 4 days after the start of daily feeding of 0.34 kg of locoweed to horses and may be present in animals exposed to toxic plants but clinically normal.[26] Pulmonary lesions associated with chronic ingestion of locoweed that may predispose to high-altitude disease (brisket disease) in cattle include alveolar emphysema, bronchiolar constriction and hypertrophy, and interlobular edema and fibrosis. Pyloric or gastric ulcers have been reported in affected cattle.[8,26] Placental edema, fetal ascites, and hydrops allantois have been described in exposed pregnant cattle.

■ Treatment

There is no known effective long-term therapy for locoweed poisoning. Animals remain affected for a prolonged period or even permanently after removal of the plants. One author recommends tranylcypromine (60 mg PO), a monoamine oxidase inhibitor, and protryptyline (60 mg PO) or reserpine (1.25 mg PO per animal once daily) for treatment of chronically affected animals.[27] The efficacy of these treatments is unknown. Addition of a mineral supplement and a natural clay (clinoptilolite) to the diet of cattle ingesting locoweed did not prevent toxicity.[28]

■ Prevention

Nonaddicted livestock normally do not eat locoweed if other forage is available. The condition may be prevented by supplemental feeding during the early spring and late summer. One report has described conditioning aversion to locoweed in horses with lithium chloride administered simultaneously with grazing on *Oxytropis sericea*.[29] Whether this is a practical management tool in large

numbers of animals has yet to be determined.

Staggers Syndromes (Grass Staggers)

Robert J. MacKay

Forage-associated staggers syndromes are common and have been associated with protective fungal secondary metabolites, bacterial antibiotic corynetoxins, or neurotoxic chemicals produced by the forage itself. Some associated plant or fungal toxins also induce agalactia, fever, low productivity, and other physiologic effects because of a prolactin-like effect.

Tremorgenic Mycotoxicoses

At least 20 tremorgenic mycotoxins are known; they are produced by several different fungi, have the same biologically active moiety, and give rise to similar clinical manifestations.[1,2] Indole-diterpenoid tremorgens are secondary fungal metabolites that act by blocking potassium outflow from cells via inhibition of cell membrane large-conductance calcium-activated potassium channels.[3,4] The most important classes of tremorgens are the *lolitrems* (perennial ryegrass staggers) and *paspalitrems* (*Paspalum* staggers, Bermudagrass staggers). Other indole-diterpene tremorgens that may be elaborated on moldy feeds by saprophytic fungi and occasionally cause staggers in livestock include penitrems, janthitrems, aflatrem, and verruculogen. The major tremorgenic mycotoxicoses are similar or identical clinically; therefore clinical signs are discussed in detail only in the Perennial Ryegrass Staggers section.

Perennial Ryegrass Staggers.

Perennial ryegrass staggers (PRS) is a syndrome of tremors and ataxia that result from ingestion of endophyte-infected perennial ryegrass *(Lolium perenne)* by horses, cattle, sheep, deer, goats, and alpacas.[5] PRS is a common condition of livestock in New Zealand and Australia and occasional outbreaks occur in Northern Europe, the northwestern United States, South America, and Europe.[6-9] The case attack rate may reach 100%, but the mortality rate is generally low and attributable only to accidents. Substantial economic losses may be incurred, however, when production animals with PRS cannot be safely moved. For example, herd- or flock-wide outbreaks have prevented milking of dairy cows and mustering of sheep for necessary procedures such as anthelmintic treatment,

shearing, or breeding.[5] Conditions that increase toxicity of perennial ryegrass pastures include high proportions of endophyte-infected plants; late seasonal growth; hot, dry summer and fall after wet spring; ryegrass domination of pastures; ambient temperatures higher than 23° C; ryegrass that is allowed to flower before consumption; and close grazing.[9] Endophytes are most abundant in the leaf sheath and florets and lowest in the blades. Disease outbreaks occurs from June to September in the northern hemisphere and from December to June in the southern hemisphere.

PRS typically appears acutely 5 to 10 days after introduction of livestock onto endophyte-rich pastures; onsets as early as 48 hours and as late as 2 weeks after exposure have been recorded. The source of tremorgenic toxins is the symbiotic endophytic fungus *Neotyphodium lolii*.[5] The fungal infection confers resistance to predation of grass by insects, including the Argentine stem weevil, and so there is selective pressure for expansion of toxigenic cultivars. *N. lolii* produces three classes of alkaloids with approximately parallel profiles of production: *tremorgens, ergopeptides*, and *peramine*. The most abundant and active indole-diterpene tremorgen produced by endophyte-infected plants is lolitrem B.[10] Lolitrem B concentrations of more than approximately 2 mg/kg (ppm) of dry matter in forage reliably cause staggers in sheep, cattle, and horses.[11] The concentration of lolitrem B in pasture increases from spring through fall. Plant infection rates below 25% (typical in northern hemisphere pastures) are associated with sporadic cases, whereas plots with 90% infection rates are common in Australasian pastures and are associated with outbreaks of PRS.

Ergovaline and other ergopeptide alkaloids (also see Chapter 54) produced by endophytes cause signs comparable with those of heat stress syndrome, a condition in cattle in the southwestern United States that graze on tall fescue infected with the endophyte *Neotyphodium coenophialum*.[9] The resulting clinical signs are diarrhea, hyperthermia, high heart and respiratory rates, poor weight gain, and reduced milk production. The high mortality rates (up to 30% of affected sheep) reported during PRS outbreaks in Australia in 1986, 1993, and 2002 have been attributed to heightened susceptibility to heat stress caused by ergopeptides in endophyte-infected perennial ryegrass.[9] Horses experimentally fed endophyte-infected *L. perenne* seeds during cool conditions in New Zealand developed limb edema and exudative heel lesions, signs that reflected the vasoconstrictive “fescue foot”–like effects of ingested ergopeptides.[11] Peramine, a pyrrolopyrazine alkaloid, is a potent insect-feeding deterrent with substantial

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protective effects against the destructive Argentine stem weevil. Strains of endophyte-free perennial ryegrass have been propagated but are difficult to maintain without extensive insecticide use. Cultivars of *L. perenne* that are infected with strains of *N. lolii* have been produced that contain peramine but not tremorgen or ergopeptide. These cultivars (e.g., AR1, AR37) therefore have multiple advantages over traditional endophyte-infected strains, in that they do not cause staggers or ergopeptide-associated production loss and substantially protect against stem weevil predation.[12] AR1 is not as broadly insect resistant as is wild-type *N. lolii,* however, and root aphid infestation is notably unaffected.

Clinical signs first occur approximately 5 to 10 days after livestock are introduced to infected pasture (or after they eat infected ryegrass seeds or straw[7,11]) and become progressively more severe until the animals are removed from the endophyte source. The carefully observed signs reported for experimentally induced PRS in horses are typical of mild to moderate signs shown by animals of all affected species during natural PRS outbreaks.[11] Initially, affected animals exhibited fine, then coarse, fasciculations and tremors of skeletal muscles, particularly those of the shoulders, chest, and thoracic limbs. Tremors were particularly apparent during eating, after exercise, or in a thoracic limb that was offloaded by the horse and rested. Fine tremors of the eyeballs were evident during ophthalmoscopic examinations but otherwise difficult to appreciate.[11] Other early clinical signs included a basewide gait, truncal sway both at rest and during walking, and rapid, stumbling, corrective foot placements. Blindfolding or elevation of the chin exaggerated these signs, a finding consistent with bilateral vestibular dysfunction. Affected horses were hyperresponsive to the withers slap used to test the laryngeal adductor (“slap”) reflex. With progression of PRS, signs of general proprioceptive ataxia—including delayed limb protraction, interference between pairs of limbs, and circumduction of pelvic limbs on the outside of circles—became apparent. The gait also became jerky and more interrupted, but hypermetria, a characteristic cerebellar sign, was not observed in these mildly and moderately affected horses. The authors speculated that signs reported in severely affected livestock—namely, limb stiffness and unpredictable, inconsistent limb movements, hypermetria, head tremor, falling, and generalized tetanic convulsions[6,13]—are consistent with cerebellar involvement.[11] The authors therefore proposed a time- and dose-related progression through the three “qualities” of ataxia (vestibular, general proprioceptive, then cerebellar) during the course of PRS in an

individual animal.[11] Of note was that normal muscle strength was preserved in affected animals, and they remained bright and alert.

In all cases, signs are exacerbated by handling. Attempts to force affected animals through gates or onto trailers may precipitate recumbency. While down, the animals exhibit rigid extension of the legs with occasional flailing, opisthotonos, and tonic-clonic convulsions. Frothy exudate from the mouth has also been described. After approximately 10 to 20 minutes, the animal recovers if left undisturbed, stands, and walks back to the herd or flock.

Recovery occurs over days to weeks; longer recoveries are typical of severely affected animals. Most animals are normal within a week of removal from toxic pasture. Treatment is not usually necessary, but it is important not to disturb or frighten animals with tremors and to handle them as infrequently and carefully as possible. If practicable, they should be kept on level ground in an area free of potential hazards, especially water hazards. If handling is necessary, hyperresponsiveness can be controlled by sedation. Tremors can be suppressed temporarily by diazepam (0.02 to 0.1 mg/kg IV for horses or 0.1 to 0.2 mg/kg IV for small ruminants).

Paspalum Staggers.

Claviceps paspali ergots parasitize *Paspalum* spp. grasses and produce paspalitrems, indole-diterpene tremorgens that cause staggers syndromes in livestock similar or identical to perennial ryegrass staggers described earlier. Susceptible grasses include dallisgrass *(Paspalum dilitatum),* bahiagrass *(Paspalum notatum),* water couchgrass *(Paspalum distichum),* and knotgrass *(Paspalum paspaloides).*[14-16] *Paspalum* staggers has been recognized in the United States, South Africa, Great Britain, Australia, and New Zealand.[14,17-19] Natural outbreaks occur most commonly in cattle, but *Paspalum* staggers has been reported in three foals and two adult horses grazing on dallisgrass in Australia,[20] and sporadic cases are observed regularly by the author in horses on bahiagrass pastures in Florida.

C. paspali first attacks the pistil of the grass flower and replaces the ovary with a sclerotium (ergot). The fungus secretes a sticky fluid, the “honeydew,” which contains a large number of spores but little toxin. The fluid hardens into a mature sclerotium containing a high concentration of tremorgenic metabolites. Toxic stands of dallisgrass or other *Paspalum* grasses can be recognized by the presence of numerous small, reddish brown or black sclerotia measuring 3 to 5

mm in diameter on the seed head of the plant. The most abundant indole-diterpene metabolite in sclerotia is paspalitrem B, but paspalitrems A and C, paspaline, and paxilline are also produced.[15,21] *C. paspali* sclerotia also produce ergot alkaloids, albeit at low concentrations (on the order of 10 µg/kg of dry weight, in comparison with 150 mg/kg for paspalitrem B in one report[22]). Particular animals apparently develop a craving for the infested seed heads and graze them selectively. Toxin production is greatest when there is a wet period after formation of the seed heads. The toxin remains active in cured hay. Mowing the toxic pastures and removing or burning the infested seed heads is effective for preventing further exposure to the tremorgen.

Clinical diagnosis is made by observation of clinical signs, visible detection of the toxic agent in the feed, or detection of indole-diterpenes by thin-layer chromatography. Animals recover spontaneously within days to several weeks after being removed from the pasture.

Bermudagrass Staggers.

Bermudagrass *(Cynodon dactylon)* occasionally becomes toxic for livestock.[19] Cattle are considered most susceptible, followed by sheep, goats, and horses. As is the case for *Paspalum* staggers, bermudagrass staggers results from ingestion of paspalitrems in grass parasitized by fungal ergots, in this case *Claviceps cynodontis*. *C. cynodontis* is closely related to *C. paspali*, and the chemical profiles of indole-diterpenoid and ergot alkaloids produced by the sclerotia of these two fungi are similar. The clinical and epidemiologic aspects of bermudagrass staggers and *Paspalum* staggers are likewise similar.[22]

Animals may develop clinical signs as early as 36 hours after consuming toxic forage. Experimentally poisoned goats have developed clinical signs 8 days after being fed 772 g/head/day of toxic hay.[23] The toxin survives drying, and hay that is cut from offending pastures may remain toxic for as long as 9 years.[24] Pastures that are toxic remain so for successive seasons unless the vegetation is burned off and the ground is tilled and reseeded. The clinical signs occur suddenly, usually simultaneously, in several animals in the herd. In some cases, most of the animals on a single pasture may be affected, whereas animals on an adjacent pasture remain normal. The mortality rate is low, and deaths usually result from self-inflicted trauma. Affected animals recover 2 days to 2 months after removal from the affected pasture or hay. Management is as for PRS.

Tremorgenic Mycotoxicoses Associated With Saprophytic Fungi

Most tremorgenic mycotoxins are synthesized by common saprophytic fungi of the genera *Penicillium* and *Aspergillus* that elaborate mycotoxins onto improperly harvested or stored livestock feeds. Some *Penicillium* spp. can also act as opportunistic plant pathogens, most notably as a cause of ear rot in corn. Ingestion of moldy cornstalks is probably the most common source of fungus-related tremors in livestock. The fungi proliferate in the corn but do not produce tremorgens until the stalks touch the ground. After production at or near the soil surface, the toxins translocate in plants through root absorption.[25] Cases associated with *Aspergillus* molds (usually *Aspergillus clavatus*) have occurred worldwide, linked to feeding on sprouted grains and the by-products of beer production, both of which provide an environment for growth of the mold.[26,27] Clinical signs are indistinguishable from those of *Paspalum*, perennial ryegrass, and bermudagrass staggers.[16,25,28,29] Indole-diterpenoid tremorgens produced by *Penicillium* and *Aspergillus* spp. can be classified into four major groups: the aflatrem-paxilline group, the verruculogen-fumitremorgen group, the territrem group, and the tryptoquivaline group. Of these, the most important fungal tremorgens are aflatrem, penitrem A, fumitremorgen B, and verruculogen. In some cases, additional non–indole-diterpenoid mycotoxins elaborated by these fungi cause a wider spectrum of clinical signs. For example, *A. clavatus* caused a highly fatal mycotoxicosis of cattle in South Africa that was associated with widespread degeneration and necrosis of skeletal muscle and CNS motor neurons.[15]

Diagnosis is by demonstration of indole-diterpenoid tremorgens by thin-layer chromatography (sometimes in combination with a mouse tremorgen assay). Mycelial elements of *Penicillium* and *Aspergillus* molds may survive degradative conditions in the GI tract and can be identified and cultured from the feces of affected animals.

Corynetoxicoses (Annual Ryegrass Toxicity, Flood-Plain Staggers, Blown Grass Staggers)

Corynetoxicoses are severe, often fatal neurologic disorders of livestock in Australia and South Africa.[30] A related syndrome occurred in Oregon from the 1940s through the 1960s but apparently has not recurred since.[31,32] Corynetoxins

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are produced by plants of several genera—including *Lolium rigidum* (annual ryegrass), *Polypogon monspeliensis* (annual beard grass), and *Lachnagrostis filiformis* (blown grass)—that are colonized by a nematode (*Anguina* sp.) and a bacterium *(Rathayibacter toxicus).*[33-35] Affected sheep and cattle with the same clinical syndrome in Oregon had been fed a fescue *(Festuca nigrescens)* infected with a grass seed nematode and a *Rathayibacter*-like organism.[31,32] Corynetoxin-producing *R. toxicus* is transported into host plants by nematode L2 larvae and ingested by sheep, cattle, and occasionally horses.[30] The colonized plant forms a hollow gall in response to larval invasion of the seed. Bacteria are thus carried into the galls, where they proliferate into a distinctive yellow to orange mass.[30] *R. toxicus* organisms produce a series of closely related corynetoxins that are glycolipids in the tunicaminyluracil class of antibiotics. Corynetoxins potently inhibit lipid-linked *N*-glycosylation of glycoprotein, and their toxicity in animals probably results from the depletion of essential *N*-glycosylated proteins. It takes up to 15 years after introduction of the nematode-bacterial complex to a pasture before clinically significant amounts of toxin are produced.[36] A method of evaluating toxic pastures has been developed; it is based both on enumeration of contaminated seedheads and on ELISA to quantify *R. toxicus.*[37]

Although the serum half-life of corynetoxins in livestock is only approximately 4 hours, repeated exposure leads to an accumulation of the toxin, and up to 12 weeks of continued ingestion may be necessary for the onset of clinical disease.[30] Also, the concentration of the toxin increases in the seedheads during the summer and is greatest as the plant dries and the seeds ripen. Outbreaks associated with the feeding of hay made from toxic pasture may occur at any time. Stock losses are highest in sheep, although cattle deaths can be substantial. Outbreaks in horses occur occasionally and generally involve only a few horses.[38,39] Clinical signs appear to reflect the cerebellar and thalamic lesions that are evident histologically.[39] All ages are affected, and morbidity and mortality rates are usually high. When an affected flock is driven, or when cattle are rounded up or otherwise stressed, some animals collapse in sternal or lateral recumbency. They often have muscle tremors, opisthotonos, head nodding, tetanic and clonic convulsions, limb extension, hypermetria, odontoprisis, nystagmus, and ptyalism. Animals may regain their footing after several minutes and stagger away with a stiff-legged, jumping, or swaying gait. These animals often wander aimlessly, exhibiting stupor and ataxia. In mildly and moderately

affected animals, clinical signs usually resolve within a week of removal from affected pasture; however, relapses may occur in animals that appear to have recovered, and it may take several months for severely affected animals to recover. Treatment with magnesium sulfate solution (50 to 100 mg/kg, IV in horses, SC in ruminants, repeated as needed) is reportedly effective in some cases.[38,40] The most practical strategy for controlling annual ryegrass toxicity is to break the nematode's life cycle by killing the ryegrass for two or three growing seasons. Otherwise, pastures remain perpetually toxic. Integrated control measures that have been recommended for prevention of annual ryegrass toxicity include applying herbicides in the spring, seeding the pastures with legumes, burning the infected pasture grasses during early autumn, and applying ryegrass-selective herbicides in the summer months, combined with heavy winter grazing.

Pathologic changes associated with corynetoxin poisoning include widespread petechial hemorrhages and jaundice and friability of the liver. Histologically, CNS changes are surprisingly mild and nonspecific. Most lesions are cerebellar with proteinaceous fluid around vessels, especially in the meninges. There is diffuse vacuolation of hepatocytes and bile duct proliferation.

Kikuyu Grass Poisoning

A multiorgan disease characterized by peracute onset obtundation, ataxia, drooling of saliva, sham drinking, ruminal distention, and colic occurs in cattle and, to a much lesser extent, sheep and goats of New Zealand and Australia that are grazing on kikuyu grass *(Pennisetum clandestinum).*[41] According to a review of nine reports involving 2719 cattle at risk, the morbidity rate was 23% and the case fatality rate was 70%.[41] The cause and pathogenesis are poorly understood.

Canarygrass Staggers (*Phalaris* Staggers)

Phalaris poisoning has been reported in Australia, New Zealand, South Africa, Norway, Argentina, and the United States, in association with the ingestion of *Phalaris* spp. grasses by sheep and cattle, most notably *Phalaris aquatica* (bulbous canarygrass or hardinggrass) and *Phalaris arundinacea* (reed canarygrass).[42] These outbreaks have been characterized by either sudden death due to peracute brain dysfunction (termed *polioencephalomalacia-like sudden death*) or myocardial dysfunction (termed *cardiac sudden death*).[43,44] Sheep are considered to be the most susceptible species, but cattle are also affected.[45] Only

the cardiac sudden death syndrome has been reported in horses.[46,47] In the United States, outbreaks of canarygrass staggers have been reported in sheep and feedlot lambs in California *(P. aquatica),*[48,49] as well as sheep and cows in Louisiana *(Phalaris caroliniana)*[50] and cows in West Virginia *(P. arundinacea).*[45]

It has been suggested that phenylethylamines or derivatives of tyramine are involved in sudden death syndromes.[42,51] Staggers occurs in either an acute and reversible form or a chronic, irreversible, and typically lethal form. The latter, more common presentation usually occurs as outbreaks. Delayed or chronic *Phalaris* staggers is associated with tryptamine alkaloids produced by the plant.[42,51] These alkaloids structurally resemble serotonin and act as serotonergic receptor agonists, and accumulation within serotonergic tracts of the CNS eventually results in staggers signs. Rapid growth of canarygrass favors the formation and accumulation of toxin. Other factors that enhance the toxicity of canarygrass pasture include fog, humidity, or rain, followed by sunny, warm weather or sunshine on nitrogen-fertilized pastures.[52] Grazing animals are not usually affected until *Phalaris* spp. grasses constitute more than 50% of the diet.[53] The concentration of tryptamine alkaloids may be reduced by curing the forage as hay. In contrast, ensiling canarygrass does not reduce the amount of toxin.[54]

Staggers occurs after exposures lasting from 5 days to 33 weeks. Signs may be delayed for as long as 4 months after removal from the toxic grass.[50] Characteristic early clinical signs in sheep are constant anxious observation of handlers and continuous twitching ear movements. Signs progress to include hyperexcitability, exaggerated responses to auditory or tactile stimuli, fine muscular fasciculations (particularly of masseter muscles), licking of the lips, wrinkling of the facial muscles, repetitive chewing, inability to swallow, flaring of the nostrils, ptyalism, nystagmus, intention tremor of the head, ear and tail twitching, basewide stance, reduced menace response, and deficient pupillary reflexes.[55] The gait of affected sheep is described as stiff-legged, with both hindlimbs moving in unison at gaits above the trot (“bunny-hopping”). Affected sheep and cattle may buckle at the knees and assume sternal recumbency with the hindquarters elevated.[45,53] They then fall into lateral recumbency and flail wildly while attempting to stand. Poisoned cattle also become uncoordinated and may have distinctive stabbing movements of the tongue and inability to prehend

forage.[56] They salivate profusely and drop feed from the mouth. Affected animals eventually die from starvation. There may be increased protein concentration (40 to 100 mg/dL) and nucleated cell count (up to 50 mononuclear cells/µL) in CSF of affected animals.[48] Animals may survive the initial signs but have neurologic signs that wax and wane for up to 10 months. For confirmation of a diagnosis, tryptamine alkaloids in suspect grasses can be quantified by ELISA.[57] Concentrations greater than 30 to 50 mg/100 g dry weight of forage are considered toxic for sheep.[52,55]

The pathologic lesions in the CNS of affected animals are characteristic and include focal, demarcated, blue-green or slate-gray discoloration in the brainstem and corticomedullary junction of the kidney; intracytoplasmic accumulations of yellow-brown pigment in the dorsal root ganglia, brainstem nuclei, and ventral horns of the gray matter of the spinal cord; neuronal loss; focal gliosis; and swelling of axonal sheaths in the ventromedial aspect of the spinal cord.[45,48,53] The pigment is thought to originate from deamination of the toxic alkylamines, but their presence is not strongly correlated with the development of neurologic deficits.[55]

Administration of cobalt to animals on toxic grass pastures is protective. In the presence of cobalt, rumen microflora inactivate toxic alkaloids. Weekly administration of 28 mg of cobalt to each animal was required experimentally to prevent clinical signs in exposed sheep.[58,59] Additional recommendations include removal of affected animals from the offending pasture, sedation with a phenothiazine tranquilizer, and administration of sodium pentobarbital or diazepam to convulsive animals. *Phalaris* plants may also contain potentially toxic concentrations of nitrate or cyanide. In any outbreak of suspected *Phalaris* toxicosis with sudden death, cyanide and nitrate poisonings should also be considered.[43]

Differential Diagnoses for Staggers Syndromes

Grass staggers is easily recognized by clinical signs. The specific plant involved must be identified through examination of the pasture forage. Tremorgenic diseases of adult cattle are common throughout most of the world. In addition to the syndromes discussed earlier, plants that may cause staggers syndromes include toxic storage syndromes, such as locoism induced by the swainsonine-containing plants *Swainsona luteola, Swainsona galegifolia, Astragalus* spp., and *Sida* spp. and the tremor syndrome induced by *Solanum dimidiatum,*

Solanum fastigiatum, and *Solanum viarum*. Hypomagnesemia causes grass staggers and has been reported to cause cerebellar degeneration under some circumstances. The genetic storage diseases α- and β-mannosidosis, generalized glycogenosis, globoid cell leukodystrophy, and neuronal lipodystrophy may also be important in the differential diagnoses for ataxic animals with tremor and cerebellar signs.

Multiple Congenital Central Nervous System Defects

Multiple congenital defects that are suspected or documented to have a heritable (genetic) basis have been described in large animals. Many, but not all, of these disorders involve signs referable to cerebellar dysfunction; others may have signs referable to spinal cord dysfunction. These defects along with others are listed in Table 35.6.

TABLE 35.6

Congenital Diseases of Large Animals With CNS Signs and Known Mode of Inheritance

Diseases With Predominant Intracranial Signs	Species and Breeds Affected	Clinical Signs/Ancillary Tests	Age at Onset	Mode of Inheritance	Referer
Ceroid lipofuscinosis	Ovine: South Hampshire, Swedish Landrace, Rambouillet	Progressive ataxia, blindness, depression, coma	Variable	Autosomal recessive	1-10
	Caprine: Nubian				
	Cattle: Devon				
	Horses: breeds not described				
Citrullinemia	Cattle: Holstein	Progressive depression, bellowing, abnormal tongue and facial movements, convulsions, death	Newborns	Autosomal recessive	11-19
		Increased blood ammonia and citrulline concentrations			
Exophthalmos and strabismus	Cattle: Jersey, Holstein,	Protrusion and crossing of the	>6 mo	Unknown	20, 21

	Brown Swiss, Shorthorn	eyes			
Cerebellar abiotrophy	Cattle: Holstein, Angus, Limousin	Intention tremors, hypermetria, basewide stance; may or may not progress	Variable	Suspected autosomal recessive	22-26
Bovine familial convulsions and ataxia	Cattle: Angus, Charolais, Polled Hereford, Angus Cross	Stillbirth/abortion with occasional dorsiflexion of the spine Intermittent cerebellar signs and convulsions	Variable, may improve with age	Autosomal dominant with incomplete penetrance	27-33
Cerebellar abiotrophy/hypoplasia	Horses: Arabians, Arabian cross	Head tremor, ataxia, hypermetria	>2 mo	Autosomal recessive	34-39
Familial ataxia	Cattle: Hereford	Ataxia, abnormal head posture, pupillary dilatation	Newborns	Unknown	40
Micrognathia/cerebellar hypoplasia	Cattle: Angus	Stillbirth, brachygnathia, cerebellar hypoplasia	Stillborn	Suspected autosomal recessive	41
Alpha mannosidosis	Cattle: Angus, Murray Grey, Simmental, Galloway, Holstein	Stunted growth, ataxia, head tremor, hypermetria	1 wk to 15 mo	Autosomal recessive	42-49
Beta mannosidosis	Cattle: Salers Goats: Anglo-Nubian	Recumbency, deafness, narrow palpebral fissures, intentional head tremor, rotatory head movements, ocular defects, joint abnormalities, domed skull	Newborns	Autosomal recessive	50-71
Generalized glycogenolysis (beta-galactosidase deficiency, GM1 gangliosidosis)	Sheep: multiple breeds Cattle: Holsteins	Lethargy, anorexia; head carried low and extended; blind, collapse when head moved	>1 mo	Suspected autosomal recessive	72-83
Bovine generalized glycogenosis (type II glycogenosis, Pompe disease)	Cattle: Shorthorn, Brahman	Weakness, tremors, ataxia, right-sided heart failure	2-3 mo	Autosomal recessive	84-93
Globoid cell leukodystrophy (Krabbe disease)	Sheep: Polled Dorset	Depression, head tremor, ataxia, hyperesthesia	>4 mo	Unknown	94, 95
Neuronal lipodystrophy	Cattle:	Depression,	>10 mo	Unknown	96-98

	Angus, Beefmaster Sheep: Breeds not described	blindness, circling, seizures, coma			
Shaker calf syndrome	Cattle: Horned Hereford	Recumbency, hypermetria, hypertonia, hyperesthesia, muscle tremors	Newborns	Unknown	99
Maple syrup urine disease	Cattle: Hereford, Polled Shorthorn	Viscous, dark, malodorous urine; fever, depression, opisthotonos, myoclonus, convulsions; spongiform changes in brain	Newborns	Autosomal recessive	100-11(
Hereditary neuraxial edema	Cattle: Polled and Horned Herefords, Hereford × Friesian	Inability to rise; hyperesthesia, myoclonus, extensor rigidity, and apnea/dyspnea when stimulated	Newborns (may be stillborn)	Suspected autosomal recessive	117-12!
Epilepsy	Cattle, horses	See text			
Narcolepsy/cataplexy	Horses, cattle, sheep	See text			
Diseases With Predominant Spinal/Motor Nerve/Muscle Signs					
Inherited myoclonus	Horses: Peruvian Paso	Myoclonus in response to stimuli, bunny-hopping gait; may not be able to stand without assistance	Newborns	Unknown; deficiency of receptors for the inhibitory neurotransmitter GABA	126
Congenital encephalomyelopathy	Horses: Quarter Horse	Inability to stand; when assisted to stand, hindlimb tremors cause the hindlimbs to bounce off the ground; increased patellar reflexes	Present at birth (i.e., newborn)	Unknown	127
Systemic neuraxonal dystrophy	Sheep: Suffolk	Progressive hindlimb ataxia leading to recumbency	>1 mo	Suspected autosomal recessive	128-12!
Weaver syndrome (bovine progressive degenerative myeloencephalopathy)	Cattle: Brown Swiss, Angler	Progressive paraparesis, hindlimb ataxia with proprioceptive deficits, muscle	>5 mo	Autosomal recessive	130-14(

		tremors, recumbency			
Progressive spinal myelinopathy	Cattle: Murray Grey	Inability to stand; progressive hindlimb hypertonia and proprioceptive deficits	Newborns	Autosomal recessive	147-14
Bovine spinal muscular atrophy	Cattle: Brown Swiss, Red Swiss, Braunvieh, Holstein	Progressive muscle atrophy leading to recumbency	>2 wk	Autosomal recessive	149-15
Spinal dysmyelination	Cattle: Braunvieh, Braunvieh Cross	Inability to stand, generalized tremors, muscle atrophy	Newborns	Autosomal recessive	158-16
Neuropathy/myopathy/glomerulopathy	Cattle: Gelbvieh	Progressive hindlimb ataxia and paraparesis, muscle atrophy, reduced anal tone; proteinuria	Few weeks to 1 yr	Unknown	161-16
Progressive ataxia	Cattle: Charolais, Charolais Cross	Progressive paraparesis and hindlimb ataxia, proprioceptive deficits; muscle/tail tremors on rising	>6 mo	Suspected autosomal recessive	163-17
Spastic paresis (Elso heel)	Cattle: multiple breeds	Intermittent extensor spasticity and hypertonia of one or both hindlimbs; hyperextension of hock during weight bearing	>3 wk	Unknown	173-19
Inherited periodic spasticity (crampy syndrome, barn cramps, Krampfigkeit)	Cattle: dairy breeds	Intermittent muscular spasms of hip and upper hindlimb muscles, simultaneous kyphosis	>3 yr	Suspected autosomal dominant with incomplete penetrance	196-20
Hereditary lethal spasms (Doddler syndrome)	Cattle: Jersey	Inability to stand, head and neck spasms when stimulated, convulsions, death	Newborns	Suspected autosomal recessive	201-20
Congenital abnormalities of the vertebrae and/or spinal cord	Multiple species	See text			

CNS, Central nervous system; *GABA,* gamma-aminobutyric acid.

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Diseases Manifesting Principally With Spinal Cord or Peripheral Nerve Signs

Equine Herpesvirus Myeloencephalopathy

Robert J. MacKay

Equine herpesvirus 1 (EHV-1) is a member of the Alphaherpesvirinae subfamily of Herpesviridae. Along with another alphaherpesvirus, EHV-4, it is a common cause of upper respiratory disease in horses (see Chapter 31); of more importance is that because of a tendency to cause cell-associated viremia and vasculitis, EHV-1 infection is associated with late-term abortion, death of neonatal foals, and spinal cord disease. Outbreaks of the last of these syndromes, known as *equine herpesvirus myeloencephalopathy* (EHM), have become more frequent and severe since the 1990s. The U.S. Department of Agriculture has suggested that EHM is an emerging disease on the basis of the following criterion: "A disease [that] changes in severity [or] type of animal that can be infected, or [reflects] other changes in pathogen behavior."[1]

■ Clinical Signs

Acute onset of ataxia and tetraparesis of variable severity most often characterizes the neurologic form of EHV-1.[2,3] Signs usually appear between 6 and 10 days after infection. The severity of clinical signs can range from subtle pelvic limb ataxia and weakness to complete recumbency without limb or head movement. Nonneurologic signs, including nasal and ocular discharge, limb edema, colic, ocular lesions, and anorexia, may also be observed.[2-7] Horses may be febrile at presentation, but most are normothermic. Fever, often biphasic in profile, is the most consistent premonitory sign of neurologic disease, although not all febrile horses develop myeloencephalopathy. Coughing and nasal discharge or abortion sometimes accompany the neurologic signs or may have occurred during the preceding 2 weeks.[5,8,9]

The neurologic signs reflect injury to the white and gray matter of the spinal cord and include limb and truncal ataxia and paresis, bladder distention, urinary incontinence, weakness of the tail and anus, and reduced perineal sensation. Affected horses may exhibit either penile paresis or persistent erection (priapism) during the first several days of clinical signs. Pelvic limbs are more

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severely affected than thoracic limbs, and signs are usually symmetric. In mild and moderately severe EHM, bladder distention is often present, with spastic detrusor tone and without urethral relaxation (dyssynergia). Bladder atony and incontinence also occur, particularly in recumbent horses, and the associated dribbling of urine leads to secondary perineal scalding. Bladder rupture has occurred in such horses. Anal sphincter and caudal rectal tone may also be reduced, with consequent obstipation and gaping of the anus.

Signs of brain dysfunction such as seizures, blindness, and cranial nerve dysfunction occur in some severe cases of EHM.[10,11] Ocular lesions such as mydriasis, hypopyon, uveitis, and optic neuritis may also be present. The occurrence of multifocal chorioretinopathy, visible several weeks after onset of neurologic signs as foci of depigmentation, appears to be a particularly sensitive indicator of previous EHV-1 viremia.[12]

The clinical signs typically stabilize within 48 hours, and in most instances recumbency, if it occurs, begins during this period. Some horses continue to deteriorate and eventually die or are euthanized. In survivors, improvement begins within the first 5 to 7 days and may continue for weeks or even months. Many horses make a full clinical recovery; however, an unknown proportion still have residual signs of limb weakness or ataxia. A horse that does not become recumbent during the first 2 days has a much better prognosis for survival.

■ Diagnosis

EHM can be diagnosed tentatively on the basis of characteristic neurologic signs, history, and supporting findings on physical examination. A CSF analysis that shows xanthochromic fluid with high protein concentration and normal or slightly high nucleated cell count (albuminocytologic dissociation) is typical and almost pathognomonic for EHM,[10,13] although in occasional cases, protein concentration is normal, mononuclear pleocytosis is present, or both occur.

Conventional, nested, or quantitative PCR amplification of EHV-1–specific gene sequences (usually glycoprotein B) in nasal swabs and EDTA-anticoagulated blood is the diagnostic technique of choice for horses with suspected EHM.[13] Both nasal swab and blood samples should be submitted at the acute stage of disease; nasal swab samples alone are sufficient to monitor for release from quarantine in some jurisdictions. Nasal swabs are more likely to collect virus than are nasopharyngeal swabs.[14] Swabs for this purpose should be approximately 6 inches long with a synthetic shaft. After collection, the swab

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should be placed in viral transport medium and sent to the diagnostic laboratory. If transport media are not available, the swab can be broken into a sterile tube and transported. Positive samples can be analyzed separately or simultaneously for a single-nucleotide variant in the viral DNA polymerase gene, DNA_{pol} D_{572}, which defines the best known and most important neuropathogenic strain of EHV-1. Real-time PCR provides quantification of viral DNA load and allows additional interpretation of the relevance of positive results.[13] These molecular diagnostic tests confirm active EHV-1 infection (and viremia when the blood test result is positive) but do not confirm the diagnosis of EHM specifically.

Additional aliquots of nasal swab and anticoagulated blood samples should also be submitted for traditional virus isolation in tissue culture. Virus isolation is important to allow full characterization of outbreak viruses, including susceptibility to candidate antiviral drugs.[15]

A fourfold or greater increase between acute and convalescent serum virus-neutralizing or complement-fixation (CF) antibody titers in samples taken 7 to 21 days apart is presumptive evidence of EHV-1 infection.[13] These tests are of limited value, however, because they do not distinguish between EHV-1 and EHV-4 responses, and results are delayed several weeks. An ELISA that distinguishes between infections with these two viruses is now available (SVANOVIR EHV1/EHV4-Ab, Svanova Biotech, Uppsala, Sweden) and is the serologic diagnostic of choice. A practical approach to an outbreak that may involve many horses is to submit serum from both clinical and in-contact/cohoused horses for serologic study and samples for PCR only from horses with clinical signs of fever or EHM. Such an approach provides additional support for the diagnosis and defines the extent of exposure to the virus during the outbreak.

■ Pathophysiology

After initial colonization of the epithelia of the upper respiratory tract, EHV-1 spreads to and amplifies in regional lymph nodes before circulating in the blood within leukocytes. The magnitude and duration of the leukocyte-associated viremia are positively related to the risk for EHM.[13,16] Virus is presumed to enter endothelial cells of small arterioles of the CNS after binding to its surface class I major histocompatibility complex receptor. Endothelial infection incites destructive innate and specific immune inflammatory responses, which in turn initiate coagulation and widespread arterial microthrombosis and hemorrhage.

Viral replication within neurons has not been demonstrated in EHM; rather, neuronal injury is secondary to ischemia that, in turn, is secondary to vasculitis and thrombosis.

■ Epidemiology

Herpesvirus infection is enzootic in the horse population. Infection usually occurs through the respiratory epithelium when the animal comes in contact with the virus in aerosolized droplets or via fomites contaminated with fluids from an abortion or in ocular, nasal, or other respiratory tract secretions.[3,10] Foals probably become infected with virus shed from their dams during recrudescence of latent infections.[13] Most horses in the United States first become infected before 1 year of age and remain infected with latent virus in the trigeminal ganglia or in lymphoid tissues around the head.[13,15] Surveys of necropsies of adult horses indicate that more than 50% of normal horses are latently infected by EHV-1 in one or both of these sites.[13]

EHM is rare, but cases have been reported worldwide. Outbreaks occur more commonly in Europe and the United States than in Australia and New Zealand.[13] Viral polymorphism undoubtedly accounts for differences in neurovirulence. Viruses with one allele of a single-nucleotide polymorphism in the viral DNA polymerase gene, D_{752},[17] were found to be 162 times more likely to cause EHM than were viruses with the alternative allele, N_{752}.[18] The mechanism for enhanced neuropathogenicity of D_{752} is related partly the fact that viremia in infected horses is of higher order than that in horses infected with N_{752}, but it is not due to greater neurotropism. It is common for horses to be latently infected with both variants (D_{752} and N_{752}), and there is no evidence that horses latently infected with the neuropathogenic strain pose a higher risk of being the source of future EHM outbreaks.[13] Polymorphism elsewhere in the genome probably also modulates neurovirulence.[9] During outbreaks, the virus appears to be spread readily, and both morbidity and mortality rates can be high.

Horses of any age, gender, and breed are susceptible. In some studies females in general, or mature pregnant or lactating mares, are most often affected.[7,16,19] The principal risk factor for development of EHM is fever, especially the second peak of a biphasic fever.[6] The onset of neurologic signs often follows closely the decline from peak temperature. Additional purported risk factors in at least some outbreaks were older age,[6,7] cooler seasons (all but summer), introduction of

horses to a herd,[7,8] and inconsistent outbreak-specific breed susceptibilities.[7,8,13] Foals are rarely affected. Mules and donkeys are infected and shed virus but in the United States apparently do not develop EHM.[20] In contrast, EHM is relatively common and highly fatal in donkeys and mules in Ethiopia.[21] Frequent (up to four times annually[6,19]) and recent[19] vaccination against EHV-1 have been reported as independent risk factors. Stress-associated recrudescence of latent infections and subsequent shedding without clinical signs has been difficult to confirm experimentally but undoubtedly is important in the initiation of some outbreaks, especially those occurring after long-distance transportation or in closed herds. Experimentally infected horses may nasally shed virus for 3 weeks or longer after infection; however, viral shedding was not found after 9 days after onset of clinical signs in 20 horses with EHM.[22]

Primary attack rates, as judged by occurrence of fever (usually defined as rectal temperature >40.6° C [101.5° F]) among at-risk horses, may be up to 90%; an average of 10% of these infected horses develop EHM, and mortality rates for horses with EHM are between 20% and 80%; a typical rate is 50%.[3,13] There is no report of EHM caused by modified live virus vaccines currently approved for use in horses.

■ Necropsy Findings

Gross and histologic lesions are not always limited to the CNS. Ocular lesions such as hypopyon, iritis, and chorioretinitis have been reported. Cystitis and scrotal edema may be present. Focal areas of hemorrhage may be found throughout the brain and spinal cord parenchyma and meninges. Vasculitis and thrombosis in the small arteries and veins of the spinal cord and brain result in ischemic lesions in the CNS.[23,24] Equine herpesvirus is infrequently cultured from the CNS, but PCR, in situ hybridization, and immunohistochemistry studies can be performed on CNS tissues obtained post mortem to confirm the presence of the virus.[13]

■ Treatment

Acyclovir is guanosine analog with in vitro activity against EHV-1 that has been used successfully for treatment of herpes simplex encephalitis in humans. Adequate blood levels of acyclovir can be achieved in horses by oral dosing with valacyclovir (30 mg/kg q8h for 2 days and then 20 mg/kg q12h) or IV

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administration of acyclovir (10 mg/kg q12h) but not by oral acyclovir.[25] Although valacyclovir is safe and effective when used as preventive treatment, limited data suggest that it is not effective in horses with ataxia (i.e., EHM).[26,27] In view of the scant evidence available, however, valacyclovir treatment is still worthwhile when economic circumstances permit. Pharmacokinetic and pharmacodynamic data have been obtained for several other antiherpetic drugs, but their effectiveness for EHV treatment has not been investigated.[26]

Supportive care is the most important aspect of treatment for EHM. Measures include bladder decompression by sterile catheterization at least twice daily for horses with bladder distention or incontinence, evacuation of the rectum, administration of intravenous or oral fluids, and enteral or parenteral nutritional support. Recumbent horses must be appropriately padded, and decubital lesions must be prevented or treated. Horses that are recumbent but able to support their weight when lifted should be managed with an abdominal sling.

Administration of antiinflammatory drugs soon after the onset of neurologic signs may be beneficial.[28] NSAIDs (e.g., flunixin meglumine, 1.1 mg/kg IV q12-24h) should be used especially if the horse is febrile or if a painful condition is clinically suspected. Corticosteroids are often used because of presumed suppression of vasculitis, and although no objective data for their efficacy are available, there is a solid theoretical basis for their use.[13,28] Dexamethasone (0.05 to 0.1 mg/kg IV or IM) can be given every 12 to 24 hours for 3 to 5 days; the dosage is then tapered for 1 to 3 days. There are unquantifiable risks related to steroid-induced immunosuppression, including increased susceptibility to bacterial infection of the urinary tract and reactivation of latent virus. Because of uncertainties as to its benefits and risks, steroid treatment should be reserved for horses that are recumbent or in imminent danger of becoming so. DMSO (1 g/kg as a 10% solution in polyionic fluids by slow IV infusion) every 12 to 24 hours is often administered, although its efficacy also has not been documented.

Administration of antibiotics should be considered if the horse is recumbent or has urinary tract or respiratory tract involvement. Chronic cystitis, sometimes associated with bacteria resistant to common antimicrobials, is a common complication of urinary incontinence and bladder catheterization in horses with EHM. Management of such cases is discussed in Chapter 34.

The lesions of EHM are characterized by extensive microvascular thrombosis,[29] and so aspirin or heparin may be used in an effort to prevent worsening of spinal cord lesions (see next section).

■ Control and Prevention

Vaccines currently used to prevent EHV-1 respiratory and abortion syndromes are not claimed to prevent EHM, and there is no reliable evidence that they do. A small study concluded that modified live virus vaccine provided modest, albeit significantly better, protection against experimentally induced EHM than did a killed low-antigen vaccine,[30] although the duration and robustness of such protection, if any, are not yet clear. Vaccination with inactivated "high-antigen" vaccines (i.e., those with a label claim for prevention of herpesvirus abortion), enhanced adjuvant vaccines, or modified live vaccine does have the important effect of reducing nasal shedding and thus potentially limiting the spread of infection during an outbreak. This rationale has also been used to justify booster vaccination of at-risk horses during an outbreak. Because of persistent evidence-based concerns about inducing or exacerbating EHM by excessive and recent vaccination, however, this practice remains controversial.[6,19]

Immunostimulants are sometimes administered to horses at risk for EHM on the basis of the theory that immune system activation will prevent viral reactivation or replication,[13] but supportive evidence is lacking. A history of nutritional supplementation with a product containing zinc protected horses exposed during an EHM outbreak from developing the disease according to a retrospective study of horses involved in the 2011 Ogden, Utah, outbreak.[19]

Valacyclovir and valganciclovir are prodrugs of the antiviral agents acyclovir and ganciclovir that have adequate bioavailability in horses when given orally.[25] Although these agents have in vitro activity against EHV-1, valacyclovir and ganciclovir were not effective at preventing EHM when either one was administered 4 to 6 days after viral inoculation (i.e., at the onset of the second temperature rise).[31] Ganciclovir, but not valacyclovir, reduced the severity of ataxia. In contrast, valacyclovir significantly reduced the severity of neurologic signs when begun either the day before challenge or at the onset of fever and continued for 1 to 2 weeks.[27] Therefore if these drugs are used for prevention, they should be begun no later than the onset of the initial fever.

Protocols for management of premises with EHM cases are now well established and tested. Comprehensive and regularly updated guidelines are available from the American Association of Equine Practitioners (AAEP; http://www.aaep.org/). In addition, the British Horserace Betting Levy Board publishes Codes of Practice on Equine Diseases (https://codes.hblb.org.uk/). In brief, the essentials of these protocols are (1) to isolate affected horses; (2) to

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monitor temperatures twice daily on all quarantined horses; (3) to submit diagnostic samples; and (4) to implement robust biosecurity procedures.[13] There is still uncertainty about the length of quarantine required after the last occurrence of fever in any horse. AAEP guidelines currently call for 28 days. A workable but expensive alternative is to require 14 days after the last fever in any quarantined horse and then test all horses for nasal shedding by PCR on swabs taken on 2 to 4 successive days.[13] It is essential that all guidelines are followed meticulously; with each new fever, a 28-day quarantine must start over. Biosecurity procedures for EHM caused by neuropathogenic and nonneuropathogenic strains should be the same.[12] Additional guidelines are available for measures designed to prevent or reduce the likelihood of outbreaks and to lessen the effect of outbreaks that do occur.[13]

Equine Protozoal Myeloencephalitis

Robert J. MacKay

Equine protozoal myeloencephalitis (EPM) is the most common infectious neurologic disease of horses in the United States. The Apicomplexa protozoan *Sarcocystis neurona* is the usual cause, with sporadic cases caused by *Neospora hughesi*.[1,2] Species of *Sarcocystis* have an obligatory two-host life cycle.[3] *S. neurona* reproduces sexually in the small intestine of the definitive host, the opossum (*Didelphis virginiana* in North America and *Didelphis albiventris* in South America), and results in the passage of oocysts/sporocysts with feces. Asexual proliferation occurs in the intermediate host and culminates in the formation of sarcocysts in muscle. The nine-banded armadillo, striped skunk, raccoon, and domestic cat are natural intermediate hosts that cover the geographic range in which EPM occurs.[4-7] The primary and secondary hosts for *N. hughesi* are not known. The horse usually functions as an aberrant dead-end intermediate host for *S. neurona:* With the exception of a single foal with *S. neurona* muscle sarcocysts,[8] only precystic stages (i.e., merozoites and schizonts) have been found in the CNS of horses with EPM.

■ Pathogenesis

The pathophysiologic and immunologic mechanisms of *S. neurona* infection in horses are not completely understood. Horses ingest the infective sporocyst stage of *S. neurona* in food and water that have been contaminated by opossum feces.

Congenital *S. neurona* infection is rare, but it is well established that *N. hughesi* may be transmitted transplacentally.[9] The mechanism of entry into the CNS of the horse is probably related to leukocyte-associated parasitemia. Once in the CNS, *S. neurona* can localize and replicate in any region, from cerebrum to spinal cord. True peripheral nerves and nerve roots are not infected; however, cranial nerves I and II (olfactory and optic), which are part of the CNS, can be affected. The location and extent of lesions determine the type and severity of clinical signs. Histologically, protozoa are usually associated with mixed inflammatory cellular responses and neuronal destruction. Schizonts (multicellular proliferative bodies) or free merozoites are common observed in the cytoplasm of neurons or mononuclear phagocytes and in capillary endothelial cells but rarely in other inflammatory or CNS cells.[3]

Both cellular and humoral immunity appear to be important for control of infection by *S. neurona*. Because of the intracellular location of the parasite, competent cell-mediated adaptive immune responses are considered essential for its elimination.

■ Epidemiology

EPM is a disease of horses that have spent time in North or South America. There are isolated reports of horses elsewhere in which EPM was diagnosed but that have no history of travel to the Americas, and the nature of infection in these cases remains unclear.[10,11] Horses of all breeds can be affected by EPM, and there is no sex bias. There are few reports of EPM in ponies or mules, which suggests that these equids may be less susceptible to EPM than are horses. Ages at onset of EPM have ranged from 2 months to at least 30 years, although it is rare in horses younger than 2 years old. One study identified an increased risk of EPM in horses aged 1 to 5 years and older than 13 years.[12] EPM typically occurs as individual cases, but clusters of cases have occasionally been reported.[13]

The reported prevalence of *S. neurona* infection as evidenced by *S. neurona* antibodies in horses in various locations throughout the United States varies from 0 to 89.2%.[14,15] Rates are generally high in areas with dense human populations, abundant water sources, and moderate rainfalls; seropositivity rates are low in arid, sparsely populated regions. The geographic variation in prevalence corresponds closely to the still-expanding range of the definitive host, the opossum. Despite the high rate of infection by *S. neurona*, the lifetime risk of a horse for developing EPM in these areas may be only approximately

1% (estimated from the mean 0.14% one-year incidence reported in the *National Animal Health Monitoring System 1998* survey[16]).

The factors that influence the relationship between infection with *S. neurona* and development of EPM are not well understood. *S. neurona* lacks the genetic diversity found among *Toxoplasma gondii* isolates, but it may nonetheless be capable of *T. gondii*–like clonal expansion of virulent strains,[17] although conclusive evidence for this has not yet been found in the setting of equine infections. Results of risk factor analysis for EPM vary by study, but factors likely to increase exposure to opossums, their environment, and their feces are consistently identified.[18-21] Other risk factors include previous diagnosis of EPM on the premises; primary use of the horse, with showhorses and racehorses at relatively high risk; recent transport; and recent adverse health events such as medical problems, parturition, and management changes. Collectively, these risk factors indicate that physiologic stress may play an important role in the onset of EPM.

■ Diagnosis

Antemortem diagnosis of EPM remains challenging. Criteria for diagnosis include finding clinical signs consistent with EPM, ruling out other diagnoses, positive response to treatment with anti-EPM drugs, and finding *S. neurona*–specific antibodies through immunodiagnostic testing. Proof of diagnosis post mortem is demonstration of protozoa in CNS lesions, often obtained with immunohistochemical staining or PCR. Even when the organism is not observed, the diagnosis is frequently made presumptively if characteristic inflammatory changes are found.[22,23]

Two types of immunodiagnostic tests are available for EPM: those that rely on threshold values of serum anti–*S. neurona* antibody (IFAT, ELISAs for antibody against various *S. neurona* surface antigens) and those that purport to detect specific antibody made within the CNS (Western blot, serum-to-CSF antibody ratios, *C* values).[24] Blood samples for serum tests are easily obtained, but the diagnostic assays are based on the yet-to-be validated principle that horses with EPM have distinctly higher serum antibody concentrations than do exposed/subclinically infected horses.[25] However, because seroprevalence of EPM is relatively low in comparison with that for *S. neurona*, a positive serum test result has a proportionally higher positive predictive value for EPM.[24] On the other hand, a negative test result is strong evidence that the horse does not

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have *S. neurona* infection and thus does not have EPM. The rationale for tests of the second type, each of which requires a clean CSF sample, is that identification of CNS-origin antibody is the only way to distinguish horses with EPM from exposed horses. The most popular tests of each type—namely, serum IFAT and ELISA for single-nucleotide surface antigens 2 and 4/3 (snSAG2,4/3)—have good (i.e., >80%) sensitivity and specificity for EPM among horses with solid postmortem diagnoses.[26,27] One drawback of the IFAT is that it is unable to differentiate between antibodies against *S. neurona* and those against *Sarcocystis fayeri* (a relatively nonpathogenic species).[28] In one study, the researchers used samples from necropsy-confirmed EPM-positive and EPM-negative cases to specifically compare results of IFAT and snSAG2,4/3 tests. Accuracy values for serum IFAT, serum snSAG2,4/3 ELISA, IFAT ratio, and snSAG2,4/3 ratio were 68%, 56%, 88%, and 97%, respectively.[23] Comparable tests for *N. hughesi* also are available commercially (*N. hughesi* IFAT and NhSAG1 ELISA) but have not been fully validated for EPM diagnosis. It is clear, on the basis of both flawed concepts and unsupportive clinical data, that neither CSF Western blot nor serum SAG1 ELISA is a reliable diagnostic test for EPM.[29-31] In contrast to the situation with Western blots, snSAG (and presumably IFAT) ratio test results are relatively robust in the presence of a small amount of contaminating blood; however, false-positive results do occur in cases of moderate or severe blood-brain barrier injury. For samples from horses with blood-brain barrier injury (as detected by high CSF albumin concentrations or high albumin quotient values[32]), additional total IgG testing is performed on the serum/CSF sample, and a *C* value is calculated.[33] CNS antibody production is indicated by *C* values greater than 1.

At the time it was last investigated, PCR testing of CSF for *S. neurona* DNA had high specificity but low sensitivity for the diagnosis of EPM.[34] False-negative findings are common because free parasitic DNA is destroyed by enzymes in the CSF and merozoites rarely enter the CSF. Testing by PCR of tissue samples is useful for postmortem diagnosis.

Ancillary procedures such as survey cervical radiographs, lameness examination, and serologic testing may be necessary to rule out competing differential diagnoses. In horses with signs of brain involvement, suggestive lesions may be seen with advanced imaging techniques.[35] Consistent abnormalities are not found in complete and differential WBC counts or in serum chemistry panels in horses with EPM. CSF values are abnormal in some

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horses with EPM. It has been reported that up to 35% of horses at a referral hospital have increased protein concentration (>65 mg/dL) or nucleated cell count (>6 cells/µL).[36] In the author's experience, in horses with mild clinical signs of EPM (i.e., those that typically are encountered in practice), a low percentage have any abnormality on routine CSF analysis. CK activity may be high in CSF, reflecting diffusion of the BB isoenzyme from damaged CNS gray matter.[37] Unfortunately, inadvertent inclusion of a small plug of epidural fat or dura during CSF collection can dramatically elevate CK activity, thus reducing the specificity of the test.

■ Clinical Signs

Protozoa may infect any part of the CNS and thus produce almost any possible neurologic sign. The disease usually begins insidiously but also may present acutely and be severe at onset. Signs of spinal cord involvement are much more common than are signs of brain disease. Horses with EPM involving the spinal cord have asymmetric (usual) or symmetric truncal and limb weakness and ataxia. If all lesions are behind the second thoracic spinal cord segment (T2), only the pelvic limbs are affected. If a lesion (or lesions) is located in front of T3, all four limbs may be affected. In the rare instance when the spinal cord behind the second sacral spinal cord segment (S2) is involved, the animal exhibits signs of cauda equina syndrome, which may include degrees of rectal, anal, bladder, and penile paralysis and reduced sensation of the skin of the tail and perineum. When gray matter of the ventral horn of the spinal cord is damaged for more than 1 to 2 weeks, obvious focal muscle atrophy and electromyographic changes in denervated muscle may develop. Common locations for atrophy in horses with EPM are the gluteal, biceps femoris, infraspinatus/supraspinatus, and serratus ventralis muscles. Lesions in the spinal cord may also result in demarcated areas of spontaneous sweating or loss of reflexes and cutaneous sensation.

Neurologic signs noticed at walking or during neurologic examination include any to all of the following: asymmetric stride length, toe dragging, circumduction of pelvic limbs, and hypometria (also described as floating or marching) of thoracic limbs. Other signs are noted only when the horse is ridden: difficulty maintaining a specific lead, cross-cantering or cross-galloping, and difficulty negotiating turns. Some signs that are usually attributed to primary musculoskeletal disease, such as back soreness or upward fixation of one or both

patellas, can be caused by weak or asymmetric use of muscle groups in horses with EPM that are in training.

A relatively common manifestation of brain disease in horses with EPM is a brainstem syndrome with signs of obtundation and asymmetric vestibular (VIII) nerve dysfunction (Fig. 35.18). There may also be facial paralysis (VII); dysphagia (X); tongue paralysis (XII); laryngeal paralysis (X); strabismus (III, IV, and V); failure of globe retraction (VI); and deviation of the mandible (VII). With involvement of the rostral brainstem or cerebrum, EPM may manifest as seizures, visual deficit/abnormal menace response, reduced perception of touch on the opposite side of the face, or behavioral abnormality.



FIG. 35.18 Obtundation, right-sided head tilt neck turn, and body lean in a 3-year-old Thoroughbred colt with peracute-onset equine protozoal myeloencephalitis.

Without treatment, EPM usually progresses. Progression to recumbency occurs over hours to years and may occur steadily or in a stop-start manner.

■ Treatment

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Since 2000, the folate inhibitor combination sulfadiazine/pyrimethamine, the triazine coccidiostats ponazuril and diclazuril, and the nitrothiazole nitazoxanide have all been licensed by the U.S. Food and Drug Administration (FDA) for the treatment of EPM, and commercial products have been launched.[9,38] Nitazoxanide was withdrawn in 2009. Multicenter studies of sulfadiazine/pyrimethamine, ponazuril, nitazoxanide, and diclazuril reported improvement rates of 57.1% to 61.5%.[38]

Label directions for dose and duration of FDA-approved drugs should be followed. Ponazuril in a loading dose of 15 mg/kg (three times the normal dose) reaches steady-state concentrations several days earlier than is the case with conventional dosing.[39] Many dosage permutations and combinations of these products and pharmacologically similar products are administered in clinical practice, although efficacies have not been investigated. A sodium salt formulation of diclazuril has been shown to have good oral bioavailability and may have potential as a feed additive.[40] Some veterinarians administer IV a compounded form of diclazuril, although there are no published data for its safety or efficacy. Of interest is that steady-state concentrations of diclazuril in plasma and CSF were not different for the low-dose rate (0.5 mg/kg) and the FDA-approved dose rate (1 mg/kg).[41] These data support the use of the 0.5-mg/kg dose as treatment or preventive. Experiments have demonstrated enhancement of the antiprotozoal effect of combinations of pyrimethamine with either diclazuril or ponazuril in treatment of other coccidian infections,[42] and so ponazuril or diclazuril is sometimes combined with sulfadiazine/pyrimethamine. Such treatments constitute unapproved or off-label use, albeit of FDA-approved products.

Another drug used commonly as an anticoccidial in calves, decoquinate, was evaluated in horses with presumptive EPM, at dosage of 0.5 mg/kg PO daily for 10 days, in combination with the immunomodulator levamisole, 1 mg/kg PO daily.[43] Success rates of 93.6% and 89.3% were reported on the basis of improved neurologic gait score at the end of treatment and reversion of serum snSAG1,5,6 titers, respectively. Decoquinate was also shown to have potent inhibitory and killing activity in vitro against two different isolates of *S. neurona*.[44] If this drug combination continues to perform well in wider use, it will obviously become an important treatment option.

Horses may exhibit relapse soon after the initial course of treatment is discontinued or up to several years after improvement or apparent resolution of

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signs. Although no data are available to guide treatment of relapses, it is common practice to change or add antiprotozoal drugs. In order to prevent future relapses, antiprotozoal therapy can be provided prophylactically. Protocols include FDA-approved formulations of sulfadiazine/pyrimethamine, 2 days/week at the standard dosage, or diclazuril daily at 0.5 mg/kg. A similar rationale can be used to treat horses only around the time of stressful events that may predispose to relapses.

Of the available drugs, only pyrimethamine has significant adverse side effects. Toxicity reflects both direct effects of the drug and its inhibition of mammalian dihydrofolate reductase, which induces folate deficiency. Signs include convulsions and recumbency, reproductive and neonatal disorders, oral ulcers, and bone marrow suppression, including (in decreasing frequency) leukopenia, neutropenia, anemia, and thrombocytopenia.[45-47] Horses treated with sulfadiazine/pyrimethamine should be fed good-quality green forage (e.g., alfalfa hay or pasture), which is likely to be rich in folate. Supplementation with folic acid during treatment confers no advantage, and some evidence from other species indicates that this practice could increase the possibility of toxicity.[46] Most cases of bone marrow suppression resolve if treatment is suspended for 1 to 2 weeks. Folic acid (100 mg daily) is appropriate for treatment of folate deficiency once pyrimethamine is discontinued. If signs are severe, treatment with folinic acid (100 mg IV or PO daily for 5 days) is indicated.

In mild acute cases of EPM (grade 1), additional therapy is unnecessary. In horses with moderate or severe signs, NSAID and antioxidant treatment is usually provided for the first 1 to 2 weeks. If the horse has grade 3 EPM or worse, a corticosteroid may be added. Vitamin E is often given throughout the period of antiprotozoal treatment for additional antioxidant effect. Oral administration of vitamin E has been shown to result in increased concentrations of α-tocopherol in serum and CSF.[48] As a relatively crude way to address putative immunodeficiency and “boost” cellular immunity, immune modulators are sometimes given to horses with EPM.

■ Prognosis

On the basis of drug efficacy studies and clinical experience, it is reasonable to expect that approximately 60% of moderately or severely affected horses will improve at least one grade after treatment. Only 10% to 20% of such horses completely recover, and 10% to 20% of successfully treated horses suffer at least

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one relapse. The outlook for mildly affected horses (grade 1) is considerably better, particularly if treatment is begun promptly. Although no data for the latter, more common class of treated horse have been published, at least 80% of such cases can be expected to improve, and at least 50% recover completely, with low possibility of recurrence.

■ Prevention

An inactivated vaccine was marketed under conditional approval by the U.S. Department of Agriculture. The conditional license lapsed in March 2008, and the vaccine is no longer available. When tested in horses dosed with *S. neurona* and stressed by transportation, vaccination did not prevent development of clinical neurologic signs.[49]

Prevention of *S. neurona* infection may be possible by daily administration of a drug such as diclazuril or ponazuril.[50,51] The disadvantage of this approach is that normal immune responses to the organism may be prevented. An alternative approach is metaphylaxis, wherein intermittent doses of drug are given to allow an initial round of protozoal proliferation and normal immune responses to take place but prevent invasion of the CNS. Ponazuril given at 20 mg/kg every 7 days but not every 14 days significantly reduced *S. neurona* antibody in the CSF of *S. neurona*–challenged horses, which suggests the potential utility of such an approach.[52]

Common-sense measures can be instituted to prevent contamination of feed with *S. neurona* sporocysts. Opossums can be trapped and removed or kept away by free-ranging dogs. Spilled grain, fallen fruit, and animal or bird feed should be removed, and horse food sources should be monitored and secured. The utility of controlling intermediate hosts in an effort to reduce environmental sporocyst load is doubtful; however, if populations of host animals on a problem premise are large, then such animals should be trapped and removed. Products useful for cleaning of areas potentially contaminated with sporocysts have been described.[53]

Cervical Stenotic Myelopathy

Robert J. MacKay

The term *wobbler* (also *wobbler syndrome*) describes horses with ataxia caused by any of a group of developmental anomalies and degenerative

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conditions involving the cervical vertebrae.[1] Several other descriptions are used in wobbler terminology. The most important of these are *cervical vertebral malformation and malarticulation, cervical stenotic myelopathy* (CSM), and the inelegant but descriptive *cervical vertebral stenotic myelopathy*. CSM is the most common noninfectious neurologic disease of horses. The prevalence of CSM among 1289 Thoroughbred horses born on four breeding operations was 1.3%.[2]

Two overlapping CSM syndromes are recognized, differing greatly in developmental histories. *Type I* is characterized by focal or multifocal stenosis of the vertebral canal, principally between C1 and C6, that is worse on flexion (*dynamic* stenosis). Affected horses are typically younger than 2 years of age. In *type II*, bony and soft tissue impingement into the vertebral canal results from remodeling of the articular process joints of the caudal cervical vertebrae (usually C5 to T1) and stenosis of the cranial vertebral orifice. This impingement is present in all positions of the neck (*static* stenosis) but may also have a dynamic component in that it worsens during hyperextension. Horses with static stenosis are usually young to middle-aged at the onset of wobbler signs.

Both syndromes probably involve some combination of aberrations in cartilage and bone development and external trauma that may precede clinical ataxia by many months (perhaps even in utero in the case of type I CSM[1]).

■ Pathogenesis

Type 1 CSM is another manifestation of the group of disorders of endochondral ossification (i.e., osteochondroses) that occur in young, growing horses and include physitis, contracted tendons, osteochondritis dissecans, subchondral bone cysts, and malformation of the cuboidal bones of the carpus and tarsus.[3] Study of wobbler matings has revealed a propensity for rapid growth and superior performance among offspring but no clear evidence that CSM was genetically predetermined.[4] Of interest is that other developmental orthopedic diseases were overrepresented. A genetic predisposition to development of CSM clearly exists, but because CSM is probably genetically and environmentally multifactorial, pure genetic influences have been difficult to discern. Because rapid growth and large size appear to be risk factors for foal osteochondrosis,[5] studies have tentatively implicated high protein and caloric intake in the development of CSM.[1] Marginally low levels of trace minerals such as copper may come into play during rapid growth.

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As a result of presumed genetic, physical, and dietary factors, osteochondrosis of the articular processes and metaphyseal growth plates occur early in affected foals. Genetic predisposition, rapid growth, maternal nutrition, calcium/phosphorus imbalance, low dietary levels of copper, and high dietary levels of zinc have all been implicated as developmental orthopedic diseases in foals, but their roles as risk factors for CSM are not clear.[6-9] Osteochondrosis of the vertebral physes of rapidly growing foals and weanlings results in multiple vertebral abnormalities, including flaring and enlargement of the caudal metaphyses and epiphyses of the vertebral bodies (equivalent to physitis of the limbs) and disparity of longitudinal growth of the vertebral bodies and dorsal laminae. These deformities cause focal stenosis of the vertebral canal and susceptibility to dynamic compression, respectively. In severe forms, the latter abnormality forces pairs of vertebrae into a permanently flexed, malarticulated, kyphotic position in which severe vertebral canal stenosis (both static and dynamic) is likely to occur. Flaring of the caudal metaphyseal-epiphyseal unit contributes to the narrow caudal orifice of the canal within an affected vertebra that is common in horses with CSM.

Osteochondrosis of the articular process joints may result in joint instability and later osteoarthritis and remodeling. Associated with degenerative joint disease of the articular process joints are gross enlargements due to osteophyte development. Affected articular processes may be relatively brittle and susceptible to trauma. Fractured articular processes are found quite frequently in diseased intervertebral joints at necropsy, although the fractures often cannot be seen in lateral radiographs. Pedicle fractures caused by trauma probably contribute to the massive asymmetric remodeling and enlargement of some of these joints. The canals within affected vertebrae may deform to a funnel shape with a small stenotic cranial orifice. There may also be hypertrophy and fibrosis of the synovial membrane and joint capsules of the articular process joints, and fibrovascular proliferation of the ligamentum flavum. These soft tissue structures or fluid-filled cysts associated with them may cause static stenosis and compression of the spinal cord and spinal nerves. Synovial and epidural cysts are prone to cause dramatic waxing and waning of clinical signs of spinal cord compression.[1]

■ Necropsy Findings

Horses with CSM have one or more focal compression–type lesions in the

cervical spinal cord.[10] The gross appearance of such lesions is of flattening and palpable softening of the cord. They are characterized histologically by swollen and disrupted axons and phagocytosis of myelin in white matter. Mild hemorrhages are sometimes observed in acute lesions. In chronically affected animals, the white matter demonstrates continued degeneration of neuronal fibers, proliferation of capillaries with prominent fibrous coats, and astrofibrosis. More severely affected horses also have neuronal necrosis, loss of cell bodies, and sometimes astrofibrosis in the gray matter. Massive focal lesions also occur with cavitating necrosis of white matter, particularly in lateral funiculi and occasionally in gray matter. Markedly asymmetric lesions are found in horses with prominently asymmetric clinical signs. Cranial to the focal lesions, neuronal fibers (axons and myelin) in ascending (proprioceptive) tracts exhibit secondary degeneration for variable distances, depending on the extent and age of the focal lesion. Caudal to the lesion, there is secondary fibers in descending (motor) tracts exhibit degeneration. This fiber degeneration results from the severing of neuronal fibers from their cell bodies by the focal lesion. It is most prominent in dorsolateral funiculi cranial to the lesion and in deep lateral and ventromedial funiculi caudal to the lesion.

According to one report, the most common histologic lesions in the articular processes of horses with CSM were osteochondrosis, osseous cyst–like structures, fibrous tissue replacement of trabecular bone, retained cartilage matrix spicules, bone cysts, and osteosclerosis.[11]

■ Clinical Signs

Most animals with type I CSM are 6 to 18 months old, whereas those with type II CSM are typically 18 months to 5 years; however, there are many exceptions to these ranges, and both conditions can occur in a single animal. In four large breeding farms, the onset of type I CSM occurred in horses aged 202 to 986 days (average, 434 days), whereas type II CSM cases began at ages 1085 to 1299 days (average, 1188 days).[12] A study of 811 horses in the United States indicated that horses of the Thoroughbred, warmblood, and Tennessee Walking Horse breeds were significantly more likely to have CSM than were Quarter Horses; Standardbreds and Arabians were significantly less likely to have CSM.[13] Large warmblood breeds are notably affected by type II CSM.[14] Males are overrepresented.[14,15] Affected horses are often well grown, and some have a history or signs of other developmental orthopedic diseases such as

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osteochondritis dissecans or physitis.

Clinical signs of ataxia and paresis typically begin insidiously but may manifest suddenly. In the latter case, there is often a history of some minor fall or training incident that confuses the diagnosis (the fall could have been a precipitating cause or a result of the disease). After signs have been recognized, they typically progress for a period of months and then may stabilize or even regress. Spontaneous complete recovery is rare[1]; waxing and waning signs are frequent. In general, horses with CSM appear physically normal; however, enlarged intervertebral joints in the caudal cervical spine and severe flexion angulations, particularly at the C2-C3 and C3-C4 levels, are occasionally externally visible and palpable. Pain in response to pressure over the transverse processes and reluctance to flex the neck laterally are common findings in horses with type II CSM. In rare cases, impingement on caudal cervical spinal sensory nerves by enlarged intervertebral joints in type II CSM is sufficient to cause signs of thoracic limb lameness.

The principal neurologic signs are ataxia, weakness, and spasticity of the limbs. These signs reflect involvement of axons of upper motor neurons and general proprioceptive tracts in the white matter of the spinal cord underlying the site or sites of compression. Because of the more superficial location of general proprioceptive tracts from the pelvic limbs, the pelvic limbs are generally more affected than the thoracic limbs.[1] Dynamic stenosis is usually associated with symmetric signs, whereas static stenosis may cause asymmetric signs. Severe arthrosis of the joints between the C6 and C7 levels or between the C7 and T1 levels occasionally causes signs more severe in the thoracic than in the pelvic limbs. The first sign noticed may be stumbling or clumsiness when the horse is moving into or out of a box stall. During exercise gallops, the rider may comment on a feeling of looseness or “losing the back end” around turns. Reluctance to change leads, cross-cantering or cross-galloping, or even falls after stumbling are other early signs in horses being ridden. With progression, affected horses may exhibit gait at the walk that is obviously stiff and uncoordinated; the prominent truncal sway; or “wobble,” which explains the common name for CSM in horses. Because of pelvic limb extensor weakness, some wobblers catch their patellas or have persistent upward patella fixation.

In addition to the signs already mentioned, careful neurologic examination usually discloses some or all of the following:

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- Abnormal pelvic movements during walking, best observed from behind, including excessive swiveling of an imaginary line on the median plane from between the tuber sacrale to the tailhead, excessive rotation of the pelvis around its long axis (visible as exaggerated amplitude of the rise and fall of the tuber coxae), and side-to-side truncal sway.
- Decreased resistance to lateral pressure exerted by pulling of the tail while the horse is walking.
- Apparent stiffness of the limbs during the swing phase of the stride in the thoracic or pelvic limbs. This may be associated with scuffing of the toes. When the horse's head is raised during walking, especially down a gentle slope, the stiff hypometric gait in the thoracic limbs may be exaggerated and is sometimes described colloquially as a “marching,” “floating,” or “tin-soldier” gait.
- Circumduction of each outside pelvic limb when the horse is walked in small circles.
- Interference between the thoracic limbs and pivoting around the pelvic limbs when the horse is moved in tight circles.
- Absence of the thoracolaryngeal (“slap”) reflex.

In horses with markedly asymmetric compression (usually horses with asymmetric caudal intervertebral arthritis), there also may be marked asymmetry of stride length between the pelvic limbs.

■ Diagnosis

Radiography of the cervical spine is the most important diagnostic tool. CSM can usually be diagnosed presumptively on plain laterolateral radiographs of the cervical spine from the finding of focal stenosis of the vertebral canal. The diagnosis is buttressed by additional demonstration of malformation, osteochondrosis dissecans, or arthrosis of the articular process joints; metaphyseal and epiphyseal flaring of the caudal aspect of vertebral bodies; relative elongation caudally of the dorsal laminae; or angulation between pairs of vertebrae. Oblique projections (usually lateral–50 degrees–ventral to laterodorsal) enable more accurate description of remodeling and other changes in the articular process joints and should be included as "standard of practice" in studies of horses with arthroses of the articular process joints.[16] Standardized measurements of articular process joints in oblique projections have been published, but poor repeatability and inaccuracy of these measurements have so far limited their usefulness.[17]

Intravertebral sagittal ratios for vertebrae behind C2 are calculated as the ratio of minimal sagittal diameter of the vertebral canal to maximal sagittal diameter of the cranial half of the vertebral body].[18] Both measurements are made perpendicular to the long axis of the vertebral canal. The denominator normalizes for variations in horse size and distance between object and image. Values for sagittal ratio of less than 0.52 from C4 to C6 and less than 0.54 at C7 are predictive of spinal cord compression with 89% sensitivity and specificity in the diagnosis of spinal cord compression, according to the original description.[18] In practice, cutoff values of 0.50 for C3-C6 and 0.52 for C7 are typically used.[1] Even horses with static stenosis, which may produce predominantly transverse compression from large joints, usually have at least one abnormal intravertebral sagittal ratio.[18]

Intervertebral sagittal ratio measurements are made between pairs of vertebrae in order to capture the effect of *fixed* flexion or extension angles on the diameter of the vertebral canal.[19] For a pair of vertebrae fixed in a kyphotic angle, the primary measurement (numerator) is the shortest distance between the caudal aspect of the dorsal lamina and the craniodorsal aspect of the vertebral body of the caudal-adjacent vertebra. For a fixed lordotic intervertebral joint, the corresponding measurement is the shortest distance between the caudodorsal aspect of the vertebral body and the most cranial point on the dorsal lamina of the caudal-adjacent vertebra. This measurement is then divided by the maximal

sagittal diameter of the cranial half of the vertebral body of the cranial-adjacent vertebra to calculate the intervertebral sagittal ratio.[19] Normal values for means and lower bounds of the 95% confidence intervals for intravertebral and intervertebral sagittal ratio from C3 to C7 have been published.[1,19] Any value below these lower bounds is highly predictive of spinal cord compression.

A semiquantitative scoring system has been developed for use in foals 3 to 7 months of age to predict the risk of developing CSM.[20] Intravertebral and intervertebral sagittal diameters are recorded as described earlier, but vertebral body length (rather than sagittal diameter) is used as denominator to render these diameters as ratios.[20] Up to 10 points are assigned for decreased sagittal ratios and up to 5 points for each of the following signs of cervical vertebral malformation: dorsal flaring of the caudal vertebral body, caudal extension of the dorsal lamina, angulation between adjacent vertebral bodies, delayed ossification, and enlargement of articular processes. A score of 12 or higher (maximum, 35) is predictive of the development of CSM. This study revealed a strong tendency for the diameter of the vertebral canal to be greater in female foals than it was in males.[20] A multicomponent and detailed system of measurements in plain and myelographic studies devised by Japanese workers[21,22] accurately identifies foals and yearlings with CSM, but it has not been widely adopted in other countries.

When plain radiographs are abnormal, contrast myelography may be used to support the diagnosis, to establish the number and locations of sites involved and the severity of lesions in each, and to define the soft tissue contribution to spinal cord compression. These factors are especially important if surgical stabilization is contemplated because myelography may reveal a site of disease different from that suspected from plain films. With the horse under general anesthesia, 30 to 60 mL of iohexol (Omnipaque) or iopamidol (Isovue) radiocontrast solution are injected slowly into the atlantooccipital subarachnoid cistern after a similar volume of CSF has been removed. After injection has been completed, the head is raised for 5 minutes to facilitate caudal flow of dye, and then the head is lowered and radiographs are taken.

Laterolateral views of the cervical spine are taken in neutral, flexed, and extended positions. Spinal cord impingement due to dynamic compression is clearly defined in lateral views if the dorsal and ventral dye columns are completely extinguished at diametrically opposed sites in flexed views. For cases of incomplete compression of the dorsal column, several different

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diagnostic criteria have been used, none of which is completely satisfactory.[23,24] The traditional standard of complete compression of the ventral dye column and 50% or more compression of the dorsal column at diametrically opposed sites is sensitive but has poor specificity (i.e., it can yield many false-positive results). Other likely, more accurate alternatives are (1) comparison with reference ranges for minimal dural diameters and minimal flexed dural diameters for horses either above or below 320 kg and (2) 30% or greater reduction in dural diameter in neutral views at the site of interest (usually intervertebral) in comparison with the midbody dural diameter in the caudal-adjacent vertebra. Sites affected in order of frequency are the C3-C4, C4-C5, and C5-C6 levels. Multiple sites may be affected in a single horse. The typical myelographic feature of *static* stenosis is focal spinal cord compression throughout the full range of vertebral motion. Any dynamic component at these caudal sites is relieved by flexion of the spine. The C6-C7 articulation is involved most frequently, and C5-C6 and C7-T1, to a lesser extent. At these sites, absolute narrowing of the minimal dural diameter or 30% reduction in comparison with the cranial-adjacent midbody measurement are the best diagnostic criteria.[1] In cases in which the plane of compression is transverse rather than dorsoventral, the dural diameter is usually abnormal; however, less objective criteria may have to be considered when measurements are normal. These include widening of the spinal cord diameter and fading of the dye columns over the area of lateral compression. Unfortunately, the diagnostic accuracy of plain radiographic or myelographic diagnoses of CSM has been unimpressive in comparison with that of postmortem spinal cord histopathologic study.[15]

Advanced imaging with CT[25] or MRI[26] have been described, but in mature horses, gantry dimensions usually limit their use to vertebrae in front of C4. The current rapid pace in development of MRI and CT equipment capable of evaluating the cervical spine of mature horses may in the near future substantially enhance the evaluation of CSM.

A technique has been described for endoscopic evaluation of the epidural and subarachnoid spaces of the cervical spinal cord, and this procedure was applied to a horse with CSM.[27,28] Although the technique may have application in selected cases, it has no place in the routine diagnosis of CSM.

Needle electromyography is most useful for investigation of muscles deprived of lower motor neuron activity, but it has little application to the diagnosis of CSM. The most promising electrodiagnostic testing application in this setting is

transcranial magnetic stimulation.[29,30] Descending motor tracts are stimulated by current pulsation from a coil placed on the scalp. The onset latency of electromyographic responses in limb muscles is related to the integrity of spinal motor pathways. Latencies for horses with CSM were significantly longer than those for normal horses.[31]

CSF analysis generally yields normal results. At most, xanthochromia and elevated protein levels (70 to 130 mg/dL) are observed.

■ Treatment

Medical.

Corticosteroids and NSAIDs may provide transient improvement in the signs of CSM but do not treat the underlying problem.

Large degenerative intervertebral joints can be seen ultrasonographically, and corticosteroid (e.g., triamcinolone or methylprednisolone acetate) can be injected intraarticularly under ultrasound guidance, as has been described.[32] The theoretical indications for this procedure include relief from pain of arthritis and reduction in the soft tissue components of arthritic joints so as to provide at least temporary reversal of their impingement on the spinal cord and spinal nerves in the case of CSM and thoracic limb lameness, respectively. Although descriptive support for all of these possibilities was provided in an observational series,[33] no fully objective evidence has been provided for reversal of the signs of CSM, and it is inconceivable that permanent relief could be provided.

Some mildly affected horses can stabilize and even improve both radiographically and clinically if confined and placed on restricted but nutritionally complete feed.[1] There are reports of complete recoveries with this conservative approach and, in one report, 30% of conservatively treated mildly affected Thoroughbreds went on to race.[34] For affected horses younger than 1 year (and preferably younger than 6 months), a restrictive “paced-growth” diet can be tried in order to retard growth rate and prevent CSM in clinically normal foals with radiographic evidence of stenosis of the vertebral canal or to treat foals with mild clinical signs of CSM.[35] This diet reduces energy intake to 65% to 75% of National Research Council recommendations and increases levels of trace minerals. The essential elements are as follows: (1) immediate weaning if the foal is still suckling and (2) feeding free-choice grass hay (e.g., coastal Bermuda hay) plus 3.5 lb daily of a ration balancer that is high in micronutrients

and low in calories (e.g., Buckeye's Gro 'N Win). At 1 year of age (based on birth date), the supplement is reduced over 1 week to 1 lb daily. Foals should be confined in a stall except for limited round-pen or equivalent turnout time, certainly without access to pasture. Good results are claimed for slightly affected foals, although breaking, training, and racing are set back several months and the foals look poor as yearlings.[35]

Surgical.

Ventral interbody vertebral fusion is the principal procedure. In this surgery, pairs of vertebrae are fused in extension by implantation of a cylindrical stainless steel or titanium basket (Cloward Bagby basket) filled with autogenous cortical bone fragments.[36,37] Osseous union of the vertebral bodies and stabilization of the articular process joints occurs after this surgery, although nonunion is an occasional postoperative problem. A modification involves use of a threaded titanium implant that screws into a prepared circular, threaded kerf around an isthmus of preserved bone. By leaving the isthmus and its blood supply intact, it is expected that complete bony fusion occurs more quickly. A plate may be secured over the implant, but this does not prevent retrograde migration of the implant.

The surgery provides immediate relief from dynamic stenosis and may improve static stenosis over months by causing atrophy of arthritic intervertebral joints. In the latter case, intraarticular administration of corticosteroid may hasten atrophy of the enlarged joint. The surgery results in improvement in neurologic status in 44% to 90% of horses with dynamic compression and 12% to 62% of treated horses return to athletic function.[36-39] Overall, the success rate offered by most surgeons is approximately 60%, with normal myelographic columns expected by 2 months after surgery and complete osseous union by 1 year postoperatively. On average an improvement of 1 to 2 grades is expected.[38] Results of surgery for dynamic compression were significantly better than those for static compression in one published series.[40] Although there is a general impression that increasing time since onset of signs, higher neurologic grade, and multiple surgical sites are negative indicators for response to stabilization surgery, published results are not consistent with regard to any of these issues.[36] Even three-site surgeries can be successful, although neck mobility is diminished.[41] The use of a locking compression plate has been described with initial promising results.[36] If the results of locking-plate surgery continue to be

positive, such procedures may become more widely available, obviating the need for the specialized equipment needed for implant surgery.[36]

Dorsal subtotal decompressive laminectomy[42] provides immediate relief for static compression but technically is extremely difficult and fraught with severe postoperative complications.

Neuroaxonal Dystrophy/Equine Degenerative Myeloencephalopathy

Robert J. MacKay

■ History and Epidemiology

Since the original description in 1976, neuroaxonal dystrophy (NAD)[1] and the related condition equine degenerative myeloencephalopathy (EDM)[2] have been reported throughout the world in horses and ponies of many different breeds and in other equids, including a donkey, Przewalski's Horses, and zebras.[3-6] The clinical signs of NAD and EDM are identical, and the associated CNS lesions are thought to be on a continuum wherein EDM lesions are more widely distributed than are those of NAD.[3,4] For the rest of this section, the condition is referred to as *NAD/EDM*.

Clinical signs usually begin within the first year of life: with only a few reported exceptions, all have begun by the age of 3 years.[7] A hereditary basis for the condition has been strongly suggested by the results of breeding studies or pedigree analyses in Morgan, Appaloosa, Quarter Horse, and Lusitano horses.[4,8,9] The mode of inheritance is suspected to be polygenic or autosomal dominant with variable penetrance.[4,5,8,10] A familial basis has also been suspected because of clustering of cases among the progeny of particular Standardbreds, Paso Finos, Norwegian Fjord horses, Arabians, Welsh ponies, and Haflingers.[6,11]

Overcrowding, pelleted feed, poor-quality hay, and lack of access to fresh green forage were thought to be risk factors on two affected premises.[12] In another study, significant risk factors were exposure to insecticides/repellents, exposure to wood preservatives such as creosote, and time spent on dirt lots.[7] Time spent on green pasture was a protective factor. In contrast, several clusters of cases in Oregon and California occurred in horses on pasture.[6,9] In the latter

instance, the pasture was growing on volcanic soil that was deficient in selenium and vitamin E.[6]

With rare exceptions,[7,13] NAD/EDM is consistently associated with marginal or low serum/plasma vitamin E concentration. Published normal ranges of α-tocopherol vary with age, location, season, diet, and use; however, a commonly accepted scheme classifies results greater than 2 µg/mL as normal, 1.5 to 2 µg/mL as marginal, and less than 1.5 µg/mL as deficient.[12,14] Healthy horses sharing feedstuffs and environment with affected horses usually also have low levels of vitamin E,[5,15] although foals in an Appaloosa family with hereditary NAD/EDM had significantly lower plasma vitamin E than did age-matched normal pasturemates,[15] and Quarter Horse foals that developed NAD/EDM had significantly lower CSF vitamin E concentrations than did heathy foals maintained on the same vitamin E–deficient diet.[5]

■ Cause and Pathogenesis

NAD/EDM most closely resembles ataxia with vitamin E deficiency of humans and other animals.[4,6,14] The neuroprotective effects of vitamin E are related to inhibition of oxidation of CNS membrane lipids and facilitation of axonal transport of macromolecules.[14] Direct support for the antioxidant role of vitamin E in horse CNS is provided by the results of global transcriptome analyses of affected and normal spinal cords that suggest a protective role for vitamin E in preventing accumulation of oxidized cholesterol (oxysterol) in the setting of lipid peroxidation and demylination.[16] Although familial isolated vitamin E deficiency of humans is caused by mutations in the α-tocopherol transfer protein gene, expression of the messenger RNA of this gene was similar between one unaffected horse and two horses with NAD/EDM from a group of related Quarter Horse weanlings and yearlings.[6] Low serum levels of vitamin E in horses with NAD/EDM is not explained by impaired intestinal absorption: oral vitamin E tolerance tests were normal in affected horses.[15]

■ Clinical Signs

NAD/EDM is characterized by an acute, occasionally insidious-onset, symmetric ataxia and paresis of the trunk and limbs. Clinical signs typically appear between the ages of 1 and 12 months but have occurred in neonates and mature horses.[3,4] Posture and gait are wide based, and affected limbs demonstrate notable

hypometria (spasticity). Signs are typically considerably more severe in the pelvic limbs, and the thoracic limbs may be clinically normal. In two reports, it was noted that limb weakness was observed only in horses with moderate or severe ataxia and was not recognized in many horses that were mildly ataxic.[4,6] Some horses with NAD/EDM adopt a two-beat lateral ("pacing") gait at walking speed. Long spinal reflexes such as the cervicofacial, laryngeal adductor (slap), and cutaneous trunci reflexes may be reduced or absent, especially in long-standing cases. Neurogenic muscle atrophy is not characteristic of NAD/EDM, and cases were reported in horses with body condition scores of 5 to 6 out of 9.[4,6] Signs of brain dysfunction were not reported until the early 2010s. Of 88 Quarter Horses with NAD/EDM (NAD), 77 were described as dull or obtunded and minimally responsive to light flashes, sudden movement, or loud noises.[6] An EEG obtained from one affected horse revealed dominant states of drowsiness to slow-wave sleep. Reduced or absent menace responses were noted in 33 of the 88 Quarter Horses and in 4 of 6 Lusitanos with NAD/EDM.[4,6] Vision, pupillary light reflexes, ophthalmologic examination findings, and electroretinograms were normal.

Signs may not worsen after initial onset; others progress for days to months before stabilizing. Only rarely does the condition progress to recumbency.

■ Laboratory Findings

There is no antemortem diagnostic test for NAD/EDM. Plasma/serum vitamin E concentrations of NAD/EDM horses and pasturemates are often marginal or low. Because vitamin E concentrations within individual horses vary considerably over time (especially if they are low), it is recommended that three blood samples be taken over the course of 24 hours.[14,15] Samples must not be visibly hemolyzed and should be stored so that the blood is not in contact with the rubber stopper. Plasma CK and AST activities may be slightly to moderately high because of increased recumbency.[9]

■ Diagnosis

Diagnosis during life is presumptive only and is made primarily by suggestive signalment and clinical signs with exclusion of competing diagnoses. NAD/EDM should be suspected in horses with symmetric limb ataxia that began within the first year of life and for which results of standard neurologic workups (cervical vertebral radiographs, CSF analysis, immunoassay for *S. neurona*

antibody) have not implicated another diagnosis. Low or marginal serum/plasma vitamin E concentration (≤2 µg/mL) is supportive of the diagnosis.

■ Necropsy Findings

Necropsy reveals no abnormal gross findings. Histologic changes develop in the spinal cord and brainstem.[4,6,9,13] Lesions in the lateral and medical cuneate, gracilis, and thoracic nuclei are characterized by spheroid formation with vacuolation, loss of somata, astrogliosis, and lipofuscin pigment accumulation. In addition, axonal necrosis and demyelination of the dorsal and ventral spinocerebellar tracts, the cuneocerebellar tracts, and and the ventromedial funiculi of the cervicothoracic spinal cord may be present. Calretinin immunohistochemical staining was used to show that the cell bodies of degenerated axons in NAD/EDM-affected horses probably are located in the dorsal root ganglia.[17] No histologic lesions were found to explain observations of dull mentation[18] and abnormal menace responses[4,6] in reported case series.

■ Treatment and Prevention

It is unlikely that NAD/EDM can be cured even if treated early. Slight to no improvement was observed in affected horses given vitamin E supplements of 2000 to 8000 IU daily.[9,12] The type of vitamin E and the method of supplementation have important effects on its bioavailability. Natural vitamin E (RRR-α-tocopherol) is up to twofold more active than synthetic vitamin E (d,l-α-tocopherol or all-rac-α-tocopherol). Absorption requires fat, and so bioavailability of vitamin E is negligible or low unless it is given with feed or vegetable oil.

In accordance with the notion that NAD/EDM is associated with some interaction between inherited metabolic defect and vitamin E deficiency, vitamin E supplementation appears to be at least partially effective prophylaxis and is recommended in circumstances that involve familial predisposition, processed feed, lack of access to pasture, and exposure to insecticides or wood preservatives. In one study, the incidence of NAD/EDM was reduced from 36% over 3 years to 9% by supplementation of foals with 1500 IU vitamin E daily.[12] Similar results were observed in two other clusters of cases.[6,12] Sensible genetic, nutritional, and other management practices alone could greatly reduce or eliminate the risk of NAD/EDM.

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Spinal Cord Trauma

Robert J. MacKay • Lisle W. George

Vertebral trauma is a relatively common cause of spinal cord dysfunction in both livestock and horses. The spinal cord is normally protected by a complex of bones and ligaments that can be conceptualized in biomechanical terms as two columns: dorsal and ventral.[1] The ventral column consists of the vertebral bodies, intervertebral disks, and dorsal and ventral longitudinal ligaments, whereas the dorsal column consists of alternating bony complexes (arches, articular processes, and dorsal spinous processes) and ligamentous complexes (supraspinous ligament, interspinous ligaments, ligamenta flava, and joint capsules). According to biomechanical models that have been used for assessment of spinal trauma in humans and small animals, acute spinal instability occurs when there is disruption of *both* of these columns by external mechanical forces. The corollary is that a single intact column provides stability. This two-column system has not been validated for large animals. Fractures of vertebral transverse processes and dorsal and ventral spinous processes and partial fractures of vertebral bodies or arches (i.e., stress fractures) do not cause spinal instability or neurologic signs.[2]

Most, but not all, traumatic spinal cord injuries are accompanied by vertebral fracture, subluxation, or dislocation.[3] Conversely, many spinal injuries are associated with pain, reduced mobility, and abnormal neck position but do not cause acute neurologic signs. In large animals, cervical spinal cord trauma is usually caused by hyperextension or hyperflexion of the spine in the sagittal plane with superimposed vectors of compression, distraction, rotation, or shear. With vertebral hyperextension, compressive force is applied to the dorsal column and distractive force to the ventral column, whereas the reciprocal forces apply to hyperflexion injuries. In all cases, the likelihood of associated spinal cord compression is higher in animals with abnormally narrow vertebral canals. Disk prolapse and fibrocartilaginous embolization of the spinal cord are rare in large animals and, when they occur, are usually associated with degenerative changes rather than with acute trauma, as may occur in dogs.[4-6] Young animals are subject to fractures involving epiphyseal or growth plates (i.e., Salter-Harris fractures). Vertebral infections may be seeded along these cartilaginous plates hematogenously or by direct traumatic implantation, and osteomyelitis may progress to the point of pathologic vertebral fracture. Poorly balanced nutrition or undernutrition decreases bone density and increases susceptibility to vertebral

fractures.

Horses

In racehorses, cranial or vertebral fractures have accounted for 2.5% to 3% of deaths at flat races and 16% to 23% of deaths at chase and hurdle starts.[7] In a 3-year study of fatal fractures/dislocations in the spine of 125 horses at racing events in Britain, 23% involved the cervical vertebrae, whereas the remainder involved the thoracolumbar vertebrae.[8] Necropsies of 60 horses with vertebral trauma in Australia showed that 33 injuries involved cervical vertebrae; 10, thoracic; 10, lumbar; and 2, sacral.[9] In general, cervical vertebrae are more prone to fractures during accidents at jumping events (e.g., cross-country, showjumping, foxhunting, steeplechasing, and hurdling). The occipitoatlantoaxial region is most often involved in the following situations: (1) broad forehead impact, as in collisions with the ground, other horses, or fixed objects; (2) rearing and flipping over backward; or (3) when major distraction forces are applied to the head, as occurs in tied horses jerking backward on a halter. The atlantal ring or body of the axis may be fractured, the dens may fracture transversely anywhere along its length (including at the synchondrosis in young horses), or the dens may subluxate or dislocate from its usual position in the fovea dentis of the atlas. Fracture of a single articular process is the most common fracture from C3 to C7. In young horses (especially those younger than 2 years), a characteristic and spectacular hyperextension fracture results in severe extension angulation of the intervertebral joint.[10,11] On the more cranial of the affected vertebrae, the dorsal lamina and caudal articular processes are fractured and lifted dorsally. It is thought that this “deroofing” lesion provides natural decompression of the spinal cord while the surprisingly sturdy dorsal half of the intervertebral disk provides residual stability of the ventral column of the cervical spine.

In the thoracolumbar spine, T1 to T3, T10 to TI6, and T18 to L6 appear to be relatively susceptible. Lumbar vertebral fractures reported in 38 Quarter Horse and 29 Thoroughbred racehorses primarily involved L5 and L6 and were the third most common musculoskeletal cause of death in Quarter Horses during the 22 years of data collection.[12] All cases had abnormalities on the ventral aspect of the vertebral bodies, which suggests that preexisting pathologic conditions at the L5-L6 junction probably predispose horses to catastrophic fracture. Foals and young horses at pasture are prone to collide with fixed objects or other horses,

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get kicked by adult horses, or pitch forward headfirst into the ground, all while running at high speed. Such accidents often occur at night. Typical hyperflexion and hyperextension injuries of the cervical spine result from these falls, and cranial thoracic and midback fractures result from striking solid objects or being kicked. Horses may suffer contiguous or noncontiguous injuries of multiple vertebrae after high-speed impacts. Any horse that falls backward or struggles violently against a caudal barrier (e.g., in a trailer) may sustain sacrococcygeal fractures with damage to the cauda equina. There are reports that avulsion of the cauda equina can be caused by lifting or dragging a recumbent horse by its tail. It is worth noting that horses may have serious spinal injuries while alone in a stall, without observed or external evidence of an accident, so trauma should always be considered in cases of acute onset of spinal cord signs, regardless of the environment.

Livestock

The common sites of spinal fractures in calves are C2 to C4, T10 to T13, and L3 to L6 vertebrae. Vertebral fractures (particularly compression fractures) are especially common in 3- to 6-month-old ruminants as a result of nutritional problems including vitamin D, calcium, and copper deficiency or low calcium-to-phosphorus ratio.[13] Nutrition-related fractures usually involve several animals and may also involve the ribs and long bones. Traumatic cervical vertebral fractures of cattle and small ruminants may be caused by injuries sustained in falls, roadway accidents, butting of other animals, collisions with moving farm machinery, predation, or accidents in tie-stalls, stanchions, or squeeze chutes.[13-15] Spinal injury is especially likely to occur if the head is restrained in the chute or stanchion when the animal falls. Fractures or dislocations of the lumbar or sacrococcygeal spine frequently occur in cattle that slip in wet cemented areas and in performance-age bucking bulls.[14,16] Many of these fractures occur in cows in estrus during mounting by herdmates. Spontaneous fractures of vertebrae weakened by congenital defects (e.g., hemivertebrae) or osteomyelitis also are common problems in calves.[17] Traumatic dislocations, subluxations, or fractures of the atlantooccipital and atlantoaxial joints of pygmy goats may occur when the horns are held during restraint. Thoracolumbar fractures, particularly with epiphyseal separation of the middle to caudal thoracic vertebrae, may occur in calves transiting the birth canal during correction of dystocia.[18-20]

These fractures are mainly related to excessive traction and rotational force.[21]

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Luxation of a sacroiliac joint in the dam may occur with the use of extreme force during manual extraction of a calf. Mature Holstein bulls and rams may have a fused thoracolumbar spine and stenotic vertebral canal because of ankylosing spondylitis. This condition results in progressive pelvic limb paresis and ataxia.[22] These animals are at risk for traumatic lumbar vertebral fracture, spinal cord injury, and recumbency if they are required to mount for semen collection or breeding.[23] As described for horses, vigorous traction on the tail (e.g., when trying to assist a downer cow to stand) has the potential to cause stretching or avulsion of the cauda nerve roots and signs of cauda equina syndrome.

■ Pathophysiology

The primary phase of spinal cord injury is the direct effect of the mechanical events of the original trauma.[24] The primary phase is irreversible, but additional rounds of primary injury can be prevented or minimized by surgery and external stabilization of the spine. The principal mechanical forces that are involved in acute traumatic injury are concussion, compression, shear, laceration, distraction, and contusion of the spinal cord. The secondary phase of spinal cord damage comprises the injurious molecular and biochemical events that are set in motion by the primary injury and occur in the first few hours after initial injury. The goal of medical therapy is to limit the damage that occurs from secondary injury. The most important events during this phase of injury are vascular damage with hemorrhage and microthrombosis, loss of autoregulation of blood flow, excessive release of the excitotoxic neurotransmitters aspartate and glutamate, increased neuronal intracellular calcium concentration, cellular damage from reactive oxygen species, and acute neutrophilic inflammation.

■ Clinical Signs

The most common sign of vertebral trauma in all large animal species is localized pain and limited mobility of the affected part. The atlantoaxial vertebral canal of horses is subject to fractures, subluxations, and dislocations, many of which do not cause signs of neurologic dysfunction, presumably because of the large cross-sectional area of the vertebral canal at this level of the spine.[25] Two quite rare disorders result from spinal cord trauma and confound the rules of neuroanatomic localization: spinal shock and Schiff-Sherrington syndrome. *Spinal shock* refers to loss of muscle tone and segmental spinal reflexes caudal to a focal severe transverse spinal cord injury, usually between

T3 and L3.[26] Although seldom described in the veterinary literature, it does occur in large animals, but, in contrast to the situation in humans, areflexia usually lasts less than 30 minutes, after which there is progressive recovery of segmental reflexes; persistence of signs is referable to a focal spinal cord lesion. With such a lesion, the thoracic limbs may be hypertonic, which reflects release from the inhibitory effect of tracts originating in the lumbar segments. This combination of paraplegia and thoracic limb stiffness is known as *Schiff-Sherrington syndrome*.[27] At least in small animals, signs regress by approximately 10 days. Spinal shock and Schiff-Sherrington syndrome may occur together or separately.

■ Diagnosis and Treatment

The first priority is the safety of attending personnel, which means that large patients that are thrashing and disoriented may need to be heavily sedated or anesthetized to allow for initial assessment, IV catheter placement, and treatment of any life-threatening conditions. Small ruminants theoretically can be taped to a backboard to immobilize them in lateral recumbency during initial procedures. Handlers must be careful not to exacerbate cervical vertebral trauma when restraining injured animals via lead rope and halter.

An indwelling IV catheter should be inserted and secured, and IV fluids and initial treatment should be provided as needed. Volume support and maintenance of normal arterial pressure and hematocrit are essential in all forms of CNS injury.[28] Any animal with spinal injury and neurologic signs should be provided with full doses of analgesics. NSAIDs (e.g., flunixin meglumine, 1.1 mg/kg IV or PO bid) have the dual advantages of analgesic effect and inhibition of potentially injurious cyclooxygenase activity.[24] Additional analgesia can be achieved if necessary by doses of butorphanol, morphine, or lidocaine or ketamine constant-rate infusions. The use of methylprednisone sodium succinate in this setting in human medicine remains highly controversial, although slight long-term benefits have been reported for a regimen of 30 mg/kg, followed by 5.4 mg/kg/h for 23 hours.[29,30] Patients are at an increased risk for pneumonia, sepsis, and hyperglycemia. The use of methylprednisolone is becoming less popular because the risks of complications outweigh the potential benefits[31]; high-dose methylprednisolone sodium succinate is not recommended in large animals with acute spinal cord injury. As is the case for brain injuries, antiinflammatory doses of dexamethasone (0.05 to 0.1 mg/kg IV or IM once

daily) should be administered routinely.

As soon as possible, a careful neurologic examination should be performed to localize the lesion. It is important that this examination be complete even if the site of injury seems obvious because multiple discontinuous spinal cord segments or the brain, or both, may be injured in a single traumatic incident.[32]

When technically possible, it is prudent to radiograph the entire vertebral column. In large animals under field conditions, views are generally restricted to laterolateral projections of the cervical vertebrae. Radiographs show the amount of spinal displacement at the time they are taken, however, not the amount of displacement that occurred at the time of injury. The two-column model can be used to assess spinal instability.[1] Myelography is usually not necessary if it is determined that the spinal injury can be treated conservatively or if there is a substantially displaced fracture or luxation that is an obvious candidate for surgery. Myelography should be performed in animals with marked neurologic deficits and normal or equivocal radiographs. Additional information can be obtained from oblique and ventrodorsal radiographic views, C-arm fluoroscopy, CT, MRI, and osseous-phase nuclear scintigraphy. Techniques that necessitate general anesthesia in a large animal with spinal instability generally should be avoided unless there is an immediate surgical option.[10]

After these initial evaluations, the clinician has sufficient information to make recommendations for euthanasia, conservative treatment, or surgical management. Obviously, humane considerations, economic issues, and the intended use of the patient are driving considerations in this situation. In all cases, if quadriplegia and loss of deep pain are present, or in view of radiographic evidence of likely spinal cord transection, early euthanasia is appropriate. Otherwise, with the issues of handler safety and humane treatment kept paramount, it is reasonable to wait 12 to 24 hours to allow time for recovery of function before delivering a hopeless prognosis and euthanasia recommendation. Once the decision has been made to continue treatment, most large animals are still managed conservatively; surgery is an option in selected cases.

Conservative Management.

For large animals with vertebral column injury, 1 to 2 months of each of the following is recommended: full-time stall confinement; stall confinement with daily hand-led walking; turnout into a small paddock or round pen during the day with stall confinement at night. Pain control and sedation should be provided

as needed. In horses that have difficulty getting to their feet, frequent use of an abdominal sling is essential. Such horses must be able to support their own weight once they are in the standing position. In cattle, a flotation tank can be used for the same purpose.

Surgery.

In the absence of evidence-based guidelines for surgical intervention in large animals, it is worth considering the potential adverse consequences of *not* performing surgery. Although conservative management has often been successful, the following negative outcomes have been observed in horses with spinal injuries managed conservatively: (1) sudden recumbency days to weeks after dens fracture, subluxation, or dislocation[2,33]; (2) limb ataxia and weakness after callus formation and joint remodeling around a fractured articular process[11]; (3) progressive torticollis, head tilt, or both after articular process and vertebral body fractures in the midcervical region; (4) limb ataxia and weakness after fibrous proliferation at the site of previous atlantoaxial subluxation; (5) abnormal head position and stiffness of the upper neck after upper cervical injury; and (6) a domino effect wherein there is progressive stenosis of the vertebral canal at the intervertebral joint or joints immediately caudal or cranial to a traumatized intervertebral joint that has healed in a marked flexed or extended angle.[11,20]

In view of these developments, reasonable indications for surgical intervention in horses are (1) prevention of neck stiffness or deformity; (2) prevention of callus formation or joint remodeling that may impinge on the spinal cord; (3) decompression, stabilization, or both of the atlantoaxial joint after dens fracture, subluxation, or dislocation[25,33,34] and (4) decompression or reduction and stabilization of vertebral fractures/subluxations in response to deteriorating neurologic signs. Techniques have been described for each of these surgical procedures (generally with successful outcomes) in the cervical spine of horses.[10,35-37] Canine surgical techniques can be adapted for use in the lumbosacral spine of valuable small ruminants, calves, and foals. In particular, the use of polymethylmethacrylate and Steinmann pins and plating of the dorsal spinous processes have wide potential application to thoracolumbar injuries in animals weighing less than 70 kg.[38] Surgical decompression of the cauda equina by dorsal laminectomy of the sacrum has been described. In adult horses, the tuber sacrale of the pelvis interfere with the approach to the first and possibly the

second sacral vertebrae, but the caudal part of the sacrum can be decompressed.[39] In foals and heifers, sacral fractures may be reduced and stabilized with plates and screws.[40]

■ Prognosis

For horses with spinal trauma without neurologic dysfunction that are treated conservatively, there is a fair to good likelihood that neurologic signs will not develop; however, there is also a fair chance that the neck will remain stiff, become deviated or rotated, or both. The prognosis for horses with spinal cord trauma associated with luxations or fractures of the vertebral body, arch, or articular processes must remain guarded to poor for return to use. Healing of such fractures frequently results in some degree of vertebral malalignment, sometimes with lordosis, kyphosis, scoliosis, or torticollis. Even after apparent healing and resolution of neurologic signs, delayed callus formation and degenerative changes in adjacent articulations can result in delayed spinal cord compression. When the injured spine is appropriately stabilized, improvement may continue for up to a year. In a small quadruped, it is estimated that even 10% survival of axons across a lesion site in the spinal cord may be compatible with walking. The limbs behind a permanent spinal cord lesion will be ataxic and weak to lateral pressure but spastic and stiff during walking and able to resist dorsal pressure.

Ankylosing Spondylitis of Holstein Bulls

Lisle W. George

Ankylosing spondylitis is an inflammatory disease of joint tissue associated with fusion of lumbar vertebrae in Holstein bulls. Approximately 4% of all Holstein bulls intended for artificial insemination are culled each year because of spondylitis.[1] The clinical onset of the condition is insidious. The first signs of the disorder are a stilted gait, reluctance to move, and dragging of the toes of the rear limbs. Affected bulls are slow to mount teaser dummies for collection. The condition is progressive, and over several months the animals develop paraparesis and ataxia. With mounting, the ankylosed area of the spine may fracture, leading to acute recumbency. Pathologic changes associated with the condition include calcification of the ventral vertebral ligaments between the T11 and L3 vertebrae. The condition appears to be hereditary. All bulls with the

condition possess the class I major histocompatibility complex BoLA A8 phenotype. In comparison, the phenotypic frequency of BoLA A8 in the general population of normal Holstein bulls is only 44%.[2]

Spinal Tumors

Robert J. MacKay • Lisle W. George • Mary O. Smith

With the exception of lymphosarcoma in cattle, tumors involving the spinal cords of domestic animals are rare. In the horse, tumors within the spinal cord or dura (i.e., intramedullary or extramedullary-intradural) have included meningioma, ependymoblastoma, angioma, angioblastoma, ganglioglioma, schwannoma, and neurofibroma.[1] Reported extradural tumors are lymphosarcoma, plasma cell myeloma, neurofibroma, fibrosarcoma, melanoma, hemangiosarcoma, and carcinoma.[1-4] The tumor that most commonly affects the spinal cord of ruminants is lymphosarcoma, but others, such as histiocytic sarcoma, glioma, neuroblastoma, and embryonal neuroectodermal tumors, have been reported.[5-9]

■ Clinical Signs

The clinical signs of tumorous invasion are usually referable to a single-site spinal cord lesion, although extradural tumors such as lymphoma can extend over multiple spinal cord segments.[9] The rate of onset of the neurologic dysfunction varies. Some neurofibromas, melanomas, and lymphosarcomas invade centripetally along the peripheral nerve rootlets. Affected patients develop slowly progressive limb ataxia and weakness caudal to the location of the lesion, which eventually leads to tetraplegia or paraplegia. In rare cases, the onset of tetraplegia may be peracute and unaccompanied by prodromal neurologic signs. Lymphosarcoma has a predilection for the lumbar segments of the spinal cord and the cauda equina in cattle older than 5 years (Fig. 35.19). A diagnosis of spinal cord tumor should be considered in cases of progressive neurologic disease characterized by flaccid tail and anus, dysuria, perineal scalding by urine, distended bladder, perineal analgesia or anesthesia, and paraparesis. Most animals with spinal tumors are mature to older adults; immature animals are affected in rare cases, mainly by embryonal tumors.[8-11]

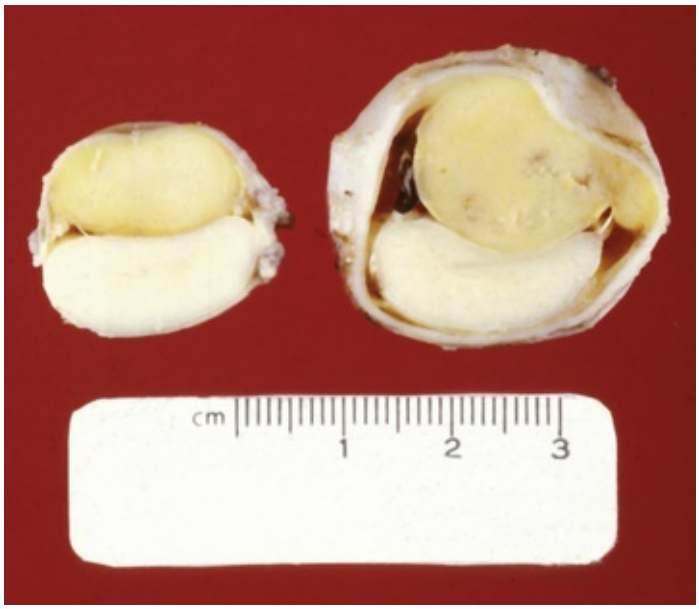


FIG. 35.19 **Epidural lymphosarcoma in a 5-year-old Holstein dairy cow. The tumor had spread from neoplastic periaortic lymph nodes and had expanded to compress the caudal lumbar and cranial sacral spinal cord segments, which resulted in signs that resembled bilateral sciatic paresis. Tumorous masses are above the compressed spinal cord in the two transverse sections shown.**

■ Clinical Pathology

Examination of CSF may be useful when the tumor has infiltrated the cauda equina and is located in the lumbosacral cistern. In these cases, tumor cells may sampled for biopsy as the needle is inserted into the lumbosacral space. In other cases the CSF may be normal, or albuminocytologic dissociation can be expected (elevated CSF protein levels with normal to mildly elevated nucleated cell count) with or without variable degrees of hemorrhage and xanthochromia. After necropsy, various immunohistochemical techniques can be used to identify the tumor type when routine histologic examination is insufficient.

■ Treatment

There is currently no treatment for most spinal cord–associated tumors of large animals; however, protocols could be adapted from those used for other forms of lymphoma in horses or for other solid tumors in small animals. In one study, a cow survived for 57 days after three treatments with L-asparaginase at 10,000 IU/m^2 surface area. The nearly 2-month period of survival allowed the investigators to successfully superovulate the cow. When treating food animals with L-asparaginase, the benefits of the antimetabolite drug must be weighed

against the potential for teratogenicity of the fetus, toxicity for humans, and the certainty of relapse in the patient.[12]

Verminous Meningoencephalomyelitis

Robert J. MacKay

Verminous meningoencephalomyelitis is caused by the meanderings of one or more parasites through the CNS and is therefore an extremely variable clinical entity. Depending on the number, size, and location of the parasites and the duration of their migration through the brain or spinal cord, a spectrum of signs is possible, ranging from a nonprogressive localizing neurologic deficit to rapidly fatal, diffuse encephalitis. Verminous meningoencephalomyelitis usually occurs sporadically and has been associated with strongylid *(Strongylus vulgaris)*, metastrongylid *(Angiostrongylus cantonensis, P. tenuis)*, filarid (*Setaria* spp.), tylenchid (formerly rhabditid; *Halicephalobus gingivalis*), and spirurid *(Draschia megastoma)* nematodes, as well as warble fly larvae (*Hypoderma* spp.).

Strongylus Vulgaris

Verminous myeloencephalitis due to *S. vulgaris* in the CNS is a rare, aberrant event resulting from embolization to the CNS of L4 or L5 larvae from verminous thrombi in the left ventricle, proximal aorta, or any of the aortic branches that supply the CNS.[1,2] *S. vulgaris* larvae in the aorta migrate subintimally upstream from locations in the proximal cranial mesenteric artery.[2] As a result of disintegration of thrombi in these aberrant locations, clot fragments and larvae migrate to the CNS. Three outcomes are possible: (1) acute massive infarction, ischemia, and edema of the brain; severe neurologic dysfunction; and death after a brief clinical course; (2) nonlethal or even subclinical embolization of the CNS that is followed by entry of one or more larvae into the CNS parenchyma, which wander therein for up to several months, producing associated neurologic signs; or (3) subclinical embolization and parasite migration. Subclinical larval migration occurs in relatively forgiving parts of the cerebral hemispheres and ends when the parasite dies or migrates out of the CNS.

A single larva can migrate through many levels of the CNS; in one case, an L5 *S. vulgaris* larva was estimated to have traveled 8 cm per day for several days

along the spinal cord of a donkey.[3] Virtually any clinical sign is possible, and signs are likely to change dramatically over time or even stop and then restart or spontaneously resolve. A larva may exit the CNS only to reenter at a different location and continue its migration. The donkey mentioned earlier was paraparetic and sitting like a dog because of larval damage through the midlumbar spinal cord; signs improved for a few days when the larva migrated out of the spinal cord, but then the animal collapsed into recumbency when the larva reentered and migrated within the cervical spinal cord.[3] Thrombosis, infarction, and tortuous hemorrhagic or discolored tracts may be evident on gross examination. Microscopic findings include linear tracts of hemorrhage lined by neutrophils, macrophages, occasional eosinophils, and reactive glial cells. CSF changes associated with *S. vulgaris* migration include xanthochromia, protein concentration ranging from 32 to 550 mg/dL, and increased nucleated cell count (42/µL to 10,000/µL).[1-4] The differential counts range from 70% to 80% neutrophils, 12% to 19% mononuclear cells, and 1% to 2% eosinophils. Verminous myeloencephalitis due to *S. vulgaris* virtually disappeared after the introduction of the macrocyclic lactone anthelmintics in the 1980s; however, the increasing practice of selective deworming may enable the reemergence of large strongyles.[5]

Hypoderma Lineatum and *Hypoderma Bovis* (Cattle Grubs)

Hypoderma lineatum (common cattle grub) and *Hypoderma bovis* (northern cattle grub) are parasites of cattle that occasionally migrate in the horse (also in goats and deer). In the late spring or early summer, adult *Hypoderma* spp. flies (known as *warble flies* or *heel flies*) deposit eggs on hairs on the limbs or lower body. First-stage larvae hatch in 5 to 7 days, penetrate the skin, and migrate in a dorsal direction along fascial planes, often following the paths of blood vessels or nerves.[6] Over approximately 1 year, migrating larvae moult once or twice and arrive in subcutaneous tissues along the back. Their dorsally directed path may sporadically take larvae through the foramen magnum or other foraminae of the skull to penetrate and meander in the brainstem. Because of the large size of *Hypoderma* spp. larvae and their propensity for migration within the caudal fossa of the skull, neurologic signs are usually severe, progressive, and fatal.[6,7] Typically, affected animals exhibit profound obtundation and signs of asymmetric cranial nerve dysfunction (e.g., head tilt and circling) that worsen quickly and lead to recumbency and death. Since the advent of pour-on and

injectable systemic organophosphate insecticides in the 1950s and macrocyclic lactones in the 1980s for systematic treatment of cattle, *Hypoderma* populations have decreased dramatically in the United States and have been eradicated in several European countries, and so intracranial myiasis is now unlikely to occur in industrialized countries. *Hypoderma diana,* a parasite of deer, has also infested horses and presumably has the potential for CNS invasion.[8]

Halicephalobus Gingivalis

H. gingivalis (previously *Halicephalobus deletrix, Micronema deletrix*) is a free-living microbivorous tylenchid nematode that feeds on bacteria in rich organic environments such as decaying vegetation, compost, or manure.[9,10] Cases of meningoencephalomyelitis caused by *H. gingivalis* occur sporadically worldwide in equids (including zebras) and occasionally in humans and cattle.[11-17] The nematode opportunistically enters the body through breaks in the mucous membranes (and possibly skin) of the nose, mouth, prepuce, and mammary gland of horses and invades and proliferates locally to cause clinically apparent granulomas.[18-23] Such masses can be locally invasive and destructive, particularly in the jaws, nasal cavity, and paranasal sinuses.[18,24] In one case a foal was apparently infected by suckling from its dam, which had *H. gingivalis* mastitis.[25] From these superficial sites, larvae or adults may enter lymphatic or venous drainage and be distributed hematogenously to various organs and tissues.

H. gingivalis has a propensity to invade and proliferate in the kidneys (Fig. 35.20), CNS, and eyes, but lesions have also been found in long bones, the heart, the lungs, the liver, the uterus, the testes, lymph nodes, and the walls of the aorta and pulmonary arteries.[23,26-28] The brain is the usual site of CNS infection, with lesser involvement of the spinal cord or, in one instance, the cauda equina.[29] The typical severe progressive neurologic signs are due to massive proliferation of nematodes adjacent to blood vessels and the associated florid perivascular granulomatous inflammation.[9] Only female nematodes are present in lesions, and reproduction is by parthenogenesis.[9]

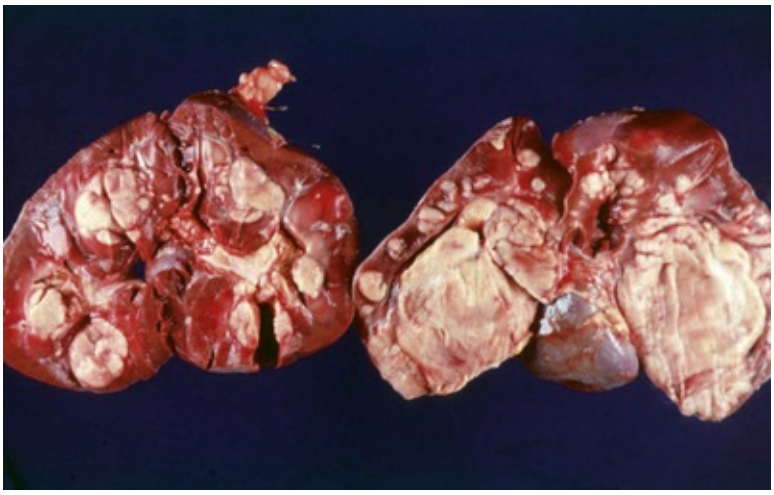


FIG. 35.20 Kidneys from a horse with disseminated *Halicephalobus gingivalis* infection, including fatal meningoencephalomyelitis.

Clinical signs of *H. gingivalis* infection of the CNS depend on the location of the lesions and include asymmetric ataxia, hypermetria in the thoracic limbs, obtundation, behavioral changes, compulsive walking, head pressing, head tilt, circling, nystagmus, recumbency, convulsions, and coma.[12-17,30-32] *H. gingivalis* meningoencephalitis is invariably fatal, regardless of treatment; affected horses die or are euthanized within several days of onset.[26,33] CSF analysis in affected horses ranges from normal to xanthochromic appearance with increased protein and mild to moderate pleocytosis of nucleated cells. Differential analyses reveal mostly mononuclear cells with lesser numbers of neutrophils and occasional eosinophils. In many (possibly most) cases of *H. gingivalis* meningoencephalitis, the animals also exhibit characteristic renal lesions.[26] The latter are usually multifocal large nodules in the renal parenchyma of one or both kidneys.[26,34] Of potential diagnostic significance in such cases are a history of weight loss, hematuria, or polyuria, or a combination of these, and findings at initial examination of nematodes in the urinary sediment, high serum creatinine and calcium concentrations, and ultrasonographically evident renal masses.[35-38] Severe progressive, usually unilateral verminous chorioretinitis or panophthalmitis may precede or coincide with the onset of signs of encephalitis.[37,39,40] Efforts to eliminate subcutaneous or renal *H. gingivalis* infections by surgery and anthelmintics are occasionally successful[21] but, unfortunately and unpredictably, are often followed within several days to weeks by the onset of encephalitis.[19,39,41-43]

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Parelaphostrongylus Tenuis

P. tenuis (the meningeal worm) is a ubiquitous parasite of white-tailed deer in the eastern United States (north of a line through the middle of the states along the Gulf of Mexico[44]). Infective larvae are ingested within infested snails and slugs, exit through the abomasum, and then migrate to the dorsal horn of the gray matter of the spinal cord, where they mature into adults before traveling along the dorsal nerve roots to the venous sinuses and subarachnoid spaces over the cerebral hemispheres. *P. tenuis* is increasingly a cause of verminous meningoencephalomyelitis due to aberrant larval migration in the CNS of other cervids, goats, sheep, and New World camelids within the same geographic range. In 2003, six equine cases with cervical scoliosis were described.[45] In each case, a unilateral multisegment contiguous lesion involved the dorsal horn of the gray matter on the convex side of the neck. In one case, cross-sections of a metastrongylid nematode were associated with the characteristic lesion, and the presumption is that all cases were caused by aberrant migration of *P. tenuis*. Five of the horses were younger than 1 year, and each exhibited acute onset of severe scoliosis after a variable prodrome with degrees of hypalgesia of the neck and cranial thorax, limb weakness, and limb ataxia, all on the side of the cervical convexity. Treatment with anthelmintics and antiinflammatories had no effect, and all affected animals were euthanized for humane reasons. An additional case, also in a young horse, was reported in 2007, this time with signs of obtundation, head tilt, circling, quadriparesis, and ataxia in all four limbs.[46] Numerous larval stages, eggs, and occasional adults of both sexes were associated with granulomatous eosinophilic inflammation in the cerebellum and adjacent brainstem. Presence of *P. tenuis* has been confirmed by PCR in lesions from the brain and spinal cord.[47,48] A *P. tenuis* nematode was extracted from the anterior chamber of a horse with signs of anterior uveitis.[49]

Angiostrongylus Cantonensis

A. cantonensis is a neurotropic metastrongylid parasite with a life cycle in rats closely analogous to that of *P. tenuis* in white-tailed deer.[50] It has long been endemic in the Pacific islands and Southeast Asia, but its range has spread into Australia, the United States, and the Caribbean. It is now well established among the wildlife of Louisiana.[51] The definitive hosts are species of wild rats that become infected by ingesting the infective larvae in slugs or snails. The larvae

migrate to the CNS to continue development before finishing the life cycle via the pulmonary vasculature. Inadvertent ingestion of infective larvae by atypical hosts such as humans, dogs, and horses may lead to aberrant migration in the CNS and signs of verminous meningomyeloencephalitis similar to those described earlier for *S. vulgaris*. Equine cases have been reported in two foals in Australia and an American Miniature Horse foal in Louisiana.[52,53] Larvae migrated in the gray and white matter of the spinal cord and brainstem. CSF analysis revealed mild pleocytosis with small numbers of neutrophils and eosinophils. Specific ELISA tests are available for testing of CSF in humans and dogs.[50]

Draschia Megastoma

D. (Habronema) megastoma is a spirurid nematode that has been found in the brainstem of a horse from the southern United States.[54] The adult worm is normally embedded in benign pyogranulomatous masses in the equine stomach, but larvae can invade wounds to cause granulating summer sores and have been reported to cause pulmonary nodules. The two unusual features of the solitary report of encephalitis are, first, the parasite found at necropsy was an adult gravid female and, second, there was a quiescent period of 6 weeks during the clinical course when clinical signs improved before the horse's condition deteriorated again.

Setaria Species

Setaria spp. are long, threadlike filarid nematodes that live without causing adverse effect in the peritoneal cavities of animals worldwide.[55] Microfilariae are released into the blood of the host and acquired by feeding mosquitoes, in which they undergo development to infectious larvae. Bovids outside the Americas are hosts to several setarial nematodes, including *Setaria digitata, Setaria labiatopapillosa,* and *Setaria marshalli*.[56-58] When inserted by mosquitoes into atypical hosts such as horses, goats, and sheep, immature *S. digitata* nematodes may migrate aberrantly through the CNS and other organs of atypical hosts.[57,59] This parasite has also migrated aberrantly in the CNS of cattle.[60] Outbreaks of so-called epizootic cerebrospinal nematodiasis, lumbar paralysis, or kumri occur during the summer or autumn when mosquito intermediate hosts are active. Outbreaks have been reported in Japan, Taiwan, China, Korea, Sri Lanka, Burma, India, Nepal, Iran, Israel, and Saudi

Arabia.[57,59,61,62] Cases in horses are sporadic and often involve older horses; in goats, young animals are usually affected, and morbidity and mortality rates are up to 100%.[57] *S. digitata* apparently does not occur in the United States[56]; however, a single case of verminous encephalomyelitis due to *S. labiatopapillosa* has been reported in this country.[63]

Clinical signs are variable and are related to mechanical and inflammatory destruction along the tracks left in the brain or spinal cord by one or more larvae.[59,64] In this regard, the pathologic features of setarial meningoencephalomyelitis are identical to those described earlier for *S. vulgaris*. Changes in the CSF associated with *Setaria* infestation include xanthochromia, pleocytosis (25 to 84 cells/µL), and a slightly increased protein concentration. The cells of one horse contained a small proportion of eosinophils and basophils, but this finding was inconsistent with other reports.

■ Treatment and Prevention

When single or a few migrating larvae are involved, the use of combinations of anthelmintics and vigorous antiinflammatory treatment has yielded successful outcomes. The latter component is probably important to prevent the effects of strong inflammatory responses against killed parasites.[50] Because penetration of the blood-brain barrier by anthelmintics is limited, high-dose benzimidazoles are often used for this purpose. Typical protocols are fenbendazole, 10 to 60 mg/kg by mouth or nasogastric tube, one to five daily doses, with dexamethasone (or equivalent), 0.05 to 0.1 mg/kg IV or IM, once daily for 3 days. Ivermectin was effective in goats with early signs of setarial myeloencephalitis[57] but has not been effective in treatment of *P. tenuis* or *H. gingivalis* cases in horses, even when used against *H. gingivalis* at a potentially toxic dose of 1.2 mg/kg (six times the recommended dose).[35] Diethyl carbamazine citrate, 40 to 100 mg/kg daily, was effective in natural and experimental setarial cases in horses.[65] Most types of verminous encephalitis are unlikely to occur in horses on a regular deworming program; however, *H. gingivalis* cases regularly occur in horses on any of a variety of regular anthelmintic regimens.

Postanesthetic Myelopathy and Encephalopathy

Robert J. MacKay

A sudden-onset progressive myelopathy that is recognized during recovery

from anesthesia has been described in horses and in a single calf.[1-6] Most of the horses initially described were large, young, and in dorsal recumbency under halothane anesthesia. There is a tendency for affected animals to be hypotensive during anesthesia. Paraparesis, ataxia, recumbency, or paraplegia is usually apparent during recovery from anesthesia but may be delayed as long as several days. Other reported signs include cutaneous hypalgesia and areflexia of the hindquarters and occasionally the thoracic limbs. Treatment is ineffective, and in all reported cases, the animals were been euthanized after a brief period during signs progressed rapidly. Lesions occur mainly in the lumbosacral spinal cord, although cervicothoracic segments also may be involved. There is malacia predominantly within gray matter (poliomyelomalacia), with associated mild to severe hemorrhage (hematomyelia) in most cases. Postanesthetic myelopathy is rare. CNS disease/myelomalacia contributed to 5% and 4% of anesthesia-related deaths in noncolic cases in the Confidential Enquiry of Perioperative Equine Fatalities (CEPEF), phases 2 and 3.[7]

Rare cases of postanesthetic encephalopathy have been described in horses.[5,8] Clinical signs include dementia, pacing and circling, cortical (“central”) blindness, ataxia, hypermetria, and recumbency. In mild cases, blindness may be the only clinical sign. The onset of signs ranged from a few hours after recovery from anesthesia to several weeks later. The major pathologic finding in affected horses that did not survive was cerebrocortical necrosis, particularly in regions of the cortex supplied by terminal arterial branches (“watershed zones”).

Although the pathogenesis of postanesthetic myelopathy is incompletely understood, it is proposed that compromise to the blood supply to the spinal cord is caused by hypotension or pressure from the abdominal viscera on the great veins (caudal vena cava, azygos vein). Systemic hypoxia, hypovolemia, and hypercapnia may underlie postanesthetic encephalopathy.[8] Factors suspected to increase the risk of postanesthetic encephalopathy include positioning in dorsal recumbency during anesthesia, use of multiple anesthetics, use of halothane for anesthesia, endotoxemia, and shock. Differential diagnoses for myelopathy include orthopedic conditions such as limb fractures, spinal fracture, myopathy, and peripheral neuropathy secondary to recumbency. The differential diagnosis for encephalopathy includes numerous metabolic, infectious, and toxic disorders. Prognosis for recovery in cases of myelopathy is poor or hopeless. In contrast, most horses with encephalopathy recover completely. The risk of these complications probably can be reduced by supporting adequate blood pressure and ventilation in patients under anesthesia, minimizing anesthesia duration, and

preventing dorsal recumbency whenever possible.

Occipitoatlantoaxial Malformation

Robert J. MacKay • Mary O. Smith

Occipitoatlantoaxial malformations (OAAMs) are a heterogeneous group of developmental defects of the first two cervical vertebrae.[1,2] They have been reported to occur in cattle, sheep, goats, and horses.[3-6]

Equine OAAMs have been classified into six groups.[1] The first, a heritable condition in Arabian horses, is characterized by symmetric atlantooccipital fusion, atlantalization of the axis, and hypoplasia of the atlantal wings.[2,7-9] A similar disorder has been reported in an Arabian-cross colt.[10] The other groups are congenital asymmetric OAAMs,[11] asymmetric atlantooccipitalfusion,[2] duplication of axis or atlas,[12] and symmetric OAAMs in non-Arabian horses.[13,14] A deletion mutation near the *HOXD3* gene was identified in one Arabian foal with OAAM but was not found in two others with atypical OAAM phenotypes.[9]

The clinical signs range from normal with or without abnormal head position to brainstem compression, sudden unexpected death, and stillbirth.[2] In typical familial cases, signs of tetraplegia or tetraparesis begin at or shortly after birth and progress at variable rates. Foals may become suddenly tetraplegic and appear to stabilize for several days but then die suddenly.[15] In rare cases, horses may not show nervous system signs until 3 years of age.[13] The signs are symmetric in most affected animals and include hyperreflexia, hypertonia, weakness, and ataxia in all four limbs. Affected animals may be reluctant to move the neck and head and show resistance to manipulation of the area. A click or crepitation may be palpated over the cranial cervical spine when the head is moved.[2,5] With asymmetric bone lesions, torticollis is common, whereas patients with symmetric lesions hold their heads in extension and frequently display the "weathervane posture." Neurologic deficits may not be apparent despite moderate torticollis.

The malformations are readily apparent radiographically (Fig. 35.21), and CT can further elucidate the anatomic abnormalities.[16] There may be subluxation of the atlantoaxial joint, ventral displacement of C2 in relation to C1, nonunited ossification center of the dens, shortened or elongated dens, shortened transverse

process of the atlas, fusion of C1 with the occipital condyles, atlantal duplication, and deviation of the basioccipital bone.[2,17] In sheep, additional malformations of the cervical vertebrae have been present concomitantly.

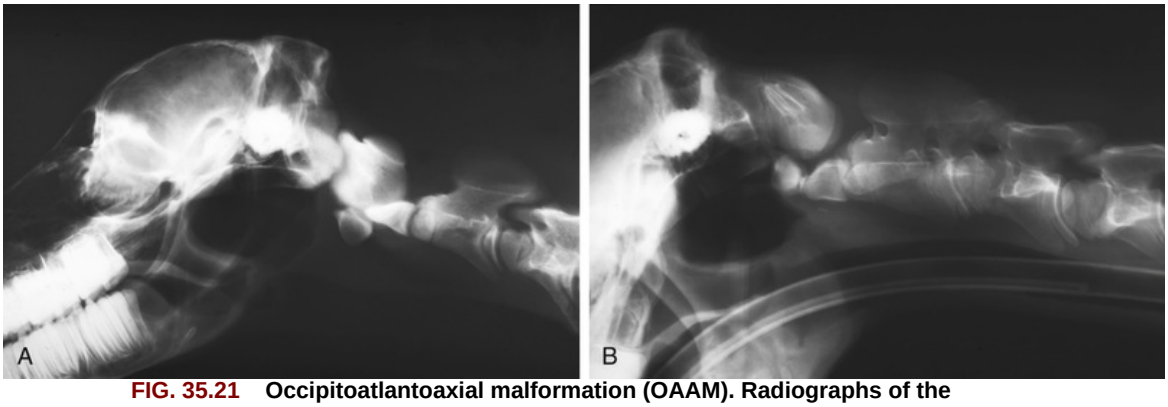


FIG. 35.21 **Occipitoatlantoaxial malformation (OAAM). Radiographs of the craniocervical region of a normal neonatal foal (A) and a 3-week-old Arabian foal with OAAM (B). In the foal with OAAM, note slightly shortened dens, ventral luxation of the dens, cranioventral movement of the body of the atlas to encroach on the guttural pouch, and fusion of the atlas to the occiput with occipitalization of its caudal surface. (Images courtesy Dr. I.G. Mayhew, Massey University.)**

Suggested approaches to treatment are surgical fusion of the atlantoaxial joints, with or without laminectomy.[13,18] Laminectomy alone has been used to alleviate spinal cord compression and clinical signs caused by occipitoatlantoaxial malformation.[19] However, long-term results of surgical intervention have been poor, with neurologic deficits persisting. Closed reduction of the luxated atlantoaxial joint has yielded similarly unsatisfactory results.[16,20] If treated, Arabian horses must not be bred because of the hereditary nature of the disease in that breed.

Congenital Vertebral Malformations

Robert J. MacKay

The vertebral column develops early in gestation via a highly orchestrated series of events comprising, sequentially, notochord formation, neural tube closure, segmentation, and vertebral formation.[1,2] Any disruption in this complex sequence by genetic defects, mechanical injury, teratogens, nutrient deficiencies, microbial infections, or maternal illness can lead to abnormalities in the structural anatomy of the spine. Most congenital vertebral malformations

(CVMs) are simple and may go undetected or are discovered incidentally during imaging procedures or at necropsy. In rare cases, a CVM is complex and has serious structural or neurologic implications. CVMs may occur as discrete abnormalities or be part of multiorgan developmental malformations involving neurologic, musculoskeletal, cardiovascular, urinary, or reproductive systems or a combination of these. When symptomatic, CVM is often fatal or life-threatening. Milder presentations predispose affected animals to spinal instability, stenosis, and spinal cord injury.

The spine is subdivided into five distinctive series (cervical, thoracic, lumbar, sacral, and caudal).[3] Vertebral variants and anomalies are most common around the boundaries between series (i.e., craniocervical, cervicothoracic, thoracolumbar, lumbosacral, and sacrocaudal).[3] Patterns of variation reflect the segmental organization of vertebral development under the influence of *Hox* genes and various growth factors.[3]

Incidental

Between 13% and 38% of horses have transpositions from C6 to C7 (or occasionally C5) of part of all of one of both ventral processes (also known as *ventral laminae of transverse processes*).[4,5] Disproportionately high numbers of Thoroughbred and warmblood horses are affected. Although this commonplace homologous variation has been considered incidental, vertebral canal stenosis and cervical pain were found significantly more often in horses with C6 ventral process transposition than in those lacking this anomaly.[5] Variations in the dorsal spinous processes of C7 and T1 and malformations of the first rib were also found in only horses with C6 ventral process transpositions.[6-8] Of 36 Thoroughbred racehorses, 8 had transitional thoracolumbar (T18-L1) vertebrae and 13 had transitional sacrocaudal vertebrae.[9] Numerous other variations in lumbosacral vertebral anatomy were noted, including intertransverse joints and articular process asymmetries. Transrectal ultrasonography reveals 10% to 20% of horses with ankylosis of L5-L6 or L6-S1 probably have transitional vertebrae at those sites.[7]

Other malformed vertebrae that may be found incidentally can result from failure of sagittal fusion of the vertebral body (i.e., butterfly vertebra[10]) or dorsal arch (spina bifida occulta). Hemivertebrae (lacking one side of the developing vertebral body) and wedge vertebrae (lacking either ventral or dorsal vertebral component) are more extreme malformations that are rarely asymptomatic.

Symptomatic

The most serious CVMs are disorders of notochord development. These commonly involve multiple different organs, in addition to potentially catastrophic CVMs, including caudal/sacral agenesis and segmental spinal dysgenesis (aplasia of vertebral bodies).[11,12] Perosomus elumbis is a sporadic lethal congenital defect of equids and livestock that includes arthrogryposis and organ malformations in addition to agenesis of vertebrae caudal to the thorax.[13-15]

CVM syndrome is an inherited condition of Holstein cattle and related breeds caused by a mutation in the gene *SLC35A3*.[16] This mutation manifests as multiple spinal deformities secondary to defective vertebral segmentation along with arthrogryposis, ventricular septal defect, and skull abnormalities. The trait was widely disseminated by the U.S. Holstein sire Carlin-M Ivanhoe Bell and resulted in tens of thousands of abortions and neonatal deaths worldwide before genetic testing was instituted.[17] There are numerous reports of congenital syndromes of calves and lambs that phenotypically are similar to CVM. In a few instances, especially when multiple animals were affected, a cause was identified. For example, gene mutations (*AGRN* gene in Angus cattle and *CHRNB1* in Danish Red cattle) that cause bovine arthrogryposis multiplex congenita syndromes have been identified.[18] Since 2011, fetal infection with Schmallenberg virus has been associated with multiple spinal deformities, arthrogryposis multiplex congenita, and multiorgan malformations in cattle and lambs in Europe.[19] Lesions are similar to those described for related bunyaviruses: Akabane virus, Aino virus, and Cache Valley virus. Other teratogenic viruses of ruminants, including bluetongue, BVD, and border disease, are not known to cause vertebral anomalies. The diagnosis of Schmallenberg viral infection can be supported by specific quantitative PCR, immunohistochemistry and serum neutralization tests on affected neonates. Arachnomelia is another similar autosomal recessive trait with multiorgan involvement and a component of defective segmentation.[20] This syndrome is found in Simmentals and Brown Swiss breeds. In addition to scoliosis and kyphosis, affected animals exhibit skull deformities and abnormally thin and elongated “spider” legs. The trait in Simmentals has been localized to a mutation in the *MOCS1* gene.[20]

Congenital scoliosis, kyphosis, lordosis, kyphoscoliosis, or torticollis are relatively common spinal deformities and, if mild, usually do not cause ataxia.[21]

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These deformities are caused by disorders of alignment or ossification of vertebral precursors (sclerotomes), which lead to asymmetric malformations of the vertebral bodies, articular processes, spinous processes, and ribs. Wedge vertebrae or hemivertebrae cause sharp-angle axial deviations that predispose to spinal cord compression.[22,23] Disordered sagittal fusion of the sclerotome dorsally or ventrally results in defects in the vertebral dorsal arch (spina bifida) or vertebral body (e.g., butterfly vertebrae). Protrusion of the meninges (meningocele), exposure of the spinal cord (myelocele), or both (myelomeningocele) are herniations through the dorsal vertebral defect (spina bifida cystica) and may be apparent as masses on the dorsal midline, either exposed or covered by skin.[24-28] Most spina bifida defects are in the lumbosacral spine, although thoracic and cervical examples occur. Spina bifida cystica is associated with neurologic and other abnormalities at and caudal to the lesion, which may be severe. It is hypothesized that chronic CSF leakage into the amnion via the vertebral defect predisposes the affected fetus to hydrocephalus and cerebellar herniations (Arnold-Chiari syndrome) that often accompany spina bifida.[29-31] An unusual case in a foal involved herniation of a myelomeningocele ventrally through a defect in the vertebral body.[32]

Interseries junctions are particularly prone to vertebral variances such as fused or transitional vertebrae (vertebrae with characteristics of adjacent segments). Many of the changes around cervicothoracic, thoracolumbar, and lumbosacral junctions appear to be asymptomatic, as described in the previous section. In contrast, many CVMs involving the craniocervical junction, including occipitoatlantoaxial malformations,[33] cause either stiffness of upper cervical joints (“weathervane posture”) or spinal cord compression and ataxia.

Finally, congenitally reduced height of vertebral arches causes vertebral canal stenosis and vulnerability to spinal cord compression.[34] Although the vertebral malformations that characterize cervical stenotic myelopathy of horses occur largely after birth, a role for congenital vertebral variations in this condition has not been excluded.

Chapters 51 and 52 contain more information about CVMs.

Myelodysplasias

Mary O. Smith • Robert J. MacKay

The following types of myelodysplasia occur in livestock[1-15]:

1. *Spinal dysraphism.* Abnormal development of the spinal cord before complete differentiation of gray and white matter; the areas of agenesis form longitudinal cystic structures instead of differentiated nervous tissue. Most of these anomalies are neural tube defects.
2. *Syringomyelia.* Longitudinal fluid-filled cavitations of the spinal cord.
3. *Hydromyelia.* Abnormal fluid-filled dilation of the central canal.
4. *Diastematomyelia.* Duplication of the gray matter at one or more segments.
5. *Rachischisis.* Complete failure of the neural tube to close; the central canal remains exposed and communicates with the integument.
6. *Meningocele.* Herniation of the meninges through a vertebral defect (usually spina bifida).
7. *Meningomyelocele.* Herniation of the meninges and dysplastic spinal cord through a spinal column defect.
8. *Myelodysplasia without vertebral defects.*

Associated abnormal neurologic signs are as described earlier for spina bifida.

Myelodysplasia has been related to genetic factors in Charolais and Hereford calves, although the mode of inheritance is unknown.[3,16] The condition has also been recognized in foals of several breeds.[15,17-19] In addition to genetic factors, causes include intrauterine bunyavirus (Schmallenberg, Akabane, Cache Valley, and Aino virus) infections, hypovitaminosis A or copper deficiency, maternal fever, or exposure to teratogens, including substances in species of *Solanum* and *Veratrum*.[15,20]

The neurologic deficits of myelodysplasia are difficult to differentiate from other spinal diseases unless the disorder is accompanied by spina bifida. Clinical recognition of myelodysplasia is usually based on the historical findings of paraplegia in a newborn calf without radiographic evidence of spinal fractures and with no myelographic evidence of spinal cord compression.

Acquired Torticollis

Robert J. MacKay • Mary O. Smith

Primary acquired torticollis with or without neurologic disease occurs in all species of domestic livestock. Causes include fracture or subluxation of the cervical vertebrae, basilar skull fractures, dystrophic muscle degeneration, unilateral cicatricial muscular contracture from injections, lupinosis, traumatic

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rupture of the cervical muscles, parasitic migration through the cervical spinal cord, hydranencephaly, asymmetric neurodegeneration, and congenital vertebral deformity.[1-6] In one study, researchers hypothesized that physical constraint within the narrow tips of uterine horns caused acquired torticollis and a variety of other deformities such as head scoliosis and limb malformations in more than 200 foals.[7] Draft horses may be predisposed to this problem, which frequently results in severe dystocia in horses. If the spinal cord is intact, no neurologic deficits result. The current epizootic of fetal Schmallenberg virus infections has caused torticollis with other malformations in calves, kids, and lambs.[8]

Treatment of traumatic torticollis should be directed at reducing the edema, relieving pain, and immobilizing the damaged structures. Muscular tears may be treated by encasing the head, neck, and proximal thorax in a fiberglass cast. Ancillary supportive treatment may include dexamethasone (0.05 to 0.1 mg/kg IM or IV daily for 2 to 3 days), methocarbamol (8 mg/kg IV tid for 5 days), and NSAIDs (e.g., phenylbutazone 2 mg/kg bid PO or IV or flunixin meglumine 1.1 mg/kg IV bid for 3 to 5 days after injury). A method of surgical correction of cervical muscle contractures through a muscle-splitting procedure has been described[9]; however, this seems unnecessary because most animals recover with only medical treatment. When torticollis is the cause of equine dystocia, delivery of the foal by cesarean section is often followed by rapid and complete anatomic and functional recovery.[7]

Tetanus

Robert J. MacKay

Tetanus is characterized by muscular rigidity and spasms. Death is common and results from respiratory compromise or tetanic convulsions. Clinical signs are caused by tetanospasmin, an exotoxin produced by the anaerobic, spore-forming, Gram-positive bacterium *Clostridium tetani.* Horses are exceptionally sensitive to tetanospasmin; cattle are relatively resistant, and small ruminants have intermediate sensitivity to the toxin. Spores are long-lived and resistant to most disinfectants and environmental extremes. They are not completely destroyed by boiling but can be eliminated by autoclaving at 115° C (239° F) for 20 minutes.[1] *C. tetani* is a ubiquitous soil inhabitant and can be isolated from feces of herbivorous domestic animals, with highest frequency in horses.[2,3] Tetanus is usually a disease of individual animals, but herd outbreaks of tetanus

in livestock have been described.[4-8]

■ Pathogenesis

The most common route of infection is inoculation of wounds with *C. tetani* spores. Deep puncture wounds contaminated by manure, soil, or rusty metal are especially likely to cause tetanus. In horses, such wounds are typically in the lower limb, although contaminated surgical sites, the postpartum uterus, injection abscesses, and infected umbilical structures are also potential sites for *C. tetani* infection.[9-11] Causative wounds are not found or reported in up to 50% of equine cases. Dairy cattle are infected most frequently after bacterial contamination of the uterus postpartum. Reestablishment of anaerobic conditions in the involuting uterus favors germination and proliferation of *C. tetani* spores. Other sites for growth of *C. tetani* in livestock include lesions caused by elastrator bands, sharp castration or tail docking, dehorning or disbudding, insertion of bull rings or ear tags, shearing, fly strike, intramuscular injection of anthelmintics or vaccines, and umbilical infections.[4,5,7,8] Outbreaks of "idiopathic tetanus" occur occasionally in young cattle, usually in association with the grazing on rough, fibrous feed, and it is likely that this is analogous to the pathogenesis of toxicoinfectious and forage poisoning forms of botulism wherein toxin is produced in wounds in the mouth or GI tract or is ingested preformed in contaminated feed.[12,13]

The crucial event in development of tetanus is germination of *C. tetani* spores, followed by vegetative growth and elaboration of exotoxins. Factors that enhance the germination and growth of *C. tetani* include necrotic tissue, pus, concomitant bacterial infection, and foreign bodies. Spores inoculated into the tissues are highly resistant to normal host defenses and may remain dormant for months or years before germinating. *C. tetani* produces at least two exotoxins: *tetanospasmin* and *tetanolysin.*[14] *Tetanolysin* damages viable tissue, thereby lowering the redox potential and creating favorable conditions for expansion of the anaerobic infection.[3] The neurotoxin tetanospasmin is a 150-kD polypeptide that is immediately cleaved by tissue proteases into active heavy and light chains connected by a single disulfide bond. It diffuses from the site of production into the vascular system and is distributed hematogenously to somatic neuromuscular junctions and autonomic ganglia, where it binds to nerve terminals. Once bound, the toxin is internalized and transported in a retrograde manner 75 to 250 mm/day in axons of both somatic and autonomic motor neurons.[15] After 1 to 14

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days, the toxin enters the CNS, reaches the neuronal cell body, traverses the synaptic cleft, and binds irreversibly to presynaptic inhibitory interneurons. Intact toxin is internalized, and then toxin light chain is released into the cytosol, where it acts to inhibit membrane fusion and recycling, events crucial in the release of the inhibitory neurotransmitters glycine and GABA.[14] The resulting disinhibition of motor neurons is the proximate cause of muscle rigidity and spasms.[3]

Preganglionic autonomic motor neurons in the lateral column of the gray matter and parasympathetic centers in the brainstem are affected by a similar mechanism but with delayed kinetic action in comparison with somatic motor neurons.[16] Both a basal increase in sympathetic activity and episodes of intense hyperactivity ("autonomic storms") occur, involving α-adrenergic and β-adrenergic receptors. During autonomic storms, the concentration of circulating epinephrine increases up to 10-fold. The resulting sympathetic overactivity causes hemodynamic instability and is an important cause of death in ventilated human patients with tetanus.[17] Its significance in large animal patients is unclear, although horses with either bradycardia or extreme tachycardia were reported as part of a large recent European case series.[18]

Neuronal binding of toxin is thought to be irreversible.[19] Recovery requires sprouting and growth of new nerve terminals, a process that is completed in weeks to months.

■ Diagnosis

Routine blood work is unhelpful, and abnormalities found are nonspecific. Gram stain of wound exudates reveal the characteristic drumstick-shaped Gram-positive bacilli in approximately 30% of human patients with tetanus,[20] but Gram stain and culture are seldom attempted in large animals with tetanus.[18] With the development of a real-time PCR assay for the tetanospasmin gene,[21] timely confirmation of *C. tetani* wound infection is now theoretically possible, and this assay may have application to veterinary cases.

Necropsy findings of animals with tetanus are nonspecific; secondary signs of musculoskeletal trauma and pulmonary congestion, atelectasis, and edema are most common.[9,10] The diagnosis can theoretically be confirmed by detection of tetanospasmin antigen in spinal cord ventral or intermediate horn cells with immunohistochemical staining in which antibody ia directed against tetanus

toxin.[22]

■ Clinical Signs

Signs occur 1 to 60 days after wound inoculation by *C. tetani* spores; most affected animals show signs between 7 and 21 days.[9,10,18,23] The incubation period varies, depending on the size of the wound, redox potential of the contaminated tissue, number of spores inoculated, and host's antitoxin titer. Probably because cranial somatic nerves are shorter than nerves to the limbs, the first signs of tetanus are associated with rigidity of muscles around the head and neck. These signs are commonly missed in livestock that are not closely watched but are usually recognized in horses. Increased tonus of the masticatory muscles (trismus), rigidity of facial expression (risus sardonicus), and neck stiffness are typical early signs.[9,24] Prolapse of the membrana nictitans begins during this phase and may be a prominent sign in the horse but is inconsistent in cattle and usually not observed in sheep.[12] The head and neck are held in an extended position, and the face has a fixed, anxious expression. The ears and commissures of the lips are retracted caudally, and the upper eyelids are elevated. Often the mouth is clamped shut and the jaws cannot be pried apart manually (lockjaw). Hyperthermia (usually <102.5° F) occurs in some animals during the early stages, and rectal temperature may rise further after tetanic convulsions.

In mildly affected animals, signs may be restricted to the head and neck; however, in most cases, generalized spasticity is evident within the first 2 days. The limbs, back, and neck are held in a characteristic rigid extended posture that resembles the legs of a sawhorse (i.e., “sawhorse” stance).[9] The tail is elevated from the ischiorectal fossa (“pump handle”). Affected animals display a stiff, toe-scuffing gait and an extended head posture. Gas bloat usually begins during the first 24 hours in ruminants and camelids, and colic is occasionally an early sign in horses.

In all cases of generalized tetanus, tonic muscle spasms develop shortly after the onset of rigidity. These can be initiated by external tactile, visual, emotional, or auditory stimuli or by voluntary movements such as posturing to acquire food or water, urinate, or defecate. The limbs and head are resistant to passive flexion, and dramatic responses to even minor stimuli manifest as hyperresponsiveness or hyperesthesia. When the face is touched, there is reflex retraction of the eye and prolapse of the nictitans.[12] This reaction is inconsistent in cattle and sheep. Attempts to chew or suckle set off rounds of masseter contractions that are easily

visible under the skin. Unmasticated feed is lodged in the cheeks or between the teeth. Even if ingesta can be moved to the pharynx, reflex pharyngeal and laryngeal spasms result in nasal regurgitation, drooling of saliva, and stridor. Aspiration pneumonia may develop as a result of impaired swallowing.

Disturbances of autonomic function have not been well documented in large animals, but heart rate and blood pressure may be increased or dramatically fluctuant with profuse sweating in horses.[9,11,18] It is not clear whether these signs represent tetanospasmin-induced sympathetic overactivity or are physiologic responses to the pain of muscle rigidity and spasms and the anxiety they cause. Signs of sympathetic overactivity are usually overlooked until after muscle spasms have been controlled. It is reported in humans that hypersalivation, increased respiratory secretion, and late-onset hypotension occur because of parasympathetic overactivity.[25]

Severely affected animals are at high risk of falling to the ground, especially during spasms. Once recumbent, they lie in lateral recumbency with the head and legs in full extension and the ears held almost parallel to the back. Frothy saliva accumulates at the commissures of the lips because the animals are unable to swallow. Spontaneous deaths are usually due to respiratory failure because of laryngeal spasm and asphyxia; contractions of the chest wall, diaphragm, and abdomen; accumulation of excessive respiratory secretions; and aspiration pneumonia. Autonomic overactivity may cause fatal cardiac dysrhythmia or heart failure and death secondary to hypertension. In advanced tetanus of cattle, ventrolateral strabismus may occur, and pupils may become dilated and fixed. Many animals die during a tetanic convulsion.

■ Treatment

The general principles that guide tetanus treatment of large animals are as follows: provide muscle relaxation, ensure good footing, eliminate the infection, neutralize the unbound toxin, maintain hydration and nutritional status, and establish active antitoxic immunity.[26]

Provide Muscle Relaxation.

All possible external stimuli, including light and noise, should be minimized. Packing the animal's ears with cotton to minimize auditory stimulation can also help reduce muscle spasms. Sedatives and muscle relaxers are administered for control of muscle spasms and rigidity.[27] The cornerstone of this approach is the

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combination of a phenothiazine-based ataractic sedative such as acepromazine with a GABA-ergic agent such as pentobarbital or diazepam.[19] An IV catheter should be placed to minimize treatment-associated stimulation.

In mildly to moderately affected animals, acepromazine (or chlorpromazine) produces obvious muscle relaxation within minutes that lasts for hours. Acepromazine also has α-adrenergic antagonist and anticholinergic actions that may help suppress autonomic overactivity.[28] Pentobarbital sodium provides additional muscle relaxation in cattle, but in horses it must be titrated carefully in order to prevent recumbency.[9,29] Phenobarbital, at a dose of 10 mg/kg IV and then by nasogastric tube q8h, provided effective muscle relaxation for a neonatal foal with tetanus whose spasms to that point had not been controlled by high and frequent doses of diazepam.[30] Large doses of diazepam or midazolam by repeated injection or constant-rate infusion are effective for control of muscle rigidity, but these drugs are expensive and impractical in many settings. The direct muscle relaxant dantrolene is used in horses for prevention of myopathy and might be useful in the treatment of tetanus. This drug has been used successfully in human tetanus.[31] Methocarbamol, glycerol guaiacolate, mephenesin, and d-tubocurarine have all been used for muscle relaxation in horses with tetanus but have been used widely.

Magnesium infusion has multiple potentially useful actions against spasms and autonomic dysfunction and is inexpensive. It blocks neuromuscular transmission, interferes with catecholamine release from nerves and the adrenal medulla, reduces receptor responsiveness to released catecholamines, antagonizes the actions of calcium, and is an anticonvulsant and vasodilator.[32,33] Magnesium has been shown to reduce the requirements for other drugs used to control muscle spasms and cardiovascular instability in human patients with tetanus.[32] Of interest is that electromyographic studies show that magnesium tends to spare the respiratory muscles, which is a marked advantage. Effective serum/plasma magnesium concentrations are 5 to 10 mg/dL. An electrocardiogram should be monitored continuously and infusion discontinued if the width of the QRS complex increases by more than 25%.

Ensure Good Footing.

The affected animal should be moved carefully to a large well-bedded stall. Feed and water should be hung so that the animal does not need to lower its head. Horses and, theoretically, cattle in danger of falling may be maintained in a body

sling, tackle and girdle, stocks, or walking frame. Appropriate caution must be exercised to ensure that such procedures do not cause the patient to become frantic.

Eliminate the Infection.

Because *C. tetani* grows in nonvascularized sites, the infection is best eliminated by surgical debridement of the affected area. If a recent wound or other infection can be identified, it must be opened, cleaned, debrided, and flushed. Penicillin (procaine penicillin G, 22,000 IU/kg IM bid) traditionally has been given to kill remaining *C. tetani* organisms and remains the drug of choice for food animals; however, penicillin might have anti-GABA and proconvulsant activities.[34] Metronidazole is now the preferred antimicrobial[28] and has outperformed penicillin in two clinical trials in human patients. It can be given at 25 mg/kg PO every 12 hours (q12h) for 3 to 5 days. If the horse's condition precludes oral medication, 50 mg/kg can be given rectally, or 10 to 20 mg/kg can be given IV, q6-8h (neonates). Use of metronidazole in food-producing animals, however, is illegal in the United States and Canada.

Neutralize the Unbound Toxin.

Tetanus antitoxin can be infiltrated into the tissues around the lesion, although this procedure is not recommended in protocols for treatment of human tetanus.[3] Despite the lack of evidence for efficacy of large doses of tetanus antitoxin, it is prudent to ensure neutralization of any residual unbound toxin by administration of at least 20 IU/kg IV, IM, or SC, repeated daily for up to 5 days. The results of intrathecal therapy as reported in small case series in horses have been inconclusive but generally not positive.[9,10,18,35] Although the data from human studies before 1991 were not supportive, meta-analysis of 12 more recent studies of both neonatal and adult cases detected a statistical survival advantage for intrathecal tetanus antitoxin over intramuscular administration.[36] A suggested protocol is 400 to 1000 IU/kg by slow installation via the lumbosacral space, including frequent cycles of aspiration of CSF into the loaded installation syringe in order to dilute the biological before delivery. Alternatively, tetanus antitoxin can be infused into the atlantooccipital cistern, but this route requires general anesthesia.

Because of severe reactions to intrathecal equine serum in ruminants, intrathecal administration of equine-origin tetanus antitoxin is contraindicated.[26]

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Administration of tetanus antitoxin has been associated with acute hepatic necrosis in horses.[37,38] The first clinical sign of this potentially fatal adverse reaction may appear 4 to 10 weeks after administration of tetanus antitoxin and has been reported in horses that received this treatment for treatment of clinical tetanus (see Acute Hepatitis in Horses section, Chapter 33).

Maintain Hydration and Nutritional Status.

The patient's hydration and food intake should be monitored daily. As mentioned, food should be placed off the ground, in an elevated feed bunk or hay net, to allow easier access. Intravenous fluids should be administered as needed to correct dehydration and electrolyte abnormalities. Alimentation via a nasogastric tube may be attempted in horses with tetanus, but because of adverse reactions, supplementation via an indwelling esophagotomy tube or IV may be necessary. A 5- to 10-cm-diameter rumenostomy should be created in affected cattle in which tetanus is worse than mild.[39] This has the dual advantage of relieving bloat and providing a portal for water and feed (usually alfalfa pellets).

Establish Active Anti-Toxic Immunity.

Clinical tetanus does not elicit a protective immune response. Affected animals should begin a primary toxoid series (see Prevention section).

■ Prognosis

The fatality rate for adult dairy cattle is up to 50% and, for horses, was between 65 and 75% in several published reports.[9,10,18,23,26] Outbreaks of tetanus associated with contaminated procedure wounds in small ruminants usually produce high mortality rates (>80%). Most affected animals that die are recumbent by 24 to 48 hours after admission to a clinic. In survivors, signs usually stabilize by 2 to 7 days, with gradual recovery over the next several weeks. However, one horse reportedly remained stiff at 6 months but was normal at 9 months after onset of signs.

On the basis of various prognostic scoring systems used for tetanus in humans[28] and the few large animal series published, negative prognostic indicators are an incubation period of less than 7 days, period of onset (time from first sign to first spasm) of less than 2 days, umbilical or uterine entry site, no vaccination within the previous year, and presence of comorbid disease. Severe signs at presentation, recumbency, or initial rapid progression of clinical

signs are all predictive of poor outcome.

■ Prevention

Because cattle are more resistant to tetanus than horses and small ruminants, they are not routinely immunized against the disease unless outbreaks have occurred previously.[26] Adult horses not previously vaccinated should be given an initial series of tetanus toxoid in two doses administered 3 to 6 weeks apart. Protective responses are usually attained within 2 weeks after the second dose. Current recommendations are to give booster doses annually thereafter or in addition at the time of injury or surgical procedure.[40] Broodmares should be revaccinated 4 to 6 weeks before foaling to provide for colostral transfer of immunity to their foals. Passively transferred antibody suppresses the IgG response of foals to toxoid vaccination at 3 months but not 6 months of age[41]; therefore it is recommended that foals from vaccinated mares be given a three-dose initial series beginning at 4 to 6 months of age, with a second dose 4 to 6 weeks later and the third dose at 11 to 12 months. Foals from nonvaccinated mares are vaccinated three times at 4-week intervals beginning at 1 to 4 months of age. Pregnant ewes and does should receive boosters with trivalent vaccine (*C. perfringens* types C and D and tetanus toxoid) approximately 4 weeks before parturition to cover lambs and kids during the early high-risk period around common husbandry procedures.[42] Young replacement animals can be given a primary series of inoculations at 1 and 2 months of age and annual boosters thereafter.

Tetanus antitoxin is produced by hyperimmunization of donor horses with tetanus toxoid. Administration of one vial of antitoxin (1500 IU) to a nonvaccinated horse should provide immediate protection that lasts for 2 to 3 weeks. Antitoxin is indicated in foals from nonvaccinated mares and in any wounded horse that has not been vaccinated within the previous year. In these cases, antitoxin and toxoid should be administered concurrently, with separate syringes at separate sites. Because the use of antitoxin is associated with hepatic necrosis (serum hepatitis) in a small number of horses, antitoxin should not be given in horses that are adequately covered by toxoid vaccination. Also, occasional failures are reported for both passive and active immunization protocols. Two of 16 foals and 10 of 74 adults developed tetanus after they were given tetanus antitoxin at birth or after injury, respectively.[18] In this same series, there were four cases in adults that had been vaccinated appropriately.

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Spinal Abscesses

Lisle W. George

■ Definition and Etiology

Most abscesses of the spinal cord originate from a preexisting osteomyelitis in a vertebral body. The bone is usually infected hematogenously. Extension of bacteria from the lungs, heart, or a septic injection site is common. Neonates frequently develop vertebral abscesses secondary to septicemia.[1,2] Ascending infections secondary to tail-docking in lambs may also occur. Some ewes chew the tails of newborns; this can lead to ascending infections of the spinal column and spinal cord as well. Bone lesions may develop from sequestra broken from as a result of vertebral fracture. Epizootics of spinal abscesses can result from injection of contaminated vaccines or mineral supplements near the spinal column. Similarly, spinal abscesses may occur along with other diseases in groups of animals that are immunocompromised.[3] Infectious agents isolated from spinal abscesses of ruminants include *C. pseudotuberculosis, T. pyogenes, M. haemolytica, Staphylococcus aureus,* and *Fusobacterium necrophorum.*[1,4-6] Agents typically found in vertebral infections of foals include β-hemolytic streptococci, *Salmonella* spp., *Actinobacillus equuli, E. coli, Rhodococcus equi,* and *Klebsiella pneumoniae.*[6-10] In rare cases, septic arthritis of the atlantooccipital joint may result from extension of a mycotic guttural pouch lesion.[11,12]

If the infectious agent remains localized in the vertebral body, the patient usually shows signs consistent with a transverse myelopathy. If the infection erodes through the dura mater, the animal develops signs of septic meningitis. If the bone infection is extensive, the vertebrae may fracture suddenly, which results in signs characteristic of spinal trauma.

■ Pathogenesis

Hematogenously derived abscesses arise because of embolization of septic thrombi into the metaphyseal arteries. These vessels have a sluggish blood flow because they become tortuous as they approach the physis. The metaphyseal vessels communicate with the ventral vertebral plexus, which in turn drains into the postcava, portal vein, and pulmonary veins. The ventral vertebral plexus does not have valves; blood flow reverses with an increase in abdominal or pleural

pressure. Regurgitated blood from infected sites in the body cavities may shower the vertebrae and spinal cord with bacteria.[4,13]

■ Clinical Signs

The neurologic deficits of animals with vertebral body abscesses without pachymeningitis (inflammation of the dura mater) are similar to those described previously for spinal fractures.[5] Animals with mildly compressive cervical abscesses show a characteristic "weathervane posture," are stiff, and are reluctant to eat food from the ground.[5,7,8] Ruminants with this lesion hold the neck in extension and attempt to prehend food from the ground by using their tongue.[5] Additional signs of spinal abscess include heat, pain, swelling, or crepitus over the affected areas and associated signs of bacteremia. Abscesses in the thoracolumbar spine cause hindlimb weakness and ataxia of variable severity, from mild gait abnormalities to complete recumbency. Stud males may be unable to breed because of weakness and pain.[14] The differential diagnosis includes trauma, aberrant parasite migration, tumor-related and pathologic fractures, hemorrhage into or around the spinal cord (e.g., postanesthetic myelopathy), myopathies, caprine arthritis–encephalitis, and fibrocartilaginous embolism.[15] Spinal abscesses can be mistaken for other painful conditions such as orthopedic disorders or traumatic reticuloperitonitis.[16]

■ Clinical Pathology and Radiographic Findings

Radiographs are the best method for obtaining a definitive diagnosis of spinal abscess. Affected vertebrae exhibit a random pattern of lucency and increased bone density characteristic of osteomyelitis, with or without adjacent soft tissue mass lesions indicative of abscess formation.[17] Diskospondylitis usually results in detectable osteolysis in the intervertebral joints.[7] Nuclear scintigraphy can be used when the bone lesions are not well defined on plain radiographs.[13] In addition, myelography may be used to detect the specific site of the spinal cord compression.

A complete blood cell count may indicate the presence of a chronic inflammatory focus, including hyperfibrinogenemia, neutrophilia, monocytosis, nonresponsive anemia, and left shift. The plasma globulin levels are often increased in affected adults but may be increased or decreased in neonates, depending on the adequacy of colostral immunoglobulin transfer.

Changes in CSF depend on the location of the abscess in the CNS tissue and the meninges. In most cases the abscess does not infiltrate through the meninges, and the CSF is normal or shows xanthochromia and mild increases in the protein concentration (60 to 120 mg/dL), with mild to no increase in nucleated cell count.[18] If the infection infiltrates into the meninges, pachymeningitis or septic myelitis will result; in affected animals, the CSF contains high numbers of WBCs (>100 neutrophils/µL) and a greatly increased protein concentration (>200 mg/dL). The CSF may clot after collection because of high concentrations of fibrinogen. Bacteria may be observed in a Gram-stained smear of CSF sediment. Spinal abscesses have been associated with *Brucella abortus* and *Mycobacterium bovis* infections in horses, and so affected horses should be tested for exposure to these organisms.[19,20]

■ Pathology

The most common sites of involvement are the costovertebral and intervertebral articulations and the vertebral body epiphyses.[21] Lumbar vertebrae are frequently involved. The bone is uneven, deformed, and softened. The abscessed area is interspersed with calcified trabeculae and pockets of necrotic debris. Sequestration of necrotic bone may occur in some cases. The meninges may be adherent to the abscessed site, and occasionally a fistulous tract may extend from the center of the abscess pocket to the subarachnoid space. In other cases the abscess is compartmentalized away from the CSF, but the proliferating bone impinges on the spinal cord.

■ Treatment and Prevention

If spinal abscessation is recognized early, prolonged antimicrobial therapy is generally effective. The results of cultures from the patient's blood, urine, feces, and CSF should guide selection of appropriate antimicrobial treatment. When bacteriologic culturing yields inconclusive results, a broad-spectrum antimicrobial should be chosen. NSAIDs may be administered for pain relief. Immobilization of the head and neck in a fiberglass cast extending from the thorax to the nose may provide support to smaller patients with a cervical abscess. Surgical drainage of the abscess and curettage of the necrotic bone may be feasible in animals with sufficient economic value to justify the procedure.[10,22] Surgical intervention in adult cattle and horses is usually difficult because of the size of the epaxial musculature and inaccessibility of the spine in

large animals.

Triaryl Phosphate Poisoning (Chronic Organophosphate Poisoning; Dying-Back Axonopathy)

■ Definition and Etiology

Ingestion of triaryl phosphates causes a neurologic disturbance of livestock characterized by a delayed neuropathy that results in incoordination and paralysis. Common sources of the triaryl phosphate esters include motor lubricants, hydraulic oils, industrial solvents, plasticizers, and automotive brake fluid. Chronic organophosphate poisoning also occurs in some families of sheep after treatment with organophosphorous anthelmintics.[1]

Triaryl phosphates have few effects on the glial cells,[2] but they have profound neurotoxic effects on the longest axons.[3] These fibers degenerate first at the distal, nonterminal areas. The degenerative lesions then spread proximally from the terminal nerve rootlets into the spinal cord until the cell body dies (dying-back axonopathy). Ingestion of 5 to 10 g/kg of triaryl phosphate causes paralysis by 19 to 36 days after exposure.[4]

■ Clinical Signs

The onset of slowly progressive neurologic signs occurs approximately 10 days to a few months after exposure.[5-7] The clinical signs of chronic organophosphate intoxication are rough hair coat, bloat, dyspnea, muscular weakness, and incoordination of the rear legs. The animals may slip on their hindlimbs and assume a dog-sitting posture. The limbs are circumducted and lack normal conscious proprioceptive responses. Affected animals become recumbent. When they attempt to rise, they do so incompletely and fall. Muscular tone and flexor reflexes may be normal, or flaccid paralysis may be evident.[6] The tail, bladder, and rectum are often paralyzed, and affected animals show signs of incontinence, constipation, and perineal scalding. Slight ventrolateral strabismus has been described, and some affected animals have been reported to become mute.[7,8] Most animals retain a normal appetite and sensorium during the development of the paralysis. Electromyographic changes in experimentally poisoned animals include increased insertional activity, positive sharp waves, and fibrillation

potentials in the muscles of the hindlimb, which are consistent with denervation of affected muscles.[9] Organophosphate-induced neuropathy has also been reported in horses, in which the most striking clinical sign was bilateral laryngeal paralysis.[10,11] Degeneration similar to that caused by delayed organophosphate toxicity in other species was most severe in the recurrent laryngeal nerves, but changes present in other peripheral nerves were milder.

■ Clinical Pathology

Clinical pathologic parameters are usually normal. The RBC cholinesterase level is low or undetectable at clinical onset but may return to normal concentrations by the time the animals display profound paralysis. The specific concentration of cholinesterase depends largely on the type of organophosphate and the patient's genetic ability to metabolize the toxic compounds. Whole-blood cholinesterase concentrations in esterase A–deficient animals remain significantly lower than in controls for at least 27 days after administration of haloxon (375 mg). In comparison, the enzyme concentrations in the plasma of normal sheep do not decrease after drug treatment.[12] Cholinesterase levels in exposed animals are not predictive of the delayed onset of neurotoxicity.[7]

■ Pathology

Laboratory confirmation of the condition is usually based on histopathologic detection of a dying-back axonopathy. Macroscopic lesions are not usually observed. Microscopic lesions are found exclusively in the CNS, and their severity appears to be dose dependent. The lesions begin distally and progress retrograde along the long, unsynapsed proprioceptive and motor tracts. The dorsospinal, cerebellar, gracile, and cuneate tracts are most susceptible to the effects of the toxins.[9] Specific lesions include demyelination, internodal axonal swelling, and wallerian degeneration. There is also a vacuolation of the large neurons of the ventral motor nucleus of the spinal cord. The mechanism of neurotoxicity is unknown, but alteration of a cell membrane protein found in neurons and some other cells has been implicated.[12-14] This protein has been designated a “neuropathy target esterase” and is thought to be “aged” by phosphorylation induced by the toxicosis.

Newer compounds in the triaryl phosphate group are less capable of causing delayed neurotoxicity, which offers some hope that the incidence of this type of toxicity may decline in the future.[14]

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■ Treatment and Prevention

Delayed organophosphate toxicity is not treatable and is irreversible. Prevention is centered on eliminating access to potential sources triaryl phosphates and ensuring secure storage and disposal of automotive lubricants and fluids.

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Motor Unit and Cauda Equina Diseases

Botulism

Robert J. MacKay

Botulism is a highly fatal disease characterized by muscle flaccidity and progressive generalized paralysis. Death results from euthanasia or respiratory failure. Clinical signs are caused by the potent botulinum neurotoxin (BoNT), an exotoxin produced by the anaerobic, spore-forming, Gram-positive bacterium *Clostridium botulinum*. Eight distinct antigenic types of BoNT and botulism have been identified: A to G, with C1 and C2 subgroups.[1,2] All but C2 are BoNT toxinotypes. Two other clostridial species, *Clostridium barati* and *Clostridium butyricum*, also produce BoNT. Mosaic recombinant toxins, with either type C or type D light chains (types CD and DC) have increasingly been identified in outbreaks of bovine botulism in Asia and Europe and probably are the dominant toxinotypes of animal botulism in Europe.[3,4]

C. botulinum spores are ubiquitous in the soil and marine sediments of most regions of the world. In general, soil-origin botulism in large domestic animals in the United States is caused by BoNT types A and B (and occasionally type C), whereas botulism caused by contamination of feed by animal carcasses is caused by BoNT types C and D. Botulism caused by *C. botulinum* type B is endemic among horses in Kentucky and in the mid-Atlantic states and accounts for most cases in the United States.[5] Almost all type A equine cases and outbreaks in the United States have occurred in western states, with Oregon and Idaho overrepresented.[6] Type C cases occur sporadically throughout the country, and type D botulism has rarely been reported in horses.[5] BoNT is acquired either by ingestion of preformed toxin (forage poisoning), germination of ingested spores in the GI tract (toxicoinfectious botulism), or contamination of wounds with spores and subsequent vegetative growth and toxin production (wound botulism).[6] Iatrogenic botulinum toxicity is an occasional cause of botulism in humans and is a potential side effect of the increasing use of BoNT for treatment of neurologic and muscular disorders in horses.[7] Forage poisoning is the most common route of infection, although shaker foal syndrome, a form of toxicoinfectious botulism caused by *C. botulinum* type B, is endemic in the United States.[5]

Horses are much more susceptible to the effects of BoNT than are cattle.[5] In fact, horses and humans are among the mammals most sensitive to the toxin.[1] Botulism in horses typically affects one or a few members of a group. In contrast, the disease in cattle is usually in the form of outbreaks.[5] These outbreaks in cattle have increasingly been associated with ingestion of poultry litter.[8-12]

■ Pathogenesis

The seven authentic BoNTs, BoNT mosaic toxins, and tetanus neurotoxin (tetanospasmin) are closely related 150-kDa proteins that differ in receptor and substrate specificities.[1] Unlike tetanospasmin, which is released alone, BoNTs are associated with a variable number of accessory proteins. It is believed that these proteins stabilize BoNTs during transit through the stomach and then may facilitate transport across intestinal epithelial cells. BoNTs are distributed hematogenously to bind to presynaptic cholinergic nerve terminals, most consequentially at the somatic neuromuscular end plate. Tissue proteases activate the toxin by cleavage into light and heavy chains connected by a disulfide bridge. After receptor-mediated internalization of BoNT in endosomes, the light chain, which is a zinc endopeptidase, is released into the cytosol, where it inactivates the SNARE (soluble *N*-ethylmaleimide–sensitive factor [NSF] attachment protein [SNAP] receptor) complex and thereby prevents docking and fusion of synaptic vesicles.[1] Vesicles containing acetylcholine are thus prevented from undergoing exocytosis and release of neurotransmitter at the neuromuscular junction. Flaccid paralysis of striated muscle is the main clinical result; however, paralysis of smooth muscle occurs, and parasympathetic effector functions fail. Once toxin is bound at the motor end plate, recovery is possible only by the sprouting of new axons and formation of new motor end plates, a process that requires weeks to complete.

Soil contamination of forage (including pasture) is the usual cause of botulism affecting one to several animals in the United States. In endemic areas of the United States, this is almost always caused by BoNT type B; cases associated with type A are also reported.[5,6] In small outbreaks or individual cases involving types C and D (or mosaic toxins), it is often not clear whether the source is carrion or soil contamination. Birds may play a role in carrying spores from a carcass to feeding areas.[5,13-15] Large outbreaks of foodborne botulism are of two types: germination of *C. botulinum* spores and bacterial growth in spoiled or

moldy forage and point contamination of feed (forage or concentrate) by animal carcasses. Spoiled forage can be in the form of hay (especially large bales) or chaff or even grass clippings stored improperly or left out to rot, but usually it involves some type of improperly fermented forage.[5,16-18] Conditions of high pH, low oxygen, and high water content favor spore germination and toxin production.[19]

Traditionally, small-grain silage (i.e., rye, wheat, oats, and barley) has been a common source of botulism for cattle,[20] but corn silage has also been implicated in several outbreaks.[15] The use of plastic film or bags to envelop (or encircle in the case of round bales) partially dried cut forage has become a popular way to produce and preserve silage and haylage for both cattle and horses. Unfortunately, plastic-wrapped forage has been the source of numerous outbreaks of botulism in both species.[5,20-22] These outbreaks have usually involved *C. botulinum* types B or A. In many cases, the plastic on the offending bale is found to be torn.[5] Accidental incorporation of an animal corpse into feed can have devastating consequences. For example, a single cat carcass that contaminated feed caused the deaths of 420 cattle.[5,23] Carcass-origin botulism is usually caused by BoNT type C, type D, or, perhaps more often, either of the mosaic variants type DC or type CD.[16,24] Rodents can be caught in a grain auger and contaminate cereal grain or be killed by hay mowers and incorporated into the center of bales.

Poultry litter has become by far the most important source of carrion-based botulism. Processed broiler litter is widely used as a cheap source of nonprotein nitrogen in feed for beef cattle and as a fertilizer for pastures and hayfields. Accidental incorporation of chicken or rodent carcasses into these litter products has resulted in botulism outbreaks all over the world, affecting up to 5500 steers and 378 sheep and goats in separate outbreaks.[8-11,25,26] For these reasons, feeding of poultry litter to cattle is now banned in Australia and Brazil and guidelines are provided for resting of pasture after litter fertilization. Even free-ranging poultry were suspected as a source of botulism in outbreaks in dairy herds in Germany and The Netherlands.[12,27-29] Type C and D botulism in cattle, including large outbreaks in Brazil, have been associated with osteophagia and sarcophagia (chewing on bones and soft tissues of decaying carcasses) by cattle with phosphorus deficiency.[19,30,31]

C. botulinum can colonize the GI tract of normal infants or adult humans whose intestinal microflora has been disrupted by intercurrent disease or

antimicrobial treatment. Shaker foal syndrome, an endemic form of toxicoinfectious botulism caused by *C. botulinum* type B, is of this type.[32] The peak age at occurrence of shaker foal syndrome is 4 weeks; 70% of cases occurr between the ages of 2 and 6 weeks.[5] The juvenile equine GI tract, possibly influenced by putative risk factors such as high milk intake, gastric ulceration, and heightened stress, is relatively hospitable to colonization and toxin production by the organism.[33,34] Toxin is detectable in the feces of approximately 30% of shaker foals but only in the acute clinical phase of the condition.[5] Normal intestinal flora of mature horses presumably inhibit colonization by *C. botulinum*. Evidence has been offered that chronic "visceral" botulism of dairy cattle in Germany is associated with GI dysbiosis and colonization of the GI tract by *C. botulinum*[35,36]; results of studies have contradicted this claim.[37,38]

■ Diagnosis

Routine bloodwork is unhelpful, and abnormalities found are nonspecific.

BoNT or spores must be present for diagnosis. The level of diagnostic support ranges from definitive to presumptive for detection of the following: (1) botulinum toxin in serum, GI contents, tissues, or wounds; (2) antibodies against botulinum toxin in the serum of convalescent animals; or (3) *C. botulinum* spores in the GI contents or suspect feed materials. Toxin is detected by the sensitive mouse bioassay and typed by mouse protection tests. In 139 horses with a clinical diagnosis of botulism, sensitivity of the mouse bioassay for detection of toxin in feces or GI contents was 32%, and specificity was 97%. In 43 cases in foals, sensitivity and specificity were 53% and 100%, respectively.[39] With mosaic toxins, mice may be protected by both type C and type D antisera, which probably explains why many outbreaks are recorded as involving both toxinotypes.[40] Detection of toxin in serum is possible only in animals with peracute onset and rapidly progressive clinical signs; the toxin is more likely to be detected in cattle than in horses.[19] Spores are detected by inoculation of mice with culture filtrate after incubation of samples anaerobically for several days in enrichment media.[6] ELISA and real-time PCR have been used on enriched samples to detect and distinguish botulinum toxins or toxin genes, respectively.[3,41,42] Sensitive duplex (BoNT types A and B) and simplex (type C) quantitative PCR assays for toxin genes return results in 4 days, in comparison

with 2 to 3 weeks for mouse bioassays, and do not require the sacrifice of laboratory animals.[43] Spores are found in the feces of approximately 34% of adult horses and 70% of foals affected with endemic type B botulism but are rarely detected in samples from normal foals or adult horses.[5] The presence of toxin antibodies in survivors has been used diagnostically in outbreaks of type C and D botulism in cattle in Australia[44] but lacked sensitivity when examined in similar outbreaks in England and Wales.[45]

Needle electromyography and decremental responses to repetitive nerve stimulation at low stimulus rates and incremental response at high stimulus rates can be used to support the diagnosis.[46-48] No obvious gross or histologic lesions are typically associated with botulism in most species.

■ Clinical Signs

The severity and rate of progression of clinical signs are dose dependent. Horses given low doses (e.g., 10^3 mouse lethal dose units) or very high doses (e.g., 10^8 units) of BoNT display the extremes of the clinical spectrum of botulism.[49] The low dose may cause only dysphagia with some progression over 5 to 7 days and then recovery with minimal treatment. In contrast, the high dose causes recumbency within 8 to 12 hours and death within 48 hours of the first detectable signs. After high experimental doses, signs may begin as soon as 12 hours after toxin challenge, whereas when low amounts of toxin have been ingested, cases may continue to develop for up to 14 days after removal of the suspect feed source.

Signs of dysphagia, lethargy, and generalized muscle weakness are the first indications of most naturally occurring cases.[50] In horses, an early sign that can be exploited diagnostically is slow, clumsy prehension and swallowing of concentrates. Normally, bright horses require less than 2 minutes to eat 250 mL of sweet feed from a shallow pan; horses with botulism might take at least twice as long. Efforts to swallow are made with the head extended and seem exaggerated and prolonged; mixtures of food and saliva are retained in the cheeks or between the teeth, or they drop out of the mouth. There are often thin trails of green-stained saliva from each nostril. Endoscopic examination of the nasopharynx usually reveals persistent displacement of the soft palate and aspiration of feed into the trachea. With progression, water runs freely from the nostrils during attempts to drink. For investigating suspected botulism in horses in areas endemic for equine grass sickness, it is important to remember that *both*

these conditions interfere with grain ingestion, and both may result in “failure” of the grain test.[50] Drooling of saliva in affected cattle is continuous, although the volume is usually not great, perhaps because of inhibition of saliva production by BoNT. In foals, dysphagia is evident as spillage of milk from the mouth and regurgitation through the external nares during attempts to suckle. Some horses present with colic, and most have reduced auscultable borborygmi. Affected cows have decreased strength and frequency of rumen contractions and firm feces.

Although animals showing the first signs of botulism may appear obtunded, it is facial muscle weakness and lack of facial expression that creates this impression. Even mildly affected animals tend to lie down more frequently than usual. With stimulation, such an animal may stand and initially walk quite normally before moving in a progressively more stilted and hypometric manner. When the patient is made to stand in one place, tremors may be apparent in the triceps muscles. As the disease progresses, tremor spreads to other antigravity muscles and increases in intensity until the animal collapses into recumbency. Prominent, generalized tremors of this type in foals in the United States with endemic toxicoinfectious botulism gave rise to the description “shaker foal syndrome.”

Tongue weakness is an important and consistent early clinical sign and, at least for type B botulism, a reliable indicator of impending limb weakness in at-risk cattle and horses. Tongue tone is assessed for this purpose as the ability of the animal to withdraw its tongue back into the oral cavity after the tip has been pulled out several inches through the interdental space. Another sign of myasthenia around the head is jaw “looseness,” evinced by cattle as lack of resistance to forced lateral movements of the lower jaw. Mydriasis and sluggish pupillary light reflexes are variable early signs; the prominence and persistence of these signs probably corresponds well with the dose and type of botulinum toxin ingested.

Between episodes of recumbency, moderately affected animals walk with a slow, shuffling, toe-scuffing gait and hold the head progressively lower.[24] Recumbent animals mount increasingly more ineffectual attempts to stand and often adopt unusual positions while recumbent; severely affected cattle often lie in sternal recumbency with both pelvic limbs extended caudally. Other animals lie in lateral recumbency with intermittent weak voluntary limb movements. Heart and respiratory rates rise during these struggles and, in some cases, respiratory efforts may seem labored, with a prolonged expiratory lift. Animals

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often die within 3 days of becoming recumbent. In survivors that remain standing, signs of limb weakness, dysphagia, and slow pupillary light reflexes completely reverse over several days to several weeks. Most persistently recumbent horses die, but in those that live and in the larger proportion of cattle that survive after becoming recumbent, efforts to stand typically resume after 1 to 4 weeks. Once such animals have successfully regained the ability to stand, they remain standing for increasingly longer periods until recovery is complete weeks to months later. Generalized but reversible muscle atrophy may be evident in long-standing cases.

The differential diagnosis for horses include any disease associated with muscular weakness and dysphagia, including infectious encephalomyelitis (EPM; EEE, WEE, and VEE; EHM; WNE); generalized myopathy (nutritional, seasonal pasture, polysaccharide storage myopathy); equine motor neuron disease (EMND); grass sickness; hyperkalemic periodic paralysis; and heavy metal toxicity. Diagnoses in cattle that should be ruled out include hypocalcemia, hypokalemia, sulfur toxicity, listeriosis, epidural lymphosarcoma, and organophosphate toxicity.

■ Treatment

Treatment involves nursing care and the use of specific anti-BoNT. Early treatment with specific antitoxin is a critical determinant of survival in horses. Of 91 untreated horses of various ages, 89 died of presumptive type B botulism,[49] whereas 27 of 28 foals[32] and more than 70% of adults[49] treated early with antitoxin survived. Among 92 adult horses with botulism that were transported to a referral hospital for treatment, the survival rate among those given antitoxin was 59%, in comparison with 10% among horses not given antitoxin.[51] The trivalent antitoxin commercially available in the United States (*C. botulinum* A, B, C [Antigen Select, Lake Immunogenetics, Ontario, N.Y.) covers cases typically observed in this country. Only one dose of antitoxin is necessary because the half-life of botulinum antitoxin (equine origin) is approximately 12 days in normal horses.[5] Unfortunately, antitoxin has minimal efficacy if used after the onset of recumbency in adult horses. The doses of antitoxin are 200 mL (≈20,000 IU) for a foal and 500 mL (≈50,000 IU) for an adult horse.[49] Clinical signs may progress for 12 to 24 hours after antitoxin administration. Horses with mild, slowly progressive disease may survive without antitoxin, as long as they are confined to stalls to restrict activity as

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much as possible.

Recumbent animals need to be kept on deep, clean bedding and, if in lateral recumbency, need to be rolled to the opposite side several times daily. Bony prominences need to be padded with pillows or circular inflatable tubes in an effort to prevent decubital ulcers. Standing horses with prominent neck weakness may suffer life-threatening edema of the head and upper respiratory tract as a result of persistently hanging their heads near to the ground. This was noted to be a feature of the presentation during an outbreak of type C botulism in horses.[22] These horses need to have their heads supported above the level of the heart for several hours daily to allow mobilization of tissue fluid. Adults that are dysphagic can be fed and watered via an indwelling stomach tube. Thoroughly soaked and suspended complete pelleted feed (e.g., Equine Senior, Purina Mills, St. Louis) can be administered indefinitely by this route. It is important to establish the patient's tolerance for bolus feedings and adjust volume and frequency of feedings accordingly. A reasonable starting point is 50% maintenance caloric requirement in 50 mL/kg water divided over four to six feedings. Caloric intake is progressively increased, and feeding frequency decreased as the animal's GI motility allows. Foals are initially fed at least 100 mL/kg of milk daily via this route, in 6 to 12 feedings, increasing to 200 mL/kg if tolerated. All recumbent animals must be in sternal position during feeding and remain sternal for at least 30 minutes after feeding. Patients without auscultable or other evidence of GI motility may be hydrated intravenously and may also be given intravenous parenteral nutrition. Recumbent adults that are being fed by nasogastric tube are at increased risk for large intestinal impactions and should be given 1 to 2 L mineral oil daily with feedings (or the equivalent twice weekly) in an effort to lubricate digesta. Recumbent male horses, including foals, are prone to retention of urine and bladder distention and must be catheterized with meticulously clean technique at least twice daily to prevent pressure necrosis and failure of the bladder wall. Animals that are able to support their own weight when assisted to a standing position should be lifted several times daily by an abdominal sling and allowed to stand with sling support for brief periods (or simply helped to their feet in the case of small ruminants). Flotation tanks may be used intermittently for this purpose in recovering cattle, especially those that are limited by recumbency-associated peripheral neuropathies.

At minimum, laboratory monitoring in recumbent horses with botulism should include daily measurements of hematocrit and total solids for hydration status,

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twice-weekly urine dipstick and specific gravity measurements to detect urinary tract infections and monitor hydration, and twice-weekly chemistry panels to assess organ function and electrolyte homeostasis. Total CO_2 values should be accorded particular attention. Values below 18 mEq/L indicate metabolic acidosis, whereas values above 35 mEq/L indicate significant metabolic alkalosis. The latter finding suggests compensation for chronic respiratory acidosis caused by respiratory paralysis or aspiration pneumonia and may prompt management changes such as improved sternal body position, frequent monitoring of respiratory function via arterial blood gas testing, or even initiation of mechanical ventilation. Horses with partial pressure of arterial oxygen (PaO_2) persistently below 65 mm Hg should be given humidified oxygen by nasal insufflation; those with partial pressure of arterial carbon dioxide ($PaCO_2$) persistently above 60 mm Hg need to be mechanically ventilated. This is generally practicable only in foals, although successful ventilation, including weaning from the ventilator, of a 425-kg horse over a period of 14 days has been reported.[52] Of 30 foals with type B toxicoinfectious botulism admitted to a referral hospital and given antitoxin, 16 required nasal insufflation with oxygen, and 8 of those 16 foals also required mechanical ventilation.[32,53]

Antibiotics are generally used only to treat known infections (e.g., aspiration pneumonia or cystitis) or to prevent or treat bacterial sepsis in heavily instrumented foals. In cases in which wound botulism is suspected, the responsible wound must be opened, drained, cleaned, and debrided, in the same approach as is used for wounds associated with tetanus. Antibiotics such as metronidazole and penicillin G that are clostridiocidal are generally not recommended for treatment of wound or infant botulism in humans, out of concern that lysed organisms will release another pulse of BoNT into the circulation.[54] Pretreatment of large animal patients with antitoxin is presumed to remove this theoretical risk. Aminoglycosides should also be avoided if possible because they may potentiate the action of BoNT and were a significant risk factor for a subsequent requirement for ventilation in cases of infant botulism.[54] Because gastric ulcers were an important feature of the original postmortem descriptions of shaker foals,[33,34] such foals are usually on a regimen of acid suppression (e.g., omeprazole, 4 mg/kg PO once daily, or sucralfate, 40 mg/kg PO every 6 hours), although the importance of this approach is unknown.

The rate of recovery from botulism depends on the toxin type and dose, the species and body weight of the patient, and the dose and timing of antitoxin.

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Dysphagic horses that are able to stand and are given antitoxin will gradually regain the ability to swallow over 1 to 14 days, with most cases resolving within 7 days.[5,49] Mydriasis usually resolves within several days, but the pupillary light reflexes may remain sluggish for weeks. Return to full limb strength often takes more than 1 month.[5,49] Few adult horses that become persistently recumbent recover unless they are provided meticulous nursing care, and most such horses should be euthanized. Decubital ulcers and secondary respiratory problems are the major complications. Recumbent foals that were treated with antitoxin and intensive care at a referral hospital were able to stand in an average of 7 days if they did not need ventilation and in 10 days if they did.[32,53] There is a belief, based on small numbers of cases, that horses with type A botulism have a worse prognosis than those with type B; in fact, only one horse with type A botulism, a 10-day-old foal, has been reported to survive.[48] If the controversial category of chronic visceral botulism is excluded,[36] death rates among cattle and other livestock with botulism are close to 100%.[30,31] This relatively high death rate among livestock needs to be interpreted in view of the general implausibility of providing specific BoNT antitoxin and intensive nursing care to affected cattle.

■ Prevention

BoNT type B toxoid (BotVax B, Neogen Corporation, Lexington, Ky.) is a safe and highly effective vaccine. The primary series is three inoculations, each 4 weeks apart, and then annual revaccination of broodmares 4 to 6 weeks before foaling to provide passive immunity to their foals. Although multivalent and BoNT type C toxoid vaccines for horses and cattle are available in many parts of the world, no vaccine of this type is licensed for horses or livestock in the United States.

Equine Motor Neuron Disease

Robert J. MacKay

EMND is an acquired neurodegenerative disorder of the ventral horns of the gray matter of the spinal cord and selected brainstem nuclei.

■ History and Epidemiology

EMND was first reported in 1990 in 11 horses from four northeastern states.[1] Hundreds more cases occurred in the northeast section of the United States over

the subsequent 20 years; fewer cases were scattered elsewhere across the country.[2,3] Additional solitary cases or outbreaks of EMND have been reported in many other countries, including Great Britain, Canada, Ireland, Switzerland, Korea, Belgium, Japan, Brazil, and The Netherlands.[2-6] The annual incidence of EMND cases in the United States peaked in 1997 and has since declined to low levels, with less than one new admission annually to Cornell University College of Veterinary Medicine's Equine Animal Hospital.[7]

The disease usually occurs sporadically, with only one case on a given premise at any time; however, one or more additional cases have occurred on the same premise within 2 years of the original diagnosis.[2] An unusual cluster of more than 80 cases occurred among horses in a city police cavalry in Brazil during the 1990s.[2] The age range of animals in reported cases is 2 to 27 years[3,8]; the mean age is 9 years, and the age at estimated maximal risk is 16 years.[9,10]

In the United States, Quarter Horse breed and age,[9] duration of residence, lack of recent rabies vaccination, exercising in a dirt paddock, a history of cribbing or coprophagia, use of pelleted feed (alone or with sweet feed), and frequent supplementation with vitamin/mineral supplements lacking vitamin E/selenium were significant nutritional risk factors in multivariate logistic regression models.[10] Of most importance is that after other significant risk factors were controlled, a strong negative association was demonstrated between serum/plasma α-tocopherol concentration and EMND risk.[11] In Europe, 13 of 32 horses with EMND had part- or full-time exposure to pasture, and yet all had low plasma levels of α-tocopherol, which suggests that bioavailability of ingested vitamin E was low in these horses.[8] A horse in Finland developed EMND despite supplementation with 300 mg α-tocopherol daily for the previous 10 years.[12] In that case, daily supplementation with excessive amounts of iron was suggested as a possible cause. In the United States, horses with EMND that had normal access to pasture had enteric or hepatic disease, which presumably resulted in malabsorption of vitamin E.[3,13] Eosinophilic enteritis associated with the presence of giant ciliated protozoa was described in five young Andalusian horses with EMND, which led the authors to speculate that these lesions either caused α-tocopherol deficiency or were the result of α-tocopherol deficiency.[14]

Although epidemiologic analyses of EMND data do not suggest a familial basis for the condition, histologic evidence of both NAD/EDM and EMND were found in two young Thoroughbreds and a Paint horse.[15] One horse had the

NAD/EDM phenotype, one had the EMND phenotype, and one had clinical signs of both conditions. These horses had a common Thoroughbred ancestor within five to six generations.

■ Cause and Pathogenesis

EMND is a spontaneous, progressive, sporadic, even solitary, condition that closely resembles progressive spinal muscular atrophy, a variant of amyotrophic lateral sclerosis (Lou Gehrig disease) of humans.[9] Although sporadic amyotrophic lateral sclerosis is probably multifactorial, it is widely believed that oxidative stress is involved in the final common pathways of neuronal injury. Evidence of systemic oxidant stress in horses with EMND includes the dominant involvement of oxidatively active type 1 myofibers in atrophied skeletal muscles and the abundant deposits of ceroid lipofuscin found in the retinal pigmented epithelium and in the endothelium of spinal cord capillaries.[3,16] Such deposits are thought to be the end products of peroxidation of membrane polyunsaturated fatty acids.[17]

In addition to the epidemiologic evidence of an association between hypovitaminosis E and EMND, the disease has been reproduced experimentally by prolonged feeding of vitamin E–deficient diets. After 21 to 28 months on a diet deficient in vitamin E but high in the pro-oxidant transition elements iron and copper, 4 of 8 horses developed clinical signs of EMND that were confirmed histologically.[18] In a separate experiment, 4 of 10 horses on the vitamin E–deficient diet but with normal iron and copper levels developed clinical signs of EMND after 18 to 37 months, and in the remaining horses, the disease was confirmed histologically via peripheral nerve biopsy or necropsy.[19] Together, the results of these experiments and epidemiologic studies confirm that a diet low in vitamin E is a strong risk factor for EMND. Left unresolved is whether vitamin E intake is the *only* responsible nutritional or management factor influencing the development of EMND in these experimental horses and in other affected horses around the world.

■ Clinical Signs

The clinical signs of EMND reflect denervation of skeletal muscles. Signs of muscle weakness and atrophy dominate the clinical presentation.[2-4,13,18] Weakness commonly occurs acutely in affected horses with noticeable muscle wasting; it is uncommon in affected horses without such wasting. In four horses

that developed EMND when fed a vitamin E–deficient diet, the mean weight loss was 92 kg at the time signs of limb weakness occurred.[2] In rare cases, the atrophy may advance insidiously without sudden weakness. Typically, there is acute onset of trembling in antigravity muscles and generalized sweating. Episodes of recumbency are frequent. When standing in one place, horses with EMND adopt a characteristic "horse-on-a-ball" stance with the limbs gathered close together under the body (Fig. 35.22).[20] Affected horses lack the strength necessary to engage the stay apparatus of the limbs when standing still; thus they constantly shift weight between limbs and have great difficulty standing in a confined area such as stocks. Acutely affected horses are more comfortable walking than standing, although even brief walking exercise may cause signs of distress such as sweating, tachypnea, and nasal flaring. Typically, at the walk, protraction phases appear somewhat short and hypometric. Horses with EMND do not have signs of ataxia such as interference between limbs or circumduction of the pelvic limbs.



FIG. 35.22 **Equine motor neuron disease in a 13-year-old Quarter Horse mare whose feet are placed close together under the body in a characteristic "horse on a ball" stance. Also note the generalized muscle atrophy, extended tail, and flared nostrils (indicative of severe exercise intolerance).**

In most horses with EMND, the head is carried below the shoulders, usually reflecting obvious wasting of the neck muscles.[2] The tail head is elevated in many cases because of atrophy and contracture of the dorsal coccygeal muscles.[2]

Widespread muscle atrophy, if not present at presentation, develops quickly (days to weeks) and is most obvious in the quadriceps, triceps, and gluteal areas.

Despite the frequent occurrence of pathologic changes in the motor nuclei of cranial nerves V and XII, noticeable atrophy of the masseters or tongue is rarely reported.[21-23]

In approximately 40% of cases, fundoscopic examination reveals a horizontal band of pigment above the optic disk at the tapetal-nontapetal junction.[2,17] The pigment may be brown-black to yellow-brown and has a reticulated or mosaic appearance. Surprisingly, problems with vision have not been reported even in EMND horses with severe pigment retinopathy.[17]

■ Laboratory Findings

Typical cases have below-range plasma/serum α-tocopherol concentrations. However, as a stand-alone test, α-tocopherol concentration is quite nonspecific[20]: Normal pasturemates of horses with experimentally induced[18] or naturally occurring[13] EMND often also have low α-tocopherol concentrations. In healthy pasture-fed horses, α-tocopherol concentrations are variable during the day and often drop transiently below the normal range.[24] For this reason, it is recommended that plasma (or serum) from serial blood collections throughout the day be combined for the purpose of α-tocopherol assay.[24] Although CSF α-tocopherol concentrations in horses with EMND have not been published, they are presumed to be lower than the published normal range of 4.1 to 13.5 ng/mL.[25,26]

Mild to moderate increases in plasma or serum CK and AST activity are found during the initial rapid progression of clinical signs, but muscle enzyme activities may be normal in chronic stable cases.

Cytologic changes in CSF are not observed in EMND; however, there may be increased total protein concentration and CK activity.[3,18] The IgG index is high in many cases, which suggests the presence of intrathecally produced IgG.

■ Ancillary Tests

Needle Electromyography.

Needle EMG can be performed in a standing or recumbent, anesthetized horse. Horses with EMND often have abnormal EMG findings, including prolonged

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insertional activity and pathologic spontaneous activity such as fibrillation potentials and trains of positive sharp waves.[20] Signs of denervation are found in facial muscles, as well as appendicular and epaxial muscles.[3] Standing EMG is preferred in order to avoid anesthesia in weak, compromised animals; however, interpretation of these studies is difficult because of movement artifacts associated with the reluctance of affected horses to stand in one place. The use of sedation and caudal epidural anesthesia (lidocaine, 0.2 mg/kg) was reported to facilitate the procedure in a horse with EMND.[21] Techniques for quantitative analysis of motor action potentials have been published, and results are abnormal in horses with EMND.[20,27,28] Regardless of the EMG technique used, abnormal results are nonspecific as to cause; they suggest only denervation or myopathy.[20]

Glucose Absorption/Metabolism Testing.

Oral glucose tolerance tests in horses with EMND yielded abnormal results in approximately 50% of reported cases, whereas results of oral xylose absorption tests were normal or slightly low.[2,13,28] It appears that increased glucose metabolism, possibly in association with increased glucose sensitivity, rather than reduced intestinal absorption, is the cause of abnormal oral glucose tolerance in horses with EMND. Euglycemic clamp results from one horse showed a 5.4-fold increase in insulin sensitivity in comparison with control horses.[29]

Nerve Biopsy.

Biopsy of the ventral branch of the spinal accessory nerve allows reliable antemortem diagnosis of EMND, at least in subacute and chronic cases.[3,30] A 5-cm section of the nerve is excised as it courses over and into the medial belly of the sternocephalicus muscle. The procedure can be performed when an anesthetized horse is either standing or recumbent and does not induce visible muscle atrophy at the surgical site. A positive histologic result is evidence of mild to severe wallerian degeneration of axons and Schwann cell proliferation. Chronic cases are marked by loss of myelinated fibers, presence of compact Büngner bands, and increased endoneurial collagen. The positive predictive value of nerve histologic findings for EMND was 77.4%, and the negative predictive value was 90%.[30] False-negative results appeared to be most likely to occur in acute cases (<2 weeks). Nerve biopsy has largely been supplanted as an initial test by evaluation of sacrocaudalis dorsalis muscle biopsies (see next

section).

Muscle Biopsy.

The initial invasive procedure of choice is biopsy of the sacrocaudalis dorsalis tailhead muscle.[3] This muscle is rich in type I myofibers, a fiber type that is highly sensitive to the effects of denervation. With the animal under local anesthesia, the muscle sample is obtained, placed on a tongue depressor, and sent chilled or in 10% formalin for histologic examination. Neurogenic atrophy is characterized by variable numbers of angular atrophied fibers. Atrophied muscle fibers are of both types, but type I fibers predominate. The results of muscle biopsy have high sensitivity for EMND (>90%) but relatively low specificity.[3] In chronic EMND cases, histologic study of nerve biopsy samples may have higher sensitivity for diagnosis than that of muscle samples.[3]

■ Diagnosis

Antemortem diagnosis of EMND is suspected on the basis of typical clinical signs, patient's age of 2 years or older, and diet low in green forage and high in carbohydrates. Needle EMG findings of denervation, especially in the deep limb muscles, are technically difficult to obtain because of movement artifact in weak horses, but they do support the diagnosis, as do mild to moderate increases in plasma CK and AST activity and low plasma α-tocopherol concentration. Evidence of denervation in muscle or nerve biopsies in the context of the preceding clinical and laboratory findings is tantamount to a definitive diagnosis of EMND. In occasional cases of insidiously progressive EMND, especially in nonendemic areas, diagnosis is made only post mortem.

■ Necropsy Findings

Although horses with EMND exhibit obvious weight loss, fat deposits noted post mortem are usually within normal limits.[1,4,20,31] Acute cases are characterized by widespread degeneration and loss of somatic motor neurons in the ventral horns of the spinal cord, accompanied by degenerative axonal changes in the ventral roots and peripheral nerves. All brainstem cranial nerve somatic motor nuclei, except those of cranial nerves III, IV, and VI, are variably involved. Most affected neurons are swollen, markedly chromatolytic, and diffusely argyrophilic; severely affected neurons are shrunken or vacuolated. Horses with cases of disease burnout (described later) demonstrate glial scars consisting of

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astrocytes and lipofuscin-laden microglia. Additional deposits of ceroid lipofuscin are found in the retinal epithelium and occasionally in the liver and intestine. Relatively minor neurodegenerative changes may be found in dorsal root ganglia. In contrast with grass sickness, minimal or no lesions are present in the autonomic nervous system. In skeletal muscles, angular atrophy affects all myofiber types, with some selectivity for type I fibers. Atrophied fibers are intermingled among normal fibers and fascicles. Involvement of the deeper muscles of the limbs may be grossly evident as pale discoloration. Histologic signs of EMND concurrent with NAD/EDM were identified in three young horses.[15] A genetic basis for these cases is suspected.

■ Treatment

The only treatment recommended for horses with EMND is vitamin E. This can be supplied in good-quality grass and alfalfa hay or by vitamin E supplementation (at 10 to 20 IU/kg/day). The water-dispersed form of natural vitamin E (RRR-α-tocopherol) is five to six times more bioavailable than synthetic vitamin E (all-rac-α-tocopherol acetate or d,l-α-tocopherol), and its administration results in rapid rises in plasma and CSF concentrations of α-tocopherol. After an initial period of at least 2 weeks' supplementation with water-dispersed RRR-α-tocopherol designed to raise plasma and CSF α-tocopherol concentrations into the normal range, treatment can be transitioned to less expensive synthetic RRR-α-tocopherol acetate for subsequent maintenance therapy.[26]

The frequent clinical observation that many horses with EMND have increased appetite may be explained by an estimate that daily caloric requirement of horses could be doubled.[20] Thus as part of the convalescent program of surviving horses, high-quality pasture, hay, and concentrate are recommended in high quantities.

■ Clinical Course

Within 6 weeks after onset of signs, approximately 40% of horses progressively deteriorate and must be euthanized; a similar number undergo marked improvement in clinical signs (usually after relocation to another premise or administration of antioxidants).[2] Some of these "recovered" horses look normal but may show relapse under the pressure of intensive training or competition.[1] In the remaining 20%, the disease appears to "burn out"; such horses survive with

permanent and obvious muscle wasting and emaciation.

Acquired Equine Polyneuropathy (Scandinavian Knuckling Syndrome)

Robert J. MacKay

Since 1995, a disease characterized by bilateral knuckling of the metatarsophalangeal joints has been observed in more than 400 horses in Sweden, Norway, and Finland. Originally known as *Scandinavian knuckling syndrome,* the condition was renamed *acquired equine polyneuropathy.*[1,2] Adult horses of any age, all breeds, and both sexes are affected. Large-fiber polyneuropathy with inflammatory demyelination-remyelination and conspicuous Schwann cell inclusions has been reported in affected horses.[2,3] The cause of the disease is unknown, although an ingested neurotoxin is considered the probable cause, possibly acting to trigger autoimmune demyelinating neuropathy.[3] Clinical signs appear mainly in late winter to spring, and almost all affected horses have been fed wrapped forage (haylage/silage). In Sweden and Norway, the disease has clustered within farms, and all cases on a particular farm occurred within 100 days of the index case on that farm.[1] The clinical signs are bilateral pelvic limb hyperflexion and collapse of the limb and knuckling of the metatarsophalangeal joints, so that the dorsum of the hooves contact the ground. Surprisingly, there is no or only slight atrophy of digital extensor muscles, and neurogenic atrophy is not found on histologic study.[3] It has been suggested that the affected nerves are type 1a and 1b sensory nerves from muscle spindles and that clinical signs of acquired equine polyneuropathy may be related to impaired reflex modulation of α motor neurons to the digital extensors of the pelvic limbs.[3] Mild and inconsistent thoracic limb weakness has been described in a few cases. The disease apparently has no cutaneous sensory or proprioceptive component, and cranial nerve abnormalities are not found clinically. In a longitudinal study of Norwegian horses with acquired equine polyneuropathy, 35% were euthanized within 6 months of diagnosis because of severe or persistent signs.[4] Of 57 surviving horses with long-term follow-up, all but 3 returned to a previous or higher level of performance. Those 3 horses experienced a relapse or new attack during the follow-up period. Possible disease-related clinical signs (intermittent pelvic limb weakness, fetlock knuckling) were reported in 14 of the surviving 57 affected horses. An apparently similar syndrome, termed *idiopathic peripheral polyneuropathy,* has

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been reported in horses in Japan[5]; however, this syndrome severely affects all limbs, and limb muscles show marked neurogenic atrophy.

■ Definition and Etiology

Robert J. MacKay

Polyneuritis Equi (Neuritis of Cauda Equina)

Polyneuritis equi is a progressive granulomatous polyganglioradiculoneuritis involving the cauda equina and, less commonly, cranial nerves and other spinal nerves.[1-4] The disease usually occurs in adult horses,[2] although it has been described in a yearling filly.[5] No breed or gender predilection has been noted.[6]

The cause of polyneuritis equi is unknown. The lesions are characterized by heavy infiltrations of cytotoxic T cells and macrophages with lesser populations of helper T cells, B cells, and plasma cells.[1,7] This pathologic process is similar to experimental allergic neuritis of rats, coonhound paralysis of dogs, and Guillain-Barré syndrome in humans, all of which are suspected of having an autoimmune basis.[1,8] Other proposed causes include a hypersensitivity reaction after systemic infection, aberrant migration of helminth larvae, and association with equine herpesvirus type 1, equine viral arteritis, or adenovirus infections.[5,6,9,10] However, conclusive evidence for any of these theories is lacking.

■ Clinical Signs

The clinical signs of polyneuritis equi reflect destruction of somatic and autonomic lower motor neurons and sensory neurons at the level of the nerve roots and dorsal root ganglia. Vague signs of dysuria and tail rubbing may precede the neurologic syndrome.[1] The onset of acute signs is marked by cutaneous and muscular hyperesthesia around the hindquarters, focused on the tailhead. Rubbing and chewing of this area is characteristic. Over days to weeks, there is progressive desensitization of previously hyperesthetic areas until the skin over the caudal rump, tail, perineum, and caudal thighs becomes anesthetic. At least initially, there may be a zone of residual hypersensitivity around the margins of the desensitized skin. Paresis of the tail, bladder, rectum, anal sphincter, and penis progresses, with neurogenic atrophy of the muscles of the tail. Fecal retention and overflow urinary incontinence reflect paralysis of rectal

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and detrusor muscles, respectively. Urine dribbling causes scalding and staining of the perineum (in mares) and hindlimbs. In males, the penis may remain dropped out of the sheath, although penile and preputial sensation is preserved. Impotence resulting from incomplete erection and inability to achieve intromission was the presenting sign in one stallion with polyneuritis equi.[11] In some cases, involvement of the lumbosacral nerve roots causes variable weakness and ataxia of the pelvic limbs and atrophy of muscles of the rump or legs. Any spinal nerve root may be affected symmetrically or asymmetrically, and so discrete areas of muscle atrophy, cutaneous desensitization, and sweating are possible anywhere along the spine. Weakness and ataxia have been observed in all four limbs of a few affected horses.[12-14]

Cranial nerves can be involved. The signs depend on the individual nerves affected and the severity of the disease. The nerves most often affected are the motor division of the trigeminal nerve (cranial nerve V; atrophy of chewing muscles), the facial nerve (VII; facial paralysis), and the vestibular nerve (VIII; head tilt and ataxia), although signs due to involvement of cranial nerves XII (tongue weakness and atrophy), III (reduced pupillary light reflex), IX, and X (dysphagia) have also been reported.[9,12-14] Signs of cranial nerve involvement are usually asymmetric.

Any disorder that affects the cauda equina may cause similar signs. These include instabilities of the caudal spine caused by luxations or fractures, EHM, sorghum-sudangrass intoxication, rabies, and other infectious diseases that involve the cauda equina or sacrocaudal spinal cord segments, as well as some primary diseases of the lower urinary tract.

■ Diagnosis

CSF may have a moderate mononuclear pleocytosis with lesser numbers of nondegenerate neutrophils and high protein concentration. Electromyographic abnormalities occur in polyneuritis equi as a result of denervation of affected muscles. Affected horses have high circulating antibodies to P2 myelin basic protein, but this test is not available commercially and is reported to be nonspecific.[15,16] The diagnosis was supported in one case by the finding of an intense mononuclear neuritis in a biopsy sample from the sacrocaudalis dorsalis muscle.[1] Thickened sacral nerves were also imaged by transrectal ultrasonography in that horse.

■ Necropsy Findings

The cauda equina is thickened, discolored, and covered with edematous tissue and fibrous material. There may be adhesions of the nerve roots or the spinal cord to the meninges and the periosteum of the vertebral canal. Subdural or epidural petechiation and hemorrhage are sometimes present.

At the microscopic level, the major finding is granulomatous inflammation of the extradural and intradural parts of the nerve roots. The nerve sheaths are thickened and infiltrated to varying degrees by lymphocytes, plasma cells, lymphoblasts, macrophages, giant cells, eosinophils, and, in rare cases, neutrophils. Nerves are obliterated by intraneural inflammation, necrosis, and endoneurial thickening. Axonal degeneration and demyelination are present in surviving nerves. Nerve bundles are separated by large amounts of fibrous tissue. There is minimal to moderate evidence of nerve regeneration.

■ Treatment and Prognosis

Treatment with corticosteroids at antiinflammatory doses early in the course of the disease may be palliative but is not curative. Immunosuppressive gold salts and cytotoxic drugs such as azathioprine have been used for the treatment of polyneuritis equi, but the efficacy of such approaches has not been reported. General supportive care should be given, including fluid therapy when necessary, and the rectum and bladder must be emptied manually and by catheter, respectively. With careful management, affected horses can be kept alive for months, but the prognosis for extended life is still regarded as hopeless; the usual cause of death is euthanasia for humane reasons.

Sorghum Toxicity

Robert J. MacKay • Mary O. Smith

■ Definition and Etiology

A syndrome of ataxia and cystitis in horses, cattle, and sheep has been linked to the consumption of annual grasses of the genus *Sorghum*.[1-4] Incriminated species have included *Sorghum bicolor* (sorghum), *Sorghum sudanense* (sudangrass), sorghum-sudan hybrids, and *Sorghum halepense* (Johnson grass, oxgrass). The causative toxin is not known, although there is evidence that chronic cyanide toxicity has a role.[5] This disease does not appear to be linked to the breed,

gender, or age of an animal.[3]

■ Clinical Signs

The first sign observed is usually ataxia of the pelvic limbs, followed by urinary incontinence. Affected animals have a swaying pelvic limb gait and a tendency to knuckle in the fetlocks. Occasional affected horses may walk with a hopping gait, in which both pelvic limbs are lifted off the ground simultaneously. Signs in horses tend to worsen on backing, and animals may fall or even become recumbent.[3] During an outbreak of the disease in cattle, 3 of 54 affected cows became recumbent, and 2 died.[6] The perineal muscles are relaxed, and urine dribbles from a flaccid, distended bladder.[4,6] In mares the vulva opens and closes repeatedly; in stallions and geldings the penis is relaxed and protrudes from the prepuce.[7] There may be paresis of the tail in affected horses and cattle. Loss of skin sensation over the hindquarters has been described in a cow, which suggests involvement of both sensory and motor nervous pathways.[6] Headshaking, ataxia, weakness, recumbency, opisthotonos, and death have been reported in affected sheep, and the rate of mortality can approach 50%.[8]

Cystitis in affected animals may be severe and occurs secondary to urine retention. Dribbling of urine onto the skin of the perineum and pelvic limbs results in scalding of the skin and dermatitis. Pyelonephritis is a common sequela to chronic cystitis and may be fatal.[2,3] Sometimes the clinical signs may be chronic; in one outbreak, horses had been showing signs for as long as 3 years.[3]

Abortion in mares, arthrogryposis as a congenital deformity of foals and lambs, and neurologic abnormalities in newborn lambs have also been linked to the feeding of *Sorghum* plants.[3,8]

■ Clinical Pathology

Diagnosis of sorghum toxicity is based on the presence of typical clinical signs in association with a history of feeding on *Sorghum* plants. No specific diagnostic test is available. Cystitis and pyelonephritis are identified by typical findings on routine urinalysis, serum biochemistry, and urine culture.

■ Pathophysiology

The precise nature of the toxic substance in *Sorghum* plants that causes this

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syndrome is unknown. Most *Sorghum* spp. are cyanogenic plants that contain the cyanogenic glycoside surrina, which, when hydrolyzed, releases hydrocyanic acid at potentially toxic concentrations.[1] Acute, sometime fatal cyanide toxicosis has been described in cattle that ingest large amounts of rapidly growing sorghum.[9,10] Chronic exposure to cyanide has been suggested as the cause of the neuropathologic changes found in animals with ataxia-cystitis syndrome.[3] Experimental long-term dosing of potassium cyanide to goats caused histologic changes in the CNS that were comparable with those of the natural disease.[5] It has also been suggested that the toxic principle in *Sorghum* plants may be a lathyrogen-like substance.[2]

■ Epidemiology

The cyanide content of *Sorghum* plants is increased by rain after drought and higher in new shoots and wet plants.[1] In one survey of the disease in horses, most cases occurred during the wet season and involved young, growing plants.[3] The period of grazing before the onset of signs ranges from 1 week to many months.[3,6]

■ Necropsy Findings

Wallerian degeneration, swelling of axons and myelin sheaths, and demyelination in a small number of nerve fibers throughout the length of the spinal cord and in the cerebellum, cerebellar peduncles, and pons have all been described, together with the presence of phagocytic gitter cells. In lambs grazing on sorghum, there were also lesions in the ventral horn gray matter of the spinal cord.[3,6,8] These changes are not associated with specific tracts. Ultrastructural studies of brains and spinal cords of affected sheep have revealed that the axonal swelling (spheroids) are composed of aggregates of neurofilaments, mitochondria, vesicular bodies, and dense bodies, enclosed within a thin myelin sheath.[8]

■ Treatment and Prognosis

Withdrawal of *Sorghum* plants from the diet of affected animals results in a gradual improvement in the clinical signs over weeks to months, although recovery may not be complete.[6,8] Death is a potential outcome, however, and mortality rates can be high in some cases.[8] There is no specific treatment for

affected animals. Supportive therapy includes antibiotics for treatment of bacterial urinary tract infections.

■ Control

Avoidance of feeding *Sorghum* plants as a predominant part of the diet or the sole diet is the only method of control. This plant has considerable feed value and does not present a major hazard when used as part of a diversified feeding regimen.

Stringhalt

Robert J. MacKay

Stringhalt is a condition of horses characterized by sudden exaggerated flexion of one or both pelvic limbs during the swing phase of locomotion. Two distinct syndromes are recognized: *classical stringhalt,* a persistent condition of individual horses involving only one limb; and *pasture-associated* or *Australian stringhalt,* which involves both pelvic limbs and occurs in outbreaks in horses at pasture. Both forms occur worldwide, but pasture-associated stringhalt is most common in Australasia, South America, and the western United States.[1-6]

■ Clinical Signs

The defining clinical sign of stringhalt is abrupt hyperflexion of the hock and stifle during attempted movement. In classical stringhalt, typically only one limb is affected; in contrast, Australian stringhalt is almost always bilateral, although signs may be asymmetric (Fig. 35.23). Stringhalt is most evident during backing, sharp turning, when the horse goes down a slope, after a sudden stop, and during the transition from standing still to walking forward.[2,7] Signs may be exacerbated by excitement, cold weather, or hard exercise.[2,8] During forward walking, the flexing limb snaps forward and upward in an adducted or sagittal plane; this feature of stringhalt distinguishes it from similar presentations of shivers, in which the limb is abducted during protraction.[9] The clinical presentation of stringhalt varies greatly, even among horses with pasture-associated stringhalt grazing on the same pasture. In mild cases, flexion is only slightly exaggerated and pelvic limb action may be completely normal at gaits above the walk. Such horses are able to perform without impairment. At the other end of the spectrum, the upper joints of the limb flex so violently that the

dorsum of the fetlock slaps against the horse's abdomen with each stride.[7] When the condition is bilateral, the result is a bouncing bunny-hopping gait in which "progression can only be accomplished with a series of bounds and plunges extremely painful to witness."[4,10] In the most severe cases, ambulation is impossible. An atypical pasture-associated stringhalt syndrome is described wherein the forelimbs are also involved and there are signs of generalized weakness.[1,2,4,11,12] Signs of obtundation, nervousness, hyperesthesia, or increased aggressiveness have occasionally been reported.[2,4,6,13] A variable proportion of horses with pasture-associated stringhalt have abnormal laryngeal movement, stridor, or abnormal vocalization.[4,5,13,14]



FIG. 35.23 Bilateral hyperflexion of the pelvic limbs in a horse with pasture-associated (Australian) stringhalt.

Onset of stringhalt is usually sudden. Signs may fluctuate but tend to worsen over several weeks in horses with pasture-associated stringhalt, before plateauing, often for several months; then they begin to improve.[2] Within 2 weeks after onset of severe pasture-associated stringhalt, atrophy of the muscles of the gaskin and, less obviously, the thigh and other parts of the body, becomes apparent.[2,15] Horses with severe or atypical pasture-associated stringhalt may develop profound generalized neurogenic muscle atrophy that results in marked weight loss despite normal appetite and food consumption.[12]

■ Clinical Pathology

No abnormal clinical pathologic findings are associated with stringhalt. EMG of affected muscles reveals increased insertion activity and abnormal spontaneous activity such as fibrillation potentials and positive sharp waves consistent with denervation.[2,14] NCV is slowed in the peroneal nerves of affected limbs, which indicates demyelination, and improves as animals recover clinically.[2]

■ Pathophysiology

The cause of classical stringhalt is unknown. Foot conditions and articular lesions of the hock or stifle are possible risk factors.[4,7,16] Trauma to the proximal dorsal metatarsus, particularly over the digital extensor tendons, often precedes classical stringhalt and probably is an important factor in the development of this form of the condition.[2,4] Months may elapse between injury and the onset of stringhalt.[17]

Since 1884,[10] most reports of pasture-associated stringhalt have implicated the common pasture weed *Hypochaeris radicata* (also known as flatweed, castear, cat's ear, or false dandelion).[1,3,4,8,12,13,16] Most outbreaks occur in late summer or autumn among horses grazing on drought-damaged pastures heavily infested with *H. radicata*. Cases often occur after weeks to months of grazing on suspect pastures.[10,13] Interestingly, some affected horses are thought to have developed a taste for flatweed, to the exclusion of other forage.[13] Several outbreaks have been associated with “true” dandelion *(Taraxacum officinale),* and one has been associated with mallow *(Malva parviflora)*.[1,4,18] During pasture-associated stringhalt outbreaks, less than 50% of populations are usually affected, but attack rates vary widely.[2,8,13] Some attempts at producing pasture-associated stringhalt by feeding cut *H. radicata* to horses have been unsuccessful; however, stringhalt was induced in a 6-month-old colt fed a daily average amount of nearly 10 kg of *H. radicata* harvested from a pasture where the disease had occurred.[3]

Pasture-associated stringhalt is a distal neuropathy primarily affecting large myelinated axons of the peripheral nervous system.[15,19] The longest nerves in the body—namely, the recurrent laryngeal nerves and the peroneal and tibial branches of the sciatic nerve—appear to be most severely affected. This also explains why tall horses are more prone to the condition than young horses, ponies, or small native Chilean breeds.[18] Shetland ponies have been affected,

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however.[8] The lesions of pasture-associated stringhalt are consistent with ingestion of a neurotoxin produced by either pasture weeds such as *H. radicata* or, less probably, by associated fungi.

Pasture-associated stringhalt and some cases of classical stringhalt probably result from interference with myotatic reflexes.[17] The immediate cause of pelvic limb hyperflexion in pasture-associated stringhalt is presumably progressive degeneration of large myelinated axons in tibial and peroneal nerve branches, including α motor neurons to skeletal muscle, 1A and 1B sensory neurons from muscle spindles, and Golgi tendon organs. Classical stringhalt may be the final common sign of a variety of insults: besides interference with limb reflexes, mechanical effects of adhesions involving the muscles and tendons of the digital extensors of the pelvic limb may occur, as may painful conditions of the hock or distal limb.

■ Pathology

In long-standing cases of pasture-associated stringhalt, affected animals exhibit variable, often severe atrophy of the muscles of the pelvic limbs, especially distally, and atrophy of the muscles of the larynx supplied by the recurrent laryngeal nerves.[1,12,19] Peripheral nerves demonstrate axonal degeneration of large diameter fibers acutely and decreased numbers of myelinated fibers in chronic cases, with perineural fibrosis and accumulation of myelin debris. Evidence of nerve regeneration, including regenerating nerve clusters, “onion bulb” formations, and Schwann cell proliferation, is usually found. Recurrent laryngeal nerves, branches of the sciatic nerves, and variably other nerves are affected with a proximal to distal gradient of increasing severity.

■ Treatment

Care should be taken to identify sources of pain (e.g., arthritis, hoof abscess, recent hoof trimming) that might account for stringhalt-like signs. Signs of stringhalt were blocked in one horse by intraarticular anesthesia of the distal tarsal joints; use of intraarticular corticosteroids permanently resolved the problem.

Several skeletal muscle relaxants have been investigated in horses with pasture-associated stringhalt. Phenytoin, an inhibitor of voltage-gated sodium channels, gives partial to complete remission of signs in horses in a dosage of 10 to 15 mg/kg PO, once or twice daily.[2,12,14] Mephenesin, which acts in the spinal

cord to specifically inhibit polysynaptic reflexes, suppressed signs in a horse with chronic pasture-associated stringhalt[7] but was ineffective in an outbreak of pasture-associated stringhalt.[1] Baclofen, an analog of the inhibitory neurotransmitter GABA, had no effect in a horse with severe stringhalt.[8,14] Taurine (10 mg PO q24h) may help with behavioral abnormalities.[13]

Although the results of the procedure are unpredictable, surgical removal of the distal muscle belly and tendon of insertion of the lateral digital extensor effects a clinical cure in a proportion of horses with either classical stringhalt or pasture-associated stringhalt.[3,4] Of four horses with classical stringhalt treated with lateral digital extensor myotenectomy, two resolved and the other two improved partially. The surgery was precluded in two other horses because of adhesions involving the tendon.[17] Responses to a survey of veterinarians in Australia indicated that more than 50% of over 100 lateral digital extensor operations had been successful in eliminating signs of stringhalt.[2] Even more impressive was that 11 of 13 horses with pasture-associated stringhalt were normal within 12 days of surgery.[5] The surgery can be performed with horses standing or in lateral or dorsal recumbency. An initial skin incision is made over the lateral digital extensor tendon immediately proximal to its junction with the long digital extensor, and the tendon is isolated and exposed. A second incision is made over the muscle belly proximal to the hock, and the muscle belly is dissected free of overlying fascia. The tendon is severed through the distal incision, and then the tendon is pulled through its sheath into the proximal incision by means of traction on the muscle. The muscle belly is then incised 2 cm proximal to the musculotendinous junction. In a modification of the technique, which may improve success rate, 7 to 10 cm of muscle is removed. After the fascial and skin layers have been closed, a bandage is applied over the surgical site and maintained, with box stall rest, for 2 to 3 weeks.

■ Prognosis

There is almost no information on outcomes for horses with classical stringhalt; however, it is commonly supposed that most cases persist, although they may improve with time. Of one series of four cases that developed after proximal dorsal metatarsal trauma, one horse recovered, two improved, and one's condition was unchanged for at least 6 months after onset of signs.[17] Many cases of pasture-associated stringhalt recover normal gait and muscle mass if removed from toxic pasture. In a series of 70 cases monitored over several years in

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France, 36 recovered in an average of 8 months, 6 died, and 14 still had stringhalt signs at least 2 years after onset.[13] The few reported deaths were in horses that were either unable to stand or unable to move to sources of water and feed; they were euthanized for humane reasons. Recovery times of 3 days to 3 years have been recorded; most horses take 6 to 12 months.[2,7] It is unclear to what extent athletic performance returns after clinical recovery from severe pasture-associated stringhalt. There is evidence that laryngeal dysfunction may persist beyond the time of recovery from gait abnormalities.

Tick Paralysis

Robert J. MacKay

■ Definition and Etiology

An ascending lower motor neuron paralysis has been described in horses, cattle, sheep, pigs, dogs, cats, and poultry in Australia, associated with feeding by ticks of the genus *Ixodes*, especially *Ixodes holocyclus*.[1-7] In the United States and Canada a similar disease occurs in dogs, humans, cattle, sheep, New World camelids, and wild animal species as a result of infestation with several *Dermacentor andersoni*.[8-10] A similar problem occurs in small ruminants in Africa, where *Ixodes rubicundus* and *Rhipicephalus evertsi* are the tick species implicated.[11-13]

■ Clinical Signs

Progressive generalized flaccid paresis develops over one to several days, terminating in recumbency. Death from respiratory paralysis may occur in as little as 24 hours in severe cases.[6] Animals may be found recumbent or may be paraparetic and ataxic in the early stages of disease. When signs are mild to moderate, the differential diagnosis includes a variety of neurologic and nonneurologic diseases such as botulism, rabies, colic, uterine torsion, trauma, myelopathies, myopathies, and metabolic disorders. Of these, only botulism progresses to the profound muscular flaccidity characteristic of tick paralysis. Both reflex withdrawal from a noxious stimulus and the blink reflex are reduced or absent, although sensory function appears normal.

Tick paralysis may be fatal when caused by *I. holocyclus* even when the ticks have been removed. In contrast, paralysis caused by *Dermacentor* spp. is usually

reversible if the ticks are removed before the animal is recumbent.[10] Paralysis in sheep does not occur when less than 0.2 *D. andersoni* ticks/kg are present but consistently occurs when more than than 0.8 ticks/kg are present.[10] One to five *I. holocyclus* ticks were found on 85% of horses with tick paralysis.[7]

■ Diagnosis

Diagnosis is based on the clinical signs and finding ticks on the affected animal. There are no pathognomonic findings in affected animals except for the presence of ticks. EMG in tick paralysis in dogs in North America reveals minimal spontaneous activity and lack of evoked CMAPs in response to motor nerve stimulation.[14] Findings in large animals are expected to be similar. CSF is normal in tick paralysis, which helps differentiate it from some, but not all, myelopathies.

■ Pathophysiology

The cause of tick paralysis is believed to be a neurotoxin in the saliva of female ticks that is inoculated into the host when the tick feeds. Nymphs and larvae in large numbers may also cause the disease. In the case of *I. holocyclus*, the toxin has been named *holocyclotoxin*.[15] The toxin or toxins elaborated by *Dermacentor* spp. have not been as well characterized. *Holocyclotoxin* acts by inhibiting release of acetylcholine from nerve terminals at the neuromuscular junction.

■ Epidemiology

The disease occurs worldwide, in association with different tick species in different areas. In North America the region from the Pacific coastal range to the Continental Divide provides especially favorable conditions for the proliferation of *D. andersoni*.[9] Tick paralysis in the United States and Canada occurs mainly in the Pacific Northwest and the Rocky Mountains, although the geographic range of the responsible tick species is much larger. The disease tends to be seasonal in both North America and Australia; most cases occur in the spring, when ticks are most active. In North America, smaller animals such as sheep and New World camelids are more often affected than cattle.[16] In Australia, affected horses were of multiple different breeds, were between 1 week and 18 years of age, and weighed from from 9 to 450 kg.[7] Tick factors probably influence

disease severity, and genetic variation within *I. holocyclus* may play a role in toxin potency.[17] A short-lived immunity has been demonstrated in dogs and sheep exposed to ticks.[10]

■ Necropsy Findings

There is no pathognomonic finding at necropsy, although the presence of ticks should increase suspicion of this disease. Death usually results from respiratory paralysis.

■ Treatment and Prognosis

Treatment is supportive after removal of every tick and topical application of an acaricide. Lack of improvement suggests that ticks remain on the animal, except in cases of *I. holocyclus* infestation, in which signs persist and may worsen for 1 to 2 days after removal of all ticks. In small animals, shaving the hair coat may be necessary to ensure detection and removal of all ticks. Areas such as the axillae and groin, in particular, provide good sites of attachment for ticks. The prognosis is good in the case of *Dermacentor*-induced paralysis when tick removal and supportive care are instituted before animals are recumbent. Fatalities occur in cases of *Ixodes*-induced paralysis despite removal of ticks. Cooling of the patient has been suggested in treatment of *I. holocyclus* toxicity, but this practice is controversial; a better approach may be to avoid warming the patient excessively.

Administration of a canine-origin hyperimmune serum has been shown to be beneficial in treatment of horses and a llama.[7,18] In horses, doses exceeding 0.5 mL/kg produced a higher odds ratio for survival than did a lower dose.[7] Adverse reactions such as anaphylaxis, bradycardia, and hypotension occur in a small number of dogs and cats treated with hyperimmune serum, but these can be avoided by of atropine.[19] Two of 95 horses given antiserum had reactions, one of which was fatal.[7]

Of 103 horses treated for tick paralysis in Australia, 27 (26%) died or were euthanized.[7] Paradoxically, the odds of survival were inversely related to the weight of the horse.

■ Control

Environmental control to reduce tick populations and routine use of acaricides

may decrease the incidence of tick paralysis.

Equine Grass Sickness

Robert J. MacKay

Grass sickness is a debilitating, often fatal, dysautonomia of equids associated with full-time access to pasture.[1] Because lesions are also found in the somatic lower motor neurons, it has been suggested that it is more accurate to describe grass sickness as a polyneuropathy rather than a dysautonomia.[2] A comparable fatal polyneuropathy has also long been recognized in the Patagonia region of South America, where it is known as *mal seco*.[3] Equine grass sickness (EGS) is endemic in Scotland, England, and Wales and has also been reported from many countries in northern Europe, Cyprus, the Falkland islands, and Colombia with isolated cases in Australia, Ethiopia, and the United States.[1,4-6]

Epidemiologic studies conducted since the early 1970s have identified high horse density, full-time grazing, a recent change in feed type or premises, previous occurrence of the disease on the premises, pasture disturbance, mechanical removal of horse manure from pastures, sandy or loamy soils, recent deworming with ivermectin, recent cool dry weather and irregular ground frosts, and good bodily condition as risk factors.[1,2,7-14] Concentrations of various herbage and soil minerals are associated with horses' risk of developing EGS.[2] Cases occur throughout the year with peak numbers in the spring and a smaller peak in the autumn. The risk of disease is highest in horses aged 2 to 7 years (peak, 5 to 6 years), although cases have been reported in horses from 2 months to 27 years of age. Horses of all breeds, ponies, donkeys, Przewalski's horses, and zebras are affected. Males and females are equally represented in surveillance data. Protective factors included contact with previous cases, daily feeding of hay or haylage, chalky soil, higher average maximal temperature, manual removal of feces from pastures, pasture grass mowing, and grazing together with ruminants.

■ Cause and Pathogenesis

Theories as to the cause of EGS have included mineral or vitamin deficiencies or exposure to toxic plants, secondary metabolites and trace minerals in pasture grass, insects, viruses, or bacterial or fungal toxins.[15,16] Although the cause of EGS is still unknown, considerable evidence has been adduced in support of

roles either for *C. botulinum* toxins or mycotoxins.

The hypothesis that mycotoxicosis is the cause of EGS is attractive because it is consistent with the observed influences of pasture grazing and climate on disease risk.[2] Since the 1990s, a hypothesis has been developed that EGS is a toxicoinfectious form of botulism involving a type C strain commonly carried by birds.[17] Strong support for this hypothesis has been provided by (1) the demonstrated association between EGS and the presence in ileal contents of *C. botulinum* type C and type C1 neurotoxin (BoNT type C)[17]; (2) the observation that horses with EGS have significantly lower serum antibodies to *C. botulinum* and BoNT type C than do pasturemate controls[18,19]; and (3) the presence of rising titers of specific IgG antitoxin in cases of chronic EGS. *C. botulinum* type C is unique among clostridial organisms in that its major toxin, BoNT type C, possesses potent and nonspecific neurotoxicity in vitro, probably via action on cellular syntaxin.[17] It has been hypothesized that toxin production and absorption occur in the ileum as a result of either overgrowth from normal intestinal flora or spore germination in association with nutritional or environmental triggers involving factors such as parasite status and changes in feed, pasture, and weather conditions.[1,4] Set against this evidence are the many clinical, epidemiologic, and biological differences between EGS and neuroparalytic botulism of horses.[2] A survey of veterinarians in Great Britain confirmed the feasibility of conducting a controlled field trial of the efficacy of *C. botulinum* type C vaccination in preventing naturally occurring EGS.[20] A candidate vaccine was selected and shown to induce significant antitoxin responses and a longitudinal vaccine study has been ongoing since 2014.[21]

■ Clinical Signs

The major clinical signs of grass sickness principally reflect dysfunction of the enteric nervous system.[1,22] They include dysphagia, gastric and small intestinal dilation, nasogastric reflux, colonic impaction, and colic. Clinical presentations are classified as acute (course of <48 hours), subacute (2 to 7 days), and chronic (>7 days).[23] Two thirds of reported cases have been acute or subacute and one third was classified as chronic.[1] Acutely affected horses may be found dead or in abdominal crisis with signs of colic, tachycardia, generalized sweating, nasogastric reflux (including spontaneous nasal regurgitation of stomach contents), absence of intestinal borborygmi, and abdominal distention. Rectal

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palpation and transabdominal ultrasonography reveal distended loops of small intestine and gas-filled large bowel. Affected horses are unable to swallow food or water, and drool from the mouth may be in the form of thick, ropy saliva. Fine muscle fasciculations similar to those that occur with EMND may affect the triceps and quadriceps.

Horses with subacute EGS survive long enough to develop colonic impactions and secondary large intestinal tympany. Chronic EGS may develop insidiously, and only a minority of these cases show mild, intermittent colic. Patchy sweating or piloerection, or both, are evident on the neck, flanks, and behind the shoulders. Typically, the appetite is reduced, and affected animals have varying degrees of difficulty in chewing and swallowing; however, salivation, accumulation of fluid in the stomach, and impaction are not usual features. Bilateral ptosis with ventral deviation of the eyelashes are often secondary to loss of sympathetic eyelid tone. Because of suppression of normal nasal secretions, some horses with mild chronic EGS have a characteristic dry crusty nasal exudate (rhinitis sicca). Fecal production is reduced, and feces are unusually firm and small. Weight loss is rapid and severe.

Acute and subacute cases are invariably fatal. Death occurs from gastric rupture, circulatory compromise, or cardiopulmonary failure; most commonly, such animals are euthanized. With appropriate nursing case, many horses with chronic (mild) EGS survive and even completely recover.[2] EGS is unlikely to recur in recovered horses.[13]

■ Diagnosis

Definitive diagnosis requires demonstration of compatible neuropathologic features within the autonomic or enteric nervous systems.[1] The antemortem sample of choice is an ileal biopsy, which is processed for hematoxylin and eosin staining with or without synaptophysin immunostaining of myenteric and submucosal enteric plexuses.[2] Lingual and rectal biopsies have been undertaken for diagnostic accuracy, and preliminary results have been promising but require prospective validation.[2]

No confirmatory blood test for EGS is available. Nonspecific abnormalities are consistent with severe dehydration, systemic inflammatory response, hypovolemia, stress, loss of GI secretions, and anorexia.[2,24] Peritoneal fluid protein concentrations may be high, although nucleated and red blood cell counts are usually normal. Altered serum concentrations of numerous acute-phase

proteins (including α_2 macroglobulin, serum amyloid A, ceruloplasmin, haptoglobin, and orosomucoid) have been recorded in horses with EGS but are nonspecific indicators of inflammation.[25]

In EGS cases with ptosis, topical application of 0.5 mL 0.5% phenylephrine eyedrops results in normalization of the eyelash angle within 30 minutes, and this result is supportive of the diagnosis.[26] Barium swallow contrast radiography, esophageal endoscopy, abdominal ultrasonography, and rectal palpation are used to identify changes consistent with dysfunction of components of the enteric nervous system.[2]

■ Treatment and Prevention

All cases of acute and subacute EGS are considered incurable and therefore necessitate euthanasia on humane grounds as soon as possible after diagnosis. For selected chronic cases, treatment involves excellent nursing care and provision of palatable, easily swallowed food and high energy concentrates. Clinical recovery occurs in approximately 70% of preselected treated cases.[1]

Current efforts at prevention involve minimization of known risk factors and introduction of suspected protective practices. Thus in endemic areas, horse owners are advised to avoid exposure to pastures where previous cases have occurred, minimize disturbance of pasture or soil, prevent overgrazing of pasture, and avoid the “overuse” of ivermectin dewormers. On the other hand, owners are encouraged to allow horses to graze with ruminants, mow pastures regularly, manually remove feces from pastures, and supplement pasture feeding with hay or haylage. These practices are particularly important during seasonal and climatic risk periods, as well as for young horses in good bodily condition, especially those recently imported.

■ Necropsy Findings

Gross necropsy findings in horses with EGS include esophageal ulceration, fluid distention of the stomach and small intestines, impaction of the large colon or cecum (or both), and the presence of inspissated mucus within the small colon and rectum. Horses with subacute and chronic cases do not have gastric and small intestinal distention but do have variable degrees of large intestinal impaction and often rhinitis sicca.[22] Histologic lesions of neuronal degeneration are most evident in the autonomic ganglia, enteric nerve plexuses, brain, and spinal cord.[23,27] There is chromatolysis, nuclear eccentricity, nuclear

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degenerative changes, cell death and neuronophagia, cytoplasmic vacuolation, and spheroid formation.

Peripheral Nerve Disorders

Robert J. MacKay • Lisle W. George

Most peripheral nerve disorders of large animals are traumatically induced, but injections, abscesses, tumors, and parasitic invasion of the nerves occur in rare cases. Damage to nerves are classified into two major functional categories.[1] Type 1 injury involves loss of function without loss of axonal continuity. Type 2 injury involves damage to axonal structures in such a way that wallerian degeneration of the axon ensues distal to the site of injury; the proximal axonal segment and the cell body remain intact. Retrograde degeneration of the proximal nerve occurs if connectivity is not reestablished.

Type 1 *(neurapractic)* lesions are characterized by a failure of conduction of the action potential across the injured axonal segment. The pathologic basis for these reversible injuries could be nerve compression, damage to the myelin sheath, or alteration of the functions of the axonal cell membrane or its channel proteins. Type 2 injuries are characterized by axonal interruption *(axonotmesis).* If there components of the connective tissue sheath and axon are also disrupted, the process is termed *neurotmesis.* Immediately after axonotmetic injury, the distal axonal segment is able to conduct action potentials; however, within 3 to 8 days after injury, the distal segment degenerates and no longer responds to electrical stimulation. In this way, neurapractic (type 1) and axonotmetic (type 2) injuries of longer than 8 days' duration can be theoretically distinguished. After axonotmesis of motor nerves, muscle reinnervation occurs by two separate mechanisms: collateral sprouting and axonal regrowth. If loss of axons to a muscle is incomplete, surviving motor axons generate sprouts from their nerve terminals, which can establish competent junctions with adjacent denervated muscle units. Reinnervation of muscle units by this process occurs within days to weeks. However, if the motor axons to a muscle are severed, reinnervation occurs by growth of collateral sprouts from the proximal stump. Axonal sprouts grow at a rate of 1 mm per day (≈1 inch per month). Because of progressive fibrous replacement of denervated muscle and retrograde degeneration of the proximal parts of affected motor neurons, reinnervation may not be possible if more than 12 months have elapsed since the original injury. However, reinnervation surgery has been successful when performed on human patients 20

years or more after denervation.[2]

Large-diameter myelinated fibers are most sensitive to compression forces. The largest axons (sensory axons), including afferent fibers conveying touch-pressure, vibration, and proprioception, are usually damaged first (which results in ataxia or inappropriate limb placement); second, the large myelinated motor axons are compromised; third, the smaller axons, which carry cutaneous and deep mechanoreceptor sensory information, are affected; last to be lost are the smallest-diameter fibers, which transmit pain sensation.

The following sections are discussions of the peripheral nerves most often damaged in large animals.

Suprascapular Nerve

Mechanical damage to the suprascapular nerve results in paralysis of the infraspinatus and supraspinatus muscles.[3] Such injuries occur most commonly when the animal collides at speed with gateposts, trees, or other objects.[4] Acute injury or local anesthesia of the suprascapular nerve is characterized by outward bowing or “popping” of the scapulohumeral joint, or both, as weight is placed on the limb. Neurogenic atrophy develops after 2 to 4 weeks, and the scapular spine becomes prominent (Fig. 35.24). The common name for this condition is “sweeney.”



FIG. 35.24 **Sweeney (neurogenic atrophy) of the left supraspinatus and infraspinatus muscles in a Quarter Horse gelding. The lesion was caused by trauma related to running into a fencepost 2 months previously.**

Brachial Plexus

Damage to the brachial plexus may result in any combination of dysfunction of the radial, pectoral, axillary, musculocutaneous, median, and ulnar nerves, although radial nerve signs usually dominate.[5,6]

Lesions of the brachial plexus are caused by trauma to the shoulder with or without scapular or rib fracture, deep penetrating axillary wounds, neoplasia or bacterial cellulitis, or forced extraction of a fetus to relieve dystocia.[7] Because of their tendency to move at high speeds, horses are most susceptible to brachial plexus injuries. The condition may occur in small ruminants after automobile accidents, carnivore attacks, or blows from larger animals.

Avulsion of the brachial plexus results in complete flaccidity, lack of reflexes, and desensitization of the affected thoracic limb. Disruption of the origins of the cervical sympathetic trunk in the caudal aspect of the plexus results in ipsilateral Horner syndrome. Lesser injuries may result in abduction of the elbow (pectoral nerve), dropped shoulder (subscapular), hyperextension of the elbow (musculocutaneous), or signs of radial paralysis (next section).[8]

Radial Nerve

The radial nerve provides motor input to a flexor of the shoulder and extensors of the elbow, carpal, and digital joints. The nerve courses over the lateral aspect of the elbow joint and is vulnerable to traumatic insult at that point. Radial nerve paralysis arises from injury to the T1 nerve root or nerve from vertebral or rib fracture, as part of a brachial plexus injury, as a result of humeral fracture, from direct trauma to the nerve over the elbow, as part of an ischemic myoneuropathy during prolonged anesthesia, or during restraint in lateral recumbency with inadequate padding of the forelimb.[7,9-11]

With radial paralysis, the limb position varies, depending on the location of the lesion in the radial nerve. Lesions at or near the elbow joint are characterized by dropped elbow, inability to protract the limb, scuffing of the toe, and flexion of all distal limb joints (Fig. 35.25). The foot is knuckled over at rest, and the animal is unable to bear weight on the leg. Lesions distal to the elbow cause knuckling of the carpus, fetlock, and pastern joints, but the animal can support weight on the affected limb if the metacarpus and distal limb are held in extension. The triceps reflex is depressed or absent. After weeks of radial

denervation, the extensor muscles of the thoracic limb exhibit atrophy. Detectable sensory deficits resulting from radial nerve paralysis tend to be vague and probably vary from patient to patient.



FIG. 35.25 High radial nerve paralysis in a horse showing knuckling of the carpus and digit and dropped elbow.

Kangaroo Gait in Sheep.

A locomotor disorder predominantly involving the thoracic limbs of lactating ewes has been reported in New Zealand, Australia, Scotland, and northern England.[12,13] Knuckling and paresis of the thoracic limbs are suggestive of radial paresis, and a high-stepping forelimb gait is also present. In advanced cases, the pelvic limbs are also involved. Limited necropsy data suggest both CNS and peripheral nerve involvement.[14,15] Affected ewes are usually of large breeds and are nursing twins. Most recover after weaning their lambs. Affected sheep are usually grazing on mixed forage, often with some concentrate supplementation. A clinically identical condition has been reported in Israel and in Australia among sheep grazing on the legume fenugreek.[16] A causative toxin

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or nutritional deficiency is suspected for both kangaroo gait and fenugreek staggers, but no toxin has yet been identified.

Femoral Nerve

The femoral nerve is distributed to the quadriceps femoris muscles and the skin of the rear limb over the medial thigh. Traumatic overextension of the hip and stifle joints from a fall or other injury or forced posterior delivery of a fetus can damage one or both femoral nerves.[17] The nerve courses too deeply to be directly affected by an external blow to the pelvic limb; however, it can be damaged by ilial, femoral, or vertebral fractures. Ischemic injury caused by prolonged stretch or increased tissue pressure during anesthesia in dorsal recumbency may cause bilateral femoral neurapraxia.[18] A similar presentation, presumably caused by compression of lumbar spinal branches by the foal in the birth canal, occurs in mares after severe prolonged dystocia.

The clinical signs of femoral nerve paralysis are related to an inability to extend and fix the stifle.[3] The reciprocal apparatus is unable to fix the stifle and hock, which results in collapse of the limb during weight bearing and constant flexion of all distal digital joints. The hoof usually remains flat on the ground. Chronic femoral denervation causes atrophy of the quadriceps femoris muscles. The patellar reflex is absent or depressed, and the patella is often displaced laterally. Hypoesthesia or anesthesia of the medial part of the rear limb extends from the proximal thigh to the medial malleolus of the tibia.

Sciatic Nerve

The sciatic nerve is the largest nerve in the body and innervates the extensor muscles of the hip, flexor muscles of the stifle, and most of the muscles of the distal limb. Sciatic nerve paralysis occurs most often in postpartum cows after forced fetal extraction.[19] Injury to the sixth lumbar nerve proximal to the lumbosacral plexus is the usual cause of so-called calving or obturator paralysis syndrome. Injection of irritating drugs into the space between the greater trochanter and the ischial tuberosity may cause a sciatic neuritis.[20] This occurs most frequently in young animals, but rare cases occur in adult cattle and small ruminants. Other causes of sciatic nerve damage are pelvic fractures, sacroiliac or coxofemoral dislocations, tumors, or abscesses located along the course of the nerve. Sciatic neuropathy is a rare complication of sacroiliac joint injections in horses.

The sciatic nerve innervates most of the musculature of the rear limb, and so the motor deficits associated with denervation are profound. At rest, the limb hangs behind the animal. The stifle is dropped and extended, and the hoof rests on its dorsum (Fig. 35.26). If the limb is positioned properly, the animal usually can bear some weight on it because of the normal function of the quadriceps muscles and the action of the reciprocal apparatus. Chronic sciatic denervation results in neurogenic atrophy of the caudal thigh muscles and all of the muscles distal to the stifle.



FIG. 35.26 **Characteristic posture of a foal with partial sciatic nerve paralysis. Note the flexion of the hocks, fetlocks, and stifle. The signs were the result of an intramuscular injection in the gluteal area.**

The sciatic nerve divides into the tibial and the peroneal nerves in the distal limb. Therefore except for the medial part of the thigh and gaskin, sciatic denervation also results in hypoesthesia and anesthesia of the entire limb distal to the stifle.

Peroneal Nerve

The peroneal branch of the sciatic nerve is distributed to the flexor muscles of

the hock joint and the extensor muscles of the digit. The nerve becomes superficial and is exposed to damage as it crosses over the lateral condyle of the fibula immediately distal to the stifle. Peroneal paralysis of this type occurs in all species of large animals and is common in postpartum dairy cattle that have been recumbent as a result of hypocalcemia or other causes and in horses because of postanesthetic ischemic myoneuropathy. The hock joint is hyperextended, the fetlock and pastern are flexed, and the dorsum of the hoof usually rests on the ground[3,21,22] (Fig. 35.27). Affected animals can bear weight when the limb is manually placed in the proper position. There is desensitization of the skin over the craniolateral aspect of the limb extending from the stifle to the hoof.



FIG. 35.27 **Calf with peroneal nerve paralysis. Note the flexed fetlock and digit and the hyperextended carpus. This condition was caused by injection of antibiotics into the peroneal nerve on the caudolateral aspect of the leg.**

Tibial Nerve

The tibial nerve supplies the extensor muscles of the hock joint (i.e., the gastrocnemius) and the digital flexors. Tibial paralysis is most often observed in periparturient cattle or neonates that have been given an injection of an irritant drug in the caudal leg at the level of the stifle. Tibial paralysis also occurs in sheep and goats and is a common sequela to dog-bite injuries. The resting limb

is held more flexed than is normal, and, although the foot contacts the ground in normal position, the metacarpophalangeal joint often partially collapses into a flexed position (i.e., “knuckles”). The limb moves in a stringhalt-like manner, with exaggerated flexion of the tarsus and stifle during protraction, followed by sudden extension to the weight-bearing phase of the stride. At rest the pelvis is asymmetric, with the affected side held lower than normal.[3] Chronic loss of tibial nerve function results in atrophy of the gastrocnemius and digital flexor muscles. The skin of the caudomedial aspect of the leg demonstrates anesthesia.

Obturator Nerve

The obturator nerve supplies the adductor muscles of the pelvic limb. The nerve is well protected in horses and small ruminants, and so injury is rare in these species. In contrast, because the cow has a relatively shallow acetabulum and poorly developed round ligament, the obturator nerve and the lumbar branches that supply it are vulnerable to injury during forced extraction of a calf to relieve dystocia. Reports of obturator nerve paralysis of cattle accompanied by knuckling and inability to support weight on the rear limbs probably represent a combination of sciatic and obturator nerve dysfunction. Coxofemoral dislocation is a common complication of obturator paralysis in cattle housed in stalls with slippery flooring.

Obturator nerve paralysis is most common in cattle and is almost exclusively a result of dystocia. The nerve injury is located in the pelvis at the level of the obturator foramen. Of all dystocias in dairy cattle, 9.2% result in paraplegia.[23] The obturator nerve innervates the adductor, pectineus, and gracilis muscles. Effects are minimal if the cow is placed on a surface that has good traction. Clinical signs of an obturator nerve injury include a hopping pelvic limb gait when the animal attempts to run and severe pelvic limb abduction or splay-leggedness when the animal stands on a slippery surface (Fig. 35.28). In severe cases, the cow may be sternally recumbent with the pelvic limbs extending laterally to each side. Experimental studies have indicated that the so-called calving paralysis syndrome is actually a result of a combination of injuries to the obturator nerve and to the sixth lumbar spinal nerve (L6), a major contributor to the sciatic and obturator nerves. Experimental sectioning of the obturator nerve alone does not produce paralysis, if the animal has secure footing.[3,19,24] Obturator nerve paralysis does not result in a cutaneous sensory deficit.



FIG. 35.28 **Cow with obturator nerve paralysis caused by relief of a difficult dystocia. Note the basewide stance and yet the apparent ease with which the cow is able to stand on the deep bedding. Note also that rope hobbles are being applied to prevent further abduction and trauma.**

Compression damage to one or more peripheral nerves during parturition or milk fever is a frequent factor in the so-called downer cow syndrome (discussed later). The condition occurs in 4 to 28% of all cases of milk fever and, before the advent of flotation tanks for treatment, was associated with a mortality rate of 20 to 67%.[25,26]

Peripheral Facial Nerve Paralysis

Facial paralysis is common in horses but uncommon in other large animals. Depending on the site of damage, some or all of the facial muscles can be affected. Complete unilateral facial paralysis in horses is evident as deviation of the nose toward the normal side, reduced flaring of the ipsilateral nostril during inspiration, and ipsilateral drooping of the lip, eyelid, and ear. Reflexes involving cranial nerve VII, such as the lip, eyelid, and menace and ear reflexes, are reduced or absent. Inability to close the eyelid causes exposure keratitis, which may be particularly severe when there is damage to the secretomotor fibers of the facial nerve at or proximal to the geniculate ganglion (keratitis sicca). The tongue protrudes out of the paralyzed side of the mouth, which

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suggests, often erroneously, a problem with lingual function. Because of paralysis of the buccinator cheek muscle, boluses of feed accumulate between the cheek and teeth, from where they may be dropped from the mouth. With chronic facial denervation in horses, neurogenic atrophy of the parotidoauricularis muscle becomes apparent as a groove behind the vertical ramus of the mandible. In cattle, because of the rigid structure of the planum nasale, muzzle deviation is not observed. In small ruminants, subtle muzzle deviation can usually be appreciated.

Injury to the facial nerve proximal to the vertical ramus of the mandible causes full facial paresis. Proximal facial nerve trauma in horses is usually caused by fractures of the vertical ramus of the mandible, stylohyoid bone, or petrous temporal bone (after a blow to the head or as a complication of THO). Damage within the facial canal is often associated with concurrent signs of vestibular nerve damage such as head tilt, nystagmus, and circling. Tear production may also be reduced or absent. Hemorrhage into the middle/inner ear, otitis media/internal guttural pouch mycosis, and parotid lymph node abscessation each can involve the adjacent facial nerve, causing ipsilateral facial paralysis. Distal facial nerve damage is usually due to direct injury from a blow or lateral recumbency or strangulation by a tight-fitting halter. The nerve or its branches are often damaged as they cross the mandible, the zygomatic arch, or both. Facial paresis after recumbency during general anesthesia is common and usually involves only the nose, lips, or both. Similar conditions occur in goats and are caused by excessive pull on neck chains while the animal is being led onto the milk stand or tied with the neck chain. In cattle, facial nerve paresis is usually the result of space-occupying masses at the caudal aspect of the mandibular ramus.

Most animals with facial nerve paralysis caused by trauma have neurapractic (type 1) nerve injury and recover within 2 weeks; those with type 2 (axonotmetic) injuries regrow axons from the site of injury at the rate of approximately 1 inch per month, and so full resolution make take several months. The paralysis is occasionally permanent. In chronic cases, food should be removed from the cheek pouches twice daily, and the tongue and fauces should be routinely examined for ulcers. Oral ulcers, if present, should be treated by flushing of the mouth.

■ Treatment

The objectives of medical treatment of peripheral nerve injury are (1) to reduce

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swelling and inflammation at the site of injury, (2) to support and stabilize the denervated area, and (3) to maintain of the general health of the animal.

In the case of lacerating trauma, the general principles of wound management apply. The wound should be cleaned, irrigated, debrided, and dressed, and ventral drainage should be established. If severed nerve ends are visible, they can be tagged for later identification and surgical repair. Medical therapy for inflammation and swelling should be initiated, especially if there is obvious tissue swelling. This may include any combination of a cyclooxygenase inhibitor (e.g., flunixin meglumine, 1.1 mg/kg IV, IM, or PO once or twice daily); DMSO (1 g/kg as a 10% solution IV or by nasogastric tube once or twice daily); and a glucocorticoid (e.g., dexamethasone, 0.05 mg/kg IV or IM once daily). An additional anti-inflammatory effect can be provided by cold water hydrotherapy or local application of skin-permeant drugs such as DMSO or diclofenac. In the presence of an open wound or other risk for bacterial infection, broad-spectrum antimicrobial therapy should be initiated. This can be directed by culture results, if available.

Fractured or dislocated bones that have the potential to further injure nerves must be reduced and stabilized. Stall rest helps prevent further injury. In the case of paralyzed limbs, a protective wrap may be necessary to prevent damage caused by dragging or improperly placing the limb. A support wrap, splint, or light cast should be maintained on a leg affected with radial paralysis so as to prevent limb contracture. A heavy support wrap, possibly with additional fetlock support, should also be placed on the opposite limb to protect against breakdown caused by prolonged increased weight bearing. If the horse has difficulty alternating between recumbency and standing, it should be supported as needed in an abdominal sling (horses and small ruminants) or flotation tank (cattle) until it is able to rise unassisted. Because of the buoyancy provided by water, affected animals (usually horses) may be able to exercise affected limbs in swimming pools. Skin over bony prominences should be padded to prevent decubital injury; such injuries must be treated aggressively if they occur.

If possible, passive range-of-motion exercises should be performed on paralyzed limbs in an attempt to preserve joint flexibility and prevent contracture. Faradic or galvanic electrical muscle stimulation, acupuncture, and hyperbaric oxygen therapy are other procedures advocated for treatment of peripheral nerve injury. Calcium gluconate can be given empirically to downer cows (500 mL SC daily), as may potassium chloride (100 g in 20 L of water given daily by stomach tube). Abduction of the rear limbs may be prevented in

cattle by application of a hobble around the metatarsus. The distance between the legs should be approximately 35.6 to 50.8 cm (14 to 20 inches) when the legs are tied together and held abducted. It is important to apply the hobbles with a nontightening bowline knot to prevent strangulation of the foot.

Surgical procedures for repair of peripheral nerves are beyond the scope of this text but are described elsewhere. In external neurolysis, the nerve is dissected from a bed of scar tissue.[1] This is indicated if there is obvious compression from fibrous tissue, and it is performed routinely in horses with suprascapular neuropathy.

Downer Cows (Alert Downers)

John A. Angelos • Bradford P. Smith • John R. Middleton

■ Definition and Etiology

Downer cows, down cows, or downers are cattle that are recumbent and cannot stand; those that can maintain sternal recumbency while continuing to eat and drink are classified as “alert downers.” Common underlying causes of recumbency in cattle include severe mastitis, metritis, musculoskeletal disease (primary musculoskeletal injuries, including fractures and torn muscles/tendons), neuropathies secondary to pelvic trauma (calving paralysis), spinal cord compression (e.g., secondary to lymphosarcoma), and metabolic disease (hypocalcemia, hypokalemia, hypophosphatemia, hypomagnesemia).[1] After the initial episode of recumbency, secondary muscle and nerve injury caused by extended periods of recumbency on a firm surface may further exacerbate the recumbency. Heavy cattle down on concrete are particularly susceptible to pressure ischemia of the muscles and nerves and to muscle and ligament tearing secondary to repeated struggling and slipping. The severity of pressure damage depends on the nature of the surface on which the animal is recumbent and the duration of compression.

Identifying underlying causes of recumbency in downer cattle represents a diagnostic challenge for the practitioner. Assessing prognosis and determining reversibility of the underlying condition are necessary for practitioners to assist producers in making treatment decisions, as well as to conform to laws and abide by ethical norms surrounding humane handling of downer animals. In short, dragging of downer livestock is considered inhumane, and downer livestock that are in distress or that do not respond to treatment should be humanely

euthanized.

■ Epidemiology and Pathogenesis

It is reported that 3.8% to 28.2% of all cows with milk fever become alert downers,[2-5] and the mortality rate is 20 to 67%.[3-7] The incidence of the condition (24 hours or longer) was 21.4 cases per 1000 cow-years in Minnesota dairy herds, with a 33% recovery rate.[7] Fifty-eight percent of downer cases occurred within a day of calving, and 97% occurred within the first 100 days after calving.[7] Because the pressure damage done to muscles and nerves is aggravated by recumbency, it is desirable to have the animal on soft bedding (e.g., sand, grass) and to have the animal stand as soon as possible.

■ Clinical Pathology

Laboratory testing for metabolic causes of recumbency would be ideal in all circumstances, but this is often not feasible or possible.

Of 16 normal cows anesthetized for 6 to 12 hours in sternal recumbency with the right hindlimb under the body, 8 were unable to stand on recovery and became alert downers.[8] Those that could stand exhibited swelling and stiffness and peroneal nerve deficits and paresis in the right hindlimb.[8] These signs typically appear in cows that have been recumbent for several hours on a hard surface. As pressure applied to a nerve increases, nerve conduction is impaired and eventually lost.[9] Serum CK values in experimental downer cows increased, starting at 12 hours and continued to increase up to 48 hours, and then decreased, even though the cow remained down.[8] The CK values at 12 and 24 hours did not differ statistically between the cows that could rise after anesthesia and the downers. After 48 hours and 96 hours, the downers had higher mean CK values than did the ambulatory cows, but the range in values was broad.[8] The clinical difference between cows that recovered and those that remained downers was attributed to damage to the sciatic nerve or its branches, particularly the peroneal nerve.[8] Peroneal nerve damage results in knuckling over at the fetlock. In another study of downers, AST levels were greatly elevated on days 4 to 7, even after CK levels fell.[10]

Serum levels of creatine phosphokinase, AST, and lactate dehydrogenase have been examined to determine whether these indices of muscle damage can help predict recovery of recumbent dairy cattle. Of the three enzymes, AST has been

shown to be most useful in predicting nonrecovery. Dairy cattle with an AST level higher than 171 IU/L are 80% more likely not to recover than a dairy cow with an AST level lower than 171 IU/L.[11]

CSF collected from recumbent adult dairy cattle with spinal cord lesions (neoplasia, trauma, or infectious process) had significantly higher total protein concentrations and total nucleated cell counts than did recumbent adult dairy cattle without spinal cord lesions, which suggests that CSF analysis may be useful in differentiating alert downer cows with spinal lesions from those without.[12] Cows with CSF protein levels lower than 0.25 g/L and total nucleated cell counts of 4.5 or lower were predicted to not have a spinal cord lesion, whereas cows with total nucleated cell counts higher than 4.5 or a protein concentration exceeding 0.39 g/L were predicted to have a spinal cord lesion, according to the statistical modeling performed in the study.[12]

■ Treatment

Many downer cattle are treated empirically for suspected metabolic abnormalities and response to treatment aids in establishing the diagnosis. Periparturient downer cows should be treated for hypocalcemia with one or more doses of calcium. Animals that become more alert but that are not standing after one or two doses of calcium are classified as alert downer cows.

Devices that aid and promote standing traditionally include hip lifters (hip clamps), slings, and inflatable bags. Although these devices help less severely affected animals stand temporarily, they do not allow the animal to stand comfortably for hours and may even cause further trauma in animals that struggle. For these reasons, the use of water flotation has been explored as a tool in the management of downer cows. Rasmussen[13] first reported on the use of a warm-water flotation system in Denmark in 1982. Commercial flotation systems practical for cows (Aqua Cow Rise System [http://www.aquacowsystem.com] and Aqua-Cow-Rise System [http://kirbymfg.com/aquacow.htm]) are marketed in the United States.

For flotation therapy to allow the best chances for recovery, the animal should first be examined to determine that it is a good candidate for flotation, by ruling out fractures, severe spinal cord compression, and severe systemic illness. Identifying and correcting electrolyte disturbances (e.g., hypocalcemia, hypophosphatemia, hypomagnesemia, hypokalemia) are required for successful application of flotation therapy. Once metabolic or systemic illnesses have been

addressed and the cow is considered strong enough to stand once supported by water, the cow is placed in the flotation tank as follows: (1) the water tank is positioned near the downer cow; (2) the wheels and tongue are detached, and both ends of the tank are removed; (3) a mat is pulled from the tub to a position beside the downer cow, and the animal is rolled or slid onto the mat; (4) the mat is winched or otherwise pulled into the tub, and the ends of the tub are put in place; they seal with rubber gaskets and large turnbuckles; and (5) the cow's head is held up a few inches by a rope halter, and a hose is inserted into the tub, which is filled with water as quickly as possible; the water temperature should be 37.7° C to 38.7° C (100° F to 102° F). Cows in lateral recumbency on the mat become sternal when 12 to 24 inches of water fills the tub and usually attempt to stand beginning when the tub is half to two-thirds full.

If no hot water is available near the cow, or if the tub is not next to dirt or grass suitable for the cow to exit on, the wheels can be put back on and the cow easily transported by trailer to a better location. In addition, it is helpful to have an assistant support the tail or have a means to pull the tail once the cow attempts to rise. This helps the cow maintain a sternal position during early efforts at struggling before the cow is actually standing. Before flotation of lactating cattle at the University of California, Davis, cows are milked, and teat ends are sealed with a rubber teat sealant; this is removed once the cow is removed from the tank before milking. The sealant is reapplied after milking in preparation for the next flotation.

Once the cow is standing in warm water, it is possible to determine which limb or limbs are paretic or painful by observing which limbs the cow is using to support weight. Most cows calm down and relax in a standing position within 5 minutes. Most will eat hay, and even primiparous heifers that have not been handled much seem to be remarkably calmed by the warm water. Unlike horses, cattle do not panic or attempt to jump out. The cow can be left in the water for 12 to 24 hours. If the water temperature drops below 35° C (95° F), some water should be released from the discharge valve and replaced with hot water; this is especially recommended in cold weather. When the decision is made to remove the cow from the tub, the water is drained, and the end of the tub facing the dirt, sand, or grass is opened. The cow is encouraged to exit *slowly* into a pen with good footing. Some cows fall as the water is let out, and others collapse once they try to walk. By observing how a cow is ambulating on exit, it is possible to determine whether hobbles should be placed onto the cow before the next flotation. If cows are considered at risk for splaying out while exiting the tank, it

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is recommended that hobbles be applied before the cow is placed in the tank.

Careful observation as the cow moves can be helpful in trying to locate anatomic or functional problems. The animal that collapses can be pulled out on the mat and left on suitable bedding, dirt, sand, or grass until refloated after a period of rest. Advanced planning on location is important for successful use of flotation therapy. Cows that can walk out into a pen may or may not be able to stand by the next day and may need to be refloated. Cows may need to be floated for up to 10 consecutive days before they can arise by themselves. If cases are carefully selected to rule out fractures, severe traumatic stifle injuries, septic arthritis, and spinal cord compression, a recuperative success rate of 46% to 90% can be expected.[13,14]

Flotation is most effective if applied early, before a downer cow develops serious myopathy and neuropathy. Studies have shown that water flotation is practical and effective, even when cattle have been down for 24 hours or longer.[1] The sooner a postparturient alert downer cow can be floated after onset of recumbency, the sooner it can resume standing. In one study of postparturient alert downer cattle treated with flotation therapy, the mean time to resumption of standing was shorter for cattle floated within 1 day of going down (mean, 2.8 days to resumption of standing) than for cattle floated after being down for 2 days or longer (mean, 5.3 days to resumption of standing).[14]

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• CHAPTER 36

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Mammary Gland Health and Disorders

Pamela L. Ruegg, Ronald J. Erskine, Consulting Editors

The presence of mammary glands is a defining characteristic of mammals. The original purpose of these specialized glands was to produce milk to feed progeny. However, milk has excellent nutritional qualities and several breeds of cattle, goats, and sheep are bred primarily to produce milk that is used for human consumption. Diseases of the mammary gland thus have important repercussions not only for animal health but also for the well-being of humans.

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Mammary Gland Health of Dairy Cattle

The global dairy industry has dramatically changed in the past quarter century. Volatile milk prices, increasing herd size and reliance on hired labor, more complex feeding and housing systems, and increased pressure for environmental stewardship have fostered greater diversity among dairy enterprises. Bovine mastitis is the most common and economically important disease of dairy herds in developed countries[1,2] and hinders realization of optimum farm productivity, milk quality, and supply of dairy foods. Mastitis remains the most common cause of antimicrobial drug therapy for cows on U.S. dairy farms.[3] In addition, an important and often unrecognized obstacle to implementation of mastitis control practices is the behavior and attitude of farmers and employees.[4] Veterinarians can play a critical role in the control of this disease as part of a quality milk team that targets drug use, environment, milking practices, and the epidemiology of mastitis within each dairy herd. Implementation of quality milk programs within dairy herds will increase productivity for dairy producers, supply milk processors with superior raw milk, offer consumers better quality dairy foods, improve cow health and well-being, establish the dairy industry as an advocate for antimicrobial stewardship, and promote a sustainable market for U.S. dairy products globally.

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Economic Impact of Mastitis of Dairy Cattle

Decreased milk production in affected mammary glands is the primary economic loss from mastitis. Inflammation causes pathologic changes in milk-secreting epithelial cells that decreases functional capacity. Depending on the type of pathogen, losses may continue into subsequent lactations. Most infections result in local inflammation or relatively mild clinical cases.[5,6] However, chronic infections can lead to agalactia in the affected quarter or, in the case of severe clinical cases, profound systemic involvement that occasionally results in death.

Somatic cell counts (SCCs) are indicators of leukocyte migration into milk that primarily occurs from infection of the mammary gland. Bulk tank somatic cell counts (BTSCCs) are strongly correlated with the proportion of infected cows within a dairy herd and are used as a measure of milk quality. Substantial economic loss may be incurred when regulatory or processor limits for BTSCCs are exceeded. Although the Pasteurized Milk Ordinance sets the BTSCC limit at 750,000 cells/mL for Grade A milk in the United States, in 2012 the U.S. Department of Agriculture (USDA) required that dairy exports to the European Union (EU) originate from farms with BTSCCs of 400,000 cells/mL or less. Because of this mandate and to be competitive for global dairy markets, 400,000 cells/mL has become the de facto limit for many milk processors, who may refuse milk from dairy operations that do not meet this standard. In addition, many producers are paid monetary premiums for low BTSCCs or are penalized for high BTSCCs. This may help explain why in 2015, BTSCCs in 96.0% of milk produced in the United States were less than 400,000 cells/mL; 68.8% of producers shipped milk below this limit for the entire year.[7] In addition, the percentage of total milk shipped with BTSCCs of less than 200,000 cells/mL during 2010 to 2016 increased from 40.6% to 52.5%.

Milk from cows with subclinical mastitis is not usually withheld from the bulk tank and thus contributes to increased BTSCCs and reduced milk quality. Proteolytic and other changes in milk due to subclinical mastitis adversely affect organoleptic qualities and the shelf life of milk and milk products. BTSCCs greater than 150,000 cells/mL are associated with decreased productivity per cow, shorter shelf life of fluid milk, and reduced yield of products such as cheese.[8,9] Overall, reduced milk production and quality associated with BTSCCs

of 200,000 cells/mL or greater has been estimated to result in an annual economic loss of $3.1 billion to consumers.[10] Individual cow milk yield is estimated to decrease by 0.5 to 0.6 kg/day for each twofold increase in SCCs over 50,000 cells/mL.[2,11] However, the magnitude of the milk decrease relative to SCC increase has been reported to be higher in later lactation and older cows.[12] More recently, losses from subclinical mastitis have been determined to be a function of the milk production potential of the cow; cows that are higher milk producers have greater milk losses from subclinical mastitis than lower producing cows.[13] Thus milk yield losses for cows with a SCC of 800,000 cells/mL range from 1 to 3.3 kg/day, or 4.3% to 8.0%, relative to cows with SCCs of 100,000 cells/mL or less.[13] Losses from subclinical mastitis are even more substantial if accumulated over an entire lactation. Cows with chronic mastitis, measured by increased consecutive Dairy Herd Improvement Association (DHIA) test days with SCCs of 100,000 cells/mL or greater, resulted in higher milk losses than cows with new infections.[14] In addition, DHIA records from more than 166,000 cow lactations in the western United States found that cows with a first test date SCC of 200,000 cells/mL or greater produced 718 kg less milk than cows with a first test date SCC less than 200,000 cells/mL.[15]

High-BTSCC milk also has a greater risk of condemnation because of violative antimicrobial residues.[16-18] In a retrospective study, the rate of antibiotic residue violations increased as herd SCC increased, and the relative risk of antibiotic residue violations (compared to herds with SCCs less than 250,000 cells/mL) was 2.4, 2.8, and 7.1 times greater for herds with SCCs of greater than 400,000, greater than 550,000, and greater than 700,000 cells/mL, respectively.[16]

Cows with chronically increased SCCs caused by intramammary infections (IMIs) are often culled prematurely as a consequence of decreased milk production. The cost of premature culling depends on the perceived value of the cow, the market prices for culled cows and replacement heifers, and the potential value of the replacement heifer.[19] Cows with an average SCC greater than 700,000 cells/mL were twice as likely to be culled as cows with an average SCC under 250,000 cells/mL, especially in herds with low BTSCCs.[20] Cows that are not culled may be segregated or require the use of milking procedures that increase labor costs. For example, cows with chronic IMIs caused by *Staphylococcus aureus* or *Mycoplasma* may need to be housed separately and milked last.

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The incidence of clinical mastitis averages between 15% and 25% of lactations, although some herds may have rates greater than 45%.[21-25] Estimates of lost milk production from a case of clinical mastitis over an entire lactation range from 110 to 552 kg, depending on the parity and stage of lactation when the case occurred.[26-28] Further losses from clinical mastitis can result from subsequent repeated episodes during the same or later lactations. In a study of 7 New York dairies, milk losses in the first 50 days following onset of clinical mastitis were 304, 128, and 92 kg for cases caused by gram-negative, gram-positive, and other pathogens, respectively.[29] Clinical mastitis also results in additional economic losses beyond milk production. In a 1700-cow dairy, cows with clinical mastitis lost 341 kg of saleable milk, compared to projected yield, during the first 60 days after case onset.[30] Nearly 75% of the milk loss was discarded because of treatment, with the remainder accounted for by lost production. Cows in their second or greater lactation, or more than 150 days in milk, incurred greater losses, although the type of causative pathogen was not associated with differences in losses.[30] The average total costs per case (US$) of gram-positive, gram-negative, and other pathogens were estimated to be $133.73, $211.03, and $95.31, respectively.[31] Premature culling resulting from unresolved clinical mastitis cases or subsequent suboptimal milk yield of the affected cow may increase these costs to as much as $600.[32]

The occurrence of both subclinical and clinical mastitis has been associated with reduced reproductive performance. In a preliminary field study, cows were almost two times more likely to have altered interestrus intervals following an episode of clinical coliform mastitis compared to herdmates without clinical mastitis.[33] Conception rates for cows with clinical mastitis between 3 weeks before and 5 weeks after insemination have been reported to be lower compared to cows without clinical mastitis.[34,35] Clinical mastitis due to gram-negative bacteria has a more detrimental effect on the probability of conception than clinical mastitis caused by gram-positive bacteria or other organisms.[36] In addition, the days to first service, services per conception, and days to conception were all increased in cows with clinical mastitis as compared to nonmastitic cows.[37] Cows with a case of clinical mastitis in the first 45 days of gestation are nearly three times more likely to abort within the next 90 days than nonmastitic cows.[38] As well, cows with increased SCCs (>150,000 cells/mL) have decreased conception rates as compared to cows with lower SCCs, and as

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the SCC increases, the odds of pregnancy decrease.[39-41] It is likely that inflammatory mediators released in response to IMI play a role in oocyte and embryonic degradation. For example, lipopolysaccharide endotoxin in cattle induces a prolonged release of inflammatory mediators, including prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), leading to uterine smooth muscle contraction and luteolysis, a gradual decline in plasma progesterone, and thus abortion, especially in the first trimester of pregnancy.[40,42]

The total cost of mastitis is impossible to quantify accurately, varies over time, and is herd dependent. Nationally, the cost of mastitis has been estimated at $200/cow/year, or $1.5 to $2 billion.[19] Costs associated with implementation of mastitis control programs can be substantial. Return on investment in mastitis control is more important than the absolute cost and ranged from –$20 to $275/cow/year in a review of nine studies.[37,43] However, this return depends on the prevalence and type of mastitis in the herd, existing control measures, and producer compliance. In summary, although the costs incurred by producers to control mastitis are significant, the benefits of reducing mastitis include improved cow health and productivity, a superior raw milk supply for processors, better quality and safer dairy foods for consumers, and a more sustainable market for dairy products globally.

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Anatomic Structures of the Bovine Mammary Gland

Cattle have a single udder that is composed of four independent mammary glands that are referred to as *quarters*. Suspensory ligaments attach the udder to the pelvic bone and abdominal muscles of the ventral body wall. The four quarters are anatomically independent with no direct physical connections,[44] but researchers have demonstrated mild inflammatory responses in apparently healthy quarters adjacent to quarters experiencing clinical mastitis indicative of some interdependence.[45] Each mammary gland consists of a teat with a single opening, small cisterns (also called sinuses) in the teat and base of the gland, a system of ducts, and secretory tissue. The secretory tissue is organized into lobes that are composed of lobules containing hundreds of microscopic alveoli lined by *mammary epithelial cells* that synthesize and secrete milk.[5] Nutrients required for milk synthesis are delivered to each mammary gland by the circulatory system and transported into epithelial cells or directly into the alveolar lumen. Milk components, including casein, lactose, and fat, are synthesized within epithelial cells and secreted into the alveolar lumen, where they combine with other constituents to form milk. Production of milk is continuous, and during the interval between milkings about 20% of the milk accumulates in the larger spaces of the udder such as the teat cistern, gland cistern, and large ducts *(cisternal fraction).* However, about 80% of the milk remains fixed by capillary forces within the alveoli *(alveolar fraction),* and removal of this fraction is dependent on achieving successful milk ejection *(milk letdown).*[46]

Milk letdown occurs in response to tactile stimulation of teats, which triggers a neurohormonal reflex, causing the pituitary gland to release *oxytocin* into the bloodstream.[46] Milk is ejected from the alveoli into the cisterns when the surrounding myoepithelial cells contract after binding oxytocin. Milk flows through the teat orifice after resistance of the teat canal (also called the *streak canal*) is overcome due to the pressure of milk in the teat, suckling by offspring, or the process of milking. Activation of the sympathetic nervous system during periods of stress or excitement can inhibit the release of oxytocin from the pituitary gland or the binding of oxytocin to myoepithelial cells, thus preventing milk ejection.[47]

The teat canal and surrounding musculoelastic tissue are the primary physical barrier to microbial invasion and also prevent leakage of milk between milkings.[48,49] The teat canal is a narrow, longitudinally folded cylinder lined with stratified squamous epithelium. The tortuous shape of the canal provides physical protection against infection, as well as *keratin*, which lines the canal and is produced by the epithelial cells. Lack of keratin in the teat canal greatly increases the risk of IMI because keratin physically plugs the teat canal, traps invading microbes, and contains bacteriocidal fatty acids and proteins.[50-52] Hyperkeratosis of the teat end; trauma-associated abrasion of the teat orifice; or teat damage from ineffective pulsation, excessive milking vacuum, or poorly fitting teat cup liners can also increase the risk of IMI.[53-55]

Because of the importance of the teat in mammary gland defense, dairy producers should routinely monitor teat condition and use a combination of genetic selection and management practices to promote teat health and sound conformation of the udder. However, it must be emphasized that cows housed on wet or soiled bedding, or udders and teats exposed to excessive water during milking preparation, are at high risk for IMI, despite good teat end health.[56-58] In addition, lack of aseptic preparation of teat ends before cannula insertion or use of multiple-dose drug preparations that are not intended for intramammary infusion can result in outbreaks of infection caused by opportunistic pathogens.[59]

Immunologic Responses to Intramammary Infection

Reducing pathogen exposure is the foundation of prevention of infectious disease, including mastitis. When exposure to pathogens is sufficient to traverse the teat canal and multiply in the milk, the ensuing response on the part of the host immune system initiates inflammation of the mammary gland, which is recognized as subclinical or clinical mastitis. If the innate and acquired immune systems effectively eliminate the invading microbes, the mastitis will be mild and transient. However, when defense mechanisms are compromised (e.g., during the periparturient period, periods of heat stress, or after transportation and commingling of animals in the herd) or when the pathogen expresses virulence factors that resist phagocytosis or intracellular destruction, severe or chronic mastitis may develop. The intensity of the inflammatory response determines whether mastitis is subclinical or clinical.

With *subclinical mastitis*, the inflammatory process does not result in visible abnormalities in the milk, mammary gland, or cow, although leukocytosis and

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other soluble changes in milk occur. With *clinical mastitis,* milk from the affected quarter is visibly abnormal, the gland may undergo marked inflammation, and the cow may exhibit signs of systemic illness. Although mastitis can result from trauma, the vast majority of mastitis is caused by IMI via the teat canal. As stated earlier, limiting exposure to pathogens at the teat end remains the primary means to prevent infection. Mastitis occurs in all herds, but herds that manage pathogen exposure will endure less mastitis.

Mammary Inflammation.

If invading pathogens are able to overcome the teat canal barrier and gain entry into the gland, a series of innate host defenses help to limit bacterial growth. Because bovine mastitis is essentially a disease of bacterial and occasional mycotic or algal pathogens, the primary effectors of mammary immunity are polymorphonuclear neutrophils (PMNs). However, as in other tissues, these phagocytes rely on a complex system of soluble and cellular mediators that recognize pathogen presence and subsequently recruit and activate phagocytes to eliminate the microbes, termed the *innate immune system.* Soluble factors include complement, lactoferrin, and acute phase proteins (such as mannose-binding lectin and C-reactive protein). Lactoferrin is an iron-binding glycoprotein produced by mammary epithelial cells and found in PMN granules.[60] By sequestering iron, lactoferrin prevents multiplication of iron-dependent microorganisms, such as coliform bacteria.[61] Mannose-binding lectin and C-reactive protein will bind to molecules specific to pathogen cell walls and help to activate the complement cascade. Innate host defenses differentiate host tissue from pathogens by recognizing molecules that are universal to many microbes but not present on host cells. These pathogen-associated molecular patterns (PAMPs) are recognized and selectively bound by serum proteins and receptors in host cells, which are called *pathogen recognition receptors* (PRRs).[62]

Toll-like receptors (TLRs) are an important class of PRRs that reside both on cell surfaces and within host cells. These receptors invoke gene expression and release of inflammatory cytokines (e.g., interleukins, tumor necrosis factor [TNF]-α) from the host cells and act as the critical link between recognition of foreign agents and initiation of the host response.[62,63] Examples of specific pathogen targets bound by TLRs include peptidoglycan and lipoteichoic acid of gram-positive bacteria (TLR-2), gram-negative lipopolysaccharide (LPS; TLR-

4), bacterial flagellin (TLR-5), and bacterial DNA as CpG oligonucleotides (TLR-9).[64] Much of the local inflammation and systemic signs (when they occur) associated with mastitis are attributable to this response. Numerous cell types, including epithelial and endothelial cells, macrophages, and other phagocytic cells possess TLRs, which can contribute to an inflammatory response.[65] The inflammatory response is further modulated by activation of eicosanoid (arachidonic acid) metabolites such as prostaglandins and leukotrienes, as well as by endocrine and adipose mediators.[66,67]

Milk from healthy mammary glands contains a low concentration of leukocytes. However, when microbial ligands (molecules) are detected by TLRs on macrophages and epithelial cells, these cells release proinflammatory cytokines, such as interleukin 1 (IL-1), IL-6, and TNF-α.[62] These mediators cause vasodilation and expression of adhesion molecules on endothelial cells, which in turn trigger an influx of neutrophils.[64] Circulating blood neutrophils must adhere to the vascular endothelium before migrating into the milk. Vascular neutrophils loosely bind and roll along the endothelium, using a surface adhesion molecule (CD62L or L-selectin).[68] L-selectin is highly expressed on the surface of normal circulating neutrophils, whereas similar molecules—E-selectin (CD62E) and P-selectin (CD62P)—are expressed on vascular endothelial cells at the site of inflammation.[68] Neutrophil CD62L is responsible for making initial contact between fast-flowing blood neutrophils and the vascular wall, which rapidly slows neutrophil movement in small postcapillary vessels, whereas endothelial CD62E and CD62P direct slow-moving neutrophils to the specific site of inflammation. Additional proinflammatory mediators, such as IL-8, leukotriene B4, and complement component 5a, serve as neutrophil chemotactic agents and promote expression of surface receptors on endothelial cells.[68] This in turn causes neutrophils to express the β_2-integrin adhesion complex CD11b/CD18. The CD11b/CD18 complex firmly anchors neutrophils to vascular and intercellular adhesion molecules.[68-70] Once bound, neutrophils migrate between the endothelial and mammary epithelial cells into the milk *(diapedesis)*, traveling along a chemotactic gradient to the site of infection.[68] During infection, neutrophils often exceed concentrations of 1 million cells/mL. Both the speed of recruitment and the extent of neutrophil influx into milk influence microbial clearance and are critical determinants of infection outcome.[64,71-73] Thus, compared to noninfected quarters, milk from infected quarters reflects the recruitment of PMNs and lymphocytes to eliminate the infection after initial

signaling by antigen processing cells such as macrophages, and chemotactic modulators from endothelial and antigen processing cells. This leads to higher absolute numbers of neutrophils, lymphocytes, and macrophages but greater proportions of PMNs and lymphocytes relative to macrophages.[74,75]

During migration and under the influence of proinflammatory cytokines (e.g., TNF-α and interferon gamma [IFN-γ], IL-17), neutrophils are further activated to become focused killer cells.[68] In this way, the leukocytes arrive at the infection site ready to recognize, phagocytose, and kill infecting pathogens. Phagocytosis is accomplished through a variety of specialized receptors on the surface of neutrophils, which are generally upregulated in response to the proinflammatory signals received during diapedesis and chemotaxis. Expression of CD14 receptors enables neutrophils to bind bacterial LPS in the presence of LPS-binding protein (LBP); this binding facilitates nonopsonic phagocytosis of gram-negative bacteria.[76] At the same time, soluble *CD14* is shed into the milk, where it neutralizes free LPS and binds to epithelial cells, enhancing chemoattractant release.[73] The most important neutrophil receptor for opsonic phagocytosis is the *Fc receptor,* which binds the Fc region of immunoglobulins (Ig), particularly IgG2 and IgM, enabling the phagocytosis of antibody-coated pathogens.[77,78] Complement component 3b is also opsonic for bovine neutrophils.[69]

Receptor binding stimulates the neutrophil to extend pseudopods and engulf the adhered pathogen into a phagosome. The phagosome fuses with cytoplasmic secretory granules to form an intracellular vesicle (phagolysosome), where degranulation and microbial killing take place. Neutrophil granules contain cationic peptides called *defensins,* which have broad-spectrum antibacterial and antifungal activities.[60,64] These proteins, along with lactoferrin, and hydrolytic enzymes contribute to oxygen-independent killing of engulfed pathogens.

To effectively respond to pathogen invasion, the lactating mammary gland of ruminants must overcome numerous deficits. The number of somatic cells (which in lactating dairy cattle are primarily leukocytes) in milk is typically less than 100,000 cells/mL in uninfected glands, which is approximately 100-fold lower than in blood. Concentrations of factors such as lactoferrin and complement are also lower in milk relative to plasma.[79] In addition, the ability of circulating macrophages in milk to re-enter tissue for antigen presentation remains speculative. As compared to blood, macrophages and neutrophils in milk have decreased phagocytic ability.[80,81] Neutrophils engulf fat globules and

casein, which reduces subsequent pseudopod formation as well as intracellular killing capacity.[73] Host-adapted pathogens (such as *S. aureus*) often have numerous virulence factors to help evade recognition and phagocytosis, which further compromises the ability of host defenses to eliminate the infection.

As mentioned earlier, postpartum cows may be particularly susceptible to infections compared to cows later in lactation. $CD4^+$ (T-helper) lymphocytes are predominantly T_h2 (downregulation of inflammation) compared with T_h1 (proinflammatory) within 3 days after calving. This alters the repertoire of cytokines produced and thus the effectiveness of phagocytic cells such as PMNs and macrophages.[82]

Specific Immune Responses.

If a pathogen survives innate host defenses, the specific (also called *acquired*) immune system is triggered. This branch of the immune system recognizes specific antigens of pathogens, and if repeated exposure occurs, an immunologic "memory" initiates a faster and more intense response with longer duration. As with neutrophils, mammary macrophages ingest and kill microorganisms. In addition to initiating inflammation and killing pathogens, macrophages and dendritic cells play a key role in processing and presenting antigen to T lymphocytes. Antigen presentation is critical to activate T-helper cells ($CD4^+$), thus enabling secretion of cytokines, activation of B lymphocytes, as well as cytotoxic ($CD8^+$), suppressor, and memory functions.[83] To date, the role of the $CD4^+$ (helper), $CD8^+$ (cytotoxic and suppressor), and CD17 (phagocyte agonist) subsets in bovine mammary immunity are best understood.[84] B lymphocytes also are critical for antigen processing and serve as precursors to immunoglobulin-producing plasma cells.

Concentrations of immunoglobulin are low in normal milk but rise in response to IMI. This increase is partly a result of local Ig production but mostly from increased permeability of vascular endothelial cells and mammary epithelial cell tight junctions, which allows an influx of plasma Ig (and other plasma proteins) into milk. Influx of opsonizing Ig (IgM and IgG2) enables efficient phagocytosis of microorganisms by neutrophils.[77,78,85] Nonopsonizing Ig (IgG1 and IgA in cattle) have other beneficial functions, such as neutralization of bacterial toxins, agglutination of bacteria, and prevention of bacterial adherence to epithelial cells. Immunoglobulins in milk also mediate antibody-dependent cell-mediated cytotoxicity by leukocytes.[83,86]

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Defense Mechanisms in the Periparturient Period.

Mammary gland defense mechanisms are greatly reduced in the periparturient period, which increases vulnerability to IMI. Indeed, both the incidence and the severity of mastitis are greater in the periparturient period than during other periods of lactation.[68,87-89] Phagocyte diapedesis and killing and lymphocyte mitogenic responses are markedly decreased during the periparturient period.[84,86,90-92] Cows infected with *S. aureus* have a subpopulation of $CD8^+$ lymphocytes within the mammary gland that suppress proliferation of $CD4^+$ lymphocytes, and this class of $CD8^+$ cells is preferentially trafficked into the gland during the postpartum period.[93]

The immunosuppression accompanying parturition is partly caused by increased circulating cortisol concentration, which impairs neutrophil margination and recruitment.[64] Neutrophils of periparturient cows also undergo apoptosis more rapidly than do neutrophils of cows in later lactation, and early onset of apoptosis reduces phagocytic and intracellular killing activity.[73] Low circulating concentrations of insulin-like growth factor 1 (IGF-1) in periparturient cows may reduce neutrophil viability and impair cytokine secretion.[89]

Nutrition of the cows during the transition period can also play a critical role in mammary immunity. Non-esterified fatty acids (NEFAs) are released from adipose tissue in response to negative energy balances that are typical for cows in the transition period from late gestation to peak milk production. Particularly before calving, cows with excessive negative energy balances and high serum NEFAs are more at risk for culling and diseases during early lactation.[94,95] In addition, elevated serum NEFAs lead to undesirable expression of proinflammatory mediators, adhesion molecules, and reactive oxygen species.[67] The altered plasma fatty acid profile in cattle during periods of negative energy balance also changes the phospholipid content in membranes of endothelial and mononuclear cells.[96] Fatty acids from membrane phospholipids are the precursors for numerous arachidonic acid metabolites, the control of which is critical for the magnitude of inflammatory responses.

Oxidative stress resulting from high energy use by high-producing dairy cows further increases the expression of oxylipid (peroxylipid and other metabolites of polyunsaturated fats) pathways. Especially because of the dynamics of lipid metabolism in dairy cows around parturition, profound changes in the

composition and concentration of oxylipids systemically and in the mammary gland may be responsible for dysfunctional inflammatory responses.[66] The key to modulating this potential problem is to manage the feeding of cows to mitigate excessive body condition loss, especially in transition cows.

Antioxidant supplementation has also been demonstrated to play an important role in mammary immune function. Antioxidants such as vitamin E, selenoenzymes, and zinc-dependent superoxide dismutase protect cells and membranes from oxidative damage that could result from expression of reactive oxygen species during phagocyte killing.[97] Phagocytosis and killing is reduced in neutrophils collected from selenium-deficient cows as compared to those collected from selenium-supplemented cows.[98] In addition, selenium deficiency resulted in more severe outcomes in cows with coliform mastitis.[99] In one herd, vitamin E supplementation above National Research Council (NRC) guidelines (4000 IU/day) to dry cows in the last 14 days before calving was reported to decrease clinical mastitis in the first 7 days of lactation.[100] However, in a larger field study in five herds, feeding dry cows 3000 IU/day of vitamin E (which also exceeds NRC recommendations) was found to increase both subclinical and clinical mastitis in the first 3 months after lactation.[101] In this field study, antioxidant status in cows fed high levels of vitamin E varied, which may reflect the dependency of plasma α-tocopherol concentrations on lipid mobilization, which itself varies with individual cow energy balance.[102] Thus while antioxidant supplementation is critical for mammary health, there is no compelling evidence to feed selenium, vitamin E, or any other nutrient of this type above NRC guidelines.

Recently, recombinant bovine granulocyte colony-stimulating factor covalently bound to polyethylene glycol (PEG rbG-CSF) administered twice subcutaneously to cows before and within 24 hours after calving was found to increase circulating numbers of PMNs. This induced neutrophilia is hypothesized to permit a more robust and timely response for cows that may be prone to postpartum infectious diseases, including mastitis.[103] In a subsequent field trial conducted in four dairies in diverse geographic locations in the United States, administration of two doses of PEG rbG-CSF to cows before and after calving reduced the overall clinical mastitis rate during the first 30 days after calving by 35% compared to control cows.[104] However, the magnitude of the decrease in clinical mastitis varied by herd. This technology may help transition cows to overcome PMN-related immune dysfunction, although other pathways

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of postpartum immune dysfunction may not be affected by this approach. In addition, clinical benefits will rely on the incidence of postpartum clinical mastitis in a herd and should not be used as a substitute for other sound transition cow management practices.

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Diagnosis and Detection of Mastitis

▪ Definitions

Technically, mastitis can be defined as any inflammation of the mammary gland (including inflammation caused by injury), but almost all mastitis occurring in dairy cows is caused by pathogenic organisms that are mostly of bacterial origin but can also include yeasts, fungi, and algae.[5] Like infections occurring in other tissues, mastitis begins with invasion by a pathogen, followed by a brief latent period and then progression to either subclinical or clinical states or resolution of the infection as a result of the cow's immune response.[105] Detection of mastitis is almost never based on identification of the precise moment of infection, but is based on observation of the resulting inflammation. Therefore recognition of mastitis is dependent on pathogen and cow characteristics that govern the magnitude of the immune response and the intensity and accuracy of the detection methods.

Subclinical mastitis is characterized by inflammation that is usually detected by enumeration of inflammatory cells in the milk. By definition, milk obtained from mammary gland quarters of cows experiencing subclinical mastitis appears visually normal but contains an abnormal number of somatic cells, with or without detectable presence of pathogenic bacteria.[5] In most instances, detection of subclinical mastitis is based on evaluation of the SCC in an appropriate milk sample. The SCC can be measured using milk collected from individual quarters or composite milk samples that are a mixture of milk from all functional glands of an individual cow. Composite milk samples are routinely used in DHIA programs for monitoring the SCC of individual cows. When composite SCC values are used, some subclinical infections will not be detected because the SCC of the composite milk will be reduced by dilution with milk from healthy quarters that contain few somatic cells.[106] When cows are not routinely tested for individual SCCs, veterinarians cannot determine important epidemiologic characteristics of subclinical infections (such as prevalence or incidence) that are necessary for implementing mastitis control programs.[107]

The distribution of cell types found in bovine milk varies depending on infection status and milk fraction.[108] The SCC of healthy quarters is quite low and usually remains well below 100,000 cells/mL.[5] However, based on detection

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of IMI (microbiologically positive milk samples), a threshold of less than 200,000 cells/mL is usually considered to be the optimal value to define a mammary quarter as healthy.[109-112] The selection of an appropriate threshold for defining subclinical mastitis is not fixed but rather is dependent on the goal of the control program. Use of a lower threshold will identify more animals with subclinical infections (increased sensitivity and fewer false negatives), whereas use of a higher threshold (increased specificity) will result in fewer false positives.[112] Regardless of threshold, review of the SCC history of a cow is much more informative as compared to observation of a single monthly value.

An SCC greater than 200,000 cells/mL does not always indicate that bacteria will be recovered from milk samples obtained from the affected gland.[113,114] The immune response indicated by the influx of leukocytes is often effective in reducing the number of bacterial colonies in milk, and about 10% to 25% of quarters that are above a threshold of 200,000 cells/mL will be apparently bacteriologically negative.[109,110,112] As the prevalence of infected quarters has declined, the predictive value of SCC relative to detection of IMI has declined. As the prevalence of pathogens that maintain long periods of subclinical IMI (such as *Streptococcus agalactiae* and *S. aureus*) has declined, the proportion of apparent "false negatives" (inability to recover bacteria from quarters that exceed the SCC threshold) has increased.[115] These culture-negative samples do not always indicate that the quarter is cured; they may indicate that the immune response has reduced the number of bacteria to below normal laboratory detection limits[114] and are essentially indicative of the chronic state of failed inflammation (inability to achieve bacteriologic cure). It is useful to educate clients that about 30% to 50% of milk samples collected from mammary glands with high SCCs will be culture negative, and thus sufficient samples should be collected to ensure meaningful diagnostic test results.

The duration of the subclinical phase of IMIs varies depending on etiology, as the magnitude of the inflammatory response is partially a function of virulence characteristics that vary among bacteria. In most herds, a greater proportion of subclinical mastitis is caused by gram-positive pathogens as compared to gram-negative pathogens (Table 36.1). Usually, gram-negative opportunistic pathogens such as *Escherichia coli* have a shorter subclinical phase as compared to gram-positive pathogens such as *S. aureus* or most IMIs caused by *Streptococcus* spp.[116] In general, approximately 25% to 35% of cows experiencing chronic subclinical mastitis caused by gram-positive pathogens may eventually exhibit

clinical symptoms.[117] For opportunistic environmental pathogens, the likelihood of a clinical episode occurring in a cow with subclinical IMI varies among pathogens. For example, about 50% of IMIs caused by streptococci may progress to clinical signs, whereas more than 80% of coliform infections will exhibit clinical signs.[116]

TABLE 36.1

Results of Selected Studies That Describe the Distribution of Bacteria Recovered from Milk Obtained from Cows With Clinical and Subclinical Mastitis in Modern Dairy Herds Located in Developed Countries

Country	Herds	Milk Samples[a]	*Staphylococcus aureus*	Other Staphylococci	*Streptococcus agalactiae*	Other Streptococci	Coliforms	Othe
Milk Samples Collected from Clinical Cases								
Holland[275]	274	2737	18%	6%	0%	25%	28%	NR[b]
UK[142]	90	480	3%	13%	0%	25%	21%	11%
New Zealand[250]	28	1332	19%	7%	0%	45%	NR	4%
Canada[143]	106	2850	11%	6%	0%	16%	15%	5%
USA[6]	51	706	3%	6%	0%	14%	35%	13%
China[572]	161	3283	10%	11%	3%	21%	33%	5%
Milk Samples Collected from Cows With Visibly Normal Milk								
Finland[210]	216	12,661[c]	3%	17%	<1%	<1%	<1%	15%
Germany[198]	80	9910	6%	9%	<1%	2%	<1%	13%
USA[398]	40	5227	4%	16%	2%	8%	2%	16%
Italy[207]	101	13,124	2%	19%	21%	12%	3%	6%

[a]Results characterized as contaminated and mixed infections were excluded.

[b]NR indicates that the study did not report that outcome.

[c]Contaminated cases are included.

It is important to diagnose both prevalence and incidence of subclinical infections within a dairy herd. Cows with IMIs that remain subclinical are known to produce considerably less milk, and they maintain a reservoir of pathogens that can result in increased exposure of otherwise healthy cows.[13,118] Subclinical infections that persist for long durations are especially costly. For example, cows that maintain subclinical mastitis across the dry period (SCC >200,000 cells/mL at the last test of the completed lactation and first test of the subsequent lactation) have been shown to produce 9.1 kg (20 lb) less milk at

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their first DHIA test day.[112]

In diagnostic laboratories, the SCC of fresh or preserved milk is usually determined using automated methods that dye and enumerate cells.[119] Overall, about half of all U.S. dairy farmers and about 75% of dairy farms containing more than 500 cows subscribe to monthly DHIA testing, so it is possible for most cows in the United States to be monitored for subclinical mastitis using SCC values of composite milk samples.[120] SCC values of individual cows are not usually normally distributed, and many DHIA centers report the SCC using a linear score transformation, which is calculated using a simple formula (LS = $\log_2$ [SCC/100] + 3) that results in a normal distribution of values. At the herd level, increased linear somatic cell scores are associated with increasing prevalence of IMI.[121] At the cow level, SCC scores are the transformed representation of actual SCC, which are linearly correlated with milk yield loss, and thus serve as the basis to estimate economic losses from subclinical mastitis.[11,13] Reviewing monthly summarized SCC values at the herd level is a critical component of udder health programs and should be part of routine activities during scheduled veterinary visits to dairy farms.[122,123]

Laboratory-based methods for identification of subclinical mastitis are considered accurate, but because they are removed from the farm, they are sometimes criticized as too slow for making cow-side decisions. To overcome this hurdle, a number of indirect measures of SCC have been developed. The California Mastitis Test (CMT) is an example of an indirect test that has been used for more than 50 years to help guide mastitis control programs.[124,125] The CMT was developed to test milk from individual quarters but is also useful for composite milk and samples obtained from bulk tanks. The CMT reagent is a mixture of a detergent and bromocresol purple, which is used as an indicator of pH. The degree of reaction between the detergent and the DNA of cell nuclei is a measure of the number of somatic cells in milk. The CMT is generally read using a five-point scale that begins with “negative” (SCC range of 0 to 200,000 cells/mL) and “trace” scores (SCC range of 150,000 to 500,000 cells/mL) and ends with a maximum score of 3 (SCC >5,000,000 cells/mL). The CMT was developed during the period when many cows had very high SCCs as a result of chronic subclinical infections caused by *S. agalactiae* and *S. aureus*. Through the adoption of standardized best management practices, the prevalence of these pathogens has decreased,[115] and SCC values of IMI caused by minor pathogens are usually not as high.[126] While the CMT continues to have considerable utility,

it is important to note that even “trace” scores indicate the presence of subclinical mastitis and the test may be difficult to read when used on milk obtained from cows in the first few days of lactation.[127]

In addition to an increased SCC, a number of changes in milk composition occur as a result of inflammation that is part of the immune response to infection.[45,128] Mild inflammatory changes can also be detected in apparently normal mammary gland quarters adjacent to quarters that are experiencing clinical mastitis.[45] Compositional changes include reduced casein, lactose, and α-lactalbumin concentrations; an influx of sodium, chloride, and plasma proteins; increased proteolytic and lipolytic activity; an increase in lactoferrin concentration and enzyme activities; and a rise in pH.[129] Many of these changes can be used as indicators of subclinical mastitis. Among the more common milk tests are those that detect albumin, sodium, chloride, lactose, or concentration of adenosine triphosphate; *N*-acetyl-β-D-glucosaminidase (NAGase) activity; antitrypsin activity; or pH. Plasma tests detect α-lactalbumin, casein, or lactose concentration.[130-133] Milk concentrations of acute phase proteins amyloid A and haptoglobin are able to distinguish healthy quarters from those with subclinical mastitis.[134] Although a variety of immunologic mediators are modified by IMI, measurement of SCC remains the most accurate method of identifying subclincally infected quarters.[132] With increases in diagnostic technology and increased emphasis on production of high-quality milk, considerable research has focused on producing tools for continuous in-line monitoring of milk quality, and these tools will increasingly be used in future dairy herds.[135] Increased use of automatic milking systems (robotic milking) has led to the search for automated methods that can consistently and accurately detect abnormal milk, but challenges remain to identify automated systems that are accurate throughout the lactation period.[136] While current testing technology generally gives accurate results, the ultimate value of any test depends on the value of the intervention that is chosen based on the test result, thus veterinary practitioners should continuously review how such tests can be best used on dairy farms.

Clinical mastitis is usually defined as production of visually abnormal milk, with or without secondary clinical signs. Detection of clinical mastitis is based on observation of foremilk prior to attaching the milking unit, but the working definition of clinical mastitis varies greatly among farm workers. While the majority of workers on larger farms routinely remove foremilk, about one third of farms containing fewer than 500 cows do not routinely remove or observe

foremilk of all cows, and in these instances detection of clinical mastitis is limited to cases with more severe signs.[21,137] To evaluate incidence of clinical mastitis, veterinarians should ask milking technicians to describe their definition and detection methods. Clinical signs of mastitis result from inflammation and may include abnormal appearance of milk (presence of clots or serum); swelling, redness, or edema of one or more quarters; and severe systemic signs such as anorexia, fever, or agalactia. As compared to subclinical mastitis, a much greater proportion of clinical cases are caused by gram-negative pathogens (Table 36.2). Like other bacterial diseases, many cases of mastitis occur as a syndrome with the infected quarters alternating between a clinical state and a subclinical state.[138] The disappearance of clinical signs indicates that inflammation has decreased and does not usually coincide with bacteriologic cure.[139] The ability to achieve a bacteriologic cure varies greatly among etiologic agents and is associated with variation in immune response among cows and the appropriateness of the therapeutic plan.[140]

TABLE 36.2

Summary of Characteristics of Common Mastitis Pathogens

Pathogen	Most Common Point of Infection in Mammary Gland	Duration of Subclinical Phase	Clinical Cases That Develop Systemic Signs	Typical SCC Response (Cells/mL)	Common Source of Infection	Risk of Cow-to-Cow Transmission	Expecte Rate of Spontar Bacteric Cure
Gram-Positive Organisms							
Staphylococcus aureus	Adheres to and invades mammary parenchyma	Long	10%-20%	Variable, ranging from 250,000 to >1,000,000	Exposure to milk from infected cows	Moderate to high	Very lov
Non-aureus staphylococci (NAS); previously coagulase-negative staphylococci	Usually mucosal surfaces	Short to moderate	2%-10%	<500,000	Teat skin	Low to moderate	Moderat high
Streptococcus agalactiae	Mucosal surfaces of ducts and cistern	Long	<1%	>800,000	Obligate udder pathogen	High	Negligit

Other *Streptococcus* spp. (*S. uberis, S. dysgalactiae,* and others)	Variable depending on species	Moderate to long	10%-20%	>500,000; varies by species	Environment and milk from infected cows	Varies by species	Low to moderat
Corynebacterium bovis	Teat canal		<1%	<200,000	Exposure to milk from infected cows	Moderate	Moderat high
Gram-Negative Organisms							
Escherichia coli	Mucosal surfaces	Short	25%-30%	>1,000,000	Environment	Low	Usually
Klebsiella spp.	Variable by strain	Moderate to long	25%-30%	>500,000	Environment and milk from infected cows	Varies by strain	Low to moderat
Serratia spp. (*S. marcescens, S. liquefaciens,* and others)	Can invade mammary parenchyma	Moderate to long	<15%	>500,000	Environment and chlorhexidine teat dips	Moderate	Moderat
Other Commonly Isolated Organisms							
Mycoplasma bovis and spp. (*M. californicum, M. bovigenitalium,* and others)	Distributes throughout udder and other organs	Long, often multiple glands affected	Variable depending on herd	>500,000	Infected cows; aerosol transmission among cows infected with respiratory disease is common	High	Low
Prototheca spp. (*P. zopfii, P. blaschakeae, P. wicherhamii,* and others)	Epithelial layer of mammary alveoli	Often long	Few	>500,000	Environment and milk from infected cows; poor hygiene during IMM treatments	Moderate	Low to moderat

IMM, Intramammary; *SCC,* somatic cell count.

Recording standardized severity scores can help veterinarians better define the pattern of clinical mastitis on individual farms.[139,140] One severity scoring system uses a three-point scale that combines the appearance of milk with the progression to additional clinical signs. A score of 1 (mild mastitis) = abnormal

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milk only; 2 (moderate mastitis) = abnormal milk and abnormal udder; 3 (severe mastitis) = systemic symptoms.[140] This system is practical and simply recorded and can be an important method to assess detection intensity. In most herds, distribution of severity of clinical mastitis is approximately 40% to 50% mild cases, 40% to 50% moderate cases, and 5% to 15% severe cases.[6,139] Veterinarians are rarely asked to treat mild and moderate cases of clinical mastitis and therefore may not understand the true incidence of clinical mastitis on many dairy farms.[141] Veterinarians need to promote the use of clinical mastitis records that allow them to monitor the occurrence of mild and moderate cases and to evaluate outcomes of mastitis treatments.

Identification of Etiologic Agents

Effective treatment and control of mastitis is based on knowledge of the etiology of the infection. As dairy farms increase in size, an increasingly diverse group of pathogens have been associated with the occurrence of mastitis.[6,142-144] Clinical signs may be suggestive of some pathogens, but it is impossible to diagnose the etiology based on the appearance of the milk, gland, or animal. Some practitioners erroneously believe that they can recognize coliform infections based on severity of the symptoms, but researchers have consistently shown that the majority of clinical cases caused by coliform bacteria present with only mild or moderate symptoms[6,145,146] and misdiagnosis of coliform infections is common.[147] Collection of an aseptically obtained milk sample and use of appropriate microbiological techniques is necessary to determine etiology.[5]

Milk Samples Collected From Individual Animals.

Milk samples may be individually collected from affected quarters (quarter milk samples) or combined from all four glands into a single vial (composite milk samples). Quarter milk samples collected from affected glands are more sensitive in detection of bacteria from subclinical infections as compared to composite milk samples, although the sensitivity of composite samples increases with the number of infected glands per cow.[148] Repeated sampling increases the likelihood of detecting glands that are intermittently shedding some pathogens.[5] The concentration of bacteria per milliliter of milk varies among pathogens. Some pathogens (such as most *Streptococcus* spp.) consistently shed large numbers of bacteria in milk. For these pathogens, the use of composite milk

samples may be acceptable because concentrations of bacteria will likely consistently exceed the microbiological detection limit.[149] For many other pathogens (such as *S. aureus* and *Mycoplasma* spp.), composite samples will often result in apparently culture-negative results because these pathogens are often shed in fewer numbers and dilution with milk from healthy quarters will result in samples that contain less than the limit of detection in most laboratories (100 colony-forming units [CFU]/mL of milk).[150]

Microbiological culture or polymerase chain reaction (PCR) testing of composite milk samples is often used to reduce the cost of routine screening of high-risk animals for the presence of existing subclinical infections with potentially contagious mastitis pathogens. Pooling 5 to 10 aseptically collected composite or quarter milk samples is another strategy that is used in some herds to further reduce costs. When either of these strategies is used, it is important to recognize that the potential for false negative outcomes is increased. The sensitivity of composite milk samples for detection of *S. aureus* and *Streptococcus dysgalactiae* was estimated to be about 73% to 77% in contrast to about 60% to 62% for *Streptococcus uberis* and non-aureus staphylococci (NAS).[151] In all instances, sensitivities increase as the number of infected mammary gland quarters increases.[151] When using pooled or composite samples, veterinarians should routinely review cow histories to identify cows with increased SCCs that are typical of subclinical infections.

Mastitis is usually caused by a single type of bacteria, and the National Mastitis Council has developed standards that specify that recovery of more than two colony types of bacteria cultured from an aseptically collected milk sample is indicative of contamination.[5] Before collection of milk samples, technicians should be trained in techniques that ensure aseptic collection of the sample; adherence to aseptic sampling procedures is even more critical when DNA-based diagnostic tests are used. To maximize the possibility of recovering bacteria from the sample, milk should be collected after the teats have been prepared for milking (application of premilking disinfectant and drying) but before the units are attached.[152] Collection of samples before milking is usually easier because cows are more likely to stand still and there is less pressure from farm workers to release the cows. Before obtaining the sample, the udders should be clean, and dry-wiping the udder with a paper or cloth towel is often helpful in reducing the possibility of contamination. Milk should be collected in sterile vials by technicians who are wearing disposable nitrile or latex gloves and using a

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standardized process. After thoroughly drying the teat using a cloth or paper towel, the teat end should be vigorously scrubbed using 70% ethyl or isopropyl alcohol. If composite samples are collected, a separate alcohol swab must be used for each teat. Sanitation is not complete until the surface of the swab remains clean after it is used.

The cap should be removed from the sample vial without touching the inside and held so that the inner surface faces down. Milk from the teat to be sampled can be directed at an angle into the sampling vial. A sample size of 3 to 5 mL is usually adequate. The cap should be replaced immediately after the sample is obtained. When sampling multiple teats, the far teats should be scrubbed before the near teats and the near teats sampled first, to avoid contamination by the sampler's arm or hand. Samples must be cooled immediately, refrigerated at 4° C, held on ice, or frozen until cultured. Failure to use aseptic technique or mishandling after collection can produce erroneous results. If samples are to be submitted to a diagnostic laboratory, they should be submitted within 24 hours of collection. If samples cannot be processed within 24 hours, they should be frozen until transported to the lab. Freezing for periods of more than 2 weeks has minimal effects on recovery of most mastitis-causing bacteria but can reduce recovery of *Mycoplasma* spp.[153]

When proper sampling and laboratory techniques are used, the recovery of bacteria from bovine milk samples is highly specific for mastitis. However, microbiological examination of milk obtained from glands affected with clinical or subclinical mastitis is not very sensitive.[114] When a single milk sample is obtained from dairy cattle exhibiting clinical or subclinical mastitis, approximately 35% to 50% of milk samples will be culture negative (see Table 36.1).[5,6] Repeated sampling of affected quarters can increase the probability of reaching a diagnosis.[5,150]

Failure to recover bacteria from a milk sample can be a result of either a successful or a failed inflammatory response. For example, the inability to culture viable bacteria from milk samples collected from quarters with chronically high SCCs may be a result of suppression of bacterial growth caused by the chronic inflammatory response. In this instance, ongoing inflammation is likely caused by chronic bacterial infection and is indicative of failed inflammatory response. In contrast, failure to recover viable bacteria from milk samples obtained from cows with clinical mastitis is often due to spontaneous clearance of bacteria prior to onset of visible clinical signs. Many of these culture-negative clinical cases are the result of successful inflammation, and if

the clinical signs are not severe, most of these cows have excellent prognoses without use of antimicrobial therapy.[140]

Laboratory Methods.

Standardized laboratory methods for identification of mastitis pathogens have been well defined by the National Mastitis Council.[5] In general, laboratory technicians inoculate media that contain nutrients required for bacterial growth, and the inoculated media are placed in an incubator that contains the appropriate atmosphere and temperature to encourage growth of the target organisms. After 24 to 48 hours, the plates are examined for growth, and the bacteria are identified using a variety of specific test methods that depend on observable characteristics of the bacteria. In most mastitis laboratories, 10 to 100 µL of each milk sample are inoculated onto a portion of a blood agar plate (5%). The inoculum volume determines the lower limit of detection. For example, one colony observed on a plate inoculated with 0.01 mL (10 µL) is equivalent to approximately 100 CFU/mL of milk, whereas one colony observed using a 0.1-mL (100-µL) inoculum is equivalent to approximately 10 CFU/mL. The use of larger (0.05- or 0.10-mL) inocula increases recovery rates for pathogens shed in low concentrations, such as *E. coli* or *S. aureus.* Other ways to increase recovery are pre-culture centrifugation,[154] incubation,[155-157] or freezing[157] of the milk, or a combination of these methods. The optimal method is pathogen dependent. Augmented methods are most useful for detecting subclinical *S. aureus* infections and reducing false-negative results for clinical mastitis samples.

After inoculation, agar plates are incubated at 37° C and observed for growth at 24 and 48 hours.[5] Although there is no absolute definition of IMI,[158] the presence of at least 100 to 300 CFU/mL is usually required to define an infection.[5,114] Identification of bacteria is made based on phenotypic characteristics of the colonies and the result of additional laboratory tests. *S. aureus* is usually differentiated from other staphylococci based on a positive coagulase reaction and other typical phenotypic characteristics, such as hemolysis.[5] Streptococci are usually identified using the Christie–Atkins–Munch-Petersen (CAMP) test and esculin reactions. When milk samples originate from cases of clinical mastitis, MacConkey agar is usually also inoculated to facilitate the rapid identification of gram-negative, lactose-fermenting organisms (coliforms). Classic microbiological techniques use additional biochemical tests for final identification at the species level, but other

techniques for identification of mastitis pathogens are increasingly used. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been shown to increase accuracy of diagnosis of NAS and streptococci.[159,160] Identification of *Mycoplasma* spp. requires the use of media containing specific nutrients not found in general media and incubation in a carbon dioxide–enhanced environment.

On-Farm Culture.

As farm size has increased and specialized workers have become more common, on-farm culture (OFC) programs have been developed.[161] Methods used for OFC are not usually the same as those used in professional diagnostic laboratories and are often performed by farm personnel who may have some technical expertise but lack formal training in microbiological methods. On most farms, OFC methods are based on the use of laboratory shortcuts and have a goal of rapidly reaching a presumed diagnosis to guide treatment.[162-164] The most basic method of OFC is the use of biplates, triplates, or quadplates that contain selective[165] agars or chromogenic media.[154] Growth on a selective agar is used to differentiate cases caused by gram-positive or gram-negative bacteria, culture-negative cases, or in some instances specific pathogens. After 24 hours of incubation, culture plates are observed, and the treatment protocol is specified based on the culture outcome.[140,163,166] Typical agars that are used include MacConkey agar (selective for growth of gram-negative bacteria); TKT agar (selective for growth of streptococci), and Factor, Baird-Parker, or KLMB media (selective for growth and differentiation of some staphylococci). Studies have indicated that using selective media in OFC systems is about 80% accurate in differentiating gram-positive and gram-negative pathogens as compared to diagnostic laboratories.[165] The use of OFC to make more specific pathogen diagnoses is not as accurate and requires additional training of personnel.

Most smaller herds do not have sufficient cases of mastitis to develop the expertise needed for OFC, and one alternative is to offer in–veterinary clinic culturing (IVCC). In these instances farmers usually collect a milk sample and immediately initiate treatment, but they may stop or modify treatment duration or the drug after receiving a preliminary microbiological diagnosis from their veterinarian within 24 hours. Development and oversight of a culture program (either OFC or IVCC) is an ideal way for veterinarians to increase involvement in mastitis control programs. Using veterinary technicians to supervise these

programs may also increase veterinary involvement and oversight of mastitis treatments. When OFC is used, veterinary technicians can visit farms to restock supplies, train farm personnel, and provide oversight and quality control.

Microbiological Analysis of Bulk Tank Milk.

Microbiological examination of bulk tank milk samples is performed using a variety of laboratory techniques depending on the objective of the testing.[5,106] Enumeration of the total number of aerobic bacteria in bulk milk is routinely performed by milk processors as part of the regulatory requirements for milk production. Standardized methods for counting bacteria may be based on culture or performed using automated counting of stained bacterial cells.[119] Processors also commonly perform additional laboratory tests to assess hygienic conditions of milk harvest and storage and may use results of these tests to determine premium payments. Comparison of the number of psychotrophic, thermoduric, or coliform bacteria from various milk samples can be used to identify problems with dirty udders, inadequate premilking preparation, cleanliness of milking equipment, or cooling stored milk.[5] Methods used for these tests are simply quantitative and do not result in identification of specific microorganisms.

Qualitative bulk tank cultures (BTCs) are usually performed to identify specific pathogens shed by cows that are being milked while affected with subclinical mastitis.[5,106] Methods of sampling, laboratory techniques, and reporting formats have not been standardized, thus it is difficult to compare results of BTCs among laboratories. Because of the variation in laboratory methods, it is best to submit bulk tank milk samples to a specialized laboratory that tests several dilutions using selective media for isolating and counting colonies. The laboratory should be informed if identification of *Mycoplasma* spp. is of interest so that the proper media and incubator conditions are used.

The interpretation of results of BTCs can be confusing, as bacteria can originate from teat skin, subclinical mastitis infections, failure of milking technicians to exclude milk from cows that have clinical mastitis, poor hygienic conditions, failure to adequately cool milk, and use of inadequately cleaned milking equipment. Because there are numerous opportunities for bacteria to contaminate bulk milk, interpretation of BTCs is based on knowledge of reservoirs of the organisms found in the milk.[5,167] Although few scientific studies have been performed to validate criteria for interpretation of BTCs, suggested interpretive criteria have been published.[5] A few organisms (*S.*

agalactiae, *S. aureus*, and *Mycoplasma bovis*) are known to originate primarily from infected cows, but many organisms have multiple potential sources. Organisms such as NAS may originate from IMI or from poorly disinfected teat skin and udders that have been contaminated by bedding sources. Non-agalactiae streptococci are commonly found in the dairy farm environment and are associated with dirty udders, but these organisms can also cause subclinical mastitis. The natural duration of subclinical IMI caused by *E. coli* is short, and there are multiple environmental sources of this organism.[116] Thus when many *E. coli* are found in bulk milk, the most likely source is contamination during the milking process.[168] When organisms that have environmental niches are found in bulk tank milk, sources other than IMI should be investigated before assuming that infected cows are the source.

The sensitivity of a single BTC for detection of herds with infected cows is generally considered to be low, and results should not be used to estimate prevalence of infected cows.[5] Positive predictive values of BTCs (detection of at least one positive cow when the organism was found in a BTC) are estimated to be more than 97% for *S. agalactiae* and *S. aureus* and more than 80% for *Mycoplasma* spp.[169] Due to low sensitivity, the inability to isolate selected mastitis pathogens from bulk milk does not indicate the absence of subclinically infected cows, and negative BTCs routinely occur in large herds that contain infected cows. The relatively low sensitivity of a single BTC for screening herds for contagious pathogens can be improved by using enhanced laboratory techniques or by increasing the frequency of sampling. The use of commingled samples that have been independently collected for 3 to 5 consecutive days is recommended to reduce false-negative results that occur as a result of variation in bacterial shedding.[167]

Molecular Testing.

The continued development of molecular techniques has the potential to improve diagnosis of mastitis; however, a full review of these technologies is beyond the scope of this chapter. A variety of molecular methods are used to diagnose mastitis pathogens, identify potential zoonotic agents in milk, identify genetic diversity of resistance genes, and investigate mastitis outbreaks and milk quality problems.[170-173] Some molecular methods are used to identify specific strains of bacteria to determine the likely source or transmission of mastitis pathogens.[174,175] Other methods are used to improve diagnosis of pathogens for

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which biochemical methods for identification of species are known to be inaccurate[176] or to more rapidly arrive at a diagnosis.[177] In general, genotypic methods of identifying bacteria are based on identification of unique sections of DNA that are compared to characteristics of known library strains. Several PCR-based methods of identifying bacteria have been developed,[172,178,179] and real-time PCR tests are widely available. One commercially available test is able to accurately detect the presence of bacterial DNA of up to 16 mastitis pathogens and the β-lactamase gene but requires the use of aseptically collected milk samples to limit the number of false-positive results.[180] In one study, use of this test resulted in identification of bacterial DNA of potential mastitis pathogens in 43% of culture-negative milk samples.[181] However, research has indicated that teat skin and teat canal flora may be the source of many minor pathogens identified in milk samples using PCR testing.[182]

The use of the commercially available reverse transcription PCR (RT-PCR) test to evaluate quality of bulk tank milk has also been investigated.[183-185] As expected, PCR testing is useful to detect the presence of obligate udder pathogens (such as *S. agalactiae*) in bulk milk, but a single PCR test of bulk tank milk is not reliable for diagnosis of mastitis pathogens.[183] Interpretation of PCR test results of bulk tank milk for bacteria that have possible environmental origins in bulk milk is difficult and not always more sensitive than bacteriologic culture.[185] PCR test results are interpreted relative to the cycling threshold (Ct) values, which indicate the number of cycles required to reach a signaling threshold. In general, the lower the Ct value, the greater the amount of the specified DNA in the sample, but similar to BTC results, PCR tests are not accurate to estimate the prevalence of infected cows within a herd.[183]

Decision making for management of milk quality based on PCR results is complicated because DNA from both live and dead bacteria is detected. Just as the occurrence of a few colonies of environmental pathogens on a blood agar plate would not be sufficient evidence to indicate that a treatment is indicated, identification of bacterial DNA from milk is not always sufficient evidence on which to base a treatment protocol. To improve the utility of diagnostic methods based on DNA, aseptic samples should be collected[180] and the medical history and SCC of the cow should be reviewed before making treatment or culling decisions. For some pathogens, such as *Mycoplasma* spp., *S. agalactiae*, or *S. aureus*, the cow history will generally support the presumed diagnosis; for other pathogens the relationship may be less apparent. It is clear that the cost of using

molecular methods will decrease, and therefore the use of these methods will increase. However, continued research is needed to help define practical ways of best using these methodologies.

Milk was long considered sterile, but researchers have been exploring the potential presence of a microbiota in milk from apparently healthy mammary quarters.[186,187] The presence of a commensal microbiota in the teat canal is well accepted,[188-190] but the mammary gland itself has long been considered to be a sterile environment.[191] Based on a limited number of studies, some researchers[192] have hypothesized that the bovine milk microbiota is composed of a complex and diverse community that includes both culturable and nonculturable organisms that are linked to intestinal flora and contribute to homeostasis and mammary gland health. Others have challenged this view,[191] describing anatomic, immunologic, and practical research suggesting that while there is considerable evidence for the existence of a teat apex microbiota, the concept of a mammary gland microbiota is incompatible with known mammary gland immunobiology and warrants critical examination. This subject is an area of very active research, and clinical applications of these techniques in udder health programs have not yet been developed.

Epidemiology of Mastitis Pathogens

Transmission and Reservoirs.

Mastitis is an infectious disease that occurs when udders become infected with pathogens, most of which are bacteria. With the exception of infections caused by a few unique microorganisms (such as *Mycoplasma* spp.), exposure of the teat sphincter to bacteria is the primary route of almost all mammary gland infections. Microorganisms that can potentially cause mastitis are typically categorized as either environmental or contagious based on the likely reservoir on the farm and the most probable source of the initial exposure.

Opportunistic organisms from the cow's surroundings are generally considered to be primarily environmental pathogens. Transmission occurs when teats are exposed to bacteria found in environmental sources such as fecal material, bedding, soil, and contaminated water.[58] Contamination of teat skin with environmental pathogens increases the probability of IMI, especially when defense mechanisms (such as the patency of the teat sphincter) are compromised. IMI with environmental pathogens can also occur when teat ends are not

sufficiently disinfected before infusing antibiotics or when a contaminated infusion preparation or cannula is used.[58,193] Gram-negative bacteria, such as *E. coli* and *Klebsiella* spp., are the most commonly isolated environmental pathogens.[6] However, many gram-positive organisms, such as *S. uberis* and *S. dysgalactiae* can be found in the cow's surroundings, and the initial infection with these pathogens is often from an environmental source. Although coliforms and streptococci are commonly isolated, many other organisms are found in the environment of cows and are capable of causing mastitis. The diversity of environmental mastitis pathogens is increasing as management of dairy farms intensifies and as a variety of bedding sources are used.[58,194] Reducing exposure to environmental pathogens is based on improving hygiene of cows, housing areas, and the milking process.[195]

Mammary glands with chronic subclinical infections are the primary reservoir of contagious mastitis pathogens. Transmission occurs when teats are exposed to bacteria found in milk that came from an infected gland. In many instances, exposure to infected milk occurs during the milking process. Infected milk droplets can be found in teat cup liners, hands of milking technicians, towels used to wash or dry teats, or milk droplets that leak onto bedding surfaces. The presence of these organisms on teat skin increases the probability of infection. In some cases, abrupt vacuum fluctuations within the milking cluster (reverse pressure gradients) can propel contagious pathogens from the milk of an infected gland into the teat canal of a healthy gland.[196] The most common contagious mastitis pathogens are host-adapted bacteria that cause long-term subclinical infections. Historically, *S. agalactiae* was considered to be one of the most important causes of contagious mastitis[197]; however, this obligate udder pathogen is controlled in most developed dairy regions and is not commonly isolated from milk samples of cows located in developed regions.[115,198,199] In recent years, *S. aureus*, and *M. bovis* have been the most prevalent contagious mastitis pathogens found in U.S. dairy herds.[200] It is important to recognize that most organisms that establish chronic subclinical IMI can be transmitted in a contagious manner. Successful control programs for contagious pathogens are based on reducing the prevalence of subclinically infected cows, thus reducing the probability that healthy cows are exposed to milk that originated from infected udders.

The classification of organisms as contagious or environmental is a broad characterization of the most common sources of initial exposure to pathogens

and does not preclude other potential routes of transmission[146] (see Table 36.2). Historically, contagious pathogens were considered to be caused by highly contagious identical clones that were transmitted only among cows, whereas environmental bacteria were often considered to consist of diverse strains that were found only in the environment.[201] However, use of DNA fingerprinting has demonstrated that it is not uncommon to find several different strains of contagious organisms such as *S. aureus* occurring in cows on a single farm.[202] Similarly, a single dominant strain of *Klebsiella* spp. isolated from multiple cases of mastitis has been reported as evidence of contagious transmission of a supposedly environmental pathogen.[203] The use of molecular methods has demonstrated that microbes are continually evolving in response to control measures and changes in farm management. While characterization of pathogens as "contagious" or "environmental" still provides a reasonable basis for initiating control programs, veterinarians should be aware of the possibilities of additional routes of transmission and the need for comprehensive control programs that may exceed the typical recommendations.

Prevalence of Mastitis Pathogens.

More than 130 organisms, including bacteria and some algae, yeasts, and fungi, have been documented to cause mastitis.[5,204] Although some regional differences in prevalence have been demonstrated, the distribution of pathogens that cause clinical and subclinical mastitis on modern dairy farms is remarkably consistent (see Table 36.1). In recent years, widespread adoption of standardized mastitis control procedures in developed dairy regions has resulted in a decreased prevalence of mastitis caused by contagious pathogens such as *S. aureus* and *S. agalactiae* (see Table 36.1).[115,142,143] Herds that fail to control these pathogens typically have failed to effectively implement well-known mastitis control procedures such as postmilking teat dipping and comprehensive use of antimicrobial dry cow therapy.[199] On most dairy farms, about 25% to 30% of milk samples obtained from cows secreting abnormal milk result in no significant growth of bacteria (see Table 36.1), usually because of an effective immune response to infection by opportunistic environmental pathogens. Coliform bacteria and environmental *Streptococcus* spp. are usually the most common pathogens identified from milk samples collected from cases of clinical mastitis on modern U.S. dairy farms (see Table 36.1).[6,28,205,206] In contrast, when milk samples are collected from cows with subclinical infections, few

coliform bacteria are identified, indicating the short duration and clinical nature of most of these infections.[116,207-210] In regions that have controlled *S. aureus* and *S. agalactiae*, NAS are often the most prevalent pathogen group associated with subclinical infections (see Table 36.1). While epidemiological studies of mastitis pathogens within regions have resulted in consistent recovery of typical groups of pathogens, the distribution of pathogens often varies among farms based on individual risk factors. The implementation of effective control programs and correct treatments is based on understanding the etiology of mastitis, and sufficient diagnostic testing should be used routinely by veterinary practitioners who are working to control mastitis.

Characteristics of Pathogens.

Pathogenesis, virulence, and prognosis of IMI are each influenced by important characteristics that vary among pathogens. General characteristics of the most common mastitis pathogens are described in Table 36.2. Depending on specific virulence factors, organisms infect different locations in the mammary gland, have differing abilities to cause systemic symptoms, vary in the expected duration of subclinical phases of infection, and differ in the expected rate of spontaneous bacteriologic cure (see Table 36.2). Understanding these differences is fundamental to the development of effective control programs.

Mastitis Caused by *Staphylococcus* Species

Staphylococcus aureus.

The genus *Staphylococcus* contains at least 50 species, and initial differentiation among species is based on their ability to coagulate plasma.[5] Historically, staphylococci that do not coagulate plasma have been referred to as coagulase-negative staphylococci (CNS), but non-aureus staphylococci (NAS) is now the preferred terminology, as the group includes some species that coagulate plasma. Among staphylococci associated with bovine mastitis, *S. aureus* and *Staphylococcus hyicus* are coagulase positive, but *S. hyicus* is usually considered to be a minor mastitis pathogen. *S. aureus* is considered a major pathogen because of its impact on SCC and widespread prevalence. *S. aureus* has been isolated from bulk tank milk of about 40% of U.S. dairy herds,[200] and about two thirds of producers who culture milk samples have reported its isolation,[21] but the prevalence and economic impact vary tremendously among herds. Most IMIs

caused by *S. aureus* are chronic and subclinical, with periodic bouts of mild clinical mastitis. However, clinical mastitis caused by *S. aureus* can result in systemic signs, or the affected mammary gland may become gangrenous. Herds with a large proportion of cows with mastitis caused by *S. aureus* tend to have higher BTSCCs and many cows with chronically increased SCCs (see Table 36.2).

IMI caused by *S. aureus* is diagnosed by isolating coagulase-positive staphylococci from milk samples of cows. When grown on appropriate media, colonies usually demonstrate hemolysis and other typical phenotypic characteristics.[5] Occasionally some *S. aureus* strains are coagulase negative, thus definitive identification requires additional diagnostic testing. There are many different strains of *S. aureus;* some herds may have a predominant strain, whereas other herds may harbor diverse strains.[202,211] Some researchers have reported that variation among strains of *S. aureus* results in differences in transmission, virulence, and antibiotic susceptibility,[212,213] whereas others have reported similar outcomes independent of strain.[214,215]

Although much is known about *S. aureus*, considerable knowledge gaps about pathogenesis still exist.[216,217] Some strains of *S. aureus* can adhere to and invade mammary epithelial cells and interstitial tissue,[213,218,219] but variation in invasive potential among strains has been noted.[220] A variety of mechanisms to avoid the immune response have been noted for *S. aureus*. The organism can resist phagocytosis by neutrophils with antiphagocytic mechanisms such as a capsule that inhibits opsonization and a surface protein (protein A) that binds the Fc portion of host Ig. Leukotoxin production enables some *S. aureus* strains to kill phagocytes[221] while other mechanisms allow *S. aureus* to survive within leukocytes and epithelial cells and induce apoptosis.[219] Some strains of *S. aureus* produce enzymes and exotoxins that damage mammary cells and result in fibrosis and abscess formation.[222] Many strains produce β-lactamase, conveying resistance to antibiotics such as penicillin and amoxicillin. Others convert to L-form or small colony variants, which can persist even after antibiotic therapy.[215,223] Certain *S. aureus* strains form biofilms, making them inaccessible to phagocytes and antibiotics,[224-226] and some but not all biofilm-associated proteins have been associated with chronic infections.[220,227] For these reasons, *S. aureus* IMIs seldom resolve spontaneously and usually respond poorly to antimicrobial therapy.[223]

Farmers who purchase replacement heifers or lactating cows without screening the animals or source herds often have herds with greater prevalence of *S. aureus* as compared to closed herds, illustrating the importance of biosecurity in mastitis control. The prevalence of infected cows within a herd is an important risk factor for new infections. Cows with chronic *S. aureus* infections or with characteristics that predict a low likelihood of cure should be culled as soon as economically feasible or segregated and milked last. Alternatives are simply to stop milking the infected gland or to induce cessation of lactation in an individual gland.

Non-aureus Staphylococci (Previously Referred to as Coagulase-Negative Staphylococci).

In most studies, NAS are the most prevalent bacteria isolated from milk samples obtained from cows with subclinical infections and from the mammary secretions of dry cows and prepartum heifers (see Table 36.1). Based on use of traditional microbiological methods of identification, there are at least 50 species of NAS, and many have been isolated from IMIs of dairy cows.[5,228,229] Epidemiological differences among various species have not been well defined. While researchers have demonstrated some variation in SCCs and persistency of IMI among NAS species, these differences have not been shown to affect milk yield,[230,231] and control programs are generally nonspecific. Historically, a thorough understanding of epidemiologic characteristics and differences in pathogenesis among NAS species has been limited by the relatively poor discriminatory ability of phenotypic or biochemical diagnostic tests.[232] The accuracy of identification of NAS associated with bovine mastitis has been improved by the use of genotypic methods (such as sequencing), and the use of MALDI-TOF MS by diagnostic laboratories has allowed for improved discrimination among species.[159,233]

Most recent surveys using modern discriminatory methods indicate that *Staphylococcus chromogenes, Staphylococcus epidermidis, Staphylococcus haemolyticus,* and *Staphylococcus simulans* are the most prevalent species associated with bovine mastitis, but variation among studies has been noted.[231,234,235] Staphylococci are the most common organisms recovered from mastitis in heifers, and a variety of NAS species have been recovered from teat skin, the streak canal, and precalving udder secretion obtained from heifers.[21,236]

IMI caused by NAS typically results in subclinical infection that is associated

with only modest increases in SCC[237]; thus despite the widespread prevalence, NAS are often referred to as "minor" mastitis pathogens.[229] Most infections caused by NAS remain subclinical, with SCCs lower than 500,000 cells/mL. However, when NAS infections persist they may be characterized by greater increases in SCCs.[238]

Although NAS account for about 15% to 20% of subclinical IMI, they are recovered from a relatively small proportion of cases of clinical mastitis, and clinical signs are usually mild (Table 36.1).[146,239] The rate of spontaneous cure is often high,[240] but intramammary treatment used for cases of clinical mastitis caused by NAS usually results in bacteriologic cure rates that exceed 80%.[229,237] The use of β-lactam–based intramammary antibiotics at dry-off is often successful in treating subclinical IMI caused by NAS. Treatment of subclinical IMI caused by NAS during lactation is unlikely to be profitable because a potential increase in milk yield after treatment has not been documented. There are no specific control measures for NAS mastitis. Effective premilking and postmilking teat dipping, comprehensive antibiotic treatment of cows at dry-off, and attention to udder and milking hygiene are recommended.

Mastitis Caused by *Streptococcus* Species

Streptococcus agalactiae.

S. agalactiae is generally considered to be an obligate udder pathogen, and control measures that focus on reducing the prevalence of infected cows have been highly effective.[241] Historically, IMI caused by *S. agalactiae* was the most common cause of bovine subclinical mastitis, and most preventive practices used on modern dairy farms were developed to aid in reducing transmission of this highly contagious organism.[197] On modern North American dairy farms, control of *S. agalactiae* has been successful, and this organism is rarely isolated from individual cow milk samples (see Table 36.1) or bulk tank milk obtained from U.S.[200] or Canadian dairy farms.[143] However, without proper attention to biosecurity and milking procedures, *S. agalactiae* can be introduced and spread rapidly through a herd, resulting in substantial economic loss. Mastitis caused by *S. agalactiae* is usually subclinical and if not treated can persist for months or years (see Table 36.2). Subclinical infection may be interspersed with bouts of mild clinical mastitis, but only rarely will cows exhibit systemic signs.

S. agalactiae adheres to epithelial cells in the mammary gland and localizes

primarily in the ducts. Milk production declines when ducts become blocked with cells and debris and the associated alveoli involute. Early treatment can result in increased milk production because the superficial nature of the infection results in minimal damage to the milk secretory cells. However, tissue damage, fibrosis, and a permanent decrease in milk production can occur if infection becomes chronic. *S. agalactiae*–infected glands tend to shed high concentrations of bacteria and somatic cells in milk. and this organism should be suspected in the rare instances when a BTSCC exceeds regulatory limits.[24]

S. agalactiae is easily isolated from milk samples and is diagnosed when esculin-negative, CAMP-positive streptococci are identified in milk samples obtained from bulk tanks or from individual cows. *S. agalactiae* is usually an obligate udder pathogen so RT-PCR is useful for rapid diagnosis of infected cows.[176] In some regions that have not successfully controlled this organism, there is evidence of adaptation to environmental niches[242]; however, this is not common. When the organism is found in bulk milk or milk samples of affected cows, a sampling plan should be developed to screen the herd to identify and treat all infected cows. Antibiotic treatment has formed the basis for control of *S. agalactiae,* and intramammary antibiotics have been found to be more efficacious as compared to intramuscular treatment using penethemate.[243] In instances where use of antibiotics is not an option (e.g., organic dairy farms in the United States), it is especially important to identify and cull infected cows. Control programs for *S. agalactiae* are based on eradication through identification, treatment, culling, and biosecurity.

Environmental *Streptococcus* Species.

A number of streptococci and closely related organisms are frequently isolated from milk samples collected from cows with clinical and subclinical mastitis (see Table 36.1). *S. uberis* and *S. dysgalactiae* are the most common streptococcal species recovered from IMI, but other species such as *Streptococcus parauberis, Streptococcus equinus, Streptococcus saccharolyticus, Streptococcus salivarius,* and *Streptococcus canis* have also been associated with mastitis.[244] In addition, there are a number of gram-positive, catalase-negative cocci such as *Enterococcus faecalis*, *Enterococcus faecium*, *Aerococcus viridans*, and several species of *Lactococcus* that have similar reservoirs and are often grouped with streptococci.[245] These streptococcal-like organisms are collectively referred to as environmental streptococci because the primary

exposure is often in cow housing areas. Streptococcal organisms can be cultured from many materials commonly used for bedding, including contaminated sand.[194] Many of the IMIs caused by environmental streptococci result in subclinical infections, and strains that become chronic may be transmissible among cows in a contagious manner.[246-248]

Environmental streptococci are shed in the feces of cattle and are often ubiquitous in the dairy farm environment.[249] Infected dogs and cats can carry *S. canis* in their respiratory and urogenital tracts and serve as potential sources of infection for cows.[246,248] *S. uberis* is found in the vagina of cows,[249] but genital tract secretions probably play little role in the transmission of infection. Teats are often exposed to environmental streptococci that are present in bedding contaminated with feces[194]; straw is well known to support growth of *S. uberis*. *S. uberis* is also well known to affect cows on pastures and is the most frequent cause of mastitis in New Zealand dairy herds.[250,251] High-traffic cow lanes and areas of pastures or lots where cows congregate and defecate harbor *S. uberis* and serve as reservoirs.[249]

Approximately 50% of IMI caused by environmental streptococci are initiated during the dry period.[252] The mammary gland is highly susceptible to environmental streptococcal infection during the early and late stages of the dry period, when mammary secretions accumulate and host defense mechanisms are compromised.[116,253,254] Risk factors for IMI caused by *S. uberis* are similar to those for IMI caused by *S. aureus*.[255] IMI is accompanied by a rapid influx of neutrophils into the mammary gland and a resultant increase in SCC. Based on experimental inoculation studies with *S. uberis*, the recruited neutrophils are unable to fully prevent bacterial multiplication. Ineffective host response probably explains the prolonged infections and persistently high SCCs seen in some cases.

Although many IMIs caused by environmental streptococci spontaneously cure within 30 days, about one third of infections persist for long periods, sometimes longer than a lactation. Up to 50% of IMIs caused by environmental streptococci may result in clinical signs,[252] but only about 10% to 20% of those cases will become systemically ill.[6,256] Recurrent episodes of clinical mastitis are common.[257] Control of IMI caused by environmental streptococci is based on reducing exposure in housing areas and ensuring that cows remain healthy, clean, and dry.

Mastitis Caused by Coliforms

Characteristics Shared Among Coliform Bacteria.

Coliform bacteria are defined as gram-negative, rod-shaped organisms that can ferment lactose.[5] These organisms are fairly easy to identify because growth on MacConkey agar results in a characteristic pink colony. *E. coli* and several other genera such as *Klebsiella*, *Enterobacter,* and *Serratia* (some of which are non-lactose fermenting) are commonly associated with bovine mastitis (see Table 36.1), whereas other coliforms such as *Citrobacter* spp. only rarely cause mastitis. Coliform organisms include both pathogenic and nonpathogenic strains that are ubiquitous in the dairy farm environment and frequently shed in feces. Within individual bacterial species, a wide variety of strains are capable of causing mastitis.[258] Teats are initially exposed to these organisms in housing or pasture areas, thus coliforms are considered to be primary environmental pathogens. Organic bedding materials, such as straw, wood chips, sawdust, recycled manure or solids from methane digesters, pelleted corncobs, and newspaper, support the growth of coliform bacteria.[259] Environmental conditions such as increased ambient temperatures and increased rainfall influence the growth of bacteria and thus the extent of teat end exposure and risk of intramammary infection. Large numbers of gram-negative organisms are present in bedding that is based on use of manure.[194,208] As compared to sand bedding, manure-based bedding materials have been associated with increased clinical and subclinical mastitis and reduced milk yield.[260] Likewise, management decisions such as increased housing density, poor stall design, failure to use sufficient bedding materials, or poor pasture management can increase the probability that teats will be exposed to coliform bacteria in manure.

In early lactation, clinical mastitis caused by coliforms may be the result of IMI acquired during the dry period.[116,261,262] However, coliform infections can be acquired at any time during lactation, particularly if the exposure is great and primary defense mechanisms, such as the patency of the teat sphincter, are compromised.

After coliform bacteria infect the mammary gland, they multiply rapidly but most do not adhere to or invade the epithelial cells.[263] If the cow's immune response is rapid and efficient, infection will be quickly eliminated and there will be little long-term impact on cow health or productivity. Although the majority of clinical cases of mastitis caused by coliform bacteria are mild, up to 30% of

cases may result in systemic signs such as anorexia, fever, or a marked drop in milk production.[6,256] On most farms, IMI caused by coliform mastitis accounts for the majority of mastitis cases accompanied by systemic signs.[264] Development of systemic signs and severe disease are primarily associated with characteristics of the cow that influence its ability to respond to the infection.[263] When influx of neutrophils is delayed or phagocytosis or intracellular killing mechanisms of neutrophils are impaired, bacterial multiplication continues, resulting in greater concentrations of inflammatory mediators and more severe clinical disease. Severe cases occur most frequently in the periparturient period and during early lactation.[72,265,266]

The outcome of clinical mastitis caused by coliform bacteria depends on the severity of the case, which usually depends on the balance between the dose (magnitude of of exposure) and the ability of the cow to response immunologically. Increased or subnormal rectal temperature, reduced rumen contraction rate and amplitude, marked dehydration, and marked depression are associated with increased risk of death, culling, or poor return to milk production.[145,267] Severe neutropenia and high bacterial concentration in the milk[145] are also indicative of a poor prognosis. Cows in early lactation do not develop neutropenia to the extent observed in later lactation; therefore the leukogram is not a good indicator of mastitis severity in early lactation.[268]

In contrast to environmental streptococcal mastitis, intramammary antibiotic treatment at dry-off is considered to be less effective in preventing coliform infections during the dry period.[269,270] The spectrum of activity of many antibiotics (β-lactams and macrolides) used for dry cows in the United States is primarily directed toward gram-positive pathogens. Infusion of internal teat sealant at dry-off reduced the incidence of new *E. coli* infections compared with infusion of antibiotics (cephalonium) in one study.[271] However, the risks of new gram-negative IMIs during the dry period and of clinical mastitis during early lactation were similar when quarters were treated with teat sealant plus antibiotics (cloxacillin) or antibiotics alone.[272] The use of internal teat sealant combined with appropriate intramammary antibiotics has been shown to result in reduced frequency of new IMI caused by coliform bacteria.[273]

Control of mastitis caused by coliform bacteria is based on reducing teat end exposure to these organisms. This is especially true for periparturient cows that may have compromised immune responses. Improving the hygienic conditions of the cows' surroundings and during the milking routine, reducing cow density,

and ensuring that cows have access to an adequate diet are fundamental steps used to reduce the incidence of coliform infections. Although coliforms are often referred to as a group, there are some important differences in pathogenicity and expected outcomes of IMI among the coliform genera.

Escherichia coli.

Most IMI caused by *E. coli* has a short duration, and these organisms are rarely isolated from cases of subclinical mastitis.[274] While many producers may believe that *E. coli* typically causes severe mastitis, research demonstrates that about one third of cases present with mild symptoms (only abnormal milk), one third present with moderate symptoms (abnormal milk accompanied by local signs in the udder), and one third present with systemic signs.[6,256] Most cases of clinical mastitis caused by *E. coli* are preceded by low SCCs, and the transient nature of most *E. coli* infection is evidenced by the rapid return of SCCs to relatively normal levels within weeks of occurrence of a clinical case.[275] Although some researchers have proposed that specific strains of *E. coli* are more pathogenic in cows,[276] genomic studies indicate that virulence traits are highly diverse among strains[277,278] and *E. coli* is considered to be a facultative opportunistic pathogen that typically originates from the gastrointestinal tract.[277] However, about 5% of *E. coli* cases can result in persistent infections that may lead to recurrent clinical mastitis in the same or another quarter.[279,280] Differences in gene expression between *E. coli* strains that cause transient versus persistent infection have been identified, and transient strains have been reported to be more sensitive to complement-mediated killing as compared to persistent strains, suggesting that both host and pathogen factors may influence response to IMI.[281]

Klebsiella Species.

Klebsiella oxytoca and *Klebsiella pneumoniae* are the two most common species associated with bovine mastitis, and molecular studies have indicated that some organisms previously identified as *Klebsiella* spp. are actually *Raoultella* spp.[282] The clinical presentation and management of mastitis caused by *Raoultella* spp. are identical to recommendations for control of mastitis caused by *Klebsiella* spp.[282] Although the distribution of severity of symptoms is similar for clinical mastitis caused by both *Klebsiella* and *E. coli*,[283] the impact of *Klebsiella*

mastitis on milk yield is significant and long lasting.[28,205] In contrast to IMI caused by *E. coli*, IMIs caused by *Klebsiella* spp. are often of much longer duration and accompanied by long duration of increased SCCs.[282] While the origin of initial IMI may be environmental, between-cow transmission can occur during periods of subclinical infection. Sawdust bedding has been implicated in outbreaks of *Klebsiella* mastitis, but *Klebsiella* species can proliferate rapidly in other bedding materials, and fecal shedding from healthy dairy cows has been documented.[284]

Serratia Species.

Serratia marcescens and *Serratia liquefaciens* are the species that are most commonly associated with bovine mastitis. Many *Serratia* species produce bright-red colonies on blood agar, but they are easily outcompeted by other pathogens and prevalence may be underestimated unless special media and cultural conditions (e.g., incubation at 20° C) are used.[285,286]

In contrast to mastitis caused by other coliforms, IMI caused by *Serratia* spp. often persists in a subclinical form for many months. Field observations and experimental infections have demonstrated that *Serratia* spp. are less pathogenic than most other coliform infections, probably because they stimulate less of an immune response.[287] In contrast to mastitis caused by other coliform bacteria, few cases of mastitis caused by *Serratia* result in severe clinical signs.[288,289] However, *Serratia* infection persists longer than *E. coli* infection. A mean duration of 55 days has been reported,[276,288] but many infections persist for 6 to 10 months.[285,289] Substantial SCC increases in cows and bulk milk are often associated with herd outbreaks of mastitis caused by *Serratia* spp.[289,290]

Serratia IMI can originate during lactation or the dry period. In one longitudinal study, 48% of *Serratia* infections were acquired during the first half of the dry period and 31% during the second half, with only 21% initiated during lactation.[288] IMI caused by *Serratia* can originate from environmental reservoirs such as organic bedding material.[285,286] However, mastitis caused by *Serratia* is frequency associated with contaminated chlorhexidine teat dips or teat dip cups.[282,291] In one outbreak that used molecular analysis to identify a source, the diversity of *Serratia* strains identified indicated that the chlorhexidine teat dips became contaminated with unique strains at each farm.[270,282] Antibiotic therapy is usually ineffective,[276,277] but up to 50% of infected quarters may eventually

self-cure.[288,289] Segregation of chronically infected cows may help to contain an outbreak.[290] Culling is recommended for cows with recurrent cases of clinical mastitis or persistently high SCCs.

Mastitis Caused by Other Organisms

Mycoplasma Species.

Mycoplasma spp. are well known pathogens of dairy cows that infect a number of organs and cause a variety of cattle diseases.[292] *Mycoplasma* spp. are associated with otitis media in calves, infections of the urogenital tract, arthritis in calves and cows, pneumonia, and mastitis. Infections caused by *Mycoplasma* spp. can be recognized in disease outbreaks that present with a range of clinical signs, including death of adult cows,[293] and often result in significant economic losses for dairy farms.[294] *Mycoplasma* has been isolated from the bulk tank milk of about 9.4% of U.S. dairy herds, but the prevalence is strongly associated with herd size and region. In 2014, the USDA's National Animal Health Monitoring System (NAHMS) reported that *Mycoplasma* was isolated from 25% of bulk tank milk samples obtained from herds that contained more than 500 cows, in contrast to 6% and 0% of herds containing 100 to 499 cows and 30 to 99 cows, respectively.[21] Risk factors for *Mycoplasma* mastitis include commingling of cattle from multiple herds, off-site rearing of calves, and stressors such as overcrowding, nonhygienic milking practices, and insufficient biosecurity programs.

Although a number of *Mycoplasma* spp. are considered pathogenic for cattle, the most common species associated with mastitis include *M. bovis*, *Mycoplasma californicum,* and *Mycoplasma bovigenitalum*.[292] *M. bovis* is the most common species associated with bovine mastitis. *Mycoplasma* species can be isolated from a variety of mucosal surfaces of both normal and ill cattle. However, there is increasing evidence that *M. bovis* is an important cause of chronic nonresponsive pneumonia in cattle.[295] While *Mycoplasma* spp. can be isolated from the nares of clinically normal cattle, several researchers have noted that the prevalence of nasal shedding is greater in herds that have problems with *Mycoplasma* mastitis as compared to herds that have not identified a *Mycoplasma* mastitis problem.[292] At the individual animal level, neither nasal nor vaginal swabs are consistently positive in clinically affected animals,[296] and use of serology to diagnose individual animals has not been shown to be

sufficiently predictive to be used in control programs.[297] Colonized cattle may remain asymptomatic or develop bronchopneumonia, otitis, polyarthritis, or mastitis. Because of the unique nature of carriage and transmission of this organism, veterinarians should review detection, diagnosis, and treatment of bovine respiratory disease as part of an investigation into mastitis outbreaks associated with *Mycoplasma* spp. In dairy herds with *Mycoplasma* mastitis, otitis media and otitis interna, respiratory disease, or swollen joints may be seen in calves, especially if unpasteurized milk is ingested.[298,299]

Transmission of *Mycoplasma* spp. is unique in that multiple routes of infection of the mammary gland are possible. Asymptomatic carrier animals may infect herdmates by shedding the organisms in nasal or vaginal secretions, feces, or milk,[292] and infected semen can serve as a route of infection in naive herds.[300] Infection can occur at milking time when teats are exposed to fomites infected with *Mycoplasma* organisms that originated from the udder of another cow. However, IMIs can also occur when *Mycoplasma* spp. are spread from other infected body sites such as the respiratory tract. In one study, intramammary inoculation of *Mycoplasma* species into a single mammary gland was followed by detection of phenotypically identical *Mycoplasma* species in extramammary body sites, blood, and noninoculated mammary glands.[301,302] Biddle and colleagues[303] found that isolates of *Mycoplasma* species from the milk, mammary gland parenchyma, and supramammary lymph nodes of infected cows all had the same pulse-field gel electrophoresis pattern and that all cows had at least one extramammary isolate with the same pattern. These findings suggest that cows with *Mycoplasma* mastitis frequently have disseminated infections and that internal transmission may occur.

The presentation of mastitis outbreaks caused by *Mycoplasma* spp. is extremely variable among farms. On many farms, most IMIs caused by *Mycoplasma* result in persistent subclinical infections. However, clinical mastitis often affects multiple glands (as a result of internal transmission of infection) and will not respond to antibiotic therapy. Many outbreaks of disease caused by *Mycoplasma* are not recognized because diagnosis depends on the use of appropriate laboratory methods. *Mycoplasma* spp. have unique growth requirements and must be cultured using appropriate media and incubation under specific conditions such as 10% carbon dioxide.[304] Prolonged freezing of milk samples reduces the concentration of viable organisms[153,305] and may result in false-negative diagnoses, but broth enrichment before culturing can enhance

detection of *Mycoplasma* species.[153] When culture is used for diagnosis, the plates must be allowed to incubate for up to 7 to 10 days, as some colonies will grow very slowly. The identification of *Mycoplasma* DNA in milk is indicative of IMI, so PCR testing is useful because a diagnosis can be achieved more rapidly.[172] PCR-based diagnostic methods have acceptable limits of detection (<100 CFU/mL) and use primers that differentiate among several *Mycoplasma* species.[172] Although PCR-based methods will be increasingly used, it is important to review the health and SCC history of PCR-positive cows to ensure that the identification based on DNA is indicative of active infection.

The recovery of *Mycoplasma* spp. from bulk tank milk is strongly suggestive of the occurrence of at least one infected animal in the milking herd.[150] However, the failure to find *Mycoplasma* in bulk milk does not indicate that the herd is free of infection. Infected cows may not be contributing to the bulk tank, they may be culled, or they may not be shedding sufficient numbers of bacteria to be detected using typical culture methods. After an infected herd is identified, the next step is to identify the infected animals by obtaining milk samples from high-risk cows. It is possible to collect samples of milk from each string during milking to narrow sampling of individual cows to groups that test positive. Individual milk samples can then be collected and pooled to identify individuals for further testing. Cows with clinical mastitis and those with high SCCs are good candidates for testing, but some infected animals may not exhibit clinical mastitis and may maintain relatively low SCC values, so diagnostic testing should continue until the bulk tank tests negative and the symptoms of an outbreak subside.

Mycoplasma organisms lack a cell wall, thus most antibiotics approved for use in dairy cattle are not effective. Antibiotic treatment during lactation or at dry-off is not useful for control of *Mycoplasma* mastitis. *Mycoplasma* spp. have the ability to inhibit the inmate immune response[306] and enhance neutrophil apoptosis,[307] thus enhancing dissemination and reducing the probability of spontaneous cure. Although some IMIs may resolve spontaneously, infected cows should be considered permanently infected. Even if repeated culturing of milk from an individual quarter yields negative results, infection might persist in an extramammary site and spread to the mammary gland. For this reason, the most common and least risky control strategy is based on an aggressive testing and culling program for all cows diagnosed with *Mycoplasma* mastitis.[308] However, even aggressive diagnosis and culling programs may not prevent

periodic *Mycoplasma* mastitis incidents if infections persist asymptomatically in extramammary sites. Some herds are able to control *Mycoplasma* mastitis without aggressive culling by implementing within-herd segregation, effective biosecurity, and excellent milking techniques. This strategy is more risky as even with these practices, airborne transmission among cows may still occur. Vaccination against *M. bovis* is possible, as bacterins are available, but the efficacy of these vaccines for control of mastitis has not been demonstrated. Vaccination against *M. bovis* is hindered because of variable expression of a diverse and ever-changing set of genes encoding variable surface lipoproteins (Vsps).[309]

Overall, control of *M. bovis* is based on identification of infected cows, prevention of transmission by excellent biosecurity, and implementation of milking and management programs that prevent new infections. As with other pathogens that can be transmitted in a contagious manner, effective postmilking teat dipping is required. *Mycoplasma* species are susceptible to most germicides found in teat dips.[310] Effective premilking and postmilking teat dipping and other measures used to prevent the spread of contagious pathogens in the milking parlor help to limit *Mycoplasma* mastitis transmission. Care must be taken to ensure that hospital pens do not become a source of transmission either through direct contact with infected cows or through fomites or airborne transmission.[311] Control of respiratory disease and provision of housing with excellent ventilation is also necessary. Pasteurization of waste milk reduces the risk of *Mycoplasma* transmission to milk-fed calves.[299]

Pasteurella multocida.

Pasteurella multocida is found in the upper respiratory tract of cattle and can be considered both normal flora and a contributor to bovine respiratory disease complex. This organism is occasionally associated with bovine mastitis. Most episodes are sporadic, but herd outbreaks can occur.[312] Mastitis caused by *P. multocida* can be recognized by increased incidence of clinical mastitis and by an increase in BTSCCs that is indicative of cows with subclinical infections. Hematogenous or lymphatic spread of *P. multocida* from the respiratory tract to the mammary gland has been proposed, and *P. multocida* has been isolated from the blood of cows with severe coliform mastitis.[313] Contamination of teats by nasal secretions (e.g., from nursing calves or intersucking cows), cow-to-cow spread at milking time, or inappropriate infusion practices may contribute to

outbreaks. Antibiotic treatment has historically been unrewarding, and infected cows are often culled. However, spontaneous resolution appears to occur in some cases. Control of herd outbreaks associated with *P. multocida* should be directed at reducing the possibility of cow-to-cow transmission at milking time and improving ventilation of cow housing areas.

Prototheca Species.

Prototheca species are unicellular algae that are widespread in nature and occur throughout the world in habitats that contain moisture and organic matter.[57] *Prototheca* spp. have been isolated frequently from feces of cows and other warm-blooded animals such as pigs and rodents.[314,315] On dairy farms, several different *Prototheca* species have been found in moist areas such as soil, mud, vegetation, and water.[314] Although *Prototheca blaschkeae* and *Prototheca zopfii* genotypes 1 and 2 have been associated with bovine mastitis,[316,317] *P. zopfii* genotype 2 is the main species associated with herd outbreaks of *Prototheca*-related mastitis.[318,319] Initial IMI is likely due to environmental reservoirs, but several risk factors for *Prototheca* mastitis have been identified.[59] Important risk factors include the use of intramammary infusions of nonapproved products and the use of internal teat sealants at dry-off. On many farms, *Prototheca* is ubiquitous in the environment, and these risk factors illustrate the importance of hygienic technique when performing intramammary infusions. When *Prototheca* is identified as a cause of mastitis, veterinarians should investigate treatment practices and ensure that teats are thoroughly cleaned before infusion and that intramammary products are not warmed by being placed in potentially contaminated farm water before infusion into the udder.

P. zopfii will grow on blood agar and can be detected by microscopic examination of Gram-stained colonies; however, the colonies are easily overgrown and may be underdiagnosed. Diagnosis can be improved by culturing milk on selective media. *Prototheca* isolation medium (PIM) contains inhibitory substances that facilitate identification of the organism and is often used in mastitis laboratories. Identification of specific genotypes is not routinely performed but can be done for research or epidemiologic purposes using several molecular techniques.[318,320]

IMI with pathogenic *Prototheca* can result in both subclinical and clinical symptoms, and the infections can occur sporadically, endemically, or acutely. Most clinical cases are of mild or moderate severity. Infected cows may become

chronically infected and experience persistently increased SCCs. Shedding of *P. zopfii* in milk can be persistent or intermittent.[321] Most *Prototheca* IMIs are probably acquired from the environment, but the possibility of transmission among cows in a contagious fashion should be recognized and prevented as part of a control program.

Treatment of mastitis caused by *Prototheca* is not recommended. *P. zopfii* is resistant to antimicrobial therapy, and infection can persist through the dry period.[198] Therefore identification, segregation, and progressive culling of infected animals are required to control *Prototheca* mastitis. On most farms, searching for point sources of environmental contamination will not be useful; however, hygienic conditions in the environment should be improved. Culling of infected cows should be coupled with identification and avoidance of contaminated environmental sites, enhanced cleaning of feed bunks and watering devices, and use of milking procedures that ensure clean teats and minimize contagious spread of infection.

Corynebacterium bovis.

Corynebacterium bovis is commonly found in the streak canal and can cause occasional IMI that results in mild increases in SCC and very little impact on milk yield.[322] It is rarely a cause of clinical mastitis. *C. bovis* can be cultured on routine media such as blood agar, but colonies may not be apparent until after 48 hours of incubation. *C. bovis* can be a frequent contaminant in milk samples, and DNA from this organism is frequently identified in association with other bacteria when PCR testing is used on milk samples.[178] This organism can be transmitted from cow to cow at milking time, but the use of premilking and postmilking teat germicides is effective in controlling transmission.

Trueperella pyogenes.

Trueperella pyogenes is the current name assigned to an organism that previously was named *Arcanobacterium pyogenes* (formerly *Actinomyces pyogenes* or *Corynebacterium pyogenes*). IMI with this organism usually results in acute purulent symptoms of clinical mastitis. In most instances, treatments are not effective, and mastitis caused by this organism has a poor prognosis.[5] Few cases remain subclinical, and the identification of this organism in bulk tank milk usually results from failure to detect and divert milk from cows with clinical symptoms. The outcome of most cases occurring in lactating cows is

loss of the quarter or culling of the cow.[323] Transmission among cows can occur by flies or through environmental exposure of teat skin, especially if teat ends are damaged.

Historically, this organism was considered one of the etiologic agents of "summer mastitis," a condition of prepartum heifers and nonlactating cows that has been recognized mainly in Europe and Japan during summer months.[324] In most cases, anaerobic bacteria (e.g., *Peptococcus indolicus*, *Bacteroides* spp., *Fusobacterium necrophorum*) and facultative anaerobes (e.g., *S. dysgalactiae*) are also involved.[324,325] Summer mastitis is characterized by a swollen, hard, painful mammary gland containing purulent, foul-smelling secretion. Acutely affected animals typically demonstrated systemic signs ranging from lethargy and reduced feed intake to high fever, severe depression, abortion, and death. Systemic administration of procaine penicillin G often resolves systemic illness, but neither systemic nor intramammary antibiotics are effective at eliminating IMI.[325] The outcome of most episodes of summer mastitis is chronic clinical mastitis or a nonfunctional quarter. Horn flies are believed to be responsible for transmitting summer mastitis. Because *T. pyogenes* is often found in the environment on farms and on body sites of cattle, teat skin contamination may predispose to infection, as occurs with coliform or environmental streptococcal mastitis, particularly if teat defenses are compromised.

Control of summer mastitis is accomplished by fly control, infusion of mammary glands with antibiotics at dry-off, appropriate environmental hygiene practices and stocking density, prevention and treatment of teat lesions, and prompt recognition and segregation of infected cows. Amputation of the teat, which facilitates drainage of secretions, increases environmental contamination and should not be done unless the cow can be segregated.

Yeast Mastitis.

Yeast are microorganisms that are ubiquitous in the environment of dairy farms, and they can cause opportunistic IMIs. Sources of exposure of teats include contact with soil, plants, and water and feedstuffs such as total mixed rations.[326] *Candida* species, *Trichosporon beigelii*, and other yeast organisms are associated with mastitis in individual cows or herds.[5] Yeast infection usually follows intramammary antibiotic treatment or teat skin injury. Outbreaks often occur when homemade infusion products or associated equipment (e.g., needles, syringes, bottles, cannulas) are contaminated or when the teat is not adequately

disinfected before infusion.[327,328] In one study, six cows treated with a homemade intramammary antibiotic solution contaminated with *T. beigelii* all developed fever, hypogalactia, and swollen mammary glands within 2 weeks, and two of the six died. When the producer continued to use homemade solutions, an additional 23 cows (over half the herd) became infected, and the herd was dispersed.[327] Yeast have been cultured from towels and teat cup liners used on infected cows, suggesting that contagious transmission may occur.[327,329]

On blood agar, yeast colonies appear similar to NAS colonies, so it is important to examine the colonies microscopically. Sabouraud dextrose agar with antibiotics is a common alternative medium that selects for yeasts. Yeast infections are not susceptible to antibiotic treatment, and infusion of antibiotics may potentiate infection. The use of antifungal agents is not allowed in the United States, but experimental use has not been demonstrated to be effective. Infection (especially with *Candida* species) often resolves spontaneously within 2 to 4 weeks,[326,329] but cows with severe or recurrent clinical mastitis, reduced milk production, or persistently high SCCs should be culled. Control of yeast mastitis includes aseptic intramammary infusion procedures; use of single-dose, commercially prepared antibiotic infusion products; segregation of infected cows at milking time; and use of individual rather than shared towels. Feeding contaminated silage or total mixed ration can promote fecal excretion of yeast and has been blamed for outbreaks of yeast mastitis in some instances.

Pseudomonas Species.

Pseudomonas spp. are considered to be environmental pathogens that are commonly isolated from water sources on dairy farms.[5] *Pseudomonas* spp. typically appear on blood agar as white or gray hemolytic colonies and may produce a grape-like odor. *Pseudomonas aeruginosa* is the most common species isolated from milk of mastitic cows. IMI with *Pseudomonas* spp. can result in severe clinical mastitis that may develop into gangrene.[330] However, chronic subclinical mastitis with periodic bouts of mild clinical mastitis is the more common presentation.

After IMI with *Pseudomonas* spp. is established, it usually persists, and antibiotic therapy is unsuccessful. This is caused in part by production of factors that inhibit host defenses and reduce antibiotic efficacy, such as biofilm.[73] Cows with persistently high SCCs or repeated bouts of clinical mastitis should be culled, or individual glands may be dried off.[311]

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IMI in cows usually occurs when teats come in contact with contaminated water, and the use of water to wash teats before milking has frequently been implicated in outbreaks of mastitis caused by *Pseudomonas* spp. Water sources should always be investigated when *Pseudomonas* spp. are responsible for outbreaks of mastitis on dairy farms. Predipping for teat disinfection rather than washing with water reduces the risk of infections caused by contaminated water sources. Similar to IMI caused by *Prototheca*, mastitis caused by *Pseudomonas* has been attributed to use of contaminated intramammary infusion products[56] or teat cannulas, inadequate teat end sanitation before drug infusion, contaminated teat wipes,[331] and exposure of cows to stagnant water. Investigation of a herd problem should focus on hygienic practices for intramammary infusion practices and reduction of exposure to water in the environmental and milking process.

Nocardia and *Mycobacterium* Species.

Nocardia species and mastitis-causing *Mycobacterium* species are saprophytes and therefore may cause IMI when teats are exposed to unhygienic environmental conditions. However, both *Nocardia* spp. and *Mycobacterium* spp. are uncommon causes of mastitis that have typically been associated with unhygienic use of intramammary infusions or use of contaminated intramammary products.[5,332,333] Both of these organisms have been associated with sporadic cases or herd outbreaks of mastitis. Symptoms are variable and can range from greatly increased SCC[334] to death. A tentative diagnosis can be made by observing acid-fast rods or gram-positive rods with branching filaments in a milk smear, but culture of aseptically obtained milk samples is required to diagnose and differentiate *Nocardia* and *Mycobacterium* species. Prolonged freezing can reduce recovery of *Nocardia* from milk samples. Antibiotic therapy is futile. *Nocardia* is a potentially zoonotic pathogen, and affected animals should be segregated and culled. Control of mastitis caused by these organisms involves proper intramammary infusion practices and general environmental hygiene.

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Prevention and Control of Mastitis

Prevention of Intramammary Infection

At the herd level, the prevalence of mastitis is a function of the incidence and the duration of IMI. Thus control programs are directed toward implementing management programs that can influence either duration of IMI or the development of new infections. After an infection is acquired, duration of IMI is influenced by inherent characteristics of the pathogens (see Table 36.2), treatment efficacy, and culling decisions. Management practices that focus on limiting duration of infection occur after financial losses attributable to infection have already been incurred. In contrast, control programs that focus on preventing the development of new infections are profitable because they reduce the losses caused by mastitis. Thus the emphasis on controlling mastitis should be directed toward implementation of management practices that prevent new infections.

Prevention is based on knowledge of where the exposure to pathogens is occurring. In general, contagious transmission occurs when teats of healthy cows are exposed to bacteria that originated from subclinically infected udders of other cows. Thus the primary principle of reducing exposure to pathogens that can be transmitted in a contagious manner is to reduce the possibility of contact with milk that came from subclinically infected cows. Successful implementation of the five-point plan is the basis for control of pathogens that can be transmitted in a contagious manner.[335] The components of the five-point plan are discussed throughout this chapter and include (1) postmilking teat dipping, (2) comprehensive use of intramammary antimicrobial therapy at the end of every lactation, (3) appropriate therapy of clinical cases, (4) proper maintenance and functioning of milking equipment, and (5) appropriate culling of chronically infected cows. The components of the five-point plan are now widely viewed as standard management procedures and are highly adopted in many developed dairy regions.[260,336,337] As a result, many regions have dramatically reduced the prevalence of IMI caused by organisms that are primarily transmitted in a contagious manner.

To address the increased incidence of mastitis caused by environmental pathogens, the National Mastitis Council has added five additional components

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focused on implementation of a comprehensive mastitis control program (http://www.dairyweb.ca/Resources/WDD82/WDD8212.pdf). The 10-point mastitis control program incorporates all components of the five-point plan and is organized in the following checklist:

Point 1: Establishment of Goals for Udder Health. As with management of reproduction, nutrition, and production, it is difficult to improve udder health without having clear goals. While the establishment of goals seems intuitive, few farmers set aside sufficient time to develop an udder health plan that includes herd-specific goals. Surveys of veterinarians and other professionals who work with dairy producers indicate that barriers to improvement in milk quality are often related to motivation and implementation rather than lack of technical knowledge or skills.[4,137,338-340] Several studies have indicated that many dairy veterinarians are only marginally involved in mastitis control programs. Upon beginning a team-based milk quality improvement program, only 24% of dairy farmers (n = 180) indicated that they used their herd veterinarian to plan milk quality programs.[137] In a companion survey, most dairy veterinarians (n = 42) interested in participating in a mastitis control program indicated that they spent less than 10% of their professional time actively working to improve milk quality.[339] Increased involvement in the development of annual udder health plans is an area of opportunity for dairy veterinarians, and the initial step can be to begin a discussion of herd-specific goals.

Point 2: Maintenance of a Clean, Dry, Comfortable Environment. Exposure to pathogens that have environmental reservoirs is strongly associated with facility and animal hygiene. Numerous hygienic practices on dairy farms have been associated with the incidence of clinical mastitis.[341-344] The rate of clinical mastitis occurring in dairy cows has been shown to be strongly associated with the cleanliness of animal housing and bedding sources.[341] The number of bacteria on teat skin is associated with bacterial count in bedding,[194,345] and a linear relationship between the rate of clinical mastitis and the number of gram-negative bacteria in bedding has been demonstrated.[182,346] Nutritional management can have an indirect influence on hygiene, as the use of high-concentrate diets has been associated with looser feces and reduced facility cleanliness.[347] Cow cleanliness can be evaluted using several scoring systems.[344,348] A four-point udder hygiene scoring (UHS) system for assessing udder hygiene has been described by Schreiner and Ruegg.[349] Cows that are scored as having dirty udders were at increased risk of IMI and increased

SCC.[344] Similarly, Reneau and colleagues[350] used hygiene scores to evaluate five body areas on dairy cows.[326] The udder and hind limb scores were significantly associated with SCC.[326] Research has demonstrated that neither UHS nor the rate of new IMIs is improved by the use of tail docking, and this practice should not be encouraged.[349,351]

Mastitis control programs should focus on reducing bacterial exposures by improving facility hygiene. In many herds, clean or recycled sand will be the recommended bedding material because it does not support as much growth of coliform bacteria as organic bedding materials do.[194,208,346,352,353] In some herds, bacterial counts can be reduced by adding lime or other bedding conditioners or by using other methods to reduce bacterial counts, but the effect is generally short lived.[354,355] The use of dried manure solids as bedding is a risky strategy because these substances are ideal to support growth of bacteria found in the intestinal tract of dairy cows.

Point 3: Proper Milking Procedures. Milking hygiene and the risk of new IMIs can be improved by ensuring that milking technicians wear disposable nitrile or latex gloves.[356-358] Essential aspects of an effective premilking routine include effective teat disinfection, examination of foremilk, sufficient stimulation to allow for effective milk letdown, complete drying of the teats, and timely attachment of the milking unit. Research has definitively established that the gold standard for premilking teat disinfection is application of an effective disinfectant for a sufficient contact time, followed by drying the teat using a single cloth or paper towel for each cow.[359-362] To ensure that clinical mastitis is detected and abnormal milk does not reach the human food chain, two or three streams of foremilk should be removed and examined before attaching milking units. Drying teats has been demonstrated to reduce bacterial counts of teat ends,[360] reduce the number of colonies of spore-forming bacteria in bulk milk,[363] and effectively reduce the risk of contaminating milk with iodine residues from predips.[359] Teats should be dried using one dry cloth or paper towel for each cow. Use of towels to dry teats on multiple cows has been associated with a greater monthly rate of clinical mastitis as compared to herds that use a single towel per cow.[137]

Modern dairy cows in high-producing herds have been selected to milk rapidly, and removal of foremilk is often sufficient stimulation to achieve milk letdown. The time between stimulation and attachment of the milking unit should be approximately 60 to 90 seconds, but disturbances in milk flow and

yield have not been reported until lag times have exceeded 3 minutes.[364,365] To prevent bimodal milk flows, premature attachment of the milking unit should be avoided.[364] To minimize stress on teat ends, milking units should be removed when milk flow rates drop to a level that indicates that most milk has been harvested. On most high-producing herds, milking units are removed when milk flow rates fall below 0.5 to 1.0 L/min. The use of automatic take-off units is encouraged, as they increase consistency of milking and allow milking technicians to focus more on premilking preparation.

The purpose of postmilking teat disinfection is to reduce the transmission of pathogens that can be transmitted in a contagious manner.[335,366,367] The principle is based on killing pathogens deposited on the teat skin during the milking process before they colonize the teat orifice and invade the gland, and effective application of postmilking teat dips can result in more than a 50% reduction in new IMIs.[368] Postmilking teat dipping is a highly adopted practice,[21,120] but it is not always properly implemented. Milking technicians should be trained to use an application method (such as use of a dip cup) that ensures that at least 75% of the teat skin is covered with an approved, commercially formulated teat disinfectant. Efficacy of the postmilking teat dip should have been demonstrated through properly performed scientific trials.

Point 4: Proper Maintenance and Use of Milking Equipment. The impact of machine milking on development of new IMIs is well known, and veterinarians should be aware of how to evaluate key indicators of milking equipment function. Improper functioning of milking machines can result in reduced resistance of the teat canal to IMI; vacuum fluctuations and liner slips may provide forces that overcome the resistance of the teat canal to bacterial invasion or dispersion of bacteria within the udder, and milking equipment can serve as fomites to transfer bacteria among cows. Providing stable teat end vacuum is a central objective of a properly functioning milking system.[369,370] A high rate of liner slips has been demonstrated to be associated with increased rates of clinical mastitis and increased risk of IMI.[370] Improperly functioning machines may cause congestion in the teat wall, which can result in slower closure of the teat canal and development of IMI.[371,372]

Point 5: Good Record Keeping. Measuring outcomes is an integral part of effective management.[373] Mastitis is a bacterial disease that occurs in individual animals, but mastitis control programs must be implemented at the herd level. Successful mastitis control depends on effective detection, accurate diagnosis,

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evaluation of appropriate treatment options, and implementation of preventive practices that address herd-specific risk factors associated with exposure to mastitis pathogens. Veterinarians who wish to reduce mastitis should regularly review herd records for SCCs and clinical mastitis and evaluate key performance indicators relative to herd goals. The program should be structured to allow for the evaluation of cow factors, environmental factors, and milking machine factors that can contribute to exposure to mastitis pathogens. An effective surveillance system for mastitis includes clear case definitions and effective mechanisms to detect both clinical and subclinical mastitis, the use of recording systems that allow for timely evaluation of risk factors, and feedback mechanisms that allow management personnel and veterinarians to develop goals and evaluate actions.

Points 6 and 7: Appropriate Management of Clinical Mastitis During Lactation and Effective Dry Cow Management. Both of these topics are discussed later in the chapter.

Point 8: Maintenance of Biosecurity for Contagious Pathogens and Marketing of Chronically Infected Cows. Biosecurity programs are designed to reduce the risk that healthy cows will be exposed to bacteria originating from other animals. The goal of mastitis biosecurity programs is to reduce the probability that teats of healthy cows will be exposed to infected milk and to enable the cow to have an effective immunologic response if exposure occurs (see Prevention Through Immunization section later). Many farmers arrange the milking order so that lower risk animals (first lactation cows or cows with lower SCCs) are milked first to reduce the risk of transmission of mastitis pathogens during the milking process. Physical segregation of chronically infected cows has been shown to be an effective method of reducing the new infection rate,[374,375] but it is dependent on using diagnostic methods that can accurately detect infected cows. Automated backflush of liners with disinfectants between cows has reduced the risk of new IMIs caused by *S. aureus*,[376] but the cost effectiveness of these systems depends on the prevalence of of infections within the herd. The use of an automated teat dipping and backflush system was shown to result in reduced bulk tank SCC and decreased new increased SCC, but the effect became more significant after 6 to 18 months of use.[377]

The prevalence of chronically infected cows is a strong predictor of risk of new infection with pathogens that can be transmitted in a contagious manner. One study demonstrated that the odds of a cow becoming infected with *S. aureus* doubled with each 5% increase in the herd prevalence of existing infection.[357]

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Chronically infected cows must be identified through routine testing of individual cows' SCCs, and microbiological analysis should be performed to identify the causative pathogens. Cows that develop chronic infections with pathogens that are refractory to treatment should be culled to reduce the risk of transmission to healthy animals.

When animals from outside sources are purchased, they should be bought from recognized individual herds (rather than sale barns), and historical information such as bulk tank culture results and individual cow SCC histories should be reviewed. Animals should be screened for *Mycoplasma* spp., and a history of recent respiratory disease should be viewed as an important risk factor for this syndrome.

Point 9: Regular Monitoring of Udder Health Status. Udder health recording systems must include monitoring programs that allow assessment of both clinical and subclinical disease. Animal health recording systems for mastitis should consist of both temporary cow-side records that are used for day-to-day decision making and permanent records (such as cow cards or computerized records) that are used to summarize trends over time.[123,354,355] The recording system should be accessible and allow the veterinarian to determine important risk factors and epidemiologic trends. The first step in monitoring subclinical mastitis is to ensure that SCC values are routinely obtained from all cows. Generally all cows with SCC values greater than 200,000 cells/mL (linear somatic cell score of approximately 4.0) are considered to have subclinical mastitis. SCCs should be reviewed monthly at both the herd level and the cow level. At the herd level, evaluation of monthly SCC patterns can be highly diagnostic for troubleshooting subclinical mastitis problems. Recommendations for key performance indicators for monitoring udder health are available.[373]

Point 10: Periodic Review of Mastitis Control Program. Dairy farming is a complex process that involves interactions between animals, nature, and people. Like other research-based businesses, the growth in knowledge about dairy management practices is extraordinary. Dairy farmers acquire information about animal health from a variety of sources, including veterinarians, nutritionists, other producers, dairy magazines, and consultants. Veterinarians visit multiple farms, see results from a wide variety of management decisions, and bring an outside perspective to farm decisions. On-farm management teams can be formed to troubleshoot specific farm issues or to meet periodically and review farm performance. A properly formed management team can aid the farmer by bringing together advisors with a range of experiences. Management teams also

allow for dialogue between consultants (such as veterinarians and dairy plant personnel) who have a shared interest in specific outcomes. The management team format is extremely successful in solving mastitis problems. Farms that participated in a team-based milk quality program in Wisconsin increased adoption of best management practices and improved mastitis control.[378]

Prevention Through Immunization

Understanding the principles of the immunologic response to immunization is helpful in successfully implementing an effective vaccination program. Lymphocytes will respond to a specific microbial antigen only if the antigen (protein) is combined with a major histocompatibility complex (MHC) molecule on the surface of host cells, a process referred to as antigen presentation.[65] Cells such as macrophages and dendritic cells are particularly efficient in antigen processing by phagocytizing, digesting, and presenting antigens on their membrane surface in conjunction with an MHC molecule. In response to antigen presentation, naive lymphocytes then undergo clonal expansion and differentiation. A specific antigen can only be presented to a lymphocyte that solely recognizes that antigen.[62] Thus successful immunization against a pathogen must link the invasion of the pathogen with recruitment of innate phagocytic cells that recognize and digest the microbe, and subsequently present one of potentially hundreds of different antigens from the pathogen on the cell surface in order to attract and activate a matching lymphocyte for that specific antigen. T-helper cells play a central role by (1) enhancing B-lymphocyte clonal expansion and differentiation to antibody-producing plasma cells, and (2) completing the inflammatory response loop by releasing cytokines such as IL-17 and IFN-γ that stimulate phagocytes to more efficiently phagocytize and kill ingested microbes. Antigen-specific antibodies that arise from the acquired immune response also enhance phagocyte function by opsonizing microbes, thus assisting in target recognition and ingestion.

The decision to use a vaccine as part of a mastitis control program should be founded on the practitioner's ability to access peer-reviewed studies and compare incidence and severity of natural infections between vaccinated animals and unvaccinated controls. Such studies should encompass a diversity of herd management practices and geographic regions. Unfortunately, such trials require large numbers of animals and long duration. Alternatively, challenge-exposure trials are often performed to assess vaccine efficacy. This type of trial requires

fewer animals and less time, and many variables such as different strains of bacteria, challenge dose, and physiologic status of the animal can be uniformly standardized. In addition, more comprehensive outcomes, including shedding of bacteria in milk, physical examination of the cow, and changes in biochemical parameters of serum and milk can be reliably measured. However, these studies may have limited application in relation to the diversity of dairy farm management and environment, as well as among pathogens.

As with therapeutics, appraisal of vaccine efficacy should *not* be made on testimonials, especially herd-level impressions of "before-and-after" responses. Assertions are often made based on perceptions that initiating a vaccine program decreased the incidence and severity of mastitis cases, lowered SCCs, increased milk production, et cetera, without using a concurrent nonvaccinated control group for comparison. This is a frequent flaw in the evaluation of autogenous bacterins, in addition to a lack of the quality control standards rigorously followed in commercial production. Mastitis incidence and SCCs within a herd can rise and fall based on many factors, including weather, changes in the proportion of younger to older animals in the herd, history of herd additions, correction of milking techniques or deficiencies in equipment, and culling decisions.

Immunization Against Specific Mastitis Pathogens

Gram-Negative Core-Antigen (*Escherichia coli* J5) Bacterins.

Gram-negative core-antigen bacterins are used on many dairy herds. The variants studied most extensively are formulated with a mutant strain of *E. coli* O111:B4 (Rc mutant, commonly termed J5) lacking the "O" antigen capsule of the cell wall but with the core lipopolysaccharide, membrane proteins, and lipid A antigens intact. These core antigens are highly conserved among gram-negative bacteria[379,380] and elicit cross-reactive anti–gram-negative antibodies in J5-vaccinated cows.[381-383] Thus dairy cattle immunized with these bacterins develop immune resistance against a wide variety of gram-negative bacteria, including mastitis-causing coliforms.

Initial studies in California determined that higher serum anti–*E. coli* J5 immunoglobulin G (IgG) was correlated with a lower incidence of clinical coliform mastitis.[384] A subsequent field trial demonstrated that cows administered three immunizations (at drying off, 30 days after drying off, and in the postpartum period) had a fivefold decrease in the rate of clinical coliform

mastitis in the first 100 days of lactation, as compared to unvaccinated cows.[385] A field trial in Ohio using a similar dose regimen reported that core-antigen immunization did not reduce the prevalence of gram-negative IMIs at calving; however, 67% of the infections present at calving in unvaccinated cows developed clinical mastitis, as compared to only 20% in the J5-vaccinated cows.[386] In addition, vaccination with J5 bacterin increased anti–*E. coli* J5 IgG in serum and milk as compared to unvaccinated controls,[386-388] although anti–*E. coli* J5 antibody titers in milk are orders of magnitude lower than in serum. Following intramammary challenge of *E. coli*, core-antigen immunization reduced the severity of infection but did not prevent infection.[386]

The pathogenesis of severe coliform mastitis is dependent on LPS-induced immune mediator responses, and a high proportion of severe coliform mastitis cases become bacteremic.[313] Thus J5 bacterins may have a greater impact on the systemic effects of coliform mastitis than on local mammary inflammation. This concept is supported by a field trial from New York that determined that two doses of J5 bacterin decreased the proportion of clinical mastitis cases that resulted in culling or death by threefold but did not reduce the overall incidence of clinical mastitis cases.[389] However, coliform mastitis cases contracted during the first 50 days of lactation resulted in less milk production loss among J5-vaccinated cattle.[390]

Gram-negative bacterins are regarded as weakly immunogenic in dairy cattle because they elicit poor amnestic IgG1 and IgG2 responses.[81] An Ontario study found that a substantial population of cows that were administered two J5 bacterin doses during the dry period had poor antibody responses and a higher incidence of mastitis in the subsequent lactation.[391] This relatively short duration of immune protection is supported by several trials.[392-394] A New York study determined that cows vaccinated with two doses of J5 bacterin lost less milk production following clinical mastitis and survived longer as compared to unvaccinated cows. However, this protection, as well as anti–J5 antibody titers, declined as lactation (and time since vaccination) progressed and did not exist by 75 days in milk.[392] In a Michigan study, hyperimmunization of cows with six doses of J5 bacterin resulted in a threefold decrease in severe clinical coliform mastitis from 42 to 126 days in milk, as compared to cows that received three doses. This suggested that supplemental immunizations extended protection beyond that offered by traditional vaccination regimens.[393] A subsequent Michigan study determined that cows immunized with five doses of J5 bacterin

had elevated anti–*E. coli* J5 antibody IgG1 and IgG2 titers, relative to unvaccinated cows, for up to 60 to 90 days longer than cows administered three doses of J5 bacterin only.[394] In addition, the best response to immunization, in terms of intensity and duration of antibody response, was gained when multiple immunizations were given as a series in different anatomic locations on the cow.[394]

Use of J5-type bacterins relies on five principles: (1) Diagnose if coliform organisms cause a substantial portion of clinical mastitis within a herd, (2) determine the severity and incidence of clinical coliform mastitis cases, (3) describe the epidemiology of the problem in the herd, (4) decrease other herd risk factors that may contribute to clinical coliform mastitis, and (5) develop a vaccination protocol that best integrates immunology with herd needs and practical limitations (Table 36.3). Veterinarians should review these steps when developing a protocol for dairy herds and periodically review progress and changes in the herd that may lead to a re-evaluation of the immunization protocol.

TABLE 36.3

Guidelines for Core-Antigen Gram-Negative Bacterin Use in Dairy Herds

1. Diagnose the cause of clinical mastitis	Does bacteriology of clinical mastitis cases frequently yield coliforms (gram-negative)?	Bacterin ineffective for gram-positive pathogens.
2. Determine the incidence of severe mastitis caused by coliforms	Are >1% clinical mastitis cases?	Bacterin reduces severity, not incidence of infection.
3. Describe affected animals	What are the risk factors associated with animals with severe coliform mastitis in the herd?	Identify if stage of lactation, age, or season is associated with the problem.
4. Decrease risk factors of exposure	Are there other critical risk factors for coliform mastitis prevention that need to be addressed?	Bacterin effects are diminished in herds with poor sanitation, cow comfort, intramammary infusion techniques, teat end health, or milking preparation.
5. Develop a protocol that best fits the herd	Will the protocol likely be followed? Is it likely to offer the best return on investment?	Immunization programs should be designed to reduce unnecessary doses and target the affected animals.

Use of *Staphylococcus aureus* Bacterins.

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Considerable effort, encompassing numerous antigens, virulence factors, and bacterial strains, has been made to develop an efficacious and practical *S. aureus* vaccine. Much of the interest has focused on vaccination of primiparous heifers. A bacterin containing a lysed culture of polyvalent phage types, including a variety of capsular serotypes, is commercially available in many regions (Lysigin). This product originated from work in Louisiana that determined that two initial doses 2 weeks apart, followed by doses at 6-month intervals, reduced IMI at calving caused by both NAS and *S. aureus*. However, a subsequent challenge-infection study determined that this bacterin did not prevent IMI, accentuate clearance of IMI, affect SCC, or milk yield post challenge.[395] The Lysigin-vaccinated heifers did have improved clinical scores and shorter duration of clinical mastitis.[395] Although immunization with Lysigin increased serum anti–*S. aureus* IgG1 in heifers, milk concentrations of IgG1, IgG2, and IgM were not affected.[396] In a subsequent report in lactating cows, representing multiple parities, two doses of Lysigin administered 14 days apart did not reduce the number of mammary quarters that developed new *S. aureus* or NAS IMI, the time after vaccination to develop new IMI, SCC, or milk antibody isotype to positive ratio.[395] The authors speculated that the bacterin may have induced insufficient opsonizing antibodies in milk to promote phagocytosis.

S. aureus vaccines would likely have limited use in many dairies, especially in herds with low prevalences of IMI, as is typical for herds with SCCs less than 200,000 cells/mL. Thus it is unlikely that *S. auereus* bacterins will have a significant impact in herds that successfully control contagious mastitis by practicing excellent milking techniques and maintaining milking equipment. Conversely, herds that immunize in lieu of good management practices are likely to have disappointing results. Investigators have administered *S. aureus* bacterins in an attempt to augment antimicrobial therapy, with conflicting results.[395,397]

Mastitis Therapy: Antimicrobial Drugs

General Concepts

Mastitis remains the most common cause of antimicrobial drug therapy for cows on U.S. dairy farms. In 2014, 21.7% of cows were treated for mastitis using antimicrobial drugs.[21] If this use represents the majority of all U.S. dairy herds, with approximately 9 million dairy cows, then nearly 1.9 million mastitis cases are treated annually. Surveys from Wisconsin and Canada estimated that between two and four doses of intramammary infusions are used per cow per year; this means that on a 1000-cow dairy, an average of 5 to 10 doses of intramammary antimicrobials would be administered daily.[398,399] Antimicrobial therapy benefits animal health and well-being, but economic losses associated with antimicrobial therapy of mastitis include drug and veterinary expenses, extended labor, and most importantly, discarded milk.[400] Unwarranted antimicrobial use in dairy cattle can result in residue violations in milk and meat and erode consumer confidence in the safety of dairy foods.

To date, the risk of emerging antimicrobial resistance among bovine mastitis pathogens has been low, particularly for drugs with high therapeutic value in human medicine.[401-403] Nonetheless, prudent administration of antimicrobials is needed on dairy farms, similar to stewardship of antimicrobial resources as advocated in human medicine. Responsible antimicrobial stewardship minimizes the emergence and dissemination of antimicrobial resistance among pathogens and preserves the therapeutic integrity of the drugs.

Mastitis therapy is often initiated empirically, without consideration of case risk factors for efficacy, and as a substitute for an integrated mastitis control program.[140,404] Standardizing mastitis therapeutic protocols should diminish spontaneous “cow-side” biases and establish uniformity for therapeutic regimens. However, farmer therapeutic decisions often differ from veterinary recommendations.[405] In a Wisconsin study across 51 herds, nearly a quarter of cows treated received an additional secondary treatment because of perceived lack of response to the initial treatment.[404] The majority of intramammary treatments were administered to cows with a microbiological diagnosis of no growth or *E. coli*, two culture outcomes that are not likely to benefit from therapy. In addition, in a survey of more than 600 herds from Michigan,

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Pennsylvania, and Florida, only about half of the respondents stated that they "frequently or always" record treatments or review treatment records before administering mastitis therapy.[406] In addition, more than 80% of the herds reported that they rarely or never use bacteriologic results for mastitis therapy decisions.

Risk factors that decrease therapeutic efficacy include increasing (1) age of the cow, (2) preexisting SCC before treatment, (3) duration of infection, (4) number of quarters infected, and (5) *S. aureus* infections.[205,223,407] In particular, chronic infections have poor therapeutic outcomes and may require extended duration of antimicrobial therapy.[400] Thus to reduce antimicrobial use associated with mastitis, we need to change behaviors and attitudes of farm personnel to (1) use bacteriology to the best of herd labor abilities, (2) determine the history of the cow and identify cow-level risk factors that may affect the efficacy of therapy, and (3) apply standardized therapy protocols that are based on sound pharmacology.

A small proportion of cows can be responsible for a large proportion of clinical mastitis episodes in a herd. Thus antimicrobial therapy is unlikely to cure infections in glands with repeated bouts of clinical mastitis episodes. Many herds tend to unnecessarily lose time and money by treating "repeat offender" clinical mastitis cases. When coupled with the lack of bacteriologic culture, thus opening the door for treatment of unresponsive pathogens, most clinical mastitis may be treated unnecessarily on many dairy farms. Veterinarians should not only direct drug selection and protocols for mastitis therapy on dairy farms, but more importantly establish selection criteria for cows to be either included or excluded for treatment. In addition, it is critical to have not only a therapy protocol, but also a protocol to determine efficacy or a "cure" after therapy. Many clinical trials in the literature, or those done on farm, evaluate therapeutic outcome in relatively short periods after treatment is completed (less than 14 days). As many cases of mastitis relapse after this period (up to 30 days is common), practitioners should adopt a long-range view of therapeutic outcomes, including subesquent SCC testing, survival in herd, loss of quarter function, and milk production, in additon to relapses.

Alternatives to antibiotic treatment include (1) euthanizing or culling the cow, (2) drying off the cow or gland, (3) administering supportive treatment alone, or (4) doing nothing. The cow's welfare must be considered when choosing among these options, to minimize pain and suffering. If supportive treatment or no treatment is chosen, the cow should be milked after healthy cows and the milk

withheld from sale for as long as it is visibly abnormal. If a single gland is dried off, antibiotics should not be infused because this may result in antibiotic residues in milk from the other glands.

Limitations of Antimicrobial Susceptibility Testing.

Antimicrobial susceptibility test results should not be used as the main basis for antibiotic selection. In most cases, susceptibility cut-points for zone diameters (for the disk diffusion test) or minimum inhibitory concentration (MIC) values are based on antibiotic concentrations in serum or interstitial fluid of people after oral or intravenous (IV) dosing; these are not equivalent to concentrations achieved in milk or mammary tissue after intramammary or systemic dosing.[408] The absolute MIC value is more useful than a dichotomous result (susceptible or resistant) based on an irrelevant cut-point. However, the reported MIC value may not reflect the MIC in milk because MICs in milk are often higher than in blood, especially for non–β-lactam drugs.[393] More recently marketed intramammary antibiotics have MIC or disk diffusion cut-points that are relevant to treatment of mastitis, but the cut-points need to be validated in vivo. Recent studies have determined that susceptibility test results (susceptible versus resistant) had no impact on the outcome (clinical cure, bacteriologic cure) of clinical mastitis episodes.[240,409,410] Interestingly, *S. aureus* isolates that are penicillinase-producing strains are less responsive to treatment even if penicillinase-resistant antibiotics are used.[411]

Treatment of Mild and Moderate Cases of Clinical Mastitis

Treatment of Clinical Mastitis Caused by Streptococci and Staphylococci.

The effectiveness and selection of antibiotic therapy depend on the pathogen causing clinical mastitis. Cows with cases of mild (severity score 1) or moderate (severity score 2) clinical mastitis and no bacterial growth in the milk are unlikely to benefit from antibiotic therapy, as are cows with a low concentration of *E. coli* in the milk. Cows with *Mycoplasma* mastitis or mastitis caused by opportunistic pathogens such as *P. aeruginosa, S. marcescens, P. zopfii,* or *Candida* spp. are unlikely to respond to antibiotic therapy.[56,57,292,412] Thus the use of antimicrobial therapy for mastitis cases caused by these pathogens should be avoided and may lead to unnecessary risks for drug residues.

On the other hand, antimicrobial drugs can enhance resolution of many cases of streptococcal or staphylococcal mastitis episodes. The prototype for therapeutic success is treatment of IMI caused by *S. agalactiae*. This organism tends to be highly susceptible to intramammary therapy with β-lactam drugs, with cure rates of 85% to 90% often reported.[196,241] This organism is essentially an obligate udder pathogen in dairy cattle, remains superficial in mammary tissue, and has a high level of susceptibility to therapy. Thus *S. agalactiae* can essentially be eradicated from a herd by simultaneously treating all infected cows, including those with subclinical infections.[241,413] This can be economical for a dairy, but only if proper prevention programs (e.g., postmilking teat dipping, dry cow treatment) are in place to prevent new infections after herd treatment.[193] For this and other gram-positive pathogens, systemic administration of antimicrobial drugs is not likely to attain any better cure rates than intramammary infusions.

Therapeutic efficacy of other gram-positive cocci, with the exception of *S. aureus*, can also be efficacious in many cases. Only 10% to 20% of clinical mastitis caused by environmental streptococci is severe.[6] Similarly, the vast majority of clinical mastitis caused by NAS is mild to moderate. Intramammary infusion of commercial products is the treatment of choice, although some strains of streptococci have been reported to be resistant to cloxacillin and pirlimycin.[401,403] Likewise, studies of naturally occurring clinical streptococcal mastitis determined that intramammary pirlimycin or amoxicillin therapy attained bacterial cures of 70% to 75% of infected quarters as compared to cures of 29% to 39% in untreated quarters, respectively.[414] However, results can vary depending on the herd, and as mentioned earlier, the duration of infection at the time of treatment has a large impact on outcome. Cures following pirlimycin therapy for NAS did not differ from untreated controls in one study (about 45%).[415] Similarly, about 66% of subclinical quarters infected with streptococci or staphylococci cured whether treated with two doses of intramammary pirlimycin or not treated.[410]

Several studies have described the potential benefits of extended intramammary therapy (beyond the traditional two doses) for the treatment of mastitis caused by streptococci and *S. aureus*.[416-418] This may be appropriate from a pharmacodynamic standpoint as all antimicrobial drugs that are labeled for intramammary use in dairy cattle (U.S.) rely on time-dependent inhibition of bacterial growth. Thus inhibitory action of the drug is more likely to be

efficacious if the concentration of the drug is maintained above the MIC for extended periods at the site of infection as opposed to at peak concentrations. Experimental *S. uberis* infections treated for 2, 5, or 8 days (q24h) with intramammary ceftiofur attained bacterial cures in 43%, 88%, and 100% of the infections, respectively.[419] Similar results were obtained for chronic streptococcal and *S. aureus* infections treated with intramammary pirlimycin.[416] In naturally occurring subclinical mastitis, two doses of intramammary ceftiofur cured 39% of infections that included all gram-positive cocci, as opposed to 66% for quarters treated with eight doses, but the sample was not sufficient to determine pathogen-specific effects.[420] However, other studies performed as noninferiority trials have found that a shorter duration of therapy (3 days) did not differ from a longer duration of therapy (5 days) relative to survival in the herd after therapy or rate of clinical cure.[206]

The decision to use extended therapy as part of a herd mastitis therapy protocol should be made carefully and when possible should be based on microbiological diagnosis (see the On-Farm Culture section earlier). The success of therapy with conventional dosing should first be considered. If deemed to be unsatisfactory, especially as indicated by high rates of relapses after therapy, extended therapy may be a viable choice. To date, the benefits of extended therapy have best been determined for infections caused by streptococci and *S. aureus*. One study has determined that extended treatment of mild cases of clinical mastitis caused by a variety of coliform bacteria increased bacteriologic cures and reduced culling but did not influence posttreatment milk yield or SCC, although the outcomes were highly herd dependent.[421] Furthermore, the ability of the herd personnel to perform aseptic infusions into the teat canal is critical. Extended therapy is associated with an increased risk of infection from opportunistic pathogens, and herds with poor infusion techniques are not good candidates for multiple doses of intramammary tubes.

S. aureus intramammary infections often result in deep-seated abscesses. Therapy is difficult, especially as resistance to antibacterials (particularly β-lactams) is more common as compared to streptococci, and *S. aureus* may survive intracellularly following phagocytosis where antibacterial concentrations are reduced.[400] In addition, *S. aureus* has numerous extracellular substances that impart an ability to survive in the presence of a hostile host immune system. Consequently, elimination of IMI caused by this pathogen is often not as successful as compared to IMI caused by other gram-positive pathogens.

Experimentally induced *S. aureus* IMI has a reported cure rate of 25% to 55% of infected quarters when evaluated 21 to 60 days after infection. However, natural infections are usually of longer duration before detection and subsequent therapy and thus more refractive to therapy. The importance of duration of infection was evident in a study that determined that intramammary penicillin and novobiocin cured 70% in quarters that had been infected for 14 days or less as compared to only 35% in chronically infected quarters.[422] Similarly, Barkema and colleagues[423] reported a wide variation in the success of therapy, near 60% in younger, newly infected animals as opposed to less than 5% in older animals with chronic infections. Even modest results of efficacy reported in the literature may be optimistic, as relapses occurring more than 30 days after treatment are common.[420] This not only reaffirms the difficulty in attaining successful therapy but also suggests a poor correlation between in vitro culture and susceptibility and therapeutic outcome in chronic IMI caused by this organism.[424]

Consequently, combinations of parenteral and intramammary treatment regimens have been advocated to eliminate a higher proportion of *S. aureus* infections. In experimental infections in lactating cows, the combined use of intramuscular procaine penicillin G and intramammary amoxicillin achieved a better cure rate (18 of 35 infected quarters) than intramammary amoxicillin did alone (10 of 40 infected quarters).[425] Dry cows with *S. aureus* IMI had improved cure rates when administered 11 mg/kg IM every 24 hours of oxytetracycline in addition to intramammary antibacterials as compared to cows administered intramammary infusions only.[426] Other studies have not found any benefit from systemic antimicrobial use to eliminate chronic infections caused by *S. aureus*.[427,428] In addition, systemic therapy for mastitis is extralabel drug use in the United States, and milk and meat withholding periods must be determined judiciously. Therapy should be administered for periods long enough (7 to 10 days) to allow effective elimination of the pathogen and would be more economical and less likely to result in residues in milk if this therapy is administered to dry cows. Depending on susceptibility testing, lipophilic antibacterial drugs that distribute well into mammary tissue, such as oxytetracycline, are the best candidates for systemic administration. Cure rates may not be much better than those attained from spontaneous cure, especially in chronic IMI, and as stated earlier, efficacy must be defined critically. Affected quarters should be monitored by culture or SCC for at least 60 days to encompass the refractory period when bacteria may not be isolated.

Using Bacteriology as a Criterion for Therapy.

Microbial culture of milk is a practical tool to identify causative agents and the foundation to better target therapeutic regimens for mastitis. A multistate study demonstrated that culture-based therapy of gram-positive and mixed isolates only, as compared to empirical therapy of all mild mastitis cases, reduced antimicrobial use by 50%.[155,163,166] Furthermore, no differences were found between mastitis cases that were assigned to the empirical therapy or culture-based treatment program in terms of recurrence of clinical mastitis (35% versus 43%), linear SCC (4.2 versus 4.4), daily milk production (30.0 kg versus 30.7 kg), and culling or death (28% versus 32%) for the rest of the lactation after the clinical mastitis case. This concept was further supported by a more recent study that found no significant differences existed between cows administered empirical therapy and culture-based therapy in days to clinical cure, milk production, survival in herd, or SCC.[429]

Thus selective treatment of mild clinical mastitis based on culture results does not affect long-term outcomes but does decrease antibiotic use. As mentioned earlier, most farms do not routinely culture milk from cows with clinical mastitis, but it is still important to determine the most frequent clinical mastitis pathogens in the herd to make appropriate treatment and prevention recommendations. It is also particularly important to determine if *Mycoplasma* species or opportunistic pathogens that are nonresponsive to antibiotic therapy are contributing to clinical mastitis.

Treatment of Severe Clinical Mastitis.

Clinical mastitis cases that include systemic involvement are considered severe (severity score 3).[205] Coliform organisms are the most common cause of severe mastitis in most dairy herds and are the common cause of cases that result in the loss of a cow from death or agalactia (see Tables 36.1 and 36.2).[6,430] Thus primary therapy for severe clinical mastitis should be directed against coliform organisms, although secondary consideration must be given to other pathogens. From a cow-side appraisal, treatment of severe clinical mastitis is a forced decision (i.e., empirical treatment is indicated). Although the basis for antimicrobial therapy is knowledge of the causative pathogen, this is not attainable for some hours after initial case recognition, and thus the practical problem is to design a therapeutic regimen on clinical impression. In addition, systemic antimicrobial therapeutic regimens currently are not labeled by the U.S.

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Food and Drug Administration (FDA). As a result, veterinarians often formulate therapeutic management of severe mastitis using extralabel drugs.

Experimental challenge models have clarified much of the pathophysiology of mastitis resulting from infection with gram-negative organisms.[99,263,387] Following infection, bacterial numbers in milk rapidly increase, and depending on the size of the challenge, peak bacterial concentrations in milk often occur within a few hours. Typically, a subsequent rapid decline in bacterial concentration follows neutrophil migration into the gland. Though often severe, experimental IMI caused by *E. coli* usually clears spontaneously and rarely is more than 10 days in duration. The resulting inflammation and leukocytosis in the affected quarter may persist for several weeks, or the quarter may become agalactic, despite the inability to isolate bacteria on culture. Although useful for determining the pathogenesis of coliform IMI, experimental challenge models should not be universally applied for therapeutic decisions. Most challenge infections do not include recently calved cows, use strains of bacteria that may not be as virulent as some of the wild types of pathogens, and are generally not administered if other possible immune stressors (metabolic or heat) are present. All of these variables could reduce the severity of clinical outcome for experimental as compared to natural infections. In addition, herd factors such as nutrition and housing can affect the outcome of naturally occurring infections, and host-adapted strains that may persist in affected cows have been identified.[282]

Many of the inflammatory and systemic changes that occur during severe coliform mastitis result from the release of LPS from the bacteria, which is released from the bacterial cell wall following phagocytosis and killing by neutrophils. As mentioned in the Mammary Inflammation section, LPS is a potent stimulator of the inflammatory cytokine response through the action of TLRs.[431-434] This results in subsequent activation of the cyclooxygenase and lipoxygenase pathways, releasing prostaglandins, leukotrienes, and thromboxanes, compounds that are potent mediators of local inflammatory and systemic circulatory events.[67] Also, endotoxin-induced cytokines, such as IL-1 and TNF-α, initiate a wide range of systemic responses, including fever, leukocytosis, protein synthesis and release by hepatocytes, and serum iron sequestration, collectively termed the acute phase response.[433,435,436] Although LPS concentration in the milk may be high, LPS is usually nearly undetectable in plasma.[437] This suggests that the fever, tachycardia, reduced rumen motility,

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and signs of shock that accompany severe coliform mastitis are not a consequence of endotoxemia but production and absorption of inflammatory mediators, such as TNF-α. The concentration of TNF-α in milk is positively correlated with coliform mastitis severity, and a high concentration of TNF-α in blood is seen only in severe responders.[87,266,438] Hematologic and plasma biochemical changes that often accompany clinical coliform mastitis include leukopenia (neutropenia, lymphopenia, monocytopenia), hypocalcemia, and reductions in plasma concentrations of zinc, copper, and iron.[268]

Consequently, in order to reduce the severity of acute coliform mastitis, either bacterial growth must be inhibited to reduce exposure of the quarter and the cow to LPS or the effects of the LPS release must be neutralized. From a practical standpoint, therapy of severe coliform infections cannot begin until clinical signs appear. Clinical recognition of coliform mastitis usually occurs after peak bacterial numbers have been attained. Thus by the time therapy is initiated, maximal release of LPS has likely occurred. This raises concerns regarding the advantages of antibacterial therapy in alleviating the effects of acute coliform mastitis. Thus the primary therapeutic concern is the treatment of endotoxin-induced shock with fluids, and other supportive care.

Antibacterial therapy may be of secondary importance relative to immediate supportive treatment of endotoxic shock, but it remains an integral part of a therapeutic regimen for severe mastitis. Because of low MIC for gram-negative rods relative to other antimicrobials, aminoglycosides were considered for many years to be a drug of choice for coliform mastitis. However, cows experimentally challenged with *E. coli* and dosed with 500 mg of intramammary gentamicin q12h did not have lower peak bacterial concentrations in milk, duration of infection, convalescent somatic cell or serum albumin concentrations in milk, or rectal temperatures as compared to untreated challenged cows.[439] In addition, gentamicin readily diffused through the milk-blood barrier as indicated by detectable concentrations in serum throughout the treatment period and the first 12 hours after the last dose. Consequently, urine gentamicin concentrations were detectable 14 days after the last infusion, and gentamicin concentrations of 1 µg/g in renal tissue were detected in cows 6 months after the trial.[439] As well, intramuscular gentamicin was not more efficacious in preventing agalactia or death resulting from severe coliform mastitis or in improving other clinical outcomes, as compared to cows receiving intramuscular erythromycin or no systemic antimicrobial therapy.[440]

Considering the lack of efficacy in controlled studies, increased sophistication of drug residue testing among regulatory agencies, zero tolerance for residues in renal tissue of culled cows, the 30- to 45-day half-life for clearance in the bovine kidney, and extended milk withdrawal periods after use of aminoglycosides, the use of this class of drugs in adult dairy cattle has little merit.

Seminal research from Colorado found that bacteremia occurs in nearly half of severe coliforms cases and increases with the severity of the clinical signs.[313,441] Numerous pathogens, in addition to mammary-derived coliforms, that are likely opportunistic invaders from the respiratory and gastrointestinal tract were also isolated from blood.[313] This is likely a consequence of the profound neutropenia that occurs in many severe coliform cases.[268] Cows that remain neutropenic for 4 or more days, or that have high metamyelocyte and myelocyte concentrations in their blood, are more likely to be bacteremic than cows with a normalizing leukon.[441] Bacteremia suggests a poor prognosis, and these cows are at greater risk of death or culling.[313] Thus a primary target of antimicrobial therapy for severe coliform mastitis should be highly perfused tissue and the selection of drugs that remain in the plasma compartment and have low MIC for gram-negative rods.

Three doses of parenteral sulfadiazine-trimethoprim failed to achieve clinical improvement in experimental *E. coli* infections.[442] However, three intramuscular doses of cefquinome, a fourth-generation cephalosporin that has better distribution into mammary tissue than sulfonamides, was found to improve clinical outcome of experimentally infected cows as compared to use of cloxacillin or ampicillin.[443] Further research confirmed the possible benefits of systemic antimicrobial administration; intravenous oxytetracycline improved the clinical outcome of cows with coliform mastitis (not necessarily severe) as compared to cows that did not receive systemic antibacterials.[444] Ceftiofur sodium, a third-generation cephalosporin, has been reported to have excellent activity against gram-negative pathogens, with a suggested MIC for *E. coli* of 0.25 to 1.0 μg/mL. Mammary tissue and milk concentrations of ceftiofur following systemic treatment remain below these concentrations, and treatment of mild clinical mastitis caused by coliform organisms with systemic ceftiofur did not affect clinical or bacteriologic outcome, probably due to the poor distribution of β-lactams into the mammary gland following systemic administration.[445,446]

However, in a study of naturally occurring cases in Michigan, cows with

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severe coliform mastitis that were administered intramuscular ceftiofur at a dose of 2.2 mg/kg once per day for 5 days were three times less likely to be lost from the herd and had significantly higher marketed milk than cows not receiving systemic antimicrobial therapy.[430] This strongly emphasizes the inclusion of bacteremia in therapeutic considerations for severe coliform mastitis.

Intramammary antimicrobial therapy should be administered for most severe mastitis cases, at least until bacterial culture results are determined. Numerous severe mastitis cases are caused by gram-positive cocci and can be difficult to distinguish from cases caused by coliforms at initial presentation. Chronic IMI caused by pathogens such as *S. aureus* can become acutely gangrenous at times of neutropenic dysfunction such as parturition.[86] Bacterial culture of cases can also help to identify other causative agents that are not likely to respond to antimicrobial therapy, including *M. bovis*, mycotic organisms, and *Prototheca* spp. Severe, overwhelming IMI that leads to bacteremia can occur from *S. marcescens*, *P. aeruginosa*, and *Bacillus cereus*.

Thus therapeutic regimens for severe clinical mastitis should (1) administer supportive care, especially for those cows displaying shock; (2) target antibacterial therapy to maintain effective concentrations in plasma with a drug that has a broad spectrum of activity; and (3) administer intramammary antibacterial drugs to reduce the effects of a gram-positive IMI, unless bacteriologic results suggest otherwise.

Summary of Antimicrobial Therapy

Judicious antibiotic use is necessary for successful mastitis treatment programs. Case selection is critically important to avoid unnecessary antibiotic use, which is costly to the producer and of concern to the public. When producers are unwilling or unable to use culture results as the basis for treatment determination, a decision may be necessary to avoid treatment completely or, alternatively, to treat all cows empirically. Antibiotic selection and the timing, dose, frequency, and duration of treatment affect the outcome. Therefore antibiotic treatment protocols should be designed with veterinary input and monitored for efficacy. Monitoring requires that farm personnel record the incidence, severity, and duration of clinical mastitis, as well as the treatments administered. The occurrence of relapses, SCCs, and targeted milk bacteriology also facilitate assessment of treatment efficacy.

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Mastitis Therapy: Supportive Treatment.

A variety of supportive measures are used in cows with severe clinical mastitis, often in conjunction with antibiotic therapy. Fluids and electrolytes are administered to correct circulatory and electrolyte disturbances (also see Chapter 44). Steroidal and nonsteroidal antiinflammatory agents are used to reduce pain, inflammation, and fever. Dairy producers and veterinarians use many other systemic and local treatments, most of which have not been scientifically evaluated or shown to be effective. This section discusses the most frequently used supportive treatments.

Fluid and Electrolyte Therapy.

Cows with severe clinical mastitis can develop fluid and electrolyte disturbances as a result of decreased feed and water intake, rumen stasis, ileus, and diarrhea. Severely affected cows, particularly those with coliform mastitis, may develop septic or endotoxic shock; death or organ damage can result from decreased effective circulating volume.

The hydration status of an adult cow is assessed subjectively by observing skin tent duration on the neck or eyelid and position of the globe in the orbit. Unfortunately, findings can be influenced by the body condition of the cow. Objective criteria for estimating the extent of dehydration have been reported for dairy calves but have not been established for adult cows.[447] Extrapolating from calves, a healthy cow should have cervical skin tenting of 2 seconds or less and no recession of the eyeball. Skin tent durations of 4, 6, or 8 seconds and eyeball recession of 2, 4, or 7 mm would correlate with 4%, 8%, and 12% dehydration, respectively. Indicators of reduced peripheral perfusion are cold extremities (ears, tail, fetlocks—only reliable at moderate ambient temperatures) and a dry muzzle or mouth.[448] Hematocrit and plasma protein concentration are not reliable indicators of hydration status in an individual cow because of the wide range of normal values and the effects of inflammation and stage of lactation on total protein concentration.

Most cows with clinical mastitis, even severe mastitis, have normal acid-base balance or metabolic alkalosis; metabolic acidosis is uncommon and associated with a poor prognosis.[441,449] Therefore there is no need for routine IV administration of alkalizing agents, such as bicarbonate or lactate. Also, oral products containing magnesium hydroxide or sodium bicarbonate should not be administered.

Fluids can be administered by the oral (intraruminal) or IV route. The oral route is least expensive and is often adequate for cows with mild to moderate dehydration. Oral fluids should be hypotonic or isotonic and should contain sodium, to create an osmotic gradient between rumen fluid and blood and enable sustained absorption of fluid and electrolytes; hypertonic oral fluids should be avoided.[450] A 600-kg cow that is 6% dehydrated needs to absorb 36 L of fluid to replace her deficit. This volume can be safely administered orally, but administration of larger volumes of hypotonic fluid may lead to intravascular hemolysis.[451] Oral fluids are not sufficient for cows with severe dehydration because they do not cause rapid resuscitation.

Ringer's solution, which is an isotonic (isosmotic), mildly acidifying solution that contains physiologic concentrations of sodium, chloride, potassium, and calcium, is the fluid of choice for rapid IV resuscitation of adult ruminants.[450] Isosmotic (0.9%) sodium chloride is an alternative that can easily be constituted using table salt and distilled water in a sterile carboy. However, administration of isosmotic crystalloid solutions is impractical in many situations because of the large volume of fluid required and the need for IV catheterization. A 600-kg cow that is 10% dehydrated requires 60 L of fluid to replace her deficit.

A more practical alternative for on-farm therapy to isosmotic IV fluid therapy is IV administration of hypertonic (7.2%, 2460 mOsm/L) saline. Hypertonic saline is administered through a large-bore needle at 4 to 5 mL/kg body weight over 4 to 5 minutes, in conjunction with oral administration of water (5 gal). Rapid administration of hypertonic saline is required to effectively create an osmotic gradient that draws fluid from the intercellular spaces and gastrointestinal tract (mainly rumen) into the vasculature. Although hypertonic saline does not have a sustained effect and will not completely correct a large fluid deficit, it rapidly increases plasma volume and improves cardiac output and tissue perfusion. Hypertonic saline has been shown to be safe in cows with endotoxic mastitis.[452,453]

Mild to moderate hypocalcemia often accompanies clinical mastitis, with the odds of hypocalcemia increasing with the severity of mastitis,[145] although other serum electrolytes are variable. Affected cows may show muscle tremors or weakness but are seldom recumbent. Calcium supplementation can be by the oral, subcutaneous (SC), or slow IV route, depending on the severity of clinical signs and the product used. Anorexic cows often become hypokalemic, especially if anorexia persists for several days. Hypertonic saline administration

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also causes a transient reduction in serum potassium concentration. Potassium chloride can be supplemented orally at a rate of up to 240 g divided two to three times daily, with lesser amounts (30 to 120 g) being satisfactory for mild to moderate hypokalemia.[454] Sodium and chloride derangements are usually mild and can be addressed by administering balanced oral or IV fluids or hypertonic saline. Blood glucose concentration is usually normal or high in cows with clinical mastitis, so dextrose should not be administered routinely. However, IV dextrose treatment may be warranted in cows with concurrent ketosis.

Anti-inflammatory Drugs.

Most of the physiologic and pathologic changes associated with clinical mastitis are a result of the inflammatory response to infection. Therefore it is logical to administer anti-inflammatory agents. Also, anti-inflammatory agents can reduce the pain associated with clinical mastitis.[455] However, the inflammatory response is necessary for resolving intramammary infection, and anti-inflammatory agents can produce detrimental side effects. Many of the agents used in other countries are not labeled for use in lactating dairy cows in the United States. The choice of anti-inflammatory agents in the United States is limited to three approved drugs—dexamethasone, isoflupredone acetate, and flunixin meglumine—although none is approved for the treatment of severe clinical mastitis.

Dexamethasone and isoflupredone acetate are inexpensive steroidal anti-inflammatory agents that have no milk-withholding requirement. Glucocorticoid drugs inhibit the production of inflammatory molecules and the adhesion molecules that facilitate transport of inflammatory cells from the bloodstream to the site of inflammation. Glucocorticoids also help to maintain microcirculation and cell membrane integrity, interfere with dissolution and disruption of connective tissue, decrease formation of histamine by injured cells, and antagonize toxins and kinins. These actions of glucocorticoid drugs could be expected to benefit mastitic cows, particularly those with mastitis caused by endotoxin-producing coliform bacteria. Glucocorticoids prevent arachidonic acid release by stabilizing cell membranes and by inducing lipocortin production. Lipocortin prevents phospholipase A2 from contacting cell membrane–associated arachidonic acid and effectively limits the precursor needed for eicosanoid production.[456] In addition, endogenous cortisol release has been identified as playing an important role in downregulating neutrophil trafficking

into the site of infection and production of inflammatory cytokines.[68]

Data on the efficacy of steroidal anti-inflammatory agents for treatment of clinical mastitis are limited to experimental mastitis trials. A single, 30-mg IM dose of dexamethasone given at the time of *E. coli* inoculation reduced local signs of inflammation, tachycardia, rumen motility impairment, and 14-day milk production loss, compared with untreated controls.[457,458] A large IV dose of dexamethasone (0.44 mg/kg) given to goats 12 hours after *E. coli* infusion reduced fever and appetite suppression but had no effect on heart rate, rumen contractions, serum biochemical parameters, SCCs, milk yield, or histopathologic changes.[459] Isoflupredone acetate (20 mg IV) administered to endotoxin-challenged cows after the onset of clinical mastitis had no beneficial effect on systemic parameters, mammary gland swelling, or milk production, compared with untreated controls.[460]

However, each of these agents has potential adverse effects. Dexamethasone can cause abortion in pregnant cows, especially after 5 months of gestation, although this would be less of a concern for cows in early lactation. Repeated dosing (0.04 mg/kg IM for 3 days) of cows with subclinical intramammary infections resulted in increased bacterial shedding and development of clinical mastitis.[461] Perhaps more problematic is the use of isoflupredone acetate because this drug reduces plasma potassium concentration and repeated doses can lead to severe hypokalemia and recumbency.[462-464]

The above studies suggest that the most likely benefit for corticosteroid treatment would be for severe coliform mastitis, and delays in therapy relative to the onset of infection may hamper efficacy. Nonetheless, dexamethasone is a potent anti-inflammatory agent, and it is difficult to extrapolate the benefit for cattle in terms of improved attitude and shock mitigation from experimental mastitis trials to naturally occurring clinical mastitis. Because of mineral corticoid effects on serum potassium, dexamethasone may be preferred over isoflupredone. In addition, corticosteroid use in chronic IMI should be contraindicated.

A variety of nonsteroidal antiinflammatory drugs (NSAIDs) are used to treat clinical mastitis worldwide.[455] However, only flunixin meglumine is approved for use in lactating dairy cows in the United States. Dipyrone and phenylbutazone are banned, and other NSAIDs can be used in an extralabel manner only if appropriately justified. The NSAIDs are not immunosuppressive but carry a risk of abomasal ulceration and renal damage. These complications

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are not well documented in cattle and presumably are minimized if treatment is of short duration, hydration is maintained, and appetite is restored. The primary mode of action of NSAIDs is to inhibit the synthesis of prostaglandins and thromboxanes by inhibition of cyclooxygenase. NSAIDs also inhibit the formation of prostaglandin E2 in the brain, which effectively reduces fever.[465]

Treatment of cows with flunixin meglumine at 0 and 3 to 5 hours after *E. coli* inoculation abolished fever and improved rumen motility, compared with untreated controls, but had no effect on gland or milk appearance, heart rate, or respiratory rate.[466] Similarly, administration of flunixin meglumine every 8 hours beginning 2 hours after endotoxin infusion reduced fever and improved gland appearance and attitude, compared with untreated controls, but had no effect on milk appearance, heart rate, rumen motility, SCC, or milk production.[467] When administered after the onset of fever and gland swelling, flunixin meglumine (2.2 mg/kg IV) reduced heart rate and rectal temperature and increased rumen motility in cows with endotoxic mastitis but had no effect on milk production or mammary gland inflammation.[468] As with the steroids, the relevance of these trial results to cows with naturally occurring clinical mastitis is uncertain. Meloxicam, administered at a dose of 0.5 mg/kg subcutaneously, was found to have a beneficial effect in relieving pain, decreasing udder edema, and reducing body temperature response following an LPS-induced clinical mastitis.[468a] Although not labelled for use in cattle in the United States, this drug may have potential in the future for analgesia and as an anti-inflammatory agent. It appears that NSAIDs can improve well-being and outcome in cows with clinical mastitis. However, specific criteria for instituting NSAID therapy, the timing of therapy relative to infection onset, and the optimal duration of treatment remain to be determined.

Oxytocin and Frequent Milking.

Oxytocin is administered to stimulate milk ejection and facilitate removal of secretions from mastitic mammary glands. Frequent milk-out (stripping) reputedly augments the removal of pathogens, toxins, and inflammatory mediators from the mammary gland. Although these are seemingly logical practices, no solid evidence exists to support their routine use, and some data suggest they can be detrimental. Oxytocin (20 IU IM twice daily for 3 days) at milking time prevented development of clinical mastitis in only two of eight cows experimentally inoculated with *S. uberis;* once clinical mastitis developed,

oxytocin was ineffective at resolving the *S. uberis* infections.[469] When initiated at the onset of clinical *S. uberis* mastitis, oxytocin (80 IU IM, followed by 20 IU IM twice daily) resulted in no clinical or bacteriologic cures by 3 or 6 days.[470] In contrast, clinical and bacteriologic cure rates of 91% and 64% were achieved by intramammary antibiotic administration by 3 and 6 days, respectively. When oxytocin was used in conjunction with intramammary antibiotics, clinical and bacteriologic cure rates at 6 days dropped to 10%, implying a significant adverse effect of oxytocin and stripping. Frequent milk-out (every 4 to 6 hours) in conjunction with oxytocin administration did not shorten the time to clinical or bacteriologic cure or resolution of systemic illness in cows with experimentally induced coliform mastitis, compared with no treatment.[471] When oxytocin administration (100 IU IM twice daily for 1 week) was compared with no treatment (udder massage only) in cows experimentally inoculated with *S. aureus*, oxytocin administration reduced bacterial concentrations in the milk but did not improve the bacteriologic cure rate or reduce SCCs.[472] Oxytocin administration increases the permeability of mammary epithelial tight cell junctions in a dose-dependent manner, which can alter milk composition in nonmastitic glands, particularly if high doses (100 IU) are administered repeatedly.[473]

Oxytocin and frequent milk-out have not been evaluated extensively in the field. In a California study, oxytocin (100 IU IM twice daily for three treatments) at milking time resulted in similar clinical and bacteriologic cure rates, as compared to intramammary antibiotics, although an untreated control group was not evaluated.[474] However, no overall benefit resulted because the oxytocin-treated cows had a higher recurrence rate of clinical mastitis, particularly environmental streptococcal mastitis.[475] In a Virginia study, frequent milk-out (six times daily) in conjunction with oxytocin administration (20 IU) did not improve clinical or bacteriologic cure rates, time to cure, or return to milk production compared with no treatment.[471] In an Illinois herd, cows treated with supportive therapy alone (oxytocin administration [all cases], frequent milk-out [moderate and severe cases], anti-inflammatory therapy [severe cases], and fluid therapy [severe cases]) had lower clinical and bacteriologic cure rates and a higher recurrence rate than cows given antibiotics in addition to the same supportive therapy.[444] Furthermore, two studies have cited that 50 IU of oxytocin administered q12h for 19 or 22 days increased residual (nonharvested) milk by 15% at each milking.[476,477] Bruckmaier[476] noted, “Cows increasingly

refused to enter the milking parlor voluntarily and had to be fetched by the milker and cow entry into the parlor remained disturbed for up to one week after the end of injections."

In summary, oxytocin administration and frequent milk-out are not likely to be effective standalone treatments for clinical mastitis, particularly mastitis caused by streptococci, and may even be detrimental. In certain circumstances, when a cow clearly will not eject milk or when garget in the milk prevents effective milk removal, these practices may be of some benefit. Otherwise, unnecessary administration of oxytocin injections and frequent milking of painful teats should be avoided for welfare reasons. Sustained use of this drug as a routine therapy is a poor substitute for good milking preparation and will likely incite cows to be reluctant to enter the milking parlor and milk out effectively, which is the opposite of therapeutic intentions with this drug.

Prevention and Treatment of Mastitis During the Dry Period

The dry (nonlactating) period of the lactation cycle is a critical time for udder health in dairy animals. The major proportion of calf growth occurs during this time, and metabolically this is the most critical time for the cow to prepare for the next lactation. Prevention of new infections during the dry period hinges on prevention of teat end exposure to environmental pathogens. Rates of new IMI of coliforms are thought to be greater in the dry period than during lactation.[58] Thus the same management practices (i.e., maintaining cows in clean, dry, comfortable housing) that prevent infections from these organisms in lactating cows apply to dry cows. The importance of dry cow management is apparent from studies that found that nearly two thirds of clinical coliform mastitis cases in the first 2 months of lactation were newly acquired infections during the dry period.[261] The rate of environmental streptococcal IMI was 5.5-fold greater during the dry period as compared to during lactation.[261]

During involution, the mammary gland undergoes marked biochemical, cellular, and immunologic changes. Involution of the mammary parenchyma begins 1 to 2 days after the end of lactation and continues for 10 to 14 days. During this time, the gland is particularly vulnerable to new IMI; in conjunction with the periparturient period, these times represent the greatest risk for new IMI in the lactation cycle of the cow.[478] The most important defense, as with lactating cows, remains the teat canal. When a cow is dried off at the end of lactation, the teat canal does not fully fill with keratin for days to months. This

contributes to the risk of infection during mammary involution, and cows that have higher milk production at dry-off are more at risk to have teats remain open throughout the dry period.[479,480] Leukocytes increase to millions per milliliter as involution progresses and then decrease prepartum. Macrophages are predominate in lacteal secretions, followed by lymphocytes and neutrophils.[478] Lactoferrin is also associated with resistance to infection during the nonlactating period.[478] Lacteal immunoglobulins increase throughout involution and function by opsonizing bacteria, neutralizing toxins, and preventing bacterial adherence.[478] Consequently, the dry period is an ideal time to attain synergy between antibacterial therapy and immune function to eliminate pathogens from the gland and not incur the extensive costs of milk withholding typical of lactating cow therapy.

Intramammary administration of antibacterials at the end of lactation (dry cow therapy) has been a standard of dairy mastitis management for 40 years, particularly as a tool to help reduce the prevalence of contagious mastitis. Cure rates for IMI caused by all gram-positive cocci (those IMIs that existed prior to the dry period but were not detected following calving), as with lactational therapy, vary from farm to farm and are dependent on pathogen. A New Zealand study determined that dry cow therapy eliminated 85%, 90%, and 90% of IMIs caused by *S. aureus*, *S. uberis*, and *S. agalactiae*, respectively, as opposed to spontaneous cures of 31%, 50%, and 29% in untreated controls.[481,482] Cures for chronic *S. aureus* IMI or gram-negative organisms may be considerably less.[427] However, a ceftiofur dry cow therapy is now labeled for use in North America, and a previous study found that cows that were dry-cow treated with a product with significant activity against gram-negative bacteria (100 mg framycetin, 100 mg penethamates, and 300 mg procaine penicillin) had decreased clinical coliform mastitis during the dry period and early lactation as compared to cows treated with cloxacillin.[273]

Because of concern regarding overuse of antibacterial drugs and potential effects on antimicrobial resistance of bacteria, selective dry cow therapy (treatment of infected cows only) versus total or blanket dry cow therapy (treatment of all cows) is debated. Although this approach does have the potential to reduce antimicrobial drug use on a dairy farm, it must also be considered how historically successful blanket dry cow therapy has been in both eliminating and preventing IMI during the dry period. Decisions should be carefully made on an individual herd basis, and results should be monitored to

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determine the success of a dry cow mastitis program based on new IMI during the dry period, probably best monitored by changes in individual cow SCCs, cures of existing infections, and impact on the rate of clinical mastitis, particularly in early lactation. If herds are considering selective dry cow therapy, it is important to consider the ability of the herd to control mastitis (i.e., herds that have BTSCCs >200,000 cells/mL should be advised to reconsider this approach). In addition, not only metrics for outcomes following adoption of selective dry cow therapy should be monitored, but also the criteria for selection of cows that should be either included or excluded for dry cow therapy.[140] Herd-specific algorithms should be designed that include at the very least individual cow SCC status before dry-off and clinical mastitis history during the previous lactation, and preferentially bacterial culture status of cows with low SCCs that might be considered to exclude from treatment. Examples of outcomes and various models for selective dry cow therapy have been reported, but the emphasis must be placed on both protocols and outcomes, which will vary greatly depending on the herd.[483-485]

In addition to the role that dry cow therapy has in eliminating existing IMI, one dry cow therapy is also thought to prevent new IMI. Early studies suggested that dry cow therapy reduced new IMI during the dry period by 50%.[482] Overall rates from multi-institution studies reported new IMI rates during the dry period as 11% to 25% of quarters in herds that practiced blanket dry cow therapy.[486] Intramammary infusion of tilmicosin reduced new infection rates by more than 33% in a Canadian study.[486] In addition, selective dry cow therapy can result in more clinical mastitis in the dry period, more new IMI during the dry period, and subsequently more clinical mastitis in early lactation as compared to cows treated with blanket dry cow therapy.[487] An internal teat sealant consisting of a bismuth subnitrate paste in a paraffin base has gained wide acceptance on many dairies to create a barrier in the teat canal during the dry period following intramammary infusion. This is an inert product with no activity or food residue risks. Numerous field studies have confirmed the efficacy of this product to reduce new infection rates over the dry period, especially when used in conjunction with antimicrobial dry cow therapy. As an example, following intramammary cloxacillin at dry-off, the combined use of the teat sealant and antimicrobial infusions resulted in 30% fewer new IMIs during the dry period and 33% fewer clinical mastitis cases from drying off until 60 days in milk, as compared to quarters that were infused with cloxacillin only.[272]

As with lactational therapy, the use of systemic administration as an adjunct to intramammary administration has stimulated interest in potential alternative therapeutic regimens. Subcutaneous norfloxacin nicotinate administered at the start of the dry period achieved a better cure rate and lower new infection rate over the dry period for *S. aureus* infections, as compared to untreated cows and cows administered intramammary cephapirin benzathine preparations.[488] However, in a Michigan study, cows administered intramuscular oxytetracycline and intramammary cephapirin did not have better cure rates for quarters infected with *S. aureus* than cows treated with cephapirin only, although this study was performed in a herd that had 50% of the cows infected with *S. aureus* with a history of long duration of infection.[427] Systemic therapy should be reserved for use in dry cows for animals of exceptional value and for infections for which cures are deemed to be difficult to attain (i.e., chronic infections). However, success rates are likely to be low and in most cases will not be worth the injection and withholding time risks, especially if extralabel drugs are administered.

Epidemiology and Management of Mastitis in Heifers

Mastitis in heifers is rarely apparent prior to calving, but few farms actively look for mastitis before parturition. Although many farms raise healthy dairy heifers, in some studies bacteria have been isolated from more than 50% of quarters of prepartum heifers.[489-491] Reviews of heifer mastitis studies indicate that the prevalence of mastitis pathogens recovered from mammary secretions obtained before the first parturition ranged from 29% to 74%, whereas the prevalence of infection at first calving ranged from 12% to 57%.[227,492] Recovery of *Mycoplasma* organisms from milk samples was not included in these studies.

Staphylococci (primarily NAS but also *S. aureus*) are the most frequent isolates recovered from heifers, but environmental pathogens such as streptococci are also frequently recovered.[227] NAS are the most common pathogens recovered from heifers and a variety of NAS species have been recovered from teat skin, the streak canal, and precalving udder secretion obtained from heifers.[227] While NAS is the most common group of bacteria recovered from postpartum heifers, many of the apparent IMIs spontaneously disappear within the first week after calving. One study indicated that 41% of mammary quarters had NAS infections between days 1 and 4 post calving but 46% of those infections had spontaneously disappeared by days 5 to 8 post

calving.[493] However, some herds may experience persistent infections with NAS in heifers, resulting in increased SCC values and potentially decreased milk production. These herds require interventions to limit long-term effects on milk quality and production.

Detection of *S. aureus* in dairy heifers usually indicates that a significant number of lactating cows are infected. Although many herds have controlled *S. aureus*, regional differences in the prevalence of infected dairy heifers have been reported.[492] The exact mechanism of how nonlactating heifers develop *S. aureus* infections is not known, but studies have demonstrated that teat canals of heifer calves can become colonized at very young ages.[494] *S. aureus* can spread to heifers when they are fed nonpasteurized milk or colostrum or when calves come in contact with objects contaminated with infected milk.[495] While ingested milk is not transmitted directly from the digestive tract to the mammary gland, it is possible that calves may lick their udder or legs and colonize the teat skin, eventually leading to increased risk of infection. *S. aureus* can also be transmitted to heifers during the immediate pre- or postpartum period. Commingling ill animals and periparturient heifers may result in exposure to infected secretions (milk, blood, feces, etc.) from sick animals. These secretions may remain infectious for variable periods of time (depending on the characteristics of the organism, the type of bedding, and the environmental conditions) and serve as a point of exposure. Milking heifers using equipment that previously has been used on infected cows is also a common route of exposure. Several studies have demonstrated that biting flies can play a role in the transmission of *S. aureus* between infected and healthy heifers.[496] It is thought that flies congregating on teat ends of infected cows can become contaminated with bacteria present in milk droplets and mechanically transfer the bacteria when they land on the teats of uninfected animals.

M. bovis is an important pathogen that often affects heifers. This organism is associated with respiratory disease, ear infections, joint infections, mastitis, and other diseases of dairy calves and cows.[497] *M. bovis* dwells primarily in the respiratory tract of cattle, often without causing apparent clinical disease in the host.[298] This organism is unique in that respiratory infections can spread through the lymphatic and blood streams to infect other mucosal tissue such as the udder. Animals colonized with *M. bovis* can develop long-term infections and infect other animals. *M. bovis* is usually introduced into herds by clinically healthy cattle that are carriers of the organism,[497] and bulls have been demonstrated to

be carriers.[498] *M. bovis* has been demonstrated to colonize developing udders of prepubertal heifers and eventually cause mastitis.[499] The feeding of waste milk from infected cows has long been considered a primary route of infection with *M. bovis.* Commingling of calves from different sources has consistently been identified as a risk factor for infection with this organism. Control of *M. bovis* in heifers is based on reducing the potential for contact with potentially infected shedders of the organism and ensuring that calves never receive unpasteurized milk. The organism's ability to colonize the respiratory tract of cattle also requires strict attention to limiting the potential for airborne transmission, thus adequate ventilation, isolation of calves from older animals or ill calves, and reduced stocking densities are commonsense precautions.

Risk Factors for Mastitis in Heifers.

Most risk factors that contribute to the development of mastitis in heifers are related to exposure of heifers to mastitis-causing organisms. The exception to this is the occurrence of udder edema. Calves that are group-housed have the opportunity for cross-suckling, leading to increased risk for transmission of contagious pathogens.[500] Several studies have shown that contact of heifers with older cows before calving (even housing in the same barn) increases the risk of clinical mastitis after calving, and separation of heifers from older cows is generally recommended.[501] The hygiene of the environment is also an important determinant of the risk of developing mastitis in heifers, and this is true for heifers raised on pasture as well as heifers raised in confinement.[502]

Prevention of Mastitis in Heifers.

Prevention of mastitis in heifers is based on reducing exposure to mastitis pathogens and enhancing the ability of the heifers' immune system to respond to exposure. Prevention of mastitis in heifers includes the following strategies: (1) Controlling the prevalence of mastitis in the existing adult herd—exposure to contagious mastitis is more likely to occur when many animals are infected as compared to when few animals are infected; (2) using individual stalls for preweaned calves; (3) culling calves that persist in suckling other calves; (4) feeding milk replacer or pasteurized milk from healthy, uninfected cows rather than waste milk; (5) controlling flies—especially important in the control of *S. aureus;* (6) milking fresh heifers first using clean milking equipment; (7) calving heifers in clean pens that have not been used to house sick cows; (8) housing

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growing and prepartum heifers in an adequately bedded area that is clean and dry and provides sufficient space for all animals; (9) feeding a well-balanced diet that enhances the immune systems of the heifers—recommended values include 1000 IU per day vitamin E during the prefresh period and adequate selenium; (10) boosting the immunity of heifers by using gram-negative J5 vaccines, which work to reduce the severity of infections caused by gram-negative bacteria such as *E. coli;* and (11) considering prepartum teat dipping several times a week for problem herds[503] or the use of internal teat sealants administered about 1 month before calving.[504]

Prepartum Treatment of Heifers.

Intramammary therapy with antibiotics is one of the tools used to control mastitis in heifers.[494] Intramammary treatment of prepartum heifers is generally considered efficacious in reducing the prevalence of infection, can result in a reduction of SCC, and in some cases has been shown to increase milk production in the subsequent lactation.[496,505-508] However, research shows that the production response is highly variable among herds and this strategy should be routinely recommended only for herds that have demonstrated problems with heifer mastitis.[509] Oliver and colleagues[510] reported cure rates of 84% and 97%, respectively, for heifers infected with NAS that received intramammary treatment using 200 mg of either sodiumcloxacillin or cephapirin sodium; the spontaneous cure rate was 27% for heifers in an untreated control group. Research has shown that administration of intramammary antimicrobial treatments during late gestation is generally highly effective and cure rates for staphylococcal infections frequently exceed 90%.[510] Intramammary products designed for both lactating and nonlactating cows (dry cow products) have been evaluated for use in precalving heifers.[494] In virtually all instances, high rates of bacteriologic cure have been reported. No significant difference in treatment efficacy was found based on treatments given during the first, second, or third trimester of pregnancy, but fewer new *S. aureus* infections were reported for animals treated in the third trimester.[506,511] However, to minimize the potential for residues after calving, treatments should be administered at least 60 days before the expected due date, and milk should be checked for residues after calving. Unlike intramammary treatments, systemic antibiotics administered to heifers have not been shown to be effective in reducing the incidence of mastitis.[512] The effect of precalving treatment on production of heifers appears

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to be variable among herds and is not performed without introducing the risk of infections caused by improper administration of the intramammary tubes. The administration of internal teat sealants or intramammary antibiotics should occur only under hygienic conditions and after effective sanitation of teat ends. This practice is generally recommended only for herds that have demonstrated problems with mastitis in heifers.

Other Conditions of the Mammary Gland

Udder Edema.

Dairy cattle frequently develop physiologic edema of the udder during the periparturient period, and heifers have increased incidence of this disorder. Physiologic udder edema must be differentiated from *pathologic* edema, which can accompany mastitis and diseases of other body systems. *Physiologic* udder edema is symmetric, is cool to the touch, and pits on palpation. It can be limited to the udder or extend cranially along the ventrum or into the perineal region. In contrast, the edema that accompanies mastitis is more focal, is asymmetric, and is accompanied by abnormal milk and an inflamed mammary gland. Intermandibular and brisket edema, which are often observed in cows with congestive heart failure or severe hypoproteinemia, do not occur in cows with physiologic udder edema.

In most cases, physiologic edema is of little consequence and resolves spontaneously after parturition. However, treatment is recommended if the udder becomes excessively large and heavy, because this threatens the integrity of the udder suspensory apparatus and predisposes to teat injury and mastitis. Severe edema also can hinder ambulation or impair milking or nursing of the teats. If the edematous udder impinges on the skin of the thigh, moist dermatitis and secondary infection may develop, and the skin may slough; this condition is referred to as *udder scald.*

The mechanism(s) of physiologic udder edema is uncertain. Supplementing the ration of prepartum dairy cows with high concentrations of sodium or potassium salts significantly increases the incidence and severity of edema.[513,509] However, serum biochemical values and fractional clearance of electrolytes are similar in affected and nonaffected cows.[514] Increased capillary hydrostatic pressure (resulting from changes in mammary blood flow and intramammary pressure that occur around parturition) might be involved, as

might incompetent valves in the cranial superficial epigastric veins draining the udder. Cows with udder edema have higher blood pressure in the cranial superficial epigastric veins than do unaffected cows, and blood pressure is inversely related to mammary blood flow.[515] Poor udder suspension can also predispose to physiologic udder edema.

First-calf heifers and high-producing cows are at greatest risk of developing udder edema. Other risk factors are not well documented. In a case-control study of heifers in Florida, the risk of udder edema increased as height of the heifer increased, was higher if calving occurred in winter than in summer, and was higher if the fetus was male rather than female.[516] Heifers with udder edema in the first lactation were more likely than unaffected heifers to develop edema in subsequent lactations.[516]

Treatment of udder edema includes preventing excessive salt intake and administering a diuretic. In the United States, furosemide is labeled for use in dairy cows, has 48-hour milk-withholding and slaughter-withholding times, and is the diuretic of choice for treating udder edema. In one study, high cranial superficial epigastric venous pressure in cows with udder edema was reduced by IV administration of furosemide (500 mg) but not by hydrochlorothiazide (250 mg) or acetazolamide (500 mg).[507,515] Repeated administration of furosemide for several days should be avoided, but if repeated dosing is necessary, cows should be monitored for signs of electrolyte imbalance. Although corticosteroids have been recommended for treatment of udder edema, their efficacy is questionable. Prepartum milking reduces the severity of edema[517] but also decreases colostral immunoglobulin concentration at calving, so an alternative source of colostrum is needed. Prepartum milking of affected heifers has also been shown to reduce the risk of developing mastitis, but care should be taken to manage energy balance to prevent the development of ketosis.[500] Milking first lactation animals four times daily did not reduce or increase udder edema scores.[518] Increased milking frequency or other testimonial treatments such as exercise have not been demonstrated to reduce udder edema. Udder supports are available for cows with extremely pendulous or heavy udders.

Bloody Milk.

It is not uncommon to observe blood in postpartum mammary secretions. Small vessels may rupture as a result of trauma or in conjunction with udder edema. The milk is usually light pink to red or brown and may contain small blood clots.

Antibiotic treatment is not indicated. Bloody milk can also accompany severe clinical mastitis or gangrenous mastitis, both of which have a poor prognosis, but physical examination of the animal will identify these conditions.

Bloody milk should be withheld from sale for human consumption. The milk usually returns to normal appearance within 1 week. However, because blood contains natural antimicrobial inhibitors, bloody milk may cause false-positive antibiotic residue test results. The IgG1 concentration of bloody colostrum is similar to that of normal-appearing colostrum, meaning that it is not necessary to discard colostrum simply because it contains blood.[519]

Teat and Skin Conditions.

Several noninfectious diseases of teats are recognized to occur.[55] The color and condition of teats can be influenced by milking equipment, overmilking, use of caustic chemicals, or environmental conditions. The development of hyperkeratosis of the teat ends is not uncommon and occurs more commonly during winter months. Hyperkeratosis is a thickening of skin that lines the teat canal and is the result of a localized hyperplasia of the stratum corneum.[48,55,520] Mild hyperkeratosis is a normal physiologic response to forces applied to the teat during milking and does not increase the risk of IMI. However, moderate and severe hyperkeratosis can become a problem. Various scoring systems have been developed to assess teat end health. In general, teats are scored on a 1 (N = no ring) to 4 (VR = very rough ring) based on the teat end callosity observed. It is recommended that herds have less than 20% scores of 3 (R = rough ring) and 4 and less than 10% scores of 4.[55] Rough teat ends not only are difficult to clean but also provide a surface for pathogenic bacteria to harbor. Hyperkeratosis is a multifactorial problem, and risk factors must be determined and addressed for individual farms. Areas to investigate that may resolve a problem with hyperkeratosis include liner compression, excessive teat end vacuum or overmilking, environmental conditions, and use of teat dips that do not provide sufficient skin conditioning.

Infectious lesion of teats have been associated with several viruses. Pseudocowpox is caused by a paravaccinia virus that can cause acute infection in cattle. This disease results in lesions that include center vesicles that ulcerate to form scabs. As the lesions heal, they result in a characteristic ring or horseshoe-shaped scab. This virus can affect the hands of milking technicians. Diagnosis is based on observation of lesions on the hands of milking technicians and teats.

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The condition is generally self-limiting within 3 to 5 weeks.

Bovine herpes mammillitis has been associated with both herpesvirus type II and herpesvirus type IV. The resulting lesions appear similar and can occur either sporadically or in an outbreak. These viruses can present with a wide range of symptoms ranging from mild edema to the development of vesicles that result in severe ulceration and the formation of painful scabs. This condition appears to be more common during winter months. Diagnosis is based on observation of clinical signs and can be confirmed by histopathology. There is no effective therapy, but teat dipping using an effective germicide is recommended. This virus can spread among animals, so affected animals should be segregated and milked with separate milking equipment.

Teat warts are not uncommon and can be caused by several different papillomaviruses. The appearance of the warts is variable, ranging from small, smooth lesions to large, frond-like protuberences. Younger animals are often more susceptible and will develop immunity. Warts are generally self-limiting and will resolve within several months. No therapy is recommended.

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Mastitis in Beef Cows

Several surveys have demonstrated that about 15% to 40% of beef cows have IMI in at least one mammary gland.[521,522] Similar to heifers and small ruminants, NAS are the predominant bacteria isolated, but *S. aureus* has been recovered from 7% to 10% of milk samples. Milk from infected glands has significantly higher SCCs as compared to milk collected from healthy glands.[521,523,524] Clinical mastitis occurs rarely and is diagnosed and treated when economically feasible, but most mild cases of clinical mastitis are likely undetected.

Several modes of transmission of mastitis pathogens have been proposed for beef cattle. Flies are believed to serve as vectors for staphylococci, and fly-induced teat scabs of beef heifers have been shown to harbor staphylococci.[525] Calves may also serve as vectors by transmitting oropharyngeal organisms to the teats or carrying bacteria-laden milk from teat to teat. Unsanitary housing conditions probably increase the risk of infection with environmental pathogens.[521,525] As with dairy cows, poor udder conformation and teat injuries may predispose to mastitis.

Several studies have demonstrated numeric or significant decreases (up to 40 kg) in weaning weights of calves from beef cows with subclinical mastitis,[521,522,524] probably as a result of reduced milk production.[523] The adverse effect on weaning weight appears to increase with the number of infected glands.[521] Use of dry cow antimicrobial therapy has been associated with decreased IMI in the subsequent calving and increased body weight gain of calves.[526] However, the economic justification for the routine use of antibiotic treatment at dry-off is lacking. Selective intramammary antibiotic treatment at weaning based on CMT reaction has been suggested, but CMT score is unlikely to be an accurate predictor of infection. Sanitary housing conditions, appropriate stocking density, and good fly control should help to minimize mastitis risk in beef cattle.

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Mastitis in Small Ruminants

General Concepts

The udders of sheep and goats differ from those of cows in that they have only two mammary glands, which are logically referred to as halves. With the exception of the relative proportion of the cisternal cavities, anatomic structures, milk secretion, and milk letdown of small ruminants are similar to cattle. Both goats and sheep have much larger cisterns as compared to dairy cows, and the cisternal fraction of milk may approach 50% to 75% for these species.[527]

Just as in dairy cows, mastitis of small ruminants is a bacterial disease that occurs in either a subclinical or a clinical state. Subclinical mastitis is an important and underrecognized disease in small ruminants. In two separate studies, an Israeli research group compared milk production and composition of healthy and NAS-infected half-udders in ewes.[528] These studies demonstrated large increases in SCCs and 30% to 50% reductions in milk yield of infected half-udders. Subclinical mastitis is generally defined by the migration of neutrophils into the mammary gland in response to bacterial infection. This response occurs in all dairy species, but the magnitude of the response and the distribution of cell types in the healthy mammary gland differ considerably among species.[529] In both sheep and cows, a significant increase in somatic cells occurs almost exclusively in response to bacterial infection of the mammary gland. The SCC response in dairy goats is not as specific to infection, and thus different interpretation criteria are necessary. The proportion of neutrophils (PMNs) and the number of cytoplasmic particles present in milk are very different in milk produced by goats as compared to milk produced by ewes or cows. Part of this difference is generally attributed to different milk secretion mechanisms. Both goats and sheep are thought to produce milk using a largely apocrine process, where the apical portion of the secretory cell is excreted into the milk. Despite similar secretory processes, the number of cytoplasmic particles found in milk obtained from both healthy and infected glands is approximately ten- to twentyfold greater for goats (about 70,000 to 300,000 cells/mL) as compared to cytoplasmic particles found in sheep milk (about 15,000 cells/mL). The large number of cytoplasmic particles necessitates the use of DNA-specific counting mechanisms to accurately enumerate somatic cells in

goat milk. Similar to dairy cows, microbiological analysis of milk samples obtained from affected glands is the only way to determine the etiology of mastitis.

Enumeration of SCC of goat milk must be performed using DNA-specific methods.[530] The CMT is based on reaction of the detergent with DNA in cells and is also considered accurate. When enumeration of SCC in goat milk is properly performed, IMI is a well-known cause of increased SCC, but the threshold used to determine infection must be determined relative to stage of lactation.[531] Milk samples obtained from infected udder-halves of goats generally exhibit SCC values greater than 500,000 cells/mL (first 90 days in milk) and greater than 1,000,000 cells/mL (later stages of lactation).[531] Important factors that must be considered when evaluating SCCs of goats include parity, stage of lactation, breed, and estrus.[532,533] In does, the ability of estrus to stimulate increased SCCs in the absence of IMI has been demonstrated in a controlled study using induced estrus.[534] In one part of the trial, the day after inducing estrus, SCC values were 1,778,000 cells/mL for does in estrus versus 363,000 cells/mL for does in the control group; both values have been converted from the reported log values. These physiologic increases were not associated with IMI or with decreased milk production, but the mechanism behind the increase was not elucidated. Overall, while several noninfectious causes for increased SCC are observed in goats, IMI remains an important cause of increased SCC. Although it is more complex to use SCC values to investigate mastitis problems in goats, the large variation observed among herds indicates that control of mastitis can result in lower bulk tank SCC, and veterinarians should work with producers to understand the factors that influence SCC in their herds.

The types and proportions of cells present in sheep milk are more similar to dairy cows than goats, and standard methods used to count somatic cells in cows' milk are considered accurate for counting somatic cells in ewes' milk. Evaluation of SCC data is considered an effective tool for diagnosing IMIs in dairy sheep.[535,536] In an uninfected half-udder, the SCC is generally lower than 200,000 to 400,000 cells/mL.[531,536] Higher counts are almost always associated with bacterial infections and indicate the presence of subclinical mastitis.[537] Individual gland SCC values increase in response to IMI in ewes, and thus bulk tank SCC values are an indication of the quality of milk and increase when the prevalence of subclinical mastitis increases.[537] Dairy sheep producers should

monitor bulk tank SCC and manage the flock to maintain a SCC of less than 300,000 cells/mL.

Mastitis in Dairy Sheep

In North America, most sheep are kept for production of meat, and most research literature discusses symptoms of mastitis occurring in ewes that are nursing lambs. In this population, only severe clinical mastitis is likely to be diagnosed. A longitudinal study of meat sheep conducted in Great Britain reported that acute mastitis affected 2% to 3% of ewes per year, but there was tremendous variability among flocks.[538] These researchers also reported that IMI occurred in 11% of lactating ewes and resulted in reduced weight gain of suckling lambs.[538] Udder conformation is a known risk factor associated with increased risk of mastitis in ewes.[539]

A lack of emphasis on milking ewes has led to an overemphasis on the occurrence of clinical mastitis and a lack of appreciation for subclinical mastitis. Although there are no national studies assessing the incidence of clinical mastitis in dairy ewes milked in the United States, based on research in other regions, clinical mastitis is thought to occur in less than 5% of ewes per year.[531,540] While few U.S. data are available to define the prevalence of subclinical mastitis, researchers believe that up to 30% of ewes in some flocks may be affected.

In almost all instances, mastitis is caused by a bacterial infection. While most bacteria can cause both clinical and subclinical mastitis, *S. aureus, Pasteurella haemolytica,* and various yeasts and molds are organisms frequently reported to be recovered from milk samples of ewes affected with clinical signs.[540] Bluebag (clinical mastitis with a hard, cold, swollen udder) is typically caused by either *P. haemolytica* or *S. aureus*. NAS are considered to be minor pathogens in dairy cows but behave as major pathogens in dairy sheep and have been frequently reported to be the most commonly isolated pathogens recovered from cases of subclinical mastitis in dairy ewes.[535,541] Subclinical infection caused by NAS and other mammary pathogens has been associated with increased SCC.[535,536] Other pathogens typically recovered from subclinical mastitis infections in ewes include *Corynebacterium* spp., yeast, *Streptococcus* spp., *Enterobacteriaceae* spp., and *S. aureus*. Yeast and mold infections in ewes are often associated with nonhygienic administration of intramammary treatments, and great care must be taken when these treatments are used.[542]

In rare instances, the lentivirus that causes ovine progressive pneumonia (OPP) has been associated with mastitis in sheep,[543] but there is no evidence that this virus has influence on the SCC of sheep milk.[531] Mammary gland symptoms are associated with lesions in secretory tissue. While it is known that this virus has an affinity for mammary glands, the disease is slowly progressive and results in weight loss, greatly reduced milk production, and other clinical signs that make it unlikely to become widespread in flocks used for dairy production.

Risk factors for subclinical mastitis are not well defined for intensively managed milking sheep in North America. European research in Mediterranean countries has indicated that most of the variation in mastitis is associated with differences in herd management.[544] In the same study, higher producing breeds were at greater risk of mastitis, and the use of dry-off treatment resulted in less mastitis.[545-547] Practices that improve udder hygiene and reduce teat exposure to bacteria are likely to result in less mastitis.

Ewes that develop clinical mastitis are often seriously ill and should be treated immediately according to protocols that have been developed in consultation with the flock veterinarian. Most treatments for severe clinical mastitis are administered systemically, and the ewe may require supportive therapy. There are no antibiotic compounds approved for treatment or prevention of mastitis in milking sheep. Drugs used for these purposes are considered by the FDA to be administered in an “extralabel” manner, and this usage must be prescribed and supervised by a licensed veterinarian. Administration of a drug that is approved for treatment of another sheep disease, such as ceftiofur for treatment of pneumonia, to treat mastitis is also considered extralabel usage. It is important to recognize that systemic administration of ceftiofur will not achieve effective inhibitory levels in the mammary glands of cows, sheep, or goats.

The use of intramammary dry-off treatment has been shown to positively influence milk yield and SCC in the subsequent lactation and is recommended.[542,547] However, administration of intramammary treatments does increase the risk of mastitis caused by yeast bacteria, and selective dry-off treatment can be recommended in flocks that have a relatively low prevalence of subclinically affected ewes. Milk samples obtained from ewes with three or more monthly SCCs of 400,000 cells/mL or greater in the previous lactation were six to eight times more likely to be positive for mastitis pathogens in the next lactation, as compared to milk samples obtained from ewes with SCCs below that threshold. That threshold may be appropriate to identify ewes that

should receive dry-off treatment.

Mastitis in Dairy Goats

Similar to ewes, the incidence of clinical mastitis is generally reported to be less than 5% of lactating does per year.[531] A study that surveyed about 300 goat dairy farms in Holland reported an incidence of clinical mastitis of 2% per year, and about two thirds of the farms culled the majority of affected does rather than treat them.[548] One interesting study conducted in Spain linked the incidence of clinical mastitis to selenium deficiency.[549] Spanish researchers reported that for does consuming a deficient diet, the incidence of clinical mastitis was 3.8% and 15.4%, respectively, for does that had been treated with slow-release barium selenite or were enrolled in a nonsupplemented control group.[549]

There are neither national surveys nor comprehensive reviews that describe the prevalence of subclinical mastitis in dairy goats in the United States or Canada. Review of existing data about the prevalence of subclinical infection is further complicated by the lack of a uniform SCC threshold and the influence of intervening factors (such as estrus) on SCC. When recovery of bacteria from milk samples is used as the gold standard to identify subclinical mastitis, several studies have indicated that half-udder prevalence of subclinical mastitis varies between about 15% and 40%.[550,551] When using a SCC threshold of 500,000 cells/mL for defining subclinical mastitis, researchers have estimated sensitivity (probability of recovery of pathogens when the SCC is higher than the threshold) as ranging from 0.69 to 0.90 and specificity (probability of not recovering pathogens when the SCC is higher than the threshold) of about 0.35 to 0.77.[550] Although some high SCC values are likely associated with physiologic changes, some reflect IMI, and it is likely that the prevalence of subclinical mastitis in many goat herds is greater than commonly recognized.

Similar to dairy sheep, researchers have consistently reported that NAS are responsible for the greatest proportion of subclinical mastitis infections occurring in this species.[531,551,552] Infections with NAS are especially prevalent in goats at parturition, with recovery of NAS from up to 17% of goats reported.[531] Similar to ewes, the early lactation spontaneous cure rate is only about 50% for IMIs caused by NAS, and up to 25% of does may remain infected 6 weeks after parturition.[531] SCC values of infected half-udders of does are always significantly greater than SCC values of healthy half-udders. Other pathogens frequently recovered from goats with subclinical mastitis include

Corynebacterium spp., *Streptococcus* spp., and *S. aureus*. The relationship between lentiviral infections (caprine arthritis encephalitis virus [CAEV]) and SCC has been reviewed,[531] and herds with greater prevalence of seropositive does have been shown to have greater SCC values. However, this relationship is considered weak and may have been a result of immunosuppression caused by CAEV infection.

Clinical mastitis in goats is often associated with infection by *S. aureus*, *Streptococcus* spp., *Pseudomonas*,[553] or miscellaneous pathogens such as yeast. In many regions of the world, IMIs are associated with infection by a variety of *Mycoplasma* spp., and milk samples obtained from goats with chronically increased SCCs should be submitted for *Mycoplasma* culture. When clinical mastitis cannot be explained by bacterial or fungal infection, *Mycoplasma* infection should be suspected. A variety of *Mycoplasma* species can cause clinical mastitis outbreaks in small ruminants. *Mycoplasma mycoides* subsp. *mycoides* (large-colony type) is an important mastitis pathogen in goats in the United States, especially in California.[554-557] *Mycoplasma putrefaciens* is involved in some outbreaks,[464] and *Mycoplasma agalactiae* is isolated on rare occasions.[556] Does with *Mycoplasma* mastitis often exhibit severe clinical illness and reduced milk yield, in addition to an inflamed udder and visibly abnormal milk; however, subclinical IMIs can occur. Adult goats and kids in herds with *Mycoplasma* mastitis may experience polyarthritis and pneumonia, and pregnant does may abort. Morbidity and mortality can be very high, with more than 90% of goats dying or euthanized in some herds.[556]

Because all mastitis treatments involve extralabel drug usage, treatment of clinical mastitis should be performed using protocols developed by a veterinary practitioner who has a valid veterinary-client-patient relationship. Treatment of systemically ill animals should focus on supportive care and appropriate antimicrobial therapy. Treatment of animals with local signs of clinical mastitis generally involves administration of commercial intramammary products and should be accompanied by microbiological assessments of at least some cases. Treatment of subclinical mastitis is unlikely to be pursued by most farms, and aggressive culling of affected animals has been shown to be associated with herds that have lower bulk tank SCCs.[548] At least one study has demonstrated that treatment of subclinical mastitis in early lactation based on CMT reaction resulted in increased bacteriologic cure but was not economically beneficial.[548] Thus treatment of subclinical infections during lactation is not currently

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recommended. However, the use of dry-off therapy has been shown to effectively cure NAS infections and result in lower SCCs in early lactation.[558] As with sheep, producers should be taught to use extreme care when disinfecting teat ends to prevent the iatrogenic development of IMI caused by yeast.

Mastitis is an important disease of small ruminants used in dairy production, and its prevalence varies with management. Most mastitis occurs in a subclinical form, and producers who do not routinely measure individual animal SCCs will be unable to determine the impact of subclinical mastitis on production and milk quality. Most subclinical mastitis in small ruminants is caused by NAS, which should be considered as major mastitis pathogens in these species. Prevention of infection is the key to control of mastitis, and good hygienic housing and milking practices are a necessity to minimize the impact of this disease. As in all dairy species, exposure of the teat end to bacteria is the mechanism for development of mastitis, and control programs are based on principles that improve hygiene and reduce exposure to potential pathogens. The prevalence of subclinical mastitis has been shown to be decreased in goat herds that practice good teat dipping and premilking teat sanitation.[559]

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Mastitis in Horses

Mares have a uniquely different anatomic structure of the udder. Similar to the bovine udder, the equine udder is composed of four independent glands; however, the pairs of glands on each side of the midline share a single teat and are referred to as halves.[560] Mastitis occurs uncommonly in horses, in part because of the relatively small size and inguinal location of the udder, which minimizes exposure to potential pathogens. Little research has been done on the prevalence of subclinical mastitis in horses, but it is not recognized to be a serious problem and a longitudinal study estimated the prevalence to be 5% to 10%.[561] SCCs in uninfected glands have been reported to be relatively low (<250,000 cells/mL), whereas SCCs of microbiologically infected glands exceed 10^6 cells/mL.[562]

Clinical mastitis occurs sporadically in lactating and nonlactating mares; signs range from mild to severe. The most common clinical mastitis pathogen is *Streptococcus zooepidemicus,* but a variety of aerobic bacteria have been isolated from the milk of affected mares.[562-564] In a retrospective study of 28 cases, gram-negative bacteria (coliform bacteria, *Pseudomonas, Actinobacillus, Pasteurella*) were isolated from 42% of milk samples.[563] Streptococci and staphylococci constituted most of the gram-positive isolates. Rarely, mastitis is caused by nonbacterial pathogens. For example, one mare developed unilateral mastitis as a component of disseminated coccidioidomycosis.[565] Verminous mastitis has even been reported.[566]

Clinical signs of mastitis in horses include an enlarged, firm, warm, painful mammary gland and edema of the udder and surrounding tissues. The mare resists milking, and secretions are abnormal in appearance (color, viscosity, consistency). About half of all mares with clinical mastitis are systemically ill, with signs such as fever, tachycardia, tachypnea, anorexia, depression, or agalactia. The mare may be reluctant to move or may adopt an abnormal gait to minimize contact between the hindlimb and the painful gland. Sedation or anesthesia is necessary to achieve a thorough examination of the udder and collection of milk in some horses.[567]

Culturing milk is required to identify definitively the causative pathogen of equine mastitis and to confirm that antibiotic selection is appropriate. However, bacteria can often be observed on cytologic examination of the milk.[563] A

differential diagnosis for a firm, enlarged, painful mammary gland is adenocarcinoma, particularly if the udder skin is ulcerated and the secretion is serosanguineous.[568-570] With adenocarcinoma, neoplastic cells may be seen during cytologic examination of the secretion, or a mammary biopsy may be required. Because bacterial mastitis and adenocarcinoma can occur simultaneously, it is important to reevaluate mares that do not respond as expected to antibiotic treatment. Fescue toxicosis should be included in the differential diagnosis for agalactia. With fescue toxicosis, the udder is not inflamed, and mares may sweat profusely, have prolonged gestation, or give birth to weak or dysmature foals.[571]

Treatment of bacterial mastitis in horses consists of intramammary and systemic antibiotics to combat infection; NSAIDs to reduce pain, inflammation, and fever; and fluids to correct dehydration. Hot packing, hydrotherapy, and frequent stripping of the affected gland are empirically justified supportive measures but may be difficult to accomplish. Furosemide can be administered if edema is substantial.

Broad-spectrum antibiotics should be given until results of cytologic examination or culture of the milk are available. Potentiated sulfonamides, or a combination of penicillin and an aminoglycoside, are reasonable systemic antibiotic choices. Because no antibiotics are labeled for intramammary administration in horses in the United States, intramammary infusion products for cattle are used. Infusion products containing ceftiofur, cephapirin, amoxicillin, or hetacillin are appropriate until the cause of the mastitis is determined. A commercial intramammary infusion product is preferable to a homemade solution because the latter carries a greater risk of unintentional contamination. Intramammary infusion of antibiotics can be difficult to accomplish in horses because of the small size of the teat orifice and the presence of two distinct lobes within each udder half. One or both lobes can be infected, so antibiotics must be directed appropriately. Antibiotic treatment should be continued for at least 5 days to avoid relapse.

The prognosis for survival of horses with bacterial mastitis is good; however, milk production may be transiently or permanently reduced. Fortunately, mastitis is usually unilateral, and recurrence is rare.[563] Most mares respond rapidly to antibiotic treatment. Although spontaneous recovery is possible, it is unethical to withhold treatment from a mare that is ill or in discomfort. The prognosis for mammary adenocarcinoma is poor, even with surgical removal of the affected mammary gland(s) and local lymph nodes, because of the high rate of

metastasis.[570]

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• CHAPTER 37

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Diseases of the Hematopoietic and Hemolymphatic Systems

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Diseases Associated With Blood Loss or Hemostatic Dysfunction

Johanna L. Watson • Debra Deem Morris

Blood loss may be acute or chronic, and the clinical and laboratory manifestations are widely different because physiologic adaptation occurs in the chronic state.

Acute Blood Loss

Common causes for acute blood loss include trauma (e.g., severe lacerations), surgical procedures (e.g., dehorning, castration), and erosion of the carotid artery by guttural pouch mycosis in horses. External hemorrhage is immediately obvious, but hemorrhage into a major body cavity may be occult (e.g., spontaneous rupture of the middle uterine artery, splenic rupture resulting from trauma or erosion of a major vessel by abscess, aneurysm, or neoplasia). Hemoperitoneum may induce signs of colic, and hemothorax is generally attended by dyspnea. Acute massive blood loss induces hypovolemic shock characterized by tachycardia, tachypnea, cold extremities, pale mucous membranes, muscle weakness, and eventual death resulting from cardiovascular collapse.

Acute blood loss does not initially cause a change in the packed cell volume (PCV) or total plasma protein, although rapid mobilization of extracellular fluid to maintain circulating blood volume causes PCV and total plasma protein to decline within 12 to 24 hours. The severity of blood loss may be partially masked by splenic contraction because shock causes activation of the sympathetic nervous system. Icterus is absent, and bone marrow erythroid hyperplasia is delayed by 3 to 4 days. Peripheral signs of erythroid regeneration in horses are limited to mild anisocytosis with a variable increase in mean corpuscular volume. Ruminants show erythrocyte polychromasia, basophilic stippling, Howell-Jolly bodies, and occasionally nucleated erythrocytes within 4 days of hemorrhage onset.

Diagnosis

Diagnosis of acute blood loss is based on clinical signs, evidence of recent

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hemorrhage, and anemia accompanied by hypoproteinemia. Hemoperitoneum and hemothorax may be suggested by ultrasound and abdominocentesis and thoracocentesis, respectively.

Treatment.

Treatment of acute blood loss should initially be aimed at stopping the hemorrhage. External hemorrhage may be managed by pressure wraps or appropriately placed ligatures, but attempting to control internal hemorrhage when the patient is a poor risk for general anesthesia may be inadvisable and the source of hemorrhage may not be found. Hypovolemic shock should be treated by prompt intravenous (IV) administration of 40 to 80 mL/kg of sodium-containing crystalloid solutions. Studies indicate that a small volume of hypertonic saline (2 to 4 mL/kg 7.2% sodium chloride) may temporarily reverse the pathophysiologic sequelae of severe hemorrhagic shock.[1-3] The total volume of crystalloid solution required is usually much greater than the volume of blood lost because crystalloid solutions distribute throughout the extracellular space. The clinical response to fluid administration should be evaluated in light of ongoing losses to determine the necessary replacement volume.

If anemia becomes life threatening, whole blood transfusion must be considered. A PCV less than 20% in an animal with acute blood loss suggests depletion of erythrocyte reserves, and persistent reduction of the PCV over a period of 24 to 48 hours to 12% or less indicates the need for blood transfusion. A low but stable PCV (12% to 20%) does not necessitate transfusion, because transfusion should be reserved for instances in which oxygen delivery to the tissues is inadequate to support life. Blood transfusion can only be viewed as a temporary therapeutic procedure because even crossmatch-compatible allogeneic erythrocytes are removed from the circulation by the mononuclear phagocyte system (MPS) within 2 to 4 days of transfusion.[4] Horses and cattle display a high degree of blood type polymorphism, and minor antigenic incompatibilities are only delineated by blood typing.[5] Serum antibodies against nonhost erythrocyte antigens (erythrocyte alloantibodies) probably mediate the short life span of transfused erythrocytes. Compatibility testing is used to avert life-threatening antigen-antibody reactions caused by major blood group mismatching.

The routine crossmatch involves incubating washed erythrocytes from donor (major) and recipient (minor) with serum from the other. Gross and microscopic examination for clumping demonstrates serum agglutinins in horses. Sensitized cattle erythrocytes do not become clumped in saline solution but do lyse in the

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presence of rabbit complement, so only a hemolytic crossmatch can be performed in this species. Not all equine erythrocyte alloantibodies act as agglutinins, and hemolysins must be detected by adding complement to the reaction mixture. Pooled rabbit serum must first be absorbed with equine erythrocytes to remove naturally occurring antibodies. The necessity for special handling and storage of rabbit serum makes hemolytic crossmatch procedures impractical for most veterinarians. These tests are best performed by veterinary hematology laboratories (e.g., Veterinary Genetics Laboratory, School of Veterinary Medicine, University of California, Davis), which usually require serum and whole blood in sodium citrate or acid-citrate-dextrose (ACD) to crossmatch.

The first transfusion of whole blood to a horse or ruminant not previously transfused or sensitized by immunization or pregnancy is usually well tolerated because natural alloantibodies are of low concentration and weak activity. After incompatible transfusions, alloantibodies develop rapidly, making subsequent transfusions more hazardous.

Blood for transfusion should be collected aseptically into sterile containers of sodium citrate (2.5% to 4%) or ACD solution and used immediately. The necessary dosage can only be estimated, but in most instances replacing 20% to 40% of the calculated blood loss is sufficient to maintain life until the bone marrow can respond. A drop in PCV from 36% to 12% in a 500-kg animal (8% body weight blood) represents a loss of 27 L of blood. In this case, 6 to 8 L of whole blood would be therapeutic and easily donated by another 500-kg individual. Blood warmed to 37° C (98.6° F) should be administered through an in-line filter to remove clots. After pretransfusion vital parameters have been recorded, 0.1 mL of blood/kg body weight is given over 5 to 10 minutes and the evaluation is repeated. If parameters and attitude are unchanged, the transfusion can be continued at a rate not to exceed 20 mL/kg/h. The recipient should be continuously monitored so that the transfusion can be stopped if adverse reactions like tachypnea, dyspnea, restlessness, defecation, tachycardia, piloerection, muscle fasciculations, or sudden collapse occur. Although these signs may not indicate anaphylaxis, severe reactions should be treated with epinephrine (0.01 to 0.02 mg/kg). Mild signs may respond to a slowed transfusion rate or administration of corticosteroids or flunixin meglumine. Because it is often impossible to delineate the cause of transfusion reactions, the safest approach is to discontinue the blood and administer isotonic crystalloid solutions.

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The prognosis is good for most cases of acute blood loss if hypovolemic shock is quickly treated and bleeding stops. Myocardial damage as indicated by elevated cardiac troponin I (cTnI) and arrhythmia has been reported with acute hemorrhage in the horse.[6] Normal bone marrow begins to replace lost cells within 5 days. Sequential PCV analysis will be necessary to determine whether blood loss is controlled. Examples of specific disorders follow.

Guttural Pouch Mycosis.

See Chapter 31 for an in-depth discussion of this and other respiratory diseases.

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Hemoperitoneum in Horses

Monica Aleman • Johanna L. Watson

Hemoperitoneum is accumulation of blood in the abdominal cavity and can be a life-threatening problem. In the horse, associated causes are trauma; postoperative abdominal hemorrhage; neoplasia; complications from pregnancy and foaling (utero-ovarian, middle uterine, and external iliac artery rupture); organ rupture; mesenteric injury; coagulopathies; ovarian hematoma; systemic amyloidosis; and idiopathic hemoperitoneum.[7-13] The underlying cause is identified in the majority of cases (78%).[13] Trauma (spleen and in mares, reproductive tract with associated vessels) and neoplasia are the most common causes of hemoperitoneum.[9,13]

A recent retrospective study of 67 horses with hemoperitoneum revealed that Thoroughbreds and Arabians were overrepresented breeds.[13] Middle-aged and older horses (>13 years of age) and females may be overrepresented.[12,13] The most common clinical signs include abdominal discomfort, lethargy, hypovolemic shock, pale mucous membranes, prolonged capillary refill time, tachycardia, and tachypnea.[12,13] Other clinical signs are anorexia, reluctance to move, weakness, trembling, cool extremities, and abdominal distention.[12]

Clinicopathologic abnormalities include anemia, neutrophilia, lymphopenia, thrombocytopenia, hypoproteinemia, hypocalcemia, and azotemia.[12] Abnormalities in clotting parameters may be observed, depending on the cause. Hemorrhagic abdominal effusion is characterized by high red blood cell (RBC) count (>2,400,000 RBC/µL), PCV (≥18%), and total protein (≥3.2 g/dL), with a normal to high leukocyte count.[12] Central venous pressure and blood lactate concentration appear to be early indicators of hypovolemia due to acute blood loss.[14] Fluid swirling and site of hemorrhage may be evident on abdominal ultrasound.

Primary goals of therapy are treating hypovolemic shock, restoring perfusion and oxygen delivery to tissues, correcting fluid deficits, stopping further blood loss, and preventing complications. Blood transfusion should be considered if anemia becomes life threatening. The use of antifibrinolytic and procoagulant agents has been reported in the literature, but controlled studies on efficacy and safety in the horse with acute blood loss are lacking. Physical activity must be

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restricted in affected patients.

The short-term outcome is strongly associated with the underlying cause.[13] Horses with neoplasia, uterine artery rupture, mesenteric injury, or disseminated intravascular coagulation (DIC) have a greater risk of not surviving. The survival rate has been reported to range from 51% to 74%.[12,13] Poor short-term outcome was significantly associated with high respiratory rate in one study.[13] Prepartum hemorrhage appears to be associated with a poorer prognosis than postpartum hemorrhage (100% vs. 20% mortality, respectively).[13]

Hemothorax

Hemothorax may occur secondary to trauma (including lung biopsy), neoplasia, and strenuous exercise (see Chapter 31).[15] Hemothorax in neonatal foals may be the result of lacerated lungs and vessels from fractured ribs (see Chapter 20).[16]

Exercise-Induced Pulmonary Hemorrhage

Exercise-induced pulmonary hemorrhage (EIPH) has not been identified as a major cause of blood loss. EIPH is associated with high-intensity exercise in horses. An estimated 14% to 75% of racehorses examined by endoscopy have EIPH.[17] On the basis of a bronchoalveolar lavage analysis, a study suggested that 100% of horses performing strenuous exercise have EIPH.[18] EIPH has been reported in various breeds. A recent study reported that the frequency of EIPH is associated with race type, distance, gender, and age. In one study, epistaxis was more common in females, older horses (vs. <2 years of age), following steeplechase races (vs. flat races), and at shorter distances (≤1600 m long).[19] Recurrence rate in that study was reported to be 4.64%. The pathophysiology of EIPH is not completely known. For a complete description of this disorder, see Chapter 31.

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Chronic Blood Loss

Johanna L. Watson • Debra Deem Morris

A number of diseases can result in chronic loss of blood that is insidious until clinical signs of anemia develop. Physiologic adaptation to gradually developing tissue hypoxia generally masks signs of anemia until the PCV is less than 15%. Causes for chronic blood loss include bleeding gastrointestinal (GI) lesions, certain renal diseases, hemostatic dysfunction, bloodsucking external parasites, and haemonchosis (especially in goats and sheep).

GI hemorrhage is usually caused by neoplasia (especially gastric squamous cell carcinoma in horses and abomasal lymphoma in cattle), parasitism, or mucosal ulceration (e.g., abomasal ulcers in cattle and nonsteroidal antiinflammatory drug [NSAID] toxicity in horses). Significant hemorrhage may occur in ruminants heavily infested with *Haemonchus contortus* shortly after they are treated with an anthelmintic. Generally, GI hemorrhage is best detected by chemical determination of fecal occult blood, because melena rarely occurs in horses, and bleeding abomasal ulcers cannot be excluded in cattle when melena is absent. Because of the low specificity of tests for fecal occult blood, the diagnosis of chronic GI blood loss is usually supported by strong clinical suspicion and ruling out other sources of hemorrhage.

Although both renal calculi and renal papillary necrosis due to NSAID therapy cause hematuria, anemia rarely results. Renal neoplasia and congenital renal vascular anomalies are rare causes of chronic blood loss anemia. Other causes of blood loss include idiopathic hematuria and idiopathic recurrent hematuria of Arabian horses.

Disorders of hemostasis can cause internal or external hemorrhage that leads to anemia if enough blood is lost. Qualitative or quantitative abnormalities of blood vessels, platelets, or coagulation factors result in hemostatic dysfunction (see next section). Loss of erythrocyte iron secondary to chronic severe blood loss may result in iron deficiency anemia. Hypoferremia or reduced serum ferritin develops with increased total iron-binding capacity and reduction in marrow iron.

The key to managing chronic blood loss is determining the primary cause; treatment of the anemia per se is rarely indicated. Iron deficiency may be alleviated by oral (PO) supplementation with ferrous sulfate, although good-quality forages contain more than adequate amounts of iron. Parenteral iron

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supplementation as iron dextran should be avoided because it has been associated with anaphylactoid reactions in large animals. Examples of specific disorders follow.

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Gastric Ulceration

Monica Aleman • Johanna L. Watson

Gastric ulceration is also known as *equine gastric ulceration syndrome* (EGUS). Although EGUS is not an important cause of blood loss, it has a high prevalence among adult horses. Thoroughbred racehorses have the greatest prevalence (range, 82% to 93%), followed by endurance horses (67%), show horses (58%), hospitalized horses (49%), and geriatric patients with abdominal pain (18%).[20-24] Gastric ulcers were found in 66.6% of pregnant and 75.9% of nonpregnant mares on a Thoroughbred breeding farm.[25] Clinical signs may include poor hair coat, decreased appetite, poor performance, nervous disposition, abdominal pain, teeth grinding, and salivation among others. Proposed causes of gastric ulceration include exercise, transportation, grazing deprivation, alternating periods of feeding and fasting, diets with high-concentrate content, and confinement. For a complete description of gastric ulceration see Chapter 32.

Right Dorsal Colitis

Right dorsal colitis (RDC) is an enteropathy associated with NSAID administration, most commonly phenylbutazone.[26,27] Other factors that may predispose to RDC are infection, immune-mediated response, genetics, and stress; pathogenesis is unknown. NSAIDs act by inhibiting cyclooxygenase (more inhibition of constitutively expressed COX-1 than inducible COX-2 expression during states of inflammation), which will cause inhibition of prostaglandin E production, resulting in hypoxic or ischemic GI mucosal damage and delayed mucosal healing.[27]

Ponies and young performance horses appear to be predisposed. Clinical signs include inappetence, lethargy, intermittent or episodic colic, diarrhea, and weight loss. Clinicopathologic abnormalities may include mild anemia, moderate to severe hypoproteinemia with hypoalbuminemia, hypocalcemia, and in some cases azotemia. Although mild anemia is seen in most cases, horses occasionally present with severe anemia and hematochezia. RDC often develops over a period of days or a few weeks. The complete discussion of diagnosis and treatment is included in Chapter 32.

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Hemostatic Dysfunction

Johanna L. Watson • Debra Deem Morris

Basic Physiology of Normal Hemostasis

The basis for understanding the pathogenesis and manifestations of hemostatic disorders is a thorough understanding of the normal physiologic mechanism of hemostasis. Hemostasis can be viewed as two interrelated components—coagulation and fibrinolysis (both with their respective inhibitors)—which function to arrest bleeding from a damaged blood vessel and maintain nutrient blood flow.

Coagulation is mediated by blood vessels, platelets, and blood procoagulant proteins. When a blood vessel is damaged, vasoconstriction occurs, followed by rapid adherence of platelets to subendothelial collagen. Platelet adhesion causes membrane conformational changes that trigger aggregation, contraction, and granule secretion (the basic platelet reaction). Platelet phospholipoprotein (platelet factor 3) provides the necessary surface to catalyze interactions among the activated coagulation proteins that result in thrombin formation. Coagulant proteins are localized to this hemostatic plug because the platelet surface protects them from plasma anticoagulants. Through an incompletely understood mechanism, platelets also prevent spontaneous hemorrhage into the skin and mucous membranes by maintaining vascular integrity.

Procoagulant proteins circulate in the blood as precursor forms (zymogens) that must be altered during coagulation to become active. Numerous communications exist between the traditional extrinsic and intrinsic pathways, although initiating mechanisms remain distinct.[26] The extrinsic system is initiated when lipoprotein tissue factor (TF) gains access to the bloodstream. TF is widely distributed in most tissues, including endothelial cells and monocytes, and it may be increased or secreted in response to numerous pathologic stimuli like bacterial endotoxin. Intrinsic coagulation is initiated when blood is exposed to a negatively charged surface (e.g., activated platelets). Because of reciprocal activation between factor XII and prekallikrein, the intrinsic coagulation pathway stimulates formation of numerous inflammatory mediators such as kinins and complement. Both coagulation pathways culminate in the formation of activated factor X (Xa) by which thrombin is generated. In addition to

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catalyzing the conversion of fibrinogen to fibrin, thrombin promotes platelet aggregation, enhances cofactor activities of factors V and VIII, and activates factor XIII and protein C.[27] Mechanisms to localize coagulation to the site of vascular injury are critical to protect against generalized thrombosis.[28] Plasma anticoagulant proteins include the serpins, which inhibit activated coagulation factors, and the protein C system, which is directed against cofactors V and VIII.[29] Antithrombin III (AT III), the main physiologic inhibitor of thrombin and Xa, normally provides 70% of the anticoagulant activity of plasma. Although not absolutely necessary, heparin accelerates AT III action by 2000-fold.[30] Activated protein C destroys factors V and VIII, ultimately limiting its own activation, which depends on thrombin and endothelial cofactor, thrombomodulin. Protein S enhances the anticoagulant ability of protein C.

The fibrinolytic system is activated at the same time as coagulation and functions to prevent tissue ischemia by limiting the extent of fibrin clot formation. Plasmin, primarily responsible for degradation of fibrin, exists in the plasma as the zymogen plasminogen. Plasminogen has a high affinity for fibrin, as does tissue plasminogen activator (tPA); because clots contain the necessary components to allow lysis from within, systemic plasmin formation is avoided. α_2-Antiplasmin (α_2-AP), the main physiologic inhibitor of plasmin, competes with the binding of plasminogen to fibrin, and the clot contains equal amounts of both glycoproteins. Because of this molar balance between α_2-AP and plasminogen, a normal blood clot does not lyse spontaneously, despite fixation of tPA. Physiologic plasminogen activator inhibitors (PAIs) are found in plasma, platelets, and endothelial cells; platelet-derived PAI protects a blood clot against premature lysis. Clot lysis is initiated if additional tPA is taken up from the surrounding tissues, and stasis upstream from the occluded vessel is a potent stimulus for release of endothelial tPA. Conversion of plasminogen to plasmin allows partial digestion of fibrin and exposure of additional plasminogen binding sites. When this additional plasminogen is converted to plasmin, the inhibitory effect of α_2-AP is overcome and clot lysis is accelerated. Plasmin hydrolyzes fibrinogen and fibrin with equal affinity, as well as numerous other procoagulants, and it can activate complement and kininogen. The physiologic actions of plasmin are limited to the fibrin clot by the affinity between the latter and plasminogen and the presence of α_2-AP in blood. Because of multiple interactions between the coagulation and fibrinolytic systems, the most important factor that determines the rate of fibrinolysis is the rate of fibrin

formation.[31]

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Inherited Coagulation Disorders

Jeffrey W. Norris

Reductions in protein levels and/or activities associated with coagulation pathways have been documented in all species of domestic herd animals. These deficiencies arise either as the result of genetic transmission or are acquired secondary to intoxication or an underlying disease process. In domestic herd animals, inherited coagulation defects have been associated with proteins in the intrinsic pathway of coagulation, specifically prekallikrein, factor XI, and factor VIII. Defects in von Willebrand factor (vWF), vitamin K−dependent coagulation proteins, and fibrinogen have also been reported. Here, attention is given to the underlying genetics associated with these deficiencies, as improvement of breeding programs is an important aspect of overall management when patients with inherited coagulation disorders are encountered.

Prekallikrein Deficiency

Deficiency of prekallikrein, which is involved in initiation of the intrinsic pathway of coagulation, has been described in families of both miniature horses in the United States and Belgian horses in Canada.[1,2] In the family of miniature horses, a 4-year-old intact male and his female sibling were identified as having approximately fivefold decreases in circulating prekallikrein activity but no history of inappropriate bleeding.[1] The family of Belgian horses was first identified when a 7-year-old stallion had inappropriate hemorrhage for 7 days following an otherwise uncomplicated castration surgery.[2] Despite packing the incision sites with gauze sponges, the horse's hematocrit decreased by 19% over this period of time.

During initiation of the intrinsic pathway of coagulation, prekallikrein and factor XII are thought to undergo coordinated activation in a reciprocal manner. Recent studies have demonstrated that these two factors play critical roles in thrombosis but not hemostasis.[3,4] This subtle role of prekallikrein in the coagulation system is consistent with observations that many patients with prekallikrein deficiency are asymptomatic, but bleeding in response to trauma (e.g., surgery) is possible.

Blood from the affected horses in these studies had prolonged activated partial

thromboplastin times (aPTTs) but normal prothrombin times (PTs).[1,2] Prekallikrein activities in plasma from the two affected miniature horses were less than 20% that of normal horses, but insufficient data were available to determine if suspected carriers had significantly reduced circulating prekallikrein activity compared with clinically normal horses.[1] In addition to the Belgian stallion with a history of inappropriate bleeding, 13 members of his family had circulating prekallikrein levels below the reference range, including two full siblings with activities <3% of normal.[2] The sire of the affected stallion was found to have 19% of normal plasma prekallikrein activity, while levels in the mare were not determined. Therefore the reliability of prekallikrein activity testing to segregate unaffected carriers from normal horses is unclear. It is also unclear whether reduced prekallikrein activity found in these horses is due to reduced levels of circulating protein. The mode of inheritanceof prekallikrein deficiency in horses, although likely autosomal recessive, and the underlying genetic mutation have not been determined.

Factor XI Deficiency

Activation of factor XI is the second step of the intrinsic pathway of coagulation, and measurable deficiencies in factor XI activity have been reported in Holstein cattle in the United States, Canada, and the United Kingdom, as well as Japanese Black cattle.[5-8] The degree of inappropriate bleeding described in cattle with this deficiency ranges from absent to severe. Where reported, inappropriate bleeding incidents have included excessive bleeding from injection sites, petechial hemorrhage, hematoma formation, gastrointestinal hemorrhage, blood in the milk, and anemia.[5,7]

Clinical laboratory tests of the coagulation system yield expected results for a patient with a defect in the intrinsic pathway. Affected cattle have normal platelet counts and PTs.[5-7] In Holstein cattle, aPTTs are prolonged and inversely correlated with plasma factor XI activity.[9] The level of factor XI antigen in these cattle is proportionate to the factor XI activity present.[10] The use of these tests for screening affected cattle is limited because of the occurrence of false negatives in the heterozygote carrier population.[8-12]

Factor XI deficiency in cattle is transmitted as an autosomal recessive trait. Two mutations in the gene encoding factor XI, *F11*, have been associated with the deficiency of this coagulation factor and can be used to discriminate

heterozygote carriers in herds.The first of these mutations to be discovered was a 76–base pair (bp) insertional mutation in exon 12 of *F11* that occurs in Holstein cattle.[13] This mutation has been reported in cattle as widely distributed geographically as the United States, Japan, Poland, and Turkey.[13-16] More recently, this mutation has been identified in frozen semen used for breeding from two Indian Sahiwal *(Bos indicus)* cattle sires.[17] In Japanese Black cattle, factor XI deficiency is associated with a 15-bp insertional mutation in exon 9 of *F11*.[8]

Factor VIII Deficiency (Hemophilia A)

Factor VIII deficiency has been reported in a range of species, including horses, cattle, and sheep. The affected breeds of horses include Thoroughbreds, Standardbreds, Quarter Horses, and Tennessee Walking horses.[18-22] In cattle, this deficiency has been found in Herefords and Japanese Brown cattle.[23,24] In sheep, affected animals were originally restricted to a specific lineage of Alpine White sheep, but more recently this lineage has been expanded to establish a laboratory model of hemophilia A in human patients.[25,26] Inappropriate bleeding incidents described in these animals include epistaxis; petechial hemorrhage; formation of intramuscular hematomas, hemoarthroses, hemopericardium, and hemoperitoneum; as well as prolonged, life-threatening bleeding at sites of invasive procedures, umbilical cords, and following castration. Icterus, pale mucous membranes, and ventral edema are additional physical examination abnormalities that have been reported in these animals. Signs relating to factor VIII deficiency present at a young age ranging between immediately after birth to time of castration.

Patients with factor VIII deficiency have marked abnormalities in both standard clinical laboratory tests and coagulation tests. The results of standard clinical laboratory testing in these animals may include anemia, hypoproteinemia, neutropenia, the presence of reticulated platelets, hyponatremia, hypekalemia, and hypochloremia. Blood from these animals invariably has prolonged aPPTs and normal PTs. In one case, hypofibrinogenemia was reported coincident with increased D-dimer levels.[21] Inappropriate bleeding has been reported in animals with factor VIII activity levels that are approximately 15% of normal and lower.[21] Female parents of affected animals may have factor VIII activity within normal limits, but in many

cases they are found to have moderate decreases in circulating factor VIII activity.[21,22,24,25,27] In cattle, marked decreases in factors IX and XI have also been reported in animals with factor VIII deficiency, although the converse has not been shown in cattle with factor XI deficiency.[22,23] The half-life of factor VIII is extended in circulation via noncovalent association with vWF, and animals with true deficiencies in factor VIII should also have normal levels of vWF.[20,27] It has not been reported if decreased circulating factor VIII activity correlates with a decrease in circulating factor VIII antigen levels in animals.

Congenital factor VIII deficiency is X-linked and recessive, with clinical disease only having been reported in male horses and cattle. In sheep, affected females have also been reported, which is consistent with reports in humans of affected females with homozygous mutations in the gene encoding factor VIII (*F8*) or heterozygous for an inactivating mutation in *F8* combined with inactivation of the X chromosome carrying the normal *F8* allele.[25,28,29] A T-to-A substitution at nucleotide 6459 in *F8* occurs in Japanese Brown cattle with factor VIII deficiency and results in the mutation of a highly conserved leucine to histidine in the C1 domain of factor VIII.[30] In the Tennessee Walking Horse with factor VIII deficiency, cDNA made from factor VIII mRNA was found to be missing the sequence encoded by exons 1 and 2.[22] Analysis of genomic DNA revealed a deletion and two single nucleotide polymorphisms (SNPs) in intron 1, which separates the two exons that were missing in the mRNA. All three of these mutations had the expected allelic variation for a maternally transmitted deficiency (i.e., homozygous in the colt and heterozygous in the mare).

Although factor replacement therapy is the most common approach to managing factor VIII deficiency in humans, experience with this approach in veterinary patients is limited. A newborn Standardbred colt with factor VIII deficiency survived for 7 months with transfusions of 1 to 3 pints of whole blood or plasma from donor horses being given at 2- to 3-day intervals over the first 3 months of life.[20] In contrast, a growing hematoma in a 9-day-old Thoroughbred colt with factor VIII deficiency improved for only 36 hours following whole blood and plasma transfusions from normal horses in conjunction with administration of antifibrinolytic therapy.[27] Overall, the prognosis for animals with factor VIII deficiency is poor, and historically most owners have chosen euthanasia.

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Von Willebrand Factor Deficiency

In addition to stabilizing factor VIII in circulation, vWF promotes platelet-endothelial adhesion at sites of vascular injury. vWF deficiency was reported in a Quarter Horse filly that had multiple instances of inappropriate bleeding from mucous membranes, conjunctiva, and injection sites during the first 6 months of life.[31]

Clinical tests of the filly's coagulation function gave subtly altered results compared with normal horses. She had a normal platelet count, normal PT, and slightly prolonged aPTT. Plasma factor VIII clotting activity measured at the low end of the normal range. vWF antigen was reduced to 18% of normal and activity was less than 10% of normal in plasma from the filly.

Coagulation function, including factor VIII and vWF activities, was normal in the filly's dam, while the stallion was unavailable for study. Evidence that the vWF deficiency was heritable was obtained by protein electrophoresis that showed abnormal vWF structures in both the filly and the mare. Several types of vWF defects are recognized in human medicine with structural abnormalities being characteristic of type 2 vWF disease. The underlying mutation that led to vWF deficiency in the filly is unknown.

In Simmental cattle, vWF deficiency was first reported in a 10-month-old heifer with epistaxis and hematoma formation.[32] Despite observations that platelet counts and clinical coagulation tests were all within normal limits, inappropriate bleeding in this cow was corrected with administration of fresh-frozen, platelet-poor plasma. vWF antigen levels were normal in the heifer, but vWF activity was 25% of normal. Consistent with a heritable disease, two siblings of the cow were reported to have decreased vWF activities (52% and 30%). However, inappropriate bleeding episodes were not reported in these siblings. Similarly, in a separate study of the genetics underlying Simmental hereditary thrombopathy, a calf with vWF deficiency that had not suffered inappropriate bleeding episodes was identified.[33] In human patients, there is poor correlation between vWF levels and bleeding symptoms.[34]

The 10-month-old heifer and one of its siblings also had platelets with markedly reduced aggregation in response to the physiologic agonist ADP.[32] This has also been observed in human patients with platelet-type von Willebrand disease, as well as in a transgenic mouse model of this form of the disease.[35,36] However, the mutation leading to vWF deficiency in Simmental cattle is unknown, and additional testing is necessary to discriminate platelet-type von

Willebrand disease from other types of vWF deficiency in these cattle.

Deficiency of Vitamin K–Dependent Factors

A combined deficiency of the vitamin K–dependent coagulation factors (factors II, VII, IX, and X) was reported in five lambs from a flock of Rambouillet sheep.[37] Signs became apparent in affected lambs at birth and included excessive subcutaneous bleeding, hemoarthroses, tissue pallor, and bleeding from the umbilicus in newborn lambs following parturition.

Extensive testing of the coagulation cascade provided evidence for a defect associated with vitamin K–dependent coagulation factors in these lambs.[37] Standard clinical coagulation tests (aPPT and PT) were prolonged in affected lambs. In plasma from these lambs, activities of factor X and protein C were undetectable, while the activities of factors II, VII, and IX were markedly decreased. However, no abnormalities in either clinical coagulation test or any of the activities from the aforementioned individual factors were detected in the sire or ewes from which the affected lambs were bred. A study of liver samples collected at necropsy from the affected lambs showed no evidence for the presence of 10 vitamin K antagonists, including warfarin. Subsequent studies found that γ-glutamyl carboxylase activities were reduced in liver samples from affected lambs compared with age-matched control lambs.[38]

The affected lambs were produced following breeding of three ewes to a single sire across multiple years. This observation combined with the reduced γ-glutamyl carboxylase activities in liver samples from the lambs suggested the deficiency was inherited.[37,38] Breeding data from the original study also supported an autosomal recessive mode of transmission.[37] Genetic analysis of the flock revealed a single nucleotide polymorphismin exon 4 of the gene encoding γ-glutamyl carboxylase, *GGCX*, with the expected allelic frequencies in the affected lambs and their parents.[38] This mutation creates a STOP codon leading to premature termination of the protein.

Fibrinogen Deficiency

Fibrinogen, factor I, deficiency can be associated with an absolute loss of total circulating fibrinogen, afibrinogenemia, or a loss of clotting capacity, dysfibrinogenemia. Afibrinogenemia has been reported in a Saanen kid.[39]

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Although the underlying genomic mutation is unknown, heritability of the afibrinogenemia was demonstrated through a backcross to the doe, which led to the hypothesis that transmission was autosomal and had incomplete dominance. A likely case of dysfibrinogenemia was reported for a Border Leicester lamb; however, heritability was not determined.[40]

Signs associated with fibrinogen deficiency are severe. The Saanen kid was reported to have experienced prolonged umbilical bleeding, hematomas, hemarthroses, anemia, and prolonged bleeding from venipuncture sites.[39] Inappropriate bleeding episodes occurred with increasing frequency in this patient, and she survived for approximately 14 months. Similar signs were reported in the Border Leicester lamb, which was euthanized after diagnosis.[40]

Clinical coagulation tests will show prolongation of both aPTT and PT in cases of fibrinogen deficiency but are not capable of discriminating fibrinogen deficiency from inherited or acquired deficiencies in vitamin K−dependent coagulation factors. Antigen amount and functional tests for fibrinogen should be used together when assessing possible cases of fibrinogen deficiency as no one test can discriminate afibrinogenemia from dysfibringenemia.[41]

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Thrombasthenias

Jeffrey W. Norris • Monica Aleman • Fern Tablin

Thrombasthenias, which are rare, often inherited, defects in platelet function, result in spontaneous or excessive bleeding. Unlike common clinical tests for specific coagulation factors, aPTT, PT, and platelet counts are unremarkable. However, prolongation of template or buccal mucosal bleeding times are common. Diagnosis frequently requires platelet-specific and genetic testing.

Glanzmann Thrombasthenia

Glanzmann thrombasthenia (GT) results from either quantitative or qualitative deficiencies of the platelet membrane integrin $\alpha_{IIb}\beta_3$ (glycoprotein IIb-IIIa). α_{IIb} and β_3 proteins, expressed by separate genes, form heterodimers that bind fibrinogen and mediate platelet aggregation.

Clinical signs are spontaneous bleeding episodes including chronic, intermittent epistaxis unrelated to exercise; petechial and ecchymotic hemorrhages; hematomas; and prolonged bleeding following surgical procedures or venipuncture. GT platelets have normal morphology, coagulation parameters, and fibrin degradation products.[1-5] GT platelets are unable to aggregate in response to collagen or ADP and blood from GT horses forms loose clots, with limited serum separation and decreased tensile strength.[1-5] Flow cytometry has documented marked decreases in $\alpha_{IIb}\beta_3$ integrin on the platelet surface.[3]

Genetic analyses of horses with GT have documented mutations in the gene encoding α_{IIb} *(ITGA2B)*. Currently, there are three documented mutations in this gene associated with GT. The first mutation to be identified in a Thoroughbred-cross gelding was a homozygous mutation in exon 2.[5] A Quarter Horse mare that was found to be heterozygous for this exon 2 missense mutation also had a 10-base pair deletion in the second *ITGA2B* allele associated with a splice site for exon 11.[6] This deletion was subsequently found to occur with homozygosity in a Peruvian Paso horse as well.[7] The third mutation in *ITGA2B* associated with GT was in an Oldenburg filly, which was homozygous for a distinct missense mutation in exon 2.[8]

Owners of GT horses should be alert for signs of bleeding requiring

supportive care and regularly monitor for anemia.[7]

Atypical Equine Thrombasthenia

Another platelet defect was identified in a Thoroughbred filly with excessive prolonged bleeding following pin-firing.[9] In addition to this index case, the Tablin laboratory identified five other Thoroughbreds with atypical equine thrombasthenia (AET).[9-11]

AET platelets form normal clots, have normal expression of the $\alpha_{IIb}\beta_3$ integrin, and aggregate normally in response to ADP.[9,10,12] However, AET platelets simulated with low-dose thrombin have significantly reduced fibrinogen binding.[10,11] AET platelets have limited prothrombinase activity and reduced factor V released from AET platelet alpha granules.[11,12]

Treatment of bleeding has been managed with the antifibrinolytic agent ε-aminocaproic acid. Thoroughbred horses with characteristics of AET should be considered at risk for excessive bleeding during surgery.

Simmental Hereditary Thrombopathy

Spontaneous bleeding in Simmental cattle, Simmental hereditary thrombopathy (SHT), was first described in animals from Canada and the United States.[13,14] Cattle present with spontaneous hemorrhage, resultant anemia, and superficial hematomas. Prolonged bleeding secondary to tattooing or ear-tagging is commonly reported by owners.

Blood from SHT cattle has diminished clot retraction and reduced aggregation in response to ADP or collagen.[14-16] SHT platelets have normal morphology and normal calcium-dependent shape change in response to ADP.[14,17] However, SHT platelets fail to aggregate in response to the calcium ionophore A23187.[14,16,17]

The genetic transmission of SHT was investigated in Canadian Simmental cattle, and a homozygous missense mutation in exon 7 of the gene encoding calcium diacylglycerol guanine nucleotide exchange factor I (CalDAG-GEFI), *RASGRP2*, was identified in a heifer. A number of clinically normal calves in this study were heterozygous for the mutation.[18,19] The mutation leads to a change in a conserved region of the catalytic domain of CalDAG-GEFI, a protein necessary for calcium-dependent activation of the integrin $\alpha_{IIb}\beta_3$.[19] SHT platelets have delayed calcium signaling resulting in delayed integrin

activation.[20]

Bovine Chediak-Higashi Syndrome

Chediak-Higashi syndrome (CHS), characterized by abnormal secretory granules in platelets, leukocytes, and melanocytes, has been identified in Holstein, Brangus, and Japanese Black cattle.[21-23] A marked reduction of CHS platelet dense granules leads to excessive bleeding.[25-27] Dense granules have markedly reduced ADP content and release disproportionately less ADP, yet platelets aggregate normally in response to ADP.[24,28,29] Importantly, CHS platelets have a slow and transient aggregation in response to collagen.[24,29] A missense mutation was identified in the gene encoding the protein lysosomal trafficking regulator, *LYST*.[30,31] The mutation is autosomal recessive, and one study found that 8.8% of Japanese Black cattle were carriers.[32]

Additional signs of CHS include hypopigmentation of skin, hair, and eyes; photophobia; and increased susceptibility to infection. Breed information combined with coat color dilution in cattle presenting with infections or inappropriate bleeding suggests CHS. However, coat color dilution in CHS Japanese Black cattle is mild and insufficient to discriminate affected from normal cattle.[27]

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Acquired Hemostatic Disorders

Johanna L. Watson

Acquired defects of hemostasis may be divided into those involving blood vessels, platelets, and coagulation factors, although some diseases affect more than one component.

Vasculitis

Vasculitis is a clinicopathologic process that involves inflammation and necrosis of blood vessel walls, regardless of size, location, or cause.[1] Vasculitis in large animals is generally a secondary manifestation of a primary infectious, toxic, or neoplastic disorder and has characteristics of hypersensitivity vasculitis in humans. The predominant involvement of small vessels in the skin (e.g., venules, arterioles) is the hallmark of hypersensitivity vasculitis.

Clinical manifestations of vasculitis include demarcated areas of dermal or subcutaneous edema that may progress to skin infarction, necrosis, and exudation.[2] Hyperemia, petechial and ecchymotic hemorrhages, and ulceration of mucous membranes are common. Although the skin and mucous membranes are predominantly involved, hemorrhage and necrosis may occur in any organ system, resulting in lameness, colic, dyspnea, and/or ataxia. Subclinical renal disease is not uncommon. Vasculitis is often associated with adverse sequelae such as cellulitis, thrombophlebitis, laminitis, and pneumonia. Characterized vasculitis syndromes with predominant cutaneous involvement include equine purpura hemorrhagica (EPH), equine viral arteritis (EVA), equine infectious anemia (EIA), and *equine granulocytic* anaplasmosis (EGA). There are also a number of vasculitis syndromes in horses for which cause, pathogenesis, and clinical course are poorly defined.[3,4] Vasculitis is apparently uncommon in ruminants but may accompany certain septicemic diseases (e.g., malignant catarrhal fever of cattle, bluetongue of sheep).[5] Hematologic and serum biochemical findings in vasculitis are determined by the underlying disease, length of illness, organ involvement, and secondary complications. Chronic inflammation may be attended by neutrophilia, mild anemia, hyperglobulinemia, and hyperfibrinogenemia. Some horses with EPH develop a moderate anemia (PCV 20% to 25%) that is thought to be caused by increased erythrocyte

destruction.[6] The platelet count is generally normal. Muscle damage may be reflected by increased serum concentrations of creatine phosphokinase (CPK) and aspartate aminotransferase (AST). The creatinine may be elevated, and urinalysis may rarely show trace hematuria or proteinuria if there is glomerulonephritis.

Definitive diagnosis of vasculitis is made by demonstration of the characteristic histopathology of involved vessels. Full-thickness punch biopsies (at least 6 mm in diameter) of skin in an affected area should be obtained and preserved in 10% formalin and Michel's transport medium. Multiple biopsies from different sites may be necessary to reach the diagnosis. The most common inflammatory pattern is neutrophilic infiltration of venules in the dermis and subcutaneous tissue, with nuclear debris in and around involved vessels (leukocytoclasis) and fibrinoid necrosis. Considerable evidence suggests that most vasculitis syndromes are mediated by immunologic mechanisms—that is, a hypersensitivity reaction to a microbe, drug, toxin, or protein.[1] In some instances, an exogenous stimulus cannot be identified and an autoimmune pathogenesis is suspected. Immune complex deposition in vessel walls, with subsequent complement activation and chemoattractant production, seems to be the major pathogenic mechanism. Immunofluorescence on biopsies preserved in Michel's medium may reveal immune complexes. Infiltrating neutrophils and macrophages release proteolytic enzymes that cause vessel wall necrosis with subsequent edema, hemorrhage, and infarction of supplied tissues. Size and physiochemical properties of immune complexes, blood flow turbulence in sites of vessel bifurcation, and hydrostatic forces in dependent areas account for preferential formation of lesions in certain disease states and anatomic locations. Horses and cattle with idiopathic vasculitis may have incomplete response to therapy with an unpredictable poor prognosis.[5,6]

Equine Purpura Hemorrhagica

Purpura hemorrhagica (PH) is a noncontagious disease of horses characterized by vasculitis leading to extensive edema and hemorrhage of the mucosa and subcutaneous tissue. The disease has been recognized as a sequela to infection with or exposure to *Streptococcus equi*, *Streptococcus zooepidemicus*, *Rhodococcus equi*, *Corynebacterium pseudotuberculosis*, and others, as well as vaccination against *S. equi*.[2,7]

Young to middle-aged horses are commonly affected (mean, 8.4 years of age;

range, 6 months to 19 years).[7] Clinical signs usually develop acutely within 2 to 4 weeks of a respiratory infection.[8] Predominant signs are well-demarcated subcutaneous edema of all four limbs, lethargy, anorexia, hemorrhages on mucous membranes, fever, and tachycardia. Other signs are tachypnea, reluctance to move, serum exudation from the skin, colic, and epistaxis.

The predominant laboratory abnormalities include anemia, neutrophilia, hyperproteinemia, hyperfibrinogenemia, hyperglobulinemia, and elevated muscle enzymes. Thrombocytopenia is rarely detected in horses with PH.

Skin biopsy shows evidence of acute leukocytoclastic or nonleukocytoclastic vasculitis with necrosis of blood vessels. The lesions are marked dermal and subcutaneous hemorrhage, protein-rich edema, and multifocal areas of dermal infarction. Small arteries and capillaries are swollen and infiltrated by degenerate or nondegenerate neutrophils. Hyaline thrombi may be observed.[7] Immune complexes have been demonstrated to be primarily composed of immunoglobulin (Ig)M or IgA and streptococcal M protein and may be present in capillaries and small blood vessels of horses with PH, leading to a type III hypersensitivity reaction.[9] Deposition of immune complexes in vessel walls and subsequent complement activation may result in cell death. Extensive hemorrhages in the dermis, subcutis, skeletal muscles, lungs, kidneys, spleen, intestinal walls, and blood vessels have been observed in postmortem examination.

Horses with infarctive PH can present with colic, lameness, muscle swelling, and stiffness.[10] Extensive GI infarction results in severe colic signs. Significant findings in these horses include leukocytoclastic vasculitis and necrosis of various tissues, neutrophilia with a left shift, hypoalbuminemia, and high serum creatine kinase.[10]

Treatment should aim to address the primary cause if identified, reduce the immune and inflammatory response, initiate antimicrobial therapy in cases of active infection or prevent infection if indicated, provide supportive care, and prevent complications. Horses with known streptococcal infection should receive penicillin (22,000 IU/kg of intramuscular [IM] procaine penicillin G twice daily, or IV potassium penicillin G q6h) or other antibiotic with excellent efficacy against streptococcal organisms for at least 2 weeks. Hydrotherapy, limb bandages, and light exercise (hand walk) have been helpful in reducing limb edema. Fluids administered IV or via nasogastric tube may be necessary for animals that become severely lethargic and fail to drink or those that develop

dysphagia from laryngeal edema. Stridor and dyspnea may indicate the need for tracheostomy. Prolonged treatment with corticosteroids (2 to 4 weeks) has resulted in favorable outcome and low relapse rate. However, some horses may require a longer course of therapy than 4 weeks. Depending on severity of clinical signs, proposed dosages are 0.04 to 0.2 mg/kg of dexamethasone (IV, IM, or PO) once (morning) or twice a day, or 0.5 to 1 mg/kg of prednisolone PO once (morning) or twice a day, with gradual reduction of the dosage.[7] It has been suggested that antimicrobials be used throughout the course of corticosteroid therapy to reduce the occurrence of secondary sepsis.[2]

Outcomes will depend on early detection, early aggressive treatment, and extent of organ involvement. Skin sloughing, laminitis, cellulitis, pneumonia, and diarrhea are common and may significantly prolong convalescence. The prognosis is fair with early aggressive therapy and supportive care; a retrospective study of 53 horses with purpura hemorrhagica reported a mortality rate of 7.5%.[7]

Equine Viral Arteritis

Equine viral arteritis (EVA) is an infectious disease characterized by panvasculitis, edema, hemorrhage, and abortion in pregnant mares. EVA is caused by an enveloped, spherical, positive-stranded RNA virus with a diameter of 50 to 70 nm. Equine arteritis virus (EAV) is a nonarthropod-borne virus classified as a member of the new order Nidovirales within the family Arteriviridae.[11] EAV was first isolated from fetal lung collected during an epizootic of abortion in Bucyrus, Ohio.[12] Clinical signs may be absent or may develop 1 to 10 days after infection and include pyrexia, lethargy, anorexia, limb edema, stiffness, rhinorrhea, epiphora, conjunctivitis, rhinitis, and abortion. Edema of several regions can be observed, including periorbital, supraorbital, ventrum, mammary gland, scrotum, and limbs.[13] Other signs include urticarial rash, abortion, respiratory signs, ataxia, mucosal eruptions, submaxillary lymphadenopathy, and intermandibular and shoulder edema. EAV can present as epidemic abortion, with occasional fatalities in foals and adults. With natural exposure, abortion rate varies widely (<10% to >60%) and can occur from 3 to 10 months of gestation.[14] Infected mares do not become EAV carriers or chronic shedders and do not appear to have fertility problems.

Laboratory abnormalities are variable and not diagnostic for EVA.

Experimentally infected mature horses had a consistent leukopenia due to neutropenia and lymphopenia.[15] After infection, EAV can be localized in macrophages and lymph nodes within 24 and 48 hours, respectively. Various tissues are affected, but blood vessels are the principal target of EAV. Within vessels, EAV localizes in endothelium, medial myocytes, and pericytes. The virus causes vasculitis with fibrinoid necrosis of the tunica media, abundant vascular and perivascular lymphocytic and lesser granulocytic infiltration with karyorrhexis, loss of endothelium, and formation of large fibrinocellular stratified thrombi.[13] Body cavity effusion is common.

The virus is mainly transmitted through aerosols from respiratory, urinary, or reproductive tract secretions of acutely infected animals. The other route of transmission is via semen from persistently infected stallions; the virus remains viable in fresh, chilled, and frozen semen.[14] Horizontal transmission via fomites is possible.[16] Natural EAV exposure results in long-term immunity to the disease. Mares and geldings eliminate virus within 60 days, but 30% to 60% of acutely infected stallions will become persistently infected, temporarily or permanently shedding virus in semen.[13] The virus is maintained in the accessory organs of the male reproductive tract (ampullae, vasa deferentia).[14] Seroprevalence for EAV is common in the Standardbred and warmblood breeds and, more recently, EAV infection has been established within some Quarter Horse populations.[17]

Laboratory diagnosis of EVA can be based on virus isolation, viral nucleic acid detection (polymerase chain reaction [PCR] assay), or serology. In the case of serology, a fourfold or more increase in serum neutralizing antibodies between acute and convalescent samples (3 weeks apart) is required for diagnosis. Stallions with positive titers of 1 : 4 should be tested for persistent infection by virus isolation from sperm-rich ejaculate.[14] Viral isolation and PCR can be attempted from respiratory secretions or fetal and placental tissues. Semen can be tested for viral shedding by culture, isolation, or PCR. Identification of carrier stallions is crucial in preventing dissemination of EAV. A modified live (ML) vaccine is commercially available (ARVAC [Zoetis Animal Health Inc, Kalamazoo, Mich., USA]). Vaccination will result in development of a serum titer that will be detected on EVA testing and cannot be distinguished from active infection. Horses vaccinated for the first time should have serum submitted to a U.S. Department of Agriculture (USDA)-approved laboratory to confirm seronegative status. After vaccination, these animals should be isolated

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for 28 days because they may temporarily shed the modified virus; however, there is no evidence that stallions vaccinated with the ML vaccine develop the carrier state.[18]

Equine Infectious Anemia

See section on hemolytic anemia.

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Anaplasma Phagocytophila Infection in Horses

John E. Madigan

Definition and Etiology

Equine granulocytic ehrlichiosis (EGE) was first reported in the late 1960s in the foothills of northern California.[1] The disease is caused by *Anaplasma phagocytophila*. This organism was formerly known as *Ehrlichia equi*, but it was reclassified in the *Anaplasma* genus on the basis of genetic analysis.[2] Recently, the agents of human granulocytic ehrlichiosis (HGE), *Ehrlichia phagocytophila* and *E. equi*, were grouped into a single species and named *A. phagocytophila*.[2] These organisms are identical based on 16S rRNA gene sequences, and they have similar morphology, host cell tropism, and indirect fluorescent antibody (IFA) response.[3]

The organism is found within vacuoles (1.5 to 5 µm in diameter) in the cytoplasm of infected granulocytes, primarily neutrophils and eosinophils. These vacuoles or inclusion bodies are pleomorphic and contain one or more coccobacillus or large granular aggregates called *morulae*. The organisms are visible under light microscopy as deep blue to pale blue gray with Giemsa or Wright-Leishman stains.

Epidemiology

Since the disease was first reported in California,[4] cases have been diagnosed in Colorado, Connecticut,[5] Florida, Illinois, Minnesota, New Jersey, New York, Oregon, Washington, Wisconsin, Canada, Brazil, northern Europe, Poland, Italy, Pakistan, South Korea, Ukraine, and Israel.[6] Equine cases occur most commonly during late fall, winter, and spring. There is no apparent gender or age predilection, but the disease appears to be less severe in younger horses. Persistent, chronic, or latent infections or carrier status have not been demonstrated and are unlikely to occur, since the presence of *A. phagocytophila* is limited to the acute phase. Therefore it is also unlikely that infected horses

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could serve as reservoirs. Anaplasma phagocytophilum is a zoonotic infection with human infection occurring via tick bite. The disease is not contagious but could be readily transmitted through the administration of infected blood. The vectors of granulocytic ehrlichiosis are *Ixodes pacificus* in California, *Ixodes scapularis* in the eastern and midwestern United States, and *Ixodes ricinus* in Europe.[7-10] Potential or proposed reservoirs are white-footed mice, chipmunks, white-tailed deer, dusky-footed wood rats, cervids, lizards, and birds.[10]

Pathogenesis

The pathogenesis of the disease is unknown. Entry of the organism occurs after inoculation from a biting tick and is presumed to be spread via blood and/or lymph. The organism has cell tropism toward neutrophils and eosinophils, where it replicates within vacuoles, forming characteristic morulae. Presumed cytolysis, induction of inflammation, cell sequestration, consumption, or destruction result in the observed clinical signs and pancytopenia.[11] Modulation of clinical signs in experimental infection in horses occurs with dexamethasone treatment.[12] This indicates that the proinflammatory response plays a role in worsening disease severity and that disease severity can be decreased by modulating proinflammatory response.[12]

Cell- and humoral-mediated immune responses develop in affected animals. Antibody titers peak at 19 to 81 days after the onset of clinical signs, and immunity likely persists for a long period of time (>2 years).[13]

Clinical Signs

Clinical signs vary depending on the stage of infection. Early signs are fever of unknown origin and partial anorexia. Further signs develop over 24 to 48 hours and include reluctance to move, fever ranging from 39.4° to 41.3° C (102.9° to 106.3° F), mild to moderate tachycardia (50 to 60 beats per minute [bpm]), lethargy, decreased appetite, limb edema, petechiation, icterus, weakness, ataxia, and recumbency (reported in one case). Secondary trauma may result from falling in severely ataxic horses. Additional presentations besides the classic signs described may occur. Several reports of cardiac arrhythmias in clinical cases have been noted with premature ventricular contractions observed. Severe rhabdomyoliss may be the presenting clinical presentation in some cases.[14,15]

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The clinical signs appear to be less profound in younger horses. The incubation period after natural infection is believed to be fewer than 14 days. The prepatent period after experimental exposure to infected ticks or inoculation with infected blood is 8 to 12 days and 3 to 10 days, respectively. The disease is self-limiting and nonfatal provided no complications develop. However, affected horses may be predisposed to secondary bacterial, fungal, and viral infections.[1] Abortions and laminitis have not been reported in affected horses.

Clinical Pathology

Laboratory alterations include anemia, leukopenia characterized by granulocytopenia and lymphopenia, and thrombocytopenia. Morulae will be observed within the cytoplasm of neutrophils and eosinophils during the infection.

Diagnosis

Definitive diagnosis is based on the presence of characteristic morulae within the cytoplasm of neutrophils and eosinophils, or positive PCR assay for *A. phagocytophila* in peripheral blood (buffy coat).[16] Morulae may be observed in less than 1% of cells in the initial stages of the infection, rising to 20% to 50% of cells a few days later. False-positive morulae identification can occur when Dohle bodies in toxic neutrophils are mistaken for morulae. Therefore careful screening of a blood film and identification of several morulae is suggested. The history of Ixodes sp tick exposure should be a critical part of the history in suspected cases. A fourfold or greater increase in IFA titer of paired samples confirms recent exposure.[17]

Pathologic Findings

Petechiae and ecchymosis of subcutaneous tissues, as well as edema of the ventral abdomen, limbs, and prepuce, are characteristic in infected animals. Proliferative and necrotizing vasculitis, thromboses, and perivascular cuffing in subcutaneous tissue, fascia, kidneys, heart, brain, lungs, ovaries, and testes have been reported.[1,11]

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Treatment, Prognosis, and Prevention

The treatment of choice is IV administration of oxytetracycline at 7 mg/kg, or oral administration of doxycycline at 20 mg/kg of body weight once a day for 5 to 7 days. Prompt response to treatment is seen within the first 24 hours. Supportive therapy may be necessary in some cases. In cases with severe ataxia, use of dexamethasone may hasten resolution of clinical signs. The disease can be self-limiting in 2 to 3 weeks if untreated. Prognosis is excellent provided no secondary complications develop. In experimental cases and reports of natural infection, there are no reports of laminitis associated with the infection. At present, prevention is limited to tick control.

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Thrombocytopenia

Johanna L. Watson • Debra Deem Morris

Thrombocytopenia (platelet count <100,000/µL) can result from one or more of three basic mechanisms: (1) decreased or ineffective platelet production; (2) abnormal sequestration (usually in the spleen); or (3) increased platelet consumption or destruction. Thrombocytopenia causes a hemorrhagic diathesis characterized by multiple sites of small vessel bleeding. Petechial hemorrhages with or without ecchymotic hemorrhages can be found on the oral, nasal, or vaginal mucous membranes, as well as on the nictitans and sclera. Epistaxis, melena, hyphema, or microscopic hematuria may occur, but spontaneous hemorrhage is uncommon unless the platelet count is less than 10,000/µL. Prolonged bleeding from wounds, injections, or surgical procedures and the propensity to form hematomas after minor trauma are common when the platelet count is below 40,000/µL. Severe thrombocytopenia produces prolonged bleeding time and abnormal clot retraction without affecting clotting times or plasma fibrinogen.

Persistent life-threatening hemorrhage caused by thrombocytopenia may be treated with a transfusion of compatible fresh whole blood or, preferably, platelet-rich plasma. The latter may be produced by centrifugation of freshly collected blood, 3 to 5 minutes at 250 *g*.[1] Blood or plasma must be used immediately, and contact with glass must be prevented to avoid platelet adhesion and activation. Platelet transfusion is a transient life-saving measure, and the ultimate prognosis for thrombocytopenia depends on the cause.

Decreased production of platelets may occur secondary to replacement of the normal marrow architecture by neoplastic or inflammatory tissue (myelophthisic disease) or bone marrow aplasia. Both conditions are characterized by peripheral pancytopenia of variable severity and are extremely unusual in large animals. Myelophthisic disease with thrombocytopenia has been described in horses with various forms of myelogenous neoplasia[2-4] and eosinophilic myeloproliferative disorder.[5]

Hypoplastic anemia with leukopenia and thrombocytopenia has been reported in horses and cattle and is discussed later in the chapter in the section on aplastic anemia. Shortened platelet life span is by far the most common cause of thrombocytopenia in large animals. Increased platelet consumption accompanies

DIC (discussed in the next section) and rare cases of vasculitis. Immune-mediated mechanisms result in platelet destruction.

Immune-mediated thrombocytopenia (IMTP) may be primary (idiopathic) or secondary to drug administration, infections, neoplasia, or other immunologic disorders. This disease is most common in horses and has been reported secondary to EIA,[6] lymphoma,[7] and autoimmune hemolytic anemia.[8] The clinical signs of IMTP include mucosal hemorrhages and the propensity to bleed from small blood vessels. Horses with idiopathic IMTP are usually bright, afebrile, and without overt hemorrhage despite severely reduced platelet numbers. Thrombocytopenia in a horse with obvious primary disease should prompt a thorough hemostatic workup to rule out DIC.

Alloimmune thrombocytopenia of neonates has been recognized as a spontaneous disease of human infants, piglets, foals, and mule foals.[9] Clinical signs include depression, loss of suckle, a bleeding tendency, blood loss, and rapidly developing anemia due to a profound thrombocytopenia. The condition occurs in multiparous dams, and immunoglobulins from the mare, found in her plasma, serum, and milk, bind to the foal's platelets. Alloimmune thrombocytopenia should be considered in neonates with severe thrombocytopenia when other causes can be excluded, and platelet antibody assays should be used to support this diagnosis. Differential considerations include neonatal sepsis, neonatal maladjustment syndrome, and neonatal isoerythrolysis. Laboratory findings of IMTP include severe thrombocytopenia (<40,000/µL), prolonged bleeding time, and abnormal clot retraction with normal thrombin time (TT), PT, APTT, and plasma fibrinogen. Fibrin(ogen) degradation products (FDPs) may be mildly increased, and anemia accompanied by hypoproteinemia develops if there is ongoing blood loss. In most cases of IMTP and other causes for shortened platelet life span, megakaryocytic hyperplasia is evident on examination of bone marrow aspirates or biopsies. The definitive diagnosis of IMTP requires demonstration of increased quantities of platelet-associated IgG or C3 or antiplatelet activity in the serum. Flow cytometric methods to detect platelet surface–associated IgG (PSAIgG) have been adapted for horses.[10] Without PSAIgG testing, the diagnosis of IMTP must be based on small-vessel hemorrhagic diathesis and severe thrombocytopenia in a horse with normal coagulation times and no other evidence of DIC. Response to therapy (see next section) supports the diagnosis. A tentative diagnosis of IMTP in the horse should prompt a thorough search for an underlying disorder, especially lymphoma.

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Platelet destruction in IMTP is mediated by antibodies coating the platelet surface that cause premature platelet removal from circulation by the MPS.[11] Autoantibodies may attach to megakaryocytes, but the latter are not necessarily destroyed because they do not circulate through the spleen or liver. In secondary IMTP the Ig bound to the platelet surface is part of an immune complex composed of antibody directed against a drug, microbe, or neoplastic antigen that is nonspecifically attached to the platelet Fc receptor. Drug-induced IMTP generally subsides within a few days of drug discontinuation, although thrombocytopenia secondary to chrysotherapy (gold therapy) may persist for weeks to years. Because gold is occasionally used to treat pemphigus foliaceus in horses, thrombocytopenia should be considered as a potential side effect. The spleen is the major site of platelet phagocytosis because (1) much antiplatelet antibody is secreted locally, (2) more than 30% of circulating platelets are normally stored there, and (3) the stagnant splenic blood flow allows sensitized platelets to pass slowly through a dense network of phagocytic cells.

When any unexplained case of thrombocytopenia is treated, all current medication should be stopped. If a drug is absolutely necessary, it must be replaced by the chemically most dissimilar substitute. Drug-induced IMTP usually responds within 14 days of drug withdrawal. Most animals with suspected IMTP improve when treated with corticosteroids. Although their precise mechanisms of action are speculative, corticosteroids improve capillary integrity, impair clearance by the MPS, decrease the number and avidity of macrophage Fc receptors, impair antiplatelet antibody production, impede platelet-antibody interactions, and increase thrombocytopoiesis.

Dexamethasone (0.04 to 0.2 mg/kg IV or IM) given once daily generally results in an elevation in the platelet count within 4 to 7 days. Once the platelet count is greater than 100,000/µL, the dose of dexamethasone can be reduced by 10% to 20% daily while the platelet count is monitored for a relapse. Occasionally, animals with IMTP are refractory to dexamethasone, in which case prednisolone (0.5 to 1 mg/kg IM twice daily) may be tried. Treatment with corticosteroids can usually be discontinued after a period of 10 to 21 days, provided the platelet count has been normal for at least 5 days. Most horses with IMTP have a favorable prognosis, and the disease resolves within 14 to 21 days. This suggests that many cases may be secondary, yet the initiating cause is rarely found. Chronic or recurrent IMTP requiring prolonged corticosteroid therapy has been reported.[12] Alternative treatment modalities for IMTP are largely unproven in horses because most cases are responsive to corticosteroids.[13-15]

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Disorders of Coagulation Factors

Johanna L. Watson • Debra Deem Morris

Normal blood coagulation proceeds in an integrated sequence that can be simplistically viewed as three key reactions: formation of activated factor X, formation of thrombin, and formation of fibrin. Other protein interactions serve to accelerate or inhibit the reaction rates of coagulation factors. Excessive use or inhibition of these proteins produces a relative deficiency that causes hemorrhagic diathesis. Alterations in the coagulation cascade, including thrombocytopenia and procoagulant and anticoagulant effects, can be observed with snakebite (e.g., rattlesnake) envenomation (see Chapter 54).

Disseminated Intravascular Coagulation

The most common form of hemostatic dysfunction in large animals is a syndrome known variously as disseminated intravascular coagulation (DIC).[1,2] The pathologic process is characterized by widespread fibrin deposition in the microcirculationand development of a hemorrhagic diathesis caused by the consumption of procoagulants and hyperactivity of fibrinolysis. Never a primary disease entity, DIC represents an intermediary mechanism of underlying disease. In large animals, DIC has been described in association with localized or systemic septic processes,[2-5] neoplasia,[2] GI disorders,[6] renal disease,[6] and hemolytic anemia.[5,7] Diffuse activation of the hemostatic system is particularly prevalent in horses with acute GI disorders that cause colic[5,6] and is a likely initiating factor for laminitis.[8,9] Clinical manifestations of DIC may fall anywhere on the spectrum from diffuse thrombosis leading to ischemic organ failure to severe hemorrhagic diathesis. The most important determinants are the rate of thrombin generation, adequacy of fibrinolysis, and functional state of the MPS, which is largely determined by peripheral circulation. Coagulopathy usually occurs in a compensated form in horses and cattle and is rarely attended by overt hemorrhage; however, microvascular thrombosis and subsequent ischemia to vital tissues leads to organ malfunction (e.g., renal failure), which contributes to the morbidity and mortality of the primary disease process.

Renal involvement is common in DIC, which produces ischemic cortical necrosis followed by acute tubular necrosis. Renal disease may be manifested by

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oliguria, depression, and ileus caused by azotemia and electrolyte imbalances. GI microthrombosis may induce colic as a result of submucosal necrosis and superficial ulceration. Spontaneous GI hemorrhage caused by DIC may cause melena in ruminants and occult fecal blood loss in horses. Pulmonary function may rarely be compromised by microvascular thrombosis in DIC, causing tachypnea and variable hypoxemia. Altered consciousness, delirium, convulsions, or coma may follow cerebral microvascular thrombosis but is not common with DIC in large animals. Although reported in both horses[10] and cattle,[7] microangiopathic hemolysis is rare in large animals with DIC because of their small erythrocyte size.

Digital ischemia frequently accompanies DIC in horses and may play a role in the development of acute laminitis. Laboratory evidence of DIC has been documented during the developmental phase of equine laminitis,[9] and digital microvascular thrombosis occurs in horses that develop laminitis with colic or septic conditions.[8] The tendency for thrombosis of major peripheral veins is another prominent manifestation of coagulopathy in horses.

As the thrombotic stimulus continues or intensifies, the tendency for hemorrhage develops because of clotting factors and platelet depletion or generation of excessive fibrinolytic by-products (FDPs). Petechial or ecchymotic hemorrhages on mucosae and sclerae and a tendency to bleed from venipuncture or after minor trauma are the principal signs. Spontaneous life-threatening hemorrhage is rare, but trauma or surgery may induce uncontrollable hemorrhage. Diseases that must be differentiated from DIC include IMTP, warfarin toxicosis (horses), moldy sweet clover toxicosis, and inherited coagulation abnormalities.

Numerous laboratory tests of hemostasis may be abnormal during DIC, but no one test consistently or specifically provides a definitive diagnosis. The lack of test sensitivity is due to the dynamic nature of DIC, the laboratory reflection of which is determined by the balance between coagulation and fibrinolytic forces, as well as MPS integrity at the time of blood sampling.

The most widely used hemostatic function tests for DIC in large animals include platelet count, plasma fibrinogen, PT, APTT, antithrombin (AT), and serum FDPs/D-dimers.[11] Because clinical manifestations of DIC vary widely, clarification of the most frequent laboratory abnormalities in large animals with DIC is hindered by lack of a definitive diagnosis in most instances. Repeated hemostatic testing is advised when there is strong suspicion for DIC. Serum

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FDPs are most often elevated by DIC, but they are usually normal in the early or compensated form of the disease. Hypofibrinogenemia is an uncommon manifestation of DIC in large animals and, when present, should strongly suggest concomitant liver dysfunction. Hemostatic function tests are totally unreliable unless blood samples are collected and handled properly.

Criteria used for diagnosis of DIC are extremely arbitrary, and laboratory results must be interpreted in light of the patient's underlying disease. The combination of thrombocytopenia with mild to moderate PT or APTT prolongation strongly suggests DIC. The clinician should seek laboratory assistance when considering the diagnosis of DIC but appreciate that the findings are often not helpful. Clinical signs and specific situations suggest the possibility of DIC, and laboratory tests are only used to provide support.

Diseases initiate DIC by two major mechanisms: (1) generation of excessive procoagulant activity within the blood or (2) contact of blood with abnormal surfaces. Many diseases that produce DIC have the propensity to cause endotoxemia. The intestinal tract in large animals normally contains large quantities of endotoxins, only a small part of which is absorbed through the portal vein and removed by the liver. Conditions that cause intestinal mucosal edema or disruption allow endotoxins to gain access to the peripheral circulation and initiate many morbid sequelae, one of which is DIC. Intestinal strangulating obstruction, thromboembolic infarction, and severe colitis induce mucosal abnormalities, allowing endotoxemia to occur. The proliferation of gram-negative bacteria within tissues and the blood is also accompanied by endotoxemia.

Gram-negative endotoxins are capable of direct factor XII activation. However, most studies indicate that the procoagulant effects of endotoxin are primarily mediated by cytokine production by mononuclear phagocytes.[12] After endotoxin stimulation, phagocytes produce a platelet-activating factor (PAF), tissue factor, prostaglandins, interleukins (ILs), tumor necrosis factor (TNF), and other mediators with procoagulant activity.[13]

The net result of any triggering mechanism for DIC is exaggerated generation of systemic thrombin, which causes widespread microcirculatory thrombosis. In addition to the cleavage of fibrinogen to produce fibrin monomers, thrombin activates factor XIII to render fibrin more resistant to fibrinolysis, enhances the cofactor activity of factors V and VIII, and induces platelet aggregation and exposure of platelet phospholipid. Circulatory obstruction produces organ hypoperfusion, leading to ischemic necrosis.

The counterbalance fibrinolytic system is also activated by DIC, and plasmin contributes to factor consumption by destroying factors V, VIII, XIIa, IX, and XI, in addition to fibrin and fibrinogen. FDPs contribute greatly to the hemorrhagic manifestations of DIC because they have antithrombin activity, interfere with fibrin monomer polymerization, and cause platelet dysfunction. Paradoxically the combination of consumption and anticoagulation predisposes to hemorrhage at the same time disseminated thromboses occur.

The MPS plays a vital role in the pathogenesis of DIC. The tissue-fixed macrophages of the spleen and liver normally remove FDPs and activated clotting factors from the peripheral circulation, and FDPs only increase when their rate of formation exceeds the ability of the MPS to clear them. Shock and hypoperfusion of the liver and spleen or diseases associated with excessive tissue debris that must be removed by the MPS (e.g., sepsis, metastatic neoplasia) reduce its ability to function effectively and predispose to or perpetuate DIC.

Therapy for DIC is highly controversial, and the only undisputed modalities are those directed toward identification and treatment of the primary disorder, along with general supportive measures to combat shock and maintain tissue perfusion.[14,15] Intravenous fluid administration helps prevent organ dysfunction after microvascular thrombosis and can correct existing acid-base or electrolyte imbalances. Septic conditions should be treated with appropriate antimicrobial agents, and necrotic tissue or purulent exudate should be removed whenever possible (e.g., immediate surgical intervention to resect nonviable bowel). Flunixin meglumine mitigates the deleterious effects of endotoxin caused by eicosanoids and is used in horses at a dosage of 0.25 mg/kg IV q8h). Corticosteroids may worsen DIC because they reduce the phagocytic action of the MPS and potentiate the vasoconstrictor effects of catecholamines.

Significant life-threatening hemorrhage is rare in large animals with DIC, but if it occurs, fresh plasma should be administered (15 to 30 mL/kg) to replace used coagulant and anticoagulant proteins. The use of low-molecular-weight heparin, over unfractionated heparin, in DIC has been recommended in various regimens to stall the disseminated microvascular thrombosis that precipitates organ failure.[11,16,17] In dogs, minidose heparin therapy (50 to 75 units/kg subcutaneously [SC] three times daily, or 5 to 10 units/kg/h) is commonly used with blood products to treat DIC.[14] Efficacy of heparin for DIC in horses is unproven. Heparin in all species can predispose to hemorrhage, thrombosis, and thrombocytopenia[16] and can cause anemia and erythrocyte agglutination in

horses.[17] If heparin therapy is considered, one must ensure there is adequate plasma AT III, which is necessary for heparin action. Because AT III is often depleted by DIC, plasma may be necessary.

The prognosis for DIC in large animals depends largely on the nature and severity of the underlying disease and how effectively the latter is treated. Once DIC has progressed to the stage where signs of coagulation dysfunction predominate, the prognosis is generally poor.

Warfarin Toxicosis

Horses may develop a hemorrhagic diathesis due to warfarin toxicosis.[18] This coumarin-derivative anticoagulant has been used by some to treat horses with navicular disease.[19] Rarely, horses and other animals may be exposed to coumarins used as rodenticides in grains or other feedstuffs. The clinical signs of warfarin toxicosis include hematomas, ecchymoses of mucous membranes, epistaxis, and hematuria. The earliest laboratory indication of warfarin toxicosis is prolongation of the PT, because the plasma half-life of factor VII is shorter than the other clotting factors.[20] As the disease progresses, the APTT becomes prolonged and the animal may develop blood-loss anemia and hypoproteinemia. The diagnosis of warfarin toxicosis is based on a history of exposure, clinical signs of large-vessel hemorrhagic diathesis, and prolonged PT with or without APTT and with no other abnormalities of the clotting profile.

Warfarin acts through competitive inhibition of vitamin K, which is necessary for liver production of clotting factors II, VII, IX, and X.[19] Factor activity is reduced in the blood at a rate dependent on its individual half-life. In most species, factors VII, IX, X, and XI have increasingly greater half-lives, accounting for the greater sensitivity of PT for the early diagnosis of warfarin toxicosis. After GI absorption, warfarin is highly bound to plasma proteins. Drugs that are normally protein bound (e.g., phenylbutazone) can enhance warfarin's toxicity by allowing a greater proportion of the administered drug to be unbound and active.[21] In the same manner, hypoalbuminemia may increase the likelihood of warfarin toxicosis. Corticosteroids and thyroxin can lower the necessary therapeutic dose of warfarin by increasing both receptor affinity and clotting factor catabolism. Drugs that induce hepatic microsomal enzyme activity (e.g., barbiturates, rifampin, chloramphenicol) can accelerate warfarin metabolism and reduce therapeutic response to a given dose. Any reduction in

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hepatic function or content of vitamin K in the diet can also precipitate warfarin toxicosis.

Treatment of warfarin toxicosis depends on clinical signs. Warfarin therapy should be stopped if the PT exceeds twice the pretherapeutic value. Vitamin K_1 (0.5 to 1 mg/kg SC or IM) must be given every 6 hours until the PT is again normal and stable. Significant hemorrhage can be controlled by giving fresh plasma to provide necessary clotting factors. If the anemia is life threatening, whole blood transfusion should be considered. Although warfarin is eliminated rapidly, some potentiated coumarins have a prolonged half-life, requiring a longer course of vitamin K therapy. With early diagnosis and prompt vitamin K treatment, the prognosis for warfarin toxicosis is good. However, it is imperative that vitamin K_3 *not* be used because it has poor therapeutic action and is highly nephrotoxic for horses.[22]

Prevention of warfarin toxicosis is based on limiting access of livestock to rodenticides and carefully monitoring the therapeutic use of warfarin in horses. Warfarin's benefits for horses are highly controversial, and many question whether its advantages outweigh the risks.

Sweet Clover Toxicosis

Sweet clover (*Melilotus* spp.) toxicosis is caused by ingestion of moldy sweet clover hay or silage containing dicoumarol. Natural coumarins in sweet clover can be converted to dicoumarol when hay or silage is improperly cured and mold forms. The toxin persists in moldy hay or silage and is palatable. This disease can occur in all species but is most commonly seen in cattle fed sweet clover hay in the Northern Plains states. Early signs include epistaxis and melena, with the development of subcutaneous hematomas and periarticular swellings as the disease progresses. Visible swellings occur at points of trauma such as the brisket, tuber coxae, or carpi and are not hot or painful, although they may cause stiffness and disinclination to move. Accidental and surgical wounds cause severe hemorrhage and may precipitate fatal blood-loss anemia.

Clinical pathology is similar to that described for warfarin toxicosis, with prolonged PT being the earliest abnormality (detected before clinical evidence of hemorrhage). The platelet count remains normal, which differentiates this syndrome from DIC and bracken fern toxicosis. Other diagnostic ruleouts include mycotoxicosis and toxicosis from trichloroethylene-extracted soybean meal. In the absence of fever and anorexia, coagulopathy should make moldy

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sweet clover toxicosis a strong tentative diagnosis in animals with a history of access. Chemical analysis for dicoumarol in suspected feed or in the blood and liver of affected animals aids in the diagnosis,[23] but the disease cannot be excluded if dicoumarol is not detected.

The pathogenesis of moldy sweet clover toxicosis is identical to that of warfarin toxicosis. Dicoumarol interferes with hepatic synthesis of clotting factors II, VII, IX, and X by inhibiting vitamin K. Usually the syndrome appears in cattle 2 to 7 days after they ingest the moldy hay. Lower levels of dicoumarol (<70 mg/kg) in feed may prolong the onset of signs for up to 3 months.

Grazing sweet clover is not dangerous. Because of its high forage yield, sweet clover is usually harvested as silage, which should carry less danger of molding when properly cured. The toxic level of dicoumarol in sweet clover feed samples is 10 mg/kg of feed.[23]

Treatment of sweet clover toxicosis involves discontinuing the use of contaminated feed and administering vitamin K_1.[21] Dosages between 0.5 and 1 mg/kg of body weight should be administered SQ or IM every 6 hours; response occurs within 24 hours. Animals with severe blood-loss anemia or ongoing hemorrhage should be treated with plasma or whole fresh blood. Sweet clover toxicosis can be prevented by careful forage preparation, followed by the inspection of hay and silage before feeding. When the disease is suspected, questionable feed should be removed from the diet.

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Diseases Associated With Increased Erythrocyte Destruction (Hemolytic Anemia)

Johanna L. Watson • Gary P. Carlson

Hemolytic disorders are characterized by an increased rate of red cell destruction, and anemia results when the rate of red cell destruction exceeds the bone marrow capacity for increased proliferative response. Although intravascular hemolysis occurs in some circumstances, these anemias are primarily due to an increased rate of extravascular erythrocyte destruction and shortened intravascular life span.

Hemolytic anemias are associated with a wide range of systemic disease processes. A list of differential considerations for possible causal factors of hemolytic anemia in large animals is presented in Box 37.1. Clinical manifestations of hemolytic anemia will vary with the degree of anemia, rate of red cell destruction, and primary or underlying disease process. However, several common clinical signs are seen in animals with severe hemolytic anemia, regardless of the cause: mucous membrane pallor, fatigue, depression, and anorexia. Clinical icterus can be quite variable depending on the rate of red cell destruction and the liver's ability to excrete bilirubin. Icterus is a characteristic feature in hemolytic anemia, but intense icterus is noted only after massive red cell destruction and is often transient. With continued low-level hemolytic processes, the liver may be able to excrete bilirubin at a rate sufficient to avoid clinical icterus. Hemolytic icterus must be differentiated from other potential causes like liver disease or anorexia in horses. If icterus is caused by hemolytic processes, clear clinical and hematologic evidence of anemia should exist. Massive intravascular hemolysis may result in an orange to reddish discoloration of the mucous membranes. Modest to marked and often variable febrile responses are frequently encountered in hemolytic anemias caused by infectious agents and during periods of active erythrocyte destruction. With advanced anemia the pulse and respiratory rates are elevated at rest. Death losses may occur, and neurologic abnormalities ranging from bizarre behavior to mania, collapse, and death may be associated with handling animals with severe anemia.

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Box 37.1

Causes of Hemolytic Anemia

Infectious Causes

Parasitic

Anaplasmosis
Babesiosis
Hemobartonellosis
Eperythrozoonosis
Theileriasis
Trypanosomiasis

Bacterial

Leptospirosis
Bacillary hemoglobinuria

Viral

Equine infectious anemia (EIA)

Immune-Mediated Hemolytic Anemia

Autoimmune hemolytic anemia
Neonatal isoerythrolysis (NI)
Drug induced: penicillin, trimethoprim-sulfamethoxazole

Heinz Body Hemolytic Anemia

Phenothiazine toxicity
Wild onion poisoning
Red maple leaf poisoning

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Other Causes

Severe cutaneous burns
L-Tryptophan-indole intoxication
Water intoxication
Postparturient hemoglobinuria
Copper poisoning
Hemolytic syndrome in horses with liver failure
Erythropoietic porphyria in Holstein cattle

The hematologic manifestations of hemolytic anemia also vary with the rate of red cell destruction, time course of the anemia, and primary or underlying disease process. Anemia may be modest to severe, and after the first few days in all species except the horse, there is usually hematologic evidence of enhanced erythropoietic response seen as increased anisocytosis, polychromasia, reticulocytosis, and the presence of nucleated red blood cells in the circulation. Morphologic abnormalities of diagnostic significance (e.g., intracellular or epicellular parasites, granulocytic inclusion bodies, Heinz bodies, spherocytes, schistocytes, or poikilocytes) may be noted on examination of stained blood smears. Responsive anemias often are accompanied by neutrophilia and a regenerative left shift. Bone marrow usually shows an active erythropoietic response with a decreased myeloid/erythroid (M:E) ratio. The serum concentration of haptoglobin is decreased, and serum lactate dehydrogenase enzyme activity may be elevated during acute hemolytic episodes. An increase in serum bilirubin concentration caused primarily by an increase in indirect reacting bilirubin is a reflection of active red cell destruction. Specific serologic diagnostic procedures are available for many of the infectious causes of hemolytic anemia. Immunohematologic procedures like the direct and indirect Coombs test provide an indication that immune-mediated processes contribute to enhanced erythrocyte destruction. It should be noted that the principal mechanisms responsible for the increased rate of red cell destruction associated with many infectious causes of hemolytic anemia (parasitic, bacterial, viral) are immunologically mediated, and affected animals may be transiently Coombs positive.

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▪ Infectious Causes of Hemolytic Anemia

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Bovine Anaplasmosis

Kristin A. Clothier

Etiology

Molecular characterization and genetic analysis of *Anaplasma* and *Ehrlichia* have resulted in identification of six species in the *Anaplasma* genus: *Anaplasma phagocytophilum* (formerly called both *Ehrlichia equi* and *Anaplasma equi*), which infects granulocytes in a wide range of mammalian species including dogs, horses, and humans*; A. marginale, A. ovis,* and *A. centrale,* which infect erythrocytes of wild and domestic ruminants; *Anaplasma bovis,* which infects monocytes of cattle and related species; and *Anaplasma platys,* which primarily affects platelets in small animal species.[1,2] Recently, a novel species has been identified in white-tailed deer and the name *Anaplasma odocolei* sp. nov. has been proposed.[1] Although many species become infected and demonstrate symptoms of disease due to *A. phagocytophilum* infection, there is no evidence that *A. marginale* or *A. ovis* is capable of infecting humans or any nonruminant mammalian species.

In livestock medicine, *anaplasmosis* traditionally refers to disease characterized by progressive anemia caused by intraerythrocytic infection with *A. marginale* in cattle and *A. ovis* in sheep and goats. In addition, *A. centrale* causes mild disease in cattle and has been used as a live vaccine to induce partial protection against *A. marginale*.[3] These organisms are obligate intracellular bacteria located either at the periphery (*A. marginale* and *A. ovis)* or center (*A. centrale)* of red blood cells (RBCs).[4,5] They reside and replicate inside parasitophorous vesicles and replicate by binary fission, with each vesicle containing four to eight organisms.[6]

Pathogenesis

Anaplasma spp. are naturally transmitted by ixodid species ticks, most commonly *Dermacentor* in the U.S. mainland and *Rhipicephalus* spp. (including tick species previously classified in the genus *Boophilus*) in tropical and subtropical regions worldwide.[1,3] When ingested by feeding ticks, *Anaplasma*

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spp. enter midgut epithelial cells, complete the first round of replication, migrate to salivary epithelial cells, undergo a second round of replication, and enter the saliva, where they can be passed to the next host. Organisms can be transmitted transstadially (from larvae to nymphs and nymphs to adults), indicating that ticks can become infective and transfer *Anaplasma* spp. to a new host after only a single molt. Transovarian transmission has not been demonstrated.[1,7]

In the host, sequential rounds of bacterial invasion of mature erythrocytes, replication, and egress result in a progressively increasing cell-associated bacteremia, with a doubling time of roughly 24 hours. Depending on the strain of *Anaplasma* spp. and host susceptibility, 10% to 90% of erythrocytes may become infected; clinical signs appear when more than 15% of erythrocytes are infected.[7,8] Bacteremia results in RBC membrane peroxidation with infected cells showing a 10-fold increase in membrane leakage over uninfected RBC.[6,8] Anemia is due to splenic and hepatic macrophage-mediated phagocytosis of infected erythrocytes.

A. marginale expresses a variety of major surface proteins (MSPs), which facilitate interactions with vertebrate and invertebrate host cells.[7,9] This plasticity facilitates development of different bacterial surface structures leading to immune evasion and persistent infection in the animal. Phylogenetic analyses of a variety of strains have demonstrated the coevolution of *A. marginale* with tick vectors.[1,7] In addition, cases have been documented in which individual animals are infected by more than one genotype of *A. marginale*.[6,7,10]

Protective immunity appears to require induction of both antibody against the outer membrane proteins and macrophage activation for enhanced phagocytosis and bacterial killing.[7] The regenerative response to anemia can be vigorous and begins by 20 days post infection. While the immune response controls the acute phase of infection, organisms are not completely cleared from the blood due to emergence of antigenic variants. Infected animals demonstrate cyclic subclinical peaks of rickettsemia and immune response with a 6- to 8-week period, establishing the chronic infection state.[6]

Epidemiology

A. marginale is the most prevalent of the tick-borne diseases of cattle worldwide and remains as a serious constraint to livestock production in tropical, subtropical, and even temperate regions.[11,12] In the United States, infection is

endemic in much of the West, Midwest, and Southeast but occurs episodically in many states.[7] As of April 1, 2014, the disease is no longer federally reportable in Canada, and testing for entry into the country is not required. The expansion of anaplasmosis into previously nonendemic regions has been attributed to widespread movement of cattle and to the effects of global warming on vector expansion.[1,7,12]

Endemic regions are maintained by the prevalence of both competent tick vectors and persistently infected carrier cattle, which are typically asymptomatic but act as efficient reservoirs for tick-borne transmission to uninfected animals.[2,4] Vector activity varies by region, but outbreaks of anaplasmosis occur most frequently in the late spring and summer when arthropod activity is highest. Wild ruminants, including antelope, bighorn sheep, and elk have been experimentally infected with *A. marginale,* but the role they play in natural transmission is unknown. Male ticks can also remain persistently infected and a source for maintaining the bacteria in endemic regions.[4,11]

While tickborne transmission is perhaps the most investigated route of spread, with at least 20 different species of ticks identified as sources of infection, other activities in which blood transfer occurs can result in infection.[3,4] Fomites (surgical instruments, dehorning equipment, ear tagging devices) are important sources of risk, particularly in nonendemic regions where tick vectors are not present. Multiuse needles and other biting arthropods are implicated in mechanical dissemination for *A. marginale*.[1,3] Iatrogenic transmission can occur anytime and can be controlled by avoiding blood contamination during veterinary medical procedures.[3,11]

Clinical Presentation

Clinical signs are highly variable, from acute severe disease to subclinical infection, and reflect variation in virulence among pathogen strains, breed resistance, and age-related host susceptibility.[4,7] The incubation period is generally 10 to 30 days but can be as long as 60 days. Primary exposure in calf hood often produces asymptomatic or mild disease resulting in slight lethargy and anorexia for 24 to 48 hours.[6,7,10] Adult cattle are highly susceptible to acute disease characterized by a high fever ranging from 39.5° to 41° C (103° to 106° F), elevated heart rate, elevated respiratory rate, anorexia, lethargy, and in dairy cows, a dramatic decrease in milk production. Initial fever may be followed by

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subnormal temperatures, dry muzzle, and decreased rumination. Cattle may stagger or become aggressive as a result of cerebral hypoxia associated with anemia. Care must be taken not to stress severely anemic cattle because this may result in collapse and death. Mucous membranes are pallid or icteric if an animal has survived for 2 to 3 days past the acute crisis.[2,7] Additional clinical signs include constipation characterized by dark brown feces covered with mucus, pollakiuria with dark yellow urine, and abortion in late-gestation animals. Because hemolysis occurs extracellularly, hemoglobinuria is not present.[3,5] Differential diagnoses include diseases that can produce anemia and/or icterus (babesiosis, bacillary hemoglobinuria, leptospirosis); hepatotoxic plant poisonings *(Senecio)*, chemicals, and other causes of liver disease; and copper poisoning in sheep.

If an animal survives the acute crisis, the convalescent period is protracted (3 to 4 weeks) depending on the severity of the anemia, and icterus and weight loss are common. Recovered animals remain infected for life and serve as a reservoir for ongoing transmission. Although *A. ovis* infection in sheep and goats is often asymptomatic, anemia occasionally becomes severe enough to produce signs similar to those seen during *A. marginale* infection of cattle, particularly if they have conditions causing immunosuppression.[7,11]

Pathology

At necropsy, there are no pathognomonic lesions for the diagnosis of disease. In acute anaplasmosis the blood is thin, watery, and fails to clot readily. Mucous membranes, subcutaneous tissues, liver, and skeletal musculature are pale; in later stages of acute disease, the same tissues may be icteric. Splenomegaly is a consistent finding; hepatomegaly and gallbladder distention are commonly but less frequently observed.[7] Urine is deep yellow, but neither hemoglobinuria nor hematuria occurs, which helps differentiate anaplasmosis from other hemolytic diseases. Occasionally petechiae may be found in the subepicardium, subendocardium, and other serous membranes. Detection of *A. marginale*–infected erythrocytes within capillaries of Giemsa-stained histologic sections can be used to confirm a diagnosis of anaplasmosis. [5]

Diagnosis

Definitive diagnosis of acute anaplasmosis requires identification of *A.*

marginale– or *A. ovis*–infected erythrocytes by microscopic examination or PCR in animals with severe anemia. *A. marginale* can best be detected in blood smears stained with Wright's, new methylene blue, or Giemsa stain.[3,5,7] The inclusion is composed of a small morula of 2 to 8 individual organisms and as little as 5% or as many as 70% of erythrocytes may be infected. Creating a blood smear from freshly collected blood in the field may increase the likelihood of detecting parasites over blood smears made from blood exposed to anticoagulants. PCR provides increased sensitivity over direct exam and can differentiate animals infected with *A. marginale*, *A.centrale*, and *A. phagocytophilum*.[13,14] A falling hematocrit provides an estimate of the severity of infection; PCV may drop precipitously within 24 to 48 hours and may decrease below 10% before death. Death can occur despite a PCV above 20% when the hemolytic crisis is acute. In protracted cases, serial monitoring of blood smears demonstrates a decrease in the percentage of infected erythrocytes and evidence of macrocytic, hypochromic red cell regeneration.[6]

Following recovery, cattle and sheep remain persistently infected with 0.000001% to 0.1% of erythrocytes affected, and detection of organisms in erythrocytes is unreliable. Serology can be used to identify persistently infected animals.[3,7] The competitive enzyme-linked immunosorbent assay (cELISA [VMRD Inc., Pullman, Wash.]) provides high sensitivity and specificity and is used for official testing by many regulatory agencies (USDA, the Office of International Epizootics, most if not all state diagnostic laboratories.)[7,11]

Treatment, Control, and Prevention

Therapy is aimed at minimizing or preventing the effects of *A. marginale* infection. Tetracyclines are the antibiotic of choice; however, once anemia is severe, treatment is often unsuccessful.[12] Short-acting oxytetracycline at 11 mg/kg IV q24h for 3 to 5 days or long-acting oxytetracycline at 20 mg/kg IM at 72-hour intervals may be effective.[2,7] Supportive therapy is important to maximize the chance of survival. If the PCV is 12% or below, whole blood transfusion (4 to 8 L) may be indicated to prevent death and shorten the convalescence period. A PCV of 8% or below indicates an unfavorable prognosis, and death often occurs despite appropriate antibiotic and supportive therapy. Antimicrobial therapy also neither eliminates persistent infection nor prevents disease, so alternative interventions are needed, especially in endemic

areas.[7,11]

Control measures used vary depending on the geographic region and type of livestock production system. In endemic regions with high transmission rates, beef cattle are often allowed to become naturally infected at a young age and remain asymptomatic carriers with minimal risk of later acute disease.[2] In regions with lower transmission rates, live blood-based vaccines may be used to ensure infection of cattle at a young age, such as the trivalent *(A. marginale, Babesia bovis, Babesia bigemina)* live vaccine used in Australia. Similarly, live vaccines based on *A. centrale* or weakly virulent strains of *A. marginale* are commonly used in Africa, Asia, and Central and South America.[3,9] These vaccines are not licensed for use in the United States, largely because of the risk of transmitting known or newly emergent pathogens contaminating the blood-based vaccine. The exception to this is the licensing of a live vaccine for use in California (AnaVac [PHL Associates, Davis, Calif.]). Importantly, live vaccines should only be used in young animals and are contraindicated for pregnant and older animals. Killed vaccines are less efficacious and require multiple immunizations but can induce at least partial protection against severe morbidity and mortality. An experimental killed vaccine (Experimental Anaplasmosis Vaccine [University Products LLC, Baton Rouge, La.) has been licensed for use in 14 states and Puerto Rico.[11]

In the absence of immunoprophylaxis, anaplasmosis is usually controlled by preventing transmission. Advances in molecular characterization may provide additional targets for successful vaccine development.[12,15] Maintenance of an *A. marginale*–free herd in nonendemic areas can be accomplished by quarantine and serologic screening of all additions using the cELISA. In endemic regions, minimizing the exposure to vectors through strategic use of pastures, insecticides, and management of herd additions, as well as preventing iatrogenic transmission, can reduce the impacts of anaplasmosis.[2,7] Restricted use of antibiotics can also prevent elimination of the carrier status, which can protect from acute disease.[11] The risk of maintaining a fully susceptible herd within an endemic region should not be taken lightly.

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Babesiosis

Johanna L. Watson • Jerry L. Zaugg

Babesiosis is a tick-borne intraerythrocytic disease of domestic and wild mammals and humans caused by protozoan parasites of the genera *Babesia* and *Theileria*. The acute disease is characterized by fever, hemolytic anemia, icterus, hemoglobinuria, and death. Although both morphologic and serologic differentiation is required for specific identification of the various disease-producing species, all can be categorized as being either “large” or “small” in size. A list of the commonly encountered *Babesia* spp., *Theileria equi*, their usual biological vectors, and livestock hosts is presented in Table 37.1. Babesiosis has a wide geographic distribution, particularly in the tropics and subtropics, largely related to the distribution of vector ticks. Of the different diseases, the economically most important infections of livestock are those of cattle and horses. Babesiosis must be reported immediately to state or federal authorities.

TABLE 37.1
Babesia Species (Babesiosis)

Organism	Livestock Affected	Principal Geographic Distribution	Morphology of Organism	Tick Vectors
B. bigemina (B. bovis)	Cattle	Americas, Europe, Africa, Australia, Middle East	4.5 × 2.5 µm (large, round, and pyriform; acute angle)	*Boophilus annulatus, B. decoloratus, B. microplus* spp.
B. bovis (B. berbera, B. argentina)	Cattle	Americas, Europe, Russia, Africa, Asia, Australia	2.4 × 1.5 µm (small and more rounded; obtuse angle)	*B. annulatus, B. microplus, Ixodes* spp.[a]
B. divergens	Cattle	Europe	1.5 × 1.4 µm (small, narrow, and obtuse angle)	*Ixodes ricinus*
B. major	Cattle	Europe, Russia, North Africa, Middle East	2.6 × 1.5 µm (similar to *B. bigemina* but smaller)	*Haemaphysalis punctata*
B. jakimovi	Cattle	Asia	2-4.6 × 1.5-2.1 µm (large, round, and pyriform)	*I. ricinus*
B. ovate	Cattle	Japan	4.5 × 2.5 µm (large, round, and pyriform)	*Haemaphysalis longicornis*
B. caballi	Horses	Americas, Europe, Russia, Asia, Africa, Middle East	3 × 2 µm (large, pyriform; acute angle)	*Dermacentor, Hyalomma, Rhipicephalus* spp.
Theileria equi (B. equi)	Horses	Americas, Europe, Russia, Asia, Africa, Middle East	1-2 µm (small and rounded; Maltese cross is characteristic)	*Dermacentor, Hyalomma, Rhipicephalus* spp.

B. motasi	Sheep and goats	Europe, Russia, Asia, Middle East	3 × 2 µm (large, pyriform; acute angle)	*D. silvarum* (?), *Haemaphysalis* spp., *R. bursa*
B. ovis	Sheep and goats	Europe, Russia, Asia, Middle East	1.5 × 1 µm (small and more rounded; obtuse)	*I. ricinus* (?), *R. bursa*, *D. reticulatis* (?)
B. trautmanni	Swine	Europe, Africa, Russia	3.5 × 2 µm (large, narrow, and long; acute angle)	*R. sanguineus* (?), *Dermacentor* spp. (?) *Boophilus* spp. (?) *Hyalomma* spp. (?)
B. perroncitoi	Swine	Europe, Africa, Asia	0.7-2 µm (small and more rounded)	Vectors unknown

[a]Suspected vector.

From Kuttler, KL: *Foreign animal diseases,* Richmond, VA, 1984, United States Animal Health Association, p 77.

Babesiosis in the Bovine

Etiology

Known variably as *bovine babesiosis, piroplasmosis, Texas fever, redwater, tick fever,* and *tristeza*, the disease may be caused by at least six *Babesia* spp. (see Table 37.1). Animals other than cattle known to be susceptible to agents of bovine babesiosis include white-tailed deer, American bison, water buffalo, reindeer, and African buffalo. Infections in these species are nominal, and except under unusual conditions, such hosts are probably not significant reservoirs.

Of greatest concern in the western hemisphere are *Babesia bigemina* and *Babesia bovis. B. bigemina* is a large *Babesia* characteristically appearing within mature erythrocytes as nonpigmented, paired, pear-shaped bodies joined at an acute angle. Irregularly shaped, round, or amoeboid forms are also seen. *B. bovis* is a small, pleomorphic *Babesia* often identified as a single round body or as paired pear-shaped bodies joined at an obtuse angle within mature erythrocytes. Of the two species, *B. bovis* is usually considered the most virulent.

Natural transmission of both species occurs primarily by the feeding of various stages of the one-host ticks of the genus *Boophilus.* Ticks are most commonly infected transovarially (vertically). The female tick becomes infected by the ingestion of parasites during engorgement. After it drops off the host, the babesial organisms reproduce within the tick's tissues. Some of the reproducing organisms are incorporated within developing tick embryos, and the disease agents are transmitted to new vertebrate hosts by the feeding of ensuing tick larvae, nymphs, or adults. Larval ticks may transmit *B. bovis,* but *B. bigemina* is

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not transmitted until the larvae have molted into the nymphal or adult stages. Both *Babesia* spp. may also be transmitted iatrogenically through blood-contaminated fomites.

Clinical Signs

Clinical signs manifest 2 to 3 weeks after tick infestation. The incubation period following blood inoculation may be fewer than 5 days to more than 3 weeks, depending on the volume of inoculum. Clinical signs of fever (40° to 42° C [104° to 107.6° F]), depression, icterus, anorexia, tachycardia, tachypnea, anemia, hemoglobinemia, hemoglobinuria, abortion, and death are seen. Anemia is caused by intravascular destruction of erythrocytes by escaping merozoites following intraerythrocytic reproduction of the babesias by binary fission. In addition, the osmotic fragility of the whole erythrocyte population increases terminally, such that massive lysis occurs even though the parasitemia may be less than 1%.[1] In addition, an immune-mediated condition may result and the spleen will remove both damaged and healthy erythrocytes from circulation. Thus the degree of anemia may exceed that expected with a low parasitemia. Anemia may occur rapidly, with 75% or more of erythrocytes destroyed in just a few days. The exit of *B. bigemina* and *B. bovis* parasites from infected erythrocytes releases two or more parasite-associated proteolytic enzymes into the plasma. These enzymes and other parasite metabolic products are believed to interact with blood components and are responsible for such clinical signs as metabolic acidosis and anoxia. Tachycardia may be dramatic and heart sounds pronounced.

Cerebral babesiosis, characterized by hyperexcitability, convulsions, opisthotonos, coma, and death, may be observed in cattle infected with either *B. bigemina* or *B. bovis*, but especially with the latter. Central nervous system (CNS) signs are due to brain anoxia resulting from severe anemia and/or erythrocyte blockage of cerebral capillaries.

Death is caused by a shocklike syndrome associated with the accumulation of toxins, release of vasoactive substances, and anemic anoxia. Most cases with cerebral involvement are fatal, but mortality is extremely variable and depends on the *Babesia* strain, host susceptibility, and management and environmental stress factors. Many cattle that survive the acute phase recover but become chronic carriers. Other survivors often experience episodes of recrudescence, eventually succumbing to the disease, or they may die from secondary infections contracted during their debilitated state.

Cattle of all breeds are susceptible to babesiosis, but *Bos indicus* breeds exhibit a definite degree of resistance to both *B. bigemina* and *B. bovis* and the tick vectors.[2] Calves possess a natural immunity to babesiosis. Such immunity was believed to be reinforced by colostral antibodies for calves born to previously infected dams.[3] However, erythrocytes of young bovines may contain factor(s) independent of antibody that provide an innate resistance to severe babesiosis.[4] Thus calves infected up to the age of 9 months experience a minimum reaction to the disease, becoming asymptomatic carriers. Carriers remain resistant to clinical disease for at least 4 years.[5] The carrier state can be overcome, however, by such stresses as calving, malnutrition, or concurrent disease.[6]

Clinical Pathology

Clinical signs observed in cattle located in enzootic areas where *Boophilus* ticks occur may provide sufficient data for a presumptive diagnosis. Other conditions that may exhibit some of the same signs as babesiosis are anaplasmosis, trypanosomiasis, theileriosis, leptospirosis, chronic copper toxicity, and bacillary hemoglobinuria. The cerebral signs may be confused with rabies and other encephalitides. A positive diagnosis requires identification of *Babesia* on Giemsa-stained thin blood smears, positive serologic tests (IFA, ELISA, CF), or molecular diagnostics (PCR).[7] In acute infection, *Babesia* spp. can usually be detected in smears made from peripheral blood. In chronic cases the numbers of parasitized erythrocytes diminish, becoming so sparse as to make detection difficult. This is especially true with *B. bovis*, which shows a marked tendency to accumulate in capillaries, particularly those of the brain. *B. bovis* may favor capillaries in the brain and kidney, because the major energy-producing pathway of *Babesia* appears to be anaerobic glycolysis. The blockage of cerebral and renal capillaries by parasitized erythrocytes results in an anaerobic condition that enables the parasites to absorb preformed substrates by pinocytosis and diffusion through their surface membranes. PCV values drop rapidly from a normal of 35% to below 10% in less than a week after the onset of clinical signs.[8] Serum potassium levels decrease in some infected animals, whereas urine potassium levels increase in nearly all cases.[9]

Specific anti-*Babesia* antibodies are detectable in cattle sera in fewer than 7 days following infection.[10] Such antibodies also exist for at least 252 days after

the disappearance of detectable parasites.[11] The CF and IFA tests are the most widely used.[10,12] The CF test follows the same basic procedure used in anaplasmosis CF testing,[11] but with a *Babesia* antigen.[12] The test is effective, but about 100 days after infection, CF antibodies drop below a reliable diagnostic level.[10] The IFA test uses the whole intraerythrocytic parasite as antigen rather than an extract and commercially prepared rabbit antibovine γ-globulin conjugated to fluorescein.[10] Other serologic tests include latex particle agglutination,[13] rapid card agglutination,[14] and enzyme-labeling immunoassay (EIA).[15] It should be noted that the immunologic assays are indirect methods and do not detect the causal organisms in samples obtained from a suspected infected animal. Recombinant DNA techniques using selected clones containing inserts of *Babesia* genomic DNA sequences are now available to be used as specific, highly sensitive DNA or RNA probes to detect the presence of the hemoparasite DNA in an infected animal or tick vector.[16]

Necropsy Findings

Postmortem findings in cattle that die peracutely are characteristic of an acute hemolytic crisis. Such findings include a generalized pallor or icterus throughout the carcass; an enlarged icteric liver; gallbladder distended with thick, dark green bile; and a markedly enlarged dark, soft spleen. Hydropericardium and subepicardial/subendocardial petechiation may be seen. The blood is thin and watery. The urinary bladder is frequently distended with dark red urine. There may be subserosal ecchymotic hemorrhages in abomasal and intestinal mucosa, and the lymph nodes are edematous. The carcass of an animal that dies after a prolonged illness is generally emaciated and icteric.

Treatment and Prognosis

After the onset of hemoglobinuria or cerebral signs, the prognosis is poor. Acute cases with PCV values above 12% usually respond well to treatment. The prognosis decreases for cases with PCV values below 10%. Successful treatment depends on early diagnosis and prompt therapy. In addition to specific treatment, supportive therapy such as blood transfusions (4 L of whole blood per 250 kg of body weight), fluids, hematinics, and prophylactic antibiotics are important. However, wild excitable cattle may best be left alone. With severe hemolytic anemias, any exertion associated with restraint and treatment may precipitate an

anoxic crisis.

The small *Babesia* spp. are more resistant to chemotherapy and may require increased dosages or additional treatments. Chemotherapy with imidocarb can be both therapeutic and prophylactic, but there are concerns with milk and meat residue. In enzootic areas its use prevents clinical infection for as long as 2 months but at the same time allows mild subclinical infections to occur, resulting in premunition immunity.[17,18]

Prevention and Control

Eradication of *Boophilus* tick vectors has provided effective control in the United States. Most procedures aimed at reducing tick infestations (i.e., acaricide applications [on host or over environment], controlled range burning, cultivation, prolonged pasture rest, and use of repellents) are beneficial. Care should be taken to prevent accidental transfer of blood from one animal to another in routine surgery (e.g., dehorning, castration, ear marking, hormone implanting) and vaccination procedures.

The most common form of immunization consists of inoculating live organisms (virulent or attenuated) into susceptible calves to induce a state of premunition. Inoculation of older animals is followed by nonsterilizing chemotherapy as needed to modify clinical effects.[19] Although a premunition approach is useful in endemic areas, it is less desirable in areas with low infection rates because the premunized carriers provide a large reservoir of infection. Subunit vaccines were proven effective in protecting against severe clinical disease.[20,21]

Babesiosis in the Horse

Etiology.

Babesiosis/theileriosis of the horse (piroplasmosis) is a febrile tick-borne disease of equids caused by *Babesia caballi* and *Theileria equi*[22] (see Table 37.1). *B. caballi* is a large *Babesia* resembling *B. bigemina,* which affects cattle. A unique characteristic of *T. equi* is that the intraerythrocytic parasites divide into four cells to form a Maltese cross.[23]

Equine piroplasmosis is widely distributed throughout the tropics and subtropics and to a lesser extent in temperate regions. The distribution roughly corresponds to that of the tick vectors. Both species are naturally transmitted by

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ticks of the genera *Dermacentor, Hyalomma,* and *Rhipicephalus. B. caballi* is passed transovarially (vertically) from one tick generation to the next. Transmission of *T. equi* apparently only occurs transstadially (horizontally); that is, one tick stage (larvae or nymphs) becomes infected, and the disease agent is passed to the next vertebrate host in the next tick stage (nymph or adult). Because of the widespread prevalence of potential tick vectors in the United States *(Dermacentor albipictus, Dermacentor iteus, Dermacentor variablis),* equine piroplasmosis could become a problem in the United States at any time.

Clinical Signs.

Apparently, all equids are susceptible to both parasite species. The zebra in Africa is naturally infected with *T. equi* but not *B. caballi*. Once infected, survivors remain chronic carriers. At least *T. equi* can be transmitted transplacentally. Clinical features following an incubation period of 5 to 28 days are fever (39° to 42° C [102° to 107.6° F]), hemolytic anemia, jaundice, hemoglobinuria, and death. Generalized signs of depression, anorexia, incoordination, lacrimation, mucous nasal discharge, swelling of the eyelids, and frequent lying down are seen. *T. equi* is considered the most pathogenic of the two species and is responsible for a greater incidence of hemoglobinuria and death. *B. caballi* causes a more persistent fever and anemia. Differential diagnoses include equine monocytic ehrlichiosis, EIA, liver failure with hemolytic anemia, and other hemolytic anemias of the horse.

Clinical Pathology.

A fever associated with anemia, jaundice, and hemoglobinuria, with the detection of parasite-infected erythrocytes in Geimsa-stained blood smears, is diagnostic. A significant increase in relative and absolute numbers of monocytes and absence of eosinophils may be observed in horses infected with *T. equi*. Hemoglobinuria is rare in animals infected with *B. caballi,* but urine is often dark yellow in color. The official testing method is the cELISA test. There is also a PCR test for both equine diseases. As with the bovine infections, both *B. caballi* and *T. equi* infections can be specifically detected with nucleic acid probes.[17]

Necropsy.

Postmortem features are similar to those seen in bovine babesiosis, but jaundice is even more prominent throughout the carcass. There is excessive fluid in the

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body cavities, especially the pericardial sac. Pulmonary edema is evident. The liver is swollen, and hepatic vessels contain large yellowish clots. The spleen is enlarged, with rounded edges.

Treatment and Prognosis.

The drug of choice for eliminating the carrier state of infected animals is imidocarb. Imidocarb at the level of 2.2 mg/kg given two times in 24 hours is effective against *B. caballi*. A 4-mg/kg IM dose given every 72 hours for four doses is effective against *T. equi* of eastern hemisphere origin.[24] However, donkeys receiving similar treatment died from drug toxicosis.[24] The higher doses of imidocarb often produce transient colic in horses. To date, attempts to consistently eliminate the carrier state of *T. equi* of Eastern European origin have been unsuccessful.[25]

Prevention and Control.

Control of tick infestations does much to reduce disease incidence, as does care to prevent blood transfer during such routine surgical procedures as castration. No vaccines effectively prevent equine babesiosis. Although premunition as used in bovine babesiosis is of limited value in some enzootic areas, it is not widely practiced. This is because early treatment without sterilization is effective, and the resulting chronic carriers resist further disease challenge. If a horse is diagnosed with *T. equi* in the United States, the veterinarian can enroll the horse in the USDA controlled treatment program to ensure appropriate quarantine, treatment, and subsequent release of cleared animals.

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Haemobartonellosis (Eperythrozoonosis)

Johanna L. Watson • Gary P. Carlson

Haemobartonella bovis is an epicellular organism closely associated with the surface of erythrocytes. It may appear as a rod shape, an ovoid, or in chains with conventional stains. *Haemobartonella*, or hemotropic mycoplasma, infection is primarily of academic interest in North America; it is rarely a cause of anemia. The organism has been found in association with other rickettsial diseases and has been experimentally transmitted in splenectomized calves. The agent may be visualized as delicate ovoid, rod, or dumbbell forms arranged in chains or tight groups or randomly distributed epicellularly throughout appropriately stained blood smears.

Eperythrozoonosis in Cattle

The causal agent is *Eperythrozoon wenyonii (Mycoplasma wenyonii).* Infection is usually latent, producing no clinical signs in normal cattle, but it may become apparent in animals that have been severely stressed by some other systemic disease. The disease can be produced experimentally if infected blood is administered to splenectomized calves. Even under experimental circumstances, clinical signs consist of mild depression, fever, and modest anemia. The disease in cattle is of little clinical consequence except for the potential for confusion should the organism be seen on stained blood films. Occasionally cattle may have swollen and tender teats and legs.[1]

Eperythrozoonosis in Sheep and Goats

The causal organism in sheep and goats is *Mycoplasma ovis (Eperythrozoon ovis),* which appears to be similar morphologically and serologically to that found in cattle. The disease can produce more prominent clinical signs in sheep, with profound depression, anemia, and significant death losses in young lambs.[2] Red cell destruction is thought to be caused by intravascular hemolysis and erythrophagocytosis.

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Theileriasis

Johanna L. Watson • Gary P. Carlson

Theileriasis is caused by a small hemoparasite of the genus *Theileria* that infects lymphocytes and erythrocytes of ruminants and is most common in tropical and subtropical climates. The organism is spread by bloodsucking arthropods, particularly ticks of the Ixodidae family. *Theileria parva* is the cause of East Coast Fever, a highly fatal disease of cattle in Africa. Other members of the genus *Theileria* (spp. *annulata, mutans, hirci,* and *ovis*) tend to be less pathogenic and produce diseases with a wider geographic distribution.[2] *Theileria cervi* has been seen in North American deer. *Theileria mutans* has been seen in erythrocytes of both cattle and deer in North America. Theileriosis due to an agent indistinguishable from *Theileria buffeli* has been described in cattle from Texas and North Carolina with parasitemia, but clinical signs were not reported.[3] *T. buffeli* was reported as the cause of hemolytic anemia in a 6-month-old Simmental calf.[4] There was serologic evidence of a high herd prevalence of *Theileria* infection, and the agent was transmitted to splenectomized calves that developed mild anemia. The organism produces a brief illness characterized by mild fever, anorexia, and modest anemia, followed by rapid recovery.

Trypanosomiasis

Johanna L. Watson • Gary P. Carlson

Trypanosomes are flagellated protozoal organisms that can produce a variety of serious diseases of humans and animals, although many are nonpathogenic. Nagana, a disease of cattle in Africa, is caused by *Trypanosoma congolensi*. *Trypanosoma evansi* is the cause of Surra, a disease of cattle in India, and *Trypanosoma equiperdium* is the cause of Dourine in horses. In North America, *Trypanosoma theileri (Trypanosoma americanum)* is the only agent reported and is principally of academic interest because it is relatively nonpathogenic. On stained blood films from cattle, small numbers of the organism can occasionally be seen free in plasma, appearing as large flagellated protozoa with undulating membranes. *Trypanosoma* is best visualized in buffy coat smears, which tend to concentrate it. *T. theileri* rarely produces clinical signs, but occasionally a fulminating parasitemia may develop, resulting in fever, depression, and

decreased milk production.

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Leptospirosis

Johanna L. Watson • Gary P. Carlson

Leptospira infections produce disease in several species including cattle, sheep, swine, horses, dogs, and humans, but the acute hemolytic syndrome associated with these infections is seen most commonly in calves and lambs. *Leptospira interrogans* serovars *pomona* and *icterohaemorrhagiae* are the serotypes usually involved in the hemolytic syndrome. Clinical signs of the hemolytic syndrome vary but generally include fever, lethargy, icterus, anemia, and petechial hemorrhages. The anemia is brought about at least in part by immune-mediated mechanisms. Cold-reacting IgM antibodies have been implicated in the hemolytic anemia seen in lambs. The degree of anemia is variable but can be severe, with evidence of bone marrow response apparent in the peripheral blood within 4 to 7 days. A moderate leukocytosis and elevation in plasma fibrinogen are often associated with the hemolytic anemia. The diagnosis is made on the basis of demonstration of the organism in the urine, PCR, and documenting an increase in serum antibody titer. Discussion of leptospirosis as a reproductive, renal, and ocular problem can be found in other chapters.

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Bacillary Hemoglobinuria (Red Water)

Johanna L. Watson • Gary P. Carlson

Bacillary hemoglobinuria is an acute hemolytic disorder caused by *Clostridium haemolyticum* (*Clostridium novyi* type D). Also known as “Nevada red water,” it has been reported as a naturally occurring disease in cattle and experimentally produced in sheep. Clinical signs develop rapidly, and death losses are often seen. Affected animals may manifest severe depression, anorexia, fever, hemoglobinemia, and hemoglobinuria. The disease is endemic in certain poorly drained areas of the western United States and is caused by ingestion of infectious spores. The organism finds a favorable environment for development in areas of preexisting liver damage that most often have been produced by migrating liver flukes. The hemolytic syndrome is produced by toxins elaborated by the organism, which also produce a characteristic focal liver lesion. The anemia produced may be marked, and both icterus and evidence of erythropoietic response may be seen in animals that survive for more than a few days. For a complete description of the disease, see Chapter 33.

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Equine Infectious Anemia

Johanna L. Watson • Brett A. Sponseller

Equine infectious anemia virus (EIAV) is an RNA virus, a member of the Retroviridae family, belonging to the lentivirus genus. It has a structure and genome organization similar to other animal and human lentiviruses and uses virally encoded *reverse transcriptase* to convert the RNA genome to a DNA intermediate that is integrated into the host's genome by another virally encoded enzyme, *integrase*. The integrated DNA intermediate, or provirus, usurps the host cell to replicate its genome, manufacture viral proteins, and assemble the virally encoded proteins into virions that subsequently bud from the cell. Thus infection by a lentivirus results in lifelong persistent infection. EIAV causes equine infectious anemia, first described in 1843 by Lignée.[1] In 1904, Vallée and Carré determined that EIA was associated with a filterable agent, making it the first animal disease determined to be caused by a virus.[2]

Identification of Equids Seropositive for EIAV

EIA is a USDA-regulated disease. In 2003, the USDA estimated that serosurveillance of nearly 2 million samples cost U.S. horse owners in excess of $48 million. USDA-accredited laboratories use a testing scheme that detects the presence of serum antibody to the virus. The Coggins test, developed by Dr. Leroy Coggins in 1970, provided the first efficient serologic test for detection of EIAV-infected animals and remains a USDA-accepted test.[3,4] There are also four licensed ELISAs, one of which is a cELISA. These ELISAs detect antibody directed at the transmembrane glycoprotein (gp45) and/or the p26 antigen.[5] All U.S. states, Canada, and Mexico accept either the Coggins test or one of the licensed ELISAs when EIA testing is required for entry. Equids that cross state lines or attend many equestrian events (e.g., shows, races) have to be seronegative for EIA. The required period of seronegativity between tests varies state by state, however. No tests based on detection of viral nucleic acid are currently USDA approved for EIA diagnosis. It has been suggested that the use of a molecular test would help identify infected horses and assist with the eradication of the disease.[6]

Serosurveillance can lead to detection of horses infected with EIAV that

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otherwise appear healthy. Indeed, most horses infected with the virus are inapparent carriers. However, blood transferred from an inapparent carrier to another horse, either through instruments (needles, nasogastric tubes, dental equipment, etc.), blood products, or by insect vectors (primarily tabanids) can lead to infection and a fatal outcome.

Equine Infectious Anemia

The clinical form of the disease is characterized by three defined temporal stages: acute, chronic, and inapparent. The acute stage occurs with the initial burst of viremia and is characterized by high fever, thrombocytopenia, and nonspecific signs of malaise including lethargy and inappetence. In experimentally infected horses, thrombocytopenia inversely correlates with virus load and occurs slightly in advance of onset of fever. Ecchymoses and petechiae may also be detected on mucous membranes. During the chronic stage, similar clinical features occur during recurrent episodes of viremia, which are interspersed with periods of clinical quiescence and low viremia. Throughout the chronic stage, clinical episodes tend to gradually diminish in severity and duration. The inapparent stage occurs once levels of viremia are immunologically contained and no clinical signs are detected. Horses experiencing clinical disease at any point may develop DIC and die. In addition, episodes of stress (e.g., transportation, racing, extreme temperatures) may precipitate clinical disease. Corticosteroids have been experimentally used to induce recrudescence of clinical disease.[7] Other chronic manifestations of EIA include development of dependent edema, weight loss, anemia, and other signs of ill thrift. Rare manifestations that may develop include leukoencephalitis and enterocolitis.[8] Expression of clinical disease, particularly during acute infection, likely involves multiple factors, including inoculating dose, virulence factors of the inoculating viral strain, immune status, and immunogenetics of the host, age, stress, and so forth. Indeed, clinical disease occurs concomitantly with high-titered viremia. Horses with high-titered viremia pose the biggest risk of transmission to uninfected horses.

Lentiviruses have a DNA-dependent RNA polymerase (reverse transcriptase) that misincorporates nucleotides, resulting in changes in the viral genome.[9] This mechanism allows for generation of viral variants that differ genetically from preexisting ones. As a result, genetic and antigenic variation of epitopes for neutralizing antibody and cytotoxic T lymphocytes allows viral escape from

adaptive immune responses.[10,11] Antigenic variation plays a central role in clinical disease recurrence throughout the chronic stage of infection and thwarts attempts to develop an effective vaccine.[9]

EIAV can replicate effectively in monocytes, dendritic cells, and tissue macrophages[12-14] and has been shown to replicate in endothelial cells. EIAV replication in endothelial cells may play a role in the development of DIC by viral damage to endothelial cells, with subsequent exposure of subendothelium.[15] This in turn could lead to platelet aggregation and formation of thrombi.[16] In addition, damaged endothelium may lead to development of dependent tissue edema by transudation of fluid through compromised small vessels.[15]

Pathology and Clinical Pathology

Necropsy examination of horses that die of EIA may demonstrate splenomegaly, lymphadenopathy, hepatomegaly, pronounced hepatic lobular architecture, ecchymoses of the mucosa and viscera, dependent subcutaneous edema, and thrombotic disease of small vessels. Histologic findings may include a mononuclear cell infiltrate of periportal regions of the liver, adrenals, spleen, lymph nodes, meninges, and lungs. Hemosiderophages are frequently detected in the spleen, lymph nodes, liver, and bone marrow. Glomerulonephritis due to immune complex deposition is commonly observed.

Clinicopathologic abnormalities will vary depending on the stage and severity of infection. During clinical disease, a frequently profound thrombocytopenia develops concurrently with each successive episode of fever. Platelet dysfunction in EIAV-infected horses has been demonstrated, possibly exacerbating bleeding tendencies and the progression to DIC in clinically affected equids.[17] Anemia due to intravascular hemolysis, extravascular hemolysis, and depression of bone marrow erythropoiesis may progressively develop during the chronic stage of infection.[18] During the inapparent stage of infection, horses typically have increased plasma total solids and globulin concentrations, mild anemia, and decreased albumin concentration.[19] Polyclonal B-cell activation is also evident, suggesting chronic antigenic stimulation despite clinical quiescence.[19] Concomitant fever and thrombocytopenia should prompt immediate consideration of EIA. A history of recurring fever is also suggestive of EIA, particularly when other causes of fever have been ruled out.

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Prevention, Control, and Regulatory Considerations

It is well recognized that seroprevalence varies with the region of the United States.[18] States considered at high risk include Texas, Oklahoma, Louisiana, and Arkansas, whereas the mid-Atlantic area, New England, Alaska, and Hawaii are considered low-risk regions. The remaining states are classified as being at intermediate risk. Despite regional differences in risk to noninfected horses, sporadic outbreaks do occur. Veterinarians should encourage all horse owners to test for EIAV, test new arrivals, and maintain good fly control.

Once a seroreactor is identified, all contact horses are quarantined and undergo testing until two negative test results at 30- to 60-day intervals are obtained for all individuals in the quarantined herd.[16] The required interval is based on the need to allow recently infected horses to seroconvert. Seroreactors may be either quarantined or euthanized, depending on state regulations. Quarantined horses must be at least 200 yards from seronegative animals, the distance shown to be sufficient to obviate viral spread by insect vectors. In addition, seroreactors remaining in permanent quarantine must be permanently identified. A USDA code number followed by the letter *A* is assigned to the quarantined horse and permanently applied to the horse in the form of a brand or lip tattoo.

Because an EIA eradication program has never been implemented in the United States, persistence of EIAV-infected horses can be expected. The vast majority of horses in the United States are not tested annually, so to encourage horse owners to voluntarily maintain vigorous surveillance testing, the veterinary community must educate them about the consequences of EIAV infection. Horse owners are often unprepared to deal with the financial and emotional losses associated with detection of a horse seropositive for EIAV.

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▪ Immune-Mediated Hemolytic Anemia

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Autoimmune Hemolytic Anemia

Johanna L. Watson • Gary P. Carlson

Definition and Etiology

Autoimmune hemolytic anemia is associated with production of autologous antibodies directed against the patient's own red cells. These antibodies combine with complement and antigens on the red cell membrane, leading to rapid removal of affected red cells from the circulation and their accelerated destruction. Autoimmune hemolytic anemia occurs rarely as a primary idiopathic disorder[1,2] but more commonly is found secondarily associated with some other primary disease process.[1] Idiopathic immune-mediated hemolytic anemia (IMHA) has been reported in a calf[2] and pony.[3]

Clinical Signs and Differential Diagnosis

The presenting clinical signs of autoimmune hemolytic anemia are quite variable depending on the degree of anemia and the animal's primary disease. Marked anemia (PCV < 15%) manifests signs typical of those seen in any animal with a severe hemolytic anemia (i.e., depression, pale mucous membranes, variable icterus, elevated heart and respiratory rate, and variable to intermittent fever). Secondary autoimmune hemolytic anemia in horses has been associated most often with some other primary problem like purpura hemorrhagica, lymphoma, other neoplasms, protein-losing enteropathy, or chronic bacterial infections.[4,5] Clinical features are typical of the primary problem, with additional findings of hemolytic anemia. In humans, exposure to a wide variety of drugs has been causally associated with development of autoimmune hemolytic anemia. There are a number of reports of an association between procaine penicillin and autoimmune hemolytic anemia in horses,[6-10] as well as a single report in a 10-year-old horse that was treated with trimethoprim-sulfamethoxazole.[11] This apparently occurs rarely, perhaps only in specific individuals, but drug history should be ascertained in all animals with an otherwise unexplained hemolytic anemia.

It should be noted that the anemia in cattle with anaplasmosis and babesiosis

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or that in horses with equine infectious anemia, piroplasmosis, or anaplasmosis is largely the result of an immune-mediated hemolytic process.

Clinical Pathology

The hemolytic process is often rapid and persistent, leading to a pronounced anemia. Hematologic features are those typically expected for a responsive hemolytic anemia. The anemia is often progressive and may become severe, even life threatening (i.e., PCV < 10%). Erythrophagocytosis and autoagglutination may be noted on blood smears. If the process has gone on for 4 days or more, hematologic evidence of active erythropoietic response may be seen in the peripheral blood of all species except the horse. This evidence of bone marrow response is a favorable prognostic indicator, even when anemia is quite advanced. A moderate neutrophilic leukocytosis is a common feature, and thrombocytopenia may be noted in some individuals if the autoimmune process is directed at platelets and megakaryocytes in addition to erythrocytes.

Diagnosis

The direct Coombs test can detect the presence of antierythrocyte antibodies and/or complement on the red cell membrane, whereas the indirect Coombs test detects antierythrocyte antibody in the serum. It is important to remember that the Coombs test is based on species-specific reagents. These reagents are commercially available in the United States for small animals and horses, but not all diagnostic laboratories will have suitable Coombs reagents for other species. Multivalent Coombs reagent directed against IgG, IgM, and complement is most commonly used. The Coombs test is usually conducted at body temperature (37° C) and can also be run in the cold. Cold-reacting antibodies are primarily of the IgM class. Unfortunately, false-negative results to the Coombs test are possible and possibly occur because of low concentrations of antibody, low binding to the red cell membrane, or prior treatment with corticosteroids. The diagnosis in these cases is contingent on ruling out other causes of a responsive hemolytic anemia and on the response to corticosteroid therapy. Direct immunofluorescence flow cytometry can be used to determine the classes of antibody bound to erythrocytes in horses and dogs with IMHA.[12]

Pathophysiology

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Autoimmune hemolytic anemia has rarely been reported as a primary or idiopathic process in large animals, but immune-mediated anemia occurs more commonly as a secondary problem (1) in association with certain types of neoplasia; (2) with a variety of viral, bacterial, rickettsial, and protozoal infections; (3) following exposure to certain drugs; or (4) in association with other immune-mediated disorders like systemic lupus erythematosus.[13] The initiating factors for this autoimmune disorder are not completely understood but may be related to alterations in the red cell membrane through direct or indirect injury, which elicits an abnormal response by the immune system. The red blood cell membrane is no longer recognized as self but is treated as a foreign antigen. Alternately, alterations in the immune system or stimulation by some other antigenic source may result in production of antibodies with a misdirected cross-reactivity with the patient's own normal red cells. Structural and functional changes in the red cell membrane are induced by the antigen-antibody reaction and complement fixation. The complement-fixing IgG or IgM antigen-antibody reaction may produce sufficient erythrocyte damage to result in intravascular lysis of erythrocytes, but more commonly, affected cells are removed from the circulation at a rapid rate by the reticuloendothelial system of the liver and spleen. Partial phagocytosis of affected cells may result in spherocyte formation. Although the presence of spherocytes on blood smears is a characteristic diagnostic feature in human and canine patients with autoimmune hemolytic anemia, the relatively small size of red cells of most large domestic animals may make it difficult to recognize spherocytes.

Treatment and Prognosis

The approach to treating autoimmune hemolytic anemia depends on causal factors. If the animal has a history of drug therapy, it is advisable to discontinue medication or change to another class of drug. Patients with primary or idiopathic autoimmune hemolytic anemia may be the best candidates for treatment. IMHAs that are secondary to other diseases can only be managed if the primary problem is amenable to treatment. Thus treatment of an IMHA in a patient with extensive lymphoreticular neoplasia is likely to be unrewarding, and thorough diagnostic efforts should precede case selection for treatment. Although immune-mediated processes are responsible for hemolytic anemia in a number of infectious diseases, therapy must be directed at the primary agent and corticosteroids are contraindicated in these diseases. Corticosteroids can cause

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recrudescence of viremia in horses with EIA.

Treatment of autoimmune hemolytic anemia is directed at providing supportive care and interrupting the immune response responsible for antibody production. This is usually accomplished with systemic glucocorticoids. For a 450-kg horse, parenteral dexamethasone is recommended at an initial dosage of 30 to 40 mg/day. This dosage is continued for 3 to 5 days and then decreased gradually over a period of 7 to 14 days, depending on response to therapy. The hematologic response to therapy should be closely monitored. If there has been no response in 5 to 7 days, the diagnosis of autoimmune hemolytic anemia should be reviewed and potential causes of bone marrow suppression should be evaluated. Once the hemolytic process is well under control, treatment can be switched to oral prednisolone, 0.5 to 1 mg/kg daily. Human patients and small animals with IMHA that is unresponsive to corticosteroids are often treated with cyclophosphamide. One case of successful management of a horse with cyclophosphamide and azathioprine when anemia failed to respond to corticosteroids has been reported.[14] Supportive care consists of providing a quiet, restful environment and good nutrition, including vitamin supplementation. Iron- and copper-containing hematinics are generally of little benefit; neither of these elements is lost with hemolytic anemia. Blood transfusion is also of little benefit because it is often impossible to find a compatible donor, and transfused cells are rapidly removed from the circulation.

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Neonatal Isoerythrolysis in Horse and Mule Foals

Johanna L. Watson • Monica Aleman

Neonatal isoerythrolysis (NI) is the most common alloimmune disease in neonatal foals (median age, 2.5 days).[15] NI is characterized by hemolytic anemia, icterus, and hemoglobinuria. Clinicopathologic abnormalities include anemia, high serum indirect and direct bilirubin concentrations, and sorbitol dehydrogenase (SDH) activity. NI is caused by a blood group incompatibility between the foal and dam. The foal inherits and expresses, from the sire, an erythrocyte antigen (alloantigen) that is not present in the mare. The hemolytic syndrome is mediated by maternal antibodies generated against foal erythrocytes (alloantibodies) absorbed from colostrum. Blood factors associated with NI in horse foals are Qa, Qb, Qc, Aa, Pa, and Dg and donkey factor in mule foals.[15] The most common antigens are Qa and Aa. Foals with NI may also present with alloimmune thrombocytopenia. For a complete description of NI, see Chapter 53.

▪ Heinz Body Hemolytic Anemia

Johanna L. Watson • Gary P. Carlson • Monica Aleman

Definition and Etiology

Acute hemolytic anemia can develop following exposure to a variety of oxidizing agents. These include chemicals such as phenothiazine, methylene blue, acetylphenylhydrazine, or plants like wild or domestic onions, members of the *Brassica* family (rape or kale), and wilted or dried leaves of the red maple *(Acer rubrum)*.[1-7] Red maple toxicosis (RMT) has been reported in horses, zebras, and alpacas.[5,8-10] Heinz body hemolytic anemia also occurs in sheep on specially formulated diets that are low in molybdenum, which results in chronic copper toxicity; as herd problems in cattle grazing rye grass *(Secale cereale)*[11] or selenium-deficient pastures in Florida[12]; and in association with selenium deficiency as a contributing factor in postparturient hemoglobinuria in cattle in New Zealand.[13] These agents produce or allow oxidative denaturation of

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hemoglobin and resultant aggregation of the protein globin, which appears as Heinz body inclusions within the red blood cells. Heinz body anemia has been seen in association with lymphoma in a horse and was possibly due to failure of the reticuloendothelial system to remove Heinz bodies, as has been reported in horses with EIA.[14]

Clinical Signs and Differential Diagnosis

Clinical signs vary with the species involved, specific toxin or toxic metabolites, amount of toxin ingested, time course of the disease process, and occurrence of complicating secondary factors like hemoglobin nephrosis and acute renal failure. Weakness, lethargy, anorexia, and exercise intolerance are the usual presenting complaints, and death losses can occur. Mucous membranes are generally pale with variable to marked icterus. Heart and respiratory rates are generally elevated, but rectal temperature is usually within normal limits. Horses with RMT may be subclinical or may present with lethargy, muddy or cyanotic mucous membranes, tachycardia, inappetence, weakness, colic, icterus, brown discoloration of the blood, and pigmenturia. Rarely, sudden death occurs.[10] Most horses develop clinical RMT during summer and fall, and the high mortality rate may relate to the combination of a rapidly progressive hemolytic anemia and formation of methemoglobin. Urine output may be reduced, and the presence of hemoglobin, methemoglobin, or bilirubin may make urine appear dark.

It is not possible to differentiate Heinz body hemolytic anemia from other potential causes of hemolytic anemia without laboratory evaluation. The absence of fever may help differentiate these anemias from infectious causes of hemolytic anemia. History of exposure to potential oxidizing agents and the fact that these toxic plants may produce death losses or clinical signs in multiple animals at the same time should help differentiate these cases from autoimmune hemolytic anemia.

Clinical Pathology

Poisoning or intoxication resulting in Heinz body formation usually causes acute and profound anemia. In the early stages a high percentage of erythrocytes may have Heinz body inclusions. Later, as these cells are removed from the circulation and replaced by young cells from the bone marrow, the relative number of affected cells may decrease markedly. Heinz bodies are round, oval to

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serrated, refractile granules usually located near the cell margin or protruding from the cell. They are best visualized with vital stains like crystal violet or new methylene blue applied to unfixed blood smears. Heinz bodies appear as bluish-green inclusions with new methylene blue stain. Fixing blood smears with methanol in preparation for staining with the classic Wright stain interferes with stain uptake, and Heinz bodies appear as a pale area within or projecting from the cell margin and can easily be missed. After the first 3 or 4 days the anemia is usually associated with hematologic evidence of an active erythrogenic response in all species except the horse. Total plasma protein usually remains within normal limits, and the Coombs test is negative. Red maple poisoning also results in depletion of red cell mass, reduced glutathione, methemoglobinemia, increased osmotic fragility, and modest elevations of liver-derived serum enzyme activities.

Rapid and profound erythrocyte destruction may lead to hemoglobinemia and hemoglobinuria. Development of renal failure secondary to hemoglobin nephrosis is a definite risk in these animals and is reflected by modest to marked increases in the blood urea nitrogen and creatinine, as well as changes in the urinalysis.[6,7] These parameters should be monitored in severely affected animals. As with other causes of hemolytic anemia, serum bilirubin, particularly indirect-reacting bilirubin, is elevated.

The clinicopathologic abnormalities of horses with RMT include anemia (PCV as low as 7.5%), eccentrocytes, Heinz bodies, and elevated plasma methemoglobin concentration.[10] Other significant findings are an inflammatory leukogram and renal insufficiency (75% and 40% of cases, respectively).[10] Mild serum total bilirubin elevation is observed in most cases, and hemoglobinuria is seen in all affected patients.

Pathophysiology

Heinz bodies are formed by precipitation of oxidatively denatured hemoglobin. The hemoglobin contained within the red blood cell is constantly undergoing mild oxidative stress associated with oxygen transport, as well as generation of superoxide radicals and hydrogen peroxide within the cell. There are a number of reducing mechanisms within the red cell to counteract these oxidative processes through production of the reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) and reduced glutathione. The occurrence of Heinz body hemolytic anemia could be viewed as a consequence of exposure to

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oxidative stresses that simply overwhelmed the cells' reductive capacity. Selenium deficiency results in a decrease in glutathione peroxidase, a selenium-containing enzyme, and selenium deficiency may in special circumstances contribute to Heinz body formation by impeding the ability of the cells to respond to oxidative stress. There are substantial species variations in the rate of Heinz body formation that relate to the chemical structure of hemoglobin and efficacy of erythrocyte-reducing mechanisms in the face of oxidative stress.[1] Red cells with Heinz bodies are less deformable than normal cells and are rapidly removed from the circulation by the reticuloendothelial system in the spleen, where they are phagocytized and broken down. Splenectomy or corticosteroid therapy may alter Heinz body clearance mechanisms, allowing significant numbers of affected red cells to remain in the circulation of otherwise normal animals.

Gallic acid is a strong oxidant present in red maple leaves and has been implicated in the oxidation of hemoglobin, methemoglobin formation, and Heinz body anemia.[5,6,15] Methemoglobin results from the oxidative change of hemoglobin iron to the nonfunctional ferric state (see discussion of nitrate poisoning in Chapter 54). This is normally prevented by glutathione reductase, ascorbic acid, and reduced glutathione. Methemoglobin cannot load or transport oxygen and, when present in sufficient quantities, results in a brown color of peripheral blood and mucous membranes. An estimation of methemoglobin concentration in a blood sample can be made by comparing the hemoglobin concentration measured by the cyanmethemoglobin method, which measures all forms of hemoglobin, and the oxyhemoglobin method, which only measures oxyhemoglobin but not other forms (e.g., methemoglobin). Methemoglobinemia and hemolytic anemia have been reported in a mare and her dam in association with decreased levels of red cell glutathione and glutathione reductase, presumably as a result of an inherited enzymatic defect.[16]

Treatment

Treatment is largely a matter of removal from the source of toxicity and provision of supportive care. Blood transfusion can be beneficial in severely anemic patients, particularly when there is insufficient evidence of active erythropoietic response. Iron-containing hematinics are of little benefit. IV fluid therapy is indicated in animals with hemoglobinuria or azotemia to reduce the potential for further renal damage. High doses of vitamin C (ascorbic acid, 50 to

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100 g IV daily), together with fluids and transfusion, were thought to aid recovery in two horses with red maple poisoning.[17] Another report suggests that vitamin C therapy may have little impact on survival of affected horses, and when methylene blue was used to treat the associated methemoglobinemia in two horses, both died.[18] Therapeutic goals should be to improve tissue oxygenation and perfusion and control inflammation and pain (e.g., with NSAIDs). Horses treated with corticosteroids have an increased likelihood of death.[10]

Prognosis

Prognosis in animals with modest anemia and evidence of response is good if the inciting factor can be controlled or eliminated. The mortality rate of experimental and naturally occurring cases of RMT in horses is said to be 60% to 65%.[18] In animals with rapidly progressive and profound anemia, prognosis is poor unless blood transfusion is undertaken. Complications are associated with hypoxia, hypoperfusion, and inflammation. Horses may develop acute renal failure, colic, pyrexia, and laminitis. A retrospective study of 32 horses reported a fatality rate of 59% but failed to show an association between mortality and severity of anemia.[10]

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▪ Other Causes of Hemolytic Anemia

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Intravascular Hemolysis Following Cutaneous Burns

Johanna L. Watson • Monica Aleman

Intravascular hemolysis has been reported in horses following severe cutaneous burns affecting more than 25% of their body surface. Blood samples on admission showed hemolysis along with abnormal RBC morphology, increased osmotic fragility, hemoglobinuria, azotemia, and hemoglobin pigment nephropathy.[1] The pathophysiology of hemolysis is unclear but suspected to be associated with the production of hydroxyl radicals by complement-activated neutrophils. Abnormal findings reported in humans include intravascular hemolysis, increased RBC osmotic fragility, decreased membrane deformability, RBC crenation, eccentrocytosis, spherocytosis, bud formation, fragmentation, and vesiculation.[2] These abnormalities are dependent on severity of burn trauma.[2] Early fluid therapy and free radical scavengers have been beneficial for burn treatment in humans, along with supportive and wound care, control of pain and inflammation, and sepsis prophylaxis. A study in mice suggests that the level of plasma free hemoglobin is related to the size and depth of burn injury, which may be difficult to determine in some cases.[3]

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l-Tryptophan-Indol Intoxication

Johanna L. Watson • Gary P. Carlson

Experimental studies in ponies have demonstrated an acute hemolytic process associated with orally administered L-tryptophan, which is converted to indol in the GI tract.[4] Intoxication was associated with an acute onset of restlessness, tachypnea, intravascular hemolysis, and hemoglobinuria. At necropsy there was evidence of hemoglobinuric nephrosis and bronchiolar degeneration in some ponies. Similar clinical signs were noted following oral administration of tryptophan at 0.35 to 0.60 g/kg, and indol at 0.1 to 0.2 g/kg.[4,5] Intravascular hemolysis was associated with increased osmotic fragility and with Heinz body formation in a few of the experimental ponies.

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Water Intoxication

Johanna L. Watson • Gary P. Carlson

Massive water intake may produce marked hypotonicity of body fluids, with subsequent intravascular hemolysis of erythrocytes.[6] This problem has been described as a naturally occurring entity in milk-reared calves when they are first given access to unlimited quantities of water.[7,8] Severe neurologic signs may be seen (e.g., depression, convulsions, coma). Respiratory distress, hemoglobinuria, and death losses occur in some cases. Clinicopathologic features include hemolytic anemia, hypoproteinemia, hyponatremia, hypochloremia, hyposmolality, hemoglobinuria, and hyposthenuria. A sudden decrease in serum osmolality is believed to result in osmotic lysis of erythrocytes.[9] Erythrocytes are most susceptible to osmotic shock when calves are between 4 and 5 months of age. Treatment is primarily a matter of temporarily restricting water and providing supportive care. Calves with marked hyponatremia (sodium of 110 mmol/L) that are manifesting neurologic signs may benefit from hypertonic saline, mannitol, and corticosteroids. The goal of treatment is restoring serum sodium to 120 to 125 mmol/L without overcorrection. Death losses can occur in as little as 2 hours, but most calves recover without long-term adverse effects.

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Postparturient Hemoglobinuria

Johanna L. Watson • Gary P. Carlson

A syndrome of intravascular hemolysis, hemoglobinuria, and anemia has been recognized in postparturient dairy cattle around the world.[10] The disease occurs sporadically, and the incidence is relatively low. Affected animals are most often high-producing multiparous cows that develop clinical signs during the first month after calving.[11] Depression, decreased feed consumption, and decreased milk production are associated with hemoglobinuria, anemia, and icterus. The anemia is often marked and after 4 or 5 days is associated with evidence of a marked erythropoietic response. The precise mechanism by which the intravascular hemolysis occurs has not been fully elucidated. The condition has been related to the marked hypophosphatemia commonly found in affected cows and moderately low phosphate levels in unaffected herdmates. Hypophosphatemia is brought about by inadequate dietary phosphorus intake in animals grazing phosphorus-deficient soils or fed fodder grown on such soils. Low intracellular phosphate concentration may interfere with energy metabolism, thus affecting cell viability and the ability of the red cells to deal with potential hemolysins (e.g., saponins from sugar beets or alfalfa). A postparturient hemolytic problem associated with copper deficiency and Heinz body formation has been described as a herd problem in New Zealand (see previous section).

Blood transfusion and supportive IV fluids are indicated in valuable cows with severe life-threatening anemia. Correcting hypophosphatemia consists of providing phosphate, initially as sodium acid phosphate ($NaH_2PO_4H_2O$), 60 g/300 mL of water IV, followed by oral supplementation with 200 to 300 g sodium phosphate salts every 12 hours. Correction of dietary imbalances is indicated.

▪ Copper Toxicosis

Johanna L. Watson • Lisle W. George

Copper is an essential nutrient for domestic animals, but excessive supplementation can result in toxicity. Copper poisoning is a common intoxication in ruminants. Reviews of the toxicodynamics and clinical syndromes have been published.[1-3] Lambs are most susceptible to the toxic

effects of copper, but poisonings have occurred in adult sheep, goats, and cattle; Merino sheep are more resistant than British breeds.[4] Cattle have been poisoned by ingesting diets containing 37 mg of copper/kg of feed for 2 years.[5] Cattle fed 12 mg or more of copper/kg of body weight have been reported to develop subclinical hepatic disease.[6]

Elemental copper is an essential trace mineral with a narrow therapeutic window. Dietary requirements for growing sheep range between 4 and 6 parts per million (ppm), yet toxicity can occur whenever sheep are exposed to diets containing as little as 10 to 20 ppm.[7-9] Phytogenous copper poisoning results from concomitant ingestion of copper at 20 ppm of food, molybdenum, and sulfate. Ingested salts of copper are absorbed through enterocytes by carrier proteins and transported to blood in loose complexes with albumin and amino acids.[10] Roughly 20% of total plasma copper is ionized copper. Between 70% and 90% of this ionic copper is internalized by hepatocytes, where it is redistributed to bile, packaged in lysosomes in protein complexes, or used for the formation of ceruloplasmin.[10] Accumulation of copper occurs because daily hepatic biliary copper excretion amounts to less than 1% of ingested copper in ruminants.[11] Hepatic storage can buffer high levels of copper intake until the sites become saturated. At that time, hepatocytes die spontaneously or in response to environmental stress or dietary changes. Hepatocyte death causes the release of large amounts of cuprous copper into the blood. Animals that have preexisting hepatitis from pyrrolizidine alkaloids store less copper and are more susceptible to the hemolytic crisis.[4,12]

Free inorganic copper is an oxidant and can participate in the Fenton reaction. Cellular damage is related to production of oxidative hydroxides and peroxides, not to copper oxidation. These reactive intermediates are thought to initiate lipid peroxidation and oxidative denaturation of proteins within erythrocytes. Oxidation of heme protein produces Heinz bodies, and oxidation of hemin produces methemoglobinemia. Vitamin E is also denatured. This latter reaction removes a potent antioxidative protective factor and enhances cellular susceptibility to additional oxidants.

The hemolytic phase of copper poisoning is often initiated by noxious stimuli that could include shipping, hierarchal change, administration of oxidative drugs, starvation, or change of housing.[13] High-protein diets have increased resistance to the hemolytic crisis in sheep, but the role of extra molybdenum intake in these supplemented animals was unclear.[9,14] The mechanistic relationship between

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stressful events and hepatocyte release of copper is unknown.

Sources of copper that have been responsible for copper accumulation in animals include trace mineralized salt, inappropriately formulated cereal grain mixtures, forages from pastures that have been fertilized by swine or chicken manure,[15] orchard pastures that have been contaminated by copper-containing fungicides, rations containing more than 20% chicken litter, or diets that contain high concentrations of palm kernel oil. Other potential sources of copper include fencing and copper piping and overdoses of parenterally administered copper salts. Dairy goats have been poisoned by supplementation of trace minerals that were formulated for dairy cattle.

The toxic dose of copper for each species is variable and depends on duration of exposure, the animal's genetics, and the amount of molybdenum being fed. Diets with copper/molybdenum ratios over 6 : 1 are more likely to result in copper poisoning than diets with lower ratios. The interaction between the two minerals may occur in the solid phase of rumen ingesta, where insoluble and nonabsorbable complexes among copper, sulfur, molybdenum, and large-molecular-mass protein complexes are formed. The highly complexed copper is unabsorbed and hence not toxic. High dietary intake of zinc and iron also inhibit absorption of copper, and although the precise mechanism of antagonism is unknown, the elements share a competitive affinity for metallothionein.[16-18] Competition for this protein could alter the storage capacity for copper. Soil sulfates reduce molybdenum absorption by plants, increasing the potential for pathologic accumulation of copper in herbivores.

The respective single toxic doses of copper for sheep and cattle range between 20 and 110 mg/kg and 220 to 880 mg/kg of body weight. Most poisonings occur after long-term, low-dose ingestion of the element. Copper poisoning can occur in sheep after 2 months of daily dosing of 3.5 mg/kg of copper, feeding a ration that contains 20 ppm of copper for several months, or after a single SC injection of copper EDTA salt at a dose of 2 mg/kg.[19] Sheep have been poisoned by subcutaneous injection of 3 to 4 mg/kg of copper-calcium EDTA but remained normal after 6 mg/kg of copper methionate.[20] One study that fed 3.7 mg/kg of copper daily for 84 days reported peak hepatic copper levels that ranged between 258 and 375 mg/kg wet weight by 26 days after the final copper feed.[21] A single dose of 50 mg of copper caused acute hemolytic crisis in sheep when treated during midpregnancy. The largest incidence of hemolytic anemia occurred in Welsh sheep, and the lower cumulative incidence was in Cheviot sheep.[22] Single

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doses of copper calcium ETDA at 25 mg/animal have killed lambs.[23] Cumulative doses of copper ranging between 12.8 and 22 g have produced hemolytic anemia in Suffolk lambs by 42 days.

Goats may show signs of copper poisoning by 144 days after daily feeding of a ration that contains 80 mg copper/kg. Placental transfer of copper occurs, but concentrations in the tissues of lambs are not toxic even during the hemolytic phase in the dam. Adult cattle may be poisoned by feeding 5 g of copper sulfate daily for as long as 4 months. Calves may be poisoned after 6 to 8 weeks of feeding milk replacer containing 115 ppm of copper.[10,24] Horses are resistant to high dietary concentrations of copper and may remain clinically normal after prolonged feeding of diets containing levels as high as 791 ppm. In those horses, hepatic concentrations of copper at the end of the feeding period reached 4000 ppm. Adult ponies that were treated once with an oral dosage of copper of 40 mg/kg did not develop hemolytic anemia.

Clinical Signs

Animals exposed to high levels of copper are asymptomatic for weeks until the onset of hepatic necrosis.[25,26] Signs develop rapidly thereafter and are reflective of coexisting anemia, myopathy, and neurologic, renal, and hepatic disease. Clinical signs include inappetence, lethargy, weakness, recumbency, cool extremities, pallor, and grayish discoloration of the mucous membranes. Affected animals have a markedly increased pulse rate, poor pulse quality, tachypnea, hypotension, and hypothermia. Urine is dark red from the presence of free hemoglobin products. Feces are dark or have yellowish discoloration but are normally formed and do not contain hemoglobin unless secondary abomasal ulceration has occurred. Animals may have marked petechiation of the conjunctival mucosa. Pregnant animals often abort secondary to hypoxemia. Recumbent patients usually expire without struggling.

Pathology

The tissues of hemolyzing animals are pale and icteric, and serous surfaces are covered by petechial and ecchymotic hemorrhages. The liver is often pale and yellow, and the lungs are firm. Kidneys turn black and have a metallic sheen due to entrapped hemoglobin. The urinary bladder of copper-poisoned animals is filled with serosanguineous urine. Microscopic changes include hemoglobinuric

and tubular nephrosis and necrosis of the splenic follicles and hepatocytes. There is also biliary ductular proliferation and pericholangitis.[21,27] Hepatic necrosis may be detectable by microscopic examination for as long as 412 days post poisoning. Microscopic brain changes in poisoned animals include spongy degeneration of the pons and brainstem.

Diagnosis

Normal hepatic concentrations in sheep have been reported as 173 ± 130 (mean ± SD) and 129 ± 59 ppm (wet matter) for adults and lambs, respectively.[28] Wet matter hepatic concentrations of copper in poisoned animals were 429 ± 249 (mean ± SD) ppm. Dry weight concentrations may be greater than 3000 ppm. Hepatic concentrations are usually high before and after the hemolytic episode, but normal hepatic copper concentrations in hemolyzing animals have been reported.[19] The correlation between plasma and hepatic copper concentrations in prehemolytic animals is poor.[29-30] Copper poisoning in animals with normal plasma concentrations and near-toxic liver levels have been reported.[31] Normal plasma copper concentrations range from 13 to 20 µmol/L (0.8 to 1.2 µg/mL).[21] Serum copper concentrations range between 0.60 and 1.50 µg/mL (0.6 to 1.5 ppm). Plasma copper concentrations that range between 2.4 and 20.0 µg/mL (2.4 to 20 ppm) are diagnostic for acute toxicosis.

Clinical Pathology

There are no consistent hematologic changes until 24 hours before the hemolytic crisis, when sudden concentrations of cytosolic hepatic enzymes rise coincidentally with a sharp rise in plasma copper concentration. Plasma copper concentrations fall rapidly following the hemolytic crisis and are often near normal by 4 days after hemolysis.[25] Copper concentrations within erythrocytes remain high.

Clinicopathologic changes that occur during the acute hemolytic crisis include Heinz body formation, intravascular hemolysis, methemoglobinemia (as much as 5%), decreased PCV, and increased concentrations of plasma bilirubin, AST, GGT, alkaline phosphatase, total bilirubin, creatine kinase, creatinine, plasma urea nitrogen, and plasma ceruloplasmin. Urine is dark brown to black and contains high concentrations of protein, blood, and hemoglobin casts.

Microscopic examination of urine may detect erythrocytic casts and inflammatory cells.[32] Sheep that survive the hemolytic episode develop reticulocytosis by 4 days after the onset of clinical signs.[33]

Hepatic concentrations of 16 mmol copper/kg of dry matter are the threshold for development of hemolytic anemia. The half-life of copper in the liver of untreated poisoned sheep has been estimated to be 175 ± 91 days,[21] and high copper concentrations in hepatic tissues can be found for as long as 100 days after initiation of the hemolytic episode.[29]

Kidney concentrations of copper in animals with hemolytic crisis are 15 and 50 ppm for dry and wet weight volumes, respectively. Sheep may have increased plasma concentrations of γ-glutamyltransferase (GGT) and AST for 3 days before the onset of hemolysis, and glutamate dehydrogenase may be increased for as long as 700 days after cessation of copper ingestion.[21] Fecal copper concentrations may exceed 10,000 ppm during the hemolytic episode.

Treatment

Animals with acute hemolytic syndrome should be insufflated with oxygen and treated with vitamin E (3 to 5 daily doses consisting of 3000 IU/dose). If PCV is below 8%, animals should be given packed washed homologous erythrocytes. Additional therapy should include D-penicillamine (Cuprimine [Merck Sharp & Dohme, Rahway, N.J.] at 52 mg/kg of body weight daily for 6 days), anhydrous sodium sulfate (1 g/sheep daily for 6 days), and ammonium molybdate (100 mg/sheep daily for 6 days). Treatment with D-penicillamine increases urinary copper excretion by 10- to 20-fold.[34] Single-dose therapy with D-penicillamine (28 mg/kg body weight) increases copper excretion, but the effect is transient and insignificant for reducing the total hepatic copper load.[35]

Dietary supplementation with 7.7 ppm ammonium molybdate also results in hepatic copper concentrations that are 40% lower than in unsupplemented controls. Addition of 7 or 15 mg molybdenum for 80 days to experimentally poisoned sheep has reduced hepatic copper concentration in sheep by 34% and 46%, respectively.[36] Copper-poisoned cattle have been successfully treated with oral sodium molybdate (3 g daily) and sodium thiosulfate (5 g daily). When introduced into the sulfur-rich rumen contents, molybdenum salts complex with high-molecular-weight proteins in the solid phase of the digesta.[37] The protein-bound thiomolybdate aggregates strongly chelate copper in insoluble and

indigestible complexes. Molybdenum salts also enhance biliary copper excretion and selectively remove copper from hepatic metallothionein.[16,38,39] For poisoned cattle, top dressing food with 500 to 1000 mg ammonium molybdate daily for 18 days markedly reduced the amount of hepatic copper.[40]

Parenterally administered ammonium tetrathiomolybdate has been recommended for treatment of acute hemolytic crises due to copper poisoning. IV administration of ammonium tetrathiomolybdate reduces both lysosomal and cytosolic copper in hepatocytes. The drug has been given as a 5% solution in sterile saline with an IV dosing schedule of either 50 to 100 mg twice weekly for up to 11 weeks, or as 3 doses consisting of 3.4 mg/kg of body weight on alternate days and beginning at the onset of hemolytic crisis.[41-45] Concomitant administration of 36 mg of xylazine IV increased copper excretion in bile by as much as 2.25-fold over controls that were treated with thiomolybdate only.[46] Parenteral administration of thiomolybdate results in transient increases of copper concentrations in blood for as long as 24 hours. Because copper is acid insoluble, the effect is to protect copper-exposed animals from hemolytic crises and reduce tissue damage during a hemolytic event.[47,48] Biweekly injection of 100 mg molybdenum as tetrathiomolybdate increased daily hepatic biliary copper excretion by a factor that ranges between 150% and 300%.[49]

Prevention

Owing to the sporadic nature of copper poisoning and lack of signs during the accumulative phase, it can be difficult to prevent. Clients should be counseled to purchase concentrates with label claims for the species being supplemented. Copper-supplemented salts should be restricted, especially in sheep. Pastures heavily contaminated by copper can be top dressed with molybdenum phosphate (113 g molybdenum/acre). Fencing and plumbing that contain copper sulfate or metallic copper should be removed from the environment. One study in sheep receiving 36 mg copper/kg daily for 18 months controlled the hemolytic crisis and associated mortality due to copper poisoning by SC injection of sterile ammonium tetrathiomolybdate (containing 3 to 4 mg molybdenum) on alternate days for three injections.[44] Addition of ammonium molybdate at 7.7 ppm and sodium sulfate at 4200 ppm reduced liver copper and decreased plasma ceruloplasmin in experimentally exposed lambs.[30]

Feeding experimentally poisoned lambs sodium molybdate and sodium sulfate

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at respective daily dosages of 20 mg and 6 g reduced hepatic copper content after 90 days.[50] Addition of 3 mg/kg of food (dry matter) molybdenum in the form of tetrathiomolybdate reduced hepatic copper accumulation by as much as 33-fold.[43]

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Hemolytic Syndrome in Horses With Liver Failure

Johanna L. Watson • Gary P. Carlson

A fulminant intravascular hemolytic syndrome has been reported as a near-terminal event in horses with either acute or chronic liver failure.[1] Marked hemoglobinemia and hemoglobinuria are associated with intense icterus, and the sclera and conjunctiva often take on a distinctive deep reddish-orange color. The onset of intravascular hemolysis is sudden and rapidly progressive. The prognosis is highly unfavorable; nearly all horses that develop this syndrome do not survive.[2]

The cause of this syndrome is unknown, but release of hepatic copper stores does not appear to be a factor. The hemolysis may be associated with increased erythrocyte osmotic fragility. Human patients with liver cirrhosis develop a hemolytic syndrome associated with alterations in the exchangeable lipoproteins of the red cell membrane. A similar mechanism has not been shown in horses, but morphologic alterations in these horses' red cells resemble the burr cells described in human patients.[3] Bile acids and their salts are markedly increased in liver failure and could play a contributing role in the hemolytic process. At necropsy, widespread hemorrhagic lesions that resemble those described for DIC are often present.[3]

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Congenital Erythropoietic Porphyria

Gary P. Carlson

A rare congenital disorder of hemoglobin production that is inherited as an autosomal recessive has been recognized primarily in Holstein cattle, but it has also been reported in other breeds.[4-7] Commonly called “pink tooth,” the disorder is characterized by slow growth rates in calves, photosensitization, and exfoliation of nonpigmented skin when exposed to sunlight, reddish-brown teeth, and modest anemia. The teeth and bones exhibit a pink fluorescence under ultraviolet light, and the presence of uroporphyrin turns urine a brownish-red color. The condition is present at birth, and the metabolic defect is a hereditary deficiency of the enzyme uroporphyrinogen III synthase (UROS), which catalyzes an essential step in the synthesis of the porphyrin structure of hemoglobin. This leads to accumulation of uroporphyrin and coproporphyrin, which deposit in the teeth, where they are concentrated in the dentin, bones, and other tissues. The anemia seen in these cattle is variable among individuals, and several factors contribute to it. Reduced intravascular red cell life span is related to the high concentration of uroporphyrin and coproporphyrin within the cells. Porphyrins may induce hemolysis and delay red cell series maturation in the bone marrow, although there is often evidence of active erythropoietic response in peripheral blood.[5]

There is no treatment for this inherited disorder, but genetic counseling is advisable. Substantial efforts have been made to reduce the incidence of this disease in the Holstein breed. Affected cattle have much lower levels of UROS than normal cattle, and carrier animals have intermediate levels of this enzyme. Despite their rather serious problems, these cattle do reasonably well if housed indoors out of direct sunlight. The principal differential consideration is chronic fluorosis, which also produces brown discoloration of the teeth, but they do not fluoresce under ultraviolet light.

Another form of altered porphyrin metabolism, erythropoietic porphyria, has been described in humans and cattle.[5] In humans the mode of inheritance is autosomal dominant, whereas in cattle the disorder appears to have a recessive pattern of inheritance and may be sex linked because it is only seen in females. The disease does not produce anemia, porphyrinuria, or teeth discoloration, but ferrochelatase (heme synthase) deficiency leads to high concentrations of

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erythrocyte and fecal protoporphyrins.

Porphyria has also been reported in swine, where it exhibits a dominant pattern of inheritance.[5] Health effects are minimal, and there is no photosensitivity, but the pigs' teeth have reddish-brown discoloration.

Finally, animals may develop acquired toxic porphyrias. This can occur with heavy metal poisonings, principally lead. Lead inhibits several key enzymes of heme synthesis. Inhibition of aminolevulinate dehydrase leads to accumulation of aminolevulinic acid, and decreased aminolevulinate dehydrase activity is a sensitive indicator of lead poisoning. Lead also inhibits ferrochelatase and leads to marked elevation of erythrocyte zinc protoporphyrin IX, making measurement of zinc protoporphyn IX levels a means of monitoring lead exposure.[5]

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Depression Anemia

Johanna L. Watson • Gary P. Carlson

The most common form of anemia in domestic animals is associated with inadequate erythropoiesis or bone marrow depression. Depression anemia can be caused by (1) deficiencies of vitamins or minerals essential for erythrocyte production, (2) systemic disease processes that interfere with normal erythropoiesis, or (3) processes that damage or displace normal bone marrow elements. Common causes of depression anemia are listed in Box 37.2. Depression anemia is mild to moderate in severity and generally is slowly progressive. Depressed erythropoiesis is occasionally associated with processes that also result in blood loss and/or an increased rate of erythrocyte destruction. When this occurs, a profound rapidly progressive and potentially life-threatening anemia can develop. With the possible exception of chronic iron or copper deficiency, depression anemia tends to be normocytic and normochromic. Bone marrow evaluation is an extremely useful diagnostic tool in animals with nutritional deficiencies or when bone marrow damage or dyscrasia is suspected.

Box 37.2

Causes of Depression Anemia

Nutritional Deficiency

Iron deficiency
Copper deficiency
Cobalt deficiency
Vitamin B_{12} deficiency
Folic acid deficiency

Anemia of Inflammatory Disease

Chronic infection
Chronic inflammation

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Fractures and severe trauma
Neoplasia

Anemia Secondary to Organ Dysfunction

Chronic liver disease
Chronic renal disease
Chronic gastrointestinal disease
Parasitism (trichostrongylosis)

Bone Marrow Damage/Dysplasia

Myeloid and megakaryocytic bone marrow hypoplasia in Standardbred horses
Bracken fern poisoning
Congenital dyserythropoiesis and keratosis in polled Hereford calves
Trichloroethylene-extracted soybean meal toxicity
Myelophthisic disorders (myeloproliferative disease, lymphoma)
Aplastic anemia

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Iron Deficiency Anemia

Johanna L. Watson • Gary P. Carlson • Monica Aleman

Iron is present in most forages and grains. In neonates, the major source of iron is colostrum (≈0.79 mg/L in mare's milk).[1] Soil, dam's feces, and milk are other important sources of iron.[1] Iron deficiency is most commonly associated with chronic blood loss due to internal or external parasitism, bleeding GI lesions, or hemostatic defects. Dietary iron deficiency is seldom the sole cause of anemia, even in neonates on an all-milk diet, unless they are raised on cement or in barns or hutches with no access to the soil. A modest anemia is anticipated in veal calves. The anemia seen in some young calves during the first few days to weeks of life is apparently the result of congenital iron deficiency.[2] Altered immune function, high incidence of infection, and reduced growth performance are reported in veal calves on low-iron diets.[3] Alterations in GI pH may alter absorption of iron by the small intestine. States of inflammation and infection cause iron sequestration, not deficiency, by the reticuloendothelial system and lactoferrin. Iron deficiency has been well documented in calves and piglets housed exclusively indoors or in hatches with no access to soil.[4] Absolute iron deficiency anemia is not commonly reported in horses.[5-8]

Circulating erythrocytes account for about two-thirds of the total iron reserves found in the body. The remaining iron stores are distributed in the liver, spleen, and bone marrow. With chronic blood loss anemia, iron depletion is first indicated by decreased marrow iron, which can be appreciated with special staining of the bone marrow with Prussian blue stain for iron. As blood loss continues and iron deficiency progresses, serum iron is decreased, whereas iron-binding capacity may actually increase. Late in this process, iron-deficient erythropoiesis results in the typical microcytic, hypochromic erythrocytes generally thought to be characteristic of iron deficiency anemia (decreased PCV, hemoglobin concentration, mean corpuscular volume, and mean corpuscular hemoglobin concentration). Other laboratory findings include echinocytosis, keratocytosis, schistocytosis, acanthocytosis, ovalocytosis, hypoferritinemia, and hypoferremia.[5-8] The observed RBC morphologic abnormalities are thought to be due to oxidative damage. Normal serum iron and iron-binding capacity for most domestic animals is 100 and 300 µg/dL, respectively.

Treatment

Treatment of iron deficiency anemia is contingent on evaluation of the cause and correction or resolution of the process responsible for chronic blood loss. Iron is usually supplied as an oral supplement or feed additive, and many commercial preparations are available. Injectable iron dextran intended for use in baby pigs should be avoided in horses and cattle, because it can induce anaphylaxis, especially if administered repeatedly.[9] An injectable iron preparation intended for use in horses was reported to result in acute iron overload, massive hepatic necrosis, and severe death losses in a group of young cattle.[10] Iron overload has resulted in acute death losses in neonatal foals fed an iron-containing microbial supplement and in hemochromatosis and extensive liver damage in adult horses.[11]

Copper Deficiency

Johanna L. Watson • Gary P. Carlson

Copper deficiency can occur as a primary problem in milk-fed animals or in pastured animals in copper-deficient areas. More commonly, copper deficiency occurs secondarily in association with other trace mineral imbalances such as dietary molybdenum excess and is influenced by the sulfur and zinc content of the diet. Copper is an essential cofactor for a wide variety of enzymatic reactions, and copper deficiency produces a constellation of clinical signs related to impairment of these reactions.[12] Clinical signs of copper deficiency are most prominent in young, growing animals and may include reduced growth rate, rough and depigmented hair, diarrhea, osteoporosis with spontaneous fractures, and anemia. In lambs, copper deficiency can produce a demyelinating syndrome known as *swayback* or *enzootic ataxia.* Copper deficiency has also been associated with hemolytic anemia in postparturient dairy cattle in New Zealand.[10] Copper plays an important role in iron transport from the gut to the marrow and in the incorporation of iron into the heme moiety. The anemia produced by copper deficiency is generally moderate and slowly progressive. It closely resembles iron deficiency in that it is usually a microcytic, hypochromic anemia. Bone marrow evaluation often reveals intracellular accumulations of iron known as *sideroblasts.* This finding indicates that the principal problem is a function of altered incorporation of iron into the erythrocyte hemoglobin rather than an actual deficiency of iron. Copper deficiency can be documented by

measuring serum copper as ceruloplasmin, erythrocyte superoxide dismutase, or the copper content of hair, liver, or kidney. Serum iron tends to be low in animals with copper deficiency. Copper can be supplied as a dietary supplement or as an injectable copper glycinate preparation.

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Vitamin B_{12} and Folic Acid Deficiency

Johanna L. Watson • Gary P. Carlson

Nearly all of the vitamins are necessary for normal erythropoiesis, but in ruminants and horses only deficiencies of vitamin B_{12} and folate have been associated with development of anemia. These two vitamins play essential roles in DNA synthesis. When deficiency of both vitamins occur, as has been experimentally produced in pigs, a marked macrocytic anemia with hypersegmented circulating neutrophils and giant metamyelocytes and neutrophils in the bone marrow may be found. In ruminants, vitamin B_{12} deficiency has been associated with grazing cobalt-deficient pastures. A macrocytic to normocytic anemia may be noted in these animals.

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Anemia of Inflammatory Disease

Johanna L. Watson • Gary P. Carlson

A depression anemia associated with characteristic disturbances of iron metabolism is often found in animals with conditions that result in a chronic inflammatory response.[13,14] These conditions include chronic internal or cutaneous infections, infectious diseases, or immune-mediated processes that result in chronic inflammation, severe traumatic injury or fractures, and active malignant neoplasia. The anemia tends to be mild, slowly progressive, and of little clinical consequence. Clinical signs relate to the primary disease process, and hematologic features are those of a mild, unresponsive anemia, often with indications of a chronic inflammatory response. Serum iron and iron-binding capacity are decreased, but marrow iron reserves and serum ferritin are increased.[14] Anemia in these animals is partially due to a modest decrease in circulating red cell life span, but it is primarily caused by major alterations in iron metabolism and depressed bone marrow response to the anemia. These alterations represent part of the body's response to inflammation, which includes release of interleukins and other mediators and production and release of acute-phase proteins from the liver. The body sequesters iron from the circulation into storage forms, primarily in the liver and bone marrow, where it is retained and relatively unavailable for erythropoiesis. This general reaction may play a protective role by denying readily available iron to potential bacterial pathogens that require iron for growth. Iron supplementation is not indicated to treat the anemia of chronic inflammation; therapeutic effort should be directed at resolving the primary disease process.

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Anemia Secondary to Organ Dysfunction

Johanna L. Watson • Gary P. Carlson

A mild to moderate unresponsive anemia can develop in patients with chronic endocrine, hepatic, renal, or GI diseases. These disorders can produce bone marrow depression by reducing absorption, processing, and distribution of elements essential for erythropoiesis; allowing elaboration or accumulation of toxic compounds; or interfering with the production or action of erythropoietin.[15,16] These effects can occur independently of the alterations in iron metabolism that characterize the anemia of inflammatory disease.[14] However, should inflammatory processes be responsible for the specific organ damage or dysfunction, the same pattern of anemia as described in the previous section would apply. Specific therapy for anemia in these patients is not indicated, and resolution of the anemia depends on successful management of the primary disease process.

Internal parasitism, particularly *Trichostrongylus* spp. in ruminants, can result in a marked anemia that is primarily the result of bone marrow depression in which failure to absorb iron, copper, and essential amino acids plays a major role.

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Myeloid and Megakaryocytic Bone Marrow Hypoplasia

Johanna L. Watson • Gary P. Carlson

Myeloid and megakaryocytic bone marrow hypoplasia has been reported in eight young Standardbred horses sired by the same stallion.[17] Clinical signs were variable and in some individual horses included nonhealing wounds, unresponsive fevers, pleuritis, pneumonia, ataxia, hemoperitoneum, and bleeding into the bowel. Seven of eight horses died or were euthanized. The principal laboratory findings were a variable red cell count from normal to modest to marked anemia, moderate to profound neutropenia, and intermittent thrombocytopenia in most of the horses. There appeared to be a cyclic variation in neutrophil and platelet counts. A familial basis for the disease is suspected.[17]

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Aplastic Anemia

Johanna L. Watson • Debra Deem Morris

Aplastic anemia is a stem cell disorder characterized by reduced marrow production of all blood components in the absence of a primary disease process infiltrating the bone marrow or suppressing hematopoiesis.[18,19] Peripheral pancytopenia secondary to marrow aplasia is apparently uncommon in horses, although idiopathic hypoplastic anemia has been reported,[20-22] as well as rare cases associated with phenylbutazone use.[15-23] Hemorrhagic diathesis caused by thrombocytopenia is often the first indication of disease, manifested by epistaxis, mucosal petechiae, or prolonged hemorrhage after trauma or injections. Pallor may be present, with other signs of anemia (e.g., reduced exercise tolerance) depending on the severity and rapidity of aplasia progression. Neutropenia causes increased susceptibility to infections, which may result in intermittent fever or weight loss. Lymphocyte production is reportedly not impaired, but absolute lymphopenia is common in aplastic anemia. Circulating lymphocytes are often highly reactive, producing the suspicion of neoplasia or a preleukemic syndrome.[15]

The diagnosis of aplastic anemia is based on the combination of peripheral pancytopenia and bone marrow hypoplasia with fatty replacement. Because the normal erythrocyte life span in horses is roughly 140 days and in cattle exceeds 160 days,[24] neutropenia with no left shift and thrombocytopenia are earlier hematologic manifestations.

The major aims in treatment of aplastic anemia are to remove the animal from suspected causative agents and provide supportive care, in the hope spontaneous remission will occur. Broad-spectrum antimicrobials are necessary to control infections. Blood transfusions are rarely indicated, and platelet transfusion should be reserved for severe bleeding episodes, which rarely occur. Bone marrow transplantation is used with some success in humans, although graft-versus-host disease poses significant risk. The latter would presumably limit this therapy in horses; too few horses with aplastic anemia have been studied to give a clear indication of prognosis.

Bracken fern toxicosis in ruminants causes bone marrow depression and subsequent pancytopenia.[24] The toxic effects of the plant are cumulative, and clinical signs occur suddenly 2 to 8 weeks after cattle gain access to the plant.

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Clinical signs include fever, melena, epistaxis, hematuria, mucosal petechiae, hyphema, and bleeding from the eyes and vagina. Hematology reveals a platelet count less than 40,000/µL and profound leukopenia with essentially no neutrophils present. Death may follow in 1 to 3 days as a result of the combined effects of multiple internal hemorrhages and bacteremia. The major toxic factor in bracken fern is thought to be ptaquiloside.[24] Necropsy of cattle with bracken fern toxicosis reveals multiple hemorrhages throughout most tissues, necrotic GI tract ulcers, and pale bone marrow. Antibiotics and blood and platelet transfusions may be appropriate, but cattle with advanced bracken fern toxicosis (platelet count <50,000/µL, leukocyte count <2000/µL) usually die.

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Paradoxical Erythroid Hypoplasia

Johanna L. Watson • Monica Aleman

Recombinant human erythropoietin (rhEPO) has been used in racehorses to enhance their athletic activity by stimulating erythrocyte production in the bone marrow. Mild to moderate anemia and paradoxical erythroid hypoplasia based on bone marrow cytology were reported in two Standardbred racehorses following rhEPO administration.[25] Serum from these horses inhibited the rhEPO-induced activity of mouse bone marrow in vitro. The degree of inhibition was inversely proportional to the amount of exogenous rhEPO added to the serum, suggesting the presence of anti-rhEPO antibodies. Anti-rhEPO antibodies to exogenous rhEPO likely cross-reacted with the horses' endogenous rhEPO. These horses were treated with corticosteroid and returned to athletic activity.

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Erythrocytosis (Polycythemia)

Johanna L. Watson • Debra Deem Morris

Absolute erythrocytosis is caused by increased erythropoiesis that creates a circulating erythrocyte mass above normal for the species. Relative erythrocytosis caused by hemoconcentration, endotoxemia, and splenic contraction (horses) must be ruled out because these conditions are much more common in large animals than absolute erythrocytosis. Diagnosis of absolute erythrocytosis is based on persistently elevated PCV, hemoglobin, and erythrocyte count without clinical evidence of shock or dehydration and without response to IV fluid therapy. Primary erythrocytosis is associated with normal arterial oxygen tension and reduced plasma erythropoietin, whereas secondary erythrocytosis is due to increased production of erythropoietin.

All disorders characterized by an absolute erythrocytosis share clinical manifestations caused by expanded blood volume and increased blood viscosity. Generalized vascular expansion and venous engorgement cause the characteristic "muddy" hyperemia of mucous membranes. A marked decrease in cardiac output accompanies blood hyperviscosity and ultimately impairs tissue oxygenation, producing the vague signs of lethargy and weight loss. There may be an increase in thrombotic complications like laminitis and renal failure.

Congenital Erythrocytosis

Familial erythrocytosis, described in cattle[1] and humans,[2] is due to autonomous erythropoietin production without a demonstrable lesion. Congenital erythrocytosis is thus a form of inappropriate secondary erythrocytosis. Chronic hypoxia should be ruled out by measuring arterial oxygen concentration. The only way to definitively differentiate secondary erythrocytosis from primary erythrocytosis is by determination of serum erythropoietin.

Acquired Erythrocytosis

Primary Erythrocytosis

Polycythemia vera, an idiopathic myeloproliferative disorder characterized by excessive proliferation of erythroid, myeloid, and megakaryocytic elements,

without an increase in the plasma erythropoietin, is rare in animals.

Secondary Erythrocytosis

Physiologically Appropriate Erythrocytosis.

In domestic animals, absolute erythrocytosis is usually secondary to chronic diseases that produce tissue hypoxia. Chronic tissue hypoxia that attends residence at high altitude, congenital heart defects that produce right-to-left shunting, and some forms of chronic pulmonary disease induce a compensatory increase in plasma erythropoietin that results in absolute secondary erythrocytosis.[3]

The partial pressure of oxygen (P_{O_2}) in capillaries must be maintained close to 40 mm Hg to ensure adequate off-loading of oxygen to tissues. At elevated altitudes, diminished atmospheric oxygen tension produces a much smaller alveolar capillary P_{O_2} gradient and an inadequate driving force for tissue oxygenation. Erythropoietin production in response to hypoxia causes erythrocytosis to increase the oxygen-carrying capacity of circulating blood. Cattle are most susceptible to the effects of high altitude, and some develop polycythemia at 1800 m above sea level. Horses develop an increased erythrocyte mass above 2200 m, especially when in training. Sheep are similar to cattle, but goats are apparently least susceptible to elevation hypoxia.

Congenital cardiac disorders that produce right-to-left shunts are a common cause for absolute erythrocytosis in large animals. Tetralogy of Fallot is the most common defect to cause shunting of unoxygenated blood into the peripheral circulation, although a number of other defects (ventricular septal defect [VSD] being the most common) may eventually result in right-to-left shunting and secondary erythrocytosis.[4]

Chronic impairment of alveolar ventilation may eventually cause erythrocytosis, although most chronic pulmonic diseases in large animals are not associated with significant hypoxemia. Equine asthma (RAO, COPD) may produce enough ventilation/perfusion mismatching to reduce the pressure of arterial oxygen below normal, but the resultant hypoxemia is insufficient to induce erythrocytosis.

Physiologically Inappropriate Erythrocytosis.

Inappropriate elaboration of erythropoietin (i.e., normal P_{O_2} and secondary

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erythrocytosis) may rarely accompany renal, hepatic, or endocrine disorders, especially those caused by neoplasia. Secondary erythrocytosis may accompany nonmalignant renal disorders, in which local intrarenal ischemia is believed to mediate increased erythropoietin production. Paraneoplastic erythrocytosis with normal serum erythropoietin is due to tumor production of androgenic steroids or a protein with erythropoietin-like action.[5] Increased plasma erythropoietin and secondary erythrocytosis has been identified in horses with hepatocellular carcinoma.[3,6] Erythrocytosis was described in a horse with hepatoblastoma[7,8] and in another with lymphoma,[9] but serum erythropoietin levels as measured by a human assay were normal in both instances. In the horse with lymphoma, erythropoietin gene expression was identified in the lymphoma tissue. Typically, the diagnosis of inappropriate secondary erythrocytosis is based on elevated serum erythropoietin in the absence of hypoxemia. Elevated serum erythropoietin may not be demonstrated because of the nature of the assay or other compounds causing erythrocytosis.

Treatment of Erythrocytosis

When erythrocytosis is not in response to an appropriate physiologic stimulus (e.g., primary erythrocytosis and inappropriate secondary erythrocytosis), phlebotomy to keep PCV below 50% is the mainstay of treatment to control hypervolemia and blood hyperviscosity. Initially 2 to 4 L of blood may have to be removed every 2 to 3 days, but as iron deficiency supervenes, the frequency of phlebotomy may be reduced. The myelosuppressive drug hydroxyurea is used in humans and dogs with *polycythemia vera*.[2,10]

Appropriate management of secondary erythrocytosis is more complex because there is a need for increased oxygen-carrying capacity of the blood. The beneficial effect of expanded red cell mass is ultimately offset by the detrimental effect of increased blood viscosity on oxygen delivery. Oxygen delivery is impaired when PCV exceeds 60%, although continued erythropoietin output may result in overcompensation. Phlebotomy is indicated when PCV is over 60%, but the optimum PCV for patients residing at high altitudes or those with right-to-left cardiac shunts must be determined by trial and error.

The long-term prognosis for patients with erythrocytosis is determined by the severity and cause of the disorder. Congenital cardiac defects, neoplastic diseases, and chronic organ insufficiency carry a guarded to poor prognosis. Familial or primary erythrocytosis may be managed by phlebotomy, although

there are no long-term follow-ups for large animals with these disorders.

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▪ Proliferative Disorders of Lymphoid and Myeloid Systems

The lymphoproliferative disorders reported in large animals are lymphoma, lymphocytic leukemia, and plasma cell myeloma. The myeloproliferative disorders are myeloid leukemias and malignant histiocytosis. The following sections will describe lymphoma, leukemia, and myeloma.

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Bovine Lymphoma

John A. Angelos

Bovine lymphoma (lymphosarcoma) is characterized in terms of the frequency of occurrence (sporadic or endemic/enzootic), age at onset, organ involvement, and associated etiologic agent. Sporadic bovine lymphoma occurs as generalized lymphadenopathy in calves (calf or juvenile form), as thymic involvement in cattle between 6 months and 2 years of age (thymic or adolescent form), and as a cutaneous form in cattle between 1 and 3 years of age. Lymphoid tumors of cattle with sporadic bovine lymphoma are of the B- or T-cell lineage.[1] The most common form of lymphoma appears endemically in adult cattle more than 2 years of age and is associated with *bovine leukemia virus* (BLV) infection and typically involves multiple organ systems; BLV-associated lymphomas of adult cattle are of the B-cell lineage.[2] BLV is an oncogenic type C retrovirus classified in the genus *Deltaretrovirus*, subfamily *Orthoretrovirinae*, and family *Retroviridae*.

Sporadic Lymphoma

Calf or Juvenile Form

The prevalence rate of juvenile lymphoma is unknown, but this form of lymphoma is rare. The cause of juvenile lymphoma is unknown and does not appear to be associated with BLV infection. The age at onset ranges from 3 to 6 months but can be seen in calves as young as 1 month or in cattle as old as 3 years. There have been reports of fetal involvement with the calf form.[3] Calves generally present with a history of slight to moderate depression, weight loss, weakness (mainly in older calves and despite good appetite), or lymphadenopathy (mainly in younger calves). The onset of signs can be sudden (within a week).

Physical examination may reveal generalized bilateral enlargement of lymph nodes (deep cervical, parotid, subiliac [prefemoral], and mandibular) and occasionally hemal nodes. Rarely, node enlargement is restricted to a regional anatomic site and not generalized. Enlarged nodes tend to be smooth and firm but are not hot or painful. In addition to enlarged lymph nodes, common

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presenting clinic signs include bloat and dyspnea. Mucous membranes are usually pale as a result of anemia. Tachycardia, tachypnea, hyperpnea, cough, and harsh respiratory sounds may be evident on auscultation. Less frequently reported signs include fever, ruminal tympany, an enlarged liver, ataxia, and diarrhea.

Hematologic features include a microcytic hypochromic anemia, a low hemoglobin (<7 g/100 mL), a low packed cell volume (typically mid-20s), and a leukocytosis primarily caused by a lymphocytosis. Bone marrow examinations may reveal an elevated myeloid/erythroid ratio with massive neoplastic infiltration. Affected calves also tend to have low serum globulin and elevated AST. Neoplastic involvement may affect a variety of organs, including the spleen, heart, kidney, liver, pancreas, uterus, and thymus. Less thymic involvement occurs versus the thymic form of lymphoma; neoplastic tissue is found only as small, microscopic nodules. Subperiosteal neoplastic infiltration may produce spinal cord compression and result in paresis. The disease is rapidly progressive and usually fatal within 2 to 8 weeks of onset.

Thymic or Adolescent Form

The thymic form of lymphoma is rare. The disease is usually seen in cattle 6 to 24 months of age but may occur in newborn calves and cattle up to 4 years of age. Clinical signs are produced by space-occupying lesions in the neck or thorax. Metastatic mammary lymphoma along with thymic lymphoma was reported in a 3-year-old beef heifer.[4] Cattle with thymic lymphoma typically present with brisket enlargement or firm swelling in the presternal area of the brisket, associated with pitting edema.[5] Loss in body condition, rumen tympany, and dysphagia are common. Bloat may occur as a result of inability to eructate rumenal gas as a result of a space-occupying lesion around the esophagus. Generalized lymphadenopathy is uncommon; rather, enlarged superficial cervical and prescapular nodes are usually observed. The jugular veins are distended and nonpulsating; there may be muffled heart sounds and diminished resonance on thoracic percussion. Tachycardia, dyspnea, coughing, or respiratory distress may be present. Fever is also a common clinical finding; however, the exact mechanism is poorly understood but could be due to tumor necrosis, inflammatory mediators, and/or secondary respiratory infections. Hematologic features are generally unremarkable. Anemia is not a consistent feature, and lymphocytosis is only seen occasionally. The course of the disease

from the time of recognition is generally from 2 to 9 weeks. The disease is fatal, often as a consequence of bloat.

Although thymic lymphoma is not associated with BLV infection, there has been one report of a BLV-positive 18-month-old heifer with thymic lymphoma. In situ PCR was used to detect the presence of BLV proviral DNA in lymphocytes of the thymus and in liver and kidney epithelium.[6]

Atypical Forms

A 7-month-old Holstein heifer with diffuse swelling over the left thigh, difficulty ambulating, and peroneal and tibial nerve deficits had an infiltrative B-cell lymphoma involving the semitendinosus, semimembranosus, and gluteal muscles.[7] This heifer was serologically positive for BLV antibody, but the possibility of maternally derived antibody could not be ruled out. In another case report, an 18-month-old Friesian heifer with cutaneous lymphoid tumors also had extensive lymphoid nodules covering the external and luminal surfaces of the trachea.[8] An 8- to 9-year-old beef cow with weight loss was reported with pleural and pericardial invasion with a lymphoid tumor of T-cell lineage; the animal tested negative for BLV by PCR.[9] Four of 10 cattle 3 years of age or younger diagnosed with sporadic lymphoma had BLV provirus in tumor DNA as detected by PCR, and a possible role for BLV in some cases of sporadic lymphoma of cattle has been suggested.[10] A 13-month-old alpaca affected with mandibular masses and weight loss of 2 weeks duration was diagnosed with disseminated small cell lymphoma involving the pancreas, kidney, liver, omentum, and the caudal vena cava; BLV proviral DNA was identified in normal liver and mandibular mass tissue adjacent to neoplastic lymphoid tissue, but it was not found in pancreatic or renal tissue.[11]

Cutaneous Form

Cutaneous lymphoma is not as age specific as the other forms of sporadic lymphoma and may affect cattle between 1 and 3 years of age. The history may reveal an initial period of 1 to 3 months, during which cutaneous swellings are observed around the anus, vulva, escutcheon, shoulders, or flank. These signs may regress and subsequently recur. Lesions are generally raised, about 2 to 3 cm in diameter with necrotic centers, and can become ulcerated and painful. Other clinical signs depend on additional organ system involvement of the tumor and may include cardiac insufficiency, with brisket edema extending along the

ventral abdomen and jugular pulsation. Pulse and respiration may be elevated as a result of anemia. Hematologic features include anemia and presence of atypical lymphocytes. The mandibular, prescapular, subiliac, and supramammary lymph nodes are usually enlarged.

At necropsy, a variety of organs may be involved, including heart, brain, skin, spinal cord, liver, lung, kidney, and abomasum. The massive lymphoid infiltration of the skin resembles the clinical manifestations of mycosis fungoides of humans. In a report of a 12-month-old red Holstein heifer with cutaneous T-cell lymphoma, serum activity of lactate dehydrogenase (LDH) was moderately increased despite normal to minimally increased activities of liver- and muscle-specific enzymes.[12]

Hemonode Enlargement (Hemal Lymph Node)

A lymphoproliferative condition associated with hemonode enlargement and some generalized lymphadenopathy has been described for cattle infected with a lentivirus[13] that is now called bovine immunodeficiency virus (BIV).[14] BIV belongs in the genus *Lentivirus*, subfamily *Orthoretrovirinae*, and family *Retroviridae*. BIV has molecular similarity to human immunodeficiency virus and is associated with persistent lymphocytosis, lymphadenopathy, central nervous system (CNS) lesions, progressive weakness, and emaciation. Infected calves may develop enlarged superficial nodes *(hemonodes)*, mainly in the cervical region anterior and dorsal to the prescapular lymph node, over the spine of the scapula, in the paralumbar fossa, and dorsal to the subiliac (prefemoral) lymph node. Lymphocytosis is possibly related to an increase in B lymphocytes. In utero transmission of BIV has also been documented.[15]

Adult Lymphoma (Bovine Leukemia Virus)

The adult, or enzootic, form of lymphoma is the most common neoplastic disease of cattle and is most commonly caused by a BLV infection. Rates of lymphoma in cattle vary considerably, probably reflecting variation in BLV infection rates. A 2007 USDA National Animal Health Monitoring System study estimated that 84% of dairy herds in the United States are infected with BLV,[16] and a 2015 study concluded that 78% of Canadian dairies were infected.[17] Rates of BLV seroprevalence in beef and dairy cattle in Japan have risen 4- and 10-fold between 1980 and 2011.[18] Although less than 5% of BLV positive cattle are

reported to develop lymphosarcoma,[19] the rate of cattle condemnations due to lymphoma appears to have increased over time.[20] Most BLV-infected cattle are asymptomatic, immune competent, and maintain adequate production.[21-23]

Epidemiology

Horizontal transmission of BLV has been demonstrated by the transfer of blood from infected cattle to susceptible cattle. Iatrogenic (reuse of common hypodermic needles between animals, reuse of syringes, dehorners, ear notchers or ear tattoo pliers, castration instruments, or even nose tongs) are considered to be risk factors in transmission; however, some studies were unable to demonstrate transmission after use of a common needle.[24-26] A role for Tabanids in BLV transmission has also been demonstrated.[27] A reduction in seroprevalence to BLV was documented following management changes that presumably reduced exposure to BLV-contaminated blood; these changes included switching from gouge to electrical burning dehorners, single use of needles and obstetrical sleeves, disinfection of tattoo equipment, replacement of whole milk feeding with high-quality milk replacer, and heat treatment of colostrum before feeding.[28,29] Infection after use of a Tb needle dipped in blood of a BLV-infected animal could be prevented by wiping the needle with cotton before injection,[30] and transmission is considered less likely if instruments are disinfected. Rectal palpation has been postulated as a means of transmitting BLV, and experimental studies found that under extreme conditions of blood contamination and mucosal irritation, BLV can be transmitted rectally.[31-35] Under conditions typical of routine palpation during pregnancy examination, however, BLV may not necessarily be transmitted to any measurable degree.[33,35,36] Risk of spread from respiratory secretions is generally considered low, yet transmission from inhalation of BLV shed in nasal secretions is considered possible.[37-40] Herd size might be positively correlated with a high rate of lymphoma, which may reflect higher rates of BLV infection in large herds or a preponderance of susceptible pedigrees in some of the herds studied.[41,42] Close contact and heavy stocking/comingling of infected and susceptible animals also increases the incidence of horizontal transmission.[43,44] The presence of persistent lymphocytosis (PL) cattle greatly increases the chances of horizontal transmission.[19] PL is defined as an absolute lymphocyte count at least three standard deviations above the normal mean count that persists for at least 3

consecutive months.

Vertical transmission from infected dams to their fetus across the placenta can occur; however, studies have shown this occurs in only up to about 10% of pregnancies.[15,45] While transmission in colostrum and milk has been shown,[15,46] colostral antibodies also impart a protective effect against BLV infection in calves from BLV-infected dams.[47] Colostrum replacers can contain BLV antibodies that temporarily impart BLV seropositivity to calves; presence of BLV proviral DNA has also been detected in colostrum replacers, but it is unlikely that infectious BLV could survive the manufacturing process.[48,49]

Susceptibility to BLV infection is associated with BoLA type,[50,51] which may explain why higher rates of lymphoma are found in certain families of cattle. The progression of disease to persistent lymphocytosis in some BLV-infected cows has been linked to a shift away from cell mediated immunity toward a humoral response.[52,53] Polymorphisms at the MHC class II BoLA-DRB3.2 gene have been associated with differing circulating proviral loads in blood of Argentinian Holstein cattle and can be used to define BLV-resistant versus susceptible genotypes in these cattle.[54]

Antigenic and molecular evidence for the presence of BLV in mammary glandular epithelium has been demonstrated.[55] The effect of BLV persistent mammary infection on the mammary gland is not completely understood. Although one study identified increased average milk production in BLV-infected versus uninfected cattle,[56] others report negative associations between milk production and BLV status.[23,57]

Diagnosis

Cattle presented with the adult or enzootic form of lymphoma usually are older than 4 years of age but may be as young as 2 years. Cattle are often presented with a history of loss in condition, an abrupt drop in milk production (over a period of a few days), enlarged peripheral nodes, exophthalmos, or partial to complete anorexia, particularly with regard to grain or concentrates. Subclinical lymphoma may be diagnosed in cows submitted for routine reproduction examinations; other signs may include diarrhea, ataxia, paresis, ketosis, and infertility.

Common sites of lymphoid tumor predilection in adult lymphoma include heart (usually right atrium), abomasum, uterus, kidney, and spinal cord (epidural

space); other common sites include the retrobulbar space and rumen/reticulum.[58] Physical examination often reveals an organ system failure resulting from tumor involvement. Thoracic auscultation may reveal cardiac dysrhythmia, tachycardia, tachypnea, and hyperpnea. Epicardial lymphosarcoma has been described in 3 dairy cows 3 to 19 months following diagnosis and treatment for idiopathic hemorrhagic pericardial effusion; at the time of initial presentation with pericardial effusion, none of 3 affected cows had cytologic evidence of neoplasia in pericardial fluid.[59] Dependent, pitting edema is common when cervical or supramammary lymph nodes are involved. Involvement of the intestinal lymphatics is often associated with generalized dependent edema anterior to the udder. Peripheral lymph nodes typically found to be enlarged are the prescapular, subiliac, and supramammary nodes. Feces may be scant, pasty, or watery and probably reflect the presence of lesions within the GI tract. Melena may be present in animals with ulceration of the abomasum and lymphoid cell infiltration in the abomasal wall. The main ultrasound finding in a case of abomasal lymphosarcoma was enlargement of lymph nodes caudal to the reticulum, as well as severe enlargement of the abomasum with thickening of the abomasal wall.[60] Rectal palpation can be useful in cases lacking peripheral node enlargement or exophthalmos. Tumor masses palpated in the abdomen typically are multiple and range in size from only slightly enlarged lymph nodes to massive lesions half a meter in diameter. The internal iliac nodes are involved in most cattle with abdominal tumors. Tumors tend to be firm but not hard and may feel slightly lobulated. Differentiation by palpation of lymphoma tumors from other masses is highly subjective. Exploratory laparotomy may be indicated as an additional diagnostic tool in difficult cases, particularly in valuable cattle.

The hemogram of cattle with lymphoma often is generally unremarkable, except in the case of PL animals in which circulating lymphocytes remain elevated for a prolonged period. Approximately 30% of cattle with BLV infection develop persistent lifelong lymphocytosis, composed mostly of B cells.[61,62] Lymphocytotic cattle have higher BLV proviral loads in peripheral blood lymphocytes than nonlymphocytotic cattle, although some nonlymphocytotic cattle may have high BLV proviral loads and could represent obstacles to successful eradication efforts.[63] Because neutrophil concentrations can be similar between BLV-antibody positive versus BLV-antibody negative cattle while lymphocyte concentrations are increased in BLV-antibody positive cattle, recommendations have been made to avoid the use of calculated

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neutrophil-to-lymphocyte ratios in favor of direct comparison of patient absolute leukocyte concentrations to updated lymphocyte reference intervals from healthy BLV-negative cattle.[64] Anemia may be present in cattle with GI hemorrhage as a result of abomasal wall lymphoma and ulceration with bleeding; such cases would also be likely to exhibit melena. Fibrinogen levels have been inconsistent in lymphoma, and therefore its measurement may be helpful only in differentiating an abscess.

Although helpful in some cases, cytology of aspirates of tumors or tumorous nodes may not always be a reliable diagnostic tool. Discrimination cannot be made between a normal node responding to an infectious agent and a node involved with neoplastic lymphocytes; in both situations, cells resembling young, poorly differentiated lymphocytes may be present. Examination of nontumorous active lymph nodes may reveal an elevated proportion of large, young lymphocytes that could resemble those of lymphoma. In a retrospective study, the sensitivity of antemortem diagnostic testing found peripheral lymph node biopsy to be 100% sensitive while fine-needle aspirate was only 41% sensitive.[58] When compared with core-needle biopsy of peripheral lymph nodes, fine-needle aspiration was more specific and more predictive for a positive test.[65] Cytology and culture of aspirates can be helpful in differentiating a tumor from an abscess. Failed attempts at collection of cerebrospinal (lumbosacral) fluid in cattle with recumbency or rear limb weakness may be associated with the presence of lymphoid tumors in the vertebral canal; cytologic examination of cells from the collection needle in such cases may reveal abnormal lymphoid cells.

At necropsy lymphomas are found enclosed in a capsular-like tissue that, when sectioned with a knife, results in an eversion of tumor stroma. Cut tumor tissue is cream colored and friable, with little binding structure. Centers of tumors may appear necrotic and mushy, whereas peripheral regions are firmer and pink to white. Histopathology provides the only definitive diagnosis. Tissue should be biopsied by surgical removal of as much of the node (or mass) as possible.

Standard serologic tests to diagnose BLV infection include agar gel immunodiffusion (AGID) and enzyme-linked immunosorbent assay (ELISA). The ELISA is more sensitive than the AGID.[66] Serologic tests identify antibodies to a BLV 51-kilodalton (kD) envelope glycoprotein (gp51) or 24 kD core protein (p24). Low antibody response to p24 was observed in cattle with

low BLV proviral loads.[63] ELISA test kits that detect antibodies in milk samples are available commercially. The use of a milk ELISA to measure anti-BLV antibodies has been used successfully to determine lactation-specific BLV prevalence in dairy herds.[67]

Diagnosis is also possible by use of PCR to detect BLV nucleic acid,[68-71] as well as by a combined PCR-ELISA that is more sensitive than staining of PCR amplicons with ethidium bromide.[72] In a majority of calves that were experimentally infected with BLV, calves became PCR positive sooner than they seroconverted (as determined by a commercial BLV antibody test).[73] However, the measurement of antibodies to p24 antigen and whole-BLV antibodies by ELISA has been suggested as a cost-effective tool in BLV control programs as compared with real-time PCR methods.[74] ELISA-positive cattle that were not detected by PCR testing have been reported; this is most likely related to a low number of infected circulating lymphocytes at the time of sample collection.[75] The PCR by itself is considered unreliable for routine detection of BLV in herds with a high prevalence of disease,[76] and the ability of PCR to detect a BLV-infected animal is improved by means of a nested PCR, which was reported to be effective in diagnosing infection when seroconversion had not yet occurred.[77] A loop-mediated isothermal amplification (LAMP) assay has also been developed to diagnose BLV infection in cattle; this test has sensitivity at least as good as the conventional single PCR and has the advantage of not requiring specialized thermal cycling equipment.[78] Novel quantitative real-time PCR methods that use Coordination of Common Motifs (CoCoMo) primers to measure proviral loads of known and novel BLV variants were found to be more sensitive than some of the more traditional real-time PCR methods and antibody-based methods to detect BLV.[79,80] A luminescence syncytium induction assay (LuSIA) has also been shown to accurately detect and quantitatively measuring bovine leukemia virus infection.[81]

The presence of antibodies to gp51 is generally considered to be a prerequisite to a diagnosis of lymphoma, except for cows during the periparturient period when circulating antibodies may fall below the level detectable by a serologic test.[82] The mere presence of BLV antibodies does not necessarily mean that an animal has lymphoma, which is found in only about 1.7% of BLV-infected cattle.[83] However, serology can be helpful in predicting the chance of lymphoma in cattle seropositive to the gp51 antigen. Sera from cattle with lymphoma

generally have high titers to the gp51 antigen (a score of 3 or 4 on AGID), compared with those of infected cattle without lymphoma (score of 1 or 2 on AGID). In addition, cattle that do not have lymphoma tend not to have antibodies to the p24 antigen of BLV, as detected by AGID. The percentage of cattle with histologically confirmed lymphoma but in which lymphoma was not diagnosed by a gp51-positive and p24-negative test result (false-negative rate of the diagnostic test) has been found to be only 0.21%, using the AGID test.[42] Unfortunately, most diagnostic laboratories do not have the capability to perform the test using the p24 antigen.

Control

Although there are not curative treatments for lymphoma in cattle, supportive therapy may be indicated to reduce discomfort and prolong life long enough to remove valuable ova/embryos or calves or to harvest semen. Presently no vaccines offer effective protection from BLV infection and control. As such, eradication of BLV requires reduction of blood transmission through iatrogenic means and through physical contact among cattle.[84] Basic disinfecting practices of instruments and equipment used on cattle such as dehorners, ear notchers, tattoo pliers, nose tongs, and others should help reduce the transmission of BLV between animals. In one study, disinfection of instruments with chlorhexidine and sodium hypochlorite was implemented as part of a set of corrective actions that were successful at reducing new cases of BLV.[44] Avoiding the reuse of hypodermic needles and syringes between animals is also recommended to reduce transmission through blood contamination. Transmission between infected and susceptible cattle can also be reduced by segregating infected and noninfected cattle,[44,85,86] and segregation of infected animals reduces seroconversion of uninfected neighbor cattle.[87] Separation of cattle by 10 feet is preferred, but a single fence may reduce sufficiently the degree of contact necessary for transmission. If potential for rectal transmission is a concern, palpation sleeves may be rinsed or replaced between cows. Although insect transmission of BLV is theoretically possible[88] and has been demonstrated experimentally by interrupted feeding of tabanids from cattle with persistent lymphocytosis to uninfected cattle,[27] studies of natural infection did not link flies with new natural infections.[89,90] Vector control to curtail stable fly feeding was, however, reported to be effective at reducing BLV transmission.[91] Although data have not shown the use of common needles to be an important means of

BLV transmission, it would be prudent to use individual sterile needles for treatment, testing, or vaccination. As animals with PL are potential sources for increasing horizontal and vertical transmission of BLV, routine testing of the herd and culling of PI animals should reduce infection rates.

Reduction of vertical transmission via milk or colostrum should address testing and culling PL- and BLV-positive cows and reducing BLV exposure of calves via infected colostrum or milk. In a sheep model of BLV infection, freezing and thawing of leukocytes from colostrum of a BLV-infected dairy cow appeared to be effective at inactivating the infectivity of BLV-infected leukocytes.[92] As calves born to BLV-positive cows are exposed to BLV during parturition, and because antibodies to BLV in colostrum from BLV-positive cattle appear to be protective against BLV infection, neonatal BLV transmission may be reduced by feeding a calf born to a BLV-positive cow the colostrum from its dam.[47] In Japan, feeding colostrum from the dam was also found to be protective against within-farm BLV transmission.[93] Because BLV proviral loads in blood rise following birth of calves to dams with high proviral loads, early identification and culling of infected calves could help prevent virus transmission.[94] Heat treating colostrum (65º C for 30 minutes) appears to be an effective means of inactivating BLV and should be considered when developing a control program.[29,95] Colostrum replacers may contain antibodies to BLV that render calves receiving such replacers to be seropositive to BLV; in one study these antibodies waned by 4 months of age.[48]

Transmission of BLV has not been shown in cows inseminated artificially using commercially prepared frozen semen.[96-100] Although infection resulting from the use of an infected bull in natural breeding may be possible,[101,102] one study found that bulls that were BLV PCR positive in peripheral blood had no evidence of BLV in semen by PCR testing.[103] Embryo transfer recipients should be tested for BLV before transfer.[104] Embryo transfer using noninfected recipients offers a means of producing phenotypically preferred cattle from BLV-infected cows and controlling in utero infection.[89,96,105,106] It is possible to produce transferrable in vitro−fertilized embryos that are free of BLV provirus from oocytes that are exposed to BLV during maturation, fertilization, or after fertilization through a washing procedure.[107]

For most herds, control and eradication of the infection would require modification of facilities, alteration of management practices, and serologic surveillance at least annually. Planning a control program should include a

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cost/benefit analysis to evaluate potential return on the investment. Knowledge of costs incurred as a result of BLV including costs of lost milk production are important in decision making relative to implementation of BLV control programs.[108,109] When considering the potential for BLV infection to cause immune suppression,[110,111] the various ways that BLV infection could cause economic losses in cattle populations are especially diverse. Financial benefit of a BLV control program has been documented in herds in which the prevalence of BLV infection is 12.5% or higher.[112] The elective culling of BLV-infected cattle based on positive lymphocyte BLV antigen expression in vitro was reported to be effective in preventing transmission of BLV infection.[113]

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Lymphoma in Horses

Krista E. Estell

Lymphoma is the most commonly occurring hematopoietic neoplasia in horses. Previously, the terms *lymphoma* and *lymphosarcoma* have been used interchangeably, with the suffix "-sarcoma" used to characterize all malignant mesenchymal neoplasias. However, in accordance with the World Health Organization classification system, the term *lymphoma* has been adopted as there is no type of lymphoid neoplasia that is not malignant.[1] In addition, lymphoma and leukemia are now considered together, as they may be manifestations of the same disease process. It is important to emphasize that benign lymphoid hyperplasia is not synonymous with lymphoma.

Lymphoma is one of the most common malignant neoplasms in the horse; in postmortem studies, its prevalence is estimated to be 2% to 5%.[2] The underlying etiology of lymphoma in horses is undetermined. In humans there is an association between lymphoma and infection with the γ-herpesvirus Epstein Barr.[3,4] There are two case reports of horses with concurrent equine herpesvirus −5 infection and lymphoma or leukemia, one of which entered clinical remission after treatment with antivirals.[5,6] Virus-like particles have been described in lymph nodes of neonatal foals with lymphoma, though a causal relationship has not been proven.[7,8]

Lymphoma can occur at any age, with reports in an aborted fetus to horses older than 30 years.[8,9] A large-scale retrospective study reports a median age of onset of all types of lymphoma to be 10 years; a previous study reviewing intestinal lymphoma reported a mean age of onset to be 17 years.[9,10] There is no apparent sex predilection, though certain breeds are more likely to develop particular subtypes of lymphoma.[10,11] Clinical signs vary depending on tumor location, but the most common include nonspecific lethargy, weight loss, pyrexia, and lymphadenopathy. When affected, lymph nodes tend to be firm, cool, and nonpainful. Specific clinical signs are dependent on the location of the tumor with diarrhea, colic, neurologic signs, lameness, osteolysis, and pathologic fractures described.[12,13] Paraneoplastic conditions including pruritus and alopecia, hypercalcemia, IMHA, and IMTP have also been reported.[14-16]

Although the hematologic features of lymphoma vary, anemia is a relatively

common finding and is thought to be due to suppression of erythropoiesis, neoplastic bone marrow infiltration, blood loss, or IMHA. A modest neutrophilic leukocytosis with an elevated fibrinogen is often seen. Atypical lymphocytes with or without elevated lymphocyte counts may be noted in the blood smears of more than 30% of affected horses, especially late in the disease course.[17] When frank leukemia is present, neoplastic cells are often, but not always, found in the bone marrow.[18,19] Serum biochemistry profiles may provide an indication of internal organ involvement. Serum protein alterations are frequently observed and include hypoalbuminemia, hyperglobulinemia with polyclonal or monoclonal gammopathy, and decreased albumin/globulin ratio.[19] Additional immunologic derangements that have been reported in horses with lymphoma include hypogammaglobulinemia, neutropenia, and lymphopenia.[15,20,21]

Though several different classification schemes exist, the World Health Organization classification system has been adopted for the accurate description of equine lymphoma. Using this classification system, tumors are characterized on the basis of anatomic location and cell lineage. In a recent retrospective study classifying 203 cases of equine lymphoma, 14 subtypes of lymphoma were identified and 13 anatomic sites were used for characterization: multicentric (involving at least 2 organs excluding the regional lymph node), gastrointestinal, cutaneous, bone marrow, nodal, splenic, hepatic, mediastinal, heart, ocular/orbital, central nervous system, oral cavity, and nasal. Multicentric (83%), cutaneous (19%), and gastrointestinal (11%) lymphoma were the most common anatomic locations identified in this study.[22]

The diagnostic sample of choice is a biopsy of the affected lymph node or organ. Lymphoma is variably exfoliative, and even if there is a considerable amount of effusion, cytology may be inconclusive. Likewise, lymph node needle aspirates may be difficult to positively diagnose. Morphologically, lymphocytes are classified as small-cell type if their nuclear diameters are 1.5 times the diameter of erythrocytes or less; cells are classified as large if their nuclei average 2 times or more the diameter of erythrocytes.[23,24] Small-cell lymphoma consists of 60% or more small cells while large-cell lymphoma consists of 60% or more large cells. The grade of lymphoma may also be assessed by determining the amount of mitoses seen within a high-powered field.[9,24]

Immunohistochemical classification to determine the cell lineage is performed using monoclonal antibodies such as CD79a and CD20 for B-cell lymphomas and CD3 and CD8 for T-cell lymphomas. All three—B-, T-, and mixed B- and T-

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cell lymphomas—have been reported in the horse.[9,23,25] Several retrospective studies have identified a total of 14 subtypes of lymphoma in horses, with T-cell–rich B-cell lymphoma (TCRBCL) the most common subtype of lymphoma in the horse.[9,17,26] T-cell–rich, large B-cell lymphoma is a neoplastic proliferation of large B cells associated with a prominent component of nonneoplastic T cells and a dense fibrovascular network that prevents tissue fragmentation during sectioning.[1] The presence of large numbers of nonneoplastic T cells within a B-cell lymphoma could result in erroneous diagnosis of a T-cell tumor or a benign reactive lymph node, particularly if a small sample is submitted. Discriminating between neoplasia and chronic inflammation with reactive lymphocytes can be difficult in some cases; molecular clonality assays can be used to make this determination. Clonality assay results indicating a polyclonal population of lymphocytes support a diagnosis of inflammation, whereas results indicating a monoclonal population support a diagnosis of neoplasia. There are several reports of polyclonal lymphoma in horses, though this likely represents lack of appropriate molecular markers (P. Moore, Personal communication, 2016). In addition, as benign clonal expansion has been reported with various infectious and immunologic conditions, results should be interpreted carefully.

In addition to immunophenotyping and tumor cell morphologic description, establishing tumor location and presence of metastasis is necessary to determine disease severity and recommend a course of treatment. A thorough diagnostic work-up includes complete blood count with cytologic review by a hematopathologist, serum biochemical assay, thoracic radiographs, and abdominal ultrasound.[27] Though tumor biomarkers are used routinely in human medicine, there is limited research on their significance in horses. A recent paper describes significant elevations in serum thymidine kinase in horses with lymphoma when compared with horses with inflammatory conditions and nonhematopoietic neoplasia, indicating that this biomarker may be a useful ancillary diagnostic in horses with suspected lymphoma.[28] Accurate lymphoma characterization and staging in human medicine have been critical to establishing effective therapeutic management plans and accurate prognoses, and as more therapeutic options are explored in horses, it is likely that accurate diagnoses will have a similar impact.

Multicentric Lymphoma

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The definition of multicentric lymphoma is lymphoma that involves two organ systems, excluding the regional lymph nodes, or involves multiple lymph nodes at distant anatomic locations. In previous literature, the term *generalized lymphoma* has been used to describe multicentric lymphoma, though this likely represents a more chronic or severe stage of disease. Multicentric lymphoma is the most commonly reported anatomic location of lymphoma; it is often difficult to determine the site of origin if the horse is presented late in disease.[9,17] Horses with multicentric lymphoma often present with lethargy, emaciation, anorexia, generalized lymphadenopathy, and edema due to impaired lymphatic drainage.[9,10] In addition to lymphoid tissue involvement, infiltration of neoplastic lymphocytes has been reported in the spleen, liver, bone marrow, intestine, bladder, kidney, lung, heart, nasopharynx, eye, ovary, uterus, brain, and spinal cord.[9,10,16,20]

Alimentary or Intestinal Lymphoma

Lymphoma is the most common neoplasia of the intestinal tract in horses, and though the entire intestinal tract may be affected by lymphoma, disease occurs most frequently in the small intestine.[10,29] Though a breed predilection has not been established for lymphoma generally, a study reviewing intestinal neoplasia showed that Arabian horses are at an increased risk of developing intestinal lymphoma as compared with other breeds.[10,30] Lymphoma arises from the lymphocytes of the lamina propria of the intestinal tract, resulting in diffuse or segmental thickening, focal masses, or scattered crater-like ulcers with raised margins on the intestinal wall.[31-33] Peripheral lymphadenopathy is generally not present, though metastases to the lungs, mesenteric lymph nodes, liver, kidney, and spleen have been reported.[10,30,31] Intestinal lymphoma is usually associated with hypoalbuminemia secondary to protein-losing enteropathy, weight loss, edema, abdominal effusion, mild recurrent colic, and diarrhea.[10,29] Affected horses frequently have abnormal glucose or xylose absorption tests, indicating small intestinal malabsorption.[32] Transabdominal ultrasound is the imaging diagnostic of choice and typically reveals thickened (>5 mm) small intestine, large colon, and/or cecum. In cases of small intestinal thickening, duodenal biopsy via a 3-m gastroscope may be diagnostic, though the small sample size limits diagnostic utility. In cases where diffuse large colon thickening is seen, rectal mucosal biopsy may yield a diagnosis of lymphoma. Abdominocentesis may be performed, with one study showing that cytologic analysis of abdominal

fluid was diagnostic in 38% of intestinal neoplasia cases.[10] It is important to note that a normal mucosal biopsy and normal abdominal fluid cytology do not preclude a diagnosis of lymphoma. The most accurate means of diagnosis for intestinal lymphoma is exploratory laparotomy and biopsy. If the segment of intestine cannot be resected with clean margins, treatment with chemotherapeutics other than corticosteroids is generally not recommended, as the neoplastic tissue often ablates the normal intestinal architecture and treatment with chemotherapy may result in GI rupture. (A. Theon, Personal communication, 2015)

Thoracic Lymphoma: Mediastinal/Thymic

Lymphoma is the most common thoracic neoplasia in horses, and it may involve mediastinal lymph nodes, pericardium, thymus, or lungs.[33,34] The prevalence of mediastinal lymphoma varies from 4.5% to 29% of all forms of lymphoma.[9] Primary and secondary (metastatic) mediastinal lymphomas have been reported, with the mediastinum and thoracic cavity commonly affected in horses with multicentric lymphoma.[17,34] Primary mediastinal lymphoma is usually seen in adult horses; however, the disease has been reported in a 1-month-old foal with a 1-week history of respiratory distress.[35] In the early stages of the disease, minimal clinical signs may be observed. Once disease has progressed, common clinical signs include nasal discharge, adventitious lung sounds, pleural effusion, thoracic ventral and limb edema, and regional lymphadenopathy at the thoracic inlet.[31,32] Other signs may include congestive heart failure, cough, pyrexia, pleurodynia, and respiratory distress.[29] Dysphagia may be observed in cases with retropharyngeal lymphadenopathy. An elevated nucleated cell count of several thousand cells/µL, with a large percentage of abnormal lymphocytes, may be evident in pleural fluid cytologic analysis. However, collection of multiple pleural fluid samples may be necessary to establish a definitive diagnosis.[36] Cytologic abnormalities include the presence of prolymphocytes, lymphoblasts, and lymphocytes with evidence of nuclear blebbing, indented and cleaved nuclei, amorphous nuclei, altered nuclei/cytoplasm ratio, or mitotic figures.[17,29] Thoracic lymphomas may be of B-, T-, or mixed-cell origin, but T-cell lymphomas are most common.[23,34]

Cutaneous Lymphoma

Cutaneous lymphoma originates in the skin-associated lymphoid tissue. Single or multiple subcutaneous firm, nonpainful nodules ranging from less than 1 cm to greater than 20 cm in diameter can develop rapidly or slowly, regionally or over most of the body surface.[11,37] The predominant subtype of cutaneous lymphoma is T-cell−rich, large B cell (TCRBCL). One retrospective study revealed a potential breed predilection for cutaneous lymphoma subtypes; Quarter Horses were diagnosed almost exclusively with TCRBCLs, while Thoroughbreds had an increased likelihood of cutaneous T-cell lymphoma (CTCL).[11] In general, TCRBCLs tended to present with multiple nodules in different anatomic areas, while CTCLs and diffuse large B-cell lymphomas tended to be single masses. In some cases, the nodules are reported to wax and wane spontaneously or in association with sex hormone levels and seasonality, which likely reflects the presence of progesterone or other hormone receptors present within the tumors.[38] There is one report of complete regression of cutaneous lymphoma following surgical removal of an ovarian tumor.[39] Depending on the anatomic location, cutaneous lymphomas may cause mechanical lameness and limb edema secondary to vascular and lymphatic obstruction. In most cases, there are no associated hematologic abnormalities and generalized lymphadenopathy and internal organ involvement are rare in the early stage of disease. If the disease is allowed to progress untreated, cutaneous lymphoma may metastasize to internal organs or result in paraneoplastic syndromes.[11,33] If only a single or few tumors are present, surgical removal with clean margins may be curative.[11] Likewise, local injection with cisplatin in sesame oil, as previously described, has also resulted in regression of the injected tumor.[40]

Angiotrophic Lymphoma

Angiotrophic lymphoma, also known as *endotheliotropic lymphoma or intravascular lymphoma*, is lymphoma of the small blood vessels that spares the surrounding tissues. It has been described in humans, dogs, and cats.[41-43] There is a single report of angiotrophic lymphoma in a 12-year-old pregnant Thoroughbred presenting with anorexia, tachycardia, and mild fever.[44] The significant laboratory abnormalities in this case were profound anemia (PCV 12%) with a negative Coomb's test, marked anisocytosis, mild lymphopenia, low IgM, and marked erythroid hyperplasia and erythrophagocytosis on bone marrow biopsy. Histologic examination revealed pulmonary and renal vessels

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crowded with neoplastic lymphoid cells with scattered mitoses. The neoplastic cells were determined to be of T-cell origin based on immunohistochemical staining. Angiotrophic lymphoma may represent an antemortem diagnostic challenge owing to the lack of circulating neoplastic lymphocytes and identifiable masses.

Treatment of Lymphoma

If possible, surgical removal of lymphoma is indicated before treatment with ancillary treatments including radiation and chemotherapy. Radiation therapy has been effective in the treatment of cutaneous and paranasal lymphoma, though access to equipment makes treatment logistically challenging.[45,46] There are limited retrospective studies and clinical trials describing chemotherapy in the horse. The largest clinical investigation is a pilot phase II study evaluating the efficacy of doxorubicin in horses. Tumor response rate for lymphoma was 100% in the study population.[47] Signs of toxicity including hyperthermia and colic were controlled by premedication with diphenhydramine and flunixin before doxorubicin administration and treatment, at the recommended dose of 70 mg/m^2.[48]

There are several case reports describing the use of single or multidrug protocols for the treatment of lymphoma. A recent case report describes surgical removal of a TCRBCL followed by treatment with lomustine (CCNU; 60 mg/m^2q 30d for 4 treatments), followed by prednisolone, resulting in clinical remission for 16 months at the time of publication.[49] Other published protocols include single or multidrug therapies including L-asparaginase (10,000 to 40,000 U/m^2, IM q14-21d), doxorubicin (50 mg/m^2 IV), vincristine (1.4 mg/m^2 IV), and rituximab (375 mg/m^2 IV). A horse with thoracic lymphoma was treated with cytarabine (170 mg/m^2 IM) 2 weeks apart, alternating with cyclophosphamide (142 mg/m^2 IV) 7 days after each dosage of cytarabine, in addition to prednisolone.[50]

Palliative therapy of lymphoma has also been achieved with corticosteroids including dexamethasone, prednisolone, and betamethasone. Ideally, pulse-dose therapy or treatment with a relatively high dose of corticosteroid for a short period of time should be implemented until tumor regression has occurred, and then the steroid should be quickly tapered. This strategy may prevent the neoplasia from becoming resistant to corticosteroid therapy. If clinical signs

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recur during steroid tapering, then the lowest dose of steroid that controls clinical signs should be administered.

Complications associated with chemotherapeutic agents in horses depend on the drug used and should be considered before the institution of therapy. Though no large retrospectives on treatment of lymphoma in horses exist, periods of remission following treatment of 8 months to 5 years have been reported.[33,49,50] The long-term prognosis for horses with lymphoma when treatment is not elected is poor.

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Leukemia in the Horse

Johanna L. Watson • Monica Aleman

Leukemia is a rare neoplasia of the hematopoietic system that originates from the bone marrow (primary leukemia). A leukemic phase (secondary leukemia) has rarely been reported in horses.[1-3] Based on the cell of origin, the major forms of leukemia include myeloid and lymphoid leukemias, which can have an acute or chronic clinical course. According to the Leukemia and Lymphoma Society, *acute leukemias* are rapidly progressing disorders that affect mostly primitive or immature cells that lack normal function, whereas *chronic leukemias* progress slowly, allowing some growth and cell maturation that may preserve limited normal function. Reported leukemias in the horse include myelomonocytic, monocytic, granulocytic, eosinophilic, and lymphocytic forms.[1,2,4-19] Based on the presence and numbers of cells in blood, other terms used are *leukemic*, *subleukemic*, and *aleukemic leukemia*. Leukemic leukemia is characterized by an increase in cell numbers in peripheral blood; subleukemic leukemia is defined by an increase in abnormal blast cells in blood, with a total white cell count within the reference range or low; and aleukemic leukemia is characterized by the presence of abnormal cells in the bone marrow but not in peripheral blood.

There is no apparent breed or gender predisposition, based on the few reported cases.[1,2,5-19] The age at onset of clinical signs ranges from 2 to 25 years. The most common clinical signs are weight loss, lethargy, anorexia, pyrexia, and lymphadenopathy if associated with lymphoma. Other signs are weakness, ventral edema, exercise intolerance, colic, and recurrent or concurrent infections.

At the initial stages of disease, laboratory features may show mild hematologic abnormalities and include one or more of the following: anemia, neutropenia, lymphopenia, thrombocytopenia, hyperproteinemia, and hyperfibrinogemia. As the disease progresses (days to months), marked leukocytosis (counts may be >200,000 WBC/µL) and hyperproteinemia will be observed in leukemic leukemias.[16] Thrombocytopenia is a common hematologic feature.[1,15,16,19] Pancytopenia and high blast cell counts (up to 1.6×10^9 cell/µL) were reported in a lactating mare with myeloblastic leukemia.[19] Pancytopenia due to severe infiltration of leukemic cells in the bone marrow, ineffective hematopoiesis, and myelofibrosis has been reported.[15] Horses with multicentric lymphoma, pancytopenia, severe leukocytosis (more than expected for severe

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inflammation), or presence of atypical or blast cells in peripheral blood should prompt the collection of a bone marrow aspirate or biopsy. Bone marrow aspirates may have normal to altered myeloid/erythroid ratio (reference range, 0.5 to 3.76) with a disproportion of atypical or poorly differentiated blast or mature cells of certain lineage. Decreased or absent megakaryocytes is a common observation.

Hyperproteinemia due to hyperglobulinemia is a consistent finding. Serum electrophoresis typically shows a polyclonal increase of β_2- and γ-globulin fractions and, in some cases, α-globulin fraction. Marked increases in serum IgG and IgA concentrations have been detected in horses with lymphocytic leukemias.[1] Deficiencies in IgA and IgM have been reported in a single horse with chronic lymphocytic leukemia.[12]

Necropsy findings may include mucosal ulceration, edema, thrombosis, and hemorrhages of various organs due to intravascular leukostasis (aggregates of leukemic cells in blood vessels), disseminated intravascular coagulopathy, and thrombocytopenia secondary to decreased production of megakaryocytes. Leukemic-induced cell lysis may occur as the result of mediators released by neoplastic cells. Peripheral and internal lymphadenopathy may also be observed.

The diagnosis is based on results of a complete blood cell count (CBC) and chemistry panel, with cytologic and histopathologic evaluation of bone marrow, immunocytochemical analysis, flow cytometry, and immunophenotyping. Previously, leukemic cells in peripheral blood and bone marrow were described on the basis of their morphology. However, this may result in leukemia misclassification, especially in acute leukemias where mononuclear blast cells comprise the leukemic clone, which may lack specific morphologic identifying features. Numerous cytologic and cytochemical stains (e.g., Wright, Giemsa, Sudan black B, peroxidase, periodic acid-Schiff, alkaline phosphatase, acid phosphatase, various esterases, and surface glycoproteins) have been used to determine leukemia type. Leukemic cells may lack specific cytochemical properties, however. Currently, the various types of leukemias are identified by specific cellular antigens, using a panel of monoclonal antibodies and flow cytometry to analyze peripheral blood and/or bone marrow. Examples are B-cell/IgM-positive, B-cell/IgM-negative, CD3/CD4/CD5-positive T-cell, CD3-negative/CD4-positive T-cell, and CD13-positive/myeloid leukemias.[1,12,16] The various monoclonal antibodies for specific equine leukocyte antigens are shown in Table 37.2.

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TABLE 37.2

Monoclonal Antibodies for Specific Equine Leukocyte Antigens (ELAs)

ELA Marker	Specificity
EqCD2	T cells
EqCD3	T cells
EqCD4	Helper T cells (T_H cells)
EqCD5	T cells
EqCD8	Cytotoxic T cells (T_C cells)
EqCD11a/18	Panleukocyte
EqCD13	Myeloid cells
CD21	Most B cells
CD79a	B cells
EqWC1	Large T-cell and neutrophil subsets
EqWC2	T cells and neutrophils
EqWC4	Minor T-cell subset
MHCI	Nucleated cells
MHCII	B cells, macrophages, dendritic cells, and a large T-cell subset
IgM	B cells

CD, Cluster of differentiation; *Eq,* equine; *IgM,* immunoglobulin M; *MHC,* major histocompatibility complex; *WC,* white cell.

The prognosis is grave, resulting in death within days to a few months after its diagnosis. Treatment of leukemia in horses has been attempted with cytosine arabinoside, cytarabine, and prednisolone, but without much success.[8,12,18]

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Myeloma in the Horse

Johanna L. Watson • Monica Aleman

Myeloma is a neoplastic proliferation of plasma cells that primarily originates in the bone marrow but may have an extramedullary source.[20] Both forms have been reported in the horse.[21-23] Accumulation of neoplastic plasma cells outside the marrow is called *extramedullary plasmacytoma*.[20] Plasmacytomas can form in several organs and tissues, including the skin. The most common extraosseous sites in horses are lymph nodes, kidneys, spleen, and liver.[21,23,24] Multiple myeloma involves bone marrow at multiple locations and other tissues, and it is the most common form of myeloma in humans.[25] In human medicine, causes of myeloma include chromosomal translocation, irradiation, and chronic antigenic stimulation.[20]

Myeloma is a rare neoplasia of the horse (only 16 cases reported in the literature), with a median age of 14 years and a range of 3 months to 25 years of age.[21-24,26-35] Almost half of the horses were Quarter Horses, but various breeds including draft horses and ponies were represented. There is no apparent gender predilection. Clinical signs vary with the degree of plasma cell infiltration, extent, and location. The most common clinical signs are weight loss, anorexia, fever, pale mucous membranes, lethargy, limb edema, and recurrent infections.[21-24,35,36] Bone pain due to osteolytic disease is the most common early sign of myeloma in humans.[25] Four horses from the literature were reported to have osteolysis. The clinical signs in these horses included paresis, cervical pain, and lameness.[24,27,29,32]

Laboratory features are anemia, hyperproteinemia due to hyperglobulinemia, hypoalbuminemia, and proteinuria. Anemia results from reduced erythropoiesis secondary to myelophthisis, blood loss, and as a result of the osmotic effect of paraproteins. Pancytopenia is observed if myelophthisis develops. Hypercalcemia has been reported in a few cases.[21,23,24] Significantly different features have been reported (hypoproteinemia, hypoglobulinemia, hypoalbuminemia, hypocalcemia) in a gelding with systemic amyloidosis and multiple myeloma, thought to be the result of severe protein-losing enteropathy.[36] Concurrent systemic amyloidosis and multiple myeloma are common in humans but extremely rare in domestic animals, with only one cat

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and one horse reported in the literature.[36,37] Serum parathyroid hormone–related protein concentration was mildly elevated in one horse with multiple myeloma.[24]

In secretory myelomas, neoplastic plasma cells are responsible for overproduction of a monoclonal Ig called *M protein* or *paraprotein.* M protein may be fragments (mainly light chains also called *Bence Jones protein*) or a complete Ig. Subclasses of IgG are the predominant paraprotein associated with myeloma in horses,[21,35] but there are three reported cases with IgA paraprotein.[23,24]

Plasma cells are relatively sparse in normal bone marrow. Involvement of marrow is usually focal rather than diffuse, requiring multiple marrow aspirates in some cases to confirm plasmacytosis. The diagnosis of multiple myeloma in humans is based on the presence of at least 10% of plasma cells in the affected tissue, monoclonal protein in serum or urine, and evidence of end-organ damage (hypercalcemia, renal insufficiency, anemia, or bone lesions). Renal insufficiency has not been reported in horses with myeloma.[21,23] Bleeding and blood hyperviscosity syndrome are common complications of multiple myeloma in humans.[25] These complications have been reported in four horses.[21,30]

The median length of survival after diagnosis in humans is approximately 3 years.[25] Owing to poor prognosis or deterioration of condition, most reported horses were euthanized within a few days to months of diagnosis. However, two horses survived for 1 and 2 years, respectively.[31,34] One horse was euthanized 3.5 years after the diagnosis for deteriorating condition.[23]

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Lymphangioma in the Horse

Johanna L. Watson • Monica Aleman

Lymphangioma is a rare tumor in horses that originates from lymphatic vessels. Morphologically, lymphangiomas are classified into three types: simplex or capillary, cavernous, and cystic.[38] This tumor may involve cutaneous tissues of the mammary gland, thigh and inguinal regions, pleural cavity, and intestines and has only been observed in young horses.[39-41] Clinical signs vary depending on tumor location. At diagnosis, these tumors were extensive; surgical removal was not attempted, and all horses were reportedly euthanized.

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▪ Other Diseases of the Hemolymphatic System

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Anthrax

Kristin A. Clothier

Anthrax is a soil-borne bacterial disease primarily affecting herbivores and most often presenting as acute septicemia with high mortality. Other animal species, including humans, can be infected. Anthrax occurs worldwide and is noteworthy because of both its impact on agriculture and potential to cause zoonotic infections. *Bacillus anthracis*, the etiologic agent of anthrax, has been classified by the Centers for Disease Control and Prevention (CDC) and USDA as a Tier 1 Select Agent because of its potential to be used as a bioterrorism agent.[1] Dissemination of genetically modified *B. anthracis* spores through the U.S. Postal Service (USPS) in 2001 demonstrated its usefulness in this capacity.[2] Possession of this organism is under federal jurisdiction and is highly regulated.

Etiology

B. anthracis is a member of the *B. cereus* group of genetically related *Bacillus* sp.[2,3] In the vegetative form found predominantly in tissues of infected animals, *B. anthracis* is a large, rectangular-shaped, gram-positive rod. Under nutritionally limiting circumstances it produces spores, facilitating survival in harsh environmental conditions including heat, drying, and chemical treatments.[3,4] Sporulation is an oxygen-dependent process and does not occur under anaerobic conditions. Although *B. anthracis* was previously thought to be an obligate pathogen, recent research demonstrates that vegetative cells can survive and replicate in soil, plant rhizospheres, and amoeba in the environment, which may enhance transmission.[4,5] Genetic transfer between members of this group has been demonstrated by the recent identification of *B. cereus* biovar *anthracis*, which contains molecular features of *B. anthracis* and *B. cereus*.[6]

Pathogenesis

Entry into mammalian hosts can occur via inhalation, ingestion, or cutaneous routes, although ingestion is most common in animal species. Grazing herbivores are often exposed via contaminated pastures or forage grown on anthrax-positive fields. Although considered less susceptible, carnivores and

omnivores can be infected by ingesting meat from infected animals or from processed food products.[4,7] Once spores are introduced, they may be phagocytosed by macrophages and trafficked to regional lymph nodes or enter the circulation. After conversion to the vegetative state, bacteria replicate rapidly, lyse host cells, and escape to the extracellular environment. Plasmid-encoded virulence factors, particularly a poly-D-glutamic acid capsule encoded on pXO1 and a three-component toxin encoded on pXO2, are keys to bacterial survival in the host.[2,8] Presence of the capsule enables the bacterium to resist phagocytosis and mask surface antigens, resulting in evasion of the host's immune system. Toxin production is enhanced by increases in CO_2 and HCO_3^- present when the bacteria moves from the environment into the host.[2,3] Lethal factor and edema factor are secreted proteins that, when bound to the common receptor binding component (protective antigen [PA]), form lethal toxin (LT) and edema toxin (ET.)[8] Upon binding to host cells, PA oligeromizes to induce endocytosis into the host cell. In the acidic endosome, PA creates a stable pore through which LF and EF enter the cytoplasm. Both toxins interfere with cell signal transduction pathways by different mechanisms: EF increases cyclic adenosine monophosphate (cAMP) production while LF cleaves and inactivates cellular proteins. In early stages of infection, enzymatic effects of EF and LF disrupt innate immune cell functions and block inflammatory cytokine responses, particularly in neutrophils, macrophages, and dendritic cells, resulting in proliferation and dissemination of *B. anthracis*.[2,3] As septicemia progresses, toxins affect endothelial cells resulting in edema, hemorrhagic shock with hypotension, and multiorgan failure.[7,8]

Epidemiology

Anthrax occurs worldwide. Frequency of outbreaks depends on geographic location with some regions of the world (Africa, Central Asia, the Middle East, South America) considered endemic for the disease. Animal outbreaks impact humans both by disrupting livelihoods and through exposure to *B. anthracis* −affected carcasses and products.[7,9] In the United States, anthrax occurs more frequently in established “zones” of certain states (Texas, Minnesota, Montana, North and South Dakota), although sporadic cases have been reported from other locations.[10] Some areas with greater incidence of disease follow old cattle trails, which may have been the primary source for contaminating those

environments.[11]

Environments favorable for maintaining anthrax spores include soils with elevated pH, high concentrations of selected cations (Ca++, Mn++), and rich in organic material.[5,8,11] Droughts followed by heavy rainfall or flooding often precede outbreaks, as do earth-disturbing activities like excavations. Topography that favors collection of runoff and establishment of temporary water storage areas (seasonal ponds) may promote the concentration of spores.[7,10] Outbreaks usually occur during warmer months of the year.

Transmission can occur by access to blood or tissues from infected animals. Bites from blood-sucking insects have been shown to contribute to anthrax spread during outbreaks.[7] Carcasses of affected wildlife are an additional source for contaminating environments because they are unlikely to be disposed of properly and scavenging animals feeding on carcasses can disseminate organisms more widely.[10,11]

Clinical Presentation

Susceptibility to infection depends on the individual animal species and the route of infection.[10] Ruminants (cattle, sheep, and goats) are most susceptible to peracute infections, and clinical signs before death may not be observed. If present, nonspecific clinical signs include fever, depression, respiratory distress, congestion of mucous membranes, and convulsions. In more protracted cases, bloody diarrhea, hematuria, and localized tissue swelling may be observed. Cutaneous infections in animals are uncommon.[7,10]

Horses may develop an acute intestinal form and present with colic, diarrhea, cyanosis, fever, and depression followed by a fatal septicemia. A more localized form, possibly initiated by insect transmission, typically involves massive edema in the neck region, which may progress to dependent edema involving the thorax, abdomen, prepuce, or mammary gland.[7]

Swine are less susceptible to infection. Oropharyngeal involvement with swelling of the head and neck is the most common presentation; edematous tissue may obstruct breathing and swallowing. Cervical lymph nodes are prominently involved.[12] An intestinal form may present as dysentery. Pregnant animals may abort.[7,10]

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Pathology

Animals that die of anthrax sometimes produce bloody exudates from body orifices and show incomplete rigor mortis. Blood often will not clot. Carcasses undergo rapid decomposition. If a carcass is opened, the spleen is frequently enlarged and has a “blackberry jam” consistency. Lymph nodes and internal organs may be edematous and hemorrhagic. Localized exposure may result in ulceration, regional lymph node involvement, or peripheral tissue edema.[12] Histologically, large numbers of bacilli are observed in affected tissues. Spleen and lymph node architectures are obscured by massive hemorrhages. The presence of intravascular organisms is typical for septicemic anthrax.[12]

Diagnosis

Initially, anthrax may be confused with other conditions that cause acute death (clostridial infections, lightning strikes, toxic or plant poisoning) and may not be recognized. If anthrax is suspected, carcasses should not be opened to prevent sporulation and further contamination of the environment. Definitive diagnosis is based on microscopic examination of blood or tissue smears (preferably collected within 24 hours after death) and bacteriologic cultures performed in the laboratory, particularly for index cases.[10] Samples that minimize potential for environmental contamination and maximize diagnostic accuracy include unclotted blood collected from superficial veins or ocular fluid collected in a sterile syringe using a large-gauge needle. An intact eye can also be removed and submitted to the laboratory for diagnostic evaluation. In the more localized form of anthrax, samples from regional lymph nodes may be required. Tissue samples containing normal bacterial flora (e.g., ear, skin, intestinal content) are not recommended for testing because recovery of normal flora may obscure the presence of *B. anthracis* in culture. Anthrax carcasses undergo rapid putrefaction and vegetative *B. anthracis* cells are destroyed during decomposition, so the time between death and sample collection can substantially affect the recovery rate of *B. anthracis*.[10,12] To ensure use of specialized diagnostic and safety procedures, always notify laboratory personnel when a case of anthrax is suspected.[8]

Gram stains performed on direct smears demonstrate typical large, gram-positive, squared-ended rods found singly or in chains of two to four cells. A polychrome methylene blue (M'Faydean) stain confirms the presence of the *B.*

anthracis capsule surrounding organisms.[8] Anthrax bacilli must be distinguished from postmortem-invading clostridial species, which have more rounded ends and are acapsular when examined with M'Faydean stain. *B. anthracis* also stains well with other common laboratory stains, including Wright and Giemsa.

Isolation of *B. anthracis* is readily made on standard sheep blood agar.[8,10] Many organisms grow on this media, so cultures of samples from sterile sites are more likely to identify *B. anthracis* if it is present. With a doubling time of 30 to 60 minutes, colonies are apparent after as little as 6 hours of incubation.[13] Typical *B. anthracis* colonies after 24 hours of incubation are large, gray-white in color, have a rough, dry texture, and are usually nonhemolytic.[8] Gram stains of young colonies show long chains (10 or more cells) of large, square-ended, gram-positive rods often described as having the appearance of a row of "railway boxcars."

Verification of isolates as *B. anthracis* is based on lack of motility, capsule production on specialized media, lysis by a specific bacteriophage (gammaphage), and confirmatory PCR for toxin and capsule genes.[8,14] Gram stains from cultures incubated for approximately 48 hours show bacteria with centrally located spores, which do not cause the cells to bulge. Cultures must be handled using at least biosafety level 2 conditions to protect laboratory personnel during confirmatory procedures.[8,14] Care should be taken to prevent exposure to air and inadvertent spore dissemination from culture plates. Other available molecular- and antigen-based rapid screening tests are primarily used by first responders in potential bioterrorist events and to discriminate between vaccine and wild-type strains. Definitive diagnosis of a *B. anthracis* isolate must be made at a CDC Laboratory Response Network (LRN) confirmatory laboratory. All positive samples must be destroyed within 7 days of diagnosis (LRN).[14]

Treatment, Control, and Prevention

Any suspected anthrax case should be reported to appropriate local or state veterinary regulatory officials as soon as possible. The peracute nature of many anthrax infections can make early intervention impossible and treatment unrewarding. Field isolates are generally susceptible to penicillin and tetracycline drugs.[10,15] If attempted, treatment should be continued for a minimum of 5 days. *B. anthracis* strains resistant to these antibiotics have been reported. Antibiotic treatment will also interfere with detection of *B. anthracis* in

laboratory specimens.[13]

Carcass management is critical in controlling anthrax outbreaks. Carcasses should not be opened or moved from the area where they are discovered and should be destroyed by either burning or deep burial. Burning carcasses is preferred to burial because it is more effective at destroying spores, but it may not be permitted in certain areas. Any contaminated bedding or soil should be handled similarly.[8,9]

In the face of an outbreak, regulatory officials will likely quarantine affected premises. All potentially exposed animals should be closely observed for signs of infection. Clinically normal animals should be vaccinated using a commercially available live acapsular vaccine (Sterne) strain (Anthrax Spore Vaccine [Colorado Serum Co., Denver, Colo.]).[8,9] Prophylactic antibiotic treatment of unaffected herdmates is sometimes practiced; however, therapy will interfere with the efficacy of attenuated vaccines and should be considered carefully in outbreak management. Vaccination should be delayed for at least 7 days after antimicrobial administration.[8,10] Treatment decisions should be undertaken only after consultation with local veterinary public health or regulatory officials. Vaccination of neighboring herds should be initiated to prevent new infections due to either exposure to similar predisposing environmental conditions or through spread from initial outbreak sources. Controlling insects and both avian and mammalian scavengers will aid in preventing dissemination to neighboring premises.[7,10]

Prophylactic vaccination of animals in endemic areas should be performed annually 4 weeks before turning animals onto pastures where outbreaks have occurred. A single dose of vaccine is given subcutaneously in the neck. In heavily contaminated areas, a second dose may be given 2 to 3 weeks later to enhance protection. Follow the vaccine manufacturer's recommendations or local regulatory officials’ instructions regarding postvaccination market withholding time for meat and discard time for milk.[9] Localized swelling may occur at the site of vaccination, particularly in horses. Goats and llamas may exhibit serious adverse reactions to the vaccine.[10]

Ensuring that pastures are of good quality so that grazing close to the soil is avoided will minimize exposure to spores. Avoiding rough feed that might traumatize mucosal surfaces will also decrease incidence rates. Use of lime or other calcium-containing products that alkalinize the soil should not be recommended.[8] If possible, avoid grazing animals on contaminated pastures

altogether and encourage alternate uses for the land.

Public Health

Naturally occurring anthrax cases in humans in the United States are rare, and when they occur, the cutaneous form is most common.[11,13] Veterinarians are included among at-risk individuals because of the potential for contact with organisms while handling infected carcasses. If anthrax is suspected, avoid activities that result in bacterial contact. Do not open carcasses for necropsy to prevent sporulation and bacterial exposure. Use proper personal protective equipment, including physical barriers (e.g., gloves) and respiratory protection, when collecting diagnostic samples and during carcass disposal. Naturally acquired inhalational anthrax in humans is rare because of the relatively high LD_{50} (8000 to 10,000 spores) required for infection. Spores greater than 5 mm in diameter will be cleared by the mucociliary escalator. The size restriction along with static charges on spores make aerosolization and inhalation to terminal airways less likely.[13] A case report from 2009 identified exposure drums made from goat hides as the likely route of human contact, indicating that animal products can be a source of infection.[16] Exposure to *B. anthracis* should always be taken seriously, and owners of affected animals should be advised to consult with their physician for advice on medical care.

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Lyme Disease

Johanna L. Watson • Monica Aleman • John E. Madigan

Lyme disease, also known as *borreliosis,* is one of the most important arthropod-borne bacterial infections in the United States. It is caused by the spirochete *Borrelia burgdorferi* and affects humans, horses, dogs, and cats.[1-4] Because Lyme borreliosis was first identified as the causative agent of an epidemic of juvenile inflammatory arthritis in children and adults in Old Lyme, Lyme, and East Haddam, Connecticut,[5,6] medical references commonly cite "Lyme disease" when referring to *B. burgdorferi* infection.

Epizootiology

B. burgdorferi is widely distributed in the northern hemisphere. Evidence of infection or exposure in horses has been reported in the United States in the Northeast, Midwest, Texas, and California.[7] Lyme borreliosis has been extensively reported in England and other European countries, nations of the former Soviet Union, China, Japan, Southeast Asia, and South Africa.[8] *B. burgdorferi* is transmitted to humans and animals by ticks belonging to the *Ixodes ricinus* complex.[9] These ticks each feed three times during the larval, nymphal, and adult stages.[5] The larvae and nymphs feed on wild animals, and adults are found most commonly on deer.[9] On the East Coast, *Ixodes scapularis* ticks are the principle vector, whereas on the West Coast *Ixodes pacificus,* the western black-legged tick, is the main vector identified.[10] *I. scapularis* is seen from the Atlantic coast to Oklahoma and Texas.[11] A much higher percentage of *I. scapularis* ticks (12% to 99%) will carry the spirochete compared with *I. pacificus,* in which the maximum number of infected ticks is 4% to 5%.[10,11] *I. scapularis* larval ticks principally acquire the spirochete from *Peromycus leucopus,* the white-footed mouse, and the nymphal stages are the major transmitters of disease to animals and humans.[12] With *I. pacificus,* the California kangaroo rat, *Dipodomys californicus,* and the dusky-footed wood rat, *Neotoma fusicipes,* are the likely enzootic reservoirs of *B. burgdorferi.*[13]

Public Health Considerations

The CDC initiated surveillance for Lyme disease in 1982, and in January 1991 it became nationally reportable. Cases have been reported from 46 states, and the annual number of Lyme disease cases has increased 18-fold, from 497 to 8803. It is now the most common tick-transmitted disease in the United States.

B. burgdorferi organisms have been recovered from the urine of feral white-footed mice *(P. leucopus).*[14] Contact transmission has been reported between white-footed mice,[14] further complicating the understanding of transmission. Lacking any proof to the contrary, it is generally believed that any potential increased risk to humans from infected animals is due to animals bringing ticks into areas of human habitation, rather than any animal transmission.[15]

Molecular Biology

Immunochemical analysis of North American strains of *B. burgdorferi* reveal two abundant surface proteins termed *outer surface protein A* (OspA, 30 to 32 kD) and *outer surface protein B* (OspB, 34 to 36 kD).[16] The 41-kD antigen is located on the flagellum and is similar to the flagellar antigens of other spirochetes.[17] All isolates to date have four to nine pieces of extrachromosomal plasmid DNA. Plasmid may code for proteins that are important in pathogenicity, because the loss of infectivity of isolates that have been heavily passaged in the laboratory correlates with the loss of particular plasmids in culture.[18] Recent work suggests that *B. burgdorferi,* like the relapsing fever–causing *Borrelia* (e.g., *Borrelia hermsii*), can vary its antigenicity, although by a different mechanism and using subtle alterations in the genome.[19]

Clinical Signs

Equids

Clinical signs are nonspecific but may include low-grade fever, stiffness, lameness in more than one limb, muscle tenderness, hyperesthesia, swollen joints, and behavioral changes.[20,21] The most common signs are lameness and hyperesthesia. These signs have been more commonly reported in performance horses. *Borrelia* may be found concurrently with *A. phagocytophilum* in *Ixodes* ticks, resulting in dual infection in the horse.[22]

Horses from endemic areas have serologic evidence of exposure.[23-26]

Attempts have been made to correlate individual cases of arthritis, uveitis, or brain infection with this organism.[25,27,28] Experimental infection has produced seroconversion and shedding of the organism in the urine and seroconversion in contact controls.[29] In the United Kingdom, most seropositive horses do not show clinical signs of disease.[30]

Ruminants

Although there are some reports in the literature of seropositive animals with arthritis, the evaluation performed on these patients makes it difficult to determine whether *B. burgdorferi* was the cause of the signs.[31] It appears many ruminants are seropositive to *B. burgdorferi* but do not have clinical signs. Whether these tests lack specificity in the ruminant or represent a host-adapted strain of the *Borrelia* organism is unknown.[32] A recent report correlates exposure of *I. scapularis* ticks in dairy cattle with titers to *B. burgdorferi*.[33] An attempt to develop a more specific test in cattle using the 41-kD flagellin antigen has been reported.[34]

Diagnosis.

A number of diagnostic methods are available, including IFA, ELISA, indirect complement fixation, and Western blot.[29,32] Culture of the organism requires special media (BSK) and is difficult but may be possible from blood, urine, or cerebrospinal fluid. Diagnosis of recent or active *Borrelia* infection has been based on high ELISA titers, positive Western blot, or PCR.[35] In an experimental infection study, *I. scapularis* ticks infected with *B. burgdorferi* were placed on healthy ponies for 7 days. These ponies developed detectable antibody at 5 to 6 weeks.[35] ELISA titers were elevated at 3 to 4 months post exposure and remained elevated for several months until euthanasia. Western blot became positive at 10 to 12 weeks post exposure.[35] Throughout the duration of the study, the organism was isolated from the skin where infected ticks were attached. Histopathologic examination revealed lymphohistiocytic nodules in the dermis, lymph node enlargement, and perivascular and perineural lymphocytic infiltrates in the skin, fascia, and perisynovial membranes. PCR was useful for detecting organisms in the skin, lymph nodes, skeletal muscle, fascia, and synovial membranes. Less commonly, organisms were detected in the heart, pericardium, kidney, bladder, and meninges.[35] Detection of serum antibodies to *B. burgdorferi*

in horses has improved (84% detection) by using an ELISA based on whole-cell and recombinant antigens.[36]

Treatment.

Antibiotic susceptibility of *B. burgdorferi* has been reported but may lack appropriate standardization.[37] *B. burgdorferi* is sensitive to tetracycline and moderately sensitive to penicillin. Amoxicillin, ceftriaxone, and imipenem are highly active against *B. burgdorferi.* Aminoglycosides, ciprofloxacin, and rifampin lack activity.[38] Doxycycline twice daily in humans has been frequently used. Probenecid and ampicillin or amoxicillin also have been used.[38] When CNS involvement is present, ceftriaxone or IV penicillin G has been used. The appropriate duration of therapy is unknown but is related to the stage of infection.

Three different antimicrobials that included ceftiofur sodium (2.2 mg/kg/day IM), doxycycline (10 mg/kg/day PO), and tetracycline (5 mg/kg/day IV) were used for a 28-day period in experimentally infected ponies.[39] High titers and *B. burgdorferi* isolation from skin biopsies confirmed infection. Antimicrobial therapy was initiated 3 months post exposure. Tetracycline was the most effective antimicrobial; it decreased antibody titers during and months after treatment, and bacterial isolation became negative in tissues. However, tissues were still positive for the spirochete on PCR.[39] The efficacy on decreasing titers of tetracycline in the clinical setting has not been highly successful.[40] Proposed treatment for *Borrelia* infection includes tetracycline (6.6 mg/kg IV q12h), doxycycline (10 mg/kg PO q12h), or ceftiofur (2.2 mg/kg IM q12h) for 3 to 4 weeks.[35]

A recombinant outer surface protein A (rOspA) subunit vaccine was shown to be effective in preventing infection in challenged horses with infected ticks.[22,41] Specific recommendations for its use in the clinical setting are lacking.

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Tularemia

Bradford P. Smith

Tularemia, an infectious disease of humans, wild animals, livestock, and pets throughout the northern hemisphere, is caused by *Francisella (Pasteurella) tularensis.* There are four major subspecies: *tularensis, holarctica*, *mediaasiatica*, and *novicida*, with *tularensis* being the most virulent.[1] The organism is a facultative, intracellular, non–spore-forming, gram-negative coccobacillus that survives frozen or in mud and water for a period longer than 1 year,[2] but it only survives for hours in carcasses. The natural hosts are rabbits and rodents, and transmission to livestock occurs chiefly through food, water,[3] ticks, fleas, deerflies, and other insects.[4] Sheep are the most frequently affected livestock species, along with dogs, cats, and humans. Massive epidemics with high mortality in range sheep have been reported.[4] One paper describes three late-term abortion outbreaks, with one also including sick/dead ewes, between 1997 and 2007 in Wyoming and South Dakota.[5]

Humans are stricken with a plague-like illness when bitten by infected ticks, fleas, or insects and from handling infected rabbits or hares or other infected animal carcasses.[6] The disease has also been called *rabbit fever, deer fly fever,* and *meat cutter's disease.*[7] Sheep shearers may become infected by bites of parasites from the sheep. Disease in horses has also been documented.[8] Oral infection from contaminated water occurs, so fresh water should be provided.[4]

The disease causes an acute septicemia, with localization and lymphadenopathy and granulomatous lesions in the organs (particularly the liver and spleen). Signs are nonspecific, as expected with bacteremia, and include fever, anorexia, lethargy, and in some cases cough, rapid respiration, or diarrhea. Stiffness and edema of the limbs may be seen. Exposure to eyes can result in oculoglandular disease.[3] The course of disease is usually 2 to 14 days.

Agglutination titers in recovered affected sheep range from 40 to 5000. Agglutination titers persist for short periods (21 days) in horses,[4] probably because they measure mainly IgM. Diagnosis is based on culture of the organism from blood or organs. Samples must be specially handled and tests done in BSL-3 laboratories.[7] Diagnosis can also be made by IFA testing or PCR[9] or ELISA.[7]

Necropsy usually reveals ticks on the carcass. Often, reddened or necrotic

areas appear in and under the skin at the site of infected bites. Regional lymph nodes may be swollen and congested. Congestion and edema of the lungs are common. Fetal lesions from abortions have multifocal pinpoint necrosis of the liver, spleen, and lung.[5] Differentials include other bacteremias such as *Mannheimia (Pasteurella) haemolytica* in sheep, *Histophilus somni* (formerly *Haemophilus somnus*) in cattle, *Mycoplasma mycoides* subsp. *mycoides* in goats, and anthrax in all livestock. Treatment early in the course of infection is effective. Aminoglycosides, tetracyclines, cephalosporins, chloramphenicol, or quinolones all are likely to be beneficial initially until results of antimicrobial susceptibility testing are available. Insecticide removal of ticks from affected animals and herdmates is important. No animal vaccine is currently available, so insect and tick control in endemic areas remains the major prevention. Because oral infection from contaminated water has also been documented, fresh water should be provided.

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Corynebacterium pseudotuberculosis Infection

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Definition

Corynebacterium pseudotuberculosis infections occur worldwide and cause external and internal caseous lymphadenitis in sheep and goats; cutaneous excoriated granulomas and mastitic, visceral, or mixed infection in cattle; and ulcerative lymphangitis and external and internal abscesses in horses.[1-4] Subacute to chronic lymphadenitis and pneumonia have been reported in humans handling infected sheep.[5,6] Several zebras in the United States developed severe or multiple internal abscesses and died weeks after being exposed to horses in California.[7] There have been reports of the disease in camels, alpacas, and buffalo.[8,9]

Microbiology

C. pseudotuberculosis infection is caused by a 2-µm, gram-positive, intracellular, nonmotile, pleomorphic, rod-shaped facultative anaerobe.[10] *C. pseudotuberculosis* grows well at 37° C on blood agar in 24 to 48 hours, and it forms small, pinpoint in diameter, whitish, opaque colonies that are surrounded by a weak zone of hemolysis. Because of the high lipid content in the bacterial cell wall, particularly corynomycolic acid, the colonies spatter in a flame and hold their shape when pushed across the surface of an agar plate.[11] High lipid content may facilitate survival of the organism in macrophages.[12] Two species-specific biotypes of *C. pseudotuberculosis* have been identified on the basis of differences in nitrate reduction[5] and DNA fingerprinting techniques.[11,13,14] Strains isolated from small ruminants are nitrate negative, strains from horses are nitrate positive, and both strains have been isolated from cattle.[1,5,13,15] From the results of DNA studies, the terms *biovar equi* for nitrate-positive and *biovar ovis* for nitrate-negative strains were proposed.[11] Molecular studies revealed that there is considerable heterogeneity of the isolates of *C. pseudotuberculosis* from

small ruminants and from horses[13,14,16] and concluded that nitrate reduction may not absolutely distinguish between the isolates, as does ribotyping.[13] On the basis of genome sequencing, sheep and goats have specific isolates throughout the world, and horses and cattle have distinct groups of isolates depending on geographic locations.[13] Natural cross-species transmission between small ruminants and horses has not been reported.

C. pseudotuberculosis produces various exotoxins: phospholipase D (PLD), sphingomyelinase, inhibitory factor of staphylococcal β-hemolysin, hemolysis factor, dermanecrotoxins, and mouse lethality toxins.[17] Phospholipase D and sphingomyelinase are important in the pathogenesis of the disease because they hydrolyze lysophosphatidylcholine and sphingomyelin, respectively, enabling degradation of the endothelial cell wall and increasing vascular permeability.[18] The synergistic activity of sphingomyelinase with the exotoxin of *Rhodococcus equi* in lysing red blood cells in agar forms the basis for the synergistic hemolysis inhibition (SHI) test. The SHI test measures IgG to PLD exotoxin.[19]

Molecular characterization of *C. pseudotuberculosis* isolates causing various clinical forms of disease, including genome sequencing, has been reported. At present, phenotypic and genotypic strain differences have not been linked to clinical disease presentation (internal or external abscesses), suggesting that other environmental or host factors determine the course of disease.[20,21]

Clinical Signs and Differential Diagnosis

Sheep and Goats

C. pseudotuberculosis causes caseous lymphadenitis (CLA) in sheep and goats worldwide. Caseous lymphadenitis is a major cause of poor production, premature culling, and mortality. Two forms of CLA exist which manifest as external and internal abscesses.[22] The infection in small ruminants is primarily characterized by suppuration and necrosis of the large superficial lymph nodes. External abscesses are found more commonly involving the mandibular, parotid, prefemoral, or prescapular lymph nodes. The exudate present in those abscesses is thick or inspissated and may appear white in sheep and greenish in goats.[4] A breed association with the type of CLA cutaneous lesion was observed in an outbreak in a commercial ram stud in Scotland.[23] The disease is commonly known as “cheesy gland” in Australia. Differential diagnosis should include

abscesses caused by other organisms, trauma, seroma, hematoma, foreign body, injection reaction, and, less commonly, tumors. *C. pseudotuberculosis* infection represents a major herd health problem, so abscess culture to determine the precise causative agent is important. Mastitis occasionally develops.[2]

Internal abscesses can be found in the lungs, kidneys, and mediastinal, bronchial, mesenteric, and lumbar lymph nodes.[22] Chronic weight loss is the most common presenting complaint. Other clinical signs are related to the organ or tissues affected. Other diagnostic procedures may be necessary for the differentiation of internal abscesses as the cause of weight loss. Signs of spinal cord compression by vertebral abscesses have been seen in lambs born in unsanitary conditions.[4] Knowledge of the local prevalence can aid diagnosis of the infection when uncommon anatomic locations are affected. The prevalence in large breeding operations in endemic areas is estimated to be between 5% and 10%.

Cattle

C. pseudotuberculosis infection in cattle occurs as a herd problem with sporadic incidence. The most common clinical form affecting cattle is cutaneous excoriated granulomas; other forms are mastitis, visceral, and mixed infections.[2] In the most common form, the lesions do not occur as abscesses but as ulcerative, exuding granulomatous lesions as large as 20 cm in diameter, with necrotic areas that are easily surgically removed, leaving granulation tissue underneath.[3,4] Lesions are usually located in the lateral exposed areas of the body: face, neck, thorax, and flanks. The exudate varies from bloody to thick greenish in color. Lesions heal spontaneously in 2 to 4 weeks and do not appear to cause significant illness or decrease milk production in cattle in California.[4] However, monthly milk production was decreased by 6% in Israeli cattle.[3] The prevalence of the infection has been reported to be up to 10% in California dairies.[4] Morbidity was reported to be up to 35% in Israeli herds.[3] Management problems like broken posts or exposed wires traumatize the skin of cattle, allowing penetration of the organism. Young cattle appeared to be less susceptible to the disease than older cattle in Israel.[3] Differential diagnoses include trauma, foreign body, and other masses like tumors. Cutaneous lesions and mastitis were seen in 6%, and cutaneous lesions with concurrent visceral involvement in 1.6% of the cases in Israel with the remainder of the cows (92%)

exhibiting only the cutaneous form.[3] The most affected organ in the visceral form was the lung.[3] The infection has been reported in bison from Egypt, resulting in severe emaciation and edema in the ventral areas and flanks.[24]

Camels and Camelids

Caseous lymphadenitis has been reported in old and new world camelids worldwide.[25] One study documented five young alpacas (aged 22 days to 14 months old) in North America with caseous lymphadenitis or subcutaneous abscesses that developed during late summer and early fall.[9] The alpacas did not appear clinically ill but developed swellings that progressed to abscesses. The abscesses (1 to 3 per alpaca) were located in the submandibular and cervical areas and in one case adjacent to the eye. Abscess excision appeared to be the most effective treatment in those cases. Differential diagnoses include abscesses caused by *Streptococcus* spp., *Corynebacterium* spp., and *A. pyogenes*.[26] Severe lymphadenitis with internal and external abscesses was reported in camels in Asia and Jordan.[8] A study of experimental infection of adult alpacas resulted in abscesses at the inoculation site and renal lymph nodes.[27]

Horses

Three forms have been described in horses: ulcerative lymphangitis and external and internal abscesses (Figs. 37.1 and 37.2). In a previous study of *C. pseudotuberculosis* infection in horses from California, ulcerative lymphangitis was diagnosed in 1%, external abscesses in 91%, and internal abscesses in 8% of the cases.[28] There appears to be no breed or sex predilection for development of infection. Ulcerative lymphangitis appears as a severe cellulitis, where the lymphatics are affected in one or more limbs, with multiple draining ulcerative lesions. Horses often develop a non–weight-bearing lameness, fever, lethargy, and anorexia. This form of the disease occurs worldwide and often becomes chronic, resulting in limb edema, lameness, weakness, and weight loss.[4] The differential diagnosis should include blunt trauma, fracture, foreign body, puncture wounds, nonseptic cellulitis, staphylococcal cellulitis, and other septic cellulitis. Musculoskeletal infection can result in marked lameness (grades 4 to 5 out of 5) and most commonly involves the axillary and triceps areas, followed by the stifle area.[29] In addition to diffuse lymphangitis of the limbs, it can also cause osteomyelitis and septic arthritis.[28,29]



FIG. 37.1 Typical ripe pectoral external abscess in a horse, containing a large pocket of pus, caused by *C. pseudotuberculosis.*



FIG. 37.2 Severe ulcerative lymphangitis in a horse leg caused by *C. pseudotuberculosis*.

The median age for horses with external abscesses is 5 years (range, 3 months to 28 years).[28] Young horses appear to be predisposed to infection; 52% of the cases in a large retrospective study in California were 5 years old or younger.[28] Few cases involved foals younger than 6 months of age, suggesting that foals born to mares in endemic areas may be protected for several months by colostral antibodies.[28] External abscesses located primarily in the pectoral and ventral abdominal regions are most commonly diagnosed in areas of the western United States (Texas, Oklahoma, New Mexico, Colorado, Nevada, Utah, California, Wyoming, Arizona, Oregon, and Washington); however, disease incidence is increasing and spreading to all regions of the United States, including Hawaii, with reports in Mexico and Western Canada.[1,4,20,28,30,31] This clinical form of external infection is commonly known as “pigeon fever” because of the large

size of pectoral abscesses, giving the appearance of a pigeon's breast. “Dryland distemper” is another name that reflects its geographical distribution in arid areas. Other common anatomic locations are the prepuce, mammary gland, axilla, inguinal region, limbs, and head.[28] Abscesses involving the head include the ears, eyelids, forehead, maxillary, and mandibular regions.[28] Severe facial suppurative cellulitis and panniculitis with skin sloughing have also been reported.[32] Other less common areas are the thorax, neck, parotid gland, guttural pouches, larynx, flanks, umbilicus, tail, and rectum.[28] Central nervous system infection has also been reported.[28,33] A large area of edema develops in the area of abscess formation. While the abscess matures, the area becomes hard and painful, and some get large, particularly in the pectoral area. These abscesses typically have a thick capsule measuring up to 10 cm, and can cause severe lameness if located in the axillary or inguinal region.[1,28] Maturation can be slow and drainage difficult to establish if the abscess lies deep to muscle. Once drainage is established by spontaneous rupture or lancing, the majority of cases resolve within 10 to 14 days, but many horses can experience a protracted course of disease lasting months with recurring abscesses. Generally, weight loss is not observed in absence of internal infection. Abscesses may contain from 5 to 400 mL of thick, tan, purulent exudate.[1] The majority of affected horses present with a single abscess rather than multiple abscesses.[28] Fever up to 40° C develops in about 25% of cases. Other signs are nonhealing wounds, lameness, ventral dermatitis, and (less commonly) depression, anorexia, mastitis, and other problems, depending on abscess location.[28] In the majority of horses (91.4%), complete recovery occurs with no recurrence of infection in subsequent years, implying a long-lasting immunity. However, 8.6% of equine infections may persist for longer than 1 year or recur as external or internal abscesses.[28] In sheep and goats, humoral and cellular immune responses develop following infection, and macrophages acquire the ability to kill the organism.[6] The case fatality for horses with external abscesses is low (0.8%).[28] The differential diagnosis for external abscess, particularly pectoral, should include trauma, seroma, hematoma, foreign body, or abscess due to a different organism.

In a large study of *C. pseudotuberculosis* infection in the horse, 8% of 538 horses developed internal abscesses.[28] In two different studies, up to 63% of horses with internal abscesses also had a history of, or concurrent, external abscesses.[28,34] In a study of 30 horses with internal abscesses, a sex

predisposition (70% female) was apparent.[34] Mean age is 8 years, with a range of 10 months to 23 years.[28,34] The most common clinical signs are anorexia, lethargy, fever (up to 41.1° C), tachycardia, and modest weight loss. Other signs are colic, pale mucous membranes, ventral and/or limb edema, ventral dermatitis, ataxia, hematuria, nasal discharge, and abortion.[28] The most commonly affected anatomic location is the liver, followed by mesentery, mediastinum, lungs, kidneys, diaphragm, spleen, pericardium, blood, and uterus.[1,28,34] A postmortem examination was performed on an aborted fetus from a mare with pneumonia and revealed *C. pseudotuberculosis* abscesses in the liver, lungs, spleen, diaphragm, kidney, and bladder.[34] Both single and multiple organ involvement has been documented.[34] Bacteremia may also occur. The case fatality for horses with internal abscesses ranges from 30% to 40%.[28,34] The differential diagnosis should include other types of abscesses, such as *Streptococcus*, *Actinomyces*, *Staphylococcus*, *R. equi* in foals, *Coccidioides immitis*, anaerobes, neoplasia, and other causes of weight loss. The clinical signs and differential diagnosis will depend on the location of the abscess.

Humans

Human infection may result from consumption of unpasteurized infected milk or milk products, continued close contact with infected animals, handling contaminated equipment, and exposure to wounds with exudates.[6,35] Human infection has been reported from strains of small ruminants.[6] Transmission from horses to humans has not been reported, but precautions should be taken when handling infected horses. Infection in humans occurs as a subacute to chronic lymphadenitis and pneumonia.[6]

Clinical Pathology and Laboratory Diagnosis

Common findings include anemia of chronic disease and an inflammatory leukogram.[28,29,34] Leukocytosis with neutrophilia and increased fibrinogen and serum amyloid A (SAA) are common features of developing bacterial infections, particularly in the case of internal abscesses.[28,29,34] Leukocytosis with neutrophilia was seen in 36% and 76% of horses with external and internal abscesses, respectively.[28] Hyperproteinemia due to increased globulins was observed in 38% and 59% of horses with external and internal abscesses,

respectively.[28] Similarly, infected cattle and small ruminants had increases in white blood cell counts.[2,3]

Peritoneal fluid from 93% of horses with abdominal abscesses was abnormal.[28] The remaining horses with abdominal abscesses and normal peritoneal fluid had abscesses located retroperitoneally involving the kidneys, without involvement of other abdominal structures. *C. pseudotuberculosis* was isolated by bacterial culture in 32% of the samples of peritoneal fluid in horses with internal abscesses,[28] and infection can also be detected by PCR. Failure to detect the organism from peritoneal fluid does not rule out the disease as infection could be in a retroperitoneal location, sequestered within a thick capsule, or suppressed by local factors or nucleated cells.[36]

The ELISA test for detection of cell wall antigens appears to have some utility for detection and control of infection in sheep.[37-40] The synergistic hemolysis inhibition (SHI) test measures IgG response to the PLD exotoxin in the patient's serum by detecting the highest dilution that will prevent hemolysis of *R. equi* exotoxin–sensitized bovine red cells when mixed with *C. pseudotuberculosis* exotoxin of a known concentration.[19,41] Increasing titers may be seen with exposure, or active external or internal infection and there exists considerable overlap in values among these groups of horses. In a case control study, SHI test results had greatest utility for determining internal *C. pseudotuberculosis* infection in horses when there was no evidence of external abscesses.[43] A high probability of internal infection with titers greater than or equal to 512 was previously reported, yet a recent case control study of 171 horses revealed higher titers were more indicative of active external or internal disease rather than internal disease specifically. The SHI test was unable to distinguish the occurrence of internal infection when external abscesses were present. Titers increase with chronicity of infection and bacterial culture is the preferred method of diagnosis for external infection. In horses *without external abscesses,* increased titers greater than 1280 are significantly associated with internal infection. Clinicians are advised against diagnosis of internal infection on the basis of SHI titer; rather, the test should be used in conjunction with other clinical and clinicopathologic evidence of inflammation.

The SHI test can be used in sheep and goats to monitor prevalence and exposure of incoming animals and to detect subclinical infections.[4,41] In horses, a low SHI titer does not rule out the disease as horses that are seronegative at the time an external abscess is drained seroconvert later. High SHI titers in horses

with internal abscesses probably reflect the chronicity of the disease and the resulting prolonged immune stimulation. In summary, high titers can be seen with both internal and external abscesses and abdominal and thoracic ultrasonography is useful for confirmation of internal infection in suspect cases.[28,34,43] Exposed herd mates can also have SHI titers in the absence of clinical infection. Prolonged seropositivity has been observed in horses and goats.[28,41,44] Other serodiagnostic tests used in sheep and goats are tube agglutination, complement fixation, and gel immunodiffusion.[17,45]

A presumptive diagnosis can be made on the basis of history, local prevalence, time of year, clinical signs, and exudate characteristics.[4] For the diagnosis of internal abscesses, the previous features must be considered, as well as the presence of an inflammatory leukogram with elevated fibrinogen, serum chemistry abnormalities, abnormal peritoneal fluid or transtracheal wash, positive blood culture, SHI titer of 512 or higher, and ultrasonographic and/or radiographic evidence of masses.[28,34] A definitive diagnosis is established by isolating the organism from abscesses or draining wounds. The organism is readily isolated and grows well in blood agar in 24 to 48 hours, even when contaminant bacteria are present.[28]

Pathophysiology and Epidemiology

C. pseudotuberculosis is a soil-borne organism that survives for long periods of time, months to years, even in direct sunlight at environmental temperatures.[6,46,47] The incidence of infection in horses varies considerably from year to year. External and internal abscesses in horses can present at any time of the year but are more commonly observed during the fall and early winter months, with the highest incidence in September, October, and November.[28] However, internal infections are more frequently seen in November through January, 1 to 2 months following the peak number of cases with external abscesses.[34] The largest numbers of equine cases have been observed during the dry months of the year, following heavy rainfall, which may result in optimal breeding conditions for insects.[1,28,30] The seasonal incidence in horses has been associated with the presence of biting insects like *Haematobia irritans* (horn fly); this insect's feeding pattern causes ventral midline dermatitis. Insect vectors involved in transmission of disease in horses (e.g., *H. irritans, Stomoxys calcitrans, Musca domestica*) were identified by detecting the PLD exotoxin

gene of *C. pseudotuberculosis* in an endemic area.[48] Disease transmission may occur by direct contact with exudates or contaminated soil or by vector-borne routes.[49] Temporal and spatial analysis indicated an incubation period of 3 to 4 weeks in horses.[50] There is no breed or sex predilection[28]; however, a retrospective study indicated a predilection for internal abscesses in females.[34] A case-control study in an endemic area revealed young adult horses (<5 years of age) had increased risk of infection.[49] Horses housed outside or with access to an outside paddock or in contact with other horses on pasture appeared to be at higher risk than stabled horses.[49]

The disease in cattle from Israel occurred during the spring and summer dry season (March to October) when the housefly population is high.[3] *C. pseudotuberculosis* was isolated from houseflies collected over an Israeli cow lesion.[51] The infection in cattle may spread by direct contact or indirectly by houseflies or fomites.[3] The disease in sheep and goats is not seasonal, and transmission is through contact of exudate from a draining abscess from animal to animal or via contaminated equipment.[1] Lambs born in contaminated surroundings can be infected through the umbilicus, mouth, or inhalation.[4] Sheep that acquire the organism orally or from shearing wounds tend to have parotid, submandibular, prefemoral, or thoracic abscesses.[4] Goats can be infected when wounds are exposed to contaminated milking equipment. The incubation period is long and variable. In experimental infections in small ruminants, the incubation period was from 2 weeks to several months.

The pathogenesis of the disease in horses is unclear, but it has been speculated that the organism enters the equine host through skin or mucous membrane abrasions or wounds, as has been confirmed in sheep.[52,53] Experimentally induced infections in small ruminants revealed that once *C. pseudotuberculosis* gains access via wounds or abrasions, the organisms spread to subcutaneous or submucosal lymphatics, where they are phagocytosed by macrophages that migrate to the invasion site to engulf them.[54] The organism survives intracellularly because of its high lipid content (corynomycolic acid), resisting the action of lysosomal enzymes.[10] *C. pseudotuberculosis* replicates in the phagolysosome; if large numbers of organisms are engulfed, phagocytic cells die. Experimental inoculation of the organism in sheep revealed a massive infiltration with polymorphonuclear leukocytes,[55] which are believed to carry the bacteria to regional lymph nodes.[4] A PLD toxin of approximately 31.5 kD,

produced by all *C. pseudotuberculosis* isolates, increases vascular permeability, causing spread of the organism regionally and systemically.[6,42,56] Development of abscesses at secondary locations in horses can occur in up to 25% of cases.[28] PLD toxin can cause lymphatic necrosis and thrombosis and may enhance survival and multiplication of the organism via complement depletion and inhibitory effects on phagocytic cells.[6] Corynomycolic acid and PLD toxin contribute to inflammation, edema, and pain during abscess development.[57] The profound reaction of these compounds is probably responsible for the formation of a thick abscess capsule that develops as phagocytes accumulate in the abscess core. The abscess eventually matures and drains, but if removal of infected material is incomplete, recurrence may be expected, particularly in small ruminants.[4] The development of internal abscesses in horses is unclear but has been postulated to result from hematogenous or lymphatic spread of bacteria from more superficial sites.[4,28,34]

Treatment and Prognosis

Important features to consider when treating external abscesses are to (1) allow the abscess to mature, (2) establish drainage, (3) collect and properly dispose of the infective exudate, (4) lavage the wound with an antiseptic solution, and (5) apply insect repellant ointments and other measures of fly control. In a retrospective study in horses, the majority of external abscesses were incised to establish drainage, then some received antimicrobial therapy after drainage in an effort to decrease cellulitis.[28] Many horses received no treatment; abscesses broke and drained without clinical intervention.[28] Other horses were only treated with antimicrobials.[28] Outcomes were successful for 99% of horses with external abscesses.[28] Horses with abscesses in the axillary region or deep within muscles have considerable pain, necessitating incision and drainage. Ultrasound is useful for localization of deep abscesses.[34]

Antimicrobial therapy for uncomplicated external abscesses is often not indicated. Horses with external abscesses that have systemic illness, recurrent infections, or poor immunity and horses with internal infection or ulcerative lymphangitis require antimicrobials until infection has completely resolved. If antimicrobials are used, long-term (minimum 4 to 6 weeks) therapy is necessary for the treatment of internal abscesses and ulcerative lymphangitis. Median resolution time for horses with internal abscesses treated with antimicrobials was

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36 to 42 days, with a maximum duration of 97 days.[28,34] The case fatality for horses with internal abscesses treated with antimicrobials was 30% to 40%, but 100% if not treated.[28,34] A study describing 35 horses with musculoskeletal infection reported surgical drainage in 60%, antiinflammatories in 97%, and antimicrobials in 86%.[29]

In vitro, *C. pseudotuberculosis* is susceptible to nearly all commonly used antimicrobials, and resistance is uncommon.[54,58-60] Trimethoprim sulfamethoxazole (30 mg/kg PO q12h), trimethoprim sulfadiazine (24 mg/kg PO q12h), and procaine penicillin (22,000 IU/kg IM q12h) are often effective for external abscesses. Horses with internal abscesses respond well to minocycline (4 mg/kg PO q12h), doxycycline (10 mg/kg PO q12h), enrofloxacin (7.5 mg/kg PO q24h), trimethoprim sulfas (doses above), and potassium penicillin (20,000-40,000 IU/kg IV q4-6h). Rifampin (5 mg/kg PO q12h) is highly effective and is used in combination with another antimicrobial (e.g., trimethoprim sulfa or enrofloxacin) due to concerns for rapid emergence of microbial resistance when used as monotherapy. Ceftiofur is less effective due to high minimum inhibitory concentrations (MIC) and therefore not recommended. Ulcerative lymphangitis should be treated aggressively with long-term antimicrobials (3 to 4 weeks). In horses, colitis is a risk of antimicrobial use. In addition, enrofloxacin is contraindicated in growing horses due to risk of cartilage damage. Fortunately, a recent study of antimicrobial susceptibility patterns (MIC) in 207 equine isolates showed no differences in MIC over 16 years.[54]

Nonsteroidal antiinflammatories (NSAIDs) to control discomfort and inflammation are often used to control the pain and/or fever while waiting for external abscesses to mature.

The prognosis for external abscesses is good. Most resolve in 3 weeks from the day of drainage.[4] The prognosis for horses with internal abscesses and ulcerative lymphangitis is guarded but improves if infection is detected early and appropriate long-term therapy is administered. Horses with musculoskeletal infection tend to have a favorable prognosis, but osteomyelitis and septic arthritis can complicate recovery.[29]

In a study in cattle, skin lesions on individual cows healed (on average) in 23 days after local or parenteral treatment; 17% of severely affected cattle were culled.[3] Simple drainage in small ruminants does not usually result in resolution of the disease and can become a potential source of infection. Dilute betadine solutions can be used for abscess lavage. Complete excision of the abscess under

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general anesthesia may be necessary to keep the abscess from draining and prevent spread of the infection to other animals.[4] The treatment of choice in small ruminants is complete surgical removal of affected lymph nodes.

Prevention and Control

Even though *C. pseudotuberculosis* infection is one of the most commonly diagnosed infectious diseases in California, little is known about its prevention and control. General recommendations to prevent its spread are isolation of infected animals, fly control, good sanitation, careful shearing practices, disinfection of contaminated fomites, and careful disposal of bedding. On small-ruminant farms, morbidity can reach 100%, with depopulation being the most economic option. Because *C. pseudotuberculosis* can survive in soil and on fomites, the potential for environmental contamination is high.[46,49]

Immunization trials using whole cells, cell wall toxoids, and bacterin-toxoid combinations have been used to prevent CLA in small ruminants.[61-65] These vaccines have been shown to provide a high degree of protection, decreasing the number of infected sheep and number of abscesses per sheep.[61-65] *C. pseudotuberculosis* toxoids are commercially available for sheep and goats (e.g., Caseous D-T [Colorado Serum Co., Denver, Colo.], Glanvac [Rhodes, New South Wales, Australia]). In horses, autogenous bacterin-toxoids have been used for many years with anecdotal success.[66,67] A bacterin-toxoid vaccine with a conditional license (Boerhinger Ingelheim, Ingelheim am Rhein, Germany) is available for horses. Vaccinated animals demonstrate increased SHI titers following a 2-dose primary series; however, conferred protection remains to be established.

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• CHAPTER 38

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Diseases of the Bones, Joints, and Connective Tissues

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Physitis (Epiphysitis)

Berkley Chesen

▪ Definition and Etiology

Physitis is a term used to describe a developmental orthopedic condition in which there is a disturbance in endochondral ossification at the physis or growth plate. Of the developmental orthopedic diseases (osteochondrosis, physitis, subchondral bone cysts, flexural limb deformities, cuboidal bone malformation, acquired angular limb deformities, and juvenile arthritis), physitis is the most common.[1,2] In one study of 1711 Irish Thoroughbred foals, 67% had signs of developmental orthopedic disease.[2] The term *physitis* may better be defined as physeal dysplasia, since there is typically no evidence of an inflammatory process.[3] Physitis has been seen in growing cattle due to copper deficiency and interactions with molybdenum, zinc, and sulfates, as well as in calves raised on slatted floors.[4] Two common antagonists of copper are zinc, which when prevalent at high levels prevents absorption of copper by the body; and molybdenum, which is found in alfalfa.[5] Other animals in which physitis has been reported include show rams being heavily fed and sheep and goats due to pregnancy-associated ephiphysitis.[4] Physitis typically affects the given physis during its active growth phases. Many factors have been implicated as causes of physitis in horses, including[4]:

1. A genetic component for faster-growing horses and for specific conformation (such as an upright and pigeon-toed appearance)
2. Overweight foals
3. Growth spurts in foals
4. Intake of high levels of carbohydrates causing hormonal changes affecting the physis
5. Improper mineral balance (such as copper or zinc deficiencies)
6. Excessive or deficient calcium intake
7. Excessive exercise, especially on hard ground, causing strain on maturing cartilage

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More recently, physitis has been implicated as a complication after treatment with a transphyseal screw for angular limb deformities in the distal radius. It was shown that a single transphyseal screw had a significantly higher complication rate of physitis when compared to the technique using screws and wires.[6]

▪ Clinical Signs

Physitis in horses is seen mainly in three specific locations at certain ages. Foals ranging in age from 3 to 6 months most commonly have signs of physitis at the distal metacarpal or metatarsal growth plate (with or without involvement of the proximal physis of the first phalanx).[7] Older foals (8 to 24 months) may have signs of physitis at the physis of the distal radius.[7] Less frequently, the distal physis of the tibia may be involved. Physitis is characterized by firm swellings, which may be warm and painful upon palpation. Typically the swellings are medial due to increased weight bearing on this portion of the limb.[7] Foals may or may not be lame. Changes radiographically include a sclerotic, roughened physis with an irregular metaphyseal shape.[2] If the physitis continues, the growth plate may close prematurely, leading to an irreversible angular limb deformity (usually a varus deformity due to the decreased growth on the medial physis).[7]

▪ Diagnosis

A diagnosis of physitis is usually made by appreciation of the clinical signs, including warm, sometimes painful, firm swellings in the above-mentioned locations. Physitis at the fetlock may appear to have an hourglass appearance if the proximal physis of the first phalanx is affected.[7] A convex appearance just proximal to the distal tibial and radial physis may be seen early in the disease process.[7] A quantitative method for detection of physitis was investigated in Thoroughbred foals.[2] This method was based on the observation that when the physis is enlarged, there is more concavity of both the metaphysis and the ephiphysis.[8] Results of this study show that epiphyseal concavity may indicate the degree of physeal swelling by using the maximum second derivative value of that contour.[2] Radiographically, physitis is characterized by a growth plate that is irregularly thickened with sclerotic adjacent bone.[2]

▪ Treatment and Prognosis

Treatment of physitis should begin with management changes. Special attention

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should be given to the nutrition of these foals and weanlings. Ensuring proper balance of minerals, especially calcium and phosphorus, and adequate amounts of trace minerals, such as copper and zinc, is necessary. Copper is required for successful crosslinking of collagen. When there is a copper deficiency, the cartilage matrix weakens and microfractures occur.[5] Because mare's milk is very low in copper, foals rely on hepatic stores gained during the last trimester of gestation.[5] One study showed that supplementation of mares with copper during gestation significantly reduced radiographic signs of physitis in their foals at 150 days of age.[9] Supplementation of foals did not affect the incidence of physitis in the same study. Due to the results of this study, supplementation of mares during the second half of gestation with copper on farms with a high incidence of physitis may be beneficial in preventing physitis in their foals.[9] A new supplement available to veterinarians, Leg Aide™, produced by Progressive Nutrition (Hopkins, Minn.), has anecdotally positive results for supplementing foals in rapid growth phases or with nutritional shortages.

A general reduction in energy is needed to slow growth rates and when necessary to decrease body weight. Total concentrate should be 0.5 to 0.75 kg/100 kg body weight for nursing foals, 1 to 1.5 kg/100 kg body weight for weanlings, and 0.5 to 1 kg/100 kg body weight for yearlings.[4] Varying degrees of discomfort are involved with physitis. For horses with very painful, warm physes, the judicious use of nonsteroidal antiinflammatory drugs (NSAIDs) is indicated. Exercise restriction, specifically stall rest, is indicated in affected horses. Without exercise restriction, these horses continue to load the physes, which may lead to permanent conformational changes, such as angular limb deformities. The prognosis for physitis is good for athleticism with early detection and treatment.

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Osteochondrosis

Jarred Williams • Jason C. Mez

▪ Definition and Etiology

Osteochondrosis is a developmental orthopedic disease characterized by failure of, or a defect in, endochondral ossification; it can lead to cartilage flaps, osteochondral fragments, or subchondral bone cysts. It is classified as a developmental orthopedic disease (DOD) along with physitis, angular limb deformities, subchondral bone cysts, flexural deformities, incomplete ossification of the cuboidal bones, and juvenile arthritis.[1] *Chondrodysplasia* and *dyschondroplasia* are more descriptive terms because they imply a primary defect in cartilage maturation, but their use is generally reserved for abnormalities of limb and vertebral development. The terms *osteochondrosis*, *osteochondritis*, and *osteochondritis dissecans* have all been used synonymously in discussing the condition. To maintain consistency and avoid confusion, the following designations are used in this discussion: *osteochondrosis* refers to the disease, *osteochondritis* refers to the synovial inflammatory response caused by the disease, and *osteochondritis dissecans* refers to the condition when a cartilaginous flap is identified.[2]

Osteochondrosis has been recognized in most domestic species, including horses, swine, and less often cattle, sheep, and goats. The focus has been osteochondrosis in horses, because of the economic impact and performance-limiting characteristics of the disease; and in swine, due to the effects on production traits[3] and development of comparative models for study of the disease.[4]

▪ Clinical Signs and Differential Diagnosis

Osteochondrosis can present with a variety of clinical signs that are frequently recognized in juvenile animals. Effusion of the affected joint with or without accompanying lameness is common. The tarsocrural and femoropatellar joints are most often affected, but the condition can be seen in any joint. In young animals, physitis (i.e., inflammation at the physeal plate) can have a similar appearance, with generalized enlargements adjacent to synovial structures. Osteomyelitis can cause a periosteal reaction that, if located in the area of a joint,

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can have a similar appearance. Septic arthritis can closely mimic the signs of osteochondrosis, but the associated lameness is often much more severe. Physitis, osteomyelitis, synovitis, and septic arthritis should all be considered in the differential diagnosis of osteochondrosis in juvenile animals. In older animals the clinician should consider synovitis, osteoarthritis, and trauma in the differential diagnosis.

Osteochondrosis is generally diagnosed in horses when they begin training programs or athletic activity. They often present with a complaint of joint effusion that can be acute or insidious. Lameness, if any, is usually mild, except in cases with large osteochondral fragments or subchondral bone cysts. Severe cases seem to be more common in the stifle, and associated clinical signs may be present in foals as young as 6 months. Reports in cattle indicate that young, intact male, purebred animals are most often affected. The typical clinical signs are lameness with associated joint effusion. Osteochondrosis in swine has been associated with a syndrome known as “leg weakness.” Affected animals can show a range of signs from mild lameness to difficulty rising and/or inability or refusal to mount.[5] Evaluation of performance data from swine herds can be a useful indicator of osteochondrosis because it has been shown to have a significant effect on production traits.[3,6] Production animals are often slaughtered prior to 2 years of age; thus recognizable clinical signs of the disease in cattle and swine may be apparent only in breeding animals.

▪ Sites of Predilection

Osteochondrosis can be found in any diarthrodial joint, but sites of predilection exist in all species affected. In horses the stifle, tarsus, and fetlock are most frequently affected, and to a lesser degree the shoulder and vertebrae. In the stifle, in order of frequency, the lateral trochlear ridge of the femur, medial trochlear ridge of the femur, trochlear groove, and distal end of the patella are affected.[7] The medial femoral condyle is the site of predilection for subchondral cystic lesions. In the tarsus, the distal intermediate ridge of the tibia, lateral trochlear ridge of the talus, and medial malleolus are affected.[7] The most common manifestations in the fetlock joint are along the dorsal aspect of the sagittal ridge and the condyles of the metacarpus or metatarsus, and of the dorsal aspect of the proximal phalanx.[8] Predilection sites in cattle are similar to those in horses, with the hock and stifle most often affected and similar distribution in the joints.[9] Swine show a slightly different pattern, with the medial condyle of the

humerus and femur most frequently affected.[6]

▪ Diagnostic Tests

Animals presenting with signs of joint effusion and lameness should undergo a thorough physical examination. A compete blood cell count (CBC) indicating a septic process, along with radiography, helps differentiate osteomyelitis, septic physitis, and septic arthritis from osteochondrosis. Horses should be observed in motion and given flexion tests when possible. Regional and intraarticular anesthesia can be used to localize the site of lameness, though often the primary sign of osteochondrosis is swelling without lameness. Swine and cattle can be observed in their normal surroundings for signs of lameness. The joint in question should be radiographed, as should the corresponding joint on the contralateral limb in the tarsocrural and femoropatellar joints, because lesions are frequently bilateral. If lesions are detected in the metacarpophalangeal or metatarsophalangeal joint, the remaining three limbs should be evaluated. Joint effusion with or without lameness is more reliably seen in cases of osteochondritis dissecans (OCD) and subchondral bone cysts than in osteochondrosis.

Swine and cattle will often present with signs of lameness and mild joint effusion. Careful physical examination of the restrained animal should localize the lesion and guide appropriate radiography. As with equine patients, the lesions are commonly bilateral, and corresponding limbs should also be radiographed. Reviewing production records of finishing or breeding swine herds may be of diagnostic value, because osteochondrosis has been shown to cause significant reductions in performance and production traits.[3]

The manifestation of osteochondrosis may not be adequately represented by clinical signs and radiographs. Clinical signs of lameness and joint effusion have been shown to precede changes within the joint, and serial radiographs may be needed to diagnose the condition.[10] Radiographic abnormalities consistent with osteochondrosis of the distal intermediate ridge of the tibia and lateral trochlear ridge of the femur can return to a normal appearance by 5 and 8 months, respectively, in warmblood foals.[11] Radiographs often underrepresent the severity or size of the lesion seen at surgery. Evaluation of osteochondrosis along the lateral trochlear ridge of the femur indicated that ultrasonography provided a better overall subjective assessment of the lesion (length, depth, and width) compared with radiography.[12]

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▪ Pathophysiology

Endochondral ossification is the process of bone formation in which cartilage scaffolds, arranged in zones, are gradually replaced by bone. It occurs at the articular/epiphyseal and metaphyseal growth plates and at secondary centers of ossification, such as the carpal and tarsal bones. Directly beneath the articular cartilage is a zone of resting chondrocytes that divide to form the next zone of proliferating chondrocytes. These proliferative cells divide rapidly, organizing into columns perpendicular to the long axis of growth. The cells swell in the hypertrophic zone, where the columns become more organized. The chondrocytes in this zone are surrounded by increasing amounts of extracellular matrix, which becomes mineralized in the zone of calcification. These columns of chondrocytes are vascularized by metaphyseal blood vessels supplying nutrients. It is on these calcified cartilage columns that bone forms, creating the primary spongiosa, which is subsequently remodeled into mature bone.

The exact pathogenesis of osteochondrosis is unclear. The traditional theory is that the process of endochondral ossification is disrupted, resulting in areas of thickened cartilage. The deeper layers of affected cartilage do not receive adequate nutrients, resulting in necrosis of the cells and failure of proper ossification. These retained cartilage “plugs” have less structural integrity than normal cartilage and are prone to damage. Specifically, shear forces acting on the abnormal cartilage can lead to fissure formation, which progress into fragments of cartilage and subchondral bone. When compressive forces predominate on an area of thickened cartilage, it is surmised that infolding of the cartilage plug occurs with normal endochondral ossification proceeding around it, possibly leading to the formation of a subchondral bone cyst.

The traditional theory of defective endochondral ossification may be a simplistic view of a more complex, multifactorial condition. Limited reparative responses of bone and cartilage make it difficult to determine whether the origin of a lesion is developmental or traumatic. One report failed to distinguish articular cartilage differences in naturally occurring osteochondrosis versus healing osteochondral fragments.[13]

Computed tomography and magnetic resonance performed on fetuses and foals demonstrated that there was greater cartilage thickness in areas of joints that commonly develop OCD. More specifically, at 8 to 9 months of gestation, the lateral trochlear ridge of the femur, medial malleolus of the tibia, and distal intermediate ridge of the tibia, all OCD-susceptible sites, had the greatest percentage of cartilage compared to unsusceptible sites. Postpartum, the

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percentage of cartilage in the medial malleolus and distal intermediate ridge of the tibia remained high. These findings suggest that greater cartilage thickness at specific joint sites could play a role in the development of OCD.[14]

Arthroscopic observations of normal-thickness cartilage defects and normal subchondral bone, as well as lesions occurring preferentially at single sites at the limits of articulation, suggest causative factors other than defective endochondral ossification.[15] The development and then spontaneous regression of osteochondrosis lesions in young animals suggest that the condition is a dynamic process that can be affected by numerous intrinsic and extrinsic factors, and a "window of susceptibility" may exist whereby lesions are constantly changing and result in the development of normal articular cartilage. Alternatively, these developmental lesions may not regress, leading to osteochondrosis.[16] It is currently impossible to predict how a lesion may behave while developing; thus treatment recommendations should be reserved until the lesion has been fully developed.

▪ Etiology

The etiology of osteochondrosis is unclear and commonly described as multifactorial. Such factors as nutrition, genetics, growth rate, failure of normal vascularization, altered or excessive biomechanical forces, and hormonal influence have been implicated.

The consistent distribution of lesions at specific anatomic sites within the joint suggests trauma or regional biomechanical forces as causative factors, particularly when the lesions are bilateral or quadrilateral. It has been established in pigs that microtrauma or disruption of the metaphyseal blood vessels supplying the developing cartilage canals causes ischemic necrosis, failure of mineralization, and a retained cartilage plug.[17] The same vascular pattern has been shown to be present in young foals, with the arterial supply crossing the ossification front from metaphyseal blood vessels to nourish the developing cartilage canals.[18-20] Therefore such failure of vascularization, resulting in ischemic necrosis of the cartilage canal and retention of a cartilage plug, appears to play a role in the development of osteochondrosis in swine and horses.[21]

Nutritional influences have been evaluated. Studies have focused on dietary energy levels and mineral composition (copper and zinc). The growth rate of the animal is directly affected by energy intake and use as well as its genetic predisposition. Animals fed high-energy diets resulting in accelerated growth

rates have a much higher incidence of osteochondrosis.[4,22-23] More specifically, foals fed with concentrates had a higher probability of developing OCD lesions, whereas foals not receiving concentrates had a higher probability of healing from existing OCD lesions.[24] In pigs, it was shown that for every 100-g increase in average daily gain during the weaning and finishing period, a 20% increase in cartilage lesions or osteochondrosis in the humeral condyle occurred.[25] This is important when considering ration planning and growth rates of replacement animals, where longevity is a greater concern than in the production animal.

Low copper levels and increased zinc concentrations have both been implicated in the etiology of the disease. Low copper is thought to play a role through lysyl oxidase, a copper-dependent enzyme essential in the crosslinking of collagen molecules. Increased levels of zinc antagonize copper and could work indirectly through a similar mechanism. There is conflicting evidence on the causative nature of low copper levels, and lesions seen in copper-deficient animals do not always mimic those of naturally occurring osteochondrosis. In addition, evidence suggests that neonatal copper levels exert a positive effect on the resolution of osteochondrosis lesions but are not directly involved in the pathogenesis of the disease.[26]

Genetics have been implicated in the etiopathogenesis of osteochondrosis in different species. A recent review article summarized the advancements in quantitative and molecular genetics in refining estimation of genetic parameters and identifying predisposing genetic loci. Whole genome scans were performed in Thoroughbred, Standardbred, French and Norwegian trotter, Hanoverian, and Dutch warmblood populations. Heritabilities were highest for tarsal osteochondrosis in Hanoverian warmbloods and Norwegian trotters, whereas in Thoroughbreds a low genetic variation seemed to be present in similar lesions. Validation studies in Spanish Purebred and Hanoverian warmblood horses corroborated osteochondrosis risk loci on horse chromosomes (ECAs) 3, 14, 27, and 29. A strong association with tarsal OCD was found for a single nucleotide polymorphism on ECA 3.[27] In pigs, Landrace and Yorkshire breeds show a high frequency of osteochondrosis, whereas domestic pigs crossed with wild hogs do not develop the disease.[4]

Numerous hormones (e.g., insulin, somatotropin, thyroxine) are involved in endochondral ossification, and alterations of these, or their derivatives, could theoretically lead to the development of osteochondrosis. The current focus of research has been on the molecular mechanisms involved in the development of

the disease. The mechanisms of normal endochondral ossification are not fully developed, further complicating an understanding of the disease process.

▪ Treatment and Prognosis

Treatment of osteochondrosis should take several factors into account: clinical signs, lesion severity, species, age, intended use, relative value of the animal, and owner expectations. Treatment options include both nonsurgical and surgical management.

Nonsurgical management should consist of rest, controlled exercise, and dietary evaluation.[24] Dietary mineral and carbohydrate levels should be evaluated carefully, and any deficiency or excess should be corrected. Systemic NSAIDs and intraarticular medications like corticosteroids, hyaluronic acid, and polysulfated glycosaminoglycans (GAGs) can be administered, but minimal clinical evidence exists to support their use. In food-producing animals the clinician must take into consideration that these are not approved treatments and that withdrawal times may not be established.

Animals with OCD are frequently treated with arthroscopic surgery. Cases with no radiographic evidence of degenerative joint disease (DJD) before surgery and minimal articular damage at arthroscopy have a favorable prognosis. Animals that show radiographic evidence of DJD before surgery or considerable damage to the articular surfaces at arthroscopy have a less favorable prognosis. There is a site predilection for performance. Lesions in the stifle have a less favorable outcome for full athletic potential than do lesions within the tarsus. In addition, surgeon experience and age of the horse at the time of surgery also affects outcome; more experienced surgeons and older horses demonstrate improved outcomes.[28] Arthroscopic approaches to the joints of cattle have been described, but the procedure is more difficult than in the horse.[9] In selected cases, reattachment of large cartilage flaps with absorbable poly-*p*-dioxanone pins has been described.[29] Dietary evaluation of surgical patients should be included and appropriate adjustments made.

Treatment of subchondral cystic lesions vary. Nonsurgical management should consist of rest, controlled exercise, and intraarticular injection of corticosteroids with or without hyaluronic acid or polysulfated GAGs. The prognosis is variable, and alternate treatments should be considered in refractory cases; these treatments include intralesional deposition of corticosteroids, arthroscopic cystic débridement, and transcystic placement of a cortical bone

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screw.

Arthroscopic-guided injections into the fibrous lining of the cyst have a 67% success rate in horses without preexisting secondary radiographic changes.[30] Arthroscopic débridement and curettage of the cystic lesion have similar success rates, and horses younger than 3 years have a better prognosis. Packing the remaining defect with either a cancellous bone graft covered by a chondrocytic growth factor or various bone substitutes has shown promise, although it is more costly and technically challenging.[29,31] Transcystic screw fixation has shown greater than 80% success rate and gained more recent acceptance as a suitable second-line treatment should intralesional injection of steroid fail.[32] Treatment of osteochondrosis in food animals is generally limited by the economic value of the animal. Show animals or valuable breeding animals may be treated by any of the methods described, and the surgical options may offer a better prognosis than nonsurgical treatment. In production herds, ration evaluation and genetic predisposition may be the most important variables to address.

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Angular Limb Deformities

Jeffrey P. Watkins

▪ Definition, Etiology, and Clinical Signs

Angular limb deformities are deviations in the axis of the forelimbs or hindlimbs in the frontal plane. *Valgus deformity* denotes a lateral deviation of the limb distal to the origin of the deformity; *varus deformity* denotes a medial deviation. The deformity is further described by naming the joint adjacent to the origin of the deformity; for example, *carpus valgus* describes an angular deformity arising in the carpal region, with lateral deviation of the metacarpus (knock-kneed conformation; Fig. 38.1).

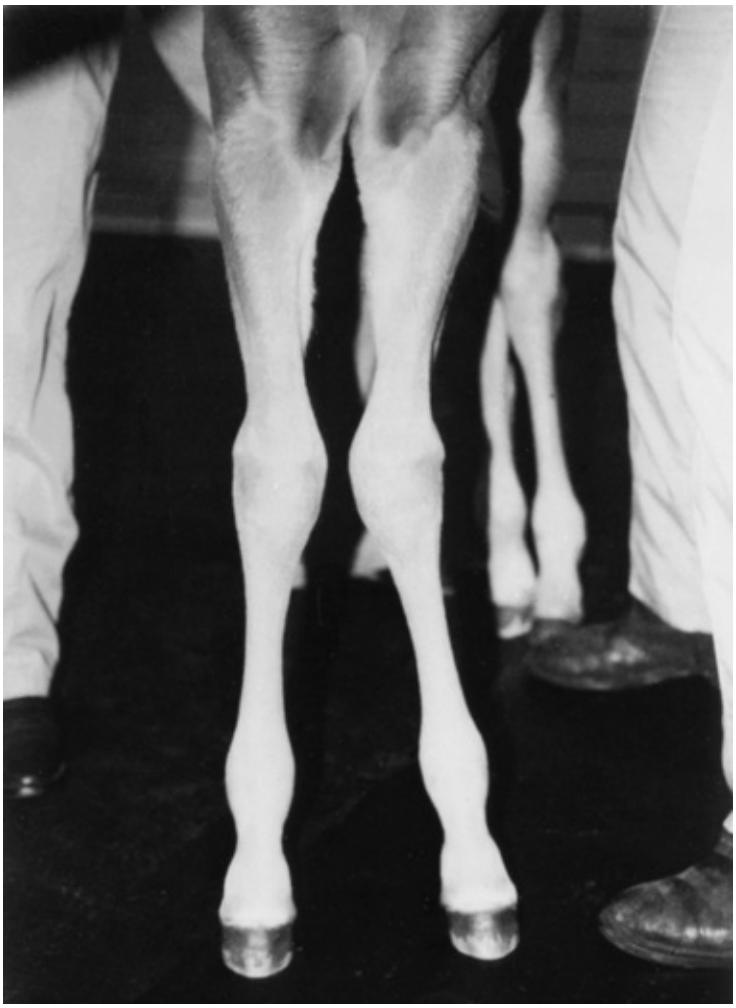


FIG. 38.1 Carpus valgus deviation.

Angular limb deformities may be either congenital or acquired. In general, they are due to laxity of periarticular supporting structures, incomplete ossification, or asynchronous physeal growth. Potential causes include intrauterine malpositioning, relative immaturity, hereditary predisposition, rapid growth, dietary imbalances, osteochondrosis, and trauma.[1-3]

Congenital angular deformities are frequently attributed to intrauterine malpositioning and laxity of periarticular supporting structures. They typically originate in the region of the carpus and tarsus, resulting in bilateral valgus deformity. It is also common to identify a “windswept” foal with valgus deformity of one limb accompanied by varus deformity of the contralateral limb. Acquired angular deformities usually occur secondary to asynchronous growth. In addition, a foal born with incomplete ossification may acquire an angular deformity secondary to crushing of the cartilaginous precursors of the cuboidal

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bones. A hereditary angular limb deformity of Suffolk, Suffolk crossbred, and Hampshire sheep is known as *spider lamb syndrome* (see the Ovine Hereditary Chondrodysplasia [Spider Lamb Syndrome] section later).

▪ Pathophysiology

Incomplete ossification is an important cause of angular deformities originating at the carpus and tarsus. The epiphyses and cuboidal bones of the carpus (ulnar, third, and fourth carpal bones) and tarsus (central and third tarsal bones) are primarily affected.[1] Most ossification of the cartilaginous precursors of these bones occurs in late gestation and is complete by the first month after birth. Prematurity or relative immaturity results in the birth of a foal before these precursors are completely ossified (Figs. 38.2 and 38.3). If laxity of the periarticular supporting structures accompanies incomplete ossification, the deformity is congenital and may worsen progressively with weight bearing as the cartilaginous cuboidal bone precursors become deformed. If laxity is not present, the foal may be born with straight legs and with unrestricted exercise acquire an angular deformity due to deformation of the precursors of the cuboidal bones during weight-bearing activity. Foals that acquire significant deformation of the developing cuboidal bones are likely to develop osteoarthritis early in life and have limited ability to perform athletically as adults.



FIG. 38.2 Premature foal with incomplete ossification of the cuboidal carpal bones, showing marked bilateral carpus valgus.

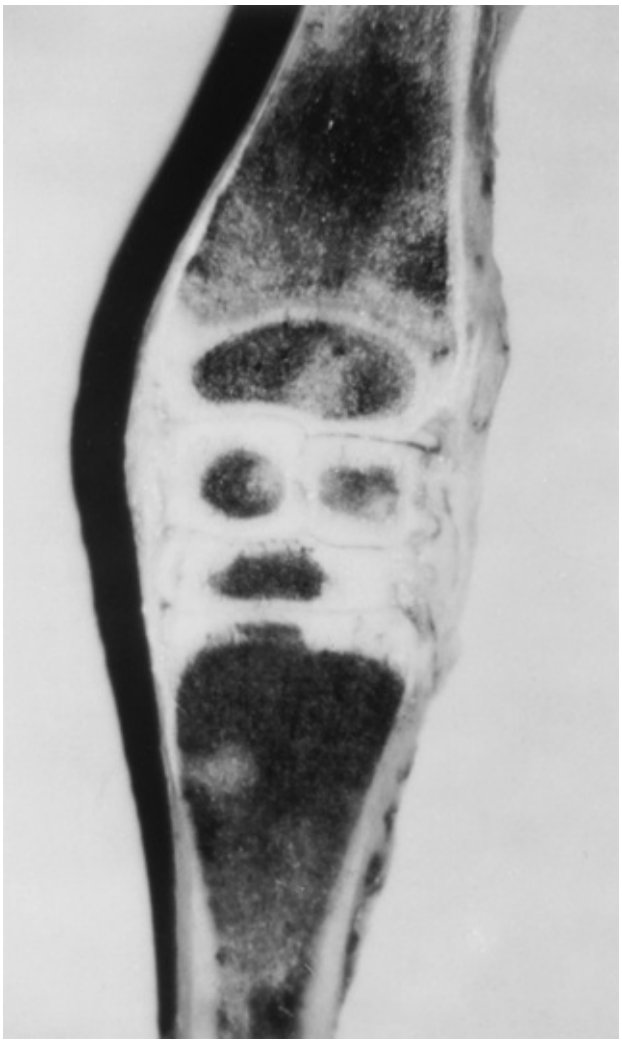


FIG. 38.3 Specimen from a foreleg of the premature foal in Fig. 38.2, cut in the frontal plane. Note the thick cartilage surrounding the centers of ossification of the cuboidal bones of the carpus.

Foals can acquire an angular limb deformity because of asynchronous growth at the metaphyseal and epiphyseal growth cartilages.[2,3] An important cause of asynchronous growth is trauma to a portion of the growth cartilage of the physis.[4] In many foals this trauma is in the form of nonphysiologic compression of the growth cartilage. Excessive exercise in foals with mild angulation and normal activity in foals with moderate to severe preexisting angular deformity may result in sufficient trauma to the growth cartilage to cause progressive deformity.

Asymmetric loading also occurs when severe lameness is present. With the change from a rectangular stance with four weight-bearing limbs to a triangular stance with three weight-bearing limbs, asymmetric, nonphysiologic loading of

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the contralateral support limb occurs, which predisposes it to developing an angular deformity. Chronic excessive loading stretches the periarticular ligamentous support on the lateral aspect of the limb. Combined with compressive forces that are concentrated along the medial aspect of the growth cartilages negatively affecting normal growth at the physis, a varus deformity often develops in the overloaded support limb.

Abnormalities of the growth cartilage that affect ossification (e.g., osteochondrosis) may also be responsible for angular deformities caused by asynchronous growth. Foals with a predisposition for rapid growth or those exposed to nutritional imbalances appear to be at greatest risk for developing the disease. Rapid growth may also result in a foal with a large body size disproportionate to its skeletal structures. This condition may cause increased compressive forces, nonphysiologic loading of the growth cartilages, and angular deformity.[4] Rarely, hypothyroidism in foals, either due to maternal influences related to excessive or inadequate dietary iodine or due to plant toxicity, has been related to delayed ossification of the cuboidal bones.[5] In addition, in the northwestern United States and adjacent area or Canada, hypothyroidism of undetermined cause in foals has been associated with skeletal abnormalities.[6]

Ruminants raised in confinement may experience endochondral dysplasia and angular limb deformities if dietary iron is high or dietary vitamin D is low[7] (rickets). Elevated dietary iron results in elevations in serum phosphorus, which in turn may inhibit 1,25-dihydroxycholecalciferol synthesis by the kidney, resulting in rickets.[5] Pregnancy-associated epiphysitis in primiparous dairy goats[8] can also result in angular limb deformities.

▪ Evaluation and Radiographic Findings

When evaluating a foal with an angular deformity, important historical information includes gestational length, age of the foal, onset and progression of the deformity, and intended use of the foal. The foal should be observed carefully while standing and walking to characterize the degree of deformity and determine the presence of compensatory problems or lameness. Physical examination includes careful palpation of the affected limb and, in neonates, determination of whether the deformity can be corrected by manual manipulation of the limb and whether there is evidence of prematurity or dysmaturity. In neonates, deformities resulting from laxity of periarticular

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supporting structures and incomplete ossification can often be corrected manually. In older foals, if deformities secondary to incomplete ossification have been left untreated and the cuboidal bones are in a collapsed configuration, or if deformities are the result of asynchronous growth, the angulation in the limb cannot be corrected manually.

Visual assessment of the forelimbs and hindlimbs from all angles is necessary, making note of the relative angulation through each joint in the sagittal plane of the evaluated limb. It should be noted that the degree of external rotation of the limb being inspected determines the position where the examiner should make his or her evaluation. In most cases external rotation is present in the limb, which necessitates examining each limb independently from a position that is slightly oblique to the median axis of the body (cranial to caudal, lateral to medial). A normal foal should have alignment of the third metabone with the phalanges, and any deviation should be considered abnormal. There is normally a mild valgus deformity in foals through the carpus and tarsus, which at weaning is in the vicinity of 5 degrees, that usually resolves as they approach their yearling year. In addition to evaluating the angulation of the hindlimb in the sagittal plane, it is important to assess hock angulation in the frontal plane. Sickle-hock conformation can be the result of incomplete ossification with collapse of the central and/or third tarsal bones.

An arthropathy should be suspected if lameness is present. A reduced range of motion and pain on passive flexion of affected joints may also be present. Collapse of incompletely ossified cuboidal bones may cause deformation of articular surfaces resulting in DJD and be manifest by the above findings. When this occurs in the carpus, the prognosis for athletic performance is guarded to poor. If the cuboidal bones of the tarsus are affected, mild collapse may not adversely affect performance, but with significant collapse, degenerative change is likely. A less common cause of lameness in foals with angular limb deformity is osteochondrosis. The prognosis for athletic performance in foals with osteochondrosis-associated angular limb deformities depends on the severity of the osteochondral lesions.

Radiographic evaluation of foals with angular deformity is important. If a diagnosis of incomplete ossification is delayed, irreparable damage may occur. In fact, a strong argument can be made for radiographic evaluation of all foals shortly after birth before uncontrolled exercise is allowed. Radiographic evaluation is mandatory to determine the degree of ossification in premature foals, twins, foals that appear to be relatively immature at birth, and foals born

with angular deformities.

In addition to assessing the maturity of the cuboidal bones, radiographic evaluation allows the examiner to identify the origin of the deformity and determine its severity. Dorsopalmar views for the carpus and fetlock and a lateromedial view of the tarsus are recommended. In the carpus and fetlock, the origin of the deformity may be subjectively determined by two geometric methods (Fig. 38.4). One method is to draw longitudinal lines bisecting the long bones above and below the joint. Where these lines intersect is the *pivot point*, which is considered the origin of the deformity; the angle of incidence of these lines is an estimation of the degree of deformity. Another method is to draw lines through the joints and adjacent physes. These lines should be parallel to each other and perpendicular to the long axis of the long bones proximal and distal to the affected joint. The origin and degree of deformity are estimated by determining where and by what degree these lines deviate from normal. Both asynchronous growth and incomplete ossification can occur concurrently, which is most easily determined with the latter method of geometric evaluation[1] (Fig. 38.5). Geometric examination to determine the degree of deformity in the tarsus is less reliable because the tibia and third metatarsus are not in the same frontal plane. The severity of the angular deformity in this location is best determined by a careful visual assessment.

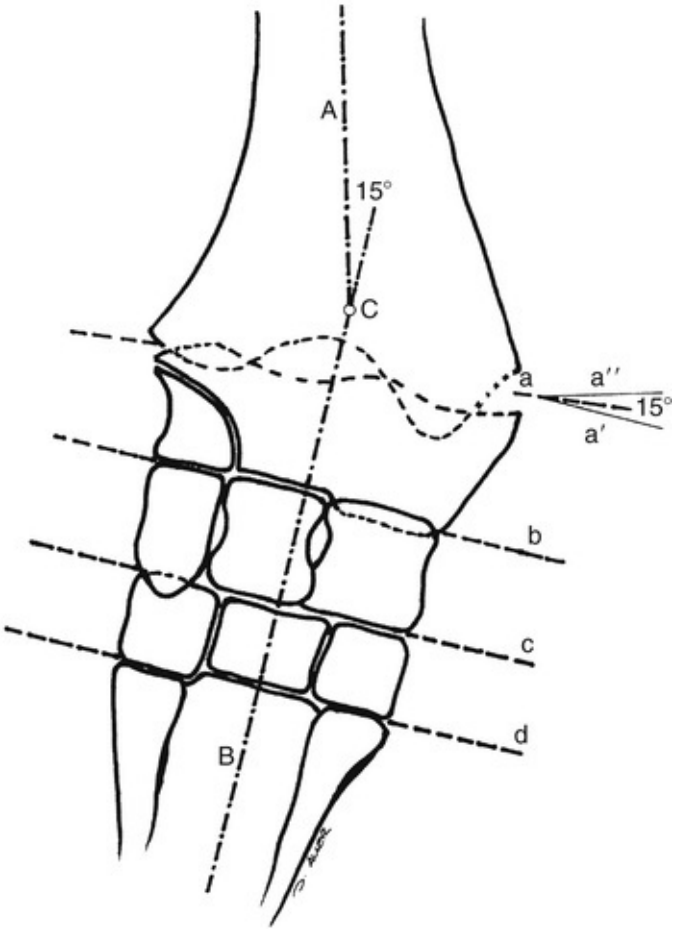


FIG. 38.4 Two methods for geometric evaluation of an angular deformity at the carpus. Lines A and B are drawn through the long axis of the radius and metacarpus, respectively. The angle of incidence is 15 degrees. Lines a, b, c, and d are drawn through the distal radius physis, antebrachiocarpal (radiocarpal), middle, and carpometacarpal joints, respectively. Line a′ is drawn parallel to line b, and line a″ is perpendicular to A. Their angle of incidence is 15 degrees. (Reprinted with permission from *Compend Contin Educ Pract Vet* 4:S330, 1982.)

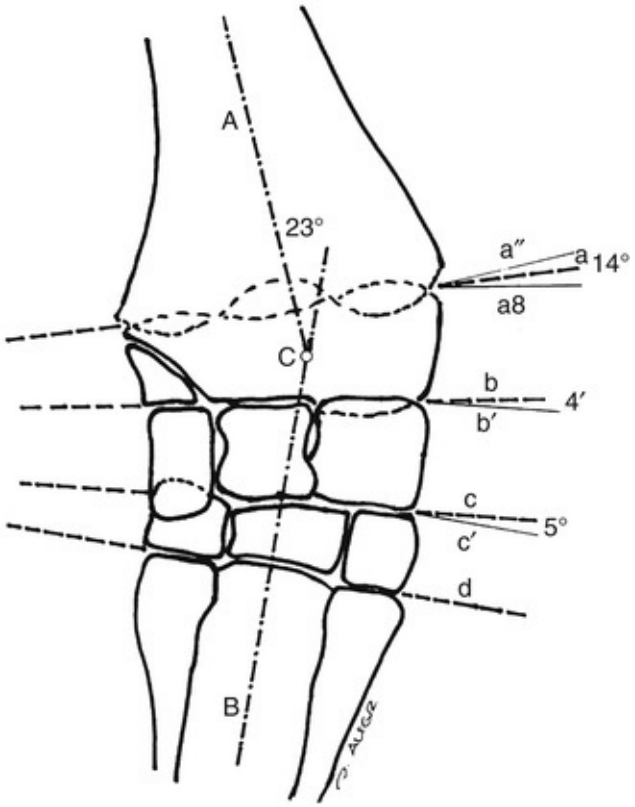


FIG. 38.5 Geometric evaluation of an angular deformity at the carpus caused by a combination of asynchronous growth and incomplete ossification. The pivot point, C, identified by lines A and B, indicates that the origin of the deformity is in the distal radial physis. However, lines a, b, c, and d are not parallel to each other, and lines a, b, and c are not perpendicular to the long axis of the metacarpus and radius. Their orientation indicates that the deformity is in the distal radial physis and the cuboidal bones as well. Note that the sum of angles a-a′, b-b′, and c-c′ equals the angle of incidence of lines A and B. (Reprinted with permission from *Compend Contin Educ Pract Vet* 4:S330, 1982.)

Radiographic findings in foals with incomplete ossification vary depending on the degree of mineralization of the precursor cuboid bones and amount of malformation that has occurred subsequent to birth. In severe cases, there may be only small, centrally located centers of ossification surrounded by radiolucent precursor cartilage (which will undergo endochondral ossification as maturity progresses). More commonly, affected cuboidal bones have a rounded contour instead of their normal angular appearance. The width of the radiolucent precursor cartilage is increased, appearing radiographically as an increase in the width of the joint space (Fig. 38.6). As ossification progresses, the bones may develop a normal anatomic shape or appear wedge shaped or crushed because of deformation of the cartilage secondary to weight bearing prior to ossifying. This

phenomenon often is noted in the ulnar, fourth, and intermediate facet of the third carpal bones in the forelimb and the central and third tarsal bones in the hindlimb. In severe cases the affected bones may be grossly deformed and, particularly in the tarsus, appear to be partially extruded from the joint (Fig. 38.7). In the tarsus, lateromedial radiographs are used to determine whether ossification is complete and malformation is present (Fig. 38.8).



FIG. 38.6 Dorsopalmar radiograph of a foal with mild incomplete

ossification of the cuboidal carpal bones. Note the difference in width of the medial aspect *(a)* and the lateral aspect *(b)* of the third carpal bone. Normally, width *a* should be approximately three-fourths the width of *b*. Also note the appearance of an increase in the width of the joint space *(c)* as a result of incompletely ossified joint cartilage.



FIG. 38.7 Dorsopalmar radiograph of a foal with incomplete ossification that was not externally supported. Severe deformation and collapse of the fourth and third carpal and proximal fourth metacarpal bones have occurred.



FIG. 38.8 Lateromedial radiograph of a tarsus from a foal with incomplete ossification. Note the lack of an angular appearance of the central tarsal bone and incomplete ossification of the third tarsal bone.

Radiographic evaluation of foals with angular deformity caused by asynchronous growth may show wedging of the epiphysis (Fig. 38.9), widening of the physis, and sclerosis adjacent to the physis. Geometric evaluation places the deviation in the metaphysis or the epiphysis of the long bone proximal to the affected joint. The joints are parallel to each other and perpendicular to the longitudinal axis of the adjacent long bones.



FIG. 38.9 Dorsopalmar radiograph of a foal with angular deformity caused by wedging in the distal radial epiphysis, the result of asynchronous growth of the epiphysis growth cartilage.

▪ Treatment and Prognosis

Neonatal foals with an angular deformity should be confined to a stall until clinical and radiographic examinations are completed. If the deformity is 10 degrees or less and radiographs reveal normal ossification, stall confinement with periods of controlled exercise is recommended. This regimen promotes continued development of the supporting structures while minimizing trauma to growth cartilages that could result if the foal were allowed uncontrolled exercise. Foals that have angular deformity severe enough to cause the hoof to break over the lateral (varus deformity) or medial (valgus deformity) wall will benefit from

the application of a hoof plate. The hoof plate is intended to extend the solar surface of the hoof to counteract the forces resulting in the abnormal breakover.

Foals with a congenital angular deformity of more than 10 degrees that can be manually corrected should be considered candidates for external support, especially if incomplete ossification is present. Patients with incomplete ossification accompanied by angular deformity that is not supported in axial alignment will often deform the cartilaginous cuboidal bone precursors with continued weight bearing. Subsequent ossification results in permanent deformity of the affected bones (see Fig. 38.7) and is often associated with end-stage osteoarthritis.

Methods of externally supporting the carpus and tarsus vary from tube casts or rigid splints to custom-made orthotic devices. Tube casts have been recommended and used successfully,[1-3] and although they provide the rigid external support necessary to maintain axial alignment while ossification progresses, several potential complications are associated with their use. The most serious is the potential for coxofemoral luxation when tube casts are used on the hindlimbs. In addition, foal skin is easily traumatized by a poorly fitting cast, and deep ulcerations may occur. Other considerations include the cost of materials and the need for constant monitoring to detect signs of a poorly fitting cast. Monitoring the status of a cast requires daily evaluation by a trained individual, and owners are seldom capable or willing to take on this responsibility; hospitalization is recommended. Rigid splints, usually fashioned from cut sections of polyvinyl chloride (PVC) pipe, are an alternative method of support. The leg is protected with a well-padded support bandage, and the splint is applied with nonelastic tape while the limb is held in alignment by an assistant. These splint bandages are changed frequently, as pressure sores beneath the splint bandage are a concern and are difficult to prevent. A splint for the tarsus may be fashioned from synthetic casting material molded lengthwise over the cranial aspect of a padded bandage centered at the joint. Once the material has dried, the splint is taped to the dorsal surface of the bandage. Alternatively, a PVC splint can be heated and bent to the desired angulation.

Regardless of the means of external support used for the carpus or tarsus, it should not extend beyond the distal metabone. Continued weight bearing by the suspensory apparatus of the fetlock helps prevent the development of fetlock hyperextension after removal of the external support. A degree of carpal hyperextension is usually present immediately after removal of external support from the forelimb, and exercise should be controlled until the tendons and

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periarticular supporting structures regain their normal tone.

Foals with an angular deformity resulting from asynchronous growth should have their exercise limited to minimize the magnitude of asymmetric loading at the growth cartilages and to encourage spontaneous correction. In these cases, reducing the magnitude of the forces acting asymmetrically at the growth cartilage should encourage compensatory growth to occur and correct the deformity. Additional therapy consists of corrective hoof trimming. Because foals with valgus deformity typically have a toe-out conformation, emphasis in the past has been to lower the lateral hoof wall of the affected limb. If this mode of therapy is vigorously pursued, compensatory varus deformity may develop in the fetlock region. This form of corrective trimming concentrates forces asymmetrically on the medial aspect of the distal metacarpal and proximal phalangeal growth cartilages. Currently, trimming the hoof level and squaring the toe to promote breakover at the toe are recommended.

Foals with angular limb deformities that fail to respond to conservative methods are candidates for surgical intervention. Animals with angular deformities arising distal to the physis were not considered candidates for surgical therapy in the past, but it has been shown that they can respond favorably to surgery.[9,10]

The decision for surgery should consider the area affected (fetlock, carpus, and/or tarsus) amount of correction required (degree of deformity), and age of the foal. In general, the more severe the deformity, the earlier the surgical intervention should be. Timing of surgery should consider the periods of rapid and predictable growth at the physis. The most rapid and predictable rate of growth occurs from birth to 10 weeks of age.[11] In the distal radius, continuous but declining growth occurs until 60 weeks of age. In the distal third metacarpal and metatarsal bones, growth rate slows dramatically by 10 weeks of age and is minimal thereafter. For these reasons, it is important to be more proactive and intervene at an early age when deformities are present in the fetlock region since there is limited time for conservative therapy to effect correction. However, there is more opportunity for correction to occur spontaneously in the carpal and tarsal region; therefore surgical intervention can be delayed in mild to moderate deformities.

Surgical manipulation of physeal growth is intended to asymmetrically alter the elongation occurring at the physis, thereby realigning the axis of the limb. Growth at the physis can be altered surgically in one of two ways: retardation or acceleration. Growth retardation is accomplished by bridging the physis with

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metallic implants. When applied to the convex side of the affected physis, growth is disallowed on the long side of the bone while continued growth on the opposite side of the bone brings the limb into alignment. As long as the implants are in place, the effect continues and is limited only by the amount of growth remaining at the physis. If the physis is still active once the limb is aligned, it is extremely important that the implants be removed, or overcorrection will occur. Techniques of transphyseal bridging include stapling, screw and wire implants, use of a small bone plate, and more recently a single transphyseal screw. Indications for transphyseal bridging include deformities that have a limited window of opportunity to correct (e.g., moderate to severe deformity in the fetlock region), those presenting after the period of rapid and reliable physeal growth, severe angulations, and based on the author's experience, deformities of the carpus and tarsus resulting from cuboidal bone malformations.

The second surgical approach to altering physeal growth, periosteal transection and elevation (stripping), is intended to accelerate growth on the concave side of the bone.[12] Reported advantages include rapid correction without the potential for overcorrection.[9,12] Because periosteal transection does not require implants, the likelihood of infection and excessive fibrosis is reduced. Implant failure is not a consideration, and a second surgery for implant removal is unnecessary. The procedure does not require specialized equipment and is technically easy to perform. In one series of foals, correction of the deformity occurred in 22 of 25 limbs treated with periosteal transection.[12] In a second series of 23 foals, 83% had straight limbs and were sound for their intended use at long-term follow-up.[9] The success rate was not affected by the origin of the deformity, degree of deviation, or presence of mild to moderate morphologic changes in the involved bones.[12] There are reports that question the efficacy of this procedure, particularly for treating carpus valgus deformities.[13,14]

Indications include mild to moderate deformities present during the rapid, reliable growth at the involved physis. Furthermore, it should be reserved for deformities in locations that will allow ample time for a second procedure to be performed if the initial treatment is not effective. The periosteum will reestablish itself, so the surgical effect is short-lived, and if correction is not adequate within 4 to 6 weeks, additional therapy is indicated.

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Ovine Hereditary Chondrodysplasia (Spider Lamb Syndrome)

Juan E. Romano, Sr.

Ovine hereditary chondrodysplasia, also known as *spider lamb syndrome* (SLS), is an inherited, semilethal musculoskeletal disease primarily affecting lambs of Suffolk or Hampshire breeding. The clinical signs are characterized by deformities affecting the appendicular and axial bones, with elongated extremities, scoliosis, abnormal rib, and sternum concavities.[1] Other signs include extreme height, fineness of bones, Roman nose with facial deformities, lack of body fat, and scarcity of muscling. At present, it is the most common inheritable skeletal disorder in sheep.[2] Males and females are affected equally[3] and called *spider lambs*, *spiders*, *monkey lambs*, and *crooked-legged or corkscrew lambs*.[4] The disease was first described in 1980 in the United States in the Suffolk breed[5,6] and then in the Hampshire breed. The disorder was also reported in Shropshire, Texel, Southdown, Oxford,[7] and Kermanian breeds.[8] It has now been disseminated into several sheep breeds that used Suffolk for breeding purposes and has propagated worldwide in the United States and Canada,[7] Australia,[9] New Zealand,[10] Brazil,[11] Germany,[11] and Iran.[8] The frequency of this disorder was reported to be 4% in Germany by detecting the mutation using blood samples.[12]

▪ Transmission

Pedigree analyses and breeding studies have established that the gene responsible for this disease has a simple autosomal recessive mode of inheritance.[13-16] The breeding of carrier animals will produce 25% of offspring with the genetic disorder.[15,16] The breeding of a spider ram in a population of carrier females produces 50% of offspring with spider lamb syndrome.[6,14] The breeding of a carrier ram with his daughters also produced offspring with this disorder. The transfer of embryos produced between a spider ram and spider donor females to normal recipient ewes resulted in all offspring with spider syndrome.[17]

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▪ Etiology

Genetic linkage between SLS and several microsatellite markers have been detected. Mapping the SLS locus was suggested to be the telomeric end of ovine chromosome 6.[7] The causative mutation was identified after positional cloning of the ovine fibroblast growth factor receptor 3 (FGFR3).[7,18] A transversion at nucleotide position 69 of ovine FGFR3 exon 17 causes a nonconservative amino substitution of nonpolar valine (V) to charge glutamate (E) at residue 700 in the second tyrosine kinase domain of the receptor. The mutation leads to loss of receptor function in homozygotes. FGFR3 acts as a negative bone growth regulator by restricting chondrocyte proliferation and endochondral bone elongation.[18,19] Heterozygous (Ss) animals are phenotypically indistinguishable from unaffected, normal (SS) animals. The genotypes of presumed heterozygous carriers of SLS are detectable only after test-mating of suspect animals to proven heterozygous carriers with subsequent evaluation of all resulting progeny or by using blood or hair follicles to detect the mutation in FGFR3.

▪ Clinical Signs

Clinical presentation of the syndrome is also highly variable, with some lambs severely affected at birth and others developing the condition in the first 6 weeks after lambing.[1] External symptoms characteristic of the disease include extreme height, fineness of bones, and lack of muscling and angular deformities of the limbs (Fig. 38.10) along with kyphoscoliosis. Affected lambs tend to be thin and arthritic, with poor muscling and insufficient weight gain. The affected individuals rarely survive and are an economic liability in market lamb production.



FIG. 38.10 Twin Suffolk lambs (12 weeks old), with normal lamb (78 lb) at left and lamb with spider lamb syndrome (37 lb) at right. Note extreme height, narrow chest, scoliosis, kyphosis, and facial deformity of the affected lamb.

The abnormalities are most frequent in the forelimb (81% to 87%), hindlimb (63% to 69%), spine (52% to 62%), and skull (19% to 35%).[20] No differences between Suffolk and Hampshire lambs were detected in the type, extent, or incidence of lesions.[20] The forelimbs and hindlimbs were characterized by mild to severe carpus (Fig. 38.11) and tarsus valgus, respectively. The most common spine abnormality was kyphoscoliosis. SLS was observed in aborted fetuses, stillborns, viable neonates, and young lambs less than 6 weeks of age.[20]



FIG. 38.11 Rotation and deviation of front legs (carpus valgus) characteristic of spider lamb syndrome in a 16-week-old Suffolk lamb.

Detection of this abnormality during pregnancy by either radiography or transabdominal ultrasonography even at the second or third tiers was not possible.[17] Diagnosis was possible only by direct examination of the fetus.[17]

▪ Laboratory Analyses

No differences in hematologic and biochemical analyses between chondrodysplastic lambs and normal flockmates were detected. Serum levels of vitamins A and E and liver levels for selenium and vitamin E were within normal parameters.[4] Trace elements in serum for iron, magnesium, zinc, and copper were no different compared with normal lambs.[4] Serum alkaline phosphatase activity has been reported either high or low in affected lambs compared with healthy lambs.[1] The only difference was a trend in a high level of skeletal muscle enzymes in serum.[4]

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Some data suggest that the regulation of insulin-like growth factor 1 (IGF-1) and IGF-binding proteins may be involved in this disorder. SLS lambs between 50 and 80 days of age showed a significant decrease in serum level of IGF-1 levels and an increase in IGF-binding proteins compared with a control group of lambs of the same age.[21]

No differences in the number of morphologic features of the chromosome were detected, and there was no evidence of deletions, duplications, translocations, or inversions when lymphocytes from clinically normal lambs and lambs affected with ovine hereditary chondrodysplasia were cultured, G-banded, and karyotyped.[22]

▪ Necropsy

The primary lesions affect the musculokeletal system. The gross lesions observed were similar to the changes noted radiographically. Lesions were observed in the skull, sternebrae, atlas, elbows, other vertebrae, and physes of the long bones, as well as other areas. The lesion noted in all locations was an excess of cartilage.[4] Marked muscle atrophy was also present. The principal lesions in bones are an increase in the width of the zone of proliferation and hypertrophy and an unevenness of the growth cartilage. A cartilage column disorder, with failure to form or maintain orderly columns of chondrocytes, is characteristic.[1] The chondrocytes and cartilage matrix appear histochemically normal and have proper ultrastructure.[23]

▪ Radiography

Chondrodysplastic lambs have characteristic radiographic patterns in the elbow, sternum, shoulder, and spine, with multiple irregular islands of ossification.[1] Radiography may be the technique of choice for identifying affected lambs prior to detecting clinical signs or when in doubt.[24] A flexed lateral radiograph of the elbow of a suspect lamb appears to be diagnostically reliable when there is a suspicion of the syndrome (Fig. 38.12).[1]



FIG. 38.12 Lateral radiograph of the front leg of a lamb with spider lamb syndrome. Note thick growth plates and multiple ossification centers near the olecranon and distal humerus.

▪ Control

The mode of inheritance for SLS is autosomal recessive, making the identification and culling of carrier (heterozygous) animals difficult due to their normal phenotype. Eliminating these heterozygous animals from affected sheep flock is possible by identifying individuals that are carriers of the mutation. This can be done by collecting peripheral blood or hair follicles and performing polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) analysis. The best approach is to perform this test in males, but depending on the objectives of the program, the test also can be run in females. Genetic testing using blood and then PCR-RFLP permits a quick and accurate detection of heterozygotes. The presence of a lamb spider is an indication that both parents are heterozygous for the disorder, so no test is required. Since the introduction of this test in 2000, a significant reduction in the incidence of

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heterozygous animals in New Zealand and the United States has been reported.[25,26]

Another possibility is to run breeding tests, which is time consuming and costly and requires adequate numbers of breeding animals to be accurate. In addition, correct identification of the animals is paramount. A ram can be progeny tested by breeding females that produced spider lambs or his own daughters. The number required to be highly accurate is 16 normal offspring from mating with a known carrier's ewes or 32 normal lambs from breeding with his own daughters. However, with these numbers the probability that the ram is a carrier is 1% or less of the cases.[27]

▪ Differential Diagnosis

A complete clinical history and physical examination as well as radiologic and pathologic examinations are essential to the diagnosis of this disease. Some of the lesions seen in spider syndrome require differentiation from abnormalities produced by viruses, chemicals, toxic plants, and nutritional factors. Infection with bluetongue and Akabane virus may result in arthrogryposis and hydranencephaly. Border disease can cause abnormalities of the nervous system, skin, fleece, and skeleton. Cache Valley virus and bluetongue can also produce these kinds of anomalies.[28] Benzimidazoles, antiparasitic drugs, have been implicated as a cause of skeletal deformities when used in pregnant ewes during specific periods.[29] Toxic plants such as locoweeds are known to cause limb deformities in utero.[30] Deficiency of vitamin D or phosphorus can cause skeletal deformities or rickets.[31] Deficiency of either zinc or manganese during gestation could lead to chondrodysplasia.[32]

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Septic (Infectious) Arthritis and Osteomyelitis

Joanne Hardy

▪ Incidence and Risk Factors

Septic arthritis can result from extension of a periarticular wound infection, traumatic inoculation, iatrogenic inoculation, or hematogenous inoculation. The hematogenous route is the most common avenue of inoculation of organisms in a joint in foals, and bacteremia and septicemia are the most important risk factors for septic arthritis in foals. In one study, septicemia was the most common cause of death (30%) in foals younger than 7 days of age; septic arthritis was identified as the cause of death in 12.5% of foals ages 8 to 31 days.[1] In adults, articular wounds are reported to be the most common cause of joint infection, followed closely by iatrogenic intraarticular injection; postsurgical infection and idiopathic (unidentified cause) infection are also reported in association with septic arthritis in adult horses.[2-4] Although uncommon, hematogenous spread from a distant focus is possible in adult horses.[5]

Establishment of infection depends on several factors, including size of inoculum, host defense, virulence of the organisms, and local joint factors. In foals, host defense is mainly associated with passively acquired immunity. Failure of transfer of passive immunity (FTPI) is the greatest risk factor for development of septicemia in foals.[6] The incidence of disease resulting from FTPI has been reported to be as high as 78%. Organism virulence is related to the ability to establish infection. Attachment factors, ability to resist phagocytosis, and resistance to cell killing all contribute to the establishment of infection. Local joint factors that may predispose to establishing or maintaining infection include low blood flow, particularly in end-capillary loops, and poor blood supply, more prominent in bone. In adults, certain intraarticular medications (e.g., corticosteroids, hyaluronate, polysulfated GAGs) have been associated with a higher risk for septic arthritis, potentially by decreasing articular defense.[7,8]

In calves, septic arthritis is associated with FTPI and septicemia and with feeding of mastitic milk *(Mycoplasma)*.[9,10] In older cattle, direct spread from a

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perisynovitis is the most common cause, and the distal interphalangeal joint (DIJ) is most often involved.

▪ Pathogenesis

Articular blood supply is provided through a main arteriole that branches to the synovial membrane and epiphysis. Blood supply to the metaphysis is provided by the nutrient artery, but in young foals transphyseal vessels exist that connect the metaphyseal and epiphyseal blood supply.[11] Experimental intravenous (IV) injection of bacteria results in rapid inoculation of articular and periarticular capillaries. Five types of hematogenous articular infection have been described: *type S* (synovial), where a septic arthritis results from inoculation of the synovial membrane; *type E* (epiphysis), where subchondral bone infection is present (Fig. 38.13); *type P* (physis), where infection of the physis occurs on the metaphyseal side of the growth plate (Fig. 38.14); *type T,* observed in premature foals, with infection of the small tarsal or carpal bones (Fig. 38.15); and *type I,* where joint invasion occurs after a periarticular soft tissue abscess (Fig. 38.16).[12] In young foals, functional transphyseal vessels allow communication of the metaphysis and epiphysis, such that bacteria localize preferentially in the synovial membrane and subchondral bone. Thus young foals predominantly have infectious arthritis types S and E. Closure of transphyseal vessels occurs after about 7 to 10 days of age, such that localization of infection to the metaphyseal vessel loops occurs in older foals.[11] Although bone inoculation can occur simultaneously with synovial inoculation in young foals, determination of bone involvement can be delayed until radiographs identify the lesions. In foals the hock, carpus, and stifle are frequently involved in hematogenous joint infection, but it is important to remember that any joints, including those of the vertebral column, can be affected. In young foals, *Actinobacillus equuli*, *Salmonella* spp., *Escherichia coli,* and other Enterobacteriaceae are often involved; in older foals, *Streptococcus* spp. and *Rhodococcus equi* are common isolates. In foals with type P (physeal) involvement, *Salmonella* and *Rhodococcus* spp. are typically involved.



FIG. 38.13 Radiograph of a foal with type E septic arthritis, showing involvement of the distal femoral epiphysis *(arrows).*

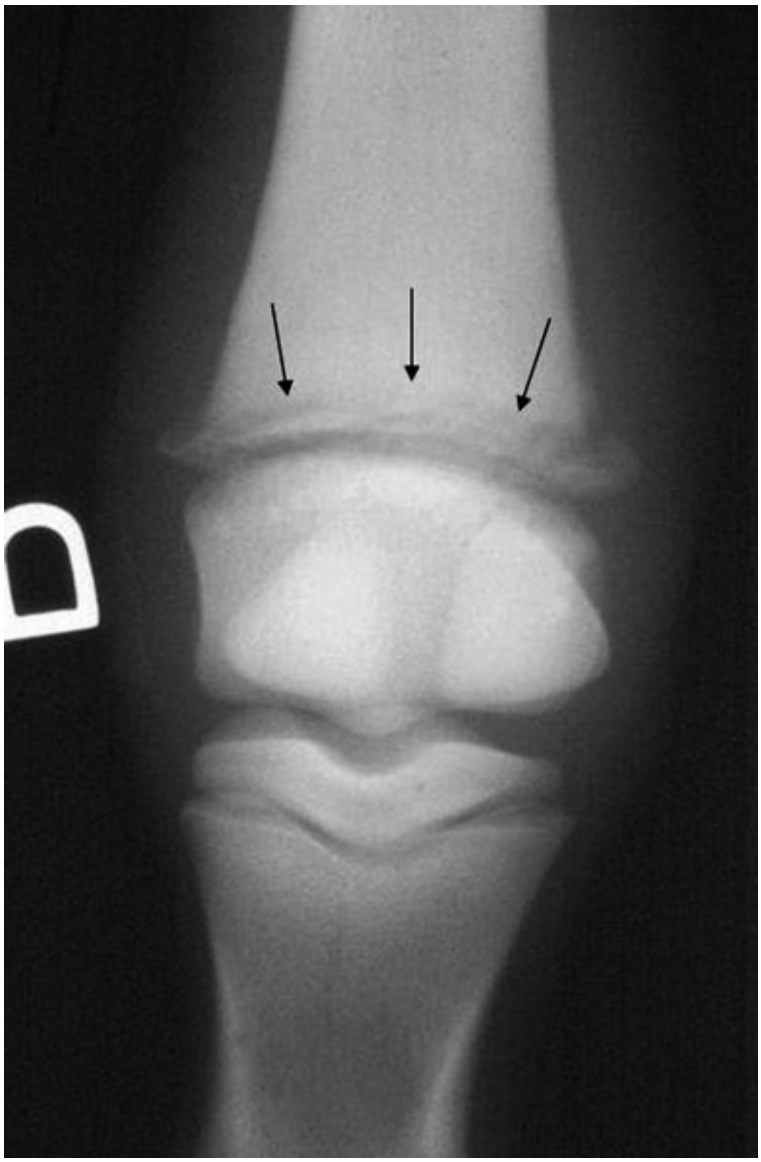


FIG. 38.14 Radiograph of a foal with type P septic arthritis, showing involvement of the distal metacarpal physis *(arrows)*.



FIG. 38.15 Radiograph of the tarsus of a premature foal with type T septic arthritis, showing involvement of the distal tarsal bones *(arrows).*



FIG. 38.16 Photograph of a foal with type I septic arthritis where a soft tissue abscess *(arrow)* dissected down into the coxofemoral joint.

In adults, inoculation of the joint from an articular wound is the most common cause of joint sepsis. The establishment of infection will depend on size of the inoculum, pathogenicity of the bacteria, and duration before treatment. In one study, 53% of horses examined within 24 hours of an open joint wound developed septic arthritis, versus 92% of horses examined within 2 to 7 days of injury and 100% of horses examined after 7 days.[13] However, two studies failed to find a relationship between interval before admission and outcome.[14,15] This suggests that many other factors influence the prognosis following joint infection. Joints of the lower limb (fetlock, coffin joint) are often involved in open joint injuries because of the poor tissue coverage in those areas.[3,16] Organisms frequently encountered in open joint wounds include Enterobacteriaceae, streptococci, and staphylococci.[3,16] These injuries are also likely to have multiple bacterial infections. Wounds near the hoof are more likely to have anaerobic infection, and *Clostridium* is the most common isolate. Fungal organisms are a rare cause of septic arthritis in horses but should be considered if isolated in pure culture more than once.[5]

Iatrogenic joint injection is the second most common cause of septic arthritis in adults, followed by postoperative infection. The tarsus is the joint most often involved in septic arthritis after joint injection, whereas the carpus is the most

common joint involved after surgery.[2,3] Staphylococci, particularly *Staphylococcus aureus*, are the most common organism isolated after iatrogenic joint injections or surgery. When *S. aureus* is isolated from a joint infection, care should be taken to determine the possibility of methicillin resistance.[17,18] The risk of septic arthritis after arthroscopic surgery is low, seen in only 8 of 627 joints (1.3%) in one study.[19] Interestingly, in these horses clinical signs did not develop until several days after discharge.

In calves, the most common isolates are *Streptococcus* spp. and *Mycoplasma bovis*.[20] In adult cattle, common pathogens involved in septic arthritis include *Mycoplasma bovigenitalium*, *Mycoplasma mycoides*, *Brucella* spp., and *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), which is most often involved.[21] In sheep, goats, and calves, *Chlamydia psittaci* polyarthritis can occur as an endemic or epidemic disease and may be accompanied by keratoconjunctivitis.[22,23] In lambs, *Erysipelothrix rhusiopathiae* is also a cause of polyarthritis, gaining systemic entrance through the stump of docked tails or a castration site. Improving hygiene during these procedures helps prevent the disease.[22] In sheep and cattle, the obligate intracellular organism *Chlamydia pecorum* has received increased recognition.[24] Involvement of this organism is thought to be underrecognized because diagnosis is based on serology and histopathology, which are not necessarily diagnostic methods used in the early stages of the disease.

▪ Diagnosis

Septic arthritis, osteomyelitis, or physitis should be ruled out in any lame foal. Foals with septicemia are at high risk of developing septic arthritis, which generally is noted clinically hours to days after the initial signs of septicemia. Although owners often complain of external trauma, septic arthritis is the most common cause of lameness in foals. In young foals with types S and E arthritis, inoculation of the synovial membrane is the first event, which the astute clinician can identify as periarticular edema. Joint effusion rapidly follows. Involvement of multiple joints is common, and identification of all affected joints is essential for successful management. Because effusion of the shoulder, elbow, or hip joints is more difficult to detect by palpation, arthrocentesis of these joints should be performed in foals with an unidentified lameness. In the stifle, femoropatellar joint involvement results in marked effusion, but femorotibial joint effusion is usually more difficult to discern. Because of the

usual communication between the femoropatellar and the medial femorotibial joint, both are typically involved concurrently. Lateral femorotibial infection is more subtle and can occur separately. Distention of the long extensor pouch is often present in lateral femorotibial infection and suggests involvement of that joint. In foals older than 7 days, physeal infection may be observed. With physeal infection, presence of concurrent synovial effusion depends on the intraarticular or extraarticular localization of the growth plate. For example, distal metacarpal physeal infection results in periphyseal edema, initially without joint effusion. The infection can break through the skin rather than involve the joint. In foals with septic arthritis, the CBC is consistent with an inflammatory response and includes a neutrophilic leukocytosis and hyperfibrinogenemia. In one study in foals, a plasma fibrinogen concentration of 900 mg/dL or higher (as measured by the heat precipitation method) was useful as an indicator of physeal or epiphyseal osteomyelitis, with positive and negative predictive values of 84.2% and 98.2%, respectively.[25]

Adult horses usually show minimal changes on the CBC and little change in systemic signs, so development of or increasing lameness after a wound, joint injection, or surgery indicates the need for further examination. In one study, the mean and median times for readmission for septic arthritis after an elective arthroscopic procedure were 47 and 20 days, respectively.[19] In that study, the authors speculated that the delay in onset of septic arthritis following surgery was an indication that joint inoculation occurred in the postoperative period rather than intraoperatively, supporting careful joint closure and continued aseptic technique when changing bandages in these horses.[19] Because of their potent antiinflammatory properties, corticosteroids may delay the onset of clinical signs of septic arthritis after joint injection. In one study of experimentally induced septic arthritis, changes in synovial fluid were present before the onset of clinical signs, and clinical signs of lameness were delayed for 3 days in these horses.[26]

Arthrocentesis is the mainstay of diagnosis of septic arthritis.[26] Table 38.1 lists the characteristics of synovial fluid according to conditions in large animals. A high protein concentration (>2.5 g/dL) and high white blood cell (WBC [leukocyte]) count are observed. Classic counts diagnostic for septic arthritis in foals exceed 30,000 cells/µL, with more than 80% neutrophils; cell counts above 10,000/µL may indicate early infection. Neutrophils are not always degenerate. Gram stain is a useful diagnostic tool because it may identify the etiologic agent

in up to 25% of cases in which culture results are negative.[27] In foals with a separate physeal infection where the physis is extraarticular, sympathetic joint inflammation and effusion can occur.[28] This manifests as a moderate increase in WBC count, with less than 90% neutrophils. The presence of such cytologic findings should alert the clinician and practitioner to the presence of physeal sepsis. Several studies have examined the usefulness of synovial fluid markers to predict joint sepsis. In one study, synovial fluid D-dimer concentration was markedly increased in septic joints, and this was not influenced by the presence of septicemia.[29] However, inclusion criteria for the study included the presence of a synovial fluid analysis consistent with sepsis, so it is not known whether D-dimer concentration would be a useful marker earlier in the disease process or when results of synovial fluid analysis are equivocal. In another study, synovial fluid equine myeloperoxidase (MPO) activity was compared in different forms of joint disease. In cases of septic arthritis, MPO activity in synovial fluid was significantly increased compared to control. Although the study concluded that synovial fluid MPO may be useful as a marker of septic arthritis in horses, further studies are needed because horses were included in the study when they already had synovial fluid analysis indicative of septic arthritis.[30] Serum amyloid A (SAA) is an acute-phase protein that is markedly increased (>1000 mg/dL) in horses with septic arthritis.[31] Interestingly, SAA concentration was not increased in synovial fluid collected after repeated intraarticular injections of amikacin in healthy horses.[32] Intraarticular injection of various substances such as antibiotics, saline, or therapeutic agents often cause a transient inflammatory reaction where total protein and nuclear cell counts are consistent with sepsis.[33] The use of SAA to differentiate inflammation from infection warrants further study. Increased lactate concentration has recently been measured and used as a rapid test for identification of septic arthritis, but the sensitivity and specificity of this measurement are currently unknown.

TABLE 38.1

Characteristics of Synovial Fluid According to Condition in Large Animal

Characteristic	Normal	Septic	Degenerative Joint Disease	Inflammatory[a]
Color	Clear	Yellow/green, serosanguineous	Yellow	Yellow to iridescent

Clarity	Transparent	Turbid	Transparent	Translucent
Fluid volume	Low	Increased[b]	Low	Increased
Viscosity	High	Low	Variable	Low (usually)
WBCs/μL	<500	>30,000	<5000	2000-10,000
PMNs (%)	<25	>75	25	>75
Total protein (g/dL)	<1	>2.5	<1	>1
Glucose	Equal to blood	<25 mg/dL	Equal to blood	25-50 mg/dL lower than blood
Gram or other stain	No bacteria seen	Bacteria may be seen	No bacteria seen	No bacteria seen

[a]May include low-grade sepsis in which bacteria are not found.

[b]Unless there is an open joint injury, in which fluid may be difficult to obtain.

PMNs, Polymorphonuclear leukocyte neutrophils; *WBCs,* white blood cells.

In adult horses with a wound localized near a synovial structure, it is crucial to identify as early as possible whether there is synovial involvement. The most convincing evidence is demonstration of synovial communication with a wound by injecting a sterile solution into the synovial structure and observing fluid exiting the wound. For this purpose, a site remote from the wound and covered with normal skin should be prepared aseptically, and depending on the structure involved, 20 to 200 mL of a sterile solution (e.g., saline, balanced electrolyte) is injected after collecting synovial fluid samples using aseptic technique.[34] If synovial involvement is detected, therapy is immediately instituted.

Radiographs of all affected joints are essential. The presence of osteomyelitis may affect prognosis and dictate prolonged antibiotic therapy. Radiographs should be repeated weekly until clinical signs resolve themselves or at any time there is deterioration in the clinical condition. Radiographs are also indicated whenever a change in therapy is planned (e.g., from IV to oral antibiotics).

Nuclear scintigraphy has been used to diagnose infectious foci in odd localizations in foals. For example, vertebral and atlantooccipital involvements have been diagnosed using this imaging modality. It must be remembered that local bone infarcts, which are often present in osteomyelitis, will result in areas of decreased rather than increased uptake. Scintigraphy using technetium-99m (^{99m}Tc)–labeled WBCs or ciprofloxacin labels has potential uses in foals with multiple-limb involvement and warrants further investigation as an imaging modality for septic arthritis.[35]

Computed tomography (CT) is a useful imaging modality to identify osteomyelitis (Fig. 38.17). It is particularly useful for imaging areas that are difficult to detail with radiography.[36] The main disadvantage is that it is

currently limited by the size of the animal.



FIG. 38.17 Computed tomography scan of a foal with septic arthritis of the left coxofemoral joint, showing osteomyelitis of the acetabulum *(arrows)* that was not radiographically evident.

Magnetic resonance imaging (MRI) has been used in foals and adults with septic arthritis.[37,38] In a limited series comprising 6 foals with infectious arthritis, 4 of the 6 had infectious lesions on MRI indicative of osteomyelitis, and only 4 of 19 lesions were detected on digital radiographs. Osseous lesions in the T2-weighted, short tau inversion recovery (STIR), and proton density MRI sequences appeared as hyperintense foci.[38] In addition, joints with infectious arthritis had heterogeneous signals within the synovial fluid, whereas all nonseptic joints had homogeneous fluid signals.[38] In adult horses with septic arthritis, MRI findings included diffuse hyperintensity within bone and extracapsular issue on fat-suppressed sequences (Fig. 38.18). The study concluded that MRI may allow earlier and more accurate diagnosis of septic arthritis in horses, particularly when the clinical diagnosis is challenging.[37]

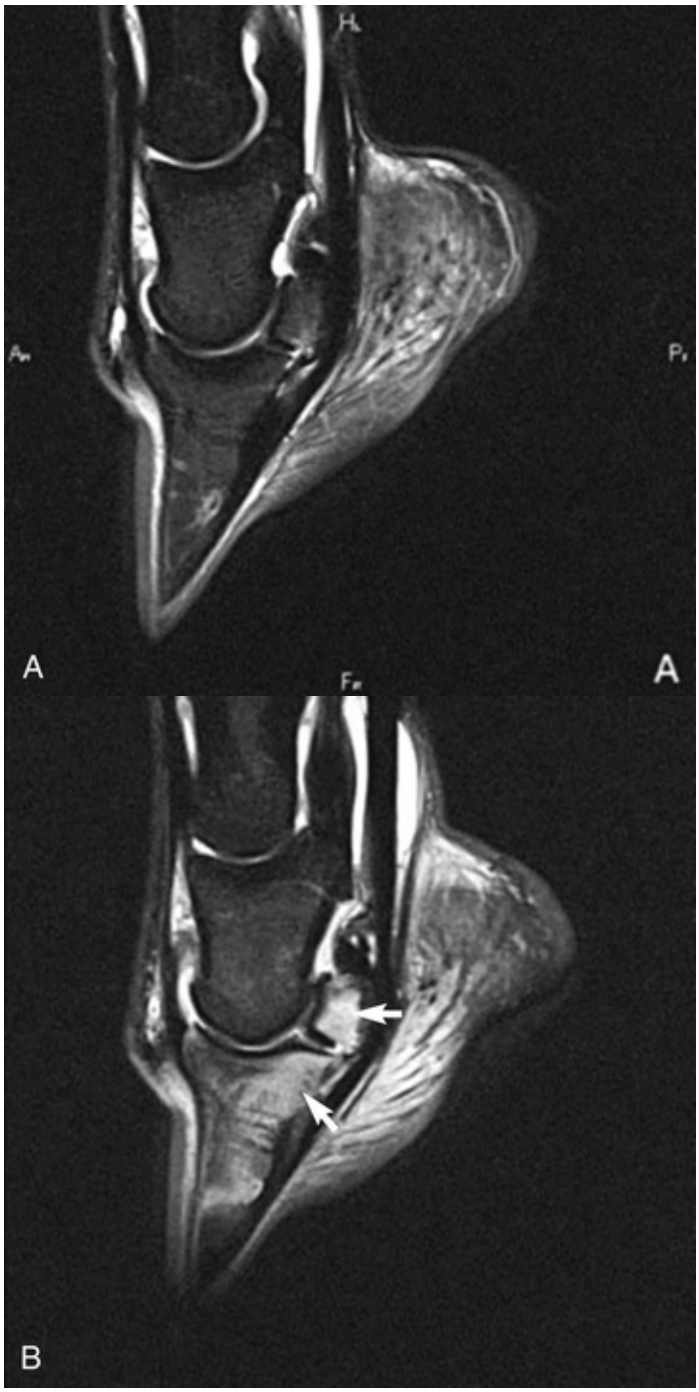


FIG. 38.18 Sagittal short tau inversion recovery weighted magnetic resonance imaging sequence of the left **(A)** and right **(B)** feet of a horse with septic navicular bursa and septic navicular bone, showing severe hyperintensity of the navicular bone and distal phalanx *(arrows).*

Identification of the organism should be attempted in all cases of septic arthritis. Gram stains, culture of synovial fluid in blood culture bottles, and culture of synovial biopsies have been suggested to increase the likelihood of

identifying the organism. In general, the positive culture rate from synovial fluid samples is approximately 50%, and synovial biopsy culture has a low yield to increase this figure.[39] Appropriate culture techniques should be used for organisms such as *Chlamydia* or *Mycoplasma* spp., and special stains may be required. Serology and histopathology are required for the diagnosis of *C. pecorum* in sheep and cattle.[24] In foals, because bacteremia or septicemia precedes the local signs, blood cultures should be obtained. In addition, any other local sites of infection should be cultured. In cases of septic physitis, needle aspiration of the affected site under radiographic or fluoroscopic guidance can be performed. In the future, other techniques for early identification of synovial sepsis may become available.[39]

▪ Treatment

Septic arthritis is an emergency. Assessment followed by institution of treatment should be done as soon as possible after problem identification. The principles of treatment of septic arthritis include systemic broad-spectrum antibiotics, local joint lavage and débridement, and local antibiotic delivery. Systemic antibiotics are best administered intravenously to ensure adequate tissue concentrations. Most often the combination of a β-lactam and an aminoglycoside or fluoroquinolone is used in adults; a β-lactam and aminoglycoside combination is most often used in foals, because fluoroquinolones may have detrimental effects on articular cartilage in young animals. In open joint injuries, particularly if an anaerobic organism is suspected, metronidazole may be added to the antibiotic regimen. Gram-positive organisms can be isolated from blood cultures in up to 33% of foals with sepsis, so gram-positive coverage is also important.[40,41] In foals with physeal involvement, Gram stain and culture of a physeal aspirate are helpful to identify the causative agent. The most common organisms isolated from septic physitis are *Salmonella* spp. and *R. equi*. If *R. equi* is identified, appropriate therapy with macrolides and rifampin should be instituted, keeping in mind that macrolide-resistant organisms have been reported; obtaining susceptibility patterns may be warranted.[42] Intestinal uptake of clarithromycin is significantly impaired when it is administered in combination with rifampin, so use of that combination should be questioned.[43] The presence of osteomyelitis warrants an antibiotic combination that reaches effective bone levels; rifampin with another antibiotic is often used. Rifampin should not be used as the sole antimicrobial because resistance is acquired rapidly with this antibiotic. Other

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antibiotics that reach effective bone concentrations include tetracyclines, chloramphenicol, fluoroquinolones, and cephalosporins. If cephalosporins are chosen, third-generation agents (e.g., ceftiofur, cefotaxime, ceftriaxone, ceftazidime) are preferred because they are more effective against gram-negative bacteria. In foals, fluoroquinolones should be reserved for organisms that are only susceptible to this class of drugs because evidence shows cartilage lesions developing in immature animals with their use.[44,45]

Local lavage of the joint or synovial structure is an important component of therapy; removal of debris, fibrin, and inflammatory mediators helps minimize damage and eliminate the organism. In foals, joint lavage can be performed under heavy sedation or short-term general anesthesia. In adults, sedation and a regional block or short-term general anesthesia can be used. Joint lavage can be performed using through-and-through needle technique; use of a pressure bag or a pump will facilitate efficient lavage of several liters of fluids through the joint. This technique may be sufficient in joints where the diagnosis was made early, where the infection is not severe, and in simple joints (fetlock, carpus). If there is poor response to treatment after one or two sequential joint lavages, arthrotomies should be performed without hesitation. Often fibrin accumulation in the affected joint precludes effective lavage and allows sequestration of bacteria. Once arthrotomies have been performed, the affected joint needs to be covered with a sterile bandage. During subsequent lavages, a teat cannula inserted in the arthrotomies may be used to lavage the joint. The arthrotomies are left to heal by second intention; the joint needs to remain bandaged until the arthrotomies are closed. Occasionally, delayed closure of the arthrotomies is necessary, particularly in arthrotomies localized over high-motion joints. In joints with multiple compartments (stifle, hock), in severe infection or osteomyelitis, in cases of longer duration, or in animals with poor response to joint lavage, arthroscopic débridement is indicated.[15] Arthroscopy has several advantages over simple needle lavage. It allows thorough débridement, removal of fibrin, and lavage of all compartments; evaluation and débridement of cartilage and underlying bone lesions; and in the case of wounds, identification and removal of foreign material. In one study, foreign material was identified on arthroscopy in 41 of 121 (43%) horses and 34% of joints with wounds involving synovial structures; these were predicted in only 15% of cases, suggesting that endoscopic evaluation is important diagnostically in wounds involving synovial structures.[15] In addition, arthroscopy may have prognostic value when radiographic lesions are equivocal. The arthroscopic portals can be left open for drainage and

subsequent lavage but must be kept under a sterile bandage.

Local or regional delivery of antibiotics is advocated for the management of septic arthritis.[46] Delivery of local antibiotics to the affected joint can be achieved by intraarticular injection, isolated IV or intraosseous (IO) infusion, isolated retrograde venous injection, continuous antibiotic delivery, or implantation of antibiotic-impregnated biocompatible materials. Intraarticular injection is the simplest method but requires repeated injections. Aminoglycosides (gentamicin, amikacin) and ceftiofur have been shown to maintain levels above the minimum inhibitory concentration (MIC) for 24 hours after a single intraarticular injection.[47,48] Intrasynovial catheter placement and repeated antimicrobial injection was described successfully in one study where a modified over-the-wire catheter system was placed directly in the synovial structure and used for antibiotic injection and lavage of the synovial structure.[4] Continuous infusion of antibiotics can also be accomplished by placing a small catheter into the affected synovial structure and attaching it to an infusion system, providing constant rate infusion of the antibiotic.[49,50]

Isolated regional IV perfusion or IO perfusion techniques are also advocated for the treatment of septic arthritis.[51,52] Although the term *perfusion* is often used in the veterinary literature, the term *infusion* should probably be used, because in most studies a single injection of the antibiotic is made at the start of the treatment period, whereas perfusion techniques establish an extracorporeal bypass system for the extremity or organ under treatment.[53] Isolated limb infusion techniques are based on isolating the area of interest with a tourniquet, followed by a single IV or IO injection of the antimicrobial. These techniques rely on transient pressure and concentration gradients to distribute a drug to the tissues. The type of tourniquet used is important; escape into the systemic circulation must be avoided during the treatment period. Wide rubber or pneumatic tourniquets are recommended.[54] An Esmarch tourniquet has also been shown to be effective.[51,53] Tourniquets should be 20% wider than the diameter of the limb on which they are used.[54] After tourniquet placement, a regional vein is catheterized using a 23-gauge butterfly catheter for isolated limb infusion. Alternatively, a long-term indwelling catheter can be placed in the vein to facilitate treatment and avoid repeated injection and possible damage to the vein.[57,58] The antibiotic is diluted in a volume of sterile fluid (20 to 120 mL have been reported) and subsequently injected, and the tourniquet is left in place for 30 to 45 minutes. In theory, the increased volume serves to increase the vascular

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pressure and therefore antibiotic distribution, but it remains unknown whether distribution of the antibiotic is a result of a pressure gradient or a concentration gradient. The increased pressure generated after a single infusion of 60 mL returned to baseline after 10 minutes in one study.[53] For IO infusion, a tourniquet is placed in a similar manner, and an IO screw is placed in the medullary cavity and used to inject the antibiotic. Alternatively, a sterile infusion line can be placed in a hole drilled into the medullary cavity. In one study, the IV infusion method had fewer complications than the IO route.[59] Several drugs have been used for IV infusion, including aminoglycosides, cephalosporins, erythromycin, enrofloxacin, vancomycin, and amphotericin B.[51,60-64] The irritating property of drugs like enrofloxacin makes their repeated use undesirable unless no alternative is available.[65]

Isolated limb retrograde venous injection (ILRVI) was compared to isolated limb infusion (ILI).[53] The ILRVI technique was similar to that reported for regional limb perfusion in horses. The ILI technique consisted of catheterization of one digital artery and vein followed by application of a tourniquet. The antibiotic was then injected over 3 minutes, followed by circulation of infusate and blood from the venous to the arterial circulation in 5-minute aliquots for 25 minutes. In the ILI technique, high pressure within the venous system was sustained for the duration of treatment, compared to the ILRVI technique. There was no difference between the two techniques in the pharmacokinetics of synovial fluid amikacin in the metacarpophalangeal joint, but significantly higher amikacin concentration was measured in the DIJ.[53] The authors concluded that either ILRVI or ILI may be used for antibiotic delivery, but that the technically less demanding ILVRI technique may be more practical.[53] Recently, time to reach maximal concentration of amikacin in the DIJ after ILVRI was shown to be only 15 minutes,[66] suggesting that tourniquet application could be shortened to 15 minutes, compared to the traditional 30 minutes. This would be an advantage when the technique is used in standing horses, who often become uncomfortable after approximately 20 minutes of tourniquet application, resulting in motion and possibly systemic leakage of the antibiotic.

Antibiotic-impregnated polymethylmethacrylate (PMMA) beads can also be used, although direct implantation into a joint can result in cartilage damage.[67-69] PMMA implants are fabricated by mixing the desired antibiotic with the powder before adding the polymerizer. Antibiotics evaluated for inclusion in PMMA include gentamicin, metronidazole, vancomycin, ceftiofur, cefazolin, and

amikacin.[70-77] Antibiotic combinations have also been used, but combining antibiotics can change their elution properties. For example, cefazolin or amikacin elute at concentrations greater than MIC for 30 days in vitro, but the combination elutes above MIC for only 6 days.[76,77] Antibiotic-impregnated biodegradable implants include synthetic and natural carriers. The advantage of these implants is that a separate procedure for their removal is unnecessary.[78-80] Synthetic carriers are degraded by hydrolysis, which may affect the antibiotic prior to its implantation.[46] Although synthetic biodegradable carriers have been evaluated in an experimental model of synovial membrane sepsis, they are not currently clinically available.[78] Gentamicin-impregnated collagen sponges consist of highly purified cattle collagen; the gentamicin molecules are embedded within the pores of the collagen. No stabilizing agents or foreign substances are added. Clinical use of successful treatment of septic arthritis in horses and cattle has been reported.[80-82] However, a recent study performed in healthy horses failed to detect sustained antibiotic release beyond that obtained with a single intraarticular injection.[83]

As high levels of antibiotics are reached within the targeted tissues with these techniques, it remains unknown whether systemic antibiotics are still required. In addition, the best dosing interval between treatments is unknown; for example, with concentration-dependent aminoglycosides, there is a transient reversible adaptive resistance for some bacteria to a second dose of aminoglycoside up to concentrations 128 times MIC. These same bacteria revert to original susceptibility when exposed to drug-free media.[53,84] Another unknown is the potential interaction of aminoglycosides and β-lactam combinations, which depending on the drug combination, can be synergistic or antagonistic. Although inactivation of certain β-lactam antibiotics by certain aminoglycosides in vitro has been documented, several studies document in vivo synergism.[85,86] Significant postantibiotic effects were detected with several antibiotic combinations.[87]

With extensive physeal lesions in foals, curettage, autologous bone grafting, and external coaptation may be required.[88,89] The addition of tricalcium phosphate granules or bioresorbable paste may be considered.[90] Angular limb deformities may result from growth disturbances or collapse of the physis on the affected side. In adults with septic arthritis and osteomyelitis, curettage of the bone lesion followed by bone grafting and external coaptation may also be

indicated.[91] Adjunctive therapies that may help alleviate inflammation include sodium hyaluronate, polysulfated GAGs, and dimethyl sulfoxide (DMSO). Sodium hyaluronate and polysulfated GAGs can be used systemically or locally, but local use should be reserved for when infection is under control because these agents decrease joint defense mechanisms.[8,92] Although DMSO has significant anti-inflammatory properties in joints, it should be used with caution because of its negative effects on cartilage metabolism.[93]

In addition to specific therapies, management of pain, stress, and other metabolic disturbances are indicated. Pain can be managed by judicious use of NSAIDs, using the smallest dose that will keep the animal comfortable. If a foal continues to show severe pain despite appropriate treatment, it is important to ensure that other joints in the limb are not involved. Other pain management modalities (e.g., opiates, fentanyl patches, epidural analgesia) can be used. It is important to remember that in foals, continued pain in one limb may result in development of a varus deformity in the contralateral weight-bearing limb owing to the tripod stance these foals acquire to maintain the weight-bearing limb under the center of gravity. Application of a lateral extension to the contralateral foot may help increase the weight-bearing surface and prevent development of this complication. Continued pain is a negative prognostic indicator in the affected foal. In adults, continued pain in one limb may result in the development of contralateral limb laminitis.[94] When continued pain in the treated limb is a problem, preventive measures (e.g., hoof support, therapeutic shoeing) should be undertaken.

Gastroprotective agents are indicated in foals and adult horses that are in pain, stressed, and receiving high doses of NSAIDs. Omeprazole is currently the only medication that has been shown to significantly prevent formation of gastric ulcers and promote healing of existing ulcers in adult horses. Although evidence for its efficacy in preventing and treating NSAID-induced ulcers is lacking, omeprazole is still indicated when NSAIDs are used in stressed animals.

In cattle, facilitated ankylosis is a reasonable alternative when the disease is too advanced, and it is a particularly good option for involvement of the DIJ. Articulations of the distal limb in general are well suited to facilitated ankylosis. In brief, the involved joint is opened and débrided of all debris, all infected tissue is curetted and removed, and a cast is applied and maintained until ankylosis is achieved.[95] Alternatively, the digit may be amputated, although a reduced production life should be expected.[96]

▪ Prognosis

In clinical studies, treatment is often limited by economic considerations, so the true long-term outcome of treatment is unknown. Outcome variables used in clinical studies range from discharge from the hospital to pasture soundness to racing potential. Owner expectations should be clear, keeping the animal's welfare in mind. The prognosis for septic arthritis should always be guarded, and owners should be informed of the high cost of treatment. In foals, factors that influence prognosis are systemic condition of the foal, number of joints involved, localization of joint involvement, severity of the infection, early versus delayed identification and institution of treatment, presence of osteomyelitis, and virulence of the organisms. In one study, 73 of 93 (78%) foals survived to discharge, but only a third reached racing performance.[97] Isolation of *Salmonella* spp. and presence of multisystem diseases were negatively associated with survival and ability to race.[97] A multidrug-resistant *Enterococcus* species was associated with unresponsive septic arthritis in three horses.[98] In another study, 58 of 69 (84%) foals survived to discharge, although signs were present for less than 24 hours in 74% of foals, only 5 foals had more than one joint involved, and only 1 foal had osteomyelitis.[99] This population of foals therefore appeared to be less severely affected. Of the affected foals, only 40.5% started in one race, and of the affected foals that were discharged, only 48.3% raced versus 66.2% in the control (sibling) group. This study concluded that even if foals are successfully discharged from the hospital, they are significantly less likely than their siblings to start in at least one race. Furthermore, these foals took significantly longer to appear on the track than their siblings. In another study of foals with osteomyelitis of hematogenous origin, 87 of 108 (80.6%) foals were discharged from the hospital, and 79 of 87 foals reached racing age.[100] Overall, 52 of 108 (48%) foals raced. Of the 21 nonsurvivors, only 1 died; the other 20 were euthanized, but none was euthanized for economic reasons. Factors associated with nonsurvival in that study included foals less than 30 days of age, critical illness, multisystem disease, multiple bone lesions, lesions of the proximal phalanx, concurrent septic arthritis, multiple septic joints, and involvement of the coxofemoral, stifle, hock, or navicular bursa. In that study, the bacterial isolate involved had no significant effect on short-term outcome.[100] In a study evaluating the factors associated with survival and racing performance in 423 neonatal Thoroughbred foals with bacteremia, the presence of septic arthritis increased the likelihood of nonsurvival by 4.54 times.[101]

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In adults with open joint injuries, the prognosis can be favorable if the joint is contaminated but not yet infected and if aggressive treatment is started immediately. However, with established infection, the prognosis should always be guarded. In one study of horses with open joint injury, 53% of those examined within 24 hours developed septic arthritis, and overall survival was 65%. In horses presented within 2 to 7 days of injury, septic arthritis developed in 92%, and survival was 38.5%; in horses examined more than 7 days after injury, septic arthritis developed in all, and survival was 50%.[13] In one study of 101 horses with heel bulb lacerations, those with involvement of synovial structures had worse outcomes than those that did not; 5 of 17 horses with synovial involvement were euthanized.[16] Horses with contaminated or infected synovial structures treated by arthroscopic débridement appeared to have a better long-term outcome, with 106 of 118 (90%) surviving and 96 (81%) returning to previous use.[16] In a study of horses with septic tenosynovitis, 40 of 51 (78%) horses were discharged, and 37 of 40 (73%) survived long term, with 21 (57%) returning to intended use.[102] Surgical technique did not influence outcome in this study. One study reported on the use of matrix metalloproteases 2 (prommp2) and 9 (prommp9) and WBC count to monitor treatment and predict outcome in horses with septic arthritis.[14] In that study, survivors had a significantly lower WBC count, prommp9, and ratio of prommp9/prommp2, with the latter being the best predictor for survival.

In cattle the prognosis for septic arthritis is generally better than in horses, probably because of the lack of expectation for athletic use. Prognosis depends on time of presentation, degree of bone involvement, and degree of extracapsular ankylosis. In two studies the success rate was reported as 72% and 85%; cattle with septic tarsi had a worse prognosis.[103,104] In another study, arthroscopic lavage and implantation of gentamicin-impregnated collagen sponges resulted in recovery in 12 of 14 cattle.[105] After arthrodesis of the DIJ, 85% success was reported.[96] For carpal arthrodesis, 87% success was reported if no carpal bone was removed, 72% success if one row of carpal bones was removed, and 35% success if both carpal rows were removed. Tarsal arthrodesis has a reported success rate of 87% in cattle.[96] A recent study indicated a positive outcome in 55% (35 of 62) of calves affected with septic arthritis.[20]

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Mycoplasma Polyarthritis in Goats

Evelyn MacKay

▪ Definition and Etiology

Mycoplasma are small bacteria without a cell wall responsible for a multitude of diseases affecting domestic ruminant herds worldwide. Pathogenic species include *Mycoplasma capricolum* (subsp. *capricolum,* subsp. *capripneumoniae*), *Mycoplasma bovis, Mycoplasma mycoides* subsp. *capri, Mycoplasma putrefaciens, Mycoplasma conjunctivae, Mycoplasma ovipneumoniae,* and *Mycoplasma agalactiae*.[1] *M. mycoides* subsp. *mycoides* LC (large colony variant) has been reclassified as *M. mycoides* subsp. *capri* based on phylogenic data.[2] It is closely related to *M. mycoides* subsp. *mycoides* SC (small colony variant), the causative agent for contagious bovine pleuropneumonia. Contagious agalactia is the common name of the disease syndrome caused by *Mycoplasma* infection of kids and does. It classically presents as a triad of clinical signs: mastitis in lactating does and polyarthritis with keratoconjunctivitis in kids, though pneumonia is common as well. *M. mycoide*s subsp. *capri* is the most common etiology in the United States, though *M. agalactiae* is more prevalent in Mediterranean countries, where it is responsible for 90% of outbreaks.[3,4] Clinical signs, disease progression, and virulence vary with strain and host factors.

▪ Clinical Signs and Differential Diagnoses

Incubation period can range from a few days to weeks, depending on species, management practices, and environmental factors. Initial signs of infection in kids include fever, lethargy, anorexia, and weakness.[5] Polyarthritis, keratoconjunctivitis, and pneumonia develop following initial bacteremia.[6] Meningitis and sudden death have been reported in some outbreaks.[7] Polyarthritis most commonly occurs in the carpal and tarsal joints; multiple joints often become warm, swollen, and painful.[3,5] Differential diagnoses include environmental organisms colonizing the joints after bacteremia. Peracute, acute, and chronic disease syndromes may develop, and *Mycoplasma* often can be cultured from the ear of asymptomatic carrier animals.[2,8]

Clinical signs in does include alterations in the appearance of milk, agalactia or drop in milk production, supramammary lymphadenopathy, fibrosis of the mammary gland, fever, anorexia, and lethargy.[1] Agalactia and mastitis of does must be differentiated from other causative agents of mastitis, including environmental coliforms, *S. aureus*, fungal organisms, and caprine arthritis encephalitis virus. Adults may also develop polyarthritis, keratoconjunctivitis, and pneumonia, and infection is not limited to females. *Mycoplasma* can colonize the reproductive tract and has been isolated from abortions and semen.[3,9] Infected herds may have decreased reproductive performance.[2]

▪ Clinical Pathology and Diagnosis

Hematologic changes are variable and may depend on severity of disease and *Mycoplasma* species. Changes in experimentally infected kids included leukopenia, decreased erythrocyte count, thrombocytopenia, decreased clotting factors, and increased clotting times consistent with disseminated intravascular coagulation.[10] Total protein and albumin concentrations may be decreased in infected animals.[6] Arthrocentesis will reveal a fibrinosuppurative arthritis.[1] Culture can be obtained from synovial fluid or milk, which requires special medium and extended time intervals for growth. *M. agalactiae* colonies typically resemble a “fried egg” on agar.

In endemic areas, a presumptive diagnosis may be based on clinical signs. Antemortem diagnosis can be made with samples of milk, blood, urine, and auricular, nasal, and ocular secretions.[3] Species and subspecies differentiation can be challenging, and techniques used include serology and molecular diagnostics such as PCR and genome sequencing.[11] Biochemical tests are not useful due to extreme similarity between species. Combination of multiple diagnostic modalities may be required for accurate differentiation.

▪ Pathophysiology and Epidemiology

Infection of kids usually occurs through ingestion of infected milk and colostrum from the doe or supplemented bovine milk in the case of *M. bovis*.[1] Disease may also spread via oral and nasal secretions of infected animals or contaminated milking equipment.[3] Polyarthritis develops after systemic bacteremia. Strain virulence, immune and nutritional status of animals, and environmental factors all play a role in severity and spread of the disease. Morbidity is often high, but

mortality varies greatly. An asymptomatic carrier introduced into the herd is often responsible for outbreaks. Disease occurs in wild ruminants, and they may represent a reservoir for transmission to domestic animals.[2]

▪ Necropsy Findings

Affected joints are swollen with decreased range of motion. Fibrin deposits and hemorrhage of the articular cartilages can be seen.[1] Microscopically, neutrophils and mononuclear cells infiltrate the synovium.[5] Gross pulmonary lesions may include diffuse interstitial pneumonia, bronchopneumonia, fibrinous pleuritis, or a combination of lesions.[5,12] Microthrombi may be present diffusely in vasculature, and microabscesses may be found in the spleen and kidney.[10]

▪ Treatment and Prognosis

Mortality and morbidity vary based on the isolate but can climb above 90% in kids. An outbreak in a dairy resulted in the euthanasia of 700 goats.[7] Treatment is often unrewarding, and resources may be best directed toward prevention and control of infection. As *Mycoplasma* lack a cell wall, treatment with antimicrobials that disrupt cell wall synesthesia are ineffective. Antimicrobials used include tetracyclines, macrolides, fluoroquinolones, and florfenicol. There is evidence of existing resistance to antimicrobials, and even susceptible isolates may not be eliminated with appropriate antimicrobial therapy.[2] Damage to joints may be permanent and crippling by the time antimicrobial therapy is initiated.

▪ Prevention and Control

A closed herd with careful screening of new animals is the best method to prevent infection. Recommended screening strategies include PCR or culture of ear swabs; serology may be performed, but asymptomatic carriers are often negative.[2,9] Hygienic milking practices help reduce spread between does, and sanitization of supplies and housing is recommended. Feeding of colostrum and milk replacers reduce likelihood of transmission to kids, though pasteurization will reduce mycoplasma numbers.[2] Culling of affected animals or complete depopulation of herds has been used in control efforts.[7,11] Killed and attenuated live vaccines exist and have shown efficacy in reducing clinical signs and shedding, but these are not commercially available in the United States.[13]

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Caprine Arthritis Encephalitis Virus

Kevin Washburn

▪ Definition and Etiology

Caprine arthritis encephalitis virus (CAEV) is an RNA-enveloped lentivirus from the Retroviridae family that infects cells of the monocyte-macrophage lineage, with clinical manifestations ranging from subclinical disease to severe encephalitis. Time from viral infection to clinical disease may vary from months to years, and because infection is lifelong, efforts to eradicate and control its prevalence and incidence are paramount to maintaining successful goat herds. Loss of productivity, death, and restrictions on the export of dairy goats are just some of the economic impacts of this disease on worldwide herds and the goat industry.

▪ Clinical Signs and Differential Diagnoses

Only about 20% of CAEV-infected goats display clinical signs of disease during their lifetime, but recognized forms of disease include a leukoencephalomyelitis, interstitial pneumonia, chronic mastitis, and debilitating polysynovitis-arthritis.[1] Leukoencephalomalacia is observed primarily in kids 2 to 6 months of age, but reports have been noted in adults.[1] This form is characterized by an ascending paresis leading to paralysis, beginning in the rear limbs and sometimes involving the forelimbs. These signs may or may not be accompanied by a mild interstitial pneumonia. Goat kids may continue to be bright, alert, and appetent. The most severe manifestation of this form of CAEV infection is progressive paresis to paralysis to urinary retention and bloating. Differentials for this form of CAEV include meningitis, meningeal worm, and trauma. Chronic interstitial pneumonia with progressive weight loss and dyspnea is another recognized form of CAEV infection. Primary ruleouts for this form include lung worms, internal caseous lymphadenitis, pulmonary abscessation, and chronic bronchopneumonia. The mammary gland is a target organ for the virus as well, resulting clinically in a firm udder with decreased milk production. Although quantity of milk is reduced, there are no apparent gross abnormalities; however, chronic bacterial mastitis should be a consideration during initial evaluation.

The most common form of CAEV infection is polysynovitis-arthritis, which is

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most frequently recognized in mature goats but has been reported in goats as young as 6 months of age. Lameness caused by this form is intermittent and insidious in onset, but eventually affected joints become painful and enlarged. Enlargement of the joints is most typically due to hyperplasia of the synovial tissues and their associated sheaths rather than increased volume of joint fluid. The carpus is most frequently involved, but the stifle, coxofemoral, atlantooccipital, and hock joints are also potential locations. Affected goats have a stiff, stilted gait and progress to walking on their carpus or recumbency. Range of motion is greatly affected, contributing to chronic soft tissue contracture. The polysynovitis-arthritis form can be accompanied by a chronic interstitial pneumonia and weight loss, as well as some degree of mammary involvement.[1] Ruleouts for this common form of CAEV include septic arthritis and chronic degenerative joint disease.

▪ Clinical Pathology and Laboratory Diagnosis

Arthrocentesis to confirm suspicion of the polysynovitis-arthritis form of CAEV infection usually yields a brown to red-tinged fluid with an increased cell count and protein. Joint fluid cell counts in affected joints are dominated by mononuclear cells, differing from bacterial synovitis, where cells consist predominantly of neutrophils. This predominance of mononuclear cells in CAEV infection is also seen in the cerebrospinal fluid (CSF) of goats affected with the leukoencephalomyelitis form. Radiographs may be a useful diagnostic tool for CAEV polysynovitis-arthritis; early cases display soft tissue swelling dorsal to the carpus. As the disease progresses, mineralization can be observed in the periarticular tissue, tendon sheaths, joint capsules, and ligaments. Roughened bone proximal and distal to the joint becomes apparent, as does periosteal reaction. A commercially available immunoenzymatic assay of antibody against surface glycoprotein was found to have a sensitivity and specificity of 86.9% and 84.4%, respectively, in its ability to discriminate between arthritic and asymptomatic goats.[2]

The U.S. Department of Agriculture (USDA) recognizes an agar gel immunodiffusion (AGID) test using ovine progressive pneumonia virus antigen as the official test for CAEV. However, an enzyme-linked immunosorbent assay (ELISA) has been developed for detection of whole virus, core, or envelope proteins. Both AGID and ELISA are considered reliable enough to be incorporated into prevention and control programs. The AGID test is reportedly

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more specific but less sensitive than the ELISA.[3] Polymerase chain reaction techniques have been developed for detection of antigen in milk, tissue, and blood. A study evaluating the performance of PCR and ELISA against viral culture for the detection of CAEV in goat kids found that PCR tended to have a lower sensitivity and higher specificity than ELISA, but combining these two tests in series or parallel may optimize the advantages and disadvantages of each technique, thereby maximizing detection.[4] Surveillance measures on goat dairies have included the use of ELISA tests on bulk milk samples that appear to be applicable for early detection of CAEV infection.[5]

A positive AGID test or ELISA in adults is synonymous with lifelong viral infection. Generally, time from infection to seroconversion ranges from 4 to 16 weeks, but some infected goats shed virus for long periods of time without seroconversion.[6] Goat kids may be transiently positive for the presence of antibodies during the first 8 to 16 weeks of life after consuming CAEV antibody–containing colostrum, but because of the nonprotective nature of maternal antibodies, such kids may seroconvert to true viral infection shed from the infected dam.

▪ Pathophysiology

The characteristic granulomatous inflammatory pathology produced in affected tissues is thought to be due to immune complexes generated by the interaction of nonneutralizing antibodies produced by lymphocytes and associated virus-infected macrophages. Localization of such inflammatory lesions occurs where tissue-associated macrophages are found. Tissues of importance for CAEV localization include the synovium, mammary gland, lung, and central nervous system (CNS), therefore the manner in which the disease manifests itself is to be expected.

▪ Epidemiology

Transmission involves the transfer of virus-laden cells from one animal to the next. Transfer of CAEV to neonates through colostrum and milk is a highly efficient natural mode of transmission.[7,8] Transmission has also been reported through direct contact, so herd owners who do not practice segregation of seropositive animals continually have difficulty controlling and eradicating the disease.[7-10] Complete separation of kids from dams immediately following parturition and during the periparturient period is necessary; evidence exists that

even kids not allowed to nurse become infected. CAEV proviral DNA has been detected in the caprine genital tract,[11] and experimental infection of goat embryos with CAEV has been reported.[12] In addition, intramammary and in utero transmission have been described.[10,13] All of the described means of acquiring the virus are potential explanations for continued transmission in herds where segregation and sound colostrum and milk management are practiced.

Maedi-visna virus (MVV), also known as *ovine progressive pneumonia*, is another lentivirus that together with CAEV is commonly referred to as *small ruminant lentivirus* (SRLV). Although sheep are most likely to display clinical signs of MVV and goats signs of CAEV, studies have shown that these viruses can be transmitted from sheep to goats and vice versa.[14] Therefore eradication programs aimed at eliminating SRLV from herds and flocks should not allow contact between sheep and goats.

A study examining the prevalence of antibody to CAEV in the United States found that 31% of all goats tested were seropositive, and 73% of herds had at least one seropositive member. Serum samples in this study were obtained from 28 states. Prevalence was highest in the western Pacific and northern plains regions on family-owned farms and increased with age. Prevalence in this study was lowest in the Angora breed.[15]

▪ Necropsy Findings

Grossly, goats affected with the polysynovitis-arthritis form of CAEV have thickened, sometimes folded synovium consistent with synovial hyperplasia due to chronic inflammation. Microscopically, synovial hyperplasia is characterized by mononuclear infiltration of lymphocytes, plasma cells, and macrophages. Synovial spaces contain fibrin, and synovial villi and collagen are necrotic.[1]

No gross lesions are apparent in the CNS of goats affected with the leukoencephalomyelitis form of CAEV, but microscopically, perivascular infiltration of lymphocytes, macrophages, and plasma cells is observed. Perivascular infiltration is often accompanied by malacia of the brain and spinal cord, in addition to loss of myelin. Occasionally, degenerative lesions are seen in the gray matter.[16]

▪ Treatment and Prognosis

Prognosis for CAEV infection varies because most goats do not show clinical disease; once signs begin, however, rapid deterioration ensues. Arthritis and

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accompanying weight loss progress, and there is no treatment. Kids or mature goats affected with the leukoencephalomyelitis form do not survive and should be euthanized for humane reasons. Reportedly, a genetically determined predisposition for development of CAEV arthritis exists and can be identified with DNA fingerprinting.[17]

▪ Prevention and Control

Prevention and control centers on colostrum and milk management, but kids should also be prevented from any contact with the dam following parturition. Heat treatment of colostrum by holding it at 45° C (113° F) for 1 hour effectively inactivates the virus.[10] Kids can then be fed pasteurized milk until weaning. Unpasteurized goats' milk from seronegative dams is a risky substitute for heat-treated milk because some seronegative goats shed virus for long periods before seroconversion occurs. Pooling of colostrum increases the prevalence of disease in goat dairies, so this practice should be restricted. Kids should be tested serologically at periodic intervals to detect and remove infected individuals. Seronegative goats should be isolated from seropositive ones by a minimum of 6 feet.[10] Sharing of feed and water troughs should not be allowed, nor should use of common needles during routine vaccination or administration of medication. During breeding, seronegative does should not be housed with seropositive bucks, but they can be hand mated and quickly re-isolated. New additions to the herd should be tested and isolated until seronegative status is confirmed prior to entry into the herd.

Despite diligent prevention and control programs based on elimination of colostrum and milk transmission, isolation of seronegative goats, and serologic monitoring, obstacles to a CAEV-free herd are often encountered. Detection of virus has been reported in properly treated colostrum.[7] Overheating colostrum denatures immunoglobulin, thereby preventing effective passive transfer of immunity, but not heating colostrum long enough or at high-enough temperatures fails to inactivate the virus. Feeding overheated colostrum may also cause diarrhea in kids.[18] Attention to time and temperature details during heat treatment of colostrum and pasteurization of milk are of the utmost importance for effective colostrum and milk management. Some farms routinely feed cow colostrum, but neonatal isoerythrolysis has been reported in kids consuming cows' milk, and the lack of goat-specific immunoglobulin transfer is less than ideal.[18] Serologic monitoring can be complicated by the fact that viral shedding

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precedes seroconversion, so all goats should be tested a minimum of twice yearly to ensure that any new cases are detected and managed accordingly. Unfortunately, no vaccine is currently available for CAEV.

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Osteoarthritis

Canaan Whitfield-Cargile

▪ Terminology

The term *osteoarthritis* (OA) is one of many terms used to describe a broad category of disease that ultimately results in bone *(osteo)* and joint *(arthron)* pathology. Other terms used to characterize this category of disease include degenerative joint disease (DJD), osteoarthrosis, osteoarthropathy, and simply arthritis. The suffix *-itis* refers to inflammation, but the role of inflammation in the etiopathogenesis of OA remains controversial in both people and animals.[1,2] While many of these terms are justified, for the purpose of clarity we will use the term OA, as it appears to be the most widely used term to describe this condition. OA is a progressive disease ultimately characterized by destruction of articular cartilage, changes in the subchondral bone, and alterations of periarticlar soft tissues including synovium, ligaments, and joint capsule, although not necessarily in that order.

Evidence exists to suggest that OA was present in the earliest examples of diarthrodial joints found in the fossil record.[3,4] Not surprisingly, OA is the most common joint disorder in people and is also highly prevalent in dogs.[5] In large animal species, OA is regularly diagnosed in horses, cattle, pigs, and small ruminants. Although there are specific causes of OA in some species (e.g., caprine arthritis encephalitis virus in goats), more often the etiology of the underlying causes remains unknown.[6] The obvious exception to this is cases of OA secondary to joint trauma, septic arthritis, or chronic increased weight bearing following injury or amputation of the contralateral limb.[7,8] Although the exact prevalence is unknown, OA is a common disease of horses often resulting in loss of use for high-end athletes and all too often progressing to debilitating pain and humane euthanasia. To highlight the prevalence of this condition in horses, one study examined the prevalence of OA in the metacarpophalangeal joint of racehorses, based on macroscopic and microscopic cartilage examination, and found that nearly one third of 2- to 3-year-olds in training had evidence of cartilage injury.[9] The cause of OA in this population of horses is unknown.

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▪ Pathophysiology and Classification

Several theoretical explanations underlie the pathophysiology of OA. As stated above, occasionally there is a clear explanation of the development of OA (i.e., following joint trauma, infection, etc.), but in most cases the cause is not clear. At a basic level, two major factors are involved in the development of OA: mechanical load and tissue turnover or metabolism. In many cases of OA, it is likely that both of these factors play a role in the etiopathogenesis, and to consider them separately is likely an oversimplification. For example, a normal load placed on a joint that has increased catabolic processes will eventually lead to the development of OA as that “normal load” overwhelms the repair capacity of that specific joint. Conversely, an abnormal load placed on a normal joint (i.e., balanced catabolic and anabolic processes) will also eventually develop OA, in part due to eventual increased turnover of components of the joint resulting in an inability for that joint to repair itself. For the purposes of this chapter, however, these processes will be considered independently.

Abnormal Biomechanical Load.

Examples of an abnormal mechanical load that overwhelms a joint's capacity for repair can be an obvious acute injury resulting in instability. Examples of these types of injuries include injury to collateral ligaments and other supporting structures of joints, fractures involving the articular surface, and injuries in the contralateral limb resulting in increased weight bearing.[10] Importantly, these examples represent a single traumatic event resulting in joint instability and eventual development of OA if not managed appropriately or, in some cases, even if managed appropriately. The other broad category of biomechanical load resulting in OA is repeated low-grade damage that occurs with routine use, resulting in repeated microdamage to the structure of a joint. At no one point are these low-grade injuries apparent, but over time this microdamage overwhelms a joint's capacity for repair and ultimately leads to development of OA. A primary example of this phenomenon is the changes that occur within the metacarpophalangeal joints of racehorses.[11] In this context, there is a wealth of evidence suggesting that stress placed on the distal end of the third metacarpal bone results in increased stiffness of the subchondral bone and eventual microcracks that may progress to condylar fractures.[12] Even if condylar fractures do not develop, the structural and molecular alterations induced by repetitive trauma lead to changes in the articular cartilage and predispose these horses to

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developing OA.[13] Similarly, abnormal biomechanical forces are placed on joints when there are anatomic abnormalities such as severe angular limb deformities and hip dysplasia in calves, among others. Although the underlying causes in these situations are obvious, this too represents a form of repetitive injury, albeit one more obvious than what occurs with the microdamage associated with performance or the forces placed on joints on a regular basis due to the shear size of many large animal species. Irrespective of the underlying biomechanical cause, the result is initiation of a series of complex biochemical and metabolic events that result in an imbalance of anabolic and catabolic processes in the joint, eventually overwhelming the repair processes. This culmination of events leads to fibrillated and ulcerated articular cartilage, eburnation and sclerosis of the subchondral bone, hyperplasia of the synovial membrane, and development of periarticular osteophytes and enthesophytes.

Tissue Metabolism.

All tissues have capacity for turnover and repair, and the tissues in the joint are no exception. OA can be thought of as an imbalance between anabolic processes (repair) and catabolic processes (turnover).[14] As discussed, factors that can upset this balance include biomechanical factors (see above), other trauma, inflammation, and sepsis. Much of the discussion examining these factors focuses on the articular cartilage, but other tissues associated with joints are also important, including synovial membrane, ligaments, and subchondral bone. Recall that synovial fluid is an ultrafiltrate of plasma, thus the synovial membrane is the bidirectional interface between the joint and the remainder of the animal. Equine synoviocytes have recently been shown to be an important player in the development of OA in horses by regulating several pathways in cartilage associated with the progression of OA.[2,15] In addition, synoviocytes are responsible for the production of several elements of synovial fluid, the critical component that along with articular cartilage is responsible for maintaining frictionless motion in joints. Taken together, these findings suggest that synoviocytes play an important role in development of OA, although their exact role and the clinical implications of these findings remain unclear.

Loss of articular cartilage is a hallmark of OA, and therefore clearly the balance of anabolic and catabolic processes in this tissue is an important aspect of OA. Articular cartilage is composed of cells, primarily chondrocytes, and an extracellular matrix (ECM) produced by these chondrocytes. The ECM consists of water (>70%), collagen (>90% type II), proteoglycan (aggrecan and aggrecan

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aggregates linked to hyaluronan). Loss of any of these components is critical, as inherent repair capacity of large (>3 to 5 mm), full-thickness defects is minimal and restoration of the critically important hyaline cartilage is difficult. Loss of articular cartilage is due to either biomechanical disruption (see above) or proteolytic enzymes synthesized by chondrocytes, synoviocytes, or other cell types that have invaded the joint in response to injury (e.g., neutrophils following joint sepsis). A major class of proteolytic enzymes involved in cartilage destruction include the matrix metalloproteinases (MMP), which are a family of more than 25 different enzymes, each with some degree of specificity to a component of the ECM. For example, MMP-1 is also called collagenase 1 and is capable of cleaving type II collagen molecules. Similarly, a disintegrin and metalloproteinase (ADAM) class of enzymes, which are closely related to MMPs, is responsible for enzymatic destruction of aggrecan molecules. Although not always clear, these enzymes are produced by chondrocytes, synoviocytes, and other cells found in joints in response to various cytokines. The principal cytokines associated with stimulating production of these enzymes are the proinflammatory cytokines interleukin (IL)-1 and tumor necrosis factor (TNF)–α. These cytokines not only induce production of these enzymes but also encourage production of other mediators of joint destruction, including prostaglandin E2, oxygen free radicals, and nitric oxide. In a normal joint under normal condition, production of these catabolic compounds is countered by production of anabolic compounds that inhibit cartilage degradation. For example, tissue inhibitors of MMPs (TIMPs) are produced by several cell types within the joint, as is IL-1 receptor antagonist, which binds to IL-1 receptors thus preventing signal transduction. Delving into the host of mediators that regulate cartilage destruction is beyond the scope of this chapter; suffice it to say that the process is complex and involves the interaction of a wealth of mediators. Identification of these mediators of OA, along with their natural inhibitors, is important as this information offers a plethora of potential therapeutic targets to prevent progression of OA (see the Treatment section later). Ultimately, however, OA develops when catabolic mediators outpace anabolic mediators, resulting in loss of ECM components, loss of chondrocytes, and eventual cartilage fibrillation and exposure of subchondral bone. In most cases the exact cause of this imbalance is not clear and is likely multifactorial. Typically the rate of disease progression and severity of OA are related to the nature and severity of the primary insult, the animal's age, the joint location, and the animal's type and level of activity.

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▪ Clinical Signs

OA can affect any joint, and therefore the clinical signs will vary greatly depending on which joint is affected. We focus primarily on OA of the appendicular skeleton, but OA is common in the axial skeleton and any diarthrodial joint. Lameness in horses is a major problem that costs the horse industry hundreds of millions of dollars each year. Lameness is also highly prevalent in other large animal species, resulting in decreased production and welfare concerns.[16] Undoubtedly, much of the lameness in horses is due to OA, although the exact locations, severity, and clinical implications of OA in horses depends on the age, use, severity, and individual response to the pathology associated with OA.[17,18] In other large animal species, lameness is the primary clinical sign of OA, although the exact manifestation of the lameness will be related to species, animal size, and severity of disease. The pain, resulting in lameness, in OA comes from several sources. As stated, the primary area of pathology is the articular cartilage. Cartilage is devoid of innervation, so the pain arises from sensory nerves in periarticular structures, including synovium, joint capsule, subchondral bone, and surrounding ligaments. Either *mechanical stimuli* or *chemical mediators* of pain stimulate these sensory nerves. An example of a mechanical stimulus resulting in pain is increased synovial fluid stretching the joint capsule and synovium. It remains unclear in both animals and people if osteophytes or bone spurs result in pain or are merely a radiographic manifestation of joint disease. Theoretically, periarticular osteophytes could result in stretching of the richly innervated periosteum, causing pain, but in people this has not been conclusively demonstrated and in some cases has been refuted.[19] In addition to lameness, other clinical signs associated with OA include synovial effusion of the affected joint, decreased range of motion, and angular limb deformities with visually obvious periarticular new bone formation as the disease becomes more severe.

▪ Diagnosis

Perineural anesthesia and intraarticular anesthesia can be useful for localizing the source of lameness and is a mainstay for the diagnosis of OA in large animals as, in most cases, physical examination alone is insufficient to confidently localize the source of pain resulting in lameness.[20] Determining the origin of lameness, however, does not confirm the cause of lameness. Diagnostic imaging demonstrating articular changes consistent with OA is the primary means of

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confirming a diagnosis of OA. Diagnostic tests that can accurately identify OA prior to the onset of irreparable articular changes have clear clinical benefit over diagnostic imaging after these changes have occurred.

Non–Imaging-Based Diagnostics.

Routine synovial fluid analysis of affected joints can distinguish pain and lameness associated with septic arthritis from OA, but in cases of OA, routine synovial analysis reveals only nonspecific changes. Therefore there has been a great deal of effort to identify specific biomarkers of early OA. Sources of these biomarkers have included serum, synovial fluid, and urine.[21] The idea of serum biomarkers is attractive, as such samples are more easily collected than synovial fluid. Examples of biomarkers that have been examined include glycosaminoglycans (GAGs), collagen degradation markers and fragments of collagen, osteocalcin, C-terminal of bone type I collagen (CTX1), and cartilage oligomeric matrix protein (COMP).[22,23] Many of these markers have shown promise in both naturally occurring OA and in vivo models of OA, but none has yet demonstrated sufficient evidence or feasibility for routine clinical use.

Imaging-Based Diagnostics.

After identification of an involved joint, many imaging strategies can be used to confirm the cause of pain, evaluate the extent of injury, and determine which treatment approaches may be warranted in light of the exact pathology found within that joint. Radiographic evaluation has been the mainstay of these approaches for decades. Radiographic changes associated with OA can include loss of joint space, subchondral bone sclerosis, subchondral cystic lesions, periarticular marginal osteophyte formation, periosteal new bone production at sites of joint capsules and ligamentous attachments (enthesophytes), and occasionally subchondral lysis. These findings can progress from no abnormalities early in the course of disease to complete fusion or ankylosis of the joint as the disease progresses. The association of radiographic findings with clinical signs is not always clear, with severe pain occasionally being associated with minimal radiographic changes and, conversely, severe radiographic changes being associated with minimal to no pain. A well-studied example of this is OA of the distal metatarsal (i.e., tarsometatarsal and distal intertarsal) joints of horses.[24] Thus more advanced imaging modalities, including cross-sectional imaging, have been attempted to more accurately assess these joints. High-field magnetic resonance imaging (MRI) is superior to low-field imaging for

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evaluating articular cartilage, although both approaches can provide useful information. MRI is superior to radiographs for detecting early changes associated with OA in both the cartilage and the periarticular structures, including subchondral bone.[25] Scintigraphy can be particularly valuable in early disease states when other diagnostic methods have not revealed bone or soft tissue changes; anatomic detail, however, will be lacking. Computed tomography is an excellent imaging modality to examine increased density of subchondral bone, a major component of the pathophysiology of OA, especially in the context of repetitive trauma.[26] The use of sonographic imaging to aid in the diagnosis of OA in horses is rapidly expanding due to the utility of this imaging technique and to the inability of perform cross-sectional imaging of many large animal species due to size. Ultrasonographic evidence of OA is limited to evaluation of the contours of the bone, as the sound beam cannot penetrate bone. Effusion, presence of osteophytes, periarticular soft tissue structures, and in some cases limited views of articular cartilage can be obtained.[27,28] Finally, surgical arthroscopic evaluation of the articular surface likely provides the best ability to evaluate the articular cartilage of joints where arthroscopic evaluation is possible. This technique provides the added therapeutic benefit of simultaneous joint lavage and is used for these purposes in all large animal species.[29,30]

▪ Treatment

Because of the importance of lameness and OA in horses and other large animal species, there has been a great deal of research into developing effecting treatment approaches. As a result, there are many choices, with seemingly more each day. Clearly the choice will depend on the inciting cause of OA, stage of disease, joint involved, species involved, and use of that animal. In general, treatment of OA should be directed at eliminating any primary causes, halting disease progression, and encouraging repair and regeneration of damaged articular cartilage. An important point is to make the diagnosis early so that effective interventions can be implemented prior to the onset of irreparable joint damage. Examples of primary causes that should be addressed include recognition and surgical intervention of osteochondritis dissecans lesions, joint sepsis, and other underlying causes amenable to treatment. Specific treatments for OA are discussed in broad categories of treatment options, recognizing that there is a great deal of overlap among these options.

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AntiInflammatory Agents.

NSAIDs are a mainstay of this class of drugs and are used ubiquitously in equine veterinary medicine in the management of OA. Prostaglandin E2 (PGE2) contributes to the pain, inflammation, and cartilage destruction that accompanies OA. Thus inhibition of the cyclooxygenase (COX) enzyme that is responsible for the breakdown of arachidonic acids into various prostaglandins is desirable from both a pain and a disease-modifying perspective. Because inhibition of COX-1, the constitutively expressed isoform of the COX enzyme, contributes to damage to the gastrointestinal (GI) tract by NSAIDs, great effort has been made to generate NSAIDs that selectively inhibit COX-2, the inducible isoform considered to cause inflammation.[31] The effectiveness of this approach remains unclear in terms of safety, but likely both classes induce the desired antiinflammatory effect in OA.

Intraarticular steroids are the most potent antiinflammatory agents available and widely used in the management of OA in horses and other large animal species.[32] These drugs are administered both systemically and intraarticularly for the management of OA, but they have been associated with progressive cartilage damage and chondrocyte cell death both in vivo and in vitro in multiple large animal species.[33] These effects seem to be somewhat steroid dependent, with some steroids (i.e., methylprednisolone acetate) being more severe than others (i.e., triamcinolone).[34] Moreover, the negative effects of steroids, especially triamcinolone, appear to be mitigated by combining these products with hyaluronan in some contexts. Thus current recommendations are for judicious use of steroids in joints, paying attention to steroid used, mobility of joint (i.e., high-motion versus low-motion), and frequency of injections to mitigate the negative effects of steroids on articular cartilage.

Therapeutics Based on Replacement of Components of Normal Joints.

Numerous medications that consist of compounds found in joints have been specifically designed and marketed for treating OA in human and veterinary patients. Examples of these include polysulfated glycosaminoglycans (PSGAGs), hyaluronan, GAG peptide complexes, and chondroitin sulfate. These types of products are variably labeled for several routes of administration, including oral, intravenous, intramuscular, and intraarticular. Many of these products exert broad biological function from antiinflammatory properties to

providing substrate to support the host repair process. Among these products, hyaluronan is the most widely studied. Most sources agree that larger molecular mass (i.e., >500 kDa) is important for any biological function to exist.[35] At masses greater than 500 kDa, hyaluronan is thought to improve the viscoelasticity of synovial fluid and exert antiinflammatory properties.[36] Much work remains to be done to clarify the effectiveness of hyaluronan, dose, ideal mass, and route of administration in regard to management of OA in large animals, although evidence exists that it is safe and appears to be beneficial in some contexts. Data on PSGAGS and similar products are equally equivocal regarding mechanisms, effectiveness, ideal product, and dosage. Despite these shortcomings, there are findings suggesting that this class of medications has benefit in the management of OA, primarily by exerting antiinflammatory properties and influencing proteoglycan degradation and production following administration. Importantly, intraarticular PSGAG administration has been shown to lower the number of bacteria required to cause synovial infection, and thus concurrent administration of intraarticular amikacin is recommended when administering PSGAGS in this manner.[37,38]

Regenerative and Biologic Therapies.

Several regenerative and biologic therapies exist for management of OA, and this is especially true for equine OA. Examples of such therapies include autologous conditioned serum (ACS), also called IL-1 receptor antagonist protein or IRAP; platelet-rich plasma (PRP); and mesenchymal stem cell (MSC) therapy. ACS is thought to inhibit the effects of IL-1 and induce several additional antiinflammatory cytokines within the joint. ACS is widely used for early OA, with both anecdotal and scientific literature supporting its efficacy, although not universally.[39,40] PRP is thought to provide a host of growth factors found in platelets to induce a beneficial change in joints affected with OA. Although strong evidence supporting its use for OA is lacking, there are data suggesting beneficial effects either alone or when combined with MSC therapy.[41,42] The therapeutic potential of MSC therapy offers an attractive means of regulating inflammation and regeneration of critical tissues lost in OA. As with PRP, data exist suggesting that this approach may offer advantages in the treatment of OA, but much work remains regarding dose, source (i.e., allogenic or autologous), timing of administration, and safety.[43,44]

In summary, a wealth of treatment options are available for the management

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of OA in large animals. Unfortunately, many of these approaches are not well understood, and work remains to determine many aspects of the management of OA in large animals. Recognition of disease, treating the underlying cause as early as possible, and making management decisions based on case specifics are a mainstay of therapy to have the best possible outcome.

▪ Prognosis

Prognosis for large animals with OA depends on the initiating factors, duration and extent of joint destruction, joint affected, species of animals, and intended use of the animal. With early and aggressive treatment, many animals can return to soundness and athletic performance. In other cases, salvage in the form of surgical arthrodesis may provide the most favorable outcome.

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Sprains, Subluxations, and Luxations

Will C. Jordan • Canaan Whitfield-Cargile

▪ Definitions

Sprains and luxations have been classified as type 2a traumatic arthritides.[1] These injuries have been categorized in three forms: mild, moderate, and severe. *Mild sprains* constitute injuries that involve the tearing or disruption of a minimal number of ligament fibers with no loss of integrity to the ligament. Hemorrhage and edema are typically present in the ligament. Injuries that involve a portion of the ligament, with loss of integrity, are considered *moderate sprains*. Laxity of the joint is often present with moderate injury, but complete separation of the ligament from the bone or complete separation of the body of the ligament is not seen. Significant hemorrhage and edema are present in the ligament. Injuries that involve tearing of the ligament, resulting in either complete separation from the bone or widening of the tendon fibers, are considered *severe sprains.* These injuries result in some form of joint instability, especially when the affected joint is manually stressed.

Luxations and subluxations are usually the result of severe sprains of periarticular or articular ligaments. *Luxations* represent the complete dislocation of the articular surfaces, whereas *subluxations* have only partial and incomplete disarticulation (Fig. 38.19).



FIG. 38.19 Dorsopalmar radiograph of a subluxated metaphalangeal joint after the joint has been manually stressed.

▪ Etiology and Pathophysiology

Sprains can be associated with acute injuries in which the ligaments are suddenly overloaded, resulting in acute failure or secondary to repetitive strains of submaximal loads resulting in less obvious breakdown but ultimately ligamentous injury. The latter results when maximal or near-maximal loads are repeatedly applied to the ligaments and associated structures, causing a degenerative type of lesion. Age can also be a contributing factor in these degenerative changes. Muscle fatigue can contribute to the weakening of adjacent structures, increasing the stresses applied to the supporting ligaments. It is suspected that most sprains of ligaments are due to acute overload, whereas tendon injury most likely occurs as a result of repetitive low-grade trauma resulting in molecular degeneration.[2] Luxations and subluxations are usually of traumatic origin, such as stepping in a hole or entrapment of a limb in a gate or fence, or subsequent to traumatic complete ligamentous disruption.[1]

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Typically, hemorrhage and edema form within the ligaments surrounding the joint capsule, or in severe lesions the hemorrhage can be periligamentous or intraarticular. Inflammation ensues, and the ligamentous or capsular lesion heals through fibrosis, forming a scar, with the predominant production of type III collagen. Type III collagen contains smaller-diameter fibrils and has fewer crosslinks than type I collagen, which is the predominant collagen type in normal tendons and ligaments. As the lesion matures, both fibril diameter and number of crosslinks increase, in addition to the proportion of type I collagen. This increases the strength of the injury, which can take weeks to months to heal but will ultimately be weaker than normal tissue.[3] Often the affected joint capsule and surrounding ligaments become fibrotic as healing occurs, resulting in decreased range of motion (ROM) in the affected joint. Secondary dystrophic mineralization of the affected soft tissue structures may occur and also adversely affect the joint's mobility.

Luxations of the coxofemoral joint in calves may be associated with calving injuries during dystocia or in cows being ridden while in estrus, or with a traumatic fall in the immediate postpartum period.[3] Shoulder joint luxations are usually the result of trauma.[4]

▪ Clinical Signs and Differential Diagnosis

Clinical signs vary depending on the severity of the sprain, location of injury, and time since the initial injury. The animal may have a history of mild lameness or decreased performance, as well as a history of a positive response to NSAIDs or stall rest. Patients with moderate to severe sprains will typically have a more pronounced, acute lameness or may be non–weight bearing on the affected limb. There may also be localized swelling, heat, increased joint effusion, or pain elicited on palpation or manipulation of the affected joint. Other signs may include abnormal limb positioning, decreased ROM, crepitus, and joint laxity. Injuries may present after an acute or traumatic insult as chronic lameness, or a chronic mild injury can present acutely with severe lameness if the collateral ligament completely ruptures. Chronic injuries are characterized by joint capsule thickening or enthesophyte formation at the origin and insertion of the affected collateral ligament.

Subluxations and luxations result in loss of joint function, loss of structural integrity of the limb, and potentially an acute varus or valgus deformity. Complete luxations in the horse are most common in the pastern, fetlock, and

hock joints.[5-8] Luxations can occur in the shoulder,[19] carpus, and coxofemoral joint, but these luxations are less common in horses.[9,10] Coxofemoral luxations are the second most common type of luxation in cattle.[3]

Differential diagnoses vary depending on the region affected and duration of injury but may include soft tissue contusion, synovitis and capsulitis, osteoarthritis, bursitis, musculotendinous injuries, fractures, physeal fractures, septic arthritis, tenosynovitis, and flexural or angular limb deformities.

▪ Diagnostic Tests

A thorough history and physical examination should be performed at presentation. The examination should include assessment of pain, swelling, heat, joint effusion, and joint instability. Patients presenting with only mild lameness should have a thorough lameness examination. Caution should be exercised in regard to perineural anesthesia, especially if there is evidence of joint laxity or instability or severe lameness, as perineural anesthesia could exacerbate the extent of joint damage or result in complete luxation once the affected area is desensitized, resulting in increased weight bearing.

Confirmatory diagnostics include diagnostic imaging to confirm sprain, luxation, or subluxation. The imaging modality of choice will vary greatly depending on species affected, size of animal, location of injury, and physical exam findings. Radiographs should be obtained to assess the joint's bony structures because concurrent fractures are common, with traumatic insults resulting in luxation. Stress views can be performed to assess the level of joint instability (see Fig. 38.19). One study reported on 17 horses with luxation or subluxation of the metacarpophalangeal (MCP) or metatarsophalangeal (MTP) joints.[5] All had rupture of at least one collateral ligament (CL) of the joint. In those horses, radiographs showed that 8 of 17 horses sustained fractures, 6 of which were avulsion fractures located at the origin of the CL. Other types of fractures identified in that study were splint bone fractures and small articular chip fractures. Fractures of the proximal or middle pastern bones can cause luxation or subluxation of the proximal or distal interpastern joint. Nuclear scintigraphy can also be used to evaluate insertional desmopathies that may not be radiographically apparent.

Ultrasonography is very useful in localizing and depicting the severity of ligamentous lesions and for confirming the association of fracture fragments identified radiographically. In acute cases, ultrasound evaluation often shows

hemorrhage within the joint capsule (Fig. 38.20). Ultrasonography is often a useful imaging modality to assess the integrity of joints that may not be amenable to radiographs such as the coxofemoral joint, where this modality can be an important component of the diagnosis.[11] Cross-sectional imaging including CT or MRI is useful in the diagnosis of joint integrity, and MRI is the gold standard for imaging and diagnosing ligamentous injuries in large animals.[12,13]

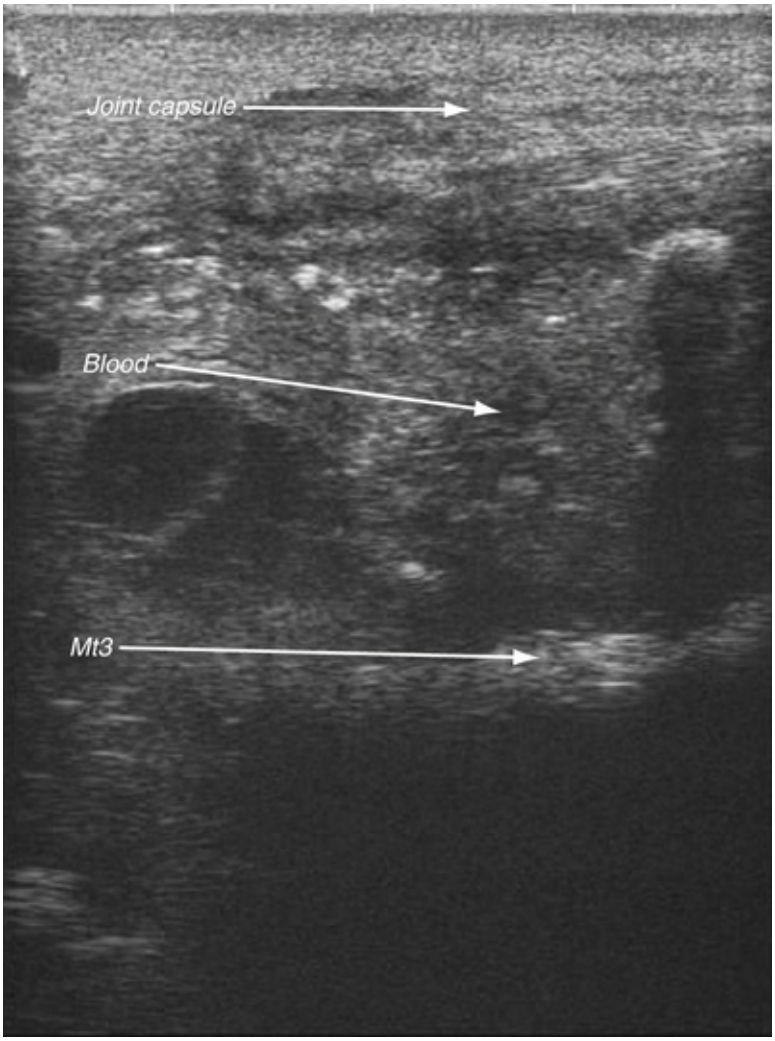


FIG. 38.20 Ultrasound image of a metacarpophalangeal joint from a horse with an acute sprain. Note the hemorrhage accumulation within the joint capsule. *Mt3,* Third metatarsal bone of fetlock joint.

▪ Treatment

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Treatment varies widely based on the severity of the injury, location, and associated structures involved. Mild sprains can be treated conservatively with support bandages, NSAIDs, polysulfated GAGs, and rest for 3 to 4 weeks, followed by a controlled exercise program before returning to normal activity. Adjunctive physiotherapies such as hydrotherapy or shock wave treatment may also be considered. Moderate sprains involving significant ligament damage may necessitate use of a cast or splint to provide joint stability during the initial healing process. Distal limb immobilization with a fiberglass cast and stall confinement was the initial treatment for 10 of 17 horses with MCP or MTP luxation and CL rupture. Duration of cast immobilization ranged from 14 to 132 days (mean = 71 days).[5]

In acute cases, hemorrhage is often present within the affected joint. This hemorrhage usually resolves after 7 to 10 days, but it can also subsequently form a fibrinous clot within the joint capsule, resulting in a chronic, mild synovitis that may necessitate treatment with intraarticular antiinflammatory agents, including sodium hyaluronic acid and triamcinolone.[14,15] Diagnostic arthroscopic surgery should be considered to evaluate articular cartilage integrity and remove persistent fibrin accumulation. If arthroscopic surgery is performed, a cast or splint should be applied to the affected limb during recovery from anesthesia to prevent luxation of the affected joint and further injury. Severe sprains may require some form of internal coaptation (surgical implants) or arthrodesis of the joint, depending on the degree of joint instability. Support of the contralateral limb should be considered for non–weight-bearing injuries.

Luxations of the coxofemoral joint in cattle can be repaired by open or closed techniques, and success depends on duration of the luxation, concurrent fractures or soft tissue injury, and age. Open reduction was reported as being more successful than closed reduction, although closed reduction should be attempted immediately after the injury if possible.[3] In select cases, femoral head otectomy can also be considered.[9,16] Shoulder joint luxations can also be reduced by closed and open techniques, with degree of injury, clinician preference, success of closed approach, and damage to other structures dictating which approach is chosen.[17,18]

▪ Prognosis

Prognosis depends on the severity of damage to the intraarticular cartilage and surrounding soft tissue structures. Horses that sustain mild joint or ligamentous

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strains have a good prognosis for returning to previous athletic use. Horses that sustain moderate or severe sprains or joint luxations usually develop secondary DJD in the affected joint, which may require intraarticular medications and NSAIDs or, in some cases, surgical arthrodesis of the affected joint. The prognosis for survival and returning to athleticism varies widely based on many of these factors. The long-term prognosis for returning to athletic performance may be poor. Eight of 17 horses with MCP or MTP joint trauma resulting in joint instability and rupture of the CL returned to riding, and one returned to jumping activity after limb immobilization and stall confinement.[5]

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Arthrogryposis

Philippa Gibbons

▪ Definition

Arthrogryposis or multiple congenital contracture can be defined as a syndrome of persistent contracture present at birth.[1] In arthrogryposis, the limb cannot be straightened manually and there is improper articular alignment or rotational deformity.[2] Arthrogryposis is one of the most common congenital defects of cattle and is found more commonly affecting the forelimbs. Arthrogryposis should be differentiated from contractures as a result of congenital tendon contracture or contracture secondary to articular fracture, ankylosis, septic arthritis, agenesis, or dysgenesis of joints.[2]

▪ Etiology

There are several etiologies for arthrogryposis, including genetic, infectious, and toxic. A congenital syndrome comprising forelimb arthrogryposis, spinal dysraphism, and cleft palate has been documented in calves of primarily Charolais origin.[3] Arthrogryposis was documented as part of the clinical findings in Holstein calves with the inherited complex vertebral malformation syndrome.[4] Various other congenital syndromes have been reported in cattle, including vertebral agenesis and arthrogryposis of the pelvic limbs in a Holstein heifer calf[5] and arthrogryposis in Herefords.[1] Arthrogryposis multiplex, or “curly calf syndrome,” is an autosomal recessive defect in Angus cattle where kyphoscoliosis and decreased muscling are also observed.[6] While not as common as in ruminants, arthrogryposis has been reported in equines, including Norwegian Fjords[7] and a Thoroughbred foal.[8] Arthrogryposis has been documented as an autosomal recessive condition in Suffolk[9] and Corriedale sheep.[10] There are no documented case reports of arthrogryposis in camelids.

Viruses of the family *Bunyaviridae* have a common tropism for fetal tissues and result in abortion, stillbirths, and arthrogryposis.[11] The viruses include Akabane virus, primarily found in Australia, Asia, and the Middle East,[11] and the Cache Valley virus in the United States.[12] Both wild and domesticated

ruminants and horses are susceptible to the Akabane and Aino viruses.[11] Concurrent defects include hydranencephaly or microcephaly, cerebellar hypoplasia, and irregular neuromuscular development.[11,13,14] More severe defects are found with infection earlier in gestation.[11,14] In 2011, a syndrome comprising fever, decreased milk yield, diarrhea, and abortion or stillbirth was reported in adult dairy cattle in Northwestern Europe.[15] Abortions, stillbirths, and live births with congenital malformations were reported in calves, lambs, and kids.[16] Congenital defects included arthrogryposis, brachygnathia inferior, spinal curvature, hydrocephalus, hydraencephalus, porencephaly, and cerebellar hypoplasia. The syndrome was found to be caused by a novel virus of the Simbu serogroup of the genus *Orthobunyavirus* and was named Schmallenberg after the town in Germany where it was first detected.[15] The virus is currently diagnosed by reverse transcription polymerase chain reaction (RT-PCR).[15,17] No vaccine is currently available. In utero infection with bluetongue virus in cattle and sheep primarily presents with hydranencephaly, although arthrogryposis, prognathia, brachygnathia, and excessive gingival tissue has been reported.[18] The pestivirus causing border disease in lambs was shown to result in several congenital abnormalities when experimentally inoculated into pregnant ewes, including arthrogryposis, tremors, brachygnathism, prognathism, and lateral deviation of joints.[19]

Arthrogryposis has been associated with the ingestion of toxic alkaloids during pregnancy, including those of the plant species *Conium, Lupinus,* and *Nicotiana*.[20] All three have been shown to also result in cleft palate deformities when fed to goats during days 30 to 60 of gestation.[20] Arthrogryposis as a result of lupine toxicity has been termed “crooked calf disease.” Congential contractures have also been reported with the grazing of sorghum pastures by sheep[21] and feeding *Veratrum californicum* at day 29 of gestation in sheep.[22]

▪ Pathogenesis

The pathogenesis of arthrogryposis is thought to be a result of denervation resulting in muscle atrophy, with the functional opposing muscles resulting in contracture.[23] Reduced numbers of ventral horn cells have been reported in cases of multiple congenital contracture.[24] Restriction of fetal movement in utero has also been proposed.[24]

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▪ Treatment and Prognosis

Animals with arthrogryposis may be aborted, stillborn, or born alive. The prognosis for survival, however, is poor. Treatment has been attempted by tenotomy of the ulnaris lateralis and flexor carpi ulnaris followed by stall confinement and bandaging.[25] In that study, a straight palmar carpal angle was achieved at the 8-month follow-up in 70% of the limbs. Outcome was improved in the less severely affected limbs.[25] Arthrogryposis in aborted or near-term fetuses commonly results in dystocia, leading to the need for manual removal of the fetus by fetotomy or cesarian section,[2,14] or in the death of the dam.[11] Severely affected animals commonly have secondary problems, including sepsis and metacarpophalangeal deformities.[25] Surviving animals should not be retained in the herd as breeding animals.

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Ankylosis

Ricardo Loinaz

▪ Definition and Etiology

Ankylosis refers to the abnormal fusion of bones in a joint, which can occur naturally or as a desired result of treatment. *Facilitated ankylosis* refers to a medical fusion and thus is different from *arthrodesis,* or surgical fusion, of two or more bones into a single structure.[1] Naturally occurring ankylosis is often the result of disease or trauma to the joint and bones involved. Septic arthritis with subsequent DJD and associated prolonged therapy, including joint immobilization, are often the inciting factors for ankylosis. *Congenital ankylosis* is the absence of an articulation, and it is a rare condition in horses and cattle, often associated with other congenital abnormalities.[2] Congenital ankylosis of the DIJ in both hindlimbs, with concurrent dysplasia of the distal sesamoid bone in all four limbs, has been reported in a 2-year-old Arabian horse.[3] In calves and foals, congenital ankylosis may occur between vertebrae or in multiple joints of the limbs, resulting in dystocia related to musculoskeletal inflexibility.[2]

Joint fusion is initiated by biomechanical and biochemical factors, leading to instability and degeneration of cartilage and chondrocytes.[2] Periarticular contracture, joint capsule fibrosis, and chronic muscle spasm all contribute to joint immobility, which leads to synovitis and cartilage destruction. Ossification of periarticular soft tissues develops, resulting in partial bone bridging across the joint. The final stage of ankylosis is complete bone bridging with trabecular bone and joint obliteration.

Common sites of ankylosis in horses include the distal hock joints (distal intertarsal [DIT] and tarsometatarsal [TMT]), the thoracolumbar intervertebral articulations, and the proximal interphalangeal (PIP) joint. These low-motion joints are more likely to achieve complete bone bridging without surgical intervention. In high-motion joints (antebrachiocarpal, midcarpal, metacarpophalangeal, scapulohumeral, and distal interphalangeal), naturally occurring complete bone bridging is rare, and the resulting cartilage degeneration leads to severe lameness. In these cases, surgical fusion or arthrodesis using internal fixation techniques is required if treatment is to be attempted.[4] Large animals with vertebral ankylosis may show neurologic deficits

caused by bony impingement on the spinal cord or by dynamic compression leading to abnormal motion or spinal ligament hypertrophy.[2]

▪ Clinical Signs and Differential Diagnosis

Indications for ankylosis include stiffness of a joint and associated immobility, degenerative joint changes, decreased range of joint motion, and varying degrees of lameness. Decreased ROM is most obvious if high-motion or multiple joints are involved. Degree of lameness can range from mild to severe, particularly in the acute phase when local inflammation contributes to the degree of lameness. Enlarged and thickened periarticular structures, conformational abnormalities, disuse atrophy of muscles or disuse osteopenia of bones, and gait stiffness may also be identified. Once bone bridging is complete and no articular cartilage remains, the condition is no longer painful, and the articulation is immobile.

Differential diagnoses include soft tissue injuries or contracture, intraarticular or periarticular adhesions, joint luxation, neoplasia, arthrodesis, spondylosis, an intraarticular mass, osteomyelitis, and fracture. Diagnosis of ankylosis should be based on a complete physical and musculoskeletal examination, lameness evaluation, and radiography. Multiple radiographic views should be available for definitive diagnosis, but additional imaging techniques such as ultrasonographic evaluation of relevant soft tissues and joint spaces, CT, and MRI may be useful and provide more detailed information that may influence the treatment option chosen.

▪ Treatment and Prognosis

Treatment in the acute phase focuses on providing comfort to the animal, because ankylosis is a chronic and progressive disease process. A complete treatment plan should be tailored to the specific case and is often determined by the presence or absence of infection or severe joint instability. Antiinflammatory medications (phenylbutazone, firocoxib, flunixin meglumine, intraarticular corticosteroids) are necessary in most cases. Additional oral joint supplements, hyaluronic acid, or polysulfated polysaccharides may also be beneficial as chondroprotectants. Although joint immobilization and a decrease in exercise are often necessary, low-level exercise appears to be beneficial in some cases because it helps increase and stimulate development of new bone formation, promoting faster and more complete ankylosis.[2] Unstable joints or actively septic joints, however, require immobilization with splints or casts to allow the

fusion to progress and improve the animal's comfort level. Animals that remain lame, have end-stage joint disease, or are not completing ankylosis naturally require surgical or chemical arthrodesis to improve the comfort level and chances of returning to performance activity.

Different methods of facilitated ankylosis can be used to promote joint fusion. The speed at which complete bone bridging occurs may be enhanced through chemical chondrocyte destruction or surgical obliteration of the articular cartilage. Chemical methods of ankylosis include the use of sodium monoiodoacetate (MIA) and ethyl alcohol, but MIA has been associated with considerable morbidity and signs of severe pain.[1] In addition, postinjection soft tissue swelling, progression of osteoarthritis to adjacent unaffected joints, severe soft tissue necrosis, variable length of convalescence, and inconsistent outcomes are why MIA-mediated ankylosis can no longer be recommended.[5] Ethyl alcohol ankylosis works via nonselective protein denaturation and cell protoplasm precipitation and dehydration. One of the first controlled studies investigating the use of ethyl alcohol in horses found that 70% ethyl alcohol injected in the TMT joint of healthy horses with no radiographic evidence of joint disease resulted in a pain-free fusion by 4 months in 8 of 16 horses and complete fusion by 12 months post injection in 15 of 16 horses.[6] A recent study evaluated the safety and efficacy of ethyl alcohol–mediated ankylosis of the DIT and TMT joints in horses with lameness localized to those joints and found a significant reduction in posttreatment lameness in all treated horses but evidence of joint collapse and progressing ankylosis by 3 months post injection.[1] Another study looked at 24 horses that received ethyl alcohol injections in the distal hock joints; 52% had improved lameness scores at 6- and 9-month follow-up, whereas 19% had deteriorated.[7] A recent study looked at 70% ethyl alcohol injection alone or in combination with lag screw placement for PIP fusion, and in both instances alcohol treatment failed to produce reliable fusion of PIP joints.[8] Another recent study looked at facilitated ankylosis of PIP joints using ethyl alcohol and reported that 50% of horses were sound and 34% were improved but not sound at time of follow-up.[9] The median time for horses to become sound enough to return to work in this study was 8 months, suggesting that ethyl alcohol–facilitated ankylosis may be more effective and work faster in DIT and TMT joints than in PIP joints.

Facilitated ankylosis via surgical débridement of articular cartilage and use of casts or transfixation casts is recommended in the initial treatment of septic PIP

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joints instead of surgical arthrodesis in the acute phase.[5] Laser-facilitated ankylosis using a neodymium-doped yttrium aluminum garnet (Nd:YAG) or a diode laser to destroy articular cartilage by superheating and vaporizing synovial fluid, resulting in chondrocyte death, can also be used for facilitated ankylosis. Experimental studies using laser-facilitated ankylosis in DIT joints found that partial ankylosis was achieved in 5 to 12 months.[5] Transarticular drilling has been used as a method for ankylosis of the DIT and TMT joints, alone or in combination with laser application, and estimates of outcomes suggest that this technique is 47% to 85% successful.[5]

Ankylosis may require 6 to 12 months for complete bone bridging after surgical or chemical treatment methods. This process can take several years if left to natural ankylosis. Prognosis depends on which joint is involved and the expectations for use of the animal. Low-motion joints have a good prognosis for returning the horse to soundness and athletic performance once the fusion process is completed. High-motion joints have a poor prognosis for return to use in horses.

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Osteomyelitis

Canaan Whitfield-Cargile

▪ Definition and Etiology

Osteomyelitis is an inflammatory disease of bone and its marrow cavity characterized by bone destruction and caused by infection.[1] The location of infection along a bone can vary and will depend on the cause of infection. Possible locations of infection include a local infection of a single region of bone such as the physis or a focal infection along the diaphysis or a more generalized infection involving several structures, including marrow, cortex, periosteum, and surrounding soft tissue.[2] If only cortical bone is affected, it is classified as osteitis. Most osteomyelitis cases in large animals are bacterial in origin, although mycotic infections have been reported.[3,4] The origin of infection can be hematogenous spread following bacteremia, especially in neonates, or extension of infection from adjacent soft tissue infection or by direct inoculation often associated with a traumatic event.

▪ Clinical Signs

Clinical signs will depend on location of infection, severity of infection, and in some cases the organism involved. Diagnosis is based on clinical findings and ultimately confirmed with diagnostic imaging with culture and histopathologic evaluation of samples from the affected bone. As stated above, there are some differences in osteomyelitis between neonates and adults. In neonates, osteomyelitis is frequently caused by hematogenous spread due to translocation of bacteria from the umbilicus or other sites of infection (e.g., respiratory, gastrointestinal). In the foal, common anatomic locations of established infections have been described and characterized by a classification system.[5] The classification system is based on anatomic location of the infection; *S-type infections* involve only the synovial membrane, *E-type infections* involve the articular epiphyseal complex, and *P-type infections* are infections of the long bone physis. Clinical signs vary based on location of infection, but typically S-type and E-type infections are associated with lameness and synovial effusion. P-type infections also appear lame, although potentially seem less severe that S-type and E-type infections, and instead of synovial effusion have soft tissue

swelling in the area of the affected metaphysis. Irrespective of location of infection, pyrexia often accompanies osseous infection of neonates. Although any structure can be involved, the high-motion joints (i.e., femoropatellar, tarsocrural, carpal, and metacarpophalngeal) are most commonly affected.

Osteomyelitis in adults is usually associated with trauma resulting in direct inoculation of deeper tissues ultimately leading to bone infection.[6] Hematogenous spread, however, does occur, and this is especially true for cases of osteomyelitis involving the axial skeleton.[7] Clearly, clinical signs will depend on site of infection. When limbs are affected, the most common clinical sign is lameness, and the degree of lameness will vary depending on location and severity of infection but is frequently mild initially and then progresses to non–weight-bearing lameness. Other clinical signs of osteomyelitis of adults include regional soft tissue swelling, pain on digital palpation, fever, and draining tracts in the case of traumatic osteomyelitis where the wound has failed to heal.[2] Time of onset of clinical signs from injury (including postoperative surgical site infection) is highly variable and may be present as early as a few days or be delayed up to 3 to 4 weeks.[8] Chronic osteomyelitis becomes more localized as the disease progresses and often results in a firm swelling over the affected area. Persistent drainage from an incision or area of granulation tissue, mild to severe lameness, or a nonhealing wound are also often seen with disease progression in chronic cases. Drainage may be persistent or intermittent and is generally characterized as purulent. Osteomyelitis, in conjunction with septic arthritis or tenosynovitis, may result in only mild lameness if the wound is open and able to decompress but will result in non–weight-bearing lameness if the wound seals due to accumulation of exudate and/or synovial fluid resulting in stretching of the joint capsule and other structures.

▪ Diagnosis

Prognosis rapidly decreases with duration of unmanaged synovial and osseous infections in all animals but especially in neonates, so prompt diagnosis is critical. In neonates, persistent lameness that is unresponsive to antiinflammatory treatment often precedes diagnosis, but lameness can be subtle during the early stages of osteomyelitis and easily mistaken for traumatic musculoskeletal injury rather than an infectious process. It is recommended that any lameness in a neonate be thoroughly evaluated for evidence of infection, including a complete physical examination, serial radiographic evaluation of any

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abnormal findings, and potentially more advanced imaging when in doubt. Additional diagnostics, especially in the case of subtle disease, include CBC, fibrinogen, and potentially other acute-phase proteins, although all of these have not been studied extensively in the context of osteomyelitis of neonates.[9] Fibrinogen greater than 900 mg/dL has been shown to be associated with septic physitis and/or osteomyelitis in foals and could help justify more advanced imaging in cases where the diagnosis is difficult. Advanced imaging, including CT and MRI, is increasingly used to diagnose or more accurately characterize the location and severity of osteomyelitis, especially in neonates, as their size greatly enhances the capability of these approaches and the complex nature of osteomyelitis in neonates frequently indicates a more advanced approach.[10,11]

In adults, osteomyelitis is difficult to diagnose with radiography in the acute stages, as radiographically apparent osseous changes will take time to develop. In fact, osteolysis does not appear on radiographs until 30% to 50% of bone mineral is lost, which may take up to 10 to 14 days after infection is established.[12] In early stages of disease, soft tissue swelling with or without gas opacities adjacent to the area of infection may be the only abnormalities noted.[13] In both adults and neonates, ultrasonography can aid in early diagnosis of osteomyelitis by detecting purulent fluid in soft tissues and periosteal involvement and can provide guidance for other confirmatory diagnostic tests, including aspiration of suspect areas for cytology and culture.[14] Radiographic signs of chronic osteomyelitis include soft tissue swelling with bone destruction and new bone formation. Infection of bone may result in the formation of an *osseous sequestrum*, an isolated portion of radiodense cortical bone that has lost local vascular supply (Fig. 38.21). The sequestrum is well defined by an outline of radiopaque productive new bone formation called an *involucrum*, which forms as a result of attempts to wall off infection.[2] An opening to the sequestrum, the *cloaca*, is usually present and allows drainage of purulent exudate to the skin surface. Sequestra are prevalent following trauma to horses, with more than 30% of wounds to the limbs resulting in sequestra formation.[15] The diagnosis of sequestra is usually made radiographically 3 weeks after initial injury and, occasionally, contrast fistulography can be useful in determining the extent of draining tract communication with bone or joints. Advanced imaging modalities provide greater diagnostic capabilities than radiography and may help in the early detection of osteomyelitis.[14] CT gives superior imaging of bone, can be reconstructed in three dimensions, and provides excellent information about

the cortical bone and medullary involvement.[1] CT is also indispensable for evaluating anatomic locations where interpretation of other imaging modalities is complicated by superimposition of complex anatomy (Fig. 38.22).



FIG. 38.21 Osseous sequestra formation on the dorsolateral aspect of the third metatarsal bone following a laceration to the level of the periosteum 2 weeks previously. Note the new bone formation (involucrum), the isolated portion of cortical bone (sequestrum), and the radiolucent area surrounding the sequestrum (cloaca).

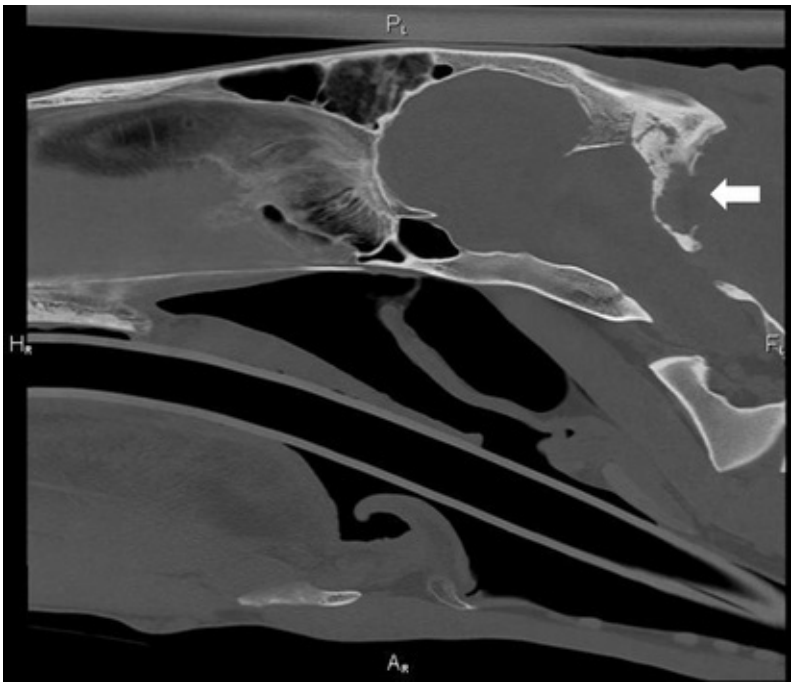


FIG. 38.22 Computed tomography demonstrating osteomyelitis of occipital bone *(arrow)* following extension of infection from nuchal bursitis.

Microbial culture and sensitivity testing should be performed to confirm a diagnosis of osteomyelitis and to guide selection of antimicrobial drugs for treatment. Samples should be collected aseptically and inoculated directly into culture media to improve the chances of obtaining bacterial growth. Swabs taken from an open draining sinus tract may include commensal bacteria that are not responsible for osseous infection. Both aerobic and anaerobic culture testing should be performed on samples when osteomyelitis is suspected. Blood culture may be useful in isolating the infectious organism in the neonate. If there is any suspicion that the osseus infection has spread to synovial structures, appropriate synovial fluid should be collected aseptically and submitted for cytology and culture and sensitivity to confirm involvement. The most commonly isolated gram-negative bacteria from foals include *E. coli, Actinobacillus* spp., and *Salmonella* spp. Gram-positive isolates include *Streptococcus* spp., *Staphylococcus* spp., and *R. equi*.[16,17] In the adult horse, members of the Enterobacteriaceae family, *Streptococcus* spp., and *S. aureus* are the most commonly isolated microorganisms in cases of osteomyelitis, septic arthritis, and tenosynovitis.[8,18]

▪ Pathophysiology

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Development of osteomyelitis is related to host factors (i.e., trauma, immune response, etc.) and microbial factors (i.e., virulence, ability to form biofilm, etc.). In the case of sequestra formation, cortical bone becomes exposed, resulting in desiccation of the periosteum, and this may result in a devitalized portion of cortical bone that, if contaminated, can become infected.[19] The host response to these bacteria involves invasion of inflammatory cells, including neutrophils that release proteolytic enzymes in an attempt to clear the invading pathogen. These enzymes are nonspecific, and thus a portion of the surrounding tissue becomes collateral damage (i.e., the cloaca). If the host is unable to eliminate the infection in a timely manner, the exudate accumulates and bacteria colonize adjacent periosteal, cortical, and medullary regions of bone and form a biofilm. A recent study demonstrated that the majority of equine wounds have evidence of biofilm formation, so this should be considered when electing treatment approaches.[20,21] Within this biofilm, bacterial microcolonies develop and bacteria become quiescent and are able to evade host immune response and medical therapies while continuing to produce matrix material.[22] These defense mechanisms are the principal reason that osteomyelitis persists without aggressive therapy.[23] These issues are compounded when foreign material (i.e., metallic implant) or necrotic tissue (i.e., sequestered bone) exists.

▪ Treatment

Early diagnosis and aggressive therapy are critical in preserving normal function to the limb in neonates affected by osteomyelitis and preventing extension of infection in all animals.[2] Left untreated, irreversible damage to the growth plate or articular cartilage may cause lifelong debilitating lameness in the affected limb in neonates. As noted above, because bacteria can evade host immune response and medical therapies by residing on necrotic tissue or, more commonly, in a biofilm, medical treatment is often unsuccessful once osteomyelitis is established, and surgical intervention is required. The goals of treatment are to physically remove bacteria, inflammatory debris, and devitalized tissue and to prevent recurrence, as physical removal of all bacteria is rarely possible and therefore recolonization occurs quickly without appropriate continued therapy.[24] Long-term medical therapy typically consisting of antibiotics is directed at preventing recurrence, although the length of time to continue and the effectiveness of long-term antibiotics remain questionable in both human and veterinary medicine.[25]

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Medical Management.

Medical management, including parenteral antimicrobials and topical wound dressings, may reduce drainage and contain infection to a single area but is rarely successful as a single treatment of osseous sequestra or osteomyelitis. Medical therapy primarily consists of antibiotics, and the selection of antibiotics should ideally be based on culture and sensitivity results. If this information is not available, empirical selection of broad-spectrum antibiotics that will have good delivery to the site of infection is indicated although less than ideal.[26] In the neonate, another facet to consider is that osteomyelitis often occurs due to other disease processes, including failure of passive transfer, pneumonia, septicemia, gastroenteritis, colitis, and omphalophlebitis, and thus appropriate diagnosis and management of these comorbidities is a critical component of managing the entire animal when treating osteomyelitis in neonates.

Surgical Management.

The goal of surgical treatment is to increase efficacy of antimicrobial treatment and host defenses by breaking down the biofilm matrix, removing necrotic debris with infected tissue, promoting vascularization of compromised tissues, and in most cases establishing drainage. For example, in cases of osseous sequestra, sequestrectomy with effective débridement can resolve infection rapidly and decrease the duration of antimicrobial therapy.[19] Successful treatment depends on removing necrotic tissue lining the draining tract, opening the cloaca to access and remove the sequestered piece of bone, and aggressive débridement of all infected bone and exudate. Cancellous bone graft or antibiotic-impregnated beads can be used to fill in large defects following sequestrum removal. For other cases of osteomyelitis, the surgical principles are the same and include the goals of débridement of all infection and necrotic tissues, removal of biofilm, and usually establishment of drainage. The surgical technique for accomplishing these goals will vary depending on the details of each case.

Local Delivery of High Concentrations of Antimicrobials.

When possible, local antibiotic delivery is preferred over systemic therapy, as local delivery techniques allow for much higher concentration of antibiotics at the site of infection while avoiding systemic toxicity. Several local delivery techniques are available, including antibiotic-impregnated beads, regional limb

perfusion (RLP) techniques, and constant rate infusion systems for synovial structures, to name a few.

Antibiotic-Impregnated Beads.

Antibiotic-impregnated beads have been used extensively to treat osteomyelitis in horses and other large animal species.[27-30] This technique has been shown to be beneficial to the treatment of orthopedic infection in both human and veterinary medicine.[31,32] Beads are most commonly made from polymethyl methacrylate (PMMA), which is not biodegradable, or plaster of Paris (POP), which is biodegradable. Although elution characteristics vary based on antibiotic, bead size, bead porosity, and nature of the site of implantation (i.e., highly exudative versus minimal exudate), PMMA elution characteristics are typically described as bimodal with a rapid release in the first 24 hours followed by low-grade, long-term release over weeks to months.[33] POP beads, by contrast, typically have rapid high concentration elution characteristics, and POP inherently possesses osteoconductive properties, making it an attractive choice for osteomyelitis, especially in situations where new beads can be easily added (i.e., open wound).[34] Antibiotic-impregnated beads can be commercially purchased or easily made. Other antibiotic-impreganated substances (i.e., collagen) exist for treating infections, and these have been occasionally used in large animals although not extensively studied.

Regional Limb Perfusion.

Regional limb perfusion of antimicrobials is an effective way to deliver a high dose of antimicrobials to an isolated area. For RLP to be effective, it is critical to have adequate venous access, appropriate tourniquet application, and adequate patient restraint. The technique involves a tourniquet placed proximal and distal (or proximal only in cases of distal limb infections) to the site of infection in order to isolate the venous system in the region of the infection from systemic circulation. The tourniquet's tightness typically occludes the venous system but only partially occludes the arterial system, resulting in a pressurized venous system that allows for antibiotics injected into this system to diffuse into the surrounding tissues and, in some cases, even poorly perfused tissues.[26] Vascular access can be obtained by placing a needle or catheter into an accessible vein located between the tourniquets. Alternatively, intraosseous access can be obtained with a cannulated screw or similar device and effective delivery of

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antibiotic can be obtained with either approach, although there appear to be differences in concentrations achieved when comparing vascular RLP with intraosseous RLP.[35,36] The exact volume of perfusate, type of tourniquet, and duration of tourniquet application is still debated.[37-42] Although many of these details still need to be optimized, a few points have become more clear: (1) volume of perfusate—it seems clear that higher volumes (60 to 100 mL) result in greater diffusion of antibiotics to the tissues, (2) antibiotic choice—although much work remains here, aminoglycosides are well studied and readily available, and their concentration-dependent action makes this class an excellent choice for RLP, (3) exangunation seems unnecessary, (4) timing of tourniquet application—greater than 20 to 30 minutes is difficult to achieve due to patient factors, and it seems there is minimal difference after 15 minutes, and (5) many other details are debatable and require more work to identify the correct decision.[39,43,44] In summary, RLP is an excellent choice for local delivery of antibiotics and should be considered when treating osteomyelitis in large animals.

▪ Prognosis

The prognosis of osteomyelitis in large animals depends on location of infection, severity of infection, synovial involvement, presence of orthopedic implant, and presence of other comorbidities, especially in neonates. Reports describing survival of adult horses with osteomyelitis vary from 10% to 100% based on many of these factors.[6,45] Similarly, reports describing survival and return to function of neonates with osteomyelitis also vary widely.[16,46] It is clear that with a prompt diagnosis, consideration of comorbidities, evaluation and management of synovial structures, initiation of appropriate therapy including removal of necrotic and infected tissue, biofilm removal and management, and appropriate use of antimicrobials with an emphasis placed on local delivery techniques, success can be achieved in many cases.

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Heel and Foot Pain

Sarah N. Sampson

▪ Introduction

Lameness associated with the foot is the most common cause of lameness in any type of horse. Predominantly this is lameness affecting the front feet, but there are also a number of horses with hind foot lameness that blocks to the heel and foot. In this section, heel and foot pain is used due to our inability to specifically localize foot pain to the navicular region with any diagnostic block other than a navicular bursa (NBSA) block. Historically, lameness that blocks to a palmar or plantar digital nerve (PDN) block (aka “heel block”) was called navicular disease. However, this term was changed to navicular syndrome once it was realized that the navicular bone is only one of many structures affected in horses that blocked to a PDN block. These navicular syndrome horses are now referred to as “heel pain” or “foot pain” horses, because we realize that a PDN block is not just blocking the navicular region. In 1996, when we started evaluating the feet of live horses with MRI, it became evident that the PDN block was actually resulting in anesthesia of many structures in the foot other than those in the navicular region. It is important to realize that in this section on heel and foot pain, all of the structures listed below can be anesthetized with a PDN block due to proximal diffusion of the block and the variable range of anesthesia achieved with this block. Depending on diffusion, it is also possible in some instances to block structures in the fetlock region.

1. Distal aspect of first phalanx
2. Middle phalanx
3. Distal phalanx
4. Collateral cartilages
5. Navicular bone (distal sesamoid bone)
6. Oblique and straight distal sesamoidean ligaments
7. Proximal and distal digital annular ligaments
8. Deep digital flexor tendon
9. Superficial digital flexor tendon branches
10. Collateral sesamoidean ligament (aka navicular suspensory ligament)

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11. Distal sesamoidean impar ligament
12. Collateral ligaments (proximal and distal interphalangeal joints)
13. Proximal interphalangeal joint
14. Distal interphalangeal joint
15. Navicular bursa
16. Digital flexor tendon sheath
17. Laminar tissue

▪ Pathophysiology

The ability to use MRI on live horses has enabled us to obtain a definitive diagnosis in horses with heel and foot pain. Due to the number of different clinical presentations as well as the number of structures that may or may not be affected, the etiology of pathologic change in the heel and foot can vary widely. For example, if a horse has unilateral deep digital flexor tendon (DDFT) pathology in the heel and no other structures are affected, this is likely a traumatic injury. Conversely, if a horse has bilateral DDFT pathology with concurrent navicular bone (NB) pathology and distal sesamoidean impar ligament (DSIL) and collateral sesamoidean ligament (CSL) desmopathy, this is more likely to be a degenerative process with a possible genetic predisposition (Quarter Horses, warmbloods, and Thoroughbreds are overrepresented and Arabians are underrepresented in horses presenting with heel and foot pain).

The exact etiology of NB pathology remains unclear, but a biomechanical theory has the most experimental support at this time and suggests that the degenerative changes in the NB result from abnormal forces exerted on the bone and its supporting ligaments (the DSIL and CSL). The podotrochlear apparatus (NB, CSL, DSIL, NBSA) and the DDFT and distal digital annular ligament (DDAL) are intimately related in the heel region from a biomechanical perspective, and these structures are often affected concurrently. Compression of the distal half of the NB by the DDFT is an important aspect of this theory. The greatest forces to the NB are applied during the propulsion phase of the stride, during extension of the distal interphalangeal joint (DIJ) just prior to toe off. The DDFT, CSL, and DSIL act to stabilize the DIJ as they are put under tension during the propulsion phase. The biomechanical force applied to the NB depends on hoof conformation and is increased in horses with low heels and decreased in horses with more substantial heels. There are also cases in which unilateral NB pathology can be due to a traumatic event, although this is much less common.

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There are also a number of very young Quarter Horses (<5 years) that have been diagnosed with severe bilateral navicular region pathology, often including NB flexor cortical erosions. These horses have often not been in any significant work, and the severity of disease cannot be explained easily using the biomechanical theory. These horses may have an even higher genetic predisposition than the Quarter Horses that develop navicular region pathology in the 10- to 12-year-old range when they have been in high-level performance for many years.

▪ History

Quarter Horses, warmbloods, and Thoroughbreds are the most common breeds affected with lameness localized to the foot with a PDN block, so signalment in regards to breed can be an important finding.[1] Most commonly, horses present with heel and foot pain between 8 and 12 years of age,[1] but they can present at any age after 2 years. Heel and foot pain can present as an insidious onset of unilateral or bilateral lameness or as an acute unilateral lameness.

Horses with an insidious onset of lameness present with poor performance complaints and/or complaints of intermittent forelimb lameness. Often these horses will have had one or more episodes of acute, obvious lameness that then improves quickly, and they are able to continue in performance for a limited period. Sometimes these horses are thought to have a foot abscess, but no drainage is seen and the horse improves temporarily. Horses with heel and foot pain may become more lame toward the end of the trimming and shoeing cycle and/or may be “tenderfooted” right after trimming and shoeing. Owners may also complain of stumbling, stiffness in the front end, pointing one front foot, and/or a shortened, choppy stride. A common history is that the horse was out of work and confined to a stall for some other reason and then was observed to be lame on one or both forelimbs on resumption of work.

Acute injuries in the heel and foot can present with a history of acute lameness during an event or when brought out of the stall or pasture. They may have improved partially with rest or not improved at all. However, with any riding or exercise, the lameness typically worsens again. As noted previously, owners may think the horse has a foot abscess and manage it accordingly until it becomes evident that the horse is not improving or the lameness continues to recur. With bilaterally lame horses, owners often think shoulder lameness exists because the horses move very stiffly. Also, horses with severe pathology can present

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similarly to a laminitic horse with slightly elevated pulses and a “walking on eggshells” look. It is important to perform a complete radiographic evaluation that includes a navicular skyline view, particularly if the horses are not sensitive over the toe to hoof testers.

▪ Diagnosis

Clinical Evaluation.

Clinical evaluation of any horse presenting for lameness begins with a thorough physical examination. The physical exam will often be normal in these horses, but some horses may have slightly increased digital pulses on the affected limbs and some horses may have palpable DIJ effusion on the affected limbs. Horses with DDFT and/or DDAL pathology in the pastern region may have thickening palpable in the palmar or plantar pastern. Abnormalities in hoof conformation are noted in many horses, but there is no correlation between the types of pathology seen within the foot and types of hoof abnormalities involving the internal structures of the foot. Horses with perfect feet can have the same pathology as horses with poorly conformed feet.

Hoof tester evaluation can be done either before or after the motion exam. Heel and foot pain horses may be negative to hoof testers, or they may have sensitivity in any area of the foot, although most commonly over the mid-frog region and heels. Hoof tester evaluation is a standard part of the lameness exam, but it does not correlate well with the type of pathology present in the foot and it is very important to remember that a negative hoof tester exam does not rule out foot pain. The hardness of the hooves, the thickness of the sole, and whether the horse is stoic can all influence whether the horse will respond to hoof tester pressure applied to the foot. Based on a group of bilateral forelimb lame horses that blocked to a PDN block, no correlation between hoof tester evaluation and MRI findings in the foot was found.[1]

Lameness Evaluation.

The lameness evaluation should be performed on smooth, hard ground. More severely affected horses can be lame at a walk (mildly lame to severely lame, depending on the pathology present). However, most horses with heel and foot pain will be sound at a walk and have mild to moderate lameness at a trot in a straight line. Horses that have a very symmetric, bilateral lameness may not look lame at a trot in a straight line but will be “choppy” or short strided.

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Circling these horses with the lame limb on the inside of the circle will commonly exacerbate the lameness when compared to movement in a straight line. Circling these horses with the lame limb on the outside of the circle may reveal lameness in the limb that is now on the inside of the circle. For example, a horse that is right front lame in a straight line may have an exacerbated right front lameness when circling to the right but then show a left front lameness when circling to the left. If a horse is unilaterally lame, it may show the same unilateral lameness in all directions.

Flexion tests performed on horses with heel and foot pain will often be positive to lower limb flexion. Occasionally the limb contralateral to the one being flexed will show increased lameness after flexion.

Diagnostic Anesthesia.

Localizing pain to the heel, foot, or pastern is commonly done with a palmar digital nerve block (1.5 to 2.0 mL/nerve). However, determining which structures are the source of pain can be challenging. It seems that the more we learn about diagnostic anesthesia, the more clouded the picture becomes. We used to believe that a PDN block localized the lameness to the heel or sole region, but this is not the case. Structures associated with the coffin joint, hoof wall, and pastern can also be desensitized with this block, depending on the amount of anesthetic diffusion that occurs.

The location of the lameness in the foot or pastern can be further defined using a DIJ (coffin joint) block, NBSA block, and/or digital flexor tendon sheath (DFTS) block in the lameness workup. When using these blocks, it is important to realize that a DIJ block can anesthetize the navicular region and a DFTS block can anesthetize some DDFT lesions within the proximal aspect of the foot. The NBSA block is the most specific block for navicular area pain, but it is also the most time consuming, so it is often not performed in a typical lameness evaluation. A positive response to NBSA block most likely reflects pathology in the navicular bursa, navicular bone, or supporting ligamentous or tendinous structures. Once the lameness has been localized to the pastern or foot region, diagnostic imaging is performed to attempt to identify the definitive cause of lameness.

▪ Diagnostic Imaging

Radiography.

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A minimum of three high-detail radiographic views should be used to evaluate the foot (lateromedial, 60-degree dorsoproximal-palmaro/plantarodistal oblique, and palmaro/plantaroproximal-palmaro/plantarodistal oblique [navicular skyline]), with additional views including a horizontal dorsopalmar view and a dorsomedial and dorsolateral 45-degree oblique view of the navicular bone and distal phalanx palmar processes. Examples of abnormal radiographic changes in the navicular bone include variation in size and shape of the synovial invaginations, cystic changes within the medullary cavity, enthesophyte formation at the wings, flexor cortical erosion, loss of corticomedullary distinction, sagittal fracture, distal border remodeling, and proximal and distal border fragments. Horses that block to a PDN block may have pathology in other bones in the pastern or foot. Examples of pathology seen in the distal phalanx include fracture, pressure necrosis from a keratoma, osteolysis, bone cyst, osteochondral fragment, and osteoarthritis associated with the DIJ. Pathologic changes can also be seen in the proximal and middle phalanges that can potentially block to a PDN block and can include bone cyst, osteoarthritis of the proximal interphalangeal (PIP) joint, and osteochondral fragments. Ossification of the collateral cartilages of the distal phalanx is common and can be associated with lameness, particularly if there is a fracture at the base of the ossified collateral cartilage. Mineralization of the soft tissue structures within the foot or pastern may also be identified and is most commonly seen associated with the DDFT just proximal to the navicular bone.

Previous studies have shown that variations in synovial invagination size and shape correlate poorly with lameness, rarely progress over time, and are inconclusive for the diagnosis of navicular bone degeneration. Radiographic abnormalities more strongly associated with lameness and relevant navicular bone degeneration include flexor cortical erosion (Fig. 38.23) and loss of the corticomedullary junction (e.g., medullary sclerosis) (Fig. 38.24). Navicular bone distal border fragments are more common, and the flexor cortex is thicker in horses with navicular pathology.[2] Although radiographic evaluation is important in the diagnostic workup of a horse showing heel and foot pain, it is not always very sensitive in defining the actual pathologic condition of the NB. Radiographs often underestimate the extent of pathology seen on necropsy in horses with navicular lesions, and many horses with lameness localized to the foot have normal radiographs even though they have multiple bone and soft tissue lesions on MRI.[1]

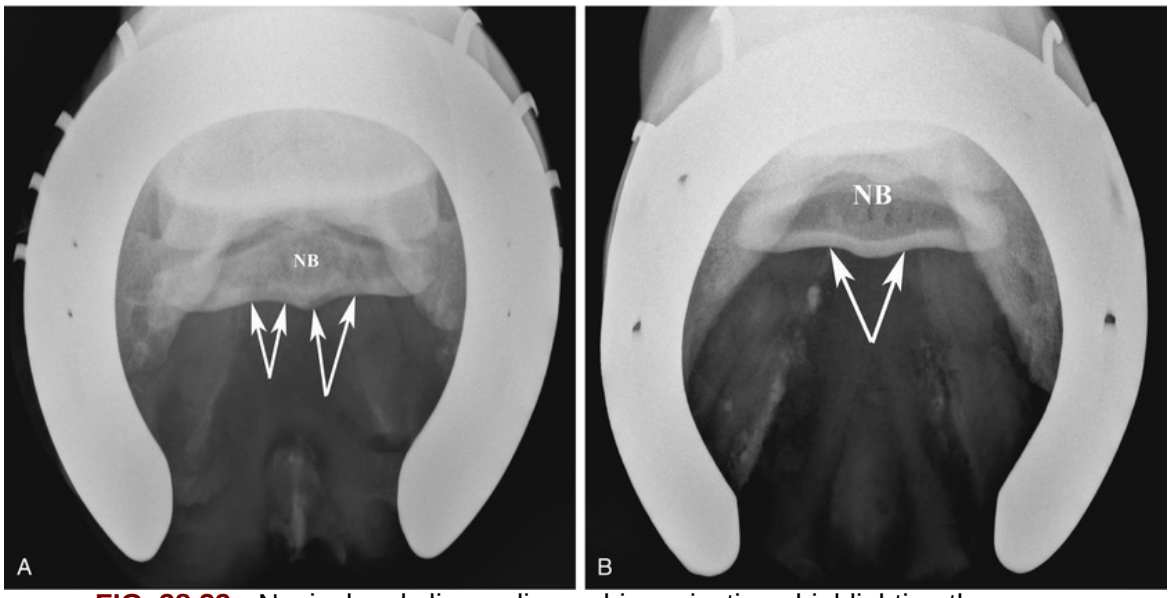


FIG. 38.23 Navicular skyline radiographic projections highlighting the flexor cortex and medullary cavity of the navicular bone *(NB).* **A,** Arrows point to two flexor cortical erosions on the flexor cortex of the NB, which is indicative of severe NB degeneration. **B,** Arrows point to a normal flexor cortex of the NB.

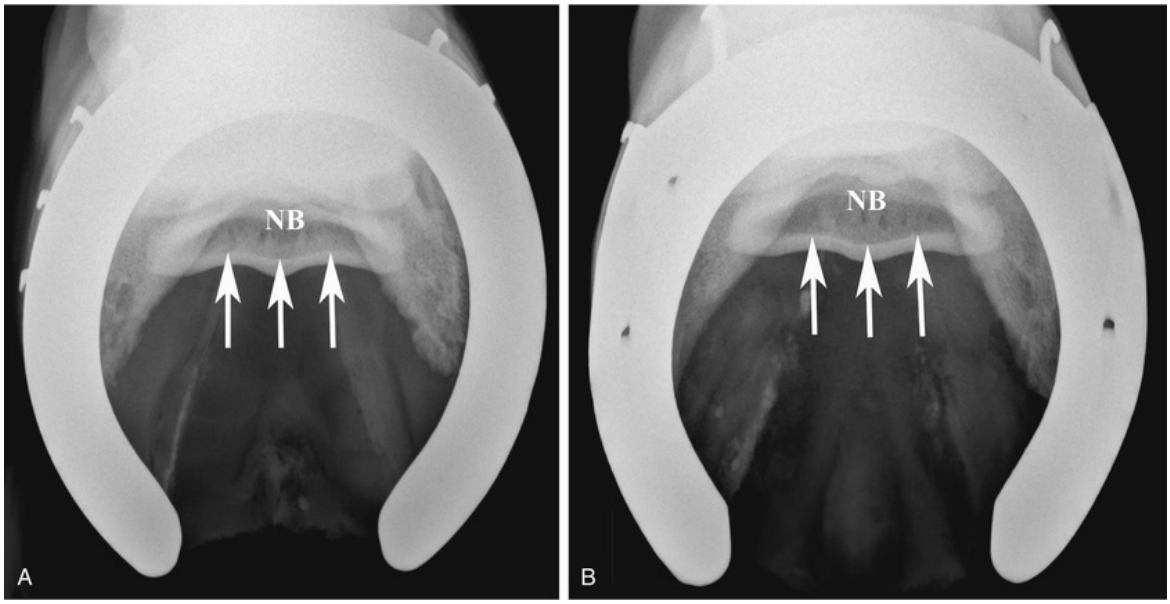


FIG. 38.24 Navicular skyline radiographic projections highlighting the flexor cortex and medullary cavity of the navicular bone *(NB).* **A,** Arrows point to the corticomedullary junction where there is loss of distinction between the flexor cortex and the medullary cavity. This is indicative of NB degeneration. **B,** Arrows point to a very distinct corticomedullary junction in

a normal horse.

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Ultrasonography.

Ultrasonography can be used to assess the structures of the pastern circumferentially, which includes the DDFT, superficial digital flexor tendon (SDFT), distal sesamoidean ligaments, proximal digital annular ligament, proximal aspect of the DDAL, proximal aspect of the DIJ collateral ligaments, collateral ligaments of the PIP joint, and periphery of the first and second phalanges.

Within the foot, ultrasonography can variably identify effusion of the NBSA, the CSL, and the proximal margin of the NB when imaged through the heel bulbs. This is very dependent on the heel conformation of the horse and access to a microconvex probe that can fit in between the heel bulbs of the horse. If the frog is pared down and the foot is soaked in water for 24 hours, a thin window on midline that is imaged through the frog can be assessed using ultrasound. If the frog is excessively hard or has a deep sulcus, poor contact between the frog and transducer may prevent propagation of the ultrasound beam.[3] Unfortunately, the images obtained through the frog are difficult to interpret, and ultrasonographic findings do not correlate well with pathologic findings on MRI. The structures partially visible in this transcuneal ultrasound window include the axial aspect of the navicular bone flexor surface, distal portion of DDFT, DSIL, and palmar aspect of the distal phalanx.[3]

Magnetic Resonance Imaging.

Magnetic resonance imaging is the gold standard in orthopedic imaging evaluation. This modality can assess both the bone and soft tissue structures of the distal limb (Fig. 38.25). It uses hydrogen protons in the body that align with the external magnetic field to assess tissue at a molecular level. Perturbation of the hydrogen atoms within the body using a radiofrequency pulse results in a grayscale image of the anatomic area imaged. Pathologic change that is not visible with ultrasonography or radiography can be identified with MRI. In regard to the foot of the horse, MRI provides a look at the internal structures of the foot that is not possible with other imaging modalities. It is used for horses with heel and foot pain when a diagnosis cannot be made with radiographs or ultrasound or when nuclear scintigraphy localizes pathology to the foot. However, many owners also request MRI in order to more fully evaluate the foot

or pastern (1) to determine if there are more than one issues, (2) to further define the severity of a previously diagnosed lesion, or (3) as a component of a prepurchase evaluation. For a definitive diagnosis in a horse with heel and foot pain that has an unremarkable radiograph and ultrasound evaluation, an MRI is the next diagnostic step.

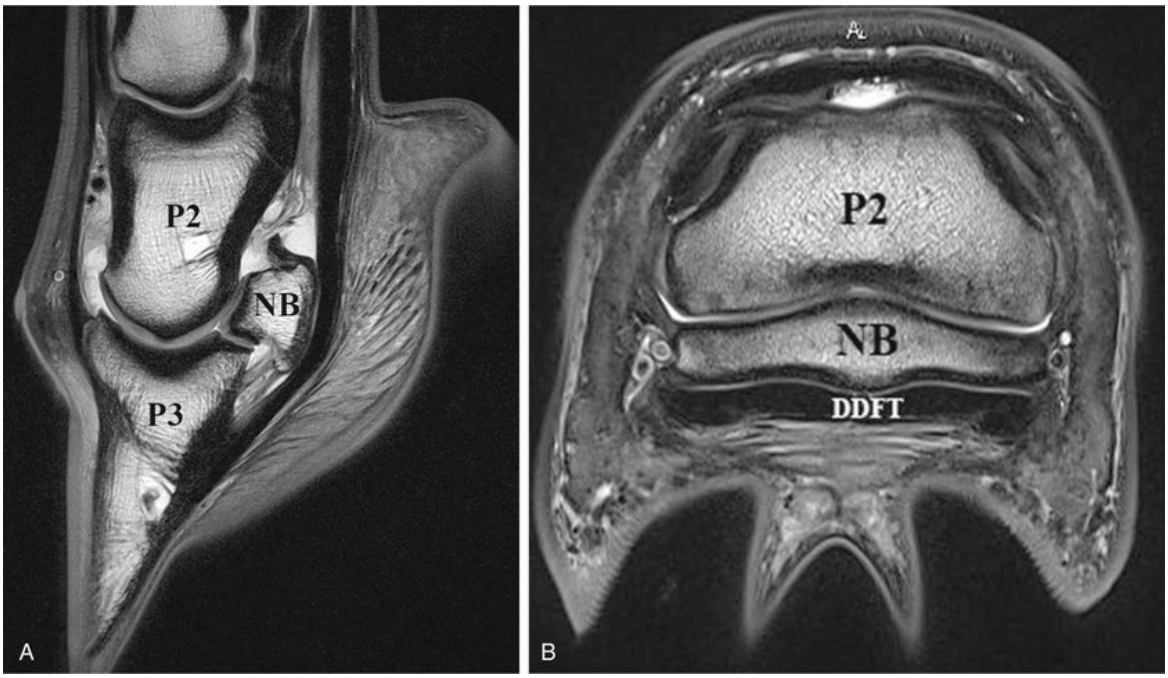


FIG. 38.25 Magnetic resonance images of the foot of a horse. **A,** Sagittal midline image of the foot. **B,** Transverse image of the foot at the level of the navicular bone *(NB). DDFT,* Deep digital flexor tendon; *P2,* middle phalanx; *P3,* distal phalanx.

Horses can be imaged in either high- or low-field-strength magnets. The higher the field strength (T; Tesla), the better the image resolution and the faster the image acquisition. All high-field magnets (≥1 T) require general anesthesia so that the horse's limbs can be placed in the bore of the magnet. Low-field magnets (≤0.3 T) can be either “standing” magnets, where the horse is sedated but standing during imaging, or magnets that require the horse to be anesthetized for the images to be acquired. The low-field, standing magnets produce the lowest-quality and lowest-resolution images due to the inherent movement of a standing horse. Motion correction software is used to decrease the image degradation, but it is not enough to make the image as clear as those obtained from a horse that is anesthetized for image acquisition. High-field-strength

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magnets have better-quality and better-resolution images, which is directly related to the field strength of the machine. High-field magnets are also much more costly to purchase, but the cost to the client to image a horse is often similar between high- and low-field magnets.

Nuclear Scintigraphy.

Nuclear scintigraphy in the horse involves intravenous injection with a radiopharmaceutical that is labelled to phosphorous and concentrates in areas of high bone turnover. This radiopharmaceutical emits gamma rays that are captured by a gamma camera during the procedure. In regard to the foot, if the navicular bone is undergoing active bone remodeling, the radiopharmaceutical will be concentrated in the navicular bone, and this will be evident on the images obtained. Increased radiopharmaceutical uptake in the foot is a good predictor of pathology, but a negative scintigraphic result does not exclude the presence of significant pathology.[4,5] Nuclear scintigraphy has been shown to have a high specificity but low sensitivity for detection of lesions of the NB, DDFT, and collateral ligaments of the DIJ when compared to MRI.[4,5] Nuclear scintigraphy can help determine the significance of pathology found with MRI, particularly if more than one structure is affected and the clinical relevance of a specific lesion is questioned.

Computed Tomography.

Computed tomography units used for horses typically involve general anesthesia, but a small number of units that can image the standing horse are being used now.

CT is used much less commonly than MRI for evaluation of the foot of the horse. It is excellent for detecting and evaluating bone pathology in the cortex or trabecula (fractures, sclerosis, peripheral remodeling), but it provides inadequate soft tissue detail when compared to MRI. It is based on density of tissue, similar to radiographs, and can show excellent peripheral bone detail, particularly for bone fragmentation, that is better than MRI, but MRI shows better internal detail of bone overall. Although less expensive than MRI, CT is less versatile and is most commonly used to assess fracture configuration or peripheral lesions of bone. CT is also used to guide some orthopedic injections and some complicated surgical procedures.

▪ Treatment

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There are numerous treatment options for horses with heel and foot pain. However, unfortunately many treatment options are only palliative, not curative. Horses with pain localized to the foot but without a definitive diagnosis will be treated based on the veterinarian's clinical evaluation and best guess as to the cause of the lameness. This decision will also take into consideration the use of the horse, the financial constraints of the owner, and any other concerns or constraints based on the individual horse-owner pair. When a definitive diagnosis is available, treatment is tailored to the structures affected, with the hope that by treating the specific cause of lameness, the prognosis for return to performance will be increased.

▪ Medical Management

Rest and Rehabilitation.

Injuries to the pastern or foot region that will most likely involve a rest and rehabilitation program include, but are not limited to, fracture, acute tendon injury, acute ligament injury, bone bruise (“edema”), and acute laminar inflammation. Depending on the structure affected and the severity of the lesion, the rest period could last from 3 to 12 months, and this is why a specific diagnosis is so important. Typically these types of lesions do not resolve with “pasture” rest, and stall or small paddock confinement is needed at the beginning of the rest and rehabilitation program. Conversely, standing a horse in a stall for 6 months is also not a reasonable rehabilitation program. When horses are rehabilitated after an injury, they should be in a controlled environment that limits their free exercise (typically a stall initially, then a small paddock, and then a larger paddock). During this confinement, it is important that the force the horses put on their limbs slowly increases in a controlled manner. A gradual increase in workload is done using hand walking, jogging in hand, and in some horses, using specific types of rehabilitation equipment based on the particular injury.

A recent study looking at 118 cases of primary DDFT injury in the pastern or foot region found that prognosis for return to use depended on injury severity, presence of concurrent injury to other structures in the foot, type of activity, and owner compliance with specific treatment recommendations.[6] Specifically, horses treated with intrasynovial corticosteroid injections and 6 months of rest and rehabilitation returned to use for a significantly longer duration than did horses treated without a rest period.[6] Also, Western performance horses returned

to use for a significantly longer duration than English performance horses.[6]

Farriery.

Therapeutic trimming and shoeing to reduce biomechanical forces on the heel region is a very important part of treatment for horses with foot and heel pain. Most often, horses will improve somewhat after corrective shoeing if they are not already shod appropriately, but they still require additional treatment to get them back in performance. The goals are to (1) restore hoof balance, (2) improve existing problems such as underrun heels, (3) reduce biomechanical forces on the heel region, and (4) protect injured areas of the foot. Although there is no standard shoeing technique for horses with heel pain, observing abnormalities in the hoof and lower limb and following basic principles can often accomplish these four goals. Proper trimming alone may restore correct hoof balance such that special shoes or pads are unnecessary. Even with proper trimming, however, many horses still require special shoes or pads to achieve the desired breakover and heel support, as well as offer protection to the bottom of the foot. The veterinarian, farrier, and owner must work together and consider the horse's hoof shape and hoof wall quality, environment, conformation, use, and severity of disease.

The configuration of the hoof capsule reflects the stresses applied to the foot during the previous year. *Hoof balance* refers to both mediolateral and dorsopalmar balance. *Dorsopalmar balance* refers to proper hoof-pastern alignment. Ideally, when viewed from the side, a line drawn through the central aspect of the first phalanx should bisect the hoof capsule, and the toe angle and heel angle should be parallel to this line. A broken back hoof-pastern axis is common in horses with long toe–low heel conformation and results in increased stress on the phalangeal joint capsules, navicular suspensory apparatus, and distal DDFT and increased pressure between the NB and DDFT.

Breakover (breakover point) of the foot is the terminal part of locomotion when the heel loses contact with the ground surface, followed by the toe. Breakover point on the bottom of the foot can be determined by finding the last point of contact of the foot or shoe with the ground near the front of the foot. A low heel angle and/or a long toe is associated with prolongation of breakover time. A high heel angle reduces breakover, causing a reduction in the forces exerted on the palmar and plantar structures of the foot and limb (e.g., navicular suspensory apparatus, DDFT).

Corrective trimming is often more important but can be more difficult than

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corrective shoeing. The toe is shortened as much as possible, and the heels are trimmed back to the widest aspect of the frog. Proper heel trimming (back to the widest aspect of the frog) increases the functional weight-bearing surface of the foot. The ground surface of the properly trimmed foot has a more rounded appearance. Palmar and plantar hoof support is essential for horses with heel pain. Full-fitting shoes provide more support by increasing the weight-bearing surface. Using a wedged shoe or pad to elevate the heels by 2 to 3 degrees after the foot is properly trimmed has been shown to decrease tension in the DDFT, reducing pressure applied to the heel region. However, each horse is an individual, and the shoeing should be tailored to each horse and adjusted, if needed, at each shoeing cycle.

Nonsteroidal Antiinflammatory Drugs (NSAIDs).

Phenylbutazone is the most common NSAID used to decrease the pain associated with lameness in the foot region. It reduces pain by inhibiting the enzyme cyclooxygenase and the subsequent cascade of prostaglandins. The recommended dosage depends on individual horse needs and severity of disease. An initial dosage of 4.4 mg/kg daily as needed for lameness can be used. Often this is used in the first 1 to 2 weeks following joint injections or shoeing changes. Many horses will require additional treatment during competition if medication rules allow and the lameness is not fully resolved with other medical treatments. Horses that are retired due to lameness that is performance limiting can be treated with low to moderate dose (2.2 to 4.4 mg/kg) phenylbutazone as needed to help with chronic pain.

Isoxsuprine Hydrochloride.

Isoxsuprine hydrochloride is a drug that causes vascular smooth muscle relaxation and may increase blood flow to the foot. Its absorption after oral (PO) administration in the horse is erratic, and its usefulness is questioned. The recommended dose of isoxsuprine is 0.6 mg/kg PO twice daily for 3 weeks; if no response is seen, the dose is increased to 1.2 mg/kg PO twice daily for 3 weeks, then once daily for 3 weeks, then every other day for an additional 3 weeks. No adverse drug reactions have been reported. At this time, isoxsuprine is not commonly used in the treatment of heel and foot pain due to the lack of evidence of efficacy.

Intraarticular Medications.

There are three synovial structures associated with the foot that can be accessed and used as a route for intraarticular medication: distal interphalangeal joint, navicular busa, and digital flexor tendon sheath (Fig. 38.26).

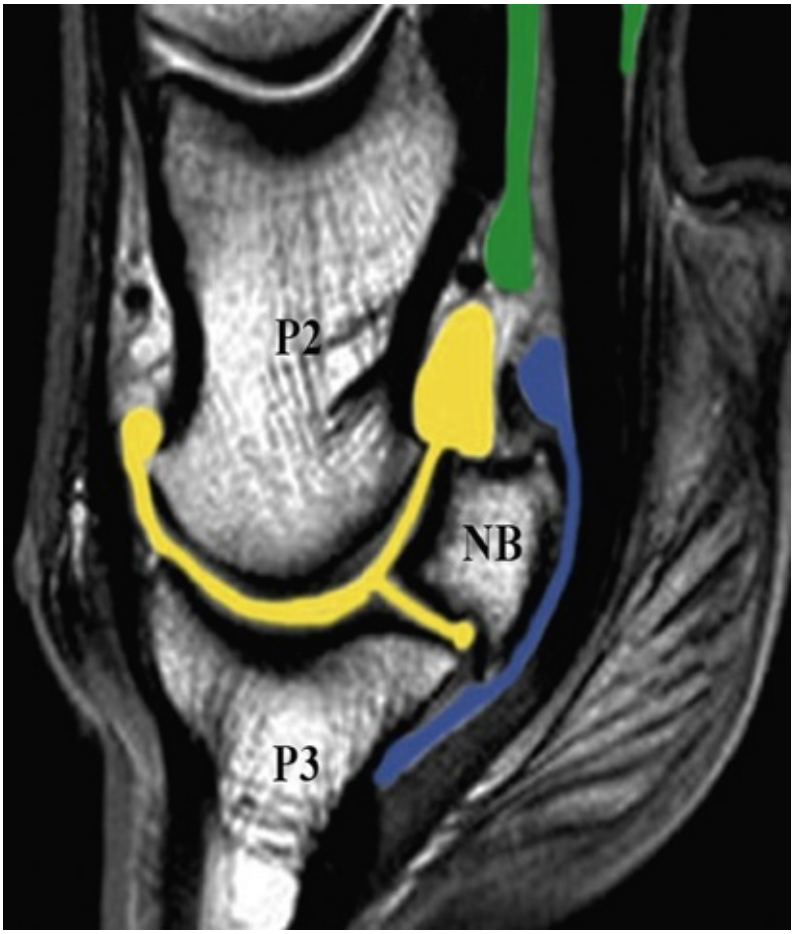


FIG. 38.26 Sagittal midline magnetic resonance image highlighting the boundaries of the distal interphalangeal joint *(yellow),* navicular bursa *(blue),* and digital flexor tendon sheath *(green).* Dorsal is to the left. *NB,* Navicular bone; *P2,* middle phalanx; *P3,* distal phalanx.

The *distal interphalangeal joint* can be medicated when there is pathology associated with the joint itself or its associated collateral ligaments. However, the DIJ also covers the dorsal surface of the CSL and DSIL, as well as the proximal, dorsal, and distal aspects of the NB where the synovial invaginations of the NB are actually contiguous with the DIJ.[7] Furthermore, triamcinolone acetonide that is injected into the DIJ in normal horses has been shown to diffuse into the NBSA in all instances.[8] Due to the broad coverage by the DIJ, this is

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often the first synovial structure medicated in horses when they are diagnosed with foot pain but do not have a definitive diagnosis. Since the DIJ is a high-motion joint, most veterinarians are injecting triamcinolone acetonide and hyaluronic acid into this synovial structure when treating horses with heel and foot pain.

The *navicular bursa* is medicated when (1) DIJ injections fail to improve the horse for a reasonable period of time, (2) there is pathology associated with the flexor cortex of the NB, (3) there is navicular bursitis, or (4) dorsal DDFT pathology is known or suspected. Navicular bursa injection should be done with radiographic guidance, and therefore this is a slightly more involved procedure than DIJ injection, it takes longer to perform, and it is typically more expensive. The navicular bursa contains fibrocartilage on the back of the NB, but no hyaline cartilage is present, thus practitioners will use either triamcinolone acetonide or methylprednisolone acetate in combination with hyaluronic acid when injecting the navicular bursa.

The *digital flexor tendon sheath* is medicated when pathology within it or in association with the sheath is known or suspected. Examples of pathology within the pastern or foot that may respond to DFTS injection include DDFT pathology within the sheath, SDFT branch tendinopathy, DDAL desmopathy,[9] and oblique and straight distal sesamoidean desmopathy.[10] Practitioners will most commonly use either triamcinolone acetonide or methylprednisolone acetate in combination with hyaluronic acid when injecting the DFTS.

A recent study evaluated 101 horses with clinical signs of heel pain that underwent MRI evaluation and had the NBSA medicated based on MRI findings associated with that region.[11] Seventy-six of 101 (75%) horses returned to their intended use for a mean of 9.6 months. Horses that had been lame for less than 6 months had a significantly better chance of returning to intended use than horses that had been lame more than 6 months.[11] Horses with primary DDFT pathology that had NBSA injections and were put through a 6-month rest and rehabilitation program responded for the longest period. If the DDFT pathology extended into the area of the DFTS, this synovial structure was also medicated. Horses with scar tissue and adhesions between the DDFT and CSL or horses with adhesions between the NB and DDFT were treated with pressurization of the NBSA with 30 to 50 mg of hyaluronic acid in an attempt to break down adhesions, but these horses were less likely to have a positive response to therapy.[11] Horses with multiple structures affected in the heel region were also less likely to respond

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well to treatment.[11]

Hyaluronan.

Hyaluronan (HA) is a normal component of synovial fluid and functions as a boundary lubricant within the joint. It also appears to have some antiinflammatory properties, but the exact mechanism is unknown. Exogenous HA inhibits chemotaxis and phagocytosis of granulocytes, reduces the stimulation of lymphocytes, and has been shown to decrease prostaglandin E2 synthesis by cultured equine synoviocytes if given intraarticularly but not systemically.[12] The antiinflammatory properties of HA appear to be dose dependent, and HA with a molecular weight greater than 500,000 Daltons may be more effective. The effect of systemic HA on pathology within the pastern or foot region is unknown. The recommended dose is 40 mg intravenously once weekly for 3 weeks, then once monthly for maintenance, but there is not substantial research in the literature at this time regarding HA administration systemically.

Polysulfated Glycosaminoglycans.

Polysulfated glycosaminoglycans (PSGAGs) are referred to as *chondroprotective agents* and have antiinflammatory properties. They decrease IL-1 and prostaglandin E2 and directly inhibit MMPs, proteinases, lysosomal enzymes, collagenase, and stromelysins. If given intraarticularly, they potentiate infection; therefore they must be given with an intraarticular antibiotic. PSGAGs given as 500 mg intramuscularly every 4 days for 7 treatments have been shown to provide positive effects (decreased joint circumference, greater carpal flexion) in a controlled study of equine carpitis.[13]

Bisphosphonates.

Biphosphonates are a class of drug that inhibits osteoclasts and are used in human medicine to treat osteoporosis. Bisphosphonates have not yet been shown to have the same inhibitory effects on osteoclasts at the doses used in horses.[14] The two bisphosphonate medications used commonly in horses are tiludronate (intravenous) and clodronate (intramuscular). One study has shown improvement in lameness using a 1 mg/kg dose of tiludronate when assessing horses with lameness that blocked to a PDN block and in which the horses had radiographic evidence of navicular bone degeneration.[15] At this time, the

improvement in lameness seen with bisphosphonates is thought to be due to an antiinflammatory effect and not a bone remodeling effect.

Extracorporeal Shockwave Treatment.

Investigated as a treatment for navicular bone degeneration in horses, extracorporeal shock wave treatment (ESWT) directs a pressure wave to a specific area of the body to increase osteogenic activity in bones and induce neovascularization. A single ESWT applied to the frog and heel bulb region does not influence lameness in horses with navicular bone disease.[16] ESWT over three treatments had no effect on pre- and postscintigraphic or radiographic images of the heel region.[17] In a study looking at collateral desmopathy of the DIJ, there was no effect of ESWT on outcome.[18] At this time, the benefit of EWST on pathology in the foot needs further investigation.

▪ Surgical Treatment

Palmar/Plantar Digital Neurectomy.

Palmar/plantar digital (PD) neurectomy is a surgical procedure that removes a section of the medial and lateral PDN between the fetlock and heel bulbs. This typically abolishes sensation in the heel and sole region of the foot. This procedure is an option for horses that block to a PDN block and are nonresponsive to medical management, with no other viable treatment options available. In a recent report in which MRI was used to guide treatment, 92% of horses responded favorably to PD neurectomy, with 80% able to return to their previous level of work for a median time of 20 months (range: 12 to 72 months).[19] Postoperative complications, including residual lameness, painful neuromas, or early recurrence of lameness, occurred in 36% of these horses.[19] Horses with DDFT pathology within the foot or pastern region are not good candidates for this procedure because they experience residual lameness or early recurrence of lameness after PD neurectomy.[19] Horses with other foot lesions or only dorsal border lesions of the DDFT had a better response to surgery.[19] In another study, 88% of horses were sound for at least 1 year after PD neurectomy.[20] Magnetic resonance imaging is used frequently to determine if DDFT pathology is present, and if so, these horses are not considered good candidates for a PD neurectomy.

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Navicular Bursoscopy.

Navicular bursoscopy is being used more often as a treatment option now that we are able to use MRI on horses and determine optimal candidates for this procedure. Optimal candidates include horses that have a primary navicular bursitis with a mild to moderate amount of fibrinous or fibrous tissue within the proximal NBSA, as well as horses that have lesions located along the dorsal border of the DDFT at the level of the proximal NBSA (Fig. 38.27). This surgical procedure allows direct visualization of pathology within the proximal NBSA, along the dorsal border of the DDFT, and along the NB flexor cortex. This procedure also enables removal of scar tissue from within the NBSA and débridement of DDFT fibrils extruding from the dorsal border due to a tendon tear. In a recent study of 92 horses undergoing navicular bursoscopy, 61% returned to work and were sound, and 42% returned to their previous level of performance.[21] Horses in this study that had extensive tearing and combination injuries of the DDFT and navicular bone identified with MRI had poor outcomes.[21]



FIG. 38.27 Transverse magnetic resonance image of a horse with a

portion of the deep digital flexor tendon torn and protruding *(arrow)* into the navicular bursa. Dorsal is to the top.

Collateral Sesamoidean Desmotomy.

This procedure involves transection of the branches of the CSL, which is the ligament that suspends the NB from the middle phalanx. When this procedure was first developed, these branches were transected at the lateral aspect of the middle phalanx through skin incisions.[22-24] In the first study, 13 of 16 (81%) horses were able to work without lameness after the procedure.[22] In the second study, 76% of horses were sound at 6 months, and 42% of horses were sound at 36 months.[23] In the third study, 12 of 17 (70%) horses were sound at 6 months following surgery.[24]

More recently, a procedure was developed to transect the CSL branches from within the palmar pouch of the DIJ using arthroscopic guidance.[25] This technique provides the ability to verify full transection of the ligament by visualization of transection and increased movement of the NB away from the middle phalanx.[25] Collateral sesamoidean desmotomy is performed when pathology associated with the suspensory apparatus (DSIL, NB, CSL) of the foot has been diagnosed but no flexor cortical erosion is present. In addition, other causes of lameness that would preclude the horse from responding positively to CSL desmotomy (e.g., DDFT pathology, navicular bursitis) need to be ruled out. Due to the specific diagnosis needed, MRI is highly recommended to determine whether this procedure would be a viable treatment option. Unfortunately, at this time there are no published reports of response to treatment using MRI as a screening tool. The hope is that by using MRI to define optimal candidates for this treatment, the prognosis for return to performance may be improved.

▪ Summary

No single treatment option is suitable for all horses with heel and foot pain. Each horse must be evaluated individually so that the structures affected, severity of disease or injury, use of horse, level of performance, and financial constraints are determined and used to guide treatment. Many treatment options are available to help these horses return to performance, but treatment can be much more successful in horses in which a definitive diagnosis has been obtained so that treatment is tailored to the individual horse. Magnetic resonance imaging is the

best diagnostic tool we have to identify pathology within the foot of horse, and it should be used if at all possible to determine the cause of the lameness.

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Spondylitis and Diskospondylitis

Sarah M. Reuss

▪ Definition

Spondylitis is inflammation of the vertebral body, whereas diskospondylitis is an inflammatory lesion that includes the intervertebral disc and its adjacent vertebrae. Although the etiologic agent may be difficult to isolate, infection is the most likely cause. Thus *vertebral osteomyelitis* and *spondylitis* are often interchangeable terms, and if the disc is involved, then *diskospondylitis* is the most appropriate term. Both spondylitis and diskospondylitis are rare in large animals but potentially career- and life-threatening when they occur. Diskospondylitis is described in swine,[1] horses, cattle,[2] goats,[3] and sheep. Neonates of all species are especially at risk for spondylitis. Diskospondylitis in large animals is most commonly reported in adult horses and cows in the cervical vertebrae.[4-6] Lesions have been less commonly identified in the thoracic,[7,8] lumbar,[9] and sacral[10] regions.

▪ Clinical Signs and Differential Diagnoses

The earliest signs of spondylitis may include fever, lethargy, stiffness, and localized spinal pain. Soft tissue swelling may be evident with paravertebral abscessation.[11] Muscle atrophy has also been reported.[8] Because diskospondylitis most commonly affects the cervical and thoracic vertebrae, neck pain and reluctance to lower the head to graze are common signs. Animals may develop an abnormal stance, with one forelimb forward and the other back, in order to graze.[7] Vertebral osteomyelitis may progress to spinal cord compression with variable degrees of ataxia, paresis, sensory and proprioceptive deficits, and recumbency. Neurologic signs are dependent on the vertebral section affected and the amount of spinal cord compression. Once present, clinical signs are usually progressive.

Clinical signs in ruminants are similar. Early signs include abnormal behavior, decreased appetite, and weight loss. Difficulty in extending the head and neck ventrally is often the reason for presentation to a veterinarian.[2] Varying degrees of neurologic deficits are reported, from occasional stumbling[2] to tetraparesis[12]

and paraplegia.[3]

Differential diagnoses for spinal pain include spondylosis, vertebral fracture, muscle strain, dorsal spinous process impingement, vertebral subluxation, vertebral infarcts, and aberrant parasite migration.[13] Additional differentials for spinal cord ataxia in horses include cervical vertebral stenotic myelopathy, equine protozoal myeloencephalopathy, herpes myeloencephalopathy, and neoplasia.

▪ Etiology and Pathogenesis

Both spondylitis and diskospondylitis are thought to be septic conditions, although etiologic isolation is not often successful. Even in cases where bacteria are not isolated, response to antimicrobials may indicate a bacterial pathogenesis.[7] Bacterial infection is more common than fungal infection, and the hematogenous route of infection is the most common. Spondylitis occurs most frequently in neonates, which may be due in part to failure of passive transfer leading to sepsis.[1] In general, spondylitis is often secondary to a preexisting focus of infection elsewhere in the body.[1] Tail docking wounds,[14] umbilical infections,[1,12] pneumonia,[10] and lung abscesses[1] are possible sources of infection. Septic thrombi embolize into the metaphyseal arteries of the vertebrae, where flow is sluggish and bacteria can colonize.[14] In adults, direct injury to the intervertebral disc and/or the vertebral end plate may contribute to the formation of diskospondylitis. The injury disrupts the vasculature, increasing susceptibility to infection. Diskospondylitis is also reported to occur secondary to spread of local infection[5] and traumatic injury.[4] Infection results in destruction and remodeling of affected bone. Inflammation of the disc and vertebrae leads to spinal cord compression and the associated neurologic dysfunction. The intervertebral disc actually may prolapse into the spinal canal.[5] Lesions are usually confined to one intervertebral space. The neurologic signs may also be secondary to the infection eroding into the meninges and causing a suppurative meningitis.

Pathogens that have been cultured from adult horses with vertebral osteomyelitis include *Brucella abortus*,[15] *Aspergillus* spp., *Streptococcus zooepidemicus*,[1] *Staphylococcus* spp.,[6,9] and *Mycobacterium bovis*.[16] Vertebral osteomyelitis isolates in foals include *R. equi*,[10,11,17] *Streptococcus* spp., *Actinobacillus* spp., *Eikenella corrodens*,[18] *E. coli*, *Salmonella typhimurium*,

Staphylococcus spp., and *Corynebacterium pseudotuberculosis.*[13] Isolates from cattle with vertebral osteomyelitis include *Aspergillus fumigatus, Bacteroides nodosus, Clostridium perfringens, Streptococcus* spp., *Staphylococcus* spp.,[2] *E. coli,*[14] *Actinomyces pyogenes, Fusobacterium necrophorum,* and *Pseudomonas* spp.[19] *Staphylococcus* spp. and *Arcanobacterium pyogenes* were cultured from the intervertebral disc of a goat.[3]

▪ Diagnosis

Diagnosis is based on clinical signs and imaging modalities. Clinicopathologic findings may include anemia, leukocytosis, neutrophilia, and hyperfibrinogenemia.[1] One retrospective study, however, found that 80% of affected horses had a normal white blood cell count.[20] Hyperproteinemia due to hyperglobulinemia may also be seen.[7] Cerebrospinal fluid is usually normal unless the osteomyelitis has progressed to meningitis. Blood and urine cultures should be obtained but are often not diagnostic.

Radiography is often the basis of diagnosis. Radiographic signs of spondylitis include bony proliferation, lysis, sclerosis, and localized soft tissue swelling.[1] Radiographic abnormalities in diskospondylitis include osteolysis of adjacent end plates with surrounding sclerosis and collapsed intervertebral disc space[9] (Fig. 38.28). Contrast radiography may be used to delineate spinal cord compression.[9] Radiographic changes may lag at least 2 to 8 weeks behind clinical signs, however, hampering the ability to make an early diagnosis.[1] With vague clinical signs, the neuroanatomic location within the vertebral column may be difficult to identify, making targeted radiographs impossible. Nuclear scintigraphy may help localize the lesion to a specific vertebral section that can then be radiographed.[1] Scintigraphy may also allow earlier detection due to the lag time in radiographic changes. Ciprofloxacin and labeled white blood cell scintigraphy may also prove useful in the diagnosis of vertebral osteomyelitis. Ultrasonography is becoming increasingly used as a diagnostic imaging modality. Abnormalities include irregular end plates or bone surfaces, wide or narrow disc spaces, vertebral step formation, and associated abscessation or muscle involvement.[9] Transrectal ultrasonography of the lumbar vertebrae may be performed, while transcutaneous studies can image the rest of the vertebral column. Advantages to ultrasound are that it can be done in the field, it can be used for needle-guided aspirates of potentially infectious lesions, and it can be

used as a screening tool to localize lesions.[9] Depending on the size of the animal and the availability of equipment, MRI and CT may also be considered, as these modalities can be used to assess the vertebral end plates, the disc, and the spinal cord.[3] CT has been used in a goat to diagnosis diskospondylitis. Bone lysis, bone proliferation, mineral opacity within the intervertebral disc, and spinal cord displacement were seen.[3]



FIG. 38.28 An 11-year-old Arabian cross gelding with fever and neck pain. The cortical margins of the caudal end plate of C5 and the cranial vertebral body of C6 are markedly thin and ill-defined. In addition, there is osteolysis and sclerosis associated with the cranial vertebral body of C5. The C5-C6 intervertebral disc space is narrow.

▪ Treatment

Long-term antimicrobial therapy is indicated for cases of vertebral osteomyelitis. Blood, urine, or tissue cultures and sensitivities may be used to guide antimicrobial choices. When that is not possible, broad-spectrum, bacteriocidal antimicrobials should be used. Long-term treatment is necessary and may last for 3 to 6 months.[10] NSAIDs can also be used for pain control. In nonresponsive cases, curettage of infected bone may be necessary.[6,10] This also provides an opportunity to collect material for bacterial culture.[10] In horses with instability

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and spinal cord compression, surgical decompression and stabilization may be indicated.

▪ Prognosis

The prognosis for horses with diskospondylitis is guarded. If there are no neurologic deficits, and thus presumably no spinal cord compression, the prognosis is more favorable. Early diagnosis and long-term treatment is essential. In one retrospective, 13 of 19 adult horses survived to discharge, with 7 returning to their previous level of performance.[20] Foals may have a worse prognosis, with only 7 of 15 surviving to discharge.[21]

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Spondylosis

Sarah M. Reuss

▪ Definition

Spondylosis is an ankylosing or degenerative condition of the intervertebral joints. Partial bridging occurs when osteophytes extend across the intervertebral space toward osteophytes on the adjacent vertebrae but a lucent line persists between the two. Complete bridging, or ankylosis, can occur without significant loss of intervertebral disc width. A variety of terms are used in veterinary medicine to describe vertebral enthesophyte formation: spondylosis deformans, vertebral osteophytosis, and ankylosing spondylosis.

▪ Etiology and Pathogenesis

In middle-aged and older animals, the thoracic and lumbar vertebrae are susceptible to chronic, progressive development of enthesophytes at the ventrolateral vertebral body margins. The exact cause is unknown but is apparently related to altered biomechanics and inflammatory mediators. One hypothesis is that spondylosis is a result of excessive dorsiflexion when the back muscles fatigue, as might be seen with exercise or breeding. There is then abnormal joint loading, mechanical stress, and degeneration of the annulus fibrosis and periarticular tissues.[1] Chemical mediators act on the periarticular ligaments and joint capsule, leading to metaplastic change, and ossification occurs within the anulus fibrosis and ventral longitudinal ligament, leading to partial bridging. Nerve roots may be compressed as they exit the intervertebral foramen, and spinal cord compression may occur if the bony proliferation extends dorsally into the vertebral canal. The cycle may continue until complete ankylosis and a continuous medullary cavity exist.[2] Partial or complete ankylosis at one site puts more stress on adjacent segments, so there is more active bone remodeling elsewhere in the vertebral column.[3] Sixty percent (14 of 23) of horses with radiographic evidence of spondylosis had more than one site involved.[4] The enthesophytes and then the ankylosed vertebral bodies are both at higher risk for fracture due to their inability to absorb normal forces. In a 22-year period in California, 38 Quarter Horse and 29 Thoroughbred racehorses that died on racetracks were diagnosed with a lumbar fracture. Closer postmortem

analysis of a subset of these catastrophic caudal lumbar vertebral fractures all had evidence of preexisting abnormalities on the ventral aspect of the vertebral bodies consistent with spondylosis.[5]

A syndrome of posterior spinal paresis has been recognized in the bull artificial insemination industry, with calcification of the thoracolumbar vertebrae and ligaments. Over time there is fusion of the lumbar vertebrae with bilateral rear limb lameness and paresis. Spondylosis in bulls is not related to force of ejaculatory thrust at service, frequency of semen collection, or high-calcium diets.[6] Despite previous thought, limited dietary calcium does not reduce the prevalence of spondylosis in bulls.[7] In one study, a highly significant serologic association was found between posterior spinal paresis and the bovine major histocompatibility complex class I antigen BoLA-A8 ($P = 0.0015$).[8]

▪ Clinical Signs and Differential Diagnoses

Spondylosis can be an incidental finding in animals with no history or clinical signs of back pain. Spondylosis can, however, account for acute, recurrent, and chronic back pain in some animals. Pain is due to inflammation, impingement, and fracture. Palpation of the spine may be resented. Horses may guard their vertebral column by using muscle contraction to not allow ventroflexion. Resentment of girthing and mounting may be noticed. Riders may report poor performance, vague lameness, or altered gait.[1] Spondylosis is rarely the cause of back pain, however, as only 3.4% (23 of 670)[4] and 2.7% (8 of 443)[9] of horses presenting for back pain were found to have spondylosis in two separate studies.

Bulls with spondylosis will have a good appetite and be afebrile, but they may have difficulty rising, be reluctant to move, and have difficulty mounting or ejaculating.[2] In both horses and cattle, once clinical signs are present, they are slowly progressive. Lameness becomes more severe, and neurologic deficits may develop with nerve root impingement or spinal cord compression. Abnormalities then include bilateral proprioceptive deficits of the hindlimbs with hoof dragging, excessive hindlimb flexion, and incoordination. Hindlimb ataxia can progress to paralysis in some animals, especially older dairy bulls.[10]

Differential diagnoses for spinal pain include muscle strain, vertebral fracture, diskospondylitis, dorsal spinous process impingement, vertebral infarct, and aberrant parasite migration. Additional differentials for cattle with hindlimb neurologic deficits include lymphosarcoma, encephalopathy, progressive degenerative myeloencephalopathy, and downer cow syndrome.[2]

▪ Epidemiology

Spondylosis in horses is most common in mature animals and reportedly occurs in a higher proportion of mares.[9] The most common location in horses is from the tenth to the fourteenth thoracic vertebrae, and most horses with spondylosis have lesions at more than one intervertebral space. The osteophytes are usually ventrolateral when found in the thoracic region, whereas they are more lateral when found in the lumbar region.[3] Transrectal lumbosacral ultrasonography has detected ankyloses of the caudal lumbar vertebrae in 10% to 20% of horses.[11]

Bulls have a higher prevalence of vertebral enthesophytes than other cattle. Middle-aged bulls can have significant pathology, with 21 of 21 dairy bulls ages 65 to 90 months having some degree of lumbar vertebral osteophytes. Thirteen of those 21 bulls had complete ankylosis of at least one intervertebral space.[10] Bulls used for artificial insemination are especially at risk, with more than 49% of those 8 years and older having spondylosis.[12]

▪ Diagnosis

Diagnosis is suggested by clinical signs. Palpation of the dorsum may elicit signs of pain. Rectal palpation may reveal ventral osteophytes if they are located on the caudal lumbar vertebrae. A thorough neurologic examination is indicated if there are hindlimb deficits. Cerebrospinal fluid is usually normal.

Standing lateral radiographs are the mainstay of diagnosis. However, diagnostic radiographs can be difficult to obtain given the depth of the vertebrae in the thoracolumbar region. If one suspects spondylosis, targeting radiographs to areas of predilection is helpful. Spondylosis in horses is typically in the midcaudal thoracic vertebrae, commonly T10 to T14, but may also affect the lumbar vertebrae.[9] In bulls, the most common locations are C3 to C5, T2 to T6, and T11 to L5. The largest osteophytes occur in older bulls at the thoracolumbar junction.[6,12] Radiographic changes include smooth bone that blends with the vertebral body and bridges apparently normal intervertebral discs. A grading system has been developed, with grade 0 being normal, grade 1 having an osteophyte from one vertebral body, and up to grade 5 having complete bridging of the intervertebral space.[4] The clinical significance of radiographic change must also be determined based on history and clinical signs, as spondylosis can be an incidental finding. Nuclear scintigraphy can be useful for determining the activity and potential clinical significance of a lesion based on the

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radiopharmaceutical uptake. Scintigraphy may also be helpful in localizing the lesion for targeted radiography. Subjective assessment of scintigraphic images had a 21.7% sensitivity but a 95.0% specificity in a recent study using radiographic change as the standard.[4] Infrared thermographic imaging was used in one bucking bull to show surface hypothermia, thus confirming spinal nerve root irritation from spondylosis seen radiographically between L2-L3 and L3-L4.[13]

▪ Treatment and Prognosis

Treatment for clinical spondylosis consists of palliative care. Systemic antiinflammatories, cryotherapy, and stall rest are recommended during the acute phase. Extended turnout is then advocated in hopes of forming an osseous union because once complete fusion occurs, clinical signs should improve. Administration of local analgesics and corticosteroid drugs may provide relief and control of localized inflammation. Epidural administration of corticosteroids with concurrent administration of systemic polysulfated glycosaminoglycans has been reported in a bucking bull, allowing clinical signs to improve enough to permit breeding.[13] However, if vertebral fractures or neurologic deficits are present, the prognosis is poor.

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Laminitis

Michelle C. Coleman

▪ Definition

Laminitis, defined as inflammation of the laminae of the hoof wall, results in degeneration, necrosis, and inflammation of the dermal and epidermal laminae in the hoof wall of equids and ruminants. The economic and welfare impacts of laminitis are high because of the associated poor prognosis, severe pain, and frequency of recurrence. Recognizing the impact of laminitis on horses and horse owners, veterinarians desire an improved understanding of laminitis, as evidenced by a 2009 survey (personal communication, Keith Kleine, AAEP Foundation) by the American Association of Equine Practitioners in which members identified laminitis as the highest priority for research funding and investigation.

▪ Etiology and Pathogenesis

Laminitis has a complex and multifactorial etiology, ultimately resulting in lamellar degradation of the suspensory apparatus of the distal phalanx.

Disease states thought to be associated with laminitis include sepsis and systemic inflammation, equine metabolic syndrome (EMS), pituitary pars intermedia dysfunction (PPID), and mechanical or traumatic overload. Septic processes including endotoxemia, gastrointestinal disease, pneumonia, and septic metritis are frequently associated with the development of laminitis. Laminitis has also been noted secondary to systemic inflammation resulting from an overload of carbohydrates, such as from overgrazing lush pastures or unrestricted access to concentrates. Excess weight bearing as a result of a contralateral limb lameness and trauma to the distal phalanx following exercise on hard ground can also result in laminitis. Exposure to a water-soluble toxin in black walnut shavings[1] and administration of corticosteroids have also been associated with the development of laminitis.[2]

In cattle, overweight heifers fed excess concentrates and housed on concrete surfaces appear to be at increased risk.

▪ Pathophysiology

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The pathophysiology of laminitis has not been fully elucidated; however, it appears to involve a combination of events that lead to lamellar degeneration, impaired biomechanical function, and debilitating pain. Several experimental models for induction of laminitis have been developed, including carbohydrate overload,[3] fructan overload,[4] black walnut extract administration,[1,5] and hyperinsulinemic models.[6,7] Distinct pathophysiologic differences between these models exist, emphasizing the complexity of the pathophysiology of disease. Together, these models support several similar and interconnected theories on the pathophysiology of laminitis, including digital hemodynamic, enzymatic, inflammatory, endocrinopathic, and mechanical or traumatic events.

The bounding digital pulses and increased hoof wall temperature in acute laminitis gave rise to one of the earliest mechanisms to receive research support, which suggests a vascular component of the disease. Early research evaluated the role of hypertension[8] and the angiographic appearance of the laminitic equine digit,[9] with the thought that increased capillary pressures secondary to venoconstriction of the digital microvasculature resulted in laminar edema, increased arteriovenous shunting, and capillary collapse.[10] Further research has implicated the role of thrombosis,[11] vascular supply,[12-15] and insulin[16] on vascular dysfunction and lamellar ischemia, with increasing interest in endothelial dysfunction.[17]

Alteration of enzymatic activity within the lamella has been proposed as another potential mechanism of laminitis. Matrix metalloproteinase enzymes (MMP-2 and MMP-9) have been isolated in increased quantities from lamellar tissue affected by laminitis,[18] affected lamellar tissue has been shown to increase transcription of MMP,[19] and MMPs have been associated with neutrophil migration into the lamellae.[20] The activation of MMPs is thought to result in separation of lamellar cells from their basement membranes; however, the mechanism by which activation occurs has yet to be elucidated. Importantly, differences in MMP activity in the various models of laminitis have been noted.[21,22]

Experimental models of equine laminitis have displayed a number of inflammatory events. The presence of endothelial activation, leukocyte infiltration, proinflammatory cytokines, leukocyte activation and chemotaxis, and activation of degradative enzymes such as MMPs have been reported in the digital lamellae in different models of laminitis. Increased expression of inducible cyclooxygenase, COX-2, suggest that prostaglandins may play a role

in laminar dysfunction.[23-25]

The role of endotoxemia in the development of laminitis remains unclear. Although systemic inflammation is a risk factor for development of laminitis, experimental endotoxin administration fails to induce the disease.[26] This could be explained by the fact that endotoxin does not act alone but rather in combination with several factors, including bacterial toxins, necrotic cell products, and proinflammatory cytokines. Endotoxin has been detected in the blood of horses following experimental carbohydrate overload[27] and is known to affect digital vascular function and platelet activation. Recent studies have hypothesized that the proinflammatory state of carbohydrate overload models is driven by an immune response to the rapid overgrowth of gram-positive and gram-negative cecal bacteria.[28]

Experimental models resulting in hyperinsulinemia reliably induce laminitis in ponies and horses.[6,7] Many theories on the pathogenesis of hyperinsulinemic laminitis exist, and it is probable that these theories are interconnected. Plasma or serum insulin concentrations can be used as predicitive[29] and prognostic[30] indicators for ponies at risk of developing laminitis. The role of insulin in glucose deprivation,[31,32] glucose excess,[33] upregulation of MMPs,[21] vascular effects,[34] and proinflammatory effects has been considered.

Laminitis has long been associated with mechanical overload on the distal phalanx, such as excessive concussion (road founder) and supporting limb laminitis. The mechanism of insult to the laminae is unknown, and currently models for studying this form of laminitis are poorly developed.

These theories of the pathogenesis of laminitis are complex and likely interconnected. The development of experimental models has accelerated our knowledge and understanding of the complex pathophysiology; however, the relationship of these models to the naturally occurring condition is unknown.

▪ Clinical Signs

Laminitis can affect a single foot or all four feet but is most commonly noted in the front feet of horses (likely due to an increased load on the forelimbs) and the hind feet of ruminants. Supporting limb laminitis occurs on the supporting forelimb or hindlimb opposite the non–weight-bearing limb. The lameness may vary in severity from subtle to prolonged recumbency due to digital pain. Because of this variability, the Obel grading system was developed to better describe severity.[35,36] Grade 1, the least severe classification, is characterized by

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shifting weight with no apparent lameness at the walk but a short-stilted trot. Horses with grade 2 lameness are willing to walk but have a stilted gait and are willing to lift a foot off the ground. Grade 3 is characterized by reluctance to ambulate and resistance to having a foot lifted off the ground. The most severe classification is grade 4, in which the horse refuses to move.[35] Shifting of weight to the hindlimbs if laminitis affects the forelimbs results in a characteristic "saw horse" stance and may be accompanied by anxiety, muscle fasiculations, anorexia, or reluctance to move in severe cases. Other clinical signs consistent with laminitis include bounding digital pulses, sensitivity to hoof testers over the sole at the toe, sensitivity to tapping of the hoof wall at the toe, heat over the dorsal surface of the hoof wall, and swelling of the coronary band. Rotation or distal displacement of the third phalanx within the hoof capsule may occur. With displacement, significant lameness often persists. A dropped sole or depression over the coronary band suggests that displacement has occurred.

Chronic laminitis results in lameness and deformation of the hoof capsule, which vary with duration of disease and type of displacement. In these cases, the sole is flat or dropped, the white line is widened, and the hoof wall shows signs of uneven growth. Irregular rings of growth may be noted around the hoof wall, more widely spaced at the heels. The abaxial white line develops apparent hemorrhages, and fissures of the hoof wall may be noted parallel to the coronary band. In ruminants, the sole softens and assumes a light-yellow discoloration.

▪ Clinical Pathology and Radiology

There are no clinicopathologic findings specific to acute or chronic laminitis, but changes may reflect an underlying disease process such as endotoxemia, enteritis, colitis, pleuropneumonia, or metritis. Changes may also be seen as a result of glucocorticoid and catecholamine release in response to pain and stress. One study showed that horses euthanized for chronic laminitis had higher white blood cell counts when compared to control horses and horses with less severe disease.[37] Baseline values for creatinine and total protein should be obtained, as these are important parameters to monitor for NSAID enteropathy.

Radiographic examination is an essential component in evaluating horses with suspected laminitis, for monitoring progress, and for providing therapeutic recommendations and prognostic information. Standard radiographic views, including lateromedial and 65-degree dorsoproximal-palmarodistal views, should be taken of all suspected digits in acute disease to serve as a baseline for

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subsequent radiographic studies and to determine if prior radiographic changes are present. Using a consistent technique is important to achieve a true lateral image and to allow accurate evaluation of radiographic parameters for comparison of serial studies. For both views, the foot should be thoroughly cleaned and placed on a wooden block such that the x-ray beam can be centered on the solar margin of the distal phalanx. A radiopaque marker placed on the middorsal hoof wall starting at the coronary band and extending distally can be useful in determining the position of the distal phalanx in relation to the surface marker.

Primary radiographic changes in acute laminitis include thickening of the dorsal hoof wall as a result of inflammation, separation of the laminae, and separation of the distal phalanx from the hoof wall. When the suspensory apparatus of the distal phalanx fails, the distal phalanx rotates away from the hoof wall or displaces distally, increasing the distance between structures. This distance can be measured as a line vertical to the parietal surface of the distal phalanx and distal to the extensor process. In normal horses, this distance should be less than 18 to 20 mm (Fig. 38.29, *A*). A ratio between this dorsal measurement and the palmar cortical length of the distal phalanx measured from the dorsodistal tip of the bone to its articulation with the navicular bone (Fig. 38.29, *B*) can be used to account for changes in magnification and size of the foot. This ratio should be less than 28% in normal horses and more than 32% in horses with displacement of the distal phalanx. Sinking of the entire distal phalanx within the horny capsule can be assessed by measuring the vertical distance between the coronary band and the extensor process of the distal phalanx (Fig. 38.29, *C*). Soft tissue swelling of the coronary band may be apparent. Palmar or plantar rotation of the distal phalanx away from the hoof wall greater than 5 degrees is indicative of capsular rotation (Fig. 38.30, *A*).



FIG. 38.29 Lateromedial radiograph of a horse with acute laminitis. **A,** Distance from the dorsoparietal surface of the distal phalanx to the dorsal surface of the hoof capsule. **B,** Length of the palmar cortex of the distal phalanx. **C,** Distance from the extensor process to the proximal aspect of the hoof wall distal to the coronary band.

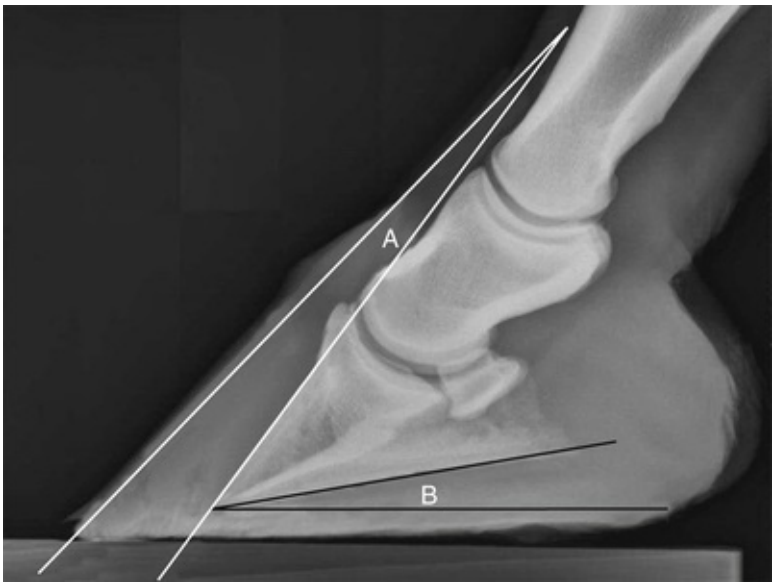


FIG. 38.30 Lateromedial radiograph of a horse with acute laminitis. **A,** Measurement of the degree of capsular rotation. **B,** Measurement of the angle of the solar margin of the distal phalanx to the ground surface of the foot.

In chronic cases, a radiolucent line may appear between the distal phalanx and the sole or hoof wall due to accumulation of serum between the dermal and epidermal laminae. The angle of the solar margin of the distal phalanx to the ground surface may be a more accurate assessment of rotation in chronic cases (Fig. 38.30, *B*). Radiographic evidence of a previous episode of laminitis may be evident in clinically normal horses. Changes may include increased thickness of the dorsal hoof wall, a radiolucent line in the dorsal hoof wall, modeling of the toe of the distal phalanx, and/or uncorrected rotation of the distal phalanx.

Positive contrast venography is useful in identifying filling defects in the digital vasculature, including the lamellar vessels, the circumflex area, and the terminal arch. Venographic studies are most valuable in early disease and may reveal damage in the hoof before radiographic changes are evident.[38]

The availability of MRI in equine medicine is increasing. High-field-strength MRI can provide detailed visualization of the laminae in the equine digit. Studies comparing digital radiography and MRI of horses with initial active laminitis suggest that measurements obtained with MRI were more sensitive and specific predictors of laminitis.[39]

▪ Epidemiology

The estimated incidence of laminitis ranges from 1.5% to 34%,[40] with an estimated lifetime risk of 15%.[41] The term *endocrinopathic laminitis* has been used to describe laminitis in horses with hyperinsulinemia, PPID, or obesity or that have been administered glucocorticoids[42] and has been recognized as the most common cause of laminitis in private equine practice.[43,44] Further, in the National Animal Health Monitoring System equine study[45] performed in 2000, horse owners in the United States reported that pasture-associated laminitis and laminitis of unknown etiology were the most common forms of laminitis.

Epidemiologic studies on the risk factors for naturally occurring laminitis in horses are limited, with inconsistent results. A recent systematic review of publications assessing the risk factors for naturally occurring laminitis revealed only an association between chronic laminitis and increasing age. Results for other horse-level factors, including gender, breed, and body weight, were inconsistent. No consistent associations have been identified with other factors, including exercise and seasonality.[46] Associations between health conditions and laminitis in hospitalized horses has been investigated, with endotoxemia the only variable for which an association was noted.[47] Several cohort studies[48,49] have

identified risk factors (e.g., hyperinsulinemia) for endocrinopathic laminitis in ponies, and a recent case control study in North America identified that generalized and/or regional adiposity, corticosteroid administration, and endocrinopathic disease were risk factors for development of pasture and endocrinopathic laminitis.[50] Duration of lameness was a risk factor for development of laminitis in the contralateral limb of horses with unilateral laminitis, and horses that developed this complication were more likely to be euthanized than horses that did not develop laminitis.[51] It is apparent that inconsistent and conflicting results regarding horses' risks of developing laminitis exist, supporting the need for well-designed observational studies to improve the strength of evidence.

▪ Necropsy

Necropsy findings depend on the duration and severity of the disease. Separation of the primary epidermal laminae of the hoof wall and the collagen fibers of the corium occurs as a result of complete degeneration of the secondary epidermal laminae. The distal phalanx may sink, rotate ventrally, or penetrate the sole. Necrotic laminae are prone to abscessation. Severe changes include fractures of the solar margin, osteomyelitis, or resorption of the distal phalanx.

▪ Treatment

An incomplete understanding of the pathophysiology and progression of laminitis limits our ability to prevent and treat the disease successfully and results in considerable controversy regarding appropriate treatment regimens. Therapy is often empiric and based on the experience of the clinician. Advancement in our knowledge of the complex pathophysiology of laminitis may result in more effective preventative and therapeutic approaches. Acute laminitis should be considered an emergency, and therapy should be initiated before or immediately following the onset of clinical signs. General principles of therapy include minimizing or eliminating predisposing factors, decreasing pain and inflammation, promoting digital circulation, reducing tension on the laminae, and reducing platelet activation and coagulation.

Eliminating Causes.

Predisposing factors to the development of laminitis should be minimized or eliminated. Following ingestion of large amounts of grain, laxatives or

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purgatives including mineral oil or activated charcoal may be administered via nasogastric tube. Exhaustion, dehydration, and hypovolemia may be treated with appropriate intravenous fluid therapy. Appropriate therapy for combating the effects of endotoxemia and septic processes, including colitis, enteritis, pleuropneumonia, metritis, and retained placenta, should be initiated and may include intravenous fluids, parental antibiotics, NSAID therapy, polymyxin B, and hyperimmune serum or plasma. Treatment and management of other conditions associated with laminitis such as PPID and EMS are discussed elsewhere in this text.

Preventative measures in suspect cases include placing the horse in a deeply bedded stall, frog support, and corrective shoeing or trimming.

Decreasing Pain and Inflammation.

Antiinflammatory therapy is recommended to decrease lamellar inflammation, edema, and pain associated with laminitis. The most common NSAID used in horses is phenylbutazone at a dose of 2.2 to 4.4 mg/kg intravenously or orally every 12 hours. Flunixin meglumine can be administered at a dose of 0.5 to 1.1 mg/kg orally or intravenously every 8 to 12 hours for its anti-inflammatory effects, or at a dose of 0.25 mg/kg intravenously every 8 hours to interrupt eicosanoid production associated with endotoxemia. Ketoprofen and firocoxib are also labeled for use in horses. Dimethyl sulfoxide (DMSO) is a free radical scavenger that aids in reduction of edema and may reduce ischemia-reperfusion injury. DMSO is typically administered at 0.1 to 1.0 g/kg intravenously diluted in a polyionic fluid to a concentration of 10% to avoid hemolysis. Pentoxifylline is a phosphodiesterase inhibitor with antiinflammatory and immune regulatory properties. It has been shown to have anti-inflammatory effects[52] both in vivo and in vitro in horses and has recently been shown to effectively inhibit MMP in horses.[53] Further, evidence suggests that pentoxifylline reduces inflammation and blood glucose concentration after diabetes induction in rats by improving insulin sensitivity, making it a potential therapy for laminitis associated with metabolic disease.[54,55] In a recent study, the analgesic effects of tramadol hydrochloride administered in combination with ketamine hydrochloride were evaluated in horses with naturally occurring chronic laminitis. Tramadol provided little analgesic effect, but analgesia was enhanced by administration of subanesthetic doses of ketamine.[56]

Promoting Digital Blood Flow.

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Venous vasoconstriction may be involved in the pathogenesis of laminitis, but several therapeutic agents that have been suggested for increasing blood flow to the digit, including isoxsuprine and nitroglycerine paste, have not proven effective. Acepromazine, a phenothiazine tranquilizer, has been shown to increase digital blood flow in clinically normal horses with a short duration of efficacy of about 30 minutes.[57] Acepromazine has been recommended at a dose of 0.03 to 0.06 mg/kg intramuscularly or intravenously every 6 to 8 hours; however, at this dosage interval, the patient should be monitored for hypotension. If this complication is documented or suspected, the dosage interval should be extended or therapy with acepromazine should be discontinued. Caution should be taken in stallions due to the risk of paraphimosis.[57]

Continuous application of cryotherapy of the distal limb, in which hoof wall surface temperatures are maintained at 5° to 10° C for 48 to 72 hours, has been shown to limit the clinical, histologic, and biochemical abnormalities associated with experimentally induced acute laminitis in the oligofructose model.[58-62] The mechanistic effect is unclear, but involvement of the inflammatory[61,63] and vascular[64] pathways is suspected. Several methods of cooling the digit have been used, including ice water immersion bath, wader boots, ice packs, and 5-L fluid bags, with variation in the hoof wall surface temperature between methods.[65]

Reducing Tension on the Laminae.

Because laminar deformity is likely due to tension placed on the suspensory apparatus of the distal phalanx, reduction of mechanical force and stabilization of the distal phalanx are essential in the treatment of acute laminitis. Horses should be confined to strict stall rest and not be exercised in the acute stages of the disease. The horse should be encouraged to lie down, and bedding in the stall, ideally sand, should be deep. Redistributing weight from the hoof wall to the bars, sole, and frog may decrease laminar tension. Various methods have been suggested, including silicone impression material (EquiFlex-Pak [Sound Horse Technologies, Unionville, Pa.]), styrofoam insulation board, Lily Pads (Nanric Inc., Lawrenceburg, Ky.), the Steward Clog (Equine Digit Support System Inc., Penrose, Colo.), and Soft-Ride boots (Soft-Ride Inc., Vermillion, Ohio). Regardless of the method of weight redistribution, it is important to remember that once the distal phalanx displaces, increased pressure over the sole where the distal phalanx displaces may cause severely increased discomfort.

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Various methods of distal limb casts have also been used to improve stability to the distal phalanx.

Decreasing tension on the deep digital flexor tendon will also help decrease tension on the laminae. This can be accomplished by elevating the heels with a wedge (i.e., the Redden Modified Ultimate Wedge [Nanric Inc., Lawrenceburg, Ky.]) or transecting the deep digital flexor tendon to reduce caudal pull on the coffin bone.

Depending on the degree of rotation and/or distal displacement in chronic laminitis, various methods of hoof care and shoeing have been used. More radical approaches, including hoof wall resection and coronary band grooving, have been historically used with varying efficacy.

Anticoagulant Therapy.

Heparin has been recommended in the treatment of laminitis to reduce microthrombi and platelet-platelet or platelet-neutrophil aggregates that are thought to form during laminitis. Heparin was recently reported to have potential antiinflammatory effects on equine endothelium exposed to neutrophil-derived myeloperoxidase.[66] Unfractionated heparin was shown to reduce the proportion of horses with proximal enteritis that develop laminitis when administered prophylactically,[67] and low-molecular-weight heparin reportedly reduced the incidence and severity of laminitis in postoperative colics.[68]

▪ Prognosis

There is little evidence-based research on prognosticating laminitic horses; however, it is likely that the prognosis of laminitis depends largely on the severity of the pathology, type of displacement, clinical signs, and underlying diseases or conditions. Prognosis may also be influenced by financial constraints, owner expectations, and owner compliance. In general, rotation is considered to have a more favorable prognosis than distal displacement, which is considered to have a more favorable prognosis than unilateral displacement. The degree of rotation and distance from the proximal margin of the extensor process of the distal phalanx to the proximal margin of the hoof were reported to be important factors in return to soundness and prognosis for survival.[69] General guidelines based on degree of lameness and rotation and progression of clinical findings proposed by Redden in 1988 can be found in the previous edition of this text. In one study, 75% of horses referred to a university veterinary hospital with

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acute laminitis did not return to athletic function, and a majority were euthanized within 1 year due to poor response to therapy or development of complications.[70]

▪ Prevention and Control

Preventative measures are aimed at decreasing risk factors for development of the disease, but our poor understanding of the etiology and pathophysiology of the disease make prevention challenging. In general, suspected risk factors such as uncontrolled grazing on lush pastures, unrestricted access to grain or concentrates, factors contributing to gastrointestinal upset including rapid changes in diet, and retained placenta should be avoided when possible.

Despite continued limitations in our understanding of laminitis, it is likely that developments in biomedical research, industrial pressures, and extensive research collaboration will continue to advance our knowledge and understanding of the pathophysiology of laminitis and improve our ability to prevent, manage, and treat the condition.

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Fluorosis

John Maas

▪ Definition and Etiology

Ingestion of excessive fluoride by cattle, sheep, and horses can result in toxicosis. Acute fluoride toxicosis is relatively rare and is the result of accidental massive ingestion of fluoride compounds such as sodium fluoride or sodium fluorosilicate. Signs of acute fluoride toxicosis include restlessness, stiffness, anorexia, agalactia, salivation, vomiting or regurgitation, urinary incontinence, diarrhea, clonic convulsions, hyperemia, weakness, severe depression, and cardiac failure. Necrosis of the gastrointestinal mucosa and high concentrations of fluoride in plasma and urine are present in acute fluoride toxicities. Chronic fluoride toxicosis is most often referred to as *fluorosis*, a general term that includes osteofluorosis and dental fluorosis. Common sources of excess fluorides in the diet are (1) water with a naturally high fluoride content, (2) forages contaminated with fluorides from nearby (upwind) industrial plants (e.g., phosphate processing plants, aluminum plants, aluminum smelters), (3) mineral sources (nondefluorinated rock phosphorus) and feed supplements with excessive fluoride content, (4) forages contaminated by soil or water (particularly sprinkler irrigation water) with a high fluoride content, and (5) volcanic activity, which can deposit fluoride-containing ash on soil or plants or in water used for agriculture.

Recent outbreaks of fluorosis have been attributed to environmental fluoride contamination by superphosphate fertilizer plants,[1] ingestion of a commercial mineral supplement containing a contaminated phosphorus source,[2] fertilizer-grade phosphorus supplements (containing large amounts of fluoride) fed to cattle for lameness attributed to a phosphorus deficiency,[3] and fluorosis in sheep and cattle attributed to water with excess fluoride used for irrigation and drinking water.[4]

▪ Clinical Signs, Differential Diagnosis, and Pathophysiology

Clinical signs of fluorosis are usually first recognized as either dental fluorosis

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or osteofluorosis. Developing teeth are very sensitive to the ingestion of excess fluorides. The deciduous teeth rarely show signs of dental fluorosis, because a partial placental barrier to the accumulation of fluorides appears to be present in the fetus. During tooth development, excess fluorides cause ameloblasts to reduce in size prematurely and the enamel epithelium to form an irregular matrix. This matrix does not calcify normally, producing defects in the mature teeth. Cattle are susceptible to dental fluorosis during enamel matrix formation, from approximately 6 months to 3 years of age. Excess fluoride intake after 3 years of age does not result in the typical fluoride-induced dental lesions. Changes in incisor teeth are observed most frequently and include chalkiness, mottling (striations or patches in enamel), hypoplasia (defective enamel), and hypocalcification. Clinical lesions can be graded from normal to excessive.[5] Factors that influence dental fluorosis include the amount of fluoride ingested, the animal's age, the duration and consistency (intermittent versus continuous) of exposure to fluoride, and the source and chemical form of fluoride ingested. Although clinically important, dental lesions should not be used as the sole criterion to determine the degree of fluorosis.

Fluoride accumulation in bone occurs over a prolonged time; osteofluorosis can eventually develop if excessive fluoride is ingested. In cattle the first palpable lesions occur on the medial surface of the proximal third of the metatarsal bones. Later, lesions can be palpated on the mandible, metacarpal bones, and ribs. Radiographically, osteofluorotic bones are thickened with a chalky, roughened, and irregular periosteal surface.

The presence of osteoporosis, osteosclerosis, hyperostosis, osteophytosis, or osteomalacia depends on the amount of fluoride ingested and the duration of exposure to fluorides. The articular surfaces are not involved in osteofluorosis and can be used to differentiate osteofluorosis from osteomyelitis, osteoarthritis, and septic arthritis. The osseous lesions eventually cause intermittent lameness and stiffness, which may affect feed intake, body condition, milk production, and reproduction. Severe dental fluorosis causes reduced feed intake and efficiency, and affected animals are sometimes reluctant to drink cold water.

▪ Clinical Pathology and Diagnosis

Diagnosis of fluorosis is difficult and complicated by many factors that affect fluoride intake and deposition. Fluorosis may be suspected by history, clinical signs, and physical examination. Radiographic findings of bone disease without evidence of joint involvement are highly suggestive of fluorosis in the live

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animal. The fluoride concentration in the urine of cattle may help approximate recent fluoride exposure. The diagnostic value of urine fluoride analysis increases as the duration of excess fluoride ingestion increases. Normal cattle have a urine fluoride concentration of about 2 to 6 mg/L (2 to 6 parts per million [ppm]) or less than 10 mg/L (ppm).[6] Cattle exhibiting moderate fluorosis have a urine fluoride concentration of about 15 to 20 mg/L (ppm). Cattle with urine fluoride concentrations of 40 mg/L (ppm) or greater or a urinary fluoride/creatinine ratio of 0.025 : 1 or greater could be suspected of ingesting a diet with a fluoride concentration of 60 ppm or greater.[5,7] The concentration of fluoride in bone is also quite helpful in the diagnosis of fluorosis (Table 38.2). Fluoride content in cancellous bone (e.g., rib, pelvis) is greater than in cortical bone. In addition, fluoride concentrations may vary in different areas of the same bone.

TABLE 38.2
Fluoride Concentration in Bones of Dairy Cattle Fed Various Levels of Sodium Fluoride[8,9]

	Fluoride in Bone (ppm; Dry, Fat-Free Basis)		
Fluoride in Feed (ppm, Dry Matter Basis)	**2 years**	**4 years**	**6 years**
0-15 (Normal conditions)	401-714	706-1138	653-1221
15-30 (No adverse effects)	714-1605	1138-2379	1221-2794
30-40 (Borderline fluorosis)	1605-2130	2379-3138	2794-3788
40-60 (Moderate fluorosis)	2130-3027	3138-4504	3788-5622
60-109 (Severe fluorosis)	3027-4206	4504-6620	5622-8676

ppm, mg/kg.

Fluoride concentration of bone is usually expressed as mg/kg (ppm) of dry, fat-free bone. However, some bone samples are ashed before fluoride determination, so it is critical to note precisely which bone was sampled, how it was prepared, and what part of the bone was analyzed. The metatarsus and metacarpus are typically analyzed for fluoride content. For all practical purposes, fluoride concentration is equal in either of these bones from the same patient.[8] Using sawdust from a longitudinal section of bovine metatarsus (dividing the bone into lateral and medial halves or dorsal and palmar halves) yields virtually the same fluoride concentration as the whole bone.[8] The fluoride concentration of the fourteenth coccygeal vertebrae (ash basis) is approximately twice that of the metacarpus (dry, fat-free weight basis).[9] This can be a practical tool for

clinical diagnosis in the live animal.

Analysis of dietary fluoride is a valuable adjunct to the diagnosis of fluorosis. The upper safe limit of fluoride in water for livestock is 2 mg/L (ppm).[10,11] This safe limit may not protect against fluorosis in all field situations because of the large number of variables involved in the pathogenesis of fluorosis. Table 38.3 lists the long-term dietary tolerances for cattle. Under field conditions, the clinician must consider all possible sources of fluoride ingestion in evaluating total intake. Because fluoride intake may be intermittent, a low dietary intake at one time may not necessarily eliminate a diagnosis of fluorosis.

TABLE 38.3

Long-Term Tolerance of Dietary Fluoride for Cattle[11]

Animal	Dietary Fluoride (ppm, Dry Matter Basis)
Dairy or beef heifers	30-40
Mature dairy cows	40
Mature beef cattle	40-50
Feedlot cattle	100

ppm, mg/kg.

▪ Treatment and Prognosis

No specific treatment is known for ruminants with severe fluorosis, and the prognosis is poor for cattle lame from extensive bony lesions. Animals removed from the offending diet or water may lose 50% of the fluoride from bone within 2 to 5 years,[12] but severe dental damage is irreversible.

▪ Prevention and Control

Prevention involves avoiding feeds, water, and supplements with excessive fluoride concentrations. Feeding aluminum sulfate at 0.5% of the total diet reduces bone fluoride storage by 30% to 40%. However, additional phosphorus must be supplied in the diet, or osteoporosis and possibly spontaneous fractures may occur. Aluminum chloride or calcium aluminate also can be fed to cattle to reduce fluoride absorption. Calcium carbonate added to soils high in fluorides aids in reducing fluoride in forages. Cereal grains do not accumulate fluorides and thus can be helpful in reducing overall fluoride consumption. In circumstances of high fluoride concentrations in water, use of flood irrigation rather than sprinkler irrigation decreases the fluoride content of crops such as

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alfalfa hay.

The effects of varying levels of dietary protein on long-term fluoride exposure have been examined. In this study the feeding of low-protein diets (75% of recommended amounts) increased the bioavailability of fluoride, but there was no significant influence on the susceptibility to fluorosis by varying the dietary protein concentration from low (75%) to normal (100%) to high (125%).

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Hypertrophic Osteopathy

M. Keith Chaffin

▪ Definition and Etiology

Hypertrophic osteopathy (HO), also known as *Marie's disease*, is an uncommon condition in horses and is characterized by symmetric proliferation of connective tissue and subperiosteal bone along the diaphyses and metaphyses of the bones of the distal extremities.[1-7] The skeletal manifestations of HO are usually secondary to a primary underlying disorder elsewhere in the horse's body, often involving a space-occupying mass.[1-3,5-7] Most often intrathoracic disorders are the primary cause[1,2,6,7]; intraabdominal and intracranial lesions have been less frequently associated with HO.[6,8,9] In addition to horses, HO has also been described in humans, dogs, cats, cattle, sheep, deer, and fowl. In humans the term *hypertrophic osteoarthropathy* is used because the articular surfaces are usually affected; in animals, however, HO does not appear to frequently affect the articular surfaces.[1,6,7]

In the horse, HO has been associated with a number of primary intrathoracic disorders, including mycobacterial pneumonia,[2,6,10] lung abscess,[1,6] suppurative pneumonia,[1,6,11] granulomatous pneumonia,[2,3] systemic granulomatous disease,[6,7] fibrosing pneumonia,[12] primary and metastatic lung neoplasia,[11,13-16] pleuritis,[2] pulmonary infarction,[17] rib fracture,[18] pleural adhesion,[2,6] pericarditis,[2,4] mediastinal lymphadenitis,[6] and equine multinodular pulmonary fibrosis.[19] Reported primary extrathoracic disorders associated with HO include ovarian neoplasia,[5,20-22] abdominal tuberculosis,[2] peritonitis,[2] pituitary adenoma,[9] pyogranulomatous dermatitis,[3] and gastric squamous cell carcinoma.[8] There is one report of HO in a mare that was thought to be associated with pregnancy; signs of HO developed during three different pregnancies and regressed each time after parturition.[11] In some cases, an underlying disorder is never identified.[2,6]

▪ Pathophysiology

The pathophysiology of HO is not completely understood.[1,6-7] Initially, blood

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flow to the distal limbs is increased, followed by fluid retention and proliferation of connective tissue. Later there is bony proliferation along the inner aspect of the periosteum.[1,6,7] The periosteal proliferation results in the bony enlargements seen clinically. The link between the primary lesion and the skeletal abnormalities is poorly understood. Proposed explanations include hormonal abnormalities, hypoxia, arteriovenous shunting, and neurologic mechanisms.[1,6,7] The neurologic theory is based on increased vagal stimulation, and the endocrine mechanism involves a variety of local and systemic hormones increasing the production of vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF), causing release of megakaryocytes from the pulmonary circulation, resulting in platelet clumping in the periosteal capillaries.[7,19] No single theory offers a completely satisfactory explanation.

▪ Clinical Signs

Horses of any age or breed and either gender can be affected with HO. Some evidence suggests that HO may be more common in male horses and large-breed horses.[6] Ponies and donkeys can also be affected.[11,14]

Common clinical signs of HO include lameness, stiff gait, and reluctance to move or trot.[1,6,7] Firm bony enlargements are present on the distal extremities. In some cases, there may be soft tissue swelling or edema adjacent to the bony enlargements. In some horses the limb swelling is warm and painful to palpation, whereas in others the swelling is cold and painless.[6] Pain can frequently be elicited by forced flexion of the major joints. Bony enlargements are usually bilateral and symmetric and often affect the cranial, lateral, and medial aspects of the affected bones.[1,6,7] All four limbs are often affected, although the forelimbs are sometimes more severely affected.[6] The metacarpal and metatarsal bones are most often affected; other sites that can be affected include the phalanges, carpus, tarsus, radius, and tibia, as well as the maxilla, facial crest mandible, and nasal bones.[2,6]

Affected horses may or may not show signs related to the primary underlying disorder, such as cough, fever, weight loss, ventral edema, tachypnea, or colic.[6] Clinicopathologic features are highly variable and depend on the underlying primary disease process. Generally, there is increased serum activity of alkaline phosphatase, associated with increased osteoblastic activity at the sites of periosteal proliferation.[6]

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Radiographically, the bony enlargements are characterized by periosteal proliferative new bone formation of the diaphysis and metaphysis of affected bones.[1-3,6,7] The periosteal reaction often exhibits an irregular palisade pattern of osteophyte formation.[1,6,7] The bony reaction may extend to the chondrosynovial junctions; the articular surfaces are usually not affected.[7] Nuclear scintigraphy may reveal focal areas of intense uptake of radiopharmaceuticals at the sites of bony enlargement.[1,4]

▪ Treatment and Prognosis

The prognosis for horses with HO is guarded and depends on the underlying disorder. In one study, 71% of horses with HO were euthanized.[6] Gradually progressive limb swelling and pain are the typical clinical course in most affected horses for which an underlying cause is either not identified or effectively managed.[7] Thus management of HO should be directed at identification and treatment of the underlying primary disorder if possible. Common methods to help identify the underlying disease include hematologic studies, serum chemistries, fibrinogen, thoracic radiography, thoracic and abdominal ultrasonography, abdominocentesis, thoracocentesis, gastroscopy, rectal examination, laparoscopy, and in some cases computed tomography.[2,6,7] Successful management of the primary underlying disorder has resulted in partial or complete regression of the skeletal disease in a limited number of equine cases.[1,3-6,19] Regression of HO is characterized by a decrease in limb swelling and lameness, and a return to athletic performance is possible if bony lesions are not advanced.[1,6] In a few idiopathic cases in which an underlying disorder was not identified, lameness and bony reactions decreased with rest, phenylbutazone, or corticosteroid therapy.[2,6]

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Fescue Foot

Meredyth L. Jones

▪ Definition and Etiology

Tall fescue *(Festuca arundinacea)* is a cool-season grass native to Western Europe and introduced into the United States perhaps as a contaminant of other seeds in the late 1800s. It is well adapted to the transitional areas between the northern and southeastern regions of the United States but can be found in areas across the country. Fescue is associated with several toxic syndromes in livestock when infected by endophyte *Neotyphodium (Acremonium) coenophialum*, a Clavicipitaceae fungus. Ergot alkaloids, most importantly ergovaline, are produced by the fungus and have vasoconstrictive effects on the feet and other extremities, leading to tissue slough. Fescue foot is considered a disease of cattle, but sheep may also be affected.[1]

▪ Clinical Signs, Diagnosis, and Differential Diagnoses

Clinical symptoms of fescue foot occur within 42 days of exposure to endophyte-infected fescue.[1] Affected cattle may arch their back and have a rough hair coat in addition to limb signs. Limb lesions occur most often in the hindlimbs, starting as a red line at the coronary band with edema,[2] and the hair is easily epilated. A gangrenous process leads to purple-black discoloration and eventual sloughing of the skin. The tips of the ears and tail may be similarly affected. Lameness becomes severe as lesions progress, and animals may knuckle and prefer not to stand. There appears to be individual variation in susceptibility to fescue toxicity and severity of lesions.

Diagnosis is based on characteristic clinical signs and documentation of high endophyte infection of fescue to which animals were exposed. A sharp line of demarcation will be present between perfused and nonperfused tissues. Histopathology reveals vascular thrombosis and necrosis of compromised tissues.

Fields can be screened for percent infection by endophytes by submitting tillers (grass shafts at ground level), seed stems, and seeds. The target laboratory for this analysis should be contacted regarding the best sample for current growth phase of the plant and sample handling instructions. Ergovaline testing

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via high-performance liquid chromatography (HPLC) is available through some reference laboratories, and samples should be shipped on ice or kept frozen until shipment.[3]

Differential diagnoses for the lesions of fescue foot include ergotism of *Claviceps purpurea,* selenium toxicity, salmonellosis, and frostbite. Sarcocystosis in cattle has been associated with hair loss at the tip of the tail.[4] In the very early phases of the disease when only redness and edema are present, traumatic injury, laminitis, and foot rot may be suspected.

▪ Pathophysiology

The toxicity of fescue is likely multifactorial and may include compounds produced by the grass itself (loline, pergoline, others); however, fungal endophytes are widely accepted as the primary mechanisms of toxicity.[5-10] *N. coenophialum* production of ergovaline, ergonine, ergosine, and lysergamide results in vasoconstriction and is noted to be the primary etiologic agent[5,6,10]; however, several other fungal types from infected fescue have produced dermal edema and necrosis when experimentally evaluated in rabbits.[11] Threshold dietary levels of ergovaline of 400 to 750 ppb in cattle and 500 to 500 ppb in sheep have been established for the production of fescue foot lesions.[1]

Studies of blood flow in sheep and cattle fed highly endophyte-infected fescue indicated that blood flow was reduced in the adrenal glands and limb skin of sheep and in the truncal skin, cerebellum, duodenum, and colon of steers.[12] Although the visible clinical lesions indicate peripheral vasoconstriction, core visceral vasoconstriction clearly occurs as well. Lesions occur most often in cooler weather,[1] which is the season favored by the grass, especially when there is snow and ice, which likely worsen vasoconstriction.

▪ Treatment and Prognosis

As soon as the disease is suspected, all animals should be removed from the pasture if possible. Once necrosis is occurring, treatment is unrewarding and euthanasia is recommended for animals whose pain cannot be controlled. Early cases may respond to supportive therapy on soft ground and local or systemic antimicrobial therapy for protection of deep digital tissues from bacterial invasion through compromised skin. The use of NSAIDs should be considered carefully. Inhibition of the COX-2 pathway may result in vasoconstriction and

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platelet aggregation, making a theoretical case for avoiding NSAIDs in cases of fescue foot.

▪ Control and Prevention

In a USDA study of fescue pastures, 61.6% were infected with endophyte nationwide, with more than 75% of pastures in the Southern United States infected.[13] In such conditions, providing legume supplementation or overseeding with clover or lespedeza, along with sufficient protein and adequate trace minerals, has shown the most consistent benefit in reducing the impact of the toxin. Feeding fescue as hay before the seed heads are out may reduce the impact, but toxic pasture grass will remain toxic even as hay. However, one study in Missouri indicated that, with stockpiling and storage of hay, endophyte levels in infected fescue were reduced, while nutritive value was retained.[14]

When starting fescue, certain strains, such as Ky-31, should be avoided for livestock, as they have high toxic potential.[15] High soil nitrogen exacerbates toxicity, and fertilization of infected cultivars should be limited. Endophyte-free cultivars of fescue do exist, and some states require the packaging of fescue seed to declare the level of endophyte infection, with target levels of 0% to 5%. Unfortunately, endophyte-free fescues are less hardy and easily overtaken by infected fescue contaminating the pasture.

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Interdigital Necrobacillosis (Foot Rot) in Cattle

Meredyth L. Jones

▪ Definition and Etiology

Interdigital necrobacillosis, also called foot rot, foul-in-the-foot, and interdigital phlegmon, is a bacterial infection of the interdigital tissues, leading to moderate to severe lameness in one or more feet of cattle. Animals at high risk include those housed in moist, muddy lots; pastures with standing water; or areas where sharp gravel, concrete, or stubble exists.[1] *F. necrophorum*, a gram-negative anaerobe, is most often associated with this syndrome. Other bacteria, including *Prevotella melaninogenica*, *Porphyromonas levii*, and *Dichelobacter nodosus*, may induce similar lesions alone or in concert with *F. necrophorum*.[2-4]

▪ Clinical Signs and Differential Diagnoses

Early cases of foot rot show mild to moderate lameness in one or more feet, most commonly the hindlimbs. On examination of the foot, there is symmetric swelling of the coronary band region that may progress upward to the level of the fetlock. The interdigital space will also be swollen, spreading the toes. One or more fissures will form in the interdigital space (Fig. 38.31), where tissue necrosis is apparent. The characteristic odor of anaerobic infection with necrosis is apparent. Exudate is present, and there may be pseudomembrane formation.



FIG. 38.31 Interdigital fissure formation and necrosis are the hallmark of interdigital necrobacillosis. The lesion will also have a foul odor and variable amounts of swelling of the interdigital space and coronary band region.

Severity of lameness may progress such that animals may refuse to bear weight on an affected limb. Young calves may hold up a limb and shake it or, when multiple limbs are affected, may walk in such a way as to appear ataxic from neurologic disease. Invasion of the tendons and synovial structures may occur if the disease is not treated appropriately early, worsening the lameness and the prognosis for recovery. Mild fever may occur, and affected cattle will increase laying time, which leads to reduction in feed intake. Animal performance is diminished, with reductions in weight gain or milk production.

Differential diagnoses include septic arthritis, sole abscess, tenosynovitis, pedal osteitis, interdigital fibroma, laminitis, and trauma.

▪ Pathophysiology

The bacteria implicated in foot rot are normal inhabitants of the ruminant gastrointestinal tract and are therefore ubiquitous in the environment in which ruminants live. The syndrome occurs when there is a breach in the skin of the foot, usually through maceration from prolonged exposure to moisture or trauma. Oxygen tension is reduced by early microbial invaders, creating an ideal environment for the anaerobic pathogens of foot rot.[5,6] From there, several mechanisms contribute to virulence and evasion of the immune response. The two subspecies of *F. necrophorum* currently recognized are biotypes A and B.

Biotype A appears to be more virulent and is more frequently isolated.[7,8] Major virulence factors associated with this organism are a high-molecular-weight leukotoxin and lipopolysaccharide (LPS).[9,10] The leukotoxin is cytotoxic to ruminant neutrophils and, when combined with LPS, protects the organism from phagocytosis.[7] *P. levii* does not stimulate a significant chemotactic response in bovine macrophages in vitro, and suppression of phagocytosis occurs even when the organism is present in low numbers.[3] These properties of *P. levii* may facilitate a local tissue environment that allows other anaerobic organisms, including *F. necrophorum*, to colonize and evade host defense mechanisms.

Bacterial production of proteases and the products of white blood cell action and destruction further destroy local tissues, allowing for deeper invasion and necrosis. Swelling and pain result from tissue necrosis. Tenosynovitis, septic synovitis, and septic arthritis may all occur as the infection advances.

Systemic inflammatory responses do occur, and serum haptoglobin levels are increased in cattle infected with foot rot.[11] Other work has shown more extensive changes to plasma protein profiles, including those involved in pathways of inflammation, complement, and coagulation.[12]

▪ Diagnosis

The diagnosis of interdigital necrobacillosis is usually clinical, based on typical swelling pattern, interdigital fissures, and odor. Lesion culture may be performed but is limited in utility due to mixed populations of environmental and fecal contaminants. Histopathology may reveal intralesional spirochetes, but this is not consistent. Serodiagnosis has been reported with indirect ELISA for the detection of leukotoxin A antibodies using the recombinant protein PL2, yielding relatively high sensitivity and specificity.[13] Lack of expected response to parenteral therapy should result in reevaluation of the diagnosis and more extensive evaluation of the foot.

▪ Treatment and Prognosis

Most uncomplicated cases of foot rot will respond to parenteral antimicrobial therapy within a few days, with return to full soundness. Antimicrobial selection should be based on animal type, withdrawal time, and dosing logistics. In the United States, commercially available preparations of oxytetracycline, florfenicol, ceftiofur, tylosin, sulfadimethoxine, and tulathromycin carry label indications for foot rot. A comparison of ceftiofur crystalline free acid (6.6

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mg/kg subcutaneously [SC] in the base of the ear once) and ceftiofur sodium daily for 3 consecutive days revealed no statistical difference in recovery rates; however, the ceftiofur sodium resulted in more labor and time required for multiple administrations.[14] Another study comparing ceftiofur and oxytetracycline found no difference in the recovery rate between the two antimicrobials, concluding that the difference in withdrawal time should be considered in the treatment choice.[15]

Local treatment is generally unnecessary in most cases, and the use of bandages should be considered in light of the environment to which the animal is returning. A wet bandage can only worsen the situation. Some cases may benefit from wound cleaning and débridement of necrotic tissue.

Antiinflammatory and analgesic therapy may result in improved appetite and ambulation, improving welfare and lessening production losses. A transdermal preparation of flunixin is approved in the United States for pain control due to foot rot.

Regardless of the medical treatments used, animals should be returned to a clean, dry environment for recovery. They should be closely monitored for return to soundness and reduction in swelling. In cases treated early, improvement is expected in 2 to 4 days after parenteral antimicrobial treatment.[16] Animals that do not respond as expected should have their diagnosis reevaluated by thorough examination of the foot to determine if another lesion is present or if the infection has extended to deeper tissues.

▪ Control and Prevention

The bacterial agents of foot rot are residents of the alimentary tract and the environment of the ruminant. Their ability to cause pathology requires damage to the skin barrier in the form of moisture leading to softening and maceration of the skin or abrasions from rocks, concrete, or stemmy or frozen forage.

General principles for control involve evaluation of the environment for potential risk factors, including low-lying areas with standing water and congregation points that collect urine and manure. Hygiene should be improved wherever possible through the use of drainage systems, manure removal, and regrading areas or by avoiding certain pastures during wet times of year.

Some owners and veterinarians may be motivated to control foot rot using in-feed antimicrobials or other additives touted to improve control. No feed additives are approved in the United States for treatment, control, or prevention

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of foot rot, and extralabel use of feed additives is prohibited by the Animal Medicinal Drug Use Clarification Act.

The utility of footbaths is limited by the availability of efficacious compounds, environmental and occupational safety, contact time, and the ability to maintain the hygiene of the footbath. It can be difficult to get cattle to stand in the footbath long enough to achieve adequate bacterial killing, whereas standing too long results in contamination with fecal material, eventually leading to inactivation.[7] Antibacterial agents and astringents, including 3% formalin, 2% copper sulfate, oxytetracycline, and lincomycin-spectinomycin formulations, traditionally have been used. Dry footbaths have also been reported and include 10% copper sulfate and slaked lime.[6] Practitioners must check state and local laws regarding the use of these substances that can cause environmental contamination and occupational health hazards.

Commercially available vaccines against *F. necrophorum* exist for use in cattle. Independent studies regarding the efficacy of these vaccines are limited. One study evaluating the incidence of liver abscess and foot rot in vaccinated versus nonvaccinated feedlot cattle showed reduced incidence of both syndromes with vaccination, but that difference was confounded by diet, with improvement only occurring in cattle fed free-choice forage.[17] The role of this dietary influence on foot rot is unknown.

Trace mineral nutrition is an important consideration when evaluating foot health on any operation. Iodine, copper, selenium, zinc, and biotin support overall foot and hoof health. Variable results have been achieved in controlling foot rot using supplementation of trace minerals and biotin.[18,19]

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Infectious Foot Rot in Small Ruminants

Philippa Gibbons

▪ Epidemiology

Lameness is a significant issue in small ruminant welfare and production. In the UK, lameness prevalence was estimated at 10.4%[1] in 2004, with 80% of lameness caused by foot rot.[2] In 2013 prevalence had decreased to 5.4%.[3] In the United States, 20.4% of sheep producers reported lameness as an important issue, and 24% of producers treated ewes for lameness.[4]

▪ Pathophysiology

Two organisms are involved in ovine foot rot: anaerobic gram-negative bacteria *Fusobacterium necrophorum*, found in the environment and feces, and *Dichelobacter nodosus*, an obligate parasite of the foot. It has been generally accepted that *D. nodosus* can survive in the environment (in feces, soil, or pasture) for only 10 to 14 days, which has influenced eradication protocols. However, survival up to 30 days has been reported,[5,6] with prolonged survival in clay soils.[5] Transmission occurs when mean daily temperatures exceed 10° C (50° F) and rainfall is greater than 50 mm per month.[7] However, in the UK foot rot has been reported year round when environmental temperatures are outside these parameters.[8] Transmission can also occur during periods of housing in warm, wet bedding.[7] Transmission of foot rot from ewes to lambs has been shown to be primarily through *D. nodosus* in the environment rather than direct transmission.[9]

Historically, *F. necrophorum* was thought to be the causative agent of interdigital dermatitis (or scald), with secondary infection with *D. nodosus* causing the sloughing of the hoof wall seen in foot rot cases.[7] Pasture conditions resulting in excoriation of the interdigital skin and maceration due to wet conditions predispose animals to developing interdigital dermatitis.[7] In recent studies, *D. nodosus* has been shown to have a primary role, with *F. necrophorum* secondary.[10,11] Current literature suggests that interdigital dermatitis and foot rot should be treated as one disease. Ten serogroups of *D. nodosus* have been identified, some of which are virulent strains. Virulence factors of *D. nodosus*

have been identified as type IV fimbriae and AprV2 proteases.[12]

Foot rot caused by *F. necrophorum* and *D. nodosus* has also been reported in cattle, horses, pigs, deer, and mouflon.[13] There is little published information about the disease in goats,[14] but foot rot is a reported cause of lameness in goats.[15] Overgrown hoof wall is more common in goats than sheep.[15] Treatment with oxytetracycline is reportedly effective in goats.[16]

▪ Clinical Signs and Differential Diagnoses

Diagnosis of foot rot is by examination of the feet. This is commonly performed by producers. Studies investigating interobserver agreement for lameness diagnosis in sheep achieved good levels of reliability when both experienced and inexperienced observers were assessed.[17] Ovine foot rot infection is characterized by lameness, foul-smelling interdigital dermatitis, and sloughing of the hoof wall as a result of separation of the hoof horn from sensitive laminae.[11] Disease can be characterized as benign, intermediate, or virulent.[7] Australian studies typically define foot rot as benign or virulent, according to determination of the virulence factors of *D. nodosus*. British studies typically characterize the disease according to clinical signs and lameness severity. Virulent *D. nodosus* has been detected in the feet of nonlame sheep, however.[1] Interdigital dermatitis (scald) is a milder form of disease primarily limited to the interdigital skin and without a foul odor.[7] Foot rot should be distinguished from contagious ovine digital dermatitis (CODD), which has low reported prevalence in the United States and results in severe lameness and underrunning of the hoof wall at the coronary band, ultimately resulting in avulsion of the hoof capsule. Treponeme bacteria are the presumed causative agent for CODD. Due to treatment differences for the two conditions, identification of the cause of lameness is important.[18] Confirmation of foot rot is achieved by laboratory testing; however, culture of *D. nodosus* can be challenging due to the fastidious nature of the bacteria. Gelatin gel, elastase, and intA PCR were used in one study,[19] but agreement between the three tests was low. Real-time PCR has also been used in individual[20] and pooled samples.[21] Quantitative PCR showed poor diagnostic specificity compared to the elastase test for one study.[22]

▪ Treatment and Prognosis

Historically, foot trimming and topical administration of antibiotics formed the

major treatment and control measures for foot rot; however, foot trimming is no longer recommended as a treatment for foot rot due to prolonged recovery in trimmed sheep.[23,24] The number of ewes bleeding post foot trimming has been associated with higher prevalence of lameness.[3] Oxytetracycline administered parenterally is the most commonly reported antimicrobial treatment.[7,23-25] Oxytetracycline is not labeled for treatment of foot rot in sheep in the United States; therefore regulations for the extralabel use of antimicrobials and withdrawal times should be followed. Sheep treated with gamithromycin showed a significant reduction in foot rot–affected feet and severity of lesions compared to those treated with oxytetracycline in a nonblinded study in Germany.[25] Whole flock treatment with Micotil (tilmicosin) was investigated in the UK. Treatment reduced but did not eliminate disease from farms. The authors did not recommend whole flock treatment with Micotil due to the failure to eliminate disease, along with concerns about use of a critically important antimicrobial.[26] Gamithromycin used on a whole flock level was successful but cannot be recommended for the same reasons.[27] Florfenicol was used on a single flock of ewes in Germany in a targeted, selective fashion, and resolution of lesions was achieved in 96% of animals.[28] Penicillin and dihydrostreptomycin combination has also been used in countries where it is available.[23]

Topical antibiotics (oxytetracycline) have been used to treat interdigital dermatitis successfully if dry conditions are maintained after treatment.[23] In a single flock study in the UK, prompt administration of parenteral oxytetracycline and topical tetracycline reduced lameness scores and improved production. Ewes had higher body condition scores and raised more lambs compared to those treated with trimming and topical antimicrobials.[29]

▪ Prevention and Control

Elimination of foot rot has been successfully achieved in Australia,[30] Norway,[31] and Switzerland.[32] The Australian eradication protocol used a combination of total destocking, inspection and culling of clinically infected animals, treatment with antibiotics, and culling and foot bathing.[30] Foot bathing took the longest time to achieve elimination and was the most labor intensive approach.[30] The Swiss eradication model involved careful claw trimming, weekly foot bathing in 10% zinc sulfate, and isolation or culling of nonresponders.[32] No antimicrobials were used. A similar protocol was used in Norway.[31] In the UK, a six-step

method has been promoted; it involves treating sheep within 3 days of becoming lame; foot inspection without foot trimming; correct diagnosis; treatment of affected sheep with parenteral and topical antibiotics, not trimming; identification of treated sheep; and culling of chronic cases.[33] Eradication of the disease has been more easily achieved where there are periods of nontransmission (dry, hot weather); therefore eradication in wet, temperate climates is challenging.[23]

Foot bathing has been used for both treatment and control. Formalin at 2% to 3%, copper sulfate at 5%, antimicrobials, and zinc sulfate at 10% have been used.[23] To be effective, foot baths should be cleaned regularly and sheep should stand on a hard surface following bathing. Concerns about foot bathing include the use of formalin in meat-producing animals, the sensitivity of sheep to copper,[34] and the use of antimicrobials in an extralabel fashion.[23] Higher concentrations of formalin can cause cracking of the hoof wall due to overhardening.[23] Due to these concerns, zinc sulfate has been the most widely promoted. Foot bathing, however, is time consuming (2 to 20 minutes of contact time for zinc sulfate, depending on concentration) and should be repeated at least once a week for 3 weeks to be effective. Foot bathing has been shown to be economically feasible if minimized to treatment and prevention of interdigital dermatitis rather than treatment of foot rot.[35]

Vaccination has been used in both treatment and control of ovine foot rot. Commercially prepared vaccinations are not available in the United States. Vaccines available in other countries include recombinant fimbrial vaccine to 10 strains of *D. nodosus*. Monovalent and bivalent fimbrial vaccines are also available. Vaccination programs are most effective when used during a period of high-risk transmission.[23] Commercially available vaccines have been shown to protect for only 10 weeks, whereas monovalent and bivalent vaccines have been shown to be protective for longer periods. This effect is presumed to be due to antigenic competition.[36] Where multiple serogroups are present in a flock, antigenic competition can be overcome by sequentially targeting the serogroups with different bivalent vaccines every 3 months.[36] A contraindication of vaccination and simultaneous treatment with the anthelmintic moxidectin has been reported.[37]

Studies have shown that susceptibility to foot rot has some heritability[38,39]; however, there is also evidence to suggest that the infection rate and environment (bacteria die more rapidly in hot, dry conditions) are more

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significant than heritability in control of the disease.[40]

Selenium supplementation has been suggested to increase speed of resolution of foot rot lesions, although in a preventative model this finding was not replicated when selenium was fed at supranutritional levels.[41,42]

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Other Infectious Conditions of the Foot

Canaan Whitfield-Cargile

Infections involving the feet of horses, cattle, and other large animal species are common and almost always caused by contamination from the environment gaining access to the soft tissue or bony structures of the foot within the hoof capsule. Typically the animal has an acute, progressive lameness such that it is almost non–weight bearing on the affected limb or will bear weight on the toe region of the foot but resist putting the heel on the ground. Other clinical signs include increased digital pulse pressure, heat, and sensitivity to hoof tester pressure over the affected area. Regional nerve blocks can be used to localize the lameness to the foot when doubt exists based on physical examination findings. Because the foot is encased in a shell of horny tissue, exudate from an infectious process often accumulates between the soft tissue and the horn. The exudate then spreads or dissects along that plane in the path of least resistance until an outlet is encountered, frequently near the coronary band and bulbs of the heels, where rupture and drainage can occur.

Problems Associated With Horseshoe Nails ("Nail Prick")

▪ History and Clinical Signs

Nail prick ("quicking") refers to penetration of the sensitive hoof structures, usually the sensitive laminae, by a driven horseshoe nail. Similarly, the term *hot nail* refers to a nail that does not necessarily penetrate the sensitive laminae but may put pressure on those tissues due to inappropriate proximity. The horse will usually react as the farrier drives or clinches the nail by jerking the foot from the farrier. In some cases, blood may appear on the nail or leak from the nail hole. It is important to realize that nail pricks occur for many reasons and are not always caused by a misdirected nail. Poorly made shoes, nails that are too large, poorly placed nail holes, and faulty nails can also result in a nail prick. Horses with poor hoof quality, thin hoof walls, or flaring hoof walls can be difficult to nail and thus are at greatest risk for nail prick. Fractious horses and young horses not previously shod may lean on the farrier or repeatedly pull the foot from the farrier, making nail driving difficult. Damage from an improperly driven nail can

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vary from minimal to serious infection, thus clinical signs also vary. Clinical signs include lameness, sensitivity to hoof testers, and increased digital pulses. Some horses will repeatedly stomp the affected foot or paw the ground immediately after shoeing. Others may point the affected limb after shoeing. Lameness may not be apparent immediately after shoeing and may occur days later when the nail hole becomes infected and the trapped pus begins to exert pressure. This delayed onset is especially common when the nail is too close to sensitive laminae but has not penetrated. The horse usually becomes acutely lame and worsens over time unless treated. Some infected nail holes will travel up the lamellae (white line) and create an abscess or soft spot at the hairline of the coronary band. The abscess will be directly aligned with the hoof wall tubules, leading to the infected nail hole, which is an important diagnostic aid.

▪ Diagnosis

Diagnosis of a misdirected nail warrants great diplomacy from the veterinarian, because many owners become unjustifiably upset with the farrier. Hoof tester examination, paying particular attention to pressure over the driven nails, is an essential diagnostic tool to locate the offending nail. Using a hammer to strike the outside hoof wall may also elicit a painful response over the nail, further increasing suspicion of that specific nail. When an abscess occurs days later, it can be very difficult to be certain that the cause of the abscess was a nail prick versus many other reasons. Unless there is irrefutable evidence of the cause of lameness and abscessation being a nail prick, it is advisable to not suggest that as a cause to avoid undue blame being placed on the farrier.

▪ Treatment

Pricks from nails can be potentially serious and require immediate treatment. If the nail prick is discovered by the farrier at the time of shoeing, the nail is removed. The nail should be examined for moisture or blood. The nail hole can be irrigated with antiseptics (i.e., povidone-iodine [Betadine] solution or hydrogen peroxide). The nail hole is then packed with iodine-soaked cotton and left open. Often the nail is redirected, and no further treatment is needed. If the horse's immunization status is not current, a tetanus vaccine should be given.

If the offending nail cannot be localized or the nail hole is infected, the shoe is removed. Hoof testers are then used to localize the painful nail hole. Frequently the pressure from the hoof testers will cause black, malodorous liquid pus to exit

from the hole. The basis of treatment is to establish drainage. The infected nail hole often requires enlargement with a loop hoof knife or curette. Ideally, a cone-shaped hole is made, with the larger opening at the bottom of the hoof to facilitate drainage. The hole is irrigated and/or the entire foot is soaked in an effort to draw out any remaining infection. An important component of treatment is to protect the foot and nail hole from the environment (e.g., mud, dirt) by keeping the foot bandaged between treatment applications. Additional medications are usually unnecessary unless involvement is extensive. Antiinflammatory medications may be beneficial to decrease pain. Once the infection has cleared, the shoe is replaced and the horse can return to previous level of activity.

▪ Prognosis

Prognosis is usually good provided that minimal damage occurs to vital structures of the foot. Establishing drainage for sepsis is important to avoid potential complications, such as third phalanx osteomyelitis or coffin joint sepsis.

Subsolar Abscess

Subsolar abscess is one of the most common causes of lameness in the horse and cow, but it is relatively rare in sheep and goats. The vast majority of lameness in cattle is attributed to hoof problems including infection.[1,2] Most often, lameness is caused by a hole or crack in the horny sole, which then becomes packed with dirt, and eventually contamination extends to and is trapped within the sensitive soft tissue beneath the sole. Animals that are housed in exceptionally moist or filthy conditions and have inadequate hoof care or overgrown feet or have underlying pathology in either the hoof or systemic conditions are more prone to this problem. For example, a common presenting complaint of horses with keratomas is repetitive subsolar abscessation, and horses with pituitary pars intermedia dysfunction (PPID) often have recurring subsolar abscesses.[3,4] Horses taken from a very dry to a very wet environment, and vice versa, also tend to have a higher incidence of sole abscesses, apparently because of the sudden change in the moisture content of the hoof and the resultant cracking of the sole. Cattle with “corkscrew claw” (a hereditary condition) or other growth deformity in the claw are more prone to sole abscess. Puncture wounds or any form of trauma that introduces contamination to the soft tissue of the sole also

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may result in abscessation.

▪ History and Clinical Signs

Subsolar abscess is a common cause of acute lameness seen in all horses. There is no signalment or breed disposition. *Gravel* is a lay term describing the assumed etiology in which a piece of gravel migrates proximally from the white line to the coronary band, leaving an infected tract. Subsolar abscesses may originate from a penetrating wound in the white line, a nail hole, or a deep subsolar bruise. Lameness is usually acute and severe (grade 3 to 4 of 5) and may worsen over time until drainage is established. The horse will often point and may not bear full weight on the affected limb. Distal limb swelling often accompanies a subsolar abscess that has not had drainage established. Systemic signs of infection (fever, lethargy) usually are not associated with subsolar abscesses unless deeper structures are involved.

▪ Diagnosis

Digital pulses are usually increased, and the hoof capsule may radiate heat. A focal painful area can usually (but not always) be located with careful hoof tester examination. Careful paring of the sole and frog may be helpful in locating the abscess, but the clinician must be careful not to damage good, healthy tissue while looking for the infection site. Foot poultices and hot-water foot baths will eventually help localize the affected area by softening the horny hoof tissue. Gray or black purulent material will leak from the infected tract (Fig. 38.32). Radiographs are useful to rule out other causes, such as third phalanx and navicular bone fracture. In some cases a gas or fluid pocket can be identified on radiographs.



FIG. 38.32 Opened subsolar abscess draining gray and black purulent material.

▪ Treatment

Treatment is aimed at establishing adequate drainage. If an opening in the tract is present at the solar surface, it should be enlarged just enough for good irrigation and drainage. This may or may not require sedation or peripheral anesthesia of the foot. If pink tissue or blood is encountered, débridement is discontinued. Large holes should be avoided to prevent solar corium protrusion, which can be a painful sequela to overzealous hoof paring. If drainage occurs at the level of the coronary band and solar surface, through-and-through lavage is beneficial. Débridement at the coronary band level should be minimal to prevent iatrogenic coffin joint contamination. Once drainage is established, protecting the opened sole from the environment is recommended and can be accomplished with a foot bandage. Daily lavage and/or foot soaks in warm water with antiseptics and/or

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salt should be continued until sepsis and inflammation are eliminated. The shoe is replaced when the affected area is dry and cornified. Large areas may require a plastic pad under the shoe for solar protection. Antibiotics and NSAIDs are rarely needed except in severe cases or if penetration of deeper structures has occurred. The patient's tetanus immunization should be considered and a toxoid administered if needed, as foot abscesses are among the most common causes of tetanus in horses.[5] Principles of treating foot abscesses are the same for all large animal species.

▪ Prognosis

Prognosis for simple subsolar abscess is excellent but worsens if complications develop in which deeper structures of the foot become involved.

Deep Penetrating Injuries to the Sole

▪ History and Clinical Signs

Most animals' environments are filled with sharp objects that can penetrate the sole, causing severe damage to structures deep within the hoof capsule. All puncture wounds should be considered potentially serious, but those involving the solar white line or caudal frog area require special attention because of potential navicular bursa, digital tendon sheath, DDFT, or distal phalanx involvement.

The clinical signs of a penetrating wound to the sole vary with the anatomic structure involved and chronicity of the injury. The animal may show minimal lameness initially at the time of injury but severe lameness once sepsis is established days later.

▪ Diagnosis

If owners find a foreign body in the bottom of the animal's foot, they should be instructed to leave the object in the foot unless there is danger of further penetration. This facilitates the ability to determine the track of the offending object, as it can be very difficult even to find the puncture wound in some cases following removal of small, sharp objects due to the elastic nature of the hoof structures and collapsing of the penetration site. Once medical attention is sought, if the object is still present then radiographs are used to determine depth of penetration and location of penetration. If the object has been removed, a

close examination of the solar surface of the hoof should commence. Systemic sedation and peripheral anesthesia using an abaxial sesamoid nerve block may be needed to thoroughly examine the penetrated equine foot. Regional IV anesthesia (Bier block) using a tourniquet is the method of choice for producing local anesthesia in cattle. A light paring of the sole and frog areas with a hoof knife may reveal a black spot indicating the penetration site. Paring should be performed carefully so that the solar corium is not injured with the hoof knife. If an entry wound is discovered, the foot is scrubbed and prepared for further diagnostic testing. A sterile flexible probe can be gently inserted into the hole and a radiograph taken to determine its depth and direction. The clinician must take care that inadvertent force or horse movement does not cause the probe to penetrate previously unaffected structures. Alternately, a less invasive and preferred method is to catheterize or place a sterile teat cannula into the hole and inject sterile radiopaque material to determine which structures are involved. Recently, advanced imaging modalities, including MRI, have been used to more accurately define the track of penetrating solar injuries.[6]

If sepsis of the podotrochlear bursa, DIJ, or digital tendon sheath is suspected or cannot be ruled out, synoviocentesis allowing for instillation of sterile saline to assess communication with the wounds and synovial fluid cytologic analysis and culture should be performed. If distal limb swelling is present, arthrocentesis should be delayed until the cellulitis subsides.

▪ Treatment

Broad-spectrum systemic antibiotics, anti-inflammatory medications, and tetanus prophylaxis are administered if penetration of deep hoof structures is suspected. If deemed necessary, antibiotics are initiated, ideally after synovial fluid has been obtained for bacterial culture. Establishment of drainage, copious lavage with sterile ionic fluid, and débridement of all necrotic tissue are indicated. Involvement of the podotrochlear bursa warrants use of navicular bursoscopy and aggressive medical therapy consisting of daily lavage of the bursa under general anesthesia and local treatment using antibiotics instilled within the bursa and regional limb perfusion. Surgical treatment such as the “street nail” procedure, which opens a window through the central frog and DDFT in the bottom of the foot to reach the navicular bursa, is a drastic and aggressive method of therapy not commonly used in favor of a less-invasive bursoscopy approach.

If the DDFT is involved (septic tendinitis), débridement and removal of frayed

and infected tendon fibers may be performed on the standing, sedated horse using a tourniquet and peripheral anesthesia or under general anesthesia, depending on horse temperament and owner financial constraints. After débridement, heel elevation with a 4- to 8-degree wedge shoe decreases weight-bearing forces on the DDFT and provides some pain relief.[7]

Deep penetrating wounds to the sole, especially the solar–white line junction, can result in infectious osteitis of the distal phalanx. The horse usually presents with a chronic, recurrent draining tract at the coronary band or solar surface and varying degrees of lameness. Infection of the distal phalanx often results from undetected soft tissue infection or dissecting subsolar abscesses. As the bone infection progresses, blood supply to the area is compromised, and the area of avascular bone separates from the parent bone, forming a sequestrum or lytic area that is apparent radiographically (Fig. 38.33). Localized third phalanx septic osteitis and sequestrum formation may not become radiographically evident for weeks after the initial penetration injury.

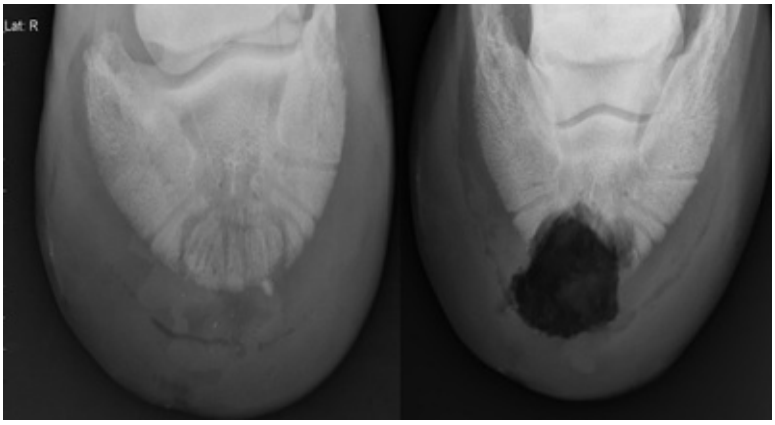


FIG. 38.33 Septic osteitis of the third phalanx before *(left image)* and after *(right image)* curettage of the infected region via a solar approach in the standing, sedated horse.

Débridement and curettage of all soft and necrotic bone can usually be performed in the standing, sedated animal if its temperament permits. The infected bone is usually discolored and soft and should be curetted to healthy bone margins (see Fig. 38.33). Systemic antibiotics may be indicated in some cases, but in most cases postoperative antibiotics can be most easily administered locally via antibiotic-impregnated beads (polymethyl methacrylate or plaster of Paris) for continued antibiotic release at the infected site. Regional

limb perfusion with antibiotics is also beneficial in some cases to treat infection locally and prevent extension to surrounding structures. A foot bandage is placed and changed every 1 or 2 days for the initial few weeks. Application of a bar shoe and hospital plate provides solar protection and decreases the labor and cost of daily bandage changes. The remaining care is as described for subsolar abscesses.

In cattle, simple sole abscesses following penetrating injury may heal quite satisfactorily without bandaging. Penetration of bone or synovial structures is managed as described above, although claw amputation is a treatment option in cattle that is not available to horses.[8] In cattle, a wooden block on the unaffected claw of the affected foot elevates the affected claw to a non–weight-bearing level and greatly reduces lameness. The block is attached with an epoxy adhesive and allowed to wear off over a period of weeks.

▪ Prognosis

Prognosis depends on severity of injury, structures involved, and chronicity of the problem before initiating treatment. Overall return to soundness has been reported to range between 36% and 60%, but horses with acute penetrating wounds that receive immediate and aggressive treatment have an excellent prognosis.[9,10] Factors that contribute to a poorer prognosis include involvement of a synovial structure, the distal phalanx, and time to presentation to the hospital. Established infection involving the podotrochlear bursa, digital tendon sheath, or distal interphalangeal joint has a poor prognosis.

Prognosis for infectious osteitis of the distal phalanx is good if sepsis is not caused by laminitis.[11] In one study, up to 24% of the distal phalanx was removed, and the horse returned to athletic soundness.[12]

Thrush

▪ Definition and Etiology

Thrush is a bacterial infection characterized by an accumulation of black, malodorous, necrotic material usually originating within the central or collateral sulci of the frog of the hoof. This degenerative condition may spread to involve deeper structures of the foot, such as the digital cushion, hoof wall, and heel bulb region, causing inflammation and breakdown of these structures.[13] This disease in horses is often considered similar to hoof rot in other large animal species.[14]

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Animals standing in soiled stalls, deep mud, swampy land, or wet pastures are at risk for developing thrush. Another predisposing factor is poor hoof conformation. Saddlebreds, Tennessee Walkers, and other gaited horses have long feet with naturally deep frog sulci and are at risk of thrush. Horses shod with full pads may develop thrush secondary to moisture and dirt collection under the pad. Other well-kept, clean horses can develop thrush for no apparent reason. Thrush is caused by a bacterial infection that appears to be most commonly associated with *Fusobacterium necrophorum;* in contrast, foot rot is associated with both *F. necrophorum* and *Dichelobacter nodosus*.[15]

▪ Clinical Signs and Diagnosis

Lameness may or may not be present, and severity can vary. Diagnosis is based on the presence of black, malodorous discharge, most often within the frog sulci. The central frog sulcus is often malformed and very deep. A painful response may occur when the affected sulci are cleaned because the degenerative process may extend to sensitive structures of the foot. If structural damage has occurred, the heels may move independently of each other, causing pain on manipulation. Horses with mechanical instability of the heels may show caudal heel pain.

▪ Treatment

The basis for treatment is removing the predisposing cause of the thrush. The horse should be moved to a clean, dry environment and have the feet cleaned daily, and if needed, proper farrier management should be pursued to correct existing problems. Any necrotic debris and undermined tissue are carefully débrided and cleaned using a hoof knife. Foot bandages may be necessary if the débridement is extensive. Infection is usually managed by topical medication. Several caustic materials have been recommended, including a combination of phenol, tincture of iodine and 10% formalin, Kopertox solution, dilute bleach, or methylene blue. Others have recommended soaking the foot in chlorine bleach (1 oz bleach per gallon water). Exercise is important to strengthen the caudal aspect of the foot and will naturally clean the feet. The best prevention for thrush involves educating the client on proper hoof hygiene.

▪ Prognosis

Prognosis is favorable if the cause of thrush can be identified and eliminated and if the condition is treated before extensive hoof damage has occurred.

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White Line Disease (“Seedy Toe”)

▪ History and Clinical Signs

The white line, visible at the sole, is created by the junction of the insensitive laminae of the hoof wall and the horn of the sole. White line disease has historically described the separation of the hoof wall from its laminar attachments. A crack or opening occurs within the white line, allowing a bacterial or fungal infection to invade the stratum medium close to the laminae, causing cavities to develop between the laminae and the outer hoof wall. Several fungal organisms have been associated with white line disease in horses.[16] In environmental conditions with too much moisture (continuous wet pastures) or in drought conditions that produce excessively dry feet, animals are at risk of developing a crack or opening in the white line. Horses with poor-quality hoof walls that split or crack may develop white line disease. In addition, horses with chronic laminitis having a thickened or stretched white line in the toe region (“seedy toe”) are predisposed to this disease.[17]

The hoof wall separation is usually a chronic condition beginning weeks or months before presentation. Horses with white line disease often show little or no lameness, and therefore the disease is not perceived as an immediate concern by many owners.

▪ Diagnosis

Visual examination of the white line, assisted by a probing instrument, will reveal a cavity with separation of the outer hoof wall from the laminae. Radiographic evaluation can determine the full extent of hoof wall separation. Often the cavity is either dry or filled with necrotic debris, which may involve a bacterial or fungal infection. The cavity is usually not painful to probing.

▪ Treatment

Treatment begins with removal of the separated outer hoof wall. After thorough débridement, large defects usually exist in the hoof wall and require protection. A heart-bar shoe redistributes weight-bearing forces to the frog and caudal region of the foot and away from damaged and weakened areas. The hoof wall defects prevent normal nailing procedures, and shoe clips can help secure the shoe to the hoof. After hoof wall removal, the exposed laminae may still have an active infectious component, requiring continued topical application of

antiseptics. Once the exposed laminae are dry and inactive, the horse may be a candidate for prosthetic hoof wall repair using an acrylic polymer.

▪ Prognosis

Prognosis depends on response to treatment and the cause of the original white line problem. Horses with poor hoof quality or seedy toe will often have disease recurrence. If the horse responds to original treatment and if environmental conditions improve, prognosis is good.

Quittor

▪ History and Clinical Signs

Quittor is a term used to describe chronic infection of the medial or lateral collateral cartilage of the distal phalanx in the horse. This condition is characterized by local inflammation and necrosis of the affected cartilage, with subsequent formation of draining tracts proximal to the coronary band. The infection is usually caused by a wound, and the horse often presents with moderate to severe lameness and a history of chronic or recurrent drainage.

▪ Diagnosis

The diagnosis is based on clinical signs and radiographic findings. Specifically, obtaining a dorsopalmar radiographic view after injecting contrast dye into the draining tract helps demonstrate the infected collateral cartilage.

▪ Treatment

Although this condition occasionally responds to medical therapy, the treatment of choice is surgical débridement with the horse under general anesthesia, the foot in full extension, and a tourniquet around the pastern. An elliptical section that includes the draining tract should be incised above the coronary band and discarded. All underlying infected soft tissue and necrotic cartilage should be excised. The incision can be closed, partially closed, or left open to allow for continued débridement if necessary, based on severity of infection and the surgeon's confidence in complete resection of affected tissues. If the condition is chronic with extensive cartilage necrosis or multiple draining tracts, the infectious process usually extends below the level of the coronary band. In these cases it is best to trephine a hole in the hoof wall at the lowest point of the

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infection. This procedure provides better drainage, facilitates débridement of the necrotic cartilage, and allows for complete closure of the surgical incision above the coronary band. The wound should be packed through the trephine hole and treated as an open wound until it heals. In cases with extensive cartilage necrosis, care should be taken to avoid accidental opening of the coffin joint. If débridement is complete and the distal interphalangeal joint has not been entered during surgery, the prognosis for the return to soundness is fair to good.[18]

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Fistulous Withers

Sarah M. Reuss

▪ Definition

Fistulous withers is a chronic inflammatory condition of the supraspinous bursa and associated tissues in horses, mules, and donkeys. The supraspinous bursa is located dorsal to the dorsal spinous processes of the second through fifth thoracic vertebrae. The normal bursa may extend laterally to the scapular cartilage, and it may be asymmetric. Normal bursal volumes range from 30 to 90 mL.[1]

▪ Clinical Signs

Affected horses may show nonspecific signs including lethargy, fever, and generalized muscle stiffness. These may progress to more specific signs of pain, heat, and swelling of the withers and cervical area. Over days to weeks, these swellings mature and rupture at one or more locations, releasing serous or mucopurulent drainage. The classically described discharge is yellowish-brown with white, yellow, or red flakes ("rice bodies").[2] Fistulous tracts may extend to the dorsal spinous processed of the vertebrae, as well as to the scapula, ribs, and occasionally the thoracic cavity. Lesions and drainage may wax and wane.

▪ Etiology and Pathophysiology

There are two forms of fistulous withers: idiopathic (or typical) and traumatic (or atypical). The more common idiopathic form results from the spread of inflammation and infection of the supraspinous bursa to surrounding structures, including the nuchal ligament and/or dorsal spinous processes. Organisms reported to be the primary cause of fistulous withers include *Brucella abortus*, *Actinomyces bovis,* and *Onchocerca cervicalis*. *B. abortus* has a predilection for synovial structures and is often associated with septic supraspinous bursitis in addition to septic atlantal bursitis ("poll evil"). In 1937, *B. abortus* was isolated from 80% of fistulous withers cases; 92% of those horses had contact with cattle, and 65% of affected horses were from farms with *Brucella*-positive cattle.[2] Currently there is some geographic variability. In New York, where the

prevalence of *B. abortus* infection in cattle is low, *B. abortus* is rarely isolated from equine cases of fistulous withers. In 1988, the prevalence of *B. abortus* in horses presented to the New York State College of Veterinary Medicine had apparently decreased, with only 2 of 14 (14%) horses having positive titers.[3] However, in Texas, where seropositive cattle are still prevalent, 9 of 28 (37.5%) horses with fistulous withers were seropositive for *B. abortus*, and these horses were more likely to be pastured with seropositive cattle.[4] Researchers have also produced fistulous withers experimentally via injection of *B. abortus* and *A. bovis* into the supraspinous bursa.[5] *O. cervicalis* has also been proposed as an etiology for fistulous withers, especially in Australia. This parasite migrates through the nuchal ligament, causing inflammation that may extend to the supraspinous bursa. Fibrous and calcified tracts develop around dead and viable parasites, causing necrosis and degeneration of the nuchal ligament.[6] *Streptomyces* spp. have also been incriminated as the cause of fistulous withers in donkeys in Sudan.[7]

The traumatic form of fistulous withers is preceded by an open wound or blunt trauma to the withers and then secondary infection. Infection may result from external contamination or from hematogenous spread to devitalized tissue. Secondary contamination of open wounds with *Streptococcus equi* subsp. *zooepidemicus*[3] or environmental microorganisms is reported.

▪ Diagnosis

A careful history must be obtained, including duration and severity of clinical signs and response to previous treatment. Physical examination with careful palpation over the withers may reveal pain, swelling, or draining tracts. CBC may show leukocytosis due to neutrophilia as well as hyperfibrinogenemia indicating chronic inflammation.

If the swelling is encapsulated and not draining, needle aspiration should be performed to obtain a sample for culture and sensitivity. Once tracts are open and draining, culture is of questionable validity due to secondary bacterial contamination. Negative cultures can also be misleading, as *B. abortus* is difficult to grow in culture and may be overgrown by other bacteria. Biopsy of inflamed tissue may also be obtained for culture and histology. Blood cultures may also be diagnostic in febrile animals.

Serologic testing for antibodies against *B. abortus* should be performed in all animals with fistulous withers due to the public health implications. The plate

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agglutination test is more sensitive and specific than the card test. *Brucella* titers are considered to be negative when they are less than 1 : 50. Ideally, paired titers should be performed, with any rise in titers performed 2 weeks apart being indicative of current infection.[8] Chronic infections may not show an increase, however, so a single high titer with compatible clinical signs should be considered diagnostic. Animals should be isolated while awaiting test results, and public health officials should be contacted if *Brucella* is suspected.

Radiographs should be obtained to determine the extent of the lesions, the presence of osteomyelitis of the dorsal spinous processes, and/or the presence of a foreign body. There may also be swelling or granular opacity of the soft tissue in the withers region.[3] Horses with positive *B. abortus* titers are more likely than seronegative horses to have radiographic evidence of osteomyelitis of the dorsal spinous processes.[4] A positive contrast fistulogram may help determine the extent of any draining tracts. Ultrasonography may also help delineate draining tracts or foreign bodies.

▪ Treatment

Medical treatment may be attempted but is often unsuccessful alone. Antimicrobial selection should be guided by culture and sensitivity results. In the absence of a culture, systemic broad-spectrum antimicrobials may be used. This should be combined with lavage of the draining tracts. Systemic antiinflammatories are also indicated to control pain.

Brucella vaccination with the S19 strain has been reported in *Brucella*-confirmed cases as an effective extralabel treatment in horses. The vaccination regimens described vary from single-dose subcutaneous injection to a series of three subcutaneous injections 10 days apart. Success rates of 70% have been reported in horses treated with S19 vaccine.[2] However, subcutaneous injection reportedly causes severe local and systemic reaction, including fever, depression, and local abscessation.[8] Intravenous administration of S19 vaccine has also been reported, but it resulted in death in 3 of 4 horses.[4] At this time, there are no approved vaccinations for use in horses, and the RB51 vaccine has not been used in equids. Also, the apparent decline in frequency of *Brucella* in fistulous withers makes vaccination of questionable value.

Medical management alone is rarely effective and usually needs to be combined with aggressive surgical débridement. Reportedly 80% of traumatic fistulous withers treated conservatively will have recurrent lesions.[9] Standing

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drainage and débridement has been performed, but general anesthesia and aggressive débridement is the preferred treatment.[3] Ostectomy and curettage of the dorsal spinous processes may be necessary. Primary closure is difficult to achieve but will provide a more cosmetic result and quicker healing time. Wounds left open to heal by second intention may take months to heal.[3] Application of maggots (freshly emerged, germ-free larvae) in combination with light surgical débridement has been reported in five cases. Four of those resolved successfully, with the remaining case being lost to tetanus before complete healing was achieved.[10]

▪ Prevention and Control

B. abortus infection, if present, carries great public health implications. Horse owners and veterinary staff must be notified of the possible exposure and take appropriate precautions. Brucellosis in humans may cause acute fever with pneumonia, spondylitis, orchitis, or pyelonephritis. Chronic brucellosis causes a transient fever in humans.[1]

Parasite control is an important aspect of prevention of fistulous withers. Horses should also be kept separate from *Brucella*-positive cattle. Proper saddle and harness fit also decreases the incidence of traumatic fistulous withers.

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Flexural Limb Deformities

Berkley Chesen

▪ Definition

Flexural limb deformities (FLDs) are defined as hyperflexion or hyperextension of a limb. Flexural deformities are described by the joint involved and occur in the sagittal plane, typically the distal interphalangeal joint, metacarpophalangeal/metatarsophalangeal joint, carpus, and rarely the tarsus. Although commonly referred to as “contracted tendons,” the tendons themselves are not truly contracted but rather functionally short relative to the adjacent bone, as only the muscular component can truly contract. Flexural limb deformities can be classified as either congenital or acquired. Flexural deformities are very common in horses and cattle. Small ruminants and camelids are much less commonly affected.

▪ Pathogenesis

Congenital flexural deformities (present at birth) are likely caused by a multitude of factors. Although intrauterine positioning has been suggested, it is likely only one cause of FLDs. Exposure of the mare during pregnancy to diseases and teratogenic agents is a possible cause of congenital FLDs. Evidence behind an absolute inciting cause is lacking, but the following have been implicated in contributing to FLds: deficiency in glycogen branching enzyme in Quarter Horse foals that is transient, ingestion of locoweed and hybrid Sudan grass, equine goiter, defective crosslinking of collagen and elastin formation from lathyrism, neuromuscular disorders, and viruses.[1-5] It is common for foals with congenital flexural deformities to have other anatomic abnormalities, such as spinal deformities that may result in dystocia. In a recent study of Thoroughbred foals in New Zealand, it was found that of 203 foals, 67% had at least one FLD (58% laxity, 38% contracted). At follow-up, 93% had improved with conservative management. Male foals were more likely than female foals to have FLDs, and gestation length was 347 ± 9 days for all foals. Age of the mare was found to be a significant factor (62% of mares younger than 12 years had foals with FLDs versus 79% of mares 12 years and older).[6]

Acquired flexural deformities typically are seen from 4 weeks to 4 months of

age, as well as in yearlings up to 2 years old. These deformities have been implicated as part of the developmental orthopedic disease complex. There are two general theories to explain how acquired flexural deformities occur. The first theory is that the tendon unit is unable to passively elongate relative to the bone.[7] In the case of the distal interphalangeal joint, the rigid deep digital flexor tendon and its accessory ligament cause a palmar rotation of the foot (club-footed) (Fig. 38.34). Flexural deformities in the metacarpophalangeal joint often occur during rapid growth in the distal radius, leading to a functional shortening superficial digital flexor muscle-tendon unit. The second theory is that longitudinal bone growth cannot create a functional shortening of tendons and that increased tension within the tendon induces pain leading to the deformity.[8] Acquired deformities are often noticed with a very acute onset (24 hours), which may add validity to the latter theory. Pain may initiate the deformity, but this can become a permanent condition if not addressed promptly, causing contracture to occur. Contracture results from fibrodesis of the joint capsule and periarticular structures.[7]



FIG. 38.34 Flexural deformity of the distal interphalangeal joint.

▪ Diagnosis

Congenital Deformities.

Digital hyperextension deformities occur in neonates due to lack of tension in

the flexor muscles. Typically these deformities correct without intervention within a few weeks. In severe cases, the palmar or plantar surfaces of the foal's pastern and fetlock area may become ulcerated due to contact with the ground if not protected.

Contractural deformities may involve one or a combination of the superficial digital flexor tendon, deep digital flexor tendon, or suspensory ligament. Congenital flexural deformities most commonly affect the carpus and metacarpophalangeal/metatarsophalangeal joint (Fig. 38.35).[9] Flexural deformities of the distal interphalangeal joint and the tarsus occur less frequently. In some pony breeds and miniature horses, lateral luxation of the patella results in the stifle showing a flexural deformity. This is usually due to a hypoplastic trochlear groove. Depending on the severity of the deformity, if the metacarpophalangeal joint is affected, the foal may or may not be able to stand.[7] Although not truly a flexural deformity, rupture of the common digital extensor tendon results in a similar appearance. This can result secondary to flexural deformities. These foals have a characteristic swelling on the dorsolateral aspect of the carpus. Often these foals bow at the carpus due to the lack of support over the lateral aspect of the carpus.[2,10] More importantly, foals with ruptured common digital extensor tendons should be checked for incomplete ossification of cuboidal bones, as these conditions often occur together.[7]



FIG. 38.35 Flexural deformity of the metatarsophalangeal joint.

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Acquired Deformities.

The most common acquired flexural deformity involves the distal interphalangeal joint and typically occurs within the first 4 months of life. The affected limb will have a more vertical hoof wall angle with a shorter toe than the unaffected limb; however, the condition is often bilateral. The heel will get longer on the affected limb, the metacarpophalangeal joint will concurrently begin to hyperextend, and the toe will undergo more wear, potentially causing issues with the white line. Two stages have been used to describe flexural deformities of the distal interphalangeal joint: stage I is defined as an angle of less than 90 degrees between the dorsal hoof wall and the sole; stage II is defined as a dorsal hoof wall that exceeds vertical.[11]

Early detection of flexural deformity of the metacarpophalangeal joint is characterized by a straight fetlock angle, or upright conformation. More severe deformity of this joint is evident by buckling at the fetlock. By placing pressure in a dorsal-palmar direction on the fetlock, the flexor tendons are stretched, allowing the practitioner to determine which structure is tightest, which is important for selecting an appropriate treatment.[7] It is also important to palpate the limb while not bearing weight to determine whether adhesions are present.

Carpal flexural deformities tend to occur within the first 6 months of life. These foals tend to be fast-growing, heavier foals (Fig. 38.36). Although not as common, flexural deformities of the proximal interphalangeal joint occur and are usually bilateral, affecting the hind limbs.[7] The exact mechanism is unknown, but it is thought that as the musculotendinous unit of the deep digital flexor complex shortens, the superficial digital flexor tendon becomes more lax.[12] This can lead to a dorsal subluxation of the joint. Often a clicking sound is appreciated when the foal walks. This condition is most often seen in weanlings with a high growth rate.[7]



FIG. 38.36 Bilateral, mild carpal flexural deformity.

Flexural deformities also occur after foals or horses are non–weight-bearing for a period of time. These deformities can be permanent if the joint undergoes "contracture" or fibrodesis (fixed without osseous ankylosis).[7]

▪ Treatment

Congenital Deformities.

Hyperextension deformities require exercise to hasten recovery. Excessive exercise is contraindicated, as this leads to fatigue and possible injury. Treatments include swimming, corrective shoeing, and light bandaging when indicated. Swimming allows muscle tone to increase without bearing weight on the limbs. If the foal's toe lifts off the ground when weight bearing, glue-on shoes with a heel extension may be indicated. It is important not to leave glue-on shoes on a growing foal for an extended period since they may prevent the foot from expanding normally; changing them every 10 days is indicated. Bandaging is necessary only in cases where the palmar or plantar surface of the pastern or fetlock is in contact with the ground to prevent ulcerations of the skin and should not be supportive of the structures. Excessive bandaging and support will only cause more laxity and should be avoided.

Treatment for congenital flexural deformities should include pain management by judicious use of NSAIDs such as phenylbutazone at 1.1 mg/kg IV or PO daily or flunixin meglumine at 1.1 mg/kg IV or PO daily. The use of gastroprotectants such as omeprazole (4 mg/kg orally daily) is strongly suggested to help avoid the ulcerogenic effects of NSAIDs.

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Oxytetracycline at a dose of 44 mg/kg diluted in physiologic saline given slowly intravenously has been used for many years in foals with flexural deformities.[13] Renal function of the foal should be taken into consideration prior to administration of oxytetracycline. There are many proposed mechanisms for how oxytetracycline works to achieve a decrease in the angle of the metacarpophalangeal joint. One mechanism proposes the chelation of calcium resulting in muscle contraction.[13] Oxytetracycline has been shown to be a neuromuscular blocking agent; however, this mechanism does not explain why other muscle groups are unaffected.[13] An in vitro study showed that oxytetracycline also works through matrix metalloproteinase 1 mRNA expression to inhibit tractional organization of collagen fibrils by myofibroblasts (the primary cell type in the DDFT and accessory ligament of the DDFT); this interaction may cause relaxation of the musculotendinous unit.[14] Regardless of the mechanism of action, foals treated with oxytetracycline should also undergo forced exercise to make the improvement permanent. Without exercise, the angle of the metacarpophalangeal joint tends to return to its previous value within 96 hours.[15]

A fairly new product on the market available to veterinarians is Leg Aide (Progressive Nutrition, Hopkins, Minn.), which has anecdotally positive results when used in conjunction with other therapies.

Toe extensions benefit the foal in two ways. First, they help protect the toe from being overworn; second, they lengthen the breakover of the foot, adding strain to the flexor tendons, potentially helping stretch them. Toe extensions may be made using acrylic hoof products or glue-on shoes with built-in extensions. In severe cases, the dorsal hoof wall should be incorporated into the shoe to prevent excessive strain at the toe and separation of the white line. Shoes and extensions should be removed within 2 weeks, as they can prevent the hoof from growing and expanding naturally in a young foal. Typically, 2 weeks is plenty of time to achieve correction. For foals with deformity of the distal interphalangeal joint, frequent rasping of the heels will help stretch the deep digital flexor tendon.

Splints and casts have been used to treat flexural deformities by giving support to the limb, thereby allowing the muscle-tendon unit to relax. When using splints, it is vital to use plenty of padding on the limb and to change the padding every time the splint is changed to ensure that pressure sores are not developing. Pressure sores can be very serious and even life threatening. Splints are made from a variety of materials but most commonly from polyvinyl

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chloride pipe that has been cut in an appropriate length and width; commercially made splints are also available. Splints are applied by placing the splint over the padding on the palmar or plantar surface of the limb. If the flexural deformity involves the distal interphalangeal joint, the splint should touch the ground. If the deformity is in the carpal region, the splint should end at the fetlock. Splints should be left in place for a period deemed adequate for the individual patient, ranging from several hours to 2 to 3 days.[7,9] One major advantage of splints over casts is that they may be removed every few hours if desired. Casts used for the lower limb are typically half-limb casts, incorporating the foot. The exception to this is for the carpal region, where a tube cast is more appropriate, ending at the fetlock. Casts should never be left in place for longer than 2 weeks at a time due to the rapid growth rate of foals. Cast sores are a very serious complication and a legitimate disadvantage to using them.

A combination of conservative treatments should be considered when treating foals with flexural deformities. If nonsurgical management does not correct the problem, surgical intervention may be necessary; however, foals with severe congenital contractural deformities have a poor prognosis. Surgery is more often attempted for foals with carpal contracture. Other congenital contractural deformities usually respond to nonsurgical treatments. Surgical correction for contractural deformities in the carpal region involves transection of the tendons of the flexor carpi ulnaris and ulnaris lateralis as well as transection of the palmar carpal fascia.[7,9] The prognosis for mild to moderate congenital flexural deformities is good for an athletic future if the foal improves over the first 2 weeks and is able to stand and nurse.[9] Flexural deformities that can be straightened manually have a better prognosis than those that cannot be straightened.

Foals with ruptured common digital extensor tendons are best treated nonsurgically. Affected foals should be confined to stall rest with the application of a splint.[10] As with any splint, it should be well padded to protect the limb. The splint will provide support to the limb and help protect immature cuboidal bones, which often accompany this condition.[7]

Acquired Deformities.

Conservative management for acquired flexural deformities is very similar to that for congenital flexural deformities. Other conservative therapies include dietary restrictions, including early weaning. Surgical management is selected

for those cases that are unresponsive to nonsurgical treatments.

For flexural deformities of the distal interphalangeal joint, desmotomy of the accessory ligament of the deep digital flexor tendon (ALDDFT) is indicated. This surgery has an excellent prognosis for full athletic potential for stage I horses. For more severe flexural deformities of this joint (stage II), a tenotomy of the DDFT may be necessary.[16] This procedure is not performed to promote an athletic career. It is acceptable for pasture soundness, breeding animals, and some light riding. Gradual rasping of the heels should be combined with any treatment for flexural deformities of the distal interphalangeal joint. Integrative therapy such as acupuncture may be considered to help achieve analgesia, muscle relaxation, and a level of sedation to help achieve physical therapy.[17] A recent study evaluated desmotomy of the ALDDFT in 13 mature horses (2 years or older) suffering from lameness isolated to the foot with FLDs of the distal interphalangeal joint.[18] Lameness was decreased in 9 of 13, with 10 of 13 performing at their level of intended use, indicating that this procedure should be considered in older horses.[18]

Acquired flexural deformities of the metacarpophalangeal joint are treated nonsurgically with a combination of NSAIDs, corrective shoeing (raising the heel with or without a vertical bar shoe with rubber dorsal tubing), and splints. Physical therapy has been used to help stretch the tendons by having the horse hop on one leg by holding the other up in a flexed position moving in a lateral direction toward the down limb.[7] If surgical correction is needed, it is important to first determine which structure is creating the tension. Most commonly the superficial digital flexor tendon is involved; however, the deep digital flexor tendon and even the suspensory ligament may be involved. For treatment of contracture of the superficial digital flexor tendon, desmotomy of the accessory ligament of the superficial digital flexor tendon is performed. If the deep digital flexor tendon is the most taught, desmotomy of the accessory ligament of the deep digital flexor tendon is completed. Both accessory ligaments may be cut when indicated.[17] In very severe cases, the suspensory branches may be transected, but this procedure is done for salvage, as it usually leads to subluxation of the proximal interphalangeal joint.[7]

Carpal flexural deformities are treated with splints and controlled exercise. Early weaning should be considered in these foals. If surgery is necessary, a tenotomy of the flexor carpi ulnaris and ulnaris lateralis in addition to splints may yield good results.

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Flexural deformities of the proximal interphalangeal joint are not as common, but can be very serious to the future athletic potential of the horse. Over time, the soft tissues around the joint will fibrose and the proximal interphalangeal joint may undergo degenerative joint disease. At this stage, a pastern arthrodesis may be necessary to achieve a pain-free and potentially sound limb. Desmotomy of the ALDDFT, as well as the tendon of the medial head of the DDFT (level of the chestnut), may benefit affected horses early in the disease process.[7,12]

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Tendinitis

Ashlee E. Watts

▪ Definition and Etiology

Tendinitis is one of the more common musculoskeletal injuries in athletic horses. Of the two flexor tendons, the SDFT is more commonly injured than the DDFT tendon. SDFT injuries occur in the forelimb far more frequently than in the hindlimb, and most injuries are in the midmetacarpal region. The prevalence of superficial digital flexor tendinitis in Thoroughbred racehorses ranges from 7% to 43%.[1] SDFT injury also occurs in Standardbred racehorses and upper-level event horses and is less commonly diagnosed in other performance horses. Deep digital flexor tendinitis is typically diagnosed in older (ages 9 to 10 years) performance horses. Injury to the distal portion of the DDFT is a major contributor to lameness in horses with foot pain,[2] and DDFT injury also occurs in the fetlock or pastern regions within the digital flexor tendon sheath (DFTS) and infrequently in the metacarpal/metatarsal region.[3,4] Desmitis of the accessory ligament of the DDFT[5] and the accessory ligament of the SDFT[6] are unusual injuries in performance horses.

The function of a tendon is to transfer activity from its associated muscle to its bony attachments on the opposite side of a joint. This allows for joint movement and locomotion. During locomotion, the elastic properties of tendons, particularly those of the SDFT, give them the ability to act like a spring, storing and releasing energy back to the limb to aid in limb advancement during movement. During gallop, substantial elongation of fibers (tendon strain) of up to 16% in the SDFT have been recorded, which is similar to the failure strains of 15% to 17% recorded in vitro, and operating this close to physiologic limits may contribute to injury of the SDFT.[7-9] The DDFT has relatively lower peak forces and strains, contributing more to flexion of the distal interphalangeal joint than to energy storage, and correspondingly has a lower injury rate.[10,11]

Tendon injury occurs when fibers are stretched beyond physiologic limits, which can be due to cumulative and degenerative fatigue failure, as is more common for the SDFT, or to a single, sudden overloading event, as is more common for the DDFT. Factors such as hard or “fast” ground, a rider's weight, and increased load when landing from a jump can also contribute to tendon

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injury by increasing the peak load on the SDFT. This accounts for the higher incidence of superficial digital flexor tendinitis in Grand Prix jumpers and upper-level event horses than in those competing at lower levels.[12] Response to tendon injury is similar to other tissue healing and includes inflammation, repair, and remodeling. During the acute inflammatory phase, hemorrhage and edema occur, and the degree of the response is determined by severity of the injury. Angiogenesis quickly follows, recruited fibroblasts produce new type III collagen, and a fibrinous scar of weak, haphazardly arranged collagen fibrils is formed. This scar tissue remodels over several months and will slowly increase the amount of collagen type I in the healed area. Controlled loading of the tendon promotes remodeling and alignment of the collagen fibrils in the direction of force (longitudinally). In a severely injured tendon the entire process can take 12 or more months, and it is likely that continued remodeling of the scar may occur over a lifetime. The healed but scarred tendon is permanently stiffer than its original state, thus re-injury is common and usually located at the periphery of the previously injured area.

▪ Clinical Signs

The classic appearance of metacarpal/metatarsal superficial digital flexor tendinitis is a convex or bowed profile of the tendon when viewed from the lateral aspect. In acute injury, swelling and heat of the tendon and peritendinous tissues can be noted but may be mild in the earliest stage of injury. A painful response to direct digital palpation can be appreciated and is best performed by holding the leg and palpating the tendon between thumb and forefinger. Unless the injury is severe, most horses with superficial digital flexor tendinitis are only mildly lame initially and rapidly improve to minimal lameness.

Horses with DDFT injuries within the DFTS are moderately lame and more lame after distal limb flexion.[4] Most horses have DFTS distention and thickening, making accurate palpation of the DDFT difficult. Injuries are usually unilateral and occur more commonly in the hindlimbs.[4] Horses with DDFT injuries within the hoof capsule have unilateral or bilateral lameness without any palpable abnormalities.[2] Injuries can be bilateral and are more frequently found in the forelimbs. Horses with desmitis of the accessory ligament of the DDFT have obvious swelling and are acutely moderately to severely lame.[5] Thickening and effusion in the carpal canal may be noted in horses with desmitis of the accessory ligament of the SDFT.

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▪ Diagnosis

Ultrasonography remains the technique of choice to confirm the diagnosis and assess the severity of SDFT injuries. The entire palmar/plantar area of the metacarpus/metatarsus should be examined in transverse and longitudinal planes. The commonly measured variables include cross-sectional area, echogenicity, and fiber alignment. The severity of the injury is determined by the length of the lesion, cross-sectional area of the tendon, cross-sectional area of the lesion, lesion echogenicity, and fiber alignment of the lesion.[13] The severity rating score has been correlated with successful outcome. The most common type of SDFT injury is a central core lesion, which appears as an anechoic lesion.[13] Acutely, the core lesion may not be visible, and ultrasound findings may be limited to peritendinous edema with a slight enlargement of the SDFT cross-sectional area. If clinical suspicion of a SDFT injury is high, the ultrasound should be repeated in 5 to 10 days to check for an ultrasonographically visible core lesion.

Diagnostic analgesia may assist the clinician in localizing the tendon injury if clinical signs are subtle or absent. This is particularly true for DDFT injury within the hoof capsule. Pain from DDFT injury in the distal metacarpal/metatarsal region usually improves after intrathecal analgesia of the DFTS.[4]

MRI is the best method of diagnosing deep digital flexor tendinitis within the hoof capsule.[2,14] Injury types include core lesions, sagittal tears, and tearing along the dorsal border; most lesions occur at or near the navicular bone.[2] Transcuneal (through the sole) ultrasonography has been reported but is not easy. Successful imaging requires meticulous foot preparation and clinician expertise.[15] Tenoscopy is the best method for detecting DDFT injury in the DFTS, although ultrasound, contrast tenograms, and MRI can also be useful.[16]

▪ Treatment

Proper treatment of tendinitis includes assessment of the injury using ultrasonography, control of the acute inflammatory episode, controlled return to function, and adjunct medical and/or surgical therapy. In acute injury, a combination of systemic NSAIDs (e.g., phenylbutazone, flunixin meglumine) and topical therapy (e.g., cold water hydrotherapy, poultice, distal limb bandage) is recommended. Box stall rest is essential during the acute phase of injury to

limit propagation of the injury, especially proximally and distally.

A variety of intratendinous and peritendinous injections have been advocated. Intralesional corticosteroids dramatically decrease the swelling and pain but cannot be recommended due to delayed tendon healing and the risk of continued injury and catastrophic injury in horses that remain in training. For metacarpal/metatarsal DDFT injuries, intrathecal injections of sodium hyaluronan into the DFTS have been beneficial.[17] The therapeutic role of regenerative medicine (e.g., stem cells derived from fat or bone marrow and platelet-rich plasma) in equine tendinitis is not fully understood. Long-term clinical efficacy has yet to be determined, but early clinical results are encouraging.[18,19] Other promising regenerative approaches that target specific pathophysiologic events in tendon injury are being developed and will likely become a standard treatment in the future.[20,21]

The surgical treatment of tendon splitting is no longer recommended due to increased damage to surrounding fibers.[22] Other surgical treatments that are recommended in specific cases are desmotomy of the superior check ligament[23,24] and desmotomy of the palmar/plantar annular ligament.[25] Superior check desmotomy may improve the likelihood that horses return to racing, but it remains somewhat controversial and may predispose horses to desmitis of the suspensory ligament.[26] Annular desmotomy has been successfully performed in horses with signs of annular ligament constriction in addition to flexor tendon injury.[25] Immediate decompression and improved gliding function are presumed benefits.

Other therapies for superficial digital flexor tendinitis that may speed accumulation of collagenous scar tissue include therapeutic ultrasound, low-power laser treatment, and extracorporeal shockwave therapy. Counterirritation (internal or external blisters) and pin firing in combination with controlled exercise or turnout in a large pasture are time-honored treatments, but their effects on tendon healing have not been helpful in studies.[22] These practices can no longer be recommended.

Controlled exercise in combination with the treatments described is of paramount importance in guiding the repair process to produce a functional tendon or tendon substitute. If exercise is excessive or uncontrolled, excess fibrous tissue is produced and remodeling is delayed. If no stress is applied, the tendon will not become well adapted for performance. Therefore a controlled incremental exercise program that is carefully monitored ultrasonographically is

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advocated. The program should be flexible and adjusted based on the severity of injury and the quality of healing. Typically, stall rest coupled with gradually increasing amounts of hand walking and trotting are recommended. Horses are monitored by regular clinical and ultrasonographic assessment until they have returned to their previous athletic function or have failed to do so. As the tendon heals, its echogenicity increases, and short linear echoes are detected. With continued healing, longer linear echoes and improved fiber alignment appear. Decrease in cross-sectional area is a good indication that the tendon is healing and remodeling. Ideally, complete repair will occur, and the tendon will no longer have a discretely visible area of injury because it has filled in with tissue that is isoechoic with normal tendon and fiber alignment is parallel to normal.

Successful treatment of DDFT injuries within the foot remains a challenge. Without surgery, long-term follow-up indicates a high rate of recurrent lameness despite prolonged periods of stall rest and corrective shoeing.[2] Surgical débridement via navicular bursoscopy appears to be helpful, especially in cases without concurrent severe navicular bone degenerative changes, although long-term follow-up is not yet available in the literature.[14] DDFT injuries within the DFTS also require surgical débridement for the best chance of healing and return to performance. This is because most DDFT injuries within a synovial environment involve the surface and epitenon of the tendon allowing synovial access to the tendon matrix, which limits healing.[27]

▪ Prognosis

Prognosis for horses with superficial digital flexor tendinitis depends on lesion severity and the type of athletic work performed. Although many horses treated with appropriate rest and controlled exercise programs will return to work, including racing, re-injury rates are high.[28,29] This is likely because of the permanent change in tendon stiffness due to accumulation of scar tissue in the healed area. Standardbreds, English sport horses, and Western performance horses appear to have a better prognosis. Horses with DDFT injuries remain problematic; prognosis is fair to poor, but as reports on bursoscopically and tenoscopically treated deep digital flexor lesions come out, the prognosis may improve.[2,4,30]

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Suspensory Ligament Desmitis

Ashlee E. Watts

▪ Definition and Etiology

The suspensory ligament (SL), also known as the *interosseous muscle*, is a strong, flat, tendinous band that contains a variable amount of muscle fibers.[1] The SL originates from the palmar carpal ligament and the proximal palmar aspect of the third metacarpus (MCIII) and in the hindlimb from the proximal plantar third metatarsus (MTIII). Coursing distally, it descends between the second and fourth metacarpal/metatarsal bones and divides into the medial and lateral branches before inserting on the abaxial aspect of the proximal sesamoid bones. The suspensory apparatus continues distally as the straight, oblique, cruciate, and short distal sesamoidean ligaments, which originate from the base of the proximal sesamoid bones and insert in the palmar pastern. The SL's main function is to prevent hyperextension of the fetlock joint.[1] Its branches also help stabilize the rotational forces on the joint. Injury to the SL occurs when it is overloaded with stress (overstretched) and its structural integrity is compromised. As with tendons, the repair process is characterized by inflammation (desmitis) and resultant fibroplasia. Healing occurs over many months, and repaired tissue is subject to re-injury due to the accumulation of scar tissue. SL desmitis is a common injury in all breeds of performance horses. Both forelimb and hindlimb injuries occur, and bilateral desmitis is not uncommon. Desmitis of the SL can be divided into three regions of interest: the proximal (origin) portion, the body, and the branches. Proximal SL desmitis is likely due to hyperextension of the carpus/tarsus in conjunction with severe overextension of the fetlock joint.[1] Straight hock conformation and hyperextension of the fetlock joint may be predisposing factors or may exacerbate the injury in the hindlimbs. Exercise in deep soft footing may also increase risk of injury.[2] Avulsion fracture, bone sclerosis, and/or enthesophyte formation in the proximal palmar/plantar MCIII/MTIII can also occur. Proximal SL desmitis occurs most frequently in sport horses, racehorses, and Western performance horses.[1] Injury to the body of the SL is less common and occurs predominantly in racehorses, specifically Standardbreds.[1,2] Desmitis of the SL branches is most common in

Standardbreds and jumping horses.[1] In the SL branches, injury is frequently associated with fetlock lameness, which suggests that the twisting motion of the fetlock predisposes horses to injury.

Catastrophic traumatic disruption of the suspensory apparatus occurs almost exclusively in the forelimbs of Thoroughbred racehorses and is the most common cause of breakdown injuries.[3] Fatigue and high speed are components of this career-ending injury. Degenerative suspensory ligament desmitis (DSLD) is a disorder characterized by progressive degeneration and enlargement of the SL, resulting in excessive fetlock hyperextension (dropping). Affected horses are generally dropped in both hind fetlocks and variably painful. The condition occurs sporadically in many breeds, usually older horses and broodmares.[1] Peruvian Paso[4] horses may be at risk and often are affected in all four limbs. The pathogenesis is unknown.

▪ Clinical Signs

Horses with proximal SL desmitis frequently have no localizing clinical signs. Heat, swelling, and edema are transient or absent, and lameness is variable. Horses with bilateral injury, especially in the hindlimbs, may have subtle gait abnormalities that are only apparent during ridden work. Lack of impulsion, resistant behavior, and loss of hindlimb activity are frequent complaints. In horses with desmitis of the body and branches of the SL, heat, pain, ligamentous enlargement, and lameness are common. Associated fetlock effusion and concurrent distal splint bone fractures may also be noted. Acute severe traumatic disruption of the suspensory apparatus results in obvious swelling, grade 4 to 5 lameness, and a hyperextended fetlock. Affected horses require first-aid treatment by application of a splint for weight-bearing stability. DSLD is characterized by bilateral chronic lameness, painful and enlarged SLs, dropped fetlocks, prolonged periods of recumbency, and reluctance to move.[1,4]

▪ Diagnosis

Perineural analgesic techniques help localize the site of lameness pain to the SL. For proximal SL desmitis, analgesia of the deep branches of the lateral palmar nerve[1,5] or lateral plantar nerve just distal to the tarsus[1,6] will alleviate lameness in the forelimb or hindlimb, respectively. Desmitis of the SL body and branches is localized using low palmar/plantar analgesia.

Ultrasonography is the imaging modality of choice for all but the proximal SL

of the hindlimb, where high field MRI is the modality of choice.[7] Lesion severity is assessed by obtaining cross-sectional and longitudinal views of the ligament and cross-sectional area measurements. Ultrasonographic changes include cross-sectional area enlargement, focal or diffuse areas of hypogenicity, core lesions, loss of normal fiber pattern, and periligamentous thickening. Mild injuries to the SL may be difficult to identify because of the wide variation in its normal ultrasonographic appearance. This is especially true in the proximal SL, since its origin is more heterogeneous than other tendons and ligaments because of variable amounts of fat and muscle tissue. Comparison between the affected and nonaffected limbs in the same horse are recommended because of individual variations and the large variation between breeds.[1]

Radiographic examination should be performed to identify concurrent bony lesions. Subchondral sclerosis, avulsion fracture, and enthesophyte formation have been identified in the proximal palmar/plantar MCIII/MTII regions of horses with proximal SL desmitis.[1,8,9] Axial exostosis along the second and fourth metacarpal/metatarsal bones[10] or fractures can contribute to SL body desmitis. Sesamoiditis and sesamoid fractures may be noted in horses with desmitis of the SL branches. In acute traumatic disruption of the suspensory apparatus, comminuted fractures of both sesamoid bones are common.

Nuclear scintigraphic findings are normal in the majority of horses with SL desmitis.[11] Increased radiopharmaceutical uptake associated with the proximal palmar/plantar MCIII/MTIII can be identified in horses with avulsion fractures and other stress-related bone injuries seen in complex SL desmitis.[8,9] MRI is not necessary but should be considered if no ultrasonographic abnormality is identified, or for the proximal SL in the hindlimb. MRI has identified fibrous adhesions between the SL and the small splint bones.[10]

▪ Treatment

Treatment of acute SL desmitis is aimed at reducing inflammation with systemic NSAIDs, local cold hydrotherapy, limb bandages, and controlled exercise. Initial clinical signs dissipate quickly even when there is significant SL fiber disruption, so it is strongly recommended to assess the ligament using ultrasonography. In uncomplicated desmitis, a controlled graded exercise program is recommended. The duration of rehabilitation will depend on the extent and severity of the desmitis. Fractures of the small metacarpal/metatarsal bones or sesamoid bones should be removed prior to rehabilitation. Horses are confined to a stall and hand

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walked daily. Ligamentous healing should be monitored every 60 days using ultrasonography. Ideally there should be a progressive reduction in cross-sectional area, improved echogenicity, and fiber alignment. Gradual increase in exercise can be prescribed depending on healing. The reparative process is slow, and return to competition or racing may not be possible for 12 to 18 months.

Damaged SLs have been injected with a wide assortment of therapeutics, and recommendations are similar to those outlined for tendinitis earlier in this chapter. Extracorporeal shockwave therapy[1,12] may be beneficial. The effects of intralesional platelet-rich plasma[13] and autologous stem cells[14] are currently under investigation, and clinical results are promising.

Successful treatment of proximal hindlimb SL desmitis is particularly challenging, and most horses treated conservatively remain lame. Neurectomy of the deep branch of the lateral plantar nerve,[1,15,16] desmotomy,[17] and fasciotomy[14-17] may be beneficial in these horses. Fasciotomy surgery allows decompression of the compartment-like syndrome that occurs when the damaged proximal SL becomes edematous and swells within the surrounding retinaculum. The deep branch of the lateral plantar nerve within the damaged SL becomes inflamed and damaged, so a neurectomy of this nerve is performed at the same time as the fasciotomy surgery.[18]

For horses with acute traumatic suspensory desmitis, it is crucial to place the affected limb in a protective splint that aligns the metacarpus with the phalanges in a straight column to prevent fetlock bending. Surgical management involves fetlock arthrodesis using a dorsal plate and wires or cables to reestablish the palmar tension band. Treatment for horses with DSLD is palliative, and rest versus turnout or barefoot versus shod does not appear to alter the long-term outcome. When there is deterioration or uncontrolled clinical signs despite treatment, options include surgical fetlock arthrodesis or euthanasia.

▪ Prognosis

Prognosis of SL desmitis depends on the location and severity of the injury. Uncomplicated cases with minimal disruption of the ligament can recover, and 90% of horses with acute proximal SL desmitis in the forelimb will return to full athletic function.[2] Complicated, chronic, or recurrent desmitis has been associated with a worse prognosis. Chronic hindlimb proximal SL desmitis has a particularly poor prognosis, and only 14% of horses treated conservatively return to full work.[2] Adjunctive medical and surgical treatments can improve prognosis

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in these problematic horses. Most horses with traumatic disruption of the SL can be salvaged for breeding after surgical repair. Prognosis for horses with DSLD is extremely poor, although these horses can also be salvaged with surgical arthrodesis of the fetlock joints.

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Fractures

Tamara M. Swor

Large animal fracture repair resulting in a successful outcome depends largely on a rapid and correct diagnosis, appropriate first-aid treatment and stabilization of the injured limb, and safe transportation to a referral surgical center. Great advances in large animal orthopedic surgery and anesthesia have allowed successful treatment of several fracture types, but some injuries still retain a poor prognosis for survival. Emergency treatment and stabilization administered by a veterinarian in the field is crucial to preserve the most treatment options and enhance the prognosis. Accurate knowledge of viable surgical and medical possibilities, and the prognosis for various fracture types, is critical during discussions with clients. The referral surgeon should be contacted early in the process by the field veterinarian and involved in decisions regarding limb stabilization, transportation, and owner financial commitments. Various medical and surgical treatment options are discussed in this section; details of specific surgical principles related to fracture repair can be found in surgical textbooks.

▪ Definition and Etiology

A *fracture* is defined as a break, crack, or rupture of a bone. In large animals, fractures are usually classified as complete or incomplete; articular or nonarticular; displaced or nondisplaced; open or closed; simple or comminuted; and transverse, oblique, or spiral. Classification by location is also common and includes terms such as *physeal, metaphyseal,* and *diaphyseal.*

Fractures in large animals are often associated with an acute traumatic event followed by sudden severe lameness. Horses may have a history of falling or running into a solid object, receiving a kick from another horse, being hit by a car, or flipping over backward (typically young animals). In another common scenario, the owner hears a loud pop or cracking sound while the horse is being lunged or is participating in an athletic activity.

Stress fractures also may occur and are often a result of cyclic loading over time, with corresponding fatigue leading to bone microfracture. Intensive training schedules create a high number of loading cycles with insufficient time to remodel and repair local areas of stressed bone (e.g., racehorse training). Specific locations of stress fractures include the distal end of the scapular spine,

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caudoproximal humeral head, craniodistomedial aspect of the humerus, medial humeral diaphysis, caudal aspect of the radius, dorsal mid-diaphyseal and distodorsolateral third metacarpal, caudal border of the ilial wing and adjacent to the pubic symphysis, proximolateral tibia, and caudal diaphysis of the tibia.[1]

Less common causes of large animal fractures include nutritional deficiencies, neoplasia, and infectious causes leading to pathologic fractures. Fractures related to difficult parturition events are seen in neonatal foals and calves.

▪ Clinical Signs and Differential Diagnosis

An animal with a long bone fracture typically will present with an acute non–weight-bearing lameness of the affected limb. Moderate to severe soft tissue swelling and inability to control the limb often accompany other clinical signs of distress, agitation, shock, and pain. Because of the horse's “fight or flight” reaction to traumatic situations, the patient will often continue attempts to place weight on the fractured limb. Fractures in locations with limited soft tissue coverage are often open (e.g., third metacarpal). Severe hemorrhage or laceration of large vessels is uncommon but may occur (e.g., pelvis).

Complete catastrophic fractures are often easily identified based on limb instability and soft tissue trauma or swelling. Proximal limb fractures may be difficult to palpate but have adjacent severe soft tissue inflammation and edema, crepitus, and difficulties in limb function. Nondisplaced or incomplete fractures may be associated with a wound or may be painful to manual palpation. Focal pain on palpation, a corresponding lameness, and a history of trauma or being kicked by another animal warrants radiographic evaluation in search of an incomplete fracture. An unrecognized incomplete fracture may progress to a complete fracture with time and movement or exercise. Physeal fractures should be considered in young animals.

Stress fractures often present with a history of acute severe lameness followed by a rapid decrease in the degree of lameness. There may also be reports of intermittent lameness that improves with stall rest. Palpation of the limb often reveals a focal area of pain, heat, and/or swelling. The horse may resist manipulation and movement of the limb.

Differential diagnoses should include hoof and sole abscesses, joint subluxation, joint luxation, nerve damage, soft tissue injury, and septic synovial structures.

▪ Clinical Evaluation

A complete physical examination should be performed on initial evaluation. Animals that are not immediately identified as having a fractured limb may be in need of systemic support. Fluid therapy, pain control, anti-inflammatory medications, and antimicrobials should be used as necessary.

Definitive diagnosis is made by taking multiple radiographic views; nuclear scintigraphy, ultrasonography, CT, and MRI may also be used (Figs. 38.37, 38.38, and 38.39). Information from imaging studies will provide fracture configuration details essential for determining prognosis. The bone involved, degree of comminution, articular involvement, physeal involvement, risk of infection, and condition of the bone fragments all affect potential repair attempts and long-term prognosis. Incomplete fractures may not be readily identified at the time of injury, and radiographs should be repeated in 10 to 14 days if a fracture is suspected.



FIG. 38.37 Lateral radiographic projection of middle phalanx fracture in

the left hindlimb. Several fracture lines appear to be present. (Courtesy Dr. Dane Tatarniuk.)



FIG. 38.38 Sagittal computed tomography image of middle phalanx fracture in the left hindlimb. Additional fracture lines are evident compared to those visualized on the radiographic projection in Fig. 38.37. (Courtesy Dr. Dane Tatarniuk.)



FIG. 38.39 Three-dimensional reconstruction of computed tomography images of middle phalanx fracture in the left hindlimb. This type of imaging allows the fracture to be assessed from all angles. (Courtesy Dr. Dane Tatarniuk.)

Stress fractures are also commonly diagnosed using radiographic evaluation and may be identified as an incomplete cortical fracture, endosteal sclerosis, or periosteal callus.[1] As with incomplete fractures, it may be difficult to identify a stress fracture by conventional radiography in the acute stages. Radiographs should be repeated in 10 to 14 days if a fracture is suspected. Other imaging modalities, especially nuclear scintigraphy or MRI/CT, may be useful in stress fracture identification.

▪ Emergency Treatment

The goals of emergency treatment include preventing further soft tissue damage, stabilizing the injured limb to decrease the patient's anxiety, minimizing further

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damage to the fractured bone ends, keeping the fracture closed, and preventing further injury and stretching to the surrounding vessels and nerves.[2] A large animal with a fractured limb should be immediately restrained and calmed. Sedatives and tranquilizers should be used with caution, however, because the desired result may be difficult to achieve if the animal is agitated or in shock. The goal of sedation should be to allow manipulation of the limb and placement of external coaptation while keeping the animal standing. Common sedatives should be used with caution to avoid creating additional ataxia; butorphanol should not be used if the horse has sustained a front limb fracture because it will make the horse lean on the forehand. If the animal is in systemic shock, an intravenous catheter should be placed and intravenous fluid support initiated. If a soft tissue wound is present, the veterinarian should assume that the fracture is open. The wound should be cleaned, topical antimicrobials used, a bandage placed to prevent further contamination, and the animal started on systemic antimicrobials. Antiinflammatory medications (e.g., phenylbutazone) should be used as necessary. If the prognosis for survival is grave, euthanasia may be suggested to the owner and might be in the animal's best interest prior to attempting transportation.

Appropriate external coaptation and stabilization of the fracture for transport can greatly influence the options available for fracture repair and the prognosis for success. Table 38.4 outlines specific emergency splints for different fractures in large animals.[2,3] Splinting techniques are designed to be placed on the standing horse and attempt to neutralize forces acting on the fractured limb. Splints should be made of a strong, lightweight material like PVC pipe or wooden boards. Bandages over fractures should be placed tightly over the injured area to decrease soft tissue swelling and minimize slippage. A layer of cotton padding should be followed by a layer of gauze or a self-adhering bandage. Multiple layers can be placed if needed (e.g., Robert Jones–type bandage). A recent study suggested that bending forces were equally neutralized with a splint over a small bandage, compared to a Robert Jones–type bandage and splint.[4] The splint should not end at the level of the fracture, should immobilize the joint above and below the fracture when possible, and should have enough padding so that no iatrogenic trauma occurs to the limb. In general, splinting techniques can be divided into categories based on fracture location.

TABLE 38.4

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Emergency Splinting Techniques for Fractures in Large Domestic Animals

Location	Species/Age	Splint
Distal phalanx	Horses, foals	No splint needed
	Cattle, calves	
Middle phalanx	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint to proximal metacarpal/tarsal 3 and cast material, Kimzey splint[a]
Proximal phalanx	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint to proximal metacarpal/tarsal 3 and cast material, Kimzey splint[a]
	Cattle, calves	No splint needed
Distal sesamoid (navicular)	Horses, foals	No splint needed
Proximal sesamoids	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint and cast material, Kimzey splint[a]
Metacarpal/tarsal 3	Horses, foals	Bandage with dorsal (front limb) or plantar (rear limb) splint and cast material, Kimzey splint[a] if fracture distal
Metacarpal/tarsal 3 and 4	Cattle, calves	Bandage with dorsal (front limb) or plantar (hindlimb) splint and cast, cast
Metacarpal/tarsal 2 and 4	Horses, foals	No splint needed
Olecranon/ulna	Horses, foals	Robert Jones–type bandage with caudal splint to lock carpus in extension
Radius	Horses, foals	Robert Jones–type bandage with lateral splint to withers, second caudal splint if needed
	Cattle, calves	
Humerus	Horses, foals	No splint needed
	Cattle, calves	
Scapula	Horses, foals	No splint needed
	Cattle, calves	
Tibia	Horses, foals	Robert Jones–type bandage with lateral splint to tuber coxae
Femur	Horses, foals	No splint needed
	Cattle, calves	
Pelvis	Horses, foals	No splint needed
	Cattle, calves	

[a]Leg-Saver splint (Kimzey Inc., Woodland, Calif.).

Distal Limb Fractures (Phalanges, Distal Metacarpus/Metatarsus).

A light cotton bandage should be placed on the affected limb from the carpus to

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the ground. A splint is then positioned on the dorsal aspect of a forelimb or the plantar aspect of a hindlimb. The toe is pointed toward the ground to align the dorsal cortices and minimize stretching of the palmar/plantar vascular and nerve structures. A second splint should be placed on the medial or lateral side of the limb if any instability is present in those directions. The splint should be secured with inelastic tape. For additional stability, several rolls of fiberglass casting tape should be placed around the entire bandage and splint structure, incorporating the hoof into the cast.

Midlimb Fractures (Midmetacarpus to Distal Radius, Midmetatarsus to Proximal Metatarsus).

A Robert Jones–type bandage should be placed on the limb from the ground to the elbow in a forelimb or from the ground to the calcaneal tuber in a hindlimb. The bandage should be less extensive in the hindlimb to facilitate splint placement. In the forelimb, splints should be placed on the lateral and caudal aspects of the limb from the ground to the elbow. In the hindlimb, splints should be placed on the lateral and caudal aspects of the limb from the ground to the calcaneal tuber. The splints are secured using inelastic tape followed by several rolls of fiberglass casting tape around the entire structure.

Upper Limb Fractures (Middle and Proximal Radius, Tarsus, Tibia).

A Robert Jones–type bandage should be placed on the limb from the ground and extend as far proximal as possible. In the forelimb, a splint should be placed on the lateral aspect of the limb from the ground to the withers. For increased stability, a second splint may be placed on the caudal or cranial side from the ground to the proximal forearm if necessary. Horses with olecranon fractures that disable the triceps muscle benefit from placement of a caudal splint to reestablish carpal extension. In the hindlimb, a splint should be placed on the lateral aspect from the ground to the tuber coxae. Splints placed high in this fashion will help minimize abduction of the limb.

High Limb Fractures (Proximal to Elbow Joint, Femur).

Fractures in these locations are covered by extensive muscle, and attempts at splinting are usually unsuccessful and unhelpful to the animal. If triceps muscle function is disabled, a splint on the caudal aspect of the carpus, locking it into extension, is beneficial.

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Transport.

Transportation of adult horses or ruminants with long bone fractures can be difficult. They should be trailered in a manner that allows them to lean on dividers for support and be tied loosely to prevent them from turning around in the trailer but still be able to use their heads for balance. When possible, horses with forelimb fractures should be transported with the head facing the rear of the trailer, and those with hindlimb fractures should be transported with the head facing the front of the trailer. These positions allow the horse to control its weight most easily with the uninjured limbs during deceleration of the trailer. Foals and calves will often elect to lie down during transport and should be allowed to do so safely in a compartment next to the mare or cow.

▪ Pathophysiology of Bone Healing

Healing of a fracture terminates in the return of the injured bone to its original form. The process of fracture healing involves several biological steps that overlap and interact with each other. Typically, three phases are recognized: inflammatory, reparative, and remodeling.[5,6] The acute *inflammatory phase* occurs in the initial 7 days after bone fracture, and chemical mediators cause chemotaxis, migration of leukocytes, and vasodilation to the injured area. These mediators protect the injury from infection and stimulate angiogenic factors. Cytokines from platelets aid in angiogenesis and mesenchymal cell growth.[5] Granulocytes and macrophages destroy invading bacteria and stimulate cell repair through the release of growth and angiogenic factors. If the inflammatory phase is impaired, fracture healing may be compromised.[5]

The *reparative phase* overlaps with the inflammatory phase and may last for up to 12 months. This phase attempts to reestablish bone union. Interfragmentary stabilization by periosteal and endosteal callus formation begins if the fractured ends are not immobilized.[6] Bony union develops as a result of endochondral and intramembranous ossification.[5,6] In the reparative phase, interfragmentary motion may greatly influence fracture healing.

The *remodeling phase* takes place both during and after the reparative phase. Osteonal remodeling allows for replacement of necrotic regions of bone. When the bone is loaded, the negatively charged concave surface will attract osteoblasts to add new bone, and the positively charged convex surface will attract osteoclasts to remove bone.[5,6] The result is the ability of a fractured bone to straighten itself by creating new bone formation on the concave surface and

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removing bone from the convex surface.

Repair of a fractured bone with the use of rigid internal fixation will inhibit naturally occurring callus formation and encourage bone to heal through haversian remodeling. *Haversian remodeling* requires that a fracture be rigidly fixed, have adequate reduction, and have an adequate blood supply.[5,6] Haversian remodeling then functions to revascularize necrotic bone at the fragmented ends of the fracture and bridge interfragmentary gaps. This form of remodeling begins 2 to 3 months after injury.

Fractured bones are often described as healing by primary (direct) or secondary (indirect) intention.[5,6] Primary bone healing occurs only with complete anatomic reduction and rigid stability. In large animal fracture repair, this is difficult to achieve because of the size of the animal and micromotion at the repair site. Secondary bone healing (most common in large animals) uses endosteal and periosteal callus formation, and new bone formed at the fracture site develops after initial formation of fibrous tissue or fibrocartilage.[5,6]

The rate of bone healing may be decreased if blood supply is inadequate, infection is present, soft tissue damage is extensive, or stability of the bone fragments is inadequate.

▪ Treatment and Prognosis

Treatment options for fractures in large animals include conservative therapy with stall rest and external coaptation (casts, splints), and surgical stabilization with open reduction and internal fixation. It is important to recognize incomplete and stress fractures and manage them appropriately with conservative therapy, preventing progression to a catastrophic fracture. In cases of incomplete fracture, the adult horse may need to be tied so that it does not cause additional stress to the fracture region by lying down and getting up repeatedly. The majority of fractures require some form of stabilization for the best chance of a successful outcome. Most horses require surgical stabilization for successful fracture repair. Ruminants are more amenable to successful fracture repair with nonsurgical options.

Conservative therapy with stall rest and external coaptation may be successful in some foals, calves, and small ruminants with complete nondisplaced fractures. Young animals have a greater and faster ability to heal bone in a reasonable amount of time, and their body weight is much less than that of a mature animal. In foals and calves, fracture configurations tend to be simpler, and the surgical

implants available for repair are of a suitable strength for the animal's size. Unique complications in young animals include premature closure of physes with fractures in these areas, systemic and local infections related to failure of antibody passive transfer, and angular limb deformities from overuse of the contralateral limb. One report described treatment using external coaptation (modified Thomas splint-cast combination) in small equids (median 127 kg) successfully as a salvage procedure.[7]

Irreparable fractures are more common in adult animals because of the greater force required for bone breakage. Proximal limb fractures in adult horses often defy successful treatment because of the severe bone comminution that occurs and because available implants are not strong enough to support the bone until it is healed, adult horses are less likely to protect the limb than foals, and laminitis formation in the contralateral limb results in overuse of the repaired limb. Stall rest with external coaptation alone is rarely associated with a good outcome; most horses need some form of internal fixation for success. Horses are often required to be athletes, and fracture repair resulting in survival but not soundness may be unacceptable. In general, ruminants have a better prognosis for survival than horses because with their less excitable temperament they protect the limb better, and complete soundness is often unnecessary for a positive outcome. In ruminants, external fixation may be a more successful option than just external coaptation because it provides increased stability but costs less than internal fixation. Open fractures in horses greatly decrease the prognosis for survival and may delay the ability to perform internal fixation. In ruminants, open fractures are less common but also carry a poorer prognosis for survival.

Implants used for surgical open reduction and internal fixation methods vary based on the specific bone involved, the animal's age, the strength of the bone fragments used in the repair, and the surgeon's preference. Common implants used in large animals include intramedullary interlocking nails, dynamic compression plates (DCPs), locking compression plates (LCPs), limited-contact DCPs, screws, wires, pins, and dynamic condylar screw plates. Table 38.5 lists specific treatment options and prognoses.

TABLE 38.5
Treatment and Prognoses for Large Animal Fractures

Fracture Location	Fracture Type	Treatment	Prognosis
Distal phalanx	Articular	Medical/surgical	Guarded

	Nonarticular	Medical	Good
Middle phalanx	Comminuted	Surgical	Guarded
Proximal phalanx	Comminuted	Surgical	Guarded
	Noncomminuted	Medical/surgical	Good
Distal sesamoid	Fragmented	Medical/surgical	Poor to guarded
Proximal sesamoids	Articular	Medical/surgical	Poor to guarded
	Nonarticular	Medical/surgical	Fair to good
Metacarpal/tarsal 3			
Lateral condyle	Nondisplaced	Surgical	Good
	Displaced	Surgical	Guarded
Medial condyle	Articular	Surgical	Guarded
Diaphyseal	Comminuted	Surgical	Guarded
Metacarpal/tarsal 3 and 4	Diaphyseal	Medical/surgical	Guarded to good
Metacarpal/tarsal 2 and 4	Distal	Medical/surgical	Good to excellent
	Proximal	Surgical	Guarded to good
Olecranon/ulna	Articular	Surgical	Good
	Nonarticular	Medical/surgical	Good
Radius	Complete	Surgical	Poor
	Complete[a]	Surgical	Guarded to good
	Incomplete	Medical	Good
Humerus	Complete	Medical	Poor
	Complete[a]	Surgical	Guarded to good
Scapula	Complete	Surgical	Poor to fair
Tibia	Complete	Surgical	Poor
	Complete[a]	Surgical	Guarded to good
Femur	Complete	Medical	Poor
	Complete[a]	Surgical	Guarded to good
Pelvis	Articular	Medical	Guarded
	Nonarticular	Medical	Guarded to good

[a]Foals, calves, and small ruminants.

Scapula.

Fractures of the scapula occur most frequently in horses 2 years of age or younger and often involve the supraglenoid tubercle. Surgical removal of the fragment or repair using lag screws, tension band wires, or DCP/LCPs has resulted in limited success. Recently, distal femoral locking plates and transverse LCPs have been used with success in a small number of horses.[8,9] Fractures involving the body of the scapula are often successfully managed conservatively in cattle.[10]

Humerus.

The humeral fracture is often in a spiral or long oblique configuration. In ruminant and equine species, both conservative and surgical treatments have been used. In foals, surgical repair may include the use of intramedullary

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interlocking nails, DCP/LCPs, or intramedullary nails. Prognosis for a closed fracture in a foal is fair to good and depends on configuration, age, and weight.[11,12] Humeral fractures in adult horses are not reparable at this time. Recent reports of horses with deltoid tuberosity or greater tubercle fractures of the humerus indicate some successful treatment results.[13,14] Conservative treatment may be successful in adult horses with nondisplaced fractures and has been used in small ruminants and foals with acceptable outcomes. Ruminants have a better prognosis in general than equine species, and calves have been treated successfully using external fixation.[15]

Radius.

The survival rate for ruminants with radial fractures repaired by external or internal fixation has been reported as 87.5%.[16] Radial fractures in foals and young horses (<1 year of age) repaired with internal fixation have a good prognosis, but in adult horses the success rate is low.[17,18] Prognosis decreases dramatically with an open fracture or surgical site infection. Animals with incomplete fractures that do not progress have a good prognosis for a full recovery with conservative management.[18]

Olecranon.

There are several different fracture configurations, and the olecranon fracture may be articular or nonarticular. These fractures are common in both young and older horses. Surgical and conservative treatments have been used with success, although internal fixation is the preferred treatment method.[19,20] Typically the fracture is repaired with a DCP or LCP applied as a tension band. The prognosis with surgical repair is good, with 75% to 87% of horses returning to athletic use, depending on the fracture type.[19-22] Conservative treatment has been reported to result in a 73% return to soundness.[23]

Femur.

Diaphyseal fractures are more common in calves, whereas proximal physeal fractures are more common in foals. Femoral fractures in calves may occur during parturition events. In young calves, these fractures have been repaired by internal fixation and femoral head and neck osteotomies with success. It has been found that calves treated surgically for femoral diaphysis fractures had fewer complications than those treated conservatively.[24] In foals, fracture repair

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with internal fixation gives the best chance of survival, and the use of intramedullary interlocking nails has shown positive results.[25] Third trochanter fractures in horses can heal with conservative management.[26] Complete femoral fractures in adult horses are not reparable at this time.

Tibia.

Tibial fractures in ruminants have been repaired using splints, external fixators, transfixation pin casts, and DCP/LCPs. Fractures repaired with external fixation in adult cattle had a 64% success rate, whereas conservative therapy yielded a 44% success rate.[27] Internal fixation is the repair method of choice in the equine species. Foals have a fair to good prognosis for survival. Adult horses have a poor prognosis for survival because tibial fractures are often open, have limited blood supply, and are often severely comminuted.

Metacarpus/Metatarsus.

In cattle, these fractures are common and have a good prognosis when treated with internal fixation, casts, or transfixation pin casts. Calves may incur distal physeal fractures after forced extraction during a dystocia, and these may be casted with good success. In horses, cannon bone fractures are frequently open because of a lack of soft tissue coverage. Treatment options include internal fixation with DCP/LCPs and screws, or transfixation pin casts. Studies evaluating outcomes in mature horses and foals with complete diaphyseal third metacarpal/metatarsal fractures treated with internal fixation found that 62% survived, although the survival rate was much higher for foals.[28] Another study reported a 67% success rate with surgical repair.[29] In racehorses, catastrophic or condylar metacarpal fracture can occur from preexisting bone injury, and repair may include DCP fixation or lag screw stabilization.[30-32]

Phalanges.

In ruminants, fractures of the proximal or middle phalanx are treated with reasonable success by applying a block to the uninjured claw or by cast application. In horses, proximal and middle phalangeal fractures have been treated by internal fixation with screws and DCP/LCPs. Prognosis for survival is good, but return to athletic function depends on the degree of osteoarthritis that develops after fixation. A recent report of proximal phalanx fractures in nonracing horses found that those treated with internal fixation had a better

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outcome than those managed conservatively.[33] Reviews of proximal phalangeal fractures in racehorses report that 50% to 75% were able to race following surgery.[34,35] Comminuted middle phalangeal fractures repaired with double plate fixation resulted in 97% of the horses discharged from the hospital and 60% able to return to useful function.[36] Severely comminuted fractures may also be treated successfully with transfixation pin casts or the Nunamaker external skeletal fixator.[37] Fractures of the distal phalanx in horses may be successfully treated with surgical fixation, hoof casts, or modification in shoeing, depending on fracture configuration. One study found that 77% of horses had a successful outcome but did not find that immobilization of the hoof influenced results.[38]

Summary.

Animals identified as having incomplete fractures should be treated conservatively with stall rest and tied to prevent them from lying down if the fracture is at risk of becoming complete (e.g., radius). Animals with stress fractures should be treated conservatively with stall rest and a careful rehabilitation program, with ongoing radiographic evaluation.

Many fractures in large animals can be repaired and allow survival of the animal. Despite recent advances in orthopedic surgery and anesthesia, some fractures in large animals are still not able to be repaired. In general, prognosis for survival is improved if the animal is young, weighs 500 pounds (225 kg) or less, the fracture is closed, appropriate emergency stabilization is implemented quickly, and prompt reduction and internal stabilization are performed.

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Spontaneous Fractures in Ruminants

Amanda K. Hartnack

▪ Definition and Etiology

Spontaneous fractures occur when a pathologic bone lesion weakens bone to the extent that fracture occurs secondary to normal forces. These are also referred to as pathologic fractures. Causes include resorption of bone, reduction of bone mass, insufficient production of bone, or local bone destruction.

▪ Clinical Signs and Differential Diagnoses

Clinical signs depend on the affected bones and may include lameness, swelling, postural changes, and angular limb deformity. Physical examination may reveal additional fractures. Commonly affected bones in ruminants include long bones, vertebrae, ribs, and mandible. Differential diagnoses include fractures of normal bones secondary to abnormal forces, septic arthritis or physitis, and osteomyelitis. Diagnosis is confirmed radiographically.

▪ Pathophysiology, Epidemiology, and Clinical Pathology

In ruminants, the underlying conditions that can lead to weakening of the bone's composite structure and subsequent fracture include bony destruction secondary to osteomyelitis or neoplasia, osteodystrophy associated with rickets in young animals, osteomalacia associated with nutritional imbalances in adults, and osteoporosis associated with copper deficiency.

Neoplasia and osteomyelitis weaken bone by dissolution of the mineral matrix, resulting in spontaneous fractures of affected bone. A variety of tumor types, including lymphosarcoma, hemangiosarcoma, liposarcoma, osteogenic sarcoma, and osteoma have been reported to cause spontaneous bone fractures in ruminants.[1-5] Radiographically, lesions may have an osteolytic, osteoblastic, osteoporotic, or mixed appearance depending on the tumor or infectious agent involved.[6,7] Localized bone infection can be traumatic or hematogenous in origin and may occur secondary to septic arthritis in calves.[7] Reported cases include vertebral body abscessation, osteomyelitis of the sternum, distal sesamoid bone, mandible, and third phalanx.[7-11] *Trueperella pyogenes* is the most common

bacterial isolate,[5,6] although osteomyelitis secondary to infection with *Actinomyces bovis* is also commonly reported in cattle.

Nutritional deficiencies or imbalances can lead to development of osteodystrophy, osteomalacia, and/or osteoporosis. These conditions can lead to spontaneous fracture, particularly of long bones and vertebrae, in some animals. Nutritional deficiencies can be classified as primary or secondary, with primary deficiencies involving inadequate intake and secondary deficiencies involving reduced nutrient absorption. Secondary deficiencies often occur when increased consumption of certain minerals such as iron, manganese, magnesium, zinc, sulfur, and molybdenum impede absorption of other nutrients. Clinically important bone diseases in ruminants are most commonly caused by deficiencies of minerals such as calcium, phosphorus, copper, and vitamin D (1,25-dihydroxycholecalciferol) due to their role in bone mineralization and collagen crosslinking.

In both young and adult animals, development of rickets due to phosphorus or vitamin D deficiency can occasionally result in spontaneous bone fracture.[13] In young animals, rickets affects the developing skeleton, resulting in abnormal endochondral ossification and defective bone formation. In adults, the pathogenesis of osteomalacia-associated disease is similar, although only bone formed during remodeling is affected, and osteoporosis can also be seen.[14] Clinical signs of phosphorus deficiency include loss of body condition, lameness, abnormal stance, spontaneous fractures, reproductive failure, and hypophosphatemia. Primary phosphorus deficiency can occur in ruminants when low levels of phosphorus are available in forage, and secondary phosphorus deficiency can result when significant imbalance exists between calcium and phosphorus concentrations in the ration.[13] Serum phosphorus levels may not reflect the severity of the disease process.[14,15] Gross postmortem findings may include brittle, porous bone and bony callus indicative of healed fractures on the ribs.

Copper deficiency has also been reported as a cause of osteoporosis leading to pathologic fracture in ruminants.[16,17] Although copper deficiency may be caused by low copper levels in the diet (primary deficiency), it is more commonly a result of high dietary molybdemum or sulfur. Deficiency occurs when molybdenum and sulfate form indigestible compounds called thiomolybdates, which bind copper.[18] In addition to spontaneous fractures secondary to osteoporosis, clinical signs of copper deficiency include lameness,

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achromotrichia, diarrhea, anemia, and poor growth.[19] In cattle, hepatic copper levels are considered the gold standard, with levels lower than 10 µg/g commonly considered deficient. Low plasma copper (<9 mmol/L) or ceruloplasmin levels are suggestive of copper deficiency (<15 IU/L).[20,21]

Other conditions that can cause spontaneous fracture in ruminants include chronic fluoride toxicity (fluorosis)[22,23] and a number of heritable conditions. These heritable conditions include osteogenesis imperfecta in Holstein Friesian calves and Charolais cattle, inherited rickets in Corriedale sheep, and hemochromatosis of Salers cattle.[24-27]

It is important to note that other management and nutritional issues may contribute to abnormal bone composition and lead to spontaneous fracture. A detailed history, physical examination, and diagnostic workup can help identify underlying conditions.

▪ Treatment and Prevention

When treating spontaneous fractures, resolution of the underlying disease is essential. The prognosis depends on the severity and location of the fracture, as well as the underlying disease process. Fractures secondary to osteomyelitis or neoplasia carry grave prognoses. However, fractures associated with metabolic bone disease have been treated successfully. As with many other conditions, prevention of spontaneous fractures is aided by proper nutritional management.

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Dorsal Metacarpal Disease in the Horse

Travis M. Tull

▪ Definition and Etiology

Dorsal metacarpal disease, or bucked shins, is a common problem in the 2- and 3-year-old training horse and is characterized by pain, heat, and periosteal proliferation in the dorsal aspect of the third metacarpal bones. Bucked shins cause lameness resulting in days lost in training, precede dorsal metacarpal stress fracture, and less commonly lead to catastrophic fracture of the third metacarpus (MCIII).[1,2] The development of dorsal metacarpal disease is directly related to the structural changes that race training induces, as the MCIII increases in size, density, and strength.[3-5] Slower gaits or speeds result in tensile strains on the dorsal aspect of the MCIII.[6] According to Wolff's law, the bone initially undergoes modeling and remodeling in response to these changes, resulting in periosteal fibrous bone on the dorsal cortices of the MCIII.[5,7] At faster race speeds, the strain on the dorsal and dorsolateral MCIII rotate, becoming compressive instead of tensile.[6,8] The bone, adapted for tensile forces, incurs microdamage that leads to pain, inflammation, lameness, and in some cases stress fracture.[2,5]

▪ Clinical Signs and Differential Diagnosis

Dorsal metacarpal disease occurs in 2- and 3-year-olds that have recently begun race training, typically after the introduction of work at race speeds.[6,7] History is important, as the disease rarely occurs in the nonracing horse and can occur in older racehorses that are changing training surfaces or beginning their career at a later age.[2,9] Affected horses demonstrate inconsistent short-strided lameness, heat, and focal pain over the dorsal cortex of the metacarpus with or without swelling.[2,9] Periosteal swelling can occur anywhere on the dorsal aspect of either limb, but generally both forelimbs or only the left MCIII demonstrate clinical signs.[9,10] Lameness often resolves with rest and NSAIDs. The lameness can be ameliorated with local analgesia such as a high ring block over the proximal dorsal MCIII. Radiographs at early onset may be inconclusive, whereas more chronic cases may have increased dorsal cortical thickness and linear lucencies

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parallel to the cortex (Fig. 38.40). Nuclear scintigraphic examination yields increased radionucleotide uptake on the dorsal cortex of the MCIII, which must be differentiated from normal uptake in an actively training horse.[11] Dorsal cortical stress fracture of the MCIII has similar presenting signs as bucked shins. Initially there may be lameness after racing or speed work that subsides with rest. There may be focal pain on palpation with variable amounts of swelling or hard periosteal callus. Radiographic signs include periosteal and endosteal proliferation and a 30- to 45-degree oblique linear lucency in the dorsolateral cortex of MCIII, most obvious on the dorsomedial-palmarolateral oblique or the lateral to medial projections.[12] The fracture line can be oriented from the outer cortex, distal to proximal, proximal to distal, in a true saucer configuration, or on occasion more than one fracture can be present (Fig. 38.41). Nuclear scintigraphy of dorsal cortical stress fracture of the MCIII coincides with moderate to intense focal radionucleotide uptake.[11]



FIG. 38.40 Dorsomedial-palmarolateral oblique radiographic projection of the left third metacarpus on a 2-year-old Thoroughbred racehorse with chronically affected bucked shins. White arrows indicate periosteal bone proliferation. Black arrows indicate linear lucency parallel to the periosteal and endosteal surface.

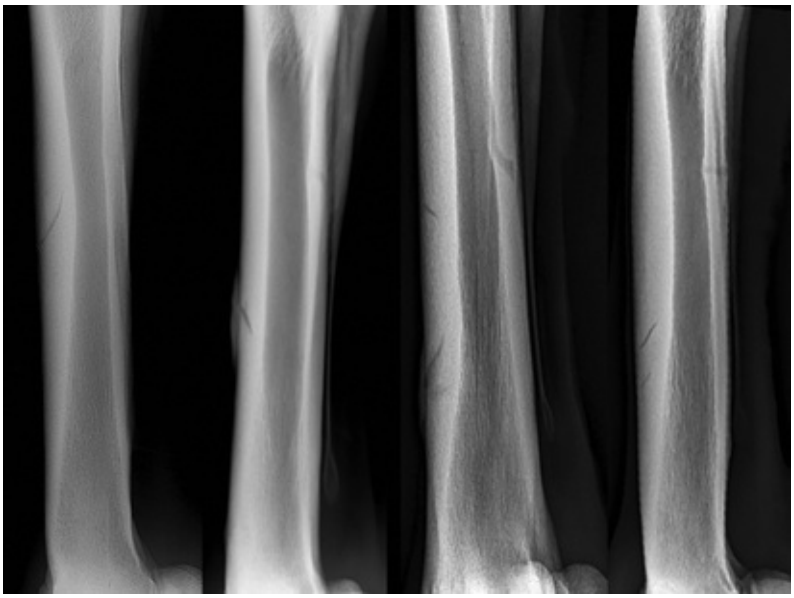


FIG. 38.41 Differing incomplete dorsal cortical stress fracture of third metacarpus configurations. From left to right, fracture line distal to proximal, proximal to distal, saucer type, and multiple fracture lines.

Differential diagnoses include trauma to the dorsal MCIII, exostoses of the second or fourth metatarsal bones, cellulitis, or osteomyelitis. Signalment, a good history of the exercise program, careful physical examination, and radiographic evaluation can readily differentiate dorsal metacarpal disease from other causes of metacarpal swelling.

▪ Pathophysiology

The musculoskeletal system of the 2-year-old racehorse undergoes significant changes in response to race training, with measurable changes in the size and geometry of the MCIII, compared to untrained horses.[3,5,13] During training the dorsal cortex of MCIII undergoes fatigue, or repetitive loading, primarily in tension.[2,6] Subsequently the bone adapts by modeling and remodeling, increasing the size of the MCIII through fibrous periosteal bone deposition.[2,6,7,14,15] As training continues with race speed work, the MCIII is subjected to compressive strains in a region adapted to tension, resulting in the clinical signs associated with dorsal metacarpal disease.[2,5,6,16] The primary histologic lesions consist of focal remodeling and periosteal/endosteal bone proliferation with edema in the subcutaneous tissues.[7] After resolution of the clinical signs of bucked shins, horses reenter training. Fibrous bone is weaker than lamellar bone, the dorsal MCIII is poorly adapted for compressive strains,

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and as with other fatigue fractures, microdamage accumulates under cyclic repetitive loading.[14] Microdamage and microcrack formation occur faster than the ability of the skeletal system to repair the damage through remodeling.[14,15] Microcracks increase in size, and macrocracks form and coalesce, leading to failure or dorsal cortical stress fracture.[14,15]

▪ Epidemiology

Dorsal metacarpal disease has been reported to affect up to 70% of juvenile Thoroughbreds at the start of training, 5% to 50% of Quarter Horses, and much less commonly the Standardbred.[1,2,9,17] It has been estimated that between 10% and 12% of horses that develop bucked shins will develop a dorsal cortical stress fracture.[2,9] Catastrophic failure of the diaphysis of the MCIII accounts for 10% of racetrack fatalities.[2] Horses trained on softer surfaces have a delayed incidence of dorsal metacarpal disease.[1,2,10] Standardbreds do not suffer from dorsal metacarpal disease nearly as frequently as Thoroughbreds, which may be related to gait and frequent training at race speeds.[2] Differences in the mechanical properties of the MCIIIs of the two breeds were not observed in vitro.[18] Dorsal cortical stress fractures occur primarily in 3-year-old Thoroughbred horses that have a history of bucked shins in their 2-year-old season.[12,19]

▪ Treatment and Prognosis

Treatment for dorsal metacarpal disease involves rest, antiinflammatories, and an altered training schedule.[2,9] The rest period is contingent on resolution of the clinical signs of heat, pain, and swelling. After clinical signs resolve, horses are slowly reintroduced to training. Based on previous research, the training schedule should be changed to incorporate more frequent, shorter, higher speed work and decreased galloping in an attempt to induce remodeling and adaptation of the MCIII for race speeds.[2,20] If clinical signs return, horses are again rested and reevaluated, and training is altered again. Counterirritation (thermocautery, cryotherapy, blistering, and periosteal scraping) and infiltration with antiinflammatories or other products are often applied in conjunction with altered training, although the majority of evidence is from clinical experience, with a paucity of research on efficacy. Extracorporeal shockwave therapy in conjunction with a modulated training regime is also reported to have with a

high success rate.[21] There has been some concern that shockwave therapy will induce analgesia and mask pain, predisposing horses to fracture, although current research has not shown significant reduction in pain.[21-24] Other therapies include local and systemic bisphosphonate therapy, although neither of the current products licensed for horses by the U.S. Food and Drug Administration are approved for animals under the age of 5 and therefore cannot be recommended. Although uncommon, if the horse fails to respond appropriately, it should be removed from training for a minimum of 60 days. Surgical intervention is the treatment of choice for mid-diaphyseal dorsal cortical stress fractures. Conservative therapy can be successful but may require a significant amount of time off, and the recurrence rate is thought to be high. Fractures that are very proximal or very distal on the MCIII do not require surgery and typically heal well. Surgical procedures described include cortical drilling (osteostixis), cortical drilling with unicortical position screw, or unicortical lag screw.[12,19,25,26] Fracture healing has been hypothesized to be promoted through the exposure of the damaged bone to medullary constituents, invoking the regional acceleratory phenomenon, or the induction of stress risers leading to osteonal repair.[12,19,27,28] Drilling alone can be performed standing, as there have been some reports of catastrophic failure after general anesthesia with this technique.[19] Methods involving screw placement performed standing require removal of the implant after 60 days.[12,26] All procedures have a similar success rate of greater than 89%, and similar fracture recurrence rates of 4% to 9%.[12,19,26] Screw placement techniques may yield a more predictable convalescence, although there have been no prospective comparative studies to date.[12]

▪ Prevention

Current research has demonstrated that the biomechanical properties and structure of the MCIII in the young training racehorse are influenced by training method and that prevention of the disease is possible through alteration of classical training methods.[2,5,10,20] Recommendations include jogging only for the purposes of warming up the horse, limiting long-distance sub-race speed gallops, and implementing more frequent short-distance breezes several times weekly.[2] The full training program has been published and implemented with a lower incidence of dorsal metacarpal disease.[2] Unfortunately, many trainers are

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reluctant to alter their methods.[29] Consequently, early identification and intervention are paramount in preventing poor performance and injury.[30] Recently, a prospective study evaluating juvenile Thoroughbred horses found that prophylactic shin scraping, while it did not prevent dorsal metacarpal disease from occurring, decreased the incidence and significantly delayed the onset of bucked shins in treated horses.[29] Future directions in decreasing the incidence of dorsal metacarpal disease should focus on the education and adoption of alternative training programs to allow the MCIII to adapt to racing speeds and pursuing interventions to lessen risk in classically trained horses.

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Silicate Associated Osteoporosis

Scott A. Katzman

▪ Introduction

Silicate associated osteoporosis (SAO), also referred to as bone fragility syndrome (BFS) or bone fragility disorder (BFD), is a progressive debilitating musculoskeletal disorder with a geographic distribution similar to that of pulmonary silicosis, primarily affecting horses in the region of the Monterey-Carmel peninsula of California, Sonoma and Napa counties, although occasional cases are identified in other regions of California.[1-3] Although SAO, BFS, and BFD tend to be used interchangeably to describe this condition, SAO is preferred, as this most accurately represent the disease process, reflecting its close association with pulmonary silicosis and similar geographic distribution.[1-3] Briefly, pulmonary silicosis in horses results from inhalation of cytotoxic, fibrogenic silicates, with cristobalite being primarily implicated in the development of the condition and geographic distribution related to exposure of horses to Miocene Monterey Shale soil of the Monterey Peninsula region of California, which contains high levels of cristobalite.[4]

Early clinical features associated with SAO include intermittent lameness affecting one or multiple limbs that cannot be localized,[1,2,5] exercise intolerance, and generalized stiffness.[1,2] In the later stages of the disease process, lameness may become severe[1,2]; scapular bowing (Fig. 38.42, *A* and *B*) and lordosis (Fig. 38.42, *C*) are common features,[1,2,5] with a pain response elicited on palpation of the scapulae[5]; and range of motion of the cervical spine may be decreased in both mediolateral and dorsoventral planes.[1,5] Generalized weight loss is also commonly observed, with varying degrees of localized muscle atrophy developing in the shoulder and gluteal regions.[1]

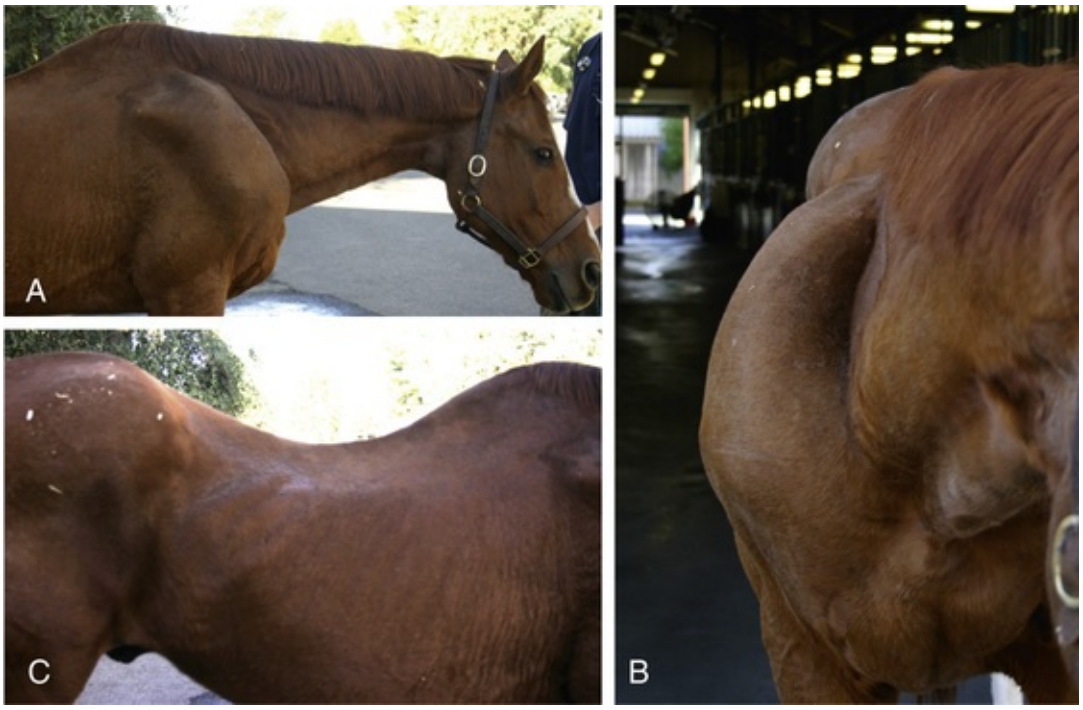


FIG. 38.42 Advanced case of SAO showing phenotypical **(A)** pronounced lateral bowing and **(B)** deformation of the scapula, as well as **(C)** marked lordosis.

Whether in the early or late stages of the disease process, the cause for progressive musculoskeletal abnormalities observed in SAO-affected horses is secondary to abnormal bone turnover and pathologic fractures affecting primarily the axial and proximal appendicular skeleton. However, clinically significant lesions have occasionally been identified in the radii and tibiae, and changes in bone morphologic and mechanical properties in affected horses have been demonstrated to develop as far distally as the distal metacarpus.[6]

Signs of respiratory tract disease are often identified on physical examination or are a noted as a historical feature and include adventitious bronchovesicular sounds on auscultation,[1] increased respiratory rate,[1] flaring of the nostrils at rest,[1] and coughing.[2] Although a direct link has not yet been elucidated, the signs of respiratory disease observed in several of these instances are suspected to be related to concomitant pulmonary silicosis, which has been confirmed in select cases. In one study describing the clinical features of 16 horses diagnosed with SAO,[1] a definitive diagnosis of pulmonary silicosis was made based on results of bronchoalveolar lavage in 3 of 7 horses for which this diagnostic was pursued, and 4 others had characteristic radiographic evidence of pulmonary silicosis[7] on thoracic radiographs. In another study, 9 of 9 horses diagnosed with

SAO on postmortem examination had cytotoxic silica dioxide polymorphs (cristobalite, quartz, tridymite) identified in lung tissue (6 of 9) and/or tracheobronchial lymph nodes (8 of 9).[3]

Treatment of SAO-affected horses is primarily palliative,[1,2] and the most devastating consequence of SAO is catastrophic fracture of an affected bone, necessitating euthanasia.[1]

▪ Etiology and Pathogenesis

To date, the etiology and pathogenesis of SAO have not been completely determined, although development of pulmonary silicosis and silicotic tracheobronchial lymphadenitis is attributed to the inhalation of the cytotoxic silicate cristobalite, which is suspected to be the etiologic agent directly responsible for SAO.[1-3] As noted previously, this is due to the similar geographic distribution between the two conditions, as well as to the diagnosis of both conditions simultaneously, as documented in several instances.[1,3] Proposed mechanisms for development of SAO include exposure to high levels of cristobalite, causing chronic systemic inflammation; dissemination of silicate-containing macrophages to bone marrow secondary to pulmonary silicosis or silicate tracheobronchial lymphadenitis; or abnormal resorption and remodeling of bone due to abnormal osteoclastic activity, comparable to Paget's disease of bone in humans.[2,3] Microscopically, bone lesions are characterized by multinucleate hypertrophied osteoclasts indiscriminately resorbing bone and associated hypertrophied osteoblasts lining bone surfaces.[3]

▪ History and Clinical Signs

There does not appear to be a breed or sex predilection for development of SAO, and it has been diagnosed in horses ranging in age from 4 to 22 years, with a mean age of approximately 10 to 14 years.[1-3,5] Due to its geographic distribution, SAO should be considered in the differential diagnosis for horses that reside or have resided in the Monterey-Carmel peninsula of California, Sonoma or Napa counties, and that are presented for any of the previously mentioned early signs of the disease (nebulous persistent or intermittent lameness, exercise intolerance, or generalized stiffness). For the horse older than 10 years that is presented with signs of advanced disease (marked lordosis, severe lameness, scapular deformation, weight loss, decreased cervical range of

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motion with or without signs of concurrent respiratory pathology), SAO should be a top differential.

It is important to remember the strong circumstantial evidence for a direct association between SAO and pulmonary silicosis and that exposure to cristobalite is responsible for the development of SAO.[2,3] It is unclear how long and at what concentration horses need to be exposed to the aerosolized silicate particles for disease to develop, and it is also unknown at what rate SAO develops following exposure[8]; however, severe multifocal osteolysis associated with SAO has been reported in a horse stabled in an endemic area after a period of only 2 years. In some instances, horses may have no known history of residing in endemic areas or may have spent only short times in these areas. In addition, there are endemic farms from which multiple horses develop SAO, and recent excavation in endemic areas can result in aerosolization of high concentrations of silicates that may be subsequently inhaled by susceptible horses, potentially accelerating the development and progression of disease. Therefore recent excavation in the vicinity of a horse presented with signs attributable to SAO as well as a history of clusters of affected horses in a small geographic area should be noted.

Because much remains unknown about the etiology and pathogenesis of SAO, it can present a diagnostic challenge, particularly in the early stages of the disease process.

▪ Diagnosis

Definitive diagnosis is made on postmortem examination. Currently, nuclear scintigraphy is the most reliable antemortem diagnostic test available for making a presumptive diagnosis of SAO.[5] Characteristic multifocal areas of increased radiopharmaceutical uptake (IRU) identified on whole body scintigraphic examination include, in descending order of prevalence, the scapulae (Fig. 38.43, *A*), ribs (Fig. 38.43, *B*), sternebrae, cervical vertebrae, tuber sacrale, ilium, ishium, and tuber coxae.[1] Less commonly, areas of focal IRU are identified in the long bones of the appendicular skeleton.[1,2] It has been established that because the majority of lesions are located from the ribs cranially, hind end scintigraphy is unnecessary in making a presumptive antemortem diagnosis.[2]

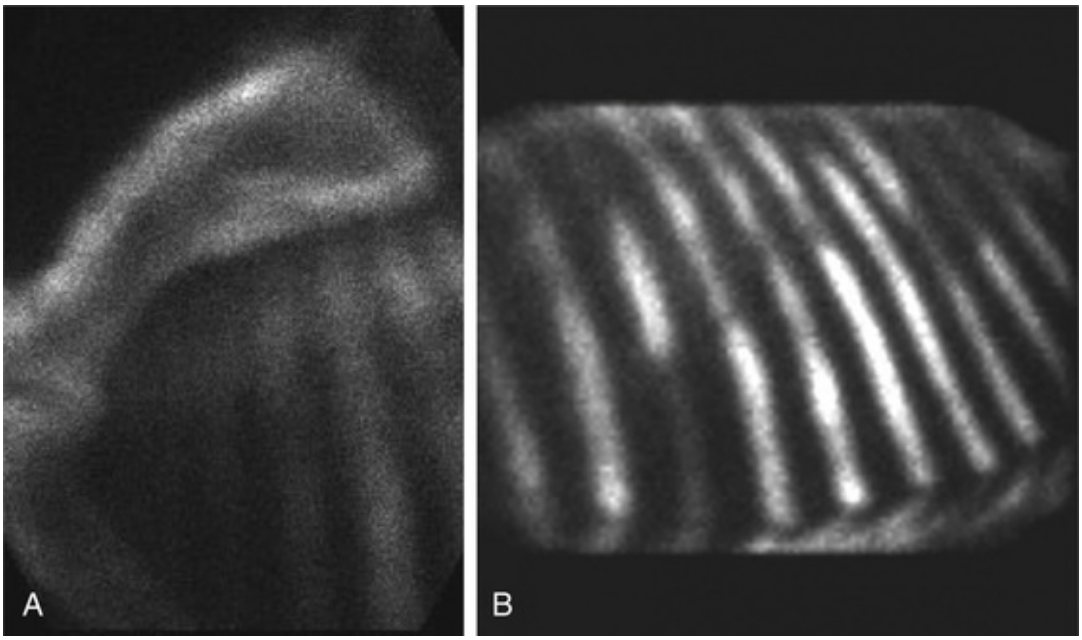


FIG. 38.43 Scintigraphic images of the same horse shown in Fig. 38.42, demonstrating **(A)** lateral bowing of the scapula with increased radiopharmaceutical uptake (IRU) in the regions of the scapular spine and caudal border of the scapula, as well as **(B)** diffuse patchy multifocal IRU noted along the length of several ribs.

Other diagnostic methods that have been investigated to evaluate their efficacy in the diagnosis of SAO include scapular ultrasonography, serum biomarkers of bone turnover, and findings on physical examination.[5] When compared to scintigraphy, it was found that in moderate to severe cases, bowing of the scapulae on physical examination and widening of the scapular spine on ultrasonographic examination were strongly supportive of a diagnosis of SAO and that serum biomarkers of bone turnover were not accurate in supporting the diagnosis.[5] In mild cases, none of these three methods were accurate, and regardless of the severity of SAO, none was as accurate as scintigraphy under any circumstance.

Bone biopsy obtained from regions of focal IRU may reveal osteopenia, fibrosis, and focal regions of bone resorption, but in some cases may be unremarkable.[1] Currently, bone biopsy is not routinely performed in the diagnosis of SAO. In addition, CBC and serum biochemistry are consistently unremarkable in these cases.

▪ Treatment

Treatment is palliative and aimed at decreasing inflammation and osteoclastic

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bone resorption. The most effective treatment to date has been intravenous administration of the nitrogen-containing bisphosphonate zoledronate at a dose of 0.057 to 0.075 mg/kg.[2,9] In one study, 9 of 10 SAO-affected horses treated with zoledronate had improvement in lameness scores or resolution of lameness.[2] Eight of ten of these horses also had a subjective decrease in radiopharmaceutical uptake on nuclear scintigraphy performed 6 months after a diagnosis of SAO based on initial scintigraphic examination.

Bisphosphonates are a class of drugs that inhibit bone resorption through osteoclast inhibition.[10] Following administration, bisphosphonates are incorporated into hydroxyapatite, the inorganic component of bone. When released from hydroxyapatite through osteoclastic resorption of bone, they induce osteoclast apoptosis, halting bone resorption. The non–nitrogen-containing bisphosphonate tiludronate has been used in the treatment of SAO, with limited, transient improvement noted after administration.[2]

One third to two thirds of bisphosphonates administered are incorporated into the skeleton, with the remainder excreted through the kidneys. Adverse systemic reactions following bisphosphonate administration are relatively rare in horses. There have been anecdotal reports of horses developing signs of acute renal failure following administration of bisphosphonates, so it is recommended to perform serum biochemical analysis to rule out preexisting renal disease prior to administration. Additional complications that have been reported following bisphosphonate administration include signs of abdominal discomfort and hypocalcemia. For these reasons, it is recommended to administer a single intravenous dose of flunixin meglumine (1.1 mg/kg) 30 minutes prior to zoledronate administration and maintain the horse on a 50% alfalfa diet to promote dietary calcium intake.[2]

In moderate to severe cases of SAO, exercise restriction is recommended to decrease the risk for catastrophic fracture, and judicious use of NSAIDs is often instituted to further reduce inflammation. In mild cases, exercise restriction and further pharmacologic intervention may not be necessary, but this must be determined on a case-by-case basis.

Finally, moving affected horses out of an endemic area may be of benefit, although doing so may not halt the progression of signs or prevent further signs from developing.

▪ Prognosis

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Prognosis is fair in the early stages, with return to athletic function possible following diagnosis and treatment. However, the owner must be warned of the risk for musculoskeletal injury secondary to decreased bone strength in these cases.

Prognosis is guarded to poor in later stages, and athletic use cannot be recommended due to the increased risk for musculoskeletal injury. In the advanced stages, SAO can be debilitating, resulting in poor quality of life. Catastrophic fractures frequently occur in these moderate to severe cases, regardless of the treatments used. These two factors, poor quality of life and catastrophic fracture, often necessitate euthanasia in advanced cases of SAO.

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Temporohyoid Osteoarthropathy

Tracy E. Norman

▪ Definition and Etiology

Temporohyoid osteoarthropathy (THO) is a disease of bony proliferation at the junction of the stylohyoid and petrous temporal bones. Several etiologies have been proposed for this condition, and the true etiology is likely variable. In some cases, bone inflammation and remodeling may occur secondary to extension of otitis media, otitis interna, or upper respiratory tract infection.[1-5] There is also evidence that many of these cases are due to primary degenerative joint disease.[6] Regardless of the cause, the result is bony proliferation of the tympanic bulla, proximal stylohyoid bone, and petrous temporal bones, often resulting in arthrosis of the temporohyoid joint and subsequent fracture of the stylohyoid and petrous temporal bones.[1-6] These fractures rarely extend into the basisphenoid and basioccipital bones, resulting in meningitis and brainstem disease.[1] Pain and inflammation associated with fracture or altered mobility of the joint and impingement on surrounding nerves result in the observed clinical signs.

▪ Clinical Signs

Horses with THO may not show clinical signs, but two clinical syndromes are associated with THO. Nonneurologic signs may be chronic and include difficulty chewing, nasal discharge, head tossing, ear rubbing, otorrhea, resentment of the bit, head shyness, and pain on manipulation of the head or ears.[1-3] Neurologic abnormalities generally include acute onset of signs of facial and vestibular nerve dysfunction, including ear droop, ptosis, muzzle deviation away from the affected side, corneal ulceration, head tilt toward the affected side, circling, ataxia, nystagmus, and collapse.[1,5,6] Auditory dysfunction is common or ubiquitous in horses with neurologic signs associated with THO but may not be appreciated on standard clinical observation.[5,7] Damage to the parasympathetic portion of the facial nerve may result in reduced lacrimation.[4] Occasionally dysphagia is also observed. Rarely, seizures or sudden death may occur secondary to fractures that extend into the cranial vault.[1] Clinical signs generally have an acute onset and may be associated with manipulation of the head for

other reasons (passage of nasogastric tube, etc.).[1]

▪ Diagnosis

Pathologic alterations at the temporohyoid joint may be identified using radiography, guttural pouch endoscopy, CT, or MRI. Otoscopic examination has been reported to identify THO.[8] Radiographs may show evidence of osseous proliferation at the temporohyoid joint on lateral and dorsoventral projections but in general are found to be less sensitive at detecting abnormalities than other diagnostic modalities.[1]

Endoscopy of the guttural pouches has been shown to be sensitive in detecting early, as well as advanced, changes at the temporohyoid joint, including soft tissue inflammation and hemorrhage, osseous proliferation, enlargement of the stylohyoid bone, and previous sites of fractures (Fig. 38.44).[1] The contralateral guttural pouch should always be evaluated, as some horses have bilateral disease. Evaluation of laryngeal function may be performed concurrently; in a recent study, 61% of horses with THO also had some degree of left laryngeal dysfunction. The association between these conditions was assessed to be most likely coincidental. Awareness of laryngeal dysfunction is important, however, especially in surgically managed cases.[7] Because endoscopy equipment is readily available and evaluations can be performed in the conscious horse, it may be the diagnostic modality of choice.

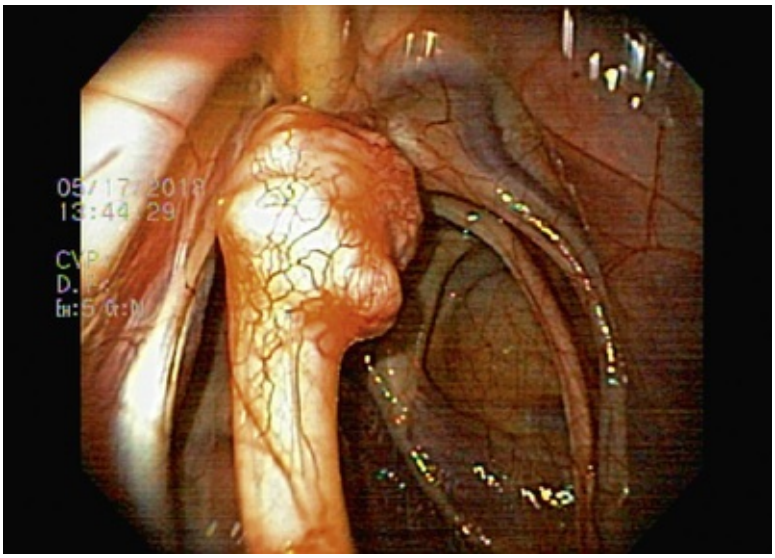


FIG. 38.44 Transendoscopic image of the right guttural pouch

demonstrating enlargement of the proximal aspect of the right stylohyoid bone consistent with temporohyoid osteoarthropathy.

CT and MRI may be indicated to provide additional information. CT allows exceptional visualization of bony proliferation and can reveal fractures that cannot be detected on plain radiographs because of superimposition of structures. Advancements in this technology and full understanding of the appearance of the topographic anatomy have increased the utility of this modality.[2,3,6]

MRI yields greater soft tissue detail than CT and is useful in documenting fluid accumulations in the middle and inner ear, as well as identifying inflammatory brain lesions.[1] The biggest impediment to the implementation of these imaging technologies is the requirement for general anesthesia and the difficulty of recovering a horse with vestibular abnormalities following the procedure.

▪ Treatment and Prognosis

Treatment of THO may include both medical and surgical management. Medical management generally includes antiinflammatory and supportive care. If ptosis and reduced lacrimation lead to exposure keratitis and corneal ulceration, tarsorrhaphy may be beneficial, and intensive medical therapy is required. If otitis is suspected, or if there is a suspected fracture into the cranial vault, the use of broad-spectrum antimicrobials with good penetration of the blood-brain barrier is indicated.

Surgical therapy for THO has been described.[1,9,10] Partial stylohyoidectomy has been used in some cases to reduce the forces on the ankylosed temporohyoid joint and prevent fracture of the petrous temporal bone.[1,9] This procedure risks damage to the adjacent nerves and may result in the formation of a bony union at the stylohyoidectomy site. An alternate technique is ceratohyoidectomy, which eliminates the lever arm that drives movement of and pressure on the temporohyoid joint. Ceratohyoidectomy is technically simpler to perform than partial stylohyoidectomy, avoids the complications of that procedure, and may be performed prophylactically or in cases in which fracture of the petrous temporal bone has occurred.[9,10]

In horses with THO, the prognosis for survival is good and for return to athletic function is fair.[1,7] Surgical management appears to result in better

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neurologic outcomes and reduced treatment times compared with medical management.[7] Improvement in neurologic function may continue for up to 2 years, but auditory loss appears to be permanent,[7] and facial nerve dysfunction also commonly persits.[1] The most common secondary complication of THO is corneal ulceration on the affected side due to poor eyelid tone and decreased lacrimation resulting in exposure keratitis. The majority of these horses should recover fully, but healing time may be protracted.[1]

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• CHAPTER 39

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Diseases of the Eye

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Ophthalmic History and Examination*

Renee T. Carter

A full ophthalmic examination should be conducted for patients presenting with a primary ocular complaint and also as part of a minimum workup for patients with neurologic changes or other unknown systemic disease processes. Prior to conducting a complete ophthalmic examination, basic information including the patient's signalment (species, breed, age, coat color, gender), use, and medical history should be obtained. A complete ophthalmic examination is then conducted in a stepwise methodical pattern to ensure that all aspects of the eye are evaluated and important diagnostic steps are not overlooked.

Reasons for presentation for ophthalmic examination include:

- Abnormal appearance of one or both eyes (i.e., asymmetry or color change)
- Presence of ocular discharge
- Presence of ocular pain
- Reduced vision or blindness
- Change in the performance or behavior of the patient
- Prepurchase examination
- Follow-up of a previously diagnosed ophthalmic condition
- Examinations for inherited ocular disorders

Ophthalmic History

A series of questions regarding the clinical signs observed, the duration and clinical course of the condition, changes in activity or behavior, previous eye problems, and whether other animals have been affected should be asked. The clinician should also obtain information on medications the owner has used to

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treat the eye (topically or systemically) and the animal's response to therapy. Potential causes for an ophthalmic or visual problem, including any possible relationship to neurologic or iatrogenic (e.g., drug-induced) disease, toxin exposure, or systemic illness, should be explored.

Instruments and Materials

A few basic instruments and materials facilitate an efficient and thorough examination. These include a focused light source (a Finoff transilluminator is preferred), direct ophthalmoscope with a cobalt blue filter, magnifying loupes, and a small pair of fixation forceps. Sterile fluorescein dye strips, Schirmer tear test strips, culture swabs, physiologic saline solution (flushing solution), topical anesthetic (0.5% proparacaine), tonometer, local anesthetic (2% lidocaine), and mydriatic solution (1% tropicamide) are often also necessary. For fundic examination, a direct or PanOptic ophthalmoscope may be used, or indirect ophthalmoscopy can be performed using a handheld lens and light source. To irrigate the nasolacrimal ducts, polyethylene tubing (5-French) should be available.

Ophthalmic Examination Procedures

General Inspection

Prior to manual restraint, the animal's activities and movements in its normal environment should be observed. This provides insight into the general well-being of the patient and its visual status. The examiner should study the animal's body condition, attitude, posture, coordination, head carriage, and ability to navigate in its normal surroundings. Animals with vision loss may be noted to spook or exhibit shying behavior on the affected side.[1] As the animal is approached, closer inspection reveals whether facial and ocular symmetry and normal eye movements are present. Signs of ocular pain (e.g., blepharospasm, apparent photophobia, epiphora) are noted, as well as size and position of the globes and the presence of ocular or nasal discharge, opacities, or masses.

Restraint

Adequate restraint is essential to conducting a complete ophthalmic examination in large animal patients. Manual restraint of small ruminants and neonates is

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usually adequate. For cattle, restraint in a chute with a head catch or in a stanchion with the head pulled laterally by nose tongs or a halter is ideal; restraint of a horse in stocks with a halter is recommended. Chemical restraint may be necessary in cattle, and use of a nose twitch and/or chemical restraint is often needed for horses. The animal's health and duration of the examination should be considered prior to the administration of chemical restraint. Chemical restraint may consist of a combination of injectable sedative (e.g., xylazine or detomidine for horses), with or without an injectable analgesic (e.g., butorphanol for horses). An auriculopalpebral (and occasionally frontal) nerve block using a local anesthetic agent such as 2% lidocaine facilitates examination, especially in patients with a painful ophthalmic condition. Neuro-ophthalmic assessment must be performed prior to administration of sedatives, analgesics, or local anesthetics (see below).

Neuro-Ophthalmic Assessment

An evaluation of the integrity of cranial nerves associated with normal ocular function is conducted (see Chapter 8).

- Menace response (a blink response) may not be present in neonates; use tracking or avoidance behavior to evaluate vision. Assess both the nasal and the temporal visual fields for each eye.
- Evaluate eyelid position and palpebral reflexes. A complete blink response to medial and lateral tactile stimuli should be present in both eyes.
- Direct and consensual pupillary light reflexes.
- Normal ocular motility when the head is moved side to side (oculocephalic reflex).

Detailed Examination

Detailed examination of ocular structures should then be performed in a predetermined pattern (i.e., anterior to posterior).[2-4] A set pattern of examination

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is recommended to avoid interfering with diagnostic tests that may have to be performed (e.g., Schirmer's test, culture). After evaluation of the animal in its normal environment, it is best to move the patient to an environment that is quiet and well lit for extraocular examination and can be darkened for intraocular examination.

Standing in front of the patient, the clinician should evaluate for alterations in the normal symmetric appearance of the eyes and periocular structures (Color Plate 39.1). Attention should be paid to lash height, pupil size and position, and globe position. If lashes are pointed downward, this may indicate ocular pain, enophthalmos, or ptosis of the eyelid; if lashes are directed upward, this may indicate exophthalmos (orbital disease) or buphthalmos.

Evaluate the size, shape, and symmetry of the pupils by retroillumination using a focal light source in a darkened environment. To perform retroillumination, stand at arm's length distance in front of the patient and obtain the tapetal reflex using a bright penlight or transilluminator. With equal illumination of the eyes, the examiner can evaluate for changes in pupil symmetry. This must be evaluated prior to dilation. Direct and indirect (consensual) pupillary light reflexes (PLRs) should then be assessed. For most patients, due to the lateral position of the eyes, it is often necessary to have an assistant aid in evaluating the consensual PLR. The assistant uses a dim light to determine if pupil movement occurs when the opposite eye is illuminated by a bright light source.[5] The examiner must recall that PLRs are not a test of vision (i.e., abnormal responses may be observed in visual animals, and normal reflexes may occur in nonvisual animals). Pupillary abnormalities that should be noted are inequality in size (anisocoria), abnormal movements (hippus), abnormal location (corectopia), or abnormal shape (dyscoria) (Color Plate 39.2).

At this point, the examiner determines whether ocular cultures or tear measurements are desired, because these procedures must be completed before further manipulations are performed and before topical pharmacologic agents are instilled.[6] Depending on clinical signs, severity of ocular disease, and species being examined, viral, bacterial, or fungal cultures may be indicated. Sterile swabs moistened with saline and appropriate enrichment broth or transport media are applied in direct contact with the tissue surface of interest to be cultured.

Palpation of the boundaries of the orbit for irregularities, asymmetry, masses, or fractures should then be performed. The globe is retropulsed to assess for increased resistance (indicating a space-occupying mass) and to inspect the

anterior aspect of the nictitating membrane (“third eyelid”) for abnormalities such as trauma or neoplasia. Retropulsion is performed by gently pressing the globe back into the orbit with a finger placed over the partially closed upper eyelid (Color Plate 39.3). Retropulsion should not be performed if the cornea is compromised by a deep ulcer or laceration to avoid rupturing the globe.

It is helpful to use a lighted otoscope head or, alternatively, a direct light source (transilluminator) and wear an Optivisor™ for further examination of the external structures of the adnexa and globe. The eyelids are inspected for integrity, position, and movement. Each eyelid is digitally everted for inspection of the margins, meibomian gland openings, and palpebral conjunctiva. Paresis, malposition (ectropion, entropion [Color Plate 39.4]), defects, masses, inflammation (swelling, ulceration, exudate), alopecia, foreign bodies, and abnormal lashes are noted.

The nictitating membranes are examined for normal position, integrity, degree of pigmentation, and the presence of follicles or masses (see Color Plate 39.3). To inspect for foreign bodies, topical anesthetic solution (0.5% proparacaine or 0.5% tetracaine) is instilled two to three times onto the ocular surface. The nictitating membrane is then grasped and manipulated with small fixation forceps, and both sides are examined for foreign bodies. Care should be taken not to damage the cartilage of the third eyelid with toothed forceps.

Normally the conjunctiva appears moist, glistening, and semitransparent. Signs of conjunctivitis are chemosis (conjunctival edema), hyperemia, and ocular discharge. Color changes of the conjunctiva usually accompany anemia (blanched, pale) or icterus (yellow, amber). Chemosis may indicate severe hypoproteinemia. Conjunctival lesions noted include focal swellings, follicles, adhesions, or masses. The sclera underlying the bulbar conjunctiva is inspected for color, contour, swellings, masses, pigmented areas, or surface irregularities.

Lacrimal system examination entails evaluation of both secretory and excretory components. Normal secretions result in a moist, glistening ocular surface. Although not typically used in large animals, Schirmer tear test strips may be used to quantify aqueous tear secretion (see the Ancillary Diagnostic Procedures section later). Schirmer's tear test is indicated in cases with a lackluster corneal appearance, persistent keratitis, or ocular discharge. To examine the excretory components, the upper and lower puncta and nasal openings of the nasolacrimal system are identified. Any overflow of tears onto the face (epiphora) is noted. Causes of increased ocular secretions (e.g., frictional irritants, foreign bodies, corneal ulcers, ocular inflammation) must be

ruled out. Causes for stimulation of lacrimal secretions must be differentiated from causes of outflow occlusion, such as congenital atresia and acquired obstruction of the nasolacrimal system.

Application of fluorescein dye can detect corneal ulceration; a cobalt blue light (available on the direct ophthalmoscope or as a filter for the transilluminator) should be used to assess for stain uptake. In addition, fluorescein dye aids in the assessment of nasolacrimal system patency. Passage of dye from the nasal opening of the nasolacrimal duct confirms patency (positive Jones test). Retrograde irrigation of the nasolacrimal duct by inserting a length of 5-French flexible tubing into the nasal punctum and flushing with saline may be necessary to differentiate insufficient drainage from excessive secretions.

The rest of the ophthalmic examination is performed in a darkened area. The examiner should perform retroillumination as previously described. Opacities will block thenormal tapetal reflex (Color Plate 39.5). Lesions can be roughly localized based on the ability to see the iris. Opacities in the anterior portion of the eye (cornea, anterior chamber) will block the ability to see the iris. Opacities in the posterior portion of the eye (lens, vitreous) will still allow the examiner to visualize the iris. A clear view of the tapetal reflex eliminates anterior chamber, lens, and vitreal opacities as the cause for vision loss in a blind eye.

The cornea is then examined by direct illumination for irregularities and opacities. Direct a focal light source across the cornea (parallel) to highlight corneal irregularities. Localization of opacities to the cornea can be conducted using this technique or alternatively with a direct ophthalmoscope or handheld slit-lamp biomicroscope. The cornea is an avascular structure that is smooth and transparent, with a moist reflective surface. Corneal lesions can often be diagnosed based on their color. Corneal edema appears as a hazy, blue corneal opacity and should be characterized as focalor diffuse (Color Plate 39.6). With severe corneal edema, raised bullae (vesicles) may be noted on the corneal surface.

Infectious keratitis is characterized by suppuration, necrosis, and stromal loss. The cornea becomes more densely opaque and acquires a creamy, off-white or yellow appearance when infiltrate is present; the margins of the opacity will be indistinct, an obvious defect in the corneal contour may be noted, and the eye will typically be painful (Color Plate 39.7). Corneal abscesses occur as focal areas of suppuration within the stroma underlying a nonulcerated cornea.

Corneal opacities may also result from focal or diffuse scarring (flat, gray,

with distinct margins), areas of corneal degeneration or dystrophy (white, chalky to refractile with distinct margins), or stretching of Descemet's membrane (Haab's striae) from elevation of intraocular pressure or previous trauma (parallel lines, resemble “railroad tracks” [Color Plate 39.8]). Inflammatory cells may aggregate on the corneal endothelium (keratic precipitates). The color corresponds to the cellular composition, appearing as multiple white, brown, or red foci, usually on the ventral aspect of the corneal endothelium. This finding indicates the presence of anterior uveitis.

Intraocular examination begins with evaluation of the clarity and depth of the anterior chamber. This can be performed using the small spot of light or slit-beam on a direct ophthalmoscope (light source directed perpendicular to the cornea and brought close until in focus); magnifying loupes may be needed. Alternatively, a handheld slit-lamp may be used. The anterior chamber is the space between the cornea and iris that contains aqueous humor. Breakdown of the blood-ocular barrier is known as anterior uveitis and results in opacification within the anterior chamber. Opacities include inflammatory products (cells and fibrin), protein (aqueous flare), red blood cells (hyphema), or white blood cells (hypopyon). (see Color Plate 39.5).

Besides the presence of exudates, loss of anterior chamber transparency may result from lens luxation, vitreal prolapse, anterior synechia, or intraocular masses (neoplasia or foreign bodies). The depth of the anterior chamber should also be evaluated. A shallow anterior chamber may be the result of leakage of aqueous humor, iris prolapse, iris bombé (forward bulging of the iris caused by iris-lens adhesions), anterior lens luxation, and phthisis bulbi. The anterior chamber will appear deep in eyes with cornea globosa, hypermature (resorbing) cataracts, buphthalmos, and posteriorly luxated lenses.

The iris is inspected for altered contour, pigmentation, mobility, neovascularization, pupil size and shape, and the presence of uveal masses (including the normal granula iridica). Granula iridica (i.e., corpora nigra) are normal structures present along the pupil margin. These structures may atrophy with chronic uveitis or become cystic. Transillumination of uveal masses may allow differentiation of solid structures (e.g., melanoma) from uveal cysts, although cysts originating from the corpora nigra in horses typically do not transilluminate (Color Plate 39.9). In animals with lightly colored or spotted hair coats, multicolored irides should be recognized as normal variants. Although uncommon, congenital iris thinning (hypoplasia) may be noted as dark, flat, or translucent areas when transilluminated. The lens-iris interface is best evaluated

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when the pupil is dilated. Iris membranes, adhesions, or strands should be characterized as congenital (persistent pupillary membranes, or PPMs) or acquired (synechiae or remnants of iris atrophy) (see Color Plate 39.2). PPMs are strands that typically originate from the iris collarette (center of the iris), whereas the edges of the iris are involved with anterior synechia.

Obscuration of the pupil space may occur with severe miosis (from acute anterior uveitis), anterior lens luxation, condensation of anterior chamber exudates (fibrin, cells), and synechiae formation (from chronic uveitis) (Color Plate 39.10). In animals with normal PLRs, complete examination of the lens and structures posterior to the lens (i.e., vitreous and fundus) may be achieved only after dilation with a mydriatic agent such as 1% tropicamide, which usually occurs 15 to 30 minutes after instillation. Once dilated, retroillumination of the ocular media to evaluate for any opacities blocking view of the tapetal reflex (as previously described) is repeated; full evaluation of the lens and fundus can also be performed.

Using a focused light, the lens is inspected for a smooth, transparent, convex anterior capsule and normal position (no part of the equator should be visible). When evaluating for lens opacities (cataracts), the examiner should direct the focused light through the axial part of the lens to establish the presence of a fundic reflex. Cataractous changes are observed as dark areas seen within the area of reflected light or white opacities when the lens is directly illuminated (see Color Plate 39.2). Cataracts may be classified according to the extent to which a fundic reflex is obstructed; a *partial reflex* indicates an incomplete cataract, whereas an *absent reflex* indicates a complete cataract. If the lens profile appears distorted (wrinkled) with numerous refractile particles present, this is typically indicative of a hypermature (resorbing) cataract.

Ophthalmoscopy must be used to examine the vitreous and fundus. The direct ophthalmoscope provides an upright image and high magnification, but it requires a close working distance and provides a small field of view, making it a poor screening tool. Using the direct ophthalmoscope, the vitreous should be in focus with a dioptric setting between +6 and +1, and the fundus is usually in focus between +1 and −2 diopters. Monocular indirect ophthalmoscopy (Panoptic) provides an upright image and moderate magnification and field of view. Indirect ophthalmoscopy provides an inverted virtual image with a less magnified view, making it a better screening tool.

The vitreous is first examined for congenital remnants (retained hyaloid structures) and opacities, including degenerative materials or exudates.

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Examination of the fundus begins with identifying the optic disk (papilla) and studying its size and shape. The shape, location, and vascular pattern of the optic disk and the appearance of the fundus vary considerably among species. In ruminants the optic disk margin typically appears irregular and fluffy, indicating myelination of axons entering the optic disk. However, it tends to be horizontally elliptical or kidney shaped and located in the tapetal portion of the fundus.[7] An optic disk with extensive myelination may be elevated above the surface of the fundus. In ruminants the major retinal arterioles are large and accompanied by venules that anastomose on the surface of the optic disk. The dorsal arteriole and venule usually intertwine as they course away from the disc over the midtapetum (Fig. 39.1). By contrast, the equine fundus is characterized by a large pink or salmon-colored horizontally elliptical or oval disc located in the nontapetum[7] (Fig. 39.2). Horses are *paurangiotic*, meaning they have vessels that extend only a short distance from the optic nerve head. The small retinal blood vessels extend radially from the margin of the disc, and no anastomotic venules are visible over the optic disk.

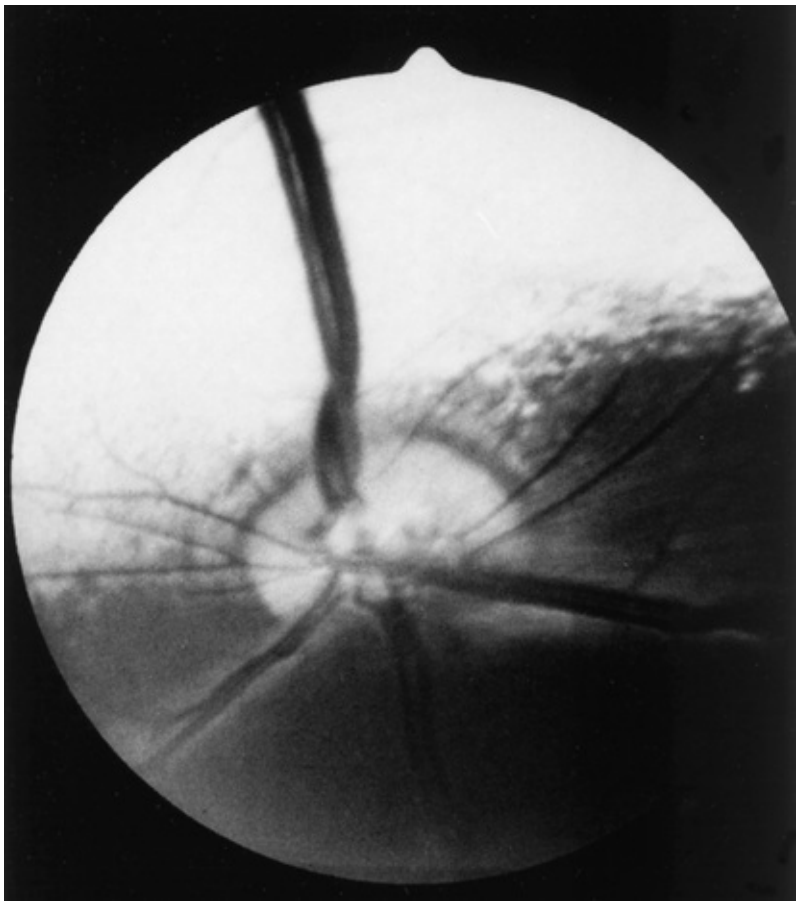


FIG. 39.1 Normal ruminant fundus characterized by a large, kidney-shaped, myelinated optic disk. Note that the large retinal arteriole and venule intertwine as they course dorsally.

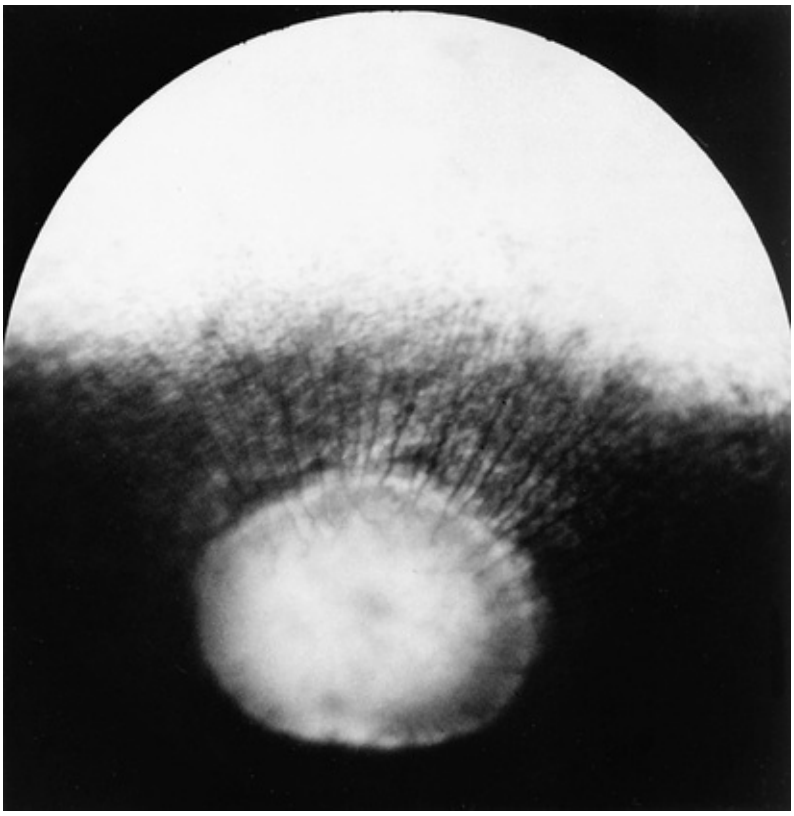


FIG. 39.2 Normal equine fundus characterized by a large, horizontally elliptical optic disk with numerous small retinal vessels entering (arterioles) and exiting (venules) the margin of the optic disk. Note that the optic disk lies in a nontapetal portion of the fundus.

In both ruminants and horses, the fibrous tapetum is present in the dorsal two thirds of the eye and is penetrated by choroidal capillaries; thus the fundus in these species is typified by dark, stippled foci called *stars of Winslow* (end-on capillaries). Coloration of the tapeta of large animals also varies considerably and may range from gold to bluish green. In animals with varied coat color, coat color dilution, and/or heterochromia irides (variable iridal color), areas of the fundi may characteristically be devoid of pigmentation and may lack a tapetum. These areas may appear orange or red because of direct visualization of the choroidal vasculature.

Abnormalities of the optic disk include hypoplasia (micropapilla), elevation (papilledema), depression (cupping), degeneration (atrophy [Fig. 39.3]), and vascular changes (e.g., congestion, attenuation, hemorrhage). The tapetal fundus is evaluated for clarity, coloration, pigmentation (Fig. 39.4), and integrity of the retinal vessels (Fig. 39.5). The nontapetal fundus is evaluated for uniformity of pigmentation. Both tapetal and nontapetal areas are assessed for retinal

elevations or separations (Fig. 39.6), hemorrhages, degenerations, disorganization (dysplasia), or scleral defects (colobomas).[7]

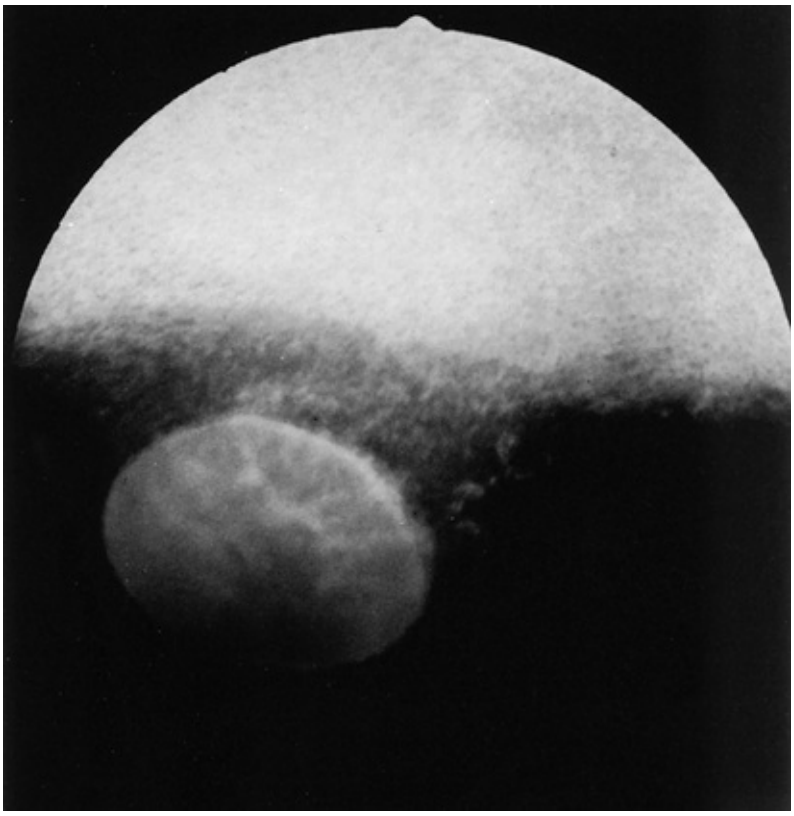


FIG. 39.3 Optic nerve atrophy (equine). Margin of disc is quite distinct because of myelin loss, which is characteristic of optic nerve atrophy. Note absence of retinal blood vessels.



FIG. 39.4 Pigmentary changes after traumatic chorioretinopathy. Irregular linear areas of hypopigmentation and hyperpigmentation are present in the tapetal fundus of a horse after ocular trauma. Pigmentary changes reflect retinal pigment epithelial disturbance from previous hemorrhage and edema. (Courtesy Dr. K.N. Gelatt.)

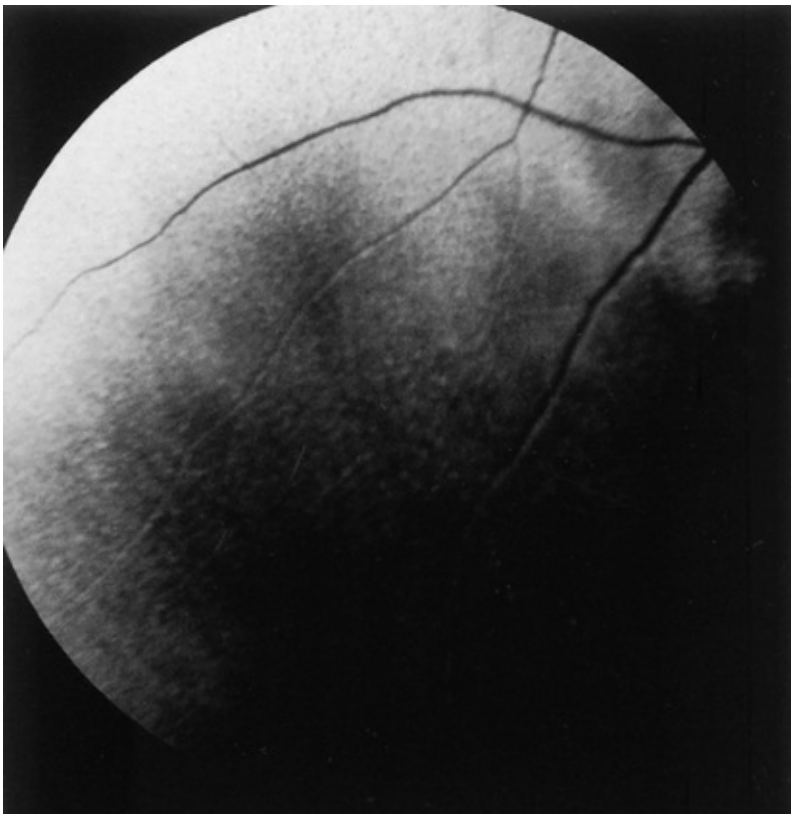


FIG. 39.5 Retinal degeneration (bovine). Peripheral retinal vessels are greatly attenuated near the tapetal-nontapetal junction. Attenuation is accompanied by hyperreflectivity of the tapetal region. These changes are consistent with generalized retinal atrophy.

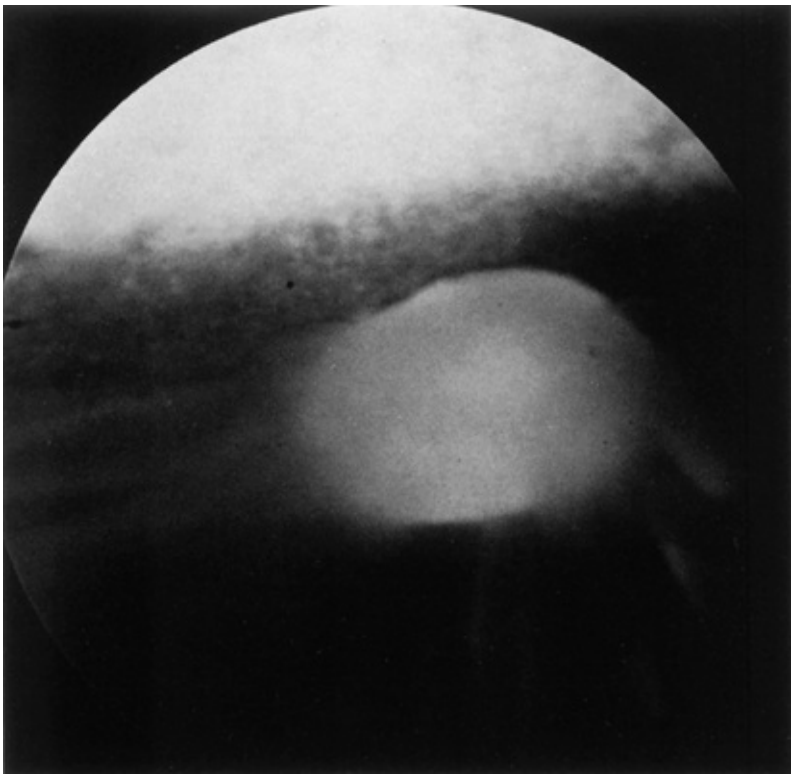


FIG. 39.6 Retinal separation (equine). Gray linear areas radiate from the optic disk into the nontapetal region of fundus. Note that the margin of the disc is quite indistinct in the affected area. Absence of retinal vessels indicates concurrent retinal degeneration.

Ancillary Diagnostic Procedures

Several additional procedures may supplement the complete ophthalmic examination. Although some ancillary procedures require specialized equipment and expertise, many may be performed in general practice.

Fluorescein and rose bengal are ocular surface stains most often used as aids in diagnosing conjunctival and corneal diseases. The tip of a sterile dye strip is moistened with saline or eye-irrigating solution, and a drop of the stain is instilled onto the eye. Fluorescein is a water-soluble dye used to detect exposed corneal stroma resulting from an epithelial defect (erosion), stromal ulceration, or descemetocele and is viewed with cobalt blue light. The pattern of fluorescein staining for a descemetocele is characterized by a donut-shaped area of positive fluorescence, with the perimeter retaining stain and the center or deepest area (Descemet's membrane) not retaining stain. Fluorescein may also be used to evaluate the patency of nasolacrimal ducts because an open duct allows the

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transmission of stain, which may be observed exiting the duct system at the nasal orifice (Jones test). Rose bengal is retained by devitalized surface cells and is therefore useful in detection of subtle abnormalities like hyperplastic or desquamating cells associated with ocular surface drying, herpetic infection, keratomycosis, or squamous cell carcinoma. Stain uptake appears pink when illuminated with white light. These stains can be performed in any order.

Although tear deficiencies are uncommon in large animals, Schirmer tear test strips may be beneficial to quantify aqueous tear production in selected cases. A sterile filter paper strip (40 × 5 mm with a notched end) is inserted into the lower conjunctival fornix. In large animals it is sufficient to measure the amount of wetting in 30 seconds (≥20 mm is normal). Tear testing is indicated in patients with a dry, lackluster corneal surface; persistent ocular discharge; or keratitis.

Cytologic evaluation of ocular surface scrapings or intraocular aspirates may differentiate between inflammatory and neoplastic diseases or in some cases may provide a definitive diagnosis. Orbital aspirates may be diagnostic in cases of exophthalmos caused by neoplasia (e.g., lymphosarcoma). Immunofluorescent or polymerase chain reaction (PCR) testing of cytologic specimens may confirm viral (e.g., infectious bovine rhinotracheitis) or *Chlamydia* infections.[3] Bacterial cultures taken from the ocular surface or from ocular aspirates, with subsequent antimicrobial susceptibility testing, may be necessary for definitive diagnosis and appropriate treatment of ocular infections. Bacterial and fungal cultures, as well as corneal cytology, are especially important tests when equine ulcerative keratitis is diagnosed. The diagnostic laboratory performing ocular cultures may offer suggestions on culture procedures, including preferred transport media and handling of samples. It is especially important to consult with the laboratory in advance when anticipating culturing for fungi, *Mycoplasma, Chlamydia*, or viral agents.

Tonometry, a means of measuring the intraocular pressure (IOP), is useful in diagnosing glaucoma (elevated IOP) and uveitis (low IOP) and in assessing response to therapy for these conditions. Tonometry is indicated in cases with corneal edema, redness, lens luxation, abnormal PLR, and cases with vision loss or a history of glaucoma. Digital tonometry (gently indenting the globe through the upper eyelid) is not considered an accurate measure of IOP; Schiøtz tonometry is not applicable to large domestic species. Applanation tonometry using the TonoPen® provides accurate and reproducible IOP readings in large animals and is routinely performed. In addition, the rebound tonometer, TonoVet®, has been used successfully in horses.[8] The clinician should be aware

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that eyelid blocks, sedation, and head position can all affect IOP readings.[9]

Biomicroscopy, using a portable handheld slit-lamp, is useful for identifying the location and nature of anterior ocular opacities. Focal irritants (e.g., ectopic cilia, small foreign bodies) and small lesions may only be visible with the magnification provided using biomicroscopy. Alternatively, use of a focal light source with magnification in the form of an otoscope or optivisor may be used for close examination.

Fundic examination may be performed relatively quickly and easily using the technique of indirect ophthalmoscopy. Monocular indirect ophthalmoscopy is performed using a handheld light source and a separate 20- or 14-diopter focusing lens for equine and bovine patients or a 28-diopter lens for smaller ruminants.

Other ancillary diagnostic procedures include electroretinography (to evaluate retinal function), visual evoked potentials (to evaluate visual pathways), and imaging procedures (radiography, ultrasonography, computed tomography [CT]). Although plain skull radiographs and some contrast studies (e.g., dacryocystorhinography) may be performed in general practice, the remaining procedures require techniques and equipment usually available only at referral centers.

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Signs of Ocular Disease*

Renee T. Carter

Clinical signs of ocular disease can be grouped into five primary categories at the time of presentation:

- Ocular or periocular asymmetry
- Ocular color change
- Ocular discharge
- Ocular pain
- Visual deficits or blindness

Patients may present with one or a combination of these clinical signs. This section provides a general description of the signs and examples of ocular diseases in which a particular sign predominates. Tables 39.1 and 39.2 summarize common signs of ocular disease in large animals.

TABLE 39.1
Causes of Important Ocular Signs in Large Animals

Changes in ocular and periocular symmetry	Eyelid disorder	Ptosis	Facial nerve paralysis Sympathetic denervation Blepharospasm
		Ectropion	Trauma, scar
		Entropion	Trauma, scar, loss of orbital volume
		Blepharitis	Parasitic Viral: pox, bluetongue Actinic/photosensitization Allergic Dermatophyte Immune-mediated
		Neoplasia	SCC, sarcoid, melanoma, papilloma, lymphoma, hemangioma, among others
		Third eyelid elevation	Increased orbital volume (space occupying lesion) Sympathetic denervation Loss of orbital volume: Microphthalmos Phthisis bulbi

			Dehydration Muscle loss Loss of orbital fat Tetanus Retraction of globe: pain Hyperkalemic periodic paralysis (flashing of eyelid) Neoplasia
	Enophthalmos	Dehydration Loss of retrobulbar fat and/or muscle Congenitally shallow orbit Sympathetic denervation Pain and associated retraction of globe Microphthalmos Globe rupture Compression of globe by periocular tumor	
	Exophthalmos	Trauma: hemorrhage, tissue swelling Orbital neoplasia Inflammatory orbital lesion: Foreign body Cellulitis Abscess Granuloma Cyst: developmental, parasitic Exogenous steroid administration (cattle) CN VI lesion (loss of retractor bulbi function) Vascular lesion Inherited: bilateral convergent strabismus with exophthalmos (B)	
	Buphthalmos	Primary or secondary glaucoma	
	Cornea globosa	Multiple congenital ocular anomalies (MCOA) syndrome (E)	
	Phthisis bulbi	Chronic inflammation or trauma	
	Globe rupture	Trauma	
	Microphthalmos	Viral: bovine viral diarrhea (BVD) Genetic: B, E Teratogenic	
	Strabismus	Extraocular muscle damage: trauma Extraocular muscle denervation: central or peripheral Congenital Inherited: bovine convergent strabismus with exophthalmus (BCSE) (B) Congenital stationary night blindness (E) Otitis media/interna	
	Retrobulbar fat prolapse		
	Anisocoria	Congenital iridial lesion	Aniridia Coloboma Hypoplasia Anterior segment dysgenesis MCOA syndrome
		Acquired iridial lesion	Synechia: anterior or posterior Iris atrophy Topical agents: tropicamide, atropine, pilocarpine Plants: containing parasympatholytic alkaloids Denervation

	Uveitis: miosis	
	Glaucoma: mydriasis	
	Retinal disorders	Retinal degeneration Retinal detachment
	Optic nerve lesion	Optic neuritis Optic nerve atrophy
	Brainstem lesion	

B, Bovine; *CN,* cranial nerve; *E,* equine; *SCC,* squamous cell carcinoma.

Data from Gosselin VB, Francoz D, Babkine M, et al.: A retrospective study of 29 cases of otitis media/interna in dairy calves. *Can Vet J* 53:957–962, 2012; and Estell K: Periocular neoplasia in the horse. *Vet Clin Equine* 33:551–562, 2017.

TABLE 39.2

Differential Diagnoses for Ocular Signs in Large Animals

	Clinical Signs/Findings	Differentials		Species Affected
Focal surface redness	Hemorrhage	Trauma		All
		Clotting disorders		All
		Piroplasmosis		E
	Hyperemic mass	Granulation tissue/healing		All
		Neoplasia	Squamous cell carcinoma Hemangiosarcoma	All
		Parasitic disease	*Habronema*	E
		Embedded foreign body		All
Diffuse redness	Conjunctivitis/keratitis	Entropion		All
		Chemical irritation		All
		Parasitic disease	*Onchocerca* *Habronema* *Thelazia* *Oestrus ovis*	E E All O
		Bacterial infections	*Chlamydia*	C, O
			Mycoplasma	C, O, B
			Branhamella	C, O, B
			Listeria	B, O, E
			Streptococcus equi	E
			Moraxella spp.	B, E
		Fungal infections		E
		Viral infections	Herpesvirus Infectious bovine rhinotracheitis (IBR)	C, B
			Bluetongue	B, O
			Equine herpesvirus 2 (EHV-2)	E
			Influenza	E
	Uveitis	Septicemia		All
		Trauma		All
		Secondary to keratitis		
		Viral	Malignant catarrhal fever	B

			Equine herpesvirus 1 (EHV-1)	E
			Adenovirus	E
			Viral arteritis	
		Bacterial infection	*Borrelia* *Leptospirosis* *Mycobacterium*	E B
		Protozoal infection	Toxoplasmosis	E
		Immune-mediated	ERU	E
		Parasitic disease	*Onchocerca*	E
	Glaucoma	Trauma		All
		Secondary to uveitis		
		Primary		
	Hemorrhage	Trauma		All
		Clotting disorders		
		Uveitis		
Cloudy Eye (Ocular Opacities)				
Cornea	Keratitis	See Conjunctivitis/keratitis above		
	Trauma			All
	Ulcers			
	Scars (healed ulcers)			
	Uveitis (see Diffuse redness abvoe)			
	Corneal edema	Anterior uveitis		All
		Glaucoma		All
		Corneal endothelial dystrophy		E
		Malignant catarrhal fever		B
Anterior chamber	Exudates, blood	Trauma		All
		Uveitis (see above)		
		Coagulopathy		
		Secondary to keratitis		
	Anterior lens luxation	Trauma		All
		Chronic uveitis		
Lens	Cataracts	Trauma		All
		Anterior uveitis		
		Viral	BVD	B
		Inherited		E
Vitreous	Exudates, blood	Trauma		All
		Retinal detachment		
		Uveitis (see above)		
		Congenital hyaloid vascular remnants		B
	Vitreal degeneration	Age-related		All
		Secondary to inflammation		
	Posterior lens luxation	Chronic uveitis (see above)		E
Ocular Discharge				All
Watery (serous)	Painful eye	Ectopic cilia, distichia	See Conjunctivitis/ keratitis by species	
		Foreign body		
		Entropion		
		Trauma		
		Ulcer/keratitis		
		Chemical irritant		

Nonpainful eye	Nasolacrimal atresia		
	Nasolacrimal obstruction (acute blockage)		
Thick (mucoid/ mucopurulent)	Foreign body	See Infectious keratoconjunctivitis by species	
	Surface tumors		
	Dacryocystitis		
	Chronic nasolacrimal blockage		
	Sinusitis		
	Bacterial infections		

B, Bovine; *BVD,* bovine viral diarrhea; *C,* caprine; *E,* equine; *ERU,* equine recurrent uveitis; *O,* ovine.

Ocular or Periocular Asymmetry

Ocular or periocular asymmetry results from unilateral changes in facial soft tissue or orbital structures, orbital volume, globe size, eyelid position, or pupil size and position (see Table 39.1). Changes in symmetry often involve a reduction or increase in volume of a certain tissue. *Reduction* in tissue volume occurs with congenital hypoplasia, cicatricial shrinkage, atrophy, or dehydration. *Increase* in tissue volume may involve the whole globe (buphthalmos) or be characterized by irregular enlargement, as seen with inflammatory or neoplastic lesions involving the globe, orbit, or eyelids. Asymmetry may also result from a neurologic dysfunction. Common examples include reduced palpebral fissure size (secondary to facial nerve paralysis), strabismus, third eyelid protrusion, and anisocoria (see Chapter 8). This section describes the common signs of ocular disease. It is not the intent to describe in detail each of the diseases that may be noted; these disorders are covered in other sections of this chapter.

Change in Globe Position

Changes in globe position affect symmetry and include exophthalmos, enophthalmos, and strabismus. Forward displacement of the eye (exophthalmos; Fig. 39.7) is often associated with a space-occupying orbital lesion (neoplasia, inflammatory, vascular, cystic) or, less often, a congenitally shallow, underdeveloped orbit. Posterior malposition of the globe (enophthalmos) may result from active globe retraction caused by pain or from loss of supporting retrobulbar soft tissues as seen in cases of muscle atrophy, loss of orbital fat, or denervation. Congenital strabismus is a developmental abnormality that results in ocular asymmetry due to deviation of normal globe position and has been

reported in Jersey, Shorthorn, Holstein, and German Brown Swiss cattle.[1,2] Strabismus can occur with exophthalmos and has also been associated with systemic disorders such as polioencephalomalacia and listeriosis.[2] Unequal orbit volume resulting in displacement of the globe or globe malposition may also occur with traumatic orbital fractures.

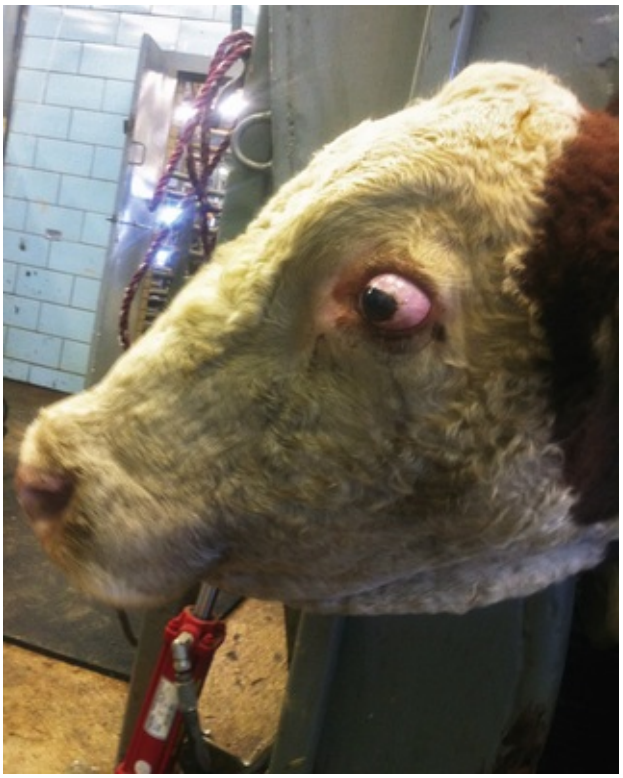


FIG. 39.7 Hereford with marked exophthalmos of the left eye that was present bilaterally.

Change in Globe Size

Unequal globe size can also account for ocular asymmetry. A congenitally small globe (microphthalmia) occurs as a genetic defect in sheep, cattle, and horses[1,3,4] and has also been associated with exposure to infectious agents and teratogens. Microphthalmia is frequently accompanied by multiple ocular anomalies and may be associated with multiple organ involvement or vertebral abnormalities.[2] Acquired variations in globe size usually result from shrinkage of the globe secondary to globe rupture or with phthisis bulbi (Color Plate 39.11) secondary

to chronic uveitis; stretching or enlargement of the globe (megaloglobus, buphthalmos) occurs with glaucoma. Cornea globosa has been reported in horses and ponies with multiple congenital ocular anomalies (MCOA) syndrome with the silver mutation and coat color.[5,6]

Changes in Eyelid Conformation

Asymmetry of the upper or lower eyelid may be due to entropion, ectropion, blepharitis, conjunctivitis, or ptosis (facial nerve paralysis or sympathetic denervation). Entropion has been reported in Simmentals[1] and as an inherited trait in sheep.[7] (see Color Plate 39.3) However, entropion most commonly occurs secondary to microphthalmos or enophthalmos (retraction of the eye with pain, reduction in orbital volume, denervation). Trauma with secondary scar formation may result in either entropion or ectropion. Nictitating membrane (third eyelid) protrusion is frequently seen secondary to active retraction of the globe in response to ocular pain, enophthalmos caused by loss of orbital contents (dehydration, malnutrition, atrophy), presence of third eyelid masses, orbital space-occupying masses, or neurologic disorders (e.g., Horner's syndrome, tetanus).

Anisocoria

Pupillary asymmetry, or anisocoria, may develop for a variety of reasons that can be grouped into (1) primary iridal lesions, including congenital iridal defects (hypoplasia, aniridia, coloboma, anterior segment dysgenesis, synechia, iris atrophy), (2) neurologic disorders (Horner's syndrome, oculomotor nerve dysfunction), (3) intraocular diseases (uveitis, glaucoma, unilateral retinal lesions), (4) diseases involving the optic nerve or brainstem, and (5) previous use of pharmacologic agents such as atropine that alter iris sphincter muscle function or exposure to plants containing parasympatholytic alkaloids.

Changes in Tissue Volume

The presence of an ocular mass may be the primary cause of ocular asymmetry. Ocular surface neoplasms are relatively common in horses and cattle. Ocular squamous cell carcinomas usually arise from nonpigmented tissues of the nictitating membrane, the lateral limbal region, or the eyelid margin where ultraviolet (UV) light exposure is highest.[8] They may appear as irregularly raised, papillary surface masses or, less often, as smooth, vascularized lesions

that invade the globe (Color Plates 39.12 and 39.13). Ulceration, exudation, and mucopurulent ocular discharge are frequent concurrent findings (see the Ocular Neoplasia section later). Periocular sarcoids are also common in horses; their appearance is variable, ranging from flat foci of alopecia to fleshy or nodular nonulcerative lesions.[9,10] Other ocular tumors occur in large domestic animals but are relatively uncommon. Dermoids and orbital cysts are congenital masses involving the periocular tissues, eye, or orbit. Other nonneoplastic ocular masses seen in large animals include firm parasitic and foreign body granulomas and soft, fluctuant subconjunctival swelling characteristic of prolapsed periorbital fat. Ocular and orbital pseudotumors have also been described in the horse.[11]

Ocular Color Change

Changes in the color of ocular or periocular tissues or the presence of opacities in the clear ocular media (cornea, aqueous humor, lens, or vitreous) are important features of ocular disease. Such changes must be differentiated from normal congenital differences in ocular pigmentation. Developmental color dilution or absence of ocular pigmentation results in light or multicolored irides (heterochromia iridis). Examples of abnormal coloration include hyperemia of conjunctival (superficial) or episcleral (deep) blood vessels associated with ocular inflammation (see Table 39.2), hemorrhage secondary to trauma or coagulopathies, pallor of the conjunctiva (which reflects severe anemia), and yellowing of the sclera and sometimes iris, indicating icterus. A change in the color of the iris may also occur with anterior uveitis.

Opacities of the ocular media may occur as either surface (corneal) or intraocular (anterior chamber, lens, or vitreous) phenomena. Brown discolorations of the cornea are the result of pigmentation, iris prolapse, embedded foreign body, or pigmented fungal plaques. Grayish scars occur from previous episodes of keratitis; infectious keratitis will present with cream- to white-colored infiltrate; corneal degeneration will appear as white deposits of lipid or mineral; vascularization occurs secondary to chronic inflammation or neoplasia; and bluish discoloration is caused by corneal edema. These color changes frequently occur in various combinations in more severe keratitis, especially those of infectious origin such as chronic keratoconjunctivitis caused by *Chlamydia* spp., *Mycoplasma* spp., or *Moraxella bovis.* Cataracts are perhaps the most obvious cause of intraocular opacities in large animals (Color Plate 39.14). Inherited cataracts have been reported in Thoroughbreds, Quarter

Horses, Morgans, and Rocky Mountain horses.[12] However, the presence of exudates within the aqueous humor or vitreous, congenital vascular remnants in the vitreous, degeneration of the vitreous, or retinal detachment may also account for intraocular opacities (see Table 39.2).

Ocular Discharge

Ocular discharge can be characterized as serous, mucoid, purulent, or hemorrhagic. The type of discharge may assist in determining the severity and chronicity of the eye disease. Serous discharge generally indicates mild eye disease, whereas mucopurulent or hemorrhagic discharge indicates more serious disorders. A notable exception to this generalization is *equine recurrent uveitis* (ERU), which is associated with serous discharge (see the Immune-Mediated Ocular Diseases section later). The nature of ocular discharge tends to change as the disease progresses or improves. This is most notable in inflammatory or infectious ocular diseases. Initially the discharge is predominantly serous, but it tends to become mucopurulent with chronicity (see Table 39.2).

Epiphora describes facial wetting and results from overflow of tears over the eyelid margin. This may result from excessive secretion of tears (e.g., painful stimulus) or from physical or functional obstruction of the nasolacrimal system. In large animals, reflex lacrimation with an associated overabundance of tears is the typical response to ocular irritation or inflammation (e.g., foreign body, lash disorders, conjunctivitis, keratitis, uveitis). When epiphora is noted, careful digital and visual examination for foreign bodies within the conjunctival fornix or under the third eyelid is indicated. Epiphora is generally one of the earliest signs of conjunctivitis, ulcerative keratitis, or anterior uveitis. In cattle with keratoconjunctivitis caused by *Moraxella bovis*, epiphora is present several days before visible corneal ulceration occurs[13] (see the Infectious Bovine Keratoconjunctivitis [IBK] section later).

If signs of painful stimuli are not noted, the patency of the nasolacrimal system should be evaluated. Developmental defects or malformations of the nasolacrimal duct system (e.g., imperforate puncta) result in epiphora secondary to impaired outflow in neonates. In these cases, the presence of epiphora may be misinterpreted as overproduction of tears. Previously undiagnosed congenital defects may also be the cause of persistent ocular discharge in adult animals. Acquired obstructions of the nasolacrimal ducts may result from infections, foreign bodies, facial trauma, nasal tumors, or sinusitis that involve the duct

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system. Whether congenital or acquired, simple nonseptic obstructions are characterized by epiphora; septic occlusions result in mucopurulent discharge from the eye or nostril on the affected side. Excessive mucus production is a feature of follicular conjunctivitis, possibly as a result of the rubbing of elevated lymphoid follicles on apposing conjunctival surfaces. Lymphoid follicles are noted in subacute or chronic forms of chlamydial conjunctivitis in sheep and with *Onchocerca* larval migration in horses. Mucoid ocular discharge may be observed concurrently with epiphora in acute ocular surface infections caused by viral or chlamydial agents. Excessive tenacious mucus may also result from inadequate secretion of the aqueous component of tears (i.e., keratoconjunctivitis sicca). Although keratoconjunctivitis sicca (KCS) is not diagnosed as commonly in large animals as it is in dogs, neurogenic KCS due to loss of parasympathetic innervation has been reported in horses, usually as a complication of guttural pouch pathology.[14] KCS has also been reported with locoweed poisoning and hypothyroidism.[15]

Purulent to mucopurulent material is characteristic when bacterial organisms are involved in the ocular disease process. Bacterial conjunctivitis occurs frequently in large domestic species and manifests as red eyes with copious mucopurulent ocular exudate. Ocular foreign bodies and surface masses (e.g., squamous cell carcinoma) may predispose to secondary bacterial infections. Mucopurulent discharge in the absence of ocular inflammation suggests infection of the nasolacrimal sac (dacryocystitis) or ducts, with reflux of exudate from the lacrimal puncta.

Sanguineous or hemorrhagic discharge most often occurs after blunt or penetrating trauma to the eye (see the Ocular Trauma section later). Foreign body penetration may damage the eyelid, conjunctiva, or globe, resulting in bleeding onto the ocular surface. In addition, bloody-tinged ocular discharge has been reported in equine piroplasmosis.[16] Corneal ulcers may rupture and result in uveal prolapse and subsequent hemorrhage on the ocular surface. Patients with conjunctivitis or ocular surface tumors may develop ulceration resulting in bloody ocular discharge. Whenever blood is noted on the surface of the eye, it is imperative that a thorough ophthalmic examination be performed to determine the cause and evaluate integrity of the globe.

Ocular Pain

Ocular pain can be manifested as blepharospasm, epiphora, photophobia, and

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periocular hyperesthesia. Animals with severe ocular pain usually resist manipulation of the eyelids or any form of ocular examination by persistently jerking the head away from the examiner and closing the eyelids tightly. In cases of persistent ocular inflammation, discomfort and pruritus may be manifested by rubbing and self-trauma to ocular or periocular structures.

Ocular pain may result from conjunctivitis, trauma, keratitis, uveitis, and glaucoma. Other causes of ocular pain include mechanical irritation from entropion, trichiasis, distichia, ectopic cilia, or foreign material.[17] Foreign bodies that cause ocular irritation in large animals are typically plant materials like seeds, hay stems, straw, twigs, bark, or thorns, although particles of sand or soil can also cause severe ocular irritation. Nonembedded particulate matter is usually entrapped by mucus and washed out of the eye by reflex tearing; it typically results only in transient discomfort. By contrast, embedded foreign material (i.e., between ocular surface layers or within ocular tissues) causes persistent ocular pain.

Blindness

Visual deficits in large animals manifest in a variety of ways. Obvious signs include bumping into objects and lack of response to visual stimuli such as light or hand motions. Another sign of blindness is reliance on stationary objects (e.g., fences, railings, other animals) to maneuver within the environment. Behavioral changes include reluctance to move or to venture into unfamiliar areas, nervousness, and spooking in response to sudden noises or movements.[18] The nonvisual animal is frequently found standing isolated from the group and may experience injury by dominant individuals in the herd and suffer from weight loss.[18] Searching nystagmus is also seen in some animals with congenital blindness.

Nonvisual animals attempt to compensate for loss of vision with their other senses, which may result in an elevated head position or a head tilt. Patients may also exhibit maximum neck extension or snorting or intensive sniffing associated with nervousness. Frequently, blind animals will show exaggerated elevation of the limbs while walking. This must be differentiated from true hypermetria (see Chapter 8). Partial loss of vision may be difficult to determine, and detection depends on observing more subtle behavioral changes such as slight head cocking or tilting, difficulty maneuvering in dim light, or shying and startling from objects on one side or objects present in some specific part of the visual

field. Conduction of a maze test will assist the clinician in the detection of partial vision loss. Animals may effectively compensate for congenital blindness or slow diminution of vision, particularly when they remain with other unaffected animals in a familiar environment. Visual disturbance may not be apparent until an affected animal is isolated or moved to an unfamiliar area.

There are numerous causes of blindness in large animals, including those that involve only the visual system and some that involve other nervous system tissues or are multisystemic (Box 39.1). A functional approach to blindness involves anatomically classifying the cause as one of the following:

Box 39.1

Guidelines for Inspection (Antemortem and Carcass) and Disposal of Animals, Carcasses, and Parts Affected With Neoplasia

A. Epithelioma of the Eye

1. Any animal found on antemortem inspection to be affected and the eye has been destroyed or obscured by neoplastic tissue and which shows extensive infection, suppuration, and necrosis, usually accompanied by foul odor, or any affected animal with cachexia, regardless of extent, shall be condemned.
2. Carcasses of animals with the eye or orbital region affected will be condemned if the affection has:
    a. Involved the osseous structures of the head with extensive infection, suppuration, and necrosis;
    b. Metastasized from the eye or orbital region to any lymph node (including the parotid lymph node), internal organs, muscles, skeleton, or other structure, regardless of the extent of the primary tumor; or
    c. Regardless of extent is associated with cachexia or evidence of absorption or secondary changes.
3. Carcasses of animals affected to a lesser degree than above may be passed for human food after removal and condemnation of the head, including the tongue, provided the carcass is otherwise

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normal.

B. Neoplasms

1. An individual organ or other part of a carcass affected with a neoplasm shall be condemned. If there is evidence of metastasis or that the general condition of the animal has been adversely affected by the size, position, or nature of the neoplasm, the entire carcass shall be condemned.
2. Carcasses affected with malignant lymphoma shall be condemned.

From Code of Federal Regulations, Title 9, Chapter 3, Parts 309.6, 311.11, and 311.12 (1-1-87 edition).

- Cloudy ocular media (light does not reach the retina)
- Retinal detachment or retinopathy
- Optic nerve or central nervous system (CNS) disorder

Assessment of PLRs aids in localization of the lesion. Cloudy ocular media can be identified on retroillumination. Animals with lesions involving the retina, optic nerve, optic chiasm, or optic tracts generally do not have a normal PLR, whereas those with more central (“higher”) lesions involving the lateral geniculate bodies, optic radiations, or occipital (visual) cortex are likely to exhibit a normal PLR (see Chapter 8).

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Ocular Trauma*

Kristina R. Vygantas

Causes of Trauma

Because the eye is anatomically prominent in horses and food animals, it is prone to blunt and sharp trauma, which can range in severity from a mild abrasion caused by a conjunctival foreign body to a severe corneal laceration with globe rupture and orbital bone fracture. Ocular injuries may result from a variety of causes, including foreign materials such as soil, sand, or stones, which may be thrown into the eye during running or by the wind; trauma from disciplinary action; scratches by vegetable matter such as hay, weed stems, tree limbs, or thorns; exposure to chemical irritants; and sudden, violent head movements during training, working, or grooming. Other sources of ocular injury include stanchions, stall or trailer latches, hooks, protruding nails, bucket handles, fencing materials, and other animals, particularly horned ruminants.

Recumbent neonates and animals with CNS disease or severe illnesses that cause depressed mentation often suffer eye injuries from abrasion by debris or bedding materials, such as sand, straw, hay, or wood shavings. These injuries may be prevented by protecting the eye from trauma through the use of a padded hood or soft mats under the head or through sedation to prevent thrashing. It is also important to keep the cornea well lubricated in dehydrated animals and/or those with reduced blinking frequency. Following ocular trauma, opportunistic or pathogenic organisms may become established in the wound bed and may cause superficial or deep corneal infections. Ocular flora native to the conjunctiva include potential pathogens that may cause severe infections.[1]

Ocular Examination in Cases of Head Trauma

The goals of examination are to determine the degree of ocular trauma and to offer a prognosis for recovery of vision and preservation of the eye. The history should elicit information as to the cause and duration of the injury, previous ocular and systemic disease or therapy, and a description of any recent sedation, anesthesia, or therapy.

Blunt or sharp facial trauma frequently results in damage to the orbit and

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globe, including fractures or soft tissue injuries of the orbit, corneal abrasions and edema, corneal or scleral rupture, hyphema, traumatic uveitis, lens luxation, traumatic cataract, vitreal hemorrhage, retinal tear or detachment, or proptosis. Therefore the integrity of the orbit and globe and presence of vision should be determined when evaluating a patient with facial trauma.

Ophthalmic examination can be performed only after adequate restraint of the head (see the Ophthalmic Examination Procedures, Restraint section earlier). Intravenous (IV) sedation, sensory and motor nerve blocks, topical anesthesia, and the use of a halter, twitch (in horses), or nose tongs (in cattle) often are necessary for adequate examination of the traumatized eye.

Trauma to the Orbit

Orbital injuries in domestic animals frequently include fractures of the orbital rim and zygomatic arch and damage to the supraorbital process of the frontal bone.[2] Fractures of the orbit may be identified by palpation, radiography, CT, or magnetic resonance imaging (MRI). Contusions or lacerations of orbital soft tissues and temporary or permanent neurologic dysfunction also may be present.

Radiographic examination of the bony orbit in large animals is technically difficult and often unrewarding with conventional radiography. Standard lateral and dorsoventral views require powerful radiographic equipment for penetration of bony structures in horses and cattle.[1] Large fractures may be identified, but distinct delineation of the bony orbit is difficult because of overlying sinus and nasal structures. An oblique view of the frontal bone is often the most helpful projection.[3] This view may be taken with a portable machine because only minimal radiographic penetration of skull structures is required. Outlining the orbit and surrounding bony structures allows identification of fractures, osteomyelitis with or without bony sequestra, and soft tissue abnormalities, including swelling and radiopaque foreign bodies. If a periorbital sinus is involved in the fracture, subcutaneous emphysema may be present. The use of digital radiography may allow enhanced visualization of the bony structures of the orbit, especially when only subtle changes are present. Digital radiography systems used in conjunction with portable equipment may provide adequate detail in standard as well as oblique projections. CT and MRI are available at many referral centers. Detail of the bony and soft tissue structures is greatly enhanced by the cross-sectional views acquired by CT, as are the structures of the calvarium, sinuses, and teeth. MRI is also beneficial in delineating soft tissue

abnormalities within the orbit and sinuses.[4-6] In a recent case report on a periorbital wooden foreign body in a horse, MRI was required to identify the embedded material.[6]

Immediate evaluation for orbital fractures should include careful examination of the globe. In cases with substantial swelling, ice packs applied to the fracture site may reduce swelling. Systemic antiinflammatory therapy (e.g., flunixin meglumine, ketoprofen, phenylbutazone) may also be given. Systemic antibiotics should be used if sinus involvement is suspected. If the fracture fragments are only minimally displaced, surgical intervention may not be required. Surgical repair should be considered if fragment displacement or entrapment of extraocular muscles has occurred or could occur.[3,7] Trauma sufficient to cause fractures may also result in neurologic dysfunction and immobility of the eyelids.

If eyelid movement is impaired, the globe must be adequately protected and lubricated until neurologic function returns. If the globe is only minimally exposed, a sterile ophthalmic lubricant may be used at least three or four times daily. In more severe cases, a nictitating membrane flap or temporary partial tarsorrhaphy may be required. If neurologic dysfunction is permanent and results in significant exposure conjunctivitis or keratitis, partial or complete permanent tarsorrhaphy should be performed.[3] Enucleation with or without placement of an orbital prosthesis may be required for severely affected eyes.

Rupture of the sclera and/or cornea is another potential consequence of blunt trauma to the orbit and globe. A recent study found that eyelid and conjunctival swelling are the most consistent clinical signs of scleral rupture in horses.[8] Other clinical features of this condition are hyphema, subconjunctival hemorrhage, uveal prolapse, and a collapsed anterior chamber (Color Plate 39.15). Ultrasonographic findings include poorly defined scleral margins and echoic or hyperechoic material in the anterior and posterior chambers and in the vitreous.[7] Trauma severe enough to cause corneal or scleral rupture is typically associated with significant intraocular damage such as retinal detachment, uveal avulsion and prolapse, and expulsive hemorrhage. Prognosis for vision and globe salvage is usually poor.

Traumatic puncture wounds of the eyelids and conjunctiva may result in orbital cellulitis and exophthalmos in food animals and horses. Pyrexia and leukocytosis may be present. If a retrobulbar abscess occurs, temporomandibular movement causes extreme pain; the animal may have the eyes partially closed,

be off feed, and stand with the neck extended. The client may observe a relatively sudden onset of exophthalmos, eyelid swelling, severe chemosis, and exposure keratitis.[3,9] With time, the cellulitis may organize into a discrete abscess that can be located by palpation or ultrasound. Fine-needle aspiration may be performed to obtain specimens for culture and susceptibility (C&S) and cytology to guide antimicrobial therapy. Therapy should consist of systemic and topical antibiotics and a systemic antiinflammatory medication. Ophthalmic ointments and lubricants should be used on the exposed cornea and conjunctiva to prevent desiccation. In many cases, the wound or abscess should be débrided or drained to facilitate healing, especially if a well-organized abscess is present.

Although traumatic proptosis is uncommon, it may occur in horses and food animals. The prognosis for return of vision is guarded to poor, depending on the extent of damage to the optic nerve and retina. If the globe is ruptured and/or the extraocular muscles are avulsed, the eye should be enucleated. If the extent of the damage cannot be evaluated initially, the globe should be repositioned, a temporary tarsorrhaphy performed, and the globe reevaluated after 7 to 10 days of therapy. Treatment should include topical broad-spectrum antibiotics, topical atropine, and systemic antiinflammatories and antibiotics. With severe fractures or serious ocular damage, consultation with or referral to an appropriate specialist is advised.

Trauma to the Eyelid

Eyelid trauma is frequently accompanied by injuries to other ocular structures. Careful ocular examination should be part of the evaluation of animals with eyelid trauma. Injuries may range from swelling (blepharedema) or orbital cellulitis to extensive lacerations and avulsion. Blepharedema may be accompanied by hemorrhage and usually resolves quickly without therapy; however, recovery may be hastened by the use of ice packs and systemically administered ketoprofen or flunixin meglumine.

Horses are particularly prone to eyelid lacerations because of the prominence of the eye and their tendency toward sudden head movements when startled. Lacerations may be categorized into those without eyelid margin involvement, those with eyelid margin involvement, and avulsions of part or all of an eyelid. For all types of eyelid injury, several basic principles should be followed. Lacerations should be treated promptly to avoid distortion from excessive swelling, infection, scarring, and loss of function. Lacerated or displaced tissue

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should not be excised. It is impossible to replace the mucocutaneous junction of the eyelid margin. If eyelid margin is sacrificed, the risk of scar formation and secondary corneal damage is high. The laceration should be thoroughly and carefully flushed with sterile saline and explored to remove all foreign material. In acute trauma, cold compresses may assist in decreasing swelling. When suturing an eyelid laceration, it is essential to preserve the eyelid margin; therefore eyelid lacerations should be repaired with minimal débridement. The vascular nature of the eyelid allows for minimal débridement even if the tissue is severely damaged. In cases of avulsion of part or all of the eyelid, a variety of blepharoplastic procedures may be performed to help restore functional eyelid margin.[10-12] For a more detailed description of the principles of surgical repair of the eyelids, an ophthalmic surgical textbook is recommended.[10,11]

Postoperative care of all eyelid lacerations should include standard wound hygiene, application of fly repellent and topical ophthalmic antibiotics, and prevention of self-trauma. In contaminated wounds, systemic antibiotic therapy is indicated for 5 to 7 days. Tetanus prophylaxis should be administered.

Improper repair of eyelid lacerations can lead to abnormal function and secondary problems, including chronic epiphora and associated dermatitis, exposure keratitis, ulcerative keratitis, cicatricial entropion or ectropion, conjunctivitis, and pigmentary keratitis.

Trauma to the Nictitating Membrane

Lacerations involving the nictitating membrane (third eyelid) should be repaired to avoid irritation and damage to the cornea. This appears to be more important in horses than in ruminants. The margin should be realigned as precisely as possible, and the lacerated conjunctiva should be repaired with absorbable small suture material such as 5-0 to 7-0 polyglactin (Vicryl [Ethicon, Somerville, N.J.]). Topical ophthalmic antibiotics should be used 3 to 6 times daily for 7 to 10 days. The entire nictitating membrane should be excised only if it is irreparably damaged.

Trauma to the Conjunctiva

Conjunctival lacerations result in swelling (chemosis) and hemorrhage. The cornea and sclera should be examined carefully for evidence of lacerations or perforation. A concurrent scleral laceration is probable if the globe is excessively

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soft on digital palpation, the anterior chamber is shallow or flat, or hyphema or subconjunctival hemorrhage is present.[8]

Chemosis and subconjunctival hemorrhage frequently resolve without therapy. However, if the chemosis is severe enough to cause exposure and desiccation, sterile ophthalmic lubricants or antibiotic ointments are indicated to prevent secondary irritation. Conjunctival lacerations rarely require closure unless they are extensive. Subconjunctival hemorrhage sustained during parturition is common in foals and calves and requires no therapy, although topical ocular lubricants or antibiotic ointments are often prescribed.

Trauma to the Cornea

Corneal injuries in horses and food animals include blunt compressive trauma, foreign body penetration, ulcerative keratitis, and lacerations. Corneal perforation often results in iris (or iris and ciliary body) prolapse. Therapy is dictated by the type and extent of corneal injury, the complications encountered, the intended use and economic value of the animal, and other financial considerations.

Blunt Trauma to the Cornea

Blunt trauma to the globe from lead shanks, whips, and other objects can result in corneal endothelial injury and subsequent edema. Signs of traumatic uveitis also may accompany such an injury. The corneal edema that results from blunt trauma to the globe may be focal, linear, or diffuse. Therapy for blunt trauma includes a topical hypertonic (5%) saline solution or ointment two to four times a day to decrease corneal edema. Flunixin meglumine or phenylbutazone at antiinflammatory dosages may also be used if uveitis is present. A linear keratopathy characterized by a nonedematous, deep, striate, refractile opacity in the cornea may represent a focal thinning or break in the Descemet's membrane in these cases. This type of lesion must be distinguished from Haab's striae, which are linear breaks in the Descemet's membrane that result from elevated IOP in glaucoma.

Corneal Foreign Bodies

Plant matter embedded in the epithelium or superficial stroma is the most frequently encountered corneal foreign body. Foreign bodies usually are easily

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removed with hydropulsion, a moistened cotton-tipped applicator, or ophthalmic forceps. Sedation, motor or sensory nerve blocks, and topical anesthesia facilitate removal. Culture and sensitivity tests and cytologic examination of corneal samples are recommended to guide antimicrobial therapy. Fluorescein staining helps evaluate the extent of corneal ulceration. While awaiting laboratory results, medical therapy should include a broad-spectrum topical ophthalmic antibiotic (e.g., bacitracin-neomycin-polymyxin three to six times daily) and atropine as needed. In horses, treatment with a topical antifungal agent (e.g., miconazole three to four times daily) may also be warranted. The prognosis is guarded until the cornea heals; the eye should be reevaluated in 24 to 48 hours.

Complications of corneal foreign bodies include bacterial and fungal infection, corneal perforation, and severe corneal scars that may restrict vision. Subpalpebral lavage systems are used in severe injuries when frequent prolonged therapy is needed or when treating intractable animals (see the Infectious Ocular Diseases, Keratitis section later).[13] Originally, the placement of the subpalpebral catheter was described in the middle tolateral fornix of the upper eyelid, although many practitioners place the lavage system in the medial aspect of the inferior eyelid, allowing the third eyelid to protect the cornea from trauma from the lavage catheter itself.[14]

Corneal Ulcers

Corneal ulcers in horses are usually initiated by trauma and should be considered contaminated by bacteria or fungi until proven otherwise. Trauma may play a lesser role in food animals, in which primary infectious etiologies are more common (see the Infectious Bovine Keratoconjunctivitis [IBK] section later). The conjunctival fornices, third eyelid, and eyelids should be carefully examined for foreign material. Diagnosis is based on cytologic examination, culture and sensitivity testing of corneal samples, and fluorescein staining of the cornea. Material for bacterial and fungal culture is collected from the ulcer with sterile rayon-tipped swabs. Cotton swabs are less satisfactory because cotton exhibits some antimicrobial properties. The eyelid margins and skin should be avoided, and better culture results are obtained if the swab is moistened with a sterile solution (sterile water or saline) before specimen collection. The most reliable results are obtained if the swabs are placed in a transport medium at the time of collection (Port-A-Cul [Becton Dickinson, Sparks, Md.]). Immediately after

collection, the swab is replaced in the tube or inoculated onto standard bacterial and fungal agar plates, or blood agar and thioglycolate broth.

Corneal scrapings for microscopic examination are collected with the use of topical anesthesia. The eyelids are retracted, and the margin of the corneal ulcer is gently rubbed with a small brush, a cytology spatula, or the blunt handle end of a Bard-Parker scalpel blade until a small amount of cellular material is collected. This material is transferred to clean glass slides, spread over a 1-cm area, and allowed to air-dry. Slides may be stained in-house with Diff-Quik and/or Gram stain to assess the presence and type of microorganisms and inflammatory cells.

Therapy of corneal ulcers is based on the removal of the cause if it is still present, control or prevention of infection with topical antimicrobials, use of topical atropine for relief of painful ciliary body spasm and prevention of synechia, and, in horses, systemic use of nonsteroidal antiinflammatory drugs (NSAIDs) such as flunixin meglumine or phenylbutazone. The initial choice of topical antibiotic should be based on the results of cytologic evaluation and modified later if necessary, according to the results of culture and sensitivity testing. If gram-positive organisms are demonstrated on corneal cytology, several surveys of bacterial susceptibility suggest that topical chloramphenicol or fluoroquinolones are a good first choice of therapy.[15] If gram-negative organisms are seen, initial empirical therapy should include a topical aminoglycoside or fluoroquinolone antibiotic,[15] but since the ocular flora is primarily gram-positive, use of broad-spectrum combinations such as bacitracin-neomycin-polymixin B should be considered. Susceptibility testing ideally should be performed for every infected ulcer given the increasing resistance seen for bacterial pathogens. If cytology demonstrates fungal hyphae, initial therapy with a topical antifungal agent should be instituted immediately. In a recent study of fungal isolates from equine ulcerative keratomycosis cases, voriconazole was shown to be the most effective antifungal drug for initial therapy.[16] Subpalpebral lavage systems greatly facilitate the delivery of topical medication to the equine eye.[13,14]

Surgical intervention should be considered in cases of deep corneal ulceration and especially when Descemet's membrane is exposed. Surgical procedures most often used for corneal ulceration include conjunctival pedicle flap and keratoplastic procedures. Ophthalmic tissue adhesives and soft contact lenses may also be used as nonsurgical therapy for deep corneal ulcers. Perforating ulcers with iris prolapse and mixed bacterial and fungal keratitis or ulcers

present for more than 2 weeks usually have a poor visual outcome.[17]

Corneal Lacerations

Corneal lacerations may be caused by sharp, protruding objects or projectiles. They can occur with or without scleral laceration and, if they are partial thickness, may be treated as corneal ulcers. By contrast, perforating corneal lacerations must be repaired surgically. Preoperative preparation includes tetanus prophylaxis (horses and goats), systemic antibiotics, and sample collection for corneal culture and sensitivity. Ocular ultrasonography is useful in determining the integrity of intraocular structures. However, care must be exercised during ocular examination, ultrasonography, and surgery and anesthesia (especially induction and recovery) because extrusion of the intraocular contents may occur if excessive pressure is exerted on the globe or if the eyelids are forced open. In some cases, complete examination of the globe should be delayed until the animal is anesthetized.

General anesthesia, adequate magnification, proper instrumentation, appropriate suture material and needles, and adequate postoperative care are necessary for successful repair of a corneal laceration. Postoperative therapy must include topical antibiotics and mydriatics or cycloplegics, along with systemic antiinflammatory agents. The prognosis for recovery of vision and preservation of the globe generally is guarded. Complications that may occur after repair of corneal lacerations include phthisis bulbi, corneal fibrosis, synechia formation, blindness, retinal detachment, cataract formation, uveitis, endophthalmitis, bacterial or mycotic keratitis, and wound dehiscence with subsequent iris prolapse.

The prognosis after surgical repair of corneal or corneoscleral lacerations is best when the animal is presented immediately with a small wound in which the cornea or sclera is sealed and the anterior chamber has reformed. Minimal hyphema, clear intraocular media, a clearly visible fundus, and laceration length of less than 15 mm are additional findings that indicate a favorable prognosis.[17] In horses the success rate when only the cornea is involved is about 70% for recovery of vision and 90% for a cosmetically acceptable globe.[18] With corneoscleral lacerations, the prognosis is much worse. In our experience, the success rate in such cases is 20% for recovery of vision and 70% for a cosmetically acceptable globe. Most phthisical globes are not considered cosmetically acceptable. Therefore enucleation should be considered initially

with severe corneoscleral lacerations because the prognosis is poor for return of vision and guarded for preservation of the globe. Several surgical procedures have been described in horses to provide a cosmetic appearance to the globe and orbit, including placement of an intraocular silicone prosthesis.[19,20]

Trauma to the Uveal Tract

Trauma to the globe can damage the iris, ciliary body, and choroid. The resulting inflammatory response may range from very mild with rapid recovery to loss of vision and chronic discomfort. Signs of inflammation of the iris and ciliary body include blepharospasm, epiphora, miosis, aqueous flare, corneal edema, fibrin in the anterior chamber, hyphema, hypopyon, low IOP, and synechia formation. Concurrent damage to the corneal epithelium may be present and must be evaluated with fluorescein dye. Damage to the choroid may also affect the retina and lead to retinal detachment or degeneration.

Traumatic uveitis is treated in a manner similar to uveitis of other etiologies. Therapy is directed toward dilating the pupil to prevent synechia formation, cycloplegia to prevent painful ciliary spasm, and controlling the intraocular inflammatory response. Topical atropine is instilled to maintain mydriasis and provide cycloplegia. Topical corticosteroids are used to decrease inflammation of the anterior segment if the corneal epithelium is intact.

The topical corticosteroids of choice are 1% prednisolone acetate or 0.1% dexamethasone. Subconjunctival injection of corticosteroids may also be beneficial in controlling inflammation. Systemic medication should include an antiinflammatory, such as flunixin meglumine, ketoprofen, phenylbutazone, or rarely, oral corticosteroids. Care must be taken to avoid secondary complications from systemic corticosteroids.

Trauma-induced hyphema usually has a good prognosis if the blood has clotted and fills less than half the anterior chamber. Stall rest, topical 1% atropine, topical corticosteroids, and systemic antiinflammatory therapy should be instituted to control the associated uveitis. If a penetrating wound is suspected, topical and systemic antibiotic therapy should be included with periodic fluorescein staining. Surgical intervention to remove large blood clots is rarely indicated because it may result in additional bleeding or may worsen the uveitis. Dilute tissue plasminogen activator (tPA; Activase [Genentech, South San Francisco, Calif.]), 25 to 50 µg, may be injected into the anterior chamber to disrupt or lyse intraocular hemorrhage and fibrin and to aid in resolution of

synechiae. For maximum effectiveness, tPA should be used within 24 to 72 hours of clot formation, although clot lysis by tPA may still occur up to several weeks after the traumatic incident.[21,22]

Chronic uveitis after ocular trauma may be associated with lens damage or the introduction of infectious or foreign agents into the eye and carries a poor prognosis. If the lens is ruptured, its surgical removal is advocated. Ocular perforation is a frequent cause of panophthalmitis in food animals and horses. Although therapy consists of systemic and topical antibiotics, as well as tetanus prophylaxis in susceptible species, panophthalmitis usually necessitates eventual enucleation.

Trauma to the Lens

Blunt or sharp trauma to the eye may damage the lens by causing lens opacity (cataract), by rupturing the lens capsule, or less often by causing a shift in position (subluxation or luxation). Release of lens protein into the eye after lens capsule rupture may induce severe granulomatous uveitis. In such cases the eye should be treated vigorously for lens-induced uveitis with topical atropine and topical and systemic antiinflammatory drugs. If the globe has been penetrated, topical and systemic antibiotics are indicated. The prognosis for preservation of vision is poor. Lens removal may be required to control the inflammatory response.

Cataracts (lens opacities) associated with ocular trauma may occur acutely or develop weeks after the initial injury. The opacity may be focal and not appreciably affect vision, or it may be complete and cause a visual deficit. If the remainder of the eye is normal, surgical removal of the cataractous lens may improve vision.[23,24] In a recent retrospective study of surgical cataract removal in horses, the highest success rate was noted in the removal of traumatic cataract, as compared with cataracts of other known etiology.[24]

Trauma Involving the Vitreous

Trauma to the eye may result in hemorrhage into the vitreous or release of inflammatory products that cause vitreal degeneration. Either circumstance can result in vitreal syneresis (liquefaction), formation of vitreal traction bands, and subsequent retinal detachment. Symptomatic treatment of inflammation is generally adequate, but vitrectomy may be beneficial in the management of

vitreal traction bands to prevent subsequent retinal detachment.[25]

Trauma to the Retina

Retinal tears, hemorrhage, edema, and detachment may be caused by trauma.[26] In cases of opaque ocular media, retinal separation may be diagnosed by ocular ultrasonography (Fig. 39.8). Retinal degeneration may follow ocular trauma. Retinal hemorrhage and edema should be treated with systemic corticosteroids. With current technology, surgical repair of retinal tears, lacerations, or detachments in food animals and horses may be feasible in selected cases.

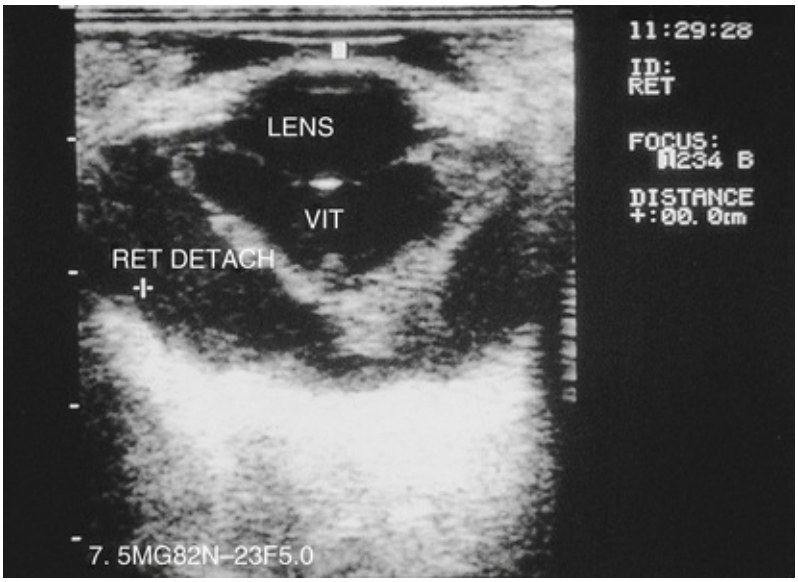


FIG. 39.8 Ocular ultrasound of a horse eye after blunt trauma to the globe. Note the characteristic V-shaped retinal detachment.

Trauma to the Optic Nerve

The pathogenesis of damage to the optic nerve is not well understood. Shearing forces at the optic foramen from displacement of the brain after severe head trauma (Fig. 39.9), direct contusion or avulsion of the optic nerve, or loss of blood supply to the nerve and subarachnoid hemorrhage probably all have roles in optic nerve injury.[27] Early examination may reveal only a dilated pupil that may be partially or completely unresponsive to light. Later, changes may include

optic nerve atrophy (Fig. 39.10) and peripapillary retinal pigmentation changes. Therapy with systemic antiinflammatory drugs may be of benefit, but severe damage is usually irreversible.



FIG. 39.9 Optic nerves and chiasm of a foal that was blind as a result of head trauma. Note the constrictions of the optic nerves caused by necrosis and degeneration. (Courtesy Dr. C.L. Martin.)

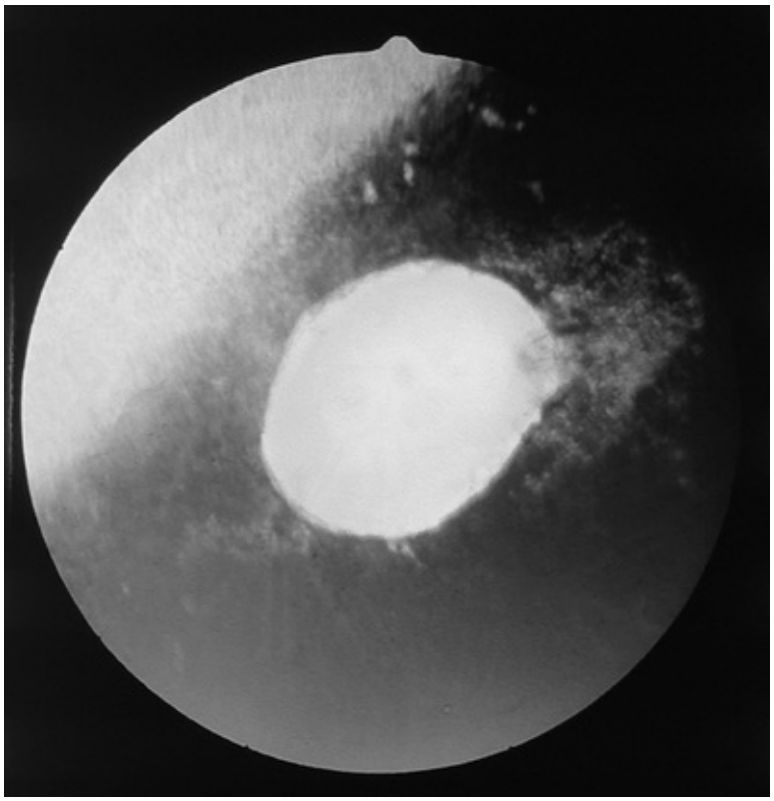


FIG. 39.10 Appearance of optic nerve 3 months after head trauma in a horse. Note the pale optic disk and peripapillary retinal degeneration. (Courtesy Dr. C.L. Martin.)

Traumatic optic nerve atrophy is usually characterized by sudden onset of unilateral or bilateral blindness, dilated fixed pupils, and a lack of menace response. In horses the traumatic episode is frequently characterized by damage to the poll from rearing over backward and striking the back of the head, from rearing up and hitting a ceiling beam, or from blunt trauma (blows) to the side or front of the face. The animal usually stands without loss of consciousness, and the injury is not considered serious by the owner at the time. Initially, blindness with a normal-appearing ocular fundus is observed.

Within 3 to 4 weeks after the trauma, examination of the fundus reveals a pale optic disk (see Fig. 39.10). Later, loss of peripapillary retinal vessels is usually evident. The optic disk often appears depressed, with increased prominence of the lamina cribrosa. Confirmation of optic nerve or optic tract lesions causing blindness may be made by the absence of a direct PLR with a normal electroretinogram. In some cases, the pathologic lesion is a rupture of the nerve axons from stretching forces produced by movement of the brain.[27] Chiasmal hemorrhage and fractures of the basisphenoid bone may be observed at necropsy.

Therapy with systemic corticosteroids (dexamethasone, 2.5 to 5 mg IV or IM) and IV dimethyl sulfoxide (DMSO) has generally not been successful,[27] although the lack of response to medical therapy appears related to the severity of the injury.

A segmental optic nerve atrophy involving one to three quadrants of the optic disk occurs in horses. The appearance is characterized by pallor, loss of normal vasculature, and increased prominence of the lamina cribrosa in the affected quadrants. The etiology is unknown, but traumatic injury is suspected in most cases. Response to medical therapy is poor.

Chemical Injury

Ocular irritation caused by insecticides and disinfectants inadvertently applied to the eye is relatively common in the farm or ranch setting. Chemical burns to the cornea and adnexa may have serious consequences and may warrant a poor prognosis for salvage of the eye. Alkali burns are more severe than acid burns. Corneal burns from acids tend to be sharply demarcated and nonprogressive, whereas alkali burns cause progressive coagulation, melting, and sloughing of the corneal stroma.[3] Chemically induced melting of the cornea must be differentiated from bacterial and fungal infections. Treatment for a suspected or known chemical burn should include lavage of the affected area with copious amounts (500 to 2000 mL) of sterile saline solution. Tap water may be used by the owner until veterinary assistance is available. It may be necessary to sedate the animal. No attempt should be made to neutralize the substance because this may cause precipitation within the cornea. The damage should then be evaluated with the aid of local nerve blocks.

Treatment should include appropriate topical antimicrobials, atropine, and a collagenase inhibitor such as autologous serum or possibly 5% to 10% acetylcysteine (Roxane Laboratories Inc., Columbus, Ohio), which inhibits collagenases and metalloproteinases by binding calcium. Hourly application of serum or acetylcysteine may be needed. Systemic antiinflammatory drugs should be used to control secondary uveitis. Therapeutic soft contact lenses have been used to protect the corneal stroma in patients with extensive corneal ulcerations.

Thermal Injury

Facial burns secondary to barn or stable fires may damage the eyelids,

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conjunctiva, and corneas. Therapy for minor burns to the eyelids is directed toward keeping the injured area moist with antibiotic dressings and protecting the cornea if eyelid dysfunction occurs. Treatment for injury to the conjunctiva or cornea should include topical antibiotic and systemic anti-inflammatory drugs in horses. Full-thickness eyelid burns may require grafting procedures to protect the cornea and minimize scarring. Third eyelid or conjunctival flaps may be required to protect the cornea until eyelid function returns.

Infectious Ocular Diseases

Caryn E. Plummer

This section describes the major infectious ophthalmic diseases of large animals (Table 39.3). Infectious bovine keratoconjunctivitis (IBK), or "pinkeye," the most common ocular disease of cattle, will be discussed in another section. Infectious ocular disease in large animals may be either the result of a pathogen primarily affecting the ocular tissues or an ocular manifestation of a systemic infection, wherein the ocular signs are secondary or concurrent to the systemic illness. As a general rule, surface ocular diseases are often primary in origin, whereas intraocular diseases are either primary or secondary. The first infections described in this section are those with predominantly ocular signs, followed by descriptions of ocular manifestations of systemic disease.

TABLE 39.3

Major Infectious Ocular Diseases of Large Animals

Agent	Common Name/Disease	Major Sign(s)	Cattle	Sheep	Goats	Horses
Mycoplasma conjunctivae	Pinkeye	Keratoconjunctivitis		++	++	
Mycoplasma mycoides subsp. *mycoides*	Pinkeye	Keratoconjunctivitis			+	
Acholeplasma oculusi (oculi)	Pinkeye	Keratoconjunctivitis		+	+	
Chlamydia psittaci	Pinkeye	Keratoconjunctivitis		++		
Branhamella (Neisseria)	Pinkeye	Keratoconjunctivitis		+	+	
Mycoplasma agalactiae		Keratoconjunctivitis		+	+	
Mycoplasma arginini		Keratoconjunctivitis		+	+	
Listeria monocytogenes		Keratoconjunctivitis	+	+		
Bovine herpesvirus type 1 (infectious bovine rhinotracheitis)		Keratoconjunctivitis	++		+	
Colesiota (Rickettsia) conjunctivae	Pinkeye	Keratoconjunctivitis		+		
Equine viral arteritis		Keratoconjunctivitis				+
Equine herpesvirus type 2		Keratoconjunctivitis				+
Mycoplasma bovoculi		Conjunctivitis	+			
Ureaplasma spp.		Conjunctivitis	+			
Equine adenovirus		Conjunctivitis				+
Moraxella spp.		Conjunctivitis				+
Streptococcus equi	Strangles	Conjunctivitis				+
Moraxella bovis	Pinkeye	Corneal ulcer	++			
Equine herpesvirus type 1	Rhinopneumonitis	Keratitis				+
Malignant catarrhal fever		Uveitis, keratitis	+			
Neonatal septicemia		Uveitis	+	+	+	+

Mycobacterium bovis	Tuberculosis	Uveitis	+			
Salmonella spp.		Uveitis				+
Borrelia burgdorferi	Lyme disease	Uveitis				+
Leptospira interrogans		Recurrent uveitis				+
Brucella abortus		Recurrent uveitis				+
Scrapie		Retinitis		+		
Histophilus somni (formerly *Haemophilus somnus*)	Infectious thromboembolic meningoencephalitis	Retinitis	+			
Bovine viral diarrhea		Retinal dysplasia, cataracts	+			
Bluetongue		Chorioretinitis, conjunctivitis	+	+		
Toxoplasma gondii		Chorioretinitis				+
Rhodococcus (Corynebacterium) equi		Panophthalmitis				+
Bovine leukemia virus		Exophthalmos	+			
Cryptococcus neoformans		Exophthalmos				+

There are many potential ophthalmic manifestations of infectious disease in large animals. Few diseases have pathognomonic or classically distinctive signs, so the combination of signalment, ocular clinical signs, systemic clinical signs, and laboratory diagnostics are necessary to confirm a diagnosis. Clinical signs associated with conjunctivitis are nonspecific to the underlying cause and include conjunctival hyperemia and chemosis. Other clinical signs may include follicle formation (often a manifestation of chronicity) and serous to mucopurulent discharge. Differentiation of primary conjunctivitis from secondary conjunctivitis resulting from other diseases (systemic disease or intraocular disease) is very important. A thorough ophthalmic examination will help with this determination.

In cattle and small ruminants, corneal disease may be initiated by an infectious agent, but infectious corneal disease in horses most often occurs secondary to corneal trauma. It can also be a manifestation of primary ocular disease or systemic disease. Signs of keratitis include pain (blepharospasm, photophobia, epiphora), ocular discharge, corneal edema, variable corneal vascularization, loss of stromal integrity (melting or keratomalacia), and secondary anterior uveitis.

Uveitis is inflammation of the uveal tract, which includes the iris, ciliary body, and choroid. Initial clinical signs may include episcleral injection, blepharospasm, photophobia, miosis, aqueous flare, hypopyon, fibrin, hyphema, and corneal edema. Intraocular inflammation can affect the entire eye and may result from direct invasion of the globe by a pathogen or as the result of a systemic inflammatory response. If untreated, uveitis can lead to permanent vision loss, cataract, secondary glaucoma, and phthisis bulbi. Some systemic

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infections may result in neuro-ophthalmic signs, such as facial nerve paralysis, Horner's syndrome, trigeminal neuropathies, nystagmus, strabismus, or ptosis. Others may cause retrobulbar disease or periorbital swelling.

This section addresses viral-, bacterial-, and fungal-mediated ocular disease; parasitic infections are addressed in a separate section. Many viral diseases affect the eye either directly or indirectly. Those that affect the globes may require direct ocular management. Other infections mediate disease primarily through cranial nerve neuropathy, and management is supportive. Any systemic bacterial infection has the potential to affect the eyes. Certain specific bacterial diseases (e.g., tetanus, botulism) may have their own distinctive ophthalmic signs, but most bacterial infections, especially when sepsis has developed, can be associated with nonspecific ocular inflammation. Fortunately, systemic fungal infections are not common in the immunocompetent animal, although ocular surface infections are common, especially in the horse. For more detailed information on the specific ocular conditions mentioned in this chapter, consult an ophthalmology textbook and the recent literature.

Conjunctivitis and Keratoconjunctivitis

■ Mycoplasmal Keratoconjunctivitis in Goats and Sheep

Definition and Etiology

Mycoplasma conjunctivae has been frequently isolated throughout the world from epidemics of keratoconjunctivitis, respiratory disease, and arthritis in goats and sheep.[1-4] *Mycoplasma mycoides* subsp. *mycoides* has been isolated from an epidemic of mastitis, arthritis, and keratoconjunctivitis in goats.[5] *Acholeplasma oculusi (oculi)* has been isolated from sheep and goats in epidemics of keratoconjunctivitis.[6,7] *Mycoplasma agalactiae* and *Mycoplasma arginini* have also been described as causing keratoconjunctivitis and systemic disease.[8]

■ Clinical Signs and Differential Diagnoses

Clinical signs of mycoplasmal keratoconjunctivitis include epiphora, conjunctival hyperemia, and occasionally follicular conjunctivitis. In experimental conjunctival inoculation with *M. conjunctivae,* clinical signs began on day 2 and lasted for 5 weeks.[9] Later in the disease, keratitis with corneal neovascularization (Color Plate 39.16) and occasionally anterior uveitis can be

seen.[1,10] One case of choroiditis and hyalitis has been described.[11] Signs can be seen in individuals, as well as in herd or flock outbreaks. The disease is usually unilateral but can be bilateral. Differential diagnoses include other infectious causes of keratoconjunctivitis, such as *Chlamydophila* spp. (sheep), *Branhamella* spp., aerobic bacteria, parasites, and infectious bovine rhinotracheitis (goats), as well as noninfectious causes such as trauma. There may be a slight variation in clinical signs experienced by sheep and goats. Although both will exhibit blepharospasm, conjunctivitis, and keratitis, sheep will occasionally develop a more severe form of the disease associated with mucopurulent conjunctivitis, corneal ulceration, and uveitis with hypopyon (Color Plate 39.17). Goats do not typically ulcerate their corneas, despite the presence of severe and vision-threatening keratitis.

■ Clinical Pathology

In conjunctival scrapings taken early in the disease, many neutrophils are seen; later, lymphocytes predominate. Plasma cells and necrotic epithelial cells are also observed.[12] Organisms can occasionally be found in epithelial cell cytoplasm in coccobacillary or varied forms.[11] Pigment granules can be mistaken for organisms.[6,12,13]

Mycoplasmal organisms can be cultured and identified from conjunctival swabs; serum antibody titers can be measured,[14,15] or PCR can be used to identify *M. conjunctivae* in conjunctival smears.[16,17] Egwu and Faull[18] describe rising serum and lacrimal antibody titers in sheep topically inoculated with *M. conjunctivae*. However, Trotter and colleagues[2] report low serum titers to *M. conjunctivae* in normal animals and no rise in titer in animals subconjunctivally inoculated with *M. conjunctivae* that subsequently developed signs of disease.

■ Epidemiology

Mycoplasmal infections apparently are transmitted directly from animal to animal, as evidenced by herd or flock outbreaks. Subclinical carrier states exist, and *M. conjunctivae* can be cultured from nonclinical animals.[19,20] There is some evidence for vector transmission (flies) as well.[21] Animals can become reinfected, but if they do, their clinical signs are usually more mild than during the initial infection. Keratoconjunctivitis can be induced in sheep with topical inoculation of *M. conjunctivae*.[18,22,23] Clinical signs were identical to natural

outbreaks and spread to uninoculated sheep. The organism can be cultured from eyes long after clinical signs abate.[9] Co-infection with other organisms may occur and result in more severe clinical signs.

■ Treatment and Prognosis

In most animals, mycoplasmal keratoconjunctivitis associated with *M. conjunctivae* is transient. Affected animals usually recover spontaneously in 10 days, although some animals seem to have recurring episodes that last for several weeks. In a controlled clinical trial, one dose (20 mg/kg) of long-acting oxytetracycline was given to experimentally inoculated lambs. This treatment seemed to hasten the cessation of clinical signs, although the results were not analyzed statistically.[24] The treatment did not, however, eliminate the *M. conjunctivae* infection and may promote a carrier state. Other drugs recommended for the ocular disease include topical oxytetracycline or oxytetracycline and polymyxin B.[1] Subconjunctival oxytetracycline is not currently recommended because it may cause a severe inflammatory reaction. In vitro antibiotic testing of *M. conjunctivae* shows that florfenicol, tylosin, oxytetracycline, streptomycin, and chlortetracycline are suitable for treatment.[25,26]

■ Prevention and Control

Introduction of new animals into a herd or flock has been implicated in starting an outbreak of keratoconjunctivitis. Therefore isolation and, if necessary, treatment of new animals are important before contact with the herd.[27-29] Transmission between species has been documented, so housing domestic sheep and goats where they might commingle with wildlife is not recommended.[27,28] No other specific recommendations have been made for prevention and control of *M. conjunctivae.*

Bovine Mycoplasmal Conjunctivitis

Mycoplasma bovoculi and *Ureaplasma* spp. have been isolated from cattle with conjunctivitis and IBK. Inoculation of normal calves with *Mycoplasma bovoculi* or *Ureaplasma* isolates produced conjunctivitis characterized by serous discharge and conjunctival hyperemia. Experimentally induced conjunctivitis ran a course of more than 1 month. Cases can be confirmed by culture or PCR

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performed on conjunctival swabs.[30] Mycoplasmal infection may predispose the animals to development of IBK from *Moraxella bovis*[31,32] (see the Infectious Bovine Keratoconjunctivitis [IBK] section later). Therefore although treatment of mycoplasmal conjunctivitis may not be warranted, it may be advisable in areas where IBK is endemic. Topical oxytetracycline ointment applied three times daily or intramuscular (IM) injection of long-acting oxytetracycline is recommended.

Other mycoplasmal organisms (e.g., *M. arginini*) can be isolated from cows' conjunctiva but are not thought to cause the disease. *Mycoplasma bovis* was found using PCR performed on normal conjunctival samples,[29] but it was not thought to cause conjunctivitis. *Mycoplasma bovigenitalium*, *Mycoplasma bovirhinis*, and *Mycoplasma bovoculi* were isolated from members of two cattle herds with conjunctivitis and bronchopneumonia.[32] However, when viral cultures were performed, bovine herpesvirus type 1 (BHV-1; also called infectious bovine rhinotracheitis [IBR]) was isolated in the same individuals. The mycoplasmal organisms may have contributed to the disease in these herds. In another cattle herd with an outbreak of respiratory disease, keratoconjunctivitis followed, and *Mycoplasma bovis*, *M. bovirhinis*, and *Mycoplasma bovoculi* were isolated in various combinations from affected calves.[33]

■ Chlamydial Keratoconjunctivitis in Sheep and Goats

Definition and Etiology

Chlamydial agents have been isolated from outbreaks of keratoconjunctivitis in sheep flocks. The agent was originally described as a strain of *Chlamydia psittaci.* The agent was called *Chlamydophila pecorum* for a period of time but is currently designated *Chlamydia pecorum*, which can also cause abortion (see Chapters 31 and 35) and polyarthritis in lambs.[34,35]

■ Clinical Signs and Differential Diagnoses

Early clinical signs consist of epiphora, chemosis, and conjunctival hyperemia. Later in the disease, follicle formation in the conjunctiva becomes prominent. Still later, corneal vascularization may be seen (Color Plate 39.18). Most cases are bilateral and symmetric.[36,37] In some flock outbreaks of keratoconjunctivitis,

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outbreaks of polyarthritis are also noted. Most lambs that develop chlamydial polyarthritis will also develop conjunctivitis.[36,37] Differentials include other infectious causes of keratoconjunctivitis, such as *Mycoplasma* and *Branhamella (Neisseria)* spp., aerobic bacteria, and parasites, as well as noninfectious causes like trauma.

■ Clinical Pathology

Early in the disease, conjunctival smears show numerous neutrophils and some lymphocytes. Later, there are more neutrophils and fewer mononuclear cells. Cytoplasmic chlamydial inclusions are occasionally seen in up to a third of the eyes scraped and can be definitively identified by fluorescent antibody staining.[34] Conjunctival epithelial cells are often necrotic. Chlamydial organisms can be cultured from conjunctival scrapings and from blood taken from sheep with polyarthritis and conjunctivitis.[36-38] In one study, titers to chlamydial antibodies were found at 1 : 16 or higher in a number of the affected lambs, although titers on normal lambs were not reported.[37] PCR can also be used to identify the organism.

■ Epidemiology

Chlamydial organisms are apparently transmitted by direct contact, as evidenced by flock outbreaks. Chlamydial organisms caused conjunctivitis in five lambs inoculated topically.[38] An uninoculated lamb housed with the five lambs also developed conjunctivitis. Lambs subsequently developed follicular conjunctivitis.[38] In another study, chlamydial organisms were injected intraarticularly, intravenously, and intramuscularly and caused polyarthritis and conjunctivitis.[39]

■ Treatment and Prognosis

In uncomplicated cases the disease is self-limiting, and eyes are normal within 2 to 3 weeks.[37] The same treatments indicated for *M. mycoides* subsp. *mycoides* (systemic oxytetracycline and, when possible, a topical tetracycline ophthalmic preparation) are also effective in treating chlamydial conjunctivitis and polyarthritis of sheep.

Branhamella (Neisseria) ovis Keratoconjunctivitis in Sheep

and Goats

Branhamella ovis is a gram-negative diplococcus similar to *Moraxella*. This agent has been cultured from the eyes of sheep and goats with keratoconjunctivitis and from normal eyes.[40-42] *B. ovis* has also been cultured from cattle with serous conjunctivitis and, rarely, keratitis.[43] Clinical signs are usually mild and include epiphora and conjunctival hyperemia. Severity of clinical signs is increased when co-infections with other organisms, such as *M. conjunctivae*, are present. Conjunctivitis but not keratitis has been experimentally induced in goats[44] and lambs,[45] and *B. ovis* could be cultured from the eyes of the lambs for up to 20 days after inoculation. Outbreaks of *B. ovis* have been successfully treated with parenteral tylosin, topical neomycin-polymyxin B, and a corticosteroid,[40] or with subconjunctival penicillin.[44]

Moraxella Conjunctivitis in Horses

Two reports have described a *Moraxella* species recovered from several horses in herd outbreaks of conjunctivitis, ocular discharge, and erosions of eyelid epithelium at the canthi.[46,47] The organism was similar but not identical to *Moraxella bovis*, and the disease was reproduced experimentally in horses by instillation of the organism into the conjunctival sac. Huntington and colleagues[47] described successful treatment of the lesions with chloramphenicol ointment, whereas Hughes and Pugh[46] described the lesions as healing spontaneously.

Keratitis

■ Bacterial Keratitis in Horses

Definition and Etiology

Bacterial keratitis occurs when a traumatic corneal ulcer becomes infected with opportunistic bacteria; no bacteria are known to *initiate* corneal ulcers in horses. The most devastating clinical manifestations are associated with *Pseudomonas aeruginosa* and *Streptococcus equi* subsp. *zooepidemicus*.[48-56] However, any bacteria that have access to the ocular surface may colonize and complicate a corneal wound.[52,53,57]

■ Clinical Signs and Differential Diagnoses

Whether infected or not, corneal ulcers cause signs of pain (blepharospasm, epiphora, photophobia). The conjunctiva is hyperemic, and the ulcerated area of the cornea retains fluorescein stain. Acute superficial ulcers are usually not infected, and the cornea maintains its normal curvature in the ulcerated area. If a superficial ulcer is slow to heal, it should be sampled for microbial C&S, since delayed healing may be a sign of an early or subclinical infection. A deep ulcer (resembling a divot in the corneal stroma) should always be assumed to be infected.

Other signs of corneal infection are rapid progression and white or yellowish infiltrate within the cornea (signifying influx of neutrophils and bacterial colonization within the corneal stroma). An ulcer that is rapidly becoming wider or deeper or begins to melt (corneal stroma softens or begins to dissolve) is highly suggestive of a bacterial infection (Color Plate 39.19). Many corneal ulcers are accompanied by some degree of anterior uveitis (miosis, aqueous flare, hypopyon, anterior chamber fibrin). The uveitis that occurs during a corneal infection tends to be much more severe than that which is present with sterile corneal wounds (see Color Plate 39.7). In cases in which the initially damaged epithelium heals over microorganisms in the corneal stroma, a bacterial stromal abscess may form.[58] Such lesions do not stain with fluorescein, and many topical antibiotics cannot penetrate the epithelial barrier to reach the site of infection. Most stromal abscesses, particularly if they are located in the deep or posterior stroma, are fungal in etiology.[59-61] Fungal keratitis may exhibit similar clinical behaviors and may become secondarily infected with bacteria.

■ Clinical Pathology

A diagnosis of a bacterial keratitis is made via corneal cytology and microbial C&S. Stained scrapings from the ocular surface wound may show intracellular and extracellular bacteria and neutrophils (Fig. 39.11). Bacterial morphology and Gram staining will guide the choice of empirical therapy while the results of C&S are pending. Bacterial organisms are definitively identified after culture of the ulcerated cornea. Aerobic culturing techniques are usually used. Culturing for anaerobic organisms may be indicated if aerobic culture does not reveal an organism and the ulcer fails to respond appropriately to medical therapy. Anaerobic infections are far less common than aerobic bacterial and fungal infections in the equine cornea.[57]

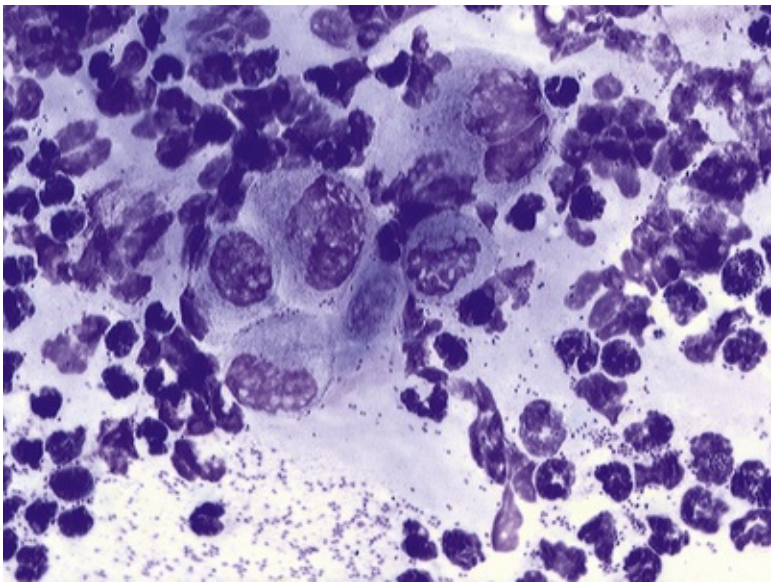


FIG. 39.11 Cytology of bacterial keratitis. Wright-Giemsa, ×100. Note the corneal epithelial cells in the center of field, numerous degenerate neutrophils, and intracellular and extracellular cocci and diplococci bacteria.

■ Pathophysiology

Bacterial keratitis is the result of pathogenic or opportunistic organisms colonizing a damaged cornea. The cornea is most likely to be damaged by mechanical trauma, but other causes such as chemical injury or corneal exposure are possible. Many different types of bacteria can be cultured from a normal eye, including *Corynebacterium*, *Streptococcus*, *Staphylococcus*, *Bacillus*, and rarely *Pseudomonas* spp. or other gram-negative bacteria.[48,50] Damage to the epithelium enables bacteria to adhere to the exposed corneal stroma, colonize, and begin replicating.[54] Some bacteria such as *Pseudomonas* elaborate collagenases and other proteoglycanolytic enzymes,[55] which results in corneal collagen destruction. Proteases and collagenases liberated by white blood cells and corneal epithelial and stromal cells also contribute to this "melting" process.[62,63] In this way, what begins as a small wound to the cornea can progress to a corneal perforation within 24 to 48 hours.

■ Treatment and Prognosis

Prognosis is guarded for any corneal ulcer that is rapidly progressing or melting. These ulcers can easily progress to corneal perforation and loss of vision or of

the eye despite timely, appropriate treatment. On the other hand, with aggressive therapy many eyes with infected ulcers can be saved and vision maintained, although scarring may be present.

In any ulcer in which a bacterial component is suspected, C&S of the ulcer and a corneal scraping for Gram staining and cytology should be taken. The horse is restrained or sedated and an auriculopalpebral block is performed. A sample for culture should be obtained with a moistened swab before any solutions or medications are applied to the eye. Following culture, a topical anesthetic is applied to the cornea, and the ulcer margins are then scraped gently with a cytology brush, a Kimura spatula, or the blunt handle end of a scalpel blade.

In cases of equine bacterial keratitis, therapeutic goals are to eliminate the bacteria, prevent or slow melting if present, and treat the concurrent uveitis.[64-66] Because this requires very frequent applications of numerous medications to a horse with a painful and often fragile eye, a subpalpebral lavage system is usually required.

Placement of Subpalpebral Lavage System.

The following equipment is necessary:

- Subpalpebral lavage (SPL) kit (MILA International [Fig. 39.12])

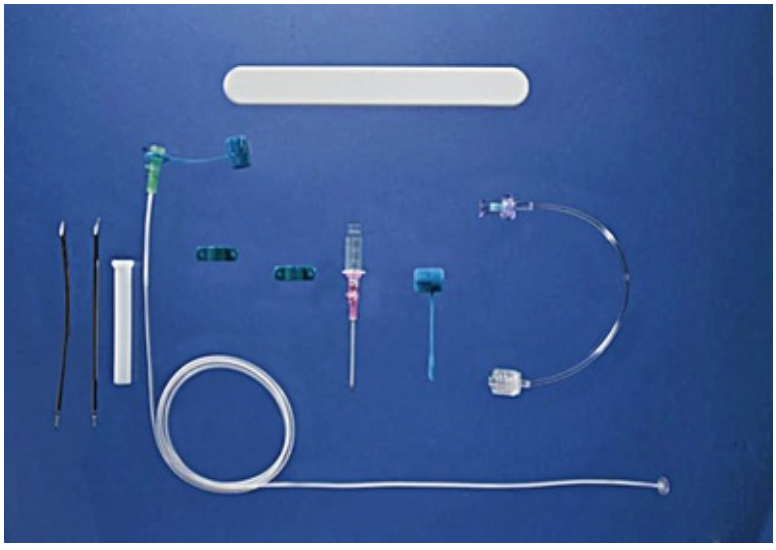


FIG. 39.12 Subpalpebral lavage kit. (Courtesy Mila International Inc.)

- White tape
- Applicator stick (tongue depressor)
- Injectable anesthetic (lidocaine, mepivacaine)
- Topical ophthalmic anesthetic (proparacaine, tetracaine)
- Monofilament nonabsorbable suture on a cutting needle

The horse should be sedated. Additional manual restraint (e.g., twitching) may be necessary depending on the animal's temperament and degree of discomfort and on the handler's comfort and experience. The auriculopalpebral nerve is blocked over the zygomatic arch to paralyze the orbicularis oculi muscle and reduce eyelid movement. If the SPL is to be placed in the upper eyelid, a supraorbital (frontal) block is performed to desensitize the eyelid. This nerve is accessed at its exit from the supraorbital foramen. If the SPL is going into the lower lid, a line block is performed along the ventral orbital rim for regional anesthesia. Topical anesthetic is then applied to the eye by directing a gentle stream onto the globe and into the conjunctival fornix with a small syringe with a 25-gauge needle broken off at the hub. The eyelid and conjunctival fornices should be flushed with a dilute Betadine solution (0.5%).

Once the periocular structures are prepared, a gloved finger or the plastic applicator stick or needle guard from the kit is advanced under the eyelid and used as a guide for the needle to which the SPL tubing is attached. The needle is directed between the eyelid and the guide and then through the skin. In the upper eyelid, it should be placed as high as possible and should grab the periosteum of the orbital rim as it exits, which will help keep the lavage footplate in place and decrease the likelihood of slippage and subsequent irritation of the cornea. While passing the needle through the skin, care must be taken not to inadvertently push the end of the needle onto or against the fragile globe. The needle and Silastic tubing are threaded through the hole in the skin until the footplate is in direct contact with the palpebral conjunctiva. Tape is used to secure the tubing to the upper eyelid, and sutures secure the tape to the skin. The tubing can be braided

through the forelock and then run down the neck through several braids to keep it secure. A small catheter is directed into the distal end of the tubing, and an injection port is fixed to the end of the catheter. The catheter and tubing are taped to an applicator stick to prevent kinking. The stick is then taped to a braid of the mane (Fig. 39.13).

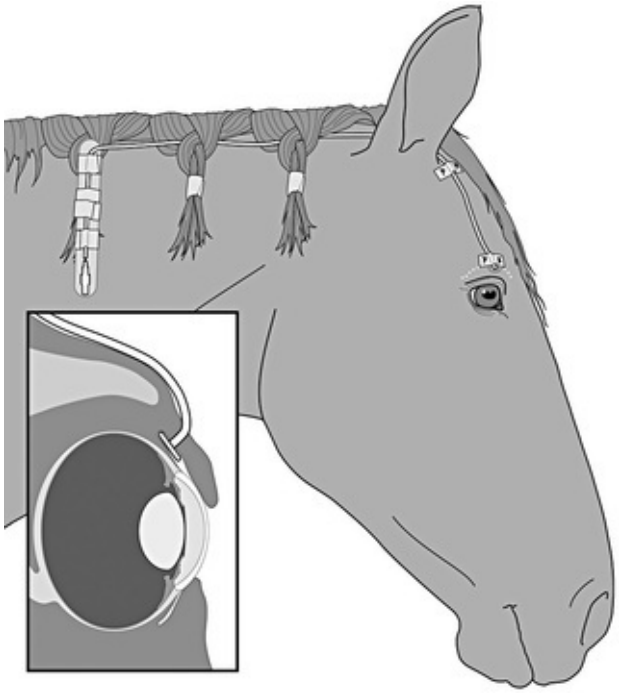


FIG. 39.13 Diagram illustrating a subpalpebral lavage system with correct positioning in superior fornix and fixation with a tape butterfly at exit site of tubing from the eyelid. Tubing is woven through braids in the mane, and injection catheter and stopcock taped to a stick applicator (tongue depressor). (Diagram courtesy Anne Gemensky-Metzler.)

Poorly placed lavage tubes or tubes that slip ventrally can rapidly produce a corneal ulcer. A displaced tube footplate can also cause topical medications to leak into the subcutaneous tissues, leading to a swollen and inflamed eyelid. Therefore the tube position should be checked at least once daily by gentle dorsal traction on the exposed tubing to ensure that it has not slipped into the conjunctival cul-de-sac. Excess traction will pull the footplate through the conjunctiva and into the eyelid itself. Most horses tolerate this system well, and well-maintained tubing may be kept in place for up to several months. Occasionally horses try to rub their heads and can damage the tubing; neck cradles or protective eye cups can be used in such horses.

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Medical/Surgical Approaches and Goals.

For noninfected ulcers a broad-spectrum preparation (e.g., neomycin-polymyxin-bacitracin, neomycin-polymyxin-gramicidin, chloramphenicol) is appropriate. In a cornea with rapidly developing keratitis or melting ulcer, the clinician should always suspect the presence of an infectious agent. Treatment should be initiated with an appropriate antibiotic, the choice of which should be based on cytologic analysis, administered every 1 to 2 hours. If rods or gram-negative organisms are observed, bacitracin-neomycin–polymixin B, aminoglycoside antibiotics (gentamicin, tobramycin), or fluoroquinolones (ciprofloxacin, ofloxacin)[67] are reasonable choices for treatment. To avoid contributing to bacterial resistance, fluoroquinolones should not be used for bacterial prophylaxis in *noninfected* ulcers. If cocci or gram-positive organisms are seen on the corneal cytology, bacitracin-neomycin–polymyxin B, neomycin–polymyxin B–gramicidin, chloramphenicol, levofloxacin or cefazolin, or penicillin or ampicillin can be used.[56,66] Cefazolin is mixed with artificial tears to a concentration of 55 mg/mL,[61] ampicillin to 10 mg/mL,[49] and penicillin G to 100,000 U/mL. If the ulcer continues to worsen, antibiotics should be changed on the basis of the initial susceptibility results, and the cornea should be recultured because organisms can become resistant to the first antibiotic used or a secondary infection can develop. For resistant organisms, susceptibility testing that gives minimum inhibitory concentration (MIC) may be very useful because higher drug concentrations are more readily and safely attainable in the ulcerated cornea than in the systemic circulation.

Keratomalacia (i.e., “melting”) must be treated with collagenase and protease inhibitors, in addition to antimicrobial medications. Autologous serum, oxytetracycline, disodium ethylenediaminetetraacetic acid (disodium EDTA; mixed with sterile water to a concentration of 0.17%), or *N*-acetylcysteine (5% to 10% in artificial tears) can be used topically for their antiprotease and anticollagenase activity, as can systemic doxycycline (10 mg/kg orally [PO] twice daily or 20 mg/kg PO once daily).[49,68] Tetanus toxoid, topical doxycycline, and ilomastat have also been applied to the diseased cornea to decrease collagen dissolution.[69]

Surgical therapy can also be used and may improve prognosis. Conjunctival pedicle grafts can be used to bring a blood supply and conjunctival fibroblasts to deep corneal ulcers, with the goal of slowing progression and aiding stromal reconstruction[56] while still allowing medication to reach the wound. A

conjunctival graft allows observation of the cornea so that treatment can be adjusted as corneal health improves or changed if the cornea continues to deteriorate. A nictitating membrane “flap” should not be used in rapidly progressing or deep ulcers because it creates a barrier to topical medications and observation of the cornea such that worsening of the ulcer goes unnoticed, repeated culturing cannot be performed, and appropriate changes in therapy cannot be instituted.

A corneoconjunctival transposition using autologous tissue or a corneal graft (penetrating keratoplasty or deep anterior lamellar keratoplasty) using donor cornea is an excellent treatment to repair very deep ulcers, descemetoceles, and perforations if melting has ceased and the ulcers are sterile.[60,61,70] Other grafting materials, such as porcine small intestinal submucosa,[71] equine amniotic membrane,[72] or bovine pericardium, may be substituted for cornea. Placement of any graft requires microsurgical instruments, techniques, training, and experience. Highly specialized techniques, such as keratectomy with a conjunctival graft, penetrating keratoplasty, posterior lamellar keratoplasty, or deep lamellar endothelial keratoplasty, are necessary to treat stromal abscesses.[53,60,73-76]

The initial desired response to appropriate therapy of a malacic ulcer is simply cessation of worsening of the ulcer. That is, the ulcer does not appear to be healing or shrinking but also is not becoming larger or deeper. This suggests that bacteria have been killed and tissue destruction has halted. Epithelium will then begin to migrate toward the center of the ulcer, covering the stroma or Descemet's membrane if it is exposed, and blood vessels will slowly begin growing into the cornea from the limbus. Once re-epithelialization is complete, new infection with microorganisms is unlikely. If surgery has not been performed, however, the area that had been ulcerated will be thinner than the surrounding stroma. This area will gradually thicken by slow reconstruction of stromal collagen by corneal fibroblasts (keratocytes) or when corneal blood vessels fill the old ulcer bed. This can take weeks to months, and until this happens, the cornea may be susceptible to traumatic rupture.

Another goal of therapy for an infected ulcer is suppression of the trigeminal nerve–mediated anterior uveitis that is associated with any corneal irritation. Topical atropine is used for this purpose because it decreases pain associated with ciliary body muscle spasm and maintains pupil dilation, which reduces the chance of posterior synechia formation. Atropine should be applied to effect (i.e., until reduced pain or pupil dilation is noted). This may be as frequently as

every 6 to 8 hours initially but should be decreased after 24 hours and used only to effect once pupillary dilation is maintained.[77] Because topical atropine is absorbed into the systemic circulation and is associated with altered gastrointestinal (GI) motility,[78] small quantities of drug should be applied (1/8- to 1/4-inch strip of ointment or 0.1 mL solution), gut sounds should be assessed frequently, and the patient should be monitored for signs of colic. Systemic NSAIDs also should be used to decrease corneal and uveal inflammation. However, these drugs do slow corneal vascularization to some extent.[79,80] Topical NSAIDs (as with corticosteroids) are contraindicated in infected ulcers. Topical corticosteroids are sometimes recommended by some to reduce corneal vascularization once epithelialization is complete. However, corneal vascularization is a critical means by which corneal stroma (and strength) is reformed, and topical corticosteroids hasten regression of granulation tissue, suggesting that this approach is inadvisable. No evidence indicates that corticosteroid administration decreases the final size of the scar, and steroids may compromise healing and predispose to local immunosuppression, additional or persistent infection, and corneal rupture.

■ Fungal Keratitis in Horses

Definition and Etiology

Fungal keratitis (or keratomycosis) occurs when an ulcerated cornea becomes infected with a mycotic organism. As with bacteria, no fungi are known to *initiate* corneal ulcers. The most common genera isolated in cases of equine fungal keratitis are *Aspergillus* and *Fusarium* spp., but many other species of other genera have been cultured.[81-86] Horses seem unusually susceptible to fungal keratitis compared with the other domestic species.

■ Clinical Signs and Differential Diagnoses

Fungal keratitis is very common in the horse, particularly in certain geographic regions (i.e., southeastern United States), but has been reported all over the world. Nonspecific signs of keratomycosis may include pain (blepharospasm, photophobia), serous to mucopurulent ocular discharge, corneal edema, variable corneal vascularization, loss of stromal integrity (melting or keratomalacia), and secondary anterior uveitis (aqueous flare, hypopyon, fibrin, miosis), which may be severe. Fungal keratitis has various clinical presentations ranging from

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superficial punctate nonulcerative keratitis, to necrotic plaques, to stromal lesions with keratomalacia and furrowing, to deeper stromal defects or deep stromal abscesses.[87,88] A superficial epithelial to subepithelial form presents with microerosions and multifocal, whitish punctate to branching subepithelial opacities that often retain rose bengal stain.[89,90] This form, if treated promptly, will usually resolve without incident. However, the forms wherein overt ulceration develops are much harder to control. Superficial fungal ulcers often appear with a roughened, gritty ulcer bed and considerable edema (Color Plate 39.20). Often this form develops into a more severe presentation wherein enzymatic destruction of corneal collagen results in a furrow or groove around the margins of the lesion.[91] This furrow is a form of corneal melting and may progress rapidly and lead to corneal perforation. In other cases of keratomycosis, a plaque of tissue that is typically an accumulation of necrotic collagen, degenerating inflammatory cells, and a mat of fungal organisms forms centrally within the ulcer bed (Color Plate 39.21).[88,91,92] A very common manifestation of fungal infection is the formation of a white or yellow deep stromal abscess, typically accompanied by corneal vascularization and edema and moderate to severe anterior uveitis (Color Plate 39.22). Fungi have an affinity for the deep corneal stroma and Descemet's membrane, and in severe cases the organisms may invade through the cornea into the anterior chamber. Fungal involvement should be suspected in any corneal ulcer that is associated with plant or organic material; has been treated with corticosteroids; does not heal as quickly as expected; does not vascularize as expected; exhibits a gritty or pigmented surface; develops a plaque, groove, or deep stromal abscess; or if the uveitis present worsens initially when topical antifungal therapy is initiated. Vascularization is usually necessary for the resolution of fungal lesions in the cornea.

■ Clinical Pathology

A diagnosis of superficial fungal keratitis is made when fungal hyphae or yeast are seen on cytologic analysis or cultured from corneal scrapings (Fig. 39.14). A diagnosis with deep keratitis or a stromal abscess may require a full-thickness corneal biopsy from which the fungus is identified using culture or histopathologic evaluation. Unfortunately, some diagnoses of fungal keratitis are made only after enucleation.[84] Fungal culture with susceptibility testing is recommended, but because results are often pending for prolonged periods,

empirical antifungal therapy is required. Recent reports have described the use of confocal microscopy in the standing horse to confirm and assess the depth of fungal keratitis.[93]

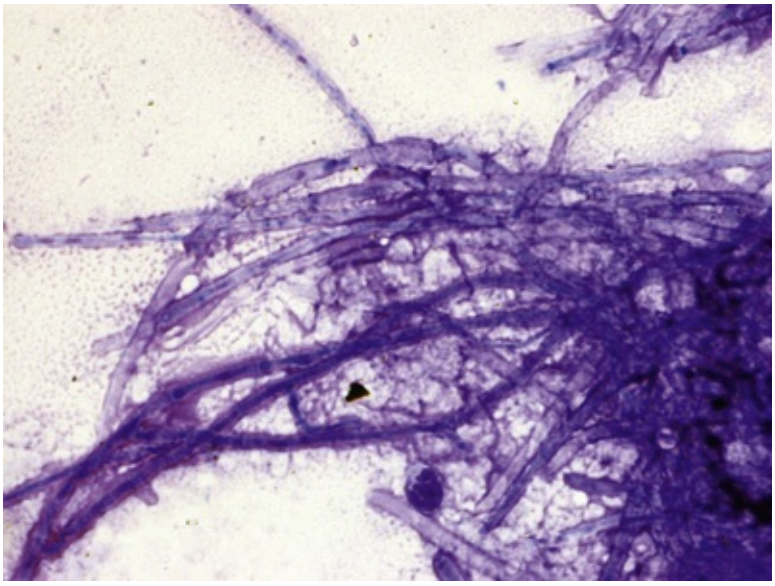


FIG. 39.14 Cytology of fungal keratitis. Diff-Quik, ×100. Note numerous basophilic septate and branching fungal hyphae. A single neutrophil serves as a reference for size of hyphae. (Image courtesy Anne Gemensky-Metzler.)

■ Pathophysiology

Fungal hyphae do not generally colonize intact corneas. An attachment may be initiated if there is a disturbance in the overlying tear film, but damage to epithelium is usually necessary for pathogenic or opportunistic fungi to begin growth in the corneal stroma. This usually results from a traumatic incident that may or may not be noticed by the owner. Use of antibiotics and corticosteroids alters normal flora and decreases the normal immune response, which may encourage fungal growth.[94] Fungi implicated in keratomycoses are usually present in the horse's environment and can be cultured from more than 90% of normal horse eyes, with *Aspergillus* spp. being the most common isolate.[81,95] There is one report in the literature of keratomycosis caused by *Candida albicans* secondary to disseminated candidiasis.[85]

■ Epidemiology

This disease is sporadic, with varying seasonal distribution and worldwide incidence.[81-88,96]

■ Treatment and Prognosis

Keratomycosis in any form typically requires extended medical therapy (generally >6 weeks, sometimes considerably longer), and if stromal loss is detected, early surgical intervention is advisable. Treatment consists of eliminating the fungus from the cornea and controlling secondary bacterial invasion and melting, along with reflex uveitis, as for bacterial keratitis. Subpalpebral lavage systems are usually essential for delivering these drugs. Healing is usually not complete until corneal vascularization has reached the infected area, except when the fungus has reached Descemet's membrane; in these cases blood vessel growth does not always stop fungal growth. Medical therapy is most effective for treating superficial disease. For deep disease, surgical therapy is often necessary in combination with medical therapy. Deep lamellar and penetrating keratoplasty probably carry the best prognosis,[74,75,88,91] although superficial keratectomy with a conjunctival graft can also be used for lesions in the anterior stroma.

A number of antifungal agents are available. Miconazole, used as the undiluted IV preparation, was once the drug of choice for many ophthalmologists. Unfortunately, it is no longer available commercially in this formulation, although it can be compounded. Natamycin (Natacyn) is manufactured as an ophthalmic suspension and is the only commercially available topical ophthalmic antifungal medication approved by the U.S. Food and Drug Administration (FDA). However, natamycin does not penetrate intact epithelium well, and some *Fusarium* spp. may be resistant to the drug.[97,98] Voriconazole administered topically in a 1% solution penetrates intact corneal epithelium and reaches therapeutic corneal concentrations; it has a relatively wide spectrum of action and is efficacious against the common fungal species.[99-101] It is probably the most commonly used antifungal agent presently.

Fluconazole may be used topically or systemically and is generally regarded to have the best penetration of the blood-brain and blood-ocular barriers among the antifungal agents. However, one study reported that fluconazole had lower in vitro activity than a number of other antifungal drugs.[98] The IV preparation is a 2 mg/mL solution, which is used undiluted as a topical preparation. Miconazole

and fluconazole do penetrate intact corneal epithelium when given topically, but drug concentrations in the stroma are higher if epithelium is absent.[102] Fluconazole can also be used subconjunctivally, intracamerally, or intravitreally. Ophthalmologists may use fluconazole systemically to treat deep corneal fungal disease because this drug does reach adequate concentrations in the aqueous humor, which may be appropriate for deep stromal or endothelial infections.[103] No toxicity studies have been performed on the horse, but anecdotal evidence does not suggest toxicities, and fluconazole has been associated with resolution of deep disease in some instances. It is not commonly used, however, because of its relatively narrow spectrum.

Compounded formulations of itraconazole/DMSO ointment have also been used for equine keratomycosis. High concentrations of itraconazole can be achieved in the corneal stroma with this preparation, even when the overlying epithelium is intact, and it has been used successfully in clinical cases.[104] In contrast to fluconazole, systemically administered itraconazole does not penetrate noninflamed equine eyes.[105]

Other drugs have been suggested as treatment for fungal keratitis. Miconazole dermatologic or vaginal creams seem to work for mild superficial disease, but no clinical trials describing their efficacy and safety for ocular use have been reported. Amphotericin B has good antifungal properties but can be very irritating. It is useful for the rare cases in which a yeast is the offending pathogen. In vitro research shows that silver sulfadiazine is fungicidal against isolates from equine patients with keratomycosis.[97] Unfortunately, in vitro results do not necessarily correlate with clinical results in patients with keratomycosis.[106-108] Corneal penetration of the drug, the horse's immune system, and the site and severity of the fungal infection all play important roles in drug choice.[97] The use of newer agents such as posaconazole, caspofungin, and anidulafungin is currently being explored.[109-111]

In addition to topical antifungal agents, therapy should proceed as with any ulcer, with topical antibiotics, antiprotease medications, and atropine, as well as systemic NSAIDs when indicated. Systemic NSAIDs should be used for the secondary uveitis, especially at the beginning of treatment when fungal death can exacerbate uveitis. However, NSAIDs slow vascularization of the cornea, and treatment with these drugs should be decreased as the uveitis is controlled.[79]

Prognosis is guarded to poor in many cases of fungal keratitis. Usually the best possible outcome is a visual eye with some degree of residual corneal

scarring. Because no evidence suggests that corticosteroids decrease the eventual size of the scar, and because they will promote the presence of residual hyphae, their use is not recommended in a healing fungal ulcer. Complications of fungal keratitis include perforation of the ulcer with loss of the eye, superinfection with bacteria, and phthisis bulbi.

Viral Keratitis in Horses

Equine herpesvirus serotype 2 (EHV-2) and serotype 5 (EHV-5) have been isolated from eyes in herd outbreaks of keratoconjunctivitis in horses.[112-116] Clinical signs in one outbreak included photophobia, epiphora and corneal neovascularization, color change, and pinpoint ulcerations; eyes healed within 2 weeks.[112] In another outbreak, conjunctivitis and multifocal superficial corneal opacities were seen; eyes healed within 2 weeks on topical idoxuridine.[113] Experimental inoculation of EHV-2 intranasally in two ponies pretreated with dexamethasone caused conjunctivitis, lymphadenopathy, and coughing.[117] Conjunctivae from both ponies was positive for virus by PCR 6 months after inoculation. EHV-2 can also be isolated from the blood of normal horses,[118] and positive PCR results can be obtained from normal eyes as well as eyes with keratoconjunctivitis, making diagnosis difficult.[116] Miller and colleagues[119] confirmed EHV-2 by fluorescent antibody staining after isolating virus from the cornea of a Thoroughbred mare with multiple superficial punctate corneal lesions. The keratitis was successfully treated with topical 1% trifluridine ophthalmic solution.

Acute cases may be moderately painful (blepharospasm, serous epiphora), with chemosis and conjunctival hyperemia. Recurrence is common and is often associated with corneal vascularization. The superficial or punctuate lesions (epithelial, subepithelial, or anterior stromal) of EHV may or may not retain fluorescein stain. Diagnosis may be difficult, and other differential diagnoses should be considered, including fungal keratitis and immune-mediated keratitis. Therapy for EHV keratitis includes topical antiviral and NSAID therapies. Idoxuridine (0.1%) and trifluridine (0.3%) limit viral replication but do not kill the virus; frequent dosing is required (4 to 12 times daily for 3 to 5 days until the condition stabilizes, then 3 to 6 times daily thereafter). A newer antiviral, 0.5% cidofovir, is effective in cats and requires only twice-daily dosing, but its use in horses has not been reported. Topical NSAIDs such as 0.03% flurbiprofen and 0.1% diclofenac are helpful for secondary uveitis and keratitis, but they should

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be used with caution because they have been reported to cause recrudescence of viral keratitis in human patients. Systemic flunixin meglumine is often helpful to improve comfort. If defects in the corneal epithelium are present, the additional use of a broad-spectrum topical antibiotic agent is indicated to prevent secondary bacterial infection.

Ocular Manifestations of Systemic Disease

Neonatal Septicemia

Neonatal septicemia in calves, foals, lambs, and kids may occur in the first few weeks after birth and may arise from umbilical infection or oral intake of bacteria. Septicemia is especially common in colostrum-deprived neonates. Secondary meningitis, polyarthritis, uveitis, and chorioretinitis may develop. Ocular signs include miosis, aqueous flare with fibrin deposition in the anterior chamber, hypopyon or hyphema, and in severe cases, panophthalmitis. Many different bacteria and fungi are capable of inducing sepsis, particularly in the immune incompetent, but some of the most commonly implicated agents include *Escherichia coli*, *Streptococcus* spp., *Pasteurella* spp., *Salmonella* spp., *Rhodococcus equi*, *Corynebacterium pyogenes*, and *Klebsiella* spp. Therapy should include systemic antibiotics (when possible, based on susceptibility testing) and treatment for uveitis (topical corticosteroids or NSAIDs, topical cycloplegics or mydriatics, and systemic NSAIDs). Prognosis, even for cases treated early, is guarded.[49,120-122]

■ Bovine Herpesvirus Type 1 (Infectious Bovine Rhinotracheitis)

Etiology

Bovine herpesvirus type 1 (BHV-1) may involve the respiratory or reproductive tracts, nervous system, or conjunctiva or may cause widespread systemic disease (see also Chapter 31). Conjunctivitis is the most common ocular manifestation of the disease, and it may occur as an isolated clinical entity or with involvement of other body systems.[123-126]

■ Clinical Signs and Differential Diagnoses

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Although conjunctivitis is frequently bilateral, it can be unilateral. Ocular discharge, initially serous and later becoming mucopurulent, is usually seen without blepharospasm. Chemosis may be severe, especially by 1 week after infection. Both the palpebral and the bulbar conjunctiva are injected, and petechial hemorrhages may occur. Multiple white plaques 0.2 to 0.5 mm in diameter may develop on the palpebral and, to a lesser extent, the bulbar conjunctival surfaces at 1 to 2 weeks after onset of clinical signs. These may coalesce later in the disease (5 to 9 days). Corneal vascularization and perilimbal edema and opacification occur in severe cases. Iridocyclitis (seen as miosis) may occasionally occur in severe cases.

Corneal changes of BHV-1 are differentiated from those of IBK (caused by *Moraxella bovis*) by their peripheral rather than central distribution and lack of corneal ulceration in BHV-1, unless BHV-1 and IBK occur concurrently in the same eye (see the Infectious Bovine Keratoconjunctivitis [IBK] section later). Corneal vascularization and opacification similar to that which occurs in malignant catarrhal fever accompanied by marked signs of anterior uveitis and other signs of generalized vasculitis has been reported occasionally.[127]

Although ocular disease with BHV-1 may occur as an isolated entity, concurrent upper respiratory tract signs, including rhinitis and dyspnea, are common. Affected animals may be pyrexic, and a fall in milk yield may occur. Abortion in pregnant animals may occur following ocular manifestations of the disease.

■ Diagnostic Procedures

BHV-1 can be recovered from infected eyes during the first 7 to 9 days of the disease but infrequently thereafter. Swabs may be taken for viral isolation in cell culture, which is probably the most reliable means of making a definitive diagnosis. Fluorescent antibody techniques may be used on conjunctival scrapings, and serology may be helpful if blood samples can be collected during the acute and convalescent stages of the disease. PCR is also being used. Histopathology to detect intranuclear inclusions is not likely to allow reliable diagnosis of the disease.[126,127]

■ Pathophysiology

Specific strains of the virus usually cause only one form of the disease (e.g., ocular form) in a herd. Ocular infection results in lymphoid hyperplasia, visible

as white plaques. On histology, these are composed of plasma cells and lymphocytes in the conjunctival stroma and subepithelial area. Mild conjunctival epithelial ulceration may occur. During the recovery phase of the disease, diphtheritic membranes secondary to conjunctival necrosis develop on the conjunctival surface.

■ Treatment and Prognosis

Recovery from the conjunctival form of the disease is spontaneous within 10 to 20 days. In certain situations, palliative treatment may be helpful. This is achieved by cleaning the ocular discharge from the lids and applying a topical broad-spectrum antibiotic to prevent secondary bacterial infection. Treatment of the conjunctival form of the disease with topical antiviral agents has not been studied and would rarely be practical or cost-effective.

■ Prevention and Control

Vaccination of susceptible animals is the most effective means to prevent and control the disease. BHV-1 vaccination programs are discussed in Chapter 48.

Bovine Herpesvirus Type 1 (Infectious Bovine Rhinotracheitis) in Goats

Goats are susceptible to BHV-1, which in some cases may result in ocular disease, particularly keratoconjunctivitis. In one goat with ocular signs, conjunctivitis and keratitis with keratoconus were seen 5 days after the onset of severe respiratory illness. BHV-1 virus was isolated from ocular and nasal discharge.[128]

Peste Des Petits Ruminants in Goats and Sheep

Peste des petits ruminants (PPR) is caused by a paramyxovirus of the *Morbillivirus* genus. This highly contagious disease affects both domestic and wild small ruminants and is characterized clinically by fever, diarrhea, depression, polypnea, conjunctivitis, lacrimation, rhinitis, erosive stomatitis, edema of eyelids, photophobia, cutaneous eruption with erythematous areas (especially noticeable in wool-free parts of the body and axilla), and lesions evolving into papules.[129,130] Ocular discharge is initially serous but becomes mucopurulent as secondary bacterial infections, which are common, develop.

Goats tend to be more severely affected than sheep, but both can suffer very high mortality rates, especially immune-incompetent juveniles.[129,130] Also known as *pseudorinderpest*, this disease is found mainly in Africa, Asia, and the Middle East.

Scrapie in Sheep and Goats

The scrapie agent causes a degenerative CNS disease in sheep and less often in goats. Barnett and Palmer[131] described two sheep with scrapie that also had multifocal hyperreflective areas in the tapetum, histologically seen as small areas of retina raised by an accumulation of eosinophilic material between photoreceptors and retinal pigment epithelium. The eosinophilic material was characterized as a complex lipid. It was not shown that scrapie had caused the lesions.[131] Subsequently, using a monoclonal antibody, a goat with natural scrapie was found to have the scrapie prion protein in the retina, without any microscopic retinal lesions.[132] A sheep experimentally infected with scrapie was also found to have prion proteins in the retina,[133] as was a sheep experimentally infected with the prion responsible for bovine spongiform encephalopathy (BSE).[134] Prion proteins can also be found in the nictitating membrane,[134,135] which may permit the antemortem diagnosis of scrapie. (See Chapter 35 for more information on scrapie.)

Bluetongue in Sheep and Cattle

Bluetongue is a disease of ruminants caused by an arbovirus that is transmitted by *Culicoides* gnats. Clinical signs include fever and vasculitis that lead to oral lesions, lameness, swollen face, pulmonary edema, and death (see Chapter 32). In pregnant ewes vaccinated with modified live virus (MLV) on day 40 of gestation, fetuses developed cerebral anomalies.[136] These anomalies have also been described in clinical cases in which ewes had been vaccinated with MLV at about 5 or 6 weeks of gestation. In addition, when the fetus was vaccinated with MLV vaccine between days 50 and 75 of gestation, lesions of retinitis and choroiditis that appeared centered around retinal vessels were noted. In some eyes, inflammatory lesions produced persistent areas of retinal dysplasia.[137]

Conjunctivitis and mucopurulent ocular discharge may be seen in cattle chronically infected with bluetongue virus. Although topical antibiotics could be applied to reduce secondary bacterial infection and reduce the ocular discharge,

this would rarely be necessary.[138] Systemically ill or congenitally infected animals may have anterior uveitis and corneal edema as a result of this infection.[139]

Bovine Viral Diarrhea

The causative agent, bovine viral diarrhea virus (BVDV), is in the genus *Pestivirus*, a member of family Flaviviridae that, in congenitally affected animals, causes retinal inflammation and necrosis. Cattle infected between days 75 and 150 of gestation may produce calves with cerebellar hypoplasia or ocular lesions. Calves with ocular signs may be blind, and nystagmus may be present. Pupillary light reflexes may or may not be absent. Other abnormalities may include microphthalmia, cataract, leukocoria (as a result of either cataract or dense white inflammatory infiltrate in the anterior vitreous), retinal hemorrhages, chorioretinitis, retinal dysplasia or folds, retinal detachment, or optic neuritis or atrophy.[140-143] The optic disk may appear atrophic, and areas of tapetal color change and hyperreflectivity may be seen, with retinal vascular attenuation. In some cases, inflammatory debris may persist in the vitreous after birth, precluding adequate fundic examination. Congenital cataracts also occur in this disease, and although the pathophysiology is unknown, they probably develop secondary to the intraocular inflammation and necrosis. Cataracts mainly involve the lens cortex.

Transplacental infection may occur when the dam is infected during pregnancy. The severity of the disease is related to fetal age at the time of intrauterine infection. Severe fetal disease and often fetal death occur in cattle infected between 50 and 100 days of gestation. Infected fetuses can also survive and become persistently infected with the virus. In these cattle, viral antigens can be found in neurons of the retina and CNS in the absence of clinical signs.[144] Ocular discharge has been reported in cases of acute or chronic cases of BVD, although the significance of these observations is uncertain.[143,145]

Serum samples collected from affected calves before ingestion of colostrum can be submitted for serologic assessment using the serum-virus neutralization test, or virus isolation can be attempted from buffy coat cells of a whole-blood sample collected into EDTA (see Chapter 32).

Bovine Leukosis

Lymphosarcoma in adult cattle is usually caused by bovine leukemia virus

(BLV), although noninfectious sporadic cases are reported in young animals. Lymphosarcoma is the most common orbital neoplasm in cattle and may result in unilateral or bilateral progressive exophthalmos.[146,147] If undiagnosed, exposure keratitis and chemosis develop. Intraocular involvement can occur, although this is less common than orbital neoplasia. Generalized lymphadenopathy or other signs of generalized lymphosarcoma usually accompany the orbital form. Specific serologic tests for BLV will confirm the diagnosis. Enucleation or exenteration is rarely indicated because of the poor systemic prognosis for affected animals. Differential considerations for progressive exophthalmos include orbital cellulitis, in some instances due to actinomycosis or actinobacillosis, frontal or maxillary sinusitis, or nasal or orbital neoplasia (especially squamous cell carcinoma).

Tuberculosis in Cattle

Tuberculosis caused by *Mycobacterium bovis* may cause granulomatous lesions in the eye of affected cattle. The uveal tract (iris, ciliary body, or choroid) is initially affected, with later expansion of granulomas into other ocular structures. Uveitis, keratitis, and chorioretinitis with retinal detachment are seen clinically.[148]

Malignant Catarrhal Fever

Malignant catarrhal fever (MCF) is a sporadic disease characterized by fever, lymphadenopathy, and generalized vasculitis resulting in inflammation of the mucosal membranes of the mouth, nose, and eye; the skin; and the GI and nervous systems, with variable but usually high mortality. The African form is caused by alcelaphine herpesvirus type 1. The North American form is caused by a similar virus, ovine herpesvirus type 2.[149,150]

Various forms of the disease are described on the basis of clinical signs (see Chapter 32). Ocular involvement is seen in the acute “head and eye” form, which is the most common presentation of the disease. Ocular signs include photophobia, epiphora, episcleral injection and scleritis, severe conjunctivitis, perilimbalcorneal edema and vascularization, anterior uveitis, and exophthalmia. Less significantly, and difficult to diagnose clinically, retinal vasculitis may develop. Corneal edema and anterior uveitis were the most commonly reported ocular signs in a recent report of cows with MCF.[151] The degree of corneal edema at initial examination did not correlate with survival; however, the

resolution of corneal edema and uveitis was associated with survival. Corneal edema and uveitis progressed despite supportive care in animals that did not survive. Bullous keratopathy may develop as a result of edema in the anterior cornea, with subsequent rupture of bullae to form painful corneal erosions.[152] The absence of central corneal ulceration distinguishes the disease from IBK, and the severity of the ocular lesions is worse than would be expected with BHV-1, BVDV mucosal disease, or bluetongue. Differentiating this disease from rinderpest could be clinically difficult in areas where both are endemic in cattle.

Serology and PCR are being used to confirm the clinical diagnosis.[153,154] The microscopic ocular lesions are those of a nonsuppurative uveitis and vasculitis. The lesions involve the conjunctiva, cornea, anterior uvea, and retinal blood vessels; the choroid is rarely involved. Serofibrinous and cellular infiltrates develop in the uvea and retina as a result of vasculitis and thrombosis. Perivascular cuffing and optic neuritis may be detected histologically.[155-157]

Prognosis for the eyes and the animal's recovery is poor.[152,158] Most importantly, in endemic areas cattle should be kept away from sheep, which may act as a reservoir for the disease, and affected animals should be isolated.[159]

Thromboembolic Meningoencephalitis

Thromboembolic meningoencephalitis (TEME) is a fatal septicemia caused by infection with *Histophilus somni* (see Chapter 35). Calves and young adult cattle can be affected, but the disease most often occurs in feedlot cattle younger than 1 year of age. The organism is capable of damaging vascular endothelial cells and activating blood clotting. Therefore most of the ocular histologic signs are related to thrombosis of retinal vessels.

Although conjunctivitis may be seen, the main ocular findings are in the fundus. Retinal hemorrhages and exudates may be focal or diffuse. Retinal infiltrates may elevate the retina and involve the vitreous. Retinal edema, hemorrhage and necrosis, vascular thrombosis, and infiltration of the retina and vitreous with neutrophils are seen histologically. Eosinophilic cytoid bodies (swollen axons) are seen in the nerve fiber layer of the retina. Retinal detachments may result from retinal edema. Later in the disease, areas of chorioretinitis result in chorioretinal scars. The anterior segment is less involved in this disease than in MCF, in which keratitis and anterior uveitis are usual.[160,161]

Leptospirosis in Horses and Cows

Leptospirosis is caused by a filamentous bacterium known as a *spirochete.* Disease is seen in most domestic animals as well as humans. Various serovars of *Leptospira interrogans sensu stricto, Leptospira kirschneri,* and *Leptospira santarosai* have been shown to affect various organs (e.g., kidneys, liver, spleen, muscles, CNS, eyes) and have been associated with abortions.[162] These organisms primarily cause a vasculitis and endotheliitis in these organs.[163]

Because leptospiral organisms cause vasculitis, it is reasonable to assume that uveitis may be present in an acute infection, and this has been reported in horses during the acute phase of leptospirosis.[164] Uveitis has also been seen experimentally in a calf during acute disease.[165] However, the role of leptospires in uveitis seen weeks to months after the acute disease remains much more controversial. Evidence for such a role is most complete in the horse, in which leptospiral uveitis and its role in equine recurrent uveitis (ERU) or "periodic ophthalmia" have been described.[166-168] ERU is an immune-mediated disorder that is the leading cause of blindness in horses (see the Immune-Mediated Ocular Diseases section later). Although the recurrent episodes of ERU are not directly caused by reinfection with microorganisms or parasites, numerous bacterial, viral, protozoal, and parasitic organisms have been implicated in the initiation of the syndrome. In one outbreak of leptospirosis on a small farm, uveitis was not seen until 18 to 24 months after the acute outbreak of leptospirosis. Treatment with systemic antibiotics did not seem to affect the uveitis. In that study, serum titers to *Leptospira interrogans* serovar *pomona* often remained high for at least 6 years.[166] In another study, uveitis was seen in 22 eyes of 18 ponies experimentally infected with *L. interrogans* serovar *pomona*. The earliest sign of uveitis was seen at 1 year after inoculation. Cataract formation and posterior synechiae were also seen, as were recurrences of overt uveitis.[167]

Recently, leptospiral organisms have been identified using PCR[168] or by culture[168-170] in the eyes of horses with ERU. A study in California using a PCR assay for *Leptospira* showed that 30 of 55 eyes (21 of 30 horses) with ERU had detectable *Leptospira* DNA in their aqueous humor.[168] In other studies, treatment with systemic antibiotics did not decrease the inflammation.[170-172] In Western Europe a total of 618 vitreous and/or aqueous samples were taken from the eyes of 501 horses with either active ERU or a history of ERU. Leptospires were isolated from 199 (32.2%) of the samples. Most belonged to serogroup

grippotyphosa, with the rest in serogroup *australis, sejroe, pomona,* or *javanica.*[169] In contrast, 36 samples of vitreous from 21 normal horses did not grow leptospires.[170] Although leptospires are involved in ERU in many horses with this syndrome, controlling or treating this disease remains a problem. The best means of symptomatic control of ERU at this time appears to be the use of ocular bioerodible cyclosporine A implants that are surgically placed within the suprachoroidal space, with the goal of controlling immune-mediated intraocular inflammation.[173] In the same study, cyclosporine was been shown to be toxic to *L. interrogans* in vitro at the same concentration that was achieved in uveal tissue with the suprachoroidal implant.[173] (See also the Equine Recurrent Uveitis section later.)

Listeria Monocytogenes in Sheep, Cattle, and Horses

Listeriosis in ruminants is manifested mainly as either an encephalitis or a septicemia in neonates, or as a reproductive problem manifested by abortion. Ocular signs with the neural form include facial nerve paralysis and ptosis, often unilateral, on the side of the central lesion; medial strabismus, often on the ipsilateral side because of involvement of the abducens nucleus; nystagmus; and amaurosis.[174] Uveitis with hypopyon has been described in chronic cases.[175]

Listeria monocytogenes has been cultured from conjunctival smears taken from sheep and cattle with keratoconjunctivitis.[176] In most of the sheep, *Branhamella (Neisseria) ovis* was also cultured. Clinical signs included conjunctival hyperemia, epiphora, photophobia, and corneal opacification. Treatment with topical chlortetracycline was curative. Walker and Morgan[177] describe two sheep that developed unilateral anterior uveitis. *L. monocytogenes* was cultured from the conjunctiva of each animal. Both animals recovered after treatment with parenteral ampicillin and topical antibiotics. *L. monocytogenes* has been cultured from the conjunctivae of three cows with keratitis (one with keratitis and uveitis) and from a corneal scraping of one horse with keratitis.[178] *L. monocytogenes* has been cultured from the cornea and conjunctiva of horses with chronic keratitis and keratoconjunctivitis.[179,180] Early treatment with broad-spectrum antibiotics may be effective in some cases.

Rabies

Rabies remains one of the most serious zoonotic diseases today.[181] It can affect

any mammal, and reports of rabies disease and death have been reported in all of the large animal species of concern in this chapter.[181,182] Ophthalmic signs of rabies are usually secondary to systemic illness and neurologic impairment and may include prolapse of the nictitating membrane, strabismus, nystagmus, and vision loss.[181-185] Prevention is the best approach to disease control, since affected animals must necessarily be destroyed once affected.[186] Fortunately, preexposure vaccination is highly effective, and postexposure (before the development of clinical signs) prophylaxis (immediate vaccination against rabies, a strict isolation period of 90 days, and administration of booster vaccinations during the third and eighth weeks of the isolation period) may be effective in unvaccinated domestic animals if administered promptly.[186]

Other Bacterial Disease in Horses

Salmonella spp. cause one of the more common and serious bacterial enteritides in foals and adult horses. It is often accompanied by septicemia in foals. Anterior uveitis and hypopyon have been seen in animals with salmonellosis, and *Salmonella* spp. can sometimes be cultured from these eyes.[187]

R. equi is a gram-positive coccobacillus that causes bronchopneumonia in young foals.[187-189] The systemic inflammatory response may result in a fibrinous anterior uveitis. Therapy involves systemic treatment of the pneumonia and topical and/or systemic antiinflammatory treatment for the uveitis.

Strangles is a respiratory infection caused by *Streptococcus equi* subsp. *equi* that can have an accompanying ocular discharge.[190] Chorioretinal depigmentation was noted in the nontapetal fundus of several horses in one group clinically diagnosed with strangles. Because these lesions repigmented with time, it was suggested that they were caused by embolism to the choroid during bacteremia.[191] One case of panophthalmitis caused by *S. equi* in a horse has been described.[192] Ten days after a bout of strangles, this horse developed anterior uveitis that progressed to corneal stromal abscesses and panophthalmitis. *S. equi* was cultured from the eye at enucleation. *S. equi* has also been isolated from infected corneal wounds in horses without systemic signs of strangles. These cases are treated aggressively, as with any bacterial keratitis.

Brucella abortus has been suggested as a cause for ERU,[187] although serum agglutination titers for *B. abortus* in normal horses and horses with ERU are

similar.[193] This organism is certainly capable of inducing intraocular inflammation, although its role in recurrence or persistence of uveitis is unknown.

A case of anterior uveitis and bilateral chorioretinitis with retinal detachments has been described in a horse from Denmark as a result of a mycobacterial infection. Acid-fast organisms were seen in both eyes as well as in numerous other organs. *Mycobacterium avium* was cultured from these organs.[194]

Other Viral Diseases in Horses

Equine adenovirus is a DNA virus that causes bronchopneumonia (type 1) or GI signs (type 2) in foals, especially if they are immunodeficient. Mucopurulent nasal and ocular discharge accompanies the respiratory system disease. Histologically, swelling and necrosis of conjunctival cells with intranuclear inclusions are seen, with accumulation of neutrophils in the lumina and adventitia of uveal blood vessels.[195] Treatment of the conjunctivitis is supportive, with lubricants and anti-inflammatory medications.

Equine viral arteritis is a rare disease caused by an RNA virus classified as Arteriviridae. Most animals are subclinically infected, but ocular and nasal discharge, rash, pyrexia, rhinitis, leukopenia, edema (palpebral, periorbital, limb, or ventral), and abortions and neonatal death are seen.[196,197] Corneal opacity and photophobia have also been described.[198] The virus characteristically causes a panvasculitis.

Borrelia burgdorferi, the agent of Lyme disease, has been most often described as causing polyarthritis in horses, cows, and dogs. However, one case of ocular disease has been reported in a pony infected with *B. burgdorferi*.[199] Unilateral anterior and posterior uveitis was noted, and spirochetes were found in the anterior chamber. Other clinical signs included arthritis and synovitis of both carpal joints. Some discuss this agent as a potential contributor to chronic immune-mediated uveitis (ERU).

Equine herpesvirus serotype 1 (EHV-1) is a cause of rhinopneumonitis in horses. It has been cultured from cases of superficial punctate keratitis in the horse; the significance of these isolations is unknown.[200] Six foals were experimentally inoculated intranasally with EHV-1.[201] All developed typical mild signs of upper respiratory infection. One foal developed vision problems 1 month after inoculation. Bilateral chorioretinitis was diagnosed. Necropsy findings included chorioretinal degeneration and demyelination of the optic

nerve and mononuclear cell infiltrate in parts of the choroid, retina, and CNS.[201] These findings are not surprising in that EHV-1 causes vasculitis and CNS disease in horses.[202] Retinal detachments and optic neuritis are possible as well. Treatment is not usually successful.

African Horse Sickness is caused by an orbivirus that is transmitted by *Culocoides* insects. It results in profound bulging of the supraorbital fossa, the soft tissue depression above the dorsal orbital rim, which is considered a hallmark of this disease.[203,204] This swelling is due to retrobulbar edema and increased vascular pressure. Chemosis and protrusion of the conjunctiva from between the palpebral fissure is often seen as well. The systemic disease is characterized by either respiratory and/or cardiac impairment and has a high rate of mortality.[203,204] Control of an outbreak in an endemic region (Africa, Middle East) involves quarantine and usually euthanasia of affected animals, vector control, and vaccination of unaffected animals.[203,204]

Equine influenza is one of the most common infectious diseases of the respiratory tract of horses. It is endemic in the equine population of the United States and throughout much of the world. This condition is highly contagious, and the virus spreads rapidly through groups of horses in aerosolized droplets dispersed by coughing. Clinical signs begin abruptly and include fever, serous nasal discharge, submandibular lymphadenopathy, and a harsh, dry, nonproductive cough.[205] Ocular signs are secondary and are usually limited to conjunctivitis with serous to mucopurulent ocular discharge.[205] The severity of clinical signs depends on the degree of existing immunity, among other factors.[206] Younger animals are most susceptible, but immunity in an older horse can be overwhelmed in animals frequently exposed at shows.[205] Vaccination of at-risk individuals is recommended.

Viral encephalitis caused by either Eastern equine encephalomyelitis (EEE) virus, Western equine encephalomyelitis (WEE) virus, or Venezuelan equine encephalomyelitis (VEE) virus is borne and transmitted by mosquito vectors and often has a seasonal presentation.[207] Any and all signs attributable to cortical and thalamic lesions may be seen with these conditions. Neurologic deficits may be asymmetric, since lesions are not necessarily symmetrically distributed. Clinical signs include altered mentation, aimless wandering, head pressing, circling, inability to swallow, irregular ataxic gait, paresis and paralysis, convulsions, and death. Ophthalmic signs include vision loss, nystagmus, strabismus, mydriasis, and abnormalities of PLRs.[207] In contrast, neurologic lesions with West Nile

virus (WNV) encephalomyelitis are more prevalent in the brainstem and spinal cord than in the cortical and thalamic regions.[208-210] Thus horses with WNV may present with signs of spinal cord ataxia, hyperesthesia, and muscle fasciculations as well. Ophthalmic signs may include vision loss, facial paralysis (with secondary exposure keratitis), anterior and/or posterior uveitis, and optic neuritis.[208-210] There is no specific therapy for viral encephalitis. Symptomatic support might include fluid therapy, antiinflammatory agents if indicated, and anticonvulsants if necessary. Topical lubricants for the eyes may be necessary.

Cryptococcosis, Histoplasmosis, and Aspergillosis in Horses

Cryptococcus neoformans is a pathogenic fungus that may cause systemic infection in horses and other mammals. Ocular signs are not usually reported in horses with cryptococcosis, although there are reports of frontal sinus granuloma with retrobulbar mass causing exophthalmos, periorbital swelling, blindness, and optic neuritis.[211-212] The chorioretinitis associated with *C. neoformans* seen in other species has not been described in the horse, cow, or small ruminant. *Cryptococcus albidus* has been cultured from the cornea of a horse with chronic keratitis.[213] Diagnosis is based on histopathologic evidence of fungal hyphae in tissue samples or on cytology, as well as a positive culture.

Histoplasma farciminosum, a fungal agent found mainly in Africa, is responsible for epizootic lymphangitis, a disease manifested with nodules and draining lesions of the subcutaneous lymphatic system.[214] A conjunctival form of this disease results from deposition of the organism on the ocular mucous membranes by biting flies. Ocular signs include serous to mucopurulent discharge, blepharedema, and conjunctival papules. Disease progression leads to ulceration of the papules, which may result in secondary keratitis and/or obstruction and erosion of the lacrimal duct. Diagnosis is mainly by cytologic analysis and culture, although serologic assays are also available. Amphotericin B is the treatment of choice, and a vaccine is available for horses in endemic areas. Organisms consistent with *Histoplasma* spp. were seen on cytology of a corneal scraping taken from a horse with chronic keratitis.[215] This horse was successfully treated with topical fluconazole.

Aspergillus spp. are considered opportunistic fungi that rarely cause systemic disease in immunocompetent horses. Aspergillosis may be a cause of guttural pouch mycosis and may also occur secondary to chronic obstructive pulmonary

disease.[216,217] Associated ocular signs can include Horner's syndrome, facial nerve palsy, and blindness resulting from ischemic optic neuritis secondary to extension of disease.[216] These organisms are ubiquitous in the environment, and horses are frequently exposed. Treatment with systemic antifungal agents may be attempted, but the prognosis is guarded and dependent on the underlying disease process and severity of the lesions. In contrast to the systemic form of the disease, local *Aspergillus* infections in the cornea are common (see the Fungal Keratitis in Horses section earlier).

Infectious Bovine Keratoconjunctivitis (IBK)

John A. Angelos

Infectious bovine keratoconjunctivitis (IBK), or “pinkeye,” is the most common ocular disease of cattle and has been identified in cattle populations worldwide. The clinical signs of IBK include corneal ulceration, corneal edema, photophobia, blepharospasm, and lacrimation (Color Plate 39.23). In less severely affected animals, recovery with or without permanent corneal scarring occurs. In the most severely affected animals, corneal rupture and lens or iris prolapse may occur, causing permanent blindness. IBK is most common in calves, typically affecting one eye, although both eyes may be affected. Estimates of annual incidence of IBK are 5% of all beef cattle, with more than 50% of herds affected.[1] Epizootic outbreaks occur, with case attack rates approaching 90% to 100% of yearling cattle.[2,3] Cattle of all breeds may be affected; however, a higher incidence is reported in Herefords,[4] and a lower incidence is reported in Brahmans and cattle with more pigmentation at the ocular margins.[5,6]

Genetic investigations of cattle affected with IBK have suggested the presence of loci that are associated with IBK.[7,8] Hereford-Friesian crossbred calves with full eyelid pigmentation had a lower incidence of IBK versus calves with less than total pigmentation.[9] Five single nucleotide polymorphisms (SNPs) on bovine chromosome 20 that are significantly associated with IBK have also been identified.[10] A relationship was also reported between a specific SNP in the Toll-like receptor 4 gene and the rate of IBK infection in Angus cattle.[11]

■ Economic Impact

Cattle with IBK have reduced weight gain that results in economic losses to

producers. Postweaning 205-day weights of bulls and heifers with IBK showed losses of 36 and 40 pounds (16 and 18 kg), respectively, over unaffected herdmates.[12] In 1169 pasture-raised calves over a 4-year period, the average weight reduction was 11 pounds (5 kg) for calves with IBK in one eye and 35 pounds (15.75 kg) for calves with IBK in both eyes.[13] A study of more than 45,000 health records of weaned calves demonstrated almost 20-pound (9-kg) lighter weaning weights in calves diagnosed with IBK versus healthy calves.[4] A retrospective population-based cohort study of approximately 1800 Angus calves over a 7-year period indicated that yearlings with evidence of IBK at weaning had reduced twelfth rib fat depth, ribeye area, and body weight versus cohorts without IBK.[14] The economic losses from reduced weight gain along with treatment-associated expenses accounted for annual losses in the United States that many years ago were estimated to be $150 million.[15]

■ Etiology and Epidemiology

Moraxella bovis is the only organism for which Koch's postulates have been fulfilled with respect to IBK[16]; however, other viruses and bacteria have been associated with IBK, including infectious bovine rhinotracheitis (IBR) virus[17,18] and *Mycoplasma* spp.[19,20] These organisms may increase risk for IBK by enhancing opportunities for corneal injury[21-23] and increasing ocular and nasal discharge, which may facilitate transmission of *Moraxella bovis*. In an outbreak of IBK in young calves, *Mycoplasma bovoculi* and *Mycoplasma bovis* were isolated from affected animals, whereas *Moraxella bovis* was not isolated.[24] In a recent study, IBR exposure as indicated by positive BHV-1 titer was not found to predispose calves to developing IBK in a herd where *Moraxella bovis* was present.[25]

For many years, a role for hemolytic gram-negative cocci in IBK pathogenesis has been suggested from the observations of researchers in the field. In 1966 hemolytic gram-negative cocci were isolated from calves with severe keratitis and corneal ulceration.[26] In Australia, *Neisseria* species were isolated in 24 of 25 outbreaks of IBK; *Moraxella bovis* was identified in only two of these outbreaks.[27] *Neisseria* (*Branhamella*) *catarrhalis* was reported in almost 45% of IBK cases, whereas *Moraxella bovis* was isolated from only 28% of IBK cases.[28] *Moraxella bovis* and *Neisseria* species were also cultured from normal eyes of cattle.[29,30] *Moraxella ovis* and *Neisseria ovis* were also reported from

cattle in Israel with IBK.[31,32] *Neisseria ovis* experimentally inoculated into the eyes of calves did not cause lesions typical of IBK, despite previous corneal irradiation.[33] *M. ovis* was reported in mule deer with keratoconjunctivitis, although experimental inoculation of *M. ovis* isolates into eyes of mule deer fawns did not cause IBK.[34] Recently, hemolytic and cytolytic activity from culture filtrates of *M. ovis* isolated from cattle with IBK has been described, suggesting a possible role for bacteria other than *Moraxella bovis* in the pathogenesis of IBK.[35]

During an IBK drug efficacy trial during summer 2002 in northern California, the majority of bacterial isolates from IBK-affected calves were found to be hemolytic gram-negative cocci.[36] Genetic and biochemical characterization of these isolates subsequently identified these organisms as a novel species that was distinct from *Moraxella bovis* and *M. ovis*; it was named *Moraxella bovoculi*.[37] It is likely that *Moraxella bovoculi* has circulated within cattle populations for many years, and until this gram-negative coccus had been shown to be distinct from *M. ovis*, it may have been misidentified by diagnostic laboratories as *M. ovis, Branhamella ovis*, *M. ovis*–like, or *B. ovis*–like. A weak causal role for *Moraxealla bovoculi* (as well as for *Moraxella bovis*) was reported in a cohort study that looked for *Moraxella bovis, M. ovis*, and *Moraxella bovoculi* DNA in swabs from eyes of beef calves.[38] However, in an experimental challenge study using a corneal scarification model for infection with the type strain of *Moraxella bovoculi*, corneal ulceration could not be demonstrated.[39] A point prevalence study that evaluated ocular flora in animals from herds in varying stages of IBK outbreaks for the presence of DNA from *Moraxella bovis*, *M. ovis*, *Moraxella bovoculi*, *Mycoplasma bovoculi*, and *Mycoplasma bovis* determined that *Moraxella bovoculi* was the only organism that correlated with clinical signs of IBK.[40] In that study, herds with high *Mycoplasma bovoculi* were more predisposed to IBK outbreaks, and authors postulated that there may be synergistic interactions between *Mycoplasma bovoculi* and *Moraxella* spp. in IBK. During 2010 to 2013 *Moraxella bovoculi* was the most frequently isolated organism from IBK-affected cattle in the central United States.[41] When the microbial community in the eyes of a cohort of calves (some of which subsequently developed IBK and some of which did not) were examined using high-throughput sequencing of 16S ribosomal RNA, *Moraxella* was found to be among the top 10 most abundant genera; however, the difference in abundance between calves that never developed IBK and those that did was not

significant.[42] Marked genetic differences were determined after whole genome sequence analysis of *Moraxella bovoculi* from cattle with IBK and from nonocular sites in asymptomatic cattle; these data suggest the presence of genetically distinct strains of *Moraxella bovoculi*.[43] In a study of ocular flora from normal goats, *Moraxella bovoculi* was the most common single bacterial species isolated.[44]

In addition to bacterial infection, other risk factors for IBK include flies, solar irradiation, and mechanical trauma from plant awns. *Moraxella bovis* survives up to 3 days on the external surface[45] and 2 days in the gut[46] of face flies *(Musca autumnalis)*. IBK was experimentally induced in cattle that were exposed to face flies that had fed on *Moraxella bovis* cultures.[47] Insecticide-impregnated ear tags or back and face rubbers to reduce fly populations have proved effective in reducing IBK in cattle populations.[48] An association between solar irradiation and IBK has also been documented.[49-51] Corneas of calves exposed to UV irradiation incur corneal epithelial cell degeneration[52] that predisposes eyes to establishment of *Moraxella bovis* and IBK. An experimental model for IBK has been developed in which calves are exposed once daily for 2 or 3 days to UV irradiation using sunlamps held 24 inches (60 cm) from the corneal surface; after the last exposure, animals are infected by instillation of *Moraxella bovis* into the eye.[53-55] Plant awns have been associated with IBK, most likely through direct mechanical damage to the cornea that facilitates infection with *Moraxella bovis* and subsequent development of IBK.

Hemolytic strains of *Moraxella bovis* are considered pathogenic. Nevertheless, nonhemolytic, nonpathogenic *Moraxella bovis* can be isolated from normal cattle,[2,56-58] from cattle exhibiting conjunctivitis,[59] and simultaneously with hemolytic *Moraxella bovis* from cattle with IBK.[58] Outbreaks of IBK typically occur annually during summer months, and such outbreaks were postulated to be caused in part by cattle harboring *Moraxella bovis* subclinically.[58,60]

■ Pathophysiology of *Moraxella Bovis*

Moraxella bovis produces many hydrolytic enzymes that may be important in facilitating ocular injury, including C4 esterase, C8 esterase-lipase, C14 lipase, phosphoamidase, phosphatase, leucine and valine aminopeptidases, and gelatinase.[61] To date, however, only two *Moraxella bovis* proteins have been

linked to pathogenicity: pili and cytotoxin. Pilin proteins of *Moraxella bovis* are of the *N*-methylphenylalanine type (type IV pili[62-64]) and enable bacteria to adhere to the corneal epithelium and colonize the surface of the cornea.[65-67] *Moraxella bovis* is capable of forming biofilms through formation of type IV pili, and disruption of these pili prevents biofilm formation.[68]

The *Moraxella bovis* cytotoxin (cytolysin/hemolysin) is a pore-forming protein that is also considered necessary for pathogenesis. Broth supernatants of hemolytic strains of *Moraxella bovis* will cause lysis of bovine erythrocytes, neutrophils, lymphoma cells, and corneal epithelial cells in vitro.[69-72] The lytic activity of *Moraxella bovis* cytotoxin occurs through calcium-dependent formation of transmembrane pores in target cell membranes.[73] Ocular lesions induced by a purified hemolytic and cytolytic fraction of *Moraxella bovis* are identical to the ocular lesions observed in naturally occurring IBK; extracts from nonhemolytic *Moraxella bovis* do not cause corneal lesions.[74]

An association between the *Moraxella bovis* cytotoxin and the RTX (***r***epeats in the structural ***t***o***x***in) family of bacterial exoproteins followed the discovery that *Moraxella bovis* cytotoxin induces the formation of pores in target cell membranes.[73] It was subsequently shown that an approximately 110-kilodalton protein in concentrated culture supernatants from cytolytic *Moraxella bovis* cultures could be recognized by a monoclonal antibody to HlyA, an RTX toxin of uropathogenic *E. coli*.[75] The presence of RTX toxins has been reported in numerous animal pathogens, including *Mannheimia haemolytica*, the agent of shipping fever pleuropneumonia in cattle[76]; *Actinobacillus pleuropneumoniae*, an agent of swine pleuropneumonia[77]; *Pasteurella aerogenes*, an abortifacient in swine and other mammals[78]; and *Actinobacillus equuli*, associated with foal septicemia.[79] Enterohemorrhagic *E. coli* O157:H7 also harbors a plasmid-encoded RTX toxin.[80]

The best-characterized RTX toxin is HlyA of uropathogenic *E. coli*. The gene encoding this toxin is assigned the abbreviation *hlyA* and is contained within a four-gene operon organized 5'-C-A-B-D-3'. The product of the RTX A gene is a structural toxin that must be activated by the RTX C gene product to become hemolytic.[81-83] The activation occurs through fatty acylation of conserved lysine residues.[84,85] After activation the toxin is secreted by membrane transport proteins encoded by the B and D genes and a third protein, TolC.[86,87] The regulation of transcription through the RTX operon in *E. coli* is a complex

process and involves the protein RfaH and JUMPStart DNA sequences.[88] As with *E. coli* hemolysin, the *Moraxella bovis* cytotoxin gene *(mbxA)* is contained within an RTX operon (*mbx* operon) that encodes activation and export proteins; this operon is absent in nonhemolytic *Moraxella bovis*.[89] The *mbx* operon defines a pathogenicity island, and acquisition or loss of *mbx* genes may explain the ability of *Moraxella bovis* to change from the hemolytic to nonhemolytic phenotype.[90] *Moraxella bovoculi* and *Moraxella ovis* have also been shown to encode RTX toxins that reside within classical RTX operons.[91] Near-complete identity between the deduced amino acid sequences of cytotoxin genes and geographically diverse *Moraxella bovis* isolates has been reported and demonstrates that there is a high degree of conservation in the gene encoding this important pathogenic factor.[92]

■ Immunity to *Moraxella Bovis*

Secretory IgA is the major immunoglobulin found in normal bovine lacrimal secretions.[93] During experimentally induced IBK, tear IgG1 and IgG2 concentrations increase.[94] Early studies suggested that calves with more severe IBK had higher lacrimal IgA titers to crude *Moraxella bovis* antigen preparations than calves with less severe IBK.[95] A subsequent study identified a predominant tear IgG response to a crude, whole-cell *Moraxella bovis* antigen in calves with naturally occurring IBK and concluded that *Moraxella bovis*–specific antibodies in lacrimal secretions did not prevent IBK in calves.[96] Enzyme-linked immunosorbent assay (ELISA) has been used to quantify nonspecific *Moraxella bovis* antigens in tears and has revealed that IgA titers are higher than IgG titers.[97] A study on a small number of calves then suggested that both lacrimal (secretory IgA) and humoral (IgG) antibodies against *Moraxella bovis* whole-cell antigen conferred resistance against IBK, versus a humoral IgG antibody response alone.[98] It was concluded that serum antibodies against *Moraxella bovis* may account for a reduction in the length and severity of clinical signs associated with IBK. Unfortunately, none of these studies adequately controlled for total antibody isotypes present in serum or ocular secretions. In addition, crude *Moraxella bovis* antigen preparations were used in these assays.

■ Experimental Vaccination

Early studies that reported reduced *Moraxella bovis* infection rates and

decreased occurrence of IBK after reexposure to *Moraxella bovis* indicated that vaccination against IBK might prevent disease.[50] Subsequent work showed that calves vaccinated intramuscularly with live *Moraxella bovis* had less severe IBK after challenge.[99] Formalin-killed *Moraxella bovis* was also reported to be as effective as live cultures in preventing experimentally induced IBK[100]; under field conditions, however, a formalin-killed autogenous bacterin was not efficacious.[101]

In an effort to identify other candidate *Moraxella bovis* vaccine antigens, researchers began to examine the use of component or subunit vaccines to prevent IBK. In early studies, *Moraxella bovis* pilin antigens were found to protect calves from homologous challenge.[102] Purified *Moraxella bovis* ribosomes were not protective.[103] Bacterin-containing pili plus corneal-degrading enzymes were protective in field trials, and protection was correlated with the corneal-degrading enzyme level in the vaccine.[104] In that study, however, the exact composition of corneal-degrading enzymes was not reported. In a later study, two commercial *Moraxella bovis* pilus-based vaccines were not protective for calves in a heterologous challenge model.[105] Although pilin is immunogenic, there is marked antigenic diversity between different pilus types because of the presence of two structural pilin genes and variability in the amino acid composition of the pilin molecule caused by inversions within pilin genes.[66,67,106,107] Limited antigenic cross-reactivity was reported between heterologous pili,[108,109] and emergence of novel pilus types can precipitate IBK outbreaks.[110] Such antigenic variability is believed to reduce the overall efficacy of pilus-based vaccines. Nevertheless, more recent work has demonstrated conserved epitopes across different pilus types,[111,112] suggesting a possible future role for conserved pilus antigens in IBK vaccines. In Australia, the prevalence of a limited number of pilus antigens in *Moraxella bovis* suggests that the use of vaccines containing certain broadly represented pilus types may help reduce losses associated with IBK.[113]

Unlike pili, the *Moraxella bovis* cytotoxin is more conserved across different *Moraxella bovis* strains. IBK-affected cattle were shown to develop systemic immune responses to cytotoxin,[114-117] and antihemolysin antibodies to one *Moraxella bovis* strain neutralized hemolysin from 33 different strains of *Moraxella bovis*.[117] A partly purified cytotoxin vaccine also protected calves against IBK after challenge with heterologous *Moraxella bovis*.[114] These reports

suggest a role for a cytotoxin-based vaccine to prevent IBK from multiple *Moraxella bovis* strains, which could therefore be superior to traditional pilus-based vaccines.

Methods to partially purify the *Moraxella bovis* cytotoxin have been published,[118] and its efficacy in a vaccine to prevent IBK has been demonstrated.[119] Calves vaccinated with the recombinant carboxy terminus of *Moraxella bovis* cytotoxin had a lower cumulative proportion of ulcerated eyes compared with saline and adjuvant control calves.[120] Along with recombinant *Moraxella bovis* cytotoxin, other recombinant cytotoxin-based vaccines to prevent IBK have been investigated, including recombinant *Moraxella bovis* pilin plus cytotoxin,[121] recombinant *Moraxella bovoculi* cytotoxin,[122] and recombinant *Moraxella bovis* pilin-cytotoxin plus recombinant *Moraxella bovoculi* cytotoxin.[123] Trends for reduced IBK in calves vaccinated with recombinant *Moraxella bovis* cytotoxin suggest promise for such recombinant vaccines, but it is likely that additional protective antigens will need to be included in such vaccines to increase their efficacy against IBK.

Although the vast majority of IBK vaccine trials have evaluated vaccines administered by a parenteral route, the use of mucosal routes of vaccine delivery has been investigated. In one study, aerosol vaccination of cattle with uncharacterized *Moraxella bovis* antigens was reportedly effective against IBK.[124] Intranasal *Moraxella bovis* pilin vaccines stimulated pilin-specific IgA in ocular secretions; the presence of such antibodies, however, could not be correlated with prevention of *Moraxella bovis* ocular infection or the development of IBK lesions.[125] An experimental intranasal recombinant *Moraxella bovis* cytotoxin-based vaccine has been developed[126,127] that appears to reduce severity of corneal ulceration associated with IBK.[128]

■ Diagnosis, Treatment, and Prevention

Diagnosis of IBK is usually based on clinical signs (see Color Plate 39.23). Ocular swabs submitted for bacterial culture can assist practitioners in identifying a specific bacterial species involved in infection and developing more specific therapeutic recommendations based on antimicrobial sensitivity data. When collecting ocular samples for culture, swabbing the periphery of active corneal ulcers and avoiding the subconjunctival cul-de-sac can help reduce contaminant overgrowth and may enhance recovery of *Moraxella* spp. (K. Clothier, personal communication). To culture *Mycoplasma* from ocular

swabs, special media and handling may be required, and it is a good idea to consult with your diagnostic laboratory prior to sample collection.

In a recent systematic review of published studies of IBK treatment with antibiotics, most treatments were considered to be effective in IBK, especially during posttreatment days 7 to 14.[129] *Moraxella bovis* is susceptible to penicillin administered subconjunctivally,[130] parenteral oxytetracycline,[131,132] florfenicol administered intramuscularly (two 20-mg/kg injections 48 hours apart) or subcutaneously (40 mg/kg once),[133,134] ceftiofur crystalline-free acid administered subcutaneously (6.6 mg ceftiofur equivalents/kg once) in the posterior aspect of the pinna,[36] and tulathromycin (2.5 mg/kg) administered subcutaneously.[135] The antibiotic sensitivities of 57 California *Moraxella bovoculi* field isolates have been reported and suggest that commonly used antibiotics for the treatment of IBK associated with *Moraxella bovis* should also be effective against *Moraxella bovoculi*.[136] Regional differences in antibiotic susceptibility among *Moraxella bovoculi* and *Moraxella bovis* exist[41,136,137] and underscore the importance of making informed treatment decisions based on antimicrobial susceptibility data. Nonantibiotic treatments of IBK have become increasingly important for purveyors of antibiotic-free cattle. A recent study found that hypochlorous acid spray can reduce pain, infection, and healing time of corneal lesions in calves experimentally infected with *Moraxella bovis*.[138]

Use of an NSAID, such as flunixin meglumine, can help relieve ocular pain and inflammation in severe cases. For individual animals in hospital settings, autologous patient serum applied topically may also assist in healing. Use of denim patches to cover an affected eye is controversial, but it is likely that such patches can relieve ocular pain associated with exposure to bright sunlight and may reduce vector spread of infectious ocular secretions in a herd setting. When applying patches, it is important to allow for ventral drainage; producers should also be advised to check under patches at least once or twice weekly to make sure an affected eye is not deteriorating. Other surgical ocular procedures such as third eyelid flaps may also be considered in severe cases.[139]

Vaccination against *Moraxella bovis* has traditionally been considered to be the foundation of a successful IBK prevention program. As with other multifactorial diseases, however, it is likely that the most effective IBK prevention program will require consideration of a variety of factors, including timing of vaccination (ideally within 4 to 6 weeks of anticipated cases); reducing risk factors (such as plant awns, foxtails, flies, and dust); supplementing trace

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minerals in deficient areas (e.g., copper and selenium); and reducing iatrogenic spread of potentially infectious material between animals (e.g., contaminated instruments, halters, and hands). To reduce fly populations, insecticide-impregnated ear tags placed on calves and topical insecticides with back and face rubbers are recommended. Clipping mature grasses before cattle are turned out may help minimize risks associated with direct mechanical corneal injury from plant awns. In areas where trace mineral deficiencies, especially of copper and selenium, are prevalent, attention to supplementation of these trace minerals is considered an important aspect of overall herd control and prevention. Neutrophils from copper-deficient calves had lower superoxide dismutase activity versus neutrophils from copper-supplemented calves, but no difference was observed in phagocytic and bactericidal activities of neutrophils from these groups.[140]

For vaccination against IBK, commercially available *Moraxella bovis* bacterins are available, but these are not universally effective. In 2017 a conditionally licensed *Moraxella bovoculi* vaccine was also released.[141] With the increase in reporting of *Moraxella bovoculi* from clinical samples following the initial report of that organism in 2007, producers and veterinarians have also sought to improve vaccination coverage by using autogenous *Moraxella bovoculi* (and/or *Moraxella bovis*) vaccines in prevention programs. While anecdotal reports that support or refute the use of *Moraxella bovis* and/or *Moraxella bovoculi* bacterins are easy to come across on discussion boards of cattle veterinarians, recently published studies investigating the efficacy of autogenous or commercial *Moraxella bovis* or autogenous *Moraxella bovoculi* vaccines reported these vaccines to be ineffective.[142-144] Some authors have also recommended the use of multivalent *Moraxella bovis*, *Moraxella bovoculi*, and *M. ovis* vaccines to prevent IBK.[145]

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Immune-Mediated Ocular Diseases

Kathryn L. Wotman • Mary Elizabeth Lassaline • Mary Belle Glaze

This section describes immune-mediated ocular disease in large animals, beginning with a review of ocular immunology, followed by discussion of immune-mediated ocular diseases including immune-mediated keratitis, eosinophilic keratitis, and equine recurrent uveitis.

Except for the conjunctiva, the eye has no lymphatic drainage. Access of antigens to potentially reactive lymphoid tissue is also restricted by the avascularity of the cornea and the presence of selective blood-ocular barriers. As unlikely as immunologically mediated abnormalities may seem under these circumstances, immune-related inflammation remains a leading cause of blindness in the horse. Reports of immune-mediated ocular disease in ruminants are rare.

Ocular Immunology

The conjunctiva represents an extension of the mucosal immune system. A variety of immune cells can be found in the conjunctival epithelium and within the substantia propria, including intraepithelial CD8+ lymphocytes and mast cells, as well as aggregates of CD4+ T-helper (Th) cells and B lymphocytes, CD1+ dendritic cells, and macrophages.[1] The conjunctiva processes ocular surface antigens with the help of regional lymph nodes. Antigen presentation is likely preceded by local tissue damage and release of inflammatory mediators that recruit inflammatory cells to the site. Under the influence of cytokines like interferon (IFN)–α, tumor necrosis factor (TNF)–α, interleukin (IL)–1, and IL-12 released by local and recruited cells, tissue dendritic cells process and carry host and pathogen molecules to regional lymph nodes to activate CD4+ Th cells. Stimulated lymphocytes migrate back to the conjunctiva (T cells) and lacrimal gland (B cells), where they participate in cell-mediated reactions and local production of IgA and to a lesser degree IgG, respectively.[1-3]

Because the globe itself is without lymphatic drainage, intraocular antigens must be processed at a distant site. These antigens pass into the systemic circulation, preferentially stimulating the spleen as well as the bone marrow and other distant lymphoid organs. After 5 to 7 days, sensitized lymphocytes migrate back to the eye and localize within the uvea and limbal conjunctiva. As with

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those on the ocular surface, these immunologically competent cells are capable of antibody production and can participate in cell-mediated reactions. Further exposure to the same antigen can provoke an anamnestic response, endowing the uveal and limbal tissues with behavior comparable to that of a regional lymph node.[4]

The intraocular immune response varies from that of a classic immune reaction, presumably to limit excessive inflammation within the eye. Anterior chamber–associated immune deviation (ACAID) is characterized by preferential stimulation of T suppressor cells that inhibit development of both CD4+ and B cells necessary in delayed-type hypersensitivity reactions and production of complement-fixing isotypes of antibody, respectively.[1,5] Cells in the uvea and corneal endothelium also express Fas ligand (FasL), which limits inflammation through apoptosis of activated leukocytes entering the eye.[1]

Each of the four major types of immunologic reactions occurs within the eye.[6] Type I (immediate) hypersensitivity is usually manifested as conjunctivitis, an acute local inflammatory reaction that follows IgE-mediated release of histamine, proinflammatory cytokines and chemotactic mediators from tissue mast cells, and synthesis of cytokines, leukotrienes, prostaglandins, thromboxane, platelet-activating factor (PAF), and kinins.[7] These mediators of the IgE–mast cell inflammatory pathway increase vascular permeability, constrict smooth muscle, dilate blood vessels, and activate leukocyte chemotaxis and the complement cascade. Allergic reactions of the lids and conjunctiva undoubtedly occur in all domestic species.

Type II (cytotoxic/cytolytic) hypersensitivity is an antibody-mediated cytolytic reaction in which the antigen is a cell surface or basement membrane component. Three basic effector pathways lead to cell destruction: (1) opsonization, with increased efficiency of phagocytic destruction; (2) antibody-dependent cellular cytotoxicity, inducing the release of enzymes capable of destroying cells and digesting basement membranes; and (3) lysis of immunoglobulin-bearing cells.[8] Conjunctival damage resulting from autoantibodies directed against epithelial basement membranes is described in equine ocular pemphigoid.

Type III (immune complex) hypersensitivity may share similar effector mechanisms with those described for cytolytic reactions, but antigen locale accounts for dissimilar disease manifestations in these two pathways.[7] This immune complex reaction may explain the clinical signs of pemphigus

foliaceus[9] and the intraocular inflammation observed in horses after influenza vaccination or contact with infected animals.[10] Antibody-mediated cell destruction has also been implicated in uveitis.[6]

Type IV (cell-mediated/delayed) hypersensitivity is an important factor in contact allergy of the lids and conjunctiva and may also play a role in ocular toxoplasmosis. The tissue destruction associated with herpetic keratoconjunctivitis in the horse has been attributed to a cell-mediated response.[6] Increasing evidence implicates delayed hypersensitivity in the pathogenesis of equine recurrent uveitis.[11,12] The reaction requires an initial antigen exposure that results in sensitization of antigen-specific T lymphocytes. Reintroduction of antigen induces interleukin production, with subsequent T-cell activation, proliferation, and cytokine production. Once activated by cytokines, recruited leukocytes display increased activity to many antigens.[13]

Allergic Blepharoconjunctivitis

In humans, several forms of allergic conjunctivitis are mediated by IgE, and histamine (H_2) receptors have been discovered on the human ocular surface.[14] The ubiquitous presence of H_2 receptors in domestic animals implies a similar distribution[2] and the potential for immediate hypersensitivity reactions of the eyelids and conjunctiva.

Affected animals demonstrate acute swelling of the eyelids and conjunctiva, accompanied by serous ocular discharge, mild conjunctival hyperemia, and pruritus. If the stimulus persists, multiple subconjunctival aggregates of lymphocytes appear as tiny semitransparent follicles within the conjunctival cul-de-sac. In contrast to bacterial conjunctivitis, crusting and purulent discharge are not typical of allergic conjunctivitis.

Diagnosis of allergic blepharoconjunctivitis is often presumptive, based only on careful and thorough elimination of all other causes of eyelid and conjunctival swelling. Trauma, orbital inflammation, neoplasia, mechanical irritants, conjunctival parasites, and other infectious agents (both ocular and systemic) should be considered. In support of an allergic etiology, conjunctival cytology may reveal eosinophils in response to mast cell degranulation.

The offending allergen may be difficult to identify. Insect stings and toxic plants (e.g., nettle) are possible causes, as are molds and pollens. Allergic conjunctivitis was described in 17 of 187 cows pastured adjacent to a field of

blossoming cotton.[15] A group of Angus-Holstein cattle demonstrated excessive lacrimation and ocular pruritus associated with familial allergic rhinitis. Several inhaled allergens have been incriminated, including capeweed, clover, dock, lucerne, pepper tree, paspalum, wattle, ryegrass, sorrel, and fungal extracts.[16] New feeds and certain drugs (e.g., oxytetracycline, penicillin, sulfonamides) may produce generalized urticaria, with accompanying eyelid and conjunctival edema.[17] Similar findings have been reported in cattle with milk allergy. Agents that directly induce mast cell degranulation through osmotic or charge interactions include hypertonic saline, NSAIDs, thiopental, opiates, neuromuscular blocking agents, mannitol, radiocontrast agents, polymyxin B, and vancomycin.[18] Occasionally, allergic conjunctivitis may be associated with a topical medication like neomycin. Clinical signs exacerbate with continued application and diminish when the medication is discontinued.

Ocular signs of hypersensitivity subside with removal of the offending allergen, but this is often impractical. Individual animals may be treated with a topical ophthalmic corticosteroid preparation, such as 0.05% dexamethasone ointment, to hasten resolution of swelling, redness, and discomfort. An agent with antiprostaglandin activity, such as oral or parenteral flunixin meglumine (Banamine®) at 0.5 mg/kg q12h, may be of benefit in the horse. Signs associated with urticaria respond to a decreasing regimen of oral prednisone or prednisolone, initiated at a dosage of 1 mg/kg once daily in the nonpregnant animal.[19] Single parenteral doses of short-acting corticosteroids, epinephrine, or antihistamines have also been used with reported success in food animals.[16]

Ocular Manifestations of Immune-Mediated Dermatoses

Pemphigus foliaceus is the most common of the autoimmune skin diseases described in horses. Lesions are often first noted on the head and lower extremities but spread to other parts of the body with time. Vesicles, bullae, pustules, erosions, and crusting are commonly noted on the skin and mucous membranes, including the eyelids and conjunctiva. Pemphigus foliaceus, bullous pemphigoid, and recently pemphigus vulgaris have been described in the horse.[20-25] Direct immunofluorescence reveals intercellular deposition of IgG and complement (C3) within the epidermis. Histopathology from biopsied lesions is reported to be more reliable, with findings of acantholytic cells with

associated neutrophilic inflammation and intraepidermal pustules.[26] In humans, a Welsh pony stallion, and recently in the equine muzzle skin, circulating autoantibodies to epidermal transmembrane proteins desmoglein 3 (Dsg3) and desmoglein 1 (Dsg1) have also been demonstrated, which leads to acantholysis, vesicle formation, and epidermal clefting.[25-27]

Ocular manifestations of pemphigus may include ulceration or crusting of the eyelids, mucoid ocular discharge, and conjunctival hyperemia with erosions. Corneal ulceration may result from mechanical trauma to affected eyelids and conjunctiva or may be a primary manifestation of disease, as has been reported in humans and a Welsh pony stallion with pemphigus vulgaris.[24,28] Diagnosis is based on clinical findings, cytology, histopathology, and positive immunofluorescence of affected skin. See the discussion of immune-mediated dermatologic disorders for therapeutic recommendations and prognosis in Chapter 53.

Other immune-mediated diseases, such as systemic lupus erythematosus (SLE) or cutaneous lupus erythematosus (CLE), occur infrequently in the horse but can affect the face and eyelids.[29,30] In addition to skin lesions, vasculitis may manifest by hemorrhages in mucous membranes, including the conjunctiva.[20,29]

Eosinophilic Keratoconjunctivitis

Eosinophilic keratoconjunctivitis (EK) is an inflammatory condition of the cornea and/or conjunctiva that can present as unilateral or bilateral ocular disease in the horse. The seasonality typically noted with EK, with a predominance of cases in one study noted during June, July, and August, suggests an environmental etiology, but the specific cause of the disorder is unknown.[31] Studies have suggested contributing factors, including climate variables (temperature, rainfall amounts, humidity levels); sex predisposition, with females being overrepresented in one study; and possible causative effects of certain types of feed.[31] As the name suggests, eosinophils on conjunctival or corneal cytology are diagnostic.[31-35] Recurrence of signs is not uncommon in subsequent years.[35]

■ Clinical Signs

Clinical signs of mild to severe blepharospasm, epiphora, characteristic caseous mucoid ocular discharge, conjunctival hyperemia, and chemosis are typically

noted at the onset of disease. Corneal lesions typically appear as raised white or pink corneal plaques. The plaques may be surrounded by corneal edema, with vascularization extending toward the ulcer and/or plaque from the limbus. Progression to corneal ulceration that extends from the limbus axially is often noted first in the ventromedial cornea quadrant underlying the third eyelid.[31-35]

■ Diagnosis

Diagnosis is based on clinical signs and cytologic findings of predominantly eosinophils on corneal or conjunctival scrapings and may include segmented neutrophils, mast cells, plasma cells, and lymphocytes. Differential diagnoses include mycotic and/or bacterial keratitis, onchocercal keratoconjunctivitis, neoplasia, foreign body granuloma, traumatic keratitis, squamous cell carcinoma, and calcific corneal degeneration.[36-39]

■ Pathophysiology

The eosinophilic inflammation found in the cornea and conjunctival surfaces suggests a type I or type IV allergic reaction. Although the inciting allergen has yet to be elucidated, parasites such as *Onchocerca* or *Habronema* spp. are often implicated, but neither has been specifically identified in a case of EK.[31,38] One proposed mechanism for EK is an allergic or inflammatory response to long-term use of ivermectin as an anthelmintic, triggering the complement cascade and cellular chemotaxis in patients with ocular onchocerciasis.[33] A recent case series of a Standardbred broodmare farm with 19 affected mares described environmental management with minimal medical intervention, including specifically fly control, as a key to decreasing incidence of disease, time to resolution of disease, and the number of recurring cases.[34] This suggests that an environmental allergen that may be associated with flies themselves or transferred by flies stimulates the type I allergic reaction. Similarities to vernal keratoconjunctivitis in humans suggest that eosinophil-granule major basic protein may play a significant role in the equine disease, inhibiting corneal epithelial migration and protein synthesis and promoting collagen degeneration.[40] Eosinophil-derived collagenase also has been reported to degrade type I collagen, the predominant collagen in the cornea.[32]

■ Treatment and Prognosis

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Given the mechanism by which EK is believed to persist (i.e., a toxic effect of eosinophilic major basic protein on the corneal epithelium leading to chronic corneal ulceration), the mainstay of treatment of EK should be prophylactic against secondary infection of corneal ulcers, including topical antibiotic therapy with a broad-spectrum drug such as ofloxacin 0.3% solution or neomycin polymyxin B bacitracin ophthalmic ointment, and in areas where fungal keratitis is prevalent, a topical antifungal as well. Treatment with immunosuppressive drugs such as prednisolone acetate or cyclosporine, although historically used to treat EK in horses, is not recommended due to the risk of infection, as well as complications associated with chronic topical steroid use.[31,33,39] Eosinophilic keratoconjunctivitis lesions remodel with minimal corneal scarring, but mean duration of treatment in one series of patients was 64 days (range of 45 to 106 days).[33] Use of topical NSAID preparations may increase the severity of clinical signs of EK in horses because of potentiation of leukotrienes, the primary promoter of eosinophilic inflammation, and thus these drugs are not recommended to treat EK.[32] Medical management and prognosis were recently evaluated in horses diagnosed and treated in the Mid-Atlantic United States and revealed an average time to resolution of 3.7 months.[35] Treatment in some horses included use of tapering doses of systemic dexamethasone starting at a rate of 0.04 mg/kg PO for 1 day, 0.03 mg/kg for 2 days, and 0.02 mg/kg once daily for 3 to 5 days.[35] A group of horses evaluated in the study was also treated with oral cetirizine, an H_1 antagonist that may be useful in decreasing the migration and adherence of eosinophils.[35,41] Horses treated with oral corticosteroids had a shorter time to resolution when compared to horses that were not given oral corticosteroids. This finding, combined with the risk of secondary corneal infection with topical steroids, suggests that systemic rather than topical corticosteroids should be used to treat EK. Treatment with oral cetirizine did not decrease time to resolution of ocular disease, but during the follow-up period these horses were significantly less likely to have recurrence of disease (1 of 13 horses [8%] had recurrence with cetirizine compared to 8 of 14 [57%] without cetirizine).[35] Excision of the corneal plaques by superficial keratectomy appears to enhance healing, attributable to removal of the eosinophil-granule major basic protein.[32,33]

Immune-Mediated Keratitis

Nonulcerative Keratitis

Chronic nonulcerative corneal opacities that vary in color and depth within the cornea without overt signs of discomfort or intraocular inflammation have been described, and they can be a diagnostic and therapeutic challenge due to difficulties in obtaining diagnostic samples from a nonulcerated cornea.[42-45] In a report of 19 horses ages 5 to 11 years diagnosed with nonulcerative keratitis, 11 horses had clinical signs for more than 12 months before referral.[42] Nonulcerative keratitis in this report was described as immune-mediated keratitis (IMK), which comprised three distinct clinical entities classified as superficial, deep/mid-stromal, or endothelial, based on the location of the corneal pathology. *Superficial keratitis* was characterized by a superficial white to yellow infiltrate with diffuse mild to moderate vascularization. *Deep/mid-stromal* lesions were described as more diffuse, with denser cellular and vascular components. A deep cellular infiltrate with mild corneal vascularization and variable degrees of diffuse corneal edema were typical of *endothelial keratitis.* Intraocular inflammation was not a feature of the disorder, regardless of lesion location.[42] Differential diagnoses include stromal abscess, EK, bullous keratopathy, subepithelial herpes keratitis, nonulcerative keratouveitis, and subepithelial keratomycosis (SEK). The infiltrates seen with SEK lie beneath the epithelial layers and may appear as punctate lesions or more geographic opacities that respond favorably to antifungal treatment.[43] Unlike what is typically noted in the equine eye with lesions due to fungal infections, SEK does not have significant blepharospasm or intraocular inflammation as a feature.[43]

An immune-mediated pathogenesis has been theorized for IMK, based on histopathologic characteristics and response to immunosuppressive therapy. Lesion appearance and description has varied, but typically within the United States, changes are described based on depth: superficial, deep/mid-stromal, and endothelial. Response to treatment and prognosis vary depending on the location of the infiltrate.[44] Regardless of lesion depth, histopathology reveals a predominantly lymphocytic-plasmacytic infiltrate, with stromal fibrosis or necrosis and vascularization. Three of five horses tested were seropositive for *Leptospira* spp. in one study.[42] Presumably the immune system is reacting to a self-antigen, antigens of a foreign protein, or an infectious agent within the cornea. Even though infectious agents have not been consistently documented in this particular disorder, immunologic cross-reaction with self-antigens (i.e., molecular mimicry) may occur, as described with leptospiral organisms or their

DNA in the equine cornea.[46,47] Keratectomies from 10 horses diagnosed withsuperficial IMK showed a predominantly cell-mediated inflammation with cytotoxic and Th cells being the most common cells noted.[48] Local immunoglobulin was also identified in the corneal samples, but this could not be directly associated with a systemic humoral response, leaving the role of this arm of the immune system in question as to the pathogenesis of IMK.[48]

Owing to the frequency at which the abnormal equine cornea is afflicted with an infectious agent (bacterial, fungal, viral), diagnostic samples (cytology, culture) should be considered prior to starting therapy with immunosuppressive agents, particularly given that typically no independent confirmation of the diagnosis of IMK, nor microbiological samples ruling out an infectious etiology, are available when the diagnosis of IMK is made. Concurrent therapy with topical antibiotics and antifungals may be warranted. Lesions of superficial stromal keratitis have been described as able to be controlled with long-term topical dexamethasone and/or cyclosporine, with the goal of reducing frequency of the topical glucocorticoid.[42,45] Tacrolimus is a more potent immunosuppressive agent than cyclosporine and could potentially be used topically to aid in decreasing the activity of T cells, but its efficacy as a sole treatment for IMK has yet to be supported with empirical results.[44] Topical ophthalmic NSAIDs (e.g., diclofenac, bromfenac, flurbiprofen) may be a reasonable alternative to topical steroids, particularly for long-term use in some cases. A similar chronic therapeutic regimen may be used in superficial and mid-stromal keratitis[45]; however, topical corticosteroids may be less effective than cyclosporine in the deeper stromal disorder and, when used in combination long-term, may offer improvement in clinical signs.[42] Lesions in 4 of 11 horses with superficial stromal IMK were treated by superficial keratectomy and conjunctival grafting; lesions resolved in all four horses without the need for ongoing medication, suggesting that surgical removal of the inciting antigen in addition to providing a direct blood supply may stop the inflammatory process.[42] Keratectomy followed by a conjunctival graft was curative in one horse with mid-stromal IMK.[42] Response to anti-inflammatory agents varies in patients with endothelial keratitis, resulting from differences in pathogenesis. Only two of four horses were controlled with constant topical dexamethasone and cyclosporine in a retrospective study from Gilger and colleagues.[42] In contrast, horses with endothelial IMK in the United Kingdom usually respond rapidly to a glucocorticoid applied topically 2 to 3 times per day and complete resolution of

clinical signs is possible.[43] In general, due to the deep location within the cornea, endothelial IMK carries a poor prognosis for response to treatment and often progresses.[44] Although retention of vision is likely in most cases of nonulcerative keratitis, long-term or even lifelong therapy is required to control the corneal disease.

The therapeutic goal for IMK is disease resolution, or at minimum slowing progression of the corneal changes and decreasing the number of medications and/or frequency of application needed to control the disease. A surgical alternative to a keratectomy of all or a portion of the affected cornea is implantation of an episcleral cyclosporine delivery device, which has shown a positive response in a report of 19 horses with IMK.[49] Keratitis was best controlled (i.e., horses were on no more than one medication) in 14 horses with either superficial IMK or endotheliitis, followed for about 6 months. However, in three horses diagnosed with mid-stromal IMK, keratitis was not controlled without additional medical and/or surgical therapy during the 5-month follow-up period after episcleral implant placement. The episcleral implant appears to reduce and in some cases may eliminate altogether the need for other topical medical therapy in horses that have previously responded to topical cyclosporine. Owners should be counseled that the implant likely lasts 1 to 1½ years and the procedure may have to repeated.[49]

Equine Recurrent Uveitis (Periodic Ophthalmia, “Moon Blindness”)

■ Definition and Etiology

Equine recurrent uveitis (ERU) is distinguished by a pattern of intraocular inflammation in which recurring episodes of acute uveitis are separated by periods of clinical quiescence. Inflammation of the iris and ciliary body (anterior uveitis or iridocyclitis) predominates in the early stages; repeated episodes damage the cornea, lens, vitreous, retina, and optic nerve. A more insidious form of ERU characterized by persistent low-grade inflammation occurs in the Appaloosa and Draft breeds of horse.

Equine recurrent uveitis is a leading cause of blindness in the horse and mule. Although the exact prevalence is unknown, estimates as high as 10% to 25% have been reported.[50,51] The financial impact on the equine industry is estimated at US$100 to $250 million annually as a result of the effects on performance and

the costs of veterinary care.[52]

Despite extensive clinical research, the specific cause of ERU is still unknown. The pathogenesis is immune mediated, and characterization of T-lymphocyte populations in affected horses documents a delayed hypersensitivity reaction as the basic immunologic mechanism underlying the recurrent inflammatory episodes.[12] Identification of the triggering antigen has proved more elusive, suggesting that the disease does not result from persistence of or repeated exposure to a single antigen, but rather to a variety of circulating antigens or native ocular antigens. *L. interrogans* serovar *pomona* is the most frequently incriminated infectious pathogen,[51] but diversification of T-cell responses to a particular antigen or group of antigens over time may result in evolution of the immune response to encompass endogenous ocular self-antigens.[9,53]

■ Clinical Signs

The ocular lesions observed in ERU vary depending on the severity and duration of the disease.[50,52,54,55] ERU can occur at any age, but the initial uveitis episode frequently occurs in horses 4 to 8 years of age. Acute episodes are painful, characterized by blepharospasm and excessive tearing. Affected eyes are often described by owners as “red” and/or “cloudy” because of changes in the conjunctiva, cornea, anterior chamber, or vitreous. Dilation of subconjunctival vessels near the limbus, termed *ciliary flush*, may intensify the generalized conjunctival hyperemia. As corneal endothelial function decreases, diffuse corneal edema gives the eye a bluish-white appearance. The cornea may also exhibit peripheral circumferential vascularization, cellular precipitates on its inner (endothelial) surface, and linear stromal opacities.

Increased uveal vessel permeability causes the aqueous humor to appear cloudy after influx of plasma proteins (flare), inflammatory cells (hypopyon), erythrocytes (hyphema), or fibrin into the anterior chamber (Fig. 39.15). The iris often appears edematous and lackluster or “muddy.” A change in iris color may be noted in breeds with lightly colored eyes, changing from blue to yellow or green in response to uveal edema, vascular congestion, and cellular infiltration (see Color Plate 39.10). Prostaglandins and other inflammatory mediators cause pupillary constriction, favoring the formation of adhesions between the iris and lens (posterior synechiae) that distort the pupillary shape. Even without adhesions, the inflamed iris responds poorly to mydriatic agents. IOP is usually

decreased because of diminished aqueous production by the inflamed ciliary body, but intermittent IOP elevations can occur.[56] The ciliary body can also deposit cellular exudates within the anterior vitreous, creating an opacity within the pupillary space that may be mistaken for cataract.

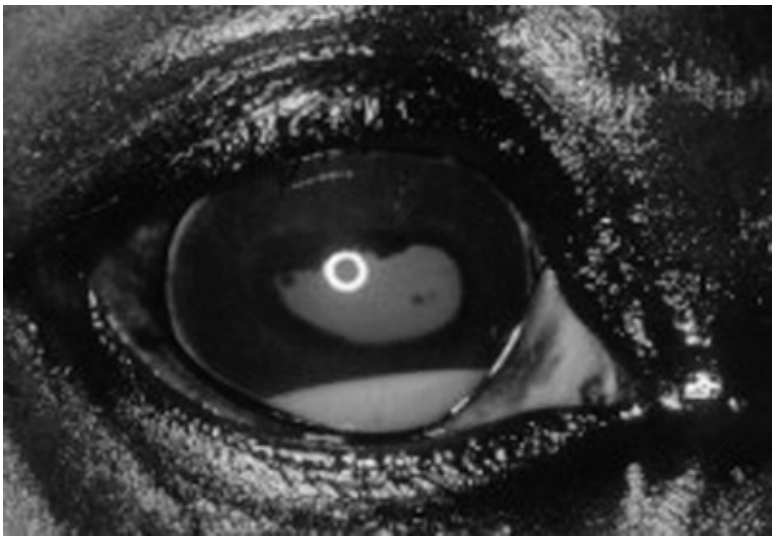


FIG. 39.15 Active uveitis characterized by hypopyon, pupillary irregularities secondary to posterior synechiae, pigment adherent to anterior lens capsule, and a dull tapetal reflection.

Active chorioretinitis causes dullness and loss of detail in affected tissues. Retinal detachment may follow choroidal exudation. Multifocal depigmented or hyperpigmented foci on either side of the optic disk are the sequelae of chorioretinitis (“chorioretinal scars”), commonly referred to as peripapillary “butterfly” lesions (Fig. 39.16).

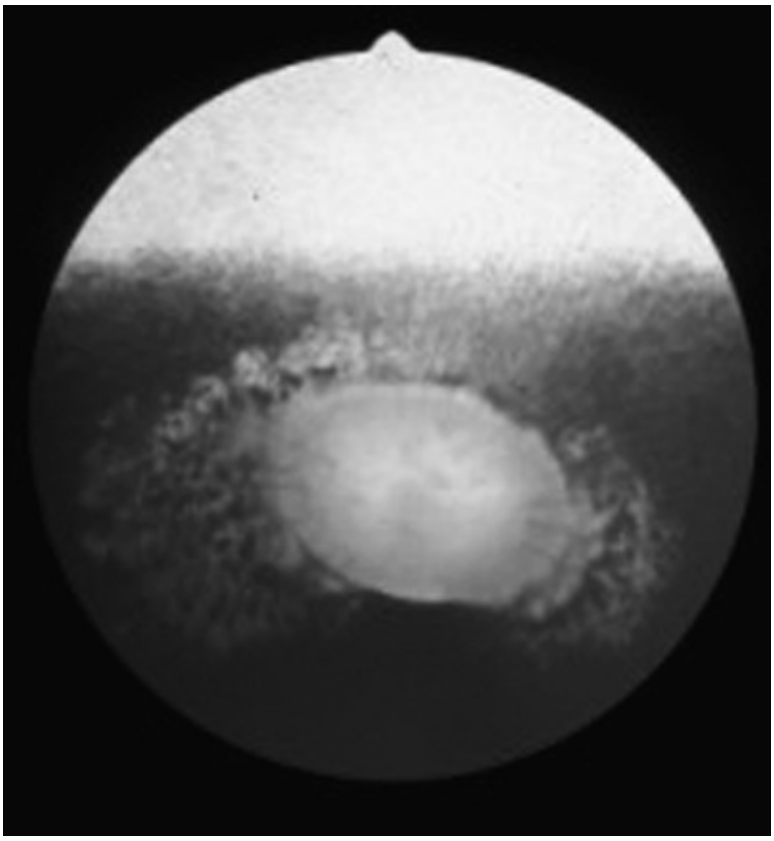


FIG. 39.16 Fundus adjacent to the optic disk takes on a mottled appearance as a result of pigment migration after previous chorioretinal inflammation from recurrent uveitis. Because of the shape, such lesions are sometimes referred to as “butterfly lesions.”

Intraocular damage increases each time inflammation recurs. Permanent corneal opacity caused by edema results if the corneal endothelium is severely compromised. Chronic recurrent uveitis is characterized by widespread posterior synechiae, iris depigmentation or hyperpigmentation, and iris atrophy. The anterior chamber may appear shallow if aqueous trapped in the posterior chamber by extensive iris-to-lens adhesions causes the iris to balloon forward (iris bombé). Most lens changes occur weeks or months after uveitis begins. Abnormalities may range from pigment flecks on the anterior lens capsule (Fig. 39.17) to dense cataracts (see Color Plate 39.2). Lens luxation often follows degeneration of the lens zonules and vitreous. Retinal detachment may also follow vitreous liquefaction or may result from traction by fibrous tissue bands within the vitreous. If retinal degeneration is substantial, the optic disk atrophies (Fig. 39.18). Permanent hypotony is followed by shrinkage of the globe (phthisis bulbi). Conversely, chronic uveitis may result in secondary glaucoma (see Color Plate 39.8). The combination of these acute and chronic ocular lesions

determines the degree of vision loss in the affected animal.

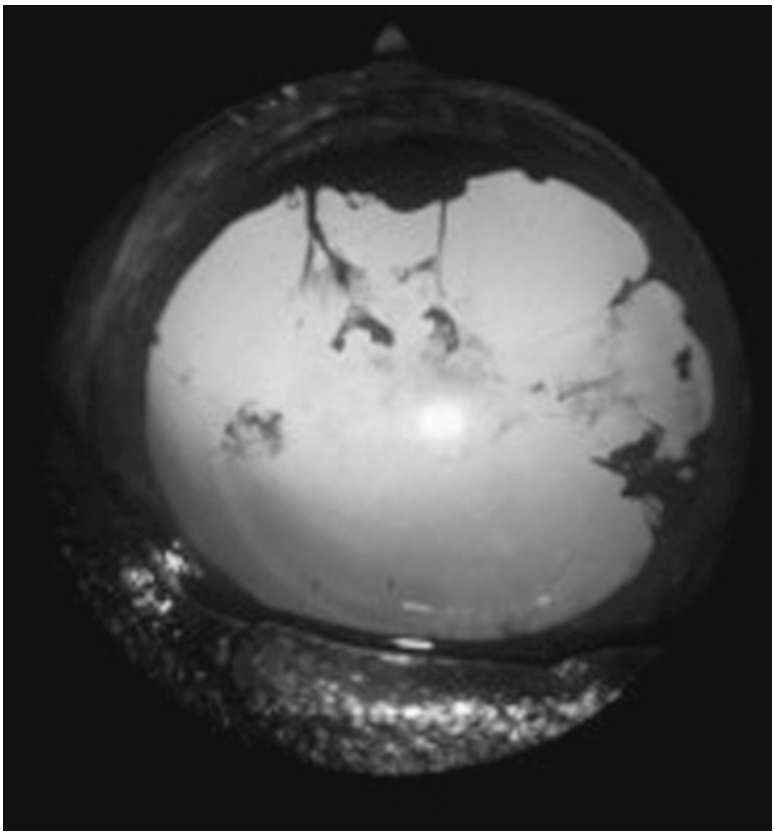


FIG. 39.17 Prior episodes of anterior uveitis are indicated by pigmented remnants on anterior lens capsule and thin adhesions of iris to lens (posterior synechiae). Pupil is pharmacologically dilated.

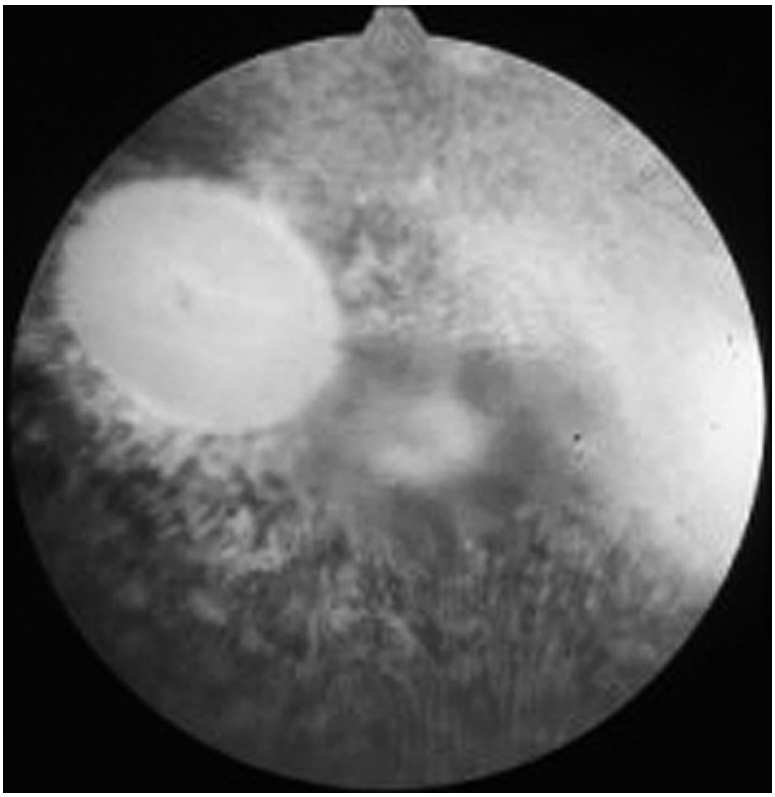


FIG. 39.18 Disk pallor and nontapetal depigmentation accompany an adjacent dark gray preretinal exudate in a horse with chronic active recurrent uveitis. This patient had poor vision.

Equine recurrent uveitis may be accompanied by transient and variable inflammation of the pineal gland.[57-60] Similar pineal inflammation has been reported in experimentally induced recurrent uveitis in laboratory animals.

■ Diagnosis

Not every case of uveitis in the horse qualifies as ERU. Diagnosis is based on a chronic, recurrent history of intraocular inflammation and the presence of characteristic ocular lesions. In cases where the history is unknown but recurrent disease is suspected, at least several of the following indicators of previous inflammation should be observed before a presumptive diagnosis of ERU is made: corneal edema or vascularization, synechiae (typically posterior), iris color change, corpora nigra atrophy or “polishing,” lens capsular pigmentation, cataract, lens luxation or subluxation, vitreous opacities or traction bands, retinal detachment, or peripapillary scarring.[50] Other causes of a red and painful eye that can mimic acute ERU include conjunctivitis, corneal ulceration, corneal stromal abscessation, keratouveitis, and glaucoma.

Serologic testing of paired serum samples for *Leptospira* spp. or other infectious agents incriminated as causes of equine uveitis (see Table 39.2) may contribute to a diagnosis of ERU, but negative titers neither exclude the diagnosis nor eliminate leptospirosis as a contributing factor to the disease.[61,62] Acute leptospiral infections are characterized by high-titer seroreactivity to at least one serovar by the eighth day[63]; the titer usually falls with time, but seroreactivity may persist for many years. Some authors suggest that a leptospiral titer of 1 : 400 or higher is of clinical importance, particularly for *L. interrogans* serovar *pomona*.[50] A higher titer in the aqueous than in the serum is indicative of intraocular antibody production and further supports a leptospiral cause for the uveitis.[64] *Onchocerca* microfilariae may be identified in conjunctival biopsies, although detection of live microfilariae does not necessarily indicate a causal relationship for uveitis.[65,66] Equine leukocyte antigen (ELA) typing may help determine susceptibility to ERU.[67]

Histopathologic lesions of the ciliary body considered pathognomonic for ERU include the presence of a thick, noncellular hyaline membrane adherent to the nonpigmented epithelium (NPE) and the presence of eosinophilic linear cytoplasmic inclusion bodies within the NPE.[68,69] Clusters of lymphocytes and plasma cells also accumulate in the posterior iris, in the ciliary body, near the ora ciliaris retinae, within the choroid, and near the optic nerve head.[52,70] Dense bundles of fibrils coupled with necrotic cells and mononuclear inflammatory cell infiltrates characterize the changes within the vitreous.[71]

■ Pathophysiology

Breed has been established as a risk factor for ERU. In a 1988 retrospective study of more than 16,000 equine patients at Cornell University, researchers determined that the Appaloosa had a significantly higher risk of developing uveitis than Thoroughbreds.[72] A subsequent New York field study substantiated the breed predilection, concluding that the Appaloosa was 8.3 times more likely to develop uveitis than all other breeds combined.[51] Within the Appaloosa breed, those with overall light hair coats and focal dark spots are more likely to develop ERU than horses with a dark, basic coat pattern and a light “blanket” over the rump.[52] Trotters and warmbloods were overrepresented in a report of 130 ERU-affected horses in Germany.[73] Of 669 mares included in a serologic study of leptospirosis, significantly fewer positive titers were found in Thoroughbreds

and Standardbreds.[74]

In humans, an immunogenetic predisposition to certain types of uveitis has been linked to the major histocompatibility complex (MHC), a closely aligned cluster of genes designated as the human leukocyte antigen (HLA) region located on a single chromosome.[75] Similar genetic loci occur in the horse, and the gene products are referred to as *equine leukocyte antigens* (ELAs). Products of these genes are glycoproteins found either on most nucleated cells (class I antigens) or restricted to accessory cells such as monocytes or macrophages (class II antigens). The immunoregulatory role of the MHC is especially important in discriminating self-peptides from those of nonself origin. Recent studies have shown an increased risk of uveitis linked with the MHC class I haplotype ELA-A9 in a group of German Warmblood horses.[67] As proposed in studies of human HLA-associated uveitis, cross-reactivity between self-antigens and ELA cell surface peptides could explain an inadvertent immunologic attack on normal cells.[76,77]

Experimental findings in ERU patients indicate that a T cell–mediated autoimmune mechanism underlies the recurrent episodes of inflammation. T lymphocytes are the predominant cell type to infiltrate the anterior uvea,[11,70] choroid,[78] and vitreous[79] of horses with ERU, and affected horses demonstrate cell-mediated immunity to retinal autoantigens and peptides.[79-81] B lymphocytes have been reported primarily in retinas from horses seroreactive for *L. interrogans* serovar *pomona*, suggesting that *Leptospira*-associated ocular inflammation may be a distinct subset of equine uveitis.[82] Equine ciliary body epithelium may play a role in recruitment and activation of leukocytes through expression of a chemotactic cytokine (chemokine),[83] although in the normal ocular microenvironment, ciliary body pigment epithelium suppresses T-cell activation by direct cell contact and the action of unidentified molecular mediators.[84] Analysis of messenger RNA (mRNA) collected from horses with uveitis demonstrates elevated levels of IL-2 and IFN-γ, indicating a Th1 response in the disease process.[85] In the absence of bacteria or viruses, this Th1 response by CD4+ uveal T lymphocytes suggests a delayed-type hypersensitivity (DTH) reaction to self-antigens or sequestered antigens in the uveal tract.[12,86] In contrast to the ocular T-lymphocyte population, systemic lymphocytes of ERU-affected horses do not exhibit a Th1 response.[12] The expression of a deviant MHC class II antigen on resident ocular cells (e.g., Muller, retinal pigment

epithelial) suggests that aberrant immune regulation may also play a role in ERU.[11,87]

Aqueous and vitreous immunoglobulin levels have been used to characterize immunologic responses within ERU-affected eyes. Using radioimmunoassay, an early study found that aqueous levels of IgG, IgM, and IgA were 50% to 120% greater in diseased eyes than in normal controls, but that the IgG/albumin ratio suggested leakage of protein through an impaired blood-aqueous barrier rather than intraocular antibody synthesis.[88] Subsequent reports support local ocular antibody production but disagree on the dominant immunoglobulin in ERU-affected eyes. Wagner and colleagues[89] found selectively increased IgA levels in the vitreous of affected horses; Eule and colleagues[90] reported substantial IgM titers in 79.6% of intraocular samples from ERU-affected eyes. In contrast to the intraocular immunoglobulins, there are no significant differences in serum immunoglobulin concentrations between healthy and ERU-affected horses.[89,90]

Both exogenous and endogenous antigens have been proposed as stimuli for these basic immunologic responses. One theory suggests that an infectious agent such as *L. interrogans* (or another, perhaps noninfectious, exogenous antigen) causes the initial iridocyclitis. Sensitized immunocompetent cells enter the uvea during this first inflammatory episode, imparting immunologic memory that is specific for the inciting antigen. Subsequent challenge of these cells by the immunogen causes recurrence of the inflammatory reaction.[6,91] However, although some reports suggest persistent infection as the cause of ERU,[92] the premise of an infectious agent that exclusively induces and maintains ERU through a classic anamnestic response does not fully account for the disorder's clinical course and response to therapy.

The role of leptospiral infection in ERU has been studied extensively in recent years. All major serogroups of *L. interrogans* have been identified in the horse and implicated as initiating factors in ERU.[51,62,93-96] In a report of 130 ERU cases in Germany, 58.8% demonstrated positive serum titers to leptospirosis, an incidence 7 to 10 times higher than the control population.[73] Anti-*Leptospira* antibodies have been found in the serum, tears, aqueous humor, and vitreous of infected horses.[62,94,97-99] Wollanke and colleagues[99] reported positive serum antibody titers to *Leptospira* serovars in 25% (24 of 97) of normal-eyed horses and 22% (50 of 227) of ERU-affected horses, but only the ERU-affected animals had positive antibody titers in the vitreous.[99] Leptospiral organisms have been cultured from the aqueous and vitreous of ERU-affected horses.[61,62,96,100,101]

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However, in one study, *Leptospira* was not frequently detectable in fixed ocular tissues of horses affected with ERU when using traditional immunohistochemical and real-time PCR techniques.[102] In another study, there were no differences in bacterial DNA detection or in serum or aqueous humor anti-*Leptospira* antibody production between clinically normal horses, horses with ERU, and horses with ocular inflammation not associated with ERU in the southeastern United States.[103]

Horses seropositive to *L. interrogans* serovar *pomona* are reportedly 13.2 times more likely to have signs of uveitis than seronegative horses.[51] Ocular signs during the acute infection are usually subtle or absent, but overt ocular inflammation develops months to years later.[104-107] Risk factors for equine leptospirosis include rodent and wildlife exposure, proximity to ponds and rivers, a dense equine population on site, and increasing age.[74,108,109]

Although direct *Leptospira*-mediated injury to the eye cannot be ruled out in the pathogenesis of ERU, a growing body of evidence instead links leptospiral infection with autoimmune responses to ocular tissue components. Complement-binding anti-*Leptospira* antibodies capable of cross-reacting with equine corneal tissue and lens have been found in the tear film and aqueous humor of horses with leptospirosis.[97,98,110] These antibodies bind corneal epithelial cells, activating complement and initiating tissue damage, a mechanism replicated in tissue culture.[111] A leptospiral protein epitope that shares antigenic determinants with the equine cornea and lens has been found in bacterial homogenates,[46] and a DNA fragment of several serovars of *L. interrogans* was determined to encode a 90-kilodalton protein that cross-reacts with equine corneal proteins.[47,112] Novel leptospiral lipoproteins, identified as LruA and LruB, stimulate local intraocular IgA and IgG production and also cross-react with equine ciliary body, lens, and retina.[113] Immunohistopathologic examination has also demonstrated leptospiral cross-reactivity with iris pigment epithelium and retina from horses with ERU.[82,114] This antigenic relationship between *Leptospira* spp. and equine ocular tissues supports the concept of molecular mimicry as a contributing factor in ERU; exposure to exogenous antigens that share molecular structural sequences with equine self-antigens initiates an autoimmune response.[10]

Toxoplasmosis, brucellosis, salmonellosis, streptococcal hypersensitivity, *E. coli*, *R. equi*, borreliosis,[115,116] intestinal *Strongylus*, and onchocerciasis have also been implicated as causes of ERU, with no consistency in culture or

serology results in affected horses.[51] Viruses suspected of a role in ERU include equine influenza virus, equine herpesvirus (EHV-1, EHV-4),[117] equine arteritis virus, and possibly equine infectious anemia.[50,52] More recent studies on vitreous and serum samples from affected horses question the role of *B. burgdorferi*, Borna disease virus, and *Toxoplasma* in ERU.[118,119]

Both humoral and cell-mediated hypersensitivities have been implicated in the lesions of ocular onchocerciasis. Immunoelectrophoretic studies have demonstrated an influx of IgG and complement (C3) into the tears of affected horses in response to larval death.[120] The resulting chemotaxis of mast cells, eosinophils, and lymphocytes perpetuates the inflammatory response and facilitates destruction of the parasite. Human patients with ocular onchocerciasis demonstrate conjunctival infiltration by CD3+ T lymphocytes and increased expression of class II MHC antigens in conjunctiva and iris,[121] as well as deficiencies in suppressor T-cell function that may interfere with the normal regulation of antibody function.[122]

In addition to the role of infectious agents in the pathogenesis of ERU, autoimmunity may occur when a normally sequestered component is exposed to lymphoid cells or when the antigenicity of a component increases as a result of a structural alteration.[123] Several endogenous ocular proteins, including retinal soluble antigen (S-antigen, or S-Ag), interphotoreceptor retinoid-binding protein (IRBP), cellular retinaldehyde-binding protein (CRALBP),[124] and uveal melanin-associated proteins, are known to induce uveitis in various animal models.[125-128] Clinical studies also implicate these potent autoantigens in the pathogenesis of some forms of human uveitis.[129-131] An autoimmune phenomenon in response to damaged uveal tissue has been proposed in the pathogenesis of ERU.[132] The isolation of S-Ag in the horse and the subsequent finding of anti-S antibodies in the aqueous humor and vitreous of horses with uveitis support the theory that this species is similarly capable of local production of antibodies to normally sequestered autoantigens.[79-81,133] Experimental uveitis with features similar to spontaneous ERU has also been induced in horses after injection of IRBP in complete Freund's adjuvant.[78] Autoantibodies to S-Ag and IRBP were found in 72% of vitreous specimens from horses with uveitis.[79] A more recent equine study concluded that retinal S-Ag is a weaker autoantigen than IRBP; T and B cells were activated after immunization with S-Ag, but only one in five horses developed uveitis or

demonstrated inflammatory cell infiltration of the uveal tract.[134] Because the retina and NPE of the ciliary body originate from neuroectoderm, it is even possible that ciliary body damage may release an S-like antigen or another uveitogenic substance.[135] Evidence suggests that response to S-Ag is predominantly T-cell dependent.[136]

Verma and colleagues[113] proposed a link between leptospiral cross-reactivity and the release of other ocular autoantigens, based on strong IgG and IgA responses to LruA and LruB lipoproteins in uveitic eyes but not in companion sera. The early phase of ERU may involve production of non–complement-fixing antibody and non-DTH T lymphocytes specific for LruA and LruB. The antibodies and cells react with the leptospiral lipoproteins, initiating a process that ultimately liberates IRBP and other ocular autoantigens.

The concept of "epitope spreading" has been offered as an explanation for the relapsing character of ERU.[137] The theory proposes that after destruction of an initial target, the immune response spreads from the first autoantigenic determinant to others not previously recognized by the immune system.[138-139] Active uveitis subsides as regulatory cells suppress the inflammation, recurring as the immune response shifts to an epitope of the same autoantigen (intramolecular spreading) or a completely different autoantigen (intermolecular spreading). A recent 22-month study of peripheral T-cell reactions in 8 horses with spontaneous ERU demonstrated intramolecular shifts to different S-Ag–derived (6 of 8) or IRBP-derived (5 of 8) epitopes and intermolecular shifts in all horses, spreading from IRBP-derived to S-Ag–derived peptides (5 of 8) or vice versa (3 of 8).[137] A shift of the immune reaction could be correlated to new uveitic episodes in 10 of 14 relapses that occurred during the observation period. The confounding factor in this theory is the shifts in immune response observed during quiescent stages, perhaps to minor uveitogenic epitopes that fail to result in overt inflammation or as part of an unknown regulatory or protective function of these T-cell clones.

Regardless of etiology, the ocular inflammatory process may attract other reactive lymphocytes to the eye. During primary uveitis, only 10% of the ocular immunoglobulin-secreting cells are specific for the inciting antigen. The remaining cells produce antibodies against immunogens that may not have entered the eye but with which the host had previous contact. As a consequence, the eye may develop recurrent inflammation after systemic exposure to any one of multiple antigens. It is therefore conceivable that subsequent episodes of

uveitis may differ etiologically, creating a perplexing clinical picture.[140]

■ Treatment

Active Inflammation.

Reduction of intraocular inflammation is the primary therapeutic objective in acute uveitis. Preservation of vision depends on successful management at this stage, when sight-threatening sequelae are minimal. If a specific cause for the uveitis is identified, it is also targeted pharmacologically. In most cases, symptomatic therapy combines corticosteroids, NSAIDs, and mydriatic or cycloplegic agents. Nonspecific suppression of T-lymphocyte activation with cyclosporine implants[141] and surgical removal of T cells and, potentially, organisms from the eye by core vitrectomy[142] are recent innovations aimed at preventing recurrence of disease.

No therapy is indicated in nonpainful eyes with lesions of chronic end-stage uveitis. Those eyes that remain painful or do not respond to therapy are candidates for enucleation or evisceration, followed by silicone prosthesis implantation in the orbit or sclera, respectively.

Corticosteroids.

The severity of the uveitis dictates the routes and frequency of corticosteroid administration. Although topical therapy is most often used, efficacy is limited by the agents' relatively short contact time with the eye. Therefore topical corticosteroids must be applied three or four times daily, even in eyes with mild clinical signs. In more severe uveitis, topical preparations should be combined with other routes of therapy. A subpalpebral lavage system should be considered when frequent application is indicated (see the Bacterial Keratitis in Horses section earlier).

Either ophthalmic solution or ophthalmic ointment is acceptable for topical use in the horse. Prednisolone acetate 1% suspension has excellent intraocular penetration and is considered the drug of choice. Potent dexamethasone preparations, 0.1% solution or 0.05% ointment, are also effective. In general, therapy should be continued for at least 2 weeks after clinical signs have resolved. Ideally, that assessment includes an objective IOP measurement to ensure resolution of ciliary body inflammation and dysfunction.

The subconjunctival injection of a repository corticosteroid preparation is an

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alternative or supplement to frequent topical therapy. Triamcinolone acetonide 4% suspension is effective for 1 to 3 weeks when injected in a 0.5- to 1-mL volume (20 to 40 mg) beneath the superior bulbar conjunctiva. Subconjunctival injection of methylprednisolone acetate suspension has a comparable antiinflammatory effect but is more likely to cause granuloma formation at the injection site. Duration of effect of either drug depends on the severity of the uveitis. Nonocular use of either drug has been linked to equine laminitis.

Intravitreal triamcinolone injection may provide a safe and effective method to control ERU. In one study evaluating the ocular distribution and toxicity of intravitreal triamcinolone, six horses were injected intravitreally with 10, 20, or 40 mg of triamcinolone. There was no evidence of overt toxicity from intravitreal triamcinolone injection in normal horses, and a single intravitreal injection resulted in ocular levels of triamcinolone for 21 days. However, the risk for bacterial infection after intravitreal injection or anterior chamber aspiration in horses appears to be high.[143]

Evaluation of inflamed eyes should always include topical application of fluorescein dye to rule out ulcerative keratitis. This precaution is especially critical when considering the use of subconjunctival corticosteroids that deliver prolonged and irreversible effects. Topical and subconjunctival corticosteroids are contraindicated in the presence of corneal ulcers because they delay healing, potentiate the destructive effects of endogenous and microbial enzymes, and predispose the cornea to secondary infection.

Nonsteroidal Antiinflammatory Drugs.

Parenteral corticosteroids may be used when topical and subconjunctival agents are ineffective in controlling inflammation, but NSAIDs are usually preferred in such cases. Use of these antiprostaglandin agents counteracts an important mediator of intraocular inflammation, minimizing the role of parenteral steroids in uveitis therapy and the attendant risk of laminitis. Flunixin meglumine (Banamine) is the NSAID of choice for the eye, administered at a dose of 0.5 to 1.1 mg/kg PO or IV twice daily for 5 days, then 0.5 mg/kg PO once or twice daily. Oral phenylbutazone at 2.2 to 4.4 mg/kg once or twice daily can be used in cases of mild uveitis or in animals that require chronic low-dose oral prophylaxis for recurrent disease. Dosage requirements for aspirin make it less practical in acute cases, but prolonged oral administration of 15 mg/kg twice daily has been used to avert relapses. Frequency of NSAID administration should be reduced as clinical response occurs because antiprostaglandins have been linked to GI

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ulceration and renal dysfunction with high doses or chronic use.

Topical ophthalmic NSAIDs are generally more costly than corticosteroids and not as potent if used alone. However, an additive antiinflammatory effect can be seen when topical NSAIDs are used in conjunction with topical corticosteroids in horses with acute or resistant uveitis. Although generally considered a safe alternative to topical corticosteroids in the presence of corneal ulceration, topical NSAIDs have been implicated in the development of melting corneal ulcers in humans. Available generic solutions include 0.03% flurbiprofen sodium and ketorolac tromethamine 0.5%. Dosage frequency is empirical, with intervals ranging from every 6 to 12 hours.

Mydriatic/Cycloplegic Agents.

A parasympatholytic mydriatic or cycloplegic agent must be used if equine uveitis is to be managed successfully. By dilating the pupil and decreasing iris-to-lens contact, the chance of posterior synechia formation—and secondary glaucoma—is reduced. An adequately dilated pupil may also promote vision during the acute episode. Ciliary spasm is relieved, making the horse more comfortable, and the iridociliary vessels return to a more normal state of permeability, with normalization of aqueous humor constituents.

Topical application of 1% atropine solution or ointment is indicated at a frequency no more than two to four times daily until the pupil dilates. The ultimate goal is to maintain mydriasis with the least frequent application possible, keeping in mind the resistance of the inflamed iris and ciliary body to the effects of atropine. Horses on an intensive parasympatholytic regimen should be strictly monitored for signs of reduced gut motility and colic because systemic effects can occur with frequent topical atropine administration.[144] Pupillary dilation may persist for 4 weeks or more after cessation of therapy.

If mydriasis is slow or incomplete, 10% phenylephrine hydrochloride solution may be used topically in conjunction with atropine.[145] Although a study in the horse suggests that phenylephrine is ineffective when combined with a parasympatholytic agent, investigators did not rule out a possible benefit if dosage or duration of therapy was increased.[146] However, frequently applied phenylephrine has been associated with the development of corneal ulcers, corneal endothelial toxicity with secondary corneal edema, and increased uveal exudation, so response to the drug should be monitored carefully.

Antibiotics.

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Because current evidence suggests an immune rather than an infectious basis for recurrent uveitis, antibiotics have assumed a secondary role in ERU management. Although topical antibiotic preparations may discourage opportunistic bacteria during intensive corticosteroid therapy, few will cross the intact cornea and reach therapeutic levels in the anterior chamber or uveal tract. In horses with positive leptospiral titers in serum or ocular fluids, systemic antibacterial therapy with oral doxycycline (10 to 20 mg/kg twice daily for 4 weeks) may minimize recurrences of uveitis.[147] In eyes with mechanical disruption of the blood-aqueous barrier, administration of enrofloxacin IV at 7.5 mg/kg q24h resulted in aqueous humor concentrations greater than the reported MIC for *L. pomona*, suggesting that enrofloxacin may be a good antibiotic choice for horses with leptospirosis-associated ERU.[148]

Other Therapies.

A novel therapeutic approach to management of equine recurrent uveitis was recently described by Fischer and colleagues.[149] Intravitreal injection of 4 mg gentamicin showed promising results in controlling chronic recurrent and persistent uveitis in 71 horses. Complications of the injections were minimal; however, progression of cataract was noted in 5.4% of the horses. Intravitreal gentamicin injections can be performed under standing sedation and may be recommended in horses with uveitis that are refractory to antiinflammatory medication, since a lesser therapeutic effect of a suprachoroidal cyclosporine implant may be seen in such patients.[159]

If leptospiral infection has been well documented in a group of horses with uveitis, vaccination against the disease may be considered. However, although in one study vaccination significantly increased the interval to recurrence (median of 126 days) compared with nonvaccinated controls (median of 86 days), the practice failed to slow the progression of disease in a group of 41 ERU-affected horses.[150] Recently, Zoetis developed the Lepto EQ Innovator® vaccine for *L. pomona* to prevent leptospirosis infection and thereby reduce the risk of abortion, acute renal failure, and development of equine recurrent uveitis. It is not advisable to administer the vaccine to horses that have already developed uveitis, since the immune response to the vaccine could potentially exacerbate the uveitis.

An intracameral injection (25 µg/0.1 mL) of tPA can be used to accelerate fibrinolysis and clear hypopyon in the anterior chamber of horses with severe

uveitis. However, tPA should be avoided in eyes with evidence of hemorrhage in the previous 48 hours.

The precise role of *Onchocerca* species in the pathogenesis of ERU is not yet determined, and considerable controversy exists regarding the necessity or benefit of microfilaricidal therapy in cases of ocular onchocerciasis (see the Ocular Parasites section later).

Acupuncture and homeopathic remedies such as poultices of chamomile and oral methylsulfonylmethane (MSM) have been used in the treatment of ERU, but the efficacy of these unconventional modalities is unknown.

■ Prevention of Disease Recurrence

Cyclosporine.

Cyclosporine A (CsA) is a noncytotoxic immunosuppressive drug that blocks transcription of IL-2 and decreases T-cell responsiveness during the initiation of inflammation.[151,152] These properties could block the nonspecific activation of T cells in recurrent episodes of ERU. With its poor inherent antiinflammatory properties, cyclosporine is likely to be more effective in preventing recurrences than treating active inflammation. Unfortunately, topical application of cyclosporine fails to achieve effective intraocular levels in horses and other species.[153] However, reports of sustained intraocular levels of CsA in ocular tissues[154,155] and resolution of clinical signs in experimental uveitis after implantation of a CsA-impregnated device into the vitreous of rabbit eyes[156] set the stage for implantation of a similar device into the anterior vitreous of horses with experimental uveitis. The CsA-containing implant significantly decreased the duration and severity of inflammation, cellular infiltration, tissue destruction, protein concentrations, and the level of transcription of proinflammatory cytokines in the experimental group.[141] The intravitreal device also prevented recurrences in 81% of horses with spontaneous ERU, but overall success was limited by complications from intraocular hemorrhage, cataract progression, and retinal detachment.[157] Because of significant risk of postoperative complications in the face of concurrent inflammation, a horse with active uveitis is not a suitable candidate for cyclosporine implantation until the inflammation is adequately controlled by conventional means.[52] Intravitreal delivery devices containing other immunosuppressive agents such as tacrolimus were also effective in suppressing inflammation after intravitreal implantation in rabbits

with experimental uveitis.[158]

To minimize ocular morbidity related to implantation, ongoing studies of cyclosporine have focused on development and evaluation of a deep scleral delivery device.[159] Superficial episcleral implantation failed to achieve substantial intraocular levels of CsA or control inflammatory episodes in ERU-affected horses. Therefore the effects of a bioerodible implant infused with CsA and inserted into the suprachoroidal space beneath a partial-thickness scleral flap 1 cm posterior to the dorsolateral limbus were studied. High concentrations of CsA were achieved in the equine ciliary body, choroid, retina, and optic nerve. In horses with severe ERU, only 15% of eyes were blind a mean of 14.2 months after implantation. In contrast, 90% of patients with severe ERU treated conventionally are blind within 1 year.[52] In vitro studies of CsA also documented a direct inhibitory effect on *Leptospira* growth at concentrations achievable within the uveal tissues after deep scleral implantation.[159]

In one retrospective study evaluating the long-term efficacy, complications, and duration of effect of suprachoroidal CsA implants in horses with ERU, the long-term maintenance of vision of these horses was demonstrated. In 151 eyes of 133 horses from the United States and Europe that had CsA devices implanted with a mean and median follow-up time of 28.9 and 26.3 months (range of 13 to 85 months), respectively, 78.8% of eyes were considered visual at last follow-up.[160] The overall mean frequency of uveitis episodes after CsA implantation was 0.09 ± SD 0.08 episodes per month. Among implanted horses, the most common complications leading to vision loss at last follow-up were persistent uveitis episodes (54%), glaucoma (22%), mature cataracts (16%), and retinal detachment (6%). Persistent uveitis episodes tended to be the highest cause of vision loss in implanted horses with less than 24 months and more than 48 months of follow-up.[160]

Core Vitrectomy.

Pars plana vitrectomy has been used to remove fibrin, inflammatory cells, and debris trapped in the vitreous and to improve vision and delay progression of clinical signs in affected horses.[12,161,162] Proponents theorize that removal of T cells or infectious organisms like *Leptospira* may reduce adverse interactions between the vitreous and the uveal tract, thereby reducing the recurrence of ERU. The technique appears more beneficial in European warmbloods with ERU than in Appaloosas with ERU in the United States. In one German study,

recurrence of ERU was prevented in 85% (29 of 34) of treated eyes followed for 5 months to 5 years, but 45% of horses developed significant cataract formation.[142] A study of vitrectomy performed in the United States was also complicated by postoperative cataract formation and progressive loss of vision, despite some decrease in recurrence of uveitis.[163] More recent reports of vitrectomy performed on more than 1200 eyes at the University of Munich described no further recurrences of ERU in 98% of patients.[164] Cataract formation and retinal detachment were reportedly rare in this group of animals. Investigators explained their success on the basis of improved patient selection and surgical expertise.

■ Prognosis

The long-term prognosis for vision in horses with recurrent uveitis is poor, although statistics of actual rates of vision loss are limited. Dwyer's 11-year study of ERU-affected horses reported that 56% of the 160 study animals experienced blindness in one or both eyes.[52] Appaloosas and *Leptospira*-seropositive horses were at increased risk for blindness over the course of the study. All seropositive Appaloosas (100%) lost vision in at least one eye; 50% were completely blind. Among seronegative Appaloosas, 72% lost vision in one or both eyes, and 29% were totally blind. Seropositive horses of other breeds lost vision in one or both eyes 51% of the time, with total blindness in only 17%. Seronegative non-Appaloosas had the best prognosis, with 34% losing vision in one or both eyes and total blindness in only 6%.

Bovine-Specific Ophthalmia

A recurrent uveitis of cattle has been described and compared to that of the horse.[165,166] As with ERU, its definitive etiology is unknown, although a viral infection was originally suggested. Clinical signs include conjunctival hyperemia, corneal edema and vascularization, inflammatory cells and hemorrhage within the anterior chamber and uveal tract, and retinal and choroidal edema and hemorrhage. The disorder is uncommon and does not share the notoriety of its equine counterpart. Therapy is directed at reducing inflammation, as described for the horse.

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Ocular Parasites*

Anne J. Gemensky-Metzler

Parasites are an often overlooked cause of ocular disease in large animals. Ocular parasitic diseases can threaten vision and reduce the economic value of the animal through decreased function, decreased production, or both. The mechanisms by which parasites damage ocular tissues are extremely varied and range from direct tissue effects of aberrant parasite migration to complex immunopathologic responses to parasitic antigens. This section reviews the major ocular parasites of large animals, with reference to the ocular tissue of primary importance. Parasitic eyelid diseases are discussed in Chapter 40.

Corneal and Conjunctival Parasitism

Ocular Onchocerciasis

Ocular disease caused by *Onchocerca cervicalis* is the result of aberrant migration of noninfective microfilariae into the palpebral, conjunctival, and corneal tissues.[1] The larvae do not appear to have a predilection for ocular tissues; rather, the eye is involved as part of a generalized subcutaneous migration. Prevalence of onchocerciasis appears to vary with region of the world. One study concluded that 50% of horses with cutaneous onchocerciasis will have ocular involvement,[2] whereas in another study roughly 50% of horses evaluated had dermal microfilariae, and of those 40% had ocular abnormalities consistent with onchocerciasis.[3]

The pathogenesis of ocular onchocerciasis in horses remains unclear, but an immune-mediated inflammatory response to microfilariae has been implicated. In humans, keratoconjunctivitis and uveitis associated with local presence of *Onchocerca volvulus* microfilariae occur only after the microfilariae die. The endosymbiont *Wolbachia pipientis* bacteria are released, inducing an intense host immune response with subsequent dermal pruritus, uveitis, and often blindness.[4,5] Studies of the immunopathogenesis of *O. volvulus* in humans found that much less corneal inflammation occurred when larvae without *Wolbachia* were injected than when larvae containing *Wolbachia* organisms were injected.[6] Because *Onchocerca* microfilariae are commonly found in equine dermal and

ocular tissues without evidence of inflammation, a similar mechanism may be involved in horses, but this has not been elucidated.

Ocular onchocerciasis occurs mostly in adult horses.[7] The older the host, the greater the exposure to the vector and the parasite, and presumably the greater the potential for ocular migration of microfilariae. Furthermore, increased immune sensitivity may occur with increased exposure to dead microfilariae.

■ Clinical Signs

Conjunctivitis and keratoconjunctivitis concentrated at the temporal limbus are the most common manifestations of ocular onchocerciasis. Acutely, chemosis and hyperemia of the conjunctiva occur, accompanied by increased lacrimation and blepharospasm. Small, raised, white nodules (0.5 to 2 mm in diameter) in the limbal conjunctiva and similar-sized punctate, subepithelial corneal opacities are often present. Corneal lesions are often wedge shaped, with the base of the triangle at the limbus, and are characterized by varying degrees of superficial and deep neovascularization and cellular stromal infiltrates. Untreated, the lesions progressively enlarge, although the rate of progression and the severity of the disease vary. With chronicity, patches of depigmentation (vitiligo) occur in the perilimbal bulbar conjunctiva. Recurrent episodes of keratoconjunctivitis are common.[1]

Migration and subsequent death of microfilariae in the uveal tract result in uveal inflammation. Both the anterior and the posterior uveal tract may be involved. The clinical signs of *Onchocerca* uveitis include apparent photophobia, epiphora, miosis, aqueous flare, inflammatory cells in the anterior chamber, and globe hypotonicity. However, these signs are not specific for onchocerciasis, and other etiologies must be considered (see Table 39.2).

Chorioretinitis reportedly is a manifestation of posterior segment involvement. Active lesions are recognized ophthalmoscopically by hyporeflective areas representing chorioretinal edema and inflammatory exudates, usually observed around the optic disk in a “butterfly-shaped” pattern.[1,3] However, aqueous and vitreous opacification often precludes accurate assessment of the fundus.

■ Diagnosis

Characteristic clinical signs are highly suggestive of *Onchocerca* keratoconjunctivitis, but definitive diagnosis requires corneal or conjunctival biopsy. Conjunctival biopsy may be collected after topical anesthesia, whereas

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general anesthesia is typically necessary for partial-thickness lamellar keratectomies to obtain corneal biopsies. A single 3- to 5-mm biopsy is divided into two samples. One sample is placed on a slide with physiologic saline, minced, and warmed to 37° C (98.6° F) to stimulate larvae movement and therefore enhance their detection. Slides are examined repeatedly over the next hour for migrating microfilariae. The organisms are 200 to 240 mm long and 4 to 5 mm in diameter, with a short, unsheathed tail. The other half of the biopsy specimen is placed in 10% buffered neutral formalin for histopathologic examination.

The presence of microfilariae in ocular tissue does not substantiate a diagnosis of *Onchocerca* keratoconjunctivitis unless evidence of a host inflammatory response exists. The cytologic response is usually pleomorphic, with neutrophils, lymphocytes, plasma cells, and eosinophils present. Varying degrees of neovascularization, pigmentation, lamellar disorganization, collagen degeneration, and calcification are present in the cornea. The overlying epithelium becomes thickened and keratinized.[8,9] The presence of eosinophils in corneal and conjunctival scrapings is suggestive of a parasite etiology, but *Onchocerca* microfilariae are rarely found. Definitive diagnosis of *Onchocerca* as the cause of uveitis is rarely possible.

The differential diagnosis for equine keratoconjunctivitis also includes squamous cell carcinoma, habronemiasis, and bacterial or fungal corneal stromal abscesses. Because horses with ocular *Onchocerca* have a generalized larval migration, they may also have dermatitis, especially of the ventral thorax.

■ Treatment

In humans chronically infected with *O. volvulus,* systemic ivermectin therapy decreases ocular microfilaria burden and improves associated ocular disease. Recently, concurrent treatment with doxycycline has been found to improve efficacy of ivermectin therapy by sterilizing adult female worms through elimination of the symbiotic *Wolbachia* bacteria.[10] Furthermore, by eliminating the *Wolbachia,* the subsequent dermal and ocular inflammatory response when microfilariae die is reduced.[6,11]

In horses, microfilaricide therapy has also been associated with increased ocular inflammation. Therefore treatment is directed at first controlling the inflammatory reaction with systemic antiinflammatory medications and then eliminating the parasite.[12] Corticosteroids have been the mainstay of this initial

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antiinflammatory treatment and may be given topically, subconjunctivally, or systemically, depending on the severity of the inflammation, extent of ocular and dermal involvement, and temperament of the horse. Like ivermectin, moxidectin has been found to be 100% effective in treatment of *Onchocerca* spp. microfilaria-associated dermatitis in horses, but without inducing the dermal edema seen after treatment with ivermectin.[13,14] Systemic NSAIDs or corticosteroids are indicated to treat and/or prevent severe uveitis with concurrent *Onchocerca* dermatitis and before larvicidal therapy. The antiprostaglandin activity of NSAIDs like phenylbutazone (2.2 to 4.4 mg/kg PO q12-24h) and flunixin meglumine (0.5 to 1.1 mg/kg PO, IM, or IV q12-24h) is beneficial, especially when corneal ulceration prohibits topical use of corticosteroids. Prednisolone, at an initial dose of 0.5 to 1 mg/kg PO daily for 5 to 7 days, is tapered as the inflammation decreases. Refractory cases have been treated for extended periods with 0.25 mg/kg PO prednisolone every other day.

When keratoconjunctivitis or uveitis is severe and/or refractory to systemic antiinflammatory treatment, topical application of corticosteroids may be indicated. However, since the corneal infiltrates associated with onchocerciasis are clinically indistinguishable from infectious organisms, extreme caution should be exercised when prescribing or administering topical or subconjunctival corticosteroids in horses. Because of superior solubility, 1% prednisolone acetate and 0.1% dexamethasone sodium phosphate are the preferred topical corticosteroid preparations. Depending on severity, lesions may be treated two to four times daily. Subconjunctival corticosteroids are also beneficial but must be used with caution if corneal ulceration exists. Therapy is tapered as the inflammation is controlled.

Elimination of the microfilariae is recommended once inflammation is controlled (see Chapter 40). Topical antibiotics are also recommended to prevent bacterial infection when corneal or conjunctival epithelial ulceration is present. With uveal involvement, topical mydriatic or cycloplegic agents such as atropine are indicated to relieve ciliary spasm and reduce the risk of posterior synechia formation.

Because systemic ivermectin or moxidectin therapy is not effective in killing adult worms, routine deworming is recommended to eliminate microfilariae and prevent maturation to adult worms.[15] Adult worms may survive in the nuchal ligament of horses for extended periods of time.[7]

Ocular Habronemiasis

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Equine ocular habronemiasis occurs when larvae from *Habronema muscae*, *Habronema microstoma*, or *Draschia megastoma* are deposited on ocular tissues. Flies serving as intermediate hosts for *Habronema* are attracted to moist areas of the body for feeding. Periocular sites with ocular discharge, such as the conjunctiva at the medial canthus, and periocular wounds provide feeding sites. As the flies feed, *Habronema* larvae are deposited on the surface of ocular tissues, migrate into the tissues, and produce a local granulomatous hypersensitivity reaction. Equine habronemiasis occurs worldwide.

■ Clinical Signs

Ocular lesions typically consist of raised, proliferative, nonhealing wounds present at the medial canthus or, less commonly, at other periocular sites. The lesions are friable and pruritic and bleed easily. Lesions often contain small (1 to 2 mm), yellow, caseated nodules (“sulfur granules”). Fistulous tracts and subdermal nodules may develop below the medial canthus.[16] Corneal neovascularization, edema, and ulceration can occur as a result of altered lid function and irritation to the cornea from contact with the rough, irregular surface of the lesion. Corneal involvement increases the degree of ocular pain and blepharospasm.

Habronemiasis lesions are typically seasonal, occurring in the warm summer months when the fly population increases. Certain horses appear to be predisposed to developing cutaneous and ocular habronemiasis, and recurrence may be seen in these animals each summer.

■ Diagnosis

Demonstration of the larvae in the granulomatous lesions or fistulous tracts is diagnostic. Biopsies of the affected tissue are directly examined for *Habronema* larvae and may also be submitted for histopathologic examination. Cytologic examination of conjunctival scrapings reveals a mixed inflammatory response, with neutrophils, eosinophils, and macrophages predominating; however, *Habronema* larvae are usually not seen. The differential considerations for these lesions include squamous cell carcinoma, sarcoids, phycomycosis, onchocerciasis, foreign body reaction, eosinophilic granuloma, and exuberant granulation tissue. Identification by PCR of *Habronema* DNA in the excised tissue may support a diagnosis of habronemiasis.[17]

■ Treatment

Until recently, routine treatment was topical, with systemic therapy reserved for severe or refractory cases. However, oral ivermectin (0.2 mg/kg) and moxidectin (0.4 mg/kg) kill both adults and larvae in the stomach and have become the treatment of choice. Lesions begin to regress in 7 days and are usually healed by 1 to 5 weeks after treatment if reinfestation is prevented.[18,19] Other effective larvicides include trichlorfon and diethylcarbamazine (DEC).

Topical, intralesional, and systemic corticosteroids may be used to decrease the inflammatory response to the larvae, but with ivermectin or moxidectin larvicidal treatment, they may not be needed. Topical antibiotics are indicated, and topical corticosteroids should be avoided if corneal ulceration is present. Débridement and drainage of granulomatous areas and fistulous tracts may increase topical drug penetration, decrease inflammation, and prevent abscess formation. Fly control and prompt treatment of disorders causing ocular discharge or exposure of fresh tissue are important in preventing habronemiasis.

Ocular Thelaziasis

Thelazia spp. nematodes in the conjunctival sac of large animals are considered commensal but can cause clinical ocular disease. *Thelazia* spp. have a worldwide distribution, with *Thelazia lacrymalis* found more often in horses and *Thelazia gulosa, Thelazia rhodesii,* and *Thelazia skrjabini* found more frequently in cattle.[20] The infection rate for cattle and horses in the United States is estimated at 15% to 38%, with horses younger than 3 years of age affected more often than adult horses.[21-24] The complete life cycle of the parasite is unknown, but *Musca autumnalis* (face fly) and other *Musca* species serve as the intermediate host or vector.[25]

■ Clinical Signs

Most horses and ruminants infested with *Thelazia* show no clinical signs. However, chronic conjunctivitis, follicular conjunctivitis, conjunctival cysts, and superficial keratitis can occur, especially in the summer months when flies are active.[26] The disease is often mild but can progress to cause corneal neovascularization, edema, and ulceration. Dacryocystitis due to parasite migration in the nasolacrimal system occurs and is more common in cattle than horses. Migration into the lacrimal gland and its ducts is seen and theoretically

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may lead to keratoconjunctivitis sicca.[24,27]

■ Diagnosis

Direct visualization of the adult *Thelazia* worms in the conjunctival sac or flushing the nasolacrimal system is diagnostic. The parasites are motile unless a topical neuromuscular blocking agent is used. Adult *Thelazia* are 8 to 18 mm long and milky white, and their cuticle contains prominent transverse striations.

■ Treatment

In cattle, both ivermectin and doramectin given systemically at 0.2 mg/kg are effective in eliminating *Thelazia*.[28-30] It is unclear whether ivermectin therapy is effective in eliminating *Thelazia* in horses, and efficacy of newer drugs such as doramectin or moxidectin has not been reported.[28] Alternatively, the parasites may be removed manually with saline flushes or forceps after topical anesthetic is administered, followed by topical ophthalmic organophosphate therapy.[30]

Ocular Elaeophoriasis

Elaeophoriasis, or “sore head,” is a disease of sheep that is caused by the nematode *Elaeophora schneideri.* Adult *Elaeophora* organisms are found in the common carotid and internal maxillary arteries of deer, where microfilariae are produced and migrate into the capillaries of the face and head. Biting flies of the genera *Hybomitra* and *Tabanus* transmit the microfilariae to new hosts. The disease is most prevalent in the fall and winter in western parts of the United States where sheep are grazed at high altitudes. *Elaeophora* infections in deer are usually not associated with clinical signs. In small domestic ruminants, bighorn sheep, and elk, however, the migrating microfilariae can cause a hypersensitivity reaction in facial and ocular capillaries.[31,32]

■ Clinical Signs

Migration of *Elaeophora* microfilariae in ocular capillaries leads to local inflammation. Although the uveal tract is affected more often, sheep with elaeophoriasis may develop chronic keratoconjunctivitis evidenced by epiphora, blepharospasm, conjunctival hyperemia, chemosis, and corneal opacities. Clinical signs of anterior uveitis caused by *Elaeophora* are nonspecific and include epiphora, blepharospasm, miosis, clouding of the anterior chamber, and

cataract formation. Ophthalmoscopic changes indicative of chorioretinitis and optic neuritis are common and include retinal edema, pigment changes in the tapetal and nontapetal fundus, optic disk edema, and optic disk atrophy.[31]

■ Diagnosis and Treatment

Diagnosis depends on demonstrating the microfilariae in skin or conjunctival biopsies. Treatment of heavily parasitized animals may cause death by occlusion of the carotid arteries with *Elaeophora* adults. Drugs used in treatment include piperazine (100 to 300 mg/kg PO), diethylcarbamazine (100 mg/kg PO), and stibophen (5 to 10 mg/kg IM for 3 to 10 days). The efficacy of ivermectin to treat *Elaeophora* is unknown. Symptomatic treatment of keratitis and uveitis is indicated.

Ocular Manifestations of Nasal Bots

Larvae of the arthropod *Oestrus ovis*, the sheep botfly, can aberrantly migrate up the nasolacrimal duct and enter the conjunctival sac, causing local inflammation. Conjunctival migration is accompanied by epiphora, conjunctival hyperemia, and chemosis. Finding the larvae within the conjunctival sac is diagnostic. Treatment consists of ivermectin, moxidectin, or eprinomectin.[33-35] Visible larvae may be mechanically removed. The nasal botfly *Gedoelstia hassleri* is reported to cause conjunctival and corneal lesions in horses in South Africa.

Ocular Manifestations of Trypanosomiasis and Piroplasmosis

Many species of the protozoal blood parasite *Trypanosoma* can infect horses and ruminants, causing fever, anemia, weight loss, edema of the ventral abdomen and limbs, sudden death, and ocular signs such as conjunctival edema, hyperemia, and petechiation.[36] Sheep and goats experimentally infected with *Trypanosoma brucei* can develop keratoconjunctivitis and panuveitis, including chorioretinitis and optic neuritis.[37,38] Demonstration of the organism in blood smears is diagnostic. Quinapyramine sulfate and chloride has been effective in treating many horses, but persistent or recurrent infections have raised concern about possible drug resistance.[36,39]

Other blood protozoans, including *Babesia* and *Theileria*, can also cause conjunctival edema, petechiation, icterus, swollen eyelids, and blood-stained

tears.

Uveal and Retinal Parasitism

Onchocerciasis, Elaeophoriasis, and Trypanosomiasis

Onchocerca cervicalis causes equine parasitic uveitis and chorioretinitis, and *Elaeophora ovis* and *Trypanosoma brucei* cause uveitis in sheep. Ocular manifestations of these diseases are discussed in the Corneal and Conjunctival Parasitism section earlier.

Toxoplasma Iridocyclitis and Retinitis

Although seropositivity for *Toxoplasma gondii* is common in horses and donkeys in some countries, associated clinical disease is uncommon and has not been reported in cattle or horses.[40] However, the intracellular protozoan parasite *Toxoplasma gondii* can cause ocular disease in small ruminants.[41] Invasion and replication in the retina and uveal tract lead to retinitis, chorioretinitis, and anterior uveitis.

■ Clinical Signs

The most common ocular findings with ocular toxoplasmosis are iridocyclitis and retinitis.[40,41] Retinitis is the primary posterior segment lesion, with secondary involvement of the choroid. Retinal degeneration, clumping of pigment in the retinal pigment epithelium and choroid, and optic disk avascularity are seen ophthalmoscopically; however, these lesions are not pathognomonic for toxoplasmosis. Orbital pain and swelling may result from parasitic invasion of extraocular muscles and orbital fat.

■ Diagnosis and Treatment

Toxoplasmosis is most commonly diagnosed by one of a variety of serologic tests for IgG and IgM antibodies or by histopathologic identification through biopsy or necropsy. Antibodies for IgG take more time to develop and may persist for years after an active infection has resolved while IgM antibodies rise and disappear sooner after recovery. Thus, titers for both IgG and IgM should be evaluated and a paired sample taken 2 to 4 weeks later may differentiate past infection or exposure (lower titers with either a decrease or no change) from

active infection (a 4-16-fold increase or sustained high titers).[40] Toxoplasmosis may be treated using sulfadiazine and pyrimethamine. Treatment may be beneficial during active infection when organisms are multiplying but is rarely effective in completely eliminating infection or clearing a subclinical infection because of the tissue encystment of organisms.[40]

Miscellaneous Intraocular Parasites

The most common intraocular parasite in horses and donkeys is *Setaria,* with *Setaria digitata* found more frequently within the eyes of horses than *Setaria equina.* Ocular infestation is presumed to result from aberrant migration of the larval stage. Although *Setaria* causes minimal inflammation in the peritoneal cavity, it can cause severe intraocular inflammation, corneal edema and blindness.[42] Diagnosis is made by visualizing the parasite in the anterior chamber and detecting microfilaria in the blood. Treatment involves symptomatic antiinflammatory and ivermectin therapy,[43,44] but surgical removal of larvae from the anterior chamber has also been reported.[45]

Other filarides found free within the anterior chamber of horses' eyes include *Dirofilaria immitis* and *O. cervicalis.*[2] Diagnosis and treatment are the same as for *Setaria.* Severe endophthalmitis resulting from intraocular infection with the free-living nematode *Halicephalobus* has been reported in a horse.[46] The ocular disease was accompanied by a fatal encephalopathy. Diagnosis was based on finding the parasite during microscopic examination of intraocular tissues.

The canine cestodes *Echinococcus granulosus* and *Echinococcus multilocularis* may form intraocular hydatid cysts in humans, but in horses and ruminants subclinical orbital involvement is more common.[47] There is no medical treatment, and surgical removal is often impossible. Diagnosis is made on histopathologic examination of affected tissues.

Coenurus cerebralis, the intermediate form of *Taenia multiceps* and *Taenia serialis,* can develop in the CNS of sheep, goats, and rarely cattle, causing a disease known as "sturdy" or "gid." Besides having abnormal gait and mentation, affected animals are often centrally blind.[48] No treatment exists, and the disease is typically fatal.

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Ocular Neoplasia*

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A wide variety of tumor types may involve the ocular or periocular tissues of food animals and horses. Except for the most common neoplasms, limited information is available regarding treatment modalities, drug dosages, overall prognosis, and prevention or control. The tendency has been to adapt information and methods used in other areas of medicine for use in large animals. Table 39.4 lists potential presenting signs and corresponding ocular neoplastic conditions or related differential diagnoses for horses, cattle, sheep, and goats. Table 39.5 categorizes ocular neoplasms that have been reported in the literature for each of these species. The greatest amount of information pertains to the horse.

TABLE 39.4

Ocular Neoplasia and Differential Diagnoses by Species Based on Presenting Clinical Signs

Clinical Sign	Equine	Bovine	Caprine	Ovine
Ocular pain	*Habronema* blepharoconjunctivitis[a] Brainstem neoplasia Ocular dermoid Ocular trauma Squamous cell carcinoma[a] Sarcoid	Brainstem neoplasia Ocular dermoid Orbital lymphosarcoma[a] Sporadic bovine leukosis Squamous cell carcinoma[a]	Brainstem neoplasia Ocular dermoid Squamous cell carcinoma	Brainstem neoplasia Ocular dermoid Squamous cell carcinoma
Exophthalmos	1 Optic nerve neuroepithelial tumor 2 Lymphosarcoma 3 Retrobulbar neoplasia	4 Enzootic adult lymphosarcoma[a] 5 Nasal and paranasal sinus neoplasia 6 Nonprogressive bilateral exophthalmos 7 Oral, maxillary, and mandibular neoplasia 8 Retrobulbar neoplasia 9 Sporadic bovine leucosis Squamous cell carcinoma[a]	Nasal and paranasal sinus neoplasia Oral, maxillary, and mandibular neophasia Squamous cell carcinoma	Adenocarcinoma of nasal cavity Nasal and paranasal sinus neoplasia Squamous cell carcinoma

Intraocular mass	Exudative optic neuritis Mastocytoma Medulloepithelioma Ocular melanoma Optic disk astrocytoma Optic nerve neuroepithelial tumor Squamous cell carcinoma Proliferative optic neuropathy Uveal or iris cyst	Ectopic lacrimal gland Ocular melanoma Squamous cell carcinoma	Ocular trauma Squamous cell carcinoma	Ocular trauma Squamous cell carcinoma
Nictitating membrane protrusion	10 Horner's syndrome 11 Ocular trauma 12 Orbital neoplasia 13 Nasal and paranasal sinus neoplasia	14 Horner's syndrome 15 Lymphosarcoma 16 Ocular trauma 17 Nasal and paranasal sinus neoplasia	18 Ocular trauma 19 Nasal and paranasal sinus neoplasia	20 Ocular trauma 21 Nasal and paranasal sinus neoplasia
Nasolacrimal duct obstruction	Cutaneous squamous cell carcinoma[a] *Habronema* blepharoconjunctivitis 22 Nasal and paranasal sinus neoplasia	23 Nasolacrimal duct occlusion 24 Nasal and paranasal sinus neoplasia	25 Nasolacrimal duct occlusion 26 Nasal and paranasal sinus neoplasia	27 Nasolacrimal duct occlusion 28 Nasal and paranasal sinus neoplasia
Ocular discharge	29 Conjunctivitis 30 Ocular trauma 31 Lymphosarcoma 32 Nasal and paranasal sinus neoplasia Retrobulbar neoplasia	33 Conjunctivitis 34 Ocular trauma 35 Lymphosarcoma 36 Nasal and paranasal sinus neoplasia Retrobulbar neoplasia	37 Conjunctivitis 38 Lymphosarcoma 39 Nasal and paranasal sinus neoplasia	40 Conjunctivitis 41 Lymphosarcoma 42 Nasal and paranasal sinus neoplasia
Periorbital or eyeball mass	43 Adenocarcinoma 44 Angiosarcoma 45 Hemangioma 46 Hemangiosarcoma 47 Lipoma 48 Lymphosarcoma 49 Mastocytoma 50 Melanoma 51 Nasal and paranasal sinus neoplasia 52 Ocular dermoid 53 Reticulum cell sarcoma 54 Retrobulbar neoplasia Sarcoid[a] Squamous cell carcinoma[a] Warts	55 Ectopic lacrimal gland 56 Fibroma 57 Fibrosarcoma 58 Ocular dermoid 59 Ocular melanoma 60 Retrobulbar neoplasia 61 Squamous cell carcinoma[a]	62 Fibroma 63 Fibrosarcoma 64 Melanoma 65 Nasal and paranasal sinus neoplasia Ocular dermoid Papillomatosis Squamous cell carcinoma	66 Fibroma 67 Fibrosarcoma 68 Melanoma 69 Nasal and paranasal sinus neoplasia Ocular dermoid Papillomatosis Squamous cell carcinoma
Buphthalmia	70 Glaucoma 71 Ocular melanoma 72 Ocular trauma 73 Medulloepithelioma Infectious bovine	74 Ocular trauma 75 Ocular melanoma		

	keratoconjunctivitis[a] Ocular melanoma Ocular trauma			
Corneal mass	Angiosarcoma Hemangioma Hemangiosarcoma Keratomycosis Ocular dermoid Squamous cell carcinoma[a]	Enzootic adult lymphosarcoma Infectious bovine keratoconjunctivitis[a] Interstitial keratitis Ocular dermoid Squamous cell carcinoma[a]	Keratomycosis Ocular dermoid Squamous cell carcinoma Fibroma	Keratomycosis Ocular dermoid Squamous cell carcinoma
Facial mass	Angiosarcoma Cutaneous habronemiasis Hemangioma Hemangiosarcoma Lymphosarcoma Mastocytoma Nasal and paranasal sinus neoplasia Ocular dermoid Ocular melanoma Oral, mandibular, and maxillary neoplasia Retrobulbar neoplasia Salivary gland neoplasia Sarcoid[a] Schwannoma of eyelids Sialoadenitis	Enzootic adult lymphosarcoma Fibroma Melanoma Nasal and paranasal sinus neoplasia Ocular dermoid Ocular melanoma Papillomatosis Retrobulbar neoplasia Sebaceous cyst Sporadic bovine leukosis Squamous cell carcinoma[a]	Fibrosarcoma Histiocytoma Melanoma Nasal and paranasal sinus neoplasia Papillomatosis Squamous cell carcinoma Fibroma Fibrosarcoma Lymphosarcoma Nasal and paranasal sinus neoplasia Ocular melanoma Papillomatosis Squamous cell carcinoma	

[a]Denotes the most prevalent and important differential diagnostic considerations.

TABLE 39.5
Ocular Neoplasms Reported in Large Animal Species

Neoplasm	Equine	Bovine	Caprine	Ovine
Adenocarcinoma	+			+
Angiosarcoma	+			
Basal cell tumor	+			
Chondroma rodens	+			
Equine sarcoid	+			
Hemangioma	+			
Lymphangioma	+			
Lymphosarcoma	+	+	+	+
Mastocytoma	+	+	+	+
Medulloepithelioma	+			
Nasal/paranasal sinus neoplasia	+			+
Ocular melanoma	+			
Optic nerve astrocytoma	+			
Optic nerve neuroepithelioma	+	+		

Papilloma	+			
Retrobulbar neoplasia	+			
Reticulum cell sarcoma	+	+	+	+
Schwannoma	+			
Squamous cell carcinoma	+	+	+	+

Despite the variety of primary and secondary neoplasms affecting the ocular and periocular tissues, most tumors produce similar effects on the eye, with tissue distortion and loss of function being the initial concerns. Strategic therapy and management goals may vary from curative or palliative (e.g., eliminating discomfort by enucleation) for individuals to elimination of the problem (e.g., culling from the herd) for a population. Tumor treatment options are often similar for neoplasms involving a particular ocular region or location. When designing a management plan, however, the specific histologic tumor type is important in determining prognosis. Classification of a tumor as “benign” versus “malignant” or “localized” (e.g., equine sarcoid) versus “systemic” (e.g., lymphosarcoma) greatly influences treatment options and management approaches. The following discussion addresses the major tumors of concern in large animals and briefly surveys miscellaneous tumors that have been associated with ocular signs.

Bovine Ocular Squamous Cell Carcinoma

■ Definition and Etiology

Bovine ocular squamous cell carcinoma (OSCC), commonly called “cancer eye,” represents the most economically important neoplasm of cattle. It is the most common tumor affecting cattle in North America, and according to estimates from federally inspected abattoirs in the United States, 12.5% of all bovine carcass condemnations were caused by OSCC.[1] The economic impact includes carcass condemnations, production losses, treatment expenditures, and management costs.

OSCC arises from the epithelial surfaces of the conjunctiva (corneoscleral junction, nictitating membrane, and palpebra) or cornea. The etiology is probably multifactorial, with genetic, environmental, and viral factors being proved or suspected.[1-3] In particular, increasing levels of solar irradiation and decreasing amounts of circumocular pigmentation are linked to an increased prevalence of OSCC.[4,5]

■ Clinical Signs and Differential Diagnoses

The gross appearance depends not only on the anatomic tumor site (because this determines the overall interaction between epithelium and underlying connective tissue elements) but also on the stage of malignancy. In general, premalignant squamous cell tumors are small, white, superficial, and elevated hyperplastic plaques or papilloma-like structures with verrucous surfaces (Fig. 39.19). In contrast, malignant tumors are more irregular, nodular, pink, erosive, and invasive in nature (Fig. 39.20). Malignant tumors with accompanying necrosis often have a characteristic foul odor (see Fig. 39.20). Squamous cell carcinomas that invade the orbit may become extensive and eventually invade bone. Often the gross appearance allows a diagnosis to be established, but at times histology is necessary to differentiate among benign tumors, carcinoma in situ, and invasive SCC. Bovine OSCC typically involves (in decreasing order of frequency) the lateral limbus, eyelid margins (especially the lower), nictitating membrane, and medial canthal regions.[1,2] (See Color Plate 39.12) Clinical signs resulting from metastatic lesions are not common, although regional lymph nodes may become infiltrated with neoplastic cells.



FIG. 39.19 Bovine ocular squamous cell carcinoma. Note the small mass involving the leading edge of the third eyelid. (Courtesy Dr. John Angelos.)



FIG. 39.20 Bovine ocular squamous cell carcinoma involving the cornea. Note the irregular and invasive growth into the cornea. The surface is rough and necrotic. (Courtesy Dr. John Angelos.)

Despite the characteristic appearance of lesions, differential considerations include conjunctival follicular hyperplasia, dermoid, fibroma, fibrosarcoma, granulation tissue, infectious bovine keratoconjunctivitis, lymphosarcoma, and mastocytoma (see Tables 39.4 and 39.5).

■ Pathophysiology

The tumor in all species develops through a series of premalignant stages (i.e., hyperplastic plaques or epidermal plaques and papillomas) to progress over months and years to a carcinoma in situ and finally to an invasive squamous cell carcinoma. Neoplastic lesions may arise without notable precursor stages. It is unlikely that tumors arise in the cornea unless previous vascularization has

occurred.[6] Spontaneous regression of 30% to 50% of bovine precancerous lesions may occur,[1] and in rare cases early OSCC may regress spontaneously. Tumors arising at the limbus are confined by the dense and poorly vascularized sclera and cornea, thus hindering metastasis to extraocular sites. Nictitating membrane tumors extend to the base of the membrane and cartilage more rapidly, with spread into the orbit and surrounding bones occurring much sooner than with tumors involving the globe. Although metastasis may eventually occur, extensive extraocular spread is limited in cattle by the practice of sending most affected animals to slaughter.

■ Epidemiology

Although OSCC has been reported in a wide variety of cattle breeds, the Hereford breed (either purebred or crossbred) is most often diagnosed with this tumor as a result of the common use of this breed as a range animal and the strong genetic trait for a white face. Thus selective breeding for partially to fully pigmented periocular skin greatly reduces the occurrence of this tumor.[1] The tumor is more common in older cattle, with the peak age prevalence being 7 to 8 years. Exposure to increasing levels of actinic radiation raises the prevalence of bovine OSCC.[4] The prevalence of ocular squamous cell tumors, including nonmalignant tumors, involving Hereford herds in regions with abundant sunlight can range from 20% to 40%. Research performed in cattle herds suggests that a high plane of nutrition or a lower-than-normal body weight in cows for the first 2 years acts to increase the prevalence.[1] The possibility that bovine OSCC may be induced by viruses (e.g., papillomavirus) warrants further research.

■ Clinical Pathology and Necropsy Findings

Definitive diagnosis is achieved by cytologic samples obtained with a spatula after topical anesthesia[1] or specimens excised for biopsy and fixed in formalin. Benign lesions typically contain superficial anucleated, keratinized squamous cells and deeper epithelial cells with enlarged nuclei and coarse chromatin clumping. Biopsies of these lesions show that the basal layer or basement membrane has not been invaded. Malignant OSCC lesions are composed of pleomorphic cells with bizarre shapes, large hyperchromatic nuclei containing large clumps of chromatin, and prominent nucleoli. Invasion across the basement membrane is noted, and keratin-pearl formation or marked anaplasia is usually

present.[6] In the event of regional lymphatic involvement, fine-needle aspiration or preferably a biopsy may demonstrate neoplastic infiltration.

Depending on the extent of tumor invasion, gross changes may be noted that involve the globe, conjunctiva and nictitating membrane, orbit, bones of the orbit, sinuses, and regional lymph nodes. In rare instances, metastasis to thoracic and abdominal organs can occur.

■ Treatment and Prognosis

Numerous modalities are available, and applications depend on availability of instrumentation, location and extent of the tumor, and value and intended function of the animal. Choices include radiofrequency hyperthermia (RDM Hypertherm [RDM International, Phoenix, Ariz.]), cryonecrosis, intralesional injection of biologic response modifiers (BRMs) such as allogeneic OSCC extract, mycobacterial cell wall fraction (Normagen [Fort Dodge Laboratories, Fort Dodge, Iowa]), *Propionibacterium acnes* (ImmunoRegulin [ImmunoVet, Tampa, Fla.]), intralesional chemotherapy with cisplatin (Platinol [Bristol-Meyers, Wallingford, Conn.]) with or without initial debulking,[7,8] radiotherapy (cesium-137, cobalt-60, gold-198, iridium, strontium-90), and surgical removal (local excision, enucleation, and exenteration with or without salivary gland and lymph node resection). Intralesional use of cisplatin (1 mg/cm^3 of tumor volume) is highly effective, but multiple injections are necessary (four times at 2- to 3-week intervals). Handling of the drug and animal after treatment must adhere to U.S. Occupational Safety and Health Administration (OSHA) guidelines,[9] and animals must not be used for food consumption. Appropriate precautions should be followed with off-label use of cytotoxic drugs. Surgical debulking with adjunctive cryonecrosis or radiofrequency hyperthermia is an effective and affordable treatment modality. Cryonecrosis is achieved with liquid nitrogen, using a probe or spray delivery system to freeze the tissues to −30° C (−22° F) twice, with complete thawing between freeze cycles. Cryotherapy is not recommended for lesions larger than 0.5 cm in diameter. Massive tissue necrosis and loss of the eyelid can be seen if the lesion is too large.

Radiofrequency hyperthermia is performed with piercing or surface probes to heat the tissues to 50° C (122° F) for 30 seconds.

Because recurrence rates range between 30.4% and 42.4%,[3,10] owner compliance to return the animal for follow-up treatment is a significant determinant in overall survival. Financial constraints are the most common

reason for cessation of treatment. Many animals that die as a consequence of OSCC are euthanized at the owner's request. The overall prognosis is determined by the degree of neoplastic involvement of normal tissue, but a guarded prognosis is usually warranted. If treatment is undertaken, intervention should begin at the earliest stages of tumor development. In animals destined for slaughter, the guidelines for condemnation of bovine carcasses affected with OSCC shown in part A of Box 39.1 should be considered.

■ Prevention and Control

In cattle, factors such as genetics, UV light, and environmental factors (e.g., wind, dust) are known to be involved in OSCC. Ocular viral infection may also be contributory. If possible, affected animals should be culled as soon as possible because most production situations preclude environmental factor modification.

Equine Ocular Squamous Cell Carcinoma

■ Definition and Etiology

Equine OSCC is the most prevalent equine ocular neoplasm (followed by equine sarcoid) and typically occurs in horses with nonpigmented eyelids.[3,11] Horses with two or more coat colors (Appaloosa, Quarter Horse, Paint) may have minimal ocular and periocular pigmentation. These breeds are at an increased risk of developing equine SCC. Thoroughbreds, Haflingers, and Draft horses (Clydesdale, Belgian, Shire) also have increased prevalence of SCC, even with adequate ocular pigmentation.[12] The amount of perilimbal and nictitating membrane pigmentation represents another important causal factor in cattle and horses that has received little attention but should be considered on prepurchase and health examinations (see Chapters 1 and 2).

■ Clinical Signs and Differential Diagnoses

Similar tissues are involved in horses as in cattle. These sites include palpebra (eyelids), limbus (corneoscleral junction), conjunctiva, nictitating membrane, and cornea (Color Plate 39.24). Some reports suggest that the nictitating membrane is more frequently involved than the corneoscleral junction.[3,11] In addition to the traditional sites, horses also are affected by corneal stromal invasive SCC. The tumor in this location appears as a nonraised mass lesion that grows directly deep into the corneal stroma (see Color Plate 39.13). The smooth

appearance may lead to clinical underestimation of the greater underlying tumor invasion.[13,14]

Differential considerations for OSCC in the horse include adenocarcinoma, adenoma, angiosarcoma, basal cell tumor, conjunctival follicular hyperplasia, dermoid, fibroma, fibrosarcoma, granulation tissue, habronemiasis, lymphosarcoma, mastocytoma, plasma cell tumors, sarcoid, and schwannoma (see Tables 39.4 and 39.5).

■ Pathophysiology

Horses demonstrate multiple tumor locations and local invasion in up to 50% of cases.[6,10] The tumor has high rates of local infiltration and recurrence.[15] Metastasis beyond extraocular sites is rare in horses but has recently been reported in local tissues, such as nasolacrimal duct, regional lymph nodes or maxillary sinus, and more distant sites, such as mediastinum. These metastases occurred without evidence of local recurrence in a delayed fashion, 18 to 42 months following initial therapy.[16,17]

■ Epidemiology

Equine OSCC in North America demonstrates an increased prevalence with increasing longitude (°W), altitude, and mean solar irradiation.[11] Breeds with a greater risk of developing OSCC include Draft breeds, especially the Belgian (odds ratio [OR] = 21.7), Appaloosa (OR = 7.9), Paint and Pinto (OR = 4.5), and grade horses (OR = 3.1). Coat colors showing an increased risk include white (OR = 26.7), cremello/palomino (OR = 13.7), gray (OR = 6.7), red/white and strawberry/white (OR = 4.7), buckskin (OR = 4.4), and chestnut/sorrel (OR = 3.8).[11] Prevalence increases with age, with the mean age of affected individuals between 9 and 13 years. Bilateral involvement may be as high as 20%.[3,10]

■ Treatment and Prognosis

Surgical excision with adjunctive therapy as described in the Bovine Ocular Squamous Cell Carcinoma section earlier is used in horses. Surgical resection is most effective early in the disease process when clean margins can be obtained. Excision of corneolimbal or corneal SCC via keratectomy followed by adjunctive therapy, such as radiation therapy or cryotherapy, is recommended over surgical excision alone because it is difficult to obtain clean margins in the

periocular area.[13,15] The most common adjunctive therapies for periocular SCC in horses include cryonecrosis (liquid nitrogen), radiofrequency hyperthermia, intralesional cisplatin or carboplatin, and radiation therapy (cesium-137, cobalt-60, gold-198, strontium-90, iridium).[18] Currently the carbon dioxide (CO_2) laser is being used for both surgical removal and adjunctive therapy following removal.[19] Photodynamic therapy (PDT) can be used alone or in conjunction with surgical removal.[20] Recurrence rates were lower following surgical debulking and PDT in comparison to surgical debulking and cryotherapy in a study by Giuliano and colleagues; however, the photosensitizer verteporfin has become increasingly difficult to obtain for veterinary use.[20,21] Recurrence rates for ocular and adnexal SCC is high (44.1%). This can be reduced to 11.9% with adjuvant radiation therapy. The anatomic site in horses with the highest recurrence rate was the limbus (corneoscleral junction) or bulbar conjunctiva.[14] Medical therapy alone is ineffective as sole treatment for ocular SCC, but it may be an effective adjunctive therapeutic modality. Mitomycin (0.4%) and 1% 5-flourouracil (5-FU) can be used as ophthalmic preparations to treat corneal and eyelid SCC.[18,22-24] When applied in an alternating regimen of 7 days on and 7 days off for the cornea, tumor regression was reported for small carcinoma in-situ masses.[12]

■ Prevention and Control

Specific preventive measures have not been systematically evaluated in horses, but recommendations include reducing UV light exposure, using fly masks with UV protection in horses (to decrease solar irradiation and environmental irritants), and avoiding breeds thought to have an increased risk of tumor development. Tattooing of lightly pigmented periocular skin has been performed in hopes of reducing the risk of UV light–induced SCC. This procedure has no deleterious effects, but true efficacy in prevention of SCC is unknown.[25]

Ovine and Caprine Ocular Squamous Cell Carcinoma

Although rarely reported, SCC of the eye and eyelids has been described in both sheep and goats. Invasive OSCC has been reported in twin goats, but etiology was not elucidated.[26] In another study of ovine and caprine cutaneous tumors,

ocular tumors (SCC) comprised 11.2% and 13.3% of tumors detected, respectively.[27]

Ocular Manifestations of Lymphosarcoma

■ Definition and Etiology

Lymphosarcoma is a fatal systemic neoplastic disease of the lymphoreticular tissue. The adult or enzootic form of bovine lymphosarcoma is likely the most devastating and common neoplasm of dairy cattle. This is a systemic disease with ocular manifestations rather than a primary ophthalmic problem. (See Chapter 37 for specific information regarding bovine lymphosarcoma and the bovine leukemia virus.) Lymphosarcoma represents the most common cause of orbital neoplasia in cattle,[28] excluding OSCC that involves the orbit by local extension. Lymphosarcoma may also affect horses[29] and goats. The etiology in horses and goats is unknown.

■ Clinical Signs and Differential Diagnoses

Clinical signs in cattle are usually associated with exophthalmos caused by orbital invasion of neoplastic lymphoid cells, subsequent exposure keratitis, and eventual proptosis[15] (Fig. 39.21). One report documented intraocular lymphosarcoma in a Holstein cow as the presenting sign of generalized lymphosarcoma.[30] Subtle exophthalmos is often overlooked because of the natural exophthalmic state of some dairy breeds. Clinical signs associated with the exophthalmos and exposure keratitis include corneal edema, vascularization, ulceration, epidermalization, conjunctival hemorrhage, chemosis, and ocular discharge. These signs may develop, progress, and change quickly once corneal protection is compromised. Other physical examination findings are discussed in Chapter 37. Differential considerations for exophthalmos include orbital cellulitis, trauma, retrobulbar hemorrhage, retrobulbar soft tissue masses, chronic sinusitis, and sinus neoplasia (see Tables 39.4 and 39.5).



FIG. 39.21 Orbital lymphosarcoma. Diffuse orbital involvement causing exophthalmos and secondary exposure keratitis of the right eye.

Equine lymphosarcoma involving the eye is usually an ocular manifestation of multicentric lymphoma. Other systemic manifestations are discussed in Chapter 37. In one study, ocular lesions were reported in 27% of horses with multicentric lymphoma.[31] Ocular manifestations of equine lymphoma include uveitis, nictitating membrane masses, chemosis and conjunctivitis, and neoplastic infiltration of the eyelids and orbit.[29,31,32] Several cases of primary ocular lymphoma have also been reported, including one horse with anterior uveitis that was attributed to solitary uveal lymphoma and a horse with corneal lymphoma associated with IMK that had been chronically treated with antiinflammatory medications.[33-35] Differential considerations should include conjunctival pseudotumor[36] or follicular conjunctivitis,[37] any chronic inflammatory disease, equine infectious anemia, equine piroplasmosis, and infectious causes of uveitis (see Table 39.3).

■ Clinical Pathology and Histopathology

Definitive diagnosis of lymphoma is based on cytologic and histopathologic findings. Equine malignant lymphoma is often composed of a heterogenous cell population consisting of B and T lymphocytes.[38] Histologic characteristics of lymphoma include compression of normal architecture, a single cell population without organized chromatin pattern, and variable nucleoli size. Tissue samples

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can also allow for immunophenotyping lymphoma into B- or T- cell origin.[39] More information on diagnosing equine lymphoma is available in Chapter 37.

■ Necropsy Findings

As with the clinical signs, necropsy findings are variable. In cattle, orbital involvement is common, with lymphoid tumors being firmly attached to the periorbita and walls of the orbit. Extraocular muscles are frequently infiltrated with tumor cells. The globe itself is typically not involved.[6] Ocular lesions occur less often in horses than in cattle. In the horse, the globe (uveal tract) can be involved in addition to extraocular tissues. As with other systemic neoplastic diseases, multiple organ involvement is usually expected with lymphoma.

■ Treatment and Prognosis

This systemic disease may be treated palliatively or definitively in an attempt to achieve remission for a time. Enucleation provides palliative treatment, and chemotherapy with corticosteroids, vincristine, and L-asparaginase may induce remission. Off-label use of these cytotoxic drugs must be approached with extreme caution, and treated animals must not be used for food consumption. Most cattle with orbital lymphosarcoma either die or are euthanized in terminal stages of disease within 6 months of diagnosis.[28,29] Horses can have a much more protracted disease course, with many presenting because of chronic illness of up to 12 months' duration.[18] A recent investigation of extraocular lymphosarcoma in 26 horses found that prognosis for remission was fair to good when complete tumor excision could be achieved and there was no eyelid or cutaneous involvement.[40] The overall long-term prognosis is unfavorable, regardless of the species involved.

■ Prevention and Control

Control of bovine lymphosarcoma depends on efforts to eradicate bovine leukemia virus, a monumental task in most cases. In other large animal species, prevention and control recommendations for lymphosarcoma are not possible until the etiology can be identified. If animals are destined for slaughter, the guidelines for condemnation of bovine carcasses affected with lymphosarcoma as shown in part B of Box 39.1 should be followed.

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Ocular Manifestations of Equine Sarcoid

■ Definition and Etiology

Equine sarcoid is a locally aggressive, nonmalignant, fibroblastic tumor of equine skin (see Chapter 40). It appears to be the most common equine cutaneous neoplasm, with 14.7% of ocular and adnexal tumors in the horse being sarcoids (all involving the eyelids), making it the second most common eyelid tumor of horses, behind SCC.[41] This neoplasm develops more frequently in sites predisposed to trauma and areas that come into contact with existing sarcoids, and it does not metastasize to internal organs. There appears to be a genetically fixed predisposition, which is probably viral induced. Bovine papillomavirus (BPV-1 and BPV-2) DNA was detected in 88% to 100% of sarcoids examined in several studies.[42,43] Breed, family, and genetic predispositions have also been identified. Quarter Horses, Appaloosas, and Arabians are at the highest risk, followed by Thoroughbreds. Standardbreds seem to have the lowest risk.[44,45]

■ Clinical Signs and Differential Diagnoses

Sarcoids involving the eyelids are classified according to the scheme used for cutaneous lesions: verrucous, fibroblastic, mixed, or occult. Tumors of the eyelids may appear smooth and nodular, crusted and nodular, ulcerated, or pedunculated (Figs. 39.22, 39.23, and 39.24). Regardless of their appearance, the tumors are nonregressing. Periocular sarcoids are subject to trauma; thus the verrucous type frequently transforms into the fibroblastic type with surface ulceration. It is difficult to differentiate sarcoid from fibroma, fibrosarcoma, neurofibroma, neurofibrosarcoma, schwannoma, or nonneoplastic granulation tissue (see Tables 39.4 and 39.5).



FIG. 39.22 Equine sarcoid. Upper eyelid exhibits a smooth nodular mass typical of many periocular sarcoids.



FIG. 39.23 Equine sarcoid involving medial aspect of eyelid. At examination or during treatment, sarcoids may become ulcerated. This tumor became ulcerated after one injection of a *Mycobacterium* cell wall preparation but subsequently resolved.



FIG. 39.24 Multiple equine sarcoids extending from the lateral canthus into periocular tissues.

■ Treatment and Prognosis

Problematic tumors can be treated by a variety of modalities, none of which is uniformly successful. Often multiple treatment sessions are required for tumor control. Treatment modalities that have been reported include surgical excision (50% success rate), cryonecrosis (30% success rate), radiofrequency hyperthermia (RDM Hypertherm), intralesional injection of a BRM (bacille Calmette-Guérin),[41] chemotherapy with intralesional cisplatin or carboplatin (with or without initial debulking),[6,7] radiation therapy (cesium-137, cobalt-60, gold-198, iridium, strontium-90), and chemotherapy (cisplatin or 5-fluorouracil) combined with surgical excision.[46] An available commercial *Mycobacterium* product (TheraCys®) can be used successfully, but the reported clinical efficacy is variable. If the sarcoid is static, flat, and hairless, it may be best left alone because any trauma—surgical or otherwise—could increase the lesion's growth rate and invasiveness. Topical therapy with the antiviral/antitumor drug imiquomod (Aldara®) may induce regression in flatter periocular sarcoids, but care should be taken to avoid contact with the conjunctival or corneal surfaces, as the preparation can induce significant ocular irritation.

Intratumoral use of cisplatin is highly effective (see Chapter 40). Response to therapy varies on the basis of tumor location, duration, severity, and previous therapeutic measures.

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Although all of these treatment modalities have been used for periocular sarcoids, it is prudent to investigate product availability when developing a treatment plan, as some products vary in their accessibility. Prognosis is favorable for equine periocular sarcoid if a complete treatment protocol is followed. As with any neoplastic disease, at the first evidence of recurrence, the animal should be reevaluated

Miscellaneous Tumors With Ocular Involvement

The tumors previously discussed represent the most significant ocular or periocular neoplasms of large animals. However, to the individual animal or owner, any tumor type represents a significant problem, even if it is rare. Thus clinicians must remember that numerous primary and secondary neoplastic processes can involve the eye and surrounding tissues. Secondary tumors may be either metastatic masses or locally invasive masses extending from sites near the eye. The greatest variety of ocular neoplastic disease has been reported in the horse (see Table 39.5).

Miscellaneous Adnexal Tumors

Adnexal tumors that have been reported include adenoma, adenocarcinoma, basal cell carcinoma, fibroma, fibrosarcoma, hemangioma,[47] hemangiosarcoma,[48] lymphoma, melanocytoma, melanoma,[49] papilloma, plasma cell tumors, mast cell tumor,[50] hemangiosarcoma,[51] and schwannoma. Depending on their location, many of these tumors are amenable to excision and adjunctive therapy, such as cryonecrosis or local chemotherapy.[49,50]

Surgical excision of small lesions, cryosurgery, radiation therapy, and intralesional cisplatin[7,8] have been the mainstay of treatment for various periocular tumors in the horse. Periocular melanomas have been reported in the horse and are usually seen in older, gray horses (Color Plate 39.24). Most of these masses are benign, and surgical excision is curative, but eyelid reconstructive procedures for larger excisions can be challenging in the horse. A malignant third eyelid melanoma in a gray horse was successfully treated with excision and local chemotherapy.[49] Oral use of cimetidine has been reported to shrink dermal melanomas,[52,53] but this has not been as successful in other studies,[54,55] so is not currently recommended. A recent retrospective study of

equine ocular and periocular hemangiosarcomas suggests that early intervention and complete excision yields a good prognosis, whereas in past case reports recurrence was more common and euthanasia of affected horses often resulted. Adjunctive therapies, such as Mitomycin C 0.04% or cryotherapy, were used in most cases in this study.[51]

Miscellaneous Ocular Tumors Involving the Globe

Reports of neoplasia involving the globe, all in horses, describe the clinical, histologic, and treatment aspects of hemangiosarcoma,[51] epibulbar melanocytoma,[56] intraocular melanoma,[57,58] medulloepithelioma,[59] and lymphangiosarcoma.[60,61] Intraocular melanomas are rare in horses and are unlikely to metastasize, but secondary glaucoma usually results in enucleation. Ocular melanocytic tumors are more prevalent in horses with a gray coat.[58,62,63] Other than vascular tumors, most primary intraocular tumors in horses do not display a severe metastatic threat. Although enucleation may be curative, histologic evaluation of excised tissues and long-term patient follow-up are necessary if accurate epidemiologic and prognostic data are to be available. Once an accurate diagnosis has been made, the clinician and owner must determine, in light of all available medical information and the proposed use of the animal, whether treatment should be curative or palliative or whether elimination of the problem from the herd should be of greater concern than care of the individual animal.

Miscellaneous Orbital Neoplasia

Orbital neoplasia usually present as gradual exophthalmos with or without blindness and mydriasis. Neuroendocrine tumors are the most frequently reported primary orbital tumor in the horse. They rarely metastasize and tend to grow slowly. Exenteration is usually curative, but care must be exercised because there is a large risk for hemorrhage.[64,65] Optic nerve tumors include neuroepithelial tumors[66] and meningioma.[67] An optic nerve neuroepithelial tumor that presented with exophthalmos displayed metastatic spread as a result of extension into the brain through the optic foramen, causing brain compression 2 months after enucleation.[66] Other tumors previously documented in the equine

orbit include multilobular osteoma (chondroma rodens),[68] fibroma,[69] angiosarcoma,[70] hemangiosarcoma,[51] medulloepithelioma,[71] malignant rhabdoid,[72] and adenocarcinoma.[65]

Any tumor involving the nasal and paranasal cavities has the potential to involve the ocular structures as the result of orbital spread. Enzootic adenocarcinoma in sheep is an example of this type of process. Although infrequently noted, exophthalmos secondary to orbital invasion of this tumor has been reported.[73]

Central blindness has been reported in a mule with an ependymoma, but could be caused by any type of neoplasia affecting the CNS, diencephalon, or occipital cortex.[74] Other forms of intracranial neoplasia can secondarily involve the eye as a result of cranial nerve dysfunction. For example, an intracranial schwannoma caused exposure ulcerative keratitis in a cow that presented with left facial paresis.[75]

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Color Plates



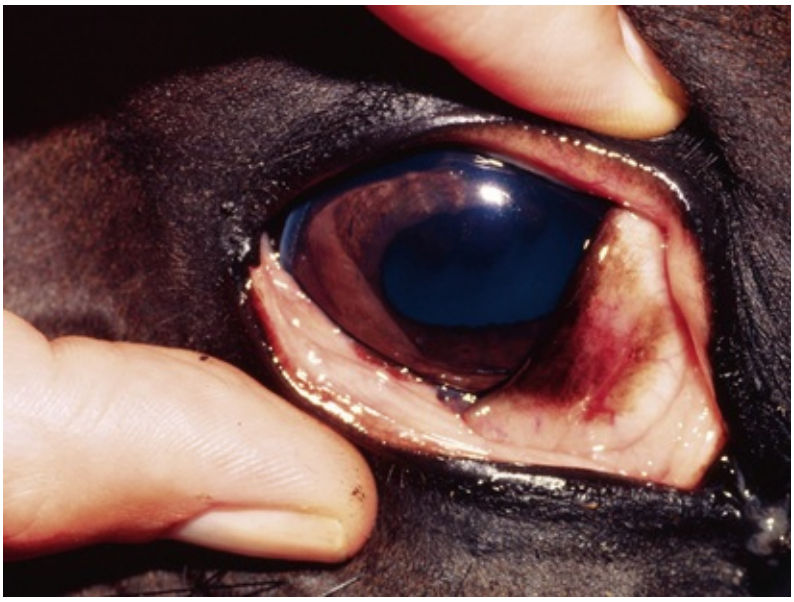
COLOR PLATE 39.1 Marked asymmetry present when standing in front of this equine patient. Left eye is buphthalmic, with elevated lashes and diffuse corneal edema secondary to glaucoma. Right eye is developing phthisis bulbi, evident by increased scleral show and decreased lash height secondary to reduced orbital tissue volume.



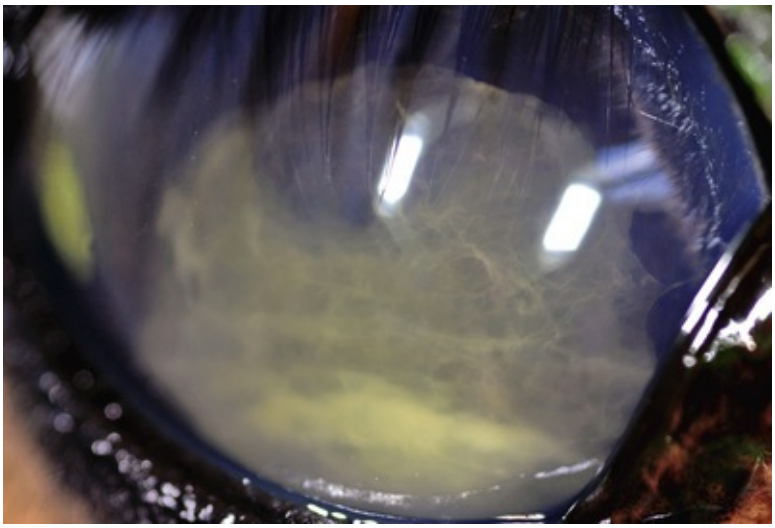
COLOR PLATE 39.2 Dyscoric pupil secondary to posterior synechia and corneal scarring with a hypermature cataract in an equine patient with equine recurrent uveitis.



COLOR PLATE 39.3 Entropion in a bovine patient; note the trichiasis present. Patient presented with blepharospasm and epiphora.



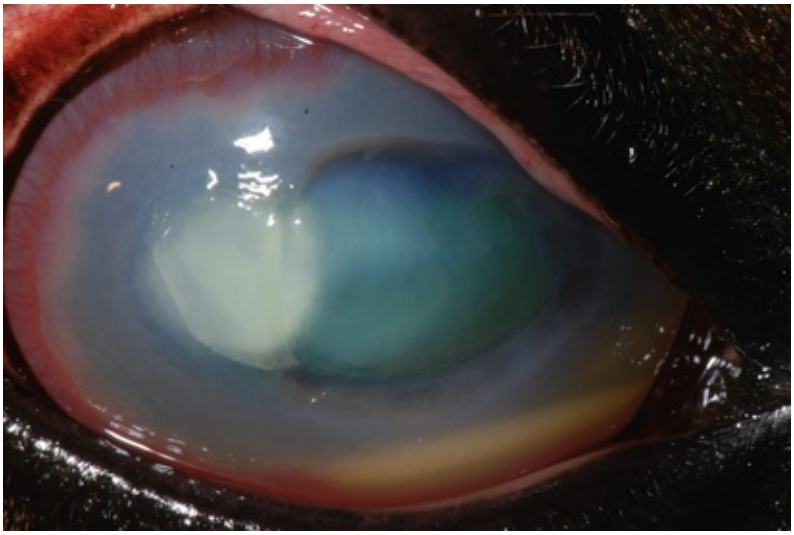
COLOR PLATE 39.4 Third eyelid elevation is noted on retropulsion of the globe. The nictitating membrane can now be thoroughly examined.



COLOR PLATE 39.5 Fibrin in the anterior chamber of a patient with anterior uveitis. Opacity is blocking the fundic reflex. Opacities in the cornea or anterior chamber will also obscure visualization of the iris.



COLOR PLATE 39.6 Diffuse corneal edema in an equine patient. Diffuse patterns of edema, which are fluorescein negative, indicate endothelial dysfunction.



COLOR PLATE 39.7 Cellular infiltration of the cornea is prominently associated with this large corneal ulceration, resulting in stromal loss. Corneal vascularization, diffuse corneal edema, and hypopyon are also present.



COLOR PLATE 39.8 Haab's striae in an equine patient with glaucoma.



COLOR PLATE 39.9 Corpora nigra cyst in an equine patient. Cysts can become large enough to obstruct vision in horses.



COLOR PLATE 39.10 Iridal color change, swelling, and miosis with blood (hyphema) and fibrin in the anterior chamber of a patient with anterior uveitis.



COLOR PLATE 39.11 Phthisis bulbi secondary to chronic equine recurrent uveitis.



COLOR PLATE 39.12 Bovine squamous cell carcinoma of lower eyelid and medial canthus with secondary corneal ulceration.



COLOR PLATE 39.13 Corneal stromal invasive squamous cell carcinoma in the horse. Note the vascularized infiltrative mass with smooth epithelial surface.



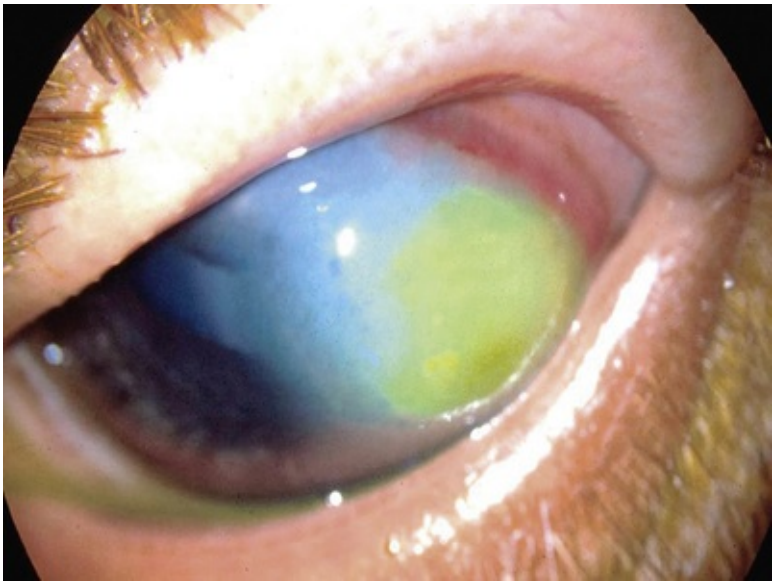
COLOR PLATE 39.14 Congenital cataract in a Thoroughbred colt.



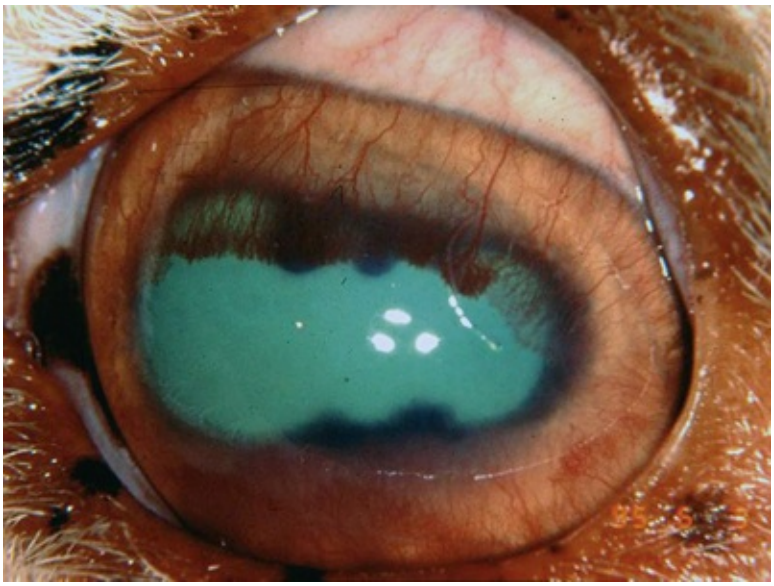
COLOR PLATE 39.15 Severe corneal laceration in a horse. This laceration was large and fibrin, iris, and intraocular contents were expelled. Lacerations such as these require enucleation.



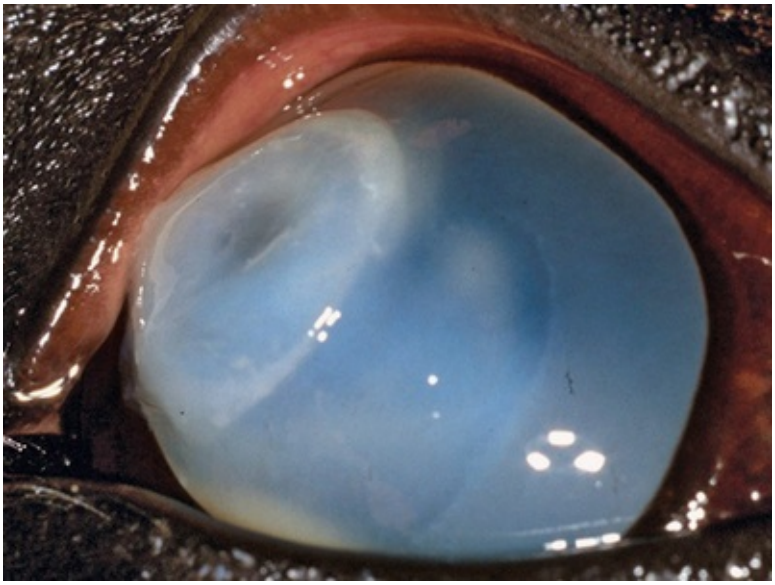
COLOR PLATE 39.16 *Mycoplasma* keratoconjunctivitis in a goat. Note the 360-degree superficial corneal vessels, diffuse corneal edema, a linear accumulation of white cellular infiltrates of the axial cornea, and miosis.



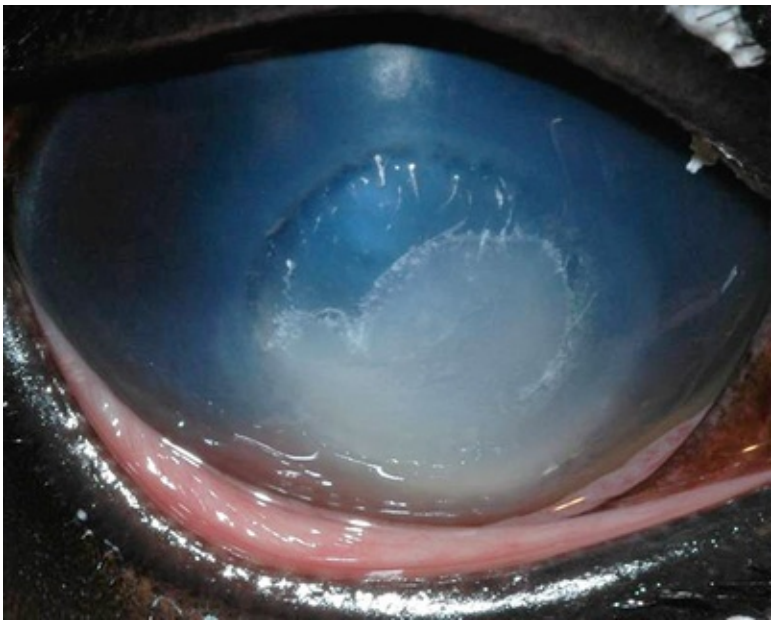
COLOR PLATE 39.17 *Mycoplasma* keratoconjuntivitis in a sheep. Note the miosis, focal corneal edema, and superonasal corneal vessels extending to the margins of a superficial corneal ulcer that has been stained with fluorescein dye.



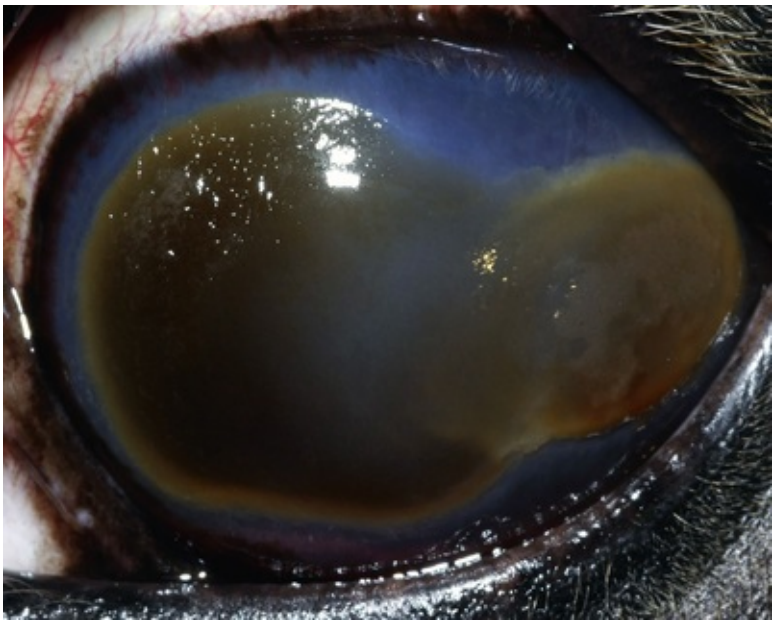
COLOR PLATE 39.18 *Chlamydia* keratoconjunctivitis in a sheep. Note the mild diffuse corneal edema, miosis, and 360-degree superficial branching corneal vessels.



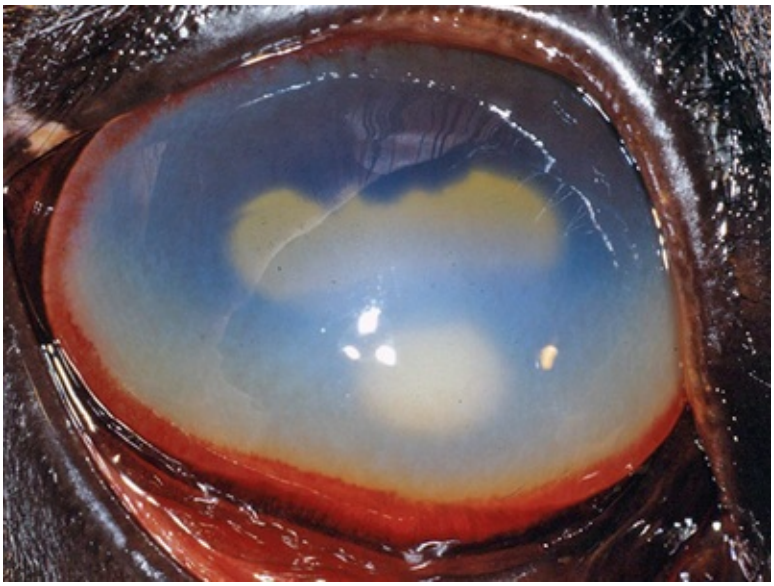
COLOR PLATE 39.19 Melting corneal ulcer, *Pseudomonas* infection. Note the diffuse corneal edema, hypoyon, and a large superonasal ulcer with cellular infiltrate around the margins and malacic corneal tissue protruding from the surface.



COLOR PLATE 39.20 Fungal keratitis with a granular white cellular infiltrate and a surrounding groove or gutter. Note the corneal vascularization inferiorly.



COLOR PLATE 39.21 Fungal keratitis with a pigmented necrotic axial plaque surrounded by active dense corneal vascularization.



COLOR PLATE 39.22 Fungal corneal stromal abscess. Note the 360-degree deep stromal corneal vessels, diffuse corneal edema, yellow cellular infiltrate of the inferior cornea, a paracentral foci of white deep stromal cellular infiltrate, and miosis.



COLOR PLATE 39.23 Infectious bovine keratoconjunctivitis. Deep corneal vascularization, cellular infiltration, ulceration, and diffuse corneal edema are noted.



COLOR PLATE 39.24 Pigmented mass of the superior eyelid in a horse that was diagnosed as having eyelid melanoma after excisional biopsy.

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*Contributions to previous editions by Cecil P. Moore and Erin S. Champagne are acknowledged.

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• CHAPTER 40

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Diseases of the Skin*

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Autoimmune Skin Disorders

Stephen D. White

Pemphigus Foliaceus

▪ Definition and Etiology

The term *pemphigus* is derived from the Greek word for “blister” and is used to describe a group of autoimmune vesiculobullous disorders characterized histologically by intraepidermal acantholysis and immunologically by intercellular deposition of immunoglobulin. Pemphigus foliaceus is the most common of this group of autoimmune diseases; in large animals it has been reported in horses,[1,2] goats,[3,4] sheep,[5] and a donkey.[6] In small animals pemphigus foliaceus has been putatively associated with drugs,[7] but this has not been identified in large animals. The factors precipitating the development of pemphigus foliaceus in large animals are unknown. The clinical lesions recognized in horses and goats are primarily scaling and crusting.

▪ Pathophysiology

Pemphigus foliaceus is characterized by the production of autoantibodies. In humans and dogs these are directed against transmembrane proteins (desmoglein-1 in humans and a minority of dogs; desmocollin-1 in most dogs[8]). The pemphigus autoantibody binds to the transmembrane protein, resulting in release or activation of one or more proteolytic enzymes. These enzymes destroy the attachments between adjoining epidermal cells. The result is *acantholysis;* the epidermal cells assume a rounded shape and separate from one another, leading to the formation of intraepidermal clefts and vesicles.[9]

▪ Clinical Signs

Pemphigus foliaceus is characterized clinically as a generalized exfoliative dermatitis (Fig. 40.1, Color Plate 40.1). Ventral or peripheral limb edema and crusts are the most common clinical signs.[1] In one study, no age, breed, or gender predilection was noted, although 80% of affected horses first exhibited signs between September and February.[1] In the horse, lesions are usually first

noted on the head, limbs, or ventrum. Initial lesions also may be associated with fever, depression, or rarely urticaria. The disease usually progresses to involve the entire body over days to weeks. The primary lesion is a pustule, but these are fragile and transient lesions. Pustules rupture soon after formation, resulting in erosions, epidermal collarettes (rings of exfoliating superficial epidermis), scale, and crust. The lesions may or may not be associated with pruritus or pain.[1,2]



FIG. 40.1 Pemphigus foliaceus in a horse; note the generalized crusts.

In the goat, pemphigus foliaceus also presents as a generalized exfoliative dermatitis. In the limited number of cases described, lesions initially were noted on the limbs, perineal region, and ventrum. The lesions consisted of crusting and scaling resulting from rupture of vesicles and bullae. Pruritus and malaise appear to be variable findings.[3]

▪ Diagnosis

Diagnosis of pemphigus foliaceus in large animals is typically based on biopsy of lesions submitted for routine histopathology. Characteristic histologic findings include intragranular to subcorneal cleft and vesicle formation associated with acantholysis. Both follicular and surface epithelia are frequently involved. Neutrophils tend to predominate in the inflammatory infiltrate, although

eosinophils may also be present.[1-3] Because certain strains of *Trichophyton* species of dermatophytes may also cause acantholysis, any histology suggestive of pemphigus foliaceus must be stained for fungi.[10] Direct immunofluorescence or immunohistochemistry as an aid in the diagnosis of pemphigus foliaceus in horses and goats has also been reported but is somewhat limited to research and academic institutions.[3,9,11] Indirect immunofluorescence testing (for pemphigus antibodies in serum) is reported to be unreliable for the diagnosis of pemphigus foliaceus in horses, although this may be due to variability in the substrate used.[9,12]

▪ Therapy

Treatment is corticosteroids at immunosuppressive doses, such as prednisolone at 1 mg/kg orally (PO) every 24 hours (q24h) or dexamethasone at 0.08 to 0.1 mg/kg PO q24h, then tapering. Oral prednisolone is preferred to prednisone because some horses are unable to metabolize prednisone into the active metabolite of prednisolone.[13] Injectable gold (Solganal [Schering, Kenilworth, N.J.]) was also used successfully, but this product is no longer available. There are anecdotal reports of benefits using another gold salt, aurothiomalate (Myochrysine [Sanofi-Aventis, Bridgewater, NJ]), 1 mg/kg intramuscularly (IM) every 7 days. Gold salts take 1 to 3 months to reach effectiveness, after which dosage frequency can be tapered to every 14 to 30 days. Adverse reactions of gold salts, although rare in the horse, include thrombocytopenia and glomerulonephropathy.

There are also reports of azathioprine (1 to 3 mg/kg PO q24-48h) being used for various autoimmune skin diseases in horses.[14,15] A potential side effect is thrombocytopenia because horses have low levels of the enzyme thiopurine methyltransferase (TPMT),[16] which is responsible for the metabolism of azathioprine in other species, including humans. However, the author has administered azathioprine (1 to 3 mg/kg PO once daily for 1 month, then q48h) to eight healthy horses with no deleterious effects.[17] Azathioprine is used as a steroid-sparing drug with corticosteroids, eventually decreasing the amount of steroid needed. Approximate cost of daily azathioprine for a 500-kg horse is $300/month.

Goats have also been treated successfully with corticosteroids (dexamethasone, prednisolone) and aurothioglucose.[3,4,11] Dosages approximate those for the horse.

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▪ Prognosis

The response to treatment in equine pemphigus foliaceus varies from patient to patient. Many horses require lifelong administration of medication to control the clinical signs; others may be weaned from medication gradually without further relapse. In one study where follow-up information was available for 13 horses, 4 were euthanized because of complications of the disease or its treatment. The reported cases of caprine pemphigus foliaceus are insufficient in number to establish a reliable prognosis.

Pemphigus Vulgaris

Pemphigus vulgaris is a rare autoimmune skin disease anecdotally reported[9] in horses and recently definitively diagnosed in a Welsh pony.[18] In that report, the diagnosis was confirmed with both direct and indirect immunofluorescence and immunoprecipitation studies, the latter identifying circulating immunoglobulin G (IgG) directed against the epidermal transmembrane protein desmoglein-3, similar to the pathogenesis in humans and dogs. Clinical signs are vesicles and ulcerations seen in mucocutaneous and cutaneous areas. Initial corticosteroid treatment improved the clinical signs, but onset of laminitis necessitated a dose decrease with a recurrence of lesions and development of oral ulcers. Despite successive adjunctive treatment with azathioprine, gold salts, and dapsone, the disease progressed, and the pony was euthanized. Necropsy showed additional lesions of the cardia of the stomach.[18]

Bullous Pemphigoid

Bullous pemphigoid is an autoimmune vesiculobullous and ulcerative disorder that affects the cutaneous basement membrane zone (BMZ). It has been rarely noted in horses.[9,19] Initiating triggers for the disease in the horse are unknown.

The pathophysiology of bullous pemphigoid in horses is assumed to be similar to that described in other mammals. Complement-activating anti-BMZ antibodies bind to a glycoprotein antigen in the lamina lucida of the BMZ. In horses this has been shown to be bullous pemphigoid antigen II (also called collagen XVII). Complement activation results in degranulation of mast cells and chemotaxis of neutrophils and eosinophils. Eosinophils release tissue-destructive enzymes with resultant injury to the BMZ, loss of dermoepidermal

adherence, and subsequent blister formation.[9]

Equine bullous pemphigoid is characterized clinically by painful, crusted, or ulcerative lesions of the skin (face and axillae), mucous membranes, and mucocutaneous junctions. Bullae are rare.[9,18] Ulceration may involve the gastrointestinal (GI) tract. The diagnosis is based on histopathologic and, when available, immunofluorescent findings. Treatment is the same as for pemphigus foliaceus; the few cases reported have not had favorable outcomes, but the author has seen a case that initially responded well to corticosteroids.

Alopecia Areata

Alopecia areata is a disease of horses and cattle typified by areas of nonpruritic alopecia.[9,20,21] One horse has been described with severe hoof dystrophy on all four legs.[22] In one report the median age was 9 years, with an age range of 3 to 15 years. Alopecia was the primary dermatologic abnormality in all horses and most commonly affected the mane, tail, and face, although any part of the body could be affected (Color Plate 40.2).[23] Histologically, a lymphocytic infiltrate surrounding the base of the hair follicle is seen, but in long-standing cases this infiltrate may not be present.[24] A mare with a T-cell lymphocytic infiltrate causing a mural folliculitis of the isthmus (central section) of the hair follicles was described.[24] Antibodies targeting the hair follicle itself have been documented.[25] Most horses regrow the hair, but this may take up to 2 to 3 years, and the disease may wax and wane, worsening most commonly in the spring and summer months.[23] Corticosteroids *may* hasten hair regrowth. Mane and tail "dystrophy" of Appaloosas and other breeds may in fact be a form of alopecia areata. Because of the circular nature of the alopecia, this disease is often mistaken for ringworm.

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Hypersensitivity Disorders

Stephen D. White

Atopic Dermatitis

▪ Definition and Etiology

Atopic dermatitis can be defined as an abnormal immunologic response to environmental allergens like pollens, barn dust, and molds. It is increasingly being recognized as a cause of pruritus in horses. The disease may be seasonal or nonseasonal, depending on the allergens involved. Age, breed, and gender predilections have not been extensively reported. A familial predisposition may be present.[1]

The presumed etiology is a type I (immediate) hypersensitivity response mediated by IgE. Evidence indicates that atopic horses do produce allergen-specific IgE[2,3]; the IgE is presumed to be directed against specific allergens. When that allergen is bound to two or more IgE antibodies on the surface of a mast cell, the mast cell releases granules containing various substances that cause erythema, vascular leaking, and pruritus.

▪ Clinical Signs

Pruritus, often affecting the face, distal legs, or trunk, is the most common clinical sign. Alopecia, erythema, urticaria, and papules may all be present. Urticarial lesions may be severe but nonpruritic. In one study of 54 horses with atopic dermatitis, 28 horses had urticaria, 8 had pruritus, and 18 had both.[3] Horses may have a secondary pyoderma typified by excess scaling, small epidermal collarettes, or encrusted papules *(miliary dermatitis).* Diagnosis of atopic dermatitis is based on clinical signs and exclusion of other diagnoses, especially parasite *(Culicoides)* allergy.

▪ Diagnosis

Diagnosis is based on clinical signs and exclusion of other pruritic skin disease. Confirmation to formulate allergen-specific immunotherapy (ASIT [hyposensitization]) is based on either intradermal testing (IDT) or serum allergy

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tests. IDT involves a series of intradermal injections of aqueous allergen extracts along with a positive (histamine) and negative (saline) control. Injections are usually performed over the lateral cervical or thoracic region, and the sites are then observed for 30 minutes to 24 to 48 hours for evidence of wheal formation. A positive reaction does not necessarily mean that the horse's clinical signs are caused by the reacting allergen, but rather that the horse has antibodies to the allergen that, on intradermal exposure, cause wheals to form. False-negative IDT reactions may occur, the most important cause of which is the use of corticosteroids, antihistamines, or phenothiazine tranquilizers before testing, especially within the previous 14 days.[4]

Horses with atopic dermatitis generally have a higher incidence of positive reactions than healthy horses, but the diagnosis (as in other species) cannot be solely made based on the IDT or serologic test alone. Such tests should be interpreted by considering the history of the disease. For example, a horse with seasonal signs is more likely to have an allergic response to seasonal allergens (pollens in summer, barn dust in winter). This interpretation will help the clinician determine which allergens might be relevant in hyposensitization, should the owners choose that treatment.[2,3,5-7]

IDT and available serologic tests look for allergen-specific IgE in the animal's blood,[8] but the latter's use on horses and other domestic species is not without controversy. One study showed no statistical difference in the efficacy of hyposensitization between horses tested with IDT and those tested with serology.[3] Preferentially, IDT and/or serologic testing are performed on horses with atopic dermatitis that have owners interested in pursuing hyposensitization. It should be remembered that, in regard to food allergy, neither serologic testing nor IDT likely has any relation to reality. Clinical research is ongoing to determine the most important allergens, their testing dilutions, and effective control substances.[9,10]

▪ Therapy

Corticosteroid treatment is usually effective in the control of pruritus or urticaria due to atopic dermatitis. The usual oral medication used is prednisolone (1 mg/kg PO q24h), although dexamethasone (0.05 mg/kg PO q24h) can also be used. The injectable dexamethasone solution may be used orally, although the clinician should remember that the bioavailability is 60% to 70% of the injectable route.

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Corticosteroids in horses may cause various adverse effects, including steroid hepatopathy, laminitis, and iatrogenic hyperadrenocorticism. Therefore other modalities of treatment may be used, such as the antihistamine hydroxyzine pamoate (200 to 400 mg/500 kg PO q12h) or cetirizine (0.2 mg/kg PO q12h); doxepin, a tricyclic antidepressant with antihistaminic effects (300 to 600 mg/500 kg PO q12h); or diethylcarbamazine syrup (6 to 12 mg/kg PO q24h). Hydroxyzine, cetirizine; and doxepin may cause either drowsiness or nervousness, although these adverse effects are uncommon. Cetirizine is expensive; because it is the active metabolite of hydroxyzine, if the latter is ineffective in an individual horse, cetirizine probably will be as well. Pyrilamine maleate, though often used in the horse, in fact has poor oral bioavailability.[11] Some clinicians have noted improvement when an essential fatty acid (EFA) product is added to the feed. Platinum Performance (Platinum Performance Inc., Buellton, Calif. [Dr. W. Rosenkrantz, personal communication, 2004]) has been used successfully in some atopic horses as an adjunctive treatment.

In general, hyposensitization injections for any manifestation of atopic dermatitis in the horse should be evaluated for efficacy for at least 12 months. The veterinarian should maintain consistent communication with the client to monitor the progress of treatment and encourage the owner to continue with the injections for the full year. Although most horses will need to be maintained on injections for life, if hyposensitization is successful, perhaps as many as 25% may be able to discontinue the treatment without recurrence.[3] Experience at the University of California, Davis, School of Veterinary Medicine (UCD-SVM) shows that about 65% to 70% of atopic horses improve with hyposensitization[3,12]; other researchers have reported even better results but in a noncontrolled study.[13]

Urticaria

▪ Definition and Etiology

Urticaria is characterized by transient focal swellings in the skin or mucous membranes called *wheals*, which represent localized areas of dermal edema. Angioedema is essentially identical but involves the subcutaneous tissues. The swelling of angioedema is diffuse, often involving the entire face and neck of the animal.

Urticaria is more frequently recognized in the horse than in ruminants.

Allergic urticaria is usually caused by atopic dermatitis (environmental allergens like pollens),[1,6,7,14] drug eruptions (especially from antibiotics[15] and nonsteroidal antiinflammatory drugs [NSAIDs]), contact allergies, and food allergies (rarely).[16]

Physical urticarias are less common and involve a nonimmunologic pathogenesis. The three most important categories are mechanically induced, such as dermatographism, essentially a "pressure" urticaria; cold urticaria; and exercise-induced urticaria. Miscellaneous diseases that can cause urticaria include dermatophytosis (initial lesions),[17] pemphigus foliaceus, "stress" (sometimes seen in racehorses immediately before a race), and vasculitis (Box 40.1). Urticaria is a recognized manifestation of milk allergy in cattle.[18]

Box 40.1

Possible Causes of Urticaria in Horses and Ruminants

Allergic Urticaria

Inhalants

Pollens, animal danders, mold spores, feather down, aerosols, smoke, dust, and volatile chemicals

Injectants

Drugs, diagnostic agents, vaccines, insect stings, serums, and blood

Ingestants

Drugs, various food items, beverages, and occult additive materials found in foods

Infections

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Foci of bacteria, fungal, viral, and parasitic infections

Contactants

Animal products, plant materials, cosmetics, plastic, and other chemicals

Drugs

Penicillin, aspirin, quinine, sulfonamides, insulin, and many others

Milk Proteins

Milk retention (cattle)

Urticaria Caused by Urticariogenic Materials

Drugs

Cocaine, morphine, codeine, atropine, quinine, thiamin, pilocarpine, polymyxin B, D-tubocurarine, dextran, dehydrocholate sodium (Decholin), and other drugs

Foods

Certain citrus fruits, strawberries, and certain fish

Toxins

Cobra venoms, jellyfish toxin, and certain plant and insect toxins

Physical Urticaria

Dermographic (induced by blunt-scratch injury)
Heat
Cold

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Light

Miscellaneous Urticaria

Erythema multiforme
Pemphigus foliaceus
Infections
Collagen vascular disease
Neoplasia
Psychogenic

▪ Pathophysiology

The wheals result from vasodilation and transudation of fluid from capillaries and small blood vessels. Both immunologic and nonimmunologic factors can trigger release of mediators from mast cells and blood basophils that will ultimately produce the characteristic wheals (Fig. 40.2). The most frequently cited immunologic mechanism of urticaria is type I hypersensitivity (IgE). Non–IgE-dependent, immune-mediated urticaria may be induced by either type II (cytotoxic, involving antibody and complement) or type III (immune complex) hypersensitivity reactions. Complement-activated urticaria may involve either immunologic or nonimmunologic mechanisms and may occur through either the classic or the alternative pathway. Urticariogenic materials can induce wheal formation without involving immunologic mechanisms by being ingested, injected, or contacting the animal. Physical agents, including mechanical injury, thermal changes, and solar radiation, may induce urticaria. An example of mechanically induced urticaria is *dermatographism* (whealing after blunt scratch injury to the skin). Local or generalized exposure to heat or cold may induce urticarial lesions in certain individuals.

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Stimulating factors	Target cells	Mediators	Urticaria
Immunologic	Tissue mast cell	Histamine	Wheals
Type I	Blood basophil	Kinine	
Type II		Products of the arachidonic acid cascade	
Type III		Acetylcholine	
Complement			
Urticariogenic materials			
Physical agents			
Idiopathic			

FIG. 40.2 Flow of pathophysiologic events in the development of urticaria.

▪ Clinical Signs and Differential Diagnosis

Wheals range from 1 to 10 cm (0.4 to 4 inches) in diameter and tend to involve the cervical and craniolateral thorax (Fig. 40.3). The animal may or may not be pruritic. Alopecia is not usually a feature of urticaria. The most important factor in distinguishing urticaria from other nodular diseases is that the individual lesions pit with pressure. This is easily demonstrated in the early stages of wheal formation, when the lesions consist primarily of dermal edema. In the later stages, when there is cellular infiltration into the dermis, the pitting is less apparent.



FIG. 40.3 Acute urticaria in a horse caused by an adverse drug reaction.

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▪ Diagnosis

Urticaria is usually a clinical diagnosis; the diagnostic dilemma is to determine the *cause* of the urticarial eruption. A skin biopsy not only will lend support to the clinical diagnosis of urticaria but also may show evidence of pemphigus foliaceus, dermatophytosis, or vasculitis. Initiation of ectoparasite control, IDT or serologic tests for atopic dermatitis, fungal culture, skin biopsy, and feed trials may all be used to determine the underlying disease.[14]

▪ Therapy

Avoiding the allergen or initiating factor or treating the underlying disease is the best therapy. When this is not possible or when the allergens cannot be identified, medical therapy should be used, as described in the Atopic Dermatitis section.

Milk Allergy

The principal cutaneous manifestation of milk allergy is urticaria and is usually seen in cows during the drying-off period. Increased intramammary pressure presumably causes milk proteins to gain access to the circulation, where they induce a type I hypersensitivity reaction.[19] The disorder is believed to be hereditary and familial, with cattle of the Channel Island breeds demonstrating increased susceptibility.

The urticarial reaction can be localized or generalized. Other clinical signs that may be noted include muscle tremors, respiratory distress, restlessness, ataxia, dullness, and even maniacal behavior. Diagnosis is made by observing an edematous swelling at the site of an intradermal injection of the cow's milk or the milk protein casein diluted 1 : 1000, in combination with the appropriate clinical signs.[19,20]

Treatment involves the use of antihistamines early in the disease. Prevention requires avoiding milk retention. An affected cow is likely to suffer recurrences of milk allergy, so culling is usually recommended.

Erythema Multiforme

Erythema multiforme (EM) has been recognized clinically in the horse and in one bull (Fig. 40.4). This is an immunologic reaction in the skin, and

programmed keratinocyte cell death (apoptosis) is the prominent change seen on biopsy. The keratinocytes may be killed specifically by killer lymphocytes. The many possible etiologic factors include infectious diseases, drugs, systemic disease, and neoplasia. In horses, drugs are probably the most frequent inducers of EM, although in many cases an underlying disease is undiagnosed.[21,22] In one bull the EM may have been caused by a pyelonephritis found on necropsy.[23] Clinical lesions are characterized by macules, papules, urticarial lesions, or vesicular bullous lesions. Individual lesions may expand peripherally, leading to formation of target-like lesions. Scaling and crusting are usually not a feature of equine EM unless the disease is characterized by erosions or ulcers. Individual lesions can persist for several days, unlike urticarial lesions. Pruritus and pain are variable but not usually seen. Lesions may occur in association with or after an infection or drug administration. The late Dr. A.A. Stannard of UCD-SVM had theorized that reticulated and hyperesthetic leukotrichia may also represent a type of EM in the horse,[22] although a recent article demonstrated histologic differences between hyperesthetic leukotrichia and EM.[24] One report associated EM in a horse with equid herpesvirus 5.[25] Interestingly, a similar disease, toxic epidermal necrolysis, has rarely been reported in cattle.[26]



FIG. 40.4 Erythema multiforme in a horse.

Differential diagnoses include urticaria, amyloidosis, and other nodular papular diseases. The diagnosis is made based on history, physical examination, and skin biopsies. Histologic changes are distinctive and often include a lichenoid pattern with keratinocyte apoptosis. Vesicular lesions may be present

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and can include more confluent areas of keratinocyte destruction with massive spongiosis and subepidermal and intraepidermal edema.

Treatment should be directed toward the underlying cause if one can be found. A drug eruption should be high on the list, and searching the history for recent drug administration is important. Although some cases of EM are self-limiting and may resolve within 1 to 3 months,[21] corticosteroid treatment as for pemphigus foliaceus may be tried. In our experience, reticulated leukotrichia does *not* resolve spontaneously and does not respond to corticosteroids.

Vasculitis

Vasculitis is a histopathologic term that implies the presence of inflammatory changes in the walls of blood vessels, and it is associated with a broad spectrum of disorders. *Cutaneous vasculitis* is recognized in horses and is most often seen as a feature of photoaggravated dermatitis, drug reactions, or purpura hemorrhagica.[27] Mules and donkeys may also be affected.[27] Affected vessels may be limited to the skin or may involve other organs, resulting in systemic disease. The cutaneous lesions are characterized by crusts, scales, edema, purpura, necrosis, and ulceration, most often affecting the legs (Fig. 40.5, Color Plate 40.3).



FIG. 40.5 Cutaneous vasculitis in a horse. **A,** Vasculitis involving forelimbs. **B,** Vasculitis involving mucous membranes of inner lip.

As a clinical entity, *photoaggravated vasculitis* seems to be more common (if poorly understood) in California and the western United States. Although previously termed *leukocytoclastic vasculitis*, the most common histologic finding is cell-poor and lymphocytic/histiocytic vasculitis.[27] It generally affects mature horses and produces lesions confined to the lower extremities that lack pigment, although pigmented legs may also be affected. Lesions are multiple and well demarcated, with the medial and lateral aspects of the pastern the most common sites. Initially, erythema, exudation, crusting, erosions, and ulcerations develop, followed by edema of the affected limbs. Some lesions may have a "punched-out" appearance. Chronic cases may develop a rough or "warty" surface. Pathogenesis is uncertain; an immune complex etiology has been suggested, and when lesions are restricted to nonpigmented areas this suggests a role for ultraviolet (UV) radiation. Drug reactions may be a potential cause.[22] One report also implicated *Staphylococcus intermedius*.[28]

It must be emphasized that cutaneous vasculitis can occur anywhere on the body and may become generalized.

The differential diagnosis is photosensitization, particularly that caused by contact. The diagnosis is confirmed by skin biopsy, which demonstrates vasculitis, often with vessel wall necrosis and thrombosis involving the small vessels in the superficial dermis. These changes may be difficult to demonstrate.

Treatment involves corticosteroids at relatively high doses (prednisolone at 1 mg/kg PO q12h or dexamethasone at 0.08 to 0.2 mg/kg PO q24h) for 2 weeks, then tapered over the next 4 to 6 weeks. Reducing UV light exposure is helpful, by bandaging affected legs, stabling inside during daylight hours, or both. In some cases, topical corticosteroids (e.g., betamethasone valerate cream 0.1% or triamcinolone spray 0.015%) may enable the horse to be weaned off systemic corticosteroids. Pentoxifylline (8 to 10 mg/kg PO q12h) may be an effective adjunct treatment. Another alternative (but more expensive) is 0.1% tacrolimus ointment q24h (Protopic [Astellas Pharma US, Northbrook, Ill.]). This disease recurs in approximately 25% of cases.[27] These horses are prone to secondary bacterial infections, and a month of antibiotic treatment (usually trimethoprim-sulfamethoxizole) is often indicated if the horse has fever or its legs are extensively swollen.

Cutaneous vasculitis seemingly is rare in ruminants; one report in calves describes lesions on the forelegs and ear tips occurring within a month on one farm. Histology showed a fibrinous-necrotic or leukocytoclastic vasculitis.

Glucocorticoid (prednisolone) therapy was effective.[29] A recent article describes systemic vasculitis (polyarteritis nodosa) in four flocks of sheep. Clinical and histologic signs involved several organ systems, including the skin.[30] Vasculitis and purpura hemorrhagica are discussed in more detail in Chapter 37.

Drug Eruption

A drug eruption is a cutaneous reaction to any agent that enters the circulation by ingestion, injection, inhalation, or percutaneous absorption. Drug eruptions may or may not be associated with systemic signs. Many drug eruptions are thought to be immunologically mediated hypersensitivity reactions, although on occasion they may occur with the initial administration of a drug and therefore without any prior sensitizing exposure, characteristic of an immunologic reaction. Drug eruptions may also occur after years of repeated asymptomatic exposure to a drug, although this is probably less common than formerly supposed. Any medication can cause a drug eruption, but the compounds most frequently incriminated include antibacterial agents (especially semisynthetic penicillins and the sulfas), phenothiazine tranquilizers, NSAIDs and antipyretics (especially phenylbutazone), local anesthetics, and anticonvulsants. In general, the more recently a drug has been given, the more likely it may be the cause of a skin disease. The clinician should try to determine a temporal association between administration of the drug and the skin disease.

Because drug eruptions can result in a wide variety of cutaneous manifestations, they must be considered in the differential diagnosis of all skin disorders. Certain clinical symptoms are more often associated with drug eruptions. Urticaria and angioedema, diffuse erythema, papular rashes, intense pruritus that responds poorly to corticosteroids (Fig. 40.6), sharply demarcated ulcers secondary to vasculitides, vesicular and bullous eruptions, and photosensitization should arouse clinical suspicion of a drug eruption. Typically, cutaneous lesions are noted 24 to 48 hours after drug administration, although there may be a longer lag interval. The eruption usually subsides within 24 to 48 hours after exposure ceases, although lesions may persist for up to 6 months after the offending agent is eliminated.[22]



FIG. 40.6 Drug eruption in a horse; note pruritus.

A diagnosis of drug eruption is based on clinical suspicion associated with an incriminating history of drug administration and by ruling out other possible causes. In a suspected case, all medications should be discontinued. If life-saving medications are being administered, a chemically unrelated compound with similar pharmacologic effects should be substituted. Administration of corticosteroids may provide some relief, but drug eruptions respond variably to corticosteroids. Although development of a cutaneous reaction after readministration of the suspected agent would support a diagnosis of drug eruption, readministration is not advisable because it can be fatal as well as unethical. Future exposure to any implicated compounds and chemically related substances should be avoided.

Contact Dermatitis

▪ Definition and Etiology

Contact dermatitis is recognized in both horses and ruminants and can be subdivided into irritant and allergic contact dermatitis. *Irritant contact dermatitis* occurs more often and is defined as a cutaneous reaction to an irritating concentration of an offending agent. The substance chemically damages the skin without immunologic mediation. The reaction may occur after a single contact with a strong irritant or after repeated contacts with a milder irritant. *Allergic contact dermatitis* represents a cutaneous reaction in a sensitized animal to a nonirritating concentration of the offending agent. Tissue damage is immunologically mediated by delayed-type hypersensitivity (type IV), so prior

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exposure is required to sensitize the skin to the material eliciting the dermatitis.[16,18] It may be difficult to differentiate between the two types of contact dermatitis, and it may not be clinically important. In our experience, the vast majority of contact dermatitis cases are iatrogenic, caused by topical products placed on the skin by veterinarians or owners.

▪ Clinical Signs

The clinical lesions associated with allergic and irritant contact dermatitis are very similar. Predisposed areas include the muzzle, extremities, and areas contacted by tack. Early lesions include erythema, edema, and vesiculation that progress to erosions, ulcerations, and crusting and ultimately to lichenification and hyperpigmentation. A gravity-induced drip pattern may be evident when the irritant is a liquid.[31]

▪ Diagnosis

A detailed history is very important—the bedding, all topical products and blankets, and other potential environmental antigens and irritants should be noted. Certain woods release various irritant oils and have been implicated when incorporated into the bedding.[32] Patch testing is possible but usually impractical. Provocative exposure is the most useful test for diagnosis of contact dermatitis, although it does not reliably distinguish between allergic and irritant contact dermatitis. It requires avoiding contact with all suspected agents for 7 to 10 days to permit clearing of the skin lesions. The patient is then reexposed to these agents on an individual basis at 7- to 10-day intervals while being observed for recurrence of the dermatitis. When a positive reaction is observed, challenge with the suspected agent should be repeated to confirm the diagnosis. The process is time consuming, requiring owner patience and cooperation.

▪ Therapy

An animal with a suspected or confirmed diagnosis of acute or irritant contact dermatitis should be placed in an environment where there is negligible chance of exposure to agents that might have produced the dermatitis. Symptomatic treatment pending spontaneous resolution includes gently washing the affected regions with water. Pentoxifylline at the dose noted earlier for vasculitis may be helpful in horses.

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Bacterial Diseases

Stephen D. White

Dermatophilosis (Streptothricosis, Rain Scald, Lumpy Wool, Strawberry Foot Rot)

▪ Definition and Etiology

Dermatophilosis is caused by an actinomycete bacterium, *Dermatophilus congolensis.* The organism is a gram-positive, non–acid-fast, branching, filamentous, aerobic bacteria that divides longitudinally and then transversely to form parallel rows of coccoid zoospores. Dermatophilosis affects horses, cattle, sheep, and goats, as well as a wide range of other mammals.[1-4]

Three conditions must be present for *Dermatophilus* to manifest: a carrier animal, moisture, and skin abrasions. Chronically affected animals are the primary source of infection, but they become a serious source of infection only when their lesions are moistened, which results in release of zoospores, the infective stage of the organism. Mechanical transmission of the disease occurs by both biting and nonbiting flies, ticks, and possibly fomites. Because normal healthy skin is impervious to infection with *D. congolensis,* some predisposing factor that results in decreased resistance of the skin, especially prolonged skin wetting by rain, is necessary for infection to occur. The organism has been isolated from the environment of affected animals. Distribution is worldwide, but frequency of occurrence of dermatophilosis varies with geographic location; areas with increased rainfall are predisposed. There is no apparent age, breed, or gender predilection.

▪ Clinical Signs

Dermatophilosis is usually seen during the fall and winter months, with the dorsal surface of the animal most often affected (Fig. 40.7, Color Plates 40.4 and 40.5). In horses, this association with the wetter months of the year has led to the term *rain scald.* Occasionally the lesions involve the lower extremities when animals are kept in wet pastures (“dew poisoning”) or if horses are left in the stall while the stall is cleaned with high-pressure water hoses. In the early stages of disease, the lesions can be felt more easily than they can be seen. Thick crusts

can be palpated under the hair coat. Removing the crusts and attached hair exposes a pink, moist skin surface, with both the removed hair and the exposed skin assuming a paintbrush shape. The undersurface of the crusts is usually concave, with the roots of the hairs protruding. In cattle and goats the older term *cutaneous streptothricosis* is sometimes still used. In sheep the condition is referred to as “lumpy wool” or “mycotic dermatitis” when wooled areas are affected and as “strawberry foot rot” when distal extremities are involved.

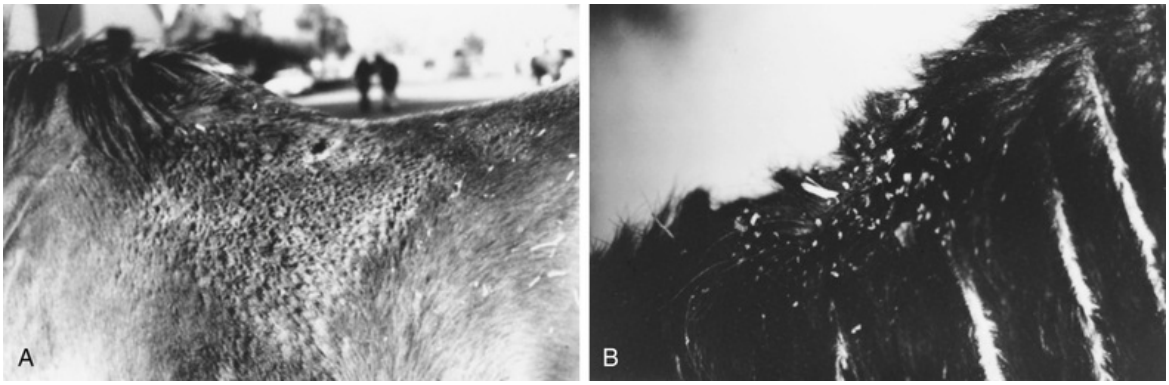


FIG. 40.7 Dermatophilosis *(Dermatophilus congolensis).* **A,** Horse with suppurative crusts and matted hair on the back. **B,** Scaling and crusting over withers and neck of a bovine.

Body areas predisposed to infection include those that are most susceptible to maceration and trauma. The distal extremities, muzzle, and entire length of the dorsum are frequently the initial sites of infection. Nonpigmented skin is also reported to be more susceptible to infection. Horses develop lesions in areas rubbed by tack, and cattle often have involvement of the udder and scrotum. Goat kids may have a tendency to develop lesions on the pinnae and under the surface of the tail. Sheep may develop a form of dermatophilosis that begins as an encrusted proliferative dermatitis at the coronet region; removal of the external crusts reveals a pink-red granulation bed that resembles the surface of a strawberry. Lesions can extend from the hoof to the hock; with loss of the crusts, ulceration occurs. Under appropriate conditions, dermatophilosis can become generalized.

▪ Diagnosis

Diagnosis is made by demonstrating the “railroad-track” cocci on impression smears. A portion of one of the crusts should be minced and mixed with a few

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drops of sterile water on a glass slide, Gram stained, and examined microscopically. Alternatively, bacterial culture or histopathology may be used for diagnosis, particularly in chronic cases. A thick crust composed of alternating layers of parakeratotic stratum corneum, dried serum, and degenerating neutrophils is the most characteristic change. A superficial folliculitis may be a prominent feature of the disease.[1] In Gram-stained sections, the branching filamentous organisms can be observed in the crusts and follicles. A recent report showed the efficacy of using real-time quantitative polymerase chain reaction (RT-qPCR) in the diagnosis of this organism.[5]

▪ Therapy

The animal should be removed from the wet environment if possible. Careful removal of possibly painful crusts, washing with iodophors or lime sulfur, and administration of antibiotics (for horses, 22,000 units/kg procaine penicillin G IM twice daily or 30 mg/kg trimethoprim-sulfamethoxizole PO twice daily) for 7 to 10 days.[4] Long-acting oxytetracycline given as a single 20-mg/kg IM dose has been reported to be effective for bovine and ovine dermatophilosis. The crusts are important in contagion, so they should be disposed of rather than brushed to the ground. Reduced tick control has been associated with increased incidence of the disease.[6]

Folliculitis, Furunculosis, and Impetigo

▪ Definition and Etiology

Bacterial *folliculitis* (superficial pyoderma) is defined as inflammation of the hair follicles secondary to a bacterial infection. *Furunculosis* is the term used to describe a follicular infection that breaks through the follicular wall (“boil”). Bacterial infection that causes subcorneal pustules but does not involve hair follicles is called *impetigo.* Folliculitis and furunculosis are often seen in horses[1,4] and goats[3] but are an uncommon problem in cattle and sheep. Impetigo is relatively common in cattle and goats.

Bacterial folliculitis is usually caused by a coagulase-positive *Staphylococcus* species. Both *Staphylococcus aureus* and *Staphylococcus pseudintermedius* (formerly *S. intermedius*) have been isolated.[7,8] In one study in horses, *S. aureus* accounted for twice as many isolates as *S. pseudintermedius;* the same study isolated some strains of *Staphylococcus hyicus* as well.[9] *Staphylococcus delphini*

has also been isolated from horses on occasion. Many isolates are resistant to penicillin G.[9] Occurrence of pyoderma has been linked to poor nutrition and husbandry in some cases.[10]

▪ Clinical Signs

Clinical signs of staphylococcal pyoderma are most often crusts, usually in a circular pattern suggestive of dermatophytosis (this may be why equine pyoderma is underdiagnosed), epidermal collarettes (circular skin lesions with an exfoliative border, as seen in dogs with superficial pyoderma), or encrusted papules similar to the miliary dermatitis reaction pattern in cats.[7] These infections tend to vary in intensity of pruritus. Histology often shows folliculitis and furunculosis, but bacterial colonies are not always seen. A truncal form of bacterial folliculitis (contagious acne, contagious pustular dermatitis, Canadian horsepox) is often associated with poor grooming and trauma from tack and saddle; warm, wet weather; and heavy work. It is painful and interferes with working and riding. It is usually caused by a coagulase-positive *Staphylococcus* species but may also be due to *Corynebacterium pseudotuberculosis*[11] (more often a cause of deep pyoderma, as discussed later). In horses, folliculitis often develops in the saddle and lumbar region, particularly in the summer. The affected area may initially be swollen and sensitive, followed by formation of follicular papules and pustules. These may become confluent or rupture, forming plaques and crusts. Deep pyoderma followed by ulceration may develop over large areas of the body, especially the neck, sides of the thorax, inner surface of the thighs, and prepuce.

A pastern bacterial infection (pastern folliculitis) is often seen. Again, the causative agent is usually a coagulase-positive *Staphylococcus* species. As with most primary pyodermas, the mechanism by which the organism gains its foothold is unknown; it is not necessarily contagion or poor sanitary conditions. The lesions are usually limited to the posterior aspect of the pastern and fetlock regions; one or more limbs may be involved. Initial lesions consist of papules and pustules. If left untreated, they coalesce and may produce large areas of ulceration and suppuration that may be quite painful. The disease is usually not associated with systemic signs, and the general health of the horse is not affected.

A relatively uncommon nodular disease termed *botryomycosis* mimics actinomycosis or a deep fungal infection but is most often caused by

Staphylococcus spp. in the horse. These may require surgical excision as well as long-term antibiotics.

▪ Public Health Considerations

In a 2000 study, methicillin-resistant coagulase-negative staphylococcal species were cultured from healthy horses in Japan. The authors concluded, “These organisms must be considered a potential threat to horses and veterinarians who care for them.”[12] In a 2006 study from the Netherlands, methicillin-resistant coagulase-negative staphylococci were found frequently.[13] The organism was usually *Staphylococcus sciuri* rather than *Staphylococcus epidermidis*, which was found in the humans in close contact with these horses. No methicillin-resistant *S. aureus* (MRSA) was found in healthy horses. A more recent article reported *S. sciuri* from a horse's skin infection.[14]

There is little public health concern about methicillin-resistant *S. pseudintermedius* (MRSP) or *S. delphini* because clustering of equine cases does not appear to be important, and zoonotic disease potential seems to be limited.

In contrast, a single strain of MRSA was isolated from *both* humans (13%) and horses (4.7%) on horse farms in Canada and New York state.[15] In looking at horses admitted to a university teaching hospital (Ontario Veterinary College), MRSA was isolated from 120 (5.3%) of 2283 horses. Of these 120 horses, 50.8% were positive at admission, and clinical infections due to MRSA were present or developed in 14 animals. Horses colonized at admission were more likely to develop clinical MRSA infection. Administration of ceftiofur or aminoglycosides during hospitalization was the only risk factor associated with nosocomial MRSA colonization. Another strain of MRSA was isolated from a small number of horses at the Veterinary University in Vienna, Austria.[16] Of further concern is the finding of nasal carriage of *S. aureus* in cattle.[17]

Of most concern is the finding of humans reporting skin lesions after contact with a community MRSA-positive affected foal, despite short-term contact with standard protective barriers. Isolates from the foal were indistinguishable from those affecting humans.[18] In another study, MRSA was isolated from 15.6% of veterinarians or technicians in large animal practice, as opposed to from only 4.4% of small animal personnel; large animal practice was the only statistically significant variable associated with colonization of MRSA.[19] On two horse farms with endemic MRSA, active screening and strict implementation of infection control protocols resulted in a rapid decrease in the number of

colonized horses. Most horses eliminated MRSA without antimicrobial treatment.[20]

▪ Therapy

The antibiotic usually used for bacterial skin infections in the horse is oral trimethoprim-sulfamethoxazole (TMS [30 mg/kg PO q12h for 2 to 6 weeks, longer for deep infections]).[7] Interestingly, dosing intervals for intravenous (IV) administration of TMS in horses may not be appropriate for use in donkeys or mules. Donkeys eliminate the drugs rapidly compared with horses.[21] In cases of staphylococcal resistance to TMS, enrofloxacin or doxycycline may be used. Doxycycline is less expensive but associated with a higher incidence of colic. Dosage is usually 10 mg/kg PO q12h. Off-label use of oral enrofloxacin formulations for poultry, ruminants, or swine has been suggested. The formulation for poultry may be used; the dose is 7.5 mg/kg PO once daily. Use of enrofloxacin in young horses (<2 years old) should be avoided because of concerns about damage to the articular cartilage.[22] One report of use of an oral gel formulation of enrofloxacin (100 mg/mL of gel) showed good clinical efficacy for infections in several organs, but almost one third of the horses had some diarrhea, and 10% had oral lesions.[23] It was hypothesized that this latter side effect could be overcome with a tap-water rinse of the oral cavity after administration; however, we have seen oral lesions and a swollen tongue, suggestive of a contact reaction, develop in a horse receiving the oral water rinse. Interestingly, enrofloxacin binds to melanin in equine hair, although the clinical implication is unknown.[24] Ceftiofur sodium (2.2 mg/kg IM or IV q12-24h) may also be used for pyoderma in horses, although its usefulness over a long period is limited by its parenteral route. In one report of 15 horses, vancomycin was used, alone or in combination with an aminoglycoside, to treat MRSA and enterococcal infections. The average vancomycin dosage was 7.5 mg/kg IV q8h over 30 minutes. The antibiotic, alone or in combination with an aminoglycoside, was safe and effective. Because of the problems with emerging resistance, we recommended that vancomycin use in horses be limited to cases where culture and susceptibility indicate effectiveness and no reasonable alternative treatment exists.[25]

For localized lesions, mupirocin ointment 2% or silver sulfadiazine cream (Silvadene) may be effective. Recently a gel with 0.4% stannous fluoride (MedEquine Gel [Dolphin International Inc., Camdenton, Mo.]) was reported as

resolving bacterial skin infections in horses.[26] As shampoos, ethyl lactate (Etiderm [Virbac, Fort Worth, Tex.]) or a *tris*-EDTA/4% chlorhexidine combination (Triz-Chlor 4 [Dechra, Overland Park, Kan.]) is helpful.

Pyoderma in ruminants has not been studied as much as in horses. In goats, lesions (often pustules that progress to crusts) usually begin on the udder and spread to the abdomen, thigh, perineum, and face. Pruritus is variable. Stress from parturition is also an important predisposing factor in goats. In sheep, a generalized staphylococcal scalded skin–like disease has been reported in lambs.[27] Staphylococcal infections associated with *Psoroptes ovis* infestation have also been noted.[28,29]

In cattle, furunculosis caused by *C. pseudotuberculosis* manifests as a locally extensive, raised, raw lesion that is frequently hemorrhagic. The lesions are almost constantly covered with a serosanguineous exudate, and palpation of the lesions usually elicits a pain response. Treatment is similar to treatment of dermatophilosis, taking into consideration culture and susceptibility results as well as withdrawal times for food animals.

Equine Staphylococcal Cellulitis

Cellulitis is a severe deep, suppurative process in which a poorly defined area of infection tends to dissect through tissue planes. Although many organisms are capable of producing cellulitis, staphylococcal cellulitis has been recognized as a specific disease entity in Thoroughbred racehorses.[30] Coagulase-positive staphylococci have been isolated from all reported cases, and, when speciated, the isolates were classified as *S. aureus.*[31] Other studies of pathogenic *Staphylococcus* spp. from horses have suggested that *S. aureus* and *S. (pseud)intermedius* are the major cutaneous pathogens,[31,32] with no significant difference in their susceptibility patterns.[31] In a retrospective study of limb cellulitis in 44 horses, coagulase-positive *Staphylococcus* spp. were cultured from 33 of 36 horses from which specimens were obtained. Horses that were febrile at admission or developed laminitis were significantly less likely to survive.[33]

The cause of staphylococcal cellulitis is uncertain. Management practices may be associated with the condition because bathing, grooming devices, or handlers can be a source of the organism.[32]

The initial symptom is acute swelling and lameness that involves one or more

limbs. Lesions progress rapidly by dissection along tissue planes. The overlying skin becomes devitalized and frequently sloughs. Accompanying systemic signs include increased rectal temperature and heart rate. Laminitis of either the affected or the contralateral limbs, osteomyelitis, and bacteremia are possible sequelae.[30] Diagnosis is based on the results of bacterial culture and biopsies for routine histopathology.

Treatment must be aggressive and initiated early in the course of the disease. Pending the results of bacterial culture and sensitivity, treatment should include broad-spectrum antibiotics like TMS. To decrease edema, promote weight bearing, and reduce the chance of laminitis, therapy should include NSAIDs, hydrotherapy, and support wraps.[30] The prognosis for complete recovery is guarded.

Equine *Corynebacterium pseudotuberculosis* Cellulitis

Solitary or multiple abscesses or nodules with many draining tracts that progress to diffuse cellulitis are often caused by *C. pseudotuberculosis;* when it affects the pectoral region it is called “pigeon fever” in the United States. This type of deep *Corynebacterium* infection may occur where caseous lymphadenitis is common in sheep or goats (although proximity to small ruminants is not a requirement), and it also may be seen seasonally when insect populations and activity are maximal. This may occur in the dry seasons, giving rise to another vernacular name, “dry land distemper”, when the process affects the inguinal region. Insect vectors seem probable, especially stable, horn, and house flies.[34] The frequency of this disease is increasing in the United States.[35] Draining nodules or abscesses are especially common in the pectoral region and occasionally affect the face, neck (Color Plate 40.6), axilla, groin, and limbs; they begin deep and enlarge, often with much edema, and rupture in 1 to 4 weeks, discharging viscid creamy pus, a major source of contamination. Abscesses most often rupture externally. Diagnosis is by clinical signs, with the infection readily identified by bacterial culture of aspirate samples from abscesses. The synergistic hemolysis inhibition test is useful for diagnosis of internal abscesses but unreliable for external abscesses.[36] Recent molecular studies of various strains of *C. pseudotuberculosis* have not shown definitive relationship between an individual strain and the location of the abscess.[37,38]

Treatment depends on location. If the abscess is in the axilla and thus painful on movement or prevents locomotion, establishing drainage is important, and antibiotics are indicated.

The antibiotics most commonly used are ceftiofur (2 to 4 mg/kg IM q12-24h), enrofloxacin (7.5 mg/kg PO or IV q24h), procaine penicillin (20,000 to 50,000 IU/kg/day), rifampin (3 to 5 mg/kg PO q12h), and TMS (30 mg/kg PO q12h).[36,39] Interestingly, there have been no changes in the minimum inhibitory concentrations of effective antibiotics over time.[40] Treating with TMS and rifampin concurrently can lead to a greater incidence of colitis and is to be avoided. If the decision is made to use antibiotics but drainage cannot be easily established (e.g., axillary abscess, with owner unwilling to allow veterinarian to use trocar and drain), antibiotics *must* be used for a minimum of 1 month. If the abscess is solitary and not causing pain or fever, antibiotics are usually unnecessary, but bringing the abscess to a head with hot packs or heat-inducing agents (ichthammol) is important. Once an abscess has drained, gentle cleaning with tamed iodines or chlorhexidine is indicated.

Early diagnosis and long-term antimicrobial treatment are important for a successful outcome in horses with internal *C. pseudotuberculosis* infection. Ultrasonographic imaging is an important technique for identifying specific organs affected, aiding in obtaining samples for a definitive diagnosis, and monitoring response to treatment. Pregnant mares with internal infections are at risk for fetal loss. Preexisting chronic organ disease may be associated with a poor prognosis.[41]

Digital Dermatitis (Papillomatous Digital Dermatitis, Bovine Digital Dermatitis, Foot Warts, Heel Warts, Hairy Foot Warts, Hairy Heel Warts, Mortellaro's Disease, Strawberry Heel Warts, Verrucous Dermatitis)

John A. Angelos • Muhammad Muzafar Makhdoomi

Digital dermatitis (DD) of cattle is an infectious, contagious, painful dermatitis of the digital skin and is a major cause of lameness in dairy cattle. Economic losses in affected animals are attributable to decreased milk production and reproductive performance, increased costs for treatment and

management, and increased culling rates.[1-4] Primarily a disease of housed dairy cattle, DD was first described in Italy in the mid-1970s[5]; however, since the mid-1990s this condition has increased in prevalence throughout the world. It has been reported in many countries, including several in Europe, the United States, Japan, Chile, Canada, Mexico, and New Zealand.[6-9] Digital dermatitis has also been found in feedlots and pasture-based dairies. Although it is difficult to assign costs to specific diseases, DD is thought to be of lower cost than sole ulcers or foot rot; however, prevalence of DD can be much higher than that of other lesions, so the total cost can be high.

▪ Clinical Signs

Roughly 80% of DD lesions occur on the plantar aspect of the hind foot, immediately proximal to the heel bulbs and adjacent to or extending into the interdigital space.[8] A 2017 study of dairy cattle in New Zealand reported that approximately 75% of affected cows were infected on one rear limb and 25% were infected on both rear limbs.[10] Less commonly, lesions occur on the plantar aspect of a forefoot and the dorsal aspect of any foot.[8] Lesions are confined to the digital skin below the level of the dewclaws.[8]

The gross appearance of lesions and the predilection for hind limbs and skin-hoof wall junctions, especially those bordering the heel bulbs and interdigital space, distinguish this disease from other causes of bovine dermatitis. The clinical appearance of DD has been classified into five stages, advancing from acute to chronic and in some cases to regression and healing.[11] The first stage describes small (~1 to 2 cm) focal lesions with a reddened circumscribed area (hence the name “strawberry heel warts”) that are extremely painful and have hairs on the periphery of each lesion that are erect and matted in exudate. The second stage has larger (2 to 6 cm) ulcerated lesions with peripheral hairs that are two to three times longer than surrounding hairs. In the third stage healing lesions have a rough, encrusted surface and are often gray in color. The fourth stage (often referred to as the “hairy” or “papillomatous” stage) consists of chronic proliferative lesions with varying degrees of hyperkeratosis characterized by black papilliform projections that vary in length from 1 mm to 3 cm. If the fifth stage is reached, it is characterized by healing of the lesion.[11] Washed surfaces are characteristically extremely painful and either red and granular, or they may appear as white-yellow, gray, brown, or black papillary areas with red, granular areas interspersed. Lesions bleed easily if traumatized.

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The time required for lesions to progress to a mature (“hairy” or papillomatous) state varies. DD lesions involving the interdigital space often occur in association with a previous interdigital fibroma. Lesions may have a foul odor[12,13] attributed to secondary anaerobic bacterial growth in exudate material (most likely *Fusobacterium necrophorum* and/or *Porphyromonas levii*).[14] Swelling of the pastern and fetlock regions is not typical in uncomplicated cases. Lameness is characteristic on dairies where DD has a high prevalence, but lameness is not consistently related to lesion size or chronicity. As such, animals can appear much lamer than one might expect given the size of the lesion. If affected digits go untreated, those with plantar or palmar lesions may become clubbed when a cow preferentially bears weight on toes while the heels overgrow.

▪ Differential Diagnoses

Differential diagnoses for an individual case of DD include interdigital necrobacillosis (foot rot; foul in the foot; interdigital phlegmon), interdigital hyperplasia (corns; interdigital fibroma), interdigital dermatitis, and traumatic injury with granulation tissue. For herd problems of lameness localized to the digit, differentials should include DD, interdigital necrobacillosis, interdigital dermatitis, laminitis, excessive sole wear from caustic or abrasive flooring, and improper or no hoof trimming. If signs of polysystemic disease exist, coronitis from viral diseases (e.g., bovine virus diarrhea, vesicular stomatitis, foot-and-mouth disease) should be considered.

▪ Epidemiology

Digital dermatitis typically spreads rapidly among adult cows, often affecting a majority of adult animals within a year after introduction. Once established in a herd, lameness is more typically seen in first and second lactation cows, commonly after entry into a milking string.[15-17] Lesions are typically seen in older cows; however, lameness in older animals is less common compared to younger cows. Bulls and yearling heifers can be affected, but these groups generally comprise a small proportion of clinical cases. Freestall herds tend to be more commonly affected than stanchion (tie stall) housed cattle or pastured cattle. DD is almost exclusively seen in dairy cattle, with no breed predilection. In endemic herds it is unlikely that eradication is possible.

Retrospective epidemiologic studies in the United States identified two

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significant risk factors in high-prevalence herds: muddy or wet conditions and purchasing replacements from off premises.[3,16] Experimental transmission of DD was demonstrated when homogenates of DD lesions were applied to the feet of calves subjected to moisture and low oxygen tension.[18] Conditions of moisture and low oxygen tension are present on confinement dairies if manure management and hygiene are inadequate. Other risk factors include use of outside hoof trimmers and not washing hoof-trimming equipment between cows.[3]

▪ Pathogenesis

A variety of anaerobic organisms have been associated with DD.[6,19-25] *Treponema* spp. spirochetes have been identified most consistently and form the majority of the colonizing bacterial flora on active lesions; these organisms also can invade the epidermis and dermis.[23,25-29] These spirochetes induce a humoral antibody response in cattle with active lesions.[30] Although DD lesions can exhibit gross and histologic similarities to viral papillomas, bovine papilloma virus has not been found in lesions.[2,8,31]

Evidence suggests that DD is a multifactorial disease involving environment, microbial, host, and management factors.[3,8,15-17,25] Rough flooring; inadequate drainage; fecal and urine accumulation on floors; dirty, wet, or uncomfortable bedding areas; and overcrowding can adversely affect digital skin health and increase the risk of DD. Transmission among cattle and between herds may be facilitated by contact between clinically and subclinically affected cows, fomites such as foot-trimming instruments, and livestock trailers and farm equipment.

Chronic and recurrent cases in otherwise healthy adult cattle are reported; immunity to DD, if it does develop, may be incomplete or temporary. Recurrence is common in individual cows following antimicrobial treatment.[11,32] Spontaneous regression of lesions and resolution of lameness, while possible, occurs rarely.

▪ Pathologic Findings

Histopathologic criteria to establish a diagnosis of DD are[8]:

- Circumscribed plaque of eroded acanthotic

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epidermis attended by parakeratotic papillomatous proliferation profusely colonized by spirochete-dominant bacterial flora
- Loss of stratum granulosum
- Invasion of stratum spinosum by spirochetes
- Infiltration of neutrophils, plasma cells, lymphocytes, and eosinophils into the dermis.

If performed, biopsies should be full-thickness 4- or 6-mm punch biopsies, washed off with sterile saline and placed in buffered formalin. Although helpful in confirming a diagnosis, histopathology is not necessary to make a diagnosis because DD lesions typically exhibit a characteristic appearance and occur in specific locations in cattle.

A biopsy study on treatment and recurrence of DD showed that clinical and histopathologic diagnoses were in agreement for active lesions before treatment.[32] Histopathology on day 28 post treatment with lincomycin or oxytetracycline, however, demonstrated that more than half of the lesions that appeared clinically resolved still had microscopic evidence of infection.[32]

▪ Treatment and Prevention

The most common methods for treating DD involve application of topical antibiotics.[8,11,32,33] There are no antibiotics currently labeled for treatment of DD in the United States; therefore adherence to extralabel drug-use regulations and observance of scientifically established withdrawal times is imperative when risk of drug residues exists.

The most commonly used therapy for DD is topical oxytetracycline or lincomycin applied in spray or powder form. To apply it topically as a spray, oxytetracycline or lincomycin is mixed with deionized or distilled water in a 2- to 4-L agricultural sprayer (25 g/L oxytetracycline, 8 g/L lincomycin) and applied directly to the heels of DD-affected cattle daily for 5 to 14 days. For topical powder treatment, 2 grams of oxytetracycline or lincomycin powder are placed on a cotton pad, applied to the affected area with an elastic bandage, and changed daily for 5 to 10 days. Both treatments elicit a rapid response consisting of dramatic lameness regression and reduction in wound size. The recurrence

rate is high enough that topical treatments may need to be repeated after 45 to 60 days for more effective control. There have been no reported antibiotic residue violations resulting from topical application of antibiotics.[34] Parenteral penicillin and ceftiofur have been reported to be efficacious[8] but may require milk withholding. Given the current restrictions on extralabel use of ceftiofur in the United States, practitioners should be mindful of following all label directions related to dose, route, frequency, and duration of therapy.

Footbaths containing a variety of products, including 5% formalin, oxytetracycline (1 to 4 g/L), lincomycin (1 to 4 g/L), copper sulfate (0.25 to 1 g/L), zinc sulfate (20%), or sodium hydroxide,[12,31,35-38] can assist in controlling the disease in infected herds; however, low-prevalence herds (<10%) may have better responses. Some authors believe that individual treatment should precede foot-bathing on contaminated farms.[37] When there is a high prevalence of DD, individual topical treatment is likely to be more effective at reducing prevalence. Contamination of footbath solutions with feces and urine can reduce effectiveness, and constant vigilance by farm workers to maintain footbath solutions is important. This problem can be reduced by placing two footbaths in tandem and spaced several feet apart, with the first containing water or a mild detergent solution for cleaning the feet and the second containing the antiseptic solution. Footbath solutions should be changed every 150 to 300 cow passages. Footbaths should be a minimum of 8 feet long and 2 to 3 feet wide, with a depth of 5 to 6 inches. The baths should be covered to limit dilution by rain and placed in an exit alley out of the milking parlor to avoid splash contamination of teat ends before milking. Additional footbaths can be placed in other locations to treat bulls, dry cows, and heifers. Footbath treatment frequency should be based on empirical evidence of efficacy every 2 to 7 days. Laws regulating the use and disposal of chemicals vary; therefore consultation with local regulatory agencies is prudent before initiating a control program on a dairy.

Improving environmental hygiene, providing dry and comfortable bedding, and improving ventilation to allow drying of stalls and alleys may reduce the incidence or severity of clinical cases. Foot-trimming equipment, mobile tilt tables, and livestock trailers should be thoroughly cleaned and disinfected to prevent potential transmission of the agents of DD between dairies. Use of iodine disinfectant containing 2.5% (weight per volume) available iodine reduced detection rates for *Treponema* spp. on hoof-trimming equipment.[39] Published vaccination studies with *Serpens* spp. or *Treponema* spp. bacterins

have not reported efficacy against DD.[33,40,41]

Interdigital Dermatitis, Heel Horn Erosion, and Heel Cracks

Interdigital dermatitis (ID) is a condition of acute or chronic inflammation confined to the epidermis of the interdigital skin. It is characterized by small circular ulcers in the interdigital epithelium, and severe cases are often characterized by ulceration, necrosis, and underrunning of the hoof horn.[42,43] It can cause varying degrees of lameness, which may be absent to moderate in severity, and can be associated with a distinct odor. A moist, white to gray serous exudate is often present. In many cases, skin irritation results in hypertrophy and may increase the growth rate of the axial hoof wall along with excessive horn production along the axial wall and sole. It is one of the most commonly diagnosed foot conditions, with prevalence running as high as 50% in affected herds.[44] Prevalence is most common on dairies with intensive stocking rates and moist, filthy conditions. In tied systems the hind digits are more commonly affected. In freestall systems lesions are observed equally between the front and hind digits. Diffuse epidermal erosion in the interdigital cleft may be seen in early cases. More chronic cases exhibit hyperkeratosis leading to a roughened appearance to interdigital skin and dorsal and palmar commissural skin folds. Chronic cases are frequently accompanied by cracks in the heel (heel horn erosion, “slurry foot,” “slurry heel”), with potential underrunning of the heel horn and subsequent severe lameness.

Some investigators have hypothesized that ID and DD are forms of the same disease complex. *Dichelobacter nodosus* may be a primary or contributory pathogen[36] along with *Treponema* spp.[45] ID and DD share certain histologic characteristics suggesting contribution or involvement by spirochetes *(Treponema)*, and both can be successfully treated and prevented with the same topical antibiotics or footbaths. However, ID can persist on dairies that practice regular foot-bathing. Slatted, rather than solid, floor systems may reduce incidence of the condition. Causative organisms may survive within deep heel cracks, which should be trimmed to reduce accumulation of debris and allow exposure to foot bath solutions.

ID differs from interdigital necrobacillosis (foot rot), in which infection extends into the dermis, leading to fissure formation, infection of deeper

structures if left untreated, and cellulitis of the pastern and fetlock regions.

In sheep, ID and virulent foot rot (VFR) are considered two different stages of the same disease complex,[46,47] with ID classified as a less severe form.[48] The same disease state is also classified as benign foot rot in Australia. Some authors designate the more severe form of disease as VFR in sheep, whereas others classify it simply as foot rot. In the UK, ID and VFR are the main causes of lameness in sheep[49] and major animal welfare issues.[50] The primary pathogen is *D. nodosus*, a gram-negative, rod-shaped anaerobic bacterium.[51-53] In sheep, ID is characterized by inflammation of the interdigital skin, resulting in lameness and loss of body condition.[54] In ID the interdigital skin appears pink and moist and is sensitive to touch, whereas VFR is characterized by underrunning of the hoof horn leading to separation of the hoof from the underlying soft tissue. The underrunning of the hoof horn begins at the junction of the skin fold with the heel that spreads anteriorly to the abaxial wall. This causes separation of the hoof horn from the laminae of the foot.[55] It is often accompanied by discharge of a grayish exudate that has a characteristic fetid odor.[51] Some authors have suggested a role of the host's acute inflammatory response to *D. nodosus* infection in leading to the development of clinical signs.[56]

The occurrence of ID is influenced by local climatic conditions.[57] In Australia a mean daily temperature greater than 10° C and a wet pasture are required for transmission of the disease. In the UK the disease can occur throughout the year and can be transmitted between sheep even when daily mean temperatures are greater than 10° C.[58] A study reported mini epidemics of ID during the spring in the UK, with increasing temperature and rainfall favoring spread of disease.[59,60]

In the UK, ID in sheep is treated with topical oxytetracycline spray (25 mg/mL) on the interdigital skin for 3 days. The use of topical antibiotic spray is highly effective at combating the disease[61,62] and leads to more than 95% recovery within 3 to 4 days.[61,63] Foot-bathing has also been used, but topical therapy is generally considered a more effective method of ID control. VFR can be difficult to treat with antibiotics, and recurrent cases of VFR can occur after 2 weeks of antibiotic treatment. VFR can be effectively controlled and eliminated from sheep flocks by vaccination with a *D. nodosus* serogroup-specific vaccine.[64]

Control and elimination programs for ID and VFR in the United Kingdom are based on empirical evidence that *D. nodosus* cannot survive off the host for more

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than 7 days.[51] Survival off the host (pasture) is dependent on moist conditions, and some authors have reported that *D. nodosus* does not survive on pasture for more than 2 weeks under warm and damp conditions. Therefore, under these conditions, sheep are not at risk of ID and VFR once pastures have been rested for 14 days. However, a recent study using qPCR reported that viable *D. nodosus* can survive for at least 40 days in soil microcosms, and the rate of survival is affected by soil type, moisture, and temperature, with lower temperatures (41° F) and clay soil favoring survival of higher loads of *D. nodosus*.[65] This is a step change in our understanding of the ability of *D. nodosus* to survive off a host. Aggressive treatment of infected sheep and preventing access of healthy sheep to *D. nodosus*–contaminated pastures for at least 40 days can potentially aid in controlling ID.

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Viral Diseases

Stephen D. White

Papillomas (Warts, Fibropapillomas)

▪ Definition and Etiology

Cutaneous papillomas or warts occur (in decreasing order of frequency) in cattle, horses, goats, and sheep.[1-4] The growths usually occur in young animals,[4] as well as on teats of mature cattle and goats, and are white, tan, or gray firm, protruding masses with a dry, horny surface. They vary in size from 1 to 500 mm and may be single or multiple. Species-specific papillomaviruses (subgroup of papovavirus) are responsible for causing warts.[5-7] It is now accepted that parts of the bovine papillomavirus (BPV) genome are found in naturally occurring equine sarcoids.[8] There are at least 10 BPV strains, designated BPV-1 through BPV-10 (Table 40.1),[9] and probably more. At least two strains of virus are currently recognized in horses.

TABLE 40.1

Distribution and Appearance of Bovine Warts by Type of Virus

Virus Strain	Usual Site	Appearance	Comments
BPV-1	Nose, teats, glans penis	Filamentous or frondlike	Can prevent breeding when on penis
BPV-2	Head, neck, brisket, occasionally alimentary tract	Pedunculated or broad-based mass	Most common typical warts
BPV-3	Atypical warts, head, neck, possibly interdigital[a]	Nonpedunculated protruding growths, delicate fronds with hair between	Persist for years
BPV-4	Alimentary tract, urinary bladder	Pedunculated mass	See Chapters 32 and 34
BPV-5	Teat	Smooth, white	Persist for years; other types may also occur on teats
BPV-6	Teat	Round and either flat or frondlike	Similar in appearance to BPV-1 when frondlike

[a]Suspected, but BPV-3 has not yet been isolated from interdigital warts. Some authors speculate that interdigital warts may be caused by yet another new BPV strain.

BPV, Bovine papillomavirus.

Modified from Hunt E: Infectious skin diseases of cattle. *Vet Clin North Am Large Anim Pract* 6:163, 1984.

▪ Clinical Signs

Warts are usually small, benign growths that appear on animals younger than 2 years, persist for 3 to 12 months, and then spontaneously regress without causing clinical signs (other than a blemish). In cattle, warts on the teats, penis, or interdigital skin[10] or in the alimentary tract may produce clinical signs of pain or occlusion. Warts usually develop in the ears of young cattle after tagging or tattooing, especially if instruments are not disinfected between individuals; these are not age related. Teat warts also predispose to environmental mastitis. Occasionally individuals with (presumed) defective cellular immunity may develop multiple extremely large warts that may result in weight loss.

In horses, warts on the face are rather common but rarely cause a significant problem (Fig. 40.8). The previously reported congenital wart in young horses has now been more properly termed a *hamartomatous lesion* (epidermal nevus) and has been shown not to be virus induced.[11]



FIG. 40.8 Typical warts (papillomas) on the nose of a yearling horse.

Warts are relatively rare in goats. They occur mainly on teats and may spread throughout the herd. A 1936 report described a herd outbreak involving the head, neck, shoulders, and forelegs in milking goats.[12] Does without adequate pigmentation on the udder develop persistent mammary gland warts that may

undergo transformation to become squamous cell carcinomas.[13] There are probably at least two different strains of goat papillomavirus (head/neck and mammary).

Warts are rare in sheep but may occur on the face or legs. Differential diagnosis in sheep and goats includes contagious ecthyma (orf), ulcerative dermatosis, dermatophilosis, and sheeppox and goatpox.

▪ Treatment and Control

Small warts can be crushed, pinched off, or surgically removed. Cryosurgery can be used on larger warts. Many regress spontaneously within a few months, even without treatment.

When show animals are involved or when animals have multiple large papillomas, tissue can be removed and made into crude autogenous vaccine (2 mL intradermally 3 times weekly) by homogenizing, grinding, freezing and thawing twice, filtering, and killing virus with 0.5% formalin. Autogenous wart vaccines are variable in their efficacy, as are commercial vaccines.[14-16] The latter rarely seem to result in effective regression of existing warts but may prevent development of new lesions if the same BPV strain is involved. Autogenous vaccines can prevent new lesions caused by the same BPV strain in a herd. There is no indication that cattle vaccines have any efficacy in other species. No wart vaccines for horses, sheep, or goats are currently marketed.

Because the viruses can be transmitted directly or via fomites, prevention involves isolation; preventing animals from rubbing on each other; and not sharing halters, brushes, and other equipment. Dipping of dehorning, tagging, and tattooing instruments in a viricidal solution between animals will also slow spread of the virus.

Aural Plaques

Aural plaques is a form of viral papilloma that often affects the inner pinna (Fig. 40.9). Nonpruritic, these plaques may also occur on the genitalia and mammary glands. The color varies from pink to grayish-white. Plaques do not resolve spontaneously, as do the “classic” papillomas seen in young horses. Biopsy or “shaving off” aural papillomas may stimulate reduction or resolution of the masses, although in some horses this may only be temporary (6 to 12 months). This has been theorized to be due to the release of “papilloma antigens” into the bloodstream during the surgical procedure, prompting an immune response

against the tumor. Imiquimod (Aldara-3M, Minneapolis, Minn.), a nonsteroidal local immune response–modifier cream, has been helpful in some cases when used 3 times weekly, every other week, for 2 to 4 months.[17] Owners should wear gloves and should be forewarned that there is frequently an impressive inflammatory reaction to the cream in the initial weeks of treatment.

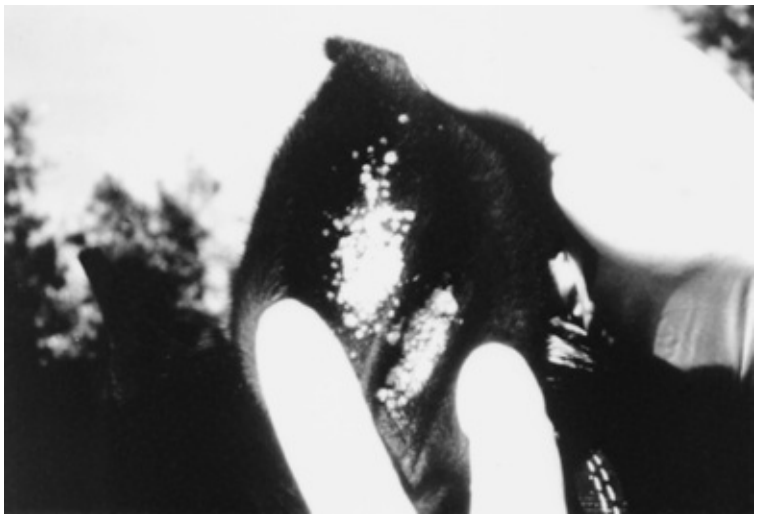


FIG. 40.9 Aural plaques on inner surface of pinna of a horse's ear.

A papillomavirus has been demonstrated in aural plaques on electron microscopy and with immunohistochemical techniques.[18]

Pseudocowpox

Pseudocowpox is a common parapoxvirus of cattle related to the viruses of contagious ecthyma (sore mouth) of sheep and goats and bovine papular stomatitis (see Chapter 32 for these diseases). All three parapoxviruses may cause nodular lesions on humans. The lesions of pseudocowpox are usually confined to the teats of cattle, and the disease is common worldwide. Cyclic waves of reinfection occur in a herd, where it causes minor teat lesions characterized initially by a small papule 2 to 3 mm in diameter, followed by crusting and circular spread of the lesion. Approximately 10 days later, the 15- to 20-mm lesion appears as a ring or horseshoe-shaped scab.[19] Lesions occasionally involve the udder, medial thighs, or scrotum. Deep ulceration is rare. There are no systemic signs of illness. The major problem associated with

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the teat lesions is an increased incidence of mastitis. The most important and common differential diagnoses are bovine herpes mammillitis and viral papillomas. Rare viruses involving the teat include vaccinia and cowpox.[19] Cowpox is a rare disease of cattle in Europe that causes ulcers and may also produce lesions in humans. Vesiculation is rare in pseudocowpox, in contrast to bovine herpes mammillitis, vaccinia, and cowpox. Recent advances in PCR technology have improved diagnostic sensitivity[20,21]; advances in vaccine technology have been reviewed elsewhere.[22]

Bovine Herpes Mammillitis (Bovine Herpesvirus, Bovine Ulcerative Mammillitis)

Bovine mammillitis teat lesions are caused by bovine herpesvirus 2 (BHV-2), which is widely disseminated in most cattle populations.[23,24] The disease may be epidemic or endemic. The virus may also cause oral lesions, udder lesions, or generalized skin disease in cattle. The teat lesions start as swollen, tender, edematous teats. Vesicles may appear in some lesions, whereas others ulcerate almost immediately. The teats become painful, and ulcers require 3 to 10 weeks to heal.[23,24] Mastitis is increased because the scabs on the teats are laden with bacteria. Diagnosis may be confirmed by isolation of the virus, the BHV-2 serum neutralization tester, or histologic demonstration of herpesvirus particles.[23,24] Therapy consists of segregation of affected animals from the rest of the herd, and affected cows should be milked last. Milkers should wash hands between cows. In severe cases, secondary infection may be controlled by topical antibiotic creams or parenteral antibiotics, with proper residue avoidance precautions in place.

Sheeppox and Goatpox

Sheeppox and goatpox are caused by capripoxviruses.[25] Both occur in Africa, Asia, and the Middle East; goatpox also occurs in parts of Europe and the United States. The two diseases are clinically similar, although sheeppox has the most severe systemic signs of the animal pox diseases. Studies have shown that the viruses are phylogenetically distinct and can be differentiated by molecular tools.[26] The diseases affect all ages, causing pyrexia, anorexia, conjunctivitis, rhinitis, and skin lesions. Prophylaxis using attenuated vaccines is the preferred

control measure because the immunity is long lasting.[25,26] Morbidity is high. Mortality may reach 80% with sheeppox but usually is low with goatpox. Humans may develop skin lesions from goatpox.

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Fungal Diseases

Stephen D. White

Dermatophytosis (Ringworm)

Dermatophytosis refers to infections of the keratinized tissues of the skin (stratum corneum layer of epidermis, hair, claws, hoof, and horns) by *Microsporum* and *Trichophyton* spp. Dermatophytosis is relatively common in the horse and in cattle, less common in goats, and rare in sheep.

▪ Etiology and Pathogenesis

The most common dermatophyte species isolated from horses are *Trichophyton equinum, Microsporum equinum, Trichophyton mentagrophytes,* and *Trichophyton verrucosum.*[1-3] *T. verrucosum* infections in humans caused by transmission from horses have been reported.[4] In ruminants the majority of dermatophytosis lesions are caused by *T. verrucosum* and to a lesser extent by *T. mentagrophytes.*[5] Transmission of the disease is usually from animal to animal by direct contact or indirectly through fomites such as grooming instruments, tack, housing, fencing, or feed bunks. The incubation period may range from 1 to 6 weeks.

Several factors may influence the susceptibility of an animal to dermatophyte infection. Age is probably most important, with younger animals more susceptible to infection. The susceptibility of young animals is most likely related to lack of prior exposure or infection and thus no immunity, as well as crowding of young animals and conditions that decrease resistance to infection (e.g., poor nutrition). Environmental factors like warmth and humidity also may play a role. Calves kept indoors or exposed to foggy weather with little or no sunlight have an increased incidence.

Under normal circumstances, dermatophytes only invade fully keratinized, nonliving tissues.[1] This results in weakened hair shafts, leading to alopecia.

In many cases, dermatophytosis is theorized to be a self-limiting disease, with the duration of infection ranging from 1 to 4 months. The spontaneous regression is at least partly related to the development of immunity, of which cell-mediated immunity is the more important. The immunity that develops is

probably not complete, and its duration is unknown.

▪ Clinical Signs

The lesions are often circular; usually appear first on the face or in the axillary/girth area; and may spread over the trunk, rump, neck, head, and limbs (Fig. 40.10). Occasionally in the horse, dermatophytoses may be limited to the pastern region. Rarely, dermatophytes may be a cause of coronary band disease in horses. The mane and tail are rarely involved. Cattle and goats are frequently affected around the eyes and face (Fig. 40.11, Color Plate 40.7).

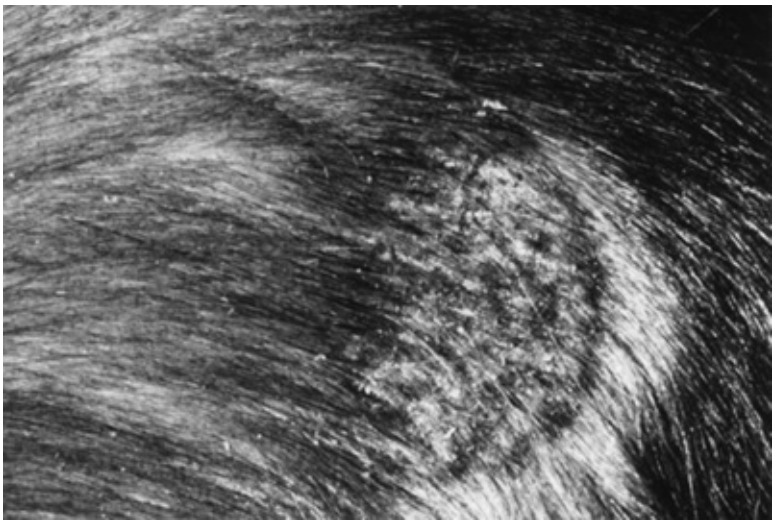


FIG. 40.10 Ringworm lesion (due to *Trichophyton* spp.) in a horse's flank area.



FIG. 40.11 Ringworm lesions (due to *Trichophyton verrucosum*) around a calf's eye.

Lesions may be superficial or deep. Superficial infections are much more common and manifest with development of thick crusts or more generally a diffuse moth-eaten appearance with desquamation and alopecia, sometimes in a ring pattern. A small crust may form over the follicle, and the hair is lost. Occasionally the initial lesions may be urticarial, progressing to multifocal, sharply demarcated areas of alopecia and scaling. The degree of pruritus varies but is usually mild or absent. Erythema is usually absent or obscured by pigmented skin. The lesions in cattle are usually characterized by excessive crusting, taking on an almost wartlike appearance.

Dermatophytosis must be considered in the differential diagnosis of any dermatoses characterized by multifocal alopecia or scaling and crusting. For a solitary lesion in horses, the occult sarcoid is the primary differential diagnosis. The two most important differential diagnoses of more extensive lesions are dermatophilosis and pemphigus foliaceus.

▪ Diagnosis

Direct microscopic examination of infected hairs is of value, but in general the most common and reliable method of diagnosing dermatophytosis is fungal culture (see Chapter 11). Broken hairs at the periphery of lesions are most satisfactory for this purpose. Large crusts should be avoided. The use of specialized indicator media is preferred. On occasion, dermatophytosis is diagnosed histopathologically. Interestingly, *Trichophyton* spp. occasionally may

cause acantholysis, mimicking pemphigus foliaceus on histopathology.[6] As with other infectious diseases, the role of PCR is being investigated for diagnostic accuracy.[7]

▪ Therapy

Although 50% captan (2 tablespoons powder in 1 gallon water) has been recommended in the past and is certainly safe for tack, its effectiveness on the animal has been questioned. Lime sulfur (LymDyp [IVX Animal Health, St. Joseph, Mo.], LymDyp DVM [Bayer, Shawnee Mission, Kan.], LimePlus dip [Dechra, Overland Park, Kan.]), 1 cup to 1 gallon of water, and bleach 1 : 10 with water are both effective but messy, odiferous, and staining. Shampoos containing miconazole, ketoconazole, and/or 3% to 4% chlorhexidine may be effective. In Europe and Canada an enilconazole rinse (Imaveral [Merial, Baie d'Urfé, Canada]) approved for horses and cattle is highly effective.

Systemic treatment is occasionally needed. The efficacy and proper dose of griseofulvin in horses has not been thoroughly researched, but we have advocated and used a dosage of 100 mg/kg PO daily for 7 to 10 days on a small number of horses. Griseofulvin is a teratogen and should not be used in pregnant mares. Alternatively, 20% sodium iodide (NaI) may be given IV (250 mL/500-kg horse once or twice every 7 days) but is also contraindicated in pregnant mares because it may cause abortion.[2]

Vaccinating cattle against *T. verrucosum* has long been successful in Eastern Europe and Scandinavia. Effective control of ringworm in cattle has been achieved in regions implementing systematic vaccination.[8] Vaccination against *T. equinum* in horses may reduce the incidence of new infections and protect a high percentage (>80%) of vaccinates from infection. These data are based on results with an inactivated vaccine containing both conidia and mycelial elements.[9] In cattle, newer vaccines consisting of recombinant protein and deoxyribonucleic acid (DNA) derived from heat shock protein 60 of *T. mentagrophytes* have shown success experimentally.[10] Such vaccines are not yet available in the United States.

Malassezia Dermatitis

The exact species of the yeast *Malassezia* growing on large animals' skin is just beginning to be investigated.[11] In one study of horses and livestock, the

Malassezia spp. isolated were identified as *Malassezia furfur, Malassezia slooffiae, Malassezia obtusa, Malassezia globosa,* and *Malassezia restricta.*[12] We have examined several mares with a *Malassezia* infection between their mammary glands that was intensely pruritic. The mares rubbed their tails and ventral abdomens. Physical examination showed a dry, greasy-to-the-touch exudate. Cytology of the exudate showed numerous yeast organisms, which were identified on culture as *Malassezia* spp. Treatment with a topical 2% miconazole/chlorhexidine shampoo was curative. We are aware of other similar cases. However, healthy nonpruritic mares may also have large numbers of yeasts in the intramammary area.[13]

Sporotrichosis

Sporotrichosis is caused by the yeast *Sporothrix schenckii,* which is most common in vegetation. The yeast becomes pathogenic in animals because of its dimorphic ability to convert from a yeastlike form at tissue temperatures between 35° and 37° C (95° and 98.6° F) to a mycelial phase (with branching, septate hyphae) at environmental or laboratory temperatures of 25° to 30° C (77° to 86° F).[14] The disease has been reported in many species of domestic animals.

The initial lesions are nodules, which frequently ulcerate, and the disease may progress to a lymphatic-cording disease. Rarely, the fungus will eventually spread to the lungs. In a retrospective study from UCD-SVM, equines were the second most common species affected, after cats.[15] Diagnosis is made by demonstrating the organism on histopathology, immunofluorescent antibody testing on affected tissues, impression smears, and culture.[15,16] This is a zoonosis, so care should be taken when handling suspected samples.

Successful therapy with a number of different systemic iodine preparations (NaI, KI) has been reported. Organic iodides have proved to have superior efficacy to inorganic iodides in treating equine sporotrichosis, with ethylenediamine dihydroiodide (organic iodide powder [Neogen Corp., Lexington, Ky.] or EDDI 20 Gr. Dextrose base [Vedco, St. Joseph, Mo.]) being a commonly used preparation. This product is in the form of a feed additive and can be mixed with a small amount of grain and administered at 1 to 2 mg/kg of the active ingredient once to twice daily for the first week, then 0.5 to 1 mg/kg once daily for the remainder of the treatment. In general, lesions will begin to regress during the first month of treatment, and therapy should be continued for *at least 1 month* beyond complete resolution of all cutaneous nodules and

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healing of any ulcerated lesions. Prematurely discontinuing therapy will invariably result in an unnecessary relapse of the disease. During treatment, the horse should be closely observed for any evidence of iodide toxicity (iodism), which includes excess scaling and alopecia, a serous ocular or nasal discharge, excess salivation, anorexia, depression, coughing, nervousness, or cardiovascular abnormalities. Should any of these signs develop, the treatment should be discontinued for 1 week, then resumed at three quarters the dosage at which the iodism was noted. In most cases the treatment is subsequently well tolerated.[17] Although both itraconazole and terbinafine have been shown to be effective in vitro against the organism isolated from a horse, there is an absence of clinical reports of their use.[18] Successful management of an infected donkey with both KI and fluconazole has been reported.[15]

Histoplasmosis

Histoplasma capsulatum var. *farciminosum* ("farcy," the cause of equine epizootic lymphangitis in East Africa) infection has been reported in donkeys, where it can have considerable economic impact.[19] Cutaneous lesions resemble those seen in sporotrichosis. Treatment has not been well established but may be similar to the treatments for *S. schenckii*.

Phaeohyphomycosis

Phaeohyphomycosis is caused by a number of ubiquitous fungi that are either saprophytes or plant pathogens. These include *Alternaria, Drechslera, Cladophialophora, Cladosporium, Phialophora,* and *Stemphylium* spp. The correct terminology currently depends on the histologic appearance of the organism, as follows[20]:

- *Chromomycosis:* any pigmented fungi
- *Chromoblastomycosis:* pigmented fungi, primarily yeast
- *Phaeohyphomycosis:* pigmented fungi, both hyphal elements and yeast

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- *Hyalohyphomycosis:* nonpigmented fungi, mainly hyphal elements

Cutaneous lesions arise from either trauma to the skin or disseminated disease. Animals with disseminated disease probably have a deficient immune system. Similar to the other deep mycoses, these lesions present as expanding nodules and draining tracts. Diagnosis is by biopsy or occasionally cytology. Histopathology shows foamy or epithelioid macrophages, and special stains will show the organisms. Veterinarians and their staff should be careful in handling material from infected animals, because the inadvertent inoculation of these organisms can cause human infections.

Treatment has generally included surgical excision or amputation if practical. Potassium iodide, as for sporotrichosis, and (if the owners can afford it) fluconazole per os at 5 mg/kg may be effective.

Zygomycosis

Similar to phaeohyphomycosis, zygomycosis is caused by a number of related fungal species that are ubiquitous saprophytes. GI and respiratory tract involvement is possible. Cutaneous lesions are thought to be caused by wound penetration. The disease typically occurs in tropical and subtropical areas. The two orders of Zygomycetes that cause disease are Mucorales, including the genera *Rhizopus* and *Mucor,* and Entomophthorales, including the genera *Conidiobolus* and *Basidiobolus.* Most cutaneous reports are in horses, although ruminants may have other organ systems affected.

The skin disease is ulcerative, nodular, and generally found on the trunk and neck. Generally, only one large nodule is present. Diagnosis is by histopathology and culture; a serum agar immunoprecipitation test has been useful in diagnosing conidiobolomycosis. Surgical removal, if possible, is preferred for treatment. Medical options include the iodides (not effective against the order Mucorales) and possibly the azoles or amphotericin B.[1]

Pythiosis

Pythium insidiosum is considered to be the causative agent of *swamp cancer,* also known as *Florida horse leech, bursattee,* and *kunker.* This organism is

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termed a *protista* and is found in tropical and subtropical areas worldwide, although its range may be expanding; it recently has been reported in a horse in northern California.[21] The pythiosis lesion occurs most often on the limbs, abdomen, neck, and lips and consists of dense granulation tissue containing masses of yellow-gray necrotic tissue, which sometimes are calcified and often are present as cores in fistulae and are removable intact. Such masses are known as *leeches* or *kunkers.* The granuloma ulcerates and extends peripherally and may reach a very large size in a short time. The overlying and adjacent skin is destroyed by both the inflammatory reaction and the self-mutilation by the horse. Important differential diagnoses are systemic fungal infections, habronemiasis ("summer sore"), and neoplasia. Although most reports in large animals are in horses, cattle, sheep, and goats may also be affected.[22-24]

Histopathologic examination of affected tissue reveals pyogranulomatous inflammation directly surrounding the organism. Isolation of organisms from the lesions is necessary for further identification and study, but histologic demonstration of the protozoa within tissues reacting to its presence is critical in establishing the causal relationship in an individual lesion. In obtaining culture, the kunkers are preferred to the actual tissue. For samples that cannot be processed immediately, acceptable handling techniques include storage at room temperature for up to 3 days, refrigeration for up to 5 days, shipping on cold packs, and storage in antibiotic solution, each combined with subsequent inoculation on selective media.[25] Recent advances in enzyme-linked immunosorbent assay (ELISA) or molecular techniques offer better potential for organism detection and identification.[26] Wide surgical excision combined with or without immunotherapy has been effective in some cases.[26-28]

Parasitic Skin Diseases

Stephen D. White

Pediculosis

Lice are obligatory ectoparasites that are generally host specific. Adults and nymphs are seldom able to live for more than a few days away from their host. Large animals suffer from infestation with several species of lice that belong to the orders Mallophaga, the biting lice, and Anoplura, the sucking lice (Table 40.2).[1]

TABLE 40.2
Lice Associated With Large Domestic Animals

Host	Mallophaga (Biting)	Anoplura (Sucking)
Horse	*Bovicola (Damalinia) equi*	*Haematopinus asini*
	Werneckiella equi equi	
Cattle	*Bovicola (Damalinia) bovis*	*Haematopinus eurysternus*
		Haematopinus quadripertusus
		Haematopinus tuberculatus
		Linognathus vituli
		Solenopotes capillatus
Goats	*Bovicola (Damalinia) caprae*	*Linognathus stenopsis*
	Bovicola (Damalinia) limbatus	*Linognathus africanus*
	Bovicola (Damalinia) crassipes	*Linognathus vituli*
Sheep	*Bovicola (Damalinia) ovis*	*Linognathus pedalis*
	Bovicola (Damalinia) caprae	*Linognathus ovillus*
		Linognathus africanus

Clinical infestations are most apparent during the winter months and reflect efficient louse reproduction during the late fall and the fact that summertime temperatures on body areas exposed to sunlight are too high for lice. Apparent carrier animals within a herd maintain populations during the “off” season and serve as a source for reinfestation of the herd during the fall.[1] The hallmark of infestation is pruritus, and many clinical changes result from self-trauma. The neck and tail are typically affected first,[2] but infestation and clinical signs may become generalized. The coat becomes dry and scaly. Patchy alopecia and crusted ulcerations result from excoriation. A heavily infested animal may

become anemic. Significant hide damage occurs as a result of excoriation, and hairballs may accumulate in the GI tract from self-grooming. Reduced productivity and weight loss result from decreased feed intake associated with restlessness. Diagnosis is usually by examination; a hand lens is useful (e.g., otoscope without cone). Interestingly, when a horse is exercised and becomes warm and sweaty, the lice will climb out toward the tip of the hair and are easier to find.[3]

Several treatment approaches exist. Ivermectin at 200 µg/kg every 14 days SC for 2 applications is effective for sucking lice but not biting lice. Application of an appropriate topical insecticide to infested animals and to all contact animals at 2-week intervals for 2 or 3 treatments is usually curative for both types of lice. Repetition of treatment is necessary to break the louse life cycle because eggs are not killed by insecticides and will hatch despite therapy. Effective topical agents include pyrethroids, permethrins, selenium sulfide, imidacloprid, phoxim, and fipronil.[3,4] Development of resistance is also possible.[5] Appropriate attention should be paid to withdrawal times in food animals. Cleaning of fomites like blankets, brushes, and rope halters is probably indicated, although lice do not live long off the host.

Trombiculidiasis

Trombiculidiasis is caused by the larval stages of mites commonly called “harvest mites” or “chiggers.” The most common species affecting large animals are *Eutrombicula alfreddugesi* (North America) and *Neotrombicula autumnalis* (Europe). The adults and nymphs are free living. The larvae feed on mammalian hosts, secreting substances in their saliva that hydrolyze the epidermis and allow extraction of tissue fluids. The individual larval stage is short, but the infestation may be ongoing with the acquisition of new larvae from the environment. In the northern hemisphere, *E. alfreddugesi* is active from late spring through early fall, whereas *N. autumnalis* is more common in late summer to mid-fall. The mites may be found in wooded areas, grass, and hay.[3,6]

The clinical signs of trombiculidiasis are crusts and papules, especially on the face, neck, and extremities. Pruritus is variable.[6] Rarely, this parasite has been implicated in headshaking in horses.[7] Diagnosis may be made early in the course of infestation by careful inspection (e.g., hand lens) and finding the minute red-orange larvae in the center of a papule. The six-legged larvae have round bodies and may be identified specifically on skin scrapings or acetate tape

preparations.[3] Although the larvae remain on the animal host for only several days, clinical signs may persist longer, so trombiculidiasis should be suspected even in the absence of mites in an animal with appropriate signs in the summer and fall.

The disorder is in theory self-limiting because of the short time of attachment of the parasite. However, if the pruritus is severe, corticosteroid administration is indicated.[3] Various products have been used on the horse to eliminate the larvae; 5% lime sulfur, fipronil, and permethrin are generally the safer parasiticides to use.

Mange

Mange is a general term for infestation by any mite species.

Psoroptic Mange

Psoroptic mange has been recognized in horses, cattle, sheep, and goats (and rabbits). The host specificity of *Psoroptes equi, Psoroptes ovis, Psoroptes natalensis,* and *Psoroptes cuniculi* is controversial; two reports state that the mites are all genetically homogeneous with little or no host specificity,[3,8] whereas another report documents an inability to transfer *P. ovis* to goats.[9] The mites do not affect people. Psoroptic mange is common in cattle but has been eradicated from horses and sheep in the United States; it is still a concern for sheep production in the United Kingdom and elsewhere in the world. The mites have a 2-week life cycle on their host but can live away from the host for up to 3 weeks. *Psoroptes* mites live on the surface of the epidermis and do not burrow. Symptomatic infestation tends to be more prevalent during the cooler months.

The hallmark of infestation in all species is pruritus. In cattle, crusted papular lesions are typically first apparent on the withers but then generalize, resulting in weight loss, secondary infections, and decreased production.[10] Horses develop papules, crusts, and alopecia most often at the base of the mane, tail, ears, and intermandibular area, with subsequent spreading to the trunk.[3] An otitis externa may be present, seemingly with *P. cuniculi.*[3] In sheep, typical lesions include papules and crusts in wooled areas, and secondary infection with *S. aureus* may occur.[11] The intense pruritus can be debilitating. Certain sheep (Merino) and cattle (Belgian Blue) breeds are more susceptible to infestation than others.[9,12] The immune response in sheep has been studied extensively, with early innate

and longer-term adaptive cutaneous immunoinflammatory responses as well as mite antigen–directed IgE being reported.[10] Goats usually have lesions restricted to the ears, although infestation and symptoms may spread to the neck and body.[13,14]

Diagnosis is based on demonstrating mites in skin scrapings and ear swabs from affected animals. Psoroptic mites are recognized by their round bodies and long, segmented pedicles.[13] Recently, serologic assays have been useful in diagnosis, especially in identifying subclinically infested animals.[15]

A number of topical insecticides have been recommended for treatment and should be applied to all affected and contact animals according to the manufacturer's guidelines. These include deltamethrin, coumaphos, diazinon, malathion, toxaphene, and lime sulfur.[6,13,16] The contaminated environment should also be treated. Ivermectin, doramectin, and moxidectin have been used for *Psoroptes* spp. in large animals at 0.2 mg/kg,[6,17-19] usually for two to three times, given subcutaneously but treatment does not always eliminate live mites from all animals. There may be lesser efficacy when using generic formulations of ivermectin.[20] It has been recommended that *P. ovis*–infested cattle be isolated for a minimum of 14 days after treatment to prevent transmission to susceptible contact cattle.[18] *Psoroptes*-infested ears in horses should not be treated topically because of the resulting discomfort; reliance is on systemic treatment. Psoroptic mange is a reportable disease in the United States.

Chorioptic Mange

Chorioptic mange, also known as *leg mange*, is common in cattle and sheep, uncommon in goats, and seen with variable frequency in horses, depending on geographic area. Draft horses may be more susceptible than other breeds. *Chorioptes* spp. are relatively host specific and include *Chorioptes bovis*, *Chorioptes texanus*, *Chorioptes ovis*, *Chorioptes equi*, and *Chorioptes caprae*.[6,13,21] The mites do not penetrate the epidermis[6] and do not affect humans.[18] They have a life cycle that spans 2 to 3 weeks and can live off the host for only a few days.[16]

This disease is variably pruritic, more so in ruminants than in horses, and less so than infestations with *Psoroptes* or *Sarcoptes* mites. Lesions consisting of papules, erythema, scaling, crusting, ulceration, and alopecia result from self-trauma. In cattle the lower aspects of the hindlimbs, the perineum (particularly

the perianal fossa), tail, and scrotum are usually affected. Sheep typically demonstrate involvement of the lower limbs and scrotum. Goats have involvement of the lower limbs. Horses typically have lesions on the pasterns, although the ventral abdomen may become involved in severe cases. In all species, infestation can become generalized.[3,6,18]

Mites are often numerous and readily demonstrated with skin scrapings. Cattle may be asymptomatic.[18] Chorioptic mange will respond to treatments described for psoroptic mange, although ivermectin and related compounds are more effective in ruminants than horses; in horses, lime sulfur or fipronil applied once weekly for at least 1 month is recommended.[3,22-27] One study in horses showed efficacy using a single dose of moxidectin 2% oral gel (Equest [Fort Dodge Animal Health, Fort Dodge, Iowa]) at the manufacturer's recommended therapeutic dose of 0.4 mg/kg body weight.[26] Other studies have not found it to be effective in eliminating the parasite in a multihorse situation.[28] Chorioptic mange is a reportable disease in the United States.

Sarcoptic Mange

Sarcoptic mange is an uncommon contagious disease of horses, cattle, sheep, and goats. The etiologic agent is *Sarcoptes scabiei;* several subspecies are relatively host specific but can be transmitted to humans. The mite burrows into the epidermis, where the egg is deposited, and its life cycle is complete in 10 to 17 days. Transmission is usually by direct contact, but the mite has a variable survival time off the host, so environmental and fomite transmission are possible.[3,6]

Clinical signs are all referable to the severe pruritus caused by the mite. Lesions include papules, scaling, crusting, ulceration, and alopecia. The head (especially the ears) and neck are usually the initial areas of involvement, although lesions become generalized.[3,6,16] Horses in areas frequented by infected wild foxes may have lesions affecting the legs and ventral abdomen.[3] Dairy cattle may have an associated udder cleft dermatitis.[29] Sheep tend to have initial involvement of the nonwool areas. The ears should always be scraped for mites; the mite is identified by its rounded body, terminal anus, short legs, and long unsegmented pedicles.[3,6,16]

Because mites may be present only in small numbers, negative skin scrapings do not rule out the disease. Diagnosis should be based on clinical suspicion and

response to therapy.[3,6,16,30]

Topical acaricides have been recommended for treatment and are applied to all affected and contact animals at 10- to 14-day intervals for 4 to 6 treatments. These include lindane (not recommended owing to toxicity in humans), coumaphos, diazinon, malathion, toxaphene, and lime sulfur.[3,6,16] Ivermectin 0.2 mg/kg SC at 2-week intervals for 2 to 4 injections (ruminants) or orally (horses) has been shown to be effective, as has injectable moxidectin and topical doramectin. The contaminated environment should also be treated. It is recommended that the state regulatory agency for livestock disease control be consulted for methods of treatment and products to use because sarcoptic mange is a reportable disease.

Demodectic Mange

Demodectic mange is a rare disorder, although it has been recognized in all large domestic species. The mites live in hair follicles and sebaceous and sweat glands and are host specific. They are not contagious between members of the same species, but *Demodex* spp. are presumably transmitted from mother to offspring during the first few days of life by direct contact with the dam. Little else is known about the life cycle of the mite.[3,6] Two species of *Demodex* are recognized in the horse.[3,30] *Demodex caballi* is a normal inhabitant of the pilosebaceous apparatus of the eyelids and muzzle and may be found in skin scrapings of these areas on horses in the absence of skin lesions. *Demodex equi* inhabits the pilosebaceous apparatus of the remainder of the body and on horses is the species that has been associated with disease. The species found on cattle, sheep, and goats are *Demodex bovis* and *Demodex ghanesis, Demodex ovis,* and *Demodex caprae,* respectively.[3,6,16,18,31]

Clinical signs are variable depending on the species affected. The disease is quite rare in horses, which may develop alopecia of the head and trunk; we have seen one case of concurrent demodicosis and chorioptic mange on the legs of a draft horse. Underlying pituitary dysfunction of the pars intermedia has been seen in some horses.[3] Pruritus and secondary pyoderma are variable. Goats and cattle usually develop nodular lesions that involve the face, shoulder, and neck.[32,33] In goats the nodular contents are white and caseous; microscopic examination for mites differentiates the lesions from *C. pseudotuberculosis.*[33] Sheep tend to develop periocular nodular lesions.

Diagnosis is based on recognizing mites with microscopic examination of skin

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scrapings or exudates obtained from nodular lesions. The mites are elongated and have short, stubby legs.[3,6,16]

No treatment has proved to be consistently effective in large animals, although relatively few case reports exist in the literature. Amitraz has not been successful in the treatment of caprine demodicosis.[33] Horses sprayed with 0.025% amitraz developed somnolence, depression, ataxia, muscular weakness, and progressive large intestinal impaction, suggesting that amitraz is contraindicated in equids.[34] Daily ivermectin has been suggested as a successful treatment for equine demodicosis, but dosages have not been codified. Oral ivermectin (0.67 mg/kg once weekly for 12 weeks) and pour-on eprinomectin (0.5 mg/kg) each successfully treated one goat with generalized demodicosis.[35] A combination of ivermectin injections of 200 µg/kg body weight twice weekly and amitraz dip once weekly has been reported as successful in cattle.[36]

Culicoides Hypersensitivity

The females of various *Culicoides* fly species ("no-see-ums," "punkies") may feed on either the dorsal or the ventral surface of the horse, affecting the mane, saddle, and rump or causing a ventral midline dermatitis in a diffuse pattern. Alopecia, papules, crusts, and erythema may all be present (Fig. 40.12). The insects induce a hypersensitivity response through salivary antigens; this condition is termed *Culicoides hypersensitivity* (Queensland itch, sweet itch) and is recognized in various areas of the world. Evidence indicates a hereditary predisposition to develop the hypersensitivity. Histopathology of lesions frequently reflects a hypersensitivity response.[37] Although many species of *Culicoides* exist, the three most commonly suspected of causing the allergic response are *Culicoides variipennis*, *Culicoides obsoletus*, and *Culicoides nubeculosus*.



FIG. 40.12 Severe *Culicoides* hypersensitivity in a horse, showing typical distribution of withers, shoulders, and head (not visible).

Numerous studies have attempted to define the nature of the hypersensitivity response. One study found serum antibodies to *Culicoides* salivary glands in both healthy horses exposed to *Culicoides* bites and horses with insect dermal hypersensitivity.[38] In contrast, no antibodies were detected in serum from native Icelandic horses that had not been exposed to *Culicoides.* Anti–salivary gland IgG antibodies were detected in both groups of horses, whereas IgE antibodies were detected only in clinically affected horses.[38] Another study compared two groups of affected Icelandic horses: those born in Iceland (no previous exposure to *Culicoides*) and transported to Europe, where they were then exposed to the flies, and those born in mainland Europe. The former had IgE and IgG antibodies to a greater number of the insects' salivary proteins.[39] Further investigation of immunoglobulins in relation to *Culicoides* found significantly more IgE-bearing cells in the dermis and epidermis of acute and chronic lesions than in skin biopsies from healthy horses.[40] Further evidence for a hypersensitivity response was demonstrated in a study in which intradermal injection of a *Culicoides* antigen extract induced T-lymphocyte and eosinophil accumulation in the skin of affected horses.[41] Other studies have supported the immunologic nature of this disease.[42-46] Two recent reports have shown some linkage between insect bite hypersensitivity (IBS) and airway disease.[47,48]

The hallmark of disease is pruritus. Although no gender predisposition has been noted, Icelandic horses may have a higher incidence of allergic reactions to the *Culicoides* insects than other breeds. The disease is uncommon in horses younger than 1 year of age, with an onset usually between 2 and 4 years.

Culicoides hypersensitivity may be seasonal, at least during the first few years of life, in temperate climates. Diagnosis is primarily by clinical signs. *Culicoides* antigens (commercially available in the United States by Greer, Lenoir, N.C.) seem useful in both diagnosis and treatment,[49-51] but this must be documented in large case studies.

Therapy is aimed at insect control, especially the following:

1. Stabling horses at sunrise and sunset, peak *Culicoides* feeding hours.
2. Ultrafine setting or screens placed in windows (60 squares to the square inch).
3. Fly control, especially keeping horses away from standing water and using permethrin repellents, usually 2% permethrin sprays. Frequently, sprays must be applied more often than the label recommends (i.e., daily, at least at first). We have had success using a nonpesticide herbal spray or roll-on (MedZone [VetShield & Sheen, Sun City, Ariz.]).
4. Overhead or stall fans (drafts interfere with insects' flight).
5. "Dresses" that physically obstruct the insects from reaching the skin.
6. Hyposensitization is controversial; success may vary with the presence of an adjuvant or the actual antigen used.
7. Oral prednisolone to manage the pruritus.

Ventral Midline Dermatitis of Horses

This is a reaction pattern in horses to ectoparasites, and not necessarily specific to any one arthropod. *Culicoides* hypersensitivity, *Onchocerca cervicalis* infestation, and black flies (Simuliidae) may cause generalized ventral midline dermatitis, whereas horn flies *(Haematobia irritans)* cause a focal dermatitis. Severe chorioptic mange may also involve the ventral midline. In all cases the lesions have variable alopecia, pruritus, and crusts. Treatment is based on eliminating or repelling the causative organism.

Other Flying Insects

Stable flies *(Stomoxys calcitrans),* black flies (Simuliidae), horn flies *(H. irritans),* horse flies (*Tabanus* and *Hybomitra* spp.), deer flies (*Chrysops* spp.), houseflies *(Musca domestica),* face flies *(Musca autumnalis),* and mosquitoes are commonly associated with irritant and allergic skin disease, as well as being

vectors of many parasites (Color Plate 40.8). They must be controlled by limiting breeding areas and by repellents; 2% permethrins are often used. It is important to remember the relationship of these various flies to the environments they favor or require for breeding and when they feed, as follows:

Horse flies, deer flies	Vegetation and water	Daytime feeders
Horn flies	Cattle	Daytime feeders
Stable flies	Manure and decaying bedding	Daytime feeders
Black flies	Running water	Morning and evening
Culicoides	Standing water, manure and decaying vegetation	Twilight to dawn
Mosquitoes	Water	Dusk to 2 hours after sunset

Screwworm Infestation

Screwworm flies cause primary myiasis; the species of importance in the Americas is *Cochliomyia hominivorax (Callitroga americana).* The fly was formerly found throughout the American tropics and subtropics from the southern United States to northern Chile.[52,53] It is no longer found in the United States or Mexico because of state, federal, and international eradication efforts.[54]

The adult fly is about three times the size of a housefly, with a metallic bluish or blue-green color.[52,54] Females are attracted to fresh wounds (castration, dehorning, branding, and shearing sites), abraded body orifices, areas soiled by discharges or excretions, and navels of newborns. They lay batches of 150 to 500 white eggs on the margin of damaged tissue in rows that overlap like shingles. Eggs hatch within 24 hours, and the larvae begin to feed in a head-downward position. Larvae are obligate parasites that require living tissue as feedstuff. They cannot develop in carrion. Larval development continues for 4 to 10 days, and at the time of their maturation they may have created a cavity 10 to 12 cm (4 to 5 inches) in diameter.[53] Mature larvae are about 2 cm in length, pink, pointed anteriorly and blunt posteriorly. The larvae then drop to the soil and pupate. The life cycle averages about 21 days and is favored by hot, humid weather.

Screwworms do not have a dormant stage in their life cycle and cannot overwinter in cold climates.[52] Thus the susceptible stage of development is the pupae, which will not survive soil temperatures below 15° C (59° F). The feeding larvae burrow deeply, creating a cavernous lesion characterized by liquefactive necrosis, profuse brownish exudate, and an objectionable odor. The syndrome is self-perpetuating in that wounds infested by screwworm larvae become increasingly attractive to gravid females. The end result is often death of

the host from secondary bacterial infection, toxemia, and fluid loss.[53]

Treatment of wounds requires clipping and cleansing, as well as destroying all larvae. Dressings containing larvicides and antiseptics should be applied. Preparations containing lindane or organophosphates have been used in an ointment or gel base. The treatment is repeated twice weekly. When large numbers of animals are affected, a 0.25% solution of coumaphos, chlorfenvinphos, or fenchlorphos may be applied to herds with a power sprayer. Calves may become ill from the spray; thus applications should be restricted to the ventral abdomen.[53] Another study showed that the curative efficacy of fipronil 1% against *C. hominivorax* larvae infestation in castration wounds was 100%.[55] Even more impressive, doramectin as a prophylactic treatment was 100% effective in prevention of *C. hominivorax* infestations.[56]

Control of screwworm flies in the United States has been achieved largely through the release of sterile males, because of the single mating tendency of the female fly. The eradication program has proceeded through Mexico south to the 21st parallel.[52] Screwworm myiasis is a reportable disease in the United States, and suspect larvae should be preserved in 70% alcohol for positive identification.[57]

Blow Fly Strike (Fleeceworms, Woolmaggots, Secondary Screwworms)

Blow flies are found throughout the western hemisphere. The species of importance include *Cochliomyia macellaria* (secondary screwworm), *Phaenicia sericata* (green bottle fly), and *Phormia regina* (black blow fly). The flies tend to be most common in the warmer regions, with the exception of *P. regina,* which is widespread throughout the cooler parts of North America and Europe.[52] Blow flies cause serious loss of sheep and wool in many countries.[54] Female flies are attracted to decaying animal matter, such as wounds infested by primary screwworms, infected sores, carcasses, and fleeces that are dampened with feces, urine, or bloody fluids.[52] They lay eggs in batches of up to 300, which hatch within hours. The larvae feed on necrotic tissue but may invade healthy tissue. Larvae develop for 3 to 5 days and, when fully mature, are white and 6 to 12 mm in length. The larvae then drop to the ground for pupation. As soil temperatures fall, larvae fail to pupate and may overwinter until the following spring. The entire life cycle is generally complete in 2 to 4 weeks under ideal conditions of

warm temperatures and high humidity.[53]

Unlike primary screwworms that feed in pocket-like aggregations, secondary screwworms tend to be dispersed throughout the infested tissue. In wool infestation the larvae may remain on the skin surface, feeding on the decomposing wool, or may penetrate the skin through small abrasions. The most common site of involvement is the breech. Infested tissue attracts more ovipositing females, and thus the syndrome is perpetuated.[52] Affected sheep are restless and do not feed. They move with their heads close to the ground, bite or kick at their wounds, and continually wriggle their tails. Affected wool is moist and brown with an obvious odor. Animals may become systemically ill and die.[57]

Treatment of individual wounds is as described for screwworms. Control involves management practices that decrease the incidence of wounds or skin irritations. Sheep are often clipped below the tail and between the hindlimbs ("crutched"), where wool is likely to become saturated with urine or feces. Castration, shearing, docking, and lambing are avoided during the summer season.[52]

Cutaneous Onchocerciasis

▪ Definition and Etiology

Cutaneous onchocerciasis in horses is a common filarial dermatitis with a worldwide distribution. Its incidence in the United States has decreased dramatically since the introduction of ivermectin for routine deworming. In a report from South America, *O. cervicalis* microfilariae were detected in midventral skin biopsy samples in 215 (17.9%) of 1200 horses examined, and the adult worms were recovered from 200 (16.6%) ligamentum nuchae from the same animals.[58]

The disease is caused by the microfilaria of *O. cervicalis* and is seen primarily in adult horses.[59,60] Adults typically are found coiled in the funicular part of the ligamentum nuchae, where they produce calcified nodules. Viviparous females may live for up to 5 years and produce large numbers of microfilariae that migrate through connective tissues to the superficial layers of the dermis. Preferential areas of microfilarial localization include the ventral midline, lower eyelid, and lateral limbus of the eye.[59] The infection is transmitted by *Culicoides*, which act as an intermediate host. The larvae are ingested by the

vector and undergo development into the third-stage (L_3) larvae in approximately 2 weeks. The L_3 larvae enter the animal host through lesions created by the feeding vector.[61] Many horses are infected with the parasite without demonstrating clinical disease.[59,61] A form of cutaneous onchocerciasis seen in donkeys in Africa and possibly in other nearby areas causes severe ulceration in the withers and neck region; it is the adult parasite (sometimes extractable by the handful) that causes this problem. This is possibly caused by the species *Onchocerca raillieti*.

▪ Pathophysiology

Pathogenesis is believed to involve a hypersensitivity reaction to antigens released by dying microfilariae.[59,61] This theory has support because not all infected horses demonstrate disease, neither the presence nor the severity of the dermatitis is correlated with the number of organisms present, and treatment with filaricides often causes a temporary exacerbation of clinical signs.

▪ Clinical Signs

Clinical signs occur most often in older horses and can include both ocular and cutaneous lesions.[59,61] Ocular lesions include uveitis, conjunctivitis, keratitis, and depigmentation of the lateral limbus.[62] Cutaneous lesions include diffuse or patchy alopecia, erythema, and scaling. Focal cutaneous depigmentation is common. Lesions tend to occur in regions where microfilariae are typically present in highest concentrations, such as the ventral midline, face (Fig. 40.13), base of the mane, anteromedial proximal forelimbs, and anterior pectoral region. An inflammatory, alopecic, or hyperpigmented area in the center of the forehead is highly suggestive of the disorder.[62] The dermatitis is generally reported as being nonseasonal and nonpruritic.[61,63]

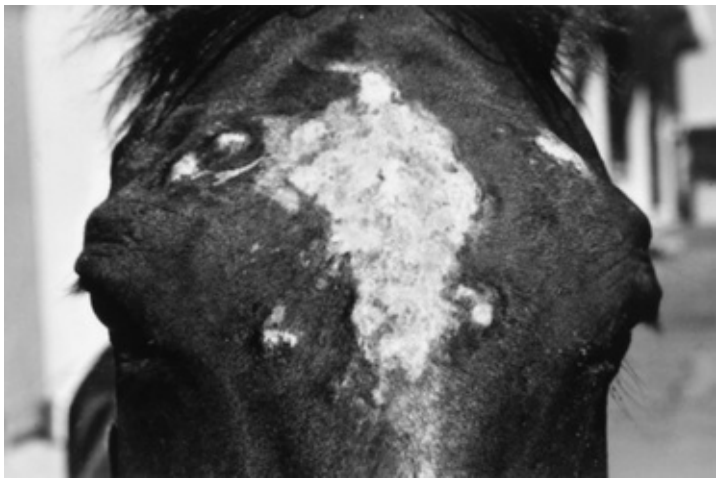


FIG. 40.13 Cutaneous onchocerciasis in a horse.

▪ Diagnosis and Histopathology

Because many normal horses have microfilariae without disease, the finding of microfilariae does not prove that they are the cause of the cutaneous lesions. In addition, because microfilariae tend to "nest" in the dermis, there is a tremendous difference in the number of microfilariae recovered from adjacent skin samples.[60,64] Thus although the absence of microfilariae makes cutaneous onchocerciasis unlikely, it does not definitively exclude it as a diagnosis. Differential diagnoses should include ventral midline dermatitis caused by the horn fly *H. irritans*, hypersensitivity reaction to *Culicoides*, dermatophytosis, and infestation with mange mites.

Ultimately diagnosis should be based on history, supportive clinical findings, exclusion of other differential diagnoses, and most importantly, response to treatment.

A positive *Onchocerca* microfilarial saline preparation demonstrates slender, delicate microfilariae that are approximately 8 × 220 µm. Typical histopathologic changes include an eosinophilic and lymphocytic perivascular dermatitis, a finding that is nonspecific and common to many other equine parasitic dermatoses (see Chapter 11). Aggregations of microfilariae may be found in the superficial dermis or perifollicular region.[59,61,64]

▪ Therapy

Ivermectin or moxidectin are the treatments of choice and are administered at 0.2 mg/kg PO.[65,66] Most horses improve within 2 to 3 weeks. Minor adverse

reactions, including fever and swelling of the periorbital, facial, and ventral midline regions, may occur in up to 25% of infected horses treated with ivermectin; moxidectin did not cause posttreatment dermal reactions in one study.[66] Severe reactions may benefit from treatment with corticosteroids, but most reactions resolve within 24 to 72 hours. Because there is no effective adulticide, recurrence may be noted as soon as 2 months after therapy. Most animals remain free of clinical signs for 6 to 12 months.[63,65] Re-treatment is recommended at 4-month intervals. Interestingly, ivermectin has been reported as having both greater and lesser GI absorption in donkeys than in horses. This awaits more clarifying studies.[67]

In cattle, onchocerciasis has been caused by the microfilariae of *Onchocerca gutturosa* and *Onchocerca lienalis* and, in Africa, *Onchocerca ochengi*.[68,69] Flies of Simuliidae are the vectors. The disease causes nodules and crust on the skin, including the teats; adult worms surrounded by neutrophils were detected free in the teat canal.[70] Ivermectin and moxidectin are effective treatments.[68]

Stephanofilariasis

Cutaneous stephanofilariasis is a filarial dermatitis of cattle. The disease is caused by organisms of the genus *Stephanofilaria* and has been observed in cattle in many countries.[71,72] Within the United States the disease is most prevalent in the western and southwestern regions, where it is caused by *Stephanofilaria stilesi.*[57,62,72] Adults and microfilariae inhabit the epidermis. The parasite is transmitted by the female horn fly *(H. irritans)* when it feeds on lesions on the ventral midline.[62] The microfilariae are ingested and develop to infective L_3 larvae in 2 to 3 weeks. The L_3 stage is introduced into the animal host on subsequent feedings.[72]

Clinical signs of cutaneous stephanofilariasis include a ventral midline dermatitis initially associated with a papular eruption. The scrotum may also be affected.[73] The lesions progress to nodules, alopecia, and crusted ulcers. There may be mild pruritus.[53] Diagnosis is based on history and appropriate clinical signs, excluding differential diagnosis and demonstration of the nematode. Biopsies may be taken as described for equine onchocerciasis, or the crust can be removed from an acute lesion and deep skin scrapings performed to recover the parasite. The tissues should be minced in isotonic saline and then examined microscopically. Multiple skin scrapings may be required to demonstrate the

parasite. Either adults or microfilariae may be found. The adult male is about 3 mm in length, and the adult female is about 6 mm in length.[70] Microfilariae are 50 µm in length.[70] Characteristic histopathologic findings include a perivascular dermatitis associated with an eosinophilia. Microfilariae may be noted in the dermis, and adults in epithelial-lined cysts at the base of the hair follicles, although both may be difficult to find.[70]

There is no approved treatment for stephanofilariasis, although approved topical organophosphates have been suggested.[60] Some authors have not recommended treatment, because clinical signs are relatively mild in many animals.[72] Cattle with zebu ancestry may be more resistant.[71]

Hypoderma (Warbles)

▪ Definition and Etiology

Infestation with the larvae of *Hypoderma* spp. is a common and serious economic problem in cattle and is recognized sporadically in horses that are pastured near cattle. Occurrences have also been reported in sheep, goats, and humans.[74] Warble flies are present in the northern hemisphere between 25 and 60 degrees latitude in more than 50 countries of North America, Europe, Africa, and Asia. *Hypoderma* spp. are not established south of the equator.[60,74] The U.S. cattle industry loses millions of dollars annually because of cattle grubs.

Two species of *Hypoderma* parasitize cattle: *Hypoderma bovis* and *Hypoderma lineatum.* The latter prefers warmer climates and is the only *Hypoderma* species present in the southern United States. Each of the species occurs in the northern United States and Canada.[60] *H. lineatum* and *H. bovis* have very similar life cycles, but the stages of *H. lineatum* tend to occur 3 to 8 weeks earlier than those of *H. bovis.* Timing of the life cycle also varies with local geographic and climatic factors.[60,74]

The adult flies are beelike in appearance, covered with dense chin bristles (hair), and are 12 to 188 mm in length, and they have nonfunctional mouthparts.[75] They have a short life span, only 1 week. Adult flies are active in the spring to early summer, with *H. lineatum* appearing 3 to 4 weeks before *H. bovis.* Female *H. lineatum* flies deposit eggs on the hairs of the legs or lower body, whereas *H. bovis* tends to deposit eggs on the rump or upper parts of the hindlimbs. Total egg production by a single female has been estimated to range

from 500 to 800.[75] The eggs hatch in 3 to 7 days, after which the larvae penetrate the skin and begin their migration through the connective tissues. *H. lineatum* larvae migrate to the subcutaneous connective tissues of the esophageal wall, whereas *H. bovis* larvae migrate toward the spinal canal. The first-stage (L_1) larvae remain in this location for 2 to 4 months during autumn and early winter. Between January and February the larvae begin a final migration through the connective tissues to the subdermal tissue of the back of the host, where they form a breathing hole through the skin. Cysts (warbles) develop around L_1 larvae. Within the cyst the larvae undergo two molts over a 4- to 6-week period. The L_3 larvae (grubs) emerge from the breathing pore, fall to the ground, and pupate. Adult flies emerge from the pupae in 1 to 3 months, and emergent adults are ready to mate almost immediately.[57,75] The life cycle is complete in 1 year. Most larvae fail to reach normal size and complete their life cycle in the horse.[74,75] A recent study suggests a humoral response from the host against the larvae while they are intact. Once the larvae are destroyed, cellular response occurs, isolating and destroying the remains of the larvae.[76]

▪ Clinical Signs

Cattle.

During the spring and summer when adult flies are active, “fly worry” may be a serious problem. Cattle exhibit a stampeding behavior called “gadding” when chased by ovipositing females, even though the flies do not bite or sting. This fear reaction results in self-injury and decreased feeding and milk production.[75] Diagnosis of warble flies in goats by ELISA has been reported, but it is not known whether this is applicable to cattle.[77]

Clinical lesions are not usually observed in association with migration of L_1 larvae unless the larvae die along the migratory path.[74] Lesions that have been associated with infestation of L_1 larvae of *H. bovis* include fat necrosis and inflammation of the connective tissues surrounding the spinal canal. Secondary periostitis, osteomyelitis, and rarely paralysis or other nervous disorders may occur. Similarly, infestation with L_1 larvae of *H. lineatum* in the submucosa of the esophagus may cause inflammation and edema in the surrounding tissues. Swallowing and eructation may be hindered, resulting in bloat and subsequent respiratory failure.[74]

Lesions most often observed with *Hypoderma* infestation are attributed to L_3 larvae. Warbles occur along the back from the shoulders to the tailhead and from the dorsal midline to a point about one third the distance down the sides. The lesions may be firm to fluctuant, raised, and painful to the touch. They measure approximately 3 cm in diameter and contain a breathing pore that usually exudes a yellowish serum. Excisional biopsy of a nodular lesion reveals the larvae within a cystlike structure that contains yellow fluid. The surrounding tissue is necrotic. Secondary infection of the cysts can result in large suppurating abscesses. The number of warbles in an infested animal may range from 1 to 300. Infestations are most serious in younger animals and become progressively less severe with age. Emergence of the grub results in healing, although carcasses retain evidence of infestation and are devalued at slaughter.[60,74] Diagnosis is usually by direct clinical examination, but immune diagnosis using pooled serum and/or milk sample is also possible.[78]

Horses.

Most horses have only one or two grubs, but heavy infestation is present in rare cases. Lesions associated with L_3 larvae include small nodular swellings that develop dorsally and frequently in the region of the withers. Most lesions have a breathing pore.[57] Differential diagnosis is most often eosinophilic granuloma (nodular collagenolytic granuloma, nodular necrobiosis), but mastocytoma, sterile nodular panniculitis, and amyloidosis should also be considered. Posterior paralysis associated with involvement of the spinal cord has been reported in both horses and cattle.[75]

The season, location of the lesions, and presence of a breathing pore are usually diagnostic. Larvae can be recovered by enlarging the breathing pore with a scalpel and extracting the grub.

▪ Therapy

When small numbers of cattle are affected with just a few grubs, manual removal of the grubs is possible by simply enlarging the breathing pore. This is usually the preferred treatment in horses as well if only one or two lesions are present. Care must be taken to remove the larvae in their entirety, because breaking the larvae and rupturing the cyst during removal can result in a severe systemic reaction.[60,74]

Systemic insecticides are the only means of eliminating the migrating larvae.

Organophosphates or the macrocyclic lactones (doramectin, eprinomectin, ivermectin, moxidectin) have been used for this purpose and are applied on the midline of the back.[74,79,80] Administration of insecticides should be timed to provide treatment in early autumn after all eggs have hatched and larvae are in the early stages of their connective tissue migration. L_3 larvae are less susceptible to insecticides, and destruction of larvae in later stages of migration increases the risk of serious secondary illness. It is advisable not to administer systemic insecticides later than 8 to 12 weeks before the anticipated first appearance of grubs along the back.[60,74] In the northern United States and Canada, treatment of cattle with systemic insecticides is not recommended from October 1 to March 1; this is when *H. bovis* larvae are in the epidural space and *H. lineatum* larvae reside in the esophagus.[60]

Sheep Keds

The sheep ked, *Melophagus ovinus,* is a wingless fly approximately 6 to 7 mm in diameter with a ticklike appearance. Sheep keds have a worldwide distribution. They primarily parasitize sheep and occasionally goats that are kept under poor management conditions.[60,81] Recently the sheep ked has been shown to be a vector of *Rickettsia raoultii* and *Rickettsia slovaca* (of the spotted fever group of organisms).[82]

The entire life cycle is spent on the host. Females live 4 to 5 months, individually laying 10 to 15 larvae that are cemented to the wool or hair. The larvae pupate in 12 hours, and the adult emerges 3 weeks later. Adults feed on blood and do not survive longer than a few days off the host. Transmission is by direct contact, and infestation is more common in the winter months.[60,61,81]

Clinical signs of infestation include pruritus with subsequent self-trauma, wool stains from the flies' fecal material, and, in severely parasitized animals, anemia. Multiple firm nodules (cockles) develop because of repeated puncture of the skin as the keds feed.[60,61] Infestation results in economic loss from a reduction in dressed carcass weights of lambs, reduced clean dry weight of fleece, wool staining, and reduced value of sheep skins because of nodular defects.[60,81,83] Diagnosis is based on demonstration of the parasite.

Therapy involves shearing all sheep in the affected flock, followed by two topical applications of malathion, diazinon, or coumaphos at 14- to 21-day intervals to kill emerging adults.[60] Because the larvae are attached to the wool or

hair some distance above the skin surface, many larvae and pupae are removed by shearing.[61,83] Imidacloprid has been shown to be effective in killing the parasite.[84] All new animals should be isolated and treated before introduction to prevent reinfestation. A control program includes annual treatment of the entire flock.

Cutaneous Habronemiasis (Equine Summer Sore)

Habronemiasis ("summer sore") is a granulomatous disease caused by the deposition of *Habronema microstoma, Habronema muscae,* or *Draschia megastoma* larvae by flies at the site of wounds or natural body moisture (sheath, eyes).[85,86] Adult parasites normally reside in the stomach, where they cause little tissue reaction, with the exception of *D. megastoma,* which produces gastric nodules of varying sizes near the margo plicatus. Females are viviparous, and larvae are passed in the feces, where they are then ingested by the larvae of flies acting as intermediate hosts. *H. muscae* and *D. megastoma* develop in the housefly, *M. domestica,* and *H. microstoma* develops in the stable fly, *S. calcitrans.*[60] The L_3 larvae are then deposited around the horse's mouth and swallowed to pass to the stomach, where they mature to adults. Cutaneous lesions occur when the larvae are deposited in damaged skin or areas of natural body moisture. The larvae cannot penetrate normal healthy skin.[61] In these aberrant locations, they are unable to mature to adults, and the resulting proliferative lesions are thought to represent a hypersensitivity reaction to the dead or dying larvae. In temperate parts of the world, habronemiasis is a seasonal disease, occurring in warm, wet weather.

Arabians, gray horses, and horses with a dilute hair coat seemingly have a predilection for this disease. The medial canthus of the eye, male genitalia, nictitating membrane ("third eyelid"), and distal extremities are the most common parts of the body affected.[85] Lesions consist of ulcers and nodules. Diagnosis is based on clinical signs, history, and the presence of calcified concretions (sulfur granules) and is confirmed by biopsy. The nodular lesions may take on the gross appearance of neoplasia. Alternatively, the larvae may infest a preexisting tumor, especially squamous cell carcinoma of the male genitalia, and a biopsy is crucial for accurate diagnosis. Characteristic histopathologic findings include granulation tissue with a diffuse infiltration of

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eosinophils and an ulcerative epithelial surface. The granulation tissue usually contains focal areas of coagulation necrosis surrounded by a dense eosinophilic infiltrate. Cross-sections of larvae can often be identified within some of the necrotic foci.[85] Rarely, larvae are found in scrapings from the lesions.[60] Larvae are not always found in the biopsy sections[85]; in these cases, if neoplasia has been ruled out, presumptive treatment for habronemiasis should be performed. A PCR assay for diagnosing habronemiasis has been developed and may hold promise in the future for cases where larvae are not found on biopsy.[87]

Treatment in the past has been either corticosteroids or organophosphates, topical or systemic. Ivermectin (0.3 mg/kg PO) has been shown to be effective and is considered the treatment of choice by many clinicians. Moxidectin (0.4 mg/kg PO) may also be used. These medications may be used once to twice in treating this disease. Systemic corticosteroids (e.g., prednisolone 1 mg/kg PO once daily for 10 to 14 days, then tapered over 2 weeks) or intralesional or topical corticosteroids are often used because of the hypersensitivity-reaction nature of the disease process. In severe cases, surgical removal or debulking of the lesion should be considered.[86]

Habronemiasis has been seen in horses routinely given ivermectin as part of their deworming program.[86] Prompt removal and disposal of manure and soiled bedding are important to eliminate vector breeding habitats. Insect repellents should be applied to affected horses. Face guards (fly masks) will also prevent infection. In general, the prognosis for resolution of individual lesions is good if the therapeutic goals are achieved.

Besnoitiosis

Donkeys have a higher reported incidence than horses for infections with the protozoal parasite *Besnoitia bennetti.*[88-91] This organism is the same species that afflicts cattle and is closely related to *Besnoitia tarandi,* which afflicts reindeer *(Rangifer tarandus).*[89] The mode of transmission has not been determined. Skin lesions affect the nares, skin, and sclera. Males and younger animals may be at greater risk.[91] Diagnosis may be from histopathology, serologic testing, and PCR. Unfortunately there is no known treatment.

Bovine besnoitiosis, due to the cyst-forming organism *Besnoitia besnoiti,* is widespread in Africa, Asia, and southern Europe, although its range may be expanding.[92] Economic losses result from decrease in cattle and milk

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production, transient or definitive sterility of bulls, laminitis, and mortality.[92-94] Goats are also affected by this parasite. Lesions are reported as warm and painful edema progressing to excessively folded skin, primarily on the legs, udder or scrotum, and head.[95] The mode of transmission is unknown, although flying insects have been suspected.[96] Diagnosis is as with donkeys; the skin of the rump may be the best place to biopsy.[97-99]

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Tumors and Cysts

Squamous Cell Carcinoma

Stephen D. White

Squamous cell carcinomas (SCCs) are tumors composed of squamous epithelial cells. They occur in all domestic species and are the most common bovine ocular tumor (see Chapter 39) and the second most common tumor recognized in the horse.[1] Although their gross appearance may vary, these tumors are usually slightly raised, broad based, and white to pink and have a cobbled or cauliflower-like surface (Color Plate 40.9). SCCs frequently occur on the penis and sheath of aged stallions and geldings (see Chapter 43). They also occur on the lips, nose, eyelids, eyes, and ears of horses. SCC often accompanies cutaneous papillomas of the udder and teats in Saanen milk goats, as well as female Angora goats in South Africa. The ears, base of the horns, perineal region, and prepuce may also be affected.[2,3] SCC is reported as the most common cancer of the ear of sheep; an outbreak primarily affecting the eyelids in 15% to 18% of a sheep population has been reported.[4] Diagnosis is by biopsy. There is increasing evidence that SCC in horses and sheep is associated with papillomavirus infection.[5-8]

The treatment of choice is wide surgical excision.[2,9,10] Solar elastosis (aggregates of thick, wavy, interwoven elastic fibers mixed with areas of degenerated collagen), when seen histologically with SCC, may lend a more favorable prognosis after complete surgical removal of lesions.[11] Other treatment modalities reported as successful include cryosurgery, radiofrequency hyperthermia, and radiation therapy.[2,12] Another study showed that topical application of 5-fluorouracil (5-FU) and intralesional cisplatin were effective in horses with SCC.[13-16] Piroxicam was successful in the long-term control of SCC with metastases in one horse.[17]

Equine Sarcoid

Alain P. Théon

Sarcoids

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Epidemiology.

The equine sarcoid was first reported by Jackson in 1936.[1] It is the most common tumor in Equidae (horses, donkeys, and mules), affecting between 1% and 3% of Equidae across the world.[2] Various sources report that histologically confirmed equine sarcoids constitute between 30% and 70% of all tumors and 70% and 90% of all skin tumors.[1,3-5] Because most estimates of incidence and prevalence are established from veterinary referral hospital data with high caseloads of affected horses, the true population base is unknown.

Sarcoids are locally aggressive, nonregressing, fibroblastic tumors of the dermis and subcutis with a variable proliferative epithelial component. This dual involvement of the epidermis and the dermis is the hallmark of sarcoids and explains the multiple and evolving clinical appearances of the tumor. The epidermal component of sarcoids shares features of a benign papilloma, and the fibroblastic component is consistent with a low grade fibrosarcoma.[6] These characteristics lead to an incorrect diagnosis of fibrosarcoma or nerve sheath tumors when the surrounding skin is not included in the tissue analyzed.[3]

Despite numerous clinical reports on sarcoids, the clinical and epidemiologic data are still puzzling. The inconsistent and sometimes conflicting data do not support any gender, breed, age, and genetic predispositions or any anatomic predilection.[2] However, paradoxical findings between studies may simply reflect the lack of histologic confirmation of the disease in most reported studies, but they may also represent regional or national variations of the clinical characteristics of sarcoids.

It is widely accepted that bovine papillomavirus (BPV) types 1 and 2 are associated with the pathogenesis of sarcoid disease. Although papillomaviruses are strictly species specific, an equine papillomavirus has not been identified in sarcoids. As opposed to other species, equine sarcoid is the only documented infection of a heterologous host by papillomavirus.[7] While BPV1 has been shown to be more prevalent in sarcoids from horses in Europe, the eastern United States, and Australia,[8-10] BPV2 has been more commonly reported in lesions from horses in the western United States and Canada.[11,12] Recently, sarcoids collected in Brazil were found to be associated with BPV13, which is genetically more than 90% homologous to BPV1 and BPV2.[13]

BPV1 and BPV2 genomes and transcripts have been found consistently in equine sarcoids.[11,14-18] Sequences of early-expressed genes of the viral genome

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including *E5*, *E6*, *E7*, and occasionally *E2* are consistently detected in sarcoid tumors and surrounding normal cutaneous margins but not in other tumor types.[19-21] Both the epithelial and the fibroblastic components of the tumor contain differential viral gene sequences that are actively transcribed.[15,17]

However, the role of BPV in the etiology of sarcoids continues to be questioned. Although equine fibroblasts can be transformed in vitro following BPV1 infection,[22,23] experimental transmission studies of sarcoids have been unsuccessful. Inoculation of sarcoid cell–free extract in cows does not induce warts, nor does it induce sarcoids in unaffected horses.[3] Experimental cutaneous infection with BPV induces fibropapillomas that are clinically similar to sarcoids. The lesions, however, regress spontaneously with production of neutralizing antibodies to the virus and presence of viral DNA sequences in white blood cells.[24,25] In contrast, histologically confirmed, naturally occurring sarcoids do not regress and are not associated with detectable serum antibody responses to BPV.[26]

The infection in horses is considered nonproductive because BPV cannot replicate in horses nor be serially passaged from BPV-induced fibropapillomas.[17,25] Full viral life cycle has never been demonstrated in Equidae, and viral particles have never been detected in lesions. Hence the disease is currently accepted as the result of an abortive cycle, dead-end infection where only early BPV gene sequences persist episomally[27,28] or are integrated in host DNA.[29]

The mode of transmission of the disease is unknown and does not require contact with cows. Intradermal injection of primary sarcoid fibroblasts containing viral episomes,[24] naked full-length BPV1 genome,[24] or transforming genes (*E5* and *E7*)[30] does not induce sarcoids in horses and donkeys. Supporting evidence for an equine-to-equine infectious cycle that maintains BPV without the need for bovine host is missing. The finding that the majority of sarcoids collected in Austria, Switzerland, the United Kingdom, and Poland harbored equid-specific BPV1 variants, and that bovines lack these variants,[31-35] further strengthens the theory that BPV is not transmitted from bovines. This is confirmed by a study where BPV DNA sequences were detected in healthy skin of horses not known to have ever been in contact with bovines.[36]

An epidemiologic BPV DNA analysis of a sarcoid outbreak in donkeys and mules in a rescue sanctuary revealed that donkeys were not the victims of an

epidemic but had accidently developed sarcoids associated with different BPV variants and were assumed to have acquired infection before their rescue.[37] In addition, evidence of a transmissible infectious cell line has not been found.[38] Because only complete BPV virions can induce transformation, contamination cannot occur by casual contact with contaminated fomites or affected horses[36] or by BPV-infected insect bites[39] or blood samples.[40] As a result, horses are considered to be nonpermissive hosts for BPV,[41] and horizontal BPV transmission remains to be documented.

The presence of viral genetic material appears to be directly associated with tumor development. However, BPV DNA sequences have also been detected in healthy skin[36] and in some cases of dermatitis.[42] In addition, the presence of viral DNA sequences has also been reported in skin swabs of unaffected horses and in peripheral blood mononuclear cells of horses with unrelated skin lesions (abscess, carcinoma, and hoof canker).[40,43] As a result, intracellular persistence of BPV transforming genes is not sufficient to produce the disease, and the role of BPV in the etiology of sarcoids continues to be questioned.[22,23]

▪ Molecular Biology

The mechanisms of cellular oncogenesis are similar to those of other transforming papillomaviruses. Cell transformation is associated with episomal or genomic integration and expression of the three transforming genes *E5, E6,* and *E7*. The gene products, *E5, E6,* and *E7,* are cell cycle regulators necessary for host cell proliferation and viral genome replication. In sarcoids, overexpression of these genes associated with persistent infection underlies cell transformation and progression into tumor cells. *E5* is always found and expressed in sarcoids. *E5* binds to and activates the platelet-derived growth factor beta receptor (PDGFβR),[44] which triggers several downstream effectors pathways controlling cell proliferation, cell survival,[44] and invasion.[45] *E6* and *E7* proteins bind to cell cycle control gene products, blocking their activity. They specifically promote cell cycle progression and prevent apoptosis and therefore immortalize the transformed cells.[33] *E6* is a transcriptional activator that inactivates the apoptotic and cell cycle arrest functions of the tumor suppressor gene *p53*. Loss of functional activity of tumor suppressor *p53* has been confirmed in sarcoid cells in culture and in tumors.[14,19,23,46,47] *P53* loss of transactivation function without *p53* mutation has been confirmed in sarcoids.[48]

E7 cooperates with *E5* as well as with *E6* in cell transformation.[49] Although *E7* lacks the binding domain of the tumor suppressor retinoblastoma protein (Rb),[50] it still inhibits apoptosis in a Rb-independent pathway, which provides transformed cells with a survival advantage.[51] The mechanisms by which *E7* and its cellular targets contribute to cellular transformation in sarcoids are not fully understood.[52]

The presence of inflammatory cells of the innate and adaptive immune system that infiltrate sarcoids provide evidence of an antitumor immune response that could eliminate abnormal cells before they can become tumorous in BPV-positive unaffected horses. Although there is evidence that the inflammatory and immune response may inhibit the development of cancer, BPV1- and BPV2-infected equids seem to lack an effective antiviral immune response to BPV and BPV-infected tumor cells. As a result, sarcoid lesions persist and progress despite the presence of cytotoxic T cells and T-helper cells in lesional and perilesional tissue.[53] It is speculated that *E5* and *E7* downregulation of the immune response may contribute to successful viral infection and allow cells to evade immune surveillance. *E5*-dependent downregulation of the surface expression of major histocompatibility complex class I (MHC I), by reducing transcription of the MHC I heavy chain gene and blocking transport of the MHC I complex to the cell, has been shown to depress adaptive immune response and allow persistence of infected cells.[54] In addition, BPV *E7* along with *E5* have been shown to block the innate immune antiviral response by downregulation of Toll-like receptor 4 (TLR4) expression.[55] Further evaluation of the defective host antitumor response ruled out a recruitment of actively immunosuppressive inflammatory cells such as regulatory T cells (Tregs). Tregs' cell density was not different in sarcoids compared to normal skin.[53]

Although the interplay between BPV *E5*, *E6*, and *E7* and their downstream targets is critical to immortalize and transform cells as well as to conceal them from the immune system, epidemiologic and experimental data indicate that persistence and overexpression of viral transforming genes are not a sufficient cause to induce sarcoid. The initiation of sarcoid appears to be due to a viral-induced inhibition of apoptosis rather than uncontrolled cell proliferation, as the markers of cell proliferation, such as cyclins and their respective kinases, are not different from those of normal skin[19,56] Additional genetic events are required for tumor cells to acquire the traits that enable them to become malignant. These events are sustained by several mechanisms, including loss of function of tumor

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suppressor genes, and driven by the host genomic instability that expedites additional mutations leading to malignancy.

Genomic instability is a hallmark of cancer progression[57] and plays a central role in sarcoid development. Increased genomic instability in sarcoids has been demonstrated by an abnormally high number of genomic aberrations found in tumor cells compared with normal unaltered skin tissue samples.[58] Similar genomic instability has been found in cultured sarcoid-derived fibroblasts, suggesting that BPV may directly stimulate genomic instability through DNA replication stress due to loss of *p53* function or through oxidative stress due to shifts in energy metabolism to support rapid proliferation.[59]

Genomic instability in sarcoids has been shown to allow accumulation of mutations of genes engaged in biological pathways common to other cancers. Growth factor signal transduction pathways, including PI3-AKT (phosphoinositide 3-kinase v-akt murine thymoma viral oncogene homolog 1)[44] and *p38* mitogen-activated protein kinase (MAPK),[45] have already been identified. Whole genome scan has been used to identify genetic variants associated with sarcoids.[58] The study confirmed an increased genomic instability already detected in tissue culture.[59,60] Aberrations of genes involved in immune response (cytokines), generation of metabolites and energy, intracellular signal transduction (PI3-AKT and MAPK pathways), and cell proliferation were identified. In addition, aberrations of common cancer genes, including *VEGF, Kit,* and *Ras*, were detected.[59]

There is good evidence that genomic instability driving progression to malignancy could be promoted by inflammation, viral integration, and epigenetic modifications. The presence of leukocytes within sarcoids provides evidence of a link with inflammation.[17] If inflammation can retard or eliminate the tumor, it can also contribute to tumor growth and survival by supplying factors that sustain proliferation and limit cell death and enzymes that facilitate invasion.[57] BPV is commonly found in inflamed equine skin conditions.[61] Although skin trauma, wound healing, and chronic irritations have been suggested as important mechanisms to allow BPV access to the dermal fibroblasts,[43] they are not required, and inflammation alone may be sufficient to allow BPV access to the dermal fibroblasts.[61] The inflammation itself may be partly a result of BPV infection, and the inability of some horses to resolve the inflammation in these areas may promote sarcoid formation.[61] The inflammatory

response may play a role in providing survival and proliferative signals to initiated cells, thereby leading to tumor promotion. One effector mechanism by which the host fights microbial infection is the production of reactive free radicals that leads to oxidative damage of all cell components and induces host DNA damage actively mutagenic for nearby cancer cells, accelerating their genetic evolution toward states of heightened malignancy, which promotes genomic instability.[57-60]

Epigenetic events are emerging as an important additional mechanism whereby the BPV transforming genes promote development of sarcoids. Epigenetic events are those that can alter phenotype without changing the genotype. Epigenetic mechanisms of silencing or activating expression of nonmutated genes involving DNA methylation and regulatory noncoding ribonucleic acids (RNAs) have been identified in sarcoids. BPV-induced aberrant DNA methylation has been associated both in vitro and in vivo with genomic instability, activation of cell proliferation genes, and silencing of genes involved with immune function.[60,62] Further, microRNA deregulation in equine sarcoid tissues resulting in abnormal expression of messenger RNA (mRNA) at the posttranscriptional level has been shown to be engaged in cancer-related pathways, including regulation of cell proliferation, apoptotic pathway, and genomic instability.[63]

The role played by BPV in the development of sarcoids may be conceptually similar to the role of a genetic predisposing mutation that favors the appearance of the tumor in affected cells. Therefore in the pathogenesis of sarcoids one can identify at least two factors. The first one is related to the effects of transforming genes' proteins, which lead to an environment of genomic instability and local immune suppression. The second factor is the accumulation of cellular genetic damages not related to BPV, needed for tumor development. In humans, viral DNA integration is another factor that plays a critical role in the deregulation of key cellular genes by insertional mutagenesis. Although integration of human papillomavirus (HPV) DNA into the host genome has been shown to positively correlate with the severity of the tumors in humans, there has been no investigation of the role of viral integration in sarcoids.

▪ Biological Behavior

Sarcoids represent a wide spectrum of fibroblastic tumors ranging from indolent, apparently benign lesions to aggressive and invasive tumors. Clinically, many

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sarcoids behave initially as benign lesions because they are slow growing, giving the false impression that the lesion is inactive. In addition, sarcoids are frequently classified as biologically benign tumors because they do not metastasize to distant organs and regional lymphatic metastasis is rare and usually associated with multiple unsuccessful treatments.[64] However, the equine sarcoid is not a benign tumor because it is a progressive disease that invades and destroys surrounding normal tissue, does not regress spontaneously, and recurs predictably after surgical mass removal.[3,33,65] Early lesions are restricted to the dermis and epidermis, but advanced lesions commonly invade the subcutis and may extend through fascia into deeper muscular structures. Considering sarcoids as benign tumors leads to inappropriate management early in the course of the disease and thus to multiple recurrences and also results in unsatisfactory cosmetic and functional outcomes as well as unnecessary expenses to control the disease.

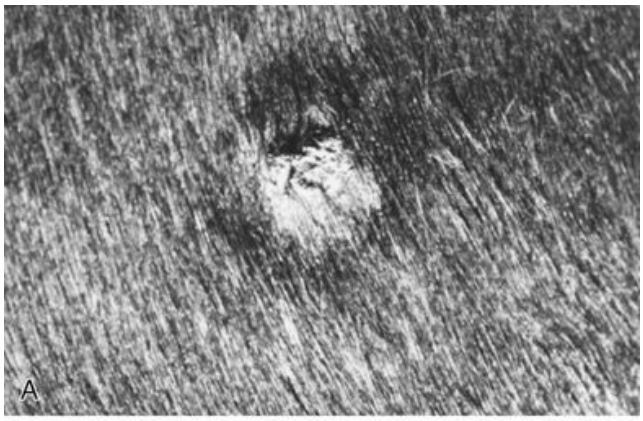
Molecular understanding of the different pathways leading to sarcoids may explain why some lesions remain quiescent for many years and eventually undergo progressive transformation to the aggressive fibroblastic type, whereas other lesions arise de novo as aggressive fibroblastic tumors.[3,6,66] The variable presence, type, and location (episomal vs. integrated) of BPV DNA and expression of BPV transforming genes in tumor cells[47] as well as the status of the host immune response, may explain the variable appearance, location, and behavior (growth rate, local invasion) of sarcoids. However, clinical manifestation of the disease is not in a simple linear correlation with BPV activity, and the correlation between viral load and disease severity remains controversial.[46]

Sarcoids share common features with soft tissue sarcomas, particularly the propensity for local invasion of surrounding tissues and infiltration of tissue planes. Tumor invasion of surrounding normal structures is believed to require matrix proteases and metalloproteases (MMPs) to allow cell migration and invasion. It has been shown that the overexpression and activation of MMPs is induced by BPV transforming proteins in equine sarcoid fibroblasts, and recently MMP overexpression by epidermal and dermal cells has also been confirmed in vivo.[47,67,68] Identifying signaling cascade controlling invasiveness may provide therapeutic targets against the most aggressive sarcoids.[44,45]

▪ Diagnosis

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Sarcoids are recognized as having different multiple clinical manifestations, including occult, verrucous, and nodular clinical types (Fig. 40.14).[3] In addition, approximately one third of affected horses have multiple sarcoids at different clinical stages at the time of diagnosis.[2] The different clinical aspects represent stages of tumor progression and reflect the relative predominance of the dermal or epidermal component. Lesions with a predominant epidermal component include occult and verrucous sarcoids. Occult sarcoids appear as an almost circular area of alopecia with a gray, scaly surface. Verrucous sarcoids may be sessile (flat variety) or pedunculated (warty variety); the skin is thickened with a dry, rough surface, with partial or total alopecia. Nodular sarcoids, also called *fibroblastic sarcoids*, range in appearance from a dermal or subcutaneous nodule to a large exophytic mass with a skin surface that eventually ulcerates. The nodular type is locally invasive, destroying adjacent tissues, and ultimately may infiltrate lymphatic vessels and nerve sheaths and disseminate to form regional metastases.[64] Mixed forms represent a transition from one type to another. The multiplicity of recognized clinical forms confirms the equivocal and progressive nature of the disease.


A


B


C

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FIG. 40.14 Equine sarcoids. **A,** Small occult sarcoid. **B,** Multiple verrucous sarcoids. **C,** Fibroblastic sarcoid.

The polymorphic appearance of sarcoids and the diverse list of differentials make the clinical diagnosis of sarcoids unreliable. The diagnosis and treatment of sarcoids require a biopsy because they are often overdiagnosed clinically. In a review of 681 horses referred to the Equine Oncology Clinic at the University of California, Davis Veterinary Medical Teaching Hospital for evaluation and treatment of clinically diagnosed sarcoids, 31% of lesions were found to be nonneoplastic dermatologic conditions.[69] After ruling out a nonneoplastic skin condition, any clinically suspicious lesion should be biopsied.[70] As with any tumor, early recognition and treatment of a small lesion is always associated with a better prognosis. It is important to keep in mind that any large and invasive sarcoid associated with a poor prognosis was, earlier in its evolution, an apparently inactive small lesion that was not recognized or was neglected. There is no contraindication for a biopsy of a suspicious skin lesion as long as definitive and effective treatment is instituted immediately after the diagnosis is made. There should be no fear about performing a biopsy of a suspected sarcoid because very effective treatments are available. However, a biopsy, like any trauma, can increase proliferation of a previously slow-growing tumor and may accelerate tumor progression. As a result, a biopsy should not be recommended if the owner is not willing to pursue treatment, if needed, because the process of biopsy without subsequent treatment has the same effect on overall prognosis as an unsuccessful attempt at treatment.

▪ Treatment

Sarcoids are low-grade fibrosarcomas and share common features of soft tissue sarcomas. They are locally invasive and tend to infiltrate into surrounding normal tissues through and along fascial planes 2 to 4 cm from the palpable tumor mass. Treatments that are used can be broadly grouped into ablative (surgery, laser vaporization, cryotherapy, hyperthermia, caustic ointments), cytotoxic (radiation therapy, chemotherapy) and biologic (immunotherapy) modalities. The overall treatment goals are (1) to destroy all tumor cells in the gross tumor and also in the normal-appearing surrounding tissues and (2) to minimize damage to healthy tissues. These goals are difficult to achieve with ablative treatment methods because they are not selective against tumor cells. A

cuff of surrounding normal tissue containing microscopic disease must be ablated to remove all tumor cells. Early complete surgical resection has a central role in the treatment of sarcoid. Alternate ablative modalities have no oncologic benefits over a well-planned conventional surgery and do not allow histopathologic evaluation of surgical margins to assess the quality of the procedure. Topical applications of escharotics with zinc chloride–based caustic ointments[*,†,‡] or 5-FU cream[§] are used empirically for treatment of sarcoids. Unfortunately, to date, no evidence-based data have been published documenting treatment efficacy against histologically confirmed sarcoids. As a result, no evidence-based information on treatment protocol, efficacy, prognosis, and toxicity is available.

Because tumor size and previous unsuccessful treatment attempts are the most important prognostic factors,[65,75] early and histologically complete surgical resection is the mainstay of treatment of sarcoids.[70] Failure to eliminate the disease results in regrowth of a tumor that is histologically and biologically more aggressive and requires wider excision than the primary lesion. As a result, it is critical to submit the resected tissue specimen for histopathologic examination to determine the status of the surgical margins. As a rule, grossly or histologically incomplete resection (i.e., positive or close pathologic margins [≤5 mm]) must be followed by a re-resection if possible or by effective adjuvant treatment. For noninvasive sarcoids resected with a pathologic margin greater than 5 mm and for invasive sarcoids resected with a pathologic margin greater than 1 cm, the risk of recurrence is low and no further treatment other than observation at regular intervals for at least 1 year is recommended. For invasive sarcoids resected with surgical margins between 5 and 10 mm, the risk of recurrence is high and adjuvant treatment may be recommended, particularly when tumor recurrence may be difficult to manage because of unfavorable anatomic location. Access to molecular techniques (PCR and RT-qPCR) designed to detect BPV *E5* or *E6* in pathologic margins will help assess the risk of recurrence and determine the need for adjuvant treatment.[76,77]

Among the nonsurgical treatments, radiation therapy and intratumoral chemotherapy with a viscous-fluid, slow-release formulation of cisplatin have well-documented efficacy against biopsy-confirmed sarcoids of all clinical types and in any location.[75,78,79] The selective effects of these treatments have the advantage of controlling the disease while avoiding disruption of anatomic structure and preserving function. When compared to radiation therapy,

intratumoral chemotherapy with cisplatin is as effective but does not have long-term side effects and does not require any special license. The overall cure rate (all stages and clinical types combined) after treatment with intratumoral cisplatin therapy used alone or as adjuvant to surgery has been reported to be as high as 96%.[75] Treatment includes a series of four intratumoral administrations of cisplatin (approximately 1 mg/cm^3 of tissue) given at 2-week intervals. Widely available and inexpensive compounded crystal is formulated in a water and sesame seed oil emulsion stabilized with sorbitan monooleate (Span 80).[75] Treatments are done on an outpatient basis under sedation, and the methods of administration and safety precautions have been described.[80] Although other antineoplastic drugs[81-83] and drug formulations[65,80,82,84] for intratumoral chemotherapy have been evaluated, cisplatin in sesame seed oil emulsion remains the most effective drug.[75] In an effort to increase duration of tumor exposure to cisplatin, cisplatin-containing biodegradable beads implanted intraoperatively[84a] have been used but have not shown any therapeutic benefit when compared to conventional intralesional cisplatin administration.[75] Attempts to increase cisplatin uptake in tumor cells by applied electroporation[85] called electrochemotherapy also failed to show any therapeutic benefit when compared to conventional intralesional cisplatin administration.[75] Further, electrochemotherapy requires general anesthesia for each treatment due to painful pulses of electric current as well as expensive equipment and complex procedures.

Systemic chemotherapy with doxorubicin* has shown preliminary evidence of efficacy for fast-growing fibroblastic sarcoids but not for indolent verrucous sarcoids.[87]

BPV-associated equine sarcoids are distinct from other equine tumors in that they express viral foreign antigens necessary to maintain the cancerous phenotype that could be targeted by the host's immune system. Because sarcoid tumor cells have the potential to be highly immunogenic, immunotherapy has been evaluated for treatment of sarcoids. Nonspecific cell-mediated immunotherapy has been used for sarcoids with inconsistent results. Treatment involves the use of immune stimulatory agents that act nonspecifically to elicit both innate and adaptive immunity and results in the induction of proinflammatory cytokines, chemokines, and other immune mediators. This in turn leads to the generation of a type 1 helper cell (Th1)–biased cell-mediated immune response and a concomitant generation of cytotoxic effector cells

against antigens in the tumor. Bacillus Calmette-Guérin (BCG) cell wall derivatives[†] and imiquimod[‡] are two nonspecific immunostimulants that have been reported for treatment of sarcoids. BCG cell wall derivatives[†] administered intralesionally[90] have been shown to be effective only for periocular sarcoids.[65,91,92] The number of treatments depends on the rate of tumor regression, and the treatment schedule depends on normal tissue toxicity; most sarcoids require two to nine treatments over several weeks.[65] Encouraging results have been reported with a biological response modifier used topically (5% imiquimod cream[89]). The ointment is recommended for the treatment of viral warts and basal cell carcinomas in humans. It was applied as a thin layer to the surface of sarcoids three times a week on nonconsecutive days for up to 32 weeks until resolution.[93] However, in our experience, imiquimod treatment was effective only for treatment of persistent cutaneous papillomas in adult horses that have an appearance similar to verrucous sarcoids and a small percentage of occult sarcoids. Treatment did not prevent progression of verrucous or fibroblastic sarcoids. In all cases treatment was associated with severe and painful inflammation of the treated area.

The continued expression of the *E5*, *E6*, and *E7* proteins by equine sarcoid tumor cells makes them excellent targets for specific immunotherapy.[17,18] Therapeutic humoral immunization has not been found effective for treatment of affected horses. Immunization against BPV1 virus-like particles in sarcoid-bearing horses[30] and donkeys[94] resulted in BPV1 neutralizing antibodies but was not therapeutically effective. Cell-mediated immunity is critical for the control of papilloma-associated tumors.[95] Therapeutic vaccines aim to control tumors by activating the patient's own cellular immune response to recognize and kill cancer cells. In humans, trials with therapeutic vaccines that target the *E6* and/or *E7* proteins using peptide or protein-based vaccines, live vector vaccines, cell-based vaccines, and DNA vaccines have been disappointing for treatment of HPV-associated tumors.[95] Although *E5* is uniformly expressed by sarcoid tumor cells, no attempt at targeting the *E5* protein has been made in veterinary medicine. The renewed interest in *E5* protein as a target for therapeutic vaccine in human medicine[96] may provide a biological rational for targeting *E5*-expressing sarcoid cells. Dendritic cells are the central players in the initiation of the adaptive immune response and play a key role in the antitumor T-cell responses. A preliminary study with autologous monocyte-derived dendritic cells (MoDCs) isolated from horses with sarcoids and loaded with tumor lysates

showed that the treatment was safe and prevented tumor recurrence after surgery in 13 of the 21 treated horses.[97] Although the data are preliminary and need to be confirmed in a larger study, they underscore the need for an increased understanding of dendritic cell biology, which will lead to further development of innovative strategies to optimize vaccine-elicited T-cell antitumor immune responses.

Although therapeutic vaccines aim to develop a strong cellular immune response to BPV antigens that are expressed in transformed cells, prophylactic vaccines aim to prevent a putative BPV infection by inducing a neutralizing antibody response. In humans, prophylactic HPV vaccines act by inducing neutralizing antibodies against the late capsid protein L1 of HPV16 and HPV18. This has led to attempts to establish a vaccine for protection against BPV1- or BPV2-associated sarcoids. Although natural or experimental infection of the skin by wild-type BPV1- or BPV2-associated sarcoid does not induce a measurable antibody response,[24] intramuscular immunization of horses with BPV1 L1 virus-like particles has been shown to elicit high titers of BPV1-neutralizing serum antibodies.[98] Virus-like particle late protein vaccine proved highly effective in protecting horses from BPV1-induced pseudosarcoid formation (short-lived papules) but not from BPV2 challenge.[99] This provides a rationale for developing a preventive vaccine that would benefit naive horses exposed to BPV1 and BPV2. However, immunization of previously exposed latent BPV1- and BPV2-carrier horses would require a vaccine that could stimulate cell-mediated immune responses to specifically target and kill the infected cells. Because it would be impossible to test horses for prior exposure to BPV prior to vaccination and horses need to be protected against both BPV1 and BPV2, the ideal vaccine would have to generate both humoral and cell-mediated immune response to BPV1 and BPV2.

Mastocytosis

Stephen D. White

In horses, mastocytosis (mast cell tumors, mastocytomas) occur in animals 1 to 18 years old (average, 9 years), with no breed predilection. A predilection for males has been proposed but is not always sustained.[1,2] In addition, multiple mast cell tumors resembling urticaria pigmentosa of humans may occur in newborn foals; these occur spontaneously and regress.[2,3]

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Equine mastocytosis is usually solitary and occurs most often on the head and trunk, although occasionally multiple tumors may be seen.[4] Lesions are 0.5 to 20 cm in diameter, well to poorly circumscribed, firm to fluctuant, dermal or subcutaneous, and may or may not be alopecic, ulcerated, and hyperpigmented. Lesions on the legs tend to be very firm and immovable.

Histology may vary from sheets of mast cells with few eosinophils (presumably early lesions) to sections showing both sheets of mast cells with numerous eosinophils and collagen degranulation. Ultrastructural features are similar to those noted in mastocytomas of other species.[5]

Clinically, most mast cell tumors in horses do not recur after being excised (22 of 25 in one study).[5] In one anecdotal case of metastasis from a tumor on the muzzle to the regional lymph nodes, the tumor and the nodes were removed, and the horse was clinically sound 3 years later. There is some debate as to whether equine mastocytomas are benign neoplasias or focal dysplasias of mast cells.

Mastocytomas are uncommon in cattle but typically occur in young calves.[6,7] One report describes a cutaneous mast cell tumor in a kid goat.[8] Although equine mastocytomas are almost always benign, mastocytosis in cattle may be malignant or benign and therefore carries a more guarded prognosis.

Melanoma

Stephen D. White

Equine Melanomas

Melanomas occur in all domestic animals, but among the large domesticated species, they are most important in the horse. Excessive exposure to sunlight has not been definitively proven to predispose horses to the development of melanoma. A disturbance in melanin metabolism associated with graying has been hypothesized to stimulate formation of new melanoblasts or to stimulate their activity, resulting in focal areas of overproduction in the dermis and epidermis, with subsequent tumor formation.[1] A higher incidence is observed in the Arabian, Lipizzaner, and Percheron breeds, probably because gray coat color occurs more often in these breeds. There is no gender predilection.

Melanocytic skin tumors of horses traditionally have been described in aging gray horses in typical locations: ventral tail, perineum, external genitalia, lip, udder, and periocular and parotid gland regions. These tumors have been the

subject of several classification schemes in attempts to correlate histopathologic appearance with clinical behavior (i.e., benign or malignant). One study distinguished three basic types of melanocytic skin tumors, as discussed next.[2]

Melanocytic nevi (melanocytoma) occur in the superficial dermis or at the epidermal-dermal junction and frequently have epithelial involvement, with nests of relatively large, mildly to moderately pleomorphic cells showing variable cytoplasmic pigmentation and occasional mitoses. More than 70% of these occur in horses younger than 6 years of age and may occur in horses of any color (not just gray). Most of these tumors occurred in atypical locations. Of 28 melanocytic nevi, only one became invasive; the rest exhibited benign behavior.

Dermal melanomas are found in the deep dermis and are composed of small, homogeneous, indistinct tumor cells, either round or dendritic, with no mitoses. (If there are multiple confluent dermal melanomas, this is referred to as *dermal melanomatosis*). About 80% of these tumors are in horses older than 6 years[2] or between 5 and 15 years[3] and are much more common in gray horses. Most of these tumors occurred in typical locations. Of 14 cases available for follow-up in one study,[2] eight had malignant behavior, as demonstrated by metastases.

In another study, clinicopathologic characteristics of cutaneous melanomas occurring in 83 Camargue-type gray-skinned horses showed that the tumors occurred most frequently underneath the tail (93.9%) and at high rates in the perianal region (43.0%), lips (33.0%), and eyelids (24.0%) but rarely in the vulva (3.8%).[4] Microscopic examination indicated that these tumors were composed mostly of melanocytes and numerous melanophages, and that these cells manifested a remarkable cellular atypia. Early stages of the tumors occurred in close association with apocrine sweat glands but not at the dermal-epidermal junction.

A clinical study was conducted on 296 gray horses of the Lipizzaner breed.[5] Of the 296 horses, dermal melanomas were present in 148 horses (50%), 68 of which were older than 15 years; 51 of these were melanoma bearing. In 75.6% of cases, melanotic tumors were detected underneath the tail. None of the affected individuals had any severe clinical effect or was handicapped in performance. The authors concluded that in contrast to melanomas in solid-colored horses, characterized by early metastases, melanomas in gray horses showed less malignancy. Affected individuals often had encapsulated nodules or structures similar to human blue nevi. This finding at least partially reflects confusion in terminology between true malignant melanomas and dermal

melanomas.

Anaplastic malignant melanomas are composed of sheets of extremely pleomorphic epithelioid cells with poor pigmentation and many mitoses. These are usually seen in horses older than 20 years and occur in horses of any color. Metastasis usually occurs first to the regional lymph nodes, then to the lungs, spleen, and liver. Hematogenous spread may also occur. Metastatic growths may be larger than the primary lesions and softer in consistency.

In regard to treatment, one study reported good success with excising dermal melanomatosis from the perineal, perianal, perirectal, or ventral tail regions.[6] In a study of three horses, cimetidine (2.5 mg/kg PO q8h) was shown to decrease the number and size of melanoma growth.[7] However, another study of 10 horses found that cimetidine had no consistent effects on either the number of tumors or the tumor surface area over the 16 weeks of treatment at 5 mg/kg PO q12h.[8] Another article noted a cure rate of 81% for melanomas treated with intratumoral injections of cisplatin.[9] A recent article reported significant tumor regression when injecting interleukin-18– and interleukin-12–encoding plasmid DNA into the tumors of horses with metastatic melanomas.[10]

Bovine Melanomas

Melanomas represented a large proportion of the cutaneous neoplasms of cattle in an older study.[11] The majority are benign, well-differentiated tumors, subcutaneous in location, and without site predilection. Dark-haired cattle are predisposed, particularly the Aberdeen Angus breed. There is no gender predilection.[11] Melanomas usually occur in young cattle and are occasionally recognized as congenital lesions.[12]

Caprine and Ovine Melanomas

Melanomas have been observed only rarely in sheep and goats.[11-14] A survey of 800,000 slaughtered goats revealed only 5 melanomas.[12] The most common site for melanomas in the goat is the perineal region,[13] although there is a case report of a malignant melanoma occurring in the coronary band region.[14] Melanomas in Angora goats histologically resemble the corresponding tumors in humans.[15]

Cutaneous Lymphosarcoma

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Stephen D. White

Equine Lymphoma

Cutaneous lymphoma has occasionally been reported in horses.[1-8] Both T-cell and B-cell forms have been reported.[9,10] Lesions present as either cutaneous or subcutaneous nodules. Diagnosis is made by biopsy and, ideally, immunohistochemistry to determine cell type.[7,8] In one horse, progesterone receptors were demonstrated on the lymphoma (B) cells, and the lesions regressed after removal of an estrogen-secreting ovarian tumor.[4] This horse also had a history of partial regression of its tumor after administration of a synthetic progestin, altrenogest (0.044 mg/kg PO once daily for 10 days). Another horse demonstrated reduction in tumor size after administration of another synthetic progestogen, megestrol acetate (0.2 mg/kg PO once daily for 8 days), as well as a local injection of 20 mg betamethasone into a mass.[5] Clearly, treatment is far from standardized, but the progesterone drugs may offer a reasonable treatment modality. Lymphosarcoma is discussed in Chapter 37.

Bovine Lymphoma

Cattle occasionally are affected by cutaneous lymphoma. The presentation is multifocal intracutaneous nodules, often accompanied by alopecia. Lymphadenopathy, leukocytosis, and lymphocytosis are often present, and internal organs may be affected.[11] The juvenile form is not necessarily associated with the bovine leukemia virus (BLV) and is of T-cell origin.[12]

Ovine Lymphoma

There are rare reports of cutaneous lymphoma in sheep.[13,14]

Cysts

Stephen D. White

Cutaneous cysts are benign lesions characterized by an epithelial wall with keratinous contents. Cutaneous cysts are subdivided into several types based on their histopathologic features.

Epidermal Cysts

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Among large animals, epidermal cysts have been reported in horses,[1] cattle,[2] and sheep.[3] These cysts may be more properly called *follicular cysts* because the epithelial lining is probably most often derived from the follicular epithelium rather than the epidermis. The cysts can be found anywhere on the body, single or multiple, congenital or acquired, and generally range in size from 0.2 to 3 cm in diameter. The cysts are covered by intact epithelium and generally do not attach to the overlying epidermis. Microscopically, epidermal cysts consist of a wall of stratified squamous epithelium surrounding a keratin-filled lumen. Epidermal appendages are not associated with the cyst wall, a feature that distinguishes epidermal from dermoid cysts.

Epidermal cysts are thought to originate from occlusion of a hair follicle or by traumatic implantation of the epidermis. A tentative diagnosis may be made by performing fine-needle aspiration of a lesion and obtaining a fluid that is clear to brownish in color. Aspiration of the contents may temporarily decrease the size of the cyst, but it typically refills. Definitive diagnosis is made by excisional biopsy, which is curative. Epidermal cysts are benign lesions, although painful inflammatory responses and ulceration may result if the cyst is ruptured, with extrusion of contents into the adjacent dermis and subcutis.

Dermoid Cysts

Dermoid cysts are very similar clinically to epidermal cysts but are much less common. Among large animals, they have been identified in horses,[1] goats,[4] and cattle.[5] In cattle, dermoid cysts may be congenital, have been reported to be as large as 10 cm (4 inches) in diameter, and are said to develop most frequently over the cranial area of the thorax[5] and in the pharyngeal region. In horses, dermoid cysts may be single or multiple and are observed most frequently along the dorsal midline between the withers and the croup. Dermoid cysts are believed to result from displacement of embryonic cells into the subcutaneous tissue. They can be distinguished histologically from epidermal cysts by the presence of epidermal appendages within the wall of the cyst and by a lumen that often contains hair and secretions from sebaceous and sweat glands in addition to keratin. As with epidermal cysts, surgical excision is diagnostic and curative.

Dentigerous Cysts

Dentigerous cysts are a congenital defect recognized in horses and are believed

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to be the result of an abnormality of the first branchial cleft.[6] Clinically, a unilateral saclike swelling that contains embryonic teeth is seen at the base of the ear. The lesion may be firmly attached to the concheal cartilage or temporal bone. Dentigerous cysts tend to fistulate. Treatment consists of surgical excision.[6] Dentigerous cysts have also been reported in sheep and are suspected of being related to a nutritional deficiency of copper.[7]

Wattle Cysts

Wattle cysts are found in goats and usually are present at the base of the wattle. Nubians and Nubian crossbreeds may be predisposed to developing these cysts. The cysts are congenital, but they may not be apparent until the animal is several months old. Tentative diagnosis is based on aspiration of clear fluid, which will temporarily decrease the size of the cyst. Surgical excision is diagnostic and curative. Histologic examination reveals a cyst wall composed of one or two layers of cuboidal to columnar epithelial cells. The cyst cavity contains homogeneous, amorphous basophilic substances.[7]

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Environmental Diseases

Stephen D. White

Frostbite

Frostbite is an uncommon injury among healthy, well-nourished animals, with all species being susceptible. It is caused by prolonged exposure to subfreezing temperatures. The length of time needed to cause frostbite depends on the ambient temperature, area of the body exposed, and health status of the animal. The areas most often affected by cold injury include the ears, tail, teats, scrotum, and distal legs.

Frozen tissue must be handled gently and thawed rapidly in warm water 38° to 44° C (100.2° to 111.1° F) as soon as possible after it is known that refreezing can be prevented. Tissue damage is greatly increased if thawing and subsequent refreezing occur (freeze/thaw–freeze/thaw syndrome). Tissue thawing is painful, and analgesics should be administered. Slow thawing is less painful than rapid thawing but results in much greater tissue damage. Frozen tissue should not be massaged during warming. Damaged areas are best left exposed during the healing process rather than covered with occlusive dressings, and premature débridement should be avoided because more tissue may be viable than first apparent. The animal should be given good supportive care and may have to be restrained to prevent self-mutilation. Management practices should be changed to prevent recurrence. Tissues previously damaged by freezing are more susceptible to cold injury when reexposed to subnormal temperatures.[1,2]

Photosensitization

Photosensitivity is an abnormal reaction of the skin when exposed to light. For photosensitization to occur, there must be (1) a photodynamic agent, (2) white or lightly pigmented skin, and (3) ultraviolet A (UVA) range (320 to 400 nm). Melanin in the skin screens UV light, thereby limiting photosensitivity reactions to the white and light-colored areas of the body.[3]

There are three generally recognized categories of causes of photosensitivity:

Type I—ingestion of a photodynamic agent

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Type II—congenital abnormalities in porphyrin or liver metabolism
Type III—liver disease due to a plant or toxin, which leads to accumulation of phylloerythrin and a breakdown product of chlorophyll.

Type I

Numerous plants contain various photodynamic agents[3-7]:

Common Name	Scientific Name	Agent
St. John's wort	*Hypericum perforatum*	Hypericin
Buckwheat	*Polygonum fagopyrum*	Fagopyrin
Perennial ryegrass	*Lolium perenne*	Perloline
Whiteheads	*Sphenosciadium capitellatum*	Unknown
Roadside leafbract	*Malachra fasciata*	Unknown
Cegadera	*Heterophyllaea* spp.	Anthraquinones
Texas snake cotton	*Froelichia humboldtiana*	Unknown
Biserrula	*Biserrula pelecinus*	Unknown

Additional reports describe photosensitivities apparently induced by the ingestion of gluten in horses and of cocoa shells in calves.[8,9]

Type II

There are two bovine diseases and one ovine disease in this category:

Congenital erythropoetic porphyria: seen in Holstein, Shorthorn, and Jamaican breeds. Commonly called “pink tooth” because of the coloration of the dentition, which will glow under a Wood's lamp, as will the urine. The cow may also have anemia. The cause is a deficiency of uroporphyrinogen III cosynthetase, which leads to a defect in the heme synthesis and an accumulation of uroporphyrin and coproporphyrin, which are photodynamic agents.

Bovine protoporphyria: seen in Limousin and Blond d'Aquitaine and Charolais breeds. Neither tooth discoloration nor anemia is present. This disease is caused by another defect in heme synthesis, as a defect in ferrochelatase, which leads to an accumulation of protoporphyrin, another photodynamic agent.

In Corriedale sheep, a congenital defect in liver function leads to an accumulation of phylloerythrin (see below under Type III).

Type III

As mammals ingest plants containing chlorophyll, this molecule is degraded by bacteria in the intestine into the porphyrin phylloerythrin. Some phylloerythrin is normally absorbed into the portal circulation, removed by the liver, and excreted by the bile. In liver disease the hepatic excretion of phylloerythrin is decreased, leading to excessive levels in the peripheral circulation and eventually in the skin, causing photosensitivity in about 25% of horses with liver dysfunction.[10-12] One of the more common reasons for liver disease in horses in the United States is ingestion of the following plants containing pyrrolizidine alkaloids:

Common Name	Scientific Name
Common groundsel	*Senecio vulgaris*
Ragwort, stinking Willie	*Senecio jacobaea*
Tarweed	*Amsinckia intermedia*
Rattleweed	*Crotalaria* spp.
Salvation Jane	*Echium lycopsis*

The following plants cause hepatic dysfunction (especially in ruminants), as they contain photosensitizing saponins, whose metabolites crystalize in the bile causing biliary blockage and cholangitis:

Common Name	Scientific Name
Puncture vine	*Tribulus terrestris*
Agave	*Agave* spp.
Signal grass	*Brachiaria decumbens*
Sacahuista, Bunchgrass	*Nolina texana*
Narthecium	*Narthecium ossifragum*

Consumption of alsike clover *(Trifolium hybridum)* may induce hepatic dysfunction (with histologic lesions distinct from those caused by pyrrolizidine alkaloids), leading to photosensitization signs (alsike clover poisoning, dew poisoning). Cases seem to be correlated to years with heavy rainfall and ingestion of the plant blossoms.[13] Finally, the saprophytic fungus *Pithomyces chartarum,* which grows on perennial ryegrass, contains the heptotoxin sporidesmin.

Ingested plants and feed should be noted and collected for future analysis. Environmental considerations include the type of pasture (or other material) with which the animal is in contact, the amount of time the animal is exposed to sunlight, any seasonality of the condition, and any other horses involved. A seasonal incidence would tend to negate liver disease; multihorse involvement should arouse suspicion of an ingested or contact photosensitizer. A thorough history of recent drug therapy should be obtained.

Physical examination usually reveals lesions limited to the hairless, white, or

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lightly pigmented areas of the skin. The involved skin is erythematous, swollen, and painful. The lesions may progress to serum exudation, thickening, fissuring, and in severe cases, necrosis and sloughing (Fig. 40.15).


A


B


C

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FIG. 40.15 Photosensitization. **A,** White blaze of a horse is selectively affected. **B,** White stocking of a horse is selectively affected. **C,** Area around eye where hair is less dense is most severely affected.

Therapy is related to etiology. Chronic liver disease carries a guarded prognosis. Removal of foodstuffs containing photodynamic agents, or removal of the animal from a pasture with plants containing these agents, will often result in full recovery if the animal is also kept out of the sun for 1 to 2 weeks. Corticosteroids are helpful in controlling inflammation and pruritus. Oral prednisolone at 1 mg/kg daily for 1 week, then halving the daily dosage for a second week, is an effective regimen in this regard.

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Skin Disorders of Unknown or Genetic Origin

Stephen D. White

Equine Seborrhea

Several possibly related equine skin diseases characterized by scaling and crust formation are referred to as *seborrhea.* Contrary to claims in the older literature, there is little evidence that seborrhea is related to excess sebum production by the sebaceous glands. Most types of seborrhea are probably diseases of abnormal cornification (development of the stratum corneum). Further, most cases reported as “generalized seborrhea” in the horse were probably pemphigus foliaceus, equine sarcoidosis (chronic granulomatous disease), or some other immune-mediated or autoimmune disease. Mane and tail seborrhea is typified by moderate to heavy scaling, with minimal or no pruritus. Some horses have considerable alopecia of the tail.

Cannon keratosis is a common equine skin condition. It involves the cranial surface of the rear cannon bone region and rarely the forelimbs. The lesions consist of areas of scaling and crusting with varying degrees of alopecia. There is no pruritus or other signs of inflammation. Cannon keratosis occurs in both males and mares, so there is no basis for the theory that the condition is caused by urine splatter (“stud crud”).[1] In one recent report, the response to treatment with four topical preparations was evaluated in an 11-year-old Morgan horse mare with histologically confirmed quadrilateral cannon hyperkeratosis. Each limb was treated for 30 days, and response to treatment was evaluated both histologically and visually. A water-based emollient and 0.1% tacrolimus ointment produced encouraging clinical responses.[2]

Linear Keratosis and Linear Alopecia

Linear keratosis and linear alopecia are rare equine dermatoses of unknown cause. There is one report in a cow.[3] Lesions do not follow blood or lymphatic vessels, nerves, or dermatomes. Because these conditions coexist in some horses, it has been suggested that they are variations of the same abnormality, and we

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have seen one case where both histologic presentations were simultaneously present in the same clinical lesion. Both conditions have been seen in a wide variety of breeds, but Quarter Horses appear to be predisposed. Most horses develop lesions between 6 months and 5 years of age.

Linear alopecia is characterized by gradual development of annular areas of alopecia, usually in a linear, vertically oriented configuration. One or more linear areas may be present. The lesions are usually 2 to 10 mm wide by a few centimeters to more than 1 m in length and occur on the neck, shoulder, and lateral thorax. Mild surface scale and crust may be present. Lesions are neither painful nor pruritic. Affected horses are typically otherwise healthy.

Linear keratosis is characterized by the gradual asymptomatic occurrence of one or more unilateral, linear, vertically oriented bands of hyperkeratotic papules that progress to marked hyperkeratosis and alopecia. We have seen one case where the lesions were confined unilaterally to the jugular furrow (Color Plate 40.10). Lesions vary from 0.25 to 3.5 cm in width by 5 to 70 cm in length and occur most often over the neck, shoulder, and lateral thorax. Lesions have also been reported to involve the legs, hip, and pectoral region. Again, affected horses are typically otherwise healthy.

These disorders are visually distinctive. Histopathologic findings in linear alopecia include early lymphocytic, infiltrative mural folliculitis and later granulomatous, infiltrative mural folliculitis. The mural infiltrate is often directed at the middle area (isthmus) of the follicle. Sebaceous glands may be involved in some cases, and complete follicular destruction and permanent alopecia are seen in severe chronic lesions. Histopathologic findings in linear keratosis include irregular to papillated epidermal hyperplasia and marked compact orthokeratotic hyperkeratosis.[4] We have seen one horse with lesions grossly diagnosed as linear keratosis, whereas the histopathology had features of both conditions.

Neither condition is known to undergo spontaneous resolution. Owners should be advised of the potential hereditary nature of these disorders. Linear alopecia has been anecdotally reported to respond to topical or systemic glucocorticoids, but recurrence is likely. Response to therapy is more likely to be seen in early lesions, when complete destruction of hair follicles has not occurred. Linear keratosis responds poorly to treatment. Topical keratolytic and keratoplastic agents, such as sulfur/salicylic acid–containing shampoos or 50% propylene glycol, can reduce the hyperkeratosis but must be continued for life. There has been some success using tacrolimus (Protopic 0.1% ointment [Astellas Pharma

US, Northbrook, Ill.]), a drug similar to cyclosporine but better absorbed through the skin, once or twice daily. Because neither condition is symptomatic, observation without treatment may be an acceptable approach. Interestingly, a report exists of a familial incidence of linear epidermal nevi in Belgian horses.[5]

Albinism

Complete and partial albinism occurs in cattle, sheep, and horses. It is a genetic defect (probably autosomal recessive) in melanin synthesis, resulting in white skin, white hair, pink eyes, and photophobia. In horses, albinism must be distinguished from *lethal white syndrome,* which is primarily a problem in Paint horses (especially, but not exclusively, in overo breedings). The defective gene has also been found in American Miniature horses, half-Arabians, Thoroughbreds, and cropout Quarter Horses (foals born to registered Quarter Horses that have too much white to register with the American Quarter Horse Association [AQHA]).[6] The Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier status (https://www.vgl.ucdavis.edu/services/horse.php).

The lethality of albinism in horses comes from the association with intestinal aganglionosis. The foals die shortly after birth. Because some white foals are not affected, euthanasia should be performed only after signs of intestinal malfunction occur. This disease is similar to Hirschsprung's disease in humans and is linked to a mutation in the endothelin-B receptor gene.[7]

Juvenile Arabian Leukoderma (Arabian Fading Syndrome, Pinky Syndrome, Hereditary Vitiligo)

Loss of melanin in the skin (depigmentation) occurs in young Arabian horses 6 months to 2 years of age (Fig. 40.16, A). The areas most frequently affected are periocular tissues, muzzle, genitalia, anus, perineum, inguinal region, and undersurface of the base of the tail. Depigmentation may persist, repigment, or wax and wane. The condition is probably hereditary.[1]

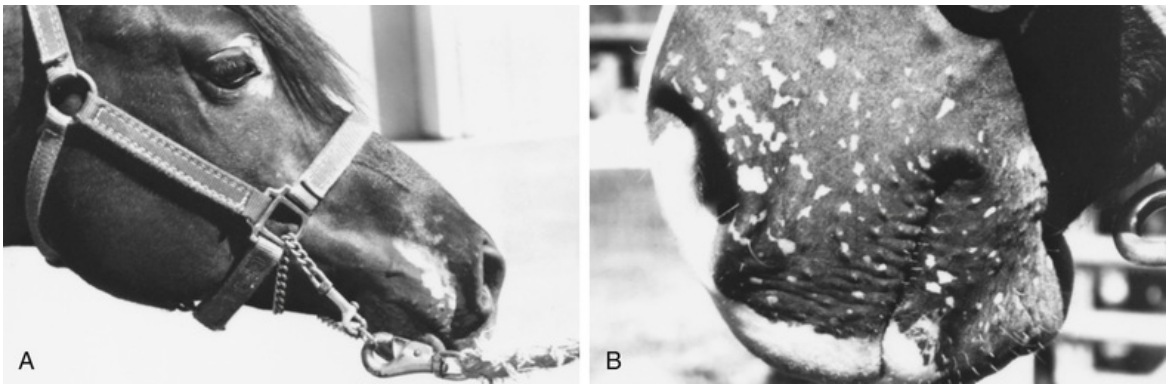


FIG. 40.16 **A,** Juvenile Arabian leukoderma. **B,** Vitiligo in a horse. (Courtesy Dr. Anthony Stannard.)

Vitiligo

This condition is best defined as "idiopathic depigmentation." Typically no trauma has occurred to produce the loss of pigment, and other skin structures are not affected (i.e., no scarring or alopecia) (Fig. 40.16, B*;* Color Plate 40.11). There is no known treatment for vitiligo. The condition may be seen in any species but is perhaps best recognized in the horse.

Reticulated and Hyperesthetic Leukotrichia

Reticulated leukotrichia occurs mainly in Quarter Horses, usually as yearlings, and occasionally in other breeds. The lesions occur on the dorsal midline and consist initially of linear crusts arranged in a characteristic crosshatch pattern (Fig. 40.17). The crusts shed, alopecia occurs, and white hair grows in permanently. There is leukotrichia without leukoderma (depigmented skin). Histologically, these lesions may resemble an epidermal form of erythema multiforme, resulting in individual keratinocyte necrosis. *Hyperesthetic leukotrichia* is a similar disease clinically, except that the crusts are extremely painful to the touch. Within a few weeks, white hairs appear in the affected areas. The crusts resolve, and the pain subsides in 1 to 3 months, but the leukotrichia persists. While anectodal cases have been linked to recent rhinopneumonitis vaccination, a recent report of a case series failed to find evidence of a link to any vaccine or medication and determined that the histology differed somewhat from erythema multiforme.[8] These diseases may recur (sometimes on a seasonal basis), and there is no known effective treatment.

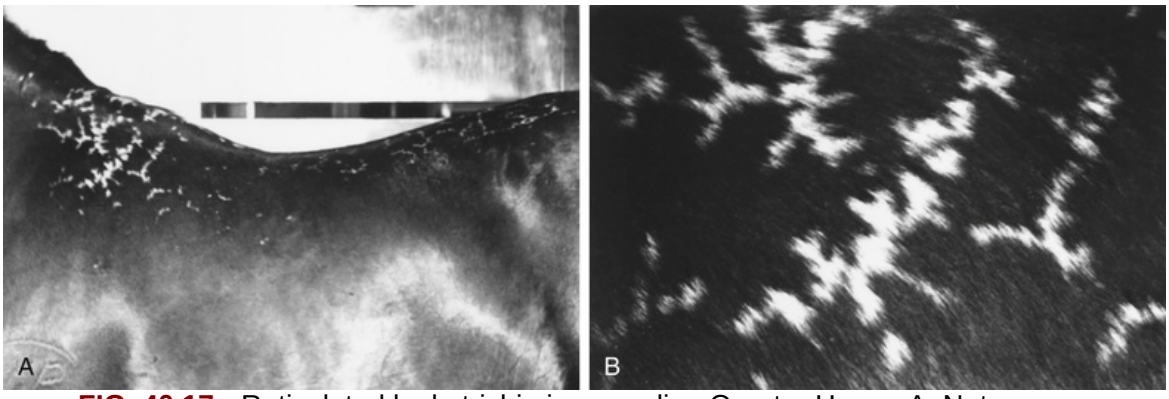


FIG. 40.17 Reticulated leukotrichia in a yearling Quarter Horse. A, Note reticulated pattern of white hairs over dorsum. B, Close up view of reticulated pattern of white hairs (leukotrichia). (Courtesy Dr. Anthony Stannard.)

Hereditary Equine Regional Dermal Asthenia (Hyperelastosis Cutis)

Hereditary equine regional dermal asthenia (HERDA) occurs early in life in horses. Most affected horses are Quarter Horses, but registered Paint horses and Appaloosas with Quarter Horse lineage have developed this disease.[9,10] Many of the Quarter Horses are from high-quality cutting lines. Reported cases have been in North America, but the disease and its associated genetic defect have been reported in Europe and South America.[11-14] The disease (or similar condition) has also been reported in a crossbred Arabian mare, a Thoroughbred gelding, a Hanoverian foal, and a Hafflinger horse.[15-18] Rarely, a similar disease has been noted in cattle, termed *dermatosporaxis;* this is caused by mutations in the procollagen I N-proteinase gene.[17,19-21]

The working hypothesis for HERDA in horses is a defect in the structure or healing process of the collagen fibers in the middle to deep dermis. Affected horses have less cutaneous tensile strength than healthy horses.[22] Typically these areas are over the back and sides of the neck (Fig. 40.18). The skin in these areas may be easily torn or stretched and often develops seromas and hematomas ("blisters" filled with either serum or blood). Healing is usually adequate but often leaves unsightly scars. Despite the regional pattern of the cutaneous signs, skin with decreased thickness was not regionally distributed in the HERDA-affected horses in one report.[23] Diagnosis is often based on the clinical signs alone; histologic findings are sometimes subtle, but "clumped" or poorly

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organized collagen fibers below the level of the hair follicles may be seen. A zone of middermal to deep dermal separation has been reported in two horses and is present in some biopsy samples.[10,24] Poorly oriented collagen fibers are sometimes seen on electron microscopy. Interestingly, affected horses may have decreased corneal thickness, increased tear production, and increased incidence of corneal ulcers, as well as loss of heart valve tensile strength.[25,26]

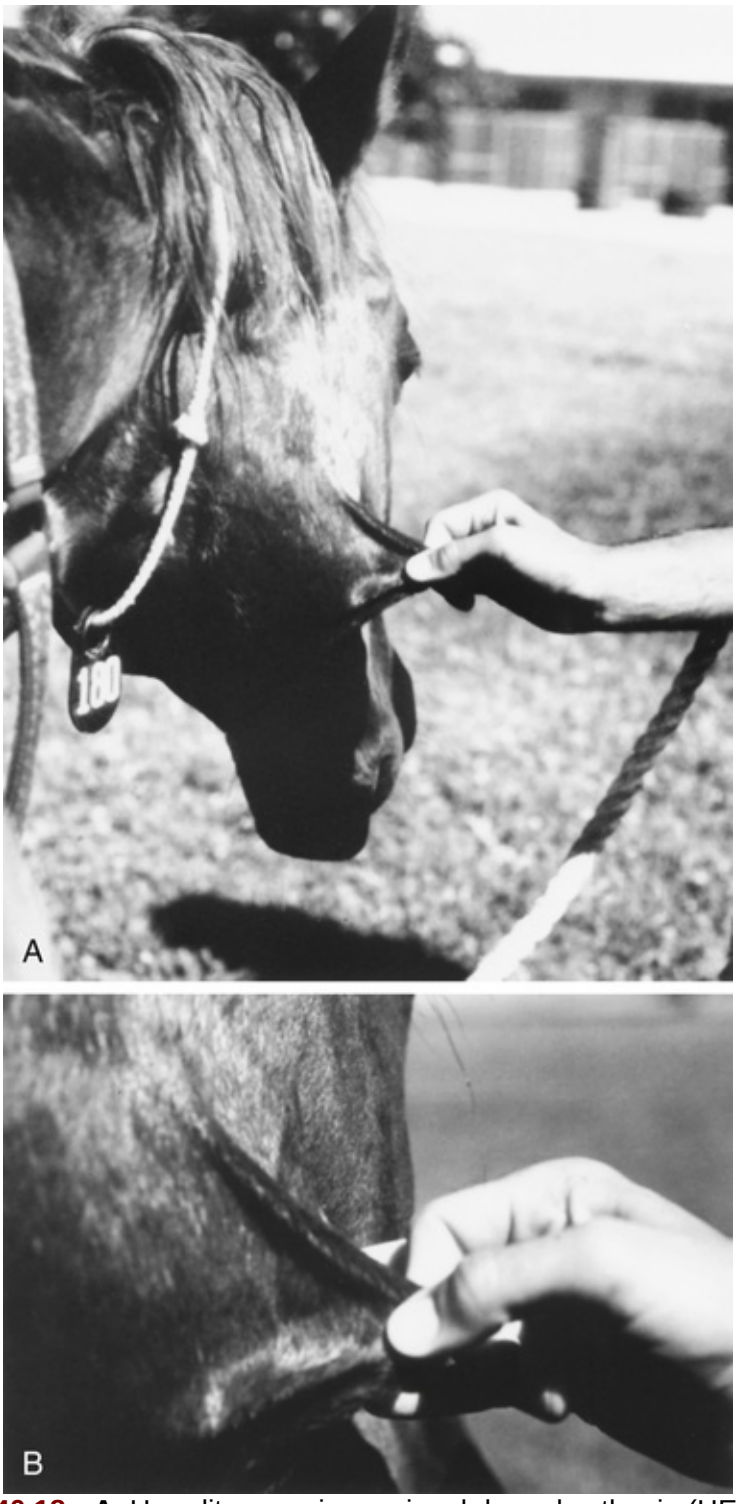


FIG. 40.18 **A,** Hereditary equine regional dermal asthenia (HERDA, hyperelastosis cutis) in a horse, showing hyperextensible skin. **B,** Close-up of A. (Courtesy Dr. Anthony Stannard.)

This condition is almost certainly present at birth, but HERDA is often not

noticed until about 2 years of age, when horses start being trained with tack and saddle, and the resulting friction and trauma induce the typical lesions.[27] As with many genetic diseases, no effective treatment or cure exists; some of these horses have been maintained as “pasture pets.”

This disease follows an autosomal recessive mode of inheritance, so for the foal to be affected, both the sire and the dam must carry the gene, and if they were bred again, there would be about a 25% chance that the next foal would also be affected.[28] Although histopathologic evaluation is informative, it is not conclusive for establishing the diagnosis. Samples of skin from the neck, croup, or back are useful for diagnosis of HERDA.[23] However, the final diagnosis must be confirmed using molecular testing.[23,29]

Recently a genetic marker was determined for this disease.[29] The marker relates to a missense mutation in equine cyclophilin B (PPIB), which in recent work has been shown to cause a functional defect in this protein, resulting in less effective catalysis of the rate-limiting step in collagen folding.[30] The Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier or affected status (http://www.vgl.ucdavis.edu/services/horse.php). Both carriers and clinically affected horses with HERDA should be removed from breeding programs. There is no known treatment.

Epidermolysis Bullosa

Epidermolysis bullosa (EB) includes a number of diseases typified in humans and animals by the common finding of blister formation after minor trauma. Most forms are congenital and apparent soon after birth. In animals and humans, subsets of EB are classified by the histologic location of the blister or cleft. These subtypes (and respective cleft location) are termed *EB simplex* (basal cell layer of epidermis), *junctional EB* (intralamina lucida or basal cell layer), and *dystrophic EB* (sublamina densa).

Junctional EB has been reported in Belgian foals of both genders; in other breeds; and in a donkey, sheep, and cattle.[31-38] Lesions are usually noted within 3 days of birth and include multiple asymmetric skin erosions and ulcers, often encrusted. Lesions may be especially prominent around the coronary bands (causing the hoof to crack and slough) and on the oral, anal, and genital mucosa. Histology and ultrastructural findings indicate a cleft in the intralamina lucida of the basement membrane zone. This is presumably caused by a defect in the

anchoring filaments that connect the basement membrane to filaments in the superficial dermis.[32] A laminin-5 (laminin 3A32) defect has been demonstrated in Belgians and in two French draft breeds, Trait Breton and Trait Comtois; the mutation is a cytosine insertion in exon 10 of the *LAMC2* gene.[39-41] Because of this knowledge, the Veterinary Genetics Laboratory at UCD offers a diagnostic test to determine carrier status in Belgian draft horses and related breeds (http://www.vgl.ucdavis.edu/services/horse.php). The defect in some ruminants has also been noted to be associated with the *LAM* gene.

Clinical presentation and the age of the foal are highly suggestive of EB diagnosis. Histology and, ideally, electron microscopy are required to confirm the diagnosis. There is no known treatment, and affected horses as well as the sires and dams of affected horses should not be bred; the mode of inheritance is autosomal recessive.

The disease previously known as *epitheliogenesis imperfecta* in Saddlebreds is now recognized as *junctional epidermolysis bullosa.* Lesions are most common on the limbs, head, and tongue. Hooves may slough in severe cases. Clinical presentation is usually diagnostic.[42-45] In moderately to severely affected animals, the disease is fatal within a few days; the foals die of septicemia or other developmental abnormalities. Mildly affected areas may heal by scar formation.

Ruminants

Epidermolysis bullosa has been reported in cattle and sheep. The simplex form has been reported in Angus and Friesian-Jersey crossbred cattle (in the latter, a keratin 5 defect was noted), junctional EB in a Charolais calf (deficient expression of an epidermal integrin), and dystrophic EB in Brangus calves.[46-49] In sheep, dystrophic EB in the white Alpine, Assaf, Suffolk, South Dorsett Down, and black face Scottish breeds has been shown or theorized to involve mutations in the gene encoding for collagen VII.[50-53] Junctional EB has been described in German black-headed mutton sheep and churra sheep, with the defect in the former traced to the formation of laminin 332, similar to the defect in the Belgian horses.[54,55] Junctional EB has also been described in Charolais, Belgian Blue, and Danish Hereford cattle; the defect in the latter two is also tied to the laminin gene.[56-58] Clinical signs of EB in ruminants are similar to those seen in horses, with ulcers, especially around the coronary band and in the oral cavity.

Eosinophilic Granuloma (Nodular Necrobiosis, Collagenolytic Granuloma)

Eosinophilic granuloma is the most common equine nontumor nodular disease in our practice. In most cases the etiology is unknown, although a hypersensitivity reaction to insect bites has been suggested. There is no apparent age, breed, or gender predilection. The disease often begins in warmer months. Lesions up to 5 cm (2 inches) in diameter may be single or multiple and most often affect the neck, withers, and back (Fig. 40.19). Skin biopsy reveals multifocal areas of abnormal-staining collagen surrounded by granulomatous inflammation containing eosinophils, lymphocytes, and histiocytes.[1] This is not thought to be caused by degeneration, but rather by degranulation of eosinophils and the coating of normal collagen fibers with the degranulated material.[59]



FIG. 40.19 Eosinophilic granuloma (nodular necrobiosis) with dermal nodules on a horse's withers. (Courtesy Dr. Anthony Stannard.)

Development of equine eosinophilic granuloma has been noted in areas of previous injections using standard silicone-coated, stainless steel hypodermic needles.[60] The reaction may occur at sites of IV and IM injections. Lesions consist of nonpainful cool, raised papules or nodules 0.25 to 1 cm in diameter at sites of previous injection. The nodule appears 24 to 48 hours after the injection, and the subsequent eosinophilic granuloma can persist for months to years. Affected horses do not develop a lesion at the site of injection if nondisposable, noncoated needles are used. The use of the noncoated needles is recommended

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for any horse that develops injection-site collagenolytic granulomas.

Horses with solitary or a few lesions may be treated by surgical excision (not in the saddle area) or glucocorticoid injections under the lesions. Triamcinolone acetonide (3 to 5 mg per lesion) is effective. It has been recommended that no more than 20 mg triamcinolone acetonide be administered at once to any horse because any more of this drug may cause laminitis.[1] Horses with multiple lesions may be treated with oral prednisolone at 1 mg/kg once daily for 2 to 3 weeks. Multiple small (<1 cm) lesions may be indicative of insect bite hypersensitivity.

Cutaneous Amyloidosis

Cutaneous amyloidosis is an uncommon nodular dermatosis of unknown etiology. There is no age, breed, or gender predilection. The condition appears to be a primary form of amyloidosis, in that concurrent inflammatory processes are not present, and amyloid (a fibrillar protein substance derived from immunoglobulins) deposition is usually restricted to the skin and occasionally the regional lymphatics, regional lymph nodes, and upper respiratory mucosa.[1,18] One case was documented as being caused by lambda light-chain deposition from an extramedullary plasmacytoma.[61] Another horse showed amyloidosis concurrent with lymphoma.[62]

Papules, nodules, and plaques on the head, neck, shoulders, thorax, or inguinal areas are firm, 0.5 to 10 cm in diameter, nonpainful, and nonpruritic. The overlying skin is normal, although it may scale or crust in severe cases (Fig. 40.20). The course of cutaneous amyloidosis is progressive and prolonged. Megestrol acetate may be an effective treatment (0.2 mg/kg PO q24h until lesions resolve). Because certain forms of primary amyloidosis in humans have a genetic basis, it may not be advisable to use affected horses for breeding until more is learned about the genetics of the equine disorder.

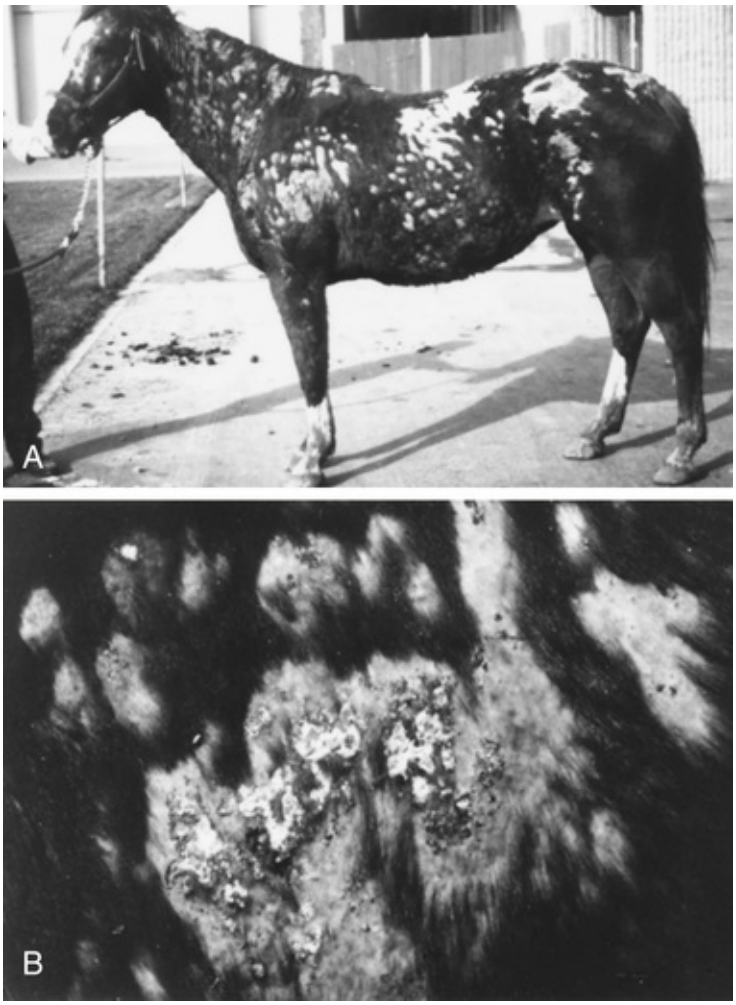


FIG. 40.20 **A,** Cutaneous amyloidosis in a horse. **B,** Close-up of skin of A. (Courtesy Dr. Anthony Stannard.)

Equine Sarcoidosis (Generalized Granulomatous Disease)

Equine sarcoidosis is characterized by skin lesions and usually concurrent systemic involvement. It is *not* a neoplastic disease and should *not* be confused with equine sarcoids.

The disease is encountered infrequently, and there is no known breed predilection. Geldings may be at increased risk.[63] The skin lesions typically are generalized scaling and crusting associated with varying degrees of alopecia (Fig. 40.21). Occasionally the disease is focal or multifocal in distribution. Rarely, the skin lesions consist of nodules or large tumor-like masses. The

different types of skin lesions may coexist. In addition to skin lesions, the most frequent presenting complaints are weight loss, decreased appetite, and a persistent low-grade fever. Lung involvement is manifested by exercise intolerance, increased resting respiratory rate, and mild dyspnea.[64-66] One report showed positive titers to *Borrelia burgdorferi* in three of four horses with equine sarcoidosis,[67] another found evidence of equine herpesvirus 2,[68] and a recent report described *Mycobacterium* DNA in the liver and skin of a horse with sarcoidosis.[69] However, other investigations, using PCR, immunohistochemistry, and histologic stains, were unable to demonstrate the presence of any causative organism.[62,70]

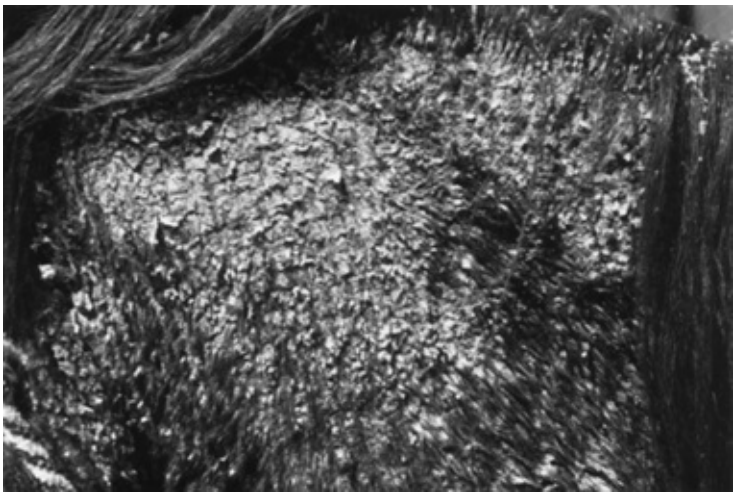


FIG. 40.21 Equine sarcoidosis (generalized granulomatous disease) in a horse. In addition to scaling and crusting skin lesions, the horse had systemic involvement. (Courtesy Dr. Anthony Stannard.)

Diagnosis is by histopathology and ruling out infectious etiologies. The major histologic change is the presence of noncaseating granulomas consisting of aggregates of epithelioid cells and multinucleated giant cells. Neutrophils, lymphocytes, and plasma cells are present in small numbers. In the skin the granulomas tend to be located in the superficial portion of the dermis. Because of the small number of horses studied and the variability of clinical signs, response to therapy has not been well documented. An abstract reported that 5 of 6 horses did well and lived longer than 1 year with prednisolone treatment.[71] Another extensive review showed that some horses did well on corticosteroid therapy (usually at doses approximating those used to treat pemphigus and other

autoimmune skin diseases); GI involvement was a sign of poorer prognosis.[63] Recently reported cases suggest that some horses with sarcoidosis may have localized rather than generalized skin disease and confirm that spontaneous resolution (seemingly when the stress of working is reduced or eliminated) may occur.[72,73]

Chronic Progressive Lymphedema

Chronic progressive lymphedema (CPL) is the term for a condition seen in Shires, Clydesdales, Belgians, and probably other draft breeds (Color Plate 40.12). It is characterized by progressive swelling, hyperkeratosis (thickening), and fibrosis (hardening) of the skin on the lower legs. This chronic progressive disease starts at an early age, progresses throughout the life of the horse, and often ends in disfigurement and disability of the limbs. Inevitably, it leads to the horse's premature death. In the Belgian draft horse, it has reduced the average life expectancy of a stallion from 20 to only 6 years.

The pathologic changes and clinical signs closely resemble a condition known in humans as *chronic lymphedema* or *elephantiasis nostras verrucosa*. The lower leg swelling is caused by abnormal functioning of the lymphatic system in the skin, which results in chronic lymphedema (swelling), fibrosis, a compromised immune system, and subsequent secondary infections of the skin. Based on preliminary research, it appears that a similar pathogenic mechanism is involved in the disease that affects these specific draft horse breeds.

The clinical signs of this disease are highly variable. The earliest lesions are characterized by skin thickening and crusting; both are often visible only after clipping the long feathering. Secondary infections develop very easily in these horses' legs and usually consist of either chorioptic mange or bacterial infections. Both dark skin and white skin on the lower legs are equally affected. These lesions are consistent with pastern dermatitis, certainly seen in other breeds. In horses with CPL, however, these lesions do not respond well to therapy.

As the disease progresses, one or two thick skin folds and sometimes multiple small, well-demarcated ulcerations develop, predominantly in the rear of the pastern region. The ulcerations are covered with adherent crusts. Manual removal of the crusts or even movement during exercise results in bleeding. These small sores may seem to respond initially to various topical medications but often reverse course, only to progress in severity and multiply in number.

Small lesions tend to coalesce into larger and more intractable (resistant to treatment) areas of skin ulceration. Over time, the lesions extend up the leg, often affecting the skin as high as the knees or hocks. These lesions are, at the very least, irritating to the horses and at times can be quite painful. Severely affected individuals often exhibit generalized swelling in all four legs.

This condition is therefore primarily a lymph system disease, and the pastern dermatitis in these draft horses is secondary to the body's inability to supply fluids properly and oxygenate the skin of the lower leg. The lymphatics break down over time, and the protein-rich fluid leaks into the tissues of the lower leg, which results in fibrosis of the tissues under the skin and thickening of the skin itself. The tissue fibrosis leads to even more blockage of fluid within the legs, inhibiting circulatory flow. This results in neovascularization, a process by which the body develops new blood vessels in a futile attempt to provide oxygen to its tissues.

Researchers suspect that a deficiency or abnormality in the connective tissue component known as *elastin* is the underlying factor and perhaps the cause of the lymphatic degeneration in these horses.[74,75] In affected animals, the lymph vessels and deep tissues of the skin do not have sufficient amounts or the proper configuration of elastin. The lack of this critical tissue element apparently instigates the progression of disease and the chronic progression of clinical signs. One report documents high levels of antielastin antibodies in affected horses.[76] A more recent report found that affected horses had increased amounts of dermal elastin in both the distal limb and the neck, whereas unaffected horses of a susceptible breed had decreased amounts. These findings support an earlier hypothesis that CPL of horses is a generalized disease. Reduced efficiency of the elastic network in supporting the dermal lymphatics may explain the development of CPL.[77]

As the condition becomes more chronic, the lower leg enlargement becomes permanent, and the swelling is firm on palpation. More of the thick skin folds and large, poorly defined, firm nodules develop. The nodules may become quite large and often are described as golf ball or even baseball sized. Both skin folds and nodules first develop in the back of the pastern area. With progression, they may extend and encircle the entire lower leg. The nodules become a mechanical problem because they interfere with free movement and are frequently injured during exercise. This disease often progresses to include massive secondary infections that produce copious amounts of foul-smelling exudates, generalized illness, debilitation, and even death.[75,76]

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In one report of possibly the same condition in several draft breeds, the authors found a perivascular dermatitis dominated by T lymphocytes with an increase in major histocompatibility complex (MHC) class II–positive, dendritic-like cells. Immunohistochemical labeling for cytokeratins CK5/6(4), CK10, and CK14 indicated a change in their expression pattern. This correlated with the degree of epidermal hyperplasia, indicating abnormal differentiation of keratinocytes. There was a statistically significant correlation between the severity of skin lesions and several other factors, including increasing age, increasing cannon circumference, prominence of anatomic structures (e.g., fetlock tufts of hairs, ergots, chestnuts), and bulges in the fetlock region.[78] Another more recent report, again looking at various draft breeds (Rhenish German, Schleswig, Saxon-Thuringian, and South German), identified a quantitative trait loci for CPL.[79]

Zinc Responsive Dermatitis

In Holstein-Friesian cattle, zinc responsive dermatitis is a hereditary autosomal recessive defect in GI zinc absorption, also known as lethal trait A 46, and is characterized by diarrhea, skin lesions, poliosis (gray hairs), and a decreased suckle reflex. Skin lesions involve inflammation and crusts around the eyes, base of ears, coronary bands, and muzzle; these may become generalized. Plasma zinc concentrations of calves are normal at birth. The histology of skin lesions shows parakeratosis.[80]

Oral administration of zinc reverses signs in 1 to 3 weeks.

Recently a similar disease, albeit one associated with a different mutation, was described in Fleckvieh cattle. Treatment is uncertain, as the mutation does not appear to involve a problem with intestinal transport of the zinc.[81]

In goats and sheep this may be caused by ingestion of alfalfa (which is high in calcium and therefore blocks zinc uptake) or overliming the soil with calcium salts, creating a zinc-deficient soil. Crusts, bilateral symmetrical alopecia, rough hair coat, abnormal claw growth with weight loss, stunted growth, abnormal (kyphotic) gait, and anorexia may all be seen.[82] Histopathology of skin shows parakeratosis and hyperkeratosis; this may be hereditary in some dairy goats.[83]

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Digital Dermatitis (Papillomatous Digital

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Color Plates



COLOR PLATE 40.1 Two-month-old Nigerian Dwarf Goat doe kid with pemphigus foliaceus.



COLOR PLATE 40.2 Two-year-old Dutch Warm Blood with alopecia areata.



COLOR PLATE 40.3 Five-year-old Thoroughbred stallion with severe vasculitis.



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COLOR PLATE 40.4 Four-month-old Spanish goat doe with dermatophilus.



COLOR PLATE 40.5 Range calf with dermatophilus.



COLOR PLATE 40.6 *Corynebacterium pseudotuberculosis* abscess on a horse's neck.



COLOR PLATE 40.7 Dermatophytosis on trunk of a Holstein cow. Lesions occurred after abdominal surgery.



COLOR PLATE 40.8 Scale and crust on a sheep's ear from biting flies, leading to eosinophilic dermatitis.



COLOR PLATE 40.9 Widespread squamous cell carcinoma on a goat's dorsum.



COLOR PLATE 40.10 Linear keratosis in a horse's jugular furrow.



COLOR PLATE 40.11 Vitiligo in a 5-year-old Quarter Horse.



COLOR PLATE 40.12 Chronic progressive lymphedema in a Gypsy Vanner horse.

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[*]Contributions to previous editions by Anne G. Evans are acknowledged.

[*]Indian Mud, Original cream company, Magnolia, AK.

[†]XXTERRA, Larson Laboratories, Inc. Fort Collins, CO.

[‡]Animex, NIES, Las Vegas, NV.

[§]Efudex 5% fluorouracil, Hoffmann La Roche Inc, Nutley, NJ.

[*]Adriamycin, Bedford Laboratories, Bedford, OH.

[†]Nomagen, Fort Dodge Laboratories, Inc., Fort Dodge, IA.

[‡]Aldara, 3M Pharmaceuticals, Minneapolis, MN.

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• CHAPTER 41

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Endocrine and Metabolic Diseases

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▪ Equine Endocrine and Metabolic Diseases

Kelsey A. Hart

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Pituitary and Hypothalamus

Dianne McFarlane

Physiology of Equine Hypothalamic-Pituitary Axis

The pituitary gland is composed of two embryologically distinct portions: an adenohypophysis, derived from invagination of the pharyngeal epithelium known as *Rathke's pouch,* and the neurohypophysis, derived from neural tissue of the hypothalamus. The adenohypophysis can be further divided into the pars distalis, pars tuberalis, and pars intermedia. The pars distalis contains five different endocrine cell types, each of which is responsible for the release of a unique hormone or set of hormones in response to hypothalamic-releasing factors delivered from the median eminence via the hypothalamic-hypophyseal portal system. The pars tuberalis is a highly vascular band of cells surrounding the pituitary stalk. The pars tuberalis is rich in melatonin receptors and is believed to be involved in regulating the seasonal rhythm of reproductive hormone production.[1] The neurohypophysis or pars nervosa is a collection of nerve axons and terminals that originate in the paraventricular and supraoptic nuclei of the hypothalamus. Oxytocin and arginine vasopressin (antidiuretic hormone) produced in the cell bodies of these nuclei are transported into the pars nervosa for storage and eventual release into the systemic circulation.

The pars intermedia of the horse incorporates tissue derived from both the adenohypophysis and neurohypophysis.[2] It is composed of a single endocrine cell type, the melanotrope. Melanotropes are directly innervated by nerve terminals of the hypothalamic periventricular dopaminergic neurons. These originate in the periventricular nucleus of the hypothalamus adjacent to the third ventricle, project through the infundibulum, and terminate in the pars intermedia (Fig. 41.1).[3] These neurons release the neurotransmitter dopamine, which acts to tonically inhibit the release of hormones from adjacent melanotropes. Dopamine released from the nerve terminals interacts at dopamine (D2) receptors on the melanotropes to inhibit cell proliferation, transcription of proopiomelanocortin (POMC), and release of POMC-derived peptides.[4] Additional regulatory signals to the pars intermedia may be delivered by direct systemic arterial supply and

from the hypothalamic-hypophyseal portal veins.[5] In addition to being under tonic inhibition, melanotropes are also positively regulated by thyrotropin-releasing hormone (TRH), which stimulates hormone release from melanotropes.[6] Additional regulatory molecules likely exist but are poorly defined in the horse.

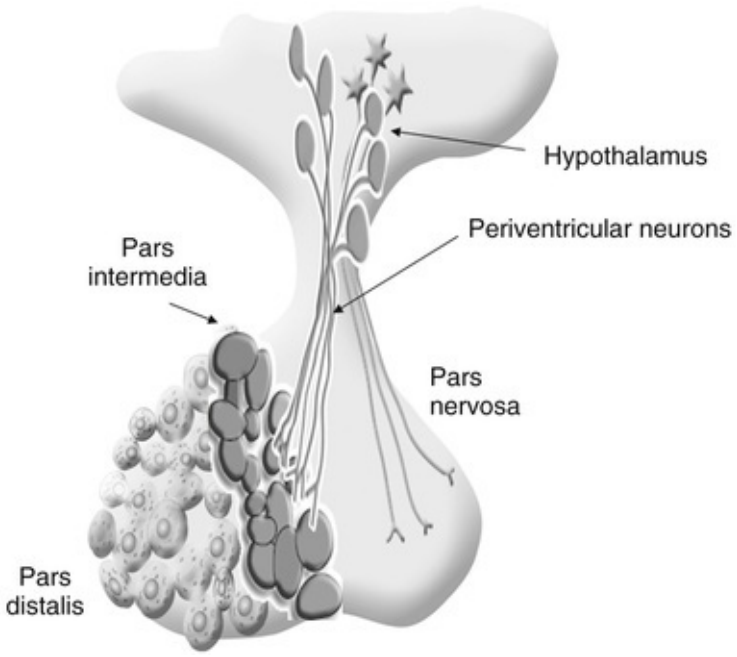


FIG. 41.1 **Physiology of the equine pituitary pars intermedia. The melanotropes of the pars intermedia produce the hormone precursor protein, proopiomelanocortin (POMC), which in the pars intermedia is cleaved into the hormones, α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-end), and corticotropin-like intermediate lobe peptide. Production of POMC in the pars intermedia is under inhibitory control by dopamine released from the nerve terminals of the periventricular neurons. The cell bodies of the periventricular neurons are in the hypothalamus, adjacent to the third ventricle.**

The primary product of the melanotrope is the hormone precursor protein POMC, which is also expressed by the corticotropes of the pars distalis. However, due to differential post-translational processing by proteases called *prohormone convertases*, each cell type secretes a different complement of POMC-derived peptides (Fig. 41.2). Due to the action of prohormone convertase I, POMC in corticotropes is primarily processed into adrenocorticotropic hormone (ACTH). ACTH circulates to the adrenal cortex, where it stimulates secretion of cortisol. Melanotropes contain active prohormone convertase I and II, and therefore POMC in the pars intermedia (PI) is cleaved into the secretory

peptides, α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-end), and corticotropin-like intermediate lobe peptide (CLIP). A small amount of ACTH may also be produced. Further processing of the peptides, including cleavage of C-terminal amino acids and *N*-acetylation, serves to control the activity of the final peptide product. For example, the most abundant form of β-end produced in the normal horse's pars intermedia is Ac-β-end (1-27), which lacks opioid activity. The most abundant β-end in horses with pituitary pars intermedia dysfunction (PPID) is β-end (1-31), which is an opioid agonist.[7]

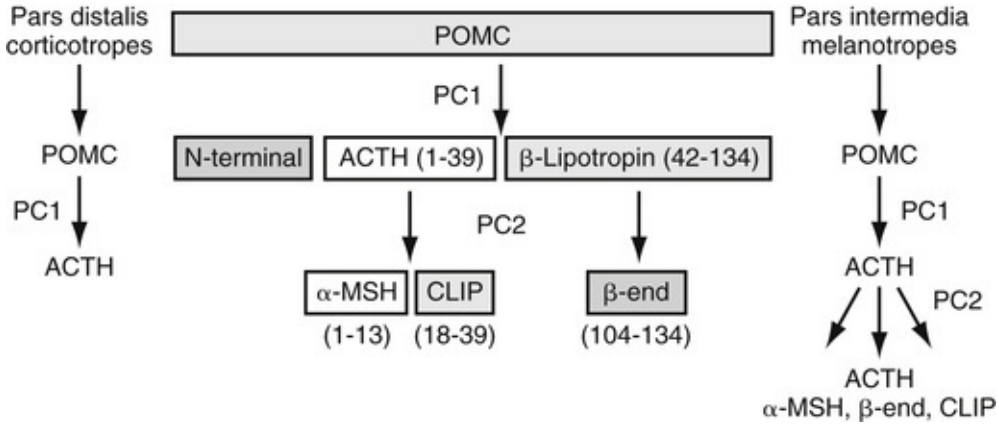


FIG. 41.2 **Proopiomelanocortin (POMC) processing. POMC is cleaved by prohormone convertase I into adrenocorticotropic hormone (ACTH) in the pars distalis and into α-melanocyte stimulating hormone, β-endorphin, and corticotropin-like intermediate lobe peptide by prohormone convertase I and II in the pars intermedia. Only a small amount of ACTH is produced by the normal pars intermedia.**

The physiologic role of the pars intermedia POMC-derived peptides, α-MSH, β-end, and CLIP, has not been extensively studied in the horse. In other species, α-MSH has several diverse actions, which are mediated through interaction with one of five distinct G-protein–coupled melanocortin receptors. α-Melanocyte stimulating hormone is named such due to its ability to induce skin pigmentation in amphibians. Its role in pigmentation is through interaction with melanocortin receptor 1 (MC1R), which is predominantly expressed in skin. In horses, mutation of the *MC1R* gene is associated with the chestnut coat color.[8] In white Camarque horses the degree of coat pigmentation is directly correlated to the plasma concentration of α-MSH.[9] α-MSH is also an integral mediator in control of energy homeostasis. MC3R and MC4R are both expressed in the central nervous system (CNS), particularly in the hypothalamus, where they function in the leptin-melanocortin pathway, regulating appetite-satiety balance and fat

metabolism.[10] Animals and humans lacking functional MC3R or MC4R are obese, and melanocortin receptor defects are a common monogenetic cause of obesity in humans.[11] Plasma α-MSH concentration in obese men has been reported to be higher than in lean men.[12] It has been suggested high plasma concentration in obese individuals may be an attempt to maintain homeostasis in individuals with a defect in MC4R. Plasma α-MSH concentration was also found to be positively correlated to obesity in horses.[13] Another function of α-MSH is as a potent anti-inflammatory agent.[14] α-MSH has been demonstrated to have multiple immune-modulating effects. Its most profound effect is in regulation of cytokine response. α-MSH inhibits activation of NF-κB by lipopolysaccharide (LPS) and interferon-γ (IFN-γ). Data in mice have suggested that α-MSH may suppress LPS-mediated inflammation by facilitating the interaction of IRAK and IRAK-M.[15] IRAK is a kinase that functions in activation of NF-κB following TLR-4 (the receptor for bacterial LPS) stimulation.[15] IRAK-M is a negative regulator of IRAK. As a result, NF-κB activation and proinflammatory cytokine release of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, and IL-6 are all decreased following α-MSH administration. Fever and other clinical evidence of inflammation are also reduced. In addition, α-MSH has been shown to inhibit human and rodent neutrophil function, including adhesion, chemotaxis, and oxidative burst.[16-17] High α-MSH plasma concentration in horses was also associated with decreased oxidative burst and adhesion.[18] β-End is a known endogenous opioid. Secretion of β-end provides analgesia and behavioral modification. It also suppresses immune responsiveness and has effects on vascular tone.[19-20] Corticotropin-like intermediate lobe peptide (CLIP, ACTH 18-34) has not been extensively studied in any species. In pancreatic islet cells in culture, CLIP was shown to be a pancreatic β-cell secretagogue, stimulating the release of insulin.[21] However, when administered to rats by either intraperitoneal or intraventricular injection, ACTH but not CLIP resulted in release of insulin and decrease in blood glucose.[22]

A distinct seasonal effect on the activity of the pars intermedia of horses and ponies has been demonstrated in horses residing in tropical and temperate environments.[23-30] Plasma α-MSH concentration is considerably higher in horses and ponies in the northern hemisphere in August through October, compared with samples collected in the winter, spring, and early summer.[23-28] Similarly, horses in the southern hemisphere experience higher plasma α-MSH

concentrations during shortening day length, from February to April.[29-30] An effect of season on α-MSH concentration has been described for humans, hamsters, and sheep.[31-33] The functional importance of the seasonal cycle is unknown, but several physiologic events occur in parallel with the α-MSH cycle. In sheep, body weight, voluntary food intake, and condition all peak simultaneously with α-MSH, with seasonal maximums occurring in September. Soay sheep with a surgically created hypothalamic-pituitary disconnection have an increase in circulating concentration of α-MSH and chronic increase in body weight.[32] These findings suggest that α-MSH or other POMC-derived peptides may play a role in metabolic preparation for winter in sheep. It is possible that horses and ponies have a seasonal increase in POMC-derived peptides to metabolically prepare them for a decrease in accessible food observed in the wild in winter. If so, dysregulation of this pathway might be associated with abnormalities in body weight and fat storage. Weight loss and abnormal fat distribution are two clinical signs associated with equine PPID. Development of a winter coat also begins as length of day decreases in the fall. The development of hypertrichosis in horses with PPID leads one to speculate that the naturally occurring seasonal increase in POMC-derived peptides contributes to development of winter coat growth. This has not been critically assessed in equids.

Equine Pituitary Pars Intermedia Dysfunction

Equine PPID is one of the most common diseases of horses and ponies 15 years and older.[34-36] PPID was originally termed *equine Cushing disease* because of features similar to human Cushing disease. However, in contrast to human Cushing disease, PPID affects the pituitary pars intermedia rather than the pars distalis, is typically not a neoplastic condition, and the adrenocortical contribution to the clinical syndrome is of much less importance. To avoid confusion, equine Cushing disease is now more correctly referred to as PPID.

In the past 2 decades the population of aged horses has increased dramatically. This, in conjunction with the vast amount of information now available online to the horse-owning public, has led to a heightened client awareness of age-associated equine health issues and a desire to promote healthy aging in their horses. As a result, diagnostic testing and treatment of horses for PPID has increased. Yet despite increased clinical recognition of this disease, much about PPID remains poorly understood.

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Pathophysiology

The pathologic hallmark of PPID is hypertrophy, hyperplasia, and microadenoma or macroadenoma formation in the pituitary pars intermedia with increased secretion of POMC peptides. Horses with PPID develop enlarged pituitaries that may exceed five times normal weight. As the pars intermedia expands, it compresses the adjacent pituitary lobes and hypothalamus, often resulting in a loss of function of these tissues. In contrast, the pars intermedia remains active in horses with PPID, secreting relatively large quantities of POMC-derived peptides into the peripheral circulation. Horses with disease may have as much as a 40-fold increase in plasma concentration of pars intermedia POMC-derived peptides.[37] Clinical signs of disease likely result from a combination of increased circulating POMC peptides and loss of neuroendocrine function of adjacent tissues.

Evidence indicates loss of dopamine inhibition is critical in the pathology of PPID. Dopamine and dopamine metabolite concentrations in the pars intermedia of PPID horses are decreased eightfold compared with age-matched controls.[7] Systemic supplementation of dopamine or a dopamine agonist to horses with PPID results in a decrease in plasma concentration of POMC peptides.[37] Horses treated with the dopamine agonist pergolide show improvement in both clinical signs and biochemical abnormalities associated with disease.[38-41] Immunohistochemistry of formalin-fixed tissue showed a fivefold decrease in pituitary dopaminergic nerve terminals and a 50% reduction in the number of dopaminergic periventricular cell bodies in the hypothalamus of PPID animals.[42] Considered together, this evidence suggests a loss of functional periventricular dopaminergic neurons—"dopaminergic neurodegeneration"—occurs in horses with PPID (Fig. 41.3). Loss of periventricular dopaminergic inhibition of the pars intermedia in other species results in pathologic changes similar to those of PPID. Surgical disruption of the periventricular hypophyseal dopaminergic tracts in rats results in increased expression of pars intermedia melanotropes.[43] In addition, D2 dopamine receptor knockout mice develop pars intermedia lesions similar to PPID.[4] These data suggest PPID is primarily a disease of hypothalamic origin, rather than the consequence of a spontaneously forming pituitary adenoma.

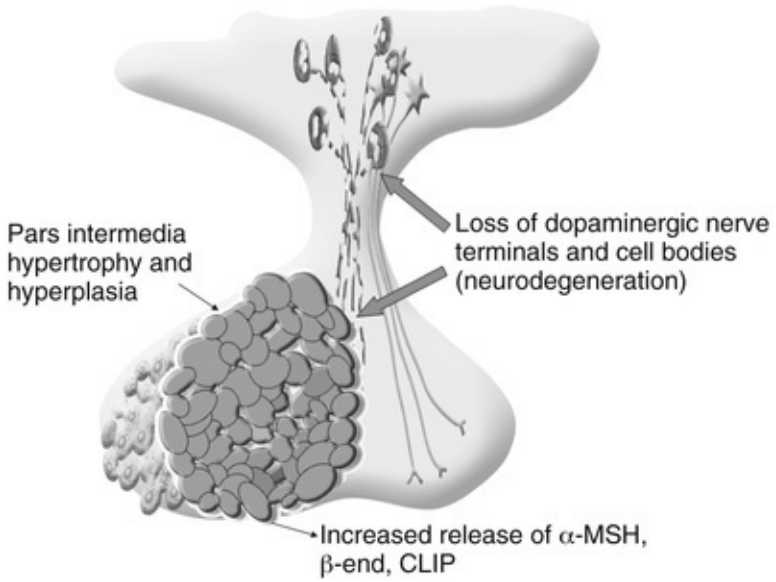


FIG. 41.3 **Pathophysiology of equine pituitary pars intermedia dysfunction. Loss of functional dopaminergic periventricular neurons leads to a decrease in dopamine at the pars intermedia. This in turns results in dysinhibition of the melanotropes of the pars intermedia. The outcome is hypertrophy and hyperplasia of the pars intermedia and increased systemic release of the pars intermedia proopiomelanocortin (POMC)-derived peptides, α-melanocyte stimulating hormone (α-MSH), β-endorphin (β-end), and corticotropin-like intermediate lobe peptide.**

One potential cause for dopaminergic neurodegeneration is oxidative stress. Oxidative stress causes modification of cellular components including proteins, DNA, and cell membrane lipids due to excessive exposure to reactive oxygen species leading ultimately to cell death or, in the case of neurons, neurodegeneration. Dopaminergic neurons are particularly vulnerable to oxidative damage because dopamine metabolism itself produces free radicals. Horses with PPID have evidence of oxidative damage, including accumulation of pars intermedia 3-nitrotyrosine[42] and decreased plasma thiol.[44] The oxidative damage in PPID does not appear to be the result of impaired antioxidant capacity because systemic and pituitary antioxidant capacity of affected horses appears unchanged.[45]

Clinical Signs

Equine PPID affects many aged equids, resulting in a variety of clinical signs including hypertrichosis (hirsutism), muscle atrophy, regional fat accumulation, polydipsia, polyuria, secondary infections, lethargy, infertility, persistent lactation, exercise intolerance, and sweating dysregulation (Fig. 41.4).[46-51] Laminitis and metabolic abnormalities including hyperglycemia and

hyperinsulinemia also occur in approximately 30% of horses with PPID.[48] It is now thought that endocrinopathic laminitis occurs in horses with PPID due to concurrent insulin dysregulation or equine metabolic syndrome (EMS), rather than as a direct result of PPID itself.

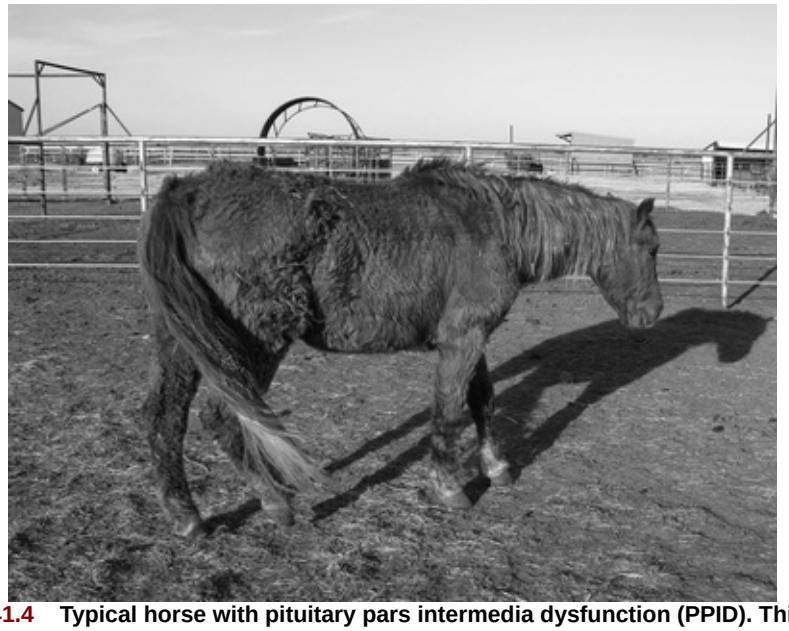


FIG. 41.4 **Typical horse with pituitary pars intermedia dysfunction (PPID). This 22-year-old Morgan mare shows obvious hypertrichosis. Other clinical signs of PPID in this horse included laminitis and weight loss despite an excellent appetite.**

The most unique clinical manifestation of PPID is an abnormally long, curly hair coat that fails to shed (previously referred to as *equine hirsutism*, although more correctly called *hypertrichosis*). Often, horse owners may report the horse sheds its winter coat slowly or incompletely in the year(s) before development of a full failure to shed. Hair may be initially retained along the legs or under the mandible (Fig. 41.5). The mechanism responsible for development of hypertrichosis in horses with PPID has not been reported. The onset of hypertrichosis in an aged horse or pony is considered essentially pathognomonic for PPID, although the author has observed similar hair coats in severely debilitated aged animals with confirmed normal pituitary pars intermedia function.



FIG. 41.5 **Coat changes vary among horses with pituitary pars intermedia dysfunction (PPID). Retained hair along the lower limbs (A), under mandible (B), and as guard hairs and tufts along trunk (C).**

In the author's experience, weight loss due to muscle mass atrophy is the most common and often the earliest clinical sign of PPID (Fig. 41.6). Despite weight loss, PPID horses often have a potbellied appearance and, as a consequence, owners may fail to notice the lost weight. Weight loss and muscle atrophy may result from several factors, including poor dentition, poor nutrition, heavy parasite burden, minimal exercise, and protein catabolism induced by increased cortisol activity. Histologic evidence of type 2 myofiber atrophy has been documented in muscle biopsies from horses with PPID, consistent with corticosteroid-associated muscle atrophy in other species.[52] Significant improvement in muscle mass was observed in a large group of horses with PPID after 6 months of treatment with pergolide mesylate, suggesting overexpression of POMC peptides contributes directly or indirectly to the mechanism of muscle atrophy.[41]



FIG. 41.6 **Horse with pituitary pars intermedia dysfunction (PPID). The major clinical sign of disease in this horse with PPID was weight loss. Muscle mass atrophy along the dorsum, with a potbelly appearance, is characteristic of PPID.**

Despite weight loss and muscle mass atrophy, horses with PPID often have abnormal accumulations of fat, most notably in the crest of the neck, tailbase, sheath, and superorbital fossa. This fat accumulation typically predates the weight loss and has a similar pattern as that observed in horses with equine metabolic syndrome (EMS). The similarity of the clinical signs and at-risk breeds of these two diseases has resulted in a misdiagnosis of PPID in animals that have EMS. Unlike what was previously postulated, these two conditions, PPID and EMS, are no longer considered mutually exclusive conditions. There has also been speculation that animals with EMS or sustained obesity with hyperinsulinemia may be at greater risk for developing PPID as they age. Although epidemiologic data are currently lacking to support this association, client-provided anecdotal data suggest this may warrant more critical assessment.

Polydipsia and polyuria (PU/PD) occurs in some horses with PPID and is typically mild in severity.[46-47,49-51] The mechanism responsible for PU/PD may include (1) compression of the pars nervosa resulting in decreased arginine vasopressin (antidiuretic hormone) production, (2) osmotic diuresis secondary to hyperglycemia and glucosuria, or (3) cortisol induced. Cortisol is thought to cause PU/PD in other species by interfering with the secretion and/or action of arginine vasopression.[53] Evidence suggests ACTH and cortisol may inhibit the renin-angiotensin-aldosterone axis as well. The mechanism of PU/PD in horses with PPID has not been extensively examined. Glucosuria is not a common

finding in horses with PPID. In one study, two PPID horses with marked hyperglycemia were found to have similar water consumption to normal horses, suggesting that osmotic diuresis is unlikely a major mechanism of PU/PD in the PPID horse.[51]

Horses with PPID have been reported to be more susceptible to infection, including endoparasitism, bacterial sinusitis, skin infections, abscesses, and respiratory infections.[46-47,54-56] The morbidity and mortality of secondary infection in equine PPID have been reported to range from 27% to 48%.[49-50,54-55] In the absence of parasite control, a heavy parasite burden is common.[56] Routine, quantitative fecal egg counts are recommended to ensure an adequate anthelmintic program. Vigilance on the part of the owner and veterinarian is important in both prevention and early recognition of infections because they may be clinically insidious. Bronchopneumonia was found at necropsy in 7 of 19 horses with PPID.[57] Bronchopneumonia should be considered in the PPID horse with fever or tachypnea.

Laminitis secondary to PPID is reported to occur in approximately 30% to 40% of diagnosed cases and can necessitate euthanasia in affected animals.[41,49-51] When adult horses with laminitis of unknown origin were examined, 30% had evidence of PPID based on the presence of clinical signs (abnormal hair coat) and diagnostic test results.[58] Although an earlier study suggested 70% of undiagnosed laminitis cases might be due to PPID, this study relied on plasma ACTH concentration measured irrespective of season and in the absence of clinical signs for the diagnosis.[59] The reliability of plasma ACTH concentration for diagnosis of presymptomatic PPID, particularly in thrifty horses in the fall, is likely poor. The pathogenesis of laminitis in PPID is not currently well understood, but endocrinopathic laminitis is the subject of ongoing investigation. Multiple lines of study support a primary role for hyperinsulinemia and insulin dysregulation in the induction of endocrinopathic laminitis.[60-65] Current data suggest that PPID is a comorbidity or risk factor rather than a primary inciting factor in the development of endocrinopathic laminitis.[48] Therefore, clients should be advised to assess all horses with insulin dysregulation (ID, equine metabolic syndrome) for PPID and all animals with PPID for ID. In horses with concurrent PPID and ID, the utmost care should be taken to manage risk factors for laminitis and minimize dietary nonstructural carbohydrates that could perpetuate ID.

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Diagnosis of Pituitary Pars Intermedia Dysfunction

Equine PPID is both common and life threatening; therefore early and accurate diagnosis with appropriate intervention is considered critical. Antemortem diagnosis of PPID currently relies on testing hypothalamic-pituitary-adrenal axis responsiveness or measurement of endogenous plasma concentrations of POMC-derived peptides such as ACTH. These tests have been the subject of recent evaluation, and the search for improved testing strategies is considered an ongoing research priority.[66] Accepted best practices for the diagnosis of PPID have evolved significantly over the past 5 years, and further changes are likely to follow.

Currently, three antemortem diagnostic tests are most commonly used in practice settings: (1) the overnight dexamethasone suppression test (DST), (2) measurement of endogenous plasma ACTH concentration, and (3) ACTH release following thyrotropin-releasing hormone stimulation. The overnight DST was long considered the “gold standard” method of antemortem PPID diagnosis.[67] In the unaffected horse, intramuscular (IM) administration of dexamethasone decreases release of ACTH from the pars distalis, resulting in a serum cortisol concentration of less than 1 µg/dL (27.59 nmol/L) 19 hours after dexamethasone (Fig. 41.7).[67] Horses with PPID fail to suppress serum cortisol concentration due to ACTH production from the pars intermedia. Although originally this test was reported to have a sensitivity and specificity of 100%, horses included in that study were selected for having end-stage PPID, resulting in a favorable bias when assessing test performance.[67] Although highly specific for PPID, the DST has shown poor performance in identifying horses with earlier PPID. In fact, the DST was only useful in identifying horses with end-stage disease (defined as those with hypertrichosis and grossly enlarged pituitary adenomas) when a random population was assessed using necropsy as the gold standard.[68]

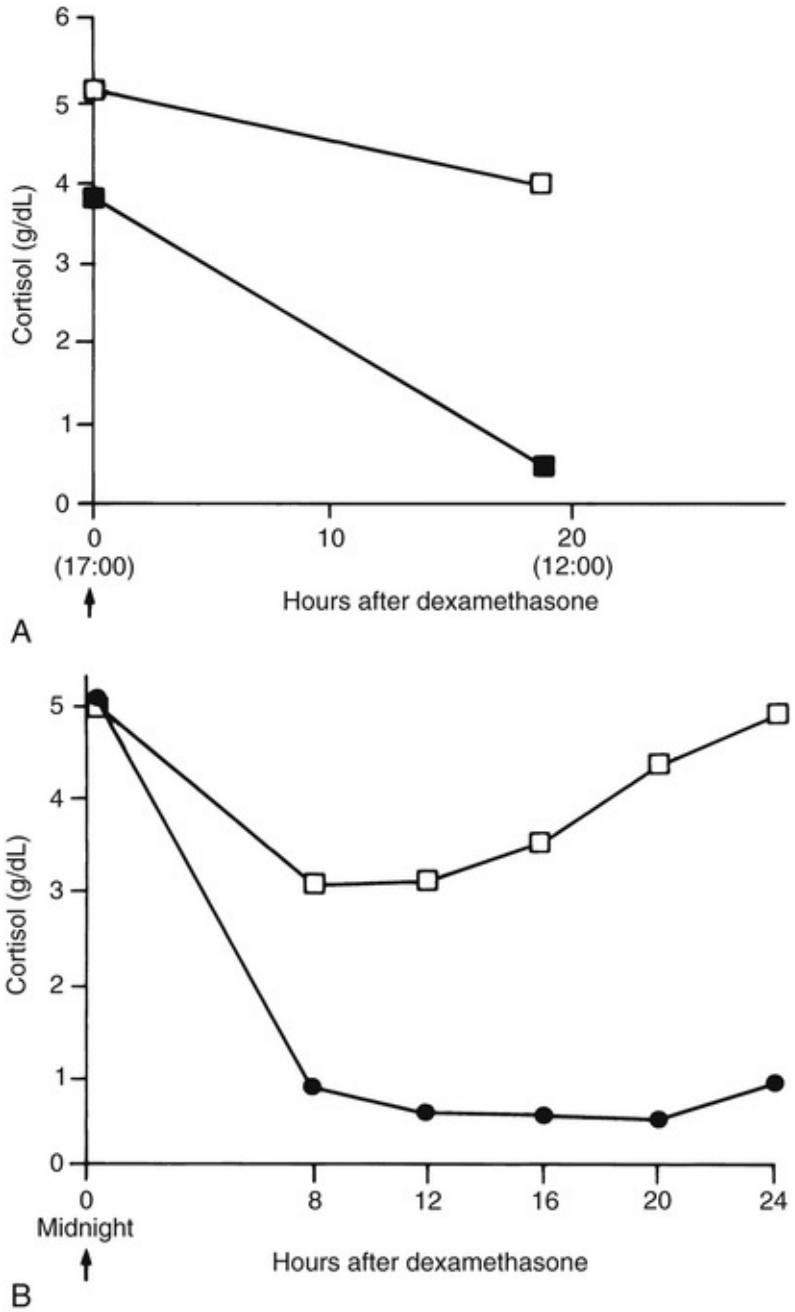


FIG. 41.7 Dexamethasone suppression test. □, Cushing; ▪, control; ↑, 40 µg/kg dexamethasone intramuscularly; **A,** overnight; **B,** standard.

Measurement of endogenous concentrations of POMC-derived peptides is also useful in the diagnosis of PPID.[69] Measurement of plasma ACTH concentration is the most commonly used method for diagnosis of PPID in ambulatory practice because it requires collection of only a single plasma sample and poses no risk to the patient. Difficulty in sample handling was long cited as a limitation of this test; however, more critical evaluation has found equine ACTH to be more stable

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in plasma than originally assumed, and as long as a plasma sample remains cooled, separation of plasma can be delayed as long as 12 hours without affecting results and without the need for special preservatives (e.g., aprotinin).[39,50,70] Measurement of plasma concentrations of ACTH was originally reported to have a sensitivity and specificity of approximately 80% to 90%.[50,69] However, evaluation of a larger, randomized equine population has found the test to have a sensitivity and specificity of approximately 70% and 80%, respectively.[68] α-MSH concentration measurement, although used in research to similarly assess pars intermedia function, is not significantly better than ACTH concentration in identification of PPID and is not commercially available.[27,68-69,71]

Seasonal variation in both static and dynamic testing of pars intermedia function has been well documented.[23-30,72-73] Testing performed in autumn, between August and October in the northern hemisphere or February and April in the southern hemisphere, yields a significantly greater hormone concentration than testing performed between November and July.[23-30,72-73] Initially, these findings led to the recommendation to avoid endocrine testing in autumn. However, further work has demonstrated that the difference in ACTH concentration between normal horses and those with PPID is much greater during autumn.[26] As a consequence, provided seasonally specific reference intervals are available, ACTH testing in autumn is more discriminating and therefore preferable to testing during other times of the year.

A positive test result in an animal with clinical signs of PPID is considered strong diagnostic evidence. However, due to the poor performance of the DST and ACTH concentration at identifying early disease, it is not uncommon for a clinician to have a suspicion of PPID in a patient that has a negative diagnostic test result. When this occurs, repeating testing at a later date or further testing using a provocative test is indicated. The dynamic test that has been shown to most accurately identify PPID is the thyrotropin-releasing hormone (TRH) stimulation test with measurement of plasma ACTH concentration.[74-76] TRH is known to be a physiologic releasing factor of the equine pars intermedia.[6] Although this test was initially performed by documenting an increase in serum cortisol concentration after TRH administration, measurement of plasma ACTH rather than serum cortisol has proven more reliable.[6,77] Plasma ACTH response is a more direct assessment of pars intermedia activity and eliminates the influence of adrenal gland response or ACTH bioactivity. It has been

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demonstrated that in PPID, immunoreactive plasma ACTH is not as bioactive as plasma ACTH from the healthy horse.[78-79] Therefore, in horses with PPID the TRH response may be attenuated at the level of cortisol release. The initial recommended protocol for the TRH stimulation test was to measure plasma ACTH concentration at time 0, 10, and 30 minutes after intravenous administration of TRH (1 mg/horse or 0.5 mg/pony).[76] However, to reduce cost and improve efficiency, most practitioners choose to collect only the 0- and 10-minute samples, as data are lacking for improved test performance with inclusion of the additional 30-minute sample. Current recommendations suggest limiting use of the TRH stimulation test to nonfall seasons.[66] Although several investigators have collected TRH stimulation data during the fall, TRH response is highly variable and may depend on such factors as breed and geographic location.[80-81] Although unlikely to be practical in most cases, advanced imaging of the pituitary using computed tomography (CT) or magnetic resonance (MR) has also been examined in a limited number of cases as a method for documenting pituitary or pars intermedia enlargement.[82-85] Accuracy of CT at estimating width, height, length, and volume of the equine pituitary gland in disarticulated heads from 25 normal horses was determined to be 81% to 93%, 58% to 71%, 88% to 99%, and 43% to 53%, respectively.[83] In a more recent study in which CT measurements were performed in a small number of live horses, accuracy was between 92% and 105%, likely due to the larger dose of contrast agent administered.[84] Despite the ability to characterize overall size of the pituitary, CT does not provide information on the internal structure of the gland, including the relative size of the pituitary lobes and presence of microadenomas. Magnetic resonance imaging is the preferred diagnostic imaging modality for pituitary masses in humans, and its usefulness in characterizing the pituitaries of horses is currently being evaluated.[85]

Necropsy Findings

Postmortem examination of the horse with PPID reveals a grossly enlarged pituitary due to hypertrophy and hyperplasia of the pars intermedia.[86-89] The normal horse's pituitary typically weighs between 1 and 3 g; the affected horse's pituitary may be two to five times this size. Enlargement may be due to an adenoma (>1 cm), which often contains areas of hemorrhage and necrosis. Alternatively, microadenomatous (≤1 cm) hyperplasia may be present. Melanotropes in the affected gland are pleiomorphic (polyhedral or spindle

shaped) with eosinophilic, granular cytoplasm.[86-89] Cells are organized into nodules, rosettes, bundles, or follicular structures separated by fine septal tissue. Pigment deposition (lipofuscin) is common in the pars nervosa, and hemosiderin may be observed when hemorrhage is present.[57] Other lesions include compression of the pars distalis, pars nervosa, or in the case of large tumors that outgrow the sella turcica, compression of the optic chiasm or hypothalamus. Associated lesions of other organs are also common, including those related to immunosuppression such as intestinal parasitism, pneumonia, abscesses, or sinusitis.[57] Laminitis may be observed in horses with PPID and insulin dysregulation; however, PPID alone is not typically associated with laminar pathology.[48] Mild enlargement of the pars intermedia is also observed in the healthy aged horse,[89] and moderate enlargement with microadenomas has been observed in clinically normal horses during the autumn.[88]

Treatment and Prognosis

Treatment of PPID is aimed at improving general health and reducing the risk of disease complications such as laminitis and infections. Management practices should be optimized for care of an aged horse. Diet and feeding practices, dental and hoof care, and deworming schedule should be assessed. Feeding of a pelleted diet designed for senior horses along with strategic deworming and correction of dental abnormalities are useful in maintaining the animal's weight and improving overall general health. Body clipping the horse that fails to shed during warm weather is critical to limit excessive sweating and avoid hyperthermia. Careful observation for evidence of infection followed by early intervention is important to avoid protracted illnesses. Due to the strong anti-inflammatory effects of POMC peptides, clinical signs of infections are often mild and don't reflect the severity of disease. Assessment of insulin regulation and vigilant attention to diet and hoof care are essential to avoid laminitis in those horses with concurrent PPID and insulin dysregulation.

Pharmaceutical interventions for PPID function by decreasing the concentration of circulating POMC peptides and/or cortisol, which theoretically should reduce the risk of disease complications beyond what can be achieved by management alone. Ideally, treatment should also reverse or retard the hyperplastic growth of the pars intermedia, thereby limiting compression of adjacent tissues.

The preferred drug for the treatment of PPID is pergolide, a dopamine agonist,

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which has been shown to improve clinical signs and diagnostic test results in treated animals.[38-40] An initial dose of 0.002 mg/kg orally every 24 hours has been recommended.[46,66] Response to the drug should be assessed by both clinical improvement and normalization of diagnostic test results. If no response is observed in 4 weeks, the dose is increased by 0.001 to 0.002 mg/kg increments monthly until clinical signs and biochemical abnormalities normalize.[46] In some horses, splitting the daily dose into two 12-hour treatments also may improve response. Complications associated with pergolide use in the horse include anorexia, colic, and diarrhea. These are typically dose dependent and often resolve spontaneously following a reduction in dose. Once an effective dose is established, endocrine testing should be repeated every 6 to 12 months to ensure hormonal control is maintained because horses may require periodic increases in dose over time. Although other dopaminergic agonists, such as bromocriptine and cabergoline, have been shown to be effective in suppressing pars intermedia activity, the only approved and well-studied dopaminergic agonist for the treatment of PPID at this time is pergolide (Prascend).[90]

Cyproheptidine, a drug with antiserotoninergic, antihistaminergic, and anticholinergic activity, was one of the original drugs used to treat horses with PPID. However, several studies using objectively measurable outcomes failed to show consistent efficacy of the drug.[38-39] In addition, although historically inexpensive, the cost of cyproheptidine has increased significantly, making pergolide the more rational current treatment choice. Cyproheptidine may be useful as an adjunct therapy in horses resistant to pergolide monotherapy. Cyproheptidine may be added at 0.3 to 0.5 mg/kg orally once daily to horses that show minimal response to a 0.006 mg/kg or higher dose of pergolide.[46] Cyproheptidine has been associated with induction of seizures in rodents and therefore may be contraindicated in horses with a history of previous seizure activity.[91]

The prognosis of horses with PPID is not well documented. Many horses live for years following diagnosis, particularly if receiving optimized management. Reports of PPID horses that have responded to pergolide for more than 5 years suggest long-term effective treatment is achievable.[92] As with all diseases, early recognition, appropriate intervention, and avoidance of complications are the keys to a positive outcome.

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Adrenal Glands

Kelsey A. Hart

Physiology of the Adrenal Gland and Hypothalamic-Pituitary-Adrenal Axis

As in other species, in the horse the paired adrenal glands lay immediately craniomedial to the kidneys. Equine adrenal glands weigh approximately 15 g each and are approximately 8 to 10 cm in length, 3 to 4 cm wide, and 1.5 cm thick, though there is much variation in adrenal size and shape among individual horses. Each gland is divided into an outer cortex that secretes corticosteroids and an inner medulla that secretes catecholamines.

The adrenal medulla functions as a neuroendocrine organ and is essentially a modified sympathetic ganglion. Preganglionic sympathetic neurons extend from the central nervous system and synapse directly on adrenal medullary chromaffin cells; when stimulated, these cells release catecholamines directly in the systemic circulation to produce a global sympathetic response. In the horse, the primary adrenal medullary catecholamine appears to be epinephrine, though norepinephrine and dopamine are also produced.[1] Diseases affecting the adrenal medulla are rare in horses—as in all species—though adrenal medullary neoplasms are reported.

The adrenal cortices are divided into three cellular zones: (1) the outer zona glomerulosa; (2) the middle zona fasiculata, which is the largest zone and comprises approximately 75% of the weight of the gland; and (3) the narrow inner zona reticularis. Cells in the zona glomerulosa are primarily responsible for the secretion of mineralocorticoids (e.g., aldosterone) in response to hypotension and electrolyte derangements (hyperkalemia, hyponatremia). Zona fasiculata cells synthesize and secrete glucocorticoids (e.g., cortisol, corticosterone, 11-deoxycortisol) in response to stimulation by adrenocorticotropic hormone (ACTH) after activation of the hypothalamic-pituitary-adrenal (HPA) axis (Fig. 41.8) by physiologic or pathophysiologic stressors. The predominant circulating glucocorticoid in the horse is cortisol.[2] Cells in the zona reticularis also secrete small amounts of glucocorticoids but primarily produce adrenal androgens such as dehydroepiandrosterone (DHEA) and androstenedione. All corticosteroid

hormones are structurally similar with a common sterol backbone and one 5-carbon and three 6-carbon rings, and they share a common synthetic pathway originating from cholesterol (Fig. 41.9). The specific corticosteroids produced by a particular adrenocortical cell depend on which specific biosynthetic enzymes are expressed in that cell (see Fig. 41.9), which varies between the three functional zones.

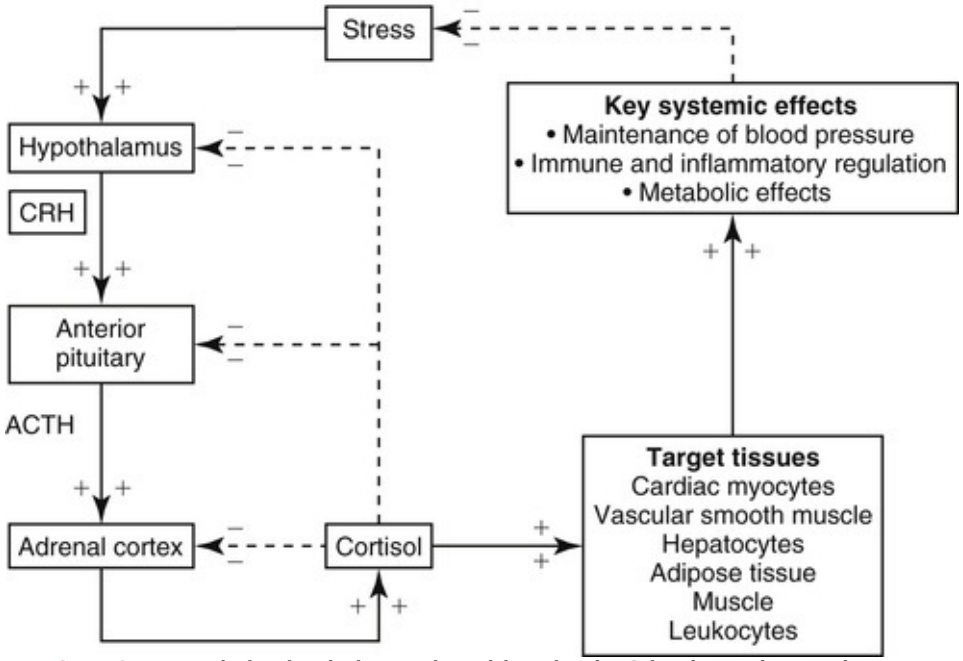


FIG. 41.8 Hypothalamic-pituitary-adrenal (HPA) axis. Stimulatory interactions are illustrated with solid arrows and + signs, and inhibitory interactions (negative feedback) are illustrated with dashed arrows and − signs. *ACTH,* Adrenocorticotropic hormone; *CRH,* corticotropic releasing hormone. (From Hart KA, Barton MH: Adrenocortical insufficiency in horses and foals. Vet Clin North Am Equine Pract 27:19–34, 2011.)

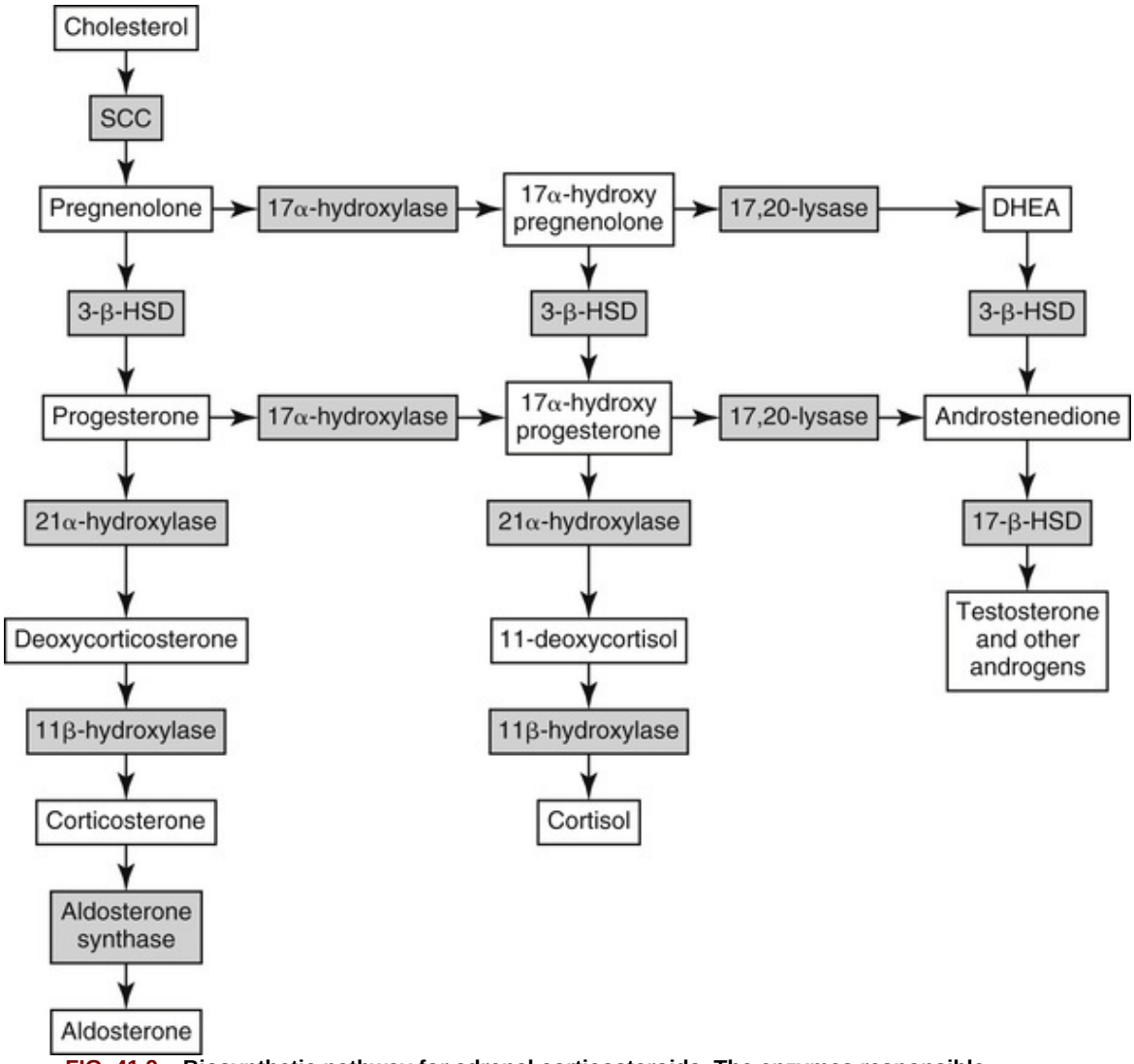


FIG. 41.9 Biosynthetic pathway for adrenal corticosteroids. The enzymes responsible for catalyzing each biotransformation are shown in the gray boxes over the arrows. *SCC,* Side chain cleavage enzyme; *3-β-HSD*, 3-β-hydroxysteroid dehydrogenase; *DHEA,* dehydroepiandrosterone. (From Hart KA, Barton MH. 2011. Adrenocortical insufficiency in horses and foals. Vet Clin North Am Equine Pract. 27:19-34)

All steroid hormones are lipophilic and thus are transported in the plasma predominantly bound to plasma proteins, including albumin and steroid-binding globulins such as cortisol-binding globulin (CBG). However, as steroid hormone receptors are located in the cytoplasm of steroid-responsive cells, it is only the free, unbound portion of circulating steroid hormones that is available to enter cells via diffusion across the plasma membrane to bind these intracellular receptors. Binding of the steroid hormone to the receptor causes conformational changes that allow dissociation of regulatory heat shock proteins, permitting the hormone-receptor complex to localize to the nucleus, bind DNA at hormone-

response-elements (HREs), and upregulate or downregulate transcription of steroid hormone-responsive genes.

Glucocorticoids are the most abundant circulating adrenal corticosteroid hormone and play an integral role in the endocrine response to stress. The HPA axis (see Fig. 41.8) is activated when physiologic, pathophysiologic, or environmental stressors activate peripheral and central nervous system components, whose signals are then interpreted and integrated in the hypothalamus. This stimulates hypothalamic paraventricular nuclei, resulting in the release of corticotropin-releasing hormone (CRH) into the hypothalamic-hypophyseal portal vessels. CRH then acts locally in the adjacent anterior pituitary gland to stimulate CRH receptors on the cell surface of pituitary corticotroph cells, resulting in the release of adrenocorticotropic hormone (ACTH, corticotrophin) into the systemic circulation.

ACTH binds cell surface receptors (melanocortin 2 receptor, MC2R) on adrenocortical cells and stimulates the adrenal glands to synthesize and secrete cortisol. MC2R is a G protein−coupled transmembrane receptor that acts via adenylate cyclase to increase cyclic AMP levels, which then activate biosynthetic enzymes necessary for cortisol synthesis, including 3-β-hydroxysteroid dehydrogenase (3-β-HSD), 17-α-hydroxylase, 21-α-hydroxylase, and 11-β-hydroxylase (Fig. 41.9). This latter enzyme catalyzes the final step in cortisol synthesis from 11-deoxycortisol and is present only in glucocorticoid-producing cells.[3]

Cortisol is not stored in adrenocortical cells but rather is secreted into the systemic circulation immediately following ACTH-induced synthesis. In most adult mammals, including horses, approximately 90% to 95% of circulating cortisol is bound to CBG and albumin.[4-8] Many cell types are sensitive to glucocorticoids, permitting cortisol to exert diverse effects necessary for maintenance of homeostasis and stress responses in both health and disease. Essential glucocorticoid-mediated physiologic responses include maintenance of blood pressure, provision of energy to tissues, and control of an appropriate inflammatory response. The sum of cortisol's systemic effects serves to reduce the physiologic stress that initially activated the HPA axis, to ultimately restore basal HPA axis tone. In addition, cortisol itself acts via negative feedback mechanisms at hypothalamic, pituitary, and adrenal levels to further downregulate HPA axis activity. Thus, with an intact HPA axis, plasma cortisol concentrations are maintained at a level appropriate for the existing degree of physiologic stress (see Fig. 41.8).

Cortisol secretion patterns in adult horses exhibit both ultradian (pulsatile) and circadian rhythms with peak secretion in the morning and the nadir in the evening, similar to many other species.[9-12] These ultradian and circadian rhythms are easily disrupted in horses by simple routine changes and illness.[9,12] Cortisol responses to ACTH stimulation testing in adult horses are described and suggest adult horses show a comparable dose-dependent effect of exogenous ACTH on cortisol concentrations as is described in other species.[11,13-15] In general, an approximately twofold to fivefold increase in cortisol concentration is observed within 30 to 90 minutes after IV administration of a 0.1 to 10 μg/kg dose of exogenous ACTH (cosyntropin) in healthy adult horses[13,15]; the magnitude of cortisol increase varies with the ACTH dose administered.

HPA axis function in the foal differs from both adult horses and other species in several key ways. Compelling evidence shows that maturation of the HPA axis occurs in the days just before parturition and continues during the first several weeks of life, much later than is described in other species.[16-19] Premature foals have lower serum cortisol and higher ACTH concentrations than full-term foals immediately postpartum.[19] These low baseline cortisol and concurrent high ACTH concentrations in premature foals imply that foals may have impaired adrenocortical sensitivity to ACTH, limited cortisol synthetic capacity, or both, as compared with adult horses.

Data from ACTH stimulation test responses in foals support this theory, as premature foals show a blunted cortisol response to exogenous ACTH, with only a 28% increase in plasma cortisol 30 to 60 minutes following stimulation, as compared with a 208% increase in normal-term foals.[16] Some evidence suggests that the fetal foal's adrenal gland may be incapable of synthesizing cortisol and some other steroid hormones until late in gestation. In contrast to most other species, fetal foals do not express substantial levels of the key steroidogenic enzymes cholesterol side chain cleavage enzyme, 17α-hydroxylase, and 3-β-HSD (see Fig. 41.9) until just before parturition in the foal,[20,21] much later than is described in other species.[22]

Furthermore, adrenocortical function may not be fully mature at birth even in full-term foals. Though increased at birth due to the stress of parturition, by 12 to 24 hours of age, mean basal cortisol concentrations are onefold to twofold lower in healthy neonatal foals than reported mean concentrations in healthy adult horses despite comparable or higher concurrent ACTH concentrations in foals.[23-27] This apparent decreased cortisol response to endogenous ACTH in the full-

term neonatal foal is supported by further evidence of limited cortisol responses to exogenous ACTH. Insulin-induced cortisol responses in foals within 12 hours of birth are less than half of the responses achieved in 7- to 14-day-old foals,[28] and healthy-term neonatal foals aged 1 to 7 days are reported to have approximately half the magnitude of cortisol response to ACTH stimulation testing than adult horses.[13,24] This decreased adrenocortical responsiveness appears to persist during the first few months of life, as 12-week-old foals show significantly greater cortisol responses to a low-dose (0.1 µg/kg) ACTH stimulation test than younger foals.[29]

Finally, foals differ from adult horses in their plasma cortisol binding capacity and cortisol secretion and metabolism patterns. In foals younger than 1 week of age, 30% to 60% of circulating cortisol is free, in contrast to 5% to 10% in adult horses.[30] This is likely due to decreased CBG concentrations in foals, as has been shown in infants.[31,32] Free cortisol is preferentially excreted and metabolized over bound cortisol,[33] so it is not surprising that increased cortisol clearance rates in foals as compared with adult horses have recently been described.[12] Healthy full-term foals appear to be able to increase their daily cortisol production rate to compensate for this increased clearance, though as serum total cortisol concentration at 1 week of age remains significantly lower in foals than adult horses,[12] foals' capacity to further and appropriately increase cortisol production in severe stress may be limited. It is likely that impaired cortisol responses in neonatal foals result from multiple factors, including decreased cortisol synthetic capacity and increased cortisol clearance and possibly other as yet undefined difference in ACTH sensitivity or activity. Regardless of the cause, this evidence of fetal and neonatal HPA axis immaturity is certain to substantially impact foals' stress responses during the neonatal period.

Mineralocorticoids (e.g., aldosterone) are produced in small quantities relative to glucocorticoids but have equally important physiologic roles. Angiotensin II —via activation of the renin-angiotensin-aldosterone system by hypovolemia/hypotension or increases in plasma osmolality—and increased plasma potassium concentration are the primary stimulants of aldosterone synthesis and secretion. ACTH is also necessary for aldosterone synthesis, but ACTH administration to healthy adult horses resulted in a decrease in plasma aldosterone concentration in contrast to increases seen in other species.[34,35]

Like glucocorticoids, aldosterone circulates in the plasma bound to albumin or

steroid-binding globulins and primarily acts by binding cytosolic mineralocorticoid receptors to alter transcription of genes necessary for sodium and potassium transport. Mineralocorticoid receptors are predominantly expressed in sodium-transporting epithelia in the distal renal tubules and colon, with lesser expression in the rest of the intestinal tract and heart. Aldosterone induces transcription of an aldosterone-regulated kinase that increases activity of apical membrane sodium channels.[36] The net effect of this is increased sodium flux across epithelial cells, resulting in increased renal and intestinal sodium and water resorption and concurrent stimulation of potassium excretion via the basolateral Na^+/K^+ ATP-ase.[36] Mineralocorticoids are vital for appropriate fluid and electrolyte balance, and mineralocorticoid deficiency rapidly results in hyponatremia, hyperkalemia, and hypovolemia.

Reported resting and exercising plasma concentrations of aldosterone in horses have been described.[37,38] In contrast to their limited cortisol responses to appropriate stimuli, newborn foals appear to be able to mount a substantial aldosterone response to hypovolemia/hyponatremia.[19,39] In fact, one study suggested that the aldosterone response in foals appears to be exaggerated in comparison with that in adult horses and may reflect differences in tubular sensitivity to aldosterone between neonates and adults.[39] However, well-established reference ranges for plasma aldosterone concentrations in foals are not currently available.

In adult males, circulating androgens are primarily of testicular origin, but in females more than half of plasma androgens may originate from the adrenal cortices. ACTH is necessary for the synthesis and secretion of adrenal androgens, but another factor (or factors) that is as yet unidentified is also required for adrenal androgen synthesis.[11] Adrenal androgens are also transported in the plasma bound to albumin and CBG and act via cytosolic steroid hormone receptors to modulate gene transcription. DHEA and androstenedione can be extraglandularly metabolized to active testosterone and estrogens and play a particular important role in early pubertal sexual development in most species. Androstenedione concentrations in adult horses are reported, and sex and age variations in adrenal androgen concentrations may be relevant but at present are poorly understood in horses and foals.[26,40] Increased adrenal androgen production is postulated to play a role in mares with estrus-related behavior problems, though this has not been definitively proven.[26]

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Adrenal Gland Disorders

Critical Illness–Related Corticosteroid Insufficiency

Critical illness–related corticosteroid insufficiency (CIRCI) (also known as *relative adrenal insufficiency*) has been described in septic foals and adult horses with colic. The condition is best understood in people and is defined as an insufficient cortisol response or inadequate cortisol activity for the existing degree of critical illness.[41-45] CIRCI is discussed in detail in the later section on endocrine dysfunction in critical illness.

Non-CIRCI Adrenocortical Insufficiency in Adult Horses

Classic adrenocortical insufficiency characterized by glucocorticoid and mineralocorticoid insufficiency and unrelated to critical illness is not well defined in horses or foals, and Addison's disease—permanent adrenocortical insufficiency secondary to immune-mediated adrenocortical destruction—has not been reported. Transient adrenal insufficiency characterized by low basal ACTH and cortisol concentrations and impaired cortisol responses to ACTH stimulation testing has been described in one horse following abrupt cessation of long-term anabolic steroid supplementation.[46] A syndrome of “adrenal exhaustion” resulting in lethargy, anorexia, and poor performance is also anecdotally described in racehorses and has been attributed to adrenal insufficiency associated with long-term anabolic steroid administration or chronic stress. Horses with presumptive adrenal exhaustion are often treated with exogenous ACTH for presumed adrenocortical stimulation, though measurement of basal cortisol concentrations and ACTH stimulation testing in race and endurance horses has not provided convincing evidence for adrenal insufficiency in these equine athletes.[47,48] The potential for iatrogenic adrenal insufficiency associated with HPA axis suppression by exogenous steroid administration, though, should be considered in horses on chronic glucocorticoid or anabolic steroid supplementation, and care should be taken to avoid abrupt cessation of such therapy. Decreased cortisol responses to ACTH are also described in mares with abnormal estrus-related behavior,[26] but the clinical significance of this behavior is not known.

In addition, the adrenal glands appear to be a shock organ in the horse and can also undergo hypoxic or ischemic damage during bouts of endotoxemia, sepsis, and systemic inflammatory response syndrome (SIRS).[15,49] Thus, there is the

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theoretical potential for protracted or permanent adrenocortical dysfunction in animals who survive critical illness, though this specific manifestation is not reported in horses or foals to date. Adrenocortical insufficiency should be considered in horses with persistent lethargy, weight loss, hyponatremia, hypochloremia, hyperkalemia, or hypoglycemia, especially if they have recently received exogenous corticosteroids or recovered from critical illness. Failure to increase serum cortisol concentration greater than or equal to 1.5- to 2-fold baseline values by 30 minutes after a low-dose ACTH stimulation test (≤0.5 µg/kg IV) or greater than or equal to 3- to 4-fold baseline values by 90 to 120 minutes after high-dose ACTH stimulation test (≥1 µg/kg IV) is consistent with a diagnosis of adrenocortical insufficiency.[13,15]

Adrenal Medullary Neoplasia

Although nonfunctional adrenal medullary nodules may be an incidental finding at necropsy in the horse, functional adrenal medullary tumors (pheochromocytoma) are also rarely reported. One recent report described finding them in 0.95% of equine necropsies across two North American university teaching hospitals between 2007 and 2014.[50-54] Pheochromocytoma can be an incidental finding at necropsy, but clinical signs resulting from increased circulating catecholamines may also be seen. Such signs include excessive sweating, agitation, colic, tachycardia, mydriasis, hyperlactatemia, hyperglycemia, and hypertension.[50] Pheochromocytomas are predisposed to hemorrhage, and hemoperitoneum secondary to ruptured pheochromocytoma is described in horses.[50,51,55] Although most cases are diagnosed at necropsy, determination of urinary catecholamine levels can be used for antemortem diagnosis if an abdominal mass and appropriate clinical signs are detected.[53] Pheochromocytomas appear to occur frequently along with other endocrine abnormalities such as thyroid adenoma, PPID, or adrenal hyperplasia, or in a multiple endocrine neoplasia syndrome described in people, small animals, and horses.[50,54,55]

Hypoaldosteronism

In people, primary hypoaldosteronism is uncommon and most frequently occurs as a result of congenital defects in some component of the aldosterone biosynthetic pathway.[11] Hypoaldosteronism is also reported in renal diseases that damage the juxtaglomerular apparatus integral to function of the RAAS, and

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peripheral resistance to aldosterone is also reported in people.[11] Such syndromes have not been described in horses, but idiopathic hypoaldosteronism is described in an alpaca.[56] In addition, hypoaldosteronism is a documented cause of renal tubular acidosis (RTA) in people[57] and should not be overlooked as a possible contributor to RTA in horses.

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Anhidrosis

Babetta Breuhaus

Description of Disease

Anhidrosis is characterized as an inability to sweat in response to appropriate stimuli. It occurs in geographic areas that experience hot, humid weather for prolonged periods of time. Clinical signs are especially likely to occur when nighttime temperatures do not fall below 70° F (21° C). Classically, anhidrosis affects horses that are not accustomed to these environmental conditions and are moved to a hot, humid area. However, partial or complete anhidrosis is also diagnosed in horses that have grown up in these same areas. It appears that horses that are worked or exercised in hot, humid conditions are more likely to develop the condition than horses that are not worked. Stress may also contribute to onset of the problem. One large epidemiologic study conducted in Florida concluded that Thoroughbreds and warmbloods, especially those with a family history of having developed anhidrosis, were more likely to develop the condition.[1] The study also supported earlier beliefs that horses that performed more strenuous work and horses that were not born in Florida were at increased risk for becoming anhidrotic. The prevalence of anhidrosis was increased, both in terms of percent of farms that housed at least one anhidrotic animal and of overall percent of affected horses, in horses residing farther south within the state.[1]

Etiology and Pathophysiology

The cause of anhidrosis is unknown. Presumably, there is an abnormality in stimulation or production of sweat. Equine sweat glands produce sweat as an ultrafiltrate from plasma; water and electrolytes are secreted into sweat gland ducts, and this fluid is transported to the skin surface as sweat. Physiologic stimulation of sweating in horses is achieved by activation of α_2-adrenergic receptors, by direct neural stimulation and from circulating catecholamines.[2-4] It is unclear whether nerve fibers act directly on the sweat glands themselves or on local capillaries, thereby altering delivery of circulating agonists.[5] Purinoceptors

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of the P2Y family may also be involved in stimulation of sweat production. Sweat glands from anhidrotic horses do not respond normally to direct stimulation, and there is histologic evidence of sweat gland atrophy.[6,7] However, it is unknown whether the observed sweat gland atrophy is the primary cause of anhidrosis or merely secondary to disuse. Histologic examination of skin from anhidrotic horses showed no evidence of neural disruption to the sweat glands,[7] and circulating concentrations of epinephrine are actually higher in anhidrotic horses than in horses that sweat normally.[8] This suggests that the problem is more likely caused by decreased ability of sweat glands to respond to stimulation, rather than failure of the thermoregulatory system to perceive the need to sweat or failure of stimulation to sweat. Cultured epithelial cells from sweat glands of anhidrotic horses had lower transepithelial resistance compared with cells derived from sweat glands of horses that were able to sweat freely.[9] In addition, cells from anhidrotic horses failed to show a change in short circuit current (indicative of chloride secretion) in response to purinoceptor or β-adrenoceptor agonists. Most theories of anhidrosis pathogenesis suggest that chronic stimulation to sweat in a hot, humid environment might lead to downregulation and/or desensitization of α_2-adrenoreceptors. The observation that only some horses living in a given environment develop anhidrosis, as well as the recent evidence of a breed and familial predisposition to the problem, suggest a possible genetic predisposition as well. It seems likely that β-adrenoceptor polymorphisms exist in horses and that certain polymorphs are more susceptible to downregulation, though scientific evidence for this theory is currently lacking.

In addition to a neural mechanism, there may also be an endocrine component to this disease. Pregnant mares were found to be somewhat less at risk of developing anhidosis than nonpregnant mares.[10] An association of anhidrosis with hypothyroidism most likely stems from the observation that thyroid supplementation helped anhidrotic horses racing in Hong Kong in the 1950s.[11] However, the author has not observed any improvement in anhidrotic pleasure horses supplemented with thyroid hormones, and measurement of thyroid hormones at rest and in response to TRH showed no difference between normal horses and horses with anhidrosis.[12]

There is evidence in some humans that acquired idiopathic anhidrosis may have an immunologic pathogenesis. Serum IgE concentration was increased in one reported case.[13] Sweat gland atrophy with infiltration by lymphocytes and

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mast cells and IgG and C3 deposition in the basement membrane has been described.[13,14] Steroid therapy improved the ability of one of these patients to sweat. An immune-mediated basis for anhidrosis has not been studied in the horse. Basement membrane was noted to be thickened in skin biopsies from 10 anhidrotic horses.[7] However, inflammation (leukocyte infiltration) was noted in only one of six anhidrotic horses housed at ambient conditions.[7]

Expression of the water channel aquaporin-5 was decreased in sweat glands from anhidrotic horses compared with sweat glands from horses that sweated normally.[15] While these results may help explain why hypohidrotic or anhidrotic horses cannot produce as much sweat as normal horses, it is not clear whether loss of these water channels is a cause or a consequence of decreased sweat gland secretory capacity. A recent review provides additional detail on the physiology and pathophysiology of equine sweat gland function and dysfunction.[16]

Clinical Signs and Differential Diagnoses

Early clinical signs of hypohidrosis include exercise intolerance, particularly in warm humid weather, and tachypnea, initially during or after exercise, and then at rest as the severity of disease increases. Owners may initially suspect that their horse has a respiratory problem. As hypohidrosis worsens or the horse becomes anhidrotic, owners realize the horse is not sweating as much as would be expected for the level of work it is performing, or it is taking longer than normal to cool out after exercise. Areas of residual sweat production often include under the mane, in the axilla or inguinal areas, and under the saddle. Dilated vessels under the skin may be noted (Fig. 41.10). A few horses exhibit extrusion of salt crystals without accompanying water (Fig. 41.11). Body temperature can increase to dangerous levels if signs are not recognized and affected horses continue to work in hot weather. The hair coat often becomes dry and thin in chronically affected horses, particularly over the face (Fig. 41.12) and cannon bones.



FIG. 41.10 Horses that cannot cool by sweat production will often show dilated peripheral skin vessels.



FIG. 41.11 **Salt crystals secreted in response to exercise (lunge test) in an anhidrotic horse. Following a lunge test, this horse excreted the salt crystals shown here, without a fluid component to the sweat. The author has observed this in two horses diagnosed with anhidrosis.**



FIG. 41.12 Chronic anhidrosis often causes facial hair loss or thinning.

Clinical Pathology and Diagnostic Tests

Hypohidrosis or anhidrosis can be included in a differential diagnosis of exercise intolerance on the basis of history and clinical signs. The diagnosis can be confirmed by performing an intradermal sweat test.[6,17-20] Six serial 10-fold dilutions of an α_2-adrenergic agonist such as terbutaline (10^{-3} w/v to 10^{-8} w/v) are prepared. Each dilution (0.1 mL) is injected intradermally along the neck or pectoral region. In normal horses, a localized area of sweat will appear at the site of injection at all concentrations, except perhaps the most dilute concentration (10^{-8}). The amount of sweat produced at each site is proportional to the concentration of terbutaline injected (Fig. 41.13). Sweating will first be noted in normal horses within 5 minutes of injection at the higher concentrations. Onset of sweat production may be delayed and amount of sweat produced reduced in hypohidrotic horses, or hypohidrotic horses may only sweat at the higher concentrations of terbutaline. Anhidrotic horses do not sweat, even at the highest concentration.



FIG. 41.13 **Terbutaline intradermal sweat test. Six serial 10-fold dilutions of terbutaline are injected intradermally along the neck. Normal horses, such as the one shown here, will sweat at the injection site of all concentrations, except perhaps the most dilute (10^{-8} w/v). In the normal horse, sweating will typically begin within 5 minutes of injection. Reduction in the amount or delay in onset of sweating is diagnostic for hypohidrosis. A complete failure to sweat in response to all terbutaline concentrations is diagnostic for anhidrosis.**

While failure to sweat in response to intradermal terbutaline injection confirms a diagnosis of anhidrosis, horses that are hypohidrotic may continue to produce sweat, even at the lower concentrations. For these horses, a lunge test will help confirm the diagnosis. Body temperature, heart rate, and respiratory rate are recorded. The horse is then lunged at a trot for 30 minutes on a hot day. During this time, the horse is observed for evidence of sweat production. Body temperature, heart rate, and respiratory rate measurements are made immediately at the end of lunging and every 10 minutes thereafter for the next 30 minutes. While the heart rate response reflects the degree of fitness, the body temperature and respiratory rate responses correlate better to the horse's ability to cool itself. If the horse's respiratory rate is not back to what it was before the onset of lunging by 30 minutes after the end of the exercise, it is highly likely that the horse is having a problem cooling.

The most likely differential diagnoses for hypohidrosis include various respiratory diseases. In the author's experience, some hypohidrotic or anhidrotic horses also have mild airway inflammation, documented most often by increased mast cells or eosinophils in bronchoalveolar lavage fluid. It is unknown whether the two problems coexist coincidentally or if there is a mechanistic link. Either way, it is likely that airway inflammation would decrease the ability of a horse to use its respiratory system to help cool itself, and this is likely to be more critical

in a horse that cannot sweat.

Treatment, Prevention, and Prognosis

The only consistently successful treatment is movement of the horse to a cooler environment, although this is not always practical or feasible. Other environmental or dietary alterations may or may not be helpful. For hypohidrotic horses or horses that are having their first episode of anhidrosis, it is important to stop any workload and decrease the stress level. Concurrent disease conditions, such as airway inflammation, should be appropriately treated. Shade, fans, misting fans, and window air conditioners can be used to try to decrease the temperature in the horse's local environment. Applying water by hose or sponging the horse with water during the hot part of the day can take the place of sweat. Electrolyte supplementation (especially KCl) has been advocated,[18,19] and various products are available commercially that appear to help some, but not all, horses. One such supplement (One AC, MCPO, Phoenix, Ariz.) contains L-tyrosine, ascorbic acid, niacin, and cobalt and claims to improve sweat production by supplying precursors to dopamine synthesis. The theory is that dopamine improves skin vasodilation, resulting in increased blood flow to sweat glands during exercise. To the author's knowledge, there are no studies at present to support or deny this claim. Other treatments that have been used with mixed success include vitamin E administration,[21,22] acupuncture, and Chinese herbs.[18,19]

Medical therapy of anhidrosis has primarily been unrewarding. Anecdotally, the α_2-adrenergic agonist clenbuterol increases sweat production in hypohidrotic horses and may be useful if used sparingly, only when weather conditions are particularly bad (i.e., extremely high heat and humidity). However, traditional recommendations are to avoid use of α_2-adrenergic agonists in hypohidrotic horses because their use theoretically might precipitate complete anhidrosis.[23] In a recent study, oral clenbuterol administration was shown to lose its beneficial effect on airway reactivity after 21 days of administration, but prolonged clenbuterol administration had no effect on results of intradermal terbutaline sweat tests.[24] However, the horses used in that study were neither hypohydrotic nor anhidrotic. The effect of prolonged α_2-adrenergic agonist administration on sweating or response to intradermal sweat tests in anhidrotic horses has not been reported. There is increasing evidence in human medicine that combination treatment of chronic airway disease with both α_2-adrenergic agonists and

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corticosteroids results in a synergistic effect, with corticosteroids helping to prevent desensitization and tolerance to α_2-adrenergic agonists and α_2-adrenergic agonists potentiating the anti-inflammatory effects of the corticosteroids.[25,26] Thus, combination therapy may be useful in hypohidrotic horses, but to date no controlled studies have been performed. Corticosteroid therapy may also be useful if there is an immune component to the pathogenesis of anhidrosis.

Once a horse has had an episode of anhidrosis, certain measures can be taken to try to prevent recurrence of the problem in subsequent years. Before the hot part of the year begins, start the horse on any supplements that have been helpful previously and make certain the horse is cardiovascularly fit. Also, make sure that any respiratory problems are under control before the onset of hot weather. As the hot season approaches, try to avoid procedures that might require administration of heavy doses of α_2-adrenergic agonists (e.g., xylazine, detomidine) that stimulate the horse to sweat. Plan to do these procedures during the cooler parts of the year. During hot periods, work the horse only during the cool parts of the day. Use external water sources to cool the horse to decrease the need for the horse to sweat.

The prognosis for hypohidrotic horses is guarded for future athletic performance in a hot environment. It is the author's opinion that the longer an anhidrotic horse has been left untreated or unmanaged, the less likely the horse will be to sweat again despite any of the treatments described earlier. However, if an underlying disease or problem can be identified and treated successfully in a horse that is just becoming hypohidrotic, the likelihood that the horse will sweat better the following season is improved.

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Thyroid Gland

Babetta Breuhaus

Thyroid Gland Physiology

Thyroid gland physiology and control of thyroid hormone secretion in horses is similar to other species. Thyroid hormones are important for growth, maturation of organ systems, and regulation of metabolism. They stimulate protein synthesis and catabolism, increase body heat production, and stimulate basal metabolic rate. The thyroid gland concentrates iodides from the blood and synthesizes and secretes both thyroxine (T_4) and tri-iodothyronine (T_3). Once secreted, thyroid hormones circulate both bound to proteins and unbound ("free"), with the free fractions being the active fractions. T_3 is more metabolically active than T_4, and although some T_3 is secreted by the thyroid gland along with T_4, the main source of T_3 in the body is from conversion of T_4 to T_3 in peripheral tissues.

Thyroid hormone secretion is regulated by the hypothalamus and pituitary. Thyrotropin releasing hormone (TRH), made in the paraventricular nucleus and released from the median eminence of the hypothalamus, stimulates release of thyroid stimulating hormone (TSH) from the anterior pituitary, which circulates to the thyroid gland to stimulate release of thyroid hormones. Plasma thyroid hormones exert negative feedback on the hypothalamus and pituitary to limit further release of TRH and TSH. Neurotransmitters that play a role in thyroid hormone regulation include α-adrenergic agonists (stimulatory) and somatostatin and dopamine (inhibitory). Glucocorticoids and the cytokines TNF and IL-1β also inhibit TSH secretion.

As most recently reviewed,[1] alterations in thyroid hormone status that have been described in horses include thyroid gland neoplasia, hyperthyroidism, and hypothyroidism. Certain drugs, diets, and physiologic or pathophysiologic states can also influence circulating thyroid hormone concentrations.

Thyroid Gland Neoplasia

Thyroid gland neoplasias are not uncommon, and it is not unusual to find them as incidental findings during necropsy of older horses.[2,3] Thyroid adenomas are

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most common, but other reported thyroid neoplasias include carcinomas, adenocarcinomas, and C-cell tumors. Although there are also scattered case reports of hypothyroid or hyperthyroid horses due to a thyroid tumor, most thyroid gland tumors are benign and nonfunctional. The glands enlarge physically, but there is no metastasis and circulating thyroid hormone concentrations remain within normal limits. As such, treatment of most thyroid gland neoplasias is unnecessary, until or unless the glands become big enough to start to interfere with swallowing or breathing. Once a thyroid gland tumor becomes enlarged enough for the owner to notice it, a reasonable approach is to measure circulating thyroid hormones (both total and free concentrations of T_4 and T_3). Provided that circulating thyroid hormone concentrations are normal, and provided that the horse is comfortable and the tumor is not big enough to interfere with alimentary or respiratory function, surgical removal is not recommended. The size of the gland should be monitored. If the gland starts to enlarge rapidly or if circulating thyroid hormone concentrations increase, then expedient surgical excision is recommended. After thyroidectomy, the horse will need to be treated with thyroid hormone supplementation to maintain circulating concentrations of thyroid hormones within the normal range.

Hyperthyroidism in Adult Horses

Hyperthyroidism is extremely rare in horses. There are three documented case reports in the literature, and all of these have been associated with thyroid gland neoplasias.[4-6] Circulating thyroid hormone concentrations are also sometimes temporarily increased in horses exposed to excess iodine, such as in a topical blister. Clinical signs of hyperthyroidism in horses include weight loss, tachycardia, tachypnea, hyperactive behavior, ravenous appetite, and cachexia. Diagnosis is confirmed by measurement of increased circulating concentrations of thyroid hormones. A T_3 suppression test can also be performed. Treatment of a hyperactive thyroid tumor has generally been thyroidectomy. It is recommended that biopsy and nuclear scintigraphy be performed before thyroidectomy to determine if both right and left sides of the thyroid gland are hyperplastic or neoplastic. If so, removal of only one side may obviate the need for postoperative thyroid hormone supplementation. It is also possible for one side of the gland to be hyperactive while the other side is normal or suppressed. In this situation, nuclear scintigraphy is important to identify which side of the gland needs to be removed. In one case report, a hyperthyroid horse was treated

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successfully with oral propylthiouracil.[6] The horse responded rapidly to treatment that was initiated at 8 mg/kg once daily and then maintained at the same dose every other day.

Hypothyroidism in Adult Horses

Hypothyroidism in the horse has been poorly understood in the past, but most now agree that primary hypothyroidism is rare. Although autoimmune thyroid disease is somewhat common in people and dogs, it has only been described in one report of histologic changes found at necropsy in a group of horses in Eastern Europe.[7] The prevalence of true hypothyroidism in adult horses is unknown but is almost certainly overestimated. Hypothyroidism has been thought to contribute to a variety of problems in the horse, including obesity, laminitis, anhidrosis, recurrent rhabdomyolysis, and poor fertility. However, documentation of hypothyroidism in such cases for the most part does not exist. Anecdotal reports of beneficial effects of thyroid hormone supplementation in these horses are also largely unsubstantiated. Despite this, many horses with these conditions receive thyroid hormone medication over extended periods of time, and many—if not all—of them do not need it. Besides the obvious waste of money, potential health risks associated with unnecessary thyroid hormone supplementation have only been minimally explored in horses.[8] In humans, thyrotoxicosis or oversupplementation with levothyroxine can result in decreased bone density, increased risk of atrial fibrillation, and possible increased risk of myocardial infarction or precipitation of congestive heart failure.[9]

Clinical signs of hypothyroidism in adult horses appear to be subtle. Traditionally, horses that gained weight easily, had cresty necks, and tended to suffer from recurrent bouts of laminitis were thought to be hypothyroid. However, in the author's experience, thyroid function tests in horses that fit this description are typically normal and it is more likely that these horses either have PPID or equine metabolic syndrome. In the few published case reports of horses that were documented to be hypothyroid based on abnormal thyroid function testing, clinical signs were primarily lethargy, exercise intolerance, and poor hair coat quality.[10-12] In experiments in which horses were made hypothyroid, either by surgical removal of the thyroid glands or by administration of antithyroid drugs,[13-25] obesity and laminitis were not reported.

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Although resting heart rate, cardiac output, respiratory rate, and rectal temperature decreased in horses after thyroidectomy,[17] and serum concentrations of triglycerides, cholesterol, and very low-density lipoproteins increased,[16] the changes were mild and absolute values remained within the normal reference interval for adult horses. For this reason, measurement of these parameters would not help identify a hypothyroid horse in the general population.

Other Alterations of Thyroid Function

Certain physiologic states, drugs, diets, and pathologic states can alter thyroid hormone synthesis, metabolism, or binding, resulting in altered serum concentrations of thyroid hormones. For example, fasting lowers circulating concentrations of thyroid hormones in many species studied, including the horse.[26] Phenylbutazone or dexamethasone administration, strenuous exercise, and diets high in energy, protein, zinc, and copper have also been shown to alter circulating concentrations of thyroid hormones in horses.[27-35]

Nonthyroidal Illness Syndrome

Nonthyroidal illness syndrome is well described in humans, dogs, and cats suffering from systemic illnesses. In humans, milder forms of illness result in decreases in serum concentrations of T_3, with T_4 remaining within the normal range or only slightly decreased. As nonthyroidal illness becomes more severe, total T_4 decreases and eventually free T_4 also begins to decrease. The magnitude of thyroid hormone suppression has been correlated to severity of disease and mortality.[36-38] Mechanisms by which thyroid hormones decrease during illness include decreased peripheral conversion of T_4 to T_3 by 5'-deiodinase, altered binding to serum carrier proteins, and hypothalamic-pituitary dysregulation or suppression.[38-42] Recent reports in adult horses and foals suggest that nonthyroidal illness syndrome is similar in horses compared with other species.[43-48] In adult horses, thyroid hormone concentrations are negatively correlated with severity of disease and TSH is not appropriately increased.[47] Total and free T3 decrease with mild disease, with total and free T4 remaining in the normal range. However, as severity of disease increases, T3 is further suppressed and T4 also begins to decrease, with some severely ill horses having virtually no measurable circulating thyroid hormones. Thus, true thyroid gland

status cannot be accurately determined in ill horses. It appears that free T4 by dialysis is least affected by illness and therefore would be the best choice if evaluation of thyroid function could not wait until an ill animal was healthy again.

Thyroid hormone concentrations, particularly T3, have also been found to be lower in sick and septic foals compared with healthy foals.[44-46,48] Thyroid hormone concentrations were inversely correlated to sepsis score,[44] and nonsurviving foals had lower concentrations of thyroid hormones compared with surviving foals.[44,48]

Fescue Ingestion

Tall fescue *(Festuca arundinaceae)* is a perennial grass that is grown commonly in the southeast because it is relatively easy to establish, has a long growing season, and has good disease and drought resistance that allow it to survive hot, humid summers. A variety of reproductive problems have been described in mares consuming fescue, and these have been shown to be caused by alkaloids produced by an endophytic fungus *(Neotyphodium coenophialum)* that lives symbiotically on the fescue plant and acts as a dopamine agonist.[49] Since TSH release from the pituitary is inhibited by dopamine,[50] it has been suggested that fescue consumption could lead to secondary hypothyroidism. Fescue ingestion was proposed as the cause of lower serum TSH concentrations in mares and foals consuming endophyte-infected fescue on a farm in central Kentucky, compared with mares and foals on a nearby farm grazing pastures that were mainly free of endophyte-infected fescue.[51] However, the author found no differences in baseline concentrations of thyroid hormones or TSH or in their responses to administration of TRH, in adult, nonpregnant horses fed endophyte-infected fescue seed for 2 months.[52] It appears that dopamine acts more as an acute modulator of TSH secretion, rather than as the primary control. In humans, while acute dopamine blockade results in increased TSH secretion and increased circulating thyroid hormones, chronic administration does not cause long-term alterations in thyroid hormone status.[50] Thus, it is likely that compensatory mechanisms override any dopaminergic effect of chronic fescue ingestion on the thyroid axis in the horse.

Syndromes Purportedly Associated With

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Hypothyroidism

Obesity

As mentioned earlier, horses that gain weight easily and have a tendency to deposit fat in the crest of the neck, over the rump and tailhead, or in the sheath have long been regarded as hypothyroid. It is now known that these horses most likely have insulin dysregulation and EMS and have normal thyroid function. Anecdotally, thyroid hormone administration to these horses usually has not resulted in substantial weight loss, especially if feed consumption is not restricted and the amount of thyroid hormone supplementation is titrated to maintain serum thyroid hormone concentrations in the normal range. However, administration of levothyroxine at a dose of approximately 0.1 mg/kg/day (48 mg) long term was associated with weight loss and increased insulin sensitivity in six healthy, euthyroid mares, despite the fact that they had access to pasture and a round bale of hay during the day and were given hay at night when they were stalled.[8,53] Although serum total T_4 concentrations increased four to five times their presupplementation concentrations, no adverse health effects were observed. Thus, when used to help obese horses lose weight, the amount of thyroid hormone given needs to be enough to make the horse mildly hyperthyroid. It is preferable for feed intake to be controlled at 1.5% to 2% of the desired body weight per day, consisting of grass hay or other feed that is low in soluble carbohydrates. It is important to understand that when thyroid hormones are administered in this manner, they are being used as a pharmacologic tool and should only be given for a short period of time; lifelong administration is not indicated.

Laminitis

A role for decreased thyroid function in the pathogenesis of laminitis was proposed but is poorly documented and remains a controversial topic. While decreased serum thyroid hormones have been associated with some horses that experience acute laminitis, it is extremely unlikely that hypothyroidism alone causes laminitis. In 13 studies in which hypothyroidism was induced by either surgical removal of the thyroid glands or administration of propylthiouracil, laminitis did not occur.[13-25] Thus, any alterations in serum thyroid hormone concentrations in horses experiencing laminitis are likely caused by factors associated with the episode of laminitis, rather than the underlying cause of

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laminitis. Such factors could include drugs used to treat laminitis (e.g., phenylbutazone), development of nonthyroidal illness syndrome, or a direct effect of factors such as endotoxin or one of the inflammatory cytokines that contribute to the onset of laminitis in some cases. In the author's experience, TRH stimulation tests performed in horses that have suffered an episode of laminitis or that have had bouts of recurrent laminitis show normal thyroid hormone responses when these tests are performed once the horse is stabilized and has been off all medications for 4 weeks.

Despite evidence of normal thyroid function in horses with laminitis, some veterinary clinicians still believe that treatment of horses with iodinated casein during an acute episode of laminitis results in improvement. These horses often are treated without prior measurement of thyroid hormones. Some are treated even when measurement shows serum thyroid hormone concentrations to be within the normal range. These horses are then often kept on thyroid hormone supplementation indefinitely. To date, no controlled studies have been performed to determine whether or not administration of thyroid hormones during acute episodes of laminitis is beneficial. However, since the action of α-adrenergic agonists on vasculature is usually vasodilatory, it is possible that thyroid hormone administration increases circulation to the foot by its ability to potentiate α-adrenergic receptor numbers and sensitivity.[54-56] Or it is also possible that thyroid hormone supplementation alters carbohydrate and fat metabolism in a way that increases insulin sensitivity.[57] Thus, any potential beneficial effect of thyroid hormone administration in horses suffering from laminitis may be pharmacologic rather than physiologic.

Anhidrosis

Anhidrosis is a condition of adult horses characterized by a decreased ability or inability to sweat in response to appropriate stimuli. The cause is unknown. Hypothyroidism has long been associated with anhidrosis, perhaps because treatment with iodinated casein was reported to help increase sweat production in anhidrotic horses in the 1950s.[58] However, the author found that baseline concentrations of thyroid hormones and TSH were normal in horses with anhidrosis.[59] Thyroid hormone responses to TRH were also normal, but TSH responses to TRH were significantly greater in anhidrotic horses than they were in horses with normal sweat production. The clinical significance of this greater TSH response to TRH in anhidrotic horses is unknown. Because equine sweat

glands are stimulated to secrete by activation of α_2-adrenergic receptors and thyroid hormones modulate adrenergic receptor function, perhaps making horses mildly hyperthyroid restores α-adrenergic receptor numbers or sensitivity or potentiates sweat responses to whatever neural stimulation remains.

Rhabdomyolysis

A link between hypothyroidism and rhabdomyolysis was suggested by a report of muscle stiffness, poor performance, and rhabdomyolysis in 4 Thoroughbred and 2 Standardbred racehorses that had low baseline T_4 concentrations.[60] The horses improved after administration of iodinated casein. However, T_4 response to TSH was normal in these horses. A subsequent study showed normal resting concentrations of T_4 but decreased T_4 response to TRH in five horses that had suffered previous episodes of rhabdomyolysis.[61] In a study of 18 Quarter Horses with polysaccharide storage myopathy and 18 Thoroughbreds with recurrent exertional rhabdomyolysis, circulating concentrations of T_4 and T_3 were within normal range. Stimulation tests were not performed.[62] Thus, a role for hypothyroidism in the pathophysiology of equine rhabdomyolysis is unclear. Because it is now known that the clinical syndrome of rhabdomyolysis is caused by more than one underlying pathophysiologic etiology, it is possible that hypothyroidism might contribute to some, but not all, cases of equine rhabdomyolysis. If hypothyroidism is suspected, thyroid function should be assessed, ideally by measuring both resting concentrations of free thyroid hormones, as well as by response to TRH or TSH. If resting concentrations of free thyroid hormones are found to be low, nonthyroidal illness syndrome due to other factors should be ruled out before thyroid hormone supplementation is prescribed.

Infertility in Mares

Thyroid hormone administration to broodmares to theoretically improve fertility has been a fairly common practice. This occurs despite a lack of evidence that the mares were actually hypothyroid in the first place or that thyroid hormone supplementation improves equine fertility. This practice presumably is an extrapolation from human medicine, where hypothyroidism in women adversely affects fertility. However, two of three fillies that had undergone thyroidectomy became pregnant without thyroid hormone supplementation,[13] and two

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additional studies including hundreds of horses failed to show an association between thyroid hormone status and conception rates in mares.[63,64] The first study[63] was performed in 329 clinically normal broodmares.[63] Resting serum T_4 concentrations were below the reference interval in 12% of the mares, within the reference interval in 86%, and increased in 6% of the mares. There was no association between serum T_4 concentration and whether or not the mare was pregnant 15 to 16 days after ovulation. There also was no association between whether or not the mare was receiving thyroid hormone supplementation (60 were, 269 were not) and pregnancy status. In the second study,[64] resting serum concentrations of total T_4 and T_3, as well as their responses to TRH, were measured in 79 Thoroughbred and Standardbred broodmares. Resting and stimulated thyroid hormone concentrations were not different between mares that did and did not become pregnant.

Although the studies referenced earlier suggest there is no association between thyroid status and fertility or infertility in the mare, hypothyroidism might contribute to infertility in a small subset of mares as in women. However, given that true hypothyroidism appears to be rare in the horse, this would have to be a small number of mares, certainly not the number of mares that are currently being routinely supplemented with thyroid hormone. Is there any basis then to the clinical impression held by some that thyroid hormone supplementation helps some mares get pregnant? Perhaps if there is, it is more related to obesity, insulin resistance, and equine metabolic syndrome than to hypothyroidism. Women with insulin resistance and metabolic syndrome are subfertile, and there is evidence that thyroid hormone administration to normal weight mares increases insulin sensitivity.[53,57] Thus, it is possible that some insulin-resistant, overweight mares are subfertile, and thyroid hormone supplementation is beneficial in those cases, not because they were hypothyroid in the first place but because it improves their insulin sensitivity. At the time of this writing, no studies have been performed to examine this hypothesis.

Assessment of Thyroid Function in Adult Horses

Thyroid glands of the horse can be assessed by measuring circulating concentrations of thyroid hormones, measuring response to stimulants such as TRH or TSH, testing the ability of administration of exogenous thyroid hormone to suppress endogenous hormone, imaging (including ultrasound, computed

tomography, magnetic resonance imaging, and nuclear scintigraphy), and biopsy.

Reference ranges for thyroid hormone concentrations in healthy adult horses and neonatal foals have been published.[1] Donkeys appear to have higher circulating thyroid hormone concentrations than do horses.[65] Because certain drugs and pathophysiologic states can lower serum concentrations of thyroid hormones in otherwise euthyroid horses, it is important that thyroid hormone measurement or function tests not be performed while horses are ill, are receiving other drugs, or are on thyroid hormone supplementation. The author recommends that thyroid hormone testing be performed in horses that have not received any medications for at least 2, and preferably 4, weeks before testing. If a horse has been receiving thyroid hormone supplementation without prior documentation of hypothyroidism, the author recommends weaning the horse off supplementation and then testing thyroid function once the horse has not received any supplementation for at least 4 weeks.

Tests that are currently available for assessment of thyroid function in the horse include measurement of total and free fractions of T_4 and T_3 and response of these hormones to administration of either TRH or TSH.[27-29,61,66-69] Although results of TRH or TSH stimulation tests are thought to provide a better indication of thyroid status than single point-in-time measurements of thyroid hormone concentrations, they can be more difficult to perform in a field setting.

To perform a stimulation test, a control blood sample is obtained, TRH (1 mg to the average 450- to 500-kg horse) or TSH (5 IU) is given intravenously, and subsequent blood samples are obtained. Most references say that T_3 should double at 2 hours, and T_4 should double at 4 hours. The author routinely performs TRH stimulation tests and prefers to measure both T_3 and T_4 before and 1, 2, and 4 hours post TRH administration in order to make sure the peaks are not missed. In 36 normal horses that participated in various studies conducted by the author, the mean increase in total T_4 was 2.2 times baseline at 4 hours. However, the range was 1.3 to 3.8 times baseline. Increases in free T_4 and free T_4 by dialysis (mean and range) were 1.7 (1.1 to 2.1) times and 1.8 (1.1 to 2.8) times at 4 hours, respectively. Increases in total and free T_3 (mean and range) were 3 (1.1 to 10.3) times and 4.2 (1 to 53) times at 2 hours, respectively. These seemingly lower thyroid hormone responses to TRH injection are in agreement with findings in a recent report of levothyroxine administration to normal horses.[70] Closer examination of data from the author's horses revealed

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that, in general, the few individuals with small increases in T_4 or T_3 either started with higher resting values or had peaks that occurred later (T_4) or earlier (T_3) than 4 or 2 hours. Individuals with lower T_4 responses in general were not the same individuals with lower T_3 responses. Thus, one must be careful when interpreting results of a TRH stimulation test. Failure of T_3 to double by 2 hours or T_4 to double by 4 hours after TRH injection does not necessarily mean that the horse is hypothyroid. Animals with high responses tended to be animals with very low resting thyroid hormone concentrations.

If single point-in-time measurement of thyroid hormones is the only option available for evaluation of thyroid status, measurement of free fractions of thyroid hormones (alone or in conjunction with measurement of total amounts of hormone) provides more useful information than measurement of total amounts of thyroid hormones alone. Measurement of serum TSH concentrations in single samples also likely will aid diagnosis of thyroid status, though a well-validated methodology for this test in horses is not commercially available.

During illness in humans, measurement of serum free T_4 by direct methods often underestimates values, when compared with measurements of free T_4 after dialysis or ultrafiltration.[71-75] This also appears to be the case in dogs[76] and horses.[43] Thus, serum concentrations of free T_4 measured by equilibrium dialysis are more likely to reflect true thyroid status in ill horses, compared with other methods of free T_4 measurement. Measurement of fT_4D instead of fT_4 may help prevent equine clinicians from misdiagnosing ill horses as being hypothyroid.

A T_3 suppression test has been described[5,6] and may be useful to confirm hyperthyroidism. A blood sample is obtained before intramuscular administration of 2.5 mg 3,5,3′-triiodothyro-L-thyronine (T_3) diluted in 5 mL sterile saline, given twice daily for 7 doses (4 days). Additional blood samples are drawn 5 minutes before each dose of T_3 and then twice daily on days 5 and 7 and in the morning of day 10. In normal horses, T_4 and T_3 measurements will be within reference range in the control blood sample. Administration of exogenous T_3 should result in a 10- to 20-fold increase in T_3 concentration, while T_4 gradually decreases, remaining suppressed for at least 5 days after the last dose of T_3. In hyperthyroid horses, control blood samples will have increased concentrations of T_4 and T_3. The increase in serum T_3 after T_3 administration is not as pronounced as in normal horses, but T_3 does remain increased throughout

the administration period. T_4 does not suppress.

Ultrasound imaging is most helpful when thyroid glands are enlarged. Ultrasound imaging can differentiate enlargement due to solid tissue versus cystic fluid. It is also useful as an aid in getting a representative biopsy sample if thyroid neoplasia is suspected. Nuclear scintigraphy is useful to demonstrate gland activity, which may or may not be equal in the right and left lobes.

Treatment of Hypothyroidism in Adult Horses

Management of horses that have been properly diagnosed as being hypothyroid or horses that have undergone thyroidectomy theoretically should be fairly straightforward. Serum thyroid hormone concentrations should be monitored, and dosages of thyroid hormone supplementation adjusted to maintain serum thyroid hormones in the normal range. This is not necessarily as simple as it sounds. T_4 is the most common form of thyroid hormone supplementation, and while T_4 administration increases serum concentrations of T_4, serum concentrations of T_3 may not change or may actually decrease if T_3 is not also given or if the horse is not truly hypothyroid. In addition, T_4 dosage recommendations have been made on the basis of thyroid hormone concentrations obtained after thyroid administration to normal horses with intact thyroid glands[77] (Chen 1984). Thyroid hormone pharmacokinetics may be different in truly hypothyroid horses; pharmacokinetic studies in horses made hypothyroid by thyroidectomy or by administration of antithyroid drugs would be useful. Until such studies are performed, the following recommendations can be made. T_4 is available in several forms. Iodinated casein contains approximately 1% T_4 and is given at 5 to 15 g/horse/day PO[13] (Lowe 1974). The recommended starting dose of levothyroxine was 20 µg/kg horse/day PO,[77,78] but a more recent study suggested that doses as high as 50 to 100 µg/kg/day are well tolerated and may be necessary.[70] If a sensitive TSH assay becomes commercially available, dosages should be adjusted to normalize TSH.

Thyroid Function in Normal Neonatal Foals

Fetal concentrations of T_3 are low.[79] In many species, fetal serum thyroid hormones increase just before birth and probably play a role in the rapid growth and organ system development that occur in late gestation. Normal neonatal

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foals have serum concentrations of thyroid hormones that are approximately 10 times adult concentrations.[48,80,81] Thyroid hormones remain high during the first week of life and then slowly decline, reaching normal adult concentrations by approximately 1 month of age. These high concentrations of thyroid hormones are thought to be important in thermoregulation, regulation of cell differentiation, and maturation of many body systems, especially the respiratory, nervous, and musculoskeletal systems. Thyroid hormones increase thermogenesis by increasing metabolic rate and, of particular relevance to the neonate, increasing heat production from brown fat.[82] Thyroid hormones also stimulate lung development and surfactant production, and these effects are potentiated by concurrent administration of glucocorticoids.[83] Skeletal growth and maturation are stimulated synergistically by thyroid hormones and growth hormone.[84] The mechanism(s) by which thyroid hormones are increased in the peripartum period is (are) unknown. One might expect the increase to be centrally driven. However, in a study by the author,[48] serum TSH concentrations were not increased in equine neonates, compared with adults, nor did they change over the first month of life, while serum thyroid hormone concentrations were declining.

Thyroid Function in Premature Foals

Premature human infants experience transient hypothyroxinemia, with serum T_4 concentrations correlated to gestational age.[85-88] In a study by the author, serum concentrations of total and free thyroid hormones and TSH, both at rest and in response to TRH, were measured in normal, healthy neonatal foals that were full term (normal foals), in hospitalized premature neonatal foals (premature foals), and in full-term neonatal foals that were ill and hospitalized for conditions similar to premature foals (sick foals) to determine the possible contributions of an immature hypothalamic-pituitary axis and nonthyroidal illness to thyroid dysfunction in premature foals.[48] Normal foals did not receive any medications. Both sick and premature foals received medications routinely used to treat conditions including (but not limited to) failure of passive transfer, sepsis, and perinatal asphyxia syndrome. Premature foals had significantly lower serum concentrations of total and free fractions of thyroid hormones than normal foals. Baseline serum concentrations of TSH were not different, but TSH responses to TRH were exaggerated in premature foals compared with normal foals. Serum

concentrations of total and free T_3 and TSH were similar in sick term foals and sick premature foals, suggesting that both of these groups of foals were experiencing nonthyroidal illness syndrome, primarily a low T_3 state. However, premature sick foals also had significantly lower total and free T4 concentrations compared with age-matched full-term sick foals, suggesting that premature foals also experience hypothyroxinemia, similar to infants. More profound alterations in thyroid function in premature foals, compared with sick term foals, may be caused by an immature hypothalamic-pituitary-thyroid axis. It remains to be seen whether early thyroid hormone supplementation in premature foals might improve short-term survivability and preserve long-term athletic function. Traditional thought has been that administration of thyroid hormones to patients with nonthyroidal illness syndrome is not beneficial and might even be detrimental. However, these beliefs have been challenged,[38,39] and the issue remains controversial. While results are variable, treatment of premature human infants with T_4 has resulted in improved IQ and neurologic development at 2 years of age[85,86] and may reduce the incidence of cerebral palsy in extremely preterm infants.[89] T_3 administration to human neonates with severe respiratory distress syndrome improved survival.[90] However, in a recent study, levothyroxine administration to premature infants was associated with development of late-onset refractory hypotension.[91] By increasing metabolism, levothyroxine therapy may lead to acute adrenal insufficiency.[92]

Congenital Hypothyroidism in Foals

Two syndromes of congenital hypothyroidism have been described in foals. Hypothyroid foals with visible goiters have been produced by mares ingesting either too much or too little iodine or by mares ingesting goitrogenic plants.[93-95] These foals are born weak, with poor sucking and righting reflexes, hypothermia, and developmental abnormalities of the musculoskeletal system, including tendon contracture or rupture and delayed bone development, particularly of the small cuboidal bones of the carpus and tarsus. Thyroid hormone supplementation to more severely affected foals may improve survivability, but dosage recommendations are scarce. Irvine recommends basing the dose on secretion rate.[84] For oral administration of T_4, this would equal 10 × 0.22 × kg bwt × 0.08 × plasma T_4 (μg/L), or approximately 2.5 mg/day PO for a

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1- to 3-day-old 50-kg foal. Because there is a time delay for T_4 to act and T_3 is more active than T_4, T_3 supplementation at one-third the calculated T_4 dose may provide more benefit initially.

A second syndrome of congenital hypothyroidism has been described in foals, primarily in the western parts of the United States and Canada.[96-100] This syndrome is characterized by thyroid gland hyperplasia, increased gestational length, and musculoskeletal abnormalities, including mandibular prognathia, flexural limb deformities of the front legs, ruptured digital extensor tendons, and incomplete ossification of the carpal and tarsal bones. Despite the prolonged gestation, other indicators of prematurity may be present, such as a silky hair coat. At the time of birth, baseline serum concentrations of T_4 and T_3 are usually within the normal neonatal ranges, but the response to TSH administration is decreased.[101] The cause is unknown but suspected to be a dietary deficiency or toxicity of the mare during gestation. Likely candidates include nitrate toxicity, iodine and/or selenium deficiency, or goitrogenic plant ingestion by the mare.[99,101] Because thyroid hormone concentrations are normal at the time of birth, thyroid hormone supplementation is usually not administered. Supportive care to try to prevent collapse of the carpal and tarsal bones is recommended.

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Equine Metabolic Syndrome

Nicholas Frank

Definitions

Equine metabolic syndrome (EMS) is a collection of risk factors for endocrinopathic laminitis, and the term *syndrome* is used because multiple factors contribute to the risk of laminitis developing in an individual horse, pony, or donkey.[1] Risk factors include ID, which is the central endocrine disorder of EMS, as well as increased adiposity, hypertriglyceridemia, altered adipokine production, and cardiovascular abnormalities. The term *insulin dysregulation* encompasses the different glucose and insulin alterations observed in affected horses, including fasting hyperinsulinemia, postprandial/postsugar hyperinsulinemia, and tissue insulin resistance (IR).[2] It is likely that EMS has a genetic basis because the syndrome has a higher prevalence in certain breeds of horse or bloodlines. For example, Andalusians, Arabians, Morgan horses, Paso Finos, ponies, and warmbloods are more likely to be affected by EMS than Standardbreds and Thoroughbreds.

If EMS susceptibility is determined by genetics, then it is essential that we identify and manage modifying factors that exacerbate the condition. Although most horses with EMS are overweight, a lean phenotype is also identified and these patients may present with the primary complaint of laminitis. It is conceivable that we will identify multiple forms of EMS in the future in the same way that researchers have recently defined different types of diabetes mellitus in humans.[3] The EMS phenotype typically develops when genetically predisposed animals encounter environmental factors that promote obesity and exacerbate ID.

It is important to distinguish EMS from pituitary pars intermedia dysfunction (PPID) yet recognize that both disorders can occur concurrently and influence one another. These disorders are compared in Table 41.1.

TABLE 41.1

Comparison of Equine Metabolic Syndrome and Pituitary Pars Intermedia Dysfunction

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Equine Metabolic Syndrome (EMS)	Pituitary Pars Intermedia Dysfunction (PPID)
Clinical Presentation	**Clinical Presentation**
Any mature horse Obesity and regional adiposity; prominent fat pads along the crest of the neck, above the tailhead, or in the prepuce/mammary gland; animals often described by owners as *easy keepers* A lean EMS phenotype is also recognized with regional adiposity Some affected horses appear normal but have excessive insulin responses to oral sugars Infertility or abnormal cyclicity in mares Subclinical or clinical laminitis; acute episodes occurring after exposure to pasture or feed with high sugar content Excessive insulin responses to oral sugars Commonly accompanied by insulin resistance	Begin evaluating horses at 10 years of age **Early PPID:** Subtle regional hypertrichosis and/or delayed shedding for a few weeks; duller, coarser hair coat Reduced muscle mass, shift in metabolism, poor performance **Advanced PPID:** Generalized hypertrichosis (hirsutism) Weight loss and skeletal muscle atrophy; rounded abdomen More pronounced fat deposits along the neck crest and in front of the tailhead in some cases Recurrent or chronic infections such as sinusitis, skin infection, dental disease, or hoof abscesses Reproductive abnormalities including infertility and persistent lactation Chronic laminitis in some cases
Pathophysiology	**Pathophysiology**
Not fully established Current theories focus on a genetic predisposition to insulin dysregulation; affected horses have excessive insulin responses to oral sugars Hyperinsulinemia might promote increased adiposity Obesity, lack of exercise, and PPID are modifying factors and lower insulin sensitivity, with insulin resistance exacerbating hyperinsulinemia Laminitis results from persistent hyperinsulinemia	Loss of dopaminergic inhibition leads to hyperplasia and hypertrophy within pituitary pars intermedia Excessive proopiomelanocortin (POMC) production with resulting increased α-melanocyte-stimulating hormone, adrenocorticotropin hormone, corticotropin-like intermediate peptide, and β-endorphin production
Management Goals	**Management Goals**
To reduce glucose and insulin responses to oral sugars by limiting the sugar content of the diet Limit access to pasture To induce weight loss if obese by restricting caloric intake To improve insulin sensitivity through weight loss and exercise Appropriate farrier care	Improvement in clinical signs and hormone concentrations through pergolide treatment Provision of supportive care including body clipping, appropriate farrier care, dentistry, and nutrition

Etiology

Genetics play a role in EMS development, and research studies provide evidence of breed differences in ID susceptibility. Jeffcott and colleagues[4] detected differences in glucose tolerance and insulin sensitivity between ponies and Standardbred horses, with fat and laminitic ponies having lower responses to exogenous insulin (and therefore lower insulin sensitivity) than Standardbreds.

Standardbred horses, mixed-breed ponies, and Andalusian cross horses also show differences in postprandial insulin responses to meals, providing further evidence of breed-related variability in glucose and insulin dynamics.[5] A more detailed examination of genetics was performed in Arabian horses using genome-wide association, and an EMS locus was identified.[6] Evidence has also been presented to suggest that EMS susceptibility follows familial lines in ponies associated with dominant expression of one or more genes with incomplete penetrance because of environmental or epigenetic factors.[7]

Environmental factors, including diet and exercise, play important roles in the development of obesity and the EMS phenotype. Feeding grain to a susceptible animal is enough to induce obesity, and the grass consumed on pasture represents a significant source of calories that contributes to weight gain. Carbohydrate intake on pasture is influenced by grazing time, the area available for grazing, and the nonstructural carbohydrate (NSC) content of pasture grasses. NSC content varies by geographic location, climate, soil quality, and season. EMS affects adult horses, and there is no reported sex predilection. Age impacts insulin metabolism in horses, as it does in other species.[8,9]

Clinical Signs and Differential Diagnoses

The medical history may provide clues that the horse is affected by EMS because genetically predisposed animals readily gain body mass and are sometimes referred to as “easy keepers” or “good doers” by their owners. Most horses, ponies, and donkeys with EMS are obese, and a thicker than normal neck crest is noted on physical examination. This form of regional adiposity is associated with ID in affected horses, and the cresty neck score can be applied to more objectively measure the amount of fat in this region.[10] Over time, regional adiposity develops in other locations such as the tail head, prepuce, or mammary glands. Many horses with EMS suffer from generalized obesity and have body condition scores of 7 or greater on a 1 (poor) to 9 (extremely fat) scale.[11] A mare suffering from EMS is shown in Fig. 41.14. Laminitis may have started to develop without the owner noticing. Horses should be turned in tight circles to detect lameness. Divergent growth rings (“founder lines”) or widening of the white line may be detected when the hooves are examined closely, and these signs provide evidence of subclinical laminitis.[12,13] Radiographs are recommended as part of the initial examination, and radiographic evidence of third phalanx displacement may be detected, even when lameness has not been

reported.



FIG. 41.14 Photograph of a 7-year-old Morgan horse crossbred mare that suffers from equine metabolic syndrome.

Clinical Pathology

Hypertriglyceridemia and mildly increased plasma gamma glutamyl transferase (GGT) activities are detected in some horses, ponies, and donkeys with EMS, but complete blood count and other plasma biochemical analysis results are normal. Hyperglycemia is occasionally detected in affected horses and it is appropriate to use the term *diabetes mellitus* when this problem persists and becomes a chronic condition. Hyperglycemia and hypertriglyceridemia are more likely to occur when horses with ID are challenged by systemic disease and hospitalization, and this is sometimes referred to as *metabolic decompensation*. Older horses with concurrent ID and PPID are susceptible to this problem, and insulin therapy may be required to control hyperglycemia and glucosuria.[14]

Low resting total triiodothyronine (tT_3) or total thyroxine (tT_4) concentrations are detected in some horses with EMS, but the significance of this finding has been overstated in the past. It is a common misconception that obese horses suffer from hypothyroidism because obesity is associated with hypothyroidism in dogs and humans. However, most animals have normal TRH stimulation test results, and low tT_3 and tT_4 concentrations, if present, should be attributed to extrathyroidal changes in thyroid hormone metabolism or low thyroid-

stimulating hormone (TSH) concentrations. Phenylbutazone is an extrathyroidal factor that significantly lowers serum tT_4 concentrations in horses because of protein binding, and this drug is commonly used to treat laminitis.[15]

Thyroid-stimulating hormone concentrations vary as the body adapts to different metabolic states, and this might also explain why low thyroid hormone concentrations are sometimes detected in horses with EMS. This is referred to as *secondary hypothyroidism* and can be confirmed by documenting low TSH concentrations. Unfortunately, diagnostic laboratories do not measure equine TSH at present, so it is difficult to confirm the diagnosis of secondary hypothyroidism. Levothyroxine supplementation is controversial in these cases, and in the author's opinion, levothyroxine supplementation should be reserved for horses with persistently low free thyroxine concentrations and abnormal TRH stimulation test results. Levothyroxine can also be administered at higher dosages for 3 to 6 months to accelerate weight loss, and that protocol is described later.

Diagnostic Testing

Measures of adiposity should be performed, including body condition score, cresty neck score, and ultrasound measurements of abdominal or subcutaneous fat depth.[16] Diagnostic testing for ID is required for all patients in high-risk breed groups, and the Equine Endocrinology Group provides current recommendations for diagnosing and managing EMS on their website (https://sites.tufts.edu/equineendogroup/). Horses are screened for ID by measuring basal (or resting) insulin concentrations under fed conditions or by performing an oral sugar test (OST).[17] The assay used to measure plasma or serum insulin concentrations should be considered before either test is performed, and a diagnostic laboratory with experience handling equine samples should be selected. Insulin concentrations have been measured by radioimmunoassay for the majority of publications on EMS, including the 2010 American College of Veterinary Internal Medicine consensus statement,[1] but some diagnostic laboratories are now using chemiluminescent or enzyme-linked immunosorbent assays to measure insulin. The reference intervals provided as follows are for insulin concentrations measured by radioimmunoassay, and adjustments must be made if other insulin assays are used.

Some clinicians prefer to screen horses by measuring basal insulin concentrations before performing an OST because of owner concerns (not

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supported by evidence) about inducing laminitis with a stimulation test. If this approach is followed, detection of high insulin concentrations confirms the diagnosis of ID, but horses with normal results must undergo dynamic testing before normal insulin status can be assumed. Insulin concentrations were previously measured under fasting conditions because this is the approach taken in human medicine,[1] but this recommendation has changed and blood samples should be collected when horses are consuming hay or grazing on pasture. Grain should be withheld for 6 hours before blood collection. When measuring basal (fed) insulin concentrations, an insulin concentration greater than 50 µIU/mL provides strong evidence of ID, concentrations in the 20 to 50 µIU/mL range provide weak evidence, and there is no evidence of ID if the insulin concentration is less than 20 µIU/mL. Note that some laboratories provide insulin concentrations in pmol/L, and an approximate conversion factor of 7 is used to convert units from µIU/mL to pmol/L.

The OST is performed by fasting the horse for a minimum of 4 hours and preferably 6 hours in order to minimize the impact of gastric emptying on test results.[18] When the OST is to be performed in the morning (8:00 and 9:00 a.m.), the horse should receive one flake of hay between 10:00 p.m. and 12:00 a.m. the night before, and then all feed should be withheld until after the test is completed. Water should also be withheld during the test. Corn syrup (Karo Light, Cordova, Tenn.) is administered by mouth using 60-mL catheter-tip syringes at a dosage of 0.15 mL/kg, and blood samples are collected 60 and 90 minutes afterwards. Plasma glucose and insulin concentrations are measured, and an insulin concentration greater than 60 µIU/mL at 60 or 90 minutes provides strong evidence of ID, concentrations in the 45 to 60 µIU/mL range provide weak evidence, and there is no evidence of ID if insulin concentrations are less than 45 µIU/mL at both time points.[5,10] Detection of plasma glucose concentrations greater than 125 mg/dL (6.9 mmol/L) at 60 or 90 minutes raises concerns about uncompensated insulin resistance or diabetes mellitus.[19]

The OST can be further simplified for use in the field by instructing the owner to administer the corn syrup themselves and then the veterinarian arrives in time to collect blood samples at 60 and 90 minutes. When the OST is repeated to monitor the progress of an individual patient with ID, only dichotomous results (ID or normal insulin status) should be considered significant because repeatability is low for absolute values.[20,21] A recent study provides evidence that a higher dose of corn syrup (0.45 mL mg/kg) improves test repeatability in

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ponies, and a cutoff value of 40 µIU/mL at 60 or 90 minutes is applied when this dose is selected and insulin concentrations are measured by Immulite chemiluminescent assay.[22]

An in-feed oral glucose test (OGT) can be selected instead of the OST, and this test is performed by fasting the horse overnight and feeding a small meal containing dextrose powder (0.75 or 1.0 g/kg body weight) mixed with water and a small quantity of chaff or low-sugar chopped forage the next morning. A blood sample is collected 120 minutes later, and an insulin concentration greater than 80 µIU/mL is consistent with ID when the 0.75 g/kg dose of dextrose is used.[23] Dextrose (1 g/kg mixed in 2 L water) can also be administered via nasogastric tube to eliminate the variability in consumption time associated with horses consuming a meal, and an insulin cutoff value of 110 µIU/mL at 120 minutes has been proposed for diagnosing ID.[24] When oral glucose test results were compared with OST results in the same group of horses and ponies, 85% agreement was detected.[25]

Basal glucose, insulin, leptin, and triglyceride concentrations can be measured to screen horses for ID, and referral laboratories may soon offer measurement of serum high-molecular-weight (HMW) adiponectin concentrations. Plasma leptin concentrations are positively correlated with body condition in equids, and the Cornell Animal Health Diagnostic Center uses a cutoff value of 10 mg/mL to define hyperleptinemia in horses. A reference interval has been reported for leptin concentrations in donkeys.[26] Serum adiponectin concentrations are negatively correlated with insulin concentrations, and low values are therefore detected in horses with ID.[21,27] Basal glucose concentrations should always be measured at the same time as insulin concentrations in case uncompensated insulin resistance or diabetes mellitus is developing.[28,29]

The combined glucose-insulin test (CGIT) can be used to measure tissue insulin sensitivity in horses. This test involves withholding feed overnight, collection of a baseline blood sample, and IV infusion of 150 mg/kg BW 50% dextrose solution, immediately followed by 0.10 IU/kg BW regular insulin.[30] Blood samples are collected at 1, 5, 15, 25, 35, 45, 60, 75, 90, 105, 120, 135, and 150 minutes post infusion. Both glucose and insulin responses must be assessed, and insulin resistance is defined by blood glucose concentrations remaining above baseline for 45 minutes or longer. The insulin response is assessed by measuring insulin concentrations at 0 (preinjection) and 45 minutes. Insulin concentrations greater than 20 µIU/mL at baseline or greater than 100 µIU/mL at

45 minutes are considered abnormal. These values reflect the amount of insulin secreted by pancreatic beta cells in response to dextrose, as well as clearance of exogenous and endogenous insulin. This test does not, however, allow assessment of the insulin response to oral sugars, which involves secretion of the incretin hormones, glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide (GIP; also known as glucose-dependent insulinotropic polypeptide). There is a small risk of inducing hypoglycemia when the CGIT is performed, so 60 to 120 mL of 50% dextrose solution should be administered intravenously if muscle fasciculations or profound weakness develops. Note that stress is an important cause of transient IR, and horses should remain calm before and during the procedure to avoid false-positive results.

Pathophysiology

Individual horses that are genetically predisposed to EMS readily gain weight and have high blood insulin concentrations. The specific genetic modification(s) present in equids with EMS have not been identified, but several hypotheses are being tested at present. One hypothesis is that affected horses have altered regulation of the incretin hormones, GLP-1 and GIP, which are secreted from the small intestine in response to ingested sugars and other nutrients, and stimulate the insulin secretion from pancreatic beta cells.[31] Incretin hormones raise insulin concentrations and slow gastric emptying as glucose concentrations increase after feeding, and both incretin hormones are degraded by the enzyme dipeptidyl transferase 4. It is therefore hypothesized that postprandial hyperinsulinemia is more pronounced in horses with EMS because of increased secretion or slowed degradation of incretin hormones. Hyperinsulinemia might then promote lipogenesis and contribute to the development of obesity in affected animals. Active GLP-1 concentrations have been measured in horses and ponies, and research is ongoing in this area.[5,21,31,32]

A second potential mechanism for hyperinsulinemia is increased secretion of insulin to compensate for rising glucose concentrations. This is the concept of compensatory hyperinsulinemia, and it fits well with our understanding of diabetes mellitus in humans. Beta cells secrete more insulin to maintain euglycemia if glucose load increases, and the animal compensates for reduced insulin sensitivity using this mechanism. Detection of higher than normal basal or OST blood glucose concentrations indicates that this compensatory mechanism is failing, and the horse has entered an uncompensated state that may

progress to diabetes mellitus. Horses with EMS typically maintain blood glucose concentrations within the reference interval, but decompensation can occur when stress or systemic disease is encountered, and hyperglycemia develops at these times. Evidence for compensated IR comes from research studies involving the administration of somatostatin analog octreotide to horses. Somatostatin inhibits insulin secretion from pancreatic beta cells, and horses with ID develop more pronounced hyperglycemia in response to octreotide injection, when compared with normal horses.[33,34] Hyperinsulinemia therefore reflects altered glucose metabolism and ID, and it is difficult to separate the effects of these disturbances on the health of the horse. Glucose load increases with increased consumption of sugars and glucogenic amino acids in the diet, as well as with tissue insulin resistance, which occurs with obesity, pregnancy, stress, systemic inflammation, PPID, and glucocorticoid administration.[2] Internal fat depots may also play a role in the pathophysiology of EMS, and the concept of internal pathologic fat must be considered. Adipose tissues secrete inflammatory cytokines as obesity progresses,[35-37] and adipokine production shifts, with increased leptin secretion and decreased adiponectin production in obese animals.[27] High-molecular-weight adiponectin concentrations are negatively correlated with insulin concentrations in horses with ID, and this may contribute to the development of insulin resistance in affected animals.[27] Adipose tissue deposits in different regions of the body might also respond differently to obesity. Higher concentrations of mRNA coding for IL-1 beta and IL-6 have been detected in nuchal ligament adipose tissue, when compared with adipose tissues from other regions of the body in horses.[35]

Insulin secreted by pancreatic beta cells enters the portal circulation, and approximately 70% of insulin is cleared from the blood as it passes through the liver in horses.[34] Decreased insulin clearance might therefore contribute to hyperinsulinemia, a hypothesis supported by the finding of low C-peptide/insulin ratios in horses with EMS.[34] Potential causes of decreased insulin clearance include a decreased number of functional insulin receptors within the liver or altered hepatocyte or endothelial cell function. Lipid accumulation within the liver is a potential mechanism linking obesity with hyperinsulinemia in horses, and mildly increased plasma GGT activities are detected in some patients. Intestinal disease, endotoxemia, and systemic inflammation also compromise liver function, potentially explaining why systemic inflammation exacerbates hyperinsulinemia.[38]

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Management

If ID is confirmed, an immediate adjustment in diet is required to lower the amount of sugar ingested. It is assumed that the risk of laminitis increases when blood insulin concentrations rise and remain increased for extended periods, so affected horses must be placed on a diet with low sugar content. Obesity, PPID, pregnancy, inadequate exercise, corticosteroid administration, and diseases inducing systemic inflammation are all modifying factors that exacerbate ID and increase the risk of laminitis. If obesity is present, the initial focus of management should be weight loss and pergolide must be prescribed if concurrent PPID is diagnosed. A thorough diet history is required, and if obesity is a factor, the diet of the horse must be adjusted to decrease energy intake. As long as hoof structures are sound, horses should be exercised to increase energy consumption and accelerate weight loss, and an exercise program consisting of daily or every other day trotting, cantering, or hillside work for 30 to 60 minutes is recommended. A more strenuous exercise regimen is required because lower intensity exercise has not been shown to improve insulin sensitivity in overweight and obese Arabian horses.[39] Body fat mass decreased in ponies that were placed on a low-intensity exercise regimen, but insulin sensitivity did not improve in all animals.[40] Swimming may be an effective method of exercising equids with EMS, and a recent study showed that plasma insulin concentrations decreased in healthy Thoroughbred horses subjected to this form of exercise.[41]

Many horses with EMS are being overfed, and removal of grain from the diet is sufficient to induce weight loss. Pasture access should be restricted in obese animals because horses with EMS often maintain the same body condition unless grass intake is limited. Recommended strategies for limiting grass consumption include (1) housing the obese horse with EMS with a companion in a small grass paddock that is one third to one half of an acre (a square with 120- to 150-ft dimensions), (2) application of a grazing muzzle during turnout, or (3) strip grazing with an electric fence. Affected horses can also be housed in a dirt paddock, but this recommendation is reserved for horses with severe hyperinsulinemia, such as those with OST insulin concentrations greater than 60 μIU/mL.

Each patient should be individually assessed before formulating a management plan. A mildly affected horse with EMS that is obese as a result of overfeeding generally responds well to energy restriction and may eventually return to pasture, as long as a grazing muzzle is used. Grazing at night or in the

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early morning is safer for horses with EMS, except after a hard frost when grasses rapidly accumulate sugars. In contrast, a severely hyperinsulinemic horse with recurrent laminitis should be held off pasture initially and then housing conditions can be adjusted, depending on subsequent test results.

If removing grain from the diet and limiting pasture access does not result in weight loss, the amount of hay fed should be progressively decreased. Hay should be fed in an amount equivalent to 1.5% to 2% of current body weight (e.g., 18 to 24 lb grass hay/day for a 1200-lb horse). If the horse is not losing weight after 4 weeks, the amount fed should be lowered to 1.5% of ideal body weight (15 lb hay/day for an ideal weight of 1000 lb). An obese horse or pony that is not losing weight after an additional 4 weeks can then be lowered to 1.0% of ideal body weight in hay (10 lb/day), but this is the minimum amount recommended. Trace minerals, protein, and vitamin E (1000 IU per day) should be provided to horses on a hay-only diet in order to maintain adequate micronutrient and protein intake.

Attention must also be paid to the sugar content of the diet if basal insulin concentrations are high or OST results confirm severe ID. In these cases, care should be taken to only feed hay with low NSC content because simple sugars and hydrolyzable starches raise insulin concentrations in affected horses. Mild and severe insulin dysregulation have not been defined through objective research, but the author has greater concern when OST insulin concentrations exceed 60 μIU/mL at 60 or 90 minutes. Many commercial laboratories analyze hay samples and report water-soluble carbohydrate (WSC) and starch percentages, which are equal to the NSC content when added together. WSCs include simple sugars and fructans, whereas cellulose and lignin are structural carbohydrates. A cutoff value of 10% has been selected for defining low NSC content, but it should be noted that this value was not derived from definitive research studies. Nevertheless, hay with less than 10% NSC on a dry matter (DM) basis is recommended for horses with ID and feeds with even lower values may be required for severely affected animals. Soaking hay in cold water for 30 to 60 minutes before feeding lowers the soluble sugar content of the feed, although results vary considerably depending on the type of hay.[42] A number of commercial products are also available as bagged hay or forage alternatives if low-NSC hay cannot be purchased. Most horse owners ask to feed a small amount of concentrate to encourage horses to enter their stalls and consume supplements. Half a measuring cup of low-NSC commercial pelleted feed can be fed to EMS horses twice daily when needed.

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Some horses with EMS have a lean phenotype, and these patients are challenging to manage because they require sufficient energy to maintain body condition, which must be accomplished with low-NSC feeds. Many of these animals have lower body condition scores, but regional adiposity is still observed and increased internal adipose tissue depots may be detected by ultrasound examination. Measuring plasma or serum leptin concentrations provides insights into the biological activity of adipose deposits because hyperleptinemia (>10 ng/mL) is detected in affected horses, and these results can be shared with horse owners to encourage compliance with management recommendations.[43] An important question to address is whether the animal is concurrently affected by PPID because this catabolic disease induces weight loss. All EMS horses older than 10 years of age should therefore undergo diagnostic testing for PPID. Other EMS horses with a lean phenotype may have been obese in the past and are lean now because of successful diet and exercise plans. Diets that provide energy in the form of fat and fiber should be selected to maintain or increase body mass in lean EMS horses, and basic feeds such as soaked molasses-free beet pulp and vegetable oil are acceptable. Commercial low-NSC pelleted feeds are also available for purchase, and vegetable oil (0.5 to 1 cup twice daily), rice bran, or a high-fat concentrate can be added to the diet if additional calories are required.

Treatment

There are two indications for pharmacotherapy to manage EMS in horses. The first is for managing obesity when other approaches have failed, and the other is for the management of hyperinsulinemia in refractory cases. Levothyroxine sodium can be prescribed for the management of obesity when this problem persists despite diet and exercise changes. Some obese horses readily lose body fat mass when placed on an energy-restricted diet, whereas others remain overweight, even when energy intake is significantly reduced. The term *weight loss resistance* is applied in these cases, and these are the same horses, ponies, and donkeys that are described as easy keepers.[44] Ponies, miniature horses, and donkeys are particularly challenging to manage and may remain obese, even after they have spent months on an energy-restricted diet. Levothyroxine sodium (Thyro-L, Lloyd, Inc., Shenandoah, Iowa) can be administered to reduce body fat mass and improve insulin sensitivity in these horses and is administered by mouth or in the feed at a dose of 0.1 mg/kg body weight once daily.[45,46] One

teaspoon of Thyro-L powder contains 12 mg levothyroxine sodium, so a horse with body mass of 500 kg receives 48 mg (4 tsp) per day. A higher dosage, 0.15 mg/kg body weight, which is equivalent to 72 mg (6 tsp) per day, may be selected if there is no change in body condition after 3 months. Treatment is continued until the horse reaches ideal body condition score or until the end of the 6-month period. When treatment is discontinued, the dosage is lowered to 0.05 mg/kg (24 mg for a 500-kg horse)/day for 2 weeks and then 0.025 mg/kg (12 mg)/day for 2 weeks. Gradual discontinuation of the drug is necessary because endogenous thyroid axis activity is suppressed while it is being administered. Medical problems have not been associated with the administration of levothyroxine to healthy horses for 12 months,[47] although some horses exhibit increased activity and mild hyperexcitability when treated. Pasture access must be restricted when horses are treated with levothyroxine; otherwise, effects on body mass are compensated for by increased feed intake.

Long-term administration of levothyroxine at lower dosages is controversial. Although obese horses often have low or fluctuating resting thyroid hormone concentrations, low thyroid hormone concentrations accompany many systemic conditions and are not associated with adverse health effects. There is little medical justification for thyroid hormone supplementation at lower dosages in horses with EMS, but it remains common practice.

The second indication for drug therapy is persistent hyperinsulinemia. Metformin and canagliflozin are used for the management of diabetes mellitus in humans, and they have also been administered to horses. Of the choices available, metformin is the least expensive and this drug can be used for the long-term management of postprandial hyperinsulinemia. Dosages selected for horses range from 15 to 30 mg/kg metformin hydrochloride given 2 to 3 times daily PO, and the drug should ideally be administered 30 to 60 minutes before feeding. Oral bioavailability of metformin is low in equids (7.1 ± 1.5% in unfed horses and 3.9 ± 1.0% in fed horses),[48] and this may explain why responses to treatment vary among individual horses. The strength of scientific evidence supporting the use of metformin in equids is weak because only three research studies have been performed to date and just two of them included affected animals.[49-51] In 2008, Durham and colleagues[49] administered metformin (15 mg/kg PO q12h) to ponies and horses with ID and reported improvement in insulin concentrations and proxies for insulin sensitivity. In contrast, Tinworth and colleagues[50] failed to demonstrate beneficial effects of metformin treatment (15 mg/kg PO q12h for 21 days) on insulin sensitivity in insulin-resistant ponies.

Short-term effects of metformin on glucose and insulin dynamics were examined by Rendle and colleagues[51] by administering a single dose of metformin (30 mg/kg) before an oral glucose challenge test. Metformin blunted increases in plasma glucose and insulin concentrations induced by administering dextrose (0.5 g/kg body weight) with a meal. Responses to metformin appear to vary among individual horses, so one approach is to assess the effect of metformin treatment on postprandial hyperinsulinemia in the individual horse by measuring insulin concentrations measured 2 hours post feeding, before and after treatment is initiated.

Canagliflozin is another option for managing hyperinsulinemia in equids, but this drug is expensive at present and this limits its use. At the time of writing, the safety and efficacy of canagliflozin has only been evaluated in one study,[53] so this drug is only recommended for severely affected patients whose health is threatened by laminitis. Canagliflozin is available as Invokana (Janssen Pharmaceuticals, Inc., Titusville, N.J.; 100 mg tablets) for use in humans. The high cost of canagliflozin limits its use in average-sized or large-sized horses, but it can be used for short-term management of acute hyperinsulinemia if, for example, a horse with ID breaks out of its enclosure and grazes on pasture or inadvertently consumes grain. In these situations, canagliflozin may be administered for 3 to 7 days with the goal of limiting the anticipated increase in insulin concentrations after acute exacerbation of ID. Long-term treatment with canagliflozin can be considered for miniature horses and small ponies, and the author prescribes canagliflozin at a dosage of 0.4 mg/kg q24h PO. Care should be taken to assess liver function and plasma triglyceride concentrations before prescribing canagliflozin. The drug should not be administered to patients with liver disease and care should be taken to monitor plasma triglyceride concentrations after treatment is initiated because canagliflozin may exacerbate hyperlipidemia in equids. Hypoglycemia, ketosis, and urinary tract infections are complications observed in humans receiving canagliflozin,[54] but these problems were not encountered in the preliminary study.[53] It should be noted, however, that canagliflozin has only been administered to a small number of horses to date, so it is possible that additional complications will be discovered if the drug gains wider use. For this reason, it is important to explain to clients that Invokana is designed for use in humans and is being used off-label in horses. Potential complications must be explained, and a good client-veterinarian relationship should exist before this new medical treatment is selected. Canagliflozin is a sodium-glucose co-transporter-2 (SGLT2) inhibitor, and

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inhibition of this transporter within the proximal tubule of the kidney increases glucose loss in the urine.[54] Blood glucose concentrations decrease in response to treatment, and the amount of insulin secreted to maintain euglycemia decreases as a result.

PPID may develop in middle-aged or older horses with EMS, and this endocrine disorder exacerbates ID. Pergolide is a dopamine receptor agonist used for the treatment of PPID in horses. It is available as Prascend (Boehringer Ingelheim Vetmedica, Inc., Ingelheim, Germany). The starting dosage is 0.002 mg/kg PO daily, and higher doses are selected for horses with more advanced PPID. Several studies provide evidence of an association between PPID and ID, but it is important to note that PPID horses can have normal insulin status, so diagnostic tests for ID must be performed to evaluate the individual animal.[55-57] Three groups are identified: equids with ID alone, those with PPID and ID, and equids with PPID alone. Medical management of PPID with pergolide typically improves insulin status in horses affected by both endocrine disorders, and this suggests that PPID exacerbates ID by increasing insulin secretion, decreasing insulin clearance, or lowering insulin sensitivity. It has been proposed that pergolide exerts an independent effect on insulin dynamics in horses, but only one study has been performed to test this hypothesis. Horses with clinical signs of EMS were placed on 1 mg pergolide/day and OST insulin concentrations decreased over time (McFarlane D.; personal communication).

Wellness Evaluations

Horses belonging to breed groups with a high risk of EMS should undergo wellness evaluations every 6 to 12 months. The minimum database for each visit includes an updated diet and exercise history; physical examination and body condition scoring; visual inspection of the hooves for signs of laminitis; basal glucose, insulin, leptin, and adiponectin concentrations; and/or OST results.

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Endocrinopathic Laminitis

Melody Anne de Laat and Cathy McGowan

Endocrinopathic laminitis is a common debilitating cause of lameness in horses and ponies associated with endocrine disorders, most notably equine pituitary pars intermedia dysfunction (PPID) and equine metabolic syndrome (EMS). Common to these disorders appears to be disturbed glucose and insulin regulation, now termed *insulin dysregulation* (ID).[1] Field studies have demonstrated the link between laminitis and insulin resistance and hyperinsulinemia since the 1980s.[2-4] In 2004, the term *endocrinopathic laminitis* was introduced "to differentiate laminitis occurring in association with proinflammatory and intestinal conditions from laminitis developing from putative hormonal influences."[5] However, it was not until experimental research unequivocally showed a direct link between hyperinsulinemia and laminitis[6,7] that the concept of laminitis being a clinical syndrome resulting from different causes really solidified.[8] The research involved development of a hyperinsulinemic model of laminitis and resulted in laminitis occurring in 100% of normal ponies or horses exposed to hyperinsulinemia (>1000 µIU/mL) while maintaining euglycemia (5 mmol/L) using a modified euglycemic-hyperinsulinemic clamp technique.[6,7] All treated ponies or horses were healthy, young, lean, and without any history of laminitis. There was no evidence of endocrine or systemic illness on blood tests before, during, or after the experiments, and no animals showed evidence of gastrointestinal involvement throughout the experiments.[6,7]

This important shift in our understanding of laminitis has allowed a wealth of new research into endocrinopathic laminitis and improved our understanding of the pathophysiology, diagnosis, treatment, and prevention of this highly prevalent form of laminitis.

Epidemiology

Endocrinopathic laminitis occurs worldwide, and it has been reported to be the most common form of laminitis[8,9]; however, a full epidemiologic understanding has been hampered by poor case definitions of laminitis, especially in distinguishing endocrinopathic causes.[10] The true frequency of endocrinopathic

laminitis across the whole population is unknown, but it can be as high as 34% in EMS-susceptible breed groups[11] and 82% in retrospective case series of PPID.[12] A more robust cohort study from the United Kingdom reported 9.9% ponies and cobs 7 years of age or older, excluding PPID and without a history of laminitis developing laminitis during a 3-year period.[13] Endocrinopathic laminitis does appear to recur with reasonable frequency, with the recurrence rate reported to range between 33% and 70% depending on the timeframe studied.[14,15] The data indicate a seasonal influence on disease occurrence, with a tendency for more new cases to occur in spring and summer when consumption of pasture high in nonstructural carbohydrates is more likely.[15,16] Even though not studied specifically for endocrinopathic laminitis, increasing age and breed have been proposed as risk factors for laminitis, while it is unclear whether a sex predisposition exists.[17-19] There are no direct data to support a genetic origin for the disease beyond the proposed genetic predisposition to underlying endocrinopathies, such as EMS/ID.[20] More simply, some studies have investigated an association between height and laminitis incidence, with the hypothesis that ponies are at greater risk of disease than horses, but the data are inconclusive.[16]

More recently, a focus on metabolic and endocrine parameters has resulted in the identification of some clear risk factors for endocrinopathic laminitis. Increased basal and dynamic serum insulin concentrations have been correlated with an increased risk of laminitis occurrence.[13,21-23] In addition, hyperleptinemia and hypoadiponectinemia increase the risk of laminitis.[13,22] Morphometric data are also supportive in some breeds, with increased BCS (≥7/9) and CNS (≥4/5) in combination with basal insulin (> 32 µIU/mL) or leptin (>7.3 ng/mL) being associated with an increased risk of pasture-associated laminitis.[22] Horses and ponies with PPID have an increased risk of both ID and laminitis. [24] Horses with PPID have 4.65 times the odds of developing laminitis and are 2.7 times more likely to have hyperinsulinemia than age-matched controls.[24]

Clinical Signs

Endocrinopathic laminitis typically results in lameness in all four limbs, which can vary from mild or even subclinical to severe debilitating pain. The degree of

lameness was graded by Obel in 1948[25] using a simple but effective scale of 1 to 4. Although this grade was developed using laminitis associated with systemic inflammatory conditions (starch overload and retained placenta; SIRS-associated), it is still relevant 60 years later for endocrinopathic laminitis.[25] Supportive findings such as typical gait, weight shifting, increased or bounding digital pulses, and pain on hoof testers may be found.[26] The hyperinsulinemic model confirmed clinical suspicion that endocrinopathic laminitis is slower in onset than SIRS-associated laminitis. Ponies and horses subjected to hyperinsulinemia developed laminitis slowly in all four limbs, with the onset of lameness associated with laminitis (Obel grade 2) by approximately 48 hours.[6,7]

It is also important to recognize that endocrinopathic laminitis can occur in the absence of pain. Experimentally, evidence of histologic lesions of laminitis was detected as early as 6 hours post exposure to hyperinsulinemia, [27] and in response to much lower circulating concentrations of endogenous insulin than in the hyperinsulinemic model,[28] which supports the contention of lamellar lesions and laminitis occurring before or without lameness. In a study of naturally occurring laminitis it was noted that hoof capsular changes such as divergent rings occurred in all histologically confirmed laminitis cases, but gross pathological changes did not correspond to the duration of lameness.[29] Divergent rings could extend the full length of the hoof wall in horses with a short history of lameness, which based on the growth rate of the hoof wall confirmed the occurrence of a preclinical stage in some horses.[29]

Histology

The hyperinsulinemic model has also facilitated more in-depth study of the pathologic lesions associated with laminitis. As early as 6 hours post exposure to hyperinsulinemia or after 48 hours of hyperglycaemia, marked elongation of the secondary epidermal lamellae is observed.[27,28] It is this lesion of epithelial cell stretching associated with a loss of cytoskeletal integrity that is the crucial early lesion in laminitis.[8] Epithelial cellular changes are observed alongside the stretching including altered orientation and shape, apoptosis, and mitosis.[30] Histopathology was less severe, and fewer inflammatory cells infiltrate than laminitis caused by systemic inflammatory diseases or carbohydrate overload models.[31]

The histology of naturally occurring endocrinopathic laminitis is similar to the

hyperinsulinemic model and shows a range of lesions with overall stretching and lengthening of primary and secondary lamellae. Abaxially (underneath the hoof wall) there is apoptosis, lamellar fusion and hyperplasia, and keratinization that may lead to tearing and separation. Axially (adjacent to P3) there is tapering of the primary and secondary lamellae in variable amounts.[29] In both experimental hyperinsulinemia and in naturally occurring endocrinopathic laminitis, the lesion is not basement membrane driven as has been proposed from research in SIRS-associated models. Early cellular changes are associated with limited and localized basement membrane damage likely to be associated with the cytoskeletal disruption within the epithelial cells.[8]

Pathophysiology

Considerable research effort has been invested in exploring the pathogenesis of endocrinopathic laminitis. While significant progress has been made, certain elements of the pathophysiology remain elusive, with uncertainty surrounding exactly which pathways engender the demise of the lamellar structure during laminitis onset. What is clear is that in cases of ID, whether from PPID or EMS, hyperinsulinemia is a catalytic factor for lamellar failure.[6,7,29,32] However, precisely how insulin drives the lamellar lesions to induce clinical laminitis remains unclear. The lamellar epithelial cells appear to be devoid of insulin receptors,[33] which suggests that an indirect action of insulin on the structure is most likely.

Early studies focused on impaired lamellar metabolism and potential interference with glucose supply during the initiation of lamellar separation.[34,35] Current consensus is that the lamellae are an insulin-independent tissue, with a profusion of the glucose transporter 1 (GLUT1).[36,37] Further, the lamellae do not appear to be rich in GLUT4, which is the principal insulin-dependent transporter and predominates in insulin-sensitive tissues such as striated muscle and adipose tissue.[36,37] GLUT1 does not rely on insulin to drive glucose uptake and predominates in highly metabolic tissues such as the brain and epithelium, where interruptions to glucose supply would be problematic.[38] As such, the lamellae appear well equipped to meet their metabolic demands.

Once it was shown that failure of glucose uptake was an unlikely catalyst for lamellar failure, investigations into the potential involvement of glucose toxicity, oxidative stress, and lamellar glycation were undertaken.[39] Despite these

processes being evident in the pathophysiology of type 2 diabetes mellitus sequelae,[40] data demonstrated that glycoxidative processes were only upregulated after the onset of lamellar pathology[39] and therefore this hypothesis was not supported.

Despite obesity, which is often associated with EMS, being a proinflammatory state, there is little evidence to support a major role for inflammation in endocrinopathic laminitis pathophysiology. Histologic studies of both naturally occurring and experimentally induced laminitis have demonstrated minimal leukocyte infiltration, unlike the marked inflammation in SIRS-associated laminitis.[31] Further, gene and protein studies of the lamellae have not reached a consensus that proinflammatory cytokines are key instigators of endocrinopathic laminitis pathophysiology.[41,42] Lastly, an active role for matrix metalloproteinases (enzymes secreted by leukocytes that degrade the extracellular matrix) in the onset of endocrinopathic laminitis has not been supported,[43] unlike in other forms of the disease.[44]

Similarly, the role of blood flow in the inception of endocrinopathic lamellar pathology is unclear. Insulin receptors are present on lamellar endothelial cells,[33] which is supportive of the potential for the vasculature to be involved in disease pathogenesis. By differential intracellular signaling through one of two different pathways, insulin is capable of stimulating the release of a key vasodilator, nitric oxide, or the potent vasoconstrictor, endothelin-1. The normal effect of insulin is vasodilation through the so-called metabolic pathway.[45] Bounding digital pulses are a common and familiar clinical sign associated with acute laminitis,[26] and their presence would seem to indicate an increase in blood flow to the hoof early in laminitis development. In agreement with this was a study that demonstrated a persistent increase in the hoof wall temperature, suggestive of vasodilation, in horses during the early stages of insulin-induced laminitis.[7] It has been suggested that an increase in blood flow to the hoof may assist in the delivery of catalytic factors, such as growth factors, inflammatory cytokines, or metalloproteinases.[46] The fact that the use of a vasodilatory agent alone was unable to induce laminitis[47] suggests that additional factors are essential for increased blood flow to potentially be causative of laminitis.

An ischemic or hypoxic pathogenesis for laminitis also makes physiologic sense and is supported by the knowledge that persistent weight bearing on one limb, which may reduce blood flow to the foot, can induce the disease.[48] While investigations in vivo of lamellar ischemia have not been attempted, data from

isolated, perfused vessel studies suggest that experimental preincubation with insulin may drive intracellular signaling away from the metabolic pathway, with aberrant vessel contraction observed in response to insulin in the lamellae.[49-50] The same effect was seen where vessels had been collected from horses with naturally occurring endocrinopathic laminitis.[51] However, ischemic lesions have not been observed histologically[27,29,30] and how ischemia may contribute to the pathogenesis of endocrinopathic laminitis remains unclear.

Perhaps the most promising line of research for uncovering the exact pathophysiology lies in understanding how aberrant intracellular signaling in the epithelial cells, especially the shift away from the metabolic pathway as has been shown in the vasculature, may be driving their demise. Insulin is a growth factor and may still exert its effect directly on the tissue, such as by signaling through, or upregulating, other receptors. Insulin can bind to insulin-like growth factor 1 (IGF-1) and hybrid insulin/IGF-1 receptors,[52] and these are both possible targets, especially considering that IGF-1 receptors have been identified on lamellar epithelial cells, and that they are differentially expressed during experimental laminitis.[33,53] Insulin may also regulate the expression of other growth factor receptors in the lamellae, such as the epidermal growth factor receptor,[54] with signaling achieved by a variety of local or circulating ligands. Activation of all of these receptors can trigger common intracellular signaling pathways that cause cellular damage via cytoskeletal disruption, leading to the well-defined initial lesion of lamellar and cellular stretching.[8,55]

Management, Prognosis, and Prevention

Endocrinopathic laminitis remains difficult to manage. However, better understanding of the cause, and in particular the relationship with ID, has allowed a focus on monitoring and management of the underlying problem to reduce recurrence in the future.[56] Further, pathologic understanding of the lesion and the potential for a subclinical phase leading to divergent hoof rings or other hoof capsular changes as an early warning[29] has meant that prevention before lameness is more achievable in some cases.

Laminitis management strategies focus on pain relief and remediation of gross hoof defects[15] (also see Laminitis section in Chapter 38). Pain relief can often be achieved with nonsteroidal antiinflammatory drugs (NSAIDs), although in severe cases opioids or multimodal analgesia may be necessary. More recently,

there has been increased interest in targeting neuropathic pain with gabapentin, although the potentially low oral bioavailability of this drug may limit its efficacy.[57,58] Restriction of movement in severe cases is important, and provision of deep bedding is recommended.[59] Additional pain relief can be achieved with hoof supports, such as moldable pads that are designed to cushion the palmar hoof surface and ease the breakover. Farriery is also recommended to reform hoof biomechanics, and specialist ongoing hoof care is often required.[59]

Treatment of the underlying endocrinopathy is also central to management, as a reduction in hyperinsulinemia is crucial for reducing the risk of recurrence. The prognosis for endocrinopathic laminitis is variable. Severe, intractable cases carry a poor prognosis, and euthanasia is often the only humane option in these animals. Milder cases with a clear underlying endocrinopathy that can be addressed and the absence of marked displacement of the distal phalanx carry a fair prognosis if appropriately and promptly managed.

Prevention of endocrinopathic laminitis should be the key focus, and identification of hoof capsular changes indicative of laminitis on clinical examination[26] should prompt appropriate endocrinologic testing. The goal should be to identify animals at particular risk of this form of laminitis in the preclinical phase and instigate strategies to reduce the likelihood of disease onset. Studies have indicated that hyperinsulinemia indicative of ID is the strongest predictor of disease.[3,4,9,11,13,29] The predictive power of insulin concentration is also apparent in animals with PPID[21,32] and has been supported more recently by the finding that an abnormal oral glucose test result was predictive of laminitis risk.[23] Combining tests for insulin, leptin, adiponectin, and morphometry may support a diagnosis of ID, but further research in this area is required.

In conclusion, the paradigm shift in our recognition and understanding of endocrinopathic laminitis has greatly improved our ability to appropriately focus management and prevention on the underlying endocrinopathy. More research will help pinpoint risk factors, improve diagnostic tests, and improve treatments for the underlying endocrinopathies, and as these are developed, so too the toolkit for preventing laminitis will grow.

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Parathyroid Gland, Calcium, and Phosphorus Regulation in Horses

Ramiro E. Toribio

Calcium

Calcium is the fifth most abundant element in the body, representing ≈1.5% of the body weight. Physiologic functions such as signal transduction, muscle contraction, hormone secretion, enzyme activation, gene transcription, cell division, cell membrane stability, cell migration, neuromuscular excitability, and blood coagulation are calcium dependent.[1-3] Processes that result in cell injury and death, such as free radical production, cytokine release, protease activation, excitotoxicity, vasoconstriction, and apoptosis, also require calcium.[2,3]

Calcium has structural and nonstructural functions, and it is found in three main compartments: the skeleton, soft tissues, and the extracellular fluid. Approximately 99% of the total body calcium (and 85% of phosphorus) is in the skeleton as hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) in a calcium–to–phosphorus ratio of 2 : 1. As part of the skeleton, calcium provides support against gravity, protects vital internal organs, and houses blood-forming elements. The skeleton is also a reservoir for calcium. Nonstructural functions are related to calcium as a regulatory ion. The remaining calcium is present in the cell membrane, mitochondria, endoplasmic reticulum, and extracellular fluid.[1-3] In blood, most calcium is in plasma as a free or ionized form (≈55%), bound to proteins (≈40%), and complexed to anions such as citrate, bicarbonate, phosphate, and lactate (≈5%) (Fig. 41.15).[1-4] In adult horses, serum ionized calcium represents 50% to 55% of the total serum calcium, while in foals ionized calcium is 43% to 56% of the total serum calcium.[2-8] Free, unbound, or ionized calcium (Ca^{2+}) is the biologically active form of calcium. Of the protein-bound calcium, approximately 80% is associated with albumin and 20% with globulins. Calcium binds to negatively charged or anionic proteins, and this affinity is pH dependent. During acidosis, increased H^+ concentrations decrease Ca^{2+} binding to anions, resulting in increased plasma Ca^{2+} concentrations. Alkalosis lowers Ca^{2+} concentrations. Hypoalbuminemia results in total hypocalcemia

(pseudohypocalcemia), with Ca^{2+} concentrations remaining within the normal range.

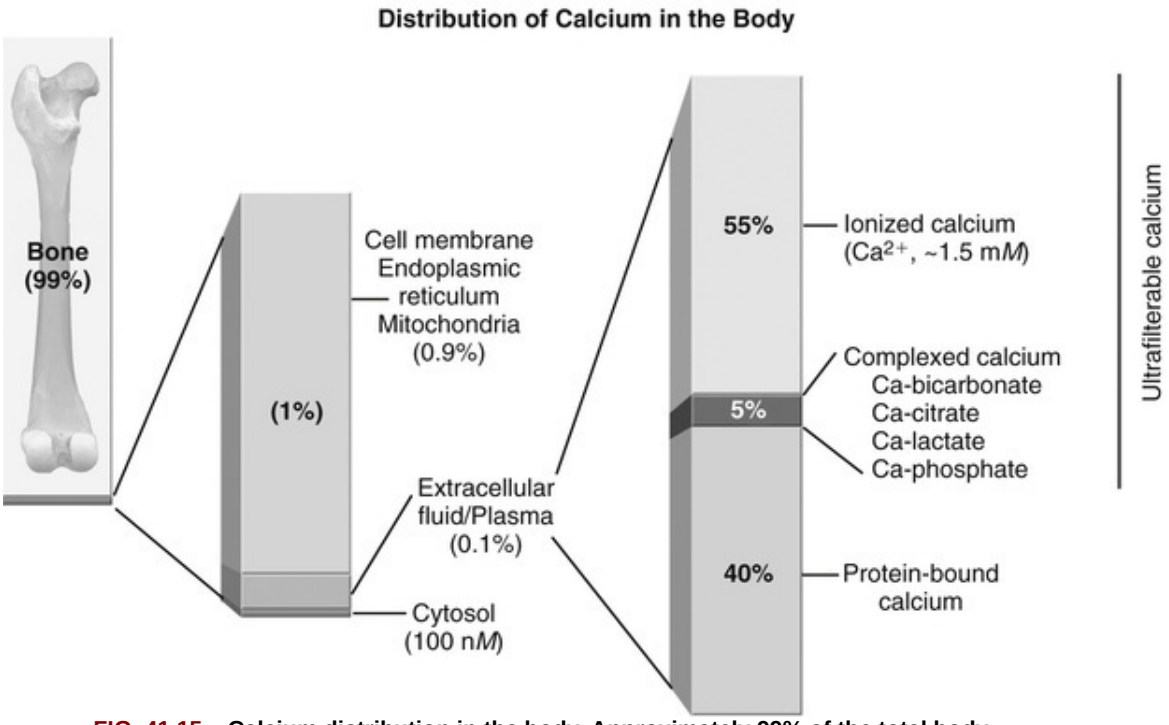


FIG. 41.15 **Calcium distribution in the body. Approximately 99% of the total body calcium is in the skeleton. The remaining calcium is present in the cell membrane, mitochondria, endoplasmic reticulum, and extracellular fluid. In blood, calcium exists in a free or ionized form (Ca^{2+}), bound to proteins, and complexed to anions such as citrate, bicarbonate, phosphate, and lactate. In horses, serum Ca^{2+} represents 50% to 55% of the total serum calcium concentration.**

Calcium and phosphorus requirements in horses depend on age, physiologic status, and amount of work or exercise performed (Table 41.2). Serum Ca^{2+} concentrations are not a reliable indicator of dietary calcium intake. A balanced diet for horses must have 0.15% to 1.5% of calcium and 0.15% to 0.6% of phosphorus in feed DM (Box 41.1). A calcium–to–phosphorus ratio less than 1 : 1 can have negative effects on calcium absorption and skeletal development; however, a calcium–to–phosphorus ratio as high as 6 : 1 for growing horses may not be detrimental if phosphorus intake is adequate.[9] Adult horses should receive approximately 40 mg of calcium/kg/day (Table 41.2). Average horses must absorb 20 to 25 mg of calcium and 10 to 12 mg of phosphorus/kg/day to meet their needs and balance losses. Calcium and phosphate content in some mineral supplements and equine feeds are presented in Tables 41.3 and 41.4.

TABLE 41.2

Calcium and Phosphorous Requirements in the Horse

	Percent in Diet		Daily Intake (Grams)	
	Ca	P	Ca	P
Foals (<6 mo)	0.80	0.55	33	20
Weanlings	0.60	0.45	34	25
Yearlings	0.50	0.35	31	22
2-year-olds	0.40	0.30	25	17
Mare, late pregnancy	0.45	0.30	34	23
Mare, lactation	0.45	0.30	50	34
Mature horses	0.30	0.20	23	14

Modified from references 2 and 95-97.

Adapted from referenes 2 and 128-130.

Box 41.1

Acceptable Ranges of Minerals and Vitamins in Feed of Horses[128,129]

Ca (%)	0.25-1.5
P (%)	0.15-0.6
Mg (%)	0.08-0.16
Vitamin D (IU/kg)	300-800

TABLE 41.3

Calcium and Phosphorous Contents of Some Mineral Supplements

	Calcium (%)	Phosphorus (%)
Calcium carbonate	34	0
Dicalcium phosphate	27	21
Monocalcium phosphate	17	21
Bone meal	30	14
Monosodium phosphate	0	22
Defluorinated phosphate	32	15
Calcium gluconate 23%	2.14	0

Adapted from references 2 and 128-130.

Modified from references 2 and 95-97.

TABLE 41.4

Mineral Composition of Some Equine Feeds on Dry Matter Basis

Source	Ca (%)	P (%)	Mg (%)
Alfalfa	1.71	0.30	0.36
Alfalfa hay	1.41	0.21	0.34
Timothy	0.40	0.26	0.16
Timothy hay	0.51	0.29	0.13
Bluegrass	0.50	0.4	0.18
Oat hay	0.32	0.25	0.29
Orchard grass	0.25	0.39	0.31
Barley	0.05	0.37	0.15
Corn	0.05	0.60	0.03
Oats	0.09	0.38	0.16
Wheat	0.05	0.42	0.14
Cottonseed meal	0.18	1.22	0.59
Linseed	0.43	0.90	0.67
Skim milk	1.36	1.09	0.13
Soybean meal	0.40	0.71	0.31
Molasses, cane	1.10	0.15	0.47
Wheat bran	0.14	1.27	0.63

Modified from NRC: Nutrient requirements, feedstuff composition, and other tables. In National Research Council (U.S.), Committee on Nutrient Requirements of Horses, editors: Nutrient requirements of horses, Washington, D.C., 2007, National Academies Press, pp 293-310.

Horses have distinctive features with regard to calcium metabolism. These include high serum total and ionized calcium concentrations,[8] a poorly regulated intestinal calcium absorption (high absorption),[10] high urinary fractional excretion of calcium,[8] low serum concentrations of vitamin D metabolites,[11-14] and decreased parathyroid gland sensitivity to Ca^{2+}.[15,16]

Most calcium absorption occurs in the small intestine.[10,17,18] Compared with other species, horses absorb a larger proportion of the dietary calcium. Horses can absorb 50% to 75% of the calcium and less than half the phosphorus in their diet, with little effect of age.[10] Calcium absorption is inversely related to dietary calcium content. High content of phosphate (or phytate, oxalate) inhibits calcium absorption; however, high dietary calcium content has minimal effect on phosphorus absorption. Oxalates reduce calcium absorption. Some plants containing harmful amounts of oxalate are listed in Table 41.5. The dietary cation-anion balance (DCAB) affects Ca^{2+} absorption in horses; a low DCAB increases intestinal Ca^{2+} absorption, while a high DCAB has the opposite

effect.[19] Glucocorticoids decrease intestinal absorption of calcium, decrease bone resorption, and increase urinary excretion of Ca^{2+} in horses.[20,21]

TABLE 41.5

Plants That Contain Oxalates[a]

Common Name	Scientific Name
Bermudagrass	*Cynodon dactylon*
Buffel grass	*Cenchrus cilaris*
Dallis grass	*Paspalum* spp.
Elephant grass	*Panicum* spp.
Foxtail grass	*Setaria* spp.
Greasewood	*Sarcobatus vermiculatus*
Halogeton	*Halogeton glomeratus*
Kikuyu	*Pennisetum clandestinum*
Kochia, summer cypress	*Kochia scoparia*
Lamb's quarters	*Chenopodium* spp.
Napier, mission grass	*Pennisetum* spp.
Pangola	*Digitaria decumbens*
Panic	*Panicum* spp.
Para grass	*Brachiaria* spp.
Pokeberry	*Phytolacca americana*
Purple pigeon grass	*Setaria incrassate*
Purslane	*Portulaca oleraceae*
Red-rooted pigweed	*Amaranthus* spp.
Rhubarb	*Rheum rhaponticum*
Russian thistle, tumbleweed	*Salsola* spp.
Setaria	*Setaria sphacelata*
Sorrel	*Rumex* spp.
Soursob, shamrock	*Oxalis* spp.
Sugar beet	*Beta vulgaris*

[a]These plants have an oxalate content higher than 0.5% of dry matter or a calcium-to-oxalate ratio of less than 0.5.

Calcium is eliminated through feces, urine, milk, sweat, and the fetus. In the kidney, approximately 60% calcium is reabsorbed in the proximal tubules by passive mechanisms and 35% is reabsorbed in the thick ascending loop of Henle and distal tubules by active mechanisms.[22] The rest (≈5%) represents the urinary fractional excretion of calcium. Endogenous losses of calcium in horses have been estimated around 20 to 25 mg/kg/body weight/day. Assuming a 50% calcium digestibility, a 500-kg horse would require 20 g of calcium to replace losses, or 40 mg/kg/day; growing and lactating horses can double these requirements. Interpretation of the urinary excretion of calcium could be difficult because horses eliminate large amounts of calcium (primarily calcium carbonate)

in urine.[2,3,23]

Phosphorus

Phosphorus represents ≈1% of body weight, with most (85%) located in the skeleton as hydroxyapatite crystals, 15% in blood and soft tissues, and less than 0.1% in the extracellular fluid. In blood, phosphorus exists as organic (intracellular) and inorganic (extracellular) phosphates. Organic phosphate consists of phosphate esters (phospholipids) bound to proteins and blood cells and represents most of the phosphorus in circulation; however, only inorganic phosphate (PO_4) is measured. PO_4 is found as ionized phosphate (≈50%), complexed with cations (Na^+, Ca^{2+}, Mg^{2+}; ≈35%), and bound to proteins (≈15%). At pH 7.4, PO_4 exists as divalent (HPO_4^{2-}) and monovalent ($H_2PO_4^-$) anions in a 4 : 1 ratio. In acidosis this ratio is 1 : 1 and can be as high as 9 : 1 during alkalosis.[24] In soft tissues, most of the phosphate is organic and intracellular. It is incorporated into nucleic acids, phospholipids, and energy compounds such as ATP and creatine phosphate. Thus, phosphate is important for muscle contraction; neurologic functions; enzyme activity; electrolyte transport; oxygen transport (2,3 DPG); intermediary metabolism of proteins, carbohydrates, and fats; gene transcription; and cell proliferation and differentiation. PO_4 regulation is closely associated to Ca^{2+} homeostasis.

Phosphorus requirements depend on age, physiologic status, and amount of work or exercise performed (Table 41.2). In horses, phosphorus absorption ranges from 20% to 55% and occurs in the small and large intestines.[17,25] Excess dietary aluminum may reduce PO_4 absorption[26-28]; however, magnesium does not seem to interfere with PO_4 absorption in horses.[29] In the kidneys, most of the PO_4 is reabsorbed in the proximal tubules by a Na^+-dependent mechanism and the urinary fractional excretion of PO_4 in horses is low (<0.5%).

Chronic excess of phosphorus results in clinical signs consistent with calcium deficiency including lameness, abnormal cartilage and bone development, fractures, and osteodystrophia fibrosa (nutritional secondary hyperparathyroidism). Acute renal failure and hypoparathyroidism are associated with hyperphosphatemia. Conditions that result in cell membrane fragility and lysis such as hemolysis, rhabdomyolysis, and tumor necrosis may cause hyperphosphatemia. Critical illness and metabolic acidosis can also increase

extracellular PO_4 concentrations in horses and foals.[30]

Hypophosphatemia occurs from inadequate intake, decreased intestinal absorption, renal waste, hyperparathyroidism, sepsis, intracellular shift, and some malignancies. Intracellular PO_4 shift is a common cause of hypophosphatemia in critically ill humans and small animals and occasionally occurs in horses with starvation, refeeding syndrome, and parenteral nutrition (hyperglycemia, hyperinsulinemia).

Chronic phosphate deficiency can be manifested as weight loss, weakness, pica (depraved appetite), lameness, and developmental orthopedic disease (DOD). Rickets, as described in other species with PO_4 or vitamin D deficiency, is not a recognized condition in foals. Serum PO_4 concentration is more indicative of dietary phosphorus intake and status than serum Ca^{2+} because PO_4 homeostasis is not as precise as that of Ca^{2+}.

Normal calcium, magnesium, phosphorus, and regulatory hormone concentrations are presented in Table 41.6. Ionized calcium concentrations are lower in foals and pregnant mares than adult horses.[5,6,23] Of interest, serum total and ionized magnesium concentrations tend to be higher in foals than adult horses.[5,6,23] Serum PO_4 concentrations and alkaline phosphatase activity are greater in foals compared with adult horses due to growth, increased intestinal absorption, bone osteoblastic activity, and bone formation.[2,6]

TABLE 41.6

Normal Calcium, Magnesium, Phosphorous, and Regulatory Hormone Concentrations in Horses

Total calcium in horses (mg/dL)	11.1-13 (2.8-3.25 mmol/L)
Total calcium in foals (mg/dL)	11-14 (2.75-3.5 mmol/L)
Ionized calcium in horses (mg/dL)	6-7 (1.5-1.75 mmol/L)
Ionized calcium in foals (mg/dL)	5.8-6.6 (1.45-1.65 mmol/L)
Phosphorus in horses (mg/dL)	2-4.8 (0.64-1.54 mmol/L)
Phosphorus in foals (mg/dL)	4.4-8.4 (1.4-2.7 mmol/L)
Total magnesium in horses (mmol/L)	0.53-0.91 (1.27-2.2 mg/dL)
Total magnesium in foals (mmol/L)	0.56-1.11 (1.34-2.66 mg/dL)
Ionized magnesium in horses (mmol/L)	0.46-0.66 (1.10-1.58 mg/dL)
Ionized magnesium in foals (mmol/L)	0.43-0.67 (1.03-1.61 mg/dL)
PTH (pmol/L)	<4 (<40 pg/mL)
Calcitonin (pg/mL)	<40 (12 pmol/L)
PTHrP (pmol/L)[a]	<3 (<30 pg/mL)
FE_{Ca} (%)	2-8

FE_P (%)	0-0.5
$25(OH)D_3$	1.90 ± 0.23 ng/mL—winter[12]
	2.43 ± 0.09 ng/mL—summer[12]
	4.2 ± 0.34 ng/mL—winter[14]
	6.2 ± 0.36 ng/mL—summer[14]
$1,25(OH)_2D_3$	18.6 ± 7.3 pg/mL—winter[14]
	18.7 ± 8.0 pg/mL—summer[14]
	55.0 ± 24.0 pmol/L[11]

[a]Measured in ethylenediaminetetraacetic acid (EDTA) plasma.

FE_{Ca}, Urinary fractional excretion of calcium; *FE_P,* urinary fraction excretion of phosphorus; *PTH,* parathyroid hormone; *PTHrP,* parathyroid hormone–related protein.

Conversion units: Calcium (mmol/L = mg/dL × 0.25; mg/dL = mmol/L × 4); magnesium (mmol/L = mg/dL × 0.4; mg/dL = mmol/L × 2.43); phosphorus (mmol/L = mg/dL × 0.323; mg/dL = mmol/L × 3.1)

Data from the College of Veterinary Medicine, Ohio State University, unless otherwise noted. Foal calcium and magnesium data from recent publications.[5,6]

Calcium and Phosphorus Homeostasis

Extracellular ionized calcium (Ca^{2+}) concentrations are regulated by a homeostatic system that includes three hormones: parathyroid hormone (PTH), calcitonin, and 1,25-dihydroxyvitamin D_3 ($1,25[OH]_2D_3$, calcitriol); three body systems (kidney, intestine, and bone); and a calcium-sensing receptor (CaR).[2,3,23] PTH increases during hypocalcemia and hyperphosphatemia while calcitonin increases during hypercalcemia (Fig. 41.16). Under physiologic conditions parathyroid hormone-related protein (PTHrP), which also activates the PTH-1 receptor, has little effect on Ca^{2+} homeostasis.[31] PO_4 regulation is closely associated with Ca^{2+} homeostasis. Extracellular ionized magnesium (Mg^{2+}) has permissive effects on calcium homeostasis by facilitating PTH secretion and action.

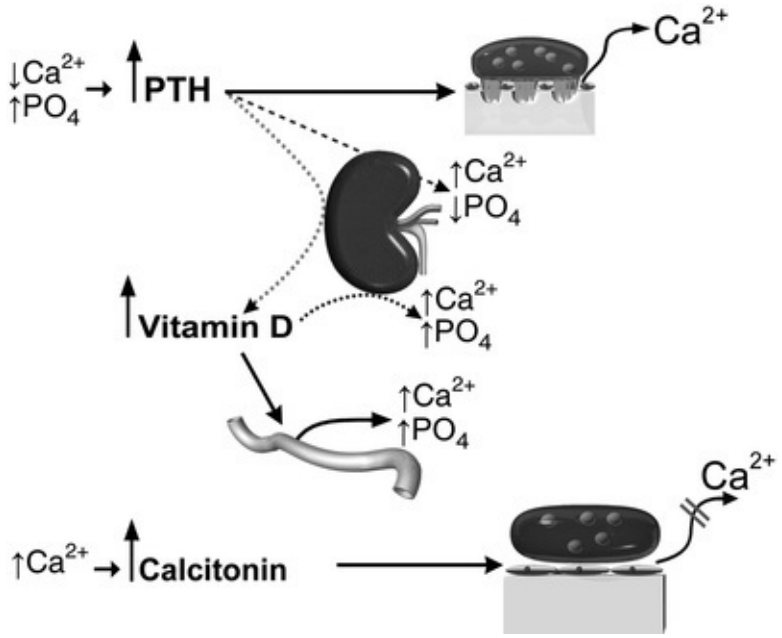


FIG. 41.16 **Calcium and phosphate homeostasis. A decrease in serum Ca^{2+} or increase in serum PO_4 concentrations increases PTH secretion. PTH increases renal Ca^{2+} reabsorption and vitamin D synthesis, decreases renal PO_4 reabsorption, and increases osteoclastic bone resorption. In turn, vitamin D increases intestinal absorption and renal reabsorption of Ca^{2+} and PO_4 and facilitates bone resorption. On the contrary, hypercalcemia decreases PTH secretion and stimulates calcitonin secretion to inhibit osteoclastic bone resorption.**

Organs involved in PO_4 homeostasis include the intestine (absorption), kidneys (excretion), and bone (storage). Extracellular PO_4 concentrations are under the control of various endocrine factors including PTH, $1,25(OH)_2D_3$, calcitonin, insulin, and the fibroblast growth factor-23 (FGF-23)/klotho axis.[3] In healthy animals, endocrine control of intestinal absorption of PO_4 is minimal, but hormones such as $1,25(OH)_2D_3$ can increase absorption in PO_4-deficient states. PTH and the FGF-23/klotho axis are considered the main regulators of PO_4 concentrations.[32-34] Information on phosphatonins (FGF-23), which inhibit renal PO_4 reabsorption and $1,25(OH)_2D_3$ synthesis in a number of species,[32-35] is limited in the horse.[30]

PTH is secreted by the chief cells of the parathyroid gland in response to hypocalcemia and hyperphosphatemia. Parathyroid chief cells detect changes in Ca^{2+} concentrations by a calcium-sensing receptor (CaR).[16,36] Through the PTH receptor, PTH increases renal Ca^{2+} reabsorption (distal nephron), decreases renal PO_4 reabsorption (proximal tubules), stimulates renal calcitriol synthesis (proximal tubules), and stimulates osteoclastic bone resorption (see Fig. 41.16).

Calcitriol ($1,25[OH]_2D_3$) increases intestinal absorption and renal reabsorption of Ca^{2+} and PO_4 and inhibits PTH synthesis and secretion.[2,3] PTH secretion is under the influence of Ca^{2+}, PO_4, and vitamin D. Biologically active intact PTH is measured with immunometric assays.

Vitamin D plays an important role in Ca^{2+} and PO_4 homeostasis and, to a lesser extent, in magnesium metabolism. Vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are secosterols derived from photolytic cleavage of the B rings of ergosterol (plants and yeasts) and 7-dehydrocholesterol (animals), respectively. Vitamin D_3 is transported to the liver by a vitamin D–binding protein (GC-globulin), where it is hydroxylated (25-hydroxylase) to 25-hydroxyvitamin D_3 ($25[OH]D_3$, calcidiol), which is then transported to the kidney to produce the active metabolite, $1,25(OH)_2D_3$ (calcitriol), by 1α-hydroxylase. In mammalians, $25(OH)D_3$ is considered the main circulating form of vitamin D. However, recent studies found that $25(OH)D_2$ was the main vitamin D metabolite in equine blood.[37,38] Hypocalcemia, hypophosphatemia, and PTH stimulate $1,25(OH)_2D_3$ synthesis by inducing renal 1α-hydroxylase activity, whereas hypercalcemia, hyperphosphatemia, FGF-23, and $1,25(OH)_2D_3$ inhibit 1α-hydroxylase.

Vitamin D stimulates intestinal absorption and renal reabsorption of Ca^{2+} and PO_4 and, to a lesser extent, of Mg^{2+}. $1,25(OH)_2D_3$ increases the expression and activity of proteins important for transcellular Ca^{2+} transport, including epithelial Ca^{2+} channels, Ca^{2+} binding proteins (calbindin D_{9k}, calbindin D_{28k}), Na^+/Ca^{2+} exchangers, and Ca^{2+}-ATPases.[2,3,39] The effects of $1,25(OH)_2D_3$ on intestinal absorption and renal reabsorption of PO_4 are mediated by Na^+/PO_4 cotransporters.[3] In addition, $1,25(OH)_2D_3$ increases Mg^{2+} renal reabsorption.[40] In bone, $1,25(OH)_2D_3$ increases bone matrix synthesis and mineralization and stimulates osteoclastic activity and bone resorption. In the parathyroid gland, $1,25(OH)_2D_3$ inhibits chief cell proliferation, PTH synthesis, and secretion.[41] Vitamin D deficiency results in rickets in young animals and osteomalacia in adults; however, the existence of rickets in the horse is not well documented.

Calcitonin is a 32–amino acid peptide secreted by the parafollicular cells (C cells) of the thyroid gland in response to hypercalcemia in a number of species, including the horse.[39,42] Calcitonin inhibits osteoclast function and bone

resorption, and it decreases renal reabsorption of Ca^{2+} and PO_4 in most species.[2,3]

Parathyroid hormone-related protein (PTHrP) is produced by almost every tissue in the body and has a broad range of functions that have little to do with Ca^{2+} homeostasis.[31] Under physiologic conditions, PTHrP functions (morphogenesis, cell differentiation) are considered to be paracrine, autocrine, and intracrine. For the most part, the endocrine functions of PTHrP are considered pathologic (humoral hypercalcemia of malignancy; HHM). HHM is a paraneoplastic syndrome that results from excessive secretion of PTHrP by some tumors. By interacting with PTH receptors, PTHrP promotes bone resorption and inhibits renal Ca^{2+} excretion, causing hypercalcemia in humans and domestic animals, including the horse.[43-48]

The *FGF-23/klotho axis* plays central functions in calcium, phosphorus, and vitamin D regulation. FGF-23 is considered the main PO_4-regulating hormone and is secreted by osteocytes in response to $1,25(OH)_2D$ and PTH.[49-51] It promotes renal PO_4 excretion by decreasing renal Na^+/PO_4 cotransporter numbers and suppressing 1α-hydroxylase activity, therefore reducing $1,25(OH)_2D_3$ synthesis.[49,51-54] FGF-23 also inhibits PTH synthesis and secretion.[49,51-54] Klotho is a protein that functions as a coreceptor for FGF-23 in the kidney and parathyroid gland.[50,51,55] Abnormalities in the FGF-23/klotho axis were recently documented in critically ill foals.[30] Foals with high FGF-23 and low klotho serum concentrations had more severe disease and were more likely to die.[30]

Organs involved in Ca^{2+} homeostasis (parathyroid gland, thyroid gland, and kidney), known as the *calcium-sensing system,* express a calcium-sensing receptor (CaR) that is activated by extracellular Ca^{2+} and to lesser affinity by Mg^{2+}.[36] CaR activation inhibits PTH secretion and stimulates CT secretion in various species, including the horse.[15,16,39] In the kidney, CaR regulates Ca^{2+} and Mg^{2+} reabsorption independently of PTH. Renal CaR activation inhibits the furosemide-sensitive $Na^+/K^+/2Cl^-$ cotransporter in the distal nephron, resulting in diuresis and urinary waste of Ca^{2+} and Mg^{2+}, in humans and horses.[36,56]

Calcium Disorders in the Horse

Calcium dysregulation in the horse is associated with hypocalcemic and hypercalcemic disorders. Equine pathologic conditions characterized by abnormal calcium homeostasis include hypoparathyroidism,[57-59] primary hyperparathyroidism,[60-62] nutritional secondary hyperparathyroidism,[63] renal failure,[64] humoral hypercalcemia of malignancy,[43-47] vitamin D toxicity,[65,66] exercise-induced hypocalcemia,[67,68] idiopathic hypocalcemia of foals,[69] cantharidiasis,[70] gastrointestinal disease,[23,70-74] and sepsis.[6,8,23,71,73,74] Low Mg^{2+} concentrations can contribute to calcium dysregulation. Other conditions that may have abnormal calcium and phosphorus regulation include calcinosis,[75] idiopathic systemic granulomatous disease (sarcoidosis),[3] and equine bone fragility syndrome.[76]

Hypocalcemic Disorders

Conditions associated with hypocalcemia in the horse are presented in Box 41.2. Calcium deficiency can be acute or chronic. Horses with acute calcium deficiency develop clinical signs associated with neuromuscular excitability and decreased smooth muscle cell contractility (Box 41.3). A decrease in extracellular Ca^{2+} concentrations increases cell membrane Na^{+} permeability, decreasing the resting membrane potential, thus making muscle cells and nerve fibers more excitable. This results in spontaneous and continuous discharges, muscle fasciculations, tremors, tetany, and seizures. Tachycardia and cardiac arrhythmias may be present, although bradycardia may develop during severe hypocalcemia. Low serum Mg^{2+} concentrations are a frequent finding in horses with hypocalcemia and can further aggravate neuromuscular excitability. Chronic calcium deficiency in general is manifested as abnormal cartilage and bone development (DOD) and lameness. When calcium deficiency is suspected, feed analysis is recommended to determine if dietary calcium and phosphorus content is adequate.

Box 41.2

Equine Clinical Conditions in Which Hypocalcemia Has Been Reported

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Acute renal failure
Bicarbonate administration
Cantharidin toxicosis (blister beetles)
Chronic renal failure
Colic
During lactation (lactation tetany)
During transport (transit tetany)
Dystocia
Endotoxemia
Endurance exercise
Enterocolitis
Furosemide administration
Heat stroke
Hypomagnesemia
Late pregnancy
Liver disease
Magnesium toxicosis
Malignant hyperthermia
Oxalate ingestion
Pancreatitis
Pleuropneumonia
Postoperative myopathy
Primary hypoparathyroidism
Retained placenta
Rhabdomyolysis
Sepsis

Box 41.3

Clinical Signs Reported in Horses With Hypocalcemia

Anxiety
Asphyxia
Ataxia

Bruxism
Cardiac arrhythmias
Colic
Convulsions
Death
Depression
Dysphagia
Dyspnea
Excitation
Hyperhidrosis
Hypersalivation
Hyperthermia
Ileus
Laryngeal spasm
Muscle fasciculation
Seizures
Stiff gait
Synchronous diaphragmatic flutter
Tachycardia
Tachypnea
Tetany
Tremors
Trismus

Synchronous diaphragmatic flutter (SDF) or “thumps” may occur in horses with hypocalcemia associated with gastrointestinal disease,[23,70] endurance exercise,[77] hypoparathyroidism,[59,78] idiopathic hypocalcemia,[69] tetany (lactation, transport),[79] sepsis,[23] blister beetle toxicosis,[70,80] retained placenta,[23,81,82] and alkalosis.[2,3] SDF develops when depolarization of the right atrium stimulates action potentials in the phrenic nerve as it crosses over the heart. Clinically, these animals have a rhythmic movement on the flank from diaphragmatic contractions that are synchronous with the heartbeat.

During alkalosis there is increased Ca^{2+} binding to albumin resulting in ionized hypocalcemia. Alkalosis also increases Mg^{2+} binding to proteins. Exercising horses may develop alkalosis from hyperventilation (respiratory alkalosis) and chloride losses in the sweat (metabolic hypochloremic alkalosis).

Hypochloremic metabolic alkalosis may develop in horses with proximal gastrointestinal disease due to luminal chloride retention or losses in nasogastric reflux. Hypomagnesemia is common in horses with SDF and hypocalcemia.

Hypocalcemic tetany is the development of sustained skeletal muscular contractions in horses with hypocalcemia. Although hypocalcemic tetany can occur in any horse with hypocalcemia, lactating mares and horses transported for long distances are at greatest risk. Lactation tetany in mares may occur anytime immediately before foaling up to the end of the lactation period. In particular, mares producing large amounts of milk and eating diets low in calcium, grazing lush pastures, or performing physical work (draft mares) are at risk. Clinical signs may include anxiety, depression, ataxia, muscle fasciculations and tremors, stiff gait, tachypnea, dyspnea, dysphagia, hypersalivation, and hyperhidrosis (Box 41.3).[2,3]

Hypocalcemic seizures, seen in foals and adult horses, are caused by decreased CNS extracellular Ca^{2+} concentrations leading to increased neuronal excitability. Clinical signs usually improve with calcium treatment, although some animals may require repeated treatments. In general, horses and foals with refractory hypocalcemic seizures have a poor prognosis for recovery.

Ileus and *retained placenta in mares* are both believed to result in part from decreased smooth muscle tone and contractility secondary to hypocalcemia.[2,3] While in skeletal muscle most of the Ca^{2+} required for contraction comes from the sarcoplasmic reticulum, in smooth muscle Ca^{2+} comes from the extracellular space.[2] For this reason, any condition that results in hypocalcemia can decrease smooth muscle contractility. Retained placenta in mares occurs in up to 10% of foalings,[81] and it has been associated with hypocalcemia.[81]

Hypoparathyroidism in horses is characterized by hypocalcemia, hyperphosphatemia, hypomagnesemia, and decreased serum PTH concentrations. Primary hypoparathyroidism results from decreased secretion of PTH, while secondary hypoparathyroidism results from magnesium depletion and sepsis. There are few documented cases of primary hypothyroidism in horses.[58,78] Hypoparathyroidism should be suspected in any horse or foal with refractory hypocalcemia. Clinical signs include ataxia, seizures, hyperexcitability, SDF, tachycardia, tachypnea, muscle fasciculations, bruxism, stiff gait, recumbency, ileus, and colic.[2,3,58,83] Laboratory findings include hypocalcemia, hyperphosphatemia, and low or normal serum intact PTH concentrations. Hypomagnesemia may be present in some horses and foals.[6,23]

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Secondary (functional or acquired) hypoparathyroidism is poorly documented in the horse; however, some critically ill foals and horses with hypocalcemia have impaired parathyroid gland function,[6,8,23] which could be a form of hypoparathyroidism secondary to inflammatory cytokines and/or hypomagnesemia.

A syndrome consistent with hypoparathyroidism, characterized by abnormally low PTH concentrations, hypocalcemia, SDF, and muscle fasciculations, has been recognized in young Standardbred and Thoroughbred horses by the author. The condition develops progressively, initially associated with poor performance and SDF. In some animals it has been reported after a surgical procedure (e.g., castration), while in others it has been linked to excessive calcium supplementation. The underlying cause of this disorder remains unknown. Suppression of mechanisms responsible for calcium homeostasis from excessive calcium administration, immune-mediated parathyroiditis, cytokines, and mutations in the calcium-regulatory system are potential explanations.

A number of critically ill foals develop a form of hypocalcemia that is refractory to calcium treatment.[69] These foals have low or normal PTH concentrations despite hypocalcemia, suggesting hypoparathyroidism. This condition has been called *neonatal idiopathic hypocalcemia*.[69] It is believed that abnormal parathyroid gland function may result from increased inflammatory cytokines.[6,69] Prognosis for survival in foals with refractory hypocalcemia is poor.

Sepsis and *endotoxemia* are the most common causes of hypocalcemia in equine patients admitted to veterinary hospitals.[6,8,23] Clinical observations also indicate that hypocalcemia is common in horses with severe gastrointestinal disease.[23,71,73] Hypocalcemia in septic patients often results from parathyroid gland dysfunction (insufficient PTH secretion), as well as intracellular calcium sequestration.[2,3,23] Inflammatory mediators known to be increased in horses and foals with sepsis and endotoxemia such as TNF-, IL-1, and IL-6 have been shown to increase CaR activation and decrease PTH secretion by equine parathyroid cells.[16]

Horses under intense *exercise* develop electrolyte and acid-base abnormalities. *Exercise-induced hypocalcemia* may result from Ca^{2+} losses in the sweat; intracellular movement of Ca^{2+}; increased Ca^{2+} binding to albumin, lactate, phosphate, and bicarbonate during alkalosis; and parathyroid gland dysfunction.[2,3,67,68]

Oxalate toxicity causes hypocalcemia by interfering with calcium absorption; a diet consisting of 1% of oxalate or higher can reduce most intestinal calcium absorption.[84] It is important that the equine diet contains less than 0.5% of oxalate or a calcium–to–oxalate ratio over 1:0. Clinical signs associated with oxalate excess are those of phosphate excess, calcium deficiency, and nutritional hyperparathyroidism. Signs of acute hypocalcemia may develop.[85] Neurologic signs from excessive bone loss and vertebral fractures have been documented.[85] Oxalates are present in several grasses and toxic plants (Table 41.5).

Equine cantharidiasis (blister beetle toxicosis) is a condition reported in the southwestern and midwestern United States and results from the ingestion of alfalfa contaminated with beetles (*Epicauta* spp.) that produce cantharidin (cantharidic acid).[70,80] Clinical signs develop from the irritant effects of cantharidin on mucosal surfaces (gastrointestinal and urinary tracts). Cantharidin often causes acute hypocalcemia and hypomagnesemia. Thus, clinical signs of severe hypocalcemia (muscle fasciculations, SDF, ataxia, dyspnea, laryngeal spasm, and cardiac arrhythmias) may be present.[70,80] It is unclear why these horses develop hypocalcemia; however, it may be a combination of severe gastrointestinal disease associated with acute renal tubular necrosis and parathyroid gland dysfunction.

Hypocalcemia and hypomagnesemia are common findings in horses with *acute renal failure*.[2,3] Reabsorption of Ca^{2+} and Mg^{2+} in the kidney is highly dependent on functional tubular cells,[2] and these cells are susceptible to various insults (hypoxia, ischemia, toxins).[22]

The pathogenesis of hypocalcemia in *exertional rhabdomyolysis* is unknown.[86] It is speculated that damage to muscle fibers during intense exercise results in Ca^{2+} influx and sequestration in the sarcoplasmic reticulum.

Treatment of Hypocalcemia

Calcium deficit, maintenance, losses, and sequestration should be considered when treating hypocalcemia. If parathyroid gland function is normal, minimal to no calcium supplementation may be required. Most horses with hypocalcemia do not show overt signs of hypocalcemia. Lack of therapy, however, can result in development of additional complications, in particular ileus. Horses with functional kidneys can rapidly eliminate large amounts of calcium, and hypercalcemia from excessive calcium administration is rare, particularly if the

horse is receiving fluid therapy. When possible, calculate the calcium deficit on the basis of Ca^{2+} concentrations (mg/dL = mmol/L × 4). From a practical standpoint, the use of standard formulas for electrolyte deficit can be used (multiplied by 10 as calcium is expressed as mg/dL). Total calcium can be used to estimate calcium deficit, keeping in mind that total calcium has more variability than Ca^{2+} concentration as it is dependent on plasma protein concentration. A horse can have total hypocalcemia, but serum Ca^{2+} concentrations may be within the normal range (pseudohypocalcemia), and calcium administration may not be necessary. It is also important to remember that 9.3% of calcium gluconate is elemental calcium, which means that a 23% solution of calcium gluconate contains 2.14% of elemental calcium or 21.4 mg/mL. Avoid the use of injectable calcium chloride as it can cause subcutaneous irritation.

Frequent monitoring of Ca^{2+} concentration and adjustment of dosage is important. Rapid administration of calcium may result in cardiovascular complications, especially in septic horses, which may be more vulnerable to the toxic effects of calcium. In our experience, horses can handle high calcium dosages. For an average-size horse with mild ionized hypocalcemia (5.0 mg/dL), we administer 50 mL of 23% calcium gluconate per 5 L of crystalloid fluids, at a fluid rate twice maintenance. Oral treatment with calcium salts is feasible in some horses with non–life-threatening, refractory hypocalcemia. Dicalcium phosphate and calcium carbonate (limestone, 200 to 300 g/day) can be used safely (Table 41.3). In horses with refractory hypocalcemia, measuring Mg^{2+} concentrations is highly recommended.

Hypercalcemic Disorders

Hypercalcemic disorders in horses are divided into two groups: (1) parathyroid gland-dependent hypercalcemia (develops due to parathyroid gland hyperfunction) and (2) parathyroid gland-independent hypercalcemia (develops despite parathyroid gland suppression). This distinction is clinically relevant in the differential diagnosis and interpretation of specific diagnostic tests, including intact PTH, PTHrP, Ca^{2+}, PO_4, and vitamin D concentrations. Parathyroid gland-dependent hypercalcemia in the horse is limited to primary hyperparathyroidism, while parathyroid-independent hypercalcemia results from various conditions (secondary hyperparathyroidism, chronic renal failure, hypercalcemia of malignancy, hypervitaminosis D, calcinosis, and idiopathic systemic

granulomatous disease).

Primary hyperparathyroidism results from an excessive and autonomous synthesis and secretion of PTH by the parathyroid gland that is not responsive to the negative feedback of Ca^{2+}. Primary hyperparathyroidism has been reported in ponies and horses,[58,60-62,87,88] and results from parathyroid adenomas or parathyroid hyperplasia. The elevated PTH concentrations increase renal Ca^{2+} reabsorption, decrease PO_4 reabsorption, increase $1,25(OH)_2D_3$ synthesis, and increase bone resorption (osteodystrophia fibrosa). Laboratory findings include hypercalcemia, hypophosphatemia, hypocalciuria, and hyperphosphaturia. PTHrP concentrations are within normal limits (low or undetectable). Clinical findings include facial bone enlargement, lameness, and a poor body condition. Radiographic findings include decreased long and facial bone density, fibrous proliferation of the maxilla and mandible, and loss of the lamina dura surrounding the molars.[60] Endoscopic examination may reveal narrowing of the nasal passages.

Nuclear scintigraphy and ultrasonography were successfully used to detect and remove a functional parathyroid adenoma in a pony.[87] Ultrasonography was useful to identify parathyroid tissue within the thyroid gland of a horse with signs and laboratory findings consistent with primary hyperparathyroidism.[88]

Postmortem findings include enlargement of the maxilla and mandible, stenosis of the nasal passages, and loosening of premolars and molars. Histologic evaluation of the parathyroid gland is important to confirm the diagnosis of primary hyperparathyroidism; however, finding the parathyroid glands in the horse is a challenge due to their small size and variable location.[2,16]

Secondary hyperparathyroidism is characterized by excessive secretion of PTH in response to hyperphosphatemia and hypovitaminosis D from chronic renal failure (renal secondary hyperparathyroidism) or hyperphosphatemia and/or hypocalcemia from nutritional imbalances (nutritional secondary hyperparathyroidism). *Renal secondary hyperparathyroidism* is not a well-recognized disease in the horse. Unlike humans and small animals in which chronic renal failure results in hyperphosphatemia, horses with chronic renal failure (CRF) often have hypophosphatemia. Moreover, the hypercalcemia in horses with CRF is the result of renal Ca^{2+} retention rather than increased PTH concentrations.[2,3,89] The increased Ca^{2+} concentrations in turn decrease PTH secretion; thus, PTH concentrations in horses with CRF frequently are below or within the normal range.[3,57] In contrast, *nutritional secondary*

hyperparathyroidism is a well-documented pathologic condition of the horse[2] and is described in more detail as follows.

Nutritional Secondary Hyperparathyroidism

Definition and Etiology

Horses fed diets low in calcium, high in phosphorus, high in oxalates, or with a phosphorus–to–calcium ratio of greater than or equal to 3 : 1 may develop nutritional secondary hyperparathyroidism, also known as bran disease, miller's disease, big head, osteodystrophia fibrosa, osteitis fibrosa, and equine osteoporosis.[2,3,63,90-94] Pastures and toxic plants with high content of oxalates (Table 41.6) predispose to secondary hyperparathyroidism. The condition remains endemic in some areas in Latin America, North America, Africa, Asia, Australia, and Europe.[63,85,90,92,95-99]

Pathogenesis

Excessive dietary PO_4 reduces intestinal calcium absorption and results in hyperphosphatemia. With advances in animal nutrition, this condition is rarely associated with excessive grain feeding, but more commonly linked to the ingestion of oxalate-rich plants. Large amounts of oxalate (oxalic acid) bind dietary calcium to form insoluble calcium oxalate (CaC_2O_4), reducing calcium absorption. Oxalate also binds magnesium, but the complex (MgC_2O_4) is more soluble than CaC_2O_4 and more likely to be absorbed. Both high-phosphorus and low-calcium diets induce parathyroid cell hyperplasia and stimulate PTH secretion in the horse.[3,100] Hyperphosphatemia directly stimulates PTH secretion and inhibits renal $1,25(OH)_2D_3$ synthesis. Because $1,25(OH)_2D_3$ inhibits parathyroid cell proliferation, low $1,25(OH)_2D_3$ concentrations contribute to parathyroid cell hyperplasia and PTH secretion. Hyperphosphatemia also results in the formation of calcium phosphate precipitates, further reducing blood Ca^{2+} and inducing additional PTH secretion. PTH increases osteoclastic activity, bone resorption, and bone loss (Fig. 41.17).[101] There is facial bone loss with excessive accumulation of subperiosteal unmineralized connective tissue (osteodystrophia fibrosa) resulting in facial enlargement (big head) (Fig. 41.18). Because this is a condition of slow progression, the homeostatic mechanisms that regulate extracellular Ca^{2+} concentrations (PTH, vitamin D, calcitonin) in general are

effective in maintaining Ca^{2+} within the normal range. These horses preserve normocalcemia at the expense of the skeletal reserves and rarely develop clinical signs of acute hypocalcemia.

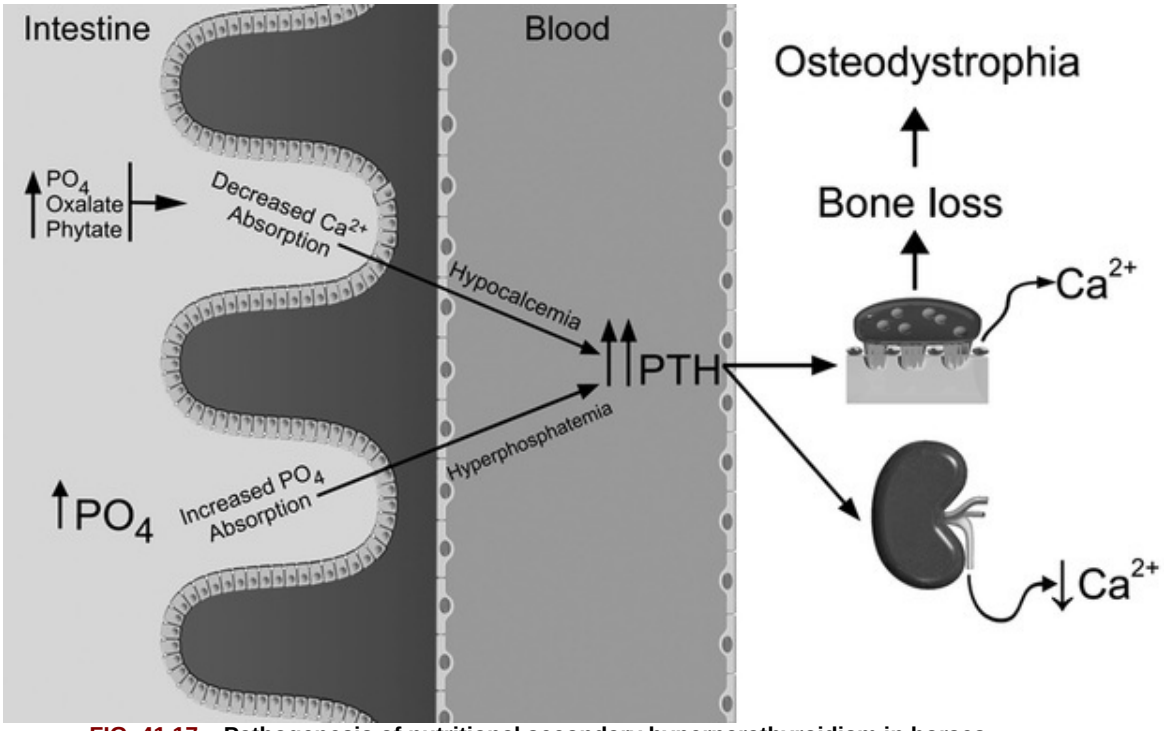


FIG. 41.17 **Pathogenesis of nutritional secondary hyperparathyroidism in horses. Excessive dietary phosphorus reduces intestinal absorption of calcium and induces hyperphosphatemia. In addition, phosphate, oxalate, and phytate bind dietary calcium to reduce absorption. Both high-phosphorus and low-calcium diets induce parathyroid cell hyperplasia and stimulate PTH secretion. PTH increases osteoclastic activity and bone resorption, resulting in bone loss (osteodystrophia fibrosa).**

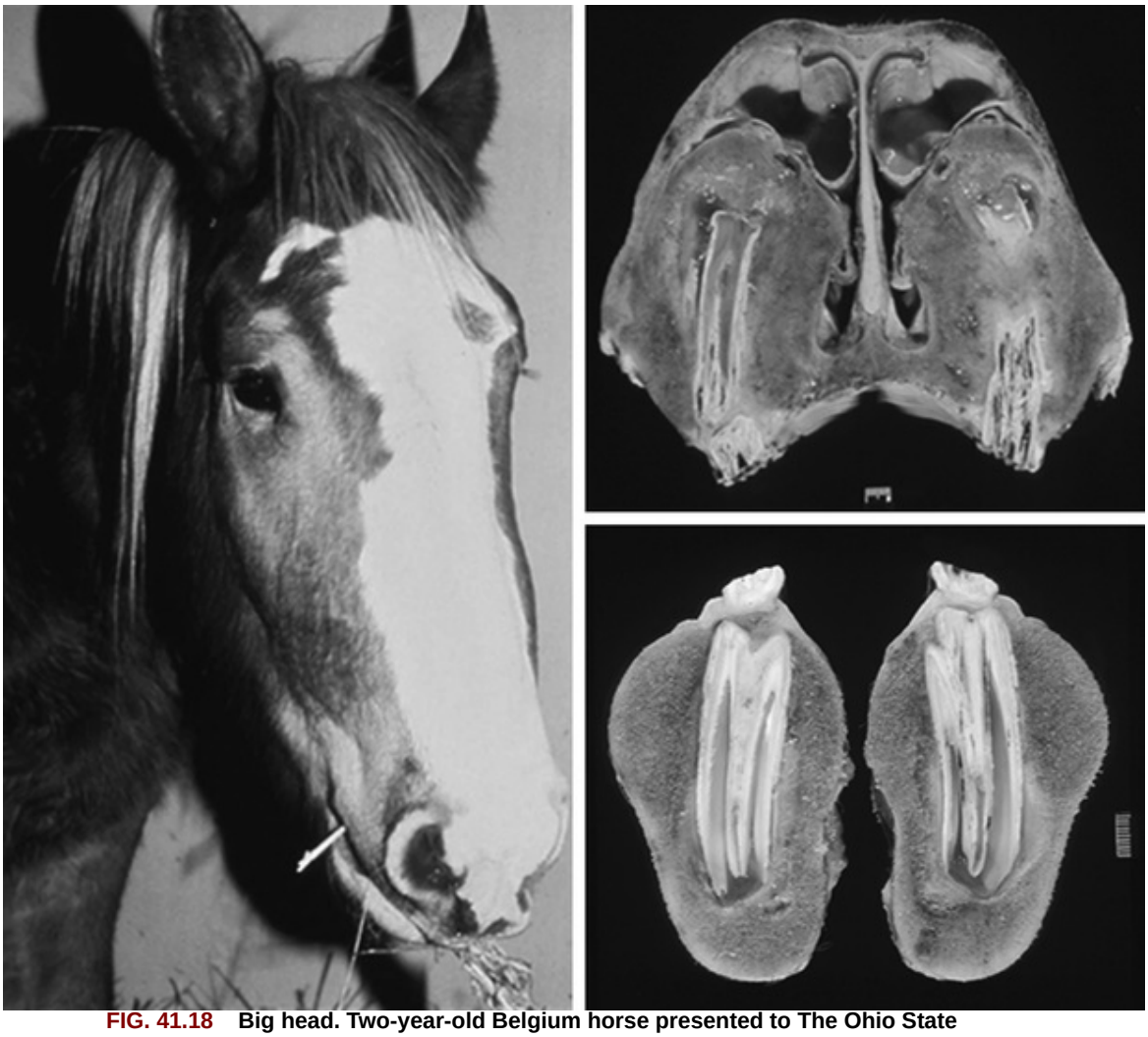


FIG. 41.18 **Big head. Two-year-old Belgium horse presented to The Ohio State University Veterinary Medical Center with clinical signs consistent with nutritional secondary hyperparathyroidism, including facial bone enlargement and upper respiratory noise. The horse was fed excessive amounts of grain. There was narrowing of the nasal passages, loss of bone mass, and excessive accumulation of unmineralized bone matrix (osteodystrophia fibrosa) in maxillary and mandibular bones.**

Clinical Signs

Clinical signs result from increased bone resorption and include unthriftiness; intermittent, shifting lameness; and a stiff gait. Younger animals may develop physitis and limb deformities. There is a typical and symmetric swelling of the facial bones; however, facial bone enlargement may not be evident in old horses (see Fig. 41.18). The facial changes and increased bone resorption around molars and premolars may result in masticatory problems. These horses are physically weak and may be in poor body condition from the pain associated with lameness

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and mastication. In severe cases, teeth may become loosened and spontaneous fractures of long bones may occur. Upper airways obstruction, dyspnea, and epiphora may be present.[3,63,90-92] Vertebral demineralization and compressive neurologic signs may occur.[85]

Acute hypocalcemia may develop from high dietary oxalate content combined with a low-calcium diet.[85] In addition, absorption of soluble oxalate can chelate calcium in circulation to worsen signs of hypocalcemia. Soft tissue mineralization was described in a foal suspected of having nutritional secondary hyperparathyroidism.[102]

Laboratory Findings

Typical laboratory changes in horses with nutritional secondary hyperparathyroidism include hyperphosphatemia, hypocalcemia or normocalcemia (hypercalcemia is unusual), and increased intact PTH concentrations, especially if the animal is eating a low-calcium or high-phosphorus or high-oxalate diet at the time of evaluation. The urinary fractional excretion of calcium is low (hypocalciuria) while the excretion of phosphorus is increased (hyperphosphaturia). Urinary excretion of phosphorus greater than 2% is common in horses ingesting oxalate-rich plants.[95] Serum alkaline phosphatase activity and collagen degradation products may be increased. Laboratory findings may be within normal limits if the animal is eating a balanced diet.

Radiologic Findings

Decreased bone density is frequent; however, bone mass must be decreased by 30% before it can be detected radiographically.[3] Decreased facial bone density along with fibrous proliferation is a consistent finding. Resorption of alveolar sockets and loss of the dental lamina dura may be present before other radiographic changes are present, and long bones are affected only in advanced cases. Radiolucency and osteopenia may be evident in long bones, vertebrae, and ribs early on; however, a patchy osteoporotic pattern may be present, in particular with chronic oxalate toxicity.[85]

Necropsy

There is increased bone resorption, bone fragility, accumulation of fibrous tissue around facial bones, obstruction of nasal passages, and parathyroid gland

hyperplasia (see Fig. 41.18).

Treatment

Diet evaluation is indicated. Eliminate or reduce any grain-based diet and avoid high-containing oxalate feeds. The addition of alfalfa to the diet may be helpful. Supplementation with calcium carbonate (limestone; $CaCO_3$) or dicalcium phosphate may result in improvement.[63] Ground limestone, which contains no phosphorus, is recommended as a good source of calcium (35%). An affected animal may require a total of 100 to 300 g/day. The diet should have a Ca:P ratio of 3 to 4 : 1. Limestone may decrease feed palatability, and adding molasses should be considered. Supplementation with vitamin D has been proposed. Horses may require 9 to 12 months for complete recovery, although some bone changes may not regress. Confinement of severely affected horses is advised. The use of NSAIDs may be indicated in some animals. Bisphosphonates have not been evaluated with this condition.

Hypervitaminosis D

Definition and Etiology

The ingestion or administration of ergocalciferol (vitamin D_2) or cholecalciferol (vitamin D_3) results in disturbances of the calcium and phosphorus metabolism in horses.[65,66,103-105] Ingestion of plants containing 1,25$(OH)_2$D-like compounds results in typical clinical signs of vitamin intoxication.[103-109] The ingestion of *Solanum glaucophyllum (S. malacoxylon)* results in a condition known as “enteque seco” in Argentina and “espichamento” in Brazil.[105,106,108,109] In Hawaii, *Solanum sodomaeum,* and the southern United States, jessamine *(Cestrum diurnum)* may cause hypervitaminosis D.[103,104,107,109] In Europe, the ingestion of golden oat *(Trisetum flavescens)* results in enzootic calcinosis.[110-112]

Pathogenesis

Hypervitaminosis D increases the intestinal absorption and renal reabsorption of calcium and phosphorus. Hyperphosphatemia is the most consistent and early laboratory finding in horses with vitamin D intoxication.[65,66,102] Serum calcium concentrations may be increased or within the normal range.[65,66,102,103,106]

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Hypervitaminosis D results in parathyroid cell atrophy and decreased PTH secretion. In addition, hypercalcemia contributes to decrease PTH secretion, lowering bone turnover. Azotemia and hyposthenuria may be present.[65,66]

Clinical Signs

Most clinical findings in horses with hypervitaminosis D are the result of hyperphosphatemia. These horses often have weight loss, poor appetite, lameness, and painful stiffness, and they are reluctant to move. Acute death from severe cardiovascular mineralization has been reported.[65,66] Polyuria and polydipsia are frequent findings. In cases with hypercalcemia, mineral deposition in the kidneys may precede mineralization elsewhere, resulting in renal failure. Lameness is probably due to calcification of ligaments and tendons.

Radiologic Findings

These horses often have increased bone density, decreased size of the medullary cavity, and increased calcification of soft tissues.

Treatment

Reducing dietary calcium intake and the use of calcium-binding agents such as sodium phytate has been proposed.[105] Glucocorticoids are used in humans with hypervitaminosis D because they may inhibit the vitamin D–mediated intestinal calcium absorption. In equids, glucocorticoids decrease intestinal absorption of calcium, increase urinary excretion of calcium, and decrease bone resorption.[20,21] Dexamethasone has been administered to horses with hypervitaminosis D with variable results. Drugs that suppress osteoclastic bone resorption (bisphosphonates) have not been evaluated in horses with hypervitaminosis D. The prognosis for horses with hypervitaminosis D is poor.

Necropsy Findings

Postmortem examination may reveal mineralization of soft tissues. Mineralization of the endothelium of the aorta and pulmonary vessels, as well as of the endocardium, is frequent. Mineralization may be found in the kidney, liver, lymph nodes, lungs, ligaments, and tendons. Osteopetrosis of epiphyses and metaphyses may be present. Atrophy of the parathyroid gland can be

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severe.[107]

Hypercalcemia of Malignancy

Humoral hypercalcemia of malignancy (HHM, pseudohyperparathyroidism) is a paraneoplastic condition in which humans and animals develop hypercalcemia associated with various types of tumors. These malignancies secrete parathyroid hormone–related protein (PTHrP), which interacts with PTH receptors to increase renal reabsorption of Ca^{2+} and bone resorption.[113] In horses, HHM has been associated with squamous cell carcinoma, adrenocortical carcinoma, lymphosarcoma, multiple myeloma, and ameloblastoma.[2,3] Laboratory findings include hypercalcemia, hypocalciuria, hypophosphatemia, hyperphosphaturia, normal or low PTH concentrations, and increased PTHrP concentrations. HHM should be suspected in any horse with hypercalcemia, no evidence of renal disease, and normal PTH concentrations.

Neonatal Hypercalcemia and Asphyxia

Clinical observations indicate that a number of critically ill newborn foals develop hypercalcemia associated with peripartum asphyxia (neonatal encephalopathy). The mechanisms underlying this problem remain unknown, although it is speculated to be associated with placental insufficiency.

Idiopathic Systemic Granulomatous Disease

This is an immune disorder documented in horses and ponies (equivalent to human sarcoidosis), in which crusty skin lesions develop along the coronary bands and mucocutaneous junctions. Granuloma formation in multiple organs is the hallmark.[114-116] Some animals may develop hypercalcemia.[114] Lesion distribution may resemble those of multisystemic eosinophilic epitheliotropic disease of horses. It has been proposed that excessive production of vitamin D or PTHrP by granulomatous cells leads to hypercalcemia in these animals.[3,114] Similar lesions have been documented in horses and cattle grazing hairy vetch *(Vicia villosa).*[117,118]

Calcinosis

Soft tissue calcification (liver, heart, kidney, lungs, vessels, muscle), hyperphosphatemia, and elevation of the calcium × phosphorus product were documented in horses with a number of pathologic conditions.[75] This disorder is different than enzootic calcinosis from the ingestion of plants with vitamin D–like activity. The mechanism by which these animals develop calcinosis is unclear, although it is likely that hyperphosphatemia plays a role.

Equine Bone Fragility Syndrome

The equine bone fragility syndrome (BFS) or silica-associated osteoporosis (SAO) is a chronic and progressive disorder of horses characterized by increased respiratory efforts, exercise intolerance, skeletal deformation, lameness, stiffness, and fractures.[119,120] (Also see the Equine Bone Fragility section in Chapter 38.) Horses of any age are affected.[119,121] Bowing of appendicular bones (scapula in particular), lordosis, and neurologic signs from vertebral deformation and spinal cord compression have been documented.[119,120] The pathogenesis remains unclear, but it has been associated with pulmonary silicosis. Radiographically, there is osteopenia and a respiratory pattern consistent with silicosis. Intracellular silica crystals (silica dioxide) in bronchoalveolar cells and pulmonary macrophages, as well as evidence of dystrophic calcification, are consistent with SAO. A high concentration of cristobalite, a fibrogenic form of silicate, is found in regions of California where the condition is more common (Monterey shale soil).[76,119,120,122] Histologically, there is excessive osteoclastic activation and bone resorption. In the respiratory tract there is pulmonary granuloma formation, fibrosis, and lymphadenitis.[76] The diagnosis of BFS is based on clinical history, clinical findings, geography, and imaging (ultrasonography, radiography, and scintigraphy). Nuclear scintigraphy is the best diagnostic modality, but scapular ultrasonography can be diagnostic in some animals.[121] Management of these horses depends on clinical signs and prevention. Nonsteroidal antiinflammatory drugs should be considered in animals with orthopedic pain considering that their use can increase the risk of fractures. Glucocorticoids may be necessary in severe pulmonary disease, but they also enhance bone loss. This is one of the few equine conditions in which bisphosphonates may be indicated.[123] Zoledronate has reduced the severity of clinical signs and scintigraphic findings in horses with BFS.[123] Decreased physical activity and dietary manipulation are recommended.

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Treatment of Hypercalcemia

Hypercalcemia as an equine emergency is rarely presented; however, the differential diagnosis of hypercalcemia is important for its treatment. Few disorders in the horse are associated with hypercalcemia (hyperparathyroidism, CRF, HHM, hypervitaminosis D). Mild to moderate hypercalcemia in general is not life-threatening, and treatment should be directed to the primary cause. Parathyroidectomy will be treatment of choice for primary hyperparathyroidism.[87] Bisphosphonates and calcimimetics (cinacalcet) are also recommended in people with hyperparathyroidism[124,125]; however, information on their use for this condition in horses is lacking. Bisphosphonates can cause renal injury in people and, anecdotally, in horses as well. In theory, calcitonin could reduce serum calcium concentrations, but this effect is transient. Surgical removal of epithelial tumors can be a successful treatment for HHM. Some horses with lymphosarcoma may show improvement with chemotherapy. Bisphosphonates and gallium nitrate have shown benefits in reducing serum calcium and bone resorption in people with HHM.[126] Bisphosphonates improved signs in horses with BFS.[123] In severe cases of hypercalcemia that may require medical treatment, initial therapy should include the administration of 0.9% saline solution and loop diuretics. Furosemide is the diuretic of choice because it inhibits the $Na^+/K^+/2Cl^-$ cotransporter in the distal tubules, increasing the urinary excretion of calcium. Thiazide diuretics are contraindicated because they stimulate calcium reabsorption. Glucocorticoid administration should be considered, in particular for horses with hypervitaminosis D.

Phosphorus Disorders in the Horse

Disorders of phosphorus homeostasis can be acute or chronic, resulting in hypophosphatemia or hyperphosphatemia. In critically ill horses hypophosphatemia is more frequent, while in foals hyperphosphatemia is more common.[6,127]

Hypophosphatemic Disorders

Hypophosphatemia develops from reduced intestinal PO_4 absorption, increased urinary PO_4 excretion, and intracellular shift of PO_4 (redistribution). Acute hypophosphatemia often reflects PO_4 redistribution from the extracellular to

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intracellular compartment and not necessarily imply total body PO_4 depletion. However, PO_4 depletion may occur in animals that have been sick for many days. From personal experience, hypophosphatemia seems to be more common in small equids, usually associated with hyperlipemia and parenteral nutrition. Intestinal PO_4 absorption is reduced by gastrointestinal disorders, hypovitaminosis D, PO_4-deficient diets, and interfering substances. Urinary excretion of PO_4 is increased with hyperparathyroidism, hypovitaminosis D, malignancies that secrete phosphatonins or PTHrP, chronic renal failure, and drugs. Sepsis, carbohydrate-rich diets, hyperglycemia, insulin administration, starvation, refeeding syndrome, hyperlipemia, and parenteral nutrition (hyperglycemia, hyperinsulinemia) decrease serum PO_4 mainly through insulin-mediated intracellular shift of PO_4 and enhanced glycolysis. Catecholamines act by a mechanism similar to insulin shifting PO_4 into the cell. Alkalosis induces hypophosphatemia by stimulating phosphofructokinase activity (glycolysis) and the need for PO_4 to synthesize ATP. In horses with a history of malnutrition, close monitoring of serum PO_4 concentrations is indicated once caloric intake resumes because they may develop refeeding syndrome. Clinical signs of acute hypophosphatemia in horses often go unnoticed. Signs are consequence of PO_4 regulatory functions on energy metabolism, cell membrane stability, and ion transport.[3] These include muscle weakness, fasciculations, dysrhythmias, neuromuscular excitability, ileus, and cell membrane fragility and lysis (hemolysis, rhabdomyolysis). Signs from mild hypophosphatemia are difficult to document. Severe hypophosphatemia can result in tissue hypoxia from reduced erythrocyte content of 2,3-bisphosphoglycerate. Chronic hypophosphatemia is rare in horses and manifests as weight loss, weakness, depraved appetite (pica), reduced bone density, DOD, lameness, and hemolysis. Ideally, therapy for hypophosphatemia would be based on the extracellular deficit, which should be overestimated because PO_4 is a major intracellular anion and cellular depletion is likely to occur in animals with prolonged hypophosphatemia. Preferred parenteral solutions include potassium phosphate and sodium phosphate. Critically ill horses can be supplemented with oral potassium phosphate or sodium phosphate (chemical grade or with phosphate-based enema solutions). Oral supplementation with dicalcium phosphate is a good option in animals with chronic phosphate deficiency.

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Hyperphosphatemic Disorders

Hyperphosphatemia develops from increased PO_4 absorption; acute renal injury; hypoparathyroidism; vitamin D toxicity; metabolic acidosis; cell lysis (hemolysis, rhabdomyolysis, tumor necrosis); or iatrogenic causes.[3] Lactic acidosis may cause hyperphosphatemia by shifting PO_4 to the extracellular compartment. Metabolic acidosis and high intracellular ATP concentrations inhibit phosphofructokinase, a key enzyme in glycolysis that uses PO_4 for carbohydrate phosphorylation. Overuse of phosphate-based enemas can cause hyperphosphatemia in foals. Unlike other species, chronic renal failure is an uncommon cause of hyperphosphatemia in horses. Inappropriate blood sample handling can result in spurious hyperphosphatemia. Hemolysis, hyperbilirubinemia, hypertriglyceridemia (hyperlipidemia), and hyperproteinemia can falsely elevate PO_4 values (pseudohyperphosphatemia). Multiple myeloma can cause pseudohyperphosphatemia from high circulating immunoglobulin concentrations. Acute hyperphosphatemia may cause hypocalcemia from interactions between PO_4 and Ca^{2+} and reduced renal synthesis of $1,25(OH)_2D$. Hyperphosphatemia is common in critically ill foals.[6,127] The pathogenesis of chronic hyperphosphatemia is described in the Nutritional Secondary Hyperparathyroidism section. Clinical signs of acute hyperphosphatemia are similar to those of acute hypocalcemia and include tetany, hyperexcitability, muscle fasciculations, colic, and dysrhythmias. Signs of chronic hyperphosphatemia are those of calcium deficiency, including lameness, orthopedic pathologies, fractures, and osteodystrophia fibrosa. Treatment of hyperphosphatemia is based on primary pathology and duration, which in some instances may not be necessary. In acute hyperphosphatemia, fluid therapy and diuretics are indicated. Dietary PO_4 restriction must be implemented in chronic hyperphosphatemia. Dialysis and phosphate binders are impractical and expensive. Calcium carbonate is a cheap phosphate binder that also provides calcium supplementation. Phosphate-binding polymers (e.g., sevelamer) are the most effective way to treat chronic hyperphosphatemia in other species, but their use is not described in horses.

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Endocrine Dysfunction in Critical Illness

Kelsey A. Hart • Ramiro E. Toribio

The endocrine response to illness is vital for ensuring organ, tissue, and cellular health during disease and includes simultaneous increases and decreases in the activity of multiple endocrine axes. Pathophysiologic stressors alter the activity of these pathways at multiple levels and through different mechanisms, with the ultimate aim of supporting the patient through the stress of illness and subsequent restoration of homeostasis. In general, the endocrine response in critical illness results in stimulation of a variety of cardiovascular, metabolic, and immune responses that help support perfusion and organ function, heal damaged tissues, and eliminate pathogens. In addition, some aspects of growth and metabolism are suppressed to free up resources to assist with meeting these goals. The endocrine response ensures that a patient responds predictably and appropriately to therapeutic interventions. Thus, clinicians depend on their patients' having intact endocrine function to aid in their recovery from a variety of diseases. This section will discuss general aspects of endocrine assessment in the critically ill patient and current perspectives on the function of specific endocrine systems in critical illness, including the hypothalamic-pituitary-adrenal (HPA) axis, renin-angiotensin-aldosterone system (RAAS) and blood volume/blood pressure regulation, endocrine pancreas and energy metabolism, thyroid axis, parathyroid gland, and growth hormone (GH) axis.

Assessment of Endocrine Function in the Critically Ill Patient

Endocrine dysfunction during critical illness can be due to a primary underlying and previously unrecognized endocrine disorder (such as undiagnosed PPID in a geriatric horse undergoing colic surgery to correct a strangulating small intestinal lesion), or secondary endocrine dysfunction can develop as a result of factors related the underlying severe illness (such as development of insulin resistance in an endotoxemic horse with colitis). The latter situation is more common, as a large number of studies have provided evidence that transient secondary dysfunction in one or more of the aforementioned endocrine systems is common in critical illness and can be associated with substantial increases in disease

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morbidity and mortality in both people and animals.[1-6] This sort of endocrine dysfunction in the critically ill patient exemplifies the “two-hit” model, with the first hit being the primary critical illness and resultant physiologic stress and suppression of endocrine function and the second hit being the inability to respond appropriately to the physiologic stress of the primary illness due to the endocrine dysfunction. It is important to note that because there is a great deal of redundancy and “cross-talk” between individual endocrine systems, dysfunction in one system can impact the function of multiple endocrine pathways. Further, a number of studies have demonstrated that endocrine intervention can improve outcomes in some critically ill patients with evidence of disturbed endocrine function.[1,4,6] Thus, accurate assessment of endocrine function is vitally important in the critical care setting.

In health, mechanisms for assessment of endocrine function include measurement of basal circulating hormone concentrations and dynamic tests, including suppression tests if overactivity of an endocrine access is suspected and stimulation tests if insufficient endocrine activity is suspected. Tests that induce physiologic stress such as the insulin tolerance test can also be used to globally assess endocrine axis function. These same assessment options are available in a clinical setting but are often too dangerous to be used in critically ill patients. Cutoff values for plasma hormone concentrations and dynamic test responses that suggest appropriate function in the unstressed patient are not applicable to the critically ill patient undergoing severe pathophysiologic stress. The critically ill patient is also in a dynamic state, with a constantly changing and evolving endocrine response,[7] so one-time responses do not always accurately represent endocrine function. Negative feedback mechanisms that govern endocrine axis function during health may not operate normally during critical illness. Availability of biologically active hormones to target tissues may be altered in illness, due to alterations in levels of hormone binding proteins, post-translational modifications, and variations in hormone metabolism. Hormone activity at the target organ might be altered by changes in receptor number, affinity, or signaling due to factors associated with the primary disease. Finally, while commercial assays are available for measurement of most of the hormones of interest in critically ill people, availability of these assays for veterinary species can be limited and turnaround time for receipt of test results may be unacceptably long for critically ill patients requiring immediate diagnosis and treatment.

Thus, endocrine assessment in the critically ill patient often requires

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assessment of function via multiple methodologies. Basal hormone concentrations from multiple levels of an endocrine axis can be assessed simultaneously, and dynamic testing can be assessed in conjunction with basal hormone concentrations to provide a more comprehensive picture of the function of the entire axis. Free, biologically active hormone concentrations can be measured if alterations in binding proteins are anticipated. Methodology for detection of hormone activity at the level of the target tissue would be ideal but is not commercially available for most hormones; thus, clinical evaluation of the patient with a high index of suspicion for evidence of endocrine dysfunction can be an important additional "test" to assess tissue hormone activity in the critical care setting. For example, as detailed later, critical illness−related corticosteroid insufficiency (CIRCI) appears to be fairly common in people with septic shock and can be treated with cortisol replacement in the form of low doses of hydrocortisone. Frequently used methodology for CIRCI diagnosis includes documentation of a low basal cortisol concentration, a decreased cortisol response to ACTH stimulation testing with a variety of protocols, or decreased free cortisol concentration. However, none of these methods are perfect and can result in false negatives and false positives, so in some intensive care units (ICUs) the decision for hydrocortisone treatment is based simply on clinical evidence of CIRCI (persistent hypotension in the face of fluid and vasopressor therapy) rather than specific endocrine test results.

In sum, because endocrine responses are necessarily, dramatically, and variably altered in critical illness, it can be difficult to define what degree of alteration is expected and appropriate and what degree is inappropriate in the critically ill patient. Currently available methodology can be used to assess endocrine function during critical illness in most patients, but expectations for universally applicable guidelines for test interpretation and diagnostic cutoff values are likely unrealistic. Rather, the astute clinician must be aware of common endocrine disturbances seen in critical illness and consider testing and/or endocrine intervention in a timely fashion to prevent development of more severe and potentially fatal complications.

HPA Axis

The HPA axis is the master regulator of various endocrine systems. It modulates cardiovascular, metabolic, and immune activity in response to physiologic needs and stressful events, with the ultimate goal of maintaining organ function. It

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regulates circulating concentrations of corticosteroid hormones, which are vital for appropriate stress responses in both health and disease. Upon stressful stimulation, the hypothalamus releases corticotropin-releasing hormone (CRH, CRF) and arginine vasopressin (AVP) into the pituitary portal system to stimulate pituitary corticotrophs to secrete adrenocorticotropic hormone (ACTH). In horses, AVP is an important releasing factor for ACTH. ACTH acts on the *zona fasciculata* of the adrenal cortices to induce the synthesis and secretion of the glucocorticoid hormones. To a lesser extent, ACTH also induces aldosterone secretion by the adrenocortical *zona glomerulosa*.

The predominant circulating glucocorticoid hormone in animals, including horses, is cortisol, though corticosterone is also present at moderate concentrations in cattle and goats. [Note: because HPA axis dysfunction in critically ill animals is best characterized in horses and the individual glucocorticoid hormones have similar effects, cortisol will be used to refer to all glucocorticoid hormones for the purpose of this review.]

Cortisol has diverse systemic effects on a variety of target tissues; during critical illness, the sum of these effects helps to maintain blood pressure, coordinate energy metabolism, and regulate the immune and inflammatory response. However, a number of studies suggest that up to 40% to 60% of people, dogs, and horses with sepsis and septic shock suffer from transient HPA axis dysfunction (CIRCI).[2,4,8,9] In these patients, the cortisol response to illness is inadequate for the existing degree of physiologic stress and ACTH concentrations. Circulating cortisol concentrations may be increased from basal levels found in healthy unstressed individuals but are still not adequate to meet demands to support and regulate cardiovascular, metabolic, and inflammatory responses.[4,10] In some patients with CIRCI, cortisol concentrations may be appropriately increased, but peripheral glucocorticoid resistance results in impaired cortisol activity in target tissues.[4,10]

The pathogenesis of CIRCI is poorly understood and is likely multifactorial. Pathophysiologic manifestations of cortisol deficiency can result from dysfunction at one or more levels of the HPA axis, including: (1) inadequate regulatory hormone (CRH, AVP, ACTH) secretion; (2) impaired adrenal sensitivity to ACTH due to receptor antagonism or downregulation; (3) impaired adrenal cortisol synthetic capacity due to loss of substrate or enzymatic failure (“adrenal exhaustion” or “loss of adrenal reserve”); or (4) impaired cortisol activity in the target tissues due to decreased glucocorticoid receptor (GR) expression or activity or intracellular conversion of cortisol to cortisone, which

cannot bind the GR.[4,10] This HPA axis dysfunction may be a result of direct injury to one or several components of the HPA axis caused by hemorrhage, ischemia, or necrosis associated with the primary illness.[4,10] In addition, the HPA axis can be suppressed by specific drugs (e.g., etomidate),[11] bacterial components such as endotoxin,[12] or the patient's own immune response.[10,13]

One key aspect of CIRCI is that the HPA axis dysfunction is transient, in contrast to absolute adrenal insufficiency (Addison's disease), which is characterized by permanent glucocorticoid and mineralocorticoid insufficiency.[4] Thus, patients with CIRCI that recover from their primary disease regain normal HPA axis function and do not require lifelong steroid supplementation. However, due to the vital role the HPA axis plays in the physiologic response to the stress of illness, the occurrence of CIRCI during critical illness substantially worsens the morbidity and mortality of the primary disease. For instance, septic people with CIRCI have significantly higher incidence of multiple organ failure and decreased survival rates as compared with septic patients with appropriate HPA axis function.[4,9,10,14-16] Thus, appropriate management of CIRCI in conjunction with treatment of the primary illness is critical.

Current understanding of HPA axis function in critically ill horses and foals is limited; to date, CIRCI is best characterized in septic neonatal foals.[17-23] Although basal ACTH and cortisol concentrations are higher in septic foals than healthy age-matched control foals and in nonsurviving foals (as one would expect with the stress of illness), several studies have reported significantly increased ACTH-to-cortisol ratios in nonsurviving septic foals.[17,19,21,23] Such high ACTH-to-cortisol ratios, with high ACTH concentrations and low corresponding cortisol concentrations, suggest cortisol synthetic failure at the level of the adrenal gland may occur in the septic full-term foal.

Findings from ACTH stimulation tests in hospitalized foals also provide evidence for adrenocortical dysfunction in this population. Peak and delta cortisol (peak–basal cortisol concentration) responses to ACTH stimulation tests do not consistently differ between healthy and ill foals, but increased disease severity and poorer prognoses were associated with decreased cortisol responses to ACTH stimulation in hospitalized foals.[20,22] Specifically, nonsurviving foals had significantly lower delta cortisol responses to low-dose ACTH stimulation as compared with survivors,[22] and foals that met criteria for CIRCI (as characterized by an inadequate delta cortisol response to a high-dose ACTH stimulation test) had a significantly greater incidence of shock, multiple organ

dysfunction syndrome, and nonsurvival than foals with an adequate cortisol response to ACTH.[20] When human diagnostic criteria for CIRCI[24] based on inadequate delta cortisol responses to high-dose ACTH stimulation were adapted and applied to hospitalized foals 1 week of age or younger, approximately 50% of all hospitalized foals and a subgroup of septic foals met these criteria.[20]

The incidence of CIRCI in critically ill horses has only been examined in one study to date, but findings suggest it may also occur in this population.[25] Twenty-four percent of severely ill horses had inappropriately low basal cortisol concentrations at hospital admission, and 85% of these horses had inadequate delta cortisol responses to ACTH stimulation.[25] Marked adrenal hemorrhage at necropsy was also seen in nonsurviving horses in this study.[25]

In concert, this evidence suggests that CIRCI occurs in critically ill and septic neonatal foals and in critically ill horses with comparable frequency and impact as in people with similar illnesses.

The clinical presentation of CIRCI is typically vague and insidious, as signs related to the primary illness usually predominate. Indeed, it is the primary illness that should prompt the clinician to consider CIRCI as a possible complicating factor because data in people, dogs, horses, and foals suggest it is more likely in certain diseases than others.[4,5,10,20,25] Recent studies in horses suggest that CIRCI should be considered as a possible complication in any critically ill horse or foal, but particularly in septic foals and horses with evidence of SIRS.[19-22,25] Clinicians should also have a high index of suspicion for cortisol insufficiency in premature foals due to the late maturation of the HPA axis and adrenal gland in foals. Human studies suggest that CIRCI also occurs in conjunction with acute respiratory distress syndrome (ARDS), massive trauma, and major surgery,[4,10] so it should also not be overlooked in horses with similar diseases.

Specific manifestations of CIRCI are directly related to inadequate cortisol support for maintenance of blood pressure, nutrient metabolism, and regulation of the immune/inflammatory response, and they can include one or more of the following: (1) persistent hypotension despite appropriate volume resuscitation and vasopressor support; (2) persistent hypoglycemia or hyperlactatemia despite glucose support and adequate perfusion; or (3) persistent signs of SIRS. Diagnostic criteria for SIRS in some groups of ill horses and foals have been investigated and include tachycardia, fever or hypothermia, leukocytosis (neutrophilia), leukopenia (neutropenia), and increased band neutrophils.[26-30]

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Specific signs of mineralocorticoid deficiency (such as persistent hyponatremia, hypochloremia, or hyperkalemia) are not a consistent feature of CIRCI but do occasionally occur.

Specific diagnostic criteria for CIRCI in horses or foals are not well defined. Indeed, determination of the ideal diagnostic criteria for CIRCI in any species is inherently difficult as quantifying a universally appropriate cortisol response to variable and constantly changing disease severity in individual patients is next to impossible. Thus, standard diagnostic criteria for CIRCI in people and infants are not widely accepted, but current recommendations include documentation of either (1) an inappropriately low basal cortisol concentration during critical illness or (2) an inadequate delta cortisol response to high-dose (supraphysiologic) ACTH stimulation testing.[24] Testing for CIRCI in people is typically done at ICU admission for patients with diseases likely complicated by CIRCI (e.g., sepsis, ARDS) or when clinical signs consistent with CIRCI, such as persistent hypotension after fluid and vasopressor support, are identified. Cutoff values for adequate basal and delta cortisol concentrations in illness are based on responses to environmental stress in healthy individuals.

In general, measurement of basal plasma hormone concentrations offers a rapid and safe means of assessing adrenocortical function in the critically ill horse or foal. There are commercial radio- and chemiluminescent immunoassays validated for measurement of plasma or serum equine cortisol concentrations.[31,32] In foals, age-related variation in HPA axis function needs to be considered when determining cutoff values for CIRCI diagnosis.[20,22,33] Specific basal cortisol cutoff values for diagnosis in CIRCI in ill foals or horses have not been critically evaluated, but basal cortisol less than 9.9 µg/dL in foals 4 hours old and younger, less than 7 µg/dL in foals 12 to 24 hours old, less than 4.4 µg/dL in foals 36 to 48 hours old, less than 2.5 µg/dL in foals hours to 7 days old, and less than 9.7 µg/dL in horses that have been used to diagnose CIRCI in recent reports.[20,25] However, due to the pulsatile nature of cortisol secretion, plasma concentrations can vary widely during a 24-hour period in both healthy and sick horses and foals with time of day, season, emotional state, and moment-to-moment changes in physiologic stressors.[34,35] Thus, correct interpretation of a single random cortisol concentration in an individual animal as appropriate or not can be difficult. Further, diagnosis of CIRCI based on a low basal cortisol concentration was not correlated with increased disease severity of decreased survival in septic foals, as was diagnosis based on ACTH stimulation testing.[20]

Assessment of cortisol concentrations in conjunction with regulatory hormone (ACTH, CRH) concentrations can provide a more comprehensive picture of HPA axis function. Plasma CRH and ACTH concentrations are easily assessed in most species via commercially available immunoassays, but as the majority of CRH is secreted into the hypothalamic-hypophyseal portal vessels rather than into the systemic circulation, accurate measurement of CRH requires sophisticated sampling methodology. In addition, while in healthy individuals ACTH and cortisol concentrations are fairly closely correlated, ACTH-cortisol dissociation is not uncommon during illness in horses and foals.[23,35] Documentation of an increased ACTH–to–cortisol ratio might be helpful for CIRCI diagnosis, especially in foals, but due to wide variation in these parameters in individual animals,[17,19-21] specific cutoff values for appropriate ACTH–to–cortisol ratios are not currently proposed for diagnosis of CIRCI in horses or foals. Even though cortisol and its ratio with ACTH concentrations are used as indicators of HPA axis function in sick foals, progesterone and dehydroepiandrosterone (DHEA) sulfate were found to be good predictors of HPA axis dysfunction and outcome in hospitalized foals.[23]

Dynamic tests like the ACTH stimulation test circumvent some of these limitations with diagnosis of CIRCI based on basal hormone concentrations. Typically, in the classic “high-dose” ACTH stimulation test, serum cortisol concentration is measured just before and 30 to 90 minutes after intravenous or intramuscular administration of a supraphysiologic quantity of ACTH (Cosyntropin, 1 to 2 µg/kg or higher).[20,40,41] This high-dose ACTH stimulation test produces a maximal adrenal response, so an inadequate increase in cortisol concentration in this test is used to diagnose both absolute, irreversible adrenal insufficiency (e.g., Addison's disease) and transient CIRCI.[4,24,36,37]

However, the high-dose ACTH stimulation test may be less sensitive for diagnosis of the transient, reversible HPA axis suppression that occurs in CIRCI. In some patients with CIRCI, the adrenal gland fails to produce an appropriate cortisol response to physiologic concentrations of ACTH but may still respond adequately to supraphysiologic ACTH concentrations.[38,39] A measurable cortisol response can be produced by administration of lower ACTH doses (0.01 to 0.2 µg/kg IM) in horses and foals,[20,22,25,40,41] and such “low-dose” stimulation tests could also be used to diagnose CIRCI in equine patients. Delta cortisol responses vary more with foal age and dose of ACTH administered, but in general an increase from basal cortisol less than onefold to twofold 30 minutes after low-

dose ACTH stimulation testing[20,22,25,40,41] and less than threefold to fourfold 90 to 120 minutes after high-dose ACTH stimulation testing[20,40,41] may be suggestive of CIRCI in horses and foals. However, one study that examined a paired low-dose/high-dose ACTH stimulation test in hospitalized foals found significant associations between increased disease severity and nonsurvival and inadequate cortisol responses to the high dose but not the low dose of ACTH.[20]

It is important to note, however, that ACTH stimulation tests only evaluate the adrenal component of the HPA axis. Therefore, patients with cortisol insufficiency due to impaired HPA axis function at the hypothalamic and/or pituitary levels may produce an appropriate cortisol response to exogenous ACTH that could be falsely interpreted as intact HPA axis function. Insulin tolerance, CRH stimulation, and metyrapone tests are preferred for global assessment of the HPA axis and diagnosis of HPA axis hypofunction and have been described in foals and horses.[42-45] However, risks associated with severe hypoglycemia and the potential for preexisting glucose/insulin derangements in critically ill horses and foals limit the utility of insulin tolerance testing in patients with potential CIRCI, and the CRH stimulation and metyrapone tests are currently limited by expense and reagent availability, so these tests are not currently recommended for diagnosis of CIRCI in horses and foals.

Finally, some of the physiologic consequences of CIRCI may be associated with cortisol resistance in peripheral tissues rather than circulating cortisol insufficiency; in fact, some patients may have impaired cortisol metabolism and ACTH-cortisol dissociation.[10,46-48] Decreased glucocorticoid receptor binding affinity is described in horses with SIRS and is associated with nonsurvival.[49] In such cases, all of the previously mentioned tests may suggest intact HPA axis function, with appropriate endogenous cortisol concentrations and normal responses to dynamic testing, despite clinical evidence of cortisol insufficiency such as persistent hypotension, metabolic derangements, or inflammatory dysregulation.

Specific therapeutic protocols for management of CIRCI in horses or foals have not been critically evaluated. It is important to remember that the goal of CIRCI treatment is *physiologic* cortisol replacement, as a number of studies in septic patients have demonstrated deleterious effects of high-dose (supraphysiologic) corticosteroid regimens in sepsis.[24] Thus, it may be ideal to avoid more potent and longer-acting corticosteroids such as dexamethasone and prednisolone in favor of hydrocortisone (which is identical to endogenous

cortisol), though these drugs are sometimes used in people with CIRCI.

In one case report, a septic foal with adrenocortical insufficiency—as evidenced by a low basal cortisol and impaired cortisol response to ACTH stimulation—demonstrated clinical improvement and eventual normalization of cortisol responses following a course of corticosteroid supplementation in addition to standard therapy for sepsis.[18] Recent evidence also suggests that in healthy 2- to 6-day-old foals, a short tapering course of hydrocortisone (1.3 mg/kg/day divided q4h IV) has potentially beneficial anti-inflammatory effects without significantly impairing innate immune function.[50] Adjustment of daily cortisol production rates in foals based on a "illness factor," as has been done in people to determine steroid supplementation regimens in CIRCI, suggests that a hydrocortisone dose of 1 to 4 mg/kg/day divided q4-6h may be appropriate for foals with CIRCI.[35] However, this or other corticosteroid regimens have not been critically evaluated in septic foals or horses with CIRCI.

Healthy newborn foals have high pregnane concentrations at birth that decrease gradually over the first 48 hours post foaling.[23,51] In the brain, progesterone, DHEA, and pregnenolone can be converted into neuroactive steroids (e.g., allopregnanolone) that promote neurogenesis, neuronal plasticity, and neuroprotection, modulate CRH and AVP synthesis, and influence the HPA axis. Neurosteroid actions in neurons and glial cell are mediated by the $GABA_A$ receptor. Increased progestogen and neuroactive steroid concentrations have been associated with disease severity, neurologic abnormalities (neonatal maladjustment syndrome [NMS]), prematurity, and mortality in hospitalized foals.[23,52] The mechanisms leading to high neurosteroid concentrations in critically ill foals remain unclear, but it has been speculated to be a consequence of altered intrauterine to extrauterine transition, as well as adrenocortical enzymatic shifts during illness.[23,52] Progesterone, 17α-hydroxyprogesterone, and allopregnanolone concentrations are often elevated in septic compared with healthy and sick nonseptic foals.[23,52] If progesterone derivatives are involved in the pathogenesis of NMS, reducing their concentrations could be beneficial. Finasteride and dutasteride are 5α-reductase inhibitors used in men for alopecia and prostatic hypertrophy to block the conversion of testosterone to 5α-dihydrotestosterone. These drugs also block the conversion of progesterone to 5α-dihydroprogesterone, a key precursor for allopregnanolone, and have been proposed as potential treatments for specific cases of NMS.

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RAAS, Blood Volume, and Blood Pressure Regulation

Hypovolemia and hypotension are common in critically ill people and animals, and regulation of blood pressure and blood volume is quite complex. The RAAS, HPA axis, and arginine vasopressin (AVP, also known as antidiuretic hormone or ADH) work independently and in concert to control these responses during both health and illness. The RAAS is activated when macula densa cells in the renal juxtaglomerular apparatus sense decreases in blood volume or blood sodium concentration or increases in plasma potassium concentration, resulting in renin release. Renin cleaves plasma angiotensinogen to angiotensin I, which is then further processed to the potent vasoconstrictor angiotensin II by pulmonary angiotensin-converting enzyme (ACE). In addition to vasoconstriction, angiotensin II induces aldosterone release from the adrenal cortices. Aldosterone increases blood volume and pressure by activating the renal tubular sodium potassium ATPase and epithelial sodium channels to enhance renal sodium and water reabsorption, as well as potassium excretion. Increases in plasma osmolality and decreases in arterial pressure are also detected by hypothalamic osmoreceptors and arterial stretch receptors, respectively, stimulating hypothalamic AVP synthesis and release from the posterior pituitary. The primary effect of AVP is the insertion of aquaporin channels in the renal medullary collecting ducts to increase water reabsorption, thus increasing blood volume and blood pressure. AVP also can directly induce arteriolar vasoconstriction and activates the HPA axis by inducing pituitary ACTH release. HPA axis activation and resultant increases in plasma cortisol further aid blood pressure regulation via direct cardiac inotropic effects and downregulation of the vasodilator nitric oxide.

In critical illness, RAAS activation is important for blood pressure and electrolyte regulation, but excessive activation can have detrimental effects. Angiotensin II has recently been demonstrated to have proinflammatory effects, and associations between angiotensin II and increased organ failure and mortality have been described.[53] Transient hyperreninemic hypoaldosteronism is observed frequently in people with septic shock and is associated with the development of acute renal failure in these patients.[54] This hypoaldosteronism could be a reflection of adrenocortical suppression in CIRCI and could play a role in persistent hypotension in affected patients, but as described earlier, specific signs of mineralocorticoid deficiency like electrolyte derangements are

uncommon in CIRCI. Information regarding specific RAAS responses in critically ill horses is limited. Hypotensive adult horses demonstrated increased aldosterone concentrations before fluid resuscitation, but aldosterone responses to hypotension appear to be exaggerated in neonatal foals.[55] RAAS activation in critically ill foals is mainly characterized by an increase in angiotensin II and aldosterone concentrations.[56] Renin activity and aldosterone concentrations were also increased in horses with experimentally induced laminitis but might represent appropriate responses to concurrent hyponatremia rather than pathologic RAAS activation.[57] Effects of RAAS on activation on inflammatory status and mortality are not described in horses or foals.

AVP concentrations are initially increased in most acutely critically ill patients, stimulated by the development of hypotension and systemic inflammation (proinflammatory cytokines are potent AVP secretagogues).[3,58] In many patients with septic shock, AVP concentrations tend to fall dramatically despite persistent hypotension, consistent with relative AVP deficiency due to both depletion of stored AVP and inhibition of AVP synthesis.[58] Tissue AVP activity may also be impaired by inflammatory responses in critical illness.[3] However, there are conflicting reports regarding associations between increases or decreases in AVP concentration and mortality in critically ill patients.[58] Increased AVP concentrations were observed in adult horses with naturally occurring hypovolemia, but not in a small group of hypotensive foals, suggesting AVP responses in foals might be immature.[55] Larger studies documented higher AVP concentrations in septic foals and an association among high AVP concentrations, hypoperfusion, and decreased survival.[59] Vasopressin infusions are sometimes used as vasopressors in hypotensive people, but variable efficacy and concerns regarding potential side effects associated with decreased skin and splanchnic blood flow limit its clinical application.[21,58] Studies investigating the safety and efficacy of vasopressin infusions in horses and foals are lacking, though vasopressin is used anecdotally as a vasopressor in some critically ill neonatal foals with reported success.

Adrenomedullin also plays a role in hemodynamics. Adrenomedullin is a vasodilator peptide of the calcitonin gene family produced by chromaffin cells of the adrenal medulla, cardiac myocytes, and cells in other tissues. It has antiapoptotic and antiinflammatory properties, attenuates ischemia and reperfusion injury, modulates vascular tone, enhances microcirculatory function, promotes angiogenesis, reduces intestinal mucosa permeability, counteracts the

RAAS, inhibits aldosterone secretion, increases natriuresis, and supports cardiovascular function during SIRS and sepsis.[60,61] Adrenomedullin concentrations are increased in people with sepsis and endotoxemia, hypertension, heart failure, and myocardial infarction.[61-63] Its production by cardiac myocytes is stimulated by TNF-α, IL-1β, angiotensin II, endothelin-1, and hypoxia. Adrenomedullin concentrations were valuable to individualize human patients who require hemodynamic support.[64] Adrenomedullin analogs have been proposed as therapeutic agents and there are ongoing clinical studies using monoclonal antibodies to the N-terminus of adrenomedullin to prolong its half-life in septic human patients.[60] A recent study found high plasma adrenomedullin concentrations in critically ill compared with healthy foals; however, concentrations were not different between septic and nonseptic foals and were not associated with survival.[65]

Thyroid Axis

In critical illness, activity of the hypothalamic-pituitary-thyroid axis is suppressed, resulting in decreased plasma triiodothyronine (T3) and thyroxine (T4) and increased reverse T3 (rT3) concentrations, a syndrome called nonthyroidal illness syndrome (NTIS) or euthyroid sick syndrome. This syndrome is well described in humans, dogs, and cats suffering from systemic illnesses, and recent reports suggest that NTIS is common in sick horses and foals.[66-69] The syndrome is described in detail earlier in the Thyroid Gland section.

Parathyroid Gland and Calcium Regulation

Calcium dysregulation is common in critically ill people and animals and is presumed to be associated with parathyroid gland dysfunction, vitamin D deficiency, or both.[70-72] Ionized hypocalcemia has been documented in septic foals and horses with intestinal disease, as well as in horses with experimental endotoxemia.[71,73] High parathyroid hormone (PTH) concentrations were found in most horses and foals with hypocalcemia and are consistent with an appropriate endocrine response to low calcium, but some hypocalcemic horses had low PTH concentrations that could be indicative of parathyroid gland dysfunction in this population.[71,73,74] In both people and foals, increased PTH

concentrations were associated with decreased survival, but factors other than hypocalcemia likely contributed to this finding as no difference in calcium concentration was found in nonsurviving foals.[71] Proinflammatory cytokines can impact PTH secretion and activity and might play a role in these calcium disturbances in critically ill horses and foals.[71] Calcitonin and PTH-related protein (PTHrP) concentrations were not different between healthy and sick foals,[71] and renal calcium excretion was not different in horses with enterocolitis,[74] suggesting these factors are not responsible for hypocalcemia in critically ill horses and foals. Procalcitonin (PCT), the precursor of calcitonin, is used in human critical care medicine as a highly specific marker of sepsis. Increased PCT concentration was documented in horses with clinical evidence of SIRS, and endotoxin administration to horses induces a rapid PCT response.[75,76]

Information on vitamin D metabolites in critically ill horses and foals is lacking. It was recently shown that hypovitaminosis D is common in critically ill foals.[77,78] Hospitalized foals had lower serum concentrations of 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D (active vitamin D, calcitriol) that were associated with hypocalcemia, disease severity, and mortality.[77,78] The mechanisms by which critically ill foals develop hypovitaminosis D remain unclear but could be a consequence of renal and intestinal losses, decreased concentrations vitamin D binding protein, and renal PTH resistance.

Another system of relevance in calcium and phosphorus homeostasis is the fibroblast growth factor-23 (FGF-23)/klotho axis. FGF-23 inhibits renal 1α-hydroxylase activity (vitamin D activation) and sodium/phosphorus cotransporter expression (promotes phosphaturia) and suppresses PTH secretion. Klotho is the coreceptor for FGF-23 and has multiple properties, including antisenescence, antioxidation, antiapoptosis, and cytoprotection. Disturbances in the FGF-23/klotho axis were recently documented in critically ill foals, and hospitalized foals with high FGF-23 or low klotho concentrations were more likely to die.[77]

Energy Axes (Endocrine Pancreas and Orexigenic System)

Insulin, glucagon, cortisol, and epinephrine are considered the main endocrine components of the energy axis; however, it is clear that this is a complex system in which many other hormones (growth hormone, ghrelin, leptin, adiponectin,

somatostatin, and incretins) are also important.

Glucose derangements are common in critically ill people and animals. In people, hyperglycemia due to previously undiagnosed diabetes mellitus or "stress hyperglycemia" is most common and is associated with increased morbidity and mortality.[1] Hyperglycemia is also common in horses with GI disease, and persistent hyperglycemia is associated with decreased survival in this population as well.[79,80] In critically ill neonatal foals, both hypoglycemia and hyperglycemia are reported and are associated with a poorer prognosis.[81] Hypoglycemia in septic neonatal foals is most likely related to decreased nursing due to illness and lack of substantial glycogen stores, but mechanisms resulting in hyperglycemia in critically ill people and animals appear to be more complication. Stresses of critical illness activate the HPA axis, sympathoadrenomedullary responses, and the GH axis, resulting in increased concentrations of the counter-regulatory hormones cortisol, catecholamines, GH, and glucagon. These hormones act directly and indirectly to increase blood glucose by increasing hepatic gluconeogenesis, inhibiting insulin release, and impairing glucose utilization in the periphery.[1] Proinflammatory cytokines like TNF-α and IL-1 are also frequently increased in critically ill patients and can induce peripheral insulin resistance in people and laboratory animals by interfering with insulin signaling.[1] Experimental endotoxemia in healthy horses has been shown to decrease insulin sensitivity.[82,83] Insulin sensitivity has not been thoroughly investigated in critically ill horses and foals to date, but one study documented higher insulin concentrations in nonsurviving septic foals[84] and a recent report found evidence of insulin dysregulation and endocrine pancreatic dysfunction in nonsurviving horses with the systemic inflammatory response syndrome.[85]

Glucose derangements have important clinical consequences in critical illness, as evidenced by the increases in morbidity and mortality discussed earlier. The consequences of hypoglycemia are obvious, as CNS function depends on glucose availability. Clinical sequelae related to hyperglycemia can be equally important, as hyperglycemia results in volume depletion through osmotic diuresis and subsequent electrolyte and acid-base derangements and perfusion impairment.[1] Hyperglycemia can also result in tissue damage via increased production of reactive oxygen species and related lipid peroxidation, damaging tissues like cardiac muscle, vascular beds, and worsening ischemia-reperfusion injury in various tissues such as ischemic intestine.[1] Hyperglycemia also alters

blood flow to certain tissues by inhibiting formation of the vasodilator nitric oxide and can cause hemostatic abnormalities through a variety of mechanisms.[1] Finally, immune function is impaired in hyperglycemia by inhibiting phagocytic and chemotactic function in macrophages and neutrophils, respectively.[1]

Because of the negative consequences associated with hyperglycemia, the effects of tight glycemic control with exogenous insulin therapy have been investigated in a number of human studies. Initial studies found a substantial reduction in mortality in patients subject to tight glycemic control protocols that aimed to keep blood glucose concentrations between 80 and 110 mg/dL in comparison with less stringent control (<180 mg/dL).[1,6,86] However, additional studies did not document such a benefit, and some studies actually found an increase in mortality and adverse hypoglycemic events with intensive insulin therapy for tight glycemic control.[1] At present, a blood glucose target of 110 to 180 mg/dL is recommended in critically ill people.[87]

To the authors' knowledge, similar studies investigating insulin therapy and blood glucose goals in animals are not described in the literature, so although the use of insulin (±glucose) infusions in critically ill horses may be indicated to combat persistent hyperglycemia in these patients, specific recommendations for blood glucose control in critically ill horses and foals are not available. There is also a unique consideration for such therapy in horses because insulin infusions at high rates have been associated with laminitis development in normal horses and ponies[88,89] and hyperinsulinemia is associated with endocrinopathic laminitis.[90] Thus, while this has only been described anecdotally, glucose and/or insulin infusions could possibly potentiate the development of laminitis in susceptible animals. The use of insulin-sensitizing drugs like metformin or pioglitazone could be useful for managing sepsis-mediated insulin resistance in horses to avoid a potential risk of insulin-mediated laminitis, but to date these drugs have not been examined in clinical equine sepsis and recent evidence suggests that their effects on insulin sensitivity in horses may be variable at best.[73,91,92]

The role of other hormonal regulators of energy metabolism—including leptin, ghrelin, GH, adiponectin, glucagon, somatostatin, and incretins—in critically ill people or animals is not well understood. These hormones are altered in many patients with critical illness, but alterations vary across studies and populations.[84,91] Glucagon concentrations are consistently elevated in septic foals, likely as a compensatory mechanism to a negative energy balance

characterized by hypoglycemia and hypertriglyceridemia.[84]

Leptin and adiponectin are hormones produced by adipose tissue (adipokines), exemplifying the important role of adipose tissue in energy endocrine homeostasis via the so-called gut-brain axis.[73,93] Leptin regulates satiety by decreasing hunger (anorexigenic) and enhances energy expenditure by increasing insulin sensitivity. Ghrelin is a GH-releasing factor secreted by P/D1 cells of the stomach and neurons in the arcuate nucleus of the hypothalamus in response to hypoglycemia and fasting to enhance hunger (orexigenic). Ghrelin also regulates food-seeking behavior to maintain energy homeostasis. Thus, ghrelin and leptin work in opposite ways at the hypothalamic level. Adiponectin participates in energy regulation by increasing insulin sensitivity and fatty acid oxidation, but it also has anti-inflammatory properties. Leptin and adiponectin blood concentrations are proportional to body condition in humans and horses.[94,95] Similar to insulin and GH during disease, resistance to leptin and adiponectin may occur in critical illness.[96]

GH Axis

The GH axis plays an important role in supporting metabolism, gut mucosal function, wound healing, and immune function during critical illness.[97] Loss of the GH pulsatile pattern is common in critically ill humans, where high plasma GH concentrations are not followed by increases in IGF-I, indicating GH resistance. However, GH deficiency may occur in some patients; either mechanism can result in relative GH insufficiency, which can increase catabolism and impair wound healing.[73,97] In critically ill people, recombinant GH supplementation has been used to decrease protein catabolism and initially appeared beneficial, though more recent studies have demonstrated associations with increased mortality, resulting in recommended cessation of the use of the compound in human ICUs.[97] GH actions are predominantly mediated via IGF-1, which is often decreased in critical illness.[73,97] GH has not been extensively studied in critically ill horses or foals, but a recent study found higher GH and lower IGF-1 concentrations in septic foals, suggesting that GH resistance may occur in this population of foals, as well as in people.[98]

Recent work in people has also demonstrated interactions between ghrelin and the GH axis—ghrelin activates the GH receptor, and in addition to hunger, it also stimulates GH secretion.[73,97] One study demonstrated higher ghrelin

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concentrations in septic compared with healthy foals; however, no association with survival was found.[98] High ghrelin and low IGF-1 (negative regulator for GH secretion) likely enhances GH secretion in critically ill foals. Ghrelin has been evaluated as a potential therapeutic agent to reduce inflammation, increase muscle mass, and treat cachexia and anorexia (anorexia nervosa) in other species. Ghrelin or related compounds may provide a means for provision of anabolic support to critically ill patients.

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▪ Ruminant Metabolic Diseases and Metabolic Modifiers

Jesse Paul Goff

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Macromineral and Bone Problems of Ruminants

Jesse Paul Goff

Introduction

Seven macrominerals, Na, K, Cl, Ca, Mg, P, and S, are considered essential for life. Inappropriate amounts of any of the macrominerals needed by ruminants can cause insufficiency and clinical disease including the "downer cow." Ca disorders, such as milk fever, are not associated with insufficient diet Ca but rather an inability of the cow to use dietary Ca and bone mineral stores of Ca at the onset of lactation. Na, K, Mg, and Cl are the major electrolytes of blood, extracellular, and intracellular fluids and influence blood volume, resting cell membrane potentials, and acid-base status. Many factors can contribute to the "downer cow syndrome" in addition to mineral challenges as outlined in Table 41.7. This chapter highlights the most common problems associated with each micromineral, focusing on identification of the problem, cause and prevention of the problem, and treatment options.

TABLE 41.7

Primary Causes of Recumbency Initiating the "Downer Cow Syndrome"

A. Mineral imbalances
1. Hypocalcemia—plasma Ca <5 mg/dL
2. Hypomagnesemia—plasma Mg <1.2 mg/dL
3. Hypophosphatemia—plasma P <1.0 mg/dL
B. Severe endotoxemia—moderate reduction in plasma Ca (5.5-7.5 mg/dL), Mg, and P
C. Dystocia—damage to obturator and L6 branch of the sciatic nerve
D. Pregnancy toxemia syndrome—low plasma Ca, Mg, P, and glucose
E. Fractures
F. Coxofemoral luxation
G. Rupture of gastrocnemius muscle
H. Lymphosarcoma of spinal cord

Calcium

The Ca concentration in adult cow blood is normally 9 to 10 mg/dL (2.25 to 2.5 mM). Blood Ca concentration in calves younger than 4 months old will generally be a little higher, 9.8 to 11 mg/dL (2.2 to 2.75 mM), which may reflect the need for more Ca to promote calcification of new bone. About half of blood Ca is bound to proteins such as albumin and globulins, and a small portion (4% to 7%) is complexed to compounds such as citrate. The remaining Ca is in the blood in an ionized form at a concentration of 1 to 1.13 mM. This is the biologically active portion of Ca in the blood. It is the predominant form of Ca in the extracellular fluids bathing the tissues. The percentage of blood Ca that is ionized is affected by blood acidity; it varies from 42% to 43% of total Ca during compensated alkalosis and reaches 47% to 48% of total Ca during compensated acidosis. The 600-kg cow's blood normally contains approximately 3.25 g Ca, and the extracellular fluids of the cow contain a total of 10.5 to 11 g Ca (Fig. 41.19).

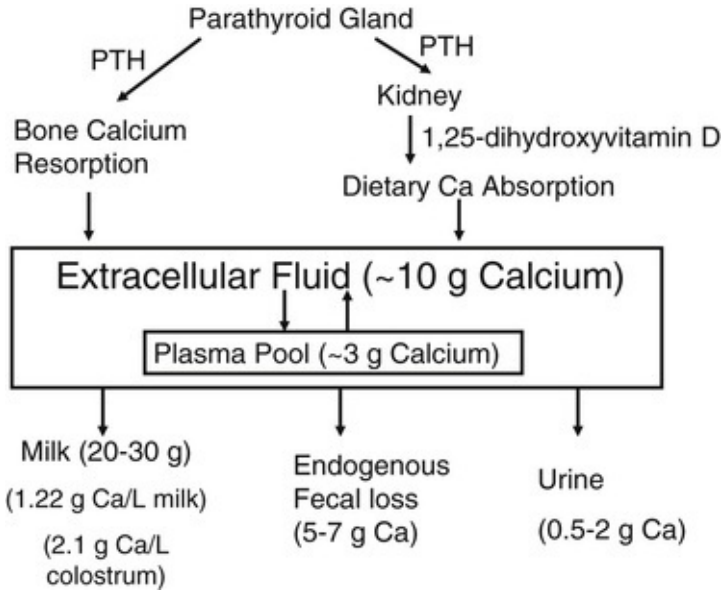


FIG. 41.19 Calcium homeostatic response of the 600-kg cow in early lactation to a decline in blood Ca concentration at the onset of lactation. *PTH,* Parathyroid hormone.

Periparturient Dairy Cow Ca Metabolism

The onset of lactation imposes a large homeostatic challenge to the dairy cow. The day before calving, the 600-kg cow uses 7 to 8 g Ca for maintenance needs

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plus another 10 g Ca to allow fetal skeleton development, for a total of about 18 g Ca. To maintain Ca balance, 18 g Ca must be absorbed from the diet. Ca in dietary forages and concentrates are generally only about 30% available. If the forage and grains of the diet supply the Ca (no limestone or other more bioavailable Ca mineral is added to the diet) and the cow is consuming about 13 kg DM/day, the diet can be as low as 0.46% Ca and will meet the Ca demands of the cow.

At calving, the 10 g Ca needed for fetal skeletal development is replaced by a much larger Ca demand for colostrum and milk production. Holsteins produce an average of 7.5 kg first milk colostrum containing about 2.3 g Ca/kg. Harvesting that colostrum removes 17 g Ca from the blood. Within an hour of removal of the colostrum, the mammary gland will take up from the blood about three quarters of the Ca needed to form the transition milk (to be removed 12 hours later at the next milking).[1] This is estimated to be another 13 g Ca. This brings the Ca lost from the blood to about 30 g Ca within a few hours of harvesting colostrum. The total Ca lost in the first day of lactation (milk Ca from first two milkings plus Ca sequestered in mammary for the next days milk) will approach 40 g Ca. Adding in the 8 g Ca maintenance requirement and the total amount of Ca leaving the blood on the day of calving approaches 46 to 48 g. This represents a 28- to 30-g Ca increase in net Ca that must enter the blood the day of calving compared with the day before calving. This represents removal of every g of Ca from the blood an additional eight to nine times during that first day compared with the day before calving. Amazingly, most cows successfully meet this challenge.

Many cows, including nearly all first-calf heifers, will suffer only a small, temporary decline in blood Ca around the time of calving as Ca homeostasis mechanisms succeed in raising the blood Ca concentration back to normal. This is initiated by the parathyroid glands, which sense any decrease in ionized blood Ca concentration and secrete parathyroid hormone (PTH). G protein–coupled PTH receptors on bone osteoblast and osteocyte and kidney cells bind the PTH, resulting in an increase in intracellular cyclic AMP concentrations to initiate various actions within the target bone and kidney cells. PTH rapidly (within minutes) reduces urinary Ca loss, which can correct small Ca imbalances. However, because urinary Ca losses are typically below 0.5 g/day, it has a limited capacity to impact Ca balance at the onset of lactation. Continued secretion of PTH will stimulate osteocytic osteolysis, which involves moving Ca from the fluid surrounding each osteocyte sitting in its lacunae through the

canalicular system and into the blood of the Haversian canal system in bone. This response is quite fast and moves about 9 g Ca into the blood of the typical cow within several hours. PTH will also stimulate renal conversion of vitamin D into the hormone, 1,25-dihydroxyvitamin D. This hormone acts on intestinal epithelial cells to stimulate active transepithelial movement of dietary Ca into the blood. This can bring large amounts of Ca into the blood, but it takes 24 to 36 hours to become fully active. Continued PTH secretion can also stimulate osteoblasts to secrete receptor activator of nuclear factor kappa-β ligand (RANKL). RANKL stimulates bone osteoclast recruitment and activation within trabecular and cortical bone. This has the potential to remove large amounts of Ca from the skeleton (over 1 kg Ca in the first 5 weeks of lactation) to help achieve Ca balance, but this process may take 48 to 72 hours to become fully active in older cows. When operating properly, the cow experiences only a small decline in blood Ca concentration (<8 mg/dL in nearly half the older cows), which lasts less than 18 hours before being restored to normal.[2]

Periparturient Hypocalcemia and Milk Fever in Dairy Cows and Goats

In some cows the Ca homeostatic mechanisms are slow to respond, resulting in moderate (blood Ca <8 mg/dL) to severe hypocalcemia (blood Ca <5.5 mg/dL) that may extend into the first 3 to 5 days of lactation. Cows with severe hypocalcemia can develop milk fever. This occurs in roughly 3% to 4% of dairy cows in the United States each year, usually within 24 hours of calving. Cows can occasionally develop milk fever before calving as a result of Ca sequestration by the mammary gland in preparation for production of colostrum. Milk fever cows exhibit muscle paresis and muscle twitching. Hypocalcemia causes neuron cell membranes to be more permeable to Na, lowering the resting membrane closer to threshold potential. The neurons are hyperexcitable, which can activate muscle twitching and tetany in the animal.

Normally, action potentials move down the axon of nerves depolarizing the terminus of the nerve axon. This opens voltage-gated Ca channels in the nerve terminus. Extracellular fluid Ca^{++} enters the neuron, causing the neuron to release acetylcholine into the synaptic cleft, resulting in muscle contraction. Hypocalcemia reduces the amount of Ca^{++} available to enter the axon terminus following an action potential, inhibiting acetylcholine release into the synaptic cleft. The result is muscle paresis. In most species, the effect of hypocalcemia on

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nerve excitability predominates and tetany is observed. However, in ruminants the effect of hypocalcemia on acetylcholine release at the myoneural junction predominates and muscle paresis is the main clinical sign.

Note that this is not always the case. In the ruminant that is severely hypomagnesemic (Mg <1.25 mg/dL) and hypocalcemic (Ca <5 mg/dL), the predominant clinical sign is tetany rather than the paresis observed in the milk fever cow fed adequate Mg. Ordinarily, Mg in the synaptic cleft of the myoneural junction competes with Ca for entry into the nerve axon following depolarization. If Ca alone is low, the entry of Ca into the axon is inhibited, causing paresis. However, in the case of the cow with grass tetany (described later), Mg in the extracellular fluids at the myoneural junction synaptic cleft is so low that even the low level of Ca in the extracellular fluids can successfully enter the axon and stimulate ACH release and muscle contraction. Because the hypomagnesemia increases excitability of nervous tissue and the myoneural junction can respond, the clinical presentation is tetany.

Early in the course of the milk fever syndrome, the cow is ataxic and muscle twitching can be observed. Eventually the cow may be unable to stand. The neck of the recumbent cow is typically tucked back into the flank. The cow is lethargic and depressed. Rumen motility will be slow to absent. The heart rate is generally increased to 80 to 100 beats per minute (bpm), but the sounds are muffled, reflecting poor cardiac output. Blood flow to the periphery is reduced. Thermoregulation is impaired, and the cow's body temperature will move toward the ambient temperature. In most cases, ambient temperature is below 38° C, so the ears feel cold and body temperature is often 36.5° C to 38° C (98° F to 100.5° F). However, in hot climates the body temperature can be dangerously elevated, which threatens life more rapidly than being hypothermic. Breathing is shallow.

Cows that develop milk fever before calving may not be able to contract the uterus enough to expel the calf. Milk may leak from the teats as the teat sphincter muscle fails to maintain muscle tone. Cows also have poor swallowing reflexes, so drenches and boluses should not be administered to them if they are recumbent. If these cows are not kept up on their sternums, rumen fluids may move up the esophagus into the pharynx and come out the nasopharynx or, worse, be aspirated on inspiration.

Blood samples obtained from milk fever cows will be low in Ca, generally below 5.5 mg/dL and usually below 4 mg/dL. Blood Mg concentrations are typically elevated (>2.3 mg/dL or 0.95 mM) due to action of PTH to enhance

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renal tubular Mg reabsorption. However, if inadequate diet Mg is fed to cows, the Mg concentration will be below 1.9 mg/dL (0.78 mM). This signals the clinician that hypomagnesemia may be a factor contributing to hypocalcemia in the cows (see later). Cows with milk fever are often hypophosphatemic with blood inorganic phosphate (P) concentration below 4 mg/dL (1.3 mM). Often, blood P is between 2.5 and 3.5 mg/dL (0.8 to 1.1 mM) in milk fever cows. Occasionally, blood P concentration will be below 1 mg/dL (0.3 mM) (see Hypophosphatemic Downer Cow section later). Blood K concentration is generally from 2.5 to 4 mEq/L, the result of inappetence and the action of PTH to reduce renal tubule potassium reabsorption. Milk fever cows will have plasma cortisol concentrations that exceed 20 ng/mL, approximately 15-fold above normal cortisol concentrations. These levels may contribute to immune suppression of the periparturient cow. Hypocalcemia can also directly impair immune cell responses, increasing susceptibility of cows to opportunistic infection of the uterus and mammary gland.

Differential diagnosis should rule out other disorders that can cause the downer cow syndrome. This includes toxic mastitis and toxic metritis, usually caused by coliform bacteria. Milk should be expelled from each teat before treatment of milk fever to rule out mastitis. Inappropriate treatment of endotoxic cows with intravenous Ca can cause death as endotoxins increase sensitivity of cardiac muscle to Ca, causing the heart to stop in systole. Trauma from calving (damage to the obturator and more commonly the L6 branch of the sciatic nerve) and pelvic or limb fractures need to be ruled out. The presence of a second calf in the uterus must also be ruled out.

Subclinical hypocalcemia, in which blood Ca is below 8 mg/dL but above 5.5 mg/dL, may affect 25% of heifers and more than half of older cows. Although not as severe as clinical milk fever, these cows are more immune suppressed than normocalcemic cows and at greater risk of metritis, ketosis, and retained placenta. The degree of hypocalcemia and the length of time the cow is hypocalcemic greatly influence susceptibility to these secondary disorders.

Pathogenesis of Milk Fever

When Ca homeostasis is working properly, the cow experiences only a small and short-lived decline in blood Ca concentration during the periparturient period. A reduced ability of bone and kidney cells to respond to PTH stimulation is implicated as the defect in Ca homeostasis that results in prolonged or severe hypocalcemia. The primary factors affecting tissue responsiveness to PTH are

metabolic alkalosis and hypomagnesemia.

Metabolic Alkalosis and Diet Cation-Anion Difference

During metabolic alkalosis the tertiary structure or shape of the PTH receptor on bone and kidney cell surfaces is changed, reducing its affinity for PTH. This reduces the amount of cyclic AMP made inside target cells inhibiting the cells from carrying out their role in Ca homeostasis (Fig. 41.20). Dietary cations, such as K^+, Na^+, Ca^{++}, and Mg^{++}, will raise the pH of the blood of the cow if they are absorbed into the blood. Dietary anions, such as chloride, sulfate, and phosphate, will acidify the blood of the cow if they are absorbed into the blood. Cations or anions in the diet that are not absorbed have no impact on blood pH. The difference in the number of mEq of cations and anions *absorbed* from the diet helps determine blood pH.[3] Cows are typically in a state of compensated metabolic alkalosis as their diet consists of forages that are typically high in K^+. Since K^+ is absorbed from the diet with nearly 100% efficiency, forage K^+ is strongly alkalinizing. Na^+ in the diet or water is also highly alkalinizing as Na^+ is also absorbed with nearly 100% efficiency. Ca^{++} and Mg^{++} cations can be present in diets in relatively high concentrations, but they are absorbed from the diet with much lower efficiency than K^+ or Na^+. Any absorbed Ca^{++} and Mg^{++} cations will also contribute to the alkalinity of the blood. Cows in a state of compensated metabolic alkalosis as a result of being fed a high K diet do not respond to PTH stimulation as well as cows placed in a state of compensated metabolic acidosis by addition of anions to their diet. Metabolic alkalosis impairs bone Ca resorption. In addition, the ability of PTH to stimulate timely production of 1,25-dihydroxyvitamin D is impaired, reducing the utilization of dietary Ca.

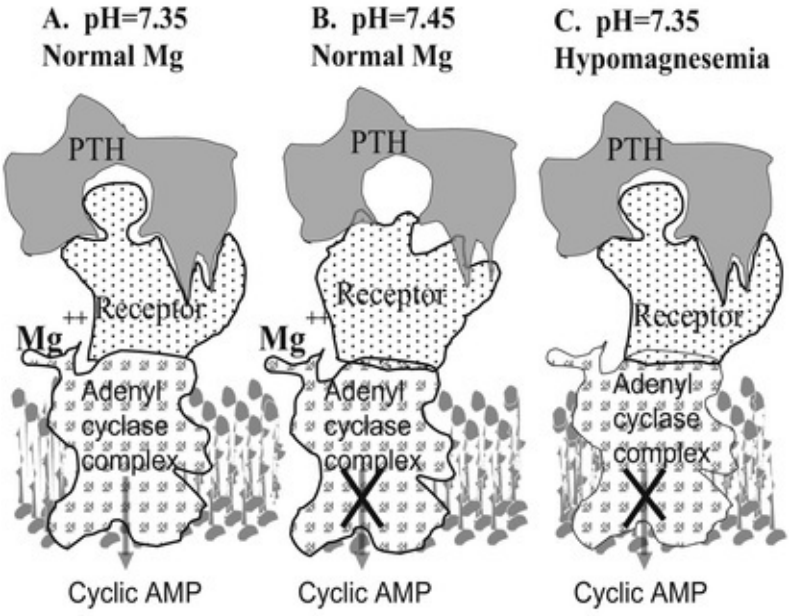


FIG. 41.20 **Parathyroid hormone (PTH) affects at the surface of target bone and kidney cells. (A) Under normal conditions, PTH released in response to hypocalcemia interacts with its receptor, located on the surface of bone and kidney cells, in a lock and key fashion. This stimulates G proteins and adenylate cyclase (adenylate cyclase complex) resulting in production of cyclic AMP, which acts as a second messenger within the cytosol of target cells. This initiates mechanisms such as bone Ca resorption and renal production of 1,25-dihydroxyvitamin D to restore blood Ca concentration to normal levels. (B) Alkalotic conditions induced by high-potassium diets induce a change in the shape of the PTH receptor protein so that it is less able to recognize and bind PTH, resulting in failure to activate the cell by producing cyclic AMP. (C) Mg is required for function of the adenylate cyclase complex. Hypomagnesemia reduces ability of PTH stimulated cells to produce cylic AMP, resulting in failure to activate the cell.**

Adjusting Dietary Cation-Anion Difference to Reduce Alkalosis in the Cow

Since K is the primary mineral causing the metabolic alkalosis that interferes with PTH function, reducing diet K content is an important step in dry cow diet formulation. Mature forages contain less potassium than young forages, and forages grown where manure or potash has been applied to the soil will have high potassium content. Cool-season grasses and legumes will remove much more potassium from the soil than they need for growth, while warm-season grasses (including corn) do not. Forages harvested when the soil is moist (spring growth) generally have higher K content than forages grown during the drier months. By restricting K application to the soil, it is possible to avoid luxury consumption of K by legumes and cool-season grasses. Producers should also be aware that forages take up Cl from the soil and it is possible to find hays that are

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low K and high (1% to 1.2%) Cl. Producers should use the lowest dietary cation-anion difference (DCAD) forage possible, not simply the lowest K forage. Forages intended for the close-up dry cow should routinely be analyzed for both K and Cl by a wet chemistry method. Near-infrared determinations of forage mineral content are not currently useful.

Anions can be added to the diet to bring the cow into a state of compensated metabolic acidosis. Diet chloride anions are absorbed with nearly 100% efficiency. Sulfate anions can also help acidify the cow, but sulfate is not absorbed as well as chloride and has approximately 60% the acidifying activity of chloride. Although phosphate anions are acidifying, they should not be added to close-up dry cow rations as they actually impair Ca homeostasis (see Phosphorus later). When sufficient anions are added to the precalving diet, they induce a compensated metabolic acidosis in the cow, improving tissue sensitivity to PTH. This restores the competency of Ca homeostatic mechanisms and facilitates a rapid return to normocalcemia after blood Ca concentration decreases at the onset of lactation.

Blood pH is difficult and expensive to measure. Urine pH generally reflects blood pH and can be determined in cows on farm to determine the degree to which an anionic diet has placed the cow in a state of compensated metabolic acidosis. Urine pH can be checked 72 or more hours after a ration change. Urine samples should be free of feces and made on midstream collections to avoid alkalinity from vaginal secretions. In cows offered feed twice daily, the timing of the urine collection does not seem critical. In cows fed limited amounts of feed so as to achieve an empty bunk, the diurnal variation in urine pH can be a full pH unit. Checking urine pH routinely allows the farm to develop confidence that the DCAD is effective and safe. Published studies where anionic salts have improved periparturient Ca status have had an anion-supplemented group of cows with urine pH below 7.0 and usually closer to 6.0.[4]

Several DCAD equations have been developed to estimate the relative effect diet macrominerals and their charges might have on the animal's blood pH. DCAD mineral concentrations are expressed as mEq of the cations and anions-per-kg diet or per-100-g diet.

1. DCAD = (Na + K) – (Cl + S)
2. DCAD = (Na + K + 0.15 Ca + 0.15 Mg) − (Cl + 0.6 S + 0.5 P)
3. DCAD = (Na + K) − (Cl + 0.6 S)

The differences in the equations reflect whether or not all macrominerals were considered and whether efficiency of absorption of the mineral from the diet was considered. One meta-analysis of published studies on periparturient hypocalcemia found the equation DCAD = (Na + K) − (Cl + 0.6 S) had the strongest ability to predict urine pH and the strongest association with milk fever incidence.[4] However, the equation DCAD = (Na + K) – (Cl + S) remains the most widely used equation.

Guidelines on the DCAD needed, expressed as (Na + K) – (Cl + S), to achieve different urine pH levels in cows are estimated below. DCAD of + 50 mEq/kg results in average urine pH of cows of approximaely 7.5. Urine pH will be around 7.0 when DCAD is approximately 0 mEq/kg and 6.3 when DCAD is approximately between −75 and −125 mEq/kg (Fig. 41.21). These are approximations, and it must be stressed that this particular DCAD equation overvalues the acidifying action of sulfate and ignores the alkalinizing action diet Ca and Mg have on blood and urine pH. Diets with anions added can be unpalatable and can depress DM intake (DMI). Commercial anion supplements that are more palatable than traditional ammonium, Ca, Mg, chloride, and sulfate salts have been developed. Even these products will depress DM intake once urine pH falls below about 5.9.[5]

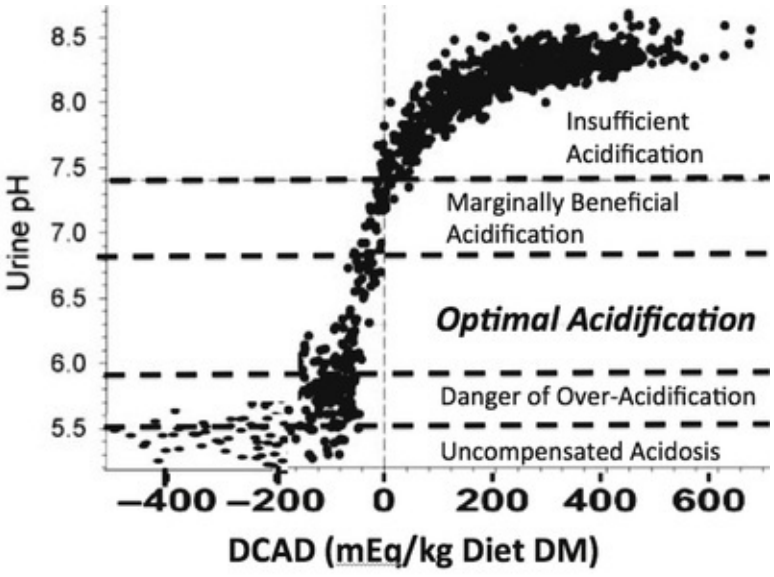


FIG. 41.21 **Effect of dietary cation-anion difference (DCAD = [Na + K] – [Cl + S]) in mEq/kg on urine pH of individual cows. Zones of expected contribution to improvement of periparturient Ca status are depicted by horizontal dashed lines. The data on cows fed diets with DCAD below −250 mEq/kg are not well represented as feed intake declines precipitously in cows fed these diets. (Adapted from Charbonneau E, Pellerin**

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D, Oetzel GR: Impact of lowering dietary cation-anion difference in nonlactating dairy cows: a meta-analysis. J Dairy Sci 89:537−548, 2006 and Constable PD, Gelfert CC, Fürll M, Staufenbiel R, Stämpfli HR: Application of strong ion difference theory to urine and the relationship between urine pH and net acid excretion in cattle. Am J Vet Res 70:915−925, 2009.)

As DCAD decreases, the degree of hypocalcemia experienced by the periparturient cow will also generally decrease. There are, however, caveats to this premise. If the addition of anions to the diet fails to acidify the cow enough to cause urine pH to be less than 7.5, there will be no demonstrable improvement in periparturient Ca status. And if the DCAD is too low, the cow is pushed into a state of uncompensated metabolic acidosis, which will greatly decrease DM consumption just before calving (see Fig. 41.21). As DCAD is reduced, the net amount of acid excreted into the urine increases until urine pH reaches about 6.3. When urine pH is below 6.3, the net acid excretion in urine is no longer well correlated to DCAD.[6] Below 6.3, the kidney begins to also excrete ammonium cations into the urine, slowing a further decline in urine and blood pH. The ammonium arises from the combining of H^+ with ammonia that diffuses into the tubular fluid as urine pH is reduced below 5.9. This ability of the kidney to neutralize the excess H^+ allows the cow to remain in a state of compensated metabolic acidosis until urine pH reaches approximately 5.5. Urine pH below 5.3 is indicative of uncompensated metabolic acidosis, which will cause severe reductions in DM intake leading to ketosis, displaced abomasum, and immune suppression.[2,5] There is evidence that dry cows with urine pH of 7.3 will be significantly less hypocalcemic than cows with urine pH of 8, but they will exhibit more hypocalcemia than cows with urine pH of 6.0. There is little evidence the degree of hypocalcemia experienced by cows with urine pH of 5.7 is less than in cows with urine pH of 6.3.

Another question revolves around the proper level of Ca to include in the diet of the cow fed anions. Anionic diets, ranging from 0.45% to 1.7% Ca, have been used successfully. Once the dietary Ca requirement of the cow has been met, the addition of Ca to precalving diets has little effect on periparturient Ca status if cows have been acidified to the same extent. However, diet Ca, especially when added as calcium carbonate, has a mild alkalinizing effect that will necessitate addition of more anions to achieve the same degree of urine acidification, which can increase the risk of DMI depression. The author prefers that prepartum diet Ca matches lactation diet Ca (0.8% to 1.1% Ca), with all of the Ca coming from forages and anion supplements.

Hypomagnesemia

A second common cause of hypocalcemia and milk fever in the periparturient cow is hypomagnesemia. Very low blood magnesium concentration (<1.2 mg/dL) can reduce PTH secretion from the parathyroid glands, which will cause blood Ca concentration to fall. This is the case when lactating beef or dairy cows are at pasture (see Magnesium section later). Less severe hypomagnesemia can alter the responsiveness of tissues to PTH. Mg must be present at adequate levels to allow the PTH/PTH receptor complex to fully activate the adenyl cyclase and allow cyclic AMP production (see Fig. 41.20). Levels below 1.7 mg/dL, which can be common particularly in the first days of lactation, do not support full activity of the adenyl cyclase linked to the PTH receptor. Cows fed adequate dietary magnesium in the prepartal ration will typically be slightly hypermagnesemic the day after parturition. When blood magnesium concentration within 24 hours after calving is not at least 1.9 mg Mg/dL, it suggests inadequate dietary magnesium.

Effect of Dietary Phosphorus on Hypocalcemia

Phosphorus (P) exists in diets and body fluids as phosphate (monobasic or dibasic PO_4^{-3}). Absorption of phosphate anions occurs primarily in the small intestine by a transepithelial process that is activated by the hormone 1,25-dihydroxyvitamin D. Because it is an anion, dietary P that is absorbed into the blood will acidify the blood. Though adding P to the diet can acidify the cow, the addition of P to the precalving diet increases the degree of hypocalcemia experienced by the periparturient cow. Serum P generally increases with dietary P. Unfortunately, a rising blood P concentration causes bone osteocytes to secrete the phosphate-regulating hormone, fibroblast growth factor 23 (FGF23), to reduce blood P. FGF23 leaves the bone, circulates in the blood, and binds to its receptor on kidney cells, where it inhibits renal enzymes involved in synthesis of 1,25-dihydroxyvitamin D and increases production of enzymes that degrade 1,25-dihydroxyvitamin D. Reducing blood 1,25-dihydroxyvitamin D concentrations reduces intestinal P absorption, causing blood P to decline (Fig. 41.22). Unfortunately, reducing production of 1,25-dihydroxyvitamin D also reduces diet Ca absorption impairing Ca homeostasis.[3] Restricting P content of precalving diets can aid Ca homeostasis. Cows fed an anionic precalving diet that was 0.21% P had a lower incidence of hypocalcemia than cows fed a 0.44%

P diet. They also maintained serum P concentrations that were within the normal range for cows (4 to 6 mg P/dL or 1.23 to 1.86 mmol/L) during the precalving period.

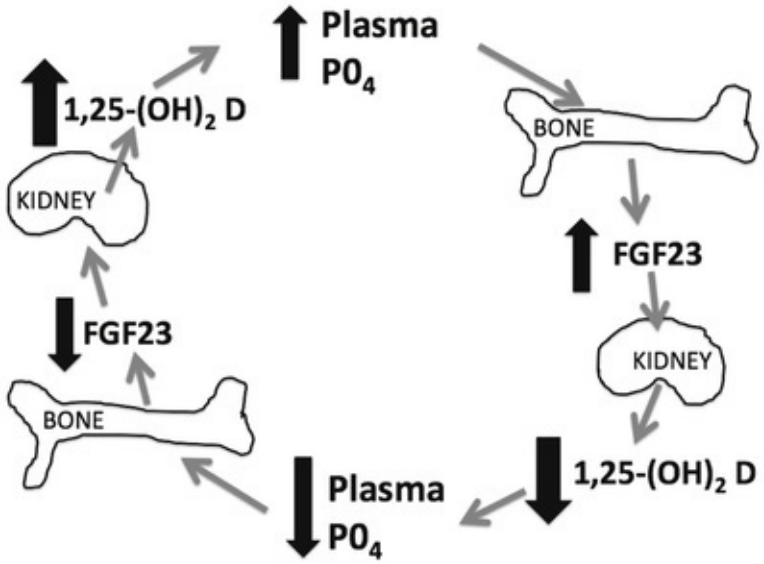


FIG. 41.22 **Increasing concentrations of phosphate in plasma and extracellular fluids cause osteocytes to secrete fibroblast growth factor 23 (FGF23) into the blood. FGF23 inhibits renal synthesis of 1,25-dihydroxyvitamin D (1,25-$[OH]_2$D), which reduces dietary phosphate absorption. Conversely, low extracellular and plasma phosphate inhibits osteocyte production of FGF23 and 1,25-$(OH)_2$D synthesis increases, stimulating increased dietary phosphate absorption to raise blood phosphate concentration.**

Dairy cows can develop a condition known as the hypophosphatemic downer cow. These cows exhibit low serum phosphate concentration, often below 1.5 mg/dL (0.46 mmol/L). When it is observed, it is generally a sequelae of milk fever (see Phosphorus section). It does not occur as a consequence of low dietary P, and steps taken to reduce milk fever incidence reduce the incidence of the hypophosphatemic downer cow as well.[2]

Using a Ca-Deficient Diet to Prevent Milk Fever

This strategy involves limiting diet Ca or diet Ca availability to levels that place the cow in negative Ca balance for 7 to 14 days before calving. Negative Ca balance stimulates the parathyroid gland to greatly increase secretion of PTH within 3 to 4 days of the diet Ca reduction. Prolonged exposure to high concentrations of PTH overcomes the tissue resistance to PTH that is caused by

metabolic alkalosis. Ca conservation and Ca mobilization mechanisms, such as renal production of 1,25-dihydroxyvitamin D and bone Ca resorption, are activated before the onset of lactation. The cow's homeostasis mechanisms are primed by the low Ca diet and ready to respond to the Ca demands of lactation.

The studies in which milk fever was effectively prevented using the “Ca-deficient diet” strategy had total diet Ca below 20 g/day and likely supplied less than 12 g absorbable Ca each day. It is difficult to feed prepartum diets that are this deficient in Ca using typical forages when cows are fed ad libitum.

Substances that bind dietary Ca and render it unavailable for absorption can allow formulation of diets that will successfully cause prepartal Ca deficiency and reduce periparturient hypocalcemia. Zeolite A is a sodium-aluminum silicate that can bind dietary Ca in prepartum diets, rendering it unavailable for absorption. Depending on DMI, it can work when diets are as high as 0.6% to 0.7% Ca (Ca intake <75 g Ca/day) to cause “Ca deficiency” and prevent milk fever. It also binds phosphate, which may be of some aid in the prevention of hypocalcemia. Zeolite A also binds Mg and cationic trace minerals (especially Cu) in the diet, but the implications to the health of the cow are unknown. A similar approach is to use rice bran that has been treated with formaldehyde so that it is able to bypass the rumen intact. The phytic acid within the rice bran binds Ca within the lumen of the small intestine, preventing it from being absorbed, improving periparturient Ca status. It also binds dietary phosphate before calving, which may also help prevent milk fever.

Exogenous Vitamin D and Parathyroid Hormone Administration

Earlier literature often recommended feeding or injecting massive doses (up to 10 million units of vitamin D) 10 to 14 days before calving to prevent milk fever. The vitamin D was converted to 25-hydroxyvitamin D, which, at very high levels, can stimulate vitamin D receptors and increase intestinal calcium absorption to help prevent milk fever. Unfortunately, the dose of vitamin D that effectively prevents milk fever is close to the level that causes metastatic calcification of soft tissues, particularly if prepartum diet Ca is high. Lower doses are not effective and may actually induce milk fever because the high levels of 25-hydroxyvitamin D suppress PTH secretion and renal synthesis of endogenous 1,25-dihydroxyvitamin D. Recent studies using administration of the vitamin D metabolite, 25-hydroxyvitamin D, have not found that this compound can reduce the incidence of hypocalcemia, though its shorter half-life

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may make it less toxic than vitamin D.

Treatment with the hormone 1,25-dihydroxyvitamin D and its analogs can be an effective means of preventing hypocalcemia. Problems with cost, timing of administration and withdrawal from treatment, and lack of FDA approval have not made these treatments practical.

Synthetic PTH peptides given daily before calving can also effectively prevent milk fever, but no commercial product is currently available. Prolonged exposure of the bone and kidney cells to the high levels of PTH overcomes tissue resistance to PTH.

Other Milk Fever Risk Factors

Heifers rarely develop clinical milk fever, though 5% to 25% of them may experience subclinical hypocalcemia, with blood Ca falling below 8 mg/dL (<2.0 mM). The incidence of clinical (milk fever) and subclinical hypocalcemia increases with each subsequent lactation. Ca homeostasis in heifers is more robust than in older cows because they are still growing. Their bones will have many more mature osteoclasts present in them. PTH needs only to activate the cells. This allows them to access more bone Ca on the first day of lactation.[1] In an older cow the PTH must first induce osteoclast production from progenitor cells and then activate the cells to resorb bone Ca. Also, as cows age there is a reduction in the number of receptors for 1,25-dihydroxyvitamin D in their intestines, which may translate into slower activation of intestinal Ca transcellular absorption.

The Channel Island (Jersey, Guernsey) and, to a lesser extent, the Swedish Red and White and Norwegian Red breeds have a higher incidence of milk fever than Holstein cows. The reasons remain unclear. Jersey cow colostrum and milk have a higher calcium content than that produced by Holstein cows, which may place a relatively larger calcium stress on the Jersey cows. In one study, Jersey cows had significantly fewer intestinal receptors for 1,25-dihydroxyvitamin D than did Holsteins, which might slow upregulation of intestinal diet Ca absorption.

Heat stress has mixed effects on acid-base physiology and therefore Ca homeostasis. During the heat of the day the cow typically has a higher respiratory rate, using movement of air in and out of the respiratory tract to reduce body heat (similar to the panting dog). This causes blood carbon dioxide levels to decrease, which lowers blood HCO_3^- anion concentration, resulting in

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respiratory alkalosis. In severe heat stress the animal may drool excessively, resulting in the loss of large amounts of salivary K (and some Na) cations from the body, which can cause metabolic acidosis. Whether respiratory alkalosis or metabolic acidosis predominates determines blood pH and susceptibility to hypocalcemia at calving.

Treatment of Cows With Milk Fever

Cows that are recumbent with hypocalcemia need to be treated with intravenous Ca as soon as possible. The proper dose is 1 g Ca/100 lb body weight given at the rate of 1 g Ca/minute. Most products on the market supply between 10.5 and 12 g Ca in a 500-mL solution. Any soluble Ca salt that dissociates to provide Ca^{++} ions will be effective. Ca gluconate and borogluconate are commonly used. Calcium chloride, while effective, is rarely used today because administration outside of the vein causes tissue necrosis. Immediately after treatment the blood total Ca concentration will be at least 14 mg/dL (3.5 mM) and often reaches 20 mg Ca/dL (5 mM). When IV Ca is administered too quickly, the heart stops in systole: this occurs when blood Ca rises above 28 mg/dL (7 mM). Some practitioners will administer Ca subcutaneously to avoid cardiac toxicity. Typically the same solution used for IV treatment is used. It must be limited to about 50 mL per injection site to avoid sterile abscess due to hypertonicity of the solution. Many of these treatments also contain glucose, which further increases the risk of a sterile abscess developing at the site of subcutaneous injection. The intravenous and subcutaneous Ca treatments will support near-normal levels of blood Ca concentration for 6 to 9 hours following treatment. Giving a subcutaneous bottle of Ca immediately following the intravenous treatment does not extend the therapeutic window and prevent relapse.

Many products also provide soluble forms of Mg and K. The 1.75- to 2.25-g Mg in these products can temporarily correct hypomagnesemia, and the K helps prevent cardiac toxicity as its action on the heart can counter the inotropic action of the Ca. Phosphorus can be found in some of these products. However, the form of phosphorus found in these products tends to be phosphite or phosphinic salts, which are biologically unavailable to the cow.

If treatment is delayed, it is possible for the cow's down side hind leg to undergo the crush syndrome in which blood flow to the limb is compromised and muscle tissue starts to become necrotic. In addition, pressure that develops between the ground and greater trochanter of the femur can damage the sciatic

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nerve, rendering the cow unable to rise even after blood Ca has been corrected. If the cow exhibits knuckling over on the down limb when she stands following IV Ca treatment, it is likely the peroneal nerve was damaged where it crosses the lateral side of the tibia. Occasionally the forelimb radial nerve can also suffer compression damage. Cold weather speeds the damage done by recumbency. Treatment of the cow with muscle and nerve damage requires that the weight be taken off the down leg. This can entail placement of the down cow in an area with deep bedding and rolling the cow from one side to the other every 3 to 4 hours until healing occurs, which may take several days. Slings, air mattresses, and other devices have been devised to help the down cow but require great dedication to achieve recovery. The cow can also be moved into a “float tank,” which uses warm water to lift the cow so she can stand in the water tank (see Chapter 35, Down Cows). Float tanks are more successful in effecting a recovery of muscle and nerve function than the other treatments described earlier. Vitamin E and selenium, B vitamins, glucocorticoids, and NSAIDs are commonly administered to down cows as adjunct therapies, but their effectiveness is not well documented.

Oral Ca risks aspiration pneumonia as the swallowing reflex is compromised. In addition, oral Ca may not raise the blood Ca fast enough to avoid the crush syndrome from developing in a recumbent cow.

Relapsing Milk Fever

About 20% of cows that have been successfully treated for milk fever with IV Ca will suffer a relapse of milk fever, often about 24 hours after initial treatment. These cows have high blood PTH concentrations but produce little 1,25-dihydroxyvitamin D at parturition, suggesting the tissues remain insensitive to PTH stimulation. Full recovery from milk fever occurs only after the cow has responded to the PTH by producing 1,25-dihydroxyvitamin D, which can be delayed for 24 to 72 hours in some cows. Some clinicians administer a second bottle of Ca subcutaneously following IV Ca treatment in the mistaken belief that this will prevent relapse. Subcutaneous or oral Ca treatment to prevent relapse will be more effective if administered 12 to 24 hours after initial IV treatment. Oral Ca treatments based on Ca chloride will also acidify the cow, improving PTH sensitivity of the tissues to help prevent relapse as well.

Oral Ca Treatments at Calving

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Ca is absorbed across the intestinal mucosa by two methods. The first method is by the active transport of Ca across intestinal cells; a process mediated by the hormone 1,25-dihydroxyvitamin D. The second method is by passive diffusion across the tight junctions that hold adjacent mucosal cells together. The concept behind oral Ca supplementation is that the cow's ability to use active transport of Ca *across* intestinal cells is inadequate to help her maintain normal blood Ca concentrations. By dosing the animal with large amounts of very soluble Ca, it is possible to force Ca across the intestinal tract by means of passive diffusion *between* intestinal epithelial cells. Best results are obtained with doses of Ca between 45 and 90 g Ca/dose. For best control of hypocalcemia, a dose is given at calving and again 12 to 24 hours later. Not all of the orally administered Ca will be rapidly absorbed via the paracellular route. Administering 50 g Ca from Ca chloride as a drench in 250 mL water is roughly equivalent to administering 4 g Ca IV.[3] Unfortunately, hypocalcemic cows have poor swallowing and gag reflexes, making them vulnerable to aspiration pneumonia. Aspiration of Ca solutions leads to severe pneumonia. Ca chloride has been used in oral Ca preparations but can be caustic as a drench. Oral boluses that are coated with fat have been developed and avoid the esophageal erosions observed with many of the oral calcium chloride drenches. Ca propionate is less injurious to tissues and has the added benefit of supplying propionate, a gluconeogenic precursor. Toxic doses of Ca can be delivered orally—the LD50 is about 200 g Ca in a soluble form!

Intravenous Ca Treatment at Calving to Prevent Hypocalcemia

Some farms routinely give older cows an intravenous bottle of Ca at calving to prevent milk fever. This raises blood Ca quite rapidly and does reduce the risk of clinical milk fever for at least the next 12 to 24 hours. However, it may shut down Ca homeostatic mechanisms on that day, causing the cow to have lower blood Ca on days 2 and 3 after calving than cows that received no intravenous Ca treatment. Oral or subcutaneously administered Ca does not appear to shut off Ca homeostasis to the same extent and may provide more effective treatment of the cow.[7]

Magnesium

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Mg is a major intracellular cation serving as a cofactor for enzymatic reactions vital to every major metabolic pathway. Extracellular Mg is vital to normal nerve conduction, muscle function, and bone mineral formation. In a 600-kg cow there is about 0.84 g Mg in the blood, 3 g Mg in all the extracellular fluids, 84 g Mg inside cells, and 210 g Mg within bone mineral. Unfortunately, bone is not a significant source of Mg that can be used in times of Mg deficit, as bone resorption occurs in response to Ca homeostasis, not Mg status. Maintenance of normal plasma Mg concentration is nearly totally dependent on continuous dietary Mg absorption.

Hypomagnesemia

Hypomagnesemia generally leads to nerve hyperexcitability, tetany, convulsion, and, too often, sudden death. Hypomagnesemia is often accompanied by and complicated by hypocalcemia. Hypomagnesemia is a common problem only in ruminants.

Cow plasma Mg concentration is normally between 1.8 and 2.4 mg/dL (0.75 and 1 mM). Normal plasma Mg concentration in sheep is between 2.2 and 2.8 mg/dL (0.90 and 1.15 mM). The kidneys play a key role in maintaining Mg homeostasis by excreting excess absorbed Mg. The renal threshold for Mg (i.e., the plasma Mg concentration at which all Mg filtered across the glomerulus is reabsorbed is 1.8 mg/dL [0.75 mM] in the cow and 2.2 mg/dL [0.90 mM]) in sheep. Plasma Mg concentrations below these levels indicate dietary Mg absorption is not sufficient. Little or no Mg will be detected in urine.

Moderate hypomagnesemia between 1.1 and 1.8 mg/dL (0.5 and 0.75 mM) is associated with reduced feed intake, nervousness, and reduced milk fat and total milk production. This can be a chronic problem in some dairy herds that often goes unnoticed. It can also predispose these animals to hypocalcemia and milk fever as described earlier.

Role of Rumen in Hypomagnesemia

Mg is well absorbed from the small intestine of young calves and lambs. As the rumen and reticulum develop, these sites become the main, and perhaps only, sites for net Mg absorption. In adult ruminants the small intestine is a site of net secretion of Mg. Mg absorption from the rumen is dependent on the concentration of Mg in solution in the rumen fluid and integrity of the Mg transport mechanisms.

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The soluble concentration of Mg in rumen fluid can be low for several reasons. Chief among these are low Mg content of forages and inadequate diet supplementation. Mg solubility also declines sharply as rumen pH rises above 6.5. Grazing animals tend to have higher rumen pH because of the stimulation of salivary buffer secretion. Forages can also contain organic compounds, such as unsaturated fatty acids, that are converted to tricarballylate, which can form insoluble Mg salts in the rumen. When high grain rations are fed, rumen fluid pH is often below pH 6.5, increasing Mg solubility and thus availability.

Two mechanisms existing in rumen epithelium allow Mg to cross the apical membrane of the stratum granulosum cells in contact with the rumen fluid. One is a Na-linked transport mechanism, which relies on a high potential difference across the apical membrane to move Mg into the cell down its electrical gradient.[8] When this transporter is fully functional, the ruminant can generally meet its Mg requirements with diets that are 0.2% to 0.25% Mg. Feeding ionophores (monensin, lasalocid) can improve activity of this Na-linked Mg transport system in the rumen, increasing Mg absorption efficiency about 10%. Lush high-moisture pastures increase the rate of passage of material, including Mg, from the rumen so that Mg may leave the rumen before it can be absorbed.

Unfortunately, the Na-linked Mg transporter is disrupted by high K and high ammonia/ammonium in the rumen fluids. High K concentration in the rumen fluid depolarizes the apical membrane of the rumen epithelium, reducing the electromotive potential needed to drive Mg thru the Mg channels in the apical membrane of stratum granulosum cells.[8] Acute exposure to ammonia/ammonium similarly depolarizes the apical membrane of the stratum granulosum cells, inhibiting Mg transport by this route. Fortunately, a second Mg transport mechanism exists in the rumen epithelium that is not dependent on the potential difference across the apical membrane and therefore unaffected by diet K. However, this transporter is Mg concentration dependent (i.e., it is most effective when rumen fluid Mg ion concentration is high). Essentially, diet Mg has to be high enough to raise rumen fluid *ionized* Mg concentration above 3 to 4 mM. This may require the diet to be greater than 0.35% Mg, depending on the source of Mg and its solubility in rumen fluid. Mg content of the close-up dry cow ration and early lactation ration should be between 0.35% and 0.4% as insurance against the possibility that the active transport processes for Mg absorption are impaired.

Cows being fed a low DCAD diet to prevent milk fever and hypocalcemia are generally fed Mg as magnesium sulfate or magnesium chloride—both are highly

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available in the rumen and generally provide adequate amounts of Mg to use either of the rumen Mg transporters effectively. However, after calving, cows are placed on a lactation diet. Forages and magnesium oxide become the sources of Mg in these diets. Magnesium oxide (MgO) is used because it can also serve as a rumen fluid alkalinizer and help maintain rumen pH during lactation. Unfortunately, there is wide variability in availability of Mg from MgO and this often causes mild hypomagnesemia in cows during the first few days of lactation.

The reactivity of MgO with acetic acid provides a simple test of the relative availability of the MgO being considered for use in rations. Place 3 g of a MgO source in a container and slowly add 40 mL 5% acetic acid (white vinegar). Cap the container, shake well for 15 seconds, and let it sit. Shake again at the 15-minute mark and then check the pH at 30 minutes. Vinegar alone has a pH of 2.6 to 2.8. The best MgO sources will bring the pH up to 8.2 and the worst to just 3.8.[2] Because pH is a log scale, this represents more than a 10,000-fold difference in the number of hydrogen ions neutralized. In an experiment with four cows with rumen fistulas, the solubility of MgO in vitro (tested in several ways) was found to parallel their solubility in the rumen and their urinary excretion—an indication that solubility predicted absorbability.[9]

Occurrence of Hypomagnesemic Tetany

Hypomagnesemic tetany is most often associated with beef and dairy cows and ewes in early lactation grazing lush pastures high in potassium and nitrogen and low in Mg and sodium. This is the most common situation, and it is often referred to as grass tetany, spring tetany, grass staggers, rye or wheat pasture poisoning and lactation tetany. Mg deficiency occurs most often in spring or fall when pastures are growing at maximal rates and is most common in lactating ruminants as milk production removes 0.15 g Mg from the blood for each liter of milk produced. Cool weather seems to play a factor as well, probably through its effects on plant Mg uptake, though there is some indication that the physiologic response of the cow to cool weather affects Mg status directly.

When plasma Mg levels fall below 0.5 mmol/L or 1.1 mg/dL, twitching is sometimes seen in the muscles of the face, shoulder, and flank. As hypomagnesemia progresses, tetanic spasms of the muscles become more common, which eventually cause the cow or ewe to stagger and fall. In most cases, the clinical signs of tetany occur only when hypomagnesemia has

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interfered with PTH secretion and function, causing secondary acute hypocalcemia.

Hypomagnesemia will slowly cause cerebrospinal fluid (CSF) Mg concentration to decline. Clonic convulsions quickly follow, with chomping of the jaws and frothy salivation. Affected animals lay with the head arched back and legs paddling. The heart rate can approach 150 bpm, and the heartbeat is often audible without a stethoscope. Respiratory rate approaches 60/min and the rectal temperature rises and can approach 40.5° C (105° F) as a result of excessive muscular activity. The eyelids flutter, and there is usually marked nystagmus. They may get up after several minutes and repeat these convulsive episodes several times before they finally die. Hypomagnesemic tetany in calves is clinically similar to that in adults and is often accompanied by moderate hypocalcemia.

Ewes are generally hypocalcemic and hypomagnesemic. Affected ewes are usually in the second to fourth weeks of lactation and are usually suckling more than one lamb. Affected ewes are generally depressed, stand with their heads down, and are reluctant to move. As hypomagnesemia and hypocalcemia progress, they suffer tetany and clonic convulsions just as in cattle. The clinical signs in goats are similar to those observed in cattle.

CSF Mg concentrations below 1 mg/dL (0.4 mM) are responsible for the clonic convulsions seen in animals with hypomagnesemic tetany. Unfortunately, blood samples obtained during or shortly after an episode of tetany may have near-normal levels of Mg as a result of muscle damage and leakage of Mg from intracellular pools complicating diagnosis. CSF Mg concentration will remain low during tetany and also can be a reliable indicator of Mg status for up to 12 hours after death. Vitreous humor Mg concentrations below 0.4 mmol/L or 1 mg/dL are also found in animals with tetany and can be a reliable indicator for 24 to 48 hours after death provided that environmental temperatures have not exceeded 23° C. Aqueous humor has not proved a reliable sample.

Urine can be collected antemortem or postmortem. Low blood Mg concentration will not exceed the renal threshold for Mg, and as a result very little Mg will be in the urine. Urine Mg concentration below 1 mM is indicative of deficiency. Urine Mg concentration above 4.4 mM is considered normal. Urine Mg between 1 and 4.4 mM is likely insufficient Mg status.

Treatment of Hypomagnesemia

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Animals exhibiting hypomagnesemic tetany need immediate treatment. This will require administering from 1.5 to 2.25 g Mg IV in the adult cow. They generally also need intravenous Ca. Most of the commercially available intravenous solutions used to treat the hypocalcemia of milk fever supply from 1.5 to 3 g Mg, usually as the chloride, borogluconate, or hypophosphite salts of Mg. Response to therapy can be disappointing, and success is related to the interval between onset of tetany and treatment. Cows should not be stimulated to rise for at least 30 minutes after treatment to avoid initiating tetany and convulsion. Cattle that will recover do so about an hour after treatment, which is the time it takes for CSF Mg concentration to return to normal. Many of these cows will relapse and require further treatment within 12 hours.

The rate of relapse can be reduced using orally administered Mg salts once the animal has regained good swallowing reflexes (to avoid aspiration pneumonia). Drenching or pumping into the rumen 100 g Mg oxide suspended in water can be effective. This provides about 52 g Mg to the animal. Adding 50 g Ca carbonate, 100 g dicalcium phosphate, and 50 g sodium chloride may enhance the effectiveness of the slurry, especially if hypocalcemia and hypophosphatemia accompany the hypomagnesemia. Alternatively, 200 to 400 mL of a 50% Mg sulfate solution can be administered by drench. Mg sulfate is more available for rumen absorption than Mg oxide. If hypomagnesemic tetany has occurred in one cow or ewe in a herd or flock, steps should be taken immediately to increase Mg intake in other members of the herd to prevent further losses. Getting an additional 10 to 15 g Mg into each pregnant cow, 20 g Mg into each lactating beef cow, and 30 g Mg into each lactating dairy cow each day, usually in a grain mix, will often prevent further hypomagnesemic tetany cases. Ewes and does can be treated with one eighth of the formulas mentioned earlier. The problem with these prevention schemes is getting the animal to actually consume the extra Mg, especially when working with animals at pasture. It can be added to a small amount of grain offered in the pasture. Mg sulfate and Mg chloride can be added to the water source, but this is only successful if the animals have no other water source to choose from.

Phosphorus

Traditionally, phosphorus in clinical medicine is abbreviated as P, although it should be understood by the reader that the biologically relevant form of phosphorus is actually inorganic phosphate, PO_4^{-3}, not elemental phosphorus. P

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is also a component of phospholipids, phosphoproteins, nucleic acids, and energy-transferring molecules such as ATP, but these are not detected as phosphate by the laboratory test used to measure blood inorganic phosphate. In the blood, phosphate ions are typically in the form of HPO_4^{-2} or $H_2PO_4^{-1}$. Moving phosphate between these two forms allows P to serve as an essential component of the acid-base buffer system of the body. P is second only to Ca as a major component of bone mineral, with the skeleton of a 600-kg cow containing about 3.9 kg P.

Phosphorus Homeostasis

Plasma P concentration is normally 4 to 8 mg/dL (1.3 to 2.6 mM). About 1.2 to 2.2 g P is present in the plasma inorganic P pool, and 5 to 8 g P is normally present in the extracellular P pool of a 600-kg cow. Intracellular P concentration is about 78 mg/dL (25 mM), and total body intracellular P content is about 185 g, with 5.5 to 6.5 g of P located within erythrocytes. Maintaining the extracellular P pool involves replacing extracellular P removed for bone and muscle growth, endogenous fecal loss, urinary P loss, and milk production with P absorbed from the diet or resorbed from bone. During late gestation, fetal skeletal development can withdraw up to 10 g P/day from the maternal P pools. About 0.3 g P is incorporated into each kg of body tissue (muscle) gained during growth of the animal. Production of milk removes about 0.9 g P from the extracellular pool/kg of milk produced. Salivary secretions remove between 30 and 90 g P from the extracellular P pool each day, though most of it is reabsorbed on reaching the small intestine. Factors affecting salivary phosphate secretion include the time spent ruminating (chewing activity) and the PTH status of the animal. PTH stimulates parotid salivary P secretion and can increase salivary phosphate concentrations twofold to threefold. Salivary phosphate secretions help buffer the rumen and supply rumen microbes with a readily available source of P necessary for cellulose digestion. Most of the salivary phosphate secreted is recovered by intestinal absorption. However, even on low-P diets a minimum of 5 g/day of secreted P is not recovered and is lost to feces. Urinary P loss is usually between 2 and 12 g/day. Bones of a 600-kg cow contain about 4 kg of P, some of which can be withdrawn and returned to the blood during osteoclastic resorption of bone.

Rumen microbes are able to digest phytic acid, so most of the phytate-bound P, the form of up to 70% of P in plants, is available for absorption in ruminants.

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P is primarily absorbed in the small intestine via an active transport process that is dependent on 1,25-dihydroxyvitamin D. This vitamin D hormone stimulates enterocytes to produce a Na^+-coupled phosphate cotransporter protein in their apical membrane, allowing efficient absorption of diet P.

Homeostasis of P

Plasma P concentrations are generally well correlated with dietary P absorption. P absorbed in excess of needs is excreted in urine and saliva. Rising serum P concentration triggers the bone osteocytes to produce the hormone fibroblast growth factor 23 (FGF23). This hormone circulates to the kidney, where it inhibits the activity of the renal enzyme that produces the hormone 1,25-dihydroxyvitmin D, and stimulates the activity of enzymes that degrade 1,25-dihydroxyvitamin D (see Fig. 41.22). The lack of 1,25-dihydroxyvitamin D reduces the active transport of P across the intestinal epithelium, lowering blood P concentration. In addition, FGF-23 also acts on renal proximal tubule cells to block Na/PO_4 cotransporters that reabsorb filtered phosphate from the tubular fluid, increasing urinary excretion of phosphate.[10]

Intestinal P absorption efficiency can be upregulated during periods of P deficiency as renal production of 1,25-dihydroxyvitamin D can be directly stimulated by very low plasma P, independent of PTH. However, the plasma P level must reach low levels (<1 or 2 mg/dL) to actually stimulate increased renal production of 1,25-dihydroxyvitamin D.

PTH, secreted during periods of Ca stress, increases renal and salivary excretion of P, which can be detrimental to maintenance of normal blood P concentrations. This is one reason that hypocalcemic animals tend to become hypophosphatemic. PTH could conceivably increase blood P concentration because it stimulates bone osteoclast mineral resorption. However, one reason the cow is hypocalcemic and secreting high levels of PTH is because the osteoclasts are not responding quickly enough to the PTH! PTH stimulates the kidney to produce 1,25-dihydroxyvitamin D, which should increase the efficiency of intestinal phosphate absorption. Complicating this further, a rise in blood P can trigger bone osteocytes to secrete FGF23 to shut off synthesis of 1,25-dihydroxyvitamin D, inhibiting intestinal absorption of Ca and P.

Acute Hypophosphatemia, Pregnancy Toxemia,

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and Downer Cows

Beef cows and ewes fed a diet marginal in P will have a chronic hypophosphatemia of 0.6 to 1.1 mmol/L or 2 to 3.5 mg/dL. In late gestation, plasma P can decline precipitously as the growth of the fetus accelerates and removes substantial amounts of P from the maternal circulation. These animals often become recumbent and are unable to rise, though they appear fairly alert and will often eat feed placed in front of them. Cows and ewes carrying twins are most often affected. Plasma P concentration in these recumbent animals is often less than 0.3 mmol/L or 1 mg/dL. The disease is often referred to as pregnancy toxemia and is usually complicated by concurrent hypocalcemia, hypomagnesemia, and in some cases hypoglycemia. Diets that are marginal in P are generally indicative of diets that are marginal in energy because grains are excellent sources of P.

At the onset of lactation in the dairy cow, the production of colostrum and milk draws large amounts of P out of the extracellular P pools. This alone will often cause an acute decline in plasma P levels. In addition, if the animal is also developing hypocalcemia, PTH will be secreted in large amounts, increasing urinary and salivary loss of P. In dairy cows, plasma P concentrations routinely fall below the normal range at parturition, and in cows with milk fever, plasma P concentrations are often between 0.4 and 0.75 mmol/L or 1.3 and 2.5 mg/dL. Plasma P concentrations usually increase rapidly following treatment of the hypocalcemic cow with intravenous Ca solutions. This rapid recovery is due to reduction in PTH secretion, which reduces urinary and salivary loss of P. Administration of Ca generally causes resumption of gastrointestinal motility, which allows absorption of dietary P and reabsorption of salivary P secretions that were sequestered within the rumen.

Some dairy cows developing acute hypocalcemia and hypophosphatemia do not spontaneously recover normal plasma P concentration. This is sometimes the case in cows that are classified as “downer cows.” This syndrome often begins as milk fever, but unlike the typical milk fever cow, plasma P remains low, often below 1 mg/dL (0.3 mM), despite successful treatment of the hypocalcemia. Protracted hypophosphatemia in these cows appears to be an important factor in the inability of these animals to rise to their feet, but why plasma P remains low is unclear. In some cases the inability to absorb the salivary phosphate is secondary to poor rumen motility, but not in all cases. Excessive cortisol secretion might be a factor in this syndrome as glucocorticoids can force

extracellular P to move inside cells.

Treatment of these “downer cows” with phosphate (PO_4^{-3})-containing solutions can effect a recovery in some animals provided they are treated before muscle and nerve damage have occurred. Unfortunately, many products suggested for intravenous use in treating this syndrome contain P as phosphite or phosphinic acid salts (PO_2^{-2}), which are biologically inactive. For proper oral treatment, the dose is 50 g P supplied in a 200-g monosodium phosphate drench. Intravenous treatment consists of 6 g P, supplied by 23 g monosodium phosphate, an amount found in many over-the-counter phosphate enema preparations sold in drugstores for human use. This author prefers to administer the phosphate dissolved in 1 L of saline. Oral treatment restores normal blood P more slowly than intravenous treatment, but the effect lasts longer. If depletion of intracellular P stores is involved in the downer syndrome, it seems likely that intravenous treatment alone will not supply enough P to replenish intracellular stores of P.

The hypophosphatemic downer cow syndrome does not appear to be caused by low P diets as affected cows are often receiving diets containing 0.4% dietary P. The best preventative measure seems to be to effective actions to avoid development of hypocalcemia. In the author's experience, hypophosphatemic downer cows are most commonly seen in the northern latitudes at the end of winter and early spring. Fluctuating temperatures caused by passing cold fronts may play a role.

Chronic P Deficiency

P deficiency is fairly common in ruminants grazing plants grown in arid climates or on tropical soils with poor soil P content or availability. While P content of the immature plant may be suitable (0.3% P-DM basis), the mature dry plants often contain less than 0.15% P. In more temperate areas, P deficiency can develop in animals grazing overly mature forages or crop residues, such as corn stalks. Sheep can, in some instances, be successfully raised on pasture that has been associated with P deficiency in cattle, suggesting that sheep are slightly more resistant to P deficiency syndromes than are cattle. This may simply reflect the higher intake/kg body weight of sheep and their habit of selecting the less mature plants, which are generally higher in P. With the exception of rickets and postparturient hemoglobinuria (discussed later), the clinical problems associated with P deficiency are general and nonspecific and can include an unthrifty

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appearance, reduced feed intake, pica, reduced rate of gain, and reduced milk production.

Impaired reproduction has often been attributed to “P deficiency.” However, in most cases cows develop P deficiency in situations that also result in concurrent energy deficiency. It is the negative energy balance that is the direct cause of reproductive failure. Unfortunately, the belief that “marginal” dietary P contributed to reproductive inefficiency has been used as justification for feeding diets that are much higher in P than is required. High-producing cows perform well in terms of milk production and fertility when fed diets containing just 0.38% P.[11]

Postparturient Hemoglobinuria

Intravascular hemolysis, anemia, and hemoglobinuria are occasionally reported during the first 6 weeks of lactation. Many, but not all, cows developing this syndrome are hypophosphatemic. Severe hypophosphatemia is postulated to depress the ability of erythrocytes to produce ATP because a key enzyme in glycolysis, glyceraldehyde-3-phosphate dehydrogenase, requires inorganic phosphate as a cofactor. Without sufficient ATP to power sodium pumps, the intracellular sodium concentration rises, the cells become more rigid and, as a result, rupture as they pass through the capillary beds.

However, hypophosphatemia alone is rarely sufficient cause for increased red blood cell fragility. Often these cows are on diets that are also deficient in selenium, copper, and energy, so attributing the cause to hypophosphatemia is likely too simplistic. Cows that have been treated for ketosis seem at greater risk of developing postparturient hemoglobinuria.

Electrolyte (Na, K, and Chloride) Issues in Ruminants

Sodium and Chloride

Sodium is the major extracellular cation of body fluids and plays a crucial role in absorption of dietary sugars, amino acids, and water. Chloride is the major anion in the body, making up more than 60% of the total anion equivalents in the extracellular fluid. Chloride helps regulate osmotic pressure of blood. Chloride is the chief anion in gastric secretions and is responsible for the low pH in the lumen of the abomasum. Chloride is actively secreted into the intestinal lumen

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by crypt epithelial cells and acts as the driving force for Na movement into the lumen of the gut to satisfy needs of Na/hexose and Na/amino acid symporters. Both Na and Cl always exist in a fully dissociated (ionized) state when in solution. Nerve and muscle resting membrane potentials are highly dependent on proper sodium and chloride concentrations. Most land vertebrates evolved without abundant diet Na. Therefore, they developed efficient and redundant mechanisms for Na absorption. Na and Cl transporters across the digestive tract epithelium are often coupled to maintain electroneutrality. Sodium and Cl can be absorbed from the rumen, small intestine, and large intestine. Nearly 100% of diet Na and more than 90% of diet Cl is absorbed.

Salt may be the only mineral compound that animals truly develop a craving for (perhaps phosphorus as well). Salt deficiency is often accompanied by observations of animals with pica, or abnormal appetite, with chewing or licking of wood, rocks, soil, urine, and bones being a common observation. Eventually osmotic and acid-base disturbances cause a reduction in appetite. Animals fail to grow, develop rough hair coats, and lactation comes to a halt. Long term, salt deficiency will cause death from dehydration. Nonlactating ruminants require 0.1% to 0.15% Na and 0.3% Cl. Lactation raises the requirement considerably to at least 0.4% Na and 0.5% Cl. For most species, the chloride requirement of the diet is adequately met by the combination of chloride from feedstuffs and from the salt added to meet the animal's sodium requirement.

Sodium and Chloride Toxicity

Sodium toxicity and chloride toxicity can occur separately. This is generally due to the effects these ions can have on acid-base physiology because, when fed separately, they can greatly affect the strong ion difference of the blood. However, when fed as sodium chloride the effects on acid-base physiology are negligible. Animals tolerate high levels of salt so long as they have free access to water to allow renal excretion of the salt. Salt will generally depress feed intake before the cow can ingest a toxic amount of salt. For most classes of cattle, voluntary intake of salt is up to 1.5 g salt/kg body weight per day. This amount of salt can be added to grain mixes to limit intake of grain/trace mineral/vitamin mixes fed ad libitum to animals at pasture.

Salt intoxication occurs in two phases. During the first phase, ingested Na and Cl are rapidly absorbed, causing a rapid rise in blood sodium and chloride concentrations, especially if water is restricted and prevents renal excretion of sodium. When plasma Na exceeds 160 mEq/L, water begins to move from the

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CSF into the plasma. If severe enough, intracellular water will be drawn from the cells in the brain causing cellular dehydration and brain shrinkage. As the brain shrinks away from the calvaria, the blood supply to brain cells can be disrupted, causing hemorrhage and thrombosis. If neuron dehydration is severe enough, convulsions and death follow. If not severe enough to kill the animal, a second phase of salt intoxication may occur over the next few days. In order to compensate for dehydration during systemic hypernatremia, brain cells try to increase the osmolarity of their intracellular spaces. This can only be partly accomplished by neuron uptake of sodium, chloride, and potassium from the CSF. However, the brain cells mostly rely on accumulation of organic osmoles such as taurine, glutamate, glutamine, and phosphocreatine within their intracellular fluids. If the hypernatremia is rapidly corrected, as might occur if water is suddenly offered to an animal that had limited access to water for a prolonged period, the osmolarity of the extracellular fluids would fall below that of the brain cell intracellular fluids. Water would tend to move across the blood-brain barrier and into the brain cells, causing them to swell. This occurs because the brain cells cannot remove the organic osmoles from the intracellular spaces as quickly as the kidneys (on ingestion of water) can correct extracellular sodium and chloride concentrations. Because the bones encasing the brain cannot expand to accommodate the edematous cells, pressure builds on the brain cells and causes necrosis of brain cells. This can cause convulsions and death. In veterinary medicine it is more common for animals to be observed in this second phase of salt intoxication. This syndrome is occasionally referred to as “water intoxication,” as the rapid restoration of normal blood osmolarity by water ingestion is often the factor precipitating clinical symptoms. Correction of severe salt toxicity or water deprivation should therefore occur over a period of 2 to 3 days so that the brain's adaptive mechanisms to prevent cellular dehydration and cerebral edema are not overwhelmed.

Potassium

Extracellular K concentration is normally 3.9 to 5.8 mmol/L and plays a vital role in osmotic equilibrium, resting membrane potential, and maintenance of acid-base balance. Intracellular K concentration is 150 to 160 mmol/L. Intracellular K is a cofactor of enzymes involved in protein synthesis and carbohydrate metabolism, and K plays a major role in intracellular osmotic and acid-base equilibrium. The ratio of intracellular–to–extracellular fluid K

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concentration is the main determinant of resting cell membrane potentials. Maintenance of normal blood K concentration requires a complex balancing act between K absorption from the diet and K removal from the blood.

Hypokalemia hyperpolarizes cells, causing resting membrane potential to be even more negative (−100 mv, inside negative, rather than the normal −90 mv), making it more difficult to reach the threshold for initiation of action potentials in nerve and muscle cells, resulting in paresis. If an action potential is successfully propagated down a motor nerve, hypokalemia, because it hyperpolarizes the resting cell membrane, will reduce the amount of acetylcholine released by the nerve ending at the motor end plate. This reduces the number of muscle fibers likely to contract, causing muscle weakness.

Moderate hypokalemia (plasma K from 2.5 to 4 mM) is often due to prolonged inappetance, often secondary to other illnesses. Ketosis is commonly the factor precipitating the inappetance. Treatment of animals with steroids that have some mineralocorticoid activity has been shown to cause K concentration to fall low enough (below 2 mM) to cause muscle weakness and recumbency, causing the hypokalemic downer cow syndrome.

Hyperkalemia is most commonly encountered in ruminants secondary to the acidosis accompanying rumen lactic acidosis, ketosis, diarrhea, renal failure, and saliva loss during heat stress. Hyperkalemia initially reduces the K concentration gradient across cell membranes, making the resting membrane potential less negative (−70 rather than the normal −90 mv). Although this makes it somewhat easier to reach threshold potential, the depolarized cells have a lower ability to open Na channels at the start of the action potential. This decrease slows the inward sodium current, particularly in cardiac muscle. The slow entry of Na into the cell early in the action potential prolongs myocardial membrane depolarization and slows impulse conduction through the myocardium; as a result, an electrocardiogram reveals a prolonged QRS duration. Hyperkalemia can have drastic effects on cardiac function. Initial bradycardia due to depolarized cardiac muscle is followed by premature ventricular contractions due to failure of cardiac conduction giving rise to ectopic initiation of ventricular contraction. Finally, the heart stops in diastole.

Potassium Homeostasis

Cattle ordinarily consume diets that contain more than enough K to meet their tissue requirements. Because more than 90% of dietary K is absorbed across the intestinal tract, preventing an excessive increase in plasma K is a daily reality.

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The kidneys are expected to excrete any excess absorbed K. Renal K excretion is controlled by aldosterone, which enhances renal secretion of K in exchange for Na ions. High blood K concentration (hyperkalemia) can directly stimulate secretion of aldosterone by the adrenal glands. However, low plasma Na and low plasma volume are more potent triggers for aldosterone secretion. Because low plasma volume is the most potent stimulant of aldosterone secretion, it is possible to have scenarios where hypokalemia develops secondary to low plasma Na and low plasma volume. Aldosterone can also increase gastrointestinal secretion of K within saliva and pancreatic secretions, which can aid the kidneys in preventing hyperkalemia. It is important to point out that dietary K can enter the extracellular fluids rapidly following a meal, while the kidney will take several hours to excrete the excess K. Another mechanism is needed to prevent hyperkalemia following a meal. This mechanism involves shifting K from extracellular to intracellular fluids. Intracellular uptake of K is mediated primarily by insulin secreted in response to elevated plasma K concentration (and also in response to hyperglycemia or a rise in blood propionate). Insulin increases the activity of the Na-K ATPase pump, particularly in the liver and skeletal muscle, increasing uptake of K by these tissues. Ketosis can cause hypokalemia as a result of inappetance. And treatment of ketosis with intravenous glucose or oral gluconeogenic precursors, such as propylene glycol, will temporarily cause hypokalemia. These treatments cause a surge in blood insulin concentration, and the insulin will drive extracellular K into intracellular compartments.

β_2-adrenergic catecholamines (i.e., epinephrine) can also drive K intracellularly. Epinephrine probably protects the animal from hyperkalemia during and following exercise. During exercise, K is lost from muscle during excitation-contraction of muscle. Stimulation of β_2-catecholamine receptors stimulates Na-K ATPase to reduce extracellular K by driving K into muscle and liver.

Another confounding problem in understanding K metabolism is its subservient relationship with acid-base balance. Because disturbances in acid-base balance are debilitating or lethal, the maintenance of a stable pH of the extracellular fluids is of paramount importance. K can move between extracellular and intracellular fluid compartments. Movement of K from the extracellular fluids to the intracellular compartment reduces the strong ion difference of the blood, making the blood less alkaline (fewer H^+). This is a compensatory mechanism that allows the animal to cope with alkalosis.

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Conversely, K leaves the intracellular fluids and enters the extracellular fluids during acidosis as a means of increasing the cation content of blood to raise the pH. (Some texts refer to this as K^+-H^+ exchange to move hydrogen ions in or out of cells.)

Blood K concentrations must be interpreted cautiously. Normal blood K concentration may not indicate normal intracellular stores of K, and abnormal blood K concentration does not necessarily indicate abnormal store or concentration of K inside cells.

Because dietary K is usually more than adequate, there is not an elaborate mechanism developed to avoid hypokalemia. Under most conditions hypokalemia is corrected by simply reducing aldosterone secretion. So long as the cow is eating, hypokalemia is generally easily avoided. However, if the cow is not eating, hypokalemia could quickly ensue, as illustrated by examining K balance in the cow.

K Balance in the Cow

In a 600-kg cow there will be approximately 1150 g K within the cells of the body and about 23 g K in all the extracellular fluids, with about 7.5 g K in the plasma pool. The maintenance requirement for K is the sum of the endogenous urinary K loss (amount of K lost in urine when cows are on a K-deficient diet, which is about 0.038 g K/kg body weight) plus endogenous fecal losses (≈6.1 g K is lost/kg DM ingested). Milk contains approximately 1.5 g K/kg, and fetal development in late gestation requires about 1 g K/day.[12]

If this cow is in early lactation and ingesting 14 kg DM/day, her maintenance requirement is about 108 g K/day. If her diet is 1.5% K, she is ingesting approximately 210 g K/day and about 189 g K is absorbed. If she is producing 15 kg milk the first day of lactation, she will use 22.5 g K for milk production. Of the 189 g K entering her body, 108 g K is used for maintenance and 22.5 g K is used for milk. This leaves 58.5 g excess K to be excreted in the urine if she is to avoid hyperkalemia.

If this cow suddenly goes off feed due to some secondary illness, K balance calculations would suggest this cow would rapidly go into negative K balance. Milk production would continue to withdraw 22.5 g K/day and the obligatory urinary K loss would be about 22 g/day for a net loss of 44.5 g K. There is some lag time between the cessation of aldosterone secretion and the cessation of K secretion by the kidneys, so the urinary loss may initially be higher than the

obligatory K loss in urine. Considering that there is only about 23 g K in all the extracellular fluids, the cow could develop hypokalemia.

However, simply fasting a cow does not constitute enough of a challenge to K metabolism to cause the severe hypokalemia associated with downer cow syndrome. Holstein nonpregnant, nonlactating cows fasted for 48 hours had a decline in plasma K from 4.9 to 4.3 mmol/L. Plasma K of beef steers fasted for up to 4 days decreased from 4.1 to 3.7 mmol/L. A greater decline in blood K due to fasting is prevented by K entering the plasma pool from muscle. Hypokalemia alone can trigger a reduction in Na-K ATPase activity in muscle, leaving more K in extracellular fluids. However, reducing pump activity does not allow the muscle to replace K that chronically leaks from the muscle cell, especially during excitation of the muscle. Intracellular K concentration eventually falls, and intracellular Na concentration increases. This response is unique to muscle. Liver and other tissue intracellular K concentration does not decrease during hypokalemia.

During prolonged fasting, muscle is broken down and the muscle protein is converted to glucose. The K within the muscle cell is released during the gradual process of muscle breakdown that occurs with fasting. During the first weeks of lactation most dairy cows are in negative protein balance and, therefore, using large amounts of muscle protein to sustain milk production.

Reduced intracellular K concentration causes a loss of muscle strength. The loss of intracellular K diminishes the amount of Ca released from the sarcoplasmic reticulum during muscle activation and, as a result, the interaction between actin and myosin to cause muscle contraction is diminished. K ions must be bound to the Ca channel proteins within the sarcoplasmic reticulum if optimal Ca is to be released into the muscle cell cytosol following depolarization of the muscle cell membrane.

Hypokalemia and “Downer Cows”

K stored in muscle will generally prevent severe hypokalemia, if the animal is only off feed for a few days (before muscle is severely depleted of K). In most reports concerning clinical cases of hypokalemia and recumbency in cows, the plasma K concentration is less than 2.5 mmol/L. In many of the affected cows, plasma K concentration is less than 1.8 mmol/L. The degree of hypokalemia observed simply from inappetance of just 4 to 5 days is unlikely to be severe enough to cause flaccid paralysis in the cow. Though inappetance greatly reduces the amount of K entering extracellular pools, it seems other factors must

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be causing depletion of extracellular and intracellular K associated with the hypokalemic downer cow.

The possibilities causing low plasma K include exaggerated renal excretion of K and excessive uptake of K by cells. The possibilities causing intracellular K depletion include prolonged fasting and exaggerated renal excretion of K.

Factors Affecting Renal K Secretion

Excessive aldosterone secretion by the adrenal gland is relatively rare in cattle. However, drugs with glucocorticoid activity are often administered to cattle in early lactation as anti-inflammatory agents or to stimulate gluconeogenesis in cows exhibiting ketosis. If those drugs also have mineralocorticoid activity, they will stimulate urinary K secretion. In the inappetant cow the muscles are releasing K to support normal blood K concentrations. If this K is being rapidly excreted by the kidney, the muscle K pool will be quickly depleted and severe hypokalemia can ensue. Isoflupredone acetate is sometimes administered to ketotic cows for its glucocorticoid activity, but it has enough mineralocorticoid activity to enhance renal K secretion. It should only be administered one time. Most hypokalemic downer cows had a history of being repeatedly injected with isoflupredone acetate over 2 to 3 days before the onset of recumbency.

Administration of diuretics, given primarily to treat udder edema, increases K excretion in the urine. Acetazolamide and the thiazide diuretics cause a large increase in urinary K loss. Furosemide, the diuretic most commonly used in cattle, increases K loss only moderately. Penicillin, aminoglycoside antibiotics, and gossypol (from cottonseed) also increase urinary K excretion to a minor extent. Though administration of diuretics and antibiotics have not been linked to hypokalemia and the downer cow syndrome in cattle, they have been implicated as the cause of cases of severe hypokalemia in man and companion animals.

Factors Increasing Transfer of K From Extracellular to Intracellular Pools.

Insulin causes a rapid uptake of K by muscle and liver. Administration of exogenous insulin was considered a factor contributing to hypokalemia in several cows developing severe hypokalemia. Endogenous insulin release occurring after intravenous administration of glucose or oral administration of glucose precursors such as glycerol, propionate, and propylene glycol will also

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shuttle K from extracellular to intracellular pools, but the effect is unlikely to be as long lived as with exogenous insulin.

β_2-adrenergic stimulation will also drive K into muscle. Stress can elicit catecholamine release in cattle. Is stress of ketosis in early lactation a precipitating factor for hypokalemia? It does not seem likely since release of epinephrine or norepinephrine is not a major feature of ketosis in cows, as it is in humans. Fever may constitute a stressor that can elicit catecholamine release. A number of the cows described with the hypokalemic downer cow syndrome did exhibit a fever during the course of the disorder.

Systemic alkalosis will cause K to leave the extracellular fluids and could be a cause of hypokalemia. Hypochloremia, with or without alkalosis, is a common feature of the cases described by Peek and colleagues[13]. Metabolic alkalosis may have precipitated the hypokalemia, but because hypochloremia is a consistent observation in affected cows, it seems more likely that gastrointestinal ileus in the animals with severe hypokalemia caused sequestration of Cl within the abomasum. This alone will cause a metabolic alkalosis and acts to drive even more K intracellularly.

Treatment of Hypokalemic Cow.

Simply restoring plasma K is not enough. A true cure also requires restoring intracellular stores of K to optimize muscle function. Intravenous treatment is necessarily slow (to avoid hyperkalemia and heart stoppage) and should be limited to 0.5 mEq/kg/h. Oral therapy with KCl has proven a more effective therapy as enough K can be delivered to replace intracellular and extracellular K. It is also less expensive. Oral treatment consists of the administration of KCl at 100 to 150 g/dose given twice daily in several gallons of water for several days. Concomitant treatment with oral glucose precursors or intravenous dextrose to cause an insulin surge can help drive the absorbed K into the cells and will help treat the underlying ketosis present in most affected cows.[14]

If dehydration is present, plasma volume needs to be corrected first. Dehydration will cause aldosterone secretion, and much of the K absorbed across the intestine will be excreted in the urine without restoring intracellular pools. Rehydration with solutions that also provide Na will also help the cow restore normal acid-base balance.

Subclinical Hypokalemia.

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Severe hypokalemia resulting in the down cow is a relatively rare phenomena, especially now that the role of repeated administration of steroids with mineralocorticoid activity is widely recognized and largely discontinued. Although intracellular stores of K have not been measured in affected cows, the course of the disease and poor response to intravenous K therapy alone suggest muscle depletion of K is a primary component of the disorder.

Moderate hypokalemia does not cause the flaccid paralysis associated with the hypokalemic downer cow syndrome. Moderate hypokalemia (2.2 to 3.9 mEq/L) is common in anorexic cattle, and severe hypokalemia is prevented by the release of K from intracellular stores in muscle.

If severe depletion of muscle K causes severe loss of muscle function and down cows, does moderate loss of K from muscle cause sluggish behavior in cows? Metabolism of K in cows is poorly researched because most diets provide more than ample supplies of K to the cow. However, the fresh cow is often faced with metabolic or infectious disease challenges that cause various degrees of anorexia. Would aggressive treatment of anorexic cows with oral KCl allow better muscle function in these cows, giving them the strength to fight for space at feed bunks, and restore them to productivity sooner?

Sulfur

Ruminants require sulfur and sulfate (SO_4^{-2}) to be in the diet to allow rumen bacteria to produce the sulfur containing amino acids, cysteine and methionine, and the B vitamins, thiamine and biotin, that the bacteria need to survive. The cow can make use of these bacterial amino acids and vitamins during digestion of the microbes once they exit the rumen. As a general rule, diets that are 0.20% to 0.23% S will satisfy the requirements of rumen bacteria. Diets consisting primarily of corn silage and corn grain risk S insufficiency. Organic sulfur in the form of the essential amino acid methionine and the B-vitamins is required by all animals. Sulfur and sulfate released during metabolism of sulfur containing amino acids can be used to produce compounds such as chondroitin sulfate and glutathione.

Of greater concern is the risk of S toxicity. In ruminants, S toxicosis presents as rapidly developing central nervous system symptoms, such as ataxia, blindness, and seizures, often followed by death. Brain lesions are most commonly described as polioencephalomalacia—swelling of the cerebrum, evidenced by flattened gyri and shallow sulci. The cerebral cortex may be

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thinned. The distribution is symmetric. Histologic section reveals a pale layer near the junction of the gray and white matter. The affected areas of the cortex will fluoresce under ultraviolet light.

Pathophysiology of S Toxicity in Ruminants

Some rumen microbes, particularly those found in cattle consuming high-concentrate diets, convert dietary sulfur to sulfide and sulfur dioxide, which can be reduced to hydrogen sulfide gas within the rumen. The hydrogen sulfide gas does not cross the rumen wall and enter the blood and would be relatively harmless if it stayed in the rumen. However, during the eructation process ruminants normally inhale a portion of the rumen gases into the lung. Hydrogen sulfide is absorbed across the lungs during eructation and causes symptoms of central nervous system disruption in the sheep. Hydrogen sulfide is a potent inhibitor of cytochrome C oxidase vital to mitochondrial respiration, and because the brain has a high energy requirement, hydrogen sulfide toxicity is associated with symptoms of central nervous system failure and brain lesions.

There is evidence that sulfur dioxide gas generated in the rumen can cleave thiamine to cause thiamine deficiency in the ruminant, leading to cerebrocortical necrosis. However, the lesions of polioencephalomalacia commonly described during sulfur intoxication of ruminants are similar, but not identical, to the cerebrocortical necrosis associated with thiamine deficiency. Further, most cases of polioencephalomalacia attributed to sulfur intoxication are not accompanied by decreased blood thiamine concentrations and do not respond to thiamine injection.[15]

Most reports of polioencephalomalacia are made in beef cattle or lambs on high-concentrate diets (90% grain) that exceed 0.4% S. Dairy cows, typically fed diets that are at least 40% forage, are rarely reported to suffer from polioencephalomalacia, despite the fact that addition of sulfate (in the form of anionic salts) to bring diet sulfur to 0.5% is commonly practiced as a means of reducing DCAD to control milk fever. Increased use of corn distiller's grains has increased diet S intake, particularly in feedlot cattle. Sulfuric acid is commonly added to the distiller's grains during processing to control pH of the fermentation, and it is used in cleaning the fermentation system. Distiller's grains can be 0.6% to 0.8% S.

Water coming from wells can often contain high concentrations of sulfur, usually in the form of sulfate. Water quality reports typically express sulfur

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content of water in units of sulfate/L. Concentrations as high as 5000 mg sulfate/L are not uncommon. The maximal safe concentration of sulfate in water is 2500 mg sulfate (or 834 mg sulfur)/L (0.08% S).

Other Possible Problems Associated With S

Many sulfur-containing compounds can be injurious to animals when ingested over the short or long term. Brassica plants (kale, cabbage, turnip, swedes) are included as a major part of the ration of ruminants in some parts of the world. These plants contain isothiocyanates that interfere with thyroperoxidase action in the thyroid gland, inhibiting thyroxine production and thus leading to hypothyroidism and goiter. Diet S can also interfere with bioavailability of diet trace minerals.

Bone Disease Associated With Ca, P, or Vitamin D Insufficiencies/Excess

Bone ash content varies somewhat with the bone examined but is generally 57% to 62% of bone dry weight. The ash will be 36% to 39% Ca, 16% to 18% P, and 5% to 7% Mg in adult animals. Ca and phosphate ions come together in a ratio of 10 Ca ions to 6 phosphate ions at the point of mineralization of the bone cartilage or osteoid matrix. Failure to supply adequate Ca, P, or vitamin D will prevent bone from mineralizing properly during bone growth in young animals and during remodeling of adult bone.

Growth Plates Allow Bones to Lengthen

Bone grows in length and width in young animals. Bone lengthens at the bone growth plates or physeal plates. A growth plate is a transverse disk of hyaline cartilage between the epiphysis and diaphysis. Chondrocytes within the growth plate become arranged into columns that run parallel to the length of the bone. The columns of chondrocytes are separated by longitudinal bars of hyaline cartilage matrix. Cells within each column are directly related to each other as they are the result of mitotic division within that column. Those chondrocytes within the growth plate that are the farthest from the diaphysis make up the zone of proliferation, where cells are rapidly dividing and extending the cartilage away from the diaphysis. The next visible stage within the growth plate is the

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zone of maturation or zone of hypertrophy. Here the chondrocytes have stopped dividing and have become enlarged. Glycogen accumulates within the cells, and their cytoplasm becomes highly vacuolated. The lacunae surrounding these chondrocytes expands, and only thin strands of cartilage matrix separate adjacent lacunae. Next, these small strands of remaining cartilaginous matrix begin to accumulate calcium phosphate deposits. This appears to be initiated by factors, such as type X collagen, produced by the hypertrophied cartilage cells. The actual process by which bone or cartilage matrix becomes mineralized is poorly understood. Some liken it to a solution that is supersaturated with calcium and phosphorus to which addition of a foreign substance initiates crystallization. In the case of bone the collagen fibers (or collagen in combination with glycoproteins or chondroitin sulfate) act as a nucleation catalyst, which transforms calcium and phosphate in solution in the tissue fluids into a solid mineral deposited on the collagen fibers. As the cartilage surrounding them calcifies, the hypertrophied chondrocytes undergo apoptosis or programmed cell death.

Finally, at the diaphyseal side of the growth plate, blood vessels invade the dead chondrocytes and calcified cartilage matrix and osteoprogenitor cells from the marrow spaces are brought into the calcified cartilage. As the lacunae are invaded, osteoblasts differentiate from the osteoprogenitor cells and form along the irregularly shaped bars of calcified cartilage that had once separated the columns of chondrocytes. A thin layer of bone matrix is deposited on the surface of the calcified cartilage. If conditions are favorable (adequate dietary calcium, phosphorus, and vitamin D), the new bone matrix quickly calcifies. This primary spongy bone area is often referred to as the metaphysis. As the growth process finishes, osteoclasts move into the metaphysis to reorganize and remodel the primary spongiosa to form true bone. Thus the rapidly dividing cells of the zone of proliferation continually advance the growth plate away from the diaphysis while osteoclasts and osteoblasts continually convert primary spongiosa to true bone at the diaphyseal side of the growth plate.

Bone Remodeling

Remodeling is necessary in large, long-lived animals to replace bone that is fatigued and accumulating microfractures. If bone remodeling came to a halt, the microfractures that accumulate would cause mechanical failure of the skeleton in about 2 years. Bone remodeling also serves another important function. It allows

the skeleton to act as a repository of minerals by allowing transfer of calcium, phosphate, and other ions in and out of bone as needed to maintain electrolyte and acid/base balance. The hormones involved in calcium and phosphate homeostasis can greatly influence the rate and extent of bone remodeling. For example, PTH increases the number of bone sites undergoing remodeling.

Only tiny units of bone undergo remodeling at any one time. While bone remodeling in compact or cortical bone differs from that in trabecular bone, the same distinct steps—activation, resorption, reversal, and formation—occur during remodeling at both sites (Fig. 41.23).

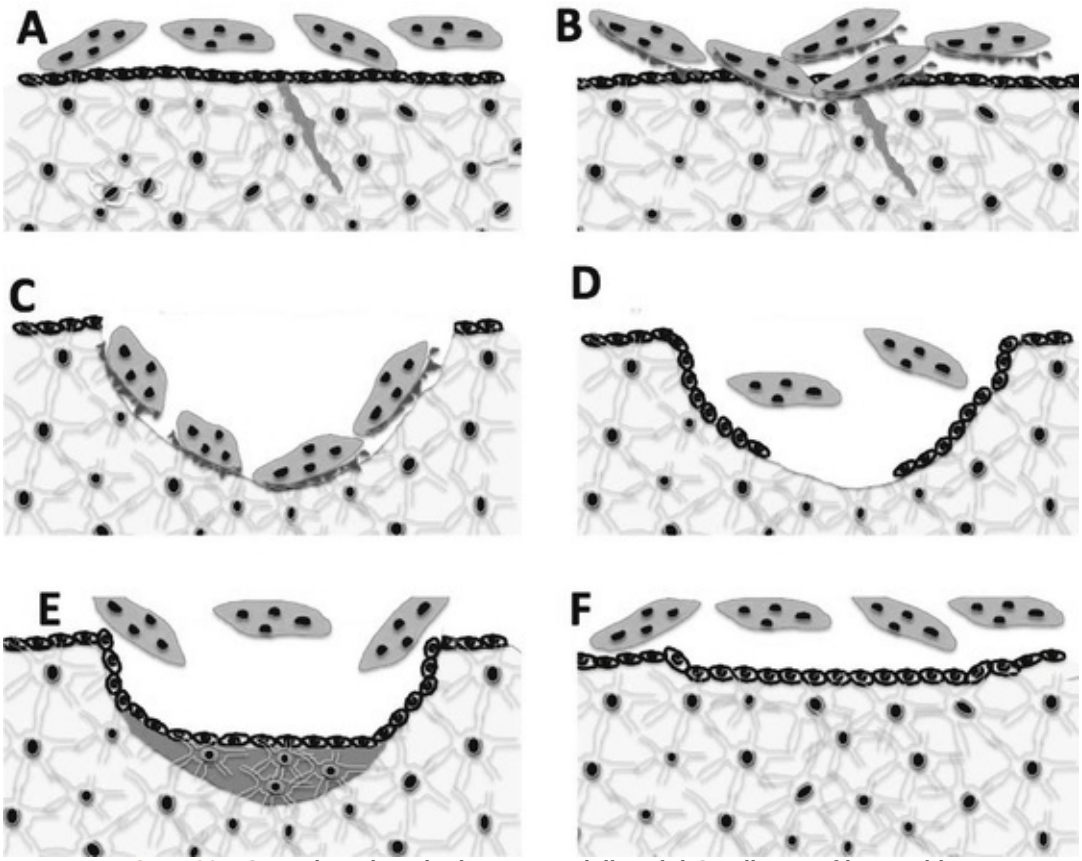


FIG. 41.23 **Steps in trabecular bone remodeling. (A) Small area of bone with a microfracture destined for remodeling. Osteocytes in bone are connected to each other and to osteoblasts at endosteal surface by canaliculi. Inactive multinucleated osteoclasts rest outside the endosteum. (B) Activation. Osteoblasts retract from area of microfracture, and osteoclasts move into the area and develop a ruffled border. (C) Resorption of bone. Osteoclasts remove a shallow bowl approximately 50 μ deep into the trabecular bone. (D) Reversal. Osteoclasts move out of resorption lacunae, and osteoblasts move into lacunae from endosteum. (E) Bone matrix formation. Osteoblasts lay down unmineralized bone matrix. (F) Bone matrix mineralization nears completion. If blood Ca and phosphate are adequate, these minerals crystallize on γ-carboxylated glutamic acid sites of matrix proteins forming new bone to replace all the resorbed bone.**

1. **Activation.** This process converts a resting or inactive bone surface into a surface to be remodeled. How a particular section of bone is chosen for remodeling is not clear. The presence of microfractures in an area is one factor that marks an area for remodeling. This “selective” remodeling appears to be directed by a signal coming from the bone. When collagen fibrils are oriented correctly, there is a very minute electrical charge oriented along the fibrils. Microfractures upset the piezoelectric charge of that portion of bone and may initiate remodeling of that piece of bone. Deterioration of bone could also elicit secretion of autocrine or paracrine factors to initiate activation of bone remodeling. During activation, the bone lining osteoblasts retracts and shrinks in the area of bone to be remodeled, exposing the bone matrix. Multinucleated osteoclasts move onto this site, and a tight bond is formed between bone matrix and the osteoclasts. Endocrine factors such as PTH can increase the rate at which bone is remodeled, though this can sometimes lead to pathology as described later.
2. **Resorption.** The osteoclasts release acids and proteolytic enzymes from their ruffled border onto the bone surface, dissolving the organic matrix of the bone. The mineral crystals are dissolved, and the minerals along with the breakdown products of the organic matrix enter the osteoclast by diffusion or specific transport processes. They are then extruded into the extracellular fluid on the opposite side of the osteoclast.

The bulk of the bone resorbed to support Ca metabolism is trabecular bone. In trabecular bone the osteoclasts resorb bone until they have formed a saucer-shaped depression in the bone that is around 50 μ in depth at its center and 200 to 300 μ in diameter. In cortical or compact bone the osteoclasts drill out a cone-shaped section of bone to create a 200 μ −diameter tunnel of varying depth (10 to 100 μ). At this point the osteoclasts quit their bone resorbing activity and leave.

3. **Reversal Phase.** This phase signals the start of the rebuilding of bone within the resorption hollow, known as a Howship's lacunae. Osteoblasts move from the bone surface down into the depths of the Howship's lacunae. Several growth factors such as insulin-like growth factor (IGF)-II and transforming growth factor–β are thought to cause osteoblasts to migrate into the Howship's lacunae to begin to replace the bone. Many

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other substances, including interleukin-1, platelet-derived growth factor, and IGF-I (somatomedin) are also considered candidates capable of initiating the reversal phase of remodeling.

4. **Formation.** Bone matrix formation begins with deposition of osteoid by the osteoblasts. This organic matrix consists primarily of type I collagen, proteoglycans, and smaller proteins typical of mature adult bone. In trabecular bone, the osteoid is laid down in discrete layers or lamellae about 3 mm thick with all the collagen fibrils within each lamellae oriented parallel to each other. In cortical bone the tunnel hollowed out by the osteoclasts is filled in from the outer circumference toward the center until only a small central canal containing blood vessels is left open. The collagen fibrils within different lamellae are oriented at an angle to the layer above or below, giving the bone added strength, an idea also used when lumber mills produce plywood.

Mineralization of the organic matrix is the final step in bone formation. It occurs after a time delay, which is about 20 days in man. Once triggered, the mineralization process is rather rapid. During the first few days of the process nearly three quarters of the total bone calcium will be deposited with the final 25% mineralization being completed months later. The total time for osteoblasts to complete the formation phase in a single Howship's lacunae approximates 150 days (Fig. 41.24, *A* and *B*).

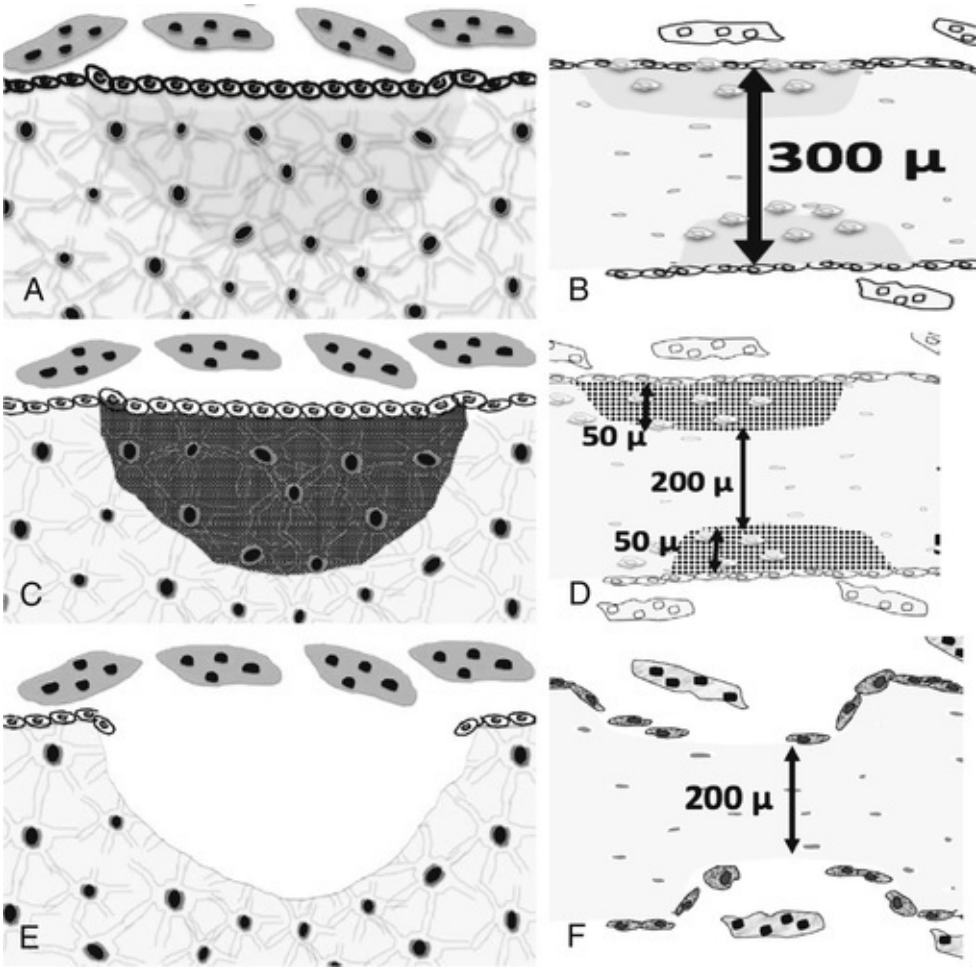


FIG. 41.24 **Mineral-related problems during bone remodeling. (A) During normal bone remodeling, the bone removed from the Howship's lacunae is completely replaced by newly formed bone. (B) A spicule of bone with remodeling sites on either side of the bone. The normal bone width and density of a spicule of bone will be the same before and after remodeling—in this case approximately 200 µ thick. (C) If the cow has not received adequate dietary phosphorus or is vitamin D deficient, the matrix is produced by the osteoblasts but fails to mineralize. (D) The remodeled area on each side of thespicule of bone area has 50 µ of rubbery matrix in each lacunae, resulting in osteomalacia, which allows bone to bend too easily. (E) If the cow receives too little dietary Ca or is in early lactation, the formation of new bone is uncoupled from the resorptive phase of bone remodeling. Neither bone matrix nor mineral is replaced. (F) The remodeled areas on each side of thespicule of bone area have not been replaced. This leads to a net loss of 50 µ of bone from each remodeling site, causing osteoporosis.**

Rickets.

Rickets is a disease of young, growing animals in which the cartilaginous matrix at the growth plate fails to mineralize. The bones fail to grow in length, leading to short stature. The physes themselves are wide with irregular borders making

joints enlarged. Rickets is a disorder of growing animals in which the newly formed osteoid and cartilage septa within the growth plate fail to mineralize. This is most often associated with vitamin D or dietary phosphorus deficiency. Rachitic animals will be hypophosphatemic and often hypocalcemic as well. Blood phosphorus concentration in young animals is generally higher than in adult animals—a reflection of their greater requirement for phosphorus to support mineralization of new growing bone. When blood phosphate concentration falls below the level required to support mineralization of the cartilage and primary spongiosa, the growth plate does not mineralize. Chondrocytes within the zone of proliferation continue to elongate the cartilage model in the growth plate. Vitamin D deficiency can reduce secretion of type X collagen by the chondrocytes within the growth plate, and this may prevent the programmed cell death of chondrocytes within the zone of provisional calcification. Since the cartilage does not calcify, blood vessels cannot move into the area to begin ossification and the physis elongates. The physis is more flexible and rubbery and gives the ends of bones an enlarged look, especially evident at the growth plates within the ribs.

Osteomalacia

During bone remodeling in adult animals, vitamin D or phosphorus deficiency causes blood phosphate concentration to fall below the level needed to mineralize newly formed bone matrix during the remodeling process. Nearly all steps in bone remodeling occur except for mineralization of the newly formed matrix. When vitamin D deficiency is the cause, the animals will be hypocalcemic as well. Serum concentration of 25-hydroxyvitamin D will be below 10 ng/mL (25 nM). The lack of phosphorus prevents mineralization but does not prevent normal bone matrix secretion by the osteoblasts (see Fig. 41.24, *C* and *D*). Pathologic changes occur much more slowly than in rickets. Over a prolonged period the bones become excessively flexible, leading to extensive joint pain in these animals. Rachitic bone and osteomalacic bone will have less bone ash per unit of bone volume or bone density. The ash will have below normal % P and % Ca content.

Osteoporosis Due to Dietary Ca Insufficiency

Animals that are in a prolonged state of negative Ca balance develop

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osteoporosis. This bone disease can be observed whenever diet Ca is inadequate, while diet P and vitamin D are adequate. Low plasma Ca concentrations (arising from dietary Ca deficiency) can cause elevated secretion of PTH. The PTH causes increased activation of bone remodeling and increased bone resorption—there will be many more Howship's lacunae formed in the bone. However, the prolonged secretion of high amounts of PTH prevents the reversal and bone formation steps of bone remodeling. Bone resorption and bone formation are no longer coupled as they are during normal bone remodeling. The result is bone that has many sites where osteoclasts have carved-out areas in the bone, giving it a moth-eaten appearance (Fig. 41.24, *E* and *F*). Bone density and ash content are greatly reduced, but the % Ca and % P in the ash are not greatly affected. The Ca content per unit of bone volume is greatly diminished. The bone does not bend as it does in rickets or osteomalacia. Instead, it becomes more brittle and is prone to fracture. Once diet Ca becomes adequate again, younger animals can restore the bone over time through renewed remodeling. Older cows may not live long enough to remodel all the sites damaged during prolonged dietary Ca deficiency.

Lactational Osteoporosis

During lactation, in virtually all species, there is an obligatory loss of bone mass from the skeleton as a result of uncoupling of bone formation from bone resorption. In this case the osteoclasts within an area of bone being remodeled resorb bone, to the normal 50-micron depth if diet Ca is adequate, or to even greater depths if the animal is also in severe negative Ca balance. However, osteoblast movement into the resorption cavity to replace resorbed bone is temporarily put on hold and no new bone is deposited. This occurs to some extent in all female mammals shortly after parturition, even when they are in positive Ca balance. However, the degree and duration of lactational osteoporosis can be magnified greatly by negative Ca balance. Once the animal has undergone the obligatory period of lactational osteoporotic bone loss (4 to 5 weeks in the cow), and if the animal is in positive Ca balance, the osteoblasts now come back into the resorption cavity and replace the lost bone. Lactational osteoporosis can help the female meet the Ca demands of lactation by uncoupling bone formation from bone resorption. In high-producing dairy cows, dietary Ca intake is generally inadequate to meet lactational Ca demands the first 4 to 6 weeks of lactation. The cow can lose as much as 13% of her skeletal mass during this period. The bone is replaced in later lactation when diet Ca intake allows the cow to enter a period of positive Ca balance.

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Nutritional Secondary Hyperparathyroidism

A deficiency of dietary Ca or diets that are excessively high in phosphate can reduce the amount of Ca that can be absorbed across the intestine into the extracellular fluids. Diets severely deficient in Ca will not supply adequate Ca to replenish Ca lost from extracellular pools. As a result, blood Ca concentration decreases and PTH secretion increases. PTH causes the kidney to reduce urinary Ca loss and increase synthesis of 1,25-dihydroxyvitamin D. But if diet Ca is too low, increasing the efficiency of intestinal Ca absorption with 1,25-dihydroxyvitamin D cannot substantially increase the amount of Ca entering the extracellular pool of Ca. In addition, a high P diet raises blood phosphate concentration, stimulating bone osteocytes to produce FGF23. The FGF23 circulates to the kidney and blocks the 1α-hydroxylase enzyme responsible for producing 1,25-dihydroxyvitamin D. This also acts to block intestinal Ca transport. The only action of PTH that can improve blood Ca concentration under these situations is to stimulate bone Ca resorption by activating more sites of bone resorption. The high PTH, high P, high FGF23, and low 1,25-dihydroxyvitamin D content of blood causes the osteoblasts that move into the Howship's lacunae to produce a more fibrous matrix than is normally produced during the bone formation phase of bone remodeling. The continued removal of bone without mineralization of the fibrous matrix results in fibrous osteodystrophy. The clinical signs of nutritional secondary hyperparathyroidism include hypertrophy of the parathyroid glands and cessation of growth in young animals. In young animals, the lack of Ca available for mineralization of bone matrix causes the growth plates to be soft, weak, and swollen. The cortices of the long bones are thin, and minor or major fractures are common. In older animals the bone of the mandible and maxilla become very malleable and teeth become loose, lending the moniker of “rubber jaw” and “bighead disease” to fibrous osteodystrophy of the bone.

Renal Secondary Hyperparathyroidism

This syndrome is due to renal failure and is occasionally observed in older cows suffering from pyelonephritis. A major function of the kidneys in most species is to remove excess phosphate from the circulation. As renal function is lost, phosphate is retained and hyperphosphatemia develops.

Hyperphosphatemia reduces the ionized Ca content of the blood. This is

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because Ca and phosphate ions normally exist in blood at concentrations that are slightly below the levels that would cause saturation of the fluids. The greatly elevated phosphate in blood of renal failure patients can exceed the equilibrium of Ca and phosphate in solution, causing a reduction of Ca from the blood. Lower blood Ca concentration increases PTH secretion. As phosphate builds up in the blood, it also stimulates bone osteocytes to produce the hormone FGF23, which blocks the activation of the 1α-hydroxylase that catalyzes conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D within the kidney.[10] Therefore, even though PTH should stimulate the remaining functional renal tissue to produce 1,25-dihydroxyvitamin D, this action of PTH is blocked by hyperphosphatemia.

As renal disease progresses, the amount of renal tissue available for production of 1,25-dyhydroxyvitamin D decreases, further compounding low blood concentrations of 1,25-dyhydroxyvitamin D. This reduces dietary Ca absorption and further depresses blood Ca concentration. This in turn stimulates increased PTH secretion and, resorbing bone Ca reserves, becomes the primary means of maintaining normocalcemia. Fibrous osteodystrophy follows the prolonged secretion of PTH when accompanied by elevated blood P and FGF23 levels.

As bone Ca is resorbed, more P is also resorbed. However, the loss of renal function prevents PTH from having its usual phosphaturic effect, exacerbating the hyperphosphatemia. A vicious cycle of higher blood P leading to increased PTH secretion and increased bone resorption ensues.

In principle, calcium deficiency differs from phosphorus deficiency in that normal osteoid is formed but fails to mineralize in phosphorus deficiency, while in calcium deficiency the normal osteoid is either not formed at all (osteoporosis if blood P and FGF23 are normal or low and blood 1,25-dihydroxyvitamin D is elevated) or replaced by fibrous tissue (fibrous osteodystrophy if blood P and FGF23 is high and 1,25-dihydroxyvitamin D is low). In adult vitamin D deficiency, it is common to see mixed lesions—areas of osteomalacia, osteoporosis, and fibrous osteodystrophy all in the same bone (Table 41.8).

TABLE 41.8

Diagnosing Acute and Chronic Macromineral Insufficiency or Imbalance in Ruminants

The tissue needed to ascertain acute problems is intended to guide diagnosis of the initial cause of recumbency in

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downer cows. All fluid concentrations are in mg/dL. “Subclinical” indicates no readily apparent outward signs of illness. “Clinical” will generally result in a “down” cow.

Mineral	**Tissues to Use**	**Normal**	**Subclinical**	**Clinical**
Ca (Acute)	Serum	8.0-10.5	5.5-7.5	<5.0
Ca (Chronic)	Serum	8.0-10.0	8.0-10.0	6.0-10.0
	Bone ash (% Ca)	37-39	35-37	<35
	Urine	>2.0	0.5-1.5	<0.1
P (Acute)	Serum	4-6	2-4	<1.0
P (Chronic)	Serum	4-6	3-4	<3.0
	Bone ash (% P)	17-20	15-17	<12
Mg (Acute)	Serum	2.0-2.3	1.3-1.7[a]	<1.1
	Vitreous humor	1.9-2.5	1.5-1.85	<1.5
	Urine	10-25	2-5	<0.5
	Cerebrospinal fluid	2-2.5	1.5-2.0	<0.5
Mg (Chronic)	Serum	2.0-2.3	1.6-1.8	<1.5

[a]These Mg levels are low enough to cause secondary hypocalcemia.

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Hyperketonemia in Dairy Cattle (Ketosis)

Jessica A.A. McArt • Daryl Nydam

Pathophysiology

Most dairy cows visit a state of energy deficit, often termed *negative energy balance* (NEB), as they transition from late gestation to early lactation. This imbalance in energy is the result of both an increase in energy requirements—more than twice as high when compared with prepartum levels[1]—and inadequate DMI. The increase in energy demand is due to lactogenesis, which is dependent on available glucose concentrations from gluconeogenesis in the liver.[2] Ruminal fermentation provides the majority of substrates for hepatic gluconeogenesis through production of volatile fatty acids (VFA), the most abundant of which are acetic acid, propionic acid, and butyric acid. Propionic acid is absorbed by the liver via portal circulation and serves as the primary metabolite for gluconeogenesis. Acetic acid is used mainly in the liver as a major source of acetyl CoA to generate ATP, and butyric acid is absorbed directly from the rumen as the ketone β-hydroxybutyrate (BHB), which can be used by multiple tissues for energy production. Several factors (e.g., nutrition, ionophore use, DMI) determine the amount and proportion of VFA produced, and when the cow's requirement for energy exceeds her productive capacity, NEB ensues. At the individual animal level, there are several metabolic adaptations to manage NEB, which include mobilization of nonesterified fatty acids (NEFA) from body fat reserves and glucose sparing for lactogenesis. However, some animals will experience excessive NEB, and it is this excess that is associated with negative downstream outcomes such as increased risk of disease development and decreases in both milk production and reproductive performance.[3-5] As some degree of NEB postpartum is physiologically normal, it is its depth, duration, and timing that influence the cow's health and performance. The metabolites NEFA and BHB are used as markers of NEB due to the relationship among energy demands, energy reserves, and the metabolic association between NEFA and BHB. Fig. 41.25 is a graphic representation of the association between these factors, which can result in excessive concentrations of BHB and the syndrome of hyperketonemia.

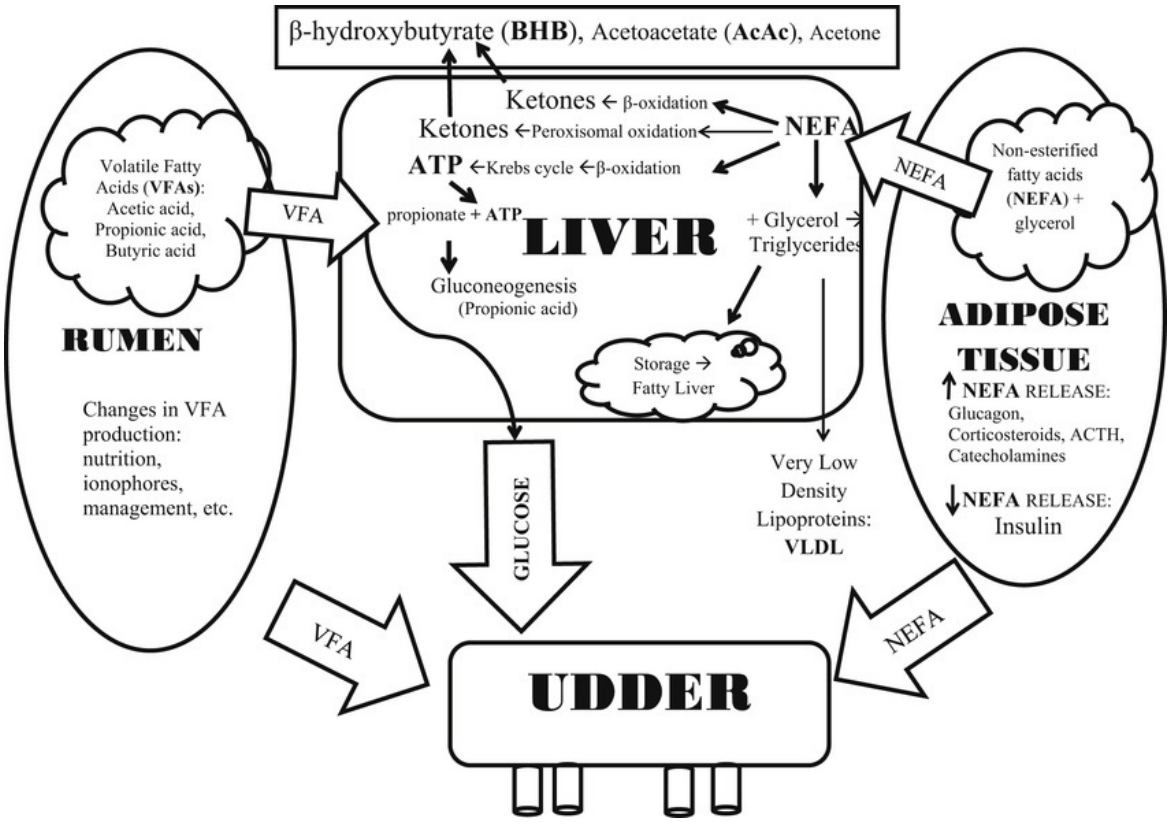


FIG. 41.25 The relationship between energy demands, energy reserves, and the metabolic association between nonesterified fatty acids (NEFA) and β-hydroxybutyrate (BHB). *ACTH,* Adrenocorticotropic hormone; *ATP,* adenosine triphosphate. (Modified from Ospina PA, McArt JAA, Overton TR, et al: Using nonesterified fatty acids and β-hydroxybutyrate concentrations during the transition period for herd-level monitoring of increased risk of disease and decreased reproductive and milking performance, Vet Clin North Am 29:387–412, 2013.)

To adapt to this increase in energy demands, glycerol and NEFA are released from adipose tissue in response to hormonal cues, such as glucagon, corticosteroids, adrenocorticotropic hormone (ACTH), and catecholamines. Insulin is the only hormone that will act to inhibit lipolysis and therefore decrease the amount of NEFA released from adipose tissue. Early in the postpartum period, there is both a decrease in insulin production and perhaps a transient state of insulin resistance.[1] This spares glucose for lactogenesis by decreasing glucose utilization in insulin-sensitive tissues and allowing continued lipolysis even when insulin concentrations increase, though the mechanistic pathways in postpartum dairy cows remain complicated.[6]

The liver receives approximately one third of cardiac output and removes approximately 15% to 20% of the NEFA in circulation. Once inside the liver,

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NEFA can follow four pathways: complete oxidation in the tricarboxylic acid cycle (TCA) pathway to produce ATP; transport out of the liver in very-low-density lipoproteins; transformation to ketones via the β-oxidation pathway or conversion to ketones through peroxisomal oxidation; or storage in the liver as triglycerides. Thus, the continual release of NEFA into circulation is not always detrimental as NEFA is a good source of energy for several tissues in the body and can be used to synthesize milk fat. However, elevated concentrations of NEFA can result in excessive accumulation of triglycerides in the liver, resulting in hepatic lipidosis. In addition to the overtly detrimental effects of hepatic lipidosis, elevated NEFA concentrations can also adversely affect immune function,[7] and an excessive amount of circulating NEFA may promote inflammation, an important factor in common diseases such as metritis and mastitis.[8] Whether NEFA directly influences this inflammatory response or acts via mechanisms that cause immune dysfunction is currently under investigation.

As mentioned earlier, formation of ketones is a normal result of NEFA metabolism in the liver, and the three major ketones produced are acetone, acetoacetate (AcAc), and BHB. Acetoacetate can spontaneously convert to acetone and CO_2 and can also be metabolized by the enzyme β-hydroxybutyrate dehydrogenase into BHB. Acetone is excreted in urine or exhaled; it is responsible for the "fruity" breath of some ketotic cows. While BHB accounts for the majority of the total ketone pool in bovines, in lactating animals with NEB, the equilibrium between AcAc and BHB may be shifted even farther toward BHB. This shift in equilibrium may be important when selecting between the nitroprusside colorimetric spot tests, which test for acetone and AcAc, versus a test that directly measures BHB.

The mammary gland is not dependent on insulin for glucose utilization. During excessive NEB, circulating NEFAs are regularly incorporated into milk fat.[9] During NEB in the postpartum period, milk fat concentrations tend to increase and milk protein concentrations tend to decrease; thus, the ratio between fat and protein can be used as an indicator of excessive NEB and as a predictor of the risk of developing metabolic diseases.[10]

Definition

Hyperketonemia, by definition, is the elevation of ketone bodies above a physiologically normal range in blood. Although historically the terms "subclinical" and "clinical" ketosis have been used to describe this metabolic

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state of ketone elevation, classification into these two categories is quite subjective. It is important to remember that expression of signs consistent with ketosis has much individual-animal variation and that manifestation of these signs most likely suggests a more severe hyperketonemia compared with cows that do not show clinical signs. Recent research has provided solid and repetitive evidence of quantitative blood BHB concentration cut-points that result in increased risks of subsequent disease development and production loss. This cut-point falls somewhere around 1.2 to 1.4 mmol/L depending on the desired sensitivity and specificity[4,5,11]; a lower cut-point results in a higher test sensitivity and lower specificity, and a higher cut-point results in a lower sensitivity and higher specificity. Thus, subclinical ketosis technically includes those cows with concentrations of BHB above 1.2 mmol/L that do not have clinical signs, and cows with clinical signs would, by definition, have clinical ketosis irrespective of what their blood concentration is (though it is often above 2.5 to 3.0 mmol/L). Hyperketonemia includes both of these categories and is the preferred term, encompassing all cows with elevated BHB regardless of expression of clinical signs. Type 1 and type 2 ketosis are terms loosely borrowed from human medicine and diabetes literature. They have limited utility in aiding our understanding of hyperketonemia in modern dairy cows or in how we prevent or treat the condition.

Clinical Signs and Differential Diagnoses

Of hyperketonemic cows, 85% to 95% have blood BHB in the 1.2 to 2.9 mmol/L range and show no aberrant clinical signs[4,12,13]; thus, we cannot detect most cases of mild or moderate hyperketonemia during a physical examination without additional diagnostic testing. Clinical signs expressed by cows with severe hyperketonemia are vague and similar to those seen with other early lactation diseases, including a loss of appetite, a decrease in milk production, and a more profound weight loss than normally seen during this period of lactation. It is important to note that the severity of hyperketonemia is not highly associated with clinical signs in that many severely hyperketonemic animals do not show clinical signs.

On physical examination, hyperketonemic animals (without concurrent disease) will have normal vital signs and may have decreased rumination frequency with more severe disease. The odor of ketones may be detected in the breath of some hyperketonemic cows, and many will have hyperketonuria. It is

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well established that hyperketonemia increases the risk of additional early lactation diseases such as metritis and displaced abomasum[4,12,13]; thus, a complete physical examination is necessary to identify or rule out other concurrent diseases.

In a very small percentage of severely hyperketonemic cows, an acute onset of bizarre neurologic signs will be evident, which can include excessive licking, flank-sucking, bellowing, circling, head pressing, and apparent blindness, and may progress to tremors and tetany. These cows are classified as having nervous ketosis and may be aggressive toward people or their surroundings, so care for personal safety is heightened during examination. Differential diagnoses for nervous ketosis include rabies, listeriosis, hypomagnesemia, and acute lead poisoning.

Epidemiology

Numerous studies have described the detrimental association of hyperketonemia with additional postpartum diseases, particularly metritis and displaced abomasum,[11-14] and culling in early lactation.[13,15,16] From an epidemiologic standpoint, it is important to know which disease occurs first to attribute the development of the secondary disease to the primary one. In most of the aforementioned studies, good effort has been made to record the temporal association of these diseases, and in the vast majority of cases, hyperketonemia has been diagnosed before metritis and displaced abomasum, such that 70% of metritis cases and 88% of displaced abomasum cases can be attributed to hyperketonemia.[17] This increased risk of disease, culling, and poor production rises not only as the severity of hyperketonemia increases, such that a cow with a BHB of 3.5 mmol/L is much more likely to develop a displaced abomasum as a cow with a BHB of 1.2 mmol/L, but also as the DIM at first diagnosis decreases (i.e., a cow first hyperketonemic at 3 DIM is much more likely to develop a displaced abomasum than a cow first hyperketonemic at 8 DIM).[13,14]

Peak incidence and prevalence of hyperketonemia (diagnosed in this case as a BHB concentration of 1.2 to 2.9 mmol/L) were found to occur at 5 DIM (Fig. 41.26) after intensive, three-times-per-week monitoring of 1717 cows on four large TMR-fed freestall dairies in New York and Wisconsin, United States.[13] A similar peak in prevalence of hyperketonemia (diagnosed as a BHB concentration of ≥1.2 mmol/L) at 1 week postpartum was reported by Duffield and colleagues[18] using data from 1010 cows on mostly component-fed tiestall

dairies in southwest Ontario, Canada. As the median time to resolution of hyperketonemia was reported to be 5 days,[13] farms that test less frequently than twice per week will underestimate the true incidence.

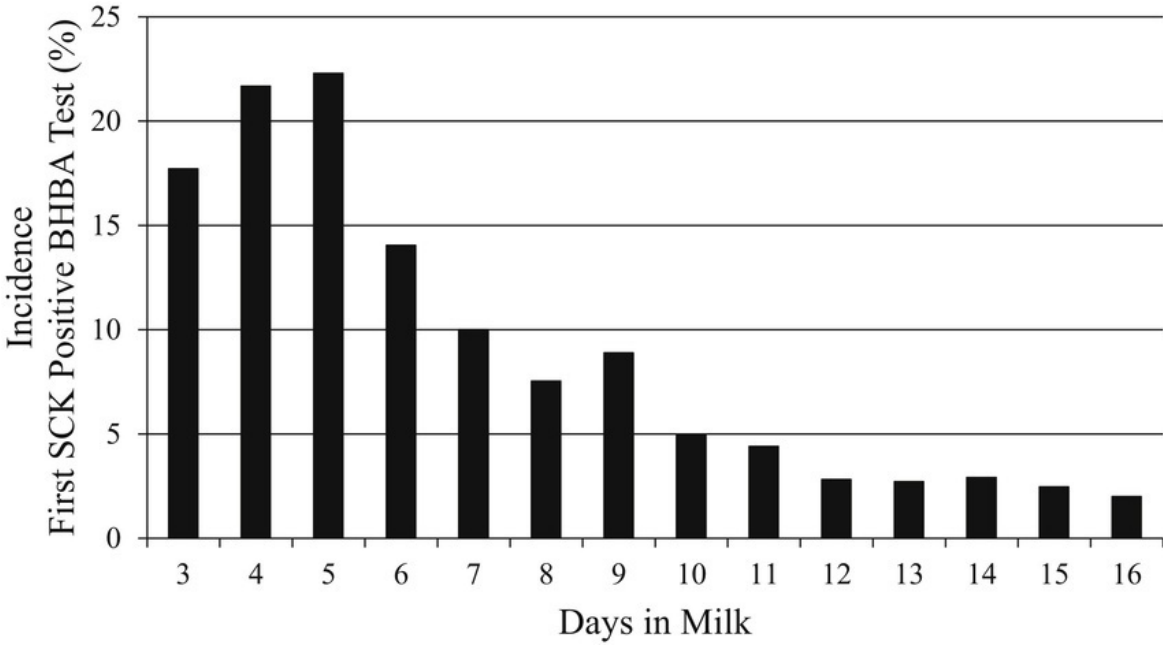


FIG. 41.26 Histogram of incidence of subclinical ketosis (SCK) in 1717 Holstein dairy cows undergoing repeated testing for SCK from 3 to 16 DIM. A positive test was defined as a blood BHBA concentration of 1.2 to 2.9 mmol/L. (Adapted from McArt JAA, Nydam DV, Oetzel GR: Epidemiology of sub-clinical ketosis in early lactation dairy cattle. J Dairy Sci 95:5056–5066, 2012.)

Two important measurements that help evaluate the frequency of a disease in a farm population are incidence risk and prevalence. Incidence risk is estimated by dividing the number of cows affected with a new case by the total number of cows that have gone through this time period (i.e., the number of cows that develop a disease at any time during a given period, among those who are at risk). For determining the incidence of hyperketonemia, a cow is no longer at risk as a new case once she has been diagnosed positive. When estimating incidence, it is necessary to follow a group of cows throughout the entire time period of interest, and testing must be completed frequently enough to ensure that all cows that develop disease will be correctly identified. For example, if a disease typically lasts 5 days, all cows at risk must be tested at least two times per week. As an example, if 15 cows within a group of 50 at-risk cows that were

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monitored between 3 and 16 days in milk (DIM) developed hyperketonemia for the first time sometime between 3 and 16 DIM, the incidence risk of hyperketonemia during that time period would be 30% (15/50).

Prevalence is a snapshot of the amount of a disease existing in a herd at a single point in time; it is determined by one test and is thus easier to estimate than incidence. Prevalence is calculated by dividing the number of disease-positive cows by the total number of cows sampled at that point in time. For example, if 20 cows were tested on a single day and three cows were hyperketonemic, the prevalence would be 15% (3/20). At the herd level, the recommendation is to test at least 15 to 20 cows in the appropriate DIM range each time a prevalence test is conducted. The recommended number of cows to test depends on the number of cows at risk, the expected herd prevalence, and the user's acceptance of the precision of the estimate and the confidence interval around the estimate. For example, if there are 50 fresh cows at risk for hyperketonemia (i.e., between 3 and 16 DIM) and you expect the prevalence to be 15%, sampling 20 cows will allow you to be 90% confident that the prevalence you obtain is ±10% of the true herd prevalence. This is a relatively small number of animals to test, but it is only useful for determining whether a herd has a very low or very high prevalence of the disease. More cows should be tested in order to more confidently estimate the true herd prevalence. For example, sampling 40 cows in the above scenario will allow you to be 95% confident that the prevalence you obtain is ±5% of the true herd prevalence.

Knowing a herd's estimated incidence of hyperketonemia is more useful than knowing the prevalence because the best strategy for testing and treating individual cows for hyperketonemia depends on the herd incidence. However, a direct determination of the herd incidence is practically challenging because it requires repeated testing of individual cows frequently enough so that all cows that develop hyperketonemia are identified. Work by McArt and colleagues[13] showed that the average duration of hyperketonemia was 5 days; thus, cows must be sampled a minimum of twice per week in order to appropriately estimate incidence. A reasonable alternative is to conduct a simple cross-sectional sample (testing herd prevalence) and then estimate the herd incidence from the herd prevalence. Fortunately, the incidence of hyperketonemia has been consistently reported to be about twice its prevalence.[13,18] For example, if 100 early lactation cows from a herd were tested and 15 of these cows had blood BHB greater than or equal to 1.2 mmol/L, the herd prevalence would be 15% and the estimated herd incidence would be 30%.

Within-herd incidence of postpartum hyperketonemia appears to range between 25% and 60% with an average of approximately 45%; across all herds in these studies, 47% of cows tested positive at least once. The results from Duffield and colleagues,[13] however, tested cows only once weekly and thus likely underestimated the true incidence. Approximately 20% of sampled cows have elevated BHB in the first 2 weeks postpartum, with within-herd prevalence ranging from 0% to 71%.[4,14] The prevalence of herds in which more than 15% of sampled cows had increased postpartum BHB concentrations of greater than or equal to 1.2 mmol/L was 40%.[4] Chapinal and colleagues[19] reported that the prevalence of herds in which more than 25% of sampled cows had increased postpartum BHB concentrations of greater than or equal to 1.4 mmol/L was 15% in 55 herds in the United States and Canada tested within a week postpartum.

These two studies also reported on within-herd alarm thresholds and subsequent outcomes. Chapinal and colleagues[19] reported reduced milk yield based on production at first Dairy Herd Improvement test of 4.4 kg per cow per day when greater than or equal to 15% of sampled animals had prepartum BHB concentrations greater than or equal to 0.8 mmol/L. In addition, herds where greater than or equal to 25% of sampled animals had postpartum BHB concentrations greater than or equal to 1.4 mmol/L had increased odds of DA. Ospina e and colleagues[4] found that herds in which greater than 15% of sampled animals had postpartum BHB concentrations greater than or equal to 1.2 mmol/L, the risk of cows with DA and clinical ketosis was higher and the herds had an increased time to pregnancy and produced less milk compared with herds with fewer animals above the threshold. Results from these studies suggest that herds with greater than or equal to 15% to 25% of sampled animals having increased prepartum or postpartum NEFA or BHB concentrations may have more difficulty with postpartum disease, poorer reproduction, and lower milk production than herds with a lower proportion of positive animals.

Economic Impact

For cows that develop any transition cow disease, the total cost of that disease can be divided between component costs and attributable costs, where the component costs are the sum of the direct and indirect costs of that particular disease and the attributable costs include the increased risk of developing another related disease. The direct costs of a disease include labor and veterinary services associated with diagnosis and treatment, therapeutic interventions, and

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discarded milk required for these interventions. Indirect costs consist of future losses such as milk production, premature culling of the cow as a result of the disease, and negative impact on future reproduction. While most people readily realize the direct costs associated with a disease, interestingly, these make up a relatively small part of the total cost of a disease.

For hyperketonemia, the average component cost per case is estimated to be $117.[17] Interestingly, the direct costs associated with the disease are only approximately 6% of the total cost, with the remaining 94% of associated costs being indirect, largely future reproductive and milk production losses. When including the costs of other diseases attributable to hyperketonemia (i.e., metritis and displaced abomasum), the total cost per case is almost $290. With herd early-lactation hyperketonemia incidences averaging 40%,[13,18] annual costs due to hyperketonemia are not trivial.

Necropsy Findings

Mortality due to hyperketonemia is uncommon unless the disease is severe in nature with an associated hepatic lipidosis, which is often the only pathologic finding during a gross necropsy examination.

Clinical Pathology and Diagnostic Tools.

The diagnostic hallmark of hyperketonemia is, as the name suggests, elevated blood ketone bodies. As BHB is the most stable ketone body in blood, its concentration is the accepted gold standard method for diagnosis of hyperketonemia. Numerous studies have assessed clinical disease incidence, culling risk, and subsequent milk production associated with various BHB cut-points to optimize use of a threshold for diagnosis of hyperketonemia, and widely used cut-points vary from 1.2 and 1.4 mmol/L.[12,14,20] As mentioned earlier, the choice of which cut-point to use depends on the user's testing purpose and desire to maximize the resulting sensitivity or specificity of the test. Recent advances in portable technology over the past decade have produced vast improvements in on-farm hyperketonemia detection with handheld point-of-care BHB meters. These can be used with whole blood, serum, or plasma and allow for an inexpensive, rapid, and accurate method for both individual cow hyperketonemia detection and herd-level disease monitoring.[21,22]

Although inexpensive, urine ketone tests, while highly specific, suffer from poor sensitivity.[23] Combined with a typical success rate of 50% when attempting

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to induce urination in a given cow, urine ketone tests lag behind handheld BHB meters in clinical utility for use in individual cow identification of hyperketonemia. Tests for milk ketones have a similar poor sensitivity, and given a comparable cost to blood BHB testing are an inferior test at the individual cow level. The poor sensitivity of urine and milk ketone tests precludes their use as a herd-level hyperketonemia monitoring tool.

Additional testing is usually unnecessary for diagnosis of hyperketonemia and rarely improves prognostic decision making, even in cases with accompanying hepatic lipidosis.

Treatment and Prognosis

Although hyperketonemia has been a commonly encountered disease for decades, few randomized, controlled studies have been conducting that assess the efficacy of frequently administered treatments.[24] The goal of such treatments are to increase the availability of glucose, whether directly administered or produced by the cow, to decrease adipose tissue mobilization and increase uptake of glucose by cells.

Administration of a glucose precursor, given as a drench, provides a source for gluconeogenesis and creates an insulin surge to facilitate glucose transport into cells. Food-grade propylene glycol is the most common product used for this purpose, and treatment with a multiday course has been shown to increase the speed of hyperketonemia resolution, reduce the risk of subsequent disease, and increase milk production.[25,26] Propylene glycol acts by increasing blood glucose concentrations through its conversion to propionate, both in the rumen and through hepatic metabolism of propanol, as well as by decreasing peripheral tissue glucose demand induced by circulating blood levels of propylene glycol and propanol.[27] A dose of 310 g (300 mL) once a day for 3 to 5 days is recommended; oral drenching is preferred over mixing in the feed to induce an insulin spike and for palatability reasons. Although glycerol can be administered as a glucose precursor and is highly metabolized in the rumen, no randomized field trials have been conducted to assess its effectiveness. A small study comparing propylene glycol with glycerol treatment in abomasally cannulated cows showed that glycerol had no benefit over propylene glycol treatment unless administered directly into the abomasum, which is not feasible in a clinical setting.[28] The importance of administering these glucose precursors as a drench rather than mixing with the feed is due to the desire of the resulting insulin

surge, which is not seen when propylene glycol is mixed with the ration. A review of multiple studies feeding propylene glycol in the ration concluded that it had no impact on milk production when administered in this way.[29] Current trials are under way to investigate the effect of new dried propylene glycol and glycerin products fed continuously via the ration during the transition period.

Propionate has been implicated as a major player in hepatic oxidation theory, the concept that feed intake is regulated by oxidation of fuels (fatty acids, propionate, lactate, and amino acids) in the liver, with higher rate of fuel oxidation suppressing feed intake.[30] Although administration of propylene glycol and other glucose precursors increases propionate availability, no studies have shown that this treatment suppresses feed intake.[29,31] However, most field trials with the statistical power needed to appropriately answer this question cannot adequately measure DMI on an individual cow basis; thus, most studies reporting a lack of association with propionate and DMI are underpowered for this analysis.

Interestingly, the success of historical therapy with an intravenous injection of glucose (in the form of dextrose) has never been assessed in a large, randomized field trial in the treatment of hyperketonemia. A recent small study showed that intravenous administration of 500 mL of 50% glucose was effective in reducing blood BHB concentrations in hyperketonemic cows for approximately 4 hours; the transient hyperglycemia from glucose administration lasted for 2 hours. However, the most effective treatment for a prolonged decrease of blood BHB concentration was seen when intravenous glucose and oral propylene glycol were given in combination.[31] There is some debate regarding the total grams of administered glucose, with some clinicians preferring 250 mL of a 50% glucose solution over 500 mL due to the potential of a resulting insulin-induced hypophosphatemia and additional electrolyte disturbances on excretion of extra glucose by the kidney. However, no hypophosphatemia or other mineral or electrolyte disturbances were seen after 3 days of treatment with 500 mL of 50% glucose.[31] It is also debated whether a continuous intravenous infusion of 2.5% or 5% glucose over a 24-hour period is preferred over multiple 50% glucose administrations. Regardless of the inability to perform a constant infusion in a commercial herd setting, there is no evidence that one infusion method is superior over the other in the treatment of hyperketonemia.

Glucocorticoids have been used for decades to treat hyperketonemia given their action in stimulating gluconeogenesis and providing glucose precursors;

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however, few studies have scientifically supported the use of glucocorticoids in the treatment of hyperketonemia. Although glucocorticoids may reduce blood BHB concentrations in the short term, particularly for mild hyperketonemia cases, their use from a subsequent disease and production standpoint has rarely been assessed. Data from a recent large field trial suggest even one dose of dexamethasone (20 mg) at diagnosis of hyperketonemia may be detrimental to cows with BHB greater than 3.2 mmol/L, and that a one-dose treatment had no positive effects on health or production outcomes at any severity level.[32] Given the lack of benefits of glucocorticoids on disease incidence or milk production in mild cases and the potential detrimental effects in more severe hyperketonemia cases, the routine use of glucocorticoids is not recommended for the treatment of hyperketonemia.

Insulin has been used as an adjust therapy for hyperketonemia in conjunction with glucose administration. However, there is limited evidence supporting its use for treatment of hyperketonemia, and the high cost of most commercial products prevents their widespread use and further investigation. Insulin suppresses adipose tissue mobilization, increases uptake of glucose by tissues, and stimulates hepatic glycolysis. Its use with glucose over several days of treatment has been shown to reduce BHB, fatty acids, and liver triglycerides; however, no studies have looked at economically important outcomes from treatment to ascertain if insulin impacts subsequent disease incidence or milk production. Recent work suggests one dose (200 IU) of glargine insulin increases milk yield in older parity hyperketonemic cows with concurrent hypoglycemia, although it was also found to decrease milk yield in the same age group of cows that were euglycemic. Given the cost and equivocal results on health and production outcomes, the routine use of insulin for the treatment of hyperketonemia is not supported.

Vitamin B_{12} has been used in the treatment of hyperketonemia, usually in the chemically synthesized form, cyanocobalamin, and often in combination with butaphosphan (Catosal, Bayer, Shawnee, Kan.). As a vitamin B_{12}-dependent enzyme, methymalonyl-coenzyme A mutase, plays an important role in the transfer of propionate into the TCA cycle, it is thought that increasing the activity of this enzyme through administration of vitamin B_{12} may increase gluconeogenesis. The few studies that have analyzed the effect of vitamin B_{12} have found that it increases ruminations in the few days after treatment and increases the cure risk in hyperketonemic cows with concurrent hypoglycemia

over that of nontreated hyperketonemic cows.[33,34] Given the low cost of vitamin B_{12}, it is often administered as an adjunctive treatment with propylene glycol at 2 to 5 mg per day, although without scientific proof of effectiveness.

The prognosis for resolution of mild hyperketonemia is excellent depending on subsequent disease development. Cows developing hyperketonemia in the first week of lactation, as well cows with more severe hyperketonemia, are at a higher risk of negative health events and poorer milk production in early lactation. Thus, both the timing of hyperketonemia development and severity can be used as prognostic indicators of subsequent disease risk.[13,32] With appropriate identification and treatment, the majority of hyperketonemic cows resolve their disease within 1 week and continue on to productive lactations. The prognoses of hyperketonemic cows that develop additional early-lactation diseases such as metritis or displaced abomasa depend on their response to treatment for the respective associated disease. Cows with accompanying severe hepatic lipidosis have a much poorer prognosis as constant and repeated nursing care is important in addition to the treatments discussed earlier, which takes considerable time and financial resources.

Herd-Level Prevention and Control

Whereas previously discussed ketone tests have great use as tools for diagnosis of hyperketonemia in individual animals, they can also be incorporated into a program for herd-level monitoring in order to assist with management decisions. It is important to note that the sensitivity and specificity of different tests can have a large impact on individual test results and, as a consequence, herd diagnosis and treatment. The probability of correctly identifying a herd as positive (i.e., having a prevalence of hyperketonemia above a certain threshold) decreases when a test with low sensitivity is used.[35] For these reasons, use of handheld blood BHB meters are suggested for herd-level monitoring.

As noted earlier, herds with a high prevalence of hyperketonemia are more likely to have a higher incidence of postpartum disease, poorer reproduction, and lower milk production. Research completed in over 150 herds in the United States and Canada suggests that this association between herd hyperketonemia prevalence and disease and production outcomes occurs when greater than or equal to 15% to 25% of animals have elevated postpartum blood BHB concentrations.[15,19] Ospina and colleagues[15] found that 40% of the 100 herds tested were above the herd alarm level. Unfortunately, hyperketonemia is an

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issue on many herds, and additional studies have found the incidence and prevalence of hyperketonemia to be quite high across herds in the United States, Canada, and Europe.

On a herd-level treatment basis, when the incidence of hyperketonemia rises above 25%, almost any testing and treatment strategy for hyperketonemia is economically beneficial. If herd-level incidence exceeds 50%, blanket treatment of all fresh cows with propylene glycol is recommended, beginning no earlier than 3 days in milk.[17] The delay of blanket treatment until a few days into lactation is important, as most cows are hyperglycemic in the immediate postpartum period, and administrations of propylene glycol, a glucose precursor, may exacerbate hyperglycemia and induce insulin dysregulation. If blanket treatment of all fresh cows is implemented, herd-level assessment of transition cow management, discussed later, is warranted, with repeated testing of fresh cows to monitor hyperketonemia prevalence at least monthly. The goal of herd-level hyperketonemia management strategies and monitoring programs are to keep the prevalence of hyperketonemia below 15%.[35]

Traditionally, nutritional management of dairy cows during the far-off dry period (i.e., approximately 60 to 30 days before calving) has received little attention, but it is a key area for hyperketonemia control. Indeed, many aspects of nutritional management (e.g., mineral nutrition beyond meeting basic nutrient requirements) appear to be less important during the far-off period compared with the close-up period. However, several studies[36-39] suggest that overfeeding cows beginning during this period leads to lower postpartum DMI, increased mobilization of body tissue, increased circulating concentrations of NEFA and BHB, and increased risk for metabolic disorders and poorer productive and reproductive performance. The recommended target diet formulation is to meet 110% to 120% of energy requirements during this period and metabolizable protein supply for Holsteins of over 1200 g/day. During the far-off period, macromineral considerations such as potassium are not of great concern; thus, a wider array of forages and feeds are acceptable to form the basis of diets.

As described earlier, controlling energy intake of close-up cows so that they meet, but do not dramatically exceed, their energy requirements during this period is a critical target. As has been well documented previously and supported by recent research,[4,15,35] energy intake below requirements as reflected by elevated NEFA concentrations during the close-up period is associated with increased incidence of postpartum metabolic disorders, lower milk production, and poorer reproductive performance. The recommended target energy intake of

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cows during the close-up period is 110% to 130% of energy requirements. For Holsteins, this is in the range of 16 to 18 Mcal/day of NEL. As a starting point, formulate the close-up diet at approximately 1.45 Mcal/kg of NEL if the group is a comingled cow/heifer group and approximately 1.38 to 1.40 Mcal/kg of NEL if the group is composed of mature animals and DMI is high. These energy densities are adjusted on the basis of actual DMI of cows on farms to achieve the overall targets for energy intake during the close-up period described earlier.

Metabolizable protein supplies of at least 1200 to 1300 g/day for cows during the close-up period should be targeted.[40] Given that lower-energy diets fed during the close-up period as described earlier typically contain limited amounts of rapidly fermentable carbohydrate (16% to 18% starch), microbial protein synthesis is limited and diets generally contain 1 to 2 kg of ruminally undegradable protein sources in order to meet the metabolizable protein recommendation outlined earlier. Furthermore, research generally supports formulation of close-up rations with methionine and lysine at levels similar to those used for lactating cows. To prevent hyperketonemia and other metabolic disorders of transition cows, it is important that neither protein nor energy are limited. This must be done while avoiding excessive energy intake.

Other management factors are certainly involved in the observed differences between farms and cows and could lead to an increased risk for hyperketonemia early in lactation. These include inadequate cow comfort, high stocking density (e.g., >80% in the close-up and fresh group), unnecessary pen moves, inadequate heat abatement, and limited access to water. Having high-quality feed (silage high in butyric acid has been repeatedly found to cause hyperketonemia, both through a reduction in DMI and a direct conversion of butyrate to BHB in the rumen) available at least 23 hours of the day, as well as management programs in place for the prevention of infectious diseases such as mastitis and uterine infection, aid in the decrease of the risk for this metabolic derailment. Mature cows, cows that had a difficult calving, and overconditioned cows are generally at an increased risk to develop hyperketonemia at the beginning of lactation.

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Bovine Somatotropin

Robert J. Collier • Dale E. Bauman

Introduction

Growth hormone (GH; somatotropin, ST) belongs to the protein family of somatolactogenic hormones produced in all mammals.[1,2] Bovine growth hormone (bGH; bovine somatotropin, bST) is the ST produced in cattle.[3,4] Although ST is named for its effects on growth, it is now known that it has a wide range of activities that are broadly classed as homeorhetic in that it coordinates metabolism to support specific physiologic states.[5,6] One of these states is lactation, and ST is also classified as a galactopoietic hormone in that it increases milk yield in established lactation.[7,8] Russian scientists were the first to extend this effect to dairy cows when they administered pituitary extract to over 2000 cows. They only gave a single injection, so the increase in milk yield lasted only a day or so, but they reported the "absolute harmlessness" of the extract and that responses were "more profitable on a well-run farm than on a farm with a poor food basis or where cattle are kept under unsatisfactory conditions."[7] In the 1940s British scientists conducted a series of studies with a goal of increasing milk supply to help alleviate chronic food shortages during World War II. They were the first to identify bST as the galactopoietic factor in pituitary extract and concluded its use "would be highly profitable to the individual farmer"; however, they also found the supply of bST was too limited to significantly impact national milk supply.[8] Additional studies with lactating cows were conducted over the decades that followed,[9,10] but these were constricted by two factors. First, supply of bST was limited to that isolated from the pituitary glands of slaughtered cows. Second, based on incorrect ideas on the mechanism of bST, scientists only worked with fat, low-producing cows (<15 lb/day).[8]

In the 1980s advances in recombinant DNA techniques made sufficient quantities of recombinant bovine growth hormone (rbST) available for the use as a milk production enhancing agent.[11,12] Approval of rbST for use in lactating dairy cows in the United States was obtained by Monsanto Company from the U.S. Food and Drug Administration (FDA) in 1993 and marketing began in 1994.The following sections will cover the chemistry, production response and

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mechanism of action, cow health and well-being, human safety, and sustainability implications of rbST use in the dairy industry.

Chemistry

Somatotropin is a peptide hormone composed of amino acids, and the sequence of these amino acids differs among species.[3] Bovine somatotropin is a protein hormone consisting of either 190 or 191 amino acids depending on the variant and having a molecular weight of 22 kDa (Fig. 41.27).[13] The mass variants of pituitary bST, associated with the presence or absence of alanine at position 191 of the molecule, are considered secretory process alterations and not genetic in nature. Additional variants have either valine or leucine at position 127, which represents a genetic difference (see Fig. 41.27).[13,14] Thus, there are four possible pituitary variants of somatotropin circulating in the blood of cattle with either alanine or phenylalanine at the carboxyl terminus and either leucine or valine at position 127 (Fig. 41.28). The distribution of these pituitary variants across the dairy breeds is shown in Fig. 41.29. Due to the presence of heterozygotes in some breeds, it is possible in some animals to have all four forms of the pituitary variants in circulation at the same time.[4] Additional mass variants occur due to dimerization of bST molecules, but these forms are considered inactive.[15] Formation of somatotropin dimers also occurs in production of rbST, but these are also inactive.[16] There is no evidence that any of the types of variants of bovine somatotropin are metabolized differently. The plasma kinetics of bST were shown to be consistent with a two-compartment model with half-lives estimated at 8.2 and 29.1 minutes for the two compartments.[17] The compartment with the short half-life appears to represent free somatotropin while the compartment with the extended half-life was believed to represent the somatotropin bound to a protein complex.[17] Free and bound bST represent 100% of total somatotropin measured by radioimmunoassay of bovine blood.

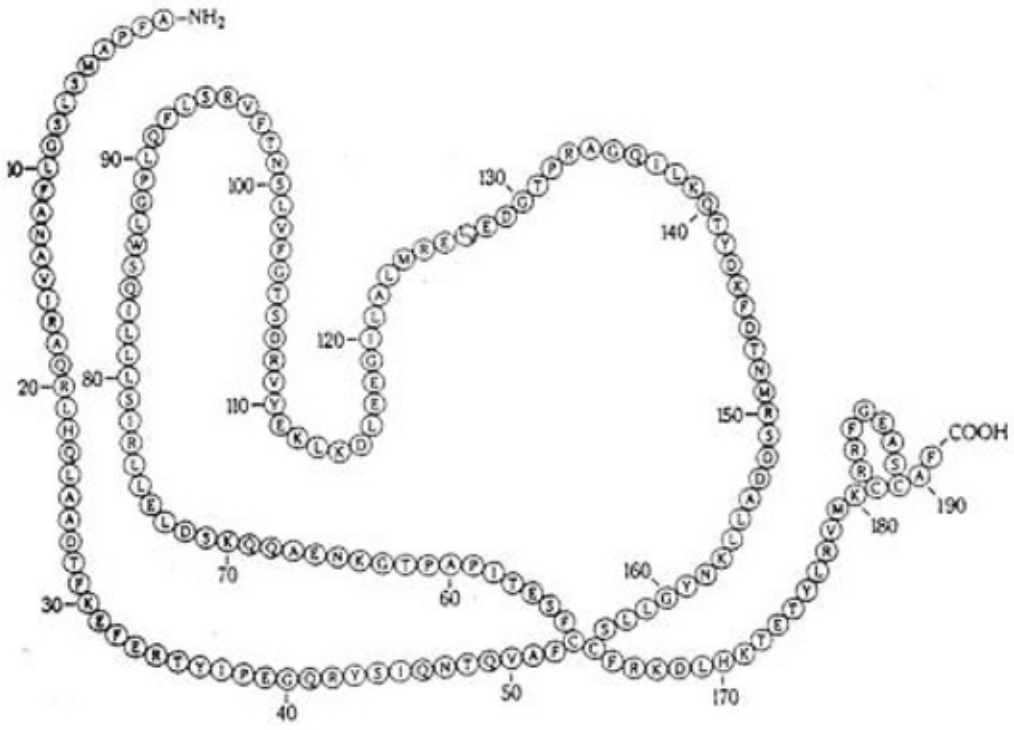


FIG. 41.27 Amino acid sequence of pituitary bovine somatotropin.

NH2-ala-phe-pro-ala-met-ser…leu(127)…phe(191)

NH2-ala-phe-pro-ala-met-ser…val(127)…phe(191)

NH2-ala-phe-pro-ala-met-ser…leu(127)…ala(190)

NH2-ala-phe-pro-ala-met-ser…val(127)…ala(190)

FIG. 41.28 Differences in carboxy terminus amino acid (alanine or phenylalanine) and position 127 (valine or leucine) of the four pituitary variants of bovine somatotropin.

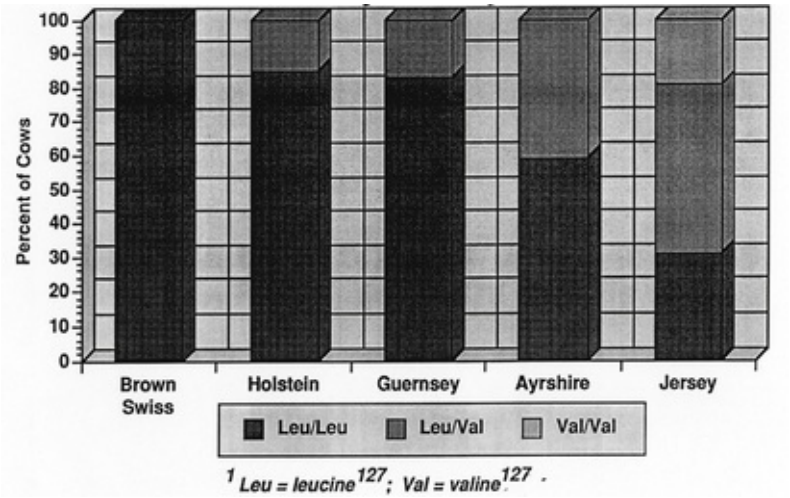


FIG. 41.29 Occurrence of the somatotropin genotypes in the five major dairy breeds. (From Lucy MC, Hauser SD, Eppard PJ, et al: Variants of somatotropin in cattle: gene frequencies in major dairy breeds and associated milk production. Domest Anim Endocrinol 10:325−333, 1993.)

Recombinant variants produced by companies seeking to use bST commercially were either the same as native bST or differed only slightly at the amino terminus.[18] The rbST currently marketed in the United States has the U.S. Adopted Name (USAN) of Sometribove; it has a single amino acid substitution of methionine for alanine at position 191 and leucine at position 127.[15] All of these recombinant variants were tested in vivo for oral activity and found to have none in laboratory rats.[11] Recombinant variants have pharmacokinetics identical to pituitary variants of bST.[17] Since the pharmacokinetics of rbST in vivo does not differ from pituitary BST, it is reasonable to assume that the degradation pathways are essentially the same for both molecules. Also, it is assumed that highly purified fragments of pituitary bST would not differ from similar fragments of rbST in biological activity. Data from lactation studies in cattle indicated no difference in response between recombinant and pituitary-derived forms of bST.[11,17] Bovine somatotropin is marketed as an oil/zinc formulation and delivered for use in dairy cattle at a label dosage of 500 mg SC every 14 days (approximately 37 mg/day) for a 500-kg cow. In safety studies, up to 300 µg/kg/day was injected into cattle.[19]

Biological actions of intact ST are well described.[11,20,21] The definition of ST's biological role has changed over time. Although first described as a regulator of growth, the term *somatotropin* does not nearly describe the pleiotropic actions of this molecule. A better term for ST is “homeorhetic

regulator." Homeorhesis is "the coordinated control of metabolism in support of a dominant developmental or physiological process."[5] Somatotropin is a key player in regulating metabolism across a variety of physiologic states and has many target tissues. Key developments contributing to our understanding of ST as a homeorhetic regulator are the identification of heterogeneity of the receptor population in both distribution and form of the receptor and its ability to alter tissue responses to acute homeostatic signals.[5,9,12,20] However, the actions of ST described to date are those initiated by the intact molecule. There are many cell types that have been identified as targets of ST, including hepatocytes, ovarian luteal cells, cells of the small intestine, bone, adipocytes, muscle, immune system cells, and cardiac cells.[21-24] The liver appears to be a key target for ST owing to its central role in regulating metabolism and its secretion of the ST mediators, insulin-like growth factors (IGFs), and their binding proteins, in response to ST binding. Binding of ST to its receptor is followed by activation of JAK, MAP, and tyrosine kinases and transfer of the cytoplasmic domain of the receptor to the nucleus while the extracellular domain, also called the somatotropin binding protein, is cleaved and enters circulation as a complex with its bound somatotropin.[27-29] Because one of the actions of ST is to increase plasma levels of IGF-1 and the IGF-1 molecule in cattle is identical to the IGF-I molecule in humans, there was great interest in the levels of IGF-1 in milk and its potential impact on the human population.[18,26] This is covered in the section on human safety.

In regard to bST activity in humans, the bovine and human growth hormones are of similar size and differ by 35% in amino acid sequence.[18,25] It is well established that although primate growth hormones can bind and activate nonprimate growth hormone receptors, the reverse is not true. The amino acid sequence required for specificity of human somatotropin for its receptor has been identified with the key interaction occurring between arg-43 of the primate receptor and asp-171 of primate somatotropin.[28-30] In nonprimate receptors this position is replaced by leucine, and histidine occupies the place of aspartate.[28-30]

Metabolism and degradation of bSTresults in a variety of "fragments" of differing molecular weights and size. Many of these have been reported to have partial growth hormone like activity.[27,31-33] However, no studies have examined kinetics of metabolism and clearance of these fragments. It is important to note that since these fragments have low affinity for the growth hormone receptor or the binding protein, they would likely reside in the plasma pool with a short half-

life.[32,33]

Production Responses and Mechanism of Action

The production of rbST represented an exciting development that improved our understanding of lactation biology and offered the opportunity for commercial use. The production and management aspects of rbST have been extensively investigated with over 500 scientific publications reporting results of controlled experiments and field trials. Several excellent reviews have summarized production and management dimensions of the response to rbST.[34-39] From a producer prospective, the use of rbST makes all cows more like the best cows in the herd. This highlights the importance of comprehensive management programs related to nutrition, reproduction, and cow health, and the need for these programs is the same for cows of comparable production regardless of whether rbST is used to achieve that production.

As a brief overview, Posilac is the commercial oil/zinc formulation of rbST approved in the United States for lactating dairy cows. It is administered by subcutaneous injection at 14-day intervals commencing on the 9th to 10th week post calving and continuing until the end of lactation.[40] Use of rbST before the 9th week of lactation is not recommended because safety studies were not conducted during this interval and because milk yield responses are more difficult to assess during this period because milk yield is still increasing, making it difficult to determine what the cow would have produced had she not been treated. There is an immediate increase in milk production when rbST treatment is initiated, which persists until rbST supplementation is discontinued. Published results from controlled experiments and field trials indicate that the increased milk production response typically ranges from 4 to 6 kg/day.[11,34-36,40] However, a lower response or even no response will occur under conditions of poor management or when animal well-being is compromised. Milk responses have been observed for all breeds and cows regardless of genetic merit. Across experiments the variation between unsupplemented and supplemented cows is similar, indicating that all cows are responding to endogenous pituitary bST and exogenous rbST in a similar manner. Some producers have injected the rbST formulation at 10-day intervals in order to increase the milk yield response. This is considered off-label use and is not recommended. However, the net effect of injecting rbST formulation at 10-day intervals is to increase the dose of rbST from 50 mg/day over a 14-day interval. This dose was included in the safety

evaluation, and the milk yield response is linear over a range of doses from 0 to 750 mg/14 days.[35]

Milk composition is of special importance, and controlled experiments and field studies have demonstrated that the nutritional components and manufacturing characteristics of milk are unaltered by the use of rbST supplementation.[12,37,41,42] Milk composition is affected by many factors including breed, genetics, diet, stage of lactation, and environment; these factors affect milk composition in an identical manner in rbST-treated cows.

Somatotropin alters the partitioning of nutrients to allow for an increase in mammary synthesis of milk.[9,12,43] Thus, effects on nutrient use in other physiologic situations were of interest. Investigations have demonstrated that lactating primparous heifers that have not attained mature growth will still do so during rbST treatment. Likewise, rbST-supplemented cows simultaneously lactating and pregnant will still shift nutrient partitioning to support fetal growth and replenishment of body reserves during the later stages of pregnancy.[37,38] Furthermore, the increase in milk yield and persistency that occurs with rbST use continues to be observed when lactation is extended in nonpregnant cows.[44]

Feed is a major expense in the dairy enterprise and a major consideration in the management of dairy cows. Compared with the immediate milk response, voluntary feed intake gradually increases over the first few weeks of rbST treatment and the magnitude of the increase matches the nutrient requirements for the extra milk.[37,38,45] Bioenergetic studies have demonstrated that nutrient requirements for maintenance and per unit of milk are not different in rbST-supplemented cows. Thus, rbST alters the partitioning and use of absorbed nutrients with little or no effect on digestive processes. Overall, dairy cows receiving rbST need to be allowed access to adequate amounts of a balanced ration, but no special diets are required.[37] Extra nutrients are required to support the increase in milk production, but these extra nutrients are all used for milk synthesis. The increase in productive efficiency that results from use of rbST is further discussed in the Sustainability section.

Milk yield per cow has progressively increased over the past 75 years, and this gain in productivity is due to adoption of new technologies and improvements in management practices. Data from a large field study demonstrate the annual gain in daily milk per cow over an 8-year period during the interval of rbST approval.[48] Herds had the characteristic annual gain in daily milk per cow during the 4-year preapproval period, but in herds that adopted rbST the yield was

increased by a similar additional increment each year during the postapproval period when rbST was used (Fig. 41.30). When adjusted for the proportion of supplemented cows, the incremental increase due to rbST was relatively constant and equal to approximately 4 to 5 kg milk per day.

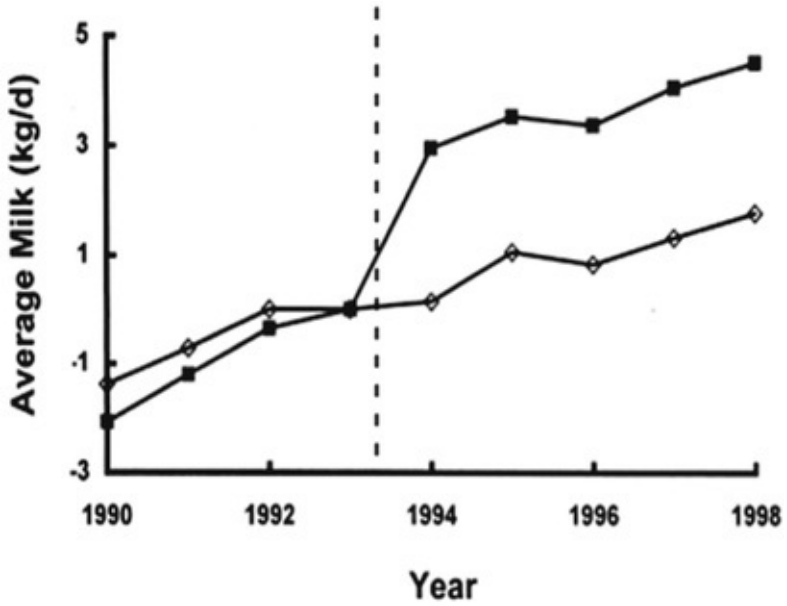


FIG. 41.30 **Improvements in average daily milk yield in Northeast dairy herds. Posilac use commenced February 1994 (dashed line) and data encompass preapproval (1990 through 1993) and postapproval (July 1994 through 1998) periods. Control herds (open diamonds) never purchased Posilac, and bST herds (closed squares) used Posilac continuously throughout the postapproval period. Data represent 340 herds with over 80,000 cows and 200,000 lactations; for comparison, daily yields are expressed relative to 1993, the year before commercial approval of rbST. (Adapted from Bauman DE, Everett RW, Weiland WH, et al: Production responses to bovine somatotropin in Northeast dairy herds. J Dairy Sci 2:2564–2573, 1999.)**

Thus, the use of rbST did not alter the rate of genetic progress in herds using rbST and the response is not altered by relative genetic merit of cows receiving rbST.

The regulation of nutrient use for milk synthesis involves two types of controls—homeostasis and homeorhesis.[5,49] Homeostatic controls regulate metabolic processes on an acute, minute-by-minute basis to maintain steady state conditions; insulin is a key homeostatic control, and its regulation of glucose utilization is of critical importance in lactation. Homeorhesis operates on a chronic, long-term basis and can be defined as the “coordinated regulation of metabolic processes to support the needs of a physiologic state.”[5] Homeorhetic controls are analogous to a symphony conductor who coordinates the

contributions of all the various instruments that make up the orchestra to produce a harmonious symphony. Somatotropin is a major homeorhetic control; during lactation, somatotropin regulates the partitioning of nutrients to support milk synthesis by altering tissue responses to homeostatic signals.[9,49] This orchestration involves most organs and tissues in the body and includes the metabolism of all nutrient classes—carbohydrates, lipids, proteins, and minerals. Thus, rbST treatment both increases milk synthesis by the mammary gland and orchestrates other body processes in a manner to provide the necessary nutrients to support the enhanced milk synthesis.[9,11,49]

Some of the major coordinated changes that occur with rbST treatment are summarized in Table 41.9. These adaptations are of special importance when rbST is first initiated because the increase in milk yield occurs immediately and the matching increase in voluntary feed intake is more gradual. Glucose provides an excellent example of the coordinated responses.[11,49] Glucose is used for milk synthesis, primarily for milk lactose, and the milk response to rbST includes increased mammary uptake and use of glucose. At the same time, acute tissue responses to insulin are shifted so that liver synthesis of glucose is increased and the use of glucose by adipose and other body tissues is reduced. The net effect is that rbST-treated cows partition more glucose to the mammary gland for increased milk synthesis, but glucose supply and use remain in balance. Thus, glucose homeostasis and the cow's well-being are maintained.[47]

TABLE 41.9

Effect of Bovine Somatotropin on Specific Tissues and Physiologic Processes in Lactating Cows

Tissue	Process affected during first few days and weeks of treatment
Mammary	↑ Synthesis of milk with normal composition
	↑ Uptake of all nutrients and milk synthesis per secretory cell
	↑ Number and maintenance of secretory cells
	↑ Blood flow and nutrient supply consistent with increase in milk yield
Liver	↑ Rates of glucose production
	↓ Ability of insulin to inhibit glucose production
Adipose	↓ Fat deposition if in positive energy balance
	↑ Fat mobilization if in negative energy balance
	↓ Ability of insulin to stimulate fat deposition
	↑ Ability of catecholamines to stimulate use of body fat reserves
Intestine	↑ Absorption of Ca, P, and other minerals required for milk
Whole body	↓ Oxidation of glucose to spare use for milk synthesis
	↑ Fatty acid oxidation if in negative energy balance

	Φ Energy expenditure for maintenance
	↑ Energy expenditure consistent with increase in milk yield (i.e., energy per unit of milk not changed)
	↑ Cardiac output consistent with increases in milk yield
	↑ Immune response
	↑ Voluntary feed intake to support increased milk
	↑ Productive efficiency (milk per unit of nutrient intake)

Changes (↑ = increased, ↓ = decreased, ϕ = no change) that occur in initial period when metabolic adjustments occur to match the increased milk synthesis.

Adapted from references 9, 11, and 20.

An additional dimension of the mechanism by which rbST increases milk production involves an improvement in the persistency of milk production.[50] Milk production typically peaks at about 60 days postpartum and then declines gradually over the remainder of the lactation cycle. The decline in lactation corresponds to a gradual loss of mammary cells referred to as cell death or apoptosis.[51] Mammary gland cell numbers are better maintained in first-lactation heifers and in cows that have a greater lactation persistency. Supplementation with rbST also improves the maintenance of actively secreting mammary cells.[51] The net effect is that the milk yield is more persistent in rbST-supplemented cows so that differences between cows receiving rbST and untreated cows tend to increase over the course of the lactation.

Health and Well-Being

As the first recombinant protein with potential use in production animals, the animal safety evaluation was extensive. In the United States this included the traditional evaluation by the FDA, as well as public hearings, science evaluations, and legislative reviews.[11,12,52] After a thorough review of well-controlled studies, the FDA Center for Veterinary Medicine (CVM) concluded that rbST could be used safely and effectively by the U.S. dairy industry. Following the initiation of commercial sales, an unprecedented postapproval monitoring program (PAMP) was initiated; this involved intensive monitoring of 28 herds (1213 cows) for the first 12 months post approval to confirm the safety evaluation conducted by the CVM.[40] Results demonstrated that health problems detected in cows treated with bST under commercial conditions were typical health events that normally occur in dairy herds. All of the conditions noted were managed routinely by accepted management practices within high-producing herds. Mastitis incidence was not increased in rbST-treated animals compared with herd-mate controls and was less than estimated from preclinical studies, and

reproductive performance was improved compared with preclinical studies.[40]

Health Canada also evaluated rbST; they requested that the Canadian Veterinary Medical Association (CVMA) evaluate if "rbST used in accordance with label directions will increase milk production without resulting in serious health problems which cannot be adequately controlled by current management practices."[53,54] In 1998 the CVMA completed a meta-analysis report,[53] and in 2003 results were published in the Canadian Journal of Veterinary Research; they concluded that use of rbST would increase yields of milk and milk components, but it would also adversely impact cow health and welfare, especially udder health, lameness, body condition, reproduction, and lifespan.[54,55] Other less rigorous evaluations also speculated that catastrophic health and welfare problems would occur in rbST-treated cows.[56,57]

Since the FDA approval, there have been several large-scale rbST investigations relating to various aspects of cow health and welfare.[40,48,58-64] Results from these investigations and over 25 years of commercial experience involving over 35 million cows on U.S. dairy farms agreed with the FDA evaluation but were at odds with the conclusions reached by the CVMA.[48,58,65] To provide an updated evaluation of the efficacy and safety of rbST, a multiuniversity expert panel was formed in 2013; they conducted a set of meta-analyses using data from peer-reviewed studies that used the commercial formulation of rbST according to the label.[66]

Variables that were analyzed to characterize the milk and milk composition responses to rbST included milk yield, percent milk fat, percent milk true protein, percent lactose, 3.5% fat-corrected milk yield, fat yield, and protein yield. Except for the percentage of lactose in milk, responses across studies were heterogeneous, indicating that unidentified factors associated with individual studies affected the magnitude of the response. Treatment with rbST increased milk and 3.5% fat corrected milk yields by about 15% over control cows. Milk composition for fat, protein, and lactose was not affected by rbST (Table 41.10). Thus, yield of these milk components increased in parallel with milk production resulting in increases of daily yields of fat and protein of 13.3% and 15.9%, respectively.[66] The increase in milk yield and the lack of effects on milk composition in this meta-analysis agrees with earlier summaries reviewed in the Production section.

TABLE 41.10

Estimates of Responses to rbST and Associated Statistics from Meta-Analysis of Continuous Traits[a]

Variables	Mean of Control Cows	Response Estimate	Standard Error of Estimate	*P* Value	95% Lower CL	95% Upper CL
Milk production & composition Milk yield (lb/day)	60.0	8.82	0.891	<0.001	7.08	10.56
Fat (%)	3.64	−0.073	0.043	0.088	0.156	0.011
Protein (%)	3.15	0.025	0.013	0.067	0.001	0.051
Lactose (%)	4.82	0.023	0.021	0.264	0.017	0.063
3.5% FCM (lb/day)	64.4	8.91	0.904	<0.001	7.143	10.67
Fat yield (lb/day)	2.38	0.317	0.046	<0.001	0.229	0.408
Protein yield (lb/day)	1.90	0.302	0.397	<0.001	0.227	0.381
Reproduction (all parities)						
Days open	104.2	−0.21	4.18	0.960	−8.39	7.98
Services per conception	1.66	−0.25	0.162	0.121	−0.57	0.07
Udder health						
Log_{10} somatic cell count	4.99[e]	−0.034	0.055	0.540	0.141	0.074
Lameness and lesions[b]						
Clinical lameness	0.38	0.13	1.14	0.991	−2.18	2.21
Lameness lesions	1.12	0.32	29.2	0.991	−55.4	56.0
Traumatic lesions	0.11	0.093	7.59	0.991	−15.5	15.7
Body condition						
Body condition score[c]	3.31	−0.064	0.031	0.037	0.124	0.004
Culling						
Culling density[d]	4.64	0.603	0.633	0.341	0.637	1.018

[a]*From St. Pierre et al.*[66]

[b]Expressed as incidence rate per 1000 cow-days at risk.

[c]Body condition score is expressed on a 1 to 5 scale, with 5 being severely overconditioned.

[d]Culling density is expressed as incidence rate per 10,000 cow-days at risk.

[e]Log_{10} somatic cell count of 4.99 = 97,734 somatic cells/mL milk.

CL, Confidence limit.

Milk somatic cell count (SCC) is an indicator of inflammation in the mammary gland, and milk SCC will increase in response to both subclinical and clinical mastitis.[67] Therefore, the meta-analysis of udder health included SCC and the incidence of clinical mastitis. Similar to what was observed for the milk responses, tests for heterogeneity indicated significance for both milk log SCC and mastitis incidence rate, indicating that unidentified factors associated with individual studies affected the observed values. In the case of SCC, the control group and rbST-treated groups did not differ and averaged nearly 100,000

SCC/mL (see Table 41.10). Likewise, mastitis incidence rate did not differ between the control and rbST-supplemented groups (see Table 41.10). Only one study[61] has conducted cultures and used intramammary infection status to ensure a balance in treatment group assignment. That study involved four herds (total cows = 555), and results indicated there were no differences between treatment groups in number of cows that developed clinical mastitis or number of days that milk was discarded because of mastitis due to use of rbST.[61]

The recent (2014) JECFA report on the effects of rbST on mastitis incidence and SCC conducted is in agreement with the results of this meta-analysis.[68] Their review of clinical and epidemiologic studies found no effect of rbST on mastitis incidence. In the case of subclinical mastitis, they reported that the "vast majority of studies reported no effect of rbST treatment on SCC values, although a few studies reported small transient increases."[68] These results are also consistent with the conclusions of public hearings conducted by the FDA Veterinary Medicine Advisory Committee.[52,69] Environmental and management factors are major causes of mastitis, and they affect both SCC and mastitis incidence.[67] In addition, genetic studies have demonstrated a small positive relationship between mastitis risk and milk production. However, high-producing herds are better managed so that effects of increased milk production are minimized or negated.[67]

Body condition was of special importance in the evaluation of health since cows need to maintain adequate body condition over the lactation cycle. In particular, it was of interest to determine whether rbST-treated cows would lose body condition due to the use of reserves to support the increased milk production. The meta-analysis consisted of BCS data obtained during and after rbST treatment for 15 studies. Mean BCS was significantly lower in cows treated with rbST compared with control cows with the difference being –0.064 ± 0.031 points (see Table 41.10). As reviewed in St. Pierre and colleagues,[18] published studies indicate that 1 point of BCS represents about 50 kg (110 lb) body weight. Thus, the difference in BCS for the rbST-treated cows observed in the meta-analysis represents about 3.2 kg (7 lb) body weight. Although significant, this difference would not be visually apparent and approximates the change in body weight associated with a typical feeding or drinking episode for a dairy cow. Thus, this updated meta-analysis indicated that treatment with rbST had little or no effect on body condition despite the increase in milk yield. The explanation for this comes from the review by Chilliard, who demonstrated that across

studies cows treated with rbST increased voluntary intake in an amount energetically comparable with the rbST-induced increases in milk yield.[45]

Altered locomotion or mobility that occurs with clinical lameness represents a range of foot and leg disorders that can result from disease, management, or environmental factors.[70] Results of the St. Pierre and colleagues[66] meta-analysis for clinical lameness found that treatment with rbST had no effect (see Table 41.10). Wherever possible, data for foot lesions were also separated into two categories—lameness lesions and traumatic lesions. Lameness lesions are lesions that directly cause clinical lameness (e.g., laminitis, sole ulcers, digital dermatitis), whereas traumatic lesions are lesions that rarely cause or result in lameness (e.g., mechanically induced skin lesions).[70] Incidence rates for either lameness lesions or traumatic lesions did not differ between controls cows and rbST-treated cows (see Table 41.10).[66]

Reproductive variables were of special interest in this evaluation. Previously, results from the PAMP study indicated that use of rbST had no effect on pregnancy rate, days open, fetal loss, cystic ovaries, or successful calving rate.[40] Results from the meta-analysis indicated a significant 5.4% improvement in pregnancy proportion in the rbST-supplemented cows for the first two breeding cycles after the voluntary wait period (Table 41.11). When compared over the full length of the trial, the pregnancy proportion was reduced 5.5% for the group receiving rbST (see Table 41.11), a reduction that was likely due to reduced estrous behavior.[64,66] The fact that rbST-treated cows were more likely to become pregnant during the first two breeding cycles, the period when cows are generally enrolled in a timed-artificial insemination (AI) protocol, suggests that rbST did not impair, and might even have a positive effect on, the reproductive performance of dairy cows during this period. In addition, use of timed AI does not require estrus observation, so the subsequent reduced pregnancy rate when timed AI is not in use again indicates estrus behavior rather than ovarian or uterine function is the issue.

TABLE 41.11

Estimates of Responses to rbST Espressed as Odds Ratios and Associated Statistics from Meta-Analyses of Noncontinuous Traits[a]

Variables	Rate of Control	Estimates of Odds	*P*	95% Lower	95% Upper

	Cows	Ratio	Value	CL	CL
Reproduction, all parties					
Pregnancy rate in LRP[b]	0.291	1.281	0.007	1.072	1.530
Pregnancy rate in ERP[c]	0.761	0.753	0.048	0.568	0.997
Fetal losses rate	0.115	1.065	0.650	0.812	1.397
Twinning rate	0.065	1.107	0.679	0.685	1.787
Cystic ovaries rate	0.065	1.171	0.425	0.795	1.725
Udder health					
Mastitis incidence rate	0.174	1.249	0.122	0.942	1.655

[a]From St. Pierre et al.[66]

[b]Limited response period (first and second AI inseminations).

[c]Extended response period (full duration of the trial).

CL, Confidence limit.

Results from the meta-analysis indicated that there was no effect of rbST on days to pregnancy, inseminations per conception, fetal losses, or twinning incidence (see Tables 41.10 and 41.11). Similarly, the incidence rate of cystic ovaries did not differ between controls and rbST-treated cows (see Table 41.11). The lack of effect on ovulation failure and cystic ovaries in dairy cows is consistent with the results from De La Sota and colleagues[71] in which rbST-treated cows had ovaries with healthy estrogen-active follicles.

Culling was also examined, and meta-analysis results indicated that culling density did not differ between controls and cows treated with rbST (see Table 41.10). Similarly, a longitudinal field study conducted over 8 years on 340 commercial dairy herds in the northeastern United States demonstrated that rbST use had no effect on “stay-ability” or herd-life.[46]

Overall, conclusions from the updated meta-analysis were consistent with FDA evaluations, the minimal reports of adverse drug experiences, numerous scientific reviews, and large-scale studies conducted on commercial dairy operations. To date, an estimated 35 million U.S. dairy cows have received the commercial formulation of rbST and results have confirmed that treatment with rbST results in increased milk yield with no adverse effects on cow health or well-being.

Because somatotropin has been shown to improve nutrient partitioning and glucose availability for milk production, it has been investigated for potential therapeutic use to prevent periparturient metabolic diseases. At the onset of lactation the dairy cow enters a period of energy deficit that is associated with

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reduced expression of key components of the somatotropin axis, as well as other metabolic regulators such as insulin. For example, the growth hormone 1A receptor population in the liver declines immediately before parturition and rises 3 to 4 days after parturition.[72] The dip in growth hormone receptor population is paralleled by a decline in plasma IGF-I concentration and a rise in plasma growth hormone concentration. These changes are associated with rapid changes in ovarian, placental, and adrenal steroid concentrations during the same time period. Thus, the uncoupling of the somatotropin axis in early postpartum dairy cows is correlated with a decrease in liver GH receptor 1A mRNA, a decrease in liver GH receptor protein, and a decline in IGF-I secretion from the liver. Radcliff and colleagues (2006) demonstrated that partial feed restriction exacerbates the decline in the growth hormone receptor 1A message in the liver and further reduces plasma IGF-I concentrations.[72] Rhoads and colleagues in 2007 further demonstrated that feed restriction depresses growth hormone action in not only liver but adipose tissue as well. Thus, the negative energy balance that occurs in early lactation inhibits the growth hormone axis in liver and adipose tissue during the transition period.[73]

Lucy and colleagues[74] in a review of this area developed the hypothesis that abnormal transition cows had lower hepatic growth hormone receptor 1A population leading to lower plasma IGF-I, which resulted in a number of secondary effects such as poor health and reproduction.

Activation of the growth hormone receptor requires dimerization of two growth hormone receptors with a single growth hormone molecule at a high affinity receptor site.[75] Each growth hormone receptor has one high affinity and one low affinity site. The high affinity sites are required for dimerization and activation of the receptor.[76] If excessive concentrations of growth hormone are present relative to available receptor sites, then all of the high affinity binding sites are occupied by single molecules of growth hormone and the receptors cannot dimerize. This appears to be a likely possibility during the transition period and early lactation when plasma growth hormone concentrations are relatively high and the available receptor population is low. Administration of low but not high doses of somatotropin during this period results in beneficial effects on reproduction and health of cattle.[77-79]

Sustainability Implications

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Sustainability is an important consideration in agricultural production, and rbST has positive benefits on the sustainability of the dairy industry. Producer gains from technologies such as rbST relate to the improvements in efficiency of nutrient use and the related environmental impact. The improvement in productive efficiency with rbST use is a consequence of the "dilution of maintenance,"[80,81] a concept illustrated in Fig. 41.31, in which the nutrient requirements of cows at different production levels are compared. A portion of consumed nutrients is utilized for maintenance; this represents a fixed cost for the cow to live and carry out normal functions. Additional nutrients are required for the synthesis of milk, and this represents a constant quantity for each increment of milk. Thus, nutrient requirements increase as milk output increases, but the fixed costs of maintenance become a smaller percent of the total requirements as milk yield increases (see Fig. 41.31). Likewise, rbST-treated cows require more nutrients to support their increased milk output, but the proportion of total nutrient intake used for milk synthesis increases and the proportion for maintenance is reduced.[5,11,80] To illustrate, consider a dairy herd of 250 cows producing at the 2017 U.S. average per cow; if rbST is used, the same herd milk output can be achieved with only 227 cows and it requires less feed, less waste, and less young stock for replacements. Alternatively, if herd size is maintained at 250 cows, the use of rbST will result in the herd's annual milk output increasing by over 275,000 gallons. Overall, the net effect is the carbon footprint for production of a gallon of milk is reduced by approximately 9% when rbST is used.[82,83]

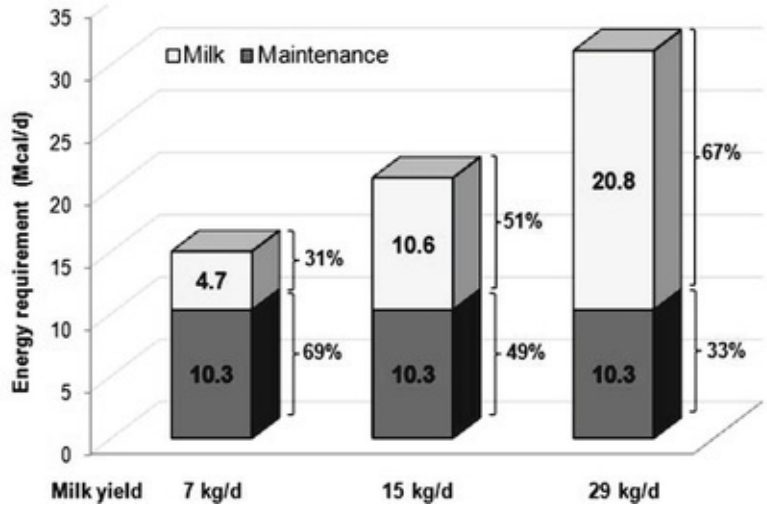


FIG. 41.31 The "dilution of maintenance" effect conferred by increasing milk production in a lactating dairy cow (650 kg body weight, 3.69% milk fat). (Adapted from Capper JL, Bauman DE: The role of productivity in improving the environmental sustainability of ruminant production systems. Annu Rev Anim Biosci 1:469–489, 2013.)

All food production has an environmental impact. Both producers and consumers gain when the environmental costs of food production are reduced. The environmental benefits of using rbST have been enumerated in national reports by USDA and EPA, as well as a series of scientific publications.[84-90] The preceding paragraph highlighted the value of rbST use for a producer herd, but the environmental benefits are particularly impressive when considered more broadly. Table 41.12 illustrates the impact if rbST is used to produce 20% of the 2017 annual milk output by U.S. dairy farms.The environmental benefits of using rbST include reductions in animal numbers, feedstuffs, water and cropland requirements, manure and animal waste outputs, and inputs of fossil fuels and electricity. Overall, the use of rbST allows the U.S. milk supply to be produced with a lower greenhouse gas and a reduced carbon footprint. To provide perspective, in this example, the reduction in carbon footprint with rbST use is equivalent to removing more than 475,000 autos/year. Furthermore, the gains in productive efficiency and environmental benefits from the use of rbST are similar and additive to those occurring with improvements in management practices and related technologies that increase the milk yield of dairy cows. Overall, these gains play an important role in the sustainability of the dairy industry.

TABLE 41.12

Environmental Impact of Using rbST-Supplemented Cows to Produce 20% of 2017 Annual Milk Production[a,b]

Item	Savings
Animals	Reduced by 183,187 (122,736 cows, 60,451 heifers)
Feed	Reduced by 247 million tons
Cropland	Reduced by 510,000 acres (797 sq. miles)
Water	Reduced by 377 billion gallons (consumed & sanitation)
Manure	Reduced by 3.58 million tons
GHG	Reduced by 2.5 million tons

[a]Table constructed by R.A. Cady based on methods detailed in references.[81,82]

[b]Based on U.S. average calving interval, days dry, 63-day start, 14-day injection interval, last dose before anticipated dry-off date. USDA-NASS Quickstats. Available at: https://quickstats.nass.usda.gov/, Accessed 20 February 18.

Human Safety

The human safety of rbST use was extensively evaluated.When considering the human food safety of bovine somatotropin, the FDA considered the “general nature of protein digestion and absorption in adults and neonates, the effects and mechanism of action of growth hormone, its effects on other growth factors and the potential for biological and oral activity in humans.”[18] Thus, oral gavage studies of both somatotropin and IGF-1 were conducted. Relative to the maximum exposure of a 10-kg infant, oral gavage doses of rbST and IGF-I were 50,000 and 200 to 2000 times greater, respectively.[18] In both cases, there were no detectable effects, which strongly indicates that any metabolites produced and taken up across the gut were not active. In agreement, a study where rats were dosed with bovine somatotropin at daily intakes from 0.04 to 4.0 mg per day demonstrated that no detectable immunoreactive bST was identified in serum of these rats.[15] Other evaluations included a Technology Assessment Conference by NIH,[84] an FDA publication in *Science*,[18] and reviews by relevant scientific societies and national medical associations.[92-95] All concluded the use of rbST presented no health or safety concerns for consumers. The human safety of milk from rbST-treated cattle has been established by 56 countries and reviewed three times by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).[68,96,97] In all three reviews the JECFA declared “rbST can be used without any appreciable health risk to consumers” and that there was no need to

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set an Acceptable Daily Intake or Minimum Residue Level for rbST.[68,97,98] There is no test to identify milk from cows supplemented with rbST, and there are no biological or nutritional differences between milk from rbST-supplemented and unsupplemented cows.[68,90,91] The most recent re-evaluation was in 2014, when JECFA reaffirmed that advancements in somatotropin biology and over 20 years of commercial use provides no evidence of any health concerns or safety risks for humans.[68,96]

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• CHAPTER 42

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Diseases of Muscle

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Examination of the Muscular System

Stephanie J. Valberg

Clinical evaluation of the muscular system requires a systematic and routine method for examination. Often a veterinarian is asked to examine an animal with a history of a relatively nonspecific disease process that may be the result of muscular dysfunction. Animals with electrolyte imbalances, pleuritis, colic, chronic wasting diseases, poor performance, weakness, and a number of lameness problems may initially have signs similar to those seen with some forms of muscular dysfunction.

A thorough history of the animal or animals involved is an integral part of characterizing the muscle disorder, particularly because many disorders are intermittent in nature and triggered by certain environmental stimuli. A careful description of the animal's muscle tone, muscle mass, gait, degree of pain,

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exercise intolerance, and weakness while experiencing clinical signs should be obtained. In addition, the duration of illness, intermittency of clinical signs, factors precipitating clinical signs, exercise schedule, diet, current medications, vaccination history, and number of other animals affected and their familial relationships should all be recorded before the muscular system is examined.

Physical Examination

Initially the animal can be observed from all aspects at a distance while the horse is standing with forelimbs and hindlimbs exactly square. The examiner should observe the size, shape, and symmetry of all muscle groups and look for muscle fasciculations. This observation helps provide impressions about tropic changes, alterations in symmetry of particular muscle groups, and spontaneous muscle activity.

The animal can then be walked, trotted, or driven and evaluated for gait abnormalities. The symmetry of the gait and evidence of lameness, weakness, stiffness, and pain associated with movement can be noted. Gait abnormalities may result from pain, muscle weakness, muscle cramping, spasticity, decreased range of joint motion, dysfunction of motor neurons, and ataxia.

Following initial visual evaluation, muscles should be palpated to obtain an overall impression of muscle tone, consistency, sensitivity, swelling, atrophy, and heat. Firm, deep palpation of the lumbar, gluteal, and semimembranosus and semitendinosus muscles may reveal pain, cramps, or fibrosis. Comparisons between muscle groups and areas of the animal can then be made to identify atrophy or swelling. Some animals are tense and demonstrate apparent evidence of myalgia when palpation is first performed. However, given time and patience, many of these animals relax, and muscles or muscle groups that at first examination appeared to be very sensitive or hypertonic may in reality be normal. By this stage it can often be determined whether individual muscles, muscle groups, a limb or limbs, or the whole body musculature is involved. The symmetry or absence of symmetry of affected muscles or muscle groups is also important. Horses should stand perfectly square when comparing bilateral muscle groups.

Fine muscle tremors can be palpated and auscultated with a stethoscope. Concurrent signs of anxiety or pain should be noted, and the animal should be reevaluated in calm surroundings if necessary. In animals with spontaneous muscle activity, muscle groups should also be percussed with a percussion

hammer. The triceps, pectoral, gluteal, and semitendinosus muscles are often easily accessed for percussion. A positive percussion sign occurs when the muscle holds a contracture for several seconds, creating a dimpled appearance below the contracted muscle (percussion myotonia) (Fig. 42.1). This occurs as the result of abnormal mechanical irritability and sustained contraction of the percussed fibers. Running a blunt instrument such as artery forceps, a needle cap, or a pen over the lumbar and gluteal muscles should illicit extension (swayback) followed by flexion (hogback) in healthy animals. Guarding against movement may reflect abnormalities in the pelvic or thoracolumbar muscles or pain associated with the thoracolumbar spine or sacroiliac joints.

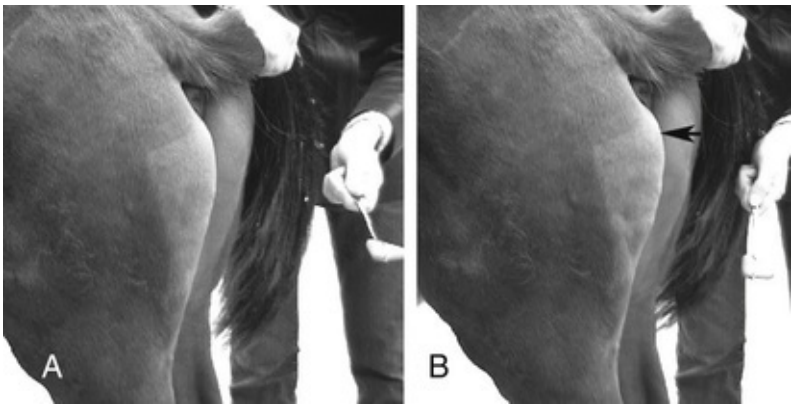


FIG. 42.1 Percussion of the semitendinosus muscle showing the muscle at rest **(A)** and an abnormal persistent firm contracture after tapping the muscle with a percussion hammer **(B)** in a horse with myotonia.

A tail pull examination while the horse is standing still and walking can be used to assess rear limb weakness. If there is evidence of weakness, differentiation between muscular and neurologic origin is ideal. This requires a detailed neurologic examination and can often be extremely difficult. In general, muscular weakness is not associated with ataxia unless it is extremely severe. Weakness is often manifested by muscle fasciculations, knuckling at the walk, frequent recumbency with difficulty rising, and shifting of weight because of an inability to fix the stifles.

If the primary abnormality identified is related to exertion, a lameness evaluation including flexion tests is often indicated as part of evaluation of the muscular system. Muscle pain may be secondary to changes in movement caused by skeletal pain. The horse should be observed at a walk or trot for any gait abnormalities and in some cases lunged for 15 minutes or ridden until

clinical signs are elicited.

Clinical Pathology

Serum Enzyme Activities and Myoglobin Concentrations

Serum enzyme activities can be extremely useful in determining whether muscle cell necrosis is a predominant feature of a suspected muscle disease. Under normal conditions the serum activities of the enzymes used to assess muscle damage are low. However, leakage of the enzymes from myocytes into the bloodstream may occur if the cell membrane is disrupted through muscle cell necrosis or if the permeability of the cell membrane is increased. A number of other factors may influence the activities of enzymes within the circulation. These include rate of enzyme production, alternative sources of the enzyme, rates of enzyme excretion and degradation, and alterations to the pathways involved in enzyme removal or inactivation.

Creatine kinase (CK), aspartate aminotransferase (AST), and lactate dehydrogenase (LDH) activities in serum are used to assess muscle damage in large animals. Serum CK offers remarkable sensitivity as an indicator of myonecrosis and is predominantly located in skeletal and heart muscle. It is intimately involved in energy production within the cytoplasm and is readily liberated into the extracellular fluid when the muscle cell membrane is disrupted. Serum CK activity increases within hours of a muscle insult and peaks within 4 to 6 hours after injury (Fig. 42.2). Limited elevations in CK may accompany training, transport, and strenuous exercise. Elevations of CK to 400 or 500 IU/L may occur when training commences or in response to moderate exercise. Extreme fatiguing exercise (e.g., endurance rides or the cross-country phase of a 3-day event) may result in CK activities being increased to more than 1000 IU/L but usually less than 8000 IU/L. These elevations are not typically reflective of an extensive myopathy, and serum activities of CK rapidly return to baseline activities (i.e., <250 IU/L in 24 to 48 hours). Recumbent animals may also have slightly elevated CK activities that are usually less than 3000 IU/L. In contrast, more substantial elevations (from several thousand to hundreds of thousands of IU/L) in the activity of this enzyme may occur with rhabdomyolysis.

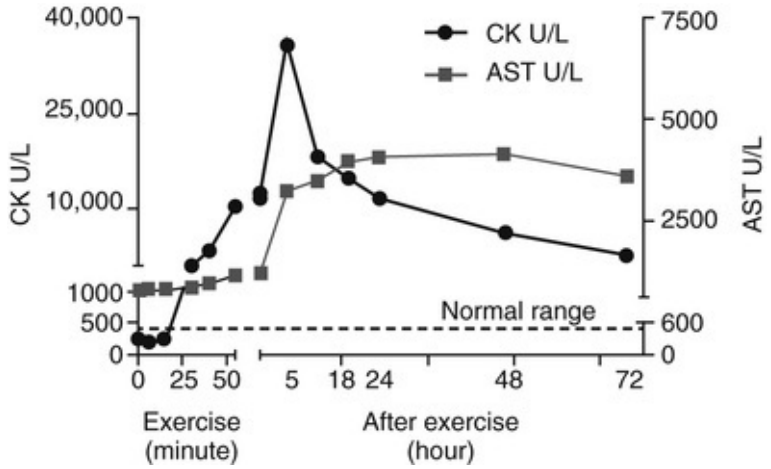


FIG. 42.2 Serum creatine kinase *(CK)* and aspartate transaminase *(AST)* activities over a 3-day period in a Standardbred trotter that developed exertional rhabdomyolysis during 55 minutes of trotting at 5 m/s. Serum CK activity increased during exercise and peaked in the sample obtained 5 hours after exercise. Serum AST was above normal range before exercise, increased after exercise, and peaked 48 hours following exercise.

Serum AST has high activity in skeletal and cardiac muscle and also in liver, red blood cells (RBCs), and other tissues. Elevations in AST are not specific for myonecrosis, and increases can be the result of hemolysis, muscle, liver, or other organ damage. Alterations in AST activity are an integral component of many serum biochemical “profiles.” AST activity rises more slowly in response to myonecrosis than does CK, often peaking 24 hours after the insult (see Fig. 42.2), and the half-life of AST is much longer than that of CK. By comparing serial activities of CK and AST in animals with suspected myopathy, information concerning the progression of myonecrosis may be derived. Thus (1) elevations in CK and AST reflect relatively recent or active myonecrosis; (2) if CK remains persistently elevated, myonecrosis is likely ongoing; and (3) elevated AST activities accompanied by decreasing or normal CK activities indicate that myonecrosis is not continuing. Elevations in serum LDH activity are not specific to skeletal muscle and can occur with rhabdomyolysis, myocardial necrosis, and/or hepatic necrosis.

Under ideal conditions samples for determination of serum CK, AST, and LDH should be harvested as soon as possible because anoxia and lysis of RBCs allows the liberation of AST and LDH. They should be kept chilled (4° C/39° F) if not taken immediately to a laboratory for analysis within 24 hours. When a delay of more than 12 hours is anticipated, freezing of the samples is desirable.

Elevations in plasma/serum myoglobin concentrations provide an indication

of recent muscle damage. Unfortunately, few laboratories can routinely measure myoglobin. Normal concentrations in resting horses have been determined by nephelometry (range 0 to 9 µg/L),[1] with measured concentrations with rhabdomyolysis ranging from 10,000 to 800,000 µg/L.[2]

Urinalysis

Urine can be obtained as a free catch sample from horses placed in stalls with fresh bedding or via catheterization. The most accurate reflection of fractional excretion of electrolytes is obtained from samples obtained without tranquilization. Urinalysis is particularly important in horses with myoglobinuria, elevations in creatinine, or suspected electrolyte imbalances. Urine specific gravity, protein content, white blood cell (WBC) count, RBC count, and evaluation of cast formation should be performed to assess the potential for concurrent renal disease. A positive Hemastix test (ortho-toluidine) in the absence of hemolysis or RBCs in urine is highly suggestive of myoglobinuria. Further differentiation of myoglobin from hemoglobin is sometimes warranted, and, where available, electrophoresis, nephelometry, or spectroscopy may be used. Spectroscopy does not always reliably distinguish between myoglobin and hemoglobin.

Electrolyte, mineral, and creatinine concentrations in urine and blood have been used to determine electrolyte balance in horses with muscle cramping or exertional rhabdomyolysis.[3] Problems often encountered, however, are the large fluctuations in daily electrolyte excretion that occur in the same horse and between horses, the interference of high urinary potassium concentrations with measures of sodium concentrations when an ion-specific electrode is used, and the presence of calcium crystals in equine urine, which artifactually decrease the calcium and magnesium measured if urine samples are not acidified.[4] Renal fractional excretions (FEs) can be calculated using the following formula:

$$FE_x = \frac{S_{Cr} \times U_x \times 100}{U_{Cr} \times S_x}$$

where *U* is urine, *S* is serum, *x* is measured electrolyte, and *Cr* is creatinine.

If urine calcium is to be determined, acidification of urine to dissolve all calcium oxalate crystals is recommended to provide exact calcium excretion.

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Determination of potassium, chloride, magnesium, and phosphorus concentrations can be performed using ion-specific electrodes or by inductively coupled plasma atomic absorption.

Normal values for FEs of electrolytes depend on a horse's diet. Normal values (%) for horses consuming grass, hay, and a sweet feed mix with available salt are FE_{Na} 0.04 to 0.08, FE_{K} 35 to 80, FE_{Cl} 0.4 to 1.2, FE_{Ca} 5.3 to 14.5, FE_{P} 0.05 to 4.1, and FE_{Mg} 14.2 to 21.4.[4,5]

Exercise Testing

Evaluation of muscle disorders that are precipitated by exercise may require an exercise challenge test. Horses should be observed for evidence of exercise intolerance, as well as muscle stiffness. An exercise test should not be used in horses with overt signs of rhabdomyolysis but rather to determine if horses not currently showing clinical signs are prone to exertional rhabdomyolysis. The goal is to induce subclinical elevations in serum CK activity. Abnormal increases in CK are more likely to occur if slow trotting is performed rather than strenuous exercise.[6] Often 15 minutes of exercise at a walk and trot in unfit horses or at a constant slow trot in fit horses will elucidate subclinical elevations of CK. If signs of stiffness develop before this, exercise should be concluded. CK activities in blood samples taken immediately after exercise do not reflect the amount of exercise-induced muscle damage. For best results, blood samples for CK activity should be taken before and 4 to 6 hours after exercise. In healthy horses, 15 to 30 minutes of light exercise rarely causes more than a threefold increase in CK activity.[7,8] Elevations greater than fivefold are indicative of exertional rhabdomyolysis. Standardized treadmill exercise testing can also be used to evaluate muscle responses and measure metabolic responses to exercise.

Electromyography

Electrodiagnostic studies detect spontaneous or evoked potentials of neurogenic or myogenic origin using electrodes positioned in the muscle. Electromyography (EMG) is particularly useful to evaluate large animals with altered muscle tone. EMG of normal skeletal muscle shows a brief burst of electrical activity when the needle is inserted (insertional activity) in muscle and then quiescence, unless motor units are recruited (motor unit action potentials) or the needle is close to a motor end plate (miniature end plate potentials). Normal muscle shows little spontaneous electrical activity unless the muscles contract or the horse moves.

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Horses with abnormalities in the electrical conduction system of muscle, or denervation of motor units, show abnormal spontaneous electrical activity in the form of fibrillation potentials, positive sharp waves, myotonic discharges, or complex repetitive discharges.[9-12] Fibrillation potentials and positive sharp waves represent spontaneous firing of muscle fibers. Myotonic discharges are bursts of complex high-frequency potentials, whereas complex repetitive discharges are similar but have fixed amplitude and frequency. They both represent abnormal simultaneous firing of groups of muscle fibers. Motor unit action potentials can be evaluated to assess their amplitude, duration, phase, and number of phases. Myopathic changes include a decrease in duration and amplitude of motor unit action potentials.[10,12] More information about the motor unit could be provided by nerve conduction velocities (NCVs); however, the inaccessibility of motor nerves makes measurement difficult in large animals. Both EMG and NCVs are used to classify the primary disease as neuropathic or myopathic, to determine the distribution of the disease, and to provide insight into the pathophysiologic mechanisms of the disease.[9,13] Equipment costs are relatively high, and expertise is required in operation and interpretation of results. Readers are advised to consult Chapter 35 before considering the use of EMG.

Nuclear Scintigraphy

Nuclear scintigraphy is useful for identification of some forms of muscle damage, particularly an area of deep muscle damage that was not suspected on the basis of clinical examination.[14] Technetium 99m methylene diphosphonate (MDP) is taken up in some damaged muscle in the horse and is best seen in the bone phase images (i.e., 3 hours after injection). Scintigraphy has been used in horses with a history of poor performance, with or without stiffness after exercise, to confirm a diagnosis of equine rhabdomyolysis.[15] The mechanism of MDP binding is unknown, but the release of large amounts of calcium from damaged muscle or the exposure of calcium binding sites on protein macromolecules in the damaged muscle may be responsible. Scintigraphy may be helpful in some cases involving focal damage to either proximal forelimb or hindlimb muscles.[14]

Ultrasonography

Diagnostic ultrasonography is potentially useful for identification of muscle

trauma, crepitus, fibrosis, and atrophy. Muscles have a rather typical striated echogenic pattern, but this varies according to the muscle group and careful comparisons must be made between similar sites in contralateral limbs, in both transverse and longitudinal images.[14] The appearance of muscle is also sensitive to the way the animal is standing and whether the muscle is under tension, so it is important that the animal is standing squarely and bearing weight evenly. Muscle fascia appears as well-defined, relatively echodense bands.[14] Care must be taken in identifying large vessels and artifacts created by them.

In an acute injury, muscle fiber disruption is seen as relatively hypoechoic areas within muscle, with loss of the normal muscle fiber striation. The jagged edge of the margin of the torn muscle may be increased in echogenicity.[14] Tears in the muscle fascia may be identified. The defect in muscle may be filled by loculated hematoma that is hypoechoic. As the muscle repairs, it becomes progressively more echogenic. Relatively hyperechoic regions may be a result of increased connective tissue or loss of muscle cell mass. Hyperechoic shadowing artifacts usually represent mineralization or gas pockets.[14]

Muscle Biopsy

Examination of muscle fibers, neuromuscular junctions, nerve branches, connective tissue, and blood vessels within a biopsy sample can provide additional information necessary to fully characterize a neuromuscular disorder.[16-18] Routine light and electron microscopic examinations, combined with histochemical evaluations, may provide insights into the particular manifestations of neuromuscular diseases and their rate of progression. A number of basic pathologic responses of muscle can be identified in paraffin-fixed sections. These include inflammatory infiltrates, muscle fiber necrosis, muscle fiber regeneration, increased number of central nuclei, variations in muscle fiber sizes and fiber shapes, vacuolar change, and proliferation of connective tissue. However, there are many pathologic alterations that cannot be detected in formalin-fixed tissue but can readily be seen in histochemical stains of fresh-frozen biopsy samples.[16-18] These include muscle fiber types and their pattern of distribution, differentiation of neurogenic atrophy from disuse atrophy or a primary myopathy, characterization of vacuolar storage material, characterization of inclusion bodies, assessment of mitochondrial density, and additional clues that may allow identification of a specific disorder or category of muscle disorders. Furthermore, formalin fixation results in artifactual

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cracking, fiber shrinkage, and leakage of substrates such as glycogen, which can affect proper interpretation of muscle pathology.

When considering collection of muscle biopsies, some general guidelines apply. Preferably, samples should be collected from what is considered abnormal or diseased muscle. A 6-mm-outer-diameter (Jørgen Kruuse A/S, Langeskov, Denmark) percutaneous needle biopsy technique can be used to obtain small muscle samples through a ¼-inch skin incision using a local anesthetic subcutaneously. If this technique is used, enough muscle should be obtained to form a ½-inch-square sample at a minimum. These samples do not, however, tolerate shipment to an outside laboratory. The optimum biopsy for shipment of histopathology tissues to a laboratory is collected using surgical or open techniques, performed under local anesthesia. Care must be exercised to infiltrate only the subcutaneous tissues, not the muscle, with the anesthetic agent. The objective is to obtain approximately a ½-inch cube of tissue; hence a suitably long skin incision is required. Two parallel incisions ½ inch apart should be made longitudinal to the muscle fibers with a scalpel. The muscle should be handled only in one corner using forceps, and crushing should be avoided. The muscle sample is then excised by cross-section incisions ½ inch apart, and the tissue is fixed appropriately. Routine histopathology samples can be placed in formalin; fresh samples can be placed in a watertight hard container after being wrapped in gauze lightly moistened with saline and shipped chilled to laboratories for freezing. On arrival at specialized laboratories, fresh samples for histochemical analysis are fixed in isopentane (methylbutane) chilled in liquid nitrogen to ensure rapid freezing and minimization of freeze artifact. Samples that potentially may be used for biochemical analysis should be immediately frozen in liquid nitrogen. Other routine histopathologic techniques may also be of diagnostic value. A special fixative may be required if such practices are to be undertaken. Samples for electron microscopy (EM) require appropriate fixation in glutaraldehyde preparations. Ideally, thin sections of muscle for EM should be clamped in vivo to maintain fibers at a resting length before they are excised. However, if pathology other than the alignment of thick and thin myofilaments is to be investigated, small muscle pieces can be excised and placed directly in appropriate EM fixative.

Responses of strips of fresh muscle to stimuli such as caffeine, halothane, and a variety of other agents can also be performed by specialized laboratories to diagnose recurrent exertional rhabdomyolysis and susceptibility to malignant hyperthermia but are not routine diagnostic procedures.[19-21]

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Classification of Muscle Disorders

Stephanie J. Valberg

A muscle disorder is usually suspected in large animals because of (1) increased, decreased, or abnormal muscle tone; (2) focal or generalized muscle damage (rhabdomyolysis); (3) muscle atrophy; or (4) exercise intolerance not associated with respiratory, cardiovascular, or skeletal causes.

Altered Muscle Tone

Increased muscle tone may be neural in origin. For example, tetanus and strychnine poisoning increase muscle tone as a result of suppressed inhibition of upper motor neurons by interneurons. Increased motor neuron firing also occurs during seizures, with electrolyte imbalances, and with equine ear tick infestation. Visual, tactile, or auditory stimuli often precipitate painful sustained motor unit activity. Other probable neural disorders that intermittently increase muscle tone include periodic spasticity and spastic paresis in cattle, stiff horse syndrome, and “shivers” in draft and warmblood horses. Focal nerve root irritation may also result in focal muscle twitching.

Increased muscle tone can also arise from myopathic disorders. Persistently enhanced muscle tone may occur because of muscle contractures, which are characterized by fixation of myofilaments in a persistently shortened position without neural input.[22] Contractures are usually extremely painful and associated with rhabdomyolysis. Contractures occur with malignant hyperthermia and some forms of exertional myopathy. Intermittent, abnormal muscle contractions without rhabdomyolysis occur when sarcolemmal ion channels within the muscle cell membrane are dysfunctional.[23,24] Caprine myotonia congenita and equine hyperkalemic periodic paralysis are examples of diseases caused by sarcolemmal ion channel dysfunction.

Moderate weakness in horses may be caused by central spinal cord disorders. More profound weakness may arise from neuropathies affecting motor neurons (equine motor neuron disease [EMND], hypocalcemia), decreased neural input at motor end plates (botulism), marked muscle atrophy (EMND) or rhabdomyolysis of postural muscles, or severe electrolyte imbalances (hypokalemia). The few operative motor units fatigue easily, resulting in muscle fasciculations, shifting of weight, low head posture, difficulty prehending grain,

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and long periods of recumbency and difficulty rising.

Muscle Atrophy

Atrophy is defined as a reduction in muscle size, specifically a reduction in muscle fiber diameter or cross-sectional area. Atrophy may occur in response to a variety of stimuli. Denervation removes the normal low-level tonic neural stimulus that is necessary to maintain muscle fiber mass. Complete denervation of a muscle results in more than a 50% loss of muscle mass within a 2- to 3-week period.[16,25] A good example of this is “Sweeney” in horses, in which the suprascapular nerve is damaged and muscles over the scapula atrophy. Other denervating conditions such as EMND show a slower and more generalized progression of gross muscle atrophy. Electromyographic abnormalities following denervation are apparent within 5 days, and it may take 3 weeks for maximal changes to develop. Increased insertional activity, positive sharp waves, and bizarre high-frequency discharges and fibrillation potentials are seen in denervated muscle.[12] Pyknotic nuclear clumps and small angular slow-twitch type I and fast-twitch type II fibers with concave sides are characteristic of neurogenic atrophy in muscle biopsies. In some cases, hypertrophy of remaining motor units may occur in neurogenic atrophy, and renervation is indicated by target fibers and fiber type grouping.

Muscle atrophy may also be caused by disuse, malnutrition, cachexia, corticosteroid excess, and immune-mediated myositis. Skeletal muscle is a plastic tissue, with approximately 1% to 5% of the contractile mass undergoing remodeling on a daily basis. If a negative nitrogen balance occurs, net protein withdrawal from the skeletal muscle mass begins within 48 to 72 hours. This type of atrophy is distinguished from neurogenic atrophy by a slower progression of atrophy, normal electromyographic findings, and muscle biopsies that are characterized by primarily atrophy of type II muscle fibers. The overall response of skeletal muscle is to maintain essential postural muscle groups, whereas less essential groups undergo significant reduction in muscle mass. With malnutrition, 30% to 50% of the muscle mass may be lost in the first 1 to 2 months.[25] Rapid atrophy is characteristic of immune-mediated myopathies in Quarter Horse–related breeds, which can result in the loss of 30% of muscle mass within 48 hours due to necrosis and atrophy of myofibers.[26]

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Muscle Necrosis

Muscle necrosis (rhabdomyolysis) as evidenced by elevations in serum CK, LDH, and AST can be focal or generalized. Many infectious, toxic, nutritional, ischemic, and idiopathic factors result in muscle fiber necrosis. When attempting to identify an etiology, it is helpful to characterize rhabdomyolysis in horses as associated with exercise or not. Specific causes of exertional and nonexertional rhabdomyolysis are listed in Boxes 42.1 to 42.3.

Box 42.1

Classification of Nonexertional Myopathies in Horses

1. Infectious
    - Viral
    - *Sarcocystis fayeri*
    - *Anaplasma phagocytophilum*
    - *Streptococcus equi*
    - *Clostridium* spp.
    - Abscesses
2. Immune mediated
    - Infarctive purpura hemorrhagica
    - Immune-mediated myositis
3. Nutritional myopathies
    - Nutritional myodegeneration
    - Selenium deficiency, vitamin E deficiency
    - Vitamin E–deficient myopathy
4. Toxic myopathies
    - Feed contaminants
    - Ionophores
    - Plant toxins
    - Trematones
    - Hypoglycin A
5. Traumatic or anesthetic

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- Focal muscle strain
- Fibrotic myopathy
- Postanesthetic myopathy

6. Muscle cramping
    - Electrolyte disturbances
    - Hypocalcemia
    - Synchronous diaphragmatic flutter
    - Ear ticks
    - Shivers
7. Myotonia
    - Myotonia congenita
    - Myotonia dystrophica
    - Hyperkalemic periodic paralysis
8. Genetic
    - Glycogen branching enzyme deficiency
    - Polysaccharide storage myopathy type 1
    - Polysaccharide storage myopathy type 2
    - Malignant hyperthermia

Box 42.2

Classification of Exertional Myopathies in Horses

1. Focal muscle strain
2. Sporadic exertional rhabdomyolysis
    - Dietary imbalances:
    - Vitamin E, selenium, electrolytes
    - Exercise in excess of training
    - Exhaustion
3. Chronic exertional rhabdomyolysis
    - Polysaccharide storage myopathy type 1
    - Polysaccharide storage myopathy type 2
    - Malignant hyperthermia
    - Recurrent exertional rhabdomyolysis

- Idiopathic exertional rhabdomyolysis

Box 42.3

Classification of Myopathies in Food Animals

1. Infectious
    - *Clostridium*
    - *Sarcocystis*
2. Nutritional
    - Selenium, vitamin E
    - Hypokalemia
3. Toxic
    - Feed additives
    - Ionophores
    - Plants
    - Gossypol, *Cassia*, white snakeroot
    - Chemical
4. Traumatic
    - Muscle crush syndrome
5. Genetic
    - Caprine myotonia
    - Bovine pseudomyotonia
    - Porcine malignant hyperthermia
    - Bovine and ovine myophosphorylase deficiency
    - Porcine RN(–) glycogen storage disease

Necrosis represents injury to organelles within a muscle fiber or within a segment of that fiber. Many myopathies associated with generalized rhabdomyolysis interrupt normal muscle metabolism, and cell death results from an inability to maintain homeostasis within the myofiber. Although a variety of external or internal insults may cause rhabdomyolysis, they often share a final common pathway leading to cell death.[27] Under normal conditions, considerable energy is expended by muscle cells to pump the calcium that accumulates in the sarcoplasm during contraction into the sarcoplasmic reticulum. If cell membrane

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function is disrupted or if the energy pathways that generate adenosine triphosphate for the calcium pump are impaired, excessive calcium may accumulate in the sarcoplasm. Although some calcium can be sequestered by the mitochondria, eventually mitochondria become overloaded and oxidative metabolism ceases; oxygen free radicals are generated; phospholipases are activated, inducing the arachidonic cascade; calcium-dependent proteases are stimulated; and complement is activated. Lipid storage disorders and antioxidant deficiencies may also cause necrosis through destruction of mitochondrial and sarcolemmal membranes. The contractile proteins within a necrotic segment are destroyed and appear homogenized with no evidence of cross-striations, and mitochondrial and sarcolemmal membranes appear disrupted. When necrosis occurs as a result of internal disruption of muscle homeostasis, the basement membrane of the cell is left intact. Macrophage infiltration and phagocytosis of necrotic debris usually occur within 16 to 48 hours of the muscle injury. Satellite cells migrate along the remaining basement membrane and form regenerative myotubes within 3 to 4 days of injury, with mature muscle fibers developing within a month of the original damage.[16]

Muscle ischemia occurs commonly with acute trauma, the compartment syndrome in recumbent animals, downer syndrome, and vascular occlusion. Compartment syndrome often involves the triceps muscle or extensors of the hindlimb because they are often compressed in down animals or during anesthesia. Hypotension during surgery contributes to the development of this syndrome. Acute muscle infarction may occur with purpura hemorrhagica or disseminated intravascular coagulation, and on postmortem examination characteristic well-demarcated areas of hemorrhagic necrosis are evident. Muscle areas in contact with the ground in recumbent animals are most susceptible to infarctions in animals with vasculitis. Clinically, acute infarctions are an extremely painful condition that may resemble colic. Chronic occlusive diseases, such as iliac thrombosis, often allow collateral circulation to develop, thereby avoiding acute signs of ischemia at rest. Although muscle has an impressive ability to regenerate, if a disease process is severe enough to disrupt the basement membrane, muscle may be replaced by connective tissue and fat. This occurs most frequently after trauma, such as following tearing of the semimembranosus or tendinosus in horses (fibrotic myopathy), and with severe infarctions.

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Disorders of Muscle Tone

There are numerous causes of increased muscle tone in large animals including forms of myotonia, ear tick infestation, and shivers in horses, as well as spastic conditions in cattle.[28-38] A condition that demonstrates enhanced muscle tone in cattle is spastic paresis,[32,33] or Elso heel. Commonly, calves between 2 and 7 months of age are affected and have an extremely straight angle to the hock and stifle. Signs reflect a decreased capacity or inability to flex the hock because of continuous tension on the gastrocnemius muscle when standing. Involvement may be unilateral or bilateral. The Holstein Friesian breed is most commonly affected, although other breeds have been found to suffer the disorder.[32-35] Spastic paresis may have a distinct familial pattern, but environmental exposure to toxins in utero have also been implicated as a cause.[32-34,36]

Clinical signs similar to spastic paresis are seen in horses with shivers, which is most commonly seen in draft horse breeds, warmbloods and warmblood crosses older than 1 year of age, and Thoroughbreds, although it may occur in light horse breeds.[37] Horses are generally taller than 16.3 hands and more often male than female. Suggested causes include genetic, traumatic, infectious, and neurologic diseases, although its exact basis is unknown. The disease primarily affects the hindlimbs and is characterized by periodic, involuntary spasms of the muscles in the pelvic region, pelvic limbs, and tail, which are exacerbated by backing up or picking up the hindlimbs. The affected limb is elevated and then abducted. It may actually shake and shiver, and the tailhead usually elevates concurrently and trembles. In more severely affected animals, on backing up the hindlimb is suddenly raised, semiflexed, and abducted with the hoof held in the air for several seconds or minutes. The tail is elevated simultaneously and trembles. After a variable period of time, the spasms subside, the limb is extended, and the foot is brought slowly to the ground. Surface electromyography indicates that both flexors and extensors fire simultaneously during backing up in horses with shivers, resulting in strong, painful muscle contractions and poorly timed relaxation.[38] There are no distinct myotonic discharges on electromyography with shivers, indicating it is not a true myotonic condition.

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Myotonic Disorders

Stephanie J. Valberg

Myotonic muscle disorders represent a heterogeneous group of diseases that share the feature of delayed relaxation of muscle after mechanical stimulation or voluntary contraction. Abnormal muscle membrane excitability appears to be the shared abnormality among myotonic disorders. The nondystrophic myotonias in large animals include myotonia congenita in horses and goats and equine hyperkalemic periodic paralysis.[28] Sarcolemmal ion channel dysfunction causes these nondystrophic myotonias. Dystrophic myotonia, a progressive disease that may also be associated with abnormalities in other body systems, has been reported in horses.[29,30] In addition, it has been noted that some horses with ear tick infestations develop percussion myotonia and painful muscle cramps.[31]

Myotonia

Clinical Signs.

Myotonia congenita in humans, horses, and goats is usually detected in the first year of life.[39-42] Affected animals commonly have conspicuously well-developed musculature and display mild to moderate pelvic limb stiffness. Gait abnormalities are usually most pronounced when exercise begins and frequently diminish as exercise continues. Bilateral bulging (dimpling) of the thigh and rump muscles is often obvious and gives the impression that the animal is well developed (Fig. 42.3). Stimulation of affected muscles, especially percussion, exacerbates the muscle dimpling below a large area of tight contraction (Fig. 42.4). Affected muscles may remain contracted for up to a minute or more with subsequent slow relaxation.[30,42] Myotonia congenita does not usually show progression of clinical signs beyond 6 to 12 months of age in horses.[30]



FIG. 42.3 Normal muscle mass in an Appaloosa foal **(A)** and spontaneous myotonic dimpling of semimembranosus muscles in a foal with myotonic dystrophy **(B).**

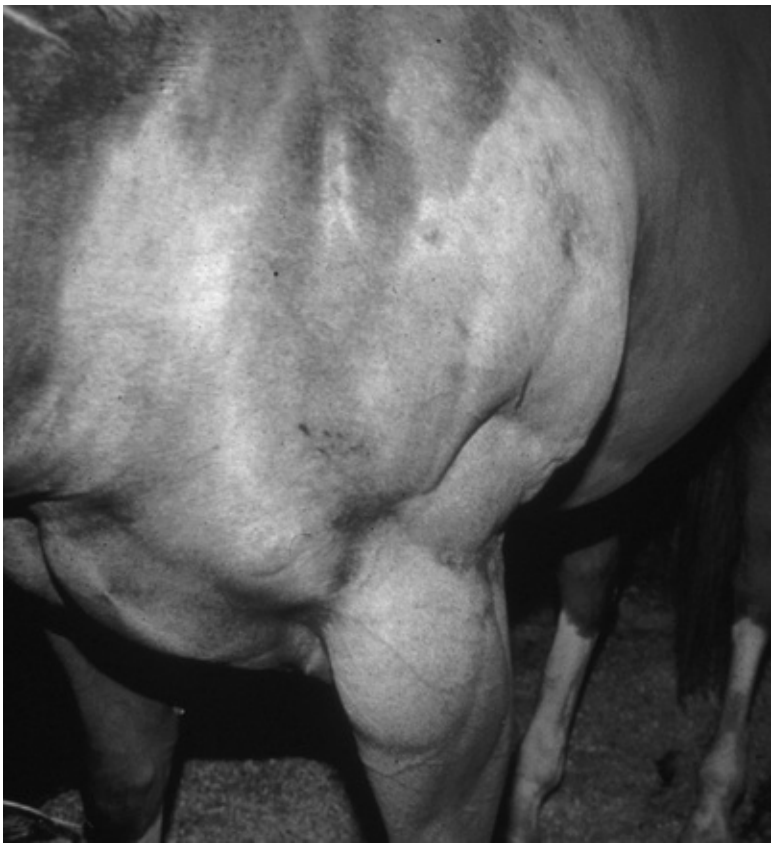


FIG. 42.4 Myotonic dimpling of the triceps in a horse with hyperkalemic periodic paralysis.

In goats, myotonia congenita appears to be an autosomal dominant mutation in the skeletal muscle chloride channel (CLCN1) that has incomplete penetrance.[24,41,43] Affected goats are commonly referred to as “fainting goats.” Signs are usually recognizable by 6 weeks of age and vary from stiffness after rest to marked general rigidity after visual, tactile, or auditory stimulation. Clinical signs remain throughout the animal's life but are not progressive.[44] An autosomal recessive c.1775A>C mutation was identified in a New Forest pony with congenital myotonia. The missense mutation results in a substitution of aspartic acid for alanine in codon 592 of the C-terminal cytoplasmic domain of the equine CLCN1 protein.[45]

Myotonia dystrophica appears to be a separate form of myotonia in horses.[29,30,46] Severe clinical signs of myotonia that progress to marked muscle atrophy and possibly involve a variety of organ systems have been observed in Quarter Horse, Appaloosa, and Italian-bred foals. Retinal dysplasia, lenticular opacities, and gonadal hypoplasia have been reported in one such Quarter Horse

foal.[29] This condition resembles myotonia dystrophica in humans, which is caused by genetic mutations involving either the *DMPK* gene or the *ZNF9* gene.[47,48] In both cases, a short segment of deoxyribonucleic acid (DNA) is abnormally repeated many times, forming an unstable region in the gene, which alters messenger ribonucleic acid (mRNA) processing. The genetic basis of myotonic dystrophy in horses is not yet known.

▪ Diagnosis

A tentative diagnosis frequently can be made on the basis of age, clinical signs (stiff gait, particularly at the onset of exercise), muscle bulging, and prolonged contractions following muscle stimulation.

Definitive diagnosis of myotonia is usually based on electromyographic examination. Affected muscle manifests pathognomonic, crescendo-decrescendo, high-frequency repetitive bursts with a characteristic “dive bomber” sound.[29,46,49] This sound is produced by the repetitive firing (after contractions) of affected muscle fibers. After a contraction diminishes, the excitability of muscle fibers is decreased and the action potentials recorded by the EMG reflect the diminution of electrical activity.[50]

Examination of muscle biopsies from foals with myotonia congenita may be normal or may demonstrate extremely variable muscle fiber dimensions up to twice those of normal age-matched controls.[42] Type I fiber hypertrophy or hypotrophy may be seen. The major changes noted with myotonic dystrophy are ringed fibers, alterations in the shape and position of myonuclei, sarcoplasmic masses, and an increase in endomysial and perimysial connective tissue.[29,30,46,51] Fiber type grouping and atrophy of both type I and type II muscle fibers may be present.

▪ Treatment

Considering that the pathophysiologic basis of myotonia in horses has not been clearly identified, recommendations for specific, effective therapy are almost impossible. In affected humans and dogs, some relief of signs has been provided by drugs such as quinine, procainamide, and phenytoin. However, responses vary among patients. Phenytoin has been reported to be efficacious in two Quarter Horses with hyperkalemic periodic paralysis and myotonic dystrophy.[49]

▪ Prognosis

Prognosis appears to be variable and dependent on the severity of clinical signs. Mildly affected animals with congenital myotonia may undergo some amelioration of clinical signs with increasing age over a period of months to years. The reason(s) for this regression of signs is unknown. Other, more severely affected horses, particularly those with dystrophic myotonia, may have progression of signs, including atrophy and fibrosis or pseudohypertrophy to the point at which the animal is no longer able to move without great pain and difficulty (Fig. 42.5). Euthanasia of such animals is often warranted. Although conclusive evidence regarding the genetic basis of dystrophic myotonia in horses is still not available, owners of affected horses should be cautioned as to the possibility of this disease being heritable.



FIG. 42.5 Marked progressive atrophy of the epaxial and gluteal muscles of a horse with myotonic dystrophy.

Hyperkalemic Periodic Paralysis

Sharon Jane Spier

Equine hyperkalemic periodic paralysis (HYPP) is caused by an inherited defect in the skeletal muscle sodium channel.[28,52-55] This myopathy manifests as abnormal skeletal muscle membrane excitability leading to episodes of myotonia, or sustained muscle contraction, and paralysis. In humans, numerous

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muscle membrane channel defects (so-called channelopathies) have been characterized, and the molecular basis for disease is well described.[40] Other reported disorders with suspected membrane defects in horses include myotonic dystrophy and congenital myotonia.[29,42] Hyperkalemic periodic paralysis was the first equine disease attributed to a specific genetic mutation and detectable through DNA technology.[54]

Hyperkalemic periodic paralysis is an autosomal dominant trait affecting Quarter Horses, American Paint Horses, Appaloosas, and Quarter Horse crossbred animals worldwide. A “syndrome” in related horses was first recognized in the 1980s by breeders and veterinarians and first reported to be similar to HYPP in humans by Cox at the American Association of Equine Practitioners convention in 1985.[55] In December 2002, this genetic disease was publicly linked to a popular Quarter Horse sire named Impressive. This prolific sire, born in 1969, has more than 500,000 offspring registered with the American Quarter Horse Association (AQHA; AQHA registrar, personal communication, 2012), and these offspring dominate the halter horse industry. Current estimates indicate that 1.5% of Quarter Horses and 4.5% of Paints are affected.[56] Notably, however, 58% of halter horses have the HYPP mutation.[55] Unfortunately, the gene frequency has not decreased in the past 20 years since genetic testing has been available to breeders, and controversy continues among horse breeders whose stock carry this gene (statistics from UCD Veterinary Genetics Laboratory HYPP Testing, 2006). Affected horses appear to have been preferentially selected as breeding stock due to their pronounced muscle development, and there is evidence of selection of HYPP-affected horses as superior halter horses by show judges.[57] In 1996 AQHA officially recognized HYPP as a genetic defect or undesirable trait. To increase public awareness of this genetic defect, mandatory testing for HYPP with results designated on the Registration Certificate began for foals descending from Impressive born after January 1, 1998. In response to requests from the membership, the AQHA Stud Book and Registration Committee ruled that foals born in 2007 and later testing homozygous affected for HYPP (H/H) are not eligible for registration. Breeders opposed to restrictions argue that the disease can be controlled through diet and medication and that these horses are highly successful in the show ring.[58]

▪ Clinical Signs

Clinical signs among horses carrying the same mutation range from

asymptomatic to daily muscle fasciculations and weakness. In the majority of horses, intermittent clinical signs begin by 2 to 3 years of age with no apparent abnormalities between episodes.[28,53] Ingestion of diets high in potassium (>1.1%), such as those containing alfalfa hay, molasses, electrolyte supplements, and kelp-based supplements, or sudden dietary changes commonly trigger episodes.[59] Fasting, anesthesia or heavy sedation, trailer rides, and stress may also precipitate clinical signs; however, the onset of signs is often unpredictable, without a definable cause. Other possible precipitating factors that have been noted in humans and horses are exposure to cold, fasting, pregnancy, and concurrent disease and rest following exercise. Exercise per se does not appear to stimulate clinical signs, and serum CK shows no change or only modest increases during episodic fasciculations and weakness.

In most cases, clinical episodes begin with a brief period of myotonia, with some horses showing prolapse of the third eyelid. Sweating and muscular fasciculations are observed commonly in the flanks, neck, and shoulders. The muscle fasciculations become more generalized as additional muscle groups are involved. Stimulation and attempts to move may exacerbate muscular tremors. Some horses may develop severe muscle cramping. Muscular weakness during episodes is a common characteristic of HYPP. Horses remain standing during mild attacks. In more severe attacks, clinical signs may progress to apparent weakness with swaying, staggering, dog sitting, or recumbency within a few minutes. Heart and respiratory rates may be elevated, and horses may show manifestations of stress (anxious appearance) yet remain relatively bright and alert during episodes. Affected horses usually respond to noise and painful stimuli during clinical manifestations of the disorder. Episodes last for variable periods, usually from 15 to 60 minutes. Several horses have died during acute episodes. Respiratory distress occurs in some animals as a result of paralysis of upper respiratory muscles, and a tracheostomy may be necessary. In addition, young horses that are homozygous for the HYPP trait have been observed to manifest a respiratory stridor and periodically may develop obstruction of the upper respiratory tract. Horses homozygous for HYPP may present for dysphagia or respiratory distress, and endoscopic findings include pharyngeal collapse and edema, laryngopalatal dislocation, and laryngeal paralysis.[60] After the episode subsides, horses regain their feet and appear normal with no apparent or minimal gait abnormalities. Although HYPP horses appear normal between attacks, electromyographic examination of affected horses reveals abnormal fibrillation potentials, complex repetitive discharges with occasional myotonic

potentials, and trains of doublets between episodes.[28,61]

▪ Etiology

HYPP results from a point mutation that causes a phenylalanine/leucine substitution in a key part of the voltage-dependent skeletal muscle sodium channel alpha subunit.[54] In horses with HYPP, the resting membrane potential is closer to firing than in normal horses.[62] Sodium channels are normally briefly activated during the initial phase of the muscle action potential. The HYPP mutation results in a failure of a subpopulation of sodium channels to inactivate when serum potassium concentrations are increased. As a result, an excessive inward flux of sodium and outward flux of potassium ensues, resulting in persistent depolarization of muscle cells and temporary weakness (Fig. 42.6).

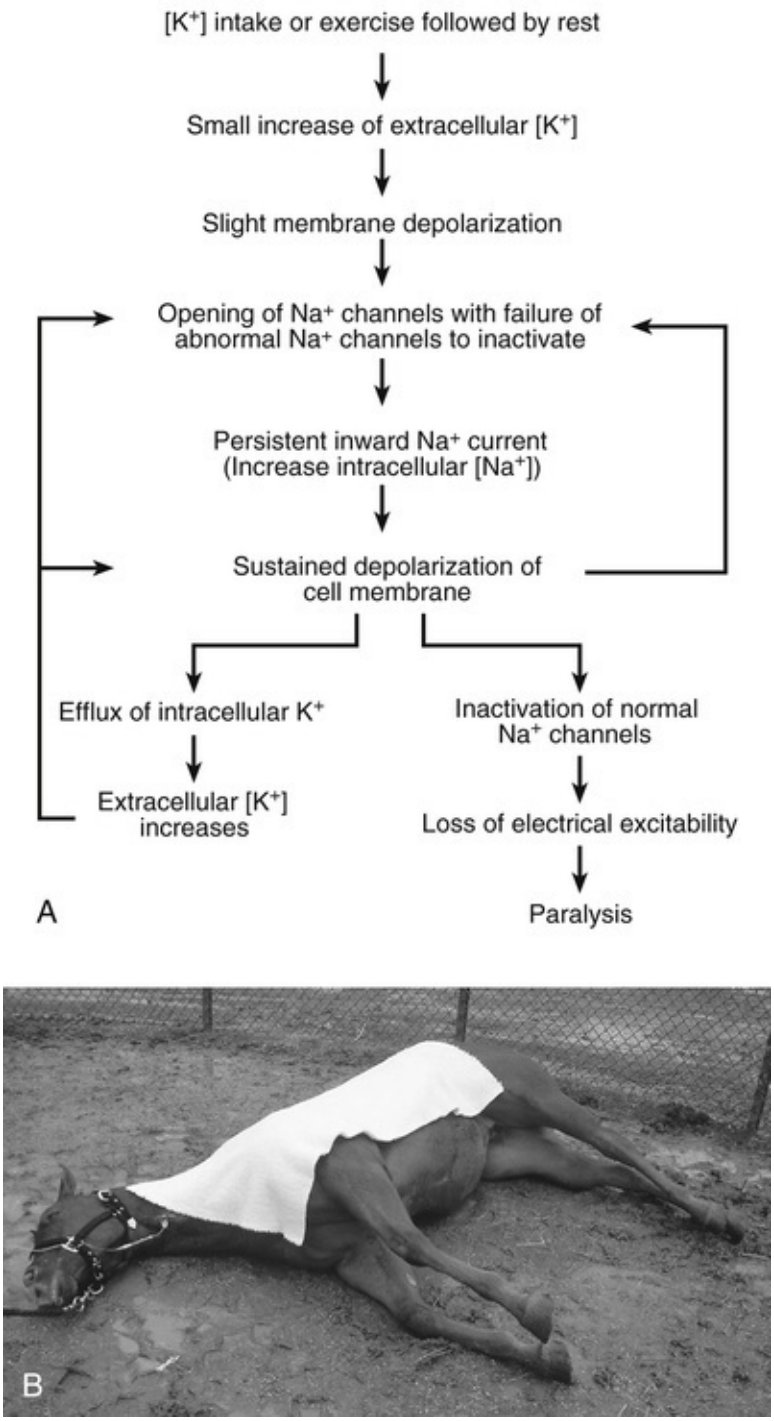


FIG. 42.6 **A,** Explanation for paralytic attacks in horses with hyperkalemic periodic paralysis (HYPP). **B,** A horse suffering from an episode of HYPP.

▪ Diagnosis

Descent from the stallion Impressive on the sire or dam's side in a horse with

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episodic muscle tremors, weakness, or collapse is strongly suggestive of HYPP. Quarter Horse foals born after 1998 that are offspring of an affected parent have a statement recommending DNA testing for HYPP on the Certificate of Registration. In most cases, hyperkalemia (6 to 9 mEq/L), hemoconcentration, and mild hyponatremia occur during clinical manifestations of the disease with normal acid-base balance.[28] Serum potassium concentration returns to normal following the abatement of clinical signs. Some affected horses may have normal serum potassium concentrations during minor episodes of muscle fasciculations.[53] Differentials for hyperkalemia include delay before sample centrifugation, hemolysis, acidosis, renal failure, severe rhabdomyolysis, and high-intensity exercise.

Because veterinarians may not be present during acute episodes, the definitive test for identifying HYPP is the demonstration of the base-pair sequence substitution in the abnormal segment of the DNA encoding for the alpha subunit of the sodium channel.[54] Submission of mane or tail hair should be made to a licensed laboratory.

▪ Treatment

Mild exercise can sometimes abort an episode in mild cases or if horses are just beginning to exhibit clinical signs. Feeding grain or corn syrup to stimulate insulin-mediated movement of potassium across cell membranes may also be helpful. Other treatment options, which may abort an episode, include intramuscular (IM) administration of epinephrine (3 mL of 0.006 mg/kg/500 kg) and administration of acetazolamide (3 mg/kg orally [PO], every 8 to 12 hours). Many horses experience spontaneous recovery from episodes of paralysis and appear normal by the time a veterinarian arrives.

In severe cases, administration of calcium gluconate (0.2 to 0.4 mL/kg of a 23% solution diluted in 1 L of 5% dextrose) will often provide immediate improvement. An increase in extracellular calcium concentration raises the muscle membrane threshold potential, which decreases membrane hyperexcitability. To reduce the serum potassium, intravenous (IV) dextrose (6 mL/kg of a 5% solution) alone or combined with sodium bicarbonate (1 to 2 mEq/kg) can be used to enhance intracellular movement of potassium. With severe respiratory obstruction, a tracheostomy may be necessary.

▪ Control

Decreasing dietary potassium and increasing renal losses of potassium are the primary steps taken to prevent HYPP episodes. Foodstuffs to avoid include high-potassium feeds such as alfalfa hay, orchard grass hay, brome hay, soybean meal, sugar molasses, and beet molasses. Optimally, later cuts of Timothy or Bermuda grass hay and grains such as oats, corn, wheat and barley, and beet pulp should be fed in small meals several times a day (Table 42.1). Regular exercise and/or frequent access to a large paddock or yard are also beneficial. Pasture works well for horses with HYPP because the high water content of pasture grass makes it unlikely that horses will consume large amounts of potassium in a short period of time. Ideally, horses with recurrent episodes of HYPP should be fed a balanced diet containing between 0.6% and 1.1% to 1.5% total potassium concentration and meals containing less than 33 g of potassium.[59,63,64] Horses will adapt to diets higher in potassium over a period of 2 weeks and will experience fewer fluctuations in potassium in blood with subsequent decreased frequency of clinical signs.[63] Because there is a wide variation in potassium concentration of forages depending on maturity and soils, it is advisable to have feeds analyzed for potassium concentrations and other nutrient requirements.[64] Table 42.1 contains examples of feeds containing varying concentrations of potassium. Supplement with vitamin E, selenium, salt, and balanced minerals where indicated to meet nutritional requirements. Commercially available complete feeds with a guaranteed potassium content may be more convenient for some HYPP horses, especially for owners with few horses.

TABLE 42.1

Examples of Feed Containing High, Medium, or Low Concentrations of Potassium (K^+)[a]

High-Potassium Feed	**K^+ (%)**	**g K^+/lb Feed**
Electrolyte supplements	30	136
Molasses	6	27
Kelp supplements	>4	>18
Alfalfa hay (90% DM)	1.4-2.4	6.4-10.9
Canary grass hay	2.6	2.6
Orchard grass hay	2.4-2.6	10.9-11.8
Soybean meal	2	9.1
Medium-Potassium Feed	**K^+ (%)**	**g K^+/lb Feed**
Fescue hay	1.7-2.1	7.7-9.5
Rice bran	1.8	8.1
Timothy hay	1.4-2.1	6.4-9.5
Coastal Bermuda hay	1.2-1.9	5.5-8.2

Kentucky bluegrass hay	1.4	6.4
Oat hay	1.4	6.4
Low-Potassium Feed	**K^+ (%)**	**g K^+/lb Feed**
Pure fats and oils	0	0
Beet pulp	0.2-0.3	0.9-1.4
Corn, oats, or barley	0.3-0.5	1.4-2.3
Pasture grass (23% DM)	0.3-0.8	1.4-3.6
Wheat	0.4	1.8
Wheat bran	1.2	5.45
Soybean hulls	1.2	5.45

[a]To decrease the frequency of episodes, avoid high-potassium feed; select feed that contains medium to low K^+. Feeding a balanced ration containing less than 1.5% K^+ and meals less than 33 g K^+ decreases fluctuations of blood K^+, lowering the frequency of HYPP symptoms.[12,15,16]

DM, Dry matter.

For horses with recurrent episodes of muscle fasciculations even with dietary alterations, acetazolamide (2 to 3 mg/kg PO, every 8 to 12 hours) or hydrochlorothiazide (0.5 to 1 mg/kg PO, every 12 hours) may be helpful. These agents exert their effects through different mechanisms; however, both cause increased renal potassium excretion. In addition, acetazolamide stabilizes blood glucose and potassium by stimulating insulin secretion. Breed registries and other associations may have restrictions on the use of these drugs during competitions, as diuretics may mask prohibited substances.

▪ Prognosis

In most cases HYPP is a manageable disorder, although recurrent bouts may occur and severe episodes can be fatal. Owners of affected horses should be strongly discouraged from breeding these animals for the long-term health of the Quarter Horse and other breeds. Because this is a dominant trait, breeding an affected horse to a normal horse results in a 50% chance of producing a foal with HYPP. All affected horses share the same mutation, regardless of whether owners have witnessed symptoms in their horses.[65] Affected horses are not suitable for young or inexperienced riders. Owners of affected horses should advise veterinarians of HYPP status before anesthesia or procedures requiring heavy sedation because these circumstances could precipitate an episode of paralysis.

HYPP-Like Syndrome

Other cases of generalized muscle fasciculations arise in horses after forced exercise or transportation, or in some cases for unknown reasons that last for an

hour or less. Horses present with fasciculations in the flanks, lateral neck, and shoulders that can gradually became more generalized. In some cases horses can progress to apparent weakness characterized by swaying, staggering, buckling at the knees, and a basewide stance. An elevated serum potassium at the time of attack has been documented in a Criollo horse.[66] The cause of this type of HYPP-like episode has yet to be determined.

Hypokalemic Myopathy in Dairy Cattle

▪ Etiology

Hypokalemic myopathy in dairy cattle occurs when serum potassium concentrations are below 2.5 mmol/L, producing severe signs of muscle weakness.[67-69] Ketosis, anorexia, and enhanced potassium excretion due to the administration of one or more doses of isoflupredone acetate to ketotic cows are common causes of hypokalemia. Isoflupredone acetate has both glucocorticoid and mineralocorticoid activity, resulting in a decrease in mean plasma potassium concentration by 25% two days after one injection (20 mg) and by 46% in cows 3 days after two injections.

▪ Clinical Signs and Diagnosis

Clinical signs of hypokalemic myopathy include severe weakness, recumbency, abnormal position of the head and neck, rumen hypomotility or atony, abnormal feces, anorexia, and tachycardia. Cardiac dysrhythmia is also common. Diagnosis is based on clinical signs combined with serum potassium of less than 2.5 mmol/L. Other common clinical chemistry abnormalities include ketosis, metabolic alkalosis, and elevated serum CK and AST activities. Muscle biopsies reveal a vacuolar myopathy.

▪ Treatment

Restoration of whole body potassium balance can be difficult, and serum potassium concentrations do not necessarily reflect muscle potassium concentrations. Recommended supplementation includes potassium chloride given orally (0.1 to 0.4 g/kg body weight), not to exceed 230 g potassium chloride orally per 24 hours. Reserve IV potassium (20 to 40 mEq potassium per liter IV solution, up to 80 mEq/L) for recumbent ruminants with severe hypokalemia and rumen atony. Do not to exceed a maximum infusion rate of 0.5

mEq/kg/h. Early treatment should also be directed at resolving the primary cause of ketosis and anorexia, as well as providing supportive care. Survival has been reported at between 22% and 79%.

Muscle Cramping

Stephanie J. Valberg • Gary P. Carlson

Muscle cramps are a painful condition that arises from hyperactivity of motor units caused by repetitive firing of the peripheral and/or central nervous system. The origin of the cramp in most cases is believed to be the intramuscular portion of the motor nerve terminals.[22,70] Most muscle cramps are also accompanied by fasciculations in the same muscle. Muscle cramps can be induced by forceful contraction of a shortened muscle, by changes in the electrolyte composition of extracellular fluid, and by ear tick infestations in horses.[22,31] In contrast, muscle contractures are painful muscle spasms that represent a state of muscle contracture unaccompanied by depolarization of the muscle membrane.[70] Muscle contractures occur with malignant hyperthermia and some forms of exertional myopathies and are invariably accompanied by markedly increased serum CK activity.

Dietary Electrolytes

Muscle stiffness, weakness, and occasional elevations in serum CK can occur when diets are deficient in sodium or potassium. These chronic deficiencies are rarely reflected in serum electrolyte concentration but may be detected by performing renal fractional excretions of electrolytes.[3] Sodium deficiency is particularly common in horses because forage and grain diets are low in sodium and chloride and high in potassium. Supplementation of the equine diet with salt is a necessity. Salt blocks may not be adequate in this regard, and loose salt (1 to 2 oz) added directly in the grain is often the best mechanism of supplementing horses with salt. Some horses may require higher dietary salt supplementation to maintain an adequate sodium balance. Balancing dietary electrolytes has been reported to decrease muscle cramping and serum CK activity in those horses with dietary deficiencies.[3]

Exhaustion in Endurance Horses

Muscle cramping in endurance horses occurs commonly during prolonged

exercise in hot weather, particularly when the humidity is high.[71,72] Under such circumstances rectal temperatures reach as high as 41° C, and horses may lose up to 15 L/h of fluids in the form of sweat that is rich in sodium, potassium, and chloride.[73,74]

▪ Clinical Signs

Affected horses demonstrate stiffness and cramping in the muscles of locomotion. Pain is a characteristic of the disorder, and affected muscle groups often undergo periodic spasms. In addition, exhausted horses are often dull, depressed, and clinically dehydrated with elevated heart and respiratory rates and persistently elevated body temperature. Common electrolyte abnormalities include a hypochloremic metabolic alkalosis with hypokalemia, hypomagnesemia, and low serum ionized calcium concentrations.[71,72,75] Synchronous diaphragmatic flutter may be seen in association with cramping.[71] Although many of the signs of muscular dysfunction are similar to those of exertional rhabdomyolysis, affected horses do not generally develop myoglobinuria.[71]

▪ Etiology

Factors contributing to cramping are dehydration, electrolyte abnormalities, and disturbances in thermoregulatory and local circulatory function. Whether this disorder is similar to heat cramps seen in human athletes is not known.

▪ Diagnosis

A variety of electrolyte abnormalities occur in affected animals.[71,75] Mild cases are distinguished by the presence of muscle cramps that subside with rest or light exercise in heat-stressed horses. In more severe cases clinical signs of dehydration and shock are often present. Horses with muscle cramping will not have marked elevations in serum CK or AST, nor will they exhibit myoglobinuria. Exhausted horses, however, may progress to develop rhabdomyolysis with marked electrolyte derangements. These horses require immediate treatment.

▪ Treatment

Under most circumstances the mild form of muscle cramping is self-limiting,

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and the signs abate with rest or light exercise. However, if evidence of other metabolic derangements exists, treatment for these disorders (e.g., plasma volume expansion with oral or intravenous isotonic polyionic fluids, cooling using water and fans) is frequently beneficial to the horse.[76] Because most horses with this condition are alkalotic, administration of solutions containing sodium bicarbonate is contraindicated. Dietary analysis should be performed to determine the extent of salt and electrolyte supplementation in affected horses. Daily direct addition of 2 oz of sodium chloride and 1 oz of potassium chloride to the feed is recommended for horses with recurrent cramping in addition to electrolyte supplementation before and after endurance rides.

Synchronous Diaphragmatic Flutter

Synchronous diaphragmatic flutter (SDF), also known as “thumps,” usually occurs in horses suffering from derangements in fluid and electrolyte balance. Inciting causes include endurance exercise, hypocalcemia, hypoparathyroidism, digestive disturbances, and possibly the administration of medications. A characteristic clinical manifestation of the disease occurs when the diaphragm contracts in synchrony with atrial depolarization.[77-79]

▪ Clinical Signs

The classic sign of SDF is a contraction or twitch in the flank region (unilateral or bilateral) as the diaphragm contracts synchronously with the heart. In severe cases this twitch may produce an audible thumping sound. The metabolic derangements leading to SDF may also be clinically apparent in some cases. These may include signs of dehydration and volume depletion. Endurance horses suffering from SDF in association with the exhausted horse syndrome may demonstrate dehydration, inappropriate sweating responses, persistently elevated body temperature, depression, anorexia, and aperistalsis.[71,72] In some horses SDF may be a chronic, recurring problem.[77]

▪ Etiology

A variety of stimuli may result in SDF. These include prolonged exercise, particularly during hot weather; hypocalcemia resulting from lactation, transit, or stress; digestive tract dysfunction; furosemide therapy; trauma; and primary hypoparathyroidism.[77,79] The most consistent metabolic derangement reported in

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horses with SDF is low serum ionized calcium concentrations usually associated with hypochloremic metabolic alkalosis.[77,78] Metabolic alkalosis may alter the ratio of free to bound calcium (increasing calcium binding to protein and decreasing ionized calcium), which possibly induces SDF.

SDF occurs in association with atrial depolarization in horses. It has been postulated that fluid, electrolyte, and acid-base derangements may disrupt the normal membrane potential of the phrenic nerve, which passes directly over the atrium, resulting in nerve discharges in response to atrial depolarization.[77,78,80]

▪ Treatment

In most cases SDF is a transient event, usually abating when the underlying cause resolves, either spontaneously or in response to treatment.[77] Most horses undergo rapid remission of signs when given calcium solutions intravenously, as described in the Hypocalcemia in Horses section later. Although hypomagnesemia is often present with SDF, horses do not respond to magnesium supplementation unless calcium is administered concurrently. Response to therapy is also reflected by improved mental status, return of appetite, and gut motility.[77]

▪ Control

Electrolyte supplementation and some dietary manipulations may help to reduce the incidence of SDF in some endurance horses suffering recurrent bouts. Providing chloride, potassium, and sodium during prolonged exercise may help to reduce fluid losses and the metabolic alkalosis that commonly accompanies this form of exercise and frequently occurs in association with SDF. Metabolic alkalosis decreases the amount of free calcium available. Supplementation of calcium and magnesium during endurance rides has been suggested as helpful in horses prone to SDF.

Alternative approaches involve reduction of dietary calcium in horses prone to SDF for a few days before an endurance ride. It is postulated that this reduction in dietary calcium stimulates the endocrine homeostatic mechanisms and increases osteoclastic activity. In the short term the horse depends less on dietary calcium and is able to mobilize substantial amounts of calcium in response to the demands imposed by the exercise; calcium losses in sweat are overcome by the release of calcium from endogenous storage pools (bone).[77] Further, horses routinely fed alfalfa hay, which has a relatively high calcium concentration, may

be more prone to the development of SDF. Limitation of this foodstuff may be indicated in chronically affected horses.

Hypocalcemia in Horses

Hypocalcemia is a relatively rare disorder in horses that has also been referred to as *lactation tetany, transport tetany, idiopathic hypocalcemia*, and *eclampsia.*

▪ Clinical Signs

Clinical signs are variable and include increased muscle tone; a stiff, stilted gait; rear limb ataxia; muscle fasciculations (especially temporal, masseter, and triceps muscles); trismus; dysphagia; salivation; anxiety; profuse sweating; tachycardia; elevated body temperature; cardiac dysrhythmias; SDF; convulsions; coma; and death.[81,82] Clinical signs may be remarkably similar to some of those seen with tetanus. This disorder may be progressive (in lactating mares in particular) over a 24- to 48-hour period, and some animals die. Clinical signs are related to the magnitude of the serum calcium concentration. Increased excitability is usually the only sign when values are below normal but above 8 mg/dL. Values of 5 to 8 mg/dL usually produce tetanic spasms and incoordination. Concentrations below 5 mg/dL usually result in recumbency and stupor.

▪ Etiology

Loss of calcium in milk, especially in mares that produce large amounts of milk, seems to predispose to this disorder.[81,82] Other factors, such as heavily lactating mares grazing lush pastures, hard work or prolonged transport, and ingestion of blister beetles (cantharidin toxicosis), may precipitate attacks. Primary hypoparathyroidism has also been diagnosed in a 3-month-old hypocalcemic warmblood foal with weakness and muscle trembling.[83]

▪ Diagnosis

Clinical signs are often highly suggestive of hypocalcemia in affected horses. Historic aspects such as lactation, previous prolonged exercise, or transport may also direct the clinician to the suspected diagnosis.[81] Definitive diagnosis depends on laboratory demonstration of hypocalcemia, with total calcium concentrations as low as 4 to 6 mg/dL in some cases. In addition, metabolic

alkalosis, hypomagnesemia or hypermagnesemia, and hyperphosphatemia or hypophosphatemia have all been found in association with hypocalcemia in horses.[81] These alterations may need correction before a return to normal function is seen in some affected animals.

▪ Treatment

Although many mild cases recover without specific treatment, in others this disorder may be life threatening. Therefore therapy should be encouraged in most cases. Treatment involves the IV administration of calcium solutions such as 20% calcium borogluconate or those recommended for the treatment of parturient paresis in cattle.[81] Administration of these solutions at the rate of 250 to 500 mL/500 kg diluted 1:4 with saline or dextrose often results in full recovery, although in some cases it may take several days.[81] Relapses do occur. These preparations should be administered slowly in conjunction with close monitoring of the cardiovascular response. Dilution in saline or dextrose before infusion decreases the chance of cardiotoxicity. Normally there is a positive ionotropic effect in response to calcium administration.[84] However, alterations in rate or rhythm provide evidence to suspend the infusion. If no response to an initial infusion occurs, a second dose may be given 15 to 30 minutes later. Most cases respond to this form of therapy, although in some cases in which signs persist, repeated treatments may be necessary.

Ear Tick–Associated Muscle Cramping

Intermittent painful muscle cramps have been described in a small number of horses with severe *Otobius megnini* infestations.[31] Muscle cramping is not associated with exercise. These horses show intermittent signs of severe muscle cramping of pectoral, triceps, abdominal, or semitendinosus and semimembranosus muscles lasting from minutes to a few hours, with severe pain that often resembles colic. Horses may fall over when stimulated. Between muscle cramps, horses appear to be normal. Percussion of triceps, pectoral, or semitendinosus muscles results in a typical myotonic cramp. Horses have elevated serum CK activities ranging from 4000 to 170,000 IU/L. Numerous ear ticks *(O. megnini)* can be identified in the external ear canal of affected horses. Without treatment for ear ticks, the spasms continue; however, local treatment of the ear ticks using pyrethrins and piperonyl butoxide results in recovery within 12 to 36 hours. Acepromazine may be helpful to relieve painful cramping.

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Nonexertional Rhabdomyolysis

Inflammatory Myopathies

Clostridial Myonecrosis

Steven M. Parish • Stephanie J. Valberg

Various species of clostridial organisms cause acute myonecrosis in many farm animal species. Infections are characterized by a rapid clinical course, fever, systemic toxemia, and high mortality.[85-87] Clostridial diseases are infectious but not contagious. Specific bacteria associated with clostridial myonecrosis include *Clostridium chauvoei (Clostridium welchii), Clostridium septicum, Clostridium sordellii,* and occasionally *Clostridium novyi* type B, *Clostridium perfringens* type A, and *Clostridium carnis.* Mixed infections involving several agents are common.[88] Synonyms for clostridial diseases include blackleg, malignant edema, false blackleg, gas gangrene, and gangrene. Although there may at times be distinct differences among the specific disease syndromes associated with the different clostridial agents, the pathophysiology of these diseases is similar enough to be covered under the general topic of clostridial myonecrosis.

▪ Clinical Signs

Commonly, clostridial myonecrosis is rapidly progressive with the development of tremors, ataxia, dyspnea, recumbency, coma, and death within 12 to 24 hours. As such, many affected animals may be found prostrate or dead.[85,86,88] Mortality may approach 100%. Affected animals who are still alive are usually severely depressed, febrile (40° to 41° C/104° to 106° F), tachypneic, anorexic, and lame. These signs are associated with a rapidly developing muscle infection and toxemia. There is usually only one primary site of infection in an affected animal. Any skeletal muscle group in the body can be involved, but most infections affect the limb or trunk muscles. Occasionally muscles such as those around the vulva, tongue, and diaphragm can be involved, or the udder in a cow may be the primary site of sepsis. Areas around recent injections are common sites of myonecrosis in the horse.[87,89] Initially the skin over the area may be swollen, hot, and discolored; however, as the disease progresses, the skin over

the area may become cool and insensitive with progressive sloughing. Crepitus may be detectable, indicating subcutaneous gas production. If a wound is present, malodorous serosanguineous fluid may discharge (Fig. 42.7). Aspiration of the swelling often reveals fluid with similar qualities.



FIG. 42.7 Clostridial myositis in the left gluteal muscle after an injection of flunixin meglumine, which has progressed to involve the biceps femoris muscle. Fenestrations were created for débridement.

Clostridial myonecrosis generally has characteristic pathologic lesions that are absent in most other conditions, making diagnosis relatively straightforward. Differential diagnoses may include other fulminant disease processes in which there is rapid debilitation or death of the animal.

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▪ Clinical Pathology

Clinicopathologic data alone are seldom specific enough to confirm the presence of clostridial myonecrosis. Hematology and serum biochemical analyses usually reflect a generalized state of debilitation and toxemia (e.g., hemoconcentration and a stress/toxic leukogram may be present). Elevations in the activities of serum CK and serum AST usually occur; however, they often do not reflect the toxicity of clostridial myonecrosis. Aspirates from the affected tissues can yield diagnostic information. It is preferable to obtain tissue specimens for direct smear examination and fluorescent antibody testing, and for anaerobic bacterial culture from affected tissues.

▪ Pathophysiology

Clostridial agents are ubiquitous in the environment and can frequently be cultured from the feces, intestinal tract, and other internal organs of a variety of species.[85] Spore-forming characteristics allow these organisms to remain in the environment for long periods, but the exact mechanisms involved in the pathogenesis of clostridial myonecrosis are not fully known. Development of clostridial myonecrosis following an intramuscular injection or penetrating wound may be the result of direct spore deposition into the tissue in association with penetration. If suitable conditions prevail within the muscle, the spores undergo a conversion into the vegetative, toxin-producing form of the organism. In contrast, the pathogenesis of the disease is more difficult to explain when a wound does not exist. It is postulated that clostridial agents gain access to the body through the alimentary tract and are present in liver and muscle in the dormant spore form.[90] Subsequently, when local tissue is devitalized and conditions become appropriate for the spores to germinate, the rapid vegetative process ensues. Muscle trauma associated with injection, transporting, herding, and handling has often been incriminated as creating a suitable environment for the development of clostridial myonecrosis. The proliferation of clostridial agents in devitalized tissues is associated with the release of powerful exotoxins responsible for the local necrotizing myositis and systemic toxemia. Toxins are released by multiplying clostridia; the toxins vary, depending on the clostridial species involved. Necrotizing (lecithinase) and hemolyzing (hemolysin) toxins, as well as neuraminidase, appear to be of greatest importance. The toxins act locally and systemically to create widespread organ dysfunction. The toxins of *C. sordellii* are the most potent of all the clostridial species, and myonecrosis

caused by this organism is fatal.

▪ Epidemiology

Clostridial agents are common in the environment, and susceptible animals are constantly exposed to them. Areas where previous death losses from clostridial disease have occurred may have a higher incidence or risk of disease because of increased environmental contamination. In cattle, clostridial myonecrosis is generally a disease of animals between 4 and 24 months of age. However, *C. sordellii* is a more common problem in older feedlot cattle in which excessive muscle bruising may occur. Younger animals are probably protected by colostral immunity and older animals by some degree of acquired immunity. Animals on high planes of nutrition and in excellent body condition are more likely to develop the disease. Infections with *C. chauvoei* occur most commonly during the warmer seasons, with the highest incidence varying from the spring to fall, depending on when calves reach the most susceptible age group. *C. septicum, C. novyi,* and *C. perfringens* type A infections can occur at any time and are usually associated with skin wounds such as injection sites, punctures, and castration wounds. The umbilicus may be a site of invasion. Infections in the genital area can occur, usually in association with a recent dystocia.

In sheep and goats, clostridial myonecrosis is most frequently associated with wounds such as those occurring after shearing, docking, and unsanitary surgical procedures. Sheep dipped for parasites after shearing may have an increased risk if the dip becomes contaminated with clostridial spores.

Most reports of clostridial myonecrosis in horses suggest an association with puncture wounds and intramuscular injection sites.[87,89] Intramuscular administration of irritating drugs (including antihistamines, anthelmintics, and phenylbutazone) may enhance the susceptibility to clostridial myonecrosis. Horses often present with or have a history of another complaint such as colic, exertional myopathy, or laminitis for which they have received injections of drugs in the preceding 48 hours.[91] Previously administered drugs (e.g., phenylbutazone) may mask the fever associated with clostridial myonecrosis, potentially confusing the diagnosis.

▪ Necropsy Findings

Swelling and autolysis are rapid in animals that have died from clostridial myonecrosis. Blood-stained fluid is often observed discharging from body

orifices. Extreme swelling and crepitus may be noted over the affected body area. When acting alone, each of the clostridial agents associated with clostridial myonecrosis produces somewhat different postmortem lesions. However, it is unwise to assume that in clostridial myonecrosis only a single clostridial agent was involved because mixed infections frequently occur.

C. chauvoei infection is characterized by engorgement of the subcutis and adjacent tissues with blood-stained fluids and gas bubbles. Cut tissue from the affected area reveals moist, dark-colored muscle in the periphery of the lesion, with lighter colored, drier muscle with gas bubbles separating the separate bundles of muscle toward the center. Other changes include severe degeneration of parenchymatous tissues caused by the systemic toxemia. The carcass usually has a foul odor similar to that of rancid butter. This odor is a characteristic of most cases of clostridial myonecrosis. The lungs are often congested with edema, and hemorrhage and a fibrinohemorrhagic pleuritis are common. The heart may be friable and show evidence of endocardial hemorrhages, particularly on the right side. The spleen may be normal or enlarged and friable. The liver is usually pale and friable and may be autolytic and porous. Lesions are similar in sheep and cattle, except that there is usually less gas and the muscles are not as dry in affected sheep.

Similar necropsy findings are found with myonecrosis caused by *C. septicum* and *C. novyi* type B. *C. septicum* and *C. perfringens* generally occur as part of mixed wound infections in which abundant malodorous, serosanguineous fluid is found at the wound site. *C. perfringens* is common in horses.

Myonecrosis resulting from *C. sordellii* is most often associated with lesions of the neck or brisket area of cattle. Death is frequently so rapid that subcutaneous gas accumulation is rare. In addition to local myonecrosis, these animals often have massive subendocardial hemorrhages in the left ventricle of the heart and hemorrhage in the trachea, bronchi, and thymus. Extensive perirenal edema and hemorrhagic renal calyces and severe congestion of the lungs are common findings.

▪ Treatment

Although clostridial myonecrosis is often fatal, aggressive specific therapy combined with supportive care may be successful in individual cases. A presumptive diagnosis of clostridial disease on the basis of history and clinical signs is usually made before obtaining the results of culture and laboratory determinations such as fluorescent antibody tests. In horses, clostridial

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myonecrosis resulting from infections with *C. perfringens* seems to be most amenable to treatment and has the best prognosis for survival, although extensive skin sloughing over the affected area is common.[87] Antibiotic therapy, aggressive surgical débridement including fasciotomy, and supportive care are the hallmarks of successful treatment.[87] With most clostridial infections, penicillin is the drug of choice. In horses, Na or K penicillin IV or procaine penicillin IM is used at a dosage of 44,000 U/kg IV every 2 to 4 hours until the animal is stable (1 to 5 days). The IV dose is then reduced to four times a day or is replaced by oral metronidazole (15 mg/kg three or four times daily). In ruminants, similar intravenous or intramuscular drug therapy is indicated. In all cases, prolonged antimicrobial therapy may be necessary.

Surgical intervention at the affected site by means of débridement or fenestration in an attempt to reduce tissue swelling, aerate the tissues, and remove necrotic tissue is considered imperative for survival in horses (see Fig. 42.7). Incisions are made through the skin and into the affected muscle to establish adequate drainage and hopefully alter the anaerobic conditions. Sufficient fenestrations should be made to establish drainage and aeration over the entire affected area.

Use of specific antitoxins is recommended when possible. However, these are often not available or not used for immediate therapy because the exact species of *Clostridium* causing the myonecrosis is not known. Cost considerations may also preclude their use. Supportive fluid therapy and use of analgesics and anti-inflammatory agents for control of pain and swelling are recommended. Short-acting corticosteroids such as dexamethasone, prednisolone, or hydrocortisone may be used for initial therapy of systemic and toxic shock, but continued use is contraindicated in the face of overwhelming sepsis. If required, specific therapy should also be directed toward any other underlying problems.

▪ Prognosis

The prognosis for life in all cases of clostridial myonecrosis is guarded to poor. The disease process is often rapidly fulminant, making treatment unrewarding. However, some animals have survived because of early diagnosis, aggressive therapy, and long-term supportive care. This is particularly true in cases involving *C. perfringens* in horses. The owner should be aware from the start of treatment that extensive skin sloughing may involve most of a limb and may force euthanasia to become a consideration at a later stage.

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▪ Prevention

Protection against clostridial myonecrosis is based on immunization procedures. Although clostridial agents are ubiquitous in the environment and frequently appear in the body of susceptible animals, rarely does adequate natural protection occur, although some colostral and acquired immunity may at times occur. Infection in unprotected animals usually follows a rapid, degenerative clinical course and terminates before the animal can generate an appropriate protective immune response. At present, only ruminants are commonly vaccinated against the agents responsible for clostridial myonecrosis. Vaccines used include multivalent bacterin toxoids containing antigens against two or more clostridial species, including *C. chauvoei, C. septicum, C. novyi, C. sordellii*, and *C. perfringens.* A rational program for protection usually involves vaccinating at an early age to establish immunity. Vaccination age is partly determined by other management factors, including when calves are handled for branding and castration, but 4 to 6 months of age is the usual time of initial vaccination. In areas of heavy exposure it may be necessary to vaccinate at 3 months and again at 4 months. In all clostridial species except *C. chauvoei,* two doses of vaccine are necessary to establish good protection. The duration of immunity is not long, and booster vaccinations should be administered every 6 to 8 months if protection is to be maintained. In many herds it is only necessary to vaccinate animals younger than 3 years of age (i.e., those animals that are at greatest risk), but in some high-risk herds it is necessary to maintain a vaccination program for the life of the animal.

Animals that die of clostridial diseases should be disposed of by deep burial, burning, or removal from the premises to avoid further contamination of the environment.

Rhabdomyolysis Associated With *Streptococcus equi*

Stephanie J. Valberg

Acute Rhabdomyolysis

Severe acute generalized rhabdomyolysis has been reported to occur in Quarter Horses younger than 7 years of age.[92,93] Affected horses have evidence of submandibular lymphadenopathy and/or guttural pouch empyema due to

Streptococcus equi. Horses develop a stiff gait, which progresses rapidly to markedly firm, swollen, painful epaxial and gluteal muscles. The majority of reported cases became recumbent and unable to rise. They developed unrelenting pain necessitating euthanasia within 24 to 48 hours of hospitalization (Fig. 42.8). Hematologic abnormalities include mature neutrophilia, hyperfibrinogenemia, and marked elevations in CK (115,000 to 587,000 U/L) and AST activities (600 to 14,500 U/L). Titers to the M protein of *S. equi* are low in affected horses, unless horses have been recently vaccinated for strangles. Titers to another protein called myosin binding protein have been high in a small number of horses that were tested.[92]



FIG. 42.8 A horse in severe pain unable to rise due to acute rhabdomyolysis concurrent with guttural pouch empyema from *Streptococcus equi*.

At postmortem examination, large pale areas of necrotic muscle are evident in hindlimb and lumbar muscles. The histopathologic lesions are characterized by severe acute myonecrosis with a degree of macrophage infiltration. Sublumbar muscles often show the most severe and chronic necrosis as indicated by greater macrophage infiltration of myofibers.

One possibile etiology is a toxic shock–like reaction arising from profound nonspecific T-cell stimulation by streptococcal superantigens with the release of high levels of inflammatory cytokines. An alternative explanation for rhabdomyolysis may be a bacteremia with local multiplication and production of

exotoxins or proteases within skeletal muscle. *S. equi* virulence factors that may account for muscle necrosis include an unidentified cytotoxic protein, several proteases, streptokinase, and streptolysin S.[94] Although *S. equi* has not been cultured in skeletal muscle from horses with rhabdomyolysis, *S. equi* bacteria have been identified in affected muscle using immunofluorescent stains for both Lancefield group C carbohydrate and *S. equi* M protein.[92] There is currently no evidence that the *S. equi* involved is an atypical genetic strain of *S. equi*.[95] Most recently, a mutation in the gene *MYH1* has been identified in association with immune-mediated myositis, and this mutation may also be responsible for cases of *S. equi*–associated myopathy (see the Immune-Mediated Myositis section).

A high mortality rate has been reported in horses receiving intravenous penicillin therapy once clinical signs of strangles and myopathy were well established. It is possible that early recognition of the signs of muscle stiffness in horses with *S. equi* infections and prompt aggressive treatment may be required for a successful outcome. Although streptococcal species are exquisitely susceptible to β-lactam antibiotics, a mortality rate of 85% has been reported in human group A streptococcal myositis despite penicillin treatment.[96] An antimicrobial that inhibits protein synthesis, such as rifampin, combined with intravenous penicillin might enhance survival rates in horses with *S. equi* rhabdomyolysis. In addition, flushing infected guttural pouches and draining abscessed lymph nodes will diminish the bacterial load. Nonsteroidal antiinflammatory drugs (NSAIDs) and possibly high doses of short-acting corticosteroids may assist in diminishing the inflammatory response. Control of unrelenting pain is a major challenge in horses with severe rhabdomyolysis. Constant rate infusion of lidocaine, detomidine, or ketamine may provide better anxiety and pain relief than periodic injections of tranquilizers. Horses should be placed in a deeply bedded stall and moved from side to side every 4 hours if they are unable to rise. Some horses may benefit from a sling if they will bear weight on their hindlimbs when assisted to stand.

Infarctive Purpura Hemorrhagica

Stephanie J. Valberg

Infarctive purpura hemorrhagica (IPH) is a severe form of purpura with a high fatality rate. In one study, prevalence of IPH was 3 of 53 cases of purpura.[97] Exposure to *S. equi* within 3 weeks of presentation, vaccination for *S. equi,* and a concurrent *Salmonella infantum* infection are reported as inciting causes. Titers

for serum enzyme-linked immunosorbent assay (ELISA) M protein may be markedly elevated.[98] The primary presenting complaint is often painful lameness with limb swelling, muscle stiffness, and/or colic. Careful physical examination reveals classic signs of purpura hemorrhagica such as petechia, oral infarctions resembling ulcers, and moderate well-demarcated limb edema; however, in addition, horses with IPH will have focal firm intramuscular swellings (Fig. 42.9). Horses with evidence of colic may have markedly decreased borborygmi and hemorrhagic gastric reflux.



FIG. 42.9 Marked swelling of the right adductor muscles of the thigh due to infarctive purpura hemorrhagica.

Hematologic abnormalities include a leukocytosis characterized by a neutrophilia with a left shift and toxic change, hyperproteinemia,

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hypoalbuminemia, and marked elevations in CK (47,000 to 280,000 U/L) and AST (960 to 7000 U/L) activities.[93,98] Peritoneal fluid obtained by abdominocentesis may be normal or may have an increased total protein, nucleated, and RBC counts if gastrointestinal infarction is present. Ultrasonographic examination of swollen muscle reveals focal hypoechoic lesions within muscle tissue. Biopsies of abnormal muscle show diffuse acute coagulative necrosis, whereas samples from palpably normal muscle tissue show no pathologic abnormalities.

Postmortem findings of horses with IPH include infarction of the skeletal musculature (Fig. 42.10), skin, gastrointestinal tract, pancreas, and lungs, as well as *S. equi* abscessation of a lymph node. Definitive histopathologic findings include leukocytoclastic vasculitis and acute coagulative necrosis resembling infarction in numerous tissues.[98] IPH resembles Henoch-Schönlein purpura in humans, which is characterized by infarctive vasculitis of the skin, kidneys, and gastrointestinal tract due to immunoglobulin A (IgA) immune complex deposition. Immune complexes are present in the sera of horses with purpura hemorrhagica that appear to be primarily composed of IgM or IgA and streptococcal M protein.[99] Deposition of complement near immune complexes in vessel walls may result in cell membrane destruction, cell death, and vascular occlusion. The distinctive feature of IPH in horses is the extensive infarction of skeletal muscle and consequently marked elevation in serum CK and AST activity.

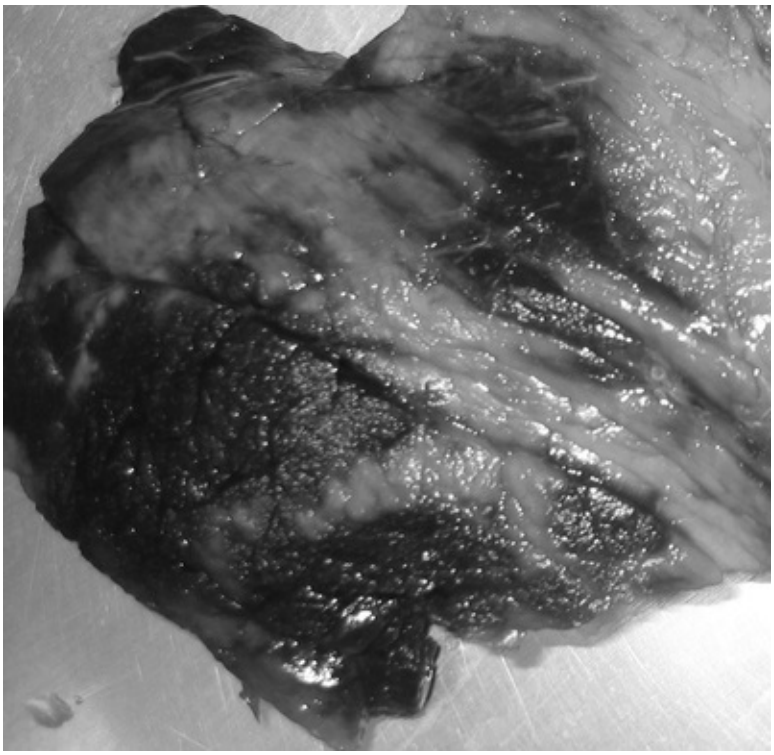


FIG. 42.10 Numerous infarctions of skeletal muscle due to infarctive purpura hemorrhagica. (Courtesy Dr. Beth Davis.)

Early recognition of signs and aggressive antibiotic and corticosteroid treatment are essential to combat the high fatality rate with IHP. Treatment of Henoch-Schönlein purpura in humans, including cases with intestinal infarctions, involves high-dose intravenous pulse therapy with methylprednisolone followed by oral corticosteroids plus immunosuppressive agents such as cyclophosphamide and azathioprine. One horse with IPH was successfully treated with penicillin, NSAIDs, and 3 weeks of dexamethasone (0.01 to 0.07 mg/kg IM or IV) followed by a 10-week tapering course of oral prednisolone (2 mg/kg initially).[95]

Immune-Mediated Myositis

Stephanie J. Valberg

The majority of horses with immune-mediated myositis (IMM) are of Quarter Horse bloodlines and are either 8 years of age or younger or 16 years of age or older.[26,100-102] In approximately 40% of horses with IMM, a triggering factor appears to have been exposure to *S. equi* or a respiratory disease. The most prominent clinical sign of IMM in Quarter Horses is rapid onset of muscle atrophy, particularly affecting the back and croup muscles (Fig. 42.11),

accompanied by stiffness and malaise. Atrophy may progress to involve 50% of a horse's muscle mass within a week and may lead to generalized weakness.

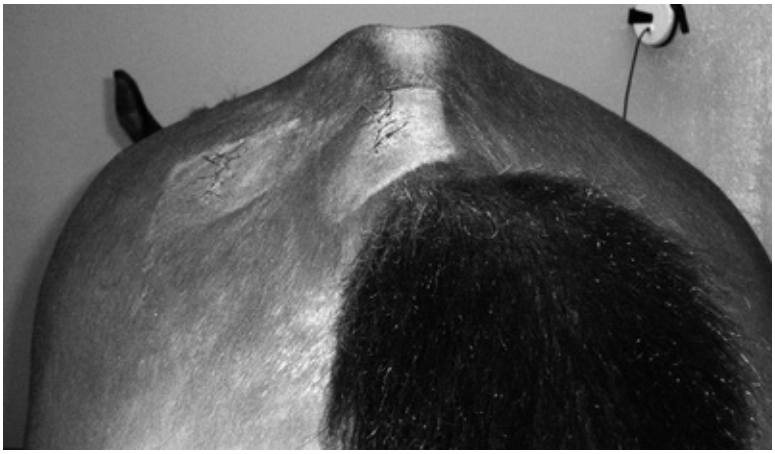


FIG. 42.11 Symmetric atrophy of the gluteal muscles with immune-mediated myositis. (Courtesy Dr. Beth Davis.)

Hematologic abnormalities are relatively minor in affected Quarter Horses unless a concurrent infection is present and are usually restricted to mild to moderate elevations in serum CK and AST activity. However, in some cases with chronic atrophy, serum muscle enzyme activities are normal. Muscle biopsy of epaxial and gluteal muscles shows lymphocyte vasculitis, angular atrophy, lymphocyte myofiber infiltration, fiber necrosis with macrophage infiltration, and regeneration. Biopsies of semitendinosus or membranous muscles may show some evidence of atrophy and vasculitis, but significant inflammatory infiltrates may be absent in these tissues. The extent of the inflammatory infiltrates in epaxial muscles is such that a diagnosis can often be established from several formalin fixed Tru-Cut samples.

The lymphocytic infiltrate seen in muscle samples from horses with IMM contains a high CD4/CD8 ratio with no evidence of IgG binding to myofibers and some upregulation of major histocompatibility Class I and II staining on muscle cell membranes.[26,103] Recently, a mutation in the gene encoding type 2X myosin heavy chain was found to be associated with IMM in Quarter Horse–related breeds.[104] Genetic testing for IMM will soon be available.

Horses with concurrent evidence of streptococcal infection should be treated with antibiotics. It is likely prudent to avoid intramuscular injections. Administration of corticosteroids appears to immediately improve signs of

malaise and inappetence and prevented further progression of muscle atrophy. Recommended dosages are dexamethasone (0.05 mg/kg IM or IV) for 3 days, followed by prednisolone (1 mg/kg PO) for 7 to 10 days, tapered by 100 mg/week over 1 month. Serum CK activity often normalizes after 7 to 10 days. Muscle mass will usually gradually recover over 2 to 3 months. Horses that are not treated with corticosteroids may develop extensive muscle atrophy, but in many cases muscle mass will gradually recover. Recurrence of atrophy in susceptible horses is common and may require reintroduction of corticosteroid therapy. Some horses develop focal residual muscle atrophy.

Equine Inflammatory Myopathies

Other causes of inflammatory myopathies exist in horses apart from IMM.[105] Piroplasmosis, for example, can produce chronic muscle atrophy characterized by muscle fiber atrophy, degeneration, and perivascular perimysial and endomysial lymphocytic infiltrates.[106] Focal symmetric atrophy of cervical muscles and lymphocytic infiltrates has also been reported in a pony with IMM.[107]

Virus-Associated Myopathy

Steven M. Parish

Necrosis of skeletal and cardiac muscle occurs frequently in association with some viral diseases. In most situations, viral-induced muscle damage represents a component of systemic multiple organ system involvement. For example, myocarditis occurs in association with foot-and-mouth disease, equine influenza, and equine infectious anemia. Other diseases causing myocarditis or skeletal muscle manifestations include bovine ephemeral fever, malignant catarrhal fever, bovine viral diarrhea, and bluetongue. Equine influenza A2 and equine herpesvirus 1 have been reported to induce primary muscle stiffness and clinical signs resembling those seen in horses with rhabdomyolysis.[108,109] Details concerning specific clinical manifestations can be found in other sections of this text.

Sarcocystosis

Steven M. Parish • Stephanie J. Valberg

Cysts of the sporozoan parasite *Sarcocystis* are commonly seen in routine

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histologic sections of the heart, esophageal, and skeletal muscle of cattle, sheep, goats, and horses. More than 90% of horses older than 8 years of age have sarcocysts in their esophageal muscles. Cysts may pose no problem, but with heavy infestations multisystemic dysfunction occurs. Experimentally induced acute disease is characterized by fever, mild anemia, chronic myositis, and muscle wasting.[110,111]

▪ Epidemiology

The life cycle of the parasite involves two hosts: carnivores as the definitive host and cattle or horses as the intermediate host. Three species of sarcocysts, *Sarcocystis cruzi*, *Sarcocystis hirsuta*, and *Sarcocystis hominis*, are known to infect cattle; Canidae, Felidae, and primates are the definitive hosts for these species. Three sarcocyst species have been described in horse muscle: *Sarcocystis bertrami*, *Sarcocystis equicanis*, and *Sarcocystis fayeri*.[112,113] Dogs have been identified as the definitive host of these equine sarcocyst species. In sheep and goats, *Sarcocystis ovicanis* and *Sarcocystis capracanis* have been described, with Canidae as the definitive host. The most common mechanism for natural infection in cattle is by ingestion of feeds contaminated with infected carnivore feces. Feedlot workers using feed bunks as toilets may be a source of exposure for feedlot cattle.

▪ Clinical Signs

Although low-level natural infection is common in cattle, when administered experimentally, a dose of 200,000 sporocysts of *S. cruzi* is necessary to cause severe clinical disease.[110] Within 4 weeks the animal develops fever (39.4° C/103° F), anorexia, salivation, weight loss, weakness, muscle fasciculations, severe depression, and sometimes death. Fever is the earliest sign and is biphasic relative to two periods of parasitemia, one occurring at 15 to 19 days and another at 25 to 42 days after inoculation. During the second febrile episode, affected calves frequently develop other clinical signs, particularly anemia. Extravascular hemolysis occurs, and hemorrhage into many tissues is common. The mechanisms involved in the hemolytic and hemorrhagic phases are likely to involve immune mechanisms. Mortality is greatest during this phase of the disease. Laboratory analysis may reveal elevations in serum urea nitrogen and bilirubin concentrations, sorbitol dehydrogenase, LDH, CK, and AST activities. If animals survive, these laboratory values usually return to normal in about 2

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weeks. Animals surviving this phase commonly continue to be inappetent and have decreased weight gains, muscle atrophy, and hair loss on the neck, rump, and tail. These changes are mediated by alterations in a variety of pathways, the net result being a partitioning away of nutrients that are used for growth.[111] The anemia is ameliorated by a regenerative process, with normal hematologic values obtained in 1 to 2 months after clinical recovery. Similar clinical findings are seen in sheep and goats. Abortion is common. A syndrome similar to that described in cattle has been reported in two horses with malaise, fever, and muscle atrophy.[112,113]

▪ Diagnosis

Diagnosis of sarcocystosis requires history, clinical signs, laboratory and serologic evaluation, and the demonstration of immature cysts in muscle biopsies. It is important to differentiate between the muscle cysts caused by *Sarcocystis* and those produced by toxoplasmosis because toxoplasmosis does not cause clinical disease in cattle.

▪ Treatment and Control

Specific treatment is effective only in the early stages of sarcocystosis in food animals. Experimental therapy with amprolium or the ionophore antibiotics before the second stage of parasitemia frequently prevents development of clinical sarcocystosis in cattle.[111] Successful treatment of one horse with sarcocystosis using phenylbutazone, trimethoprim-sulfamethoxazole, and pyremethamine has been reported.[113] Control involves preventing gross contamination of cattle and equine feeds with carnivore feces. The common use of ionophore antibiotics (e.g., growth promotants and coccidiostats) in cattle is also likely to help reduce the incidence of sarcocystosis.[114]

Nutritional and Toxic Rhabdomyolysis

Nutritional Myodegeneration

John Maas • Stephanie J. Valberg

▪ Definition and Etiology

Nutritional myodegeneration (NMD; also known as white muscle disease, stiff

lamb disease, and nutritional muscular dystrophy) is an acute myodegenerative disease of cardiac and skeletal muscle caused by a dietary deficiency of selenium or vitamin E.[115-118] This syndrome occurs in most farm animal species but is most commonly found in young, rapidly growing calves, lambs, kids, and foals, particularly those born to dams that consumed selenium-deficient diets during gestation. An in utero form of NMD may occur with affected animals showing clinical signs soon after birth. The disease has also been reported in yearling and adult cattle and occasionally adult horses. Selenium and vitamin E appear to be synergistic in preventing NMD. However, on the basis of prophylaxis and response to treatment, selenium deficiency appears to be more important.

▪ Clinical Signs

There are two distinct syndromes of NMD: a cardiac form and a skeletal form. The cardiac form is associated with acute signs of myocardial decompensation, whereas the skeletal form results in stiffness, weakness, and difficulty in ambulation.

The cardiac form of NMD usually has a sudden onset of depression, weakness, respiratory distress, rapid irregular heartbeat, severe debilitation, and often death within 24 hours. Occasionally an animal responds to therapy, but it often fails to thrive because of residual myocardial damage. Animals with predominantly cardiac signs can also manifest mild skeletal muscle problems associated with NMD. Lesions are present in the heart, diaphragm, and intercostal muscles.

The skeletal form of NMD frequently has a slower onset characterized by muscular weakness, stiffness, trembling, and recumbency with notably hard and painful muscles on palpation. Commonly affected muscle groups may include the gastrocnemius, semitendinosus, semimembranosus, and biceps femoris and muscles of the lumbar, gluteal, and neck regions. If the diaphragm and intercostal muscles are affected, the animal may show respiratory distress and evidence of increased abdominal effort when breathing. The muscles of the tongue may be involved, resulting in dysphagia. Dysphagia, especially in foals and lambs, may be the only sign. Some animals exhibit what appears to be abdominal pain with violent thrashing. Animals with skeletal NMD often respond favorably to treatment and rest. Improvement is evident after a few days, and within 3 to 5 days animals can often stand and walk.

Differentiation of NMD from other diseases causing sudden death or recumbency is important. Infectious diseases resulting in septicemia, pneumonia,

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and toxemia may have similar presenting signs. Acute heart failure resulting from cardiac anomalies; cardiotoxic agents such as those found in plants (oleander, cassia, yew, white snakeroot, and gossypol toxicity from cottonseed); and the ionophore antibiotics should also be considered. Other diseases causing stiffness of gait, weakness, and recumbency with no change in mental status must be differentiated from NMD. Spinal cord compression, cerebellar disease, suppurative and nonsuppurative meningitis or myelitis, polyarthritis, neurotoxins such as organophosphates, tetanus, pelvic fractures, and parasitic myositis all can cause recumbency. Clostridial myositis and traumatic injuries to muscles, long bones, and joints should be considered. Diseases characterized by abdominal pain may resemble NMD because they may also cause stiffness of gait, weakness, and recumbency.

▪ Clinical Pathology

Significantly elevated CK, AST, and LDH activities and myoglobinuria occur during the acute phase of myodegeneration. Progressively decreasing activities of CK can be used as a prognostic indicator of a reduction in the myodegenerative process. In foals, other reported abnormal laboratory findings include variable hyperkalemia, hyperphosphatemia, hyponatremia, and hypochloremia.[118] Evidence of dehydration, reflected by elevated serum protein concentrations and hemoconcentration, is common in nonambulatory animals unable to nurse or drink water.

The selenium status of an animal or members of a group can be determined by laboratory analysis of tissue biopsies and whole blood (Table 42.2). Vitamin E status in serum or plasma is satisfactory for assessing intermediate to long-term nutritional status; however, short-term supplementation or injections can confuse interpretation of circulating levels of selenium or vitamin E. Tissue biopsies and tissue specimens obtained at slaughter and necropsy provide an indication of storage and can also be used to assess herd status and success of supplementation. Whole blood selenium analysis is preferred over plasma and serum.[119] Whole blood selenium concentrations ranging from 0.07 to greater than 0.1 ppm (µg/mL) are considered normal in large animals. Normal liver concentrations of selenium are 0.9 to 1.75 µg/g of dry weight (DW), 0.9 to 3.5 µg/g DW, and 1.05 to 3.5 µg/g DW for cattle, sheep, and horses, respectively.[120] Selenium-dependent glutathione peroxidase (GSH-Px) formed in the RBCs during erythropoiesis also provides an index of body selenium status. Cross-

reacting enzymes, such as glutathione reductase, are not found in erythrocytes. Adequate GSH-Px activities are greater than 30 U/mg of hemoglobin per minute in cattle, 60 to 180 U/mg of hemoglobin per minute in sheep, and 20 to 50 U/mg of hemoglobin per minute in horses. However, GSH-Px reference values are only specific to the laboratory where the analysis is performed and must be validated by comparison with blood selenium concentration. The activity of GSH-Px in RBCs of domestic species remains constant for 4 to 6 days when maintained at 39° F (4° C); after this time, significant decreases occur. The critical concentration of vitamin E (α-tocopherol) in plasma is 1.1 to 2 ppm (μg/mL) in large animals. Vitamin E deteriorates rapidly in plasma samples. Therefore plasma or serum samples for α-tocopherol analysis need to be put on ice immediately, protected from light by wrapping in tin foil, and stored (−21° F/ −70° C) if analysis is to be delayed.

TABLE 42.2

Deficient, Marginal, and Normal Concentrations of Whole Blood Selenium and GSH-Px Activities in Sheep and Cattle[67,71]

Whole Blood Selenium (ppm)	GSH-Px (U/mg Hb/min)	Category	Interpretation
0.01-0.04	0-15	Deficient	Selenium supplementation is always beneficial
0.05-0.06	15-25	Marginal	Selenium supplementation is often beneficial
≥0.07	25-500	Normal	Selenium supplementation is never beneficial

GSH-Px assays are performed by different procedures in individual laboratories, and quantitative relationships between blood selenium concentrations and blood GSH-Px activities can vary. These numeric relationships are site specific, and interpretation must account for these differences.

GSH-Px, Glutathione peroxidase; *Hb,* hemoglobin; *ppm,* parts per million.

▪ Pathophysiology

The effects of selenium and vitamin E deficiency have been postulated to result, at least in part, from the destruction of cell membranes and proteins leading to a loss of cellular integrity.[115,121] Selenium, which has been shown to be an essential component of at least five selenoproteins[122] (three GSH-Px enzymes; a

deiodinase in liver and kidney that converts T_4 to T_3; and selenoprotein P, a plasma protein of unknown function), and vitamin E (α-tocopherol) serve as biologic antioxidants. During normal cellular metabolism, highly reactive forms of oxygen (free radicals) are produced. These include hydrogen peroxide, hydroperoxides, lipoperoxides, superoxide, various hydroxy radicals, and singlet oxygen. Vitamin E is active within the cell membrane as a lipid-soluble antioxidant that scavenges free radicals that otherwise might react with unsaturated fatty acids to form lipid hydroperoxides. In contrast, GSH-Px destroys hydrogen peroxide and lipoperoxides that have already been formed and converts them to water or relatively harmless alcohols. Other enzymes such as catalase and superoxide dismutase are also involved in this protective process.

Apparently important interrelationships exist among the selenium and vitamin E status of the animal, the level of polyunsaturated fatty acids (PUFAs) in the diet,[115,121] and NMD, particularly in ruminants.[115] PUFAs of dietary origin can undergo peroxidation to hydroperoxides forming toxic free radicals. During active growing periods, pasture grasses and plants contain high concentrations of linolenic acid, a PUFA. Under normal conditions the rumen is thought to be important in saturating dietary unsaturated fatty acids. However, concentrations of PUFAs in the plasma often increase in calves recently turned out to pasture, possibly enhancing the chance of free radical formation and tissue damage. This indicates that the capacity of the various protective mechanisms can be overwhelmed by dietary factors such as high levels of PUFA. Not surprisingly, selenium- or vitamin E–deficient animals may be at a greatly increased risk of tissue oxidative damage when exposed to such diets. However, the potential for induction of NMD by this process should not be overemphasized because calves on a milk diet may be severely affected.

The precise interrelationships among selenium, vitamin E, other metabolic factors, and triggering mechanisms in NMD are not fully understood because many animals deficient in selenium or vitamin E have no evidence of muscle disease. In certain situations, deficiencies of both selenium and vitamin E are necessary for disease to occur. In other animals NMD can occur when a deficiency of only one of the agents is present and the other is normal in blood and tissues.

▪ Epidemiology

NMD occurs in all farm animals and is seen most commonly in young, rapidly

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growing calves, lambs, kids, and foals. The occurrence of NMD in very young animals usually reflects a deficiency in their dams during a substantial portion, if not all, of the gestation period. The selenium and GSH-Px values of neonatal calves tend to be similar to those of their dams.[123,124]

Marginally to severely selenium-deficient areas occur throughout a large portion of the United States and other countries of the world. Forages and grains produced in the northeastern and eastern seaboards and northwestern regions of the United States are particularly deficient because of low soil levels of selenium. Acid soils and those originating from igneous (volcanic) rock are often selenium deficient, as are those having high sulfur content or soils treated with sulfur-containing fertilizers. Sulfur inhibits selenium uptake by plants and absorption by animals. Different forages in a specific area will also vary in their selenium content. Legumes take up less selenium than do grasses. Also, forage selenium concentrations are lowest during periods of rapid growth such as in the spring and during times of highest rainfall.

Vitamin E deficiency occurs most commonly when animals are fed poor-quality hay, straw, or root crops. Grain treated with propionic acid and having high moisture content is commonly vitamin E deficient. Storage of grain crops for extended periods results in marked decreases in their vitamin E content. Calves fed milk replacers containing fish oil, linseed oil, or soybean or corn oil, all of which increase the dietary levels of unsaturated fatty acids, require increased dietary supplementation of vitamin E to avoid deficiency. In contrast, cereal grains, green growing pastures, and properly prepared hay usually have adequate vitamin E.

In young ruminants the majority of NMD cases occur in calves, 2 to 4 months of age, during the spring and summer months in association with exercise when at pasture, although congenital and perinatal cases do occur. Histologic lesions consistent with NMD have also been seen in late-term aborted fetuses.[120] These findings are suggestive of an in utero form of NMD in large animals. Yearling cattle housed during the winter, fed diets high in grain with high moisture content, and then turned out in the spring may also be affected. Lambs born in confinement and turned out to pasture at 1 to 3 weeks of age frequently develop signs of NMD. Stresses such as transport, herding, and driving can also precipitate signs of NMD. In horses, NMD generally occurs during the first year of life with most cases observed from birth to weaning.[116,125]

▪ Necropsy Findings

Bilaterally symmetric myodegeneration is a consistent finding in NMD. Skeletal muscle degeneration is characterized by pale discoloration and a dry appearance of affected muscle, white streaks in muscle bundles, calcification, and intramuscular edema (Fig. 42.12). The white streaks seen in muscle bundles represent bands of coagulation necrosis or, in chronic cases in which insults may have occurred weeks before, may represent fibrosis and calcification. Affected muscle bundles are often adjacent to apparently normal or minimally affected muscle. The color of normal muscle in young calves is pale because of reduced myoglobin concentrations; therefore close inspection and histologic examination are necessary in cases of suspected NMD. Cardiac muscle undergoes changes similar to those of skeletal muscle. In calves the left ventricle and septum are most frequently involved (Fig. 42.13), but in lambs both ventricles are usually involved. Myocardial degeneration usually extends through the full thickness of the ventricular wall.

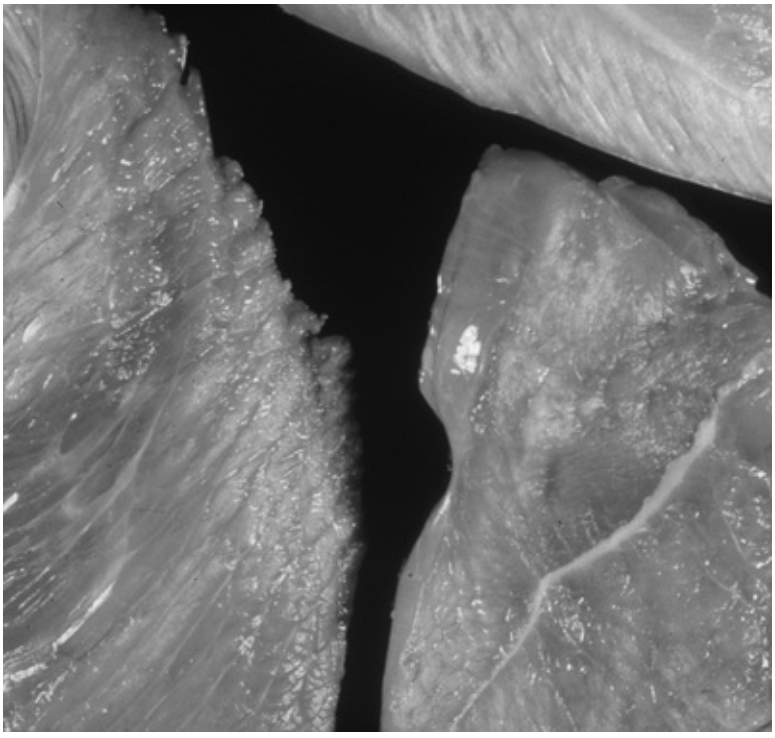


FIG. 42.12 White streaks within diffusely pale skeletal muscle due to nutritional myodegeneration.

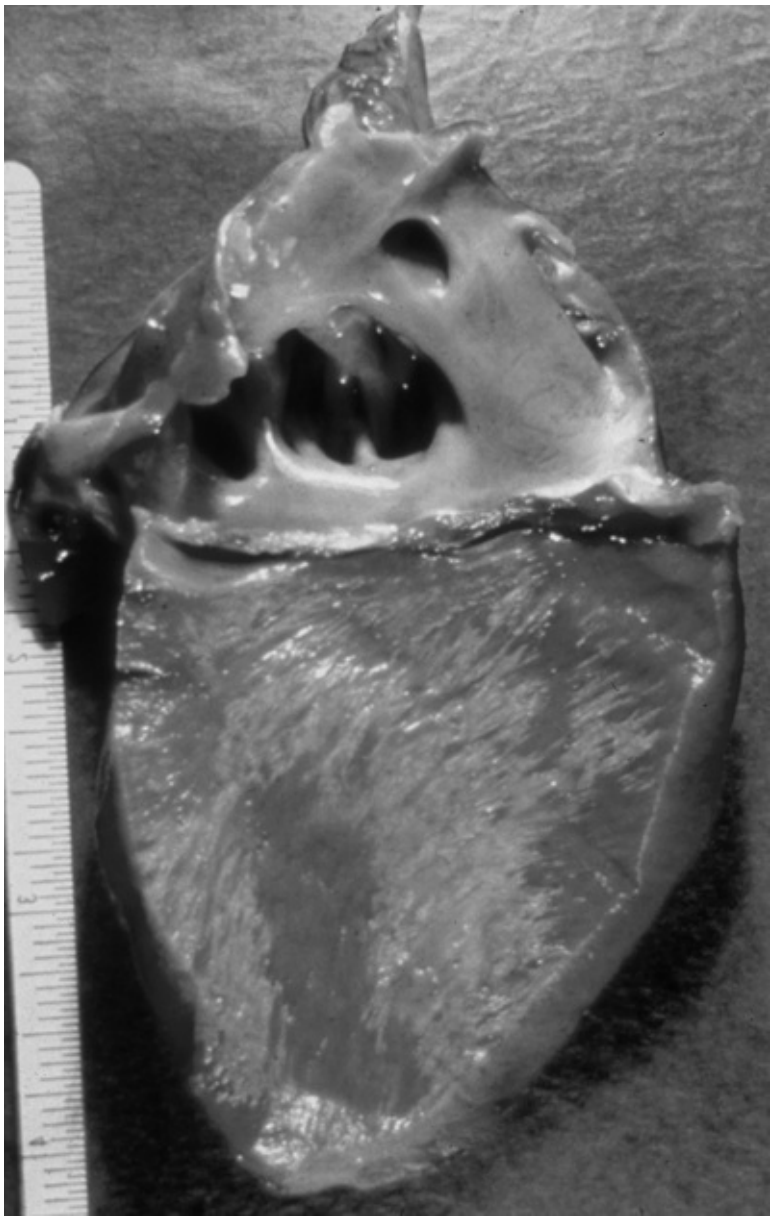


FIG. 42.13 Pale areas of muscle necrosis in the myocardium of a calf with nutritional myodegeneration.

Histologically, affected muscle fibers may be hypercontracted and fragmented with some mineralization of muscle fibers and others undergoing macrophage infiltration. In yearling cattle, type I muscle cells are more frequently affected.

▪ Treatment and Prognosis

In the cardiac form of NMD, myocardial damage is often extensive and incompatible with life. In contrast, the skeletal form of NMD is more generally amenable to treatment, although the prognosis for clinical recovery from the

skeletal form of NMD is guarded and depends often on whether secondary complications such as respiratory disease develop. In all cases of NMD, therapy should involve specific supplementation with selenium and vitamin E and general supportive care.

Alleviation of selenium-responsive NMD requires the use of injectable selenium products. These are available with selenium concentrations varying from 1 to 5 mg/mL, with all products containing 50 mg/mL (68 IU) of vitamin E as DL-α-tocopheryl acetate. The label dose for selenium is 0.055 to 0.067 mg/kg (2.5 to 3 mg/45 kg) body weight given intramuscularly or subcutaneously. Dosage of these injectable products should not be greatly increased above the label dose to prevent an inadvertent selenium toxicosis. However, when using the vitamin E/selenium combinations, the amount of vitamin E in these combination products is present as a preservative for the solution and is therefore insufficient for vitamin E supplementation. Oral supplementation is the general approach to provide additional dietary levels of vitamin E. Vitamin E can be obtained from natural or synthetic sources, which differ in bioavailability. In order for α-tocopherol acetate to be used in the body, the ester has to be removed and the α-tocopherol made water dispersible by the action of bile salts (micellization), which can limit α-tocopherol acetate absorption in the horse. To further enhance the bioavailability of α-tocopherol, water-dispersible formulations of vitamin E have been developed. The biopotency of these compounds in horses is much greater than synthetic vitamin E. When tested, two of the commercially available water-dispersible natural vitamin E products had a bioavailability 5.59 (Elevate WS [Kentucky Performance Products, Versailles, Ky.]) and 6.13 (Nano-E [Kentucky Equine Research, Versailles, Ky.]) times higher than synthetic vitamin E acetate (D-α-tocopheryl acetate). Recommended levels of supplementation for calves range from 15 to 60 mg of DL-α-tocopheryl acetate per kg of dry feed. For horses, a daily supplement of 600 to 1800 mg per os of DL-α-tocopheryl acetate has been recommended.[125]

Studies with injectable selenium show that absorption and distribution occur rapidly.[126] It is thought that incorporation of selenium into heart, skeletal muscle, and other tissues may be rapid and could account for the rapid improvement in clinical signs seen in reversible cases. The discovery of four new selenoproteins may help explain these clinical observations.[122] This improvement can occur even though blood GSH-Px activity rises slowly because of the delay caused by erythropoiesis and release of RBCs from the bone marrow.[126] However, platelet GSH-Px activity rises within hours and may be a more accurate reflection of

changes in muscle and other tissues.

Supportive therapy may include administration of antibiotics to help combat secondary pneumonia and infected decubital lesions that are common in recumbent patients. Provision of adequate energy intake and attention to the fluid and electrolyte balance are of critical importance if recovery is to be successful.

▪ Prevention and Control

The prevention and control of NMD are achieved through supplementation of both selenium and vitamin E. The use in ruminants of rumenoreticular boluses, which release a precise amount of selenium daily, has been commonplace in many countries of the world; however, current guidelines should be checked to ensure they are not permitted. These slow-release boluses can replace supplementation by salt mixtures or by injections and are extremely valuable in extensive grazing systems. Alternatively, individual animals can be supplemented by periodic (30- to 60-day intervals) injections of selenium/vitamin E preparations to help maintain body concentrations and assist in transplacental transfer of selenium to the fetus.

Oral supplementation for horses at 1 mg of selenium per day increases blood selenium concentrations above levels known to be associated with NMD.[127] Supplementation of pregnant mares is advised in areas known to be selenium deficient; however, only limited selenium may cross the placenta.[117] Supplementation during lactation increases the levels of selenium in milk and thus provides a potential means of selenium supplementation in foals; however, evidence in cattle indicates that this increased level of selenium in milk may not meet nutrient requirements.

Regardless of the method of supplementation, periodic blood (or tissue) sampling of animals at risk is recommended to ensure desired levels of selenium. In high-risk areas, samples should be taken every 60 to 90 days to determine selenium status in susceptible animals and every 6 to 12 months to monitor supplementation. On the basis of these assessments, adjustments to the rate or extent of selenium supplementation may be made.

Feeding animals properly prepared and stored hay and grain or allowing them access to high-quality green forage should ensure adequate vitamin E intake.

Masseter Muscle Myodegeneration

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Adult horses with selenium deficiency may be clinically normal or can present with acute clinical signs of bilateral swelling of the masseter muscles, trismus, dysphagia, and salivation.[128-131] Although postural and locomotor muscles may appear normal on clinical examination, postmortem of horses with masseter muscle myonecrosis has shown histopathologic evidence of bilateral symmetric lesions in muscles of the hind and thoracic limbs. Tachycardia and dysrhythmias may indicate the presence of myocardial damage. Accompanying clinical pathologic findings include pigmenturia, elevated serum AST and CK activity, and elevated cardiac troponin concentrations. Ultrasonography can be used to determine the extent of masseter muscle swelling or atrophy, as well as the presence of myocardial dysfunction. Prognosis is guarded, but there are individual reports of successful treatment. Important aspects of treatment include nutritional support via stomach tube, IV fluids, analgesics, IM selenium (0.055 to 0.067 mg/kg), and oral vitamin E (1000 to 5000 IU/day). Progression to bilateral muscle atrophy is common and may resolve after a period of months. Without early treatment, permanent trismus can occur due to muscular atrophy and fibrosis. Ruleouts for masseter swelling include parasites—most commonly *Trichinella spiralis*, *Halicephalobus* species, or *Haycocknema perplexum*[132]—trauma, and fibrosis due to trauma or chronic abscessation.

Vitamin E–Deficient Myopathy

Some horses with clinical signs of EMND and a deficiency in vitamin E are not diagnosed antemortem with EMND because they lack evidence of neurogenic atrophy in the sacrocaudalis dorsalis (SC) muscle. A recent study suggests that many such undiagnosed cases are the result of a specific myogenic presentation of vitamin E deficiency.[133] With vitamin E–deficient myopathy, the clinical presentation resembles EMND; however, sacrocaudalis muscle lacks evidence of neurogenic atrophy but contains an abnormal moth-eaten staining pattern of mitochondria. Muscle α-tocopherol concentrations from affected horses are low, but serum α-tocopherol concentrations are inconsistently low. This vitamin E–deficient myopathy has likely been missed previously because formalin-fixed biopsy specimens are most often evaluated for a diagnosis of EMND and mitochondrial staining is not possible with this fixative. The observed generalized weakness in the horses with abnormal mitochondrial stains could be due to a reversible manifestation of skeletal muscle mitochondrial oxidative stress associated with vitamin E deficiency. Horses can recover completely after

vitamin E therapy (5000 IU/day per os for >3 weeks) (Fig. 42.14). Vitamin E–deficient myopathy could be an entity unto itself or a predecessor to development of EMND, but this distinction was not evaluated in the study because all horses successfully responded to vitamin E therapy, precluding a postmortem examination.



FIG. 42.14 A horse with vitamin E–deficient myopathy before **(A)** and after **(B)** 6 months of vitamin E treatment. Before vitamin E treatment, notice the marked generalized muscle atrophy; following treatment, notice the normal muscle mass.

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Toxic Causes of Rhabdomyolysis

Stephanie J. Valberg

Ingestion of toxic substances in feed or forage is a common cause of toxic rhabdomyolysis.

Ionophores.

Ionophores are commonly added to feeds for their growth promotion and coccidiostat properties. Species differences in sensitivity to ionophores and the variety of ionophores on the market have led to several cases of ionophore-induced toxicosis. Rhabdomyolysis and cardiomyopathies are common sequelae to ionophore toxicosis. Experimental studies have indicated that LD50 values for monensin are 2 to 3, 12, 17, 26, and 21 to 36, for horses, sheep, pigs, goats, and cattle, respectively. Feed concentrations of 100 g/ton and 400 g/ton have been fatal to sheep and cattle, respectively.[134,135] Newborn calves dosed with 100 mg lasalocid twice daily, for cryptosporidiosis, experience muscle necrosis.[136] Other ionophores include naracin, salinomycin, and laidlomycin. Ionophores are quickly eliminated from the body after exposure.

Chemical Toxins.

Several chemical agents have been associated with muscle necrosis on rare occasions. Parenteral products, insecticides, and feed contaminants have been implicated. Muscle necrosis has been reported in cattle and pigs after receiving injections of lidocaine, diazepam, digoxin, levamisole, nitroclofene, pentazocine, thiazinamium, chloramphenicol, and oxytetracycline and in horses after injectable ivermectin administration. One of 70 horses poisoned with blister beetles developed muscle necrosis.[137] Animals with organophosphate toxicosis, particularly parathione, may develop muscle necrosis.[138-140] Several miniature horses being fed a complete feed containing tetrachlorovinphos, a feed-through fly control agent, were reported to develop chronic myonecrosis involving masseter, tongue, neck, respiratory and postural muscles, and occasionally cardiac muscle.[141] Affected horses showed signs of lethargy, dysphagia, fasciculations, tachypnea, and tachycardia. Muscle tissue showed evidence of chronic myonecrosis and lipid accumulation. Myonecrosis was attributed to acetylcholine accumulation at muscarinic and nicotinic sites producing oxidant

stress. Low selenium concentrations may contribute to the toxicosis.

Toxic Plants.

Gossypol is of greatest significance in swine. Monogastrics, including young calves, should not ingest feed containing more than 200 ppm gossypol. Mature ruminants may tolerate 20 g of gossypol/head/day. This normally amounts to 5 to 6 lb of whole cottonseed per head per day.[142] Two common forage toxins that cause myonecrosis are *Cassia* spp. and tremetone-containing plants. *Cassia obtusifolia* (sicklepod) is prevalent in the southeastern United States, and ingestion of seeds by swine, ruminants, or horses may cause a degenerative myopathy and cardiomyopathy with evidence of myofiber atrophy, segmental necrosis, and mitochondrial disruption.[142] White snakeroot *(Eupatorium rugosum)* grows in shaded areas of the eastern and central United States, and rayless goldenrod *(Isocoma wrightii)* is common in the Southwest on open pastures. These tremetone-containing plants can cause a fatal cardiomyopathy and severe skeletal muscle degeneration in horses when ingested at 0.5% to 2% of body weight.[143,144] Other grazing livestock are likely to be affected by ingestion of these plants at 2% of body weight. Tremetone remains active in hay and in the stalks of the dead plants on pasture, so both the fresh and the dried form of the plants should be kept from livestock.[145] Microsomal activation of the toxin in the liver may be necessary for toxic effects.[143]

Marshmallow Toxicity

Marshmallow *(Malva parviflora),* also known as small-flowered mallow, cheeseweed mallow, and little mallow, is a common weed found in pastures of grazing animals with extensive distribution, including in regions of Europe, Asia, North and South America, Australia, and New Zealand. The two cyclopropene fatty acids, malvalic acid and sterculic acid, are thought to be the main toxic components of plants.[146] Horses consuming marshmallow with little else to eat developed signs of sweating and muscle fasciculations progressing to recumbency and had elevated serum CK, AST, and lactate.[146] Increases in serum cyclopropene fatty acids, large increases in C14 to C18 acylcarnitine concentrations, and smaller increases (up to eightfold) in other acylcarnitines such as C2 to C5 suggest that the toxin disrupts long-chain fatty acid metabolism.[146]

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Seasonal Pasture Myopathy and Atypical Myopathy

Epidemiology.

A highly fatal acquired lipid storage myopathy of pastured horses occurs in the fall and less often in the spring in Europe and central and northeastern parts of North America.[147-151] Affected horses are usually young or new to affected pastures and kept on wooded pastures for more than 12 hours a day without additional feed provided. Windy weather often precedes outbreaks.[152,153]

▪ Clinical Signs

Clinical signs develop acutely and include muscular weakness, sweating, fasciculations, stiffness, tachycardia, tachypnea, recumbency, and when urine is observed, myoglobinuria. A rapid rise in respiratory rate is usually followed by collapse and death from respiratory or cardiac failure.

▪ Diagnosis

The most notable change in serum biochemistry is a marked increase in serum CK and AST activity, which is often accompanied by hyperglycemia, lactic acidemia, and in some cases elevated serum troponin I concentrations.[154] A definitive diagnosis can be made by a pattern of accumulation of serum acylcarnitines and urine organic acids and glycine conjugates typical of a deficiency in multiple acyl-CoA dehydrogenases, as well as isolation of the conjugated toxic metabolite methylene cyclopropyl acetic acid (MCPA) and hypoglycin A in blood or urine.[155-158] Serum vitamin and selenium, as well as urine tremetone, concentrations are normal. Postmortem findings include extensive necrosis in deep postural and respiratory muscles and, in 50% or more of cases, in myocardium. Frozen sections of myocardium, intercostal, diaphragm, or deep postural muscles show marked intracellular lipid accumulation in oxidative fibers (oil red O stain).[147,150]

▪ Pathophysiology

Seeds of *Acer* species trees such as the box elder *(Acer negundo)* and the European sycamore maple *(Acer pseudoplatanus)* (Fig. 42.15) contain the toxic nonproteogenic amino acid hypoglycin A.[157-159] Hypoglycin A is metabolized in the liver to MCPA, and MCPA CoA irreversibly binds to multiple acyl-CoA

dehydrogenases, enzymes that are essential for metabolism of short- and medium-chain fatty acids and branched chain amino acids. Accumulation of fat esters can damage muscle cell membranes, and an energy deficiency also arises from an inability to metabolize fat.



FIG. 42.15 Box elder seeds that contain the toxin hypoglycin A, which causes seasonal pasture myopathy.

▪ Treatment and Prognosis

Less than 75% of horses survive.[153] Early aggressive fluid therapy and antioxidant and anti-inflammatory treatment, including dimethyl sulfoxide, vitamin E, vitamin C, riboflavin, and NSAIDs, are indicated.[147] Although many older horses are asymptomatic on pastures with *Acer* species trees, young horses or new horses should not be pastured with box elder or European sycamore maple trees in the fall. Provision of additional feed or reducing grazing time during the fall may also decrease the incidence of pasture-associated myopathies.

Traumatic Rhabdomyolysis

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Compartment, Downer, and Muscle Crush Syndromes of Cattle

David R. Hodgson • Stephanie J. Valberg

Muscle damage commonly accompanies the downer syndrome in large animals. The downer syndrome is discussed in greater detail in Chapter 35. Animals weakened by disorders such as hypocalcemia are more prone to tearing adductor or semitendinosus and membranosus muscles in attempts to rise.[25,160] Initial traumatic laceration of muscle leads to edema and inflammation, both of which may exacerbate local tissue degenerative changes. In addition, the weight of a recumbent animal on dependent muscle groups creates significant increases in intramuscular pressure, resulting in decreased perfusion and ischemia of muscle and nerve. Signs of weakness and peroneal or tibial nerve paralysis most commonly accompany this type of injury. Mild elevations in serum CK can be expected in cows that are recumbent, but elevations greater than 5000 U/L usually indicate traumatic muscle damage. Treatment requires correcting the underlying cause of recumbency, fluid therapy if renal damage is evident, NSAIDs, good nursing care, adequate footing and bedding, and lifting or rolling the animal several times a day. Aquatherapy using float tanks for cattle also appears to be beneficial in relieving the pressure on muscle groups.

Postanesthetic Myoneuropathy

Postanesthetic myoneuropathy is a condition that has become much more prevalent since the advent of inhalation general anesthesia. The disorder can be categorized as occurring in two forms: (1) localized myopathy-neuropathy and (2) generalized myopathy somewhat similar to malignant hyperthermia.

Localized Myoneuropathy

Clinical Signs.

Localized myopathy-neuropathy occurs in about 6% of horses undergoing general anesthesia.[148] It is most prevalent in muscles that are in contact with a hard surface during anesthesia or those in which arterial blood supply is compromised through positional occlusion. Commonly affected muscles include triceps, deltoid, masseter, hindlimb extensors, or if the horse has been in dorsal recumbency, the hindlimb adductor and gluteal muscles.[160-162] Injury can also occur to nerves in these areas, resulting in temporary radial, peroneal, or femoral

nerve paralysis (Fig. 42.16). Clinical signs may be apparent on recovery or may be delayed for periods of up to 30 to 60 minutes after the horse has recovered from anesthesia. Affected muscles may be swollen, hot, and painful on deep palpation, and the horse is often reluctant to bear weight on the affected limb. Myasthenia (weakness) of affected muscles is common, particularly with peripheral nerve involvement. In some horses this condition may limit the animal's ability to stand for some time following anesthesia. The loss of muscle strength, particularly when involving adductor muscles, can contribute to orthopedic injury during repeated attempts to rise. Many horses with mild to moderate muscle injury recover over a period of hours to days even if untreated.[162]



FIG. 42.16 Postanesthetic myoneuropathy showing paralysis of the right femoral and peroneal nerves.

▪ Etiology

A variety of factors acting alone or in combination has been suggested to contribute to this disorder. The most important factors include duration of anesthesia, ischemia, and hypoperfusion as a result of prolonged immobility, muscle compression, systemic hypotension, and hypoxia.[162-166] There is increased lactate efflux from dependent muscles during anesthesia in horses that develop a myopathy, supporting the contention that these muscles experience compromised perfusion.[165,167,168] Halothane anesthesia has a greater propensity than isoflurane to compromise tissue oxygen delivery even in nondependent

muscles.[164] If mean arterial pressure is allowed to fall below 70 mm Hg for several hours during inhalation anesthesia, particularly if mechanical ventilation is used, the incidence of postanesthetic myopathy increases substantially.[166,167]

▪ Diagnosis

Diagnosis is based on a history of anesthesia or prolonged recumbency, clinical signs, and possibly clinical pathology examinations. Laboratory findings include elevations in serum CK and subsequently serum AST and serum LDH activities. Elevations in CK activities of thousands to tens of thousands of IU/L are commonly demonstrated in horses with moderate forms of the myopathy.

▪ Treatment

Horses demonstrating only minor localized manifestations of the myopathy usually have an uncomplicated recovery with little or no treatment.[162] Supportive care, including the use of anti-inflammatory drugs, dimethyl sulfoxide, and dantrolene sodium 2 to 4 mg/kg PO q8h to q24h for up to 48 hours, is often sufficient in mild to moderate cases.[168] Significant muscle atrophy may develop over the ensuing 3 to 4 weeks but will usually resolve within 2 to 3 months. Treatment of more severe cases is outlined under generalized reactions.

▪ Control

Correct positioning and judicious use of padding and water- or air-filled mattresses can reduce dependent muscle pressure by up to 50%, thereby aiding in the reduction of this disorder. In addition, by elevating the upper limb during anesthesia, the pressure on the lower limbs is significantly reduced. Pulling the lower forelimb forward also markedly reduces pressure in the dependent triceps muscle. When the horse is in dorsal recumbency, padding under the shoulders and hips is absolutely imperative.

Maintaining anesthesia at the lightest plane possible for a specific surgical procedure is beneficial in prophylaxis. Similarly, if possible, maintaining systemic mean arterial blood pressure above 80 to 85 mm Hg during anesthesia is advisable. The use of ionotropic agents such as dobutamine during anesthesia has been useful in reducing the occurrence of anesthetic myopathies. Administration of dantrolene sodium (2 to 4 mg/kg PO) 1 hour before induction of anesthesia may result in a reduction in the incidence of this myopathy;

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however, it should be noted that decreased cardiac output can occur in conjunction with higher dantrolene doses.

Generalized Anesthetic Reactions

Clinical Signs.

Postanesthetic reactions involving multiple muscle groups can result in clinical signs of anxiety, hyperthermia, tachycardia, tachypnea, profuse sweating, and myoglobinuria.[163,164] Horses may not be able to rise and may struggle violently, resulting in prolonged, traumatic recoveries. In some cases a progressive increase in body temperature and muscular contractures may develop under anesthesia, and a fulminant metabolic and respiratory acidosis may be noted.[20,169,170] These animals can die within a matter of hours. In some cases, shock and pigmenturia may lead to renal failure.

▪ Pathogenesis

The generalized form of myopathy cannot be explained by the compartmental syndrome alone. Halothane and succinylcholine have been the most frequently implicated inciting agents for generalized anesthetic-induced myonecrosis in all susceptible species, including the horse.[19,169,170] There appear to be several possible explanations for generalized anesthetic reactions. In some cases, systemic hypotension and hypoxemia may create local ischemic lesions, with the pathologic changes becoming more generalized as a result of the stress of anesthesia and the sensitivity of muscle cells to anesthetic agents or muscle relaxants.[162,166] In other cases, malignant hyperthermia[19,169-171] may be responsible for clinical signs of muscle contracture, heat production, and systemic acidosis resulting from excessive calcium release by the sarcoplasmic reticulum. In swine, malignant hyperthermia is caused by a genetic mutation in the ryanodine receptor 1 *(RYR1)* gene.[172] A mutation in the same gene has been identified in Quarter Horses. Horses with this mutation may develop fatal malignant hyperthermia following halothane anesthesia.[173,174] A further possible cause of generalized anesthetic myopathies is the triggering of severe myonecrosis in horses with an underlying exertional myopathy. Horses with recurrent exertional rhabdomyolysis may be at risk for excessive release of calcium from the sarcoplasmic reticulum during halothane anesthesia, and horses with polysaccharide storage myopathy may develop rhabdomyolysis due to

metabolic changes with anesthesia.[19,20,175,176]

▪ Diagnosis

Diagnosis is based on clinical signs, particularly in horses undergoing inhalation anesthesia. Routine monitoring of body temperature during anesthesia may aid in the early detection of MH. Some animals may also demonstrate metabolic and respiratory acidosis and hyperkalemia.[173] Genetic screening for MH in Quarter Horses and American Paint Horses may be warranted before elective procedures.

▪ Treatment

Severely affected cases provide a significant therapeutic challenge. Aims of therapy should include (1) relief of pain, (2) correction of fluid and electrolyte abnormalities, (3) attempts to prevent ongoing necrosis, and (4) high-quality nursing care. Many of the same principles described for treatment of exertional rhabdomyolysis can be used for treatment of postanesthetic myoneuropathy. In severely affected recumbent horses, pain relief and sedation may help prevent struggling and progression of the myopathy.[162,163] Detomidine combined with butorphanol is effective in reducing struggling. Violent struggling only exhausts the horse and increases the potential for further injury and muscle damage. Constant rate infusions of butorphanol, opioids, or detomidine may aid in pain control where practical. Similarly, administration of NSAIDs may help to reduce ongoing degenerative changes in muscle. Dantrolene sodium 2 to 4 mg/kg PO q8h to q24h decreases release of calcium from the sarcoplasmic reticulum, helping to break the cycle of muscle damage. Volume expansion and diuresis may prevent renal toxicity.[162]

The most common metabolic derangement with anesthetic-related myopathies is a metabolic and/or respiratory acidosis. If specific therapy for metabolic acidosis is necessary, intravenous administration of sodium bicarbonate can be used. For optimum results, doses are calculated on the basis of the results of acid-base analysis. If facilities for acid-base analysis are not available and the horse appears severely compromised, IV administration of sodium bicarbonate at a dosage of 0.5 to 1.0 mEq/kg slowly is recommended. If hyperthermia and contracture develop during anesthesia, discontinuation of anesthesia is advisable. Additional attempts to cool the animal with alcohol or cold-water baths may also be indicated. Administration of a large amount of soluble, lyophilized dantrolene sodium for intravenous administration may alleviate clinical signs in these

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horses. However, availability and expense of the agent in this form restrict its use. A dosage rate of 1 mg/kg IV may be appropriate, although more controlled studies are required.[162]

Good nursing care is important in severely affected horses. This involves providing well-padded areas on which horses can lie. Prevention or minimization of trauma around the eyes and appropriate care of decubital sores are important. Recumbent animals may require frequent turning to allow reperfusion of compressed muscle masses. Continued fluid therapy with polyionic fluids and possibly caloric supplementation may be indicated. The use of slings and pools to assist recumbent animals to rise has also been tried.[162] Recovery from the myopathy may occur with no apparent residual lesions. In contrast, recovery from some severe forms of the disorder may be accompanied by muscle atrophy, fibrosis, and scarring.[162]

▪ Prevention

The principles described for localized myoneuropathies apply to the prevention of generalized anesthetic-related myopathies. In addition, dantrolene sodium has been shown to reduce the incidence of MH in susceptible humans and pigs. Similar effects might be anticipated in horses. Because of limited controlled studies, the dosage rate for prevention of MH in the horse is not clearly defined. Administration at a rate of 4 mg/kg PO 1 to 2 hours before anesthesia may be beneficial in reducing the incidence of MH; however, 6 mg/kg may cause decreased cardiac output and hypotension.[168,177]

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Exertional Myopathies in Horses

Local Muscle Strain

Stephanie J. Valberg

Lumbar and Gluteal Muscles

Strain of lumbar and gluteal muscles is common in jumpers, dressage, harness horses, and Thoroughbreds. Deep palpation of epaxial and gluteal muscles results in pain and dorsiflexion of the spine. Several factors may predispose horses to muscle strains, such as an inadequate warm-up, preexisting lameness, exercise to the point of fatigue, and insufficient training. Lameness can be mild, and horses usually are reluctant to engage their hindquarters during exercise. A specific gluteal syndrome has been described in which the accessory head of the middle gluteal muscle becomes acutely painful to palpation.[178] With accessory gluteal head involvement horses become progressively more lame during exercise and will refuse to continue exercise. Horses that show pain but resist dorsiflexion, ventroflexion, and lateral bending on manipulation may have a myopathy secondary to an underlying disorder of the spine or sacroiliac joint.

Adductor Muscles

The gracilis muscle can be torn in horses and cause severe pain and, occasionally, recumbency.[179,180] A careful physical examination reveals swelling of the medial thigh and pain on palpation. Ultrasonography identifies the extent of disrupted muscle fibers. Adequate rest, NSAIDs, and cold therapy form the basis for acute treatment. Stretches and hand walking once the initial pain has dissipated are beneficial combined with application of heat or ultrasound therapy. Exercise should be resumed gradually, preceded by an appropriate warm-up period in a long and low frame. Adequate conditioning should be ensured before starting strenuous exercise. Saddles should be checked for proper fit.

Semitendinosus and Semimembranosus Muscles

Semitendinosus and semimembranosus muscles are frequently damaged in working Quarter Horses, and in chronic cases this can result in a fibrotic

myopathy.[181-183] Tearing of the semitendinosus and sometimes the semimembranosus, biceps femoris, and gracilis muscles at the point of a tendinous insertion is usually associated with work that requires abrupt turns and sliding stops. Horses caught in ropes or fences may struggle violently enough to induce sufficient trauma, allowing subsequent development of the myopathy. In one report, 5 of 18 horses developed this condition secondary to intramuscular injections.[183]

Affected muscles in acute cases are painful on deep palpation and may appear warm. Chronically hardened areas within the muscle may represent fibrosis and ossification. The lameness in chronic cases is usually most apparent at the walk and is characterized by an abrupt cessation of the anterior phase of the stride of the affected limb, causing the leg to jerk suddenly to the ground rather than continue its forward motion. Pain is not a feature in chronic fibrotic myopathy, and manipulative tests have little, if any, effect on the degree of dysfunction. The stride has a short anterior phase with a characteristic hoof-slapping gait. The gait reflects a mechanical hindlimb lameness that restricts normal function. Radiographs may indicate ossification of affected muscles.[183]

▪ Diagnosis

Serum activities of CK and AST are usually only mildly elevated. In addition to palpation, diagnosis can be confirmed by ultrasonography, thermography, or scintigraphy. Light microscopic evaluation of muscle biopsies is frequently normal in acute cases. Chronically fibrous replacement of muscle fibers is apparent.

▪ Treatment

Several surgical procedures for correction of fibrotic myopathy have been described.[169,183]

Exertional Rhabdomyolysis

Stephanie J. Valberg

Exertional rhabdomyolysis (ER) is probably the most common muscle disorder in horses. It is a frequent cause of poor performance in a variety of breeds, including Standardbreds, Thoroughbreds, warmbloods, Arabians, Morgans, Quarter Horses, Appaloosas, and Paints. ER is a complex syndrome

that likely has numerous causes. Numerous terms such as tying-up, chronic intermittent rhabdomyolysis, azoturia, Monday morning disease, paralytic myoglobinuria, and exercise-associated myositis have been used for this syndrome.

▪ Clinical Signs

Classically, horses develop a stiff, stilted gait, with excessive sweating and a high respiratory rate during or after exercise (Fig. 42.17). Most commonly, signs are seen after only 15 to 30 minutes of light exercise. Following exercise, horses may stretch out as if to urinate, become extremely reluctant to move their hindquarters, and in severe cases show signs of colic or become recumbent. Attempts to move more severely affected animals may result in extreme pain, obvious anxiety, and possible exacerbation of the condition. Firm, painful muscles may be palpated over the back and hindlimb muscles. Scintigraphic evaluation of horses with rhabdomyolysis following exercise shows symmetric damage to the gluteal, semitendinosus, and semimembranosus muscles.[15] Myoglobinuria is a classic feature of more severely affected horses. Endurance horses often show other signs of exhaustion, including a rapid heart rate, dehydration, hyperthermia, synchronous diaphragmatic flutter, and collapse.[71]



FIG. 42.17 Exertional rhabdomyolysis in a horse showing signs of pain, stiffness, sweating, and elevated respiratory rate.

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▪ Etiology

A number of factors appear to precipitate episodes of ER. Some successful athletic horses may experience one or two isolated episodes of rhabdomyolysis during their lifetime, suggesting that environmental influences play an important role in sporadic cases.[184-188] Other horses may have chronic episodes of rhabdomyolysis that compromise their ability to compete. An inherent muscle dysfunction precipitated by certain triggering factors likely contributes to rhabdomyolysis in these horses.[7,189,190] Thus ER is a description of a syndrome that has many causes. To identify the cause in individual horses, it may be helpful to initially subdivide cases into those with no intrinsic muscle abnormality (extrinsic or sporadic form) and those with a suspected intrinsic abnormality of muscle function (intrinsic or chronic form). Causes for sporadic and chronic exercise-induced muscle damage are listed in Box 42.2.

Sporadic Exertional Rhabdomyolysis

Most cases of ER can be diagnosed on the basis of the animal's history and clinical signs. Confirmation of rhabdomyolysis requires determination of abnormally elevated serum CK and/or AST. Serum CK is often in the tens to hundreds of thousands of IU/L and AST in the thousands to tens of thousands. The degree of elevation in enzymes reflects the time lapse between rhabdomyolysis and obtaining a blood sample, as well as the extent of myonecrosis. Myoglobinuria is a common finding in severely affected horses. Horses with sporadic forms of ER develop rhabdomyolysis because of an extrinsic event or recurring extrinsic events that induce muscle damage with exercise. Usually a horse is presumed to have sporadic ER the first time it develops ER.[14] If ER recurs once the horse has been rested and gradually returned to exercise, an investigation of an inherent chronic form of ER is usually pursued. Causes of sporadic ER include focal or generalized trauma to muscle, exercise performed beyond any training adaptation or performed to the point of exhaustion, and dietary imbalances that affect muscle function.

▪ Signalment, History, and Diagnosis

Horses with sporadic ER may be of any age, breed, or sex and involved in a wide variety of athletic disciplines.[184] Sporadic ER usually occurs in horses with a history of adequate performance before onset of ER, and a familial history is absent. A diagnosis is made by history, clinical signs, and elevations of serum

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muscle enzymes. Once external perturbations that affect muscle function are corrected, complete resolution and a successful return to performance are expected. Resolution occurs following a reasonable period of rest, provision of a balanced diet, and a gradual introduction of a training program matched with performance demands. If over time ER recurs despite reasonable management, a diagnosis of chronic ER becomes more likely and further diagnostic testing is appropriate.

▪ Causes

Overexertion.

A history of an increase in work intensity without a foundation of consistent training for this level of exercise is usually the basis for suspecting a training imbalance as a cause of ER. Signs of muscle stiffness and gait changes range from mild to severe, and severity is reflected by variable elevations of serum CK activity.[14] Overexertion is a well-described cause of ER in polo horses, with 81% of cases of ER attributed to overexertion and 30% of cases occurring after a day of rest.[188] The incidence of ER is as high as 9% in the United States polo horses, with most of these horses having only one episode of ER early in the polo season.[188]

Pathologic changes are often not evident in light microscopic evaluation of muscle biopsies from individuals performing unaccustomed exercise, but electron microscopy shows significant disruption of the alignment of muscle contractile proteins within muscle fibers. In more severe cases, overt segmental damage to myofibers may be apparent in muscle biopsy. Repetitive overuse of muscles, such as occurs with overtraining, may result in exercise intolerance and is associated with pathologic changes such as increased muscle fiber size variation and centrally located myonuclei in muscle biopsies.[191]

Exhaustion.

Exhaustion occurs most commonly in endurance horses or racehorses exercising in hot, humid weather. Signs of heat exhaustion include weakness, ataxia, rapid breathing, muscle fasciculations, sweating, and in severe cases collapse. The body temperature may be elevated to 105° to 108° F. Muscles are frequently not firm on palpation, although serum CK activity can be markedly elevated and myoglobinuria may be noted.[71]

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Dietary Imbalances.

Episodes of ER may be triggered by diets with a high nonstructural carbohydrate (NSC) content and low forage content,[192,193] as well as by diets deficient in electrolytes. They may be exacerbated by inadequate selenium and vitamin E. Electrolyte balance within the body is difficult to determine accurately. One suggested means to practically assess electrolyte balance in horses is to measure urinary fractional excretion of electrolytes.[194] Measurement of urinary electrolyte excretion as an indicator of electrolyte balance is complicated because marked variation can occur from diet, exercise, and sampling technique among individuals, as well as within individuals from day to day.[4] Furthermore, the high calcium crystal concentration of alkaline equine urine requires acidification to accurately assess calcium and magnesium content.[4] The high potassium content interferes with sodium analysis using conventional ion-specific electrodes.[7] Thus although popular in the 1990s,[3,194,195] urinary fractional excretion is now rarely performed in the United States unless there is a strong suspicion that body depletion has occurred and a laboratory with gas chromatography mass spectrometry analysis of acidified urine can be located. It is important to ensure that horses receive sodium chloride in the diet, with higher concentrations needed in horses that compete in hot, humid weather. Between 30 and 50 g/day combined with 15 to 25 g of “lite” salt containing potassium chloride is recommended for horses exercising in hot, humid conditions and sweating extensively. The entire diet should be adequately balanced with calcium and phosphorus (Ca/P ratio of 2:1 is ideal).

Whole blood selenium concentrations measured in ethylenediaminetetraacetic acid (EDTA) or heparin tubes are of value in assessing selenium status in animals housed in areas where soil is deficient in selenium. In cases where selenium has been administered before blood collection, glutathione peroxidase activity can be used to assess potential selenium deficiency.[196] Vitamin E concentration should be measured in serum samples kept chilled and protected from light; however, variability in serum levels can be quite large, and repeat sampling is recommended if marginal levels are identified in the first sample tested. Horses with ER are infrequently deficient in selenium and vitamin E, and alone it may not be responsible for ER[197]; however, anecdotal reports suggest that in some cases supplementation may help to further prevent episodes of ER.

▪ Treatment

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Treatment of ER is directed at relieving anxiety and muscle pain and replacing fluid and electrolyte losses. Tranquilizers such as acepromazine (0.04 to 0.06 mg/kg IM or IV), xylazine (0.5-1.1 mg/kg IV), or detomidine (0.02 to 0.04 mg/kg IV) combined with butorphanol (0.01 to 0.04 mg/kg) provide excellent sedation and analgesia. For horses with extreme pain and distress, a constant rate infusion of detomidine, lidocaine, or butorphanol may provide additional pain relief. NSAIDs such as ketoprofen (2.2 mg/kg IV), phenylbutazone (2.2 to 4.4 mg/kg IV or PO), and flunixin meglumine (1.1 mg/kg IV or PO) are frequently used to relieve pain but should be used with caution on dehydrated animals. Intravenous or intragastric dimethyl sulfoxide (as a <10% solution) is used as an antioxidant, anti-inflammatory, and osmotic diuretic for severely affected horses. Methylprednisolone sodium succinate (2.2 to 4.4 mg/kg) has been advocated by some veterinarians in the acute stage if horses are recumbent. Muscle relaxants such as methocarbamol (5 to 22 mg/kg IV slowly) seem to produce variable results, possibly depending on the dosage used. The administration of dantrium sodium (2 to 4 mg/kg PO) in severely affected horses may decrease muscle contractures and possibly prevent further muscle necrosis. The dose can be repeated q8h to q24h if necessary. Overdosing produces muscle weakness.

Severe rhabdomyolysis can lead to renal compromise due to ischemic and combined nephrotoxic effects of myoglobinuria, dehydration, and NSAIDs. In mildly dehydrated horses, provision of free-choice electrolytes and water or administration of fluids via a nasogastric tube may be adequate. Horses with moderate to severe dehydration require IV administration of balanced polyionic electrolyte solutions. Hyperkalemia can occur with severe rhabdomyolysis, necessitating the use of isotonic sodium chloride. If hypocalcemia is present, then supplementing IV fluids (100 to 200 mL of 23% calcium borogluconate) is recommended, but serum calcium should not exceed a low normal range. Affected animals are usually alkalotic, making bicarbonate therapy inappropriate. In severely affected animals, regular monitoring of serum creatinine is advised to assess the extent of renal damage.

Following rhabdomyolysis, horses should be stall rested on a hay diet for a few days. Small paddock turnout in a quiet area for a few hours twice a day is then helpful. Horses may be hand walked at this time, but more than 5 to 10 minutes at a time may induce another episode of rhabdomyolysis. For horses with sporadic forms of tying-up, rest with regular access to a paddock should continue until serum muscle enzyme concentrations are normal. For chronic cases of tying-up, this much rest may not be appropriate. Training should be

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resumed gradually, and a regular exercise schedule that matches the degree of exertion to the horse's underlying state of training should be established. Endurance horses should be supplemented with electrolytes and water during an endurance ride and monitored particularly closely during hot, humid conditions.

▪ Management

Because the inciting cause is usually temporary in sporadic cases, most horses respond to a few weeks of rest, dietary adjustments, and a gradual increase in training. Regular access to a paddock once stiffness subsides and weekly monitoring of serum CK activity are recommended. Horses are much more susceptible to a second episode of ER in the 2 weeks following an acute episode, and allowing horses the ability to calmly determine their own exercise through turnout often avoids exacerbating rhabdomyolysis. If that is not feasible, hand walking needs to performed with caution and limited to no more than a few minutes initially. While the horse is rested, the diet can be assessed to ensure that the ration is fed in an amount recommended by the manufacturer for the corresponding level of exercise. This will ensure that the proper balance of vitamins and minerals is provided. If excessive calories are provided when fed at the manufacturer's recommended levels, the diet should be switched to a less calorie-dense vitamin/mineral balanced diet. A salt block or 30 to 50 g (1 to 3 tablespoons) of salt per day will provide the necessary additional sodium chloride, with the amount fed depending on the heat, humidity, and intensity of exercise. Once serum CK returns to normal, training can be resumed gradually. A regular exercise schedule, beginning with 20 minutes or less of exercise per day, is gradually increased to eventually match the expected amount of daily exercise to the underlying state of conditioning.

Chronic Exertional Rhabdomyolysis

Horses that have repeated episodes of ER from a young age, from the time of purchase, or after they are put back into training after a long period of rest may have an underlying intrinsic abnormality of muscle function. Many horses with intrinsic muscle defects will have repeated episodes of ER with minimal exercise even when the dietary and training recommendations for sporadic ER are followed. Five specific intrinsic causes of ER have been identified to date (see Box 42.2). Idiopathic ER represents other causes of ER that have yet to be identified. In all of these intrinsic forms of chronic ER, it appears that specific

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environmental stimuli are necessary to trigger muscle necrosis in genetically susceptible animals. Horses cannot be cured of their susceptibility to this condition, but if the specific form of ER is identified, changes in management can be implemented in order to minimize episodes of rhabdomyolysis.

Polysaccharide Storage Myopathy

Polysaccharide storage myopathy (PSSM) was first recognized as a specific myopathy in Quarter Horse–related breeds in 1992[198]; however, there are individual cases of abnormal polysaccharide inclusion reported in equine muscle dating back to 1979.[17,199,200] The remarkable feature of the first horses reported to have PSSM was twofold-higher muscle glycogen concentrations than normal horses and abnormal granular amylase-resistant inclusions in histologic sections.[198] Similar biopsy findings were reported in Belgian and Percheron draft horses in 1997.[201] Since that time, many hundreds of horses of a variety of breeds have been diagnosed with PSSM.

▪ Terminology

Several acronyms are used for polysaccharide storage myopathy besides PSSM,[202] including EPSM or EPSSM (equine polysaccharide storage myopathy).[192,203] Considerable controversy existed as to whether these acronyms encompassed one muscle condition.[192,193,204] In 2008 a mutation in the glycogen synthase 1 *(GYS1)* gene was found to be highly associated with the presence of amylase-resistant polysaccharide in skeletal muscle from Quarter Horses with PSSM.[205] Genetic testing of hundreds of horses previously diagnosed with PSSM by muscle biopsy revealed that the majority of cases of PSSM characterized by amylase-resistant polysaccharide in skeletal muscle had this genetic mutation.[206] However, some cases previously diagnosed with PSSM by muscle biopsy, particularly those with excessive amylase-sensitive glycogen, did not possess the genetic mutation. This suggested that there are at least two forms of PSSM.[206,207] For clarity, the form of PSSM caused by a *GYS1* gene mutation is now called *type 1 (PSSM1)*, whereas the form of PSSM not caused by the *GYS1* mutation and whose origin is yet unknown is now called *type 2 (PSSM2)*.[207] PSSM1 is likely the same disorder described as “azoturia” or “Monday morning disease” in workhorses in the nineteenth and twentieth centuries.[208]

Type 1 Polysaccharide Storage Myopathy

Etiology.

PSSM1 is caused by a single-base-pair mutation in the *GYS1* gene resulting in an arginine to histidine substitution at codon 309. Horses with PSSM1 have a gain of function in glycogen synthase enzyme (in basal and stimulated states) because of an autosomal dominant mutation in the *GYS1* gene encoding glycogen synthase.[205] The higher than normal activity in both basal states and when activated by insulin and glucose 6-phosphate appears to have a novel link to the regulation of energy generation in muscle fibers. A deficit in energy metabolism represented by high myofiber inosine monophosphate was demonstrated in individual muscle fibers of horses with PSSM1 after light exercise in association with high serum CK activity.[209]

▪ Prevalence

PSSM1 is estimated to have emerged approximately 1600 years ago when the great horse was being developed from European draft and light horse breeds to carry knights with heavy armor into battle.[205] The highest prevalence of PSSM1 appears to occur in draft horses derived from Continental European breeds (Table 42.3).[210] In fact, many Continental European drafts are homozygous for the dominant PSSM1 trait (90% prevalence of PSSM in Trekpaards, with 40% of tested Belgian Trekpaards homozygous). North American Belgians and Percherons also have a high prevalence of PSSM1, with 36% and 54% of horses affected, respectively.[211] In contrast, the prevalence of PSSM is low in United Kingdom–derived breeds such as Shires and Clydesdales,[211] but PSSM1 is present in other U.K. horse breeds such as Irish Draught, Cob, and Connemara.[212] Numerous other breeds, more than 20 in fact, have the *GYS1* mutation responsible for PSSM1.

TABLE 42.3

Number of North American and European Horses Tested and the Percentage of Horses Testing Positive (Heterozygous and Homozygous) for the *GYS1* Mutation in Breeds Sampled Using Random and Nonrandom Sampling

Random Sampling	Breed	Number Tested	Prevalence (%)
North America	Percheron	149	62
(McCue and colleagues, 2010)[211]	Belgian	149	39
	Clydesdale[a]	132	0
	Shire	195	0.5
	Quarter Horse	335	6.6
	Paint	195	7.7
	Appaloosa	152	5.9
	Morgan	214	0.9
	Thoroughbred	96	0
	Arabian	100	0
	Norwegian Fjord	46	0
	Icelandic Pony	45	0
Nonrandom Sampling	**Breed**	**Number Tested**	**Prevalence (%)**
Europe	Belgian Trekpaard	38	92
(Baird and colleagues, 2010)[210]	Netherlands Trekpaard	23	74
	Comtois	88	80
	Breton	51	63
	Swedish Ardenner	29	38
	Rheinisch-Deutsches Kaltblut	44	68
	Sud-Deutsches Kaltblut	265	20
	Hannoverian	214	0
(Isgren and colleagues, 2010)[215]	Standardbred	36	0

[a]Both randomized and nonrandomized samples.

Prevalence estimates of PSSM1 in Quarter Horses range from 6% to 10% of the breed and 6% to 8% for Paints and Appaloosas.[56,213] The highest frequency of PSSM1 occurs in halter Quarter Horses (28% affected), and the lowest frequency occurs in racing Quarter Horses.[56] The *GYS1* mutation has been identified in approximately 72% of Quarter Horses diagnosed with PSSM by muscle biopsy and in 18% of warmbloods of a variety of types diagnosed with PSSM by muscle biopsy.[214] The prevalence of PSSM1 is very low to nonexistent in light horse breeds such as Arabians, Standardbreds, and Thoroughbreds (see Table 42.3).[215]

▪ Risk Factors

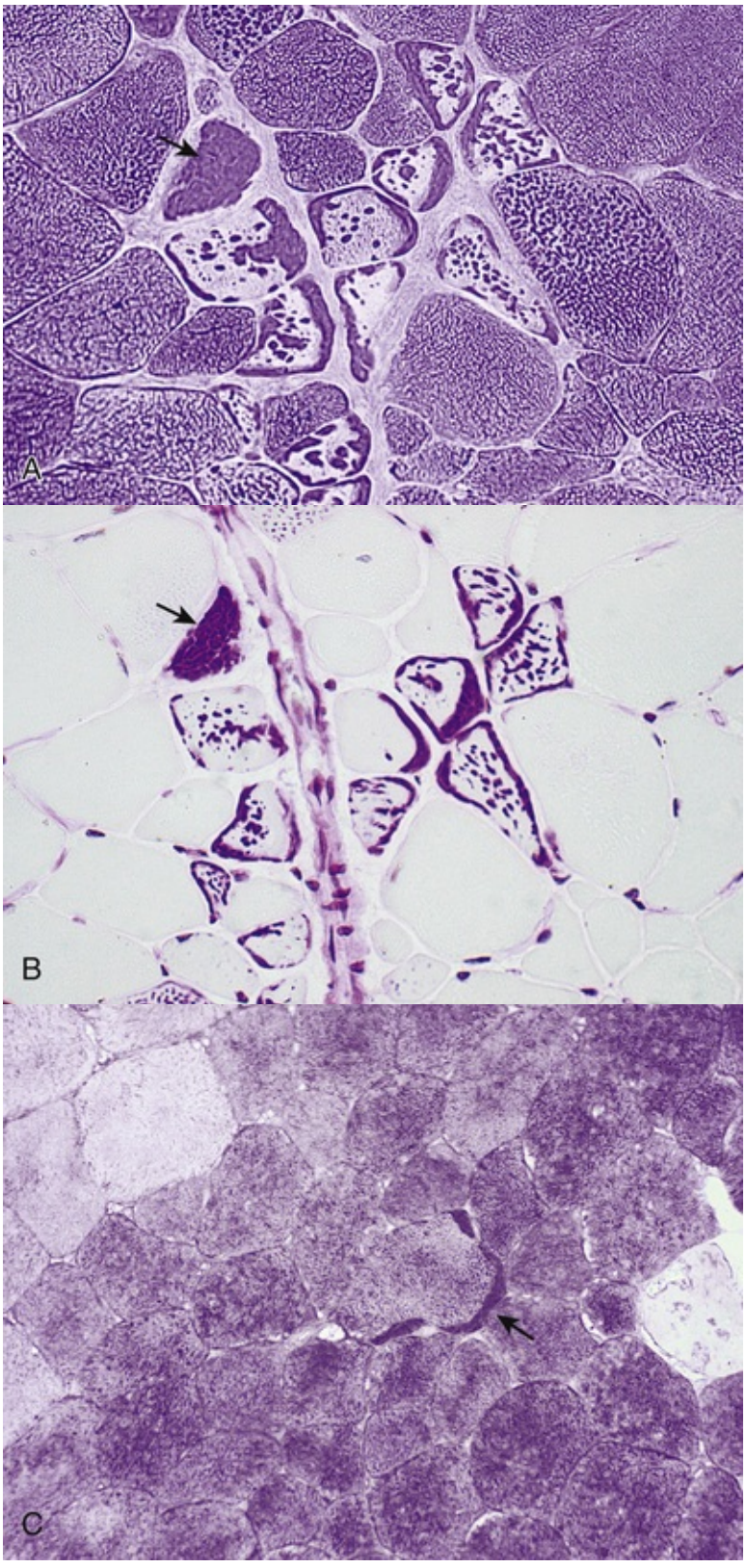
Some horses with PSSM1 are asymptomatic, whereas other horses routinely show stiffness with exercise.[216,217] In a family of warmbloods sired by a stallion with the *GYS1* mutation, the mutation resulted in a sevenfold-higher risk of developing ER, with 34% of horses with the *GYS1* mutation lacking clinical signs of PSSM1.[217] The reason for variability in clinical signs of PSSM1 probably lies in the influence of diet, exercise, other environmental factors, and other genes on the expression of the disease.[192,218,219] There is no significant

temperament, body type, or gender predilection for PSSM1.[8] The most common trigger for clinical signs of PSSM1 is less than 20 minutes of exercise at one time.[189,217] Clinical signs occur most commonly at a walk and trot, particularly if the horse has been rested for several days before exercise or is unfit. Diets high in NSCs also increase the risk of muscle pain and stiffness in PSSM1 horses.[218,220] About 40% of owners feel there is a seasonal incidence to the development of clinical signs, which some have attributed to quality of grass available at the time.[189,221] Although exercise is by far the most common trigger for PSSM, Quarter Horse and Paint foals and weanlings may develop rhabdomyolysis in conjunction with a systemic illness.[222]

▪ Diagnosis

A high degree of suspicion of a diagnosis of PSSM1 arises from clinical signs and persistent elevations in serum CK and AST activities.[8,198,218] If horses have normal serum muscle enzymes at rest, an exercise test consisting of a maximum of 15 minutes lunging at a walk and trot may help to determine if subclinical ER is present.[7] Supportive evidence would include a minimum of a threefold elevation in CK activity 4 hours after exercise.

Muscle biopsy provides one means to diagnose PSSM1.[18,198,223] The distinctive features of PSSM1 in muscle biopsy samples are numerous subsarcolemmal vacuoles and dense, crystalline periodic acid–Schiff (PAS)–positive, amylase-resistant inclusions (Fig. 42.18, *A* and *B*). A diagnosis can be made irrespective of diet and proximity of sampling to recent episodes of rhabdomyolysis. A false-negative diagnosis of PSSM1 by muscle biopsy may occur if biopsy samples are small or if horses are younger than 1 year of age.[224]


A
B
C

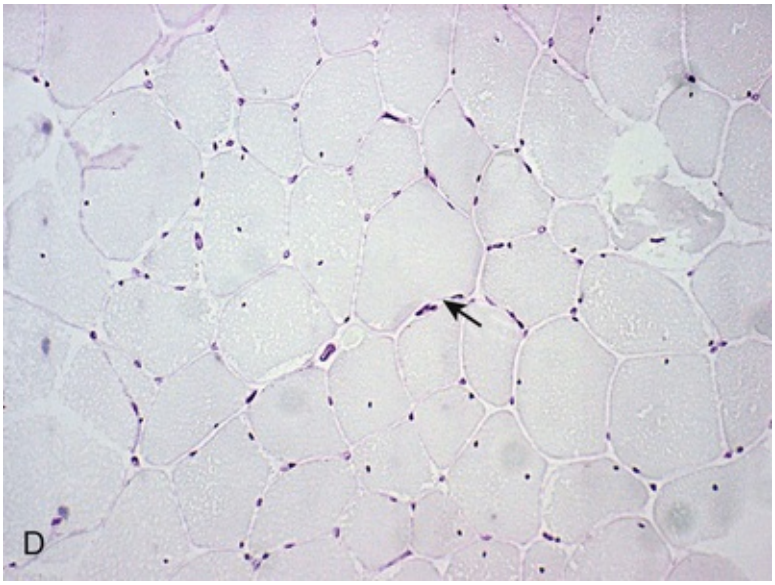


FIG. 42.18 Consecutive sections of a gluteal biopsy from a horse with type 1 polysaccharide storage myopathy (PSSM) stained with **(A)** periodic acid–Schiff (PAS) stain for glycogen and **(B)** amylase-PAS stain. *Arrows* show typical aggregates of intensely staining polysaccharide, which are resistant to amylase digestion. **(C)** PAS stain and **(D)** amylase-PAS stain of a gluteal biopsy from a horse with type 2 PSSM. *Arrows* show an aggregate of polysaccharide under the sarcolemma, which is sensitive to amylase digestion.

The gold standard for diagnosis of PSSM1 is genetic testing for the *GYS1* mutation performed on whole blood or hair root samples. It is important to note that in draft horses of Continental European origin, the very high prevalence of PSSM in essence means that there is a high chance that any clinical sign could be falsely associated with the disease PSSM1.[210] Thus clinical judgment is required to determine whether the clinical signs of the animal could reasonably be associated with a myopathic process.

▪ Clinical Signs

Acute.

On average, horses show signs of PSSM1 at 5 years of age; however, this can range from 1 to 14 years of age.[189] Acute clinical signs occur when horses are calm and include tucking up of the abdomen, fasciculations in the flank, muscle stiffness, sweating, reluctance to move forward, and overt firm muscle contractures (Fig. 42.19).[189] The hindquarters are frequently affected, but back, abdomen, and forelimb muscles may also be involved. Signs of pain can last for

more than 2 hours, and about 10% of cases become recumbent.[189] Less common signs of PSSM in Quarter Horses include gait abnormalities, mild colic, and muscle wasting. During an acute episode of ER, horses with PSSM1 often have markedly elevated serum CK activity of greater than 35,000 U/L, and myoglobinuria may be present. Severe colic-like pain post exercise and myoglobinuric renal failure are less common presenting complaints.[8,225]



FIG. 42.19 Typical stance of a horse with polysaccharide storage myopathy after 10 minutes of walking and trotting. Note the tucked-up abdomen and camped-out stance that were concurrent with firm muscles, fasciculations in the flank, and elevated serum CK activity.

Chronic

Light Breeds.

Chronic signs of PSSM1 in riding horses include a lack of energy when under saddle, reluctance to move forward, stopping and stretching out as if to urinate (see Fig. 42.19), and a sour attitude toward exercise.[189] Horses may have a combination of low-grade reluctance to exercise, poor performance, and repeated episodes of ER.[217,226] PSSM1 may also present in dressage and showjumpers as chronic back pain, failure to round over fences, and fasciculations or pain on palpation of lumbar muscles.[227,228] The range of severity of clinical signs of PSSM1 can be wide, with complete incapacitation in rare cases. Serum CK activities are often elevated in unmanaged horses, even

when horses are rested.[8] The median CK and AST activities for all PSSM1 Quarter Horses with muscle biopsies submitted to the Equine Neuromuscular Diagnostic Laboratory were 2809 and 1792 U/L, respectively.

A small number of Quarter Horses and Paints have both the *GYS1* mutation and the genetic mutation for malignant hyperthermia *(RYR1).*[219] This results in particularly severe signs of ER and a limited response to diet and exercise changes. During an episode of ER, excessively high body temperatures may develop, and sudden death can occur in horses with the *RYR1* mutation. This combination occurs most often in halter and pleasure horses.

Draft Horse and Draft Crosses.

The average age of draft horses diagnosed with PSSM is about 8 years of age. Many draft horses with PSSM are asymptomatic.[216] Signs of severe rhabdomyolysis and myoglobinuria may occur in horses that are fed high-grain diets, exercised irregularly with little turnout, or put under general anesthesia.[175,189] Rhabdomyolysis can be so severe that it leads to recumbency and death.[175] Other signs of PSSM in draft horses include progressive weakness and muscle loss resulting in difficulty rising in horses with normal serum CK activity. Clinical signs appear to be more severe in homozygotes.[229] Although the condition shivers was previously attributed to PSSM, a recent study found no causal association between these two conditions.[216] The median serum CK and AST activities in draft horses from which biopsies were sent to the Equine Neuromuscular Diagnostic Laboratory were 459 and 537 U/L, respectively.

▪ Pathophysiology

A high-NSC diet increases the propensity to develop muscle pain with aerobic exercise in PSSM1 horses.[192,218] A potential scenario in PSSM1 horses on high-NSC diets could be that nutrient switches do not fully activate enzymes such as pyruvate dehydrogenase during exercise, limiting adequate acetyl-CoA for oxidative metabolism. Although acetyl-CoA could also be supplied by fatty acid oxidation, PSSM horses on high-NSC diets have low plasma nonesterified free fatty acid concentrations, possibly due to suppression of lipolysis by high insulin.[218] A further factor reducing fatty acid oxidation in PSSM horses on high-NSC diets could be that high muscle citrate concentrations direct acetyl-CoA away from the citric acid cycle toward malonyl-CoA, the committed step

for fatty acid synthesis.[230] In addition, accumulation of malonyl-CoA causes inhibition of carnitine palmitoyltransferase, the key enzyme necessary to transport long-chain fatty acids into the mitochondria for β-oxidation.[231,232] Thus PSSM horses fed high-NSC diets may be unable to generate sufficient acetyl-CoA from either carbohydrate or fat metabolism to fuel muscle contraction during submaximal exercise. The common occurrence of clinical signs during the first 20 minutes of exercise may be because, at this stage of exercise, muscles rely heavily on glycogen and glucose for energy. Low dietary starch and fat supplementation decrease muscle citrate concentrations and increase plasma free fatty acid concentrations, which may well facilitate muscle fat metabolism in PSSM1 horses.[233]

Type 2 Polysaccharide Storage Myopathy.

Much less is known about type 2 PSSM because, as it turns out, previous research on PSSM has largely involved horses with type 1 PSSM. Current knowledge of type 2 PSSM is based on retrospective evaluation of cases diagnosed with PSSM by muscle biopsy that are now known to be free of the *GYS1* mutation and on a few years of prospective clinical cases.[223,227]

▪ Prevalence

Approximately 28% of cases of PSSM diagnosed by muscle biopsy in Quarter Horses have PSSM2 because they do not have the *GYS1* mutation.[206] Type 2 PSSM seems to be common both in high-performance Quarter Horse types such as barrel racing, reining, and cutting horses and in pleasure and halter horses. In the United Kingdom approximately 35% of PSSM cases diagnosed by muscle biopsy have PSSM2.[212] Type 2 PSSM also occurs in Paints, Appaloosas, and Morgans. About 80% of cases of PSSM diagnosed by biopsy in warmbloods have PSSM2.[206] Breeds affected include Dutch Warmblood (highest prevalence), Swedish Warmblood, Selle Français, Hanoverian, Friesian, Westphalian, Canadian Warmblood, Irish Sport Horse, Gelderlander, and Icelandic horses. Many other light breeds have also been diagnosed with PSSM2, including Standardbreds, Thoroughbreds, and Arabians.

▪ Pathogenesis

The cause or causes of PSSM2 are currently unknown. Muscle glycogen

concentrations are not as high as those found in PSSM1, and glycogenolytic enzyme defects have not been identified in the few cases where enzymes were measured.[223] To date, the only reported abnormality in muscle ultrastructure is an increase in normal beta glycogen particles.[207] It may well be that a group of conditions currently captured under the term *type 2 PSSM* have separate etiologies but share common findings of glycogen accumulation and poor performance. A heritable predisposition is suspected in Quarter Horses but yet to be proven.

▪ Clinical Signs

Acute.

In Quarter Horses, Thoroughbreds, Standardbreds, and Arabian horses, exertional rhabdomyolysis is the most common clinical sign of PSSM2.[223] In warmblood horses, episodes of exertional rhabdomyolysis are more intermittent in nature.[223]

Chronic.

Chronic signs of PSSM2 are often most closely related to poor performance rather than recurrent ER and elevations in serum CK activity. An undiagnosed gait abnormality, sore muscles, and drop in energy level and willingness to perform after 5 to 10 minutes of exercise are common complaints in horses with PSSM2.[223] Warmbloods with PSSM2 may also have painful, firm back and hindquarter muscles, reluctance to collect and engage the hindquarters, poor rounding over fences, gait abnormalities, and slow onset of atrophy. The mean age of onset of clinical signs in warmbloods is between 8 and 11 years of age, with the median CK and AST activities being 323 and 331 U/L, respectively.

▪ Diagnosis

PSSM2 must be diagnosed by muscle biopsy where increased or abnormal PAS-positive material that is usually amylase sensitive is apparent (see Fig. 42.18, *C* and *D*).[207] Determination of what constitutes an abnormal amount of amylase-sensitive glycogen is subjective, the specificity of the diagnosis may be low, and false-positive diagnoses may occur. Consideration should be made for state of training because highly trained horses have increased glycogen storages as a normal response to training. Further, glycogen is commonly found near

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capillaries in normal horses, and PAS-positive sarcoplasmic masses can be found in 60% of healthy horses, so these should not be diagnostic criteria for PSSM2.[234] Formalin-fixed sections show a greater deposition of subsarcolemmal glycogen and precipitation of glycogen in one area of a fiber even in healthy horses, and these should not be considered diagnostic criteria for PSSM2.[18] Other histopathologic features that may be present with PSSM2 include centrally located nuclei, subsarcolemmal vacuoles, muscle necrosis, macrophage infiltration of myofibers, regenerative fibers, and fiber atrophy.[223] Some laboratories grade polysaccharide accumulation as mild, moderate, and severe, where mild accumulation represents a category that has a higher chance of being a false-positive diagnosis. Mild PSSM cases in particular should receive a full physical examination to ensure that there are no other underlying causes for performance problems.

Management of Type 1 and Type 2 Polysaccharide Storage Myopathy.

Owners need to be aware that any horse diagnosed with PSSM will always have an underlying predilection for muscle soreness. The best that can be done is to manage horses in the most appropriate fashion to minimize clinical signs. With adherence to both diet and exercise recommendations provided in this chapter, at least 70% of horses show notable improvement in clinical signs and many return to acceptable levels of performance.[189,192,227] There is, however, a wide range in the severity of clinical signs shown by horses with PSSM; those horses with severe or recurrent clinical signs will require more stringent adherence to diet and exercise recommendations in order to regain muscle function.

Rest.

PSSM horses that are confined for days to weeks following an episode of rhabdomyolysis often have persistently elevated serum CK activity.[224] In contrast, PSSM horses kept on pasture with little grain supplementation often show few clinical signs of rhabdomyolysis and have normal serum CK activity.[224] As a result, a common recommendation for horses with PSSM is to limit stall confinement to less than 48 hours after an episode of rhabdomyolysis and then provide turnout in paddocks of gradually increasing size. Providing horses with as much free exercise as possible on pasture appears to be beneficial in the long term. If pasture is lush, a grazing muzzle may be necessary.[226]

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Following an acute episode, excitable horses may require tranquilization before turnout to avoid excessive galloping. Hand walking horses initially recovering from an episode of PSSM for more than 5 to 10 minutes at a time may trigger another episode of rhabdomyolysis.

Exercise.

The beneficial response to low-starch, fat-supplemented diets only occurs if it is instituted in conjunction with a regular incremental exercise program.[218] Regular daily exercise in PSSM horses over a 3-week period has been shown to produce a dramatic decrease in serum CK responses to exercise, whereas stall confinement often causes elevations in serum CK activity post exercise.[218,224] One common adaptation to daily training is an increase in oxidative capacity in skeletal muscle. The activity of these enzymes, however, was equally low in control Quarter Horses. Whether the beneficial effect of daily exercise on PSSM horses is a result of improved oxidative enzyme capacities or enhanced substrate flux or both has not been elucidated.

Exercise Regimens.

Important principles to follow when starting exercise programs in PSSM horses include to (1) provide adequate time for adaptation to a new diet before commencing exercise; (2) recognize that the duration of exercise, not its intensity, is of primary importance; (3) ensure the program is gradually introduced and consistently performed; and (4) minimize any days without some form of exercise. If horses have experienced a moderate to marked episode of rhabdomyolysis recently, 2 weeks of turnout and diet change are often beneficial before recommencing exercise. Exercise should be relaxed, and the horse should achieve a long, low frame without collection. For many horses this is most readily done in a round pen or on a lunge line, but it can be done under saddle if needed. Successive daily addition of 2-minute intervals of walk and trot beginning with only 4 minutes of exercise and working up to 30 minutes after 3 weeks is often recommended.[8,14] If horses had minor elevations in 4-hour postexercise CK with the 15-minute exercise test, they may begin at 15 minutes of exercise. Owners often do not recognize that walking the horse for 10 minutes or more initially can trigger muscle soreness in PSSM horses. Advancing the horse too quickly often results in an episode of rhabdomyolysis and repeated frustration for the owner. Work can usually begin under saddle after 3 weeks of ground work and can gradually be increased by adding 2-minute intervals of

collection or canter to the initial relaxed warm-up period at a walk and trot. Unless a horse shows an episode of overt rhabdomyolysis during the initial 4 weeks of exercise, reevaluating serum CK activity is not helpful for the first month. This is because it is common to have subclinical elevations in CK activity when exercise is reintroduced, and a return to normal levels often requires 4 to 6 weeks of gradual exercise.[8] Keeping horses with PSSM fit seems the best prevention against further episodes of rhabdomyolysis.

Diets for Polysaccharide Storage Myopathy.

The basis for designing PSSM diets is the belief that lowering the daily starch and sugar intake and increasing dietary fat content will decrease the glucose load, increase the availability of nonesterified fatty acid for muscle metabolism, and lower serum insulin concentrations.[218] Quarter Horses naturally have little lipid stored within muscle fibers. The end result would thus be decreased uptake of glucose into muscle cells, less substrate available for—and stimulation of—glycogen synthesis, and normalization of substrate flux. Owners report that this type of diet improves clinical signs of muscle pain, stiffness, and exercise tolerance in draft horses, warmbloods, Quarter Horses, and other breeds.[189,192,217,227] Dietary change appears to have less impact on alleviating gait changes such as shivers.[227]

Caloric Balance.

The horse's caloric requirements at an ideal body weight are the most important considerations in designing the diet for PSSM. This is because many horses with PSSM are easy keepers and may be overweight at the time of diagnosis. Adding excessive calories in the form of fat to an obese horse may produce metabolic syndrome and is contraindicated. If necessary, caloric intake should be reduced by using a grazing muzzle during turnout, feeding hay with a low NSC content at 1% to 1.5% of body weight, providing a low-calorie ration balancer, and gradually introducing daily exercise. Rather than provide dietary fat to an overweight horse, fasting for 6 hours before exercise can be used to elevate plasma free fatty acids before exercise and alleviate any restrictions in energy metabolism in muscle.

Selection of Forage.

Quarter Horses have been shown to develop a significant increase in serum

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insulin concentrations in response to consuming hay with an NSC of 17%, whereas insulin concentrations are fairly stable when fed hay with 12% or 4% NSC content.[220] Because insulin stimulates the already overactive enzyme glycogen synthase in the muscle of PSSM1 horses, selecting hay with 12% or less NSC is advisable. The degree to which the NSC content of hay should be restricted below 12% NSC depends on the caloric requirements of the horse. Feeding a low-NSC hay of 4% provides room to add an adequate amount of fat to the diet of easy keepers without exceeding the daily caloric requirement and inducing excessive weight gain. For example, a 500-kg horse on a routine of light exercise generally requires 18 Mcal/day of digestible energy (DE). Fed at 2% of body weight, a 12% NSC mixed grass hay almost meets the daily caloric requirement by providing 17.4 Mcal/day. Thus with a 12% NSC hay there is only room for 0.6 Mcal of fat per day (72 mL of vegetable oil) in order to achieve 18 Mcal of energy. In contrast, a 4% NSC Blue Grama hay would provide 13.5 Mcal/day, which would allow a reasonable addition of 4.5 Mcal of fat per day (538 mL of vegetable oil).

Selection of Fat Source.

High-fat diets increase plasma free fatty acid concentrations and thus the availability of fats for oxidation in skeletal muscle.[218] Long-chain fat diets also appear to increase glycogenolytic, glycolytic, and oxidative flux in PSSM1 muscle as shown by higher glucose 6-phospate, lower lactate, and higher pyruvate concentrations in the muscle of PSSM1 horses fed and trained on a commercial high-fat diet (Re-Leve [Kentucky Equine Research, Versailles, Ky.]) compared with sweet feed.[220] Thus one means to overcoming limitations in delivery of oxidative substrates in PSSM1 horses is to provide ample long-chain fat in the diet. The major sources of dietary fat for horses are vegetable based, including vegetable oils and rice bran or animal-based fat (tallow [solid rendered fat of cattle and sheep], lard, fish oil). Vegetable oils are highly unsaturated, very digestible (90% to 100%), and very energy dense. Suitable forms include soybean, corn, safflower, canola, flaxseed, linseed, peanut, and coconut. Controlled research studies in exercising PSSM horses have shown a decrease in muscle pain and serum CK in response to the addition of corn oil[233] and also a concentrate of soybean oil and rice bran (Re-Leve).[218] The amount of oil added in these trials constituted at least 13% of daily DE. Some veterinarians have advocated that as much as 25% of DE be fed in the form of fat to PSSM

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horses.[193] As discussed earlier, the principal consideration here should be whether this provides excessive calories and additional weight gain because feeding 13% DE as fat may well be effective in reducing muscle pain. Limited research has been performed on the form of oil to feed PSSM horses. Whether there is any direct beneficial effect on skeletal muscle of providing energy in the form of omega-3 versus omega-6 fatty acids has yet to be determined. Due to the potential additional oxidant stress of fats, vitamin E (1000 to 5000 U/day) should be fed to horses receiving high-oil diets.

Low-Starch, High-Fat Concentrates.

Although oils are energy dense and inexpensive, they have the disadvantages of being messy, unpalatable to some horses, prone to rancidity in warm temperatures, and difficult to feed in large amounts. As such, a number of concentrates that contain fats have been developed. The important principle to be met by such feeds is that the starch and sugar components are low enough and the fat supplementation high enough to ensure that in the total diet, the calories supplied by NSC comprise no more than 10% to 15% of the daily DE and the calories supplied by fat comprise about 12% to 15% of daily DE.[218] Common fat sources used in such concentrates include, in addition to the oils mentioned earlier, stabilized rice bran or animal fats. Rice bran and its products are palatable to most horses, have a moderate NSC content approximately 25% by weight, contain approximately 20% fat by weight, as well as vitamin E, and are naturally high in phosphorus. The NSC component of rice bran can vary if the manufacturing process is not careful to exclude the white rice grain. Commercial rice bran products occur as powder or an extruded pellet and are considerably more stable in warm temperatures compared with animal fat and vegetable oils. A number of well-balanced, low-starch, high-fat commercial diets are suitable for horses with PSSM.[218] Some commercial feeds meet the recommended nutritional needs of PSSM horses in one pelleted ration. These feeds typically contain at least 10% to 15% fat by weight and less than 20% NSC by weight. Some feed companies offer similar nutritional content by blending two or more manufactured feeds or by supplementing with oils or rice bran. At present, the NSC content of equine feed products is not consistently listed on the feed tag, and consultation with the feed manufacturer is necessary to obtain this information. Nutritional support is available through most feed manufacturers in designing an appropriate diet. There is a great deal of variation in individual tolerance to dietary starch; however, horses with more severe clinical signs of

PSSM appear to require the greatest restriction in starch intake.

Expectations.

The beneficial effects of low-starch, high-fat diets require that horses are trained daily to enhance enzymes involved in fat and glucose metabolism. It is important to note that a horse diagnosed with PSSM will always have an underlying predilection for muscle soreness, and the best that can be done is to manage horses to minimize clinical signs. With adherence to both diet and exercise recommendations, 70% to 75% of Quarter Horses and warmbloods show notable improvement in clinical signs, and many return to acceptable levels of performance.[189,193,226,227] There is, however, a wide range in the severity of clinical signs shown by horses with PSSM; those horses with severe or recurrent clinical signs will require more stringent adherence to diet and exercise recommendations in order to regain muscle function. PSSM horses that also have the mutation for malignant hyperthermia do not respond as well to diet and exercise recommendations and may continue to develop ER with the possibility of a fatal episode.[207]

Myofibrillar Myopathy

Myofibrillar myopathy (MFM) is a recently identified disorder in horses presenting with exercise intolerance or intermittent ER that is defined by specific histopathology.[235-237] First and foremost, MFM horses have cytoplasmic aggregates of the cytoskeletal protein desmin in scattered muscle fibers. Desmin functions to align sarcomeres at the Z-disc and tether them to the cell membrane. Other ultrastructural derangements evident in electron microscopy include disrupted myofibrillar alignment, ectopic accumulation of cytoskeletal proteins and Z-disc degeneration. In some cases, MFM is also characterized by cytoplasmic aggregates of glycogen similar to PSSM2.[235,237] This is likely because pools of glycogen form within disrupted myofibrils. MFM may represent a more extreme subset of PSSM2. Muscle glycogen concentrations in horses with MFM are similar to controls.

Warmblood horses diagnosed with MFM have an insidious onset of exercise intolerance notable by 6 to 8 years of age characterized by lack of stamina, unwillingness to go forward, inability to collect, abnormal canter transitions, and inability to sustain a normal canter.[237] Unresolved hindlimb lameness, stiffness, muscle pain, and, rarely, an episode of ER are reported. Serum CK and AST

activities are usually within normal limits unless samples are taken in conjunction with ER.[237]

Arabian endurance horses diagnosed with MFM usually have a history of intermittent elevations in serum CK activity after endurance rides (>10,000 U/L) or during exercise that follows a week or more of rest.[235,236] Horses do not necessarily always show the same degree of pain, sweating, and reluctance to move as is frequently seen in other forms of acute ER. Myoglobinuria can be observed in horses with only mild muscle stiffness. Between episodes, the heart rate, lactate, CK, and AST responses to exercise are normal.[236]

The best means to manage horses with MFM has yet to be determined. Many horses have been managed in a way similar to horses with PSSM2. There is no information to suggest that limiting NSC or the addition of fat is necessarily of benefit to horses with MFM. The addition of an amino acid supplement (whey based) is currently being tried as a mechanism to enhance turnover and regeneration of myofibrils within muscle cells.[237]

Recurrent Exertional Rhabdomyolysis

The term *recurrent exertional rhabdomyolysis* (RER) describes a subset of ER that is believed to be due to an abnormality in the regulation of muscle contraction and relaxation.[7,19,21,238] Research into RER has primarily been performed in Thoroughbreds and, to a lesser extent, Standardbreds.[21,187,215,239] Scientific studies of RER have used a small number of horses that share common clinical signs of ER and have abnormal muscle contracture tests.[19-21] Broader epidemiologic and genetic studies have assumed that the same pathophysiologic basis for ER exists in the majority of Thoroughbreds and Standardbreds with similar clinical signs. Whether this is true or not will require more research. There are reports of some Arabians and warmbloods with ER that may also suffer from RER on the basis of overlapping histories, clinical signs, muscle biopsy findings, and response to management.[227]

▪ Pathogenesis

Rhabdomyolysis is triggered suddenly during exercise in RER horses, which results in a sharp rise in serum myoglobin and CK activity.[6] Clinically, the triggering event is often associated with excitement in a horse that already has an underlying nervous temperament.[187,215,239] Serum cortisol concentrations are

higher in RER horses than normal horses before exercise and increase during an episode of ER.[240] Serum concentrations of epinephrine and norepinephrine are normal before an episode but increase dramatically in horses with marked elevations in serum CK activity.[240]

Exercise and Excitement.

In Standardbreds, ER commonly begins after 15 to 30 minutes of jogging at 5 m/s, although clinical signs may not be apparent until after exercise.[6,215] In Thoroughbreds exercising on the treadmill, ER most commonly develops with intervals of walk, trot, and canter and is less common if horses are allowed to gallop.[241,242] At the racetrack, ER occurs commonly when RER horses are held back to a paced gallop.[243] During eventing, RER commonly occurs after the excitement of the steeplechase or early in the cross-country phase when horses are held to a predetermined speed. ER rarely occurs when horses are allowed to achieve maximal exercise speeds, such as in racing.[187,215,242-244] A day or more of rest before this type of exercise results in higher serum CK activity post exercise.[215,242]

There is no basis for an association between RER and lactic acidosis.[242]

Intracellular Calcium Regulation.

Horses with RER are believed to have an intrinsic abnormality in intramuscular calcium regulation that is intermittently manifested during exercise.[19,245] Basal muscle intracellular calcium concentrations in RER horses are similar to healthy horses on the basis of assays in muscle cell cultures.[245] Higher intracellular calcium concentrations have been measured in horses of unspecified breeds during an episode of ER[246]; however, this also could be secondary to any insult that impairs energy generation or cell membrane integrity. Contracture testing has been performed in horses using surgically excised bundles of semimembranosus[21] or external intercostal muscle.[247] Waldron-Mease and colleagues[248] and Beech and colleagues[21] found that caffeine contracture thresholds were lower in semimembranosus muscle from Thoroughbreds and Standardbreds susceptible to RER versus breed-matched controls. Lentz and colleagues studied intact external intercostal muscle fibers from six Thoroughbreds with RER and found a lower contracture threshold for triggering agents such as potassium, caffeine, and halothane compared with control

horses.[19] An abnormality in intracellular calcium regulation was also supported by a muscle cell culture study of RER Thoroughbred horses.[245] A lower threshold for induction of myoplasmic calcium release by caffeine was found in myotube cultures from six RER Thoroughbreds compared with controls. Thus all of these studies supported an abnormality in intracellular calcium regulation in most of the Thoroughbred or Standardbred horses studied. However, studies of isolated muscle membranes have not conclusively identified any specific abnormalities in intracellular calcium regulation in RER horses.[171] Further, genetic linkage analysis using 96 horses in 4 families of Thoroughbred horses segregating for RER did not find an association linking RER with the calcium regulatory genes *RYR1* (ryanodine receptor), *SERCA* (SR ATPase), or *DHPR1* (dihydropyridine receptor).[249] Thus in spite of many detailed investigations of a small number of horses, the exact defect in regulating muscle contraction in RER horses has yet to be identified.

▪ Prevalence and Risk Factors

Assuming that the majority of cases of ER at racetracks are due to RER, the prevalence in Thoroughbred racehorses is remarkably similar around the world, with estimates ranging from 4.9% in the United States[239] to 5.4% in Australia[184] to 6.7% in the United Kingdom.[187,244] The annual incidence of ER in Standardbred racehorses in Sweden is 6.4%.[215] Exercise obviously increases the prevalence of RER in horses, and episodes are observed more frequently once horses achieve a level of fitness.[215,239]

In Standardbreds and Thoroughbreds, mares more commonly have RER than males,[187,215,239] but no general correlation has been observed between episodes of rhabdomyolysis and stages of the estrus cycle.[250] There is an interaction between age and gender in RER Thoroughbred horses such that the proportion of affected females to males is much higher in young horses compared with older age groups.[239] Swedish Standardbreds with RER, which do not begin racing until 3 years of age, did not show the same age association with RER as Thoroughbreds.[215] Temperament has a strong effect on the expression of RER in both Standardbreds and Thoroughbreds, with nervous horses, particularly fillies, having a higher incidence of rhabdomyolysis than calm horses.[187,215,239] Young fillies are more likely to have a nervous temperament than mares or male horses. Diet also has an impact, with Thoroughbred horses fed more than 2.5 kg of grain

per day being more likely to show signs of RER.[241,242] One study also found a higher prevalence of rhabdomyolysis among Thoroughbred horses with lameness.[243] A few days of rest before exercise increases the degree of elevation on serum CK activity with the next exercise session and in practice predisposes horses to an episode of ER.[242]

▪ Genetics

A genetic susceptibility to RER has been suggested for Thoroughbred horses.[190,251-253] Standardbred trotters with a history of RER actually have faster racing times from a standstill start than those without a history of RER, suggesting the trait may have beneficial and deleterious effects.[215] The variable penetrance of RER, however, and other potential modifying genes have made a genetic basis for RER suspected but difficult to identify.[254]

▪ Diagnosis

A presumptive diagnosis of RER is based on clinical signs of muscle pain and the presence of risk factors commonly associated with RER. Muscle histopathology is nonspecific in RER horses; either no abnormalities or evidence of centrally located nuclei in mature fibers and potentially waves of myofiber degeneration or regeneration is found.[7] There is a notable absence of abnormal amylase-resistant polysaccharide, although increased subsarcolemmal amylase-sensitive glycogen may be present.[7] The value of a muscle biopsy as a diagnostic tool in horses with suspected RER is largely confined to particularly recurrent unmanageable cases where a need arises to rule in or out other forms of ER. Serum CK and AST activities serve as the basis for detecting muscle degeneration, and they often show intermittent abnormal elevations that return to normal relatively quickly during the course of training. If CK elevations are mild, there are a number of factors to consider. Timing of the sample with regard to the onset of ER and exercise are important. Reliability is improved by obtaining blood samples at a standardized time after exercise, preferably 4 to 6 hours when CK peaks, and consistently with regard to exercise on the preceding day because serum CK activity is higher on exercise days that are preceded by a day or more of rest.[186] In addition, normal values need to be adjusted for the age and sex of horses. Two-year-old fillies generally have greater fluctuations in serum CK activity during race training than 3-year-old fillies or geldings.[186]

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▪ Management

Prevention of rhabdomyolysis in horses susceptible to RER is complex, and multiple factors need to be changed to decrease episodes. These factors include the environment, the exercise regimen, and diet. In addition, medication may be necessary at times to prevent further episodes of muscle damage.

Environment.

Because excitement and nervousness often trigger rhabdomyolysis, stressful situations in the environment that can be modified need to be identified. This may involve a change to a smaller barn with fewer horses and fewer handlers, compatible companions, and a more consistent daily routine. Many stressed RER-susceptible horses respond to a regular routine, including feeding first before other horses and training first before other horses, especially if the horse becomes impatient while waiting. Other horses respond to being housed in a quiet area of the barn next to calm, companionable horses. The use of hot walkers, exercise machines, and swimming pools needs to be evaluated on an individual basis because some horses develop rhabdomyolysis when using this type of equipment. Horses that develop rhabdomyolysis at specific events, such as horse shows, may need to be reconditioned to decrease the stress level associated with such events or tranquilized as part of the accommodation process. Providing daily turnout with other horses seems to be beneficial for RER horses and may decrease anxiety and thereby the likelihood of rhabdomyolysis.

Exercise.

Although a period of rest is recommended for sporadic forms of ER until serum CK normalizes, it is not recommended for horses with RER.[14] Daily exercise is important in preventing episodes of rhabdomyolysis, and therefore when serum CK is less than about 3000 U/L, horses are returned to regular daily exercise. Horses with more severe episodes of rhabdomyolysis may require additional time off in a paddock before gradually resuming exercise. Once back in training, some form of daily exercise is recommended. Avoiding fighting to hold racehorses to slower speeds during galloping may decrease rhabdomyolysis in RER-susceptible Thoroughbreds. Interval training and reduction of jog miles to no more than 15 minutes per session will benefit Standardbreds. For horses under saddle, a relaxed warm-up with intermittent periods of long, low

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stretching may be of benefit, and continued breaks to stretch between episodes of collection are recommended. Event horses may require training that incorporates calm exposure to speeds achieved during the steeplechase or cross-country phase, especially when used in an interval training program.

Diet.

A nutritionally balanced diet with appropriate caloric intake and adequate vitamins and minerals are the core elements of managing RER. For RER Thoroughbreds and Standardbreds in training, the challenge is usually supplying enough calories in a highly palatable form to meet their daily energy demands. This is in part because they often require more than 30 Mcal of digestible energy (DE) a day (5 kg sweet feed, 1.5% of body weight in hay) and, due to their nervous temperament, they may be more discriminating in their eating habits. Out of the total daily calories required by RER horses, research suggests that less than 20% DE be supplied by NSCs (starch and sugar) and at least 20% of DE be supplied by fat.[242]

Selection of Forage.

Thoroughbred horses do not appear to show the same significant increase in serum insulin concentrations in response to consuming hay with an NSC of 17% that is seen in Quarter Horses (Borgia L, 2010 PhD thesis, University of Minnesota). This fact combined with the high caloric requirements of racehorses may mean that it is not as important to select hay with very low NSC content in RER Thoroughbreds as it is in PSSM horses. Anecdotally, some trainers find that horses with RER have more frequent episodes on alfalfa hay. The nervous disposition of some RER horses may predispose them to gastric ulcers, and thus frequent provision of hay with a moderate NSC and mixed alfalfa content may be indicated.

Low-Starch, High-Fat Concentrates.

When RER Thoroughbreds are fed a moderate caloric intake (24 Mcal/day) in the form of high-starch concentrates (2.5 kg of corn, oats, wheat middlings, and molasses), they show little elevation in serum CK activity with exercise.[241] Most Thoroughbred racehorses, however, are fed at least 5 kg of high-starch concentrate per day at 30 Mcal or more per horse per day, and at this level of feeding postexercise serum CK activity rises significantly.[242] The discovery that substitution of fat for starch in a high-calorie ration significantly reduces muscle

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damage in exercising RER horses was a major advance in nutritional management of RER.[242] Practically, however, it was difficult to achieve the desired caloric intake of racehorses because the maximum amount of fat that finicky Thoroughbreds will happily consume is limited often to 600 mL of vegetable oil or 5 lb/day of balanced rice bran. Management of RER horses was significantly improved when a palatable means to provide the amount of fat required by fit, finicky RER Thoroughbreds was developed. A controlled trial using a specialized feed developed for RER (Re-Leve: 13% fat by weight and 9% NSC) determined that NSC should be no greater than 20% of daily DE and that 20% to 25% of daily DE should be provided by fat for optimal management of RER horses fed 30 Mcal or more per day.[242] No beneficial effect on serum CK activity occurred when sodium bicarbonate (4.2% of the pellet) was added to a high-starch pellet feed.[242] The amount of fat in the diet of an RER horse depends on its caloric requirements. Over and above hay at 1.5% to 2% of body weight and 2.5 kg of grain, any additional calories should be supplied by fat.

The benefit of a fat diet does not appear to be a change in muscle metabolism. Muscle glycogen and lactate concentrations before and after exercise are the same in RER horses fed a low-starch, high-fat diet compared to those fed a high-starch diet.[242,255] Rather, low-starch, high-fat diets in RER horses may decrease muscle damage by assuaging anxiety and excitability, which are tightly linked to developing rhabdomyolysis in susceptible horses. Low-starch, high-fat diets fed to fit RER horses produce lower glucose, insulin, and cortisol responses and lead to a calmer demeanor and lower preexercise heart rates.[256] Neurohormonal changes may develop in response to high serum glucose, insulin, and cortisol concentrations, resulting in an anxious demeanor. Although a calm demeanor is desired during training, some racehorse trainers feeding low-starch, high-fat feeds prefer to supplement with a titrated amount of grain 3 days before a race to potentially increase liver glycogen and increase a horse's energy during the race.

Expectations.

Studies in RER horses show that significant reductions or normalization of postexercise serum CK activity occurs within a week of commencing a low-starch, high-fat diet.[242] Days off training in a stall are discouraged because postexercise CK activity is higher following 2 days of rest compared with values taken when performing consecutive days of the same amount of submaximal exercise.

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Supplements.

Horses require daily dietary supplementation with sodium and chloride in the form of either loose salt (30 to 50 g/day) or a salt block. Additional electrolyte supplementation is indicated in hot, humid conditions. A myriad of supplements that are purported to decrease lactic acid buildup in skeletal muscle of RER horses are sold. These include sodium bicarbonate, B vitamins, branched-chain amino acids, and dimethylglycine. Because lactic acidosis is no longer implicated as a cause for rhabdomyolysis, it is difficult to find a rationale for use of these supplements.

Medications.

Low doses of tranquilizers such as acepromazine before exercise have been used in RER horses prone to excitement.[257] A dose of 7 mg IV 20 minutes before exercise is reported to make horses more relaxed and manageable. Reserpine and fluphenazine, which have a longer duration of effect, have also been used for this purpose. Horses given fluphenazine may occasionally exhibit prolonged bizarre behavior. Use of tranquilizers may be necessary only when horses are in their initial phase of training and accommodating to a new environment. Horses obviously cannot compete on these medications, and withdrawal times must be observed.

Dantrium sodium acts to decrease release of calcium from the ryanodine receptor in skeletal muscle and is used to treat malignant hyperthermia. Controlled and field studies have shown that oral dantrolene can significantly decrease signs of rhabdomyolysis in RER horses.[168,258,259] One study indicated that horses need to be fasted to achieve measurable blood levels of dantrolene,[168] but more recent controlled trials suggest that absorption of dantrium is superior in fed versus fasted horses.[258] Administration of 4 mg/kg of dantrium PO 1 hour before exercise to RER-susceptible horses fed high-grain diets resulted in significantly lower serum CK activity 4 hours after exercise compared with placebo.[168] A dose of 800 mg of dantrium was given to Thoroughbred horses in the United Kingdom 1 hour before exercise and resulted in significantly lower postexercise CK activity than a placebo.[259]

Phenytoin has been reported to be effective in preventing rhabdomyolysis in horses with RER.[260] Phenytoin acts on a number of ion channels within muscle and nerves, including sodium and calcium channels. Therapeutic levels vary, so oral doses are adjusted by monitoring serum levels to achieve 8 µg/mL, not to

exceed 12 µg/mL.[260] Drowsiness and ataxia are evidence that the dose of phenytoin is too high, and the dose should be decreased by half. Initial dosages are 6 to 8 mg/kg PO twice a day for 3 to 5 days, and if the horse is still experiencing rhabdomyolysis but is not drowsy, the dose can be increased by 1-mg/kg increments every 3 to 4 days. Most horses require a dose of 10 to 12 mg/kg PO twice daily (bid). Phenytoin is a monoaminoxidase activator and can affect dosages of other medications. Unfortunately, long-term treatment with dantrolene or phenytoin is expensive, and these drugs must be withdrawn before competition.

Hormone Therapy.

Various hormones, ranging from thyroxine to progesterone and testosterone, have been given to horses with RER. Initial studies linking low T3 and T4 concentrations in horses with ER have not been substantiated.[261-263] Some mares appear to exhibit signs of rhabdomyolysis during estrus, and it may well be of benefit in these horses to suppress estrous behavior using progesterone injections. Testosterone and anabolic steroids have been used at racetracks to prevent signs of RER, but their use is no longer permitted.

Adjunct Therapies.

Massage, myofascial release, mesotherapy, stretching, aqua treadmills, and hot/cold therapy performed by experienced therapists may be of benefit in individual cases.[264-266] Their use may promote relaxation and normal muscle tension and build muscle strength.

Malignant Hyperthermia

Malignant hyperthermia (*RYR1* mutation) in Quarter Horses and Paints has also been linked to exertional rhabdomyolysis.[173,174] It is caused by an autosomal dominant mutation that exists in exon 46 of the skeletal muscle *RYR1* gene on ECA 10.

▪ Prevalence and Risk Factors

Malignant hyperthermia is a rare disorder in Quarter Horses and Paints, affecting less than 1% of the breed. Halter and pleasure horse lines have the highest prevalence. Rhabdomyolysis may be induced by exercise and anesthesia but can

be extremely intermittent in nature.[173]

▪ Clinical Signs

Horses with the *RYR1* mutation may intermittently show signs of ER and high body temperatures.[173,174] Some horses affected with malignant hyperthermia have died suddenly after an episode of ER. Horses with the *RYR1* mutation may also have the *GYS1* mutation associated with PSSM1.[219] Such horses have more severe episodes of ER, higher serum CK activity after exercise, and a more moderated response to the diet and exercise regimens recommended for PSSM1.[219]

▪ Diagnosis

Genetic testing is recommended in Quarter Horses and Paints with difficult-to-manage forms of PSSM or a family history of postanesthetic complications. Muscle biopsy is not particularly useful for diagnosing malignant hyperthermia. Biopsies may contain mild myopathic changes, including increased variation in fiber sizes, centrally located nuclei, fiber necrosis, glycogen depletion, and ringbinden fibers.[174]

▪ Treatment

The nature of ER with horses positive for malignant hyperthermia is so intermittent that it is hard to justify premedication with dantrolene before exercise.

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Hereditary and Congenital Myopathies

Stephanie J. Valberg

Mitochondrial Myopathy

A deficiency of complex I, the first step in the mitochondrial respiratory chain, has been identified in a young Arabian filly that was presented for veterinary attention with clinical signs similar to ER.[267] In contrast to cases of ER, however, this horse showed no changes in serum CK following exercise. A marked lactic acidosis developed even with light exercise, and maximum oxygen consumption was drastically reduced, resulting in marked exercise intolerance. Histopathologic evaluation of muscle biopsies showed an abnormal increase in mitochondrial density, and biochemical analyses revealed a complex I deficiency. The horse has shown slowly progressive signs of muscle atrophy but has otherwise remained healthy at rest.

Glycogen Branching Enzyme Deficiency

Glycogen branching enzyme deficiency (GBED) is a glycogen storage disorder causing abortion, seizures, and muscle weakness in Quarter Horse–related breeds.[268-270] It represents a separate glycogen storage disorder from PSSM. GBED is caused by a nonsense mutation in exon 1 of the *GBE1* gene at codon 102, which introduces a premature stop codon.[270] Nine percent of the breed is a carrier of this autosomal recessive mutation, and 3% of abortions are attributed to this disease in Quarter Horses.[268] The prevalence of carriers is particularly high in pleasure horses, with 26% of pleasure horses carrying the *GBE1* mutation.[56] Most foals diagnosed with GBED have presented with hypothermia, weakness, and flexural deformities of all limbs at 1 day of age. Ventilatory failure may also be a presenting sign in addition to recurrent hypoglycemia and collapse. All foals have died from either euthanasia because of muscle weakness or suddenly because of apparent cardiac arrhythmia. Persistent leukopenia, intermittent hypoglycemia, and high serum CK (1000 to 15,000 U/L), AST, and γ-glutamyltransferase (GGT) activities are features of affected foals. Gross postmortem changes are not evident, and routine hematoxylin and eosin stains of

tissues may be normal or show basophilic inclusions in skeletal muscle and cardiac tissues. Frozen sections of muscle, heart, and liver show a notable lack of normal PAS staining for glycogen, as well as abnormal PAS-positive globular or crystalline intracellular inclusions (Fig. 42.20). Branching enzyme activity is minimal in skeletal and cardiac muscle, as well as in liver. A diagnosis is best obtained by confirming the presence of the genetic mutation in tissue samples or by identifying typical PAS-positive inclusions in muscle or cardiac samples.[269,270]

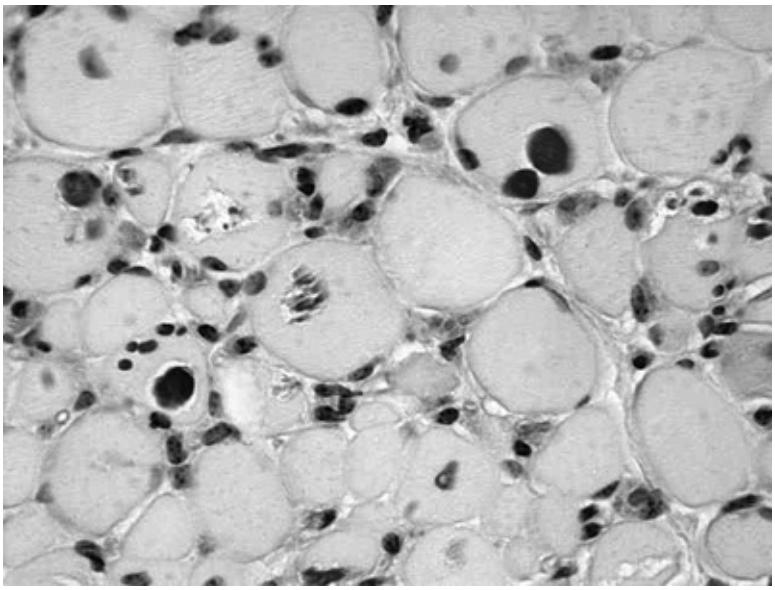


FIG. 42.20 Periodic acid–Schiff (PAS) stain of skeletal muscle from a foal with glycogen branching enzyme deficiency. Note the lack of normal diffuse dark staining for glycogen and the presence of globular and crystalline PAS-positive inclusions.

Centronuclear Myopathy in a Foal

Progressive muscular weakness, lameness and atrophy including ventroflexion of the neck, ptosis, and lip droop have been described in an Arabian-cross foal that died by 5 months of age.[271] Electromyography revealed fibrillation potentials, positive sharp waves, and complex repetitive discharges. Muscle biopsy findings were consistent with centronuclear myopathy that is associated with abnormal distributions of T-tubule and triad structures.

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Phosphorylase Deficiency in Charolais Cattle

A deficiency of the enzyme myophosphorylase (McArdle's disease) has been identified in Charolais cattle in the United States and New Zealand and in sheep in Australia.[272-275] Cattle show exercise intolerance and often collapse when forced to exercise. Serum CK is elevated, and severe rhabdomyolysis clinically resembling white muscle disease may be present. Screening for myophosphorylase can be performed by histochemical staining for phosphorylase activity in frozen sections of muscle biopsies. Confirmation of the autosomal recessive disease is obtained by biochemical analyses or identification of the base pair sequence defect. In Charolais a C-to-T substitution, which changes an encoded arginine (CGG) to tryptophan (TGG) at codon 489, is present, and in sheep a splice-site mutation is present in intron 193. This disease should be considered a differential diagnosis for white muscle disease in animals that are found to have normal vitamin E and selenium status. An ovine form of myophosphorylase deficiency has also been described.[276]

Pseudomyotonia in Cattle

Chianina and a Dutch Improved Red and White crossbreed heifer that have a form of pseudomyotonia characterized by delayed relaxation of muscle have been identified.[277,278] Clinical signs include exercise-induced muscle stiffness with normal response to muscle percussion. In contrast to myotonia, electromyography and muscle histochemistry are normal. Missense mutations have been identified in the *ATP2A1* gene encoding the sarcoplasmic reticulum SERCA1 protein.

Porcine RN(–) Glycogen Storage Disease

The RN(–) (rendement Napole) phenotype is common in Hampshire pigs. Clinically, pigs appear normal; however, the 70% increase in glycogen content in skeletal muscle causes poor meat content at slaughter. It is due to an autosomal dominant mutation in the protein kinase AMP-activated gamma 3 subunit gene *(PRKAG3)*, which encodes the gamma 3 isoform of AMP-activated protein kinase.[279] The mutation affects meat quality of pigs by increasing the glycogen content of muscle.

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• CHAPTER 43

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Diseases of the Reproductive System

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▪ Female Reproductive Disorders

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Nonpathogenic Infertility

Breeding Season

Mares

The mare is a seasonally polyestrous animal, breeding during seasons of long day length. Annual breeding and nonbreeding seasons are divided by fall and spring transitional periods, which are characterized by erratic reproductive behavior and irregular estrous cycles.

Clinical Signs

During the breeding season, mares ovulate every 21 days (range 19 to 22 days).[1] Estrus (5 to 7 days but variable) is characterized by the presence of an ovarian follicle, serum progesterone level of less than 1 ng/mL, and sexual receptivity. During estrus the cervix is palpably relaxed and the uterus is edematous. One or two follicular waves occur per cycle, and preovulatory follicles are 45 to 60 mm in diameter, often with a cone-shaped appearance on ultrasonography.[2] Ovulation occurs 24 to 48 hours before the end of estrus and may be accompanied by ovarian sensitivity.[1] The ruptured follicle is replaced by a corpus luteum (CL). Diestrus (luteal phase) is predictable in length because regression of the CL, caused by release of endometrial prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$), occurs 14 to 15 days after ovulation.[3] During diestrus and early pregnancy the cervix is tight and the uterus has increased tone. Diestrous ovulations occur and may be fertile.[4] First postpartum estrus (“foal heat”) begins in the week after foaling, and ovulation occurs in most mares 7 to 15 days postpartum.

Ruminants

Cows.

Cows are polyestrous, but seasonal differences in fertility may be caused by climate. The estrous cycle averages 21 days (range 17 to 25 days), and the duration of estrus averages 12 to 16 hours (range 6 to 24 hours). Cows are unique among domestic animals in that they ovulate spontaneously after the end

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of estrus, 24 to 30 hours after the beginning of estrus.[5]

In the absence of a bull, estrus can be detected in cows by their homosexual (bisexual) activity. Cows that stand to be mounted by another cow are in estrus (standing heat). Secondary signs that may be helpful in detecting estrus include restlessness and increased activity, vulvar hyperemia and edema, and a clear mucous discharge. Errors in heat detection are a common cause of infertility on large dairy farms.[6] The optimum time for insemination of cows is between 16 and 24 hours after the onset of estrus. Insemination of cows based on standing to be mounted results in a higher pregnancy rate than if it is based on secondary signs of estrus. Well-managed dairy cows with uncomplicated periparturient experiences may ovulate approximately 20 to 25 days after calving, whereas beef cows with nursing calves usually do not ovulate until 40 or more days after calving. The presence of the calf appears to be responsible for the difference in return to cyclicity.[7]

Sheep.

Coarse-wooled breeds of ewes are seasonally polyestrous during the autumn and winter (short photoperiod) in temperate climates. Ovulation can be induced in seasonally anestrous ewes by artificial simulation of day length and temperatures characteristic of autumn (reduced photoperiod and reduced ambient temperature), but the long latency period required for response to manipulation of light and temperature makes the procedure impractical. Ewes of fine-wooled breeds may be polyestrous throughout the year if adequately nourished. The estrous cycle of ewes averages 17 days (range 14 to 19 days), and the duration of estrus averages 36 hours. Ovulation occurs spontaneously 24 hours after the onset of estrus. Ewes display few, if any, signs of estrus unless a male is present. The primary signs of estrus include seeking the ram and standing for mating. Secondary signs include restlessness and rapid tail switching; vulvar edema and discharge of clear cervical mucus may be observed occasionally. Lambing ordinarily occurs during the anestrous season; therefore ewes do not return to estrus until the next breeding season.

Goats.

Does in temperate climates are seasonally polyestrous from late summer until early spring (short photoperiod). Onset of the breeding season in yearling does can be advanced by exposing them to 19 hours of artificial light per day for 70 days beginning in mid to late winter. Termination of artificial light results in a

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relative decrease in day length and stimulation of estrus and ovulation.[8] Alternatively, the breeding season may be hastened by exposing does to 14 to 18 hours of light per day for 3 months, followed by a reduction to 6 hours of light per day. The estrous cycle averages 21 days, and estrus lasts 18 to 36 hours. Ovulation occurs spontaneously 24 hours after the onset of estrus. An intact male or male pheromone is usually necessary for estrus detection. The primary signs of estrus are seeking the buck and standing for service. Secondary signs of estrus in does include rapid tail switching, restlessness, increased frequency of urination and vocalization, transient decrease in appetite and milk production, and edema and hyperemia of the vulva. As in sheep, parturition takes place during the anestrous season, and return to cyclicity in does is delayed until the next breeding season.[8]

Camelids.

South American camelids bred in North America are nonseasonal. In keeping with management decisions, they are often bred in a seasonal manner to avoid having newborn crias during the hottest or coldest months of the year. Some consider the South American camelids to be polyestrous, whereas others argue that they do not have a true estrous cycle.[9] These discrepancies arise from the fact that camelids are induced ovulators. Cyclic ovarian activity (e.g., transition from estrus to diestrus) is caused by coital activity. Unbred female camelids essentially exhibit estrous behavior continually, with perhaps short, occasional, unpredictive intervals of 1 to 2 days of decreased receptivity. Follicular waves in alpacas and llamas last around 17 days. Small follicles (<3 mm) are always present on the surface of the ovaries. After recruitment, follicles grow to approximately 5 mm in size. Dominance is established when one of the follicles reaches the size of 6 mm, and the female will show signs of receptivity to the male as long as a dominant follicle is present. The sizes of preovulatory follicles are 9 to 13 mm and 8 to 12 mm in the llama and alpaca, respectively. Females maintain fertile, dominant follicles for an average of 8 days before undergoing regression. Usually the next follicular wave has already produced the next dominant follicle before the previous preovulatory follicle begins to regress. For this reason, the female camelid usually maintains estrous behavior continually until she is mated.[9]

Cystic Follicular Degeneration

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Cows

Ovarian cysts are follicle-like ovarian structures that arise because of failure of ovulation of a dominant follicle.[1] They are usually larger than 25 mm in diameter and persist in the absence of a CL for 10 days or more. Follicular cysts have thin walls and may be single, multiple, or multilocular structures on one or both ovaries. Partially luteinized cysts tend to be single, unilateral structures with thicker walls because of the presence of luteal tissue.

The mechanism by which ovulation fails and cysts develop is not known. Failure of ovulation may result from inadequate release of gonadotropins or ovarian dysfunction. Increased stress of conditions such as retained placenta, metritis, and hypocalcemia around the time of calving and postpartum ketosis has been associated with an increased prevalence of cystic follicular degeneration (CFD), as has a hereditary predisposition.[2] Negative energy balance in high-producing dairy cows, as well as prolonged suckling in beef cows, may inhibit lutenizing hormone (LH) release from the pituitary and subsequent failure of ovulation.

Clinical Signs and Diagnosis

Approximately 70% to 80% of cows affected by CFD are anestrus, whereas 20% to 30% display frequent or intense estrus (nymphomania). Cystic ovarian disease affects 10% to 30% of dairy cows. The condition is rare in commercial beef cows because of rigid culling for reproductive failure.

The physical appearance of cows with CFD depends on the duration of the condition. No changes are apparent after a short time, but in long-standing cases relaxation of the pelvic ligaments may result in prominence of the tailhead and masculine characteristics such as a crested neck.

The diagnosis of CFD is based on an accurate history and clinical examination. A history of constant or frequent estrus, short interestrous intervals, or anestrus may suggest CFD. Examination of the ovaries by palpation per rectum reveals the presence of enlarged fluid-filled structures raised above the surface of the ovary that greatly increase total ovarian size. Ovarian cysts are larger (>25 mm) than preovulatory follicles (15 to 25 mm). Differentiation between a single large cyst and several smaller cysts on the same ovary may require ultrasonographic examination, as does recognition of the presence of partially luteinized cysts (based on peripheral progesterone concentrations). Ovarian cysts appear to be dynamic structures; those that develop early in the

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postpartum period may regress without treatment, and a normal estrous cycle may follow, or another cystic structure may develop.

During palpation of the ovaries, several normal structures may complicate the diagnosis of CFD. Normal preovulatory follicles may approach 25 mm in diameter and have palpable characteristics similar to those of small cysts. During the follicular phase of the estrous cycle, however, the uterus responds to palpation by becoming more turgid, whereas the uterus of a cow with CFD is typically flaccid and unresponsive. In neglected cases of CFD, mucometra may develop and must be differentiated from pregnancy. During the first 5 to 7 days of the estrous cycle, the developing CL may be smooth and soft and is commonly mistaken for an ovarian cyst. More mature CLs are solid and liver-like in consistency, often feature a palpable ovulatory papilla at the apex, and are more easily differentiated from ovarian cysts. However, 10% to 20% of mature CLs may lack an ovulatory papilla, making them more easily confused with ovarian cysts. Ultrasonography is generally more accurate in identifying subtle structural differences than transrectal palpation. Salpingitis, hydrosalpinx, oophoritis, ovarian abscesses, ovarian neoplasms, and cysts of the fimbria are other causes of enlargement of the ovary and surrounding structures that must be differentiated from ovarian cysts.[3]

Histories that may erroneously suggest CFD include apparently short interestrous intervals because of inaccurate detection of estrus. Oxytocin administered to stimulate milk letdown may result in short interestrous intervals that may spuriously be suggestive of CFD. The estrous cycle may be shortened by approximately 1 week by administering 100 IU of oxytocin per day on days 2 through 6[4] or on days 3 through 7 or 8.[5]

Clinical Pathology

Plasma progesterone concentrations are low in cows with follicular cysts. Partial luteinization may occur, and progesterone concentrations may increase over time but remain lower than those of cows with normal CLs. Estrogen concentrations in the plasma of cows with CFD are variable.

Treatment and Prognosis

The goal in treating CFD is to induce luteinization of the cyst and reestablish normal estrous cycles. Several methods have been recommended.

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Spontaneous Recovery.

Spontaneous recovery from CFD occurs in up to 60% of cows that develop CFD before the first ovulation after calving but in only approximately 20% of cases that develop after the first postpartum ovulation. Evaluation of therapeutic agents for CFD may be confounded by spontaneous recovery.

Luteinizing Hormone.

Recommended doses of human chorionic gonadotropin (hCG) range from 5000 IU either intravenously (IV) or intramuscularly (IM) to 10,000 IU IM. Among cows treated with a single dose of hCG, 65% to 80% establish a normal estrous cycle within 3 to 4 weeks; a second or third dose may be required in cows that do not respond after 3 to 4 weeks or in cases in which nymphomania persists. Anaphylaxis after repeated treatments with a larger protein hormone such as hCG can occur. Antibodies to hCG may reduce the effectiveness of sequential treatments. Therapeutic response to follicular cysts, both endocrinologically and clinically, is essentially equivalent between hCG and gonadotropin-releasing hormone (GnRH).

Gonadotropin-Releasing Hormone.

Currently the most common treatment for ovarian cysts, especially follicular cysts, is an injection of GnRH (100 µg IM). Cows that respond to this treatment have an average interval to estrus of one estrous cycle or 18 to 24 days. The treatment to breeding interval can be shortened by administering GnRH at the time of diagnosis, followed by a luteolytic dose of prostaglandin 10 days to 2 weeks later. With this regimen, it is not critical whether the cyst is follicular or luteal or even whether it is a misdiagnosed large, smooth CL with or without a fluid-filled central cavity. Most veterinarians agree that accurate differential diagnosis by rectal palpation among follicular cysts, luteal cysts, and some CLs can be a problem.

Prostaglandin $F_{2\alpha}$.

Luteal cysts can be treated with the luteolytic activity of $PGF_{2\alpha}$. The advantages are the quicker return to estrus for those cows able to respond and the lower cost of $PGF_{2\alpha}$. Cysts that luteinize in response to GnRH regress at a time similar to that of normal CLs. Treatment with $PGF_{2\alpha}$ may be used to reduce the interval from treatment with GnRH to estrus from 18 to 24 days to an average of 12 to 14

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days by administering $PGF_{2\alpha}$ at 9 days after GnRH. Most clinicians are only approximately 50% accurate in determining the degree of luteinization of cysts by palpation per rectum; therefore measurement of concentrations of progesterone in milk or of plasma from affected cows allows the selection of GnRH or hCG for treatment of follicular cysts and $PGF_{2\alpha}$ for the treatment of luteinized cysts. Ultrasonography can also be used to make an accurate diagnosis.[6]

Manual Rupture.

Thin-walled follicular cysts may be ruptured inadvertently during examination of the ovaries, and some practitioners intentionally may attempt cyst rupture. Recovery rates after manual rupture have rarely been studied in well-designed controlled experiments but are generally within the range reported for spontaneous recovery. Deliberate manual rupture of ovarian cysts is considered an obsolete form of treatment by some veterinary clinicians, but others routinely use the procedure—especially as an initial treatment for cysts found during the voluntary waiting period. Manual rupture of cysts may be followed by hemorrhage and adhesions between the ovary and surrounding structures. These complications appear to be much more common with the use of digital pressure to enucleate CLs (also no longer performed) than with manual rupture of ovarian cysts.

Ewes and Does

Cystic ovaries appear to be more common in goats than in sheep. In one study 12% of goats had cystic ovaries when examined at a slaughterhouse.[7] The condition is often overdiagnosed by owners observing nymphomania or abnormal cyclicity. Treatment typically consists of administering exogenous ovulation-hastening drugs (hCG and GnRH).[8] LH surge is noted usually within 2 hours of GnRH administration. Ten days later, $PGF_{2\alpha}$ may be administered to bring the doe into heat (roughly 2 to 2.5 days after administration).

Camelids

Hemorrhagic follicles are observed in nonbred llamas and usually regress within 22 days.[9] Follicles larger than 12 mm are considered by some authors as pathologic cysts. These structures may, however, be anovulatory follicles. They

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may have a negative influence on the emergence of other follicular waves, but this influence seems to last for only approximately 8 days.[10]

Poor Nutrition

As with other species, poor body condition, depressed energy intake, and decreased vitamin and mineral intake suppress reproductive activity in ewes and does. Lowered energy balance results in poor or weak signs of estrus, depressed ovulation, abnormal cycle, and delayed puberty. Deficiencies in energy, protein, vitamins A and E, phosphorus, and many trace minerals (iodine, copper) are commonly seen. These deficiencies are most commonly associated with irregular estrous cycles.

Ovarian Reserve and Anti-Mullerian Hormone

The mammalian ovarian reserve declines with age, and antral follicle count (AFC) is thought to be predictive of ovarian reserve and fertility.[1] Plasma levels of anti-mullerian hormone (AMH) have been directly correlated with AFC in multiple species, including mares.[2,3] Based on these findings, AMH has been suggested as a promising indicator of ovarian reserve (and therefore "reproductive age").[4,5] In the female, AMH is produced by granulosa cells in developing follicles and serves in the regulation of primordial follicular recruitment and development into primary follicles, preserving the ovarian reserve.[6-8] The mechanisms for the role of AMH in folliculogenesis are still being understood; however, it has been demonstrated that AMH restricts follicular development by decreasing the sensitivity to follicle stimulating hormone (FSH) in granulosa cells.[9,10] Finally, perhaps the more commonly known clinical application of AMH in mare reproductive health is as a reliable marker for the presence of granulosa cell tumors.[11]

Plant Toxicity

Ergot Alkaloids

The consumption of fescue infected with *Neotyphodium coenophialum* is associated with decreased reproductive efficiency (see Chapter 12). The ergot alkaloids have been shown to affect prolactin production in ewes and to increase

the interval from introduction of the ram to conception.

Estrogen-Producing Plants

Sheep appear to be sensitive to the effects of phytoestrogens. Clinical observations include infertility, irregular and prolonged heat cycles, lowered conception rates, and early embryonic death.

Heat Stress

Fertility in lactating cows is decreased during the hot seasons of the year. Heat stress may cause decreased estrus detection, impair follicular development, disrupt function of the reproductive tract, affect oocyte competence, and lead to early embryonic death. Embryos develop resistance to heat shock as they age. Bovine morulae to blastocyst stages are unaffected by heat shock.[1]

Anestrus

The causes of anestrus are multiple and include diseases of the reproductive and other systems. In addition, the problem is complicated by management factors that cause estrus to pass undetected, even though the animal's estrous cycles and estrous behavior are normal. Common causes of anestrus in mares are summarized in Table 43.1.

TABLE 43.1

Differential Diagnosis of Anestrus in Mares

Cause	Uterus	Cervix	Ovaries	Peripheral Progesterone	Season	Other Laboratory Tests	Tre
Pregnancy	Increased tone during early pregnancy; enlarged; positive signs of pregnancy by palpation or ultrasound	Tightly closed	Normal size during early pregnancy; out of reach of examiner in late stages	Elevated throughout pregnancy until just before term	Any season; may be more common in spring and summer	Equine chorionic gonadotropin; Cuboni test	Usu re th at m
Prolonged	Normal size,	Tightly closed	Normal size;	Elevated	Any	Progesterone	PGI

diestrus	increased tone and tubularity; may be similar to early pregnancy		prolonged corpus luteum is embedded within ovary	throughout prolonged life span (30-90 days)	season; may be more common in summer		
Seasonal anestrus	Normal size; flaccid; difficult to palpate	Varies from tightly closed to open	Both are small and firm, may or may not have small follicles	Low until first corpus luteum develops	Late autumn, winter, early spring	Progesterone	Arti lig fo br se
Unobserved estrus	Normal size	Characteristic cyclic changes; relaxed and open during estrus	Development of one (or more) follicles; ovulation	Elevated for ≈14 days; low for ≈7 days	Spring, summer, autumn		Imp m te ar st se ex P(
Pyometra	Variable enlargement	May be open, closed, or stenotic; purulent discharge may be present	Normal size, follicular development may be present	Erratic profiles; some are elevated for prolonged periods, others may have luteal regression	Any season	Endometrial cytology; bacterial culture; antibiotic sensitivity	Dra ar P(
Undernutrition	Normal size	Varies from tightly closed to open; no cyclic changes	Bilaterally small and firm	Low	Any season	Hematology; clinical chemistry as indicated; fecal flotation	Imp nu st pa cc cc di
Granulosa-theca cell tumor	Normal size	Varies	One enlarged, multicystic; other small and atrophic	Low	Any season	Peripheral inhibin concentrations are elevated in ≈90%, testosterone in ≈50%, and AMH in >90% of mares with granulosa-theca cell tumor	Sur re ne ov
Gonadal dysgenesis	Small	Varies	Small, firm, atrophic	Low	Any season	Karyotype	Nor

AMH, Anti-mullerian hormone; *$PGF_{2\alpha}$,* prostaglandin $F_{2\alpha}$.

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Mares

Puberty

The mare likely undergoes puberty between the ages of 12 and 24 months. Because the horse is not an agricultural production animal, there has been little interest in studying the onset of puberty as in other species, where hastening puberty increases production. Most mares are not bred until they are at least 3 years old, thus making prepubertal status an unlikely differential diagnosis for infertility.

Seasonal Anestrus

Clinical Signs and Diagnosis

The mare is a seasonally polyestrous animal, showing anestrus during the shorter days of the year and cycling regularly during the longer days. Length of anestrus varies from one to several months, although some mares, particularly in the tropics, may cycle year-round.[1] In California, Australia, and South Africa 18% to 25% of mares cycle year-round.[2-4] Anestrous mares may be indifferent to teasing and do not show regular estrous behavior. Ovaries are small and firm on palpation, and the uterus is flaccid with a thin endometrium. The cervix has mild tone and may be indistinct. On speculum examination of the vagina, the vaginal mucosa is pale and dry, and the cervix usually appears closed but is occasionally open or may be easily opened. Mares that experience seasonal anestrus will go through a transition period in late winter and early spring, characterized by the development of waves of antral follicles that regress without ovulation because the ovulatory surge of LH is absent.[5] Transitional mares exhibit signs of estrus, including clitoral “winking,” tail flagging, and urinating in the presence of the stallion. Eventually, increasing LH concentration coincides with a large follicle, resulting in ovulation. After the first ovulation of the season, the mare will continue to ovulate on successive estrous cycles. A transition period is also observed during the fall as the mare changes from a polyestrous condition to the winter anestrus. Differential diagnoses for seasonal anestrus are listed in Table 43.1.

Treatment and Prognosis

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As day length increases, most mares ovulate and begin regular cyclicity without treatment. Methods to advance the onset of regular ovulatory periods can be both managerial and pharmacologic and are discussed in the following sections.

Artificial Lighting.

The vernal transition can be moved but not shortened beyond its physiologic length of 6 to 8 weeks by exposure of mares to artificial light. A common artificial lighting regimen is to expose the mares to 16 hours of light and 8 hours of dark by extending the photoperiod in the evening starting in late November to initiate ovulation by February (in the northern hemisphere). Light should be added to the end of the day, or split between the beginning and end of the day, as opposed to adding light only at the beginning of the day.[6] An alternative regimen is to expose mares to 1 hour of artificial light 9.5 to 10.5 hours after the onset of darkness.[7] Use of one 200-watt incandescent bulb or two 40-watt fluorescent tubes at a height of 7 to 8 feet in a 12- × 12-foot box stall has been recommended.[8] Paddock lighting has been described.

Recently, research has evaluated the effectiveness of a mask fitted with a single low-intensity blue light as a method to induce the onset of cycling.[8] The masks were compared with mares not under lights and with mares stalled under lights using a conventional protocol. The study found that the masks were able to achieve the same results as the traditional protocol, bringing mares out of seasonal anestrous earlier than the control group.

Exposure to Stallions and Social Environment.

Alterations in social environment can alter the timing of ovulation in several species. Recent work has investigated social factors and the cessation of seasonal anestrus in mares. The group found that anestrus mares exposed to a stallion several times per week ovulated earlier and more frequently than anestrus mares never exposed to stallions.[9]

Gonadotropin-Releasing Hormone.

Treatment with GnRH or a GnRH analog for mares in anestrus or spring transition has been shown to induce ovulation.[10-15] Twice-daily injections of a GnRH agonist induced ovulation in a majority of mares within 2 to 3 weeks.[14] Mares that are in deep anestrus (January and February, northern hemisphere) can be expected to return to anestrus after treatment.

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Dopamine Antagonists.

Domperidone and sulpiride have been reported to stimulate follicular activity and advance the first ovulation of the year in seasonally anestrous mares.[16] However, the efficacy of dopamine antagonists in advancing follicular growth and ovulation in anestrous mares has been questioned recently, and it has been suggested that adjustments in light and climatic conditions may influence the efficacy of the treatment.[17,18]

Steroids.

Exogenous progestins suppress the release of LH from the anterior pituitary and may be used for estrous regulation during the vernal transition. After treatment of mares for 10 to 14 days, withdrawal of progestin may result in LH release from the pituitary and estrus beginning in 4 to 5 days, with ovulation within 10 days after cessation of treatment. Mares should be in mid to late transition and have a follicle at least 25 mm in size to respond to treatment. Progestins will not induce estrus or ovulation in anestrous mares.[19] The recommended dose of progesterone in oil is 150 to 300 mg daily by IM injection. The synthetic progestin altrenogest is administered orally (PO) at 0.044 mg/kg daily. Progestins may be used in combination with extended photoperiod and gonadotropins. Products that are ineffective or unavailable include repositol progesterone, melengestrol acetate, chlormadinone acetate, proligestone, medroxyprogesterone acetate, hydroxyprogesterone acetate, and norgestomet implants.

Synchronization of the first ovulation (or any ovulation during the cyclic season) can be accomplished by the administration of a combination of progesterone in oil (150 mg/day IM) and estradiol-17β (10 mg/day IM) once daily for 10 days.[20] Treatment is most effective if given after mares have been under lights for 45 to 60 days. $PGF_{2\alpha}$ should be given on the last day of steroid treatment. Treated mares will ovulate within 8 to 10 days after the last treatment.

Gonadotropins.

At a dose of 2500 to 3000 IU, hCG may induce ovulation within 48 hours when administered to a mare with a follicle larger than 35 mm in diameter[21] and may reduce time to first ovulation in transitional mares, particularly when used in combination with lights and/or progesterone treatment. Ovulation response here is less predictable than that induced with hCG during the breeding season.

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Based on a recent study, treatment of seasonally anestrous mares with recombinant equine FSH (reFSH) is effective in stimulating development of follicles and advancing the first ovulation of the year.[22] Treatment with FSH resulted in multiple ovulations but was not successful in inducing continued cyclicity.

Follicular Aspiration.

Ultrasound-guided transvaginal follicular aspiration of follicles less than 35 mm in diameter has been shown to hasten the onset of cyclicity in transitional mares.[23] Follicular aspiration resulted in the formation of an active CL, and subsequent treatment with $PGF_{2\alpha}$ resulted in estrous behavior and ovulation of a dominant follicle.

Prolonged Luteal Phase and Pseudopregnancy

Mares that experience embryonic loss in the presence of endometrial cups (days 35 to 150 of gestation) are said to be *pseudopregnant* (*pseudopregnancy* may also refer to the condition in which a conceptus was lost after maternal recognition of pregnancy and before the development of endometrial cups, resulting in prolonged luteal life). Despite the loss of the fetus and placental tissue, endometrial cups remain in place and continue to secrete equine chorionic gonadotropin (eCG) for a similar period to that in a pregnant mare, to 100 to 150 days of gestation.[24] The primary and secondary CLs may regress after embryonic loss, allowing the mare to return to cyclicity,[25,26] or remain during eCG secretion, maintaining high levels of peripheral progesterone and preventing the mare from cycling. Persistent endometrial cups throughout pregnancy and during the following breeding season have been described.[27]

Treatment and Prognosis

In untreated mares, cyclic activity is often reestablished after the cessation of eCG secretion. Repeated daily injections of $PGF_{2\alpha}$ products have been reported to cause luteal regression in pseudopregnant mares,[28] but only CLs older than 5 days respond to the treatment, which may prevent mares returning to estrus. Pregnancies have occurred in the face of high eCG,[29] but fertility of treated mares is usually low.

Lack of Behavioral Estrus (Silent Estrus)

Behavioral estrus may not be detected in otherwise normal mares as a result of inadequate estrus detection or a failure on the part of the mare to show obvious signs of estrus. The latter may occur in up to 15% of mares on well-managed farms.[1] Inadequate estrus detection may result from human apathy or ignorance or from use of a low-libido or inexperienced stallion. Teasing mares as a group may make detection of estrus more difficult, especially for nervous mares, mares with foals, and mares of low social rank. Use of anabolic steroids may suppress behavioral estrus.

Clinical Signs and Diagnosis

The mare fails to show estrus on adequate teasing with a stallion. Differential diagnoses are listed in Table 43.2.

TABLE 43.2

Irregularities of the Equine Estrous Cycle: Differential Diagnosis

Etiology	Distinguishing Features
Failure to Cycle With Low Progesterone	
Winter anestrus	Season; inactive ovaries
Gonadal dysgenesis	Small, hard, inactive ovaries; karyotype; underdeveloped tubular tract; small body
Pituitary adenoma	Systemic signs; inactive ovaries
Granulosa-theca cell tumor	See “Prolonged or Irregular Behavioral Estrus”
Behavioral	Intimidated by stallion; recently foaled; low social rank
Failure to Cycle With High Progesterone	
Pregnancy	Presence of embryonic vesicle or fetus
Persistent CL	CL fails to regress; responds to $PGF_{2\alpha}$
Diestrous ovulation	CL immature at time of endogenous $PGF_{2\alpha}$; responds to exogenous $PGF_{2\alpha}$
Pseudopregnancy	Conceptus loss after maternal recognition of pregnancy; responds to exogenous $PGF_{2\alpha}$
Iatrogenic	History of exogenous progestin or nonsteroidal antiinflammatory drug administration
Pyometra	Uterus palpably enlarged
Short Luteal Phase	
Uterine infection	Pyometra or endometritis causing premature endogenous $PGF_{2\alpha}$ secretion
Systemic endotoxemia	Systemic signs; endotoxin-mediated release of endogenous $PGF_{2\alpha}$
Iatrogenic	History of uterine manipulation, infusion, invasive procedure, or exogenous $PGF_{2\alpha}$
Prolonged or Irregular Behavioral Estrus	

Transitional period	Season; variable ovarian activity
Granulosa-theca cell tumor	Affected ovary large and multicystic, contralateral ovary small; elevated inhibin, AMH, and/or testosterone; anestrus, nymphomaniac or stallion-like behavior
Gonadal dysgenesis	Occasionally irregular cyclicity; as above
Behavioral nymphomania	Otherwise normal mare
Normal mare	Mares in winter anestrus and pregnancy may show estrous signs

AMH, Anti-mullerian hormone; *CL,* corpus luteum; *$PGF_{2\alpha}$,* prostaglandin $F_{2\alpha}$.

Treatment and Prognosis

Management should be examined to ensure a competent teasing routine. When approached by a stallion, mares in estrus stand still with ears held forward; they may elevate the tail, rhythmically evert the clitoris ("winking"), assume a squatting posture, urinate, and lean against the teasing chute toward the stallion. Mares that are in diestrus move about and hold their ears back; they may strike, kick, squeal, swish their tails, and forcefully void small amounts of urine. Experienced personnel should handle both stallion and mare. The teaser stallion should have adequate libido without being aggressive. Transrectal palpation and ultrasonography should supplement teasing. Some mares are indifferent to teasing, and records of sequential palpation must be relied on for breeding. Progesterone concentrations of less than 1 ng/mL are consistent with estrus but may also occur in anestrous mares. Mares that fail to show behavioral estrus should be bred by artificial insemination (AI) if allowed by the breed register or with appropriate restraint used for natural cover.

Behavioral Nymphomania

Abnormal estrous behavior and aggression may be demonstrated by otherwise normal mares at any stage of the estrous cycle. Ovarian tumors should be considered as an important differential diagnosis.[1]

Clinical Signs and Diagnosis

Exaggerated signs of estrus occur, initially during estrus and then throughout the cycle. Mares may develop behavioral anomalies and become aggressive. Differential diagnoses are listed in Table 43.2. It is important to differentiate abnormal estrous behavior from unrelated systemic or behavioral problems.[2]

Treatment and Prognosis

Exogenous progestins have been used to limited effect. Short-term dexamethasone treatment (5 to 10 mg) may alleviate signs for 3 to 4 days. The prognosis for resolution after bilateral ovariectomy is unpredictable, as it may be successful in some cases and exacerbate the undesired behaviors in others.[3]

Ruminants

Common causes of anestrus in cows are summarized in Table 43.3.

TABLE 43.3

Differential Diagnosis of Anestrus in Cows

Cause	Uterus	Ovaries	Peripheral Progesterone	Treatment
Pregnancy	Enlarged; positive signs of pregnancy	Corpus luteum in ovary ipsilateral to pregnant uterine horn	Elevated throughout	Usually none required; $PGF_{2\alpha}$ or $PGF_{2\alpha}$ + dexamethasone if unwanted pregnancy
Unobserved estrus	Normal; characteristic tone during estrus; postovulatory edema	Development and regression of corpora lutea and follicular waves diagnosed by sequential examinations	Elevated during diestrus and low for ≈3 days before ovulation and ≈4 days after ovulation	Improve estrus detection; estrus detection aids; synchronize estrus with $PGF_{2\alpha}$; teaser animals
Cystic follicular degeneration	Normal in acute cases; later flaccid mucometra may develop in chronic cases	Fluid-filled cyst(s) >25 mm in diameter; no corpora lutea; unilateral or bilateral; single or multiple cysts	Variable; low in cases of follicular cysts; slight elevation in cases of partially luteinized cysts	Spontaneous recovery; GnRH or hCG to induce luteinization of follicular cysts; $PGF_{2\alpha}$ for partially luteinized cysts; manual rupture
Pyometra	Variable enlargement; fluid movable from horn to horn, normal to thick uterine wall; no positive signs of pregnancy	Corpus luteum in one ovary, frequently contralateral to larger uterine horn	Elevated throughout	$PGF_{2\alpha}$
Mummified fetus	Leather-like fetus within involuted uterus; no positive signs of pregnancy	Corpus luteum in ipsilateral ovary	Elevated throughout	$PGF_{2\alpha}$; usually slaughter, advisable for economic reasons
Undernutrition	Normal	Small; static; no cyclic changes detected on sequential	Low until corpus luteum forms	Improve quality and quantity of ration

		examinations		
Granulosa-theca cell tumor	Normal	One ovary enlarged; other low atrophic	Low	Surgical removal of neoplastic ovary
Freemartinism	Small to nonexistent	Small to nonexistent	Low	No possible treatment
Ovarian hypoplasia	Very small to near normal	Very small to near normal; unilateral or bilateral; partial or complete	Variable; depends on degree of hypoplasia	No possible treatment

GnRH, Gonadotropin-releasing hormone; *hCG,* human chorionic gonadotropin; *$PGF_{2\alpha}$,* prostaglandin $F_{2\alpha}$.

Unobserved or Silent Estrus

Cow

Failure of a cow to display, or a manager to observe, the signs of estrus contributes significantly to reproductive inefficiency. When the presenting history suggests anestrus (failure to have a normal estrous cycle), the clinician must determine if the cause is failure of the manager to detect estrus in normal cows or failure of the cow to cycle because of some abnormal process. In dairy herds approximately 90% of cows presented for examination because of a history of anestrus have evidence of normal cyclic ovarian changes, whereas only approximately 10% are affected by an abnormality that suspends the estrous cycle (i.e., only ≈10% are in true anestrus).

Nearly 90% of well-managed dairy cows have initiated normal-length estrous cycles by 60 days after calving, but only approximately 60% are detected correctly to be in estrus by that time.[1] Rates of estrus detection by twice-daily observation range from 50% to 73% depending on the skill of the observer.

Mounting activity and estrous behavior are reduced by hot and cold ambient temperatures and during the times of milking and feeding. More mounts are observed when cows are kept on dirt than on concrete. Estrous behavior varies with the time of day and may be an inverse reflection of extraneous activity interfering with cow behavior. In one study, 43% of cows showed heat between midnight and 6 AM; 22% between 6 AM and noon; 10% between noon and 6 PM; and 25% between 6 PM and midnight.[2]

Estrus in dairy cows averages 7 to 16 hours but ranges from 0.5 to 36 hours. Sixty-five percent of cows are in estrus for less than 16 hours, and 25% are in estrus for less than 8 hours.[3] The number of mounts per hour ranges from 2 to 8,

and the total number of mounts during estrus ranges from 11 to 56. Total number of mounts per estrus increases with the number of cows simultaneously in estrus.

Clinical Signs and Diagnosis

Dairy herds in which infertility is caused by inaccurate estrus detection are usually characterized by prolonged intervals from calving to first breeding and between services; insemination intervals of 10 to 15 days and 30 to 35 days; records of examinations that confirm cyclic ovarian changes but in which observation of estrus is not recorded; and finding more than 15% of cows presented for pregnancy examination to be nonpregnant. Insemination during the luteal phase of the estrous cycle may occur in 10% to 20% of cows and is not likely to result in conception; insemination of pregnant cows may be followed by abortion.

The diagnosis of unobserved estrus requires sequential examination of affected cows and accurate records. Other causes of anestrus are eliminated. Conditions such as cystic follicles, pyometra, mummified fetuses, granulosa-theca cell tumors, and segmental aplasia that cause anestrus affect individual animals. Anestrus caused by undernutrition is characterized by depressed milk production and low body condition score.

Treatment and Prognosis

$PGF_{2\alpha}$ is widely used in clinical management of unobserved estrus. Mature CLs (≈day 6 through day 18 of the estrous cycle) are responsive to $PGF_{2\alpha}$-induced luteolysis. Estrus occurs an average of 3 days (range 2 to 5 days) after administration of $PGF_{2\alpha}$, depending on the follicular status of the ovaries at the time of injection. The endocrine events surrounding the controlled estrus are indistinguishable from those surrounding spontaneous estrus and ovulation. Treatment with $PGF_{2\alpha}$ shortens the intervals from treatment to first breeding and from treatment to conception but has no effect on fertility. The benefits of $PGF_{2\alpha}$ treatment are limited by inaccurate palpation of the temporary ovarian structures, injection during the wrong phase of the cycle, and failure of the manager to observe estrus in treated cows (timed AI can be used to overcome this problem).

Measurement of progesterone concentrations in milk samples taken on the day of breeding is useful in herds with a history of reduced fertility to confirm that cows being inseminated are not in the luteal phase of the estrous cycle. If more than an occasional cow presented for insemination has an elevated concentration

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of progesterone, the methods of estrus detection should be reviewed. Enzyme immunoassay kits for measuring concentrations of progesterone in milk and plasma of cows and other female animals have been described and are commercially available.

Various heat detection aids have been developed. Several of these use devices mounted on the tailhead that record when a cow has stood to be ridden. Pressure-sensitive devices that are glued to the tailhead and change color after sustained pressure by the weight of a mounting cow are commonly used. Similarly, pressure-sensitive devices glued to the tailhead can send a record of riding events directly to a computer. Chalk, cattle crayon marker, or paint applied to the tailhead are inexpensive aids that rub off when the animal is mounted when she is in heat. These methods require daily maintenance and twice-daily evaluation to function effectively. Detection aids that measure changes in activity (pedometers), mucous conductivity, or body temperature can be used successfully. Accuracy is enhanced when measurements are related to previous estrous activity and progesterone concentrations.[4]

Prevention and Control

Because unobserved estrus is primarily a problem of management, efforts to reduce time lost from delayed breeding are directed at improving efficiency of heat detection. Accurate records are required to identify cows that have not been observed in estrus by 40 days after calving. Cows not observed in estrus by 40 days after calving should be examined, and abnormalities of the reproductive organs that cause anestrus treated as indicated. The time of estrus can be predicted by palpation of the temporary ovarian structures, or estrus can be controlled with $PGF_{2\alpha}$. The most significant benefit of a planned herd health program is stimulation of improvements in management that decrease the interval from calving to conception as a result of improved estrus detection.

Anestrus after insemination is frequently interpreted as a clinical sign of pregnancy. However, unobserved estrus in cows that have failed to conceive or have experienced early embryonic death (postservice anestrus) contributes significantly to increased calving intervals. Clinical management of postservice anestrus depends on diligent observation of cows 18 to 24 days after breeding and identification of nonpregnant cows as early as possible after the infertile service so that they may be reinseminated with minimum delay. Nonpregnant cows may be accurately identified by ovarian palpation or ultrasonography for

absence of a mature CL, by low milk or plasma progesterone at the time of the first expected postservice estrus (≈21 days after breeding), or by palpation of the uterus per rectum before the second expected postservice estrus (30 to 42 days after breeding). Biochemical markers for pregnancy, such as pregnancy-associated glycoproteins (including pregnancy-specific protein B), have been validated as early as 28 days post insemination with a sensitivity and specificity of 93.9% and 95.5%, respectively.[5]

Ewe

The breeding season of most breeds of sheep maintained at temperate latitudes is restricted to late summer, autumn, and early winter, although some breeds cycle all year long. There is almost no homosexual interaction among ewes; therefore a male must be present to stimulate display of estrus.

Introduction of a ram (either intact or vasectomized) into a flock of ewes advances the breeding season. Most ewes ovulate by 3 to 6 days after introduction of rams. The induced ovulation is seldom accompanied by estrus, but the subsequent estrus approximately 17 days later is ovulatory and fertile. The “ram effect” is lost when rams are allowed to associate with ewes throughout the year.

Return to estrus after mating may be detected in a flock of ewes by fitting the ram with a brisket device that marks serviced ewes. Return of an excessive number of ewes to service after breeding alerts the owner to the possibility of infertility.

AI of ewes is rare in the United States but more popular in other countries. Laparoscopic AI is required due to the tortuous nature of the ewe's cervix and therefore is a more complicated procedure than in other species. Detection of estrus for AI depends on the use of teaser rams mingled with the ewes or led through the flock several times daily.

Doe

The breeding season of does is similar to that of ewes (i.e., it surrounds the autumnal equinox). During periods of short daylight, the normal estrous cycle of does is 20 to 21 days. Homosexual interaction among estrous does rarely occurs, so signs of estrus must be elicited by teasing. Signs of estrus may also be evoked by exposure to male pheromones by way of a “buck jar” prepared by rubbing a cloth over the scent glands caudomedial to the horns of a mature buck during the

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breeding season and storing the cloth in a tightly closed container. If estrus is not observed in does exposed to a mature buck or to a buck jar during the physiologic breeding season, pregnancy or pseudopregnancy might be considered as possible causes of anestrus. Severely parasitized or inadequately nourished does do not have normal estrous cycles. Deficiencies of phosphorus, iodine, and manganese have been suggested as causes of anestrus in does.

Introduction of bucks into a flock of does early in the breeding season results in initiation of estrous cycles and some degree of synchrony of estrus approximately 10 days after introduction of the bucks. In contrast to ewes, however, the first ovulation after exposure to males is accompanied by estrus and fertile mating.

Camelids

Most female South American camelids, although showing signs of ovarian cyclicity as early as 5 months of age, have decreased fertility until approximately 15 months of age. A female camelid should be at least 60% of her expected adult weight before she is bred. Male camelids have a preputial attachment of the penis that is not separated until 2 to 3 years of age. However, some males may detach as early as 15 months of age. Before this time they will show mounting behavior but will not be capable of intromission.

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Infertility Caused by Abnormalities of the Female Genital Organs

Abnormalities Caused by Problems With Sexual Differentiation

Sexual differentiation occurs in three stages, each stage dependent on the previous one:

1. Chromosomal (genotypic or genetic) sex is determined at fertilization in mammals by the type of sex chromosome contributed by the sperm (X or Y). In mammals, females are XX and males are XY.
2. Gonadal sex is regulated by the *Sry* (sex-determining region of the Y chromosome) gene, which produces a protein called the *HY antigen,* as well as other sex-linked and autosomal genes downstream of *Sry.* Activation of this pathway induces testis formation in the bipotential gonads. The X-linked *Dax1* gene suppresses testis formation.
3. Phenotypic sex is regulated by substances produced in the male testes to cause regression of the female tract and formation of the male tract or, in the absence of a testis, formation of the female tract.

Chromosomal sex is determined at fertilization. All normal mammalian oocytes contribute an X chromosome in addition to one of each representative autosomal maternal chromosome. Sperm cells contribute either an X or a Y sex chromosome in addition to one of each representative autosomal paternal chromosome. Abnormalities in chromosomal sex occur because of nondisjunctional errors during either mitosis or meiosis. Fig. 43.1 shows some examples of chromosomal sex anomalies.

			Sperm					
			Normal		Abnormal			
			X	Y	XY	XX	YY	O
Eggs	Normal	X	XX	XY	XXY	XXX	XYY	XO
	Abnormal	XX	XXX	XXY	XXXY	XXXX	XXYY	XX
		O	XO	YO	XY	XX	YY	O

FIG. 43.1 Examples of chromosomal sex abnormalities.

Monosomy X (XO)

Monosomy X is also known as *Turner syndrome.* Owing to the lack of a Y chromosome and the consequent *Sry* gene, but the presence of the *Dax1* gene on the present X chromosome, the phenotype is female. Monosomy X is the most commonly reported chromosomal abnormality in mares. Animals with this syndrome often have a history of poor performance and lack of or sporadic reproductive cyclicity. Ovaries are typically inactive, small, smooth, and firm. The uterus and cervix are usually hypoplastic. Externally the mare's genitalia may appear normal or underdeveloped.

XXY Syndrome

The genotype for XXY syndrome is part of Klinefelter syndrome. Because of the presence of a Y chromosome and the consequent *Sry* gene, affected individuals are phenotypically male, but probably owing to the presence of two copies of the *Dax1* gene on the two X chromosomes, they generally have hypoplastic genitalia and reproductive organs. It is thought that some factor (*Dax1* or some other) on the X chromosome must escape the inactivation process, which happens early in development (around day 7 or 8 in the horse). Testicular development and spermatogenesis are inhibited, resulting in small, flaccid testes and azoospermia. The testes may be retained or descended, but they are often small and soft. The penis may be normal or smaller than usual. Affected males often show normal libido and sexual behavior. Low testosterone concentrations may be noted. Infertility always accompanies this syndrome. Reports have been made in numerous species, including the horse.[1,2]

XXX

More is not better. A report of an infertile mare with the 65,XXX genotype confirms this.[3] The mare had bilaterally small, inactive ovaries and a hypoplastic uterus and cervix.

Mosaics.

Mosaics are individuals that have at least two cell lines with different karyotypes arising from the same zygote (Fig. 43.2).

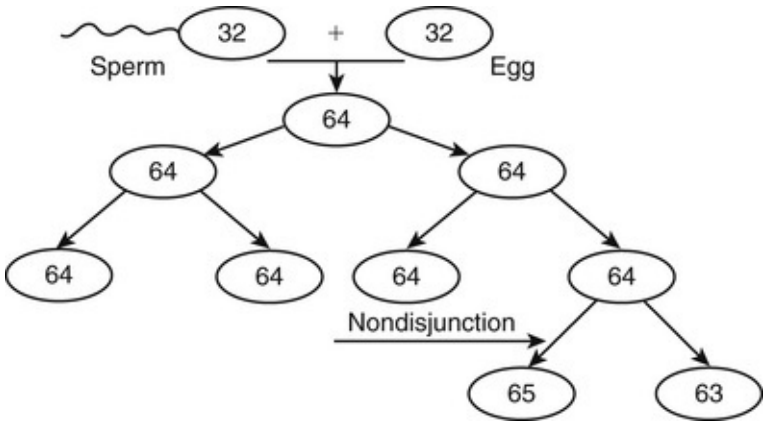


FIG. 43.2 Process of how a mosaic may occur. The haploid sperm and egg form a diploid zygote. Through the process of mitosis, diploid cells are replicated to always produce the same number of chromosomes. If, however, a chromosome pair does not separate during anaphase, called a nondisjunction event, cell lines that do not reflect a correct representation of the genome will be created and potentially propagated. If this happens with the sex chromosomes in the germ cell line, fertility of the individual or its offspring may be affected.

Phenotypes vary in accordance with the degree of mosaicism. Varying degrees of hermaphroditism and pseudohermaphroditism have been reported in many domestic species. Mosaics often have mixed gonadal dysgenesis, with an ovary and a testis, or ovotestes, owing to sex chromosome mosaic cell lines.[4,5] These are true hermaphrodites.

Chimeras

Chimeras are individuals having cell lines from two different embryonic sources. This can occur experimentally or from the natural fusion of blastocysts in utero. The possibility has been reported from a suspected double ovulation and fertilization followed by blastomere fusion in the horse (64,XX/64,XY and

63,XO/64,XY genotypes reported). Freemartinism is a common occurrence in ruminants, resulting in chimeric twins.

Freemartins

Freemartinism is a phenomenon in ruminants in which an infertile female is twin to a male. The dizygotic occurrence happens when the blastodermic vesicles of the two zygotes fuse early in development (day 18 to 20 in cattle) and share embryonic tissue. The placentas fuse (day 30 to 50 in bovines), and they share blood throughout gestation. This occurs before gonadal differentiation at day 40 to 50. Both individuals are XX/XY chimeras. The *Sry* gene of the male twin causes the freemartin gonads to develop at least partially toward the male testis. The degree of differentiation varies with each freemartin, and many freemartin gonads remain undifferentiated. The shared circulation allows testosterone and AMH from the male twin, and possibly from the chimeric freemartin, to affect the freemartin genitalia, and so she lacks a cervix, uterus, uterine tubules, and cranial vagina. The vulva is fairly normal. The yearling freemartin fails to exhibit estrus, the udder and teats remain small, and the freemartin externally resembles a steer (only with a vulva). Clinical diagnosis can be made by establishing a blind end to the vagina (no cranial vagina, no cervix) and confirmed with genotyping or use of polymerase chain reaction (PCR) to detect the Y chromosome in a phenotypic female. Among heifers born co-twin to a male, 92% will be freemartins.[6]

The male twin may develop into a fertile adult, but these individuals show a higher incidence of infertility than bulls with a 60,XY genotype. Most male twins to freemartins become steers.

Freemartinism is less common in sheep than in cattle, but it does occur. It has also been reported in goats and pigs. With increased fecundity in modern animals, the authors observe the phenomenon more often than was reported in the past. This is because ovine freemartinism is rare with twins or triplets but much more common with quadruplets or quintuplets. A notable difference between ovine and bovine freemartinism is the marked masculinity of the ovine freemartin. Gonads within the inguinal canal resemble normal prepubertal testes, and those within the abdomen resemble cryptorchid testes from rams of normal XY gonadal sex. Many ovine freemartins also have epididymides, vasa deferentia, vesicular glands, and even cremaster muscles.

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Gonadal Sex

Chromosomal sex determines gonadal sex. The Y chromosome has very few genes, and all of the ones studied play a role in sex differentiation. The gene located at the sex-determining region on the Y chromosome *(Sry)* has a DNA binding domain high-mobility group (HMG) box. It produces a protein called the *HY antigen,* and its action appears to be regulated by the transcription of other genes. Their actions initiate differentiation of bipotential embryonic gonadal tissue into testicular tissue. Other genes act downstream of *Sry* to support gonadal differentiation; these include *Sox9, Gata4*, *Wt1,* and *Sf1*, which act synergistically to promote testicular differentiation. *Sox9* is a powerful promoter of testicular tissue differentiation. It is hypothesized that *Sry* upregulates *Sox9*. In the absence of the *Sry* gene, the dual copies of the *Dax1* gene on the X chromosomes suppress the formation of testicular tissue by antagonizing the *Sry* gene and the synergy between *Sf1* and *Wt1*. Another gene, *Wnt4,* has been shown to support female development, and the absence of this gene in female mice results in masculinization.[7] This evidence refutes the notion that female development is strictly a default process caused by the absence of *Sry.* Further research is elucidating other factors that actively promote the formation of ovarian tissue (e.g., *Rspo1* β-catenin signaling). Factors affecting *Sry,* or any of the other genes downstream of *Sry,* or any factors governing female development will affect phenotypic sex.

Abnormalities of Gonadal Sex: Sex Reversals

Sex reversals occur when the chromosomal sex and gonadal sex do not agree with each other. XX sex-reversed males and XY sex-reversed females are reported in many domestic species. These individuals are either XX males (testicular tissue), XY females (ovarian tissue), or true hermaphrodites (both ovarian and testicular tissue on separate gonads or the same gonad [ovotestes]). Sex reversals are relatively common in the horse and are considered to occur both sporadically and with familial inheritance.

XY Sex-Reversed Females (Gonadal Dysgenesis).

XY sex-reversed females have been reported to arise because of an absent or mutated (and nonfunctional) *Sry* gene. It is believed that the Sry chromosome is missing because of an abnormal meiotic exchange with the X chromosome. It is thought that in the sire, two crossing-over events occur between X and Y

chromosomes during spermatogenesis. The offspring are subsequently infertile, and their external genitalia have a normal female appearance. The ovaries and uterus tend to be hypoplastic or even completely undifferentiated (“streak gonads”). These animals may be true hermaphrodites (ovotestes) or XY females (only ovarian tissue).

Sry-Positive XX Sex-Reversed Males.

XX sex-reversed males conversely may arise from a translocation of the *Sry* gene onto the X chromosome. These animals may be true hermaphrodites or XX males (only testicular tissue). This condition has been reported in ruminants but not in horses.

Sry-Negative XX Sex-Reversed Males.

There are reports in horses of *Sry*-negative XX sex-reversed males.[8,9] The exact mechanism of masculinization is still uncertain. Possibilities include Y-specific sequences other than *Sry* (which would require an XY individual with an inactivated or absent *Sry* gene), XX/XY chimerism within the testicular tissue, and a mutation in an autosomal or X-linked gene farther down the cascade of genes responsible for sex determination. XX sex-reversed males may have ambiguous sexual characteristics and may be true hermaphrodites or XX males (only testicular tissue).

Goats (especially Alpine, Saanen, and Toggenburg) present another classic, common example of *Sry*-negative XX sex-reversed males. Either the “polled” (hornless) gene is closely linked to an intersex locus or the polled gene itself is pleomorphic and controls both the hornless and intersex traits. This close linkage or pleomorphism is called the *polled/intersex syndrome* (PIS). A partial reason for the sex reversal is the deletion that affects a noncoding RNA (Pisrt1) and a transcription factor (FoxL2). The mechanism of testis induction has not been discovered yet. Elucidating this mechanism may be a big step in describing autosomal sex-determining factors in other species, including humans. The intersex gene is currently thought to work by mimicking the *Sry* gene and codes for the HY antigen.

The polled gene shows a dominant autosomal inheritance pattern, whereas the intersex trait shows an autosomal recessive inheritance pattern. A single dose of the P polled gene is enough to cause the polled trait, but a double dose is required to cause intersexuality in XX individuals. Therefore PP animals are hornless and infertile (if XX; fertile if XY); Pp individuals are hornless and

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fertile, and pp individuals are horned and fertile. Intersex individuals are always sterile and have a shortened vagina, large clitoris, bucklike head and neck, buck odor, and buck behavior. The gonads are testes or ovotestes and may be scrotal, inguinal, or abdominal. Even very masculinized intersexes with scrotal testes are azoospermic. A PP polled goat that has an XY genotype is usually initially fertile but often develops sperm granulomas later in life. The only way to avoid the intersex condition is to always breed a polled individual to a horned individual.

Phenotypic Sex

Gonadal sex determines phenotypic sex. Initially each embryo has both mullerian (paramesonephric) ducts and wolffian (mesonephric) ducts. Within testicular tissue, *Sox9* triggers Sertoli cells to secrete mullerian-inhibiting substance (MIS; also known as *anti-mullerian hormone* [AMH]), which initiates the irreversible regression of the paramesonephric ducts. The action of MIS or AMH is further regulated by other genes and their proteins (Sf-1, Gata factors, Wt-1, Dax-1, and FSH). Wt-1 and Sf-1 synergistically enhance AMH transcriptional activity. Gata-4 enhances AMH promoter activity by directly binding to DNA and by synergistically interacting with Sf-1.

Leydig cells secrete testosterone that is converted by 5α-reductase to dihydrotestosterone. These two steroids promote the differentiation of male genitalia. Testosterone influences the differentiation of the wolffian ducts into the internal male genitalia (vasa deferentia and epididymides), whereas dihydrotestosterone stimulates the formation of the seminal vesicles and male urethra from the urogenital sinus, and the penis from the genital tubercle. In the absence of these testicular hormones, the wolffian ducts regress and the mullerian ducts become the female internal genitalia.

In the presence of two X chromosomes, the double dose of Dax-1 has an inhibitory effect on the synergistic relationships between Sf-1 and Wt-1 and Gata-4, preventing their support of AMH production.[10] The primitive sex cords (gonadal cords) degenerate in the medulla and remain in the cortex (opposite in the horse). Subsequently there is no communication between the gonad and the mesonephros. In the absence of AMH, the mullerian ducts persist as the oviducts and fuse to form the uterus and cranial vagina. In the absence of testosterone, the wolffian ducts regress. Vestigial traces of these are located in the mesentery of the ovary, the epoophoron, the paroophoron, and Gartner's ducts. The tissues that form the round ligament of the uterus are analogous to the male gubernaculum.

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Abnormalities of Phenotypic Sex

Abnormalities of phenotypic sex occur when the chromosomal and gonadal sex agree (XX with ovaries or XY with testes) but the external and/or internal genitalia do not correlate or are ambiguous. Affected animals are the male and female pseudohermaphrodites. The condition can occur because of insensitivity of androgen receptors or because of any abnormality along the pathway that may affect the intervening hormones, such as the conversion of 5α-reductase to dihydrotestosterone.

Testicular Feminization.

Testicular feminization is reported in domestic species, including the horse.[11] Patients have external genitalia that are either female or ambiguous in appearance. The vagina may be blind-ending, or the uterus may be hypoplastic. The gonads are testicles, although they are usually abdominal or inguinal. Male behavior may be reported in horses. The problem lies in the gene for the androgen receptor, located on the X chromosome received from the dam. This X-linked recessive inheritance has been demonstrated in both humans and horses. Affected individuals are male pseudohermaphrodites. The condition has been diagnosed in multiple horse breeds. Serum testosterone concentration is often increased because of loss of negative feedback; a subnormal testosterone response to an hCG test is expected.

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Abnormalities of the Ovaries

Mares

Abnormally Small Ovaries

The most common causes of bilaterally small ovaries in the mare are (1) seasonal anestrus, (2) hypothalamopituitary dysfunction, (3) severe malnutrition, (4) immaturity, (5) advanced age, (6) use of anabolic steroids, and (7) gonadal dysgenesis. Clinical signs and treatment of seasonal anestrus, hypothalamopituitary dysfunction, and malnutrition are discussed elsewhere in this chapter.

Immaturity and Advanced Age

The average age at which fillies reach puberty is 18 months, with a wide range of 10 to 24 months. Fillies younger than 2 years of age with inactive ovaries and a flaccid and relaxed reproductive tract may be too young to cycle and should be reexamined later. The condition should be differentiated from gonadal dysgenesis, and karyotyping may be indicated if puberty is delayed beyond 24 months.

Older mares (>20 years) not only frequently begin cycling later in the season than do younger mares but also often have a longer follicular phase and, subsequently, a longer interovulatory interval.[12,13] Equine serum AMH levels that are related to antral follicle count have been shown to increase with age.[14] Some mares reach ovarian senescence when they grow older [12,15,16] and typically have small, inactive ovaries (follicles <5 mm) and a flaccid uterus and cervix. Although senescent mares may still show behavioral signs of estrus (similar to those of anestrous or ovariectomized mares), ovarian function is completely absent.

Oocytes collected from aged donor mares, cultured, and transferred to young recipient mares were less likely to result in pregnancy than oocytes from young donor mares.[17] Furthermore, oocytes obtained from old mares and examined using transmission electron microscopy had more morphologic abnormalities than oocytes from young mares. Results from these studies suggest that oocyte quality declines as mares age, and this factor will contribute to poor fertility in

older mares.

Treatment and Prognosis

No treatment is available for age-related ovarian inactivity. Because aged mares often experience a delayed seasonal onset of ovarian activity, they benefit from an artificial light regimen starting 60 to 90 days before the breeding season. GnRH has been used to stimulate follicular growth in mares with poor follicular development attributable to anestrus or transition. Several researchers have examined the effects of GnRH administered at different doses and intervals to stimulate follicular development in mares. In general, the number of mares responding to GnRH therapy increases as the size of follicle increases or the time of year at the onset of therapy advances.

Exogenous Hormone Treatment.

Anabolic steroids are derivatives from androgens that have been altered to provide high anabolic activity with minimal androgenic side effects. A suppression of gonadotropin secretion has been documented when mares have been treated with these drugs.[18] Anabolic steroid administration may affect both estrous behavior and ovarian size and function. The treatment of mares with low doses of anabolic steroids can cause aggressive or stallion-like behavior, whereas high doses can inhibit ovarian activity and result in failure of follicular development and ovulation.[18] Prolonged treatment of prepubertal mares with anabolic steroids results in hypertrophy of the clitoris.[19] Ovarian inactivity in mares treated with anabolic steroids is often reversible, and pituitary and ovarian function eventually return to normal in most mares after withdrawal of the treatment. However, mares intended for breeding should not be treated with anabolic steroids.

Progestins are commonly given to cycling mares for the suppression of estrus or synchronization of ovulation. Mares may continue to ovulate during progestin administration, especially if treatment is started late in the luteal phase. A high incidence of persistent CL formation has been observed in mares that ovulate during progestin treatment.[20] Administration of the potent GnRH agonist deslorelin acetate to induce ovulation has been associated with delayed follicular development and a prolonged interovulatory interval.[21,22] Deslorelin acetate is effective in inducing ovulation, but treatment appears to cause a temporary downregulation of FSH secretion. The low FSH concentrations have been

associated with a prolonged period of decreased follicular growth. Administration of $PGF_{2\alpha}$ 7 to 8 days after ovulation appears to increase the risk of delayed follicular development. It has been suggested that $PGF_{2\alpha}$ administration “resets” the timing of the estrous cycle during a period when limited follicular activity is present.

Treatment and Prognosis

Removal of the deslorelin implant after ovulation has been detected to decrease the incidence of prolonged interovulatory intervals.[23]

Gonadal Dysgenesis.

Chromosomal abnormalities occur in all breeds of horses. Mares are usually small and phenotypically female. The ovaries are small, firm, smooth, and inactive. The tubular tract is thin and flaccid. Endometrial hypoplasia is a common finding. Diagnosis is confirmed by physical findings and karyotype. Mares with gonadal dysgenesis are sterile, and there is no treatment.

Pituitary Pars Intermedia Dysfunction.

Mares with hypertrophy, hyperplasia, or adenoma formation in the pars intermedia of the pituitary (pituitary pars intermedia dysfunction [PPID]) have been reported to have abnormal estrous cycles, infertility, or both.[24,25] The mechanisms by which PPID causes reproductive abnormalities have not been determined. Potential causes may be destruction of the gonadotrophs of the anterior pituitary owing to compression by the enlarged pars intermedia and/or suppression of gonadotropin secretion owing to elevated levels of glucocorticoids or androgens produced by the adrenal cortex.[26] In support of the glucocorticoid hypothesis, administration of dexamethasone to intact mares results in reduced estrous behavior, LH concentrations, follicular growth, and incidence of ovulation.[27] In addition, administration of dexamethasone to ovariectomized mares results in suppression of pituitary LH and FSH secretion,[28] and treatment of pony mares with dexamethasone during the winter eliminates estrous behavior.[29] However, others have shown that abnormally high levels of cortisol secretion has a minimal effect on fertility.[30] Many PPID horses are insulin resistant, and insulin is believed to play a role in the regulation of ovarian steroidogenesis and follicular development.[31] Obese mares with reduced

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insulin sensitivity have been shown to have prolonged interovulatory periods. Insulin resistance therefore may be one mechanism by which PPID mares exhibit abnormal ovarian function.[32] Most horses diagnosed with PPID are older, with the average age being approximately 20 years. Consequently the decrease in reproductive efficiency in mares with PPID may be partly a result of advanced age.

Clinical signs of PPID include hirsutism and abnormal hair-coat shedding patterns, polyuria, polydipsia, and hyperhidrosis.[33] Diagnostic tests for PPID include measurements of serum glucose, insulin, adrenocorticotropic hormone (ACTH), and cortisol levels; dexamethasone suppression; ACTH stimulation; and thyrotropin-releasing hormone response.[34] The measurement of single samples for basal cortisol or ACTH concentrations is of limited value in the diagnosis of PPID.

Treatment and Prognosis

The medical management of PPID includes the administration of pergolide mesylate, a dopamine receptor agonist, at a dose of 0.002 to 0.01 mg/kg every 24 hours (1 to 5 mg/500 kg) in an adult horse. Because of its dopaminergic agonist effect, treatment with pergolide mesylate should be avoided in late pregnant and lactating mares. Treatment of pregnant mares can be discontinued at 30 days before expected foaling until 1 month postpartum, and the mares should be monitored for adequate milk production. Foals should be supplemented with a milk replacer when insufficient milk production is suspected in the dam. The serotonin antagonist cyproheptadine has also been used, but it may not be as efficacious as pergolide. The dose of cyproheptadine is 0.25 mg/kg every 24 hours, given once in the morning.

Equine Metabolic Syndrome.

Equine metabolic syndrome (EMS) is not clearly defined, and intense research in this area is expected to shed further light on the understanding of this condition in horses. Altered circulating concentrations of leptin and adiponectin have been observed in horses with EMS, and an effect on reproductive cycles in mares has been suggested, but existing data are not conclusive.[35-37] In fact, moderately obese mares are more likely to cycle year-round compared to lean mares.[38]

EMS has been associated with regional obesity, insulin resistance, and laminitis.[39] A presumptive diagnosis is often based on body condition score and

signs of regional obesity, history of laminitis, and insulin resistance.[40]

Treatment and Prognosis

Controlled diet and exercise are important components in the management of mares with suspected EMS. Medical treatment with metformin at a dose of 15 to 30 mg/kg and levothyroxin sodium at a total dose of 48 mg has been suggested.[39] However, scientific evidence of the safety and efficacy of these drugs is insufficient in horses. Metformin has not been evaluated for safety in pregnant mares, but it is considered safe to use in pregnant women.[41] The effect of human maternal hyperthyroidism on the fetus should be considered before levothyroxin is used in pregnant mares.

Abnormally Enlarged Ovaries

The most common causes of enlarged ovaries in the mare are (1) tumors, (2) anovulatory follicles, (3) ovarian hematomas, and (4) pregnancy.

Ovarian Tumors

Most equine ovarian tumors can be categorized as sex cord–stromal tumors (granulosa-theca cell tumors), epithelial tumors (cystadenomas), or germ cell tumors (dysgerminomas and teratomas), and mares can present with more than one tumor type.[1]

Granulosa-Theca Cell Tumors.

The granulosa-theca cell tumor (GCT) is the most common ovarian tumor in the mare (Fig. 43.3),[2] and 10% of all neoplasms in horses are GCTs. It is usually slow growing, unilateral, and benign; however, malignant tumors have been reported.[3] It occurs in mares of all ages and parity[2,4] and is occasionally found in pregnant mares.[2,5] The tumor arises from the steroidogenic cells of the follicle, resulting in abnormal secretion of inhibin and testosterone.

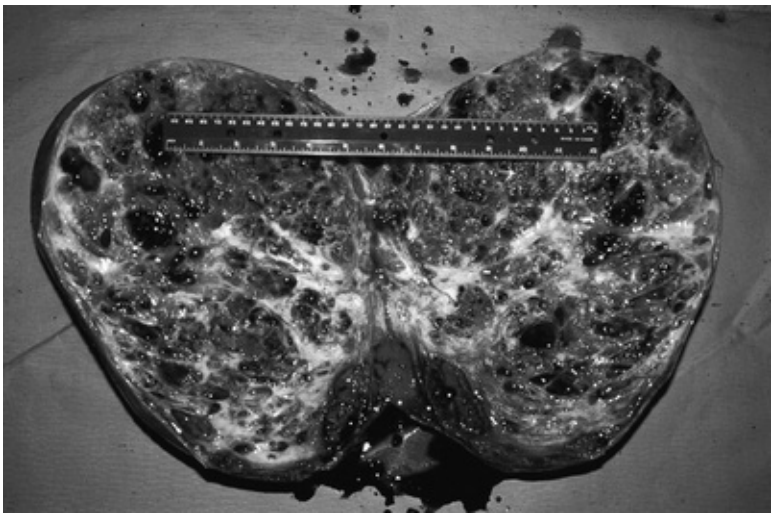


FIG. 43.3 Granulosa cell tumor removed from a mare.

Clinical Signs and Diagnosis

Diagnosis of GCTs is made based on ultrasonographic findings, histologic evaluation, hormone profile analysis, and behavioral observations. Transrectal ultrasonographic examination of the affected ovary often reveals a multicystic or honeycombed structure, but the tumor may also occur as a solid mass or as a single large cyst. In most cases the GCT affects only one ovary, and the contralateral ovary is usually small and inactive, although mares with a GCT on one ovary and a functional contralateral ovary have been reported.[6]

GCTs are hormonally active, and clinical diagnostic assays for the detection of a GCT include the measurement of inhibin (α-inhibin), testosterone, progesterone, and AMH.[7-11] α-Inhibin is elevated in approximately 90% of the mares with a GCT.[8,10] It has been hypothesized that inhibin produced by the GCT is responsible for inactivity of the contralateral ovary through the suppression of pituitary FSH release,[12] but the poor correlation between dimeric inhibin and the presence of GCT raises questions about the mechanism by which the contralateral ovary is suppressed in affected mares.[10,13] Serum testosterone in a single blood sample can be expected to be elevated (100 to 200 pg/mL) in approximately 50% to 60% of affected mares. Daily fluctuations in testosterone concentrations have been reported, and repeated samples may have to be obtained on different days in order to detect elevated testosterone.[10] Progesterone concentrations in mares with a GCT are almost always below 1 ng/mL because normal follicular development, ovulation, and CL formation do

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not occur. Serum levels of AMH in mares with GCTs are consistently higher than in normal cyclic and pregnant mares, and this provides an excellent tool in the diagnosis of GCT.[11] As a result of hormone secretion from the tumor, mares may show anestrus, constant estrus, irregular estrus, or stallion-like behavior. Physical changes such as an enlarged clitoris, increased muscle mass, and the development of a crested neck have been associated with GCTs, and other clinical signs such as colic, lameness, and weight loss have been observed.[2]

Treatment and Prognosis

Treatment for GCTs is removal of the affected ovary.[14] Surgical approaches for tumor removal include colpotomy, flank and ventral midline laparotomy, and laparoscopy. The prognoses for both life and reproductive use are good. The time from surgery to return to cyclicity varies, but most mares cycle in the year after ovariectomy.

Cystadenomas.

The most common tumor of the surface epithelium of the equine ovary is cystadenoma. They are rare, benign, normally hormonally inactive tumors from the surface epithelium of the ovulation fossa. The tumor is unilateral, and the contralateral ovary is normal.

Clinical Signs and Diagnosis

Mares with cystadenomas cycle normally from the opposite ovary and may become pregnant if bred. Rectal palpation and ultrasonography reveal the presence of one enlarged multicystic ovary, which may appear similar to a GCT, and one normal ovary; however, final diagnosis is histologic.

Treatment and Prognosis

Although cystadenomas are benign tumors and do not affect the reproductive performance of the mare, they are usually surgically removed if diagnosed. The prognoses for both life and reproductive performance are excellent.

Germ Cell Tumors.

Dysgerminomas and teratomas are rare ovarian tumors of germ cell origin. Both tumors are unilateral and hormonally inactive.

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Clinical Signs and Diagnosis

Both tumors make the affected ovary unilaterally enlarged and multicystic. Dysgerminomas are malignant and do often metastasize to the peritoneal and thoracic cavities. Teratomas may arise from all three germinal layers, and the neoplastic ovary may contain bone, cartilage, teeth, hair, muscle, and nerves. Teratomas do not cause clinical signs, interrupt the estrous cycle, or alter the behavior of the mare. Diagnosis of dysgerminomas and teratomas is made using ultrasonography and histologic evaluation of the affected ovary.

Treatment and Prognosis

Surgical removal is recommended for both dysgerminomas and teratomas. The prognosis for teratomas is usually good, but it is poor for mares diagnosed with dysgerminomas.

Anovulatory Follicles

Clinical Signs and Diagnosis

Ovulation failure is a normal physiologic event for the mare during the spring and fall transition periods, but it may also occur occasionally during the physiologic breeding season. Persistent anovulatory follicles (PAFs) may be quite large (5 to 15 cm in diameter), persist for up to 2 months, and result in abnormal estrous behavior and prolonged interovulatory intervals.[15] The cause of ovulation failure is still being determined, but it has been suggested to be due to gonadotropic stimulation insufficient for ovulation,[16] reduced estrogen production by the follicle,[17] blockage of the ovulation fossa,[18] repeated use of ovulation-inducing drugs,[19] alterations of the matrix metalloproteinase system,[20] and defects in the normal ovarian proangiogenic activity.[21] PAFs have been reported to occur in approximately 8.2% of estrous cycles, and significantly more mares 16 to 20 years of age developed anovulatory follicles than mares 6 to 10 years of age.[22] The formation of an anovulatory follicle was preceded by development of normal endometrial folds or edema in 78.3% of these cases. Initial growth patterns of follicles destined to become anovulatory were usually normal, and the first indication of a problem was the detection of echogenic particles within the follicular fluid.[22]

PAFs may contain blood and have been called *hemorrhagic anovulatory*

follicles. The hemorrhage can be detected ultrasonically as scattered free-floating echogenic spots within the follicular fluid. The follicular fluid may form a gelatinous, hemorrhagic mass within the follicular lumen. Ultrasonographically these structures may contain echogenic fibrous bands traversing the follicular lumen (Fig. 43.4).[23] A thickening of the follicular wall may be observed in anovulatory follicles. This thickening is often associated with luteinization of the follicular wall, and 85.7% of PAFs were found to be luteal structures based on elevations in plasma progesterone concentrations.[22]

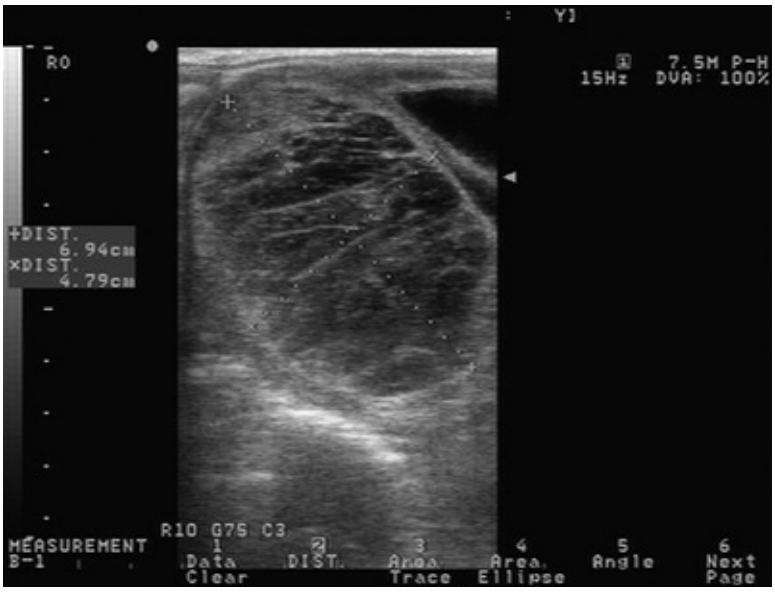


FIG. 43.4 Transrectal ultrasonographic image of a persistent anovulatory follicle in a mare.

Treatment and Prognosis

Treatment with hCG or a GnRH agonist to induce ovulation or luteinization of the anovulatory follicle is generally not effective. The administration of prostaglandins may result in the destruction of the luteal cells in mares with luteinized PAFs. Most nonluteinized PAFs spontaneously regress in 1 to 4 weeks. Pregnancy does not usually occur if a persistent follicle eventually spontaneously ovulates or is induced to ovulate. This is likely a result of degeneration of the oocyte over time. Pregnancy obviously will not occur if the follicle becomes hemorrhagic or luteinized without ovulation.

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Ovarian Hematoma

Clinical Signs and Diagnosis

Hemorrhage into the follicular cavity is a normal occurrence at ovulation. Occasionally hemorrhage is severe, resulting in the formation of an ovarian hematoma that may be 10 cm in diameter or larger. Diagnosis can be made using transrectal palpation and ultrasonography, and the condition presents as an enlarged ovary that is initially irregularly hypoechoic and then echogenic with organization of the hematoma. Ovarian hematoma should not be mistaken for a GCT, since the ovulation fossa usually remains distinguishable on the affected ovary, and the contralateral ovary remains active.

Treatment and Prognosis

Ovarian hematomas regress spontaneously over a period of weeks or months. The functional life span of the luteal tissue in a hematoma is normal, and ovarian activity is unaffected.[24] Because the affected ovary is not permanently damaged and the contralateral ovary is unaffected, the prognosis for fertility is undiminished.

Pregnancy

Multiple secondary CLs form in pregnant mares at 40 to 180 days of gestation, resulting in bilaterally enlarged ovaries that may be mistaken for ovarian pathology.

Clinical Signs and Diagnosis

Ovarian enlargement is commonly bilateral. Pregnant mares may show stallion-like behavior associated with increased testosterone production from the fetus during midgestation. Pregnancy should always be considered in a mare with stallion-like behavior, elevated serum testosterone concentrations, and enlarged ovaries. Pregnancy is diagnosed by rectal palpation and ultrasonographic examination.

Persistent Corpus Luteum

The CL usually regresses 14 to 15 days after ovulation. Although luteal cells appear to be sensitive to $PGF_{2\alpha}$ almost immediately after ovulation, complete

luteolysis and return to estrus in response to endogenous or exogenous $PGF_{2\alpha}$ will not occur until 5 days after ovulation. Because the functional CL is lysed by $PGF_{2\alpha}$ from the endometrium, the CL will continue to function in the following situations.

1. The equine conceptus produces a $PGF_{2\alpha}$ inhibitor factor, which is secreted as early as day 11 to 13 after ovulation.[25] The factor prevents $PGF_{2\alpha}$ from being synthesized and secreted from the endometrium. This results in a prolonged luteal phase of the primary CL until the development of endometrial cups and secretion of eCG ensure the presence of functional luteal tissue in the pregnant mare.
2. Embryonic loss after the time of maternal recognition of pregnancy can result in a persistent CL for a variable period of 35 to 90 days.[26]
3. Destruction of the endometrium in infectious and inflammatory conditions such as pyometra may cause insufficient synthesis of $PGF_{2\alpha}$ and prolonged luteal life.[27]
4. Late diestrous ovulation will result in a CL that is insufficiently mature to respond to endogenous $PGF_{2\alpha}$ release.
5. Nonsteroidal antiinflammatory drugs may inhibit endometrial $PGF_{2\alpha}$ synthesis, resulting in a prolonged luteal phase.[28]
6. Repeated treatment with oxytocin before upregulation of oxytocin receptors occurs (before day 13) has resulted in a prolonged luteal phase.[29,30]
7. Spontaneous CL persistence has been proposed as a clinical entity[26] but has not been adequately documented and is an area of controversy.[31]

Clinical Signs and Diagnosis

A persistent CL may be suspected clinically in mares that are not expressing normal estrous behavior during the physiologic breeding season, and it must be differentiated from mares with silent heat. Diagnosis is made by transrectal ultrasonographic examination of the ovaries. The CL appears as a well-defined hyperechoic structure on the ovary. Mares with a persistent CL will have good cervical and uterine tone on palpation, and the cervix will appear tight and dry on vaginal speculum examination because of the influence of progesterone. The diagnosis may be confirmed by analysis of plasma progesterone concentrations

or a clinical response to prostaglandin administration. Progesterone concentrations greater than 1 ng/mL are indicative of the presence of active luteal tissue. Differential diagnoses are listed in Table 43.4.

TABLE 43.4

Unilaterally Large Ovary: Differential Diagnosis

Etiology	Distinguishing Features
Granulosa-theca cell tumor	Sonographically multilocular, high inhibin, AMH and/or testosterone; small contralateral ovary
Other ovarian tumor	See text
Ovarian hematoma	Ovulation fossa still palpable, cycles normally
Ovarian abscess	Large, hard ovary; sonographically echogenic
Ovarian follicle	Normal cycling mare, ovulates
Anovulatory hemorrhagic follicle	Free-floating echogenic spots

AMH, Anti-mullerian hormone.

Treatment and Prognosis

After pregnancy has been ruled out with sonographic examination, luteolysis can be achieved with administration of 5 to 10 mg of the α-progstaglandin product dinoprost tromethamine or similar prostaglandin analog. The mare must be at least 5 days post ovulation to respond reliably to treatment, although administration of the drug 3 days post ovulation can be effective.[32] If the mare is treated with $PGF_{2\alpha}$ in the presence of a mature diestrous follicle (≥35 mm), she may ovulate the follicle without signs of estrus in response to declining progesterone concentrations that allow LH to be secreted from the anterior pituitary. An ultrasonographic or rectal examination of ovarian follicular activity should therefore always be performed before $PGF_{2\alpha}$ is administered to induce estrus.

Shortened Luteal Phase (Premature Luteolysis)

Premature (<15 days) luteolysis is associated with an early onset of estrus and a decrease in the interovulatory interval. The most common cause of premature luteolysis in the mare is endometritis. Inflammation of the endometrium results in an acute activation of inflammatory mediators. One of these mediators is $PGF_{2\alpha}$, which in addition to its inflammatory effect also may cause luteolysis

and return to estrus. Consequently a mare that exhibits a shortened diestrus should be examined for endometritis. Manipulation of the reproductive tract for uterine biopsy has also been found to cause premature luteal regression.[33]

Luteal Insufficiency

Primary luteal insufficiency implies a deficiency in progesterone production. Luteal insufficiency has been suggested to be a cause of subfertility in mares.[34] Maintenance of pregnancy in some habitually aborting mares after administration of exogenous progestogens offers circumstantial evidence that progesterone insufficiency may be responsible for some cases of pregnancy loss. However, the concept of primary luteal insufficiency as a cause of early pregnancy loss is controversial and not supported by conclusive scientific data.

Luteal insufficiency secondary to $PGF_{2\alpha}$ release in mares with endotoxemia has been reported[35] and should be considered in pregnant mares with gram-negative infection and/or endotoxemia-associated colic. Reports on the effect of exogenous administration of $PGF_{2\alpha}$ during the periovulatory period suggest that $PGF_{2\alpha}$ can delay the formation of a functional CL. Suboptimal concentrations of progesterone were found in mares after treatment with $PGF_{2\alpha}$ during the first 2 days after ovulation.[36-39] Although the CL eventually became functional and progesterone concentrations had returned to normal levels at day 14, pregnancy rates were significantly lower in treated mares.[37,38]

Clinical Signs and Diagnosis

The minimum concentration of progesterone required to maintain pregnancy in the mare has been suggested to be 2 ng/mL.[35] Repeated samples are necessary to diagnose luteal insufficiency because progesterone is released episodically.

Treatment and Prognosis

The most common treatment for luteal insufficiency is supplementation with the synthetic progestogen altrenogest (Regu-Mate®) at a dose of 0.044 mg/kg PO once daily. Options for duration of altrenogest supplementation include treatment until day 80 to 120 of pregnancy or longer and measurement of endogenous progesterone level greater than 2 ng/mL (progesterone and altrenogest do not cross-react on radioimmunoassay [RIA]) or treatment until the

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end of gestation. It is important to emphasize the need to monitor fetal well-being when mares are kept on progestin supplementation to maintain pregnancy. A case of mummification of a 5-month-old fetus in a pregnant mare at term has been reported.[40] The mare had been maintained on altrenogest throughout gestation.

Ruminants

Prolonged Luteal Function

Cow.

Spontaneous prolongation of luteal function in the presence of a normal, nongravid uterus does not occur in cows. However, several conditions affecting the uterus do suspend the luteolytic mechanism, resulting in prolonged luteal function, persistently elevated progesterone concentrations, and anestrus. Common causes of prolonged luteal function in cows include pregnancy, pyometra, mummified fetus, and segmental aplasia, including uterus unicornis.

Clinical Signs and Diagnosis

Pregnancy resulting from an unobserved or unrecorded breeding must always be considered as a possible cause of anestrus. Examination of the uterus by transrectal palpation or ultrasonography for one of the positive signs of pregnancy (fetal membrane slip, amnionic vesicle, placentomes, or fetus) must precede administration of $PGF_{2\alpha}$.

Pyometra is characterized by accumulation of variable amounts of mucopurulent exudate within the uterine lumen, failure of luteolysis, and subsequent anestrus. An enlarged uterus as a result of fluid accumulation and a thickened uterine wall in the absence of any positive signs of pregnancy can be used to differentiate uterine enlargement caused by pregnancy from that caused by pyometra. Fluid associated with pyometra is more viscous than fetal fluid and can be manipulated from horn to horn. Because the cervix is nearly always closed, there is generally no vaginal discharge.

Fetal mummification is occasionally encountered in dairy and beef cows and is characterized by fetal death, failure of expulsion, absorption of fetal fluids, and persistence of the CL. Cows with fetal mummification are usually presented when they do not deliver a calf at the expected time. The condition can be

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differentiated from pregnancy by palpation per rectum of a dried, leather-like fetus within the involuted uterus. Fetal membranes cannot be slipped, and fetal fluids and placentomes are absent.

Clinical Pathology

No remarkable changes in hematology and clinical chemistry are associated with pregnancy, mummified fetus, or pyometra in cows. In all three conditions, peripheral concentrations of progesterone remain elevated above 1 ng/mL of plasma until spontaneous luteolysis occurs or the condition is treated.

Treatment and Prognosis

Unwanted pregnancy is seldom encountered in dairy cows, but when cows or heifers are mated by accident or to an undesired sire, abortion may be reliably induced with $PGF_{2\alpha}$ products (25 mg of dinoprost tromethamine or 500 µg of cloprostenol, two injections 8 to 12 hours apart) after 7 days and before 150 days of gestation or with a combination of $PGF_{2\alpha}$ and dexamethasone (20 mg) beyond 150 days of gestation. The $PGF_{2\alpha}$ products are also the treatment of choice for pyometra in cows. Mummified fetuses are usually expelled 3 to 5 days after treatment with $PGF_{2\alpha}$. The mummy may pass through the cervix, but the vagina is likely to be dry and may not dilate sufficiently, so the mummified fetus may be retained. If the mummified fetus is not expelled by 5 days after treatment, a vaginal examination should be performed and the mummy delivered by gentle traction if necessary. The prognosis for fertility after delivery of a mummified fetus is fair, but slaughter is often recommended for economic reasons.

Ovarian Hypoplasia

Ovarian hypoplasia occurs sporadically as an autosomal recessive trait in the cow. The condition has incomplete penetrance; therefore it may be partial or complete and unilateral or bilateral. The affected gonad varies in size from a cordlike thickening in the cranial edge of the mesovarium to a bean-sized structure. The tubular genital organs remain infantile in animals with complete bilateral hypoplasia or may develop to near normal size in heifers with unilateral or partial hypoplasia. Individuals affected with complete bilateral ovarian hypoplasia are sterile, whereas those affected by partial or unilateral hypoplasia may be subfertile. With partial hypoplasia the uterine pole of the ovary is

typically affected. On direct observation by laparotomy or laparoscopy or on slaughter, the uterine pole is flat and triangular and shows converging striations. The affected part is devoid of follicles. Animals with partial ovarian hypoplasia can be expected to have a reduced superovulatory response to gonadotropin treatment. Heifers with abnormal karyotypes are also affected by ovarian hypoplasia. The condition should be differentiated from nonfunctional ovaries and anestrus associated with malnutrition or debilitating diseases. Treatment of ovarian hypoplasia is not successful.

Ovarian Tumors

Granulosa Cell Tumor

Cow.

Although rare, various ovarian neoplasms have been described in cows; granulosa cell tumors appear to be most common.[1]

Clinical Signs and Diagnosis

Granulosa cell tumors are characterized by unilateral ovarian enlargement, with the affected ovary being greater than 10 cm in diameter. The surface may be smooth or coarsely lobulated. Function of the contralateral ovary may be suppressed. The behavior of affected cows ranges from anestrus to nymphomania to bull-like behavior. Udder development and lactation may occur in affected heifers. Hormonal profiles, including estrogen and testosterone, may be variable among cows with granulosa cell tumors. Although inhibin has not been validated for use in cows, AMH is secreted by neoplastic granulosa cells and can be a useful diagnostic measurement.[1] Few bovine granulosa cell tumors are malignant, and they rarely metastasize. Among the other ovarian neoplasms that have been reported in cattle are dysgerminomas, interstitial cell tumors, and teratomas. Causes of ovarian enlargement that must be differentiated from ovarian neoplasia include ovarian cysts, oophoritis, ovarian abscesses, and parovarian cysts.

Treatment and Prognosis

The treatment for ovarian neoplasia in cattle is surgical removal of the affected

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ovary; however, cows may not be as fertile as mares after removal of the tumor.

Ewe.

Granulosa cell tumors have been reported, but tumors of the genital organs of ewes appear to be rare. Animals with ovarian tumors may exhibit all types of behavioral and physiologic abnormalities (nymphomania, inappropriate lactation). Diagnosis is based on transabdominal or transrectal ultrasonographic evaluation of the ovaries. Treatment is ovariectomy.

Doe.

Ovarian neoplasia appears to be rare in does as well. Granulosa cell tumors and dysgerminomas have been reported.

Ovarian Hemorrhage

Cow

Ovulation tags develop after ovulation, resulting from blood loss associated with rupture of the follicle. Fine adhesions may develop between the ovarian surface and surrounding structures. Most ovulation tags resolve spontaneously and have no effect on fertility. Severe ovarian hemorrhage may follow attempts to manually enucleate the CL. Adhesions between the ovary and its bursa interfere with their normal function. Enucleation of CLs for treatment of anestrus and pyometra has been superseded by treatment with $PGF_{2\alpha}$ products.

Oophoritis

Cow

Inflammation of the ovary may follow traumatic manipulations, such as enucleation of CLs and attempts to drain fluid from ovarian cysts, and ascending infections from the uterus. Oophoritis may also accompany brucellosis, mycoplasmosis, and tuberculosis.

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Infertility Caused by Abnormalities of the Female Tubular Genitalia

Salpingitis

Inflammation of the oviducts is characterized by macroscopic enlargement. Lesions are frequently bilateral and consist of infiltration by lymphocytes, plasma cells, and neutrophils, and desquamation of epithelial cells.

Most cases of salpingitis follow infections of the uterus. Necrotizing and granulomatous salpingitis may follow infection by *Trueperella pyogenes* (formerly *Arcanobacterium pyogenes*), *Mycobacterium tuberculosis*, and *Brucella abortus*. Mild inflammation of the uterine tubes that does not usually result in permanent damage accompanies uterine infection caused by *Campylobacter fetus* subsp. *venerealis* and *Tritrichomonas foetus*. Salpingitis may be a sequela to manipulations of the ovaries and uterine tubes by palpation per rectum, transvaginal ovum pickup, aggressive irrigation of an infected uterus, and inappropriate treatment with estrogenic hormones. Migrating larvae of *Strongylus edentatus* have been proposed as a possible cause of nonobstructive infundibulitis in mares, but their role is speculative.

Pyosalpinx is characterized by segmental accumulation of pus within the lumen of the oviduct after mechanical blockage of either end. Pyosalpinx frequently follows severe cases of uterine infection and may be complicated by perimetritis and localized peritonitis.

Hydrosalpinx is characterized by accumulation of thin mucus within the lumen of the oviduct. Hydrosalpinx and adhesions to perisalpingial tissues are common sequelae to chronic salpingitis.

Clinical Signs and Diagnosis

The usual history associated with diseases of the uterine tubes is one of infertility. Additional history may include uterine infection or traumatic therapy such as uterine irrigation, enucleation of CLs, or administration of exogenous estrogen during CL function. Salpingitis is an uncommon clinical finding in the mare. However, in one study up to 88% of mares were found to have macroscopic lesions in the oviduct, including adhesions, fibrous bands, and parovarian cysts, which may or may not have affected fertility.[1] Accumulations

of cells and debris may form intraluminal masses; however, their role in infertility has not been adequately tested.[2] Similarly, moderate lesions of uterine tube disease may escape diagnosis by physical examination in cows, but the results of abattoir studies suggest that lesions of the oviducts are not uncommon. In cows, lesions involving adhesions among the ovary, ovarian bursa, oviduct, and surrounding tissues may be identified per rectum by inserting two or three fingers into the ovarian bursa and rolling the oviduct between the fingers and thumb. Easy identification of the oviduct by palpation per rectum is sometimes considered indicative of abnormalities. Diagnosis of diseases of the oviducts in ewes and does is impossible by physical examination. Although a history of infertility after one of the predisposing causes might suggest oviductal lesions, diagnosis is made by exploratory laparotomy, peritoneoscopy, or necropsy.

Lesions of the oviductal or perisalpingial tissues must be differentiated from other causes of abnormal enlargements such as ovarian neoplasia, parovarian cysts, cystic ovarian disease, and ovarian hematomas. Neoplasia of the oviducts in domestic animals is extremely rare.

Clinical Pathology

Several tests that determine oviductal patency of mares[3,4] and cows[5] have been described, but neither the starch test nor the phenolsulfonphthalein dye test is reliable or consistently diagnostic. For suspected unilateral blockage, each uterine horn may be catheterized individually with a Foley catheter placed at the base of the horn on different days.[6]

Embryo Recovery

Embryo recovery after either a single ovulation or superovulation is objective evidence that one or both uterine tubes are patent and functional. Improved reproductive performance of cows may follow uterine lavage; therefore embryo recovery as a diagnostic test may have therapeutic benefits as well.[7]

Treatment and Prognosis

Treatment of diseases of the oviducts is not likely to be successful. Appropriate treatment for concurrent uterine infections should be instituted. A period of sexual rest may be beneficial and is indicated in valuable animals. The prognosis for reproduction in cases of bilateral obstruction of the oviducts is poor. In vitro fertilization of ova harvested from affected females is a therapeutic option.

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Affected females can also serve as embryo recipients.

Prevention and Control

Traumatic manipulation of the ovaries, irrigation of the endometrial cavity with large volumes of fluid (>100 mL in heifers or 150 mL in cows) or irritating chemicals, and administration of estrogenic hormones to luteal phase females should be avoided. Because abnormalities of the oviducts are frequently associated with uterine infections, reduction of the prevalence of uterine infections results in fewer tubal infections as well.

Uterine Abnormalities

Retained Fetal Membranes

Mares.

Retention of the fetal membranes beyond a period of 3 hours is an abnormal occurrence in the mare. The mare has an epitheliochorial placenta characterized by diffuse microvilli that interdigitate with endometrial crypts. After delivery, blood flow through the placental vessels is reduced. Placental microvilli shrink and disengage from endometrial crypts. The pathophysiology of the disease is poorly understood but may involve disturbances of normal prepartum endocrine events or myometrial contractility. The condition is more common after abortion, dystocia, cesarean section, and fetotomy. Partial placental retention may be localized to well-defined areas of continued placental attachment. The most common site of partial retention is the previously nongravid horn.

Equine placentas should be spread on a flat surface after expulsion and examined to ensure that the complete membrane is present. Areas of placental necrosis are common near the tips of the uterine horns, and the fragile area may be incarcerated by the rapidly contracting uterus.

Clinical Signs and Diagnosis

Retained fetal membranes (RFMs) are usually visible at the vulva. However, small tags of placental tissue may remain attached to the uterus without being apparent and may be a nidus for infection, resulting in severe metritis, endotoxemia, and laminitis hours to days postpartum.

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Treatment and Prognosis

The severity of sequelae makes early intervention essential. Treatment should begin if fetal membranes are not passed within 3 hours of foaling. Most instances respond to vigorous early pharmacologic treatment. Occasional cases require several days of persistent treatment.

Manual Removal.

Manual removal should be avoided because trauma induces placental tearing, leaving microvilli in endometrial crypts.

Oxytocin.

Oxytocin induces myometrial contractions, which may aid placental expulsion. Oxytocin may be administered by IV injection (5 to 20 IU every 30 to 60 minutes) or IM injection (10 to 20 IU every 30 to 60 minutes), or it may be infused slowly (30 to 80 IU in 500 mL of warm saline IV over 30 to 60 minutes). Care should be taken to avoid higher doses, which may result in signs of abdominal pain and will cause tetanic rather than orchestrated uterine contraction.

Allantochorionic Infusion.

If the allantochorion is intact, the allantochorionic cavity may be filled to distention with 3 to 4 gallons of warm saline or water through the cervical star.[1] The opening in the placenta is held closed manually until the mare exerts abdominal pressure. Oxytocin may be used in conjunction with this treatment.

Uterine Lavage.

If the allantochorion is not intact, uterine lavage with an isotonic saline solution will clear debris, will trigger myometrial contractions, and may help free the retained fragment of the fetal membrane. The isotonic saline solution may be infused into the uterus through an equine nasogastric tube (dedicated to reproductive use) manually held in place. Approximately 5 L may be placed in the uterus of a full-grown, postpartum mare at one time, but care should be taken to observe the mare for signs of discomfort and to gauge the amount of fluid felt within the uterus. During fluid infusion the operator may carefully explore the uterus manually, searching for RFM remnants. Once the uterus is relatively full of fluid, the fluid is siphoned out. Care must be taken to protect the fragile

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endometrium from damage incurred by the strong suction force of the siphon. The operator's hand should guard the end of the tube from direct contact with the endometrium. This process should be repeated until the effluent is clear. Uterine lavage should be performed at least once daily until 12 to 24 hours after the RFM remnants are retrieved.

Adjunct Therapy.

Concurrent therapy directed at controlling or minimizing common sequelae to retained placenta is often indicated.

1. *Antimicrobials.* Bacterial infections are commonly associated with prolonged (>6 to 8 hours) retention of the fetal membranes. The bacterial population is frequently mixed and likely to include β-hemolytic streptococci and coliforms. In prolonged cases, bacterial culture and sensitivity should be performed. Broad-spectrum antibiotics known to be effective against commonly isolated organisms are indicated. Drugs that have been recommended for systemic administration include amikacin, ampicillin, gentamicin, kanamycin, penicillin, ticarcillin (with gentamicin for *Pseudomonas* infection), and trimethoprim-sulfamethoxazole. Intrauterine administration of antibiotics and antiseptics depresses phagocytic activity of uterine neutrophils, and many chemicals irritate the endometrium. Drugs that have been suggested include those recommended for systemic administration.
2. *Antiinflammatory drugs.* Laminitis may be a sequela to metritis and is commonly associated with RFMs. Treatment with administration of antiinflammatory drugs such as phenylbutazone or flunixin meglumine is indicated to reduce the likelihood and severity of laminitis. Polymyxin B may also be indicated in cases in which preliminary signs of laminitis are noted because of its antiinflammatory and antiendotoxic effects. Additional therapy for laminitis should be administered as indicated.
3. *Other treatments.* Caslick's surgery may be indicated in some cases of RFMs to control aspiration of air. Tetanus may complicate RFMs, and prophylaxis with tetanus antitoxin in unvaccinated animals or tetanus toxoid in previously vaccinated animals is indicated.

Some cases of RFMs are refractory to treatment, and membranes may remain

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firmly attached to the endometrium for several days. Aggressive attempts at manual removal should be eschewed because severe endometrial damage may follow. Persistent treatment with uterine lavage antibiotics, antiinflammatory drugs, and oxytocin is indicated until the placenta is expelled and bacterial infection of the uterus is controlled.

The prognosis for RFMs is generally good but is reduced if treatment is delayed or if retention is accompanied by infection with virulent pathogens. Sequelae to RFMs include metritis, endometrial fibrosis, invagination of a uterine horn, uterine prolapse, and laminitis.

Ruminants

Cow

The cotyledonary placenta of cows is usually expelled within 3 to 8 hours after calving and is considered retained if not expelled by 12 hours. RFMs are more commonly seen in dairy than in beef breeds. In dairy cattle the reported prevalence ranges from 8% to 12% after spontaneous delivery of single calves. RFMs are more likely after deliveries of male calves or twins and deliveries complicated by dystocia. Parturition after a shorter- or longer-than-normal gestation is accompanied by an increase in the incidence of RFMs.[2]

The cause of RFMs in cattle is failure of fetal cotyledons to separate from crypts of maternal caruncles; the process of separation normally begins during the last months of pregnancy. Villi shrink after blood flow is interrupted by rupture of the umbilical vessels. Strong myometrial contractions continue during the third stage of labor, and changes in the size and shape of maternal caruncles contribute to separation of the placenta from the endometrium. In addition to mechanical factors, elevated collagenase, in response to increasing relaxin and estrogen prior to parturition, promotes collagen breakdown at the cotyledon-caruncle interface. A number of factors have been associated with separation failure, including induced parturition, abortion, dystocia, cesarean section, twinning, and nutritional deficiencies (selenium, vitamin E, vitamin A). The precise reasons for separation failure are unknown.

Clinical Signs and Diagnosis

The majority of affected cows show no serious clinical signs other than a transient decrease in appetite and milk production. However, 20% to 25% of

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cows affected by RFMs develop moderate to severe metritis. The most overt clinical signs are malodorous discharge and placental tissue hanging from the genital tract. RFMs are usually expelled by 4 to 10 days after calving when the caruncular tissue has become necrotic and is sloughed. Some affected cows show signs of endotoxemia, including depression, fever, ruminal stasis, and inappetence, as a result of RFMs.

Treatment and Prognosis

A variety of treatments have been suggested for RFMs in cows, including aggressive attempts at manual removal, myometrial stimulants, intrauterine and systemic antibiotics (alone or in combination with other approaches), and no therapy whatsoever. Because the processes that culminate in RFMs begin during late gestation, it is expected that treatment initiated at calving has little effect on the loosening process. Most treatments for RFMs are directed toward controlling the intrauterine bacterial population.

Manual Removal.

Manual removal of the placenta is indicated only when gentle traction is sufficient to withdraw the membranes in a short time. Attempts at manual removal are contraindicated if the patient shows clinical signs of septicemia. Trauma caused by manual removal inhibits phagocytosis by uterine neutrophils and predisposes to severe sequelae, including endometritis, septic metritis, peritonitis, and a delay to first ovulation.[3]

Myometrial Stimulants.

Administration of a single dose of oxytocin does not reduce the prevalence of RFMs in cows that calve spontaneously or in cows that require assistance at delivery.[4,5] Cows with RFMs have an elevated plasma concentration of estrogen during the period of retention; therefore administration of additional estrogen for treatment of RFMs may be of questionable value.[6] Intravenous calcium solutions are indicated in cases of RFMs secondary to hypocalcemia. Because a relatively small proportion of RFMs are due to myometrial atony, myometrial stimulants may not be beneficial in many cases.[3]

Prostaglandin.

In one trial, treatment with fenprostalene (a prostaglandin) resulted in a shorter

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period of retention in treated cows, reduced the number of treatments subsequently required for metritis, and slightly reduced the intervals to first service and conception.[7] However, other researchers found that fenprostalene produced no changes in myometrial activity between days 1 and 4 after calving and concluded that uterotonic agents are unlikely to hasten placental expulsion, because uterine effort is already increased in animals that have RFMs.[8] An imbalance between synthesis of $PGF_{2\alpha}$ and Prostaglandin I_2 (PGI_2) between 30 and 60 minutes after parturition has been demonstrated in cows affected by RFMs.[9] Prostaglandin at the time of calving does not reduce the incidence of RFMs or improve reproductive performance.[10]

Antibiotics.

Intrauterine tetracycline may reduce fertility,[11] or the reproductive performance of treated cows may be as good as that of untreated herdmates. Intrauterine treatment with 4 to 6 g of oxytetracycline per day until the placenta is expelled may reduce the prevalence of metritis associated with RFMs, but pyometra may develop in treated cows.[12] The placenta is released only after necrosis of the caruncles, which may be delayed by the presence of intrauterine antibiotics. Systemic antibiotics are indicated in cases of RFMs in which the cow has a fever, is off feed, or has a drop in milk production. Multiple studies have demonstrated that the effects of systemic antibiotics are just as good as intrauterine antibiotics alone or a combination of systemic and intrauterine antibiotics in terms of systemic health and future fertility. Ceftiofur (2.2 mg/kg IM or subcutaneously [SC] q24h for 3 to 5 days) given to febrile cows with retained membranes has shown a beneficial effect in future reproductive parameters and may reduce the incidence of acute metritis.[3,13,14]

Cows that retain their membranes for more than 12 hours after calving are more likely to develop metritis than are cows that promptly expel the membranes. However, reproductive performance of cows that rapidly return to normal after RFMs is similar to that of their unaffected herdmates, indicating that in the absence of a secondary reproductive abnormality, RFMs have a minimum effect on future fertility.

Collagenase.

An alternative approach to the treatment of RFMs is the injection of collagenase into the umbilical arteries of the retained membranes.[15] This treatment is aimed

directly at the lack of cotyledonary proteolysis, and although effective, it is expensive and often not economically justifiable. Intrauterine infusion of collagenase is not effective.

Ewe and Doe

Fetal membranes are considered retained in ewes and does if not expelled within 12 hours after delivery of the last fetus. The prevalence in does is approximately 6% after spontaneous delivery but may be higher when delivery is complicated by dystocia or abortion. Selenium deficiency has been suggested as a cause.

The clinical signs of RFMs in ewes and does are usually obvious. Does may ingest their placentas, complicating identification of cases of partial retention. RFMs may accompany retention of a fetus within the uterus, and does and ewes should be carefully examined.

Other tissues that may be exposed from the vulva in association with parturition are a prolapsed uterus, a prolapsed or everted urinary bladder, prolapse of some portion of the digestive tract through a uterine rupture, prolapsed rectum, prolapsed vagina, or a twin fetus.

Treatment and Prognosis

Manual separation of cotyledons from caruncles is impossible in ewes and does; therefore manipulative attempts to remove the placenta are limited to gentle traction on exposed membranes at daily intervals. Treatments with broad-spectrum systemic antibiotics, oxytocin (10 to 20 IU) at 12-hour intervals until the placenta is expelled, and antiinflammatory drugs have been suggested. Prophylaxis against tetanus is indicated.

Camelids

The placenta is usually passed within 1 to 2 hours of parturition. Camelid placentas resemble equine placentas (diffuse, microcotyledonary, epitheliochorial), with the exception that the left horn is almost always the pregnant horn. RFMs in camelids are most commonly seen as sequelae to dystocia or other disorders of parturition. Treatment is similar to that described for the mare.

Uterine Infections

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Mare

Endometritis

A failure of the uterine defense mechanisms to effectively eliminate an antigen (bacteria or spermatozoa) and inflammatory products from the uterus results in persistent endometritis, which is a major cause of reduced fertility in broodmares.[16] In the normal mare the uterus is well protected from external contamination by physical barriers consisting of the vulva, vestibule, vagina, and cervix, and any compromise of these barriers may predispose the mare to a chronic uterine infection.[17] Breeding is another source of uterine contamination. Intrauterine deposition of semen causes an inflammatory reaction resulting from bacterial contamination of the ejaculate or from spermatozoa.[18] Approximately 10% to 15% of a normal population of Thoroughbred broodmares developed persistent endometritis after breeding.[19] AI with frozen semen resulted in 16% to 25% persistent inflammation after breeding.[20,21] Natural resistance to experimentally induced bacterial contamination has been demonstrated in young mares, whereas a population of multiparous and barren mares developed persistent endometritis after bacterial contamination of the uterus.[22,23] On the basis of these studies, mares have been classified as either susceptible or resistant to persistent uterine infection.[22] Endometritis has severe effects on the fertility of affected mares. A persistent inflammation may interfere directly with the survival of an embryo or may cause premature luteolysis and embryonic loss because of increased $PGF_{2\alpha}$ concentrations.[24]

Several classes of immunoglobulins have been isolated from the equine uterus. Although antibody-mediated uterine defense may be important for effective elimination of bacterial contaminants from the uterus in susceptible mares, concentrations of immunoglobulins in uterine secretion are similar or even elevated compared with those of resistant mares.[25-29] Polymorphonuclear neutrophils (PMNs) are the first inflammatory cells to enter an inflamed site. Chemoattractive properties of uterine fluid have been described in vitro in horses, and the uterus responds quickly to an antigen with release of PMN-chemotactic mediators, which results in a rapid migration of PMNs into the uterine lumen.[30] Complement products and leukotriene B4 (LTB4), Prostaglandin E (PGE), and $PGF_{2\alpha}$ may all serve as chemoattractants for PMNs in the uterus.[30-34] Studies on the role of local uterine factors in PMN function

suggested that an impaired phagocytosis by uterine PMNs in susceptible mares is the result of insufficient opsonization in uterine secretion rather than a primary dysfunction of the PMNs.[35]

Recent work by researchers at the University of Kentucky found that breeding, as well as a bacterial infection with *Escherichia coli*, resulted in an upregulation of both proinflammatory and inflammatory modulating cytokines in the endometrium. A transient upregulation of proinflammatory cytokines was observed in resistant mares, whereas a sustained expression of proinflammatory cytokines coupled with an altered ratio of proinflammatory and modulating cytokines was observed in susceptible mares.[36] An imbalanced cytokine expression was also observed in susceptible mares following breeding. Inflammatory modulating cytokines were expressed at a significantly lower level at 6 hours after breeding in susceptible mares when compared with resistant mares, leading the authors to conclude that susceptible mares may have a deficiency in their ability to regulate endometrial inflammation.[37]

Mechanical aspects of the uterine defense system are currently believed to be a major contributor in uterine clearance of bacteria and inflammatory products.[38-40] Through use of intrauterine inoculations of a combination of radioactive-labeled microspheres and bacteria, impaired uterine clearance was demonstrated in susceptible mares but not in resistant mares.[38] Studies using scintigraphic measurements of intrauterine clearance of radioactive colloids further defined a delayed physical clearance in susceptible mares.[39] Through use of electromyography (EMG) to register myometrial activity, it was observed that the impaired uterine clearance in susceptible mares was caused by reduced myometrial activity in response to the inflammation.[39] This may be explained by an accumulation of nitric oxide (NO) in susceptible mares following breeding.[41] NO is an inflammatory mediator that causes smooth muscle relaxation. The dependent position of the mare's uterus may also interfere with effective clearance.

Based on pathogenesis, persistent endometritis can be divided into (1) sexually transmitted diseases (STDs), (2) persistent uterine infection, and (3) persistent breeding-induced endometritis.

Sexually Transmitted Diseases.

Contagious equine metritis (CEM) is an example of a true STD.[42,43] The disease is caused by *Taylorella equigenitalis*, a highly contagious and pathogenic

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microorganism. Although the present status of a mare's uterine defense mechanism is important for the manifestation of the disease, this bacterium is highly resistant and capable of overcoming the mare's normal disease barriers.

Persistent Uterine Infection.

Bacteria most commonly isolated from the uterus of the mare are β-hemolytic streptococci (*Streptococcus zooepidemicus* and *Streptococcus equisimilis*), *E. coli, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae.* Other aerobic bacteria isolated from the reproductive tracts of mares include α-hemolytic streptococci, *Corynebacterium* spp., *Staphylococcus* spp., *Enterobacter* spp., *Actinobacter* spp., *Proteus* spp., *Citrobacter* spp., *Candida* spp., and *Aspergillus* spp. and are the organisms most commonly associated with yeast or fungal endometritis. The role of viruses, mycoplasmas, ureaplasma, and anaerobic bacteria in endometritis is poorly understood. *P. aeruginosa, K. pneumoniae,* and possibly *S. zooepidemicus* and *E. coli* can be sexually transmitted in horses, but the consequences of exposure to these microorganisms are determined by the particular strain involved and active participation of all facets of the mare's uterine defense mechanisms. In contrast to a true STD, persistent infectious endometritis is often the result of contamination of the uterus by the mare's fecal and genital flora in combination with compromised uterine defense.[44,45] It has been proposed that endometrial biofilms are responsible for chronic infectious endometritis that appears to be nonresponsive to conventional treatment.[46] A bacterial biofilm is a complex aggregation of microorganisms. They are characterized by structural heterogenicity, genetic diversity, complex community interactions, and an extracellular matrix of polymeric substances, which greatly increases resistance to antibiotic therapy.[47] Although uterine biofilms have not yet been identified in the clinical setting in horses, an experimental model to study biofilms in the equine endometrium has recently been developed. Workers inoculated mares with a uterine infusion of *P. aeruginosa* and later successfully identified biofilms within the mares' endometrial folds.[48] An alternative explanation for persistent bacterial endometritis has been offered by Petersen and colleagues.[49] The authors suggested that bacteria can persist in the endometrial glands and the uterine wall in a dormant state. This would increase their resistance to antibiotic therapy. Another study investigated potential mechanisms of persistent uterine infections with *S. zooepidemicus* and hypothesized that the bacteria can enter epithelial cells and evade diagnosis and

attempts to treat and resolve the infection.[49] More work needs to be done to further understand the ways in which bacteria infect and survive in the equine endometrium.

Persistent Breeding-Induced Endometritis.

Intrauterine deposition of semen causes an inflammatory reaction resulting from spermatozoa.[50,51] The mechanism of the induced inflammation is similar to endometritis caused by bacteria, involving activation of the complement cascade.[51] The role of spermatozoa in breeding-induced endometritis implies that a transient uterine inflammation is a physiologic reaction to semen, and it appears to be a normal process by which excess sperm and bacterial contamination are eliminated from the mare's reproductive tract.[45,52] Transport of spermatozoa from the uterus to the oviduct is completed within 4 hours after breeding, and only a small portion of the ejaculated or inseminated semen reaches the oviduct.[53,54] The rapid transport of spermatozoa to the oviduct coincides with increased uterine activity.[52] Increased myometrial contraction in response to breeding is also responsible for rapid sperm elimination from the uterus through the cervix.[55] Not all excess spermatozoa are removed from the uterus through this mechanism. The remaining spermatozoa have to be eliminated by means of other uterine clearance mechanisms, such as PMN-phagocytosis of spermatozoa.[45] However, the condition may develop into a persistent inflammation in mares with impaired uterine clearance.[38,39] If sperm elimination and all physical and chemical reactions that are involved in the induced inflammation persist beyond the time when the embryo enters the uterus at 5 days after ovulation, embryonic loss will occur because of an incompatible inflammatory uterine environment. The incidence of persistent breeding-induced endometritis has been reported to be approximately 10% to 15% in a normal population of Thoroughbred broodmares and up to 25% in mares bred by AI with thawed frozen semen.[19,20]

In contrast to spermatozoa, seminal plasma has a suppressive effect on complement activation, PMN-chemotaxis, and phagocytosis.[56] A function of seminal plasma may be to act as an inflammatory inhibitor or modulator in the uterus, which may be of importance with regard to the transient nature of breeding-induced endometritis. The duration of breeding-induced uterine inflammation was shown in a study to be shorter when seminal plasma was included in an insemination dose, compared with when all seminal plasma was

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removed and replaced by a commercial semen extender.[57] Although the peak numbers of PMNs were the same for both groups, significantly fewer PMNs were recovered from the uterus at 24 hours compared with 6 and 12 hours after insemination when seminal plasma was included. In contrast, there was no significant difference in the number of uterine PMNs at 6, 12, and 24 hours of insemination in the absence of seminal plasma. Another function of seminal plasma in breeding-induced endometritis may be to protect spermatozoa from being phagocytosed and destroyed in an inflammatory environment. PMNs are present in the uterine lumen by 0.5 hours after breeding, but sperm transport is not completed until 3 to 4 hours later.[53] In addition, when mares are inseminated twice within a 24-hour period, semen from the second insemination is introduced into an inflammatory environment. This environment is detrimental to sperm motion characteristics, and motile sperm cells appear to bind to PMNs, forming large clusters of PMNs and spermatozoa. Addition of seminal plasma has been shown to reduce the binding between spermatozoa and inflammatory cells in vitro.[58] Recent data suggest that a specific protein in equine seminal plasma, CRISP-3, selectively protects viable but not dead spermatozoa from PMN-binding and phagocytosis.[59,60] Selective protection of viable spermatozoa from PMN-binding and phagocytosis increases their survival in a hostile uterine environment and ensures that a sufficient number of spermatozoa reach the oviduct for fertilization while effective sperm elimination of nonviable spermatozoa can be maintained.

Diagnostic Approach

History compatible with endometritis includes infertility after breeding to a fertile stallion. Mares with severe endometritis may have shortened interestrous intervals and may show vaginal discharge. Physical and speculum examination may show anatomic defects of the vulva or cervix. Excessively easy passage of a vaginal speculum may indicate loss of integrity of the vestibulovaginal sphincter. Discharge from the cervix and vaginal inflammation may be apparent. Transrectal palpation and ultrasonography may reveal accumulations of luminal fluid (Fig. 43.5). Diagnostically, it may be difficult to identify susceptibility to breeding-induced endometritis before breeding. Some mares have free fluid present in the uterine lumen before breeding, but most mares are not diagnosed until after they have been bred. If susceptibility to persistent breeding-induced endometritis is suspected, the mare should be monitored closely by

ultrasonography per rectum at 6 to 12 hours after breeding, if possible, and at a minimum within 24 hours after breeding. If free fluid is present in the uterine lumen, the mare should be considered to have persistent mating-induced endometritis. Clearance of charcoal particles from the uterus within 48 hours of inoculation and the use of scintigraphy to measure uterine clearance have been suggested to be useful in identifying mares that are susceptible to persistent breeding-induced endometritis.[39,61] However, these methods may not be practical under field conditions. Recent attempts to identify genetic markers for susceptibility to persistent endometritis are encouraging and may aid clinicians in identifying susceptible mares in the future.[62]

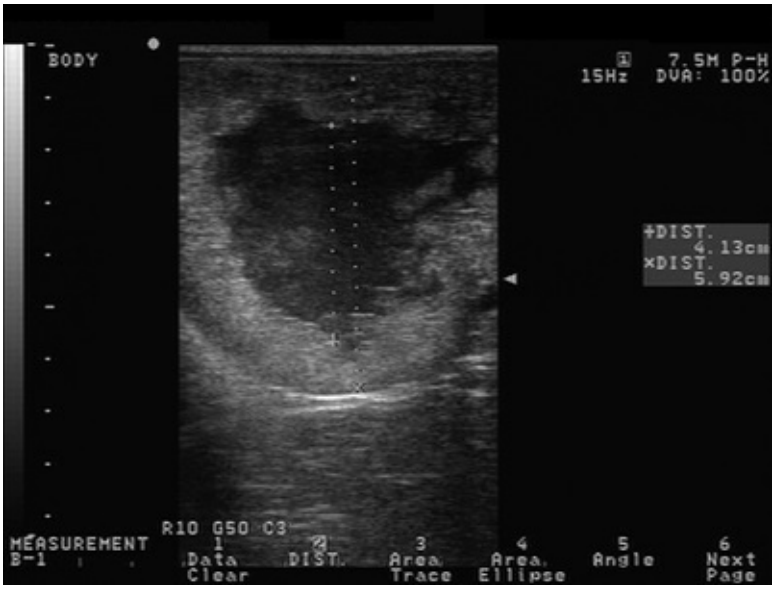


FIG. 43.5 Transrectal ultrasonographic image of uterine intraluminal fluid accumulation in a mare with endometritis.

Microbiology.

Quantitative aerobic bacterial culture of the uterine lumen is necessary to identify potential pathogens and for antibiotic sensitivity testing. Samples can be obtained using a swab, low-volume uterine lavage, or an endometrial biopsy, and they should be taken during estrus. If a uterine swab is used, the swab should be transported in a nonnutritive medium to the laboratory. Inadvertent contamination of cultures with bacteria from the lower reproductive tract is common, so the culture instrument should be guarded until it is within the

uterus.[63] A false-positive bacterial sample result may be obtained as the result of contamination (even when double-guarded swabs are used), and culture results should always be interpreted together with results from endometrial cytology. Samples obtained through a vaginal speculum may decrease the risk of contamination. The use of low-volume lavage (50 to 100 mL) has been suggested to be a sensitive method to obtain an endometrial sample for culture.[64,65] It is important to use a closed system to infuse and recover fluid from the uterus in order to avoid environmental contamination when this method is used. False-negative results are frequently obtained even under optimal circumstances, and laboratory results should always be interpreted with consideration given to clinical findings. Use of culture and histologic interpretation of an endometrial biopsy appears to be the most accurate method to diagnose persistent infectious endometritis.[66] Cultures may also be performed on endometrial biopsy samples. Culture samples for *T. equigenitalis* should be taken from the endometrium, cervix, clitoral fossa, and sinuses. Samples should be placed in Amies medium with charcoal or Stewart medium and be kept refrigerated until delivered to the laboratory.

Endometrial Cytology.

PMNs migrate into the uterine lumen in response to inflammation, so endometritis is rapidly and accurately diagnosed by examination of exfoliated endometrial cells. A sample may be taken with a guarded swab, with a cytology brush, or by low-volume lavage. Air-dried smears are stained with new methylene blue or modified Wright-Giemsa stain. Epithelial cells may be shed singly or in rafts. Arbitrary definitions of endometritis have been established based on relative numbers of PMNs or numbers of PMNs per high-power field. Using these criteria, more than one PMN per 10 epithelial cells is consistent with endometritis. Evaluating the number of PMNs per microscopic field, Riddle and colleagues observed that mares with more than two PMNs per 100× magnification microscopic field had significantly lower pregnancy rates than mares with fewer than two PMNs per 100× field.[67] Mares with more than five PMNs per 100× field had the greatest reduction in pregnancy per cycle. The authors also found that bacterial infection with *E. coli* was less likely to be associated with a positive cytology compared with mares infected with *S. zooepidemicus.* Presence of bacteria on a cytology slide may indicate infection but can also be the result of a contaminated slide or staining fluid. Bacteria

phagocytosed by PMNs are true indicators of an infection. Endometrial cytology from normal mares may contain PMNs and spermatozoa for 24 to 36 hours after breeding. It has been suggested that eosinophils are associated with fungal endometritis and pneumovagina, but the importance of this finding is unclear. Urine crystals indicate urovagina.

Endometrial Biopsy.

Endometrial biopsy is an accurate diagnostic and prognostic tool for endometritis. The biopsy sample should be taken during the breeding season, should be of adequate size, and should be either fixed in Bouin solution for 24 hours and then transferred to 10% formalin or immediately put in 10% formalin. Chronic endometritis is characterized by infiltration of the endometrium with mononuclear cells and deposition of layers of fibrosis around endometrial glands. Fibrosis of the endometrium is a degenerative change and is permanent. This pathology has been associated with susceptibility to persistent endometritis and delayed uterine clearance.[68,69] The severity of endometrial changes is inversely related to reproductive performance. A system to classify histologic changes has been described and is widely used (Table 43.5). Special stains such as periodic acid–Schiff and Gomori methenamine silver may be used to identify the presence of fungi in endometrial biopsies. Special staining can be used to detect degenerative vascular changes such as elastosis.

TABLE 43.5

Endometrial Biopsy Grade and Fertility Prognosis (Kenney and Doig)

Biopsy Category	Degree of Change	Predicted Foaling Rate (%)
I	None	80-90
IIA	Mild	50-80
IIB	Moderate	10-50
III	Severe	<10

From Kenney and Doig: Equine endometrial biopsy. In Morrow DA, ed: *Current therapy in theriogenology*. W.B. Philadelphia, 1996, Saunders, pp 723-729.

Transrectal Ultrasonography.

The presence of free intraluminal fluid before breeding strongly suggests susceptibility to persistent endometritis.[70] Ultrasonographic examination of the uterus is helpful to assess both the quantity and the quality of accumulated fluid

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in the uterine lumen. Normal mares may retain fluid for up to 6 to 12 hours after mating. If fluid is present at 12 hours or more after breeding, the mare should be considered to have a persistent mating-induced endometritis.[71] Increased echogenicity of the fluid is associated with the presence of inflammatory cells and debris.

Hysteroscopy.

Examination of the uterine lumen with an endoscope provides information about the degree of inflammation in addition to evidence of foreign bodies, transluminal adhesions, intraluminal masses, and endometrial cysts.

Treatment

Sexually Transmitted Diseases.

Mares with CEM should be treated with intrauterine infusions of antibiotics based on sensitivity tests, in combination with local treatments of the clitoral fossa and sinuses. Best results can be expected when treatment is initiated when the mare is in estrus and is combined with uterine lavage if inflammatory debris or intraluminal fluid is present. Cleansing of the vulva and the clitoris daily for 5 days with a 4% chlorhexidine or nitrofurazone ointment has been recommended.[72] Sinusectomy can also be performed.[73] Import regulations in countries free from CEM serve to prevent outbreaks of the disease. The spread of CEM on farms in endemic countries is best prevented by implementation of strict hygiene, screening of breeding stallions before the breeding season, and the use of AI, if allowed by the breed registry.

Persistent Uterine Infection.

Treatment of mares with persistent uterine infections needs to be directed toward the underlying breakdown of the uterine defense and against the microbial agent. The first therapeutic concern should be to remove predisposing causes, such as a breakdown of external genital barriers. Persistent uterine infection frequently follows degenerative or traumatic anatomic changes and loss of integrity of the barriers of ascending infection. Therefore Caslick's surgery, repair of cervical damage and perineal lacerations, and correction of urovagina should precede specific endometrial treatment. All potential sources of contamination, including intrauterine passage of diagnostic and treatment implements, should be minimized. In some mares, recovery follows with sexual rest and no further

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treatment. Mares that are susceptible to persistent uterine infections should be bred using minimal contamination techniques to avoid bacterial contamination of the uterus.[74] Antibiotics may be administered by either local or systemic routes. Intraluminal fluid and inflammatory debris should be removed by uterine lavage before local treatment. Drugs and doses are summarized in Table 43.6. Treatment should be based on sensitivity. Mares should be treated during estrus when natural defense is maximal, and strict aseptic technique should be used. The volume of fluid used for antibiotic therapy depends on the size of the uterus. A total volume of 30 to 60 mL is usually sufficient. Treatment should continue daily for 4 to 6 days during the duration of estrus. Repeated contamination may indicate an unsuccessfully resolved predisposing cause. The clitoral fossa should always be considered as a primary location of bacteria grown in these cases. If culture results from the endometrium and clitoral fossa match, the clitoral fossa should be cleaned and treated locally with antibiotics. Removal of the primary microorganism may result in overgrowth of a second bacteria or fungus (superinfection). Critical studies of the efficacy of systemic antibiotics are limited, although effective concentration of amikacin has been measured in the endometrium after systemic administration.[75] Parenteral administration may be easier, and the opportunity to introduce uterine contamination or cause uterine irritation with treatment is eliminated. Treatment of fungal infections is generally more challenging than treatment of bacterial infections. Culture and sensitivity will determine the choice of antifungal drugs (see Table 43.6). Fungal endometritis may require daily intrauterine infusions for 7 to 10 days to effectively resolve the infection. To avoid intrauterine infusions in the presence of high circulating concentrations of progesterone, treatment can be initiated 1 or 2 days after an injection of PGF2α in diestrual mares and continued until 1 or 2 days after ovulation. A single dose of a benzoylphenyl urea (lufenuron) has been suggested to effectively treat mares with fungal endometritis.[76]

TABLE 43.6

Antibacterial Drugs Used for Intrauterine Administration for Treatment of Uterine Infections in Mares

Drug	Dose (Intrauterine Administration)	Comments
Amikacin sulfate	2 g	Gram-negative spectrum; buffer with equal volume of 7.5% bicarbonate

Ampicillin	3 g	Gram-negative spectrum; may irritate the endometrium
Carbenicillin	2-6 g	Gram-negative spectrum; may irritate the endometrium; buffer with equal volume of 7.5% bicarbonate
Gentamicin sulfate	1-3 g	Gram-negative spectrum; buffer with equal volume of 7.5% bicarbonate
Kanamycin sulfate	1-3 g	*Escherichia coli*, spermatocidal
Neomycin sulfate	3-4 g	Useful against sensitive *E. coli*
Potassium penicillin G	5000-10,000 U	*Streptococcus zooepidemicus*
Polymyxin B	1 million U	*Pseudomonas*
Ticarcillin	6 g	Broad spectrum
Ticarcillin/clavulanic acid	6 g/200 mg	Broad spectrum
Ceftiofur	1 g	Broad spectrum *(S. zooepidemicus)*
Antimycotics		
Nystatin	500,000 U	Dissolve in 30 mL 0.9% saline solution; daily for 7-10 days
Clotrimazole	500 mg	Suspension or cream; daily for 1 week
Miconazole	500 mg	Effective against yeast
Amphotericin B	200-250 mg	Daily for 1 week
Vinegar	2%	20 mL wine vinegar to 1 L 0.9% saline solution; used as uterine lavage
Lufenuron	540 mg (single dose)	Suspend in 60 mL sterile saline solution

Antimicrobial Alternatives and Supplemental Treatments.

Although suitable antibiotics are the most effective treatment against infectious endometritis, recent research has focused on situations where this treatment alone is not sufficient to eliminate bacterial growth from the uterus. Suggested presence of biofilms, dormant bacteria in the deeper layers of the endometrium, and other barriers may prevent antibiotics from reaching their target and effectively eliminating bacteria.[77-79] Although further evidence may be needed to conclusively confirm some of these hypotheses, their suggestive presence in the uterus have given rise to multiple treatment options to accompany or replace traditional antibiotics. The medical value of most of these treatments is often anecdotal rather than evidence based.

N-*acetylcysteine (NAC):* This mucolytic substance has been used to reduce the viscosity of mucus in the uterus. In addition, NAC has been suggested to have antiinflammatory, antioxidant, and antibacterial activity.[80] Typically, 30 mL of a 20% solution NAC (200 mg/mL) is diluted in 150 mL of saline and infused into the uterine lumen during estrus, followed by ecbolic treatment or uterine lavage 12 hours after treatment. The treatment protocol has been suggested to be beneficial both 24 to 48 hours prior to breeding and 24 hours prior to antibiotic

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treatment. Repeated lavage may be indicated if the effluent fluid is cloudy.[81] When used together with antibiotics, the interaction with antimicrobials should be kept in mind. NAC enhances the efficacy of β-lactams but reduces the antibacterial activity of aminoglycosides, fluoroquinolones, and erythromycin. Oral treatment with NAC at 10 mg/kg did not reduce viscosity of uterine mucus; however, an antiinflammatory effect was observed in one study.[82] NAC was also suggested to decrease biofilm biomass and reduce bacteria within biofilms of *E. coli* isolates in vitro.[79] The same effect, however, was not observed for other bacteria. Intrauterine treatment with NAC is sufficiently proven to be safe and has been suggested to improve pregnancy rates, although the pregnancy data were not supported by controlled experimental conditions.[77]

EDTA-Tris: Tricide® (a third-generation chelator) chelates calcium and magnesium within the bacterial cell wall, which may potentiate the effect of the antibiotic.[83] It has been suggested to potentiate the effect of antibiotics on some bacteria, but its effect to disrupt gram-negative biofilms is less clear.[79] Treatment protocols often consist of intrauterine infusions of 250 to 750 mL Tricide followed by uterine lavage with a buffered saline solution the next day. The treatment is repeated until the effluent fluid is clear, at which time the mare is treated with local antibiotics for 5 days. Tricide can also be added to antibiotics but is not recommended for use together with ceftiofur, penicillin K, or Timentin due to precipitation in the solution.[81]

Cationic steroid antimicrobial (CSA): Ceragyn® belongs to a class of peptides that cause depolarization of bacterial cell wall membranes and activate apoptotic pathways. These peptides have been used for various conditions in human medicine because of their biofilm breakdown and broad-spectrum antimicrobial activities. Ceragyn (60 mL; 1 vial) is labeled for use up to 24 hours before or 12 to 48 hours after breeding. The drug has become increasingly popular among equine practitioners, but the authors have not been able to find conclusive data from controlled studies to support its effect on equine endometritis.

Hydrogen peroxide: H_2O_2 has a bactericidal effect on most uterine pathogens. A 1% solution (20 mL of a 3% H_2O_2 solution diluted in 60 mL lactated Ringer's solution [LRS]) has been suggested to be effective

on biofilms in vitro.[79] Information regarding the efficacy of H_2O_2 treatment is anecdotal and needs to be supported by controlled in vivo studies.

bActivate: A proprietary substance marketed as bActivate® has been shown to activate dormant *Streptococcus* spp. from the equine endometrium.[78] Dormant bacteria are not sensitive to antibiotics, but after confirmed activation with bActivate, evidenced by a positive culture, mares can successfully be treated with intrauterine infusion of antibiotics. However, fertility data from controlled studies are needed to confirm claims of improved fertility following treatment.

Immune Modulators.

The immune response of the equine endometrium has been investigated following bacterial inoculation, and treatment protocols aimed at restoring a normal immune response in susceptible mares have been reported.[84]

Bacterial cell wall extracts: Cell wall extracts of *Mycobacterium phlei* (MCWE) as well as *Propionibacterium acnes* have been investigated regarding their effect on the uterine immune system and reproductive performance. Fumoso and colleagues[85] found that MCWE treatment of susceptible mares at the time of breeding resulted in an endometrial immune environment similar to that of resistant mares at 24 hours after AI. In a follow-up study,[86] the authors concluded that MCWE treatment was effective in eliminating inoculated bacteria from the uterus in 70% of treated mares at 7 days after infusion. In another study,[84] the immune response between 3 and 72 hours after intrauterine inoculation of *E. coli* was characterized; cytokine expression in MCWE-treated mares was not different from that of untreated mares, but messenger RNA (mRNA) expression of serum amyloid A was suppressed in treated mares. Clinically, MCWE had a favorable effect on the clearance of pathogens and fluid retention.[84] These results supported a comprehensive clinical study in which problem mares were treated with *P. acnes* extract (Settle®); the authors found a 10% increase in pregnancy rates compared to untreated controls.[87] However, the mares received additional treatments and the effect of stallion fertility was not considered in that

study.

Plasma: Intrauterine infusion of autologous or heterologous plasma has been used to treat mares with infectious endometritis.[88] The rationale for the treatment was to add immunoglobulins and complement to assist the mares in eliminating pathogens from the uterus. Supplementation of fresh or cryopreserved PMNs into the uterine lumen in mares with persistent endometritis has also been proposed as an alternative treatment to antibiotics.[89-91]

Persistent Breeding-Induced Endometritis.

Management of mares susceptible to persistent breeding-induced endometritis should include limiting uterine exposure to semen and bacteria and assisting the uterus to physically clear contaminants and inflammatory products after breeding.[30,92] Preexisting uterine infections should be resolved before the mare is bred. Exposure to semen should be limited to a single breeding per cycle, if possible. This can be accomplished by closely monitoring follicular development and hormonal treatment to induce ovulation of mature follicles.

Woodward and colleagues[37] found that the imbalance of proinflammatory cytokines and inflammatory cytokines in response to semen in susceptible mares is present already within 3 to 6 hours after insemination. This information should serve as a guideline for timing of treatments in susceptible mares after insemination.

Uterine lavage: Infusion of 1 to 2 L of buffered saline solution after breeding is effective in removing accumulated fluid and inflammatory products from the uterus. Because sperm transport to the oviduct is completed within 4 hours after breeding, uterine lavage 6 to 24 hours after breeding will not have a negative effect on fertility.[53] The uterine lavage is typically repeated until the recovered effluent fluid is clear. The treatment is often combined with an ecbolic drug in order to facilitate recovery of the infused fluid.[81,90,92]

Manual dilation of the cervix in mares with poor cervical dilation may help these mares more effectively clear the uterus of fluid.

Ecbolics.

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The administration of ecbolic drugs after breeding is effective in overcoming impaired myometrial contractility in susceptible mares.[93-95]

Oxytocin: Low doses of oxytocin appear to be more effective than high doses.[96] A common treatment protocol is 10 to 20 IU of oxytocin 4 to 6 hours after breeding, repeated every 6 to 8 hours until the intraluminal fluid has disappeared. The half-life of oxytocin is relatively short, resulting in approximately 50 minutes of myoelectric activity after the administration of 10 IU.[97]

Carbetocin: Carbetocin is a long-acting oxytocin analog with an extended half-life after administration of 0.175 mg IV.[98] Limited data are available on the efficacy of carbetocin versus oxytocin.

Prostaglandin: $PGF_{2\alpha}$ has considerably longer duration on uterine contractility compared to oxytocin.[95] Treatment is not recommended after ovulation, since $PGF_{2\alpha}$ and its analogs can cause a delay in the formation of a functional CL when administered within 2 days after ovulation.[36-39] It is the authors' observation that luteolytic doses of $PGF_{2\alpha}$ are excessive and may cause myometrial "cramp" initially rather than a physiologic contraction that would be more suitable for removing fluid from the uterus. A suitable dose of $PGF_{2\alpha}$ and its analogs for treatment of equine endometritis has not been established. In severe cases of persistent breeding-induced endometritis, ecbolic treatment is often combined with uterine lavage with 1 to 2 L of buffered saline 6 to 12 hours after breeding.[81]

Social interaction with a stallion: Social interaction with a stallion may facilitate normal uterine clearance following breeding. Audio, visual, and physical exposure of mares to a stallion stimulated pituitary oxytocin release and caused uterine contractions.[100] This observation was confirmed in a subsequent report.[101] Housing susceptible mares close to a tease stallion after breeding may therefore enhance normal uterine activity and clearance.

Immune Modulators.

The immune response of the equine endometrium has been investigated following insemination,[37] and treatment protocols aimed at restoring a normal

immune response in susceptible mares after breeding have been reported.

Corticosteroids: Several studies support a positive clinical effect of corticosteroids on persistent breeding-induced endometritis. A single dose of dexamethasone (50 mg at the time of breeding) was found to improve pregnancy rates in mares with more than three risk factors for susceptibility to persistent breeding-induced endometritis.[102] Researchers from Belgium did not observe a positive effect of treatment with 10 mg or 20 mg of dexamethasone 6 to 12 hours after AI in a large group of unclassified mares,[103] emphasizing the importance of correctly identifying mares as susceptible to persistent endometritis before implementing treatment regimens. Furthermore, mares with a history of excessive postbreeding inflammation had significantly higher pregnancy rates when treated with acetate 9-α-prednisolone (0.1 mg/kg) twice daily compared to control cycles.[104]

Although the immune modulation appears to favor resolution of inflammation, it does not mimic that of resistant mares.[105] Recent observations suggest that dexamethasone suppresses the proinflammatory cytokine interleukin-1β (IL-1β) in susceptible mares at 6 hours after breeding.[106] However, no effect was observed for modulating cytokines, which previously had been suggested to differ between susceptible and resistant mares.[37]

Nonsteroid antiinflammatory drugs (NSAIDs): Because of its modulating effect on inflammation, treatment of susceptible mares with NSAIDs has been studied.[107] Oral administration of Vedaprofen (2 mg/kg) the day before AI, and of 1 mg/kg twice daily until one day after ovulation, had no effect on fluid accumulation or uterine cytology but resulted in higher pregnancy rates. It should be noted that the mares were also treated with oxytocin (20 IU) three times per day. More research is needed to determine the potential value of this treatment protocol.

Bacterial cell wall extracts: Studying the immune response to semen, Woodward and colleagues[105] found that MCWE downregulated mRNA expression of IL-1β in susceptible mares at 6 hours after AI, supporting previous observations by Fumuso and colleagues.[108] As noted under infectious endometritis, a comprehensive clinical study suggested that treatment of problem mares with *P. acnes* extract (Settle®) resulted in a

10% increase in pregnancy rates compared to untreated controls.[87] However, the mares received additional treatments and the effect of stallion fertility was not considered in that study.

Plasma: The use of plasma products has recently been directed toward immunomodulation rather than elimination of pathogens from the uterus. Platelet-rich plasma (PRP) was shown to modulate the uterine inflammatory response to semen,[109,110] including downregulation of mRNA coding for proinflammatory cytokines and NO.[111] The protocol for treatment with PRP entails separation of 180 mL of whole blood by a special centrifugation system (Angel Cytomedix, Inc., Gaithersburg, Md.) followed by resuspension of the PRP in 10 mL plasma before the mix is being infused into the uterus at 24 to 36 hours prior to breeding.

Lactoferrin: Recombinant human lactoferrin (rhLF) has been demonstrated to be safe to administer in the equine uterus and modulates breeding-induced inflammation.[112] It was concluded that intrauterine treatment with 250 µg/mL rhLF may assist susceptible mares to resolve the breeding-induced inflammation in a timely fashion. Clinical trials are needed to confirm this observation.

Electroacupuncture has been used clinically to increase uterine contractility in mares with delayed uterine clearance. Anecdotal reports are encouraging, and further research is necessary.

It is important for the clinician to keep in mind that a transient inflammatory response to semen is normal. Postbreeding treatment of these mares most likely will not improve fertility but may cause even further contamination and interfere with pregnancy. Only 10% to 25% of all broodmares develop a pathologic, persistent form of breeding-induced endometritis.[19-21] Attention should be given to identifying and managing these mares appropriately in order to optimize reproductive efficiency.

Chronic Degenerative Endometritis (Endometriosis).

Degenerative changes of the endometrium such as periglandular fibrosis and glandular dilation are often seen in older multiparous mares. The condition is associated with susceptibility to persistent endometritis[68] and may result from repeated uterine inflammation. However, the condition has also been observed in older mares without any known history of endometritis, suggesting that

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degenerative fibrosis of the endometrium can be a process of aging rather than inflammation.[113] Because of the possibility of a noninfectious cause of the disease, it was suggested that the condition should be called endometriosis, rather than degenerative endometritis.[113] It is not clear why mares with fibrotic degenerative changes to the endometrium have an impaired physical uterine clearance mechanism. Sclerotic changes in the uterine vascular bed impair blood flow to both the endometrium and the myometrium, which may explain the effect on uterine clearance.[114]

Several treatments have been suggested for degenerative fibrosis of the endometrium, but consistent results have not been reported. Infusion of dimethyl sulfoxide (DMSO) into the uterine lumen has produced inconsistent results in mares with chronic degenerative endometritis.[115,116]

The use of mesenchymal autologous stem cells and autologous conditioned serum has been explored in experimental models as potential treatment alternatives for susceptible mares and mares with degenerative endometrosis.[117-119] A modulation of the inflammatory response to semen was reported as was an indication that regenerative treatment strategies have the potential to restore degenerative changes to the endometrium.

Prognosis and Prevention.

Prognosis for fertility after endometritis varies with the severity of inflammation and fibrosis and the inciting cause. Prognosis should take into account the age of the mare, the level of reproductive management, the cause (if known), and the most probable response to treatment.

Metritis

Metritis is classically defined as inflammation of all layers of the uterine wall. Metritis occurs in the first 2 weeks after foaling and commonly follows abortion, dystocia, and RFMs. Equine metritis is often accompanied by endotoxemia and laminitis. Transluminal adhesions between endometrial folds may follow severe metritis.

Clinical Signs and Diagnosis

Metritis is characterized by uterine accumulation of postpartum secretions, bacteria, and the products of inflammation, with discharge from the cervix and possibly the vulva. Discharge is usually fluid and red-brown and may be fetid.

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Systemic signs of depression accompanied by neutropenia and leukopenia are apparent with development of endotoxemia. Differential diagnoses include normal lochia and causes of profound depression in the postpartum period as a result of uterine tears and acute abdominal disorders.

Treatment and Prognosis

Treatment is directed toward removing contamination and microorganisms from the uterus while providing systemic treatment for endotoxemia. Broad-spectrum systemic antibiotics, antiinflammatory drugs, and fluid therapy are indicated. Uterine contamination may be removed by gentle intraluminal infusion of warm water or saline and siphoning off of uterine contents. Vigorous lavage should be avoided, particularly during acute systemic disease. Prognosis depends on severity of clinical signs. If metritis is diagnosed quickly and treatment is instituted, prognosis for fertility and systemic health is good. Prognosis is guarded once endotoxemia and laminitis develop.

Pyometra

Pyometra in mares is an accumulation of purulent exudate in the lumen of the uterus. Impedance to mechanical uterine outflow, such as cervical fibrosis and adhesions of cranial parts of the tract ventrally into the abdomen, often contributes to the development of pyometra. If endometrial irritation causes release of endogenous endometrial $PGF_{2\alpha}$, diestrus will be shortened. In some mares, endometrial destruction is so severe that $PGF_{2\alpha}$ release is inadequate and luteal life is prolonged.[27] A variety of bacteria may be involved, including *E. coli*, *Pseudomonas* spp., and *Streptococcus* spp. Cultures may also be negative.

Clinical Signs and Diagnosis

A purulent vaginal or cervical discharge may be seen. The mare may demonstrate a short diestrus, a normal interestrous interval, or a prolonged diestrus. Some mares with pyometra have mild leukopenia and normocytic-normochromic anemia, secondary to mild suppression of erythropoiesis. Transrectal palpation and ultrasonography reveal a fluid-filled uterus. The uterine wall may be thin and flaccid or thick.

Treatment and Prognosis

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Treatment should involve correction of predisposing causes, fluid evacuation, and local antibiotic treatment. Evacuation of large amounts of fluid from the uterus may result in redistribution of fluid and circulatory shock. The mare should be monitored for signs of circulatory shock, and intravenous fluid may be administered during evacuation of large amounts of fluid from the uterus. The prognosis for life is excellent; however, the prognosis for return to normal fertility is guarded to poor because the conditions that predispose to development of pyometra in mares (cervical stenosis and adhesions) are difficult to treat and because severe endometrial destruction may develop. Endometrial biopsy should precede vigorous treatment. Hysterectomy should be considered if treatment is unsuccessful and if discharge is unacceptable or if adhesions impair athletic ability.

Ruminants

Bovine Uterine Infection

Deliveries complicated by dystocia or RFMs may be followed by severe bacterial infections of the uterus. The most sanitary environment possible should be provided for calving. The use of a clean pasture may be most appropriate on some farms, whereas the use of roomy, well-bedded, indoor maternity pens that are cleaned after each delivery may be appropriate on others.

Cows with abnormalities such as hypocalcemia, dystocia, and RFMs around the time of calving are more likely to develop uterine infections than are cows that calve normally. Routine treatment of cows with antibacterial drugs and chemicals has not been shown to be beneficial and may in fact reduce fertility. Postpartum uterine infections may be prevented, or the number of such infections reduced, by strict attention to sanitation in the calving environment and during assistance with delivery, along with proper management during the dry period.[1]

Bovine uteri are normally contaminated by a wide variety of microorganisms during the puerperium. Most of the organisms are transient residents of the reproductive tract and are soon eliminated from the involuting uteri of normal cows. *T. pyogenes* can persist in the uteri of cows and act with *Fusobacterium necrophorum* and *Prevotella* (formerly *Bacteroides*) spp. to cause uterine infections. Coliforms, *P. aeruginosa,* hemolytic streptococci, and gram-positive and gram-negative anaerobic bacteria are also frequently isolated from animals with postpartum uterine disease. *T. pyogenes* and *Clostridium* spp. occasionally

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colonize the postpartum uterus synergistically, causing severe gangrenous metritis. Other organisms that appear to have little effect on fertility may colonize the uterus and produce penicillinase, thus influencing the selection and route of administration of drugs used to treat uterine infections.[2,3]

Clinical Signs and Diagnosis

Lochia is normally expelled during the first 2 weeks after calving and may range from dark red or brown to white to clear. If uterine involution is delayed, discharge of lochia may continue until 30 days after calving. Discharge of lochia is not abnormal unless the fluid is fetid or the cow develops other abnormal clinical signs. Abnormalities of uterine involution cannot be diagnosed by palpation per rectum during the first several days after calving when both normal and abnormal uteri are out of reach and cannot be safely retracted. By 10 to 15 days after calving, the entire uterus can be palpated if involution is normal. Fluid should not be palpable within the uterine lumen by 14 to 18 days after calving. Gross reduction in size and histologic repair of the endometrium are complete in dairy cows by 40 to 50 days after calving.

Postpartum metritis in cows is characterized by the presence of variable amounts of lochia within the uterine lumen that may be discerned by palpation per rectum. A vaginal discharge is usually present, but it may become obvious during palpation. Septic or puerperal metritis is characterized by clinical signs of toxemia that may include fever, depression, partial or complete anorexia, and laminitis. Milk yield is depressed, and cows may be unwilling or unable to rise. Some cases may be complicated by tenesmus. Vaginitis and cervicitis may accompany metritis. Discharges associated with septic metritis vary from scanty white mucus to copious amounts of red to red-black, watery, malodorous fluid. In some cases inflammation may spread through the uterine wall and cause perimetritis and peritonitis.[4] Septic metritis in ewes and does is characterized by fever, depression, anorexia, and tenesmus.

Endometritis in cattle is usually observed between 2 and 8 weeks after calving. Discharge can range from white pus to estrual mucus. Purulent exudate may be observed only with palpation or may be found in the cranial vagina and cervical canal on examination with a speculum. The history may indicate that the cow has failed to conceive after several services but the patient is otherwise healthy.

Culture of endometrial fluid is not usually done in individual cases of bovine

uterine infection but may be indicated to determine the antibiotic susceptibility of microorganisms on a particular farm or as a part of the diagnostic plan when the incidence of postpartum metritis or endometritis increases suddenly.

Endometrial biopsies are rarely used in cows but have been recommended when complete evaluation is required of the reproductive tracts of cows that do not conceive or that conceive but do not complete their pregnancies.

Treatment and Prognosis

To be useful in treating uterine infections in cows, an antibiotic must be active against the primary uterine pathogens (*T. pyogenes* and gram-negative anaerobes), in the presence of organic debris, and in the anaerobic environment of the postpartum bovine uterus.[5] Oxytetracycline is active against many of the microorganisms that infect the bovine uterus, and its activity is only slightly reduced by organic debris and absence of oxygen. Intrauterine treatment with administration of 4 to 6 g of oxytetracycline per day has been used; however, some preparations of oxytetracycline irritate the endometrium, cervix, and vagina. Intrauterine antibiotic treatment of dairy cows results in residues in their milk.[6] For example, oxytetracycline has been found in milk from 44[7] to 96[8] hours after intrauterine administration, and thus an appropriate withdrawal period should be enforced and milk residue testing should be conducted.

Penicillin by systemic administration is effective for treatment of uterine infections in cows. Doses of penicillin required to reach the minimum inhibitory concentration of *T. pyogenes* are 10,000 to 20,000 IU/kg/day. Systemic ceftiofur (2.2 mg/kg IM or SC q24h for 3 to 5 days) achieves adequate concentrations in the uterus and is effective in treating bovine metritis.[9,10]

Treatment of septic or puerperal metritis should be directed toward controlling septicemia. Large doses of broad-spectrum systemic antibiotics are indicated, along with fluids and other supportive therapy. Attempts to remove RFMs or irrigate the uterus are contraindicated during the acute phase of the disease. After the patient has recovered from acute septicemia, intrauterine therapy may be considered.

Antiseptic Chemicals.

A variety of antiseptic chemicals have been infused into the uterine lumen of cows in attempts to treat metritis and endometritis, but few controlled trial evaluations are available. The potential for endometrial damage by these

chemicals needs to be considered carefully.

Uterine Lavage.

Lavage of the uterine lumen with large volumes of warm saline (40° to 45° C [104° to 118° F]) removes accumulated fluid and debris. Uterine lavage has been used as an adjunct to antibiotic, antiseptic, and plasma treatment. Catheters designed for nonsurgical embryo recovery are suitable for uterine lavage. Saline is infused into the endometrial cavity in 0.5- to 1-L increments, allowed to reflux through the catheter, and collected for inspection. A milk hose and larger fluid volumes may be used in cattle with larger postpartum uteri, but care must be taken not to enter far into the uterus because it is friable and easily perforated. Massage or partial retraction of the uterus by palpation per rectum may be necessary to increase fluid recovery. The uterine lumen is lavaged repeatedly until the fluid returning through the catheter is no longer turbid.

Prostaglandins.

In cows, repeated administration of $PGF_{2\alpha}$ results in shortened estrous cycles and may mimic the shortened luteal phase of patients with acute endometritis. $PGF_{2\alpha}$ therapy alone may be sufficient in mild cases of endometritis, or it may be used in combination with intrauterine or systemic therapy. In cases of chronic bovine endometritis, treatment with $PGF_{2\alpha}$ one or two times at 10- to 14-day intervals decreased the number of days open.[11]

The prognosis in cows for recovery from endometritis is usually good if the condition does not progress to a more severe form of uterine disease. Septic metritis after dystocia or RFMs may result in permanent impairment of reproductive function, laminitis, or death of the patient despite aggressive therapy.

Pyometra

In dairy cows, pyometra is likely to develop in cows that ovulate before microorganisms that infect the uterus during the postpartum period are eliminated. The CL that develops after the first postpartum ovulation at approximately 15 to 18 days after calving persists, possibly because the abnormal uterine contents suspend release of $PGF_{2\alpha}$ from the endometrium or sequester it within the uterine lumen. The uterus is brought under the influence of progesterone, which depresses phagocytic activity of uterine neutrophils and

closes the cervix, allowing the bacterial infection to persist.[12] Pyometra rarely endangers the general health or life of affected cows. Postcoital pyometra may be caused by *T. foetus* in natural breeding dairy and beef herds.[13]

$PGF_{2\alpha}$ is the treatment of choice for bovine pyometra. Treatment is followed in 3 to 6 days by uterine evacuation in 85% to 90% of treated cows. Response to $PGF_{2\alpha}$ treatment may be bolstered with a repeat injection in 6 to 12 hours. After endometrial lesions are allowed to heal for 30 days, fertility is restored in most patients.

Treatment of cows with GnRH after calving is controversial. In herds with a high prevalence of postpartum uterine infections, treatment with GnRH may decrease fertility by inducing ovulation and CL development; thus the uterus is brought under the influence of progesterone before contaminating bacteria are removed, leading to pyometra.

Perimetritis

Perimetritis may occur in all species as a sequela to severe uterine infections, uterine rupture, penetration of the vagina during mating, traumatic insemination or obstetric procedures, and cesarean section.[14] Perimetritis is characterized by inflammation of the peritoneal surface of the uterus and may be accompanied by localized or diffuse peritonitis. Adhesions then develop between the uterus and other pelvic and abdominal organs.

Clinical Signs and Diagnosis

The clinical signs of perimetritis are those of peritonitis and may include fever, depression, partial or complete anorexia, stasis of the gastrointestinal tract, and evidence of abdominal pain. Abdominal pain is typified by colic in mares and by grinding the teeth (odontoprisis) in cows. In cows the condition should be differentiated from traumatic reticuloperitonitis, displacements of parts of the digestive tract, abomasal ulcers, postpartum metritis, and abdominal fat necrosis. Perimetritis in mares must be differentiated from other causes of colic. Antemortem diagnosis of perimetritis is difficult in sheep and goats that are presented mainly with fever, depression, anorexia, and odontoprisis.

Clinical Pathology

Cases of acute perimetritis are accompanied by leukopenia, neutropenia, and a

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degenerative left shift. Further evidence of peritonitis is obtained when peritoneal fluid is obtained by paracentesis and examined for its cellular and microbiologic content.

Treatment and Prognosis

The cause of perimetritis should be treated if possible. Cases of severe metritis should be treated appropriately, and uterine ruptures sutured if possible. Repair of uterine ruptures inaccessible by flank incisions may be facilitated by intentional prolapse of the uterus after administration of epinephrine, provided the tear is not too close to the cervix (see next section). Treatment with broad-spectrum systemic antibiotics is indicated. Lavage to remove peritoneal exudate has been recommended but is difficult to accomplish, especially in cows in which the rumen, abomasum, and greater omentum make ventral drainage almost impossible and in which fibrinous peritonitis with loculation of infection occurs rapidly. Other supportive treatments such as intravenous fluids and antiinflammatory drugs should be administered.

The prognosis depends on the severity of lesions. Fatalities can occur despite prompt treatment, and surviving animals may be infertile because of mechanical interference with gamete transport caused by adhesions between the genital organs and other pelvic and abdominal tissues. In general, the prognosis for fertility in affected animals is fair at best.

Prevention and Control

Perimetritis occurs sporadically in individual animals; therefore prevention depends on avoiding the causes. Immature females, especially heifers and fillies, should not be allowed at pasture with adult males to prevent undesired mating complicated by penetration of the vagina. Traumatic obstetric, insemination, and uterine lavage procedures must be avoided. Uterine tears that occur at parturition must be sutured immediately. Postpartum metritis must be treated promptly and appropriately before it progresses to perimetritis.

Small Ruminants

Uterine infections may follow dystocia and RFMs in sheep and goats, but these infections are not frequently a cause of infertility because in most cases parturition is followed by a few months of sexual rest before the next breeding season. In ewes, RFMs and metritis follow abortion caused by *Listeria*

monocytogenes, *Campylobacter* spp., and *Chlamydophila abortus.*

Ewes and does affected with metritis are usually treated with systemic antibiotics such as penicillin, sulfamethazine, oxytetracycline, or ceftiofur. Early and aggressive treatment is indicated.

Camelids

Metritis and Endometritis

When camelids breed, the penis is inserted through the cervix and deep into the uterine horns. Unnecessary mating, or overbreeding, is the most important factor causing damage to and contamination of the uterus.[15] Other major contributing factors include RFMs, rectal vaginal tears, and unsanitary obstetric manipulations.[15]

Chronic endometritis will often not cause evident clinical signs, whereas acute, postpartum endometritis may cause fever, depression, and signs of shock. A thick, mucoid lochial discharge is normal in the postpartum female for up to a week postpartum. In contrast, thin, watery, fetid discharge is a sign of endometritis.[15]

Transrectal ultrasonography and vaginoscopy are helpful in diagnosing endometritis and metritis. Inflamed, thickened uterine walls and hyperechoic, intraluminal fluid may be present on ultrasound examination. Vaginoscopy may reveal cervical discharge. Transrectal ultrasonography may usually be performed in llamas. In alpacas, because of smaller size, an extension probe is necessary to facilitate transrectal ultrasonographic evaluation.

Uterine culture and cytology samples from the llama may be obtained using methods similar to those used in the mare and cow. A double-guarded swab prevents environmental contamination. In the alpaca, the swab should be passed through the cervix via visualization using a vaginoscope. These diagnostics should be performed during the peak follicular phase to ensure ease of passage through the open cervix and more reliable test results.[15] The most common bacteria isolated from the uteri of camelids with endometritis are *E. coli*, *S. zooepidemicus*, β-hemolytic streptococci, *Enterococcus*, coagulase-negative *Staphylococcus*, *Proteus* spp., *Enterobacter aerogenes*, *K. pneumoniae*, and *T. pyogenes*.[15]

Uterine biopsy can be a useful diagnostic tool for evaluation of metritis and endometritis in camelids. Endometrial biopsy samples in llamas may be obtained

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as in the mare. The left horn is perhaps better to target unless a particular pathology is suspected in the right horn, because camelid pregnancies almost always occur in the left horn.[15] Pathologic changes, evaluation, and prognosis are all assumed to be similar to those in the mare.

Treatment for endometritis and metritis is also similar to that described for the mare. Uterine lavage with a warm, isotonic saline solution and oxytocin injection (5 to 10 IU) are the major components of treatment. Intrauterine antibiotic infusion is done after uterine lavage. The most common antibiotics used are penicillin K (1.5×10^6 U), gentamicin sulfate (200 to 300 mg), and ceftiofur sodium (250 to 500 mg).[15] Antibiotics should be diluted in sterile water or saline (saline should not be used with ceftiofur) and given once daily for 5 to 7 days. Females should be evaluated after cessation of treatment and completion of 2 weeks of sexual rest.

Prevention of endometritis often requires a "minimum contamination breeding technique."[15] This entails monitoring follicular growth via transrectal ultrasound until the follicle is of preovulatory size, breeding only once, following breeding with an injection of hCG (750 IU) or GnRH, and administering an intrauterine infusion of antibiotics 24 hours after breeding. Females should be evaluated for pregnancy 12 to 14 days after breeding.

Further preventative measures include performing prebreeding examinations on all maiden animals to avoid breeding animals that are too young or do not have follicular activity; breeding only females that exhibit strong receptive behavior (as opposed to mere submissive behavior); performing complete gynecologic examinations on all females with a history of infertility, obstetric problems, or postpartum complications; and observing strict rules of hygiene during breeding and obstetric manipulations.[15]

Pyometra

Pyometra caused by delayed uterine involution may be observed shortly after parturition. Chronic pyometra is often associated with vaginal or cervical adhesions that may be sequelae to trauma after dystocia or aggressive obstetric manipulation.[15]

Anatomic Defects as a Cause of Uterine Infection

The most common anatomic defect associated with genital infections in camelids is pneumovagina. Other defects include urovagina and perineal lacerations. These defects should be corrected to prevent contamination with environmental and fecal organisms.

Endometrial Cysts and Lacunae

Mares

Endometrial cysts and lymphatic lacunae are common degenerative changes of the endometrium that are more prevalent in mares older than 11 years of age than in younger mares.[16] Endometrial cysts can originate from endometrial glands or obstructed lymphatics. Glandular cysts are small (<10 mm) and believed to be the result of periglandular fibrosis. Lymphatic cysts can reach several centimeters in diameter. The cause of lymphatic cysts is not fully understood, but lacunae are thought to arise after interference with normal lymph drainage from the genital tract.

Clinical Signs and Diagnosis

Endometrial cysts can be visualized by ultrasonography or hysteroscopy. Cysts may mimic pregnancy when mares are examined per rectum by palpation or ultrasonography.[17]

Sequential examination reveals that the size of endometrial cysts remains static, whereas amniotic vesicles enlarge. Large, discrete, fluid-filled cysts may be identified by palpation of the uterus per rectum. Smaller cysts and lacunae may be observed in endometrial biopsy sections. Uteri affected by lymphatic lacunae are enlarged and have a thicker wall than normal.

Treatment and Prognosis

Endometrial cysts do not require treatment unless they are suspected to interfere with pregnancy. Endometrial cysts have been suggested to cause embryonic death and abortion if large or numerous. However, there is no proven association between the presence and number of cysts and fertility.[16] Obliteration of endometrial cysts using endoscopic-guided laser surgery or electrocoagulation removes the cysts permanently, but the long-term effect on fertility has not been critically evaluated. Needle aspiration, mechanical rupture of the cyst, uterine curettage, and intrauterine infusion of hypertonic saline solution have all been

suggested to effectively remove endometrial cysts. However, the cysts often recur after treatment.

Uterine Prolapse

Uterine prolapse occurs when the previously gravid uterine horn becomes invaginated after delivery of the fetus(es) and protrudes from the vulva.

Mares

Uterine prolapse is an uncommon sequela to normal foaling, dystocia, or RFMs in the mare. The tip of the previously gravid horn invaginates to form uterine eversion. Eversion is accompanied by pain and abdominal straining. The myometrium may contract around the ring of invaginated tissue. Transrectal palpation confirms the diagnosis, and the everted tissue may be replaced manually. Eversion may progress to complete uterine prolapse, accompanied by rapid onset of systemic signs.

Treatment and Prognosis

The prolapsed uterus should be washed with clean saline and replaced manually in the standing mare as rapidly as possible. Replacement is aided by sedating the mare and administering epidural anesthesia. The uterus should be supported on a clean sheet held at the level of the pelvis. The uterus should be replaced, beginning with the uterine body and working gradually, replacing the tip of the horns last. Correct positioning of the uterus is important to prevent the prolapse from recurring. Replacement should be followed by treatment with broad-spectrum antibiotics, antiinflammatory drugs, and intravenous isotonic fluids. Treatment with oxytocin (10 to 20 IU IM) facilitates uterine involution. Prognosis is related to development of sequelae such as uterine tears, metritis, and endometrial damage.[18]

Ruminants

In cows, most cases of uterine prolapse occur within a few hours after calving. The condition is invariably associated with hypocalcemia, which results in lack of uterine tone and delayed cervical involution. In addition, dystocia frequently precedes uterine prolapse.

Elective uterine prolapse can be induced within 6 to 12 hours after calving by

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administering epinephrine to relax the uterus for the repair of uterine tears. A 10-mL amount of epinephrine (1:1000) is diluted to 250 mL in sterile saline and administered slowly IV. After 100 mL of the solution has been given, the operator reaches through the cervix, grasps the uterine wall and caruncles, and everts the uterine horn toward the cervix. When sufficient uterine tissue has entered the cervical canal, the patient responds by straining, which assists in completion of the prolapse. Epidural anesthesia is administered to abolish further straining after the prolapse is complete.

Uterine prolapse in does has been associated with dystocia, hypocalcemia, and lack of exercise. The predisposing factors are probably similar for ewes.

Clinical Signs and Diagnosis

Clinical signs of uterine prolapse are obvious, with maternal caruncles exposed on the uterine endometrium. The membranes may remain attached. Immediately after prolapse occurs the tissues are nearly normal, but within a few hours they become enlarged and edematous. The endometrium is usually contaminated with feces and bedding material. In some cases the prolapsed tissue may be lacerated or severely traumatized and may contain loops of intestines.

Clinical signs that may accompany uterine prolapse include straining, abdominal pain, restlessness, anorexia, and increased pulse and respiratory rates. Parturient paresis is common in affected dairy cows. In most patients these signs are transitory, but shock may complicate some cases.

Clinical Pathology

Uterine prolapse in cows is frequently accompanied by hypocalcemia and a significant increase in the packed cell volume.[19]

Treatment and Prognosis

The prolapsed tissue should be protected from further damage by wrapping it in wet towels or covering it with a plastic bag. Beef cows should be restrained where they are found, to prevent trauma to the uterus or rupture of the large uterine vessels should an animal try to escape on arrival of the clinician. Treatment of hypocalcemia is usually indicated before replacement of the uterus if the cow is recumbent and semicomatose; otherwise calcium gluconate is administered after replacement. Epidural anesthesia (3 to 5 cc of 2% lidocaine) is frequently, but not always, required.

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The prolapsed tissue is washed with a mild presurgical scrub. The membranes are removed if they can be easily separated from the endometrium but are left in place if removal is difficult. Some clinicians recommend that cows stand during replacement, whereas others have found that the organ can be replaced in recumbent cows if the patient is placed on her sternum with the hind legs drawn straight out behind. The prolapse is placed between the extended limbs. In fresh cases, replacement is relatively easy and is begun at the cervical pole of the organ; the dorsal and ventral parts are massaged alternately back into their normal position. After the ovarian pole has been replaced, the previously prolapsed horn must be straightened and eversion of the uterus corrected; this can be done manually or by intrauterine infusion of warm saline. Administration of clenbuterol is reported to relax the uterus, facilitate replacement, and reduce the need for epidural anesthesia, but its use is illegal in the United States. If the patient has been neglected, accumulated fluid must be reduced by lubricating the tissue with an emollient ointment and then carefully but vigorously massaging the tissue from the ovarian pole toward the cervical pole. The hygroscopic action of sugar when applied liberally to prolapsed uteri is of questionable value.

Oxytocin (5 to 40 IU IM or IV) is frequently administered to stimulate myometrial contractions after the uterus has been replaced. Metritis is a frequent sequela, and appropriate antibiotic treatment is indicated in most cases. Temporary closure of the vulva with heavy sutures after replacement may not be necessary but is practiced by many clinicians. If replacement of the prolapsed uterus is impossible or the tissue is severely traumatized, amputation may be indicated; in this case it is important that the uterine arteries be double ligated.[20] Euthanasia may also be considered in such instances.

The prognosis varies but is generally favorable if there has been no serious damage to the uterus. Fatalities can occur in cases complicated by shock or by rupture of large uterine vessels. The culling rate from infertility of cows with uterine prolapse is higher than that of their herdmates, and the calving interval is prolonged in affected cows. Barring hypocalcemia, the risk of uterine prolapse at a subsequent calving is no greater than for other cows in the herd.

Prevention and Control

Because the condition is associated with hypocalcemia in cows, provision of a properly balanced ration before calving is indicated. Although uterine prolapse can occur after an apparently normal delivery, it is more commonly associated with dystocia and forced extraction; therefore prolapse should be anticipated,

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and the dam observed so that affected patients may receive prompt treatment. Oxytocin (5 to 40 IU IV or IM) may be administered after a dystocia to increase uterine tone and potentially prevent prolapse.

Camelids

Uterine prolapse in camelids is usually a consequence of dystocia, RFMs, or excessive obstetric manipulation. Treatment is the same as described for other species.

Uterine Tumors

Neoplasia uncommonly affects the uterus of domestic animals. Leiomyomas are usually benign and arise from the outer smooth muscle of the uterus without need for a preparatory event. Leiomyomas are not necessarily associated with reproductive failure, and tumors and fetuses can coexist.

The multicentric form of lymphosarcoma may affect the uterus of cattle. Lymphosarcoma also affects does, but a predilection for the uterus is not apparent. Uterine walls affected by lymphosarcoma may contain discrete neoplastic nodules or be diffusely infiltrated.

Carcinomas, chorionepitheliomas, fibromas, fibrosarcomas, rhabdomyosarcomas, and adenosarcomas are rarely reported. Regardless of tumor type, tumors must be differentiated from normal fetuses, mummified or macerated fetuses, placentomes, abscesses, and fat necrosis.

Segmental Defects

Segmental aplasia (white heifer disease) occurs sporadically in all breeds of cattle. In most cases the cranial parts of the genital tract (ovaries, uterine tubes, and cranial part of the uterine horns) are normal, and endometrial secretions from the parts of the uterine horns accumulate because normal drainage through the cervix is impeded. Various defects may be found in affected animals, ranging from nearly complete absence of tubular genital organs to an imperforate hymen that blocks secretion drainage from a normal genital tract.

Clinical Signs and Diagnosis

Segmental aplasia may be associated with a history of anestrus if fluid accumulation within the uterine horns interferes with release of $PGF_{2\alpha}$ and

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luteolysis. Other presenting history may involve infertility or difficulty in AI. On palpation per rectum, various degrees of aplasia may be recognized. Fluid-filled parts of the uterine horns may suggest pregnancy, from which they must be differentiated. An imperforate hymen may bulge from the vulvar cleft and may be confused with vaginal prolapse, prolapse or eversion of the urinary bladder, cystic vestibular glands, or neoplasia of the vulva or vagina.

Treatment and Prognosis

The only form of segmental aplasia amenable to treatment is that in which an imperforate hymen occludes an otherwise normal tract. Incision of the hymen is followed by drainage of accumulated secretions and may allow the tract to function normally.

Paramesonephric Duct Aplasia

Aplasia of one paramesonephric duct leads to development of one uterine horn (uterus unicornis). The condition is found in cattle but is rare. Subfertility is the result of prolonged periods of anestrus caused by a persistent CL on the ovary ipsilateral to the missing uterine horn (no local luteolytic signal). The condition can be managed with exogenous $PGF_{2\alpha}$ in the hope that ovulation will occur on the intact side. Alternatively, the unaccompanied ovary can be surgically removed.

Uterus Didelphis

The caudal parts of the paramesonephric ducts may not fuse properly in cattle, causing duplication of various parts of the caudal tubular tract. Abnormalities of fusion are most common in and around the cervix. The entire cervix may be duplicated, or the cervix and vagina may be normal, with the exception of the presence of a band of tissue extending dorsal to ventral across the external os of the cervix. Partial failure of fusion may involve a part of the cervix, and the affected animal may possess a single uterine body and internal cervical os, duplication of a part of the cervical canal, and a doubled external cervical os. Uterus didelphis results when the cervix and uterine body are completely duplicated. Affected cows may conceive after natural service or if artificially inseminated through the cervix and uterine horn ipsilateral to the ovary about to ovulate. Affected animals may be unable to carry a pregnancy to term because of

lack of placental attachment in the nongravid horn.

Hydrometra (Pseudopregnancy in Small Ruminants)

Hydrometra occurs sporadically in sheep and goats and is characterized by accumulation of several liters of clear fluid within the uterus, abdominal distention, persistence of a CL, and subsequent anestrus.[20] Previous breeding is not necessary, but the condition may develop after mating, and does are frequently assumed to be pregnant. It can also occur after early embryonic loss in goats or sheep. The cause of hydrometra is unknown, but a deficiency in production or release of $PGF_{2\alpha}$ from the endometrium has been postulated, as has exposure to phytoestrogens. The clinical signs of hydrometra mimic those of pregnancy. The diagnosis is suspected if the goat fails to show estrus when it cannot possibly have been bred but is in a herd where heat detection is good. Serum progesterone concentrations are elevated, and abdominal enlargement suggestive of pregnancy may occur. Blood-based biochemical pregnancy markers will be negative. Amplitude-depth ultrasound for pregnancy is positive because of fluid in the uterus. Transabdominal ultrasound reveals anechoic fluid but no fetus or caruncles in the uterus. The animal should be rechecked if fewer than 40 days have elapsed since the last possible breeding, as early pregnancy is possible in such cases. In advanced hydrometra, large anechoic fluid-filled compartments are seen separated by undulating tissue walls, which represent the uterus coiled back on itself. Spontaneous correction is common and varies from red discharge suggestive of early abortion to expulsion of accumulated fluid approximately 150 days after an infertile mating, so-called cloudburst. No fetus or placenta is passed. Treatment of false pregnancy is with prostaglandin. The clinician needs to keep in mind that this will induce abortion if the ewe or doe has a true pregnancy. An initial dose of 5 to 10 mg of dinoprost (Lutalyse) or 125 to 250 µg of cloprostenol (Estrumate) is given and repeated in 12 days. Estrus and emptying of the uterus occur in 1.5 to 4 days. Oxytocin (50 IU bid for 4 days) is normally reserved for females that retain fluid in the uterus after prostaglandin therapy. The doe frequently becomes pregnant within a few days to weeks after termination of a false pregnancy if a buck is available. Sometimes hydrometra recurs. Suggestions for prevention have included selenium supplementation and breeding on the first heat of the season. The prevalence is surmised to be increased in herds where breeding is delayed in order to obtain

winter milk and in does manipulated hormonally to breed out of season.[20] Routine pregnancy diagnosis of sheep and goats with transabdominal ultrasound should be advised to permit rebreeding during the same season.

Cervical Abnormalities

Cervicitis

Inflammation of the cervix usually accompanies endometritis and vaginitis and is frequently secondary to trauma associated with dystocia and obstetric operations. The mucus-secreting epithelium of the cervix is more resistant to bacterial infection than is the epithelium of the uterus and vagina.

Mares

The equine cervix is a straight tube made up of layered circular and longitudinal muscle. During estrus it relaxes, and the external os lies on the floor of the anterior vagina. During diestrus or pregnancy, under the influence of progesterone, the cervix is closed and the external os is elevated off the vaginal floor. Cervicitis or inflammation of the cervix may be iatrogenic or may occur secondary to trauma associated with parturition or dystocia or as an extension of vaginitis or endometritis. Endometritis and infertility follow if the cervix lacks anatomic integrity.

Clinical Signs and Diagnosis

Infertility and history of an inciting cause such as urine pooling or dystocia may be the only signs of cervicitis in the mare. Cervical hyperemia and edema may be apparent on speculum examination in acute cervicitis. In more chronic injuries, direct digital examination of the cervix of the mare in diestrus may reveal transluminal adhesions or anatomic defects.

For treatment and prognosis in mares, see discussion under Ruminants.

Ruminants

Similarly, in cows cervicitis is secondary to uterine infections and follows trauma associated with parturition and obstetric manipulations. Infection is usually caused by microorganisms normally present in the cranial vagina such as *E. coli*, streptococci, staphylococci, and *T. pyogenes.*

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Cervicitis in does and ewes is uncommon but may occur secondary to vaginal and uterine infections and obstetric trauma.

Clinical Signs and Diagnosis

Examination of cows with a vaginal speculum reveals swelling and edema of the external cervical os. The mucous membrane is hyperemic and inflamed. Mucopurulent exudate may be present in the cervical canal or in the cranial vagina. Hypertrophy of the cervix is common in Bos indicus breeds and their crosses and may be a normal finding; therefore cervical size as detected by palpation per rectum may or may not indicate inflammation. Inflammation of the cervix without contemporary endometritis may not affect fertility. Cervicitis may occur in pregnant cows.

The clinical signs of cervicitis in does and ewes are similar to those in cattle and must be observed with a small vaginal speculum.

Treatment and Prognosis

Most cases of cervicitis resolve spontaneously when coexisting endometritis and vaginitis improve. Exudate can be flushed from the cervical canal and cranial vagina with warm saline lavages, and a nonirritating antibiotic ointment applied to the affected tissue. Caustic chemicals should not be placed in contact with the cervical mucosa. Aggressive treatment with systemic antibiotics is indicated in cases complicated by infection with anaerobic bacteria.

The prognosis for most cases of simple cervicitis is fair to good. However, inflammation of the cervix in mares may progress to more severe cervical abnormalities. Cervical damage is a serious threat to future reproductive performance in mares. Anaerobic infections of the cervix may be fatal.

Prevention and Control

Obstetric manipulations and operations must be temperate. When the cervix does not dilate properly during parturition, a cesarean section is preferred over forced extraction.

Cervical Lacerations

Mares

Cervical lacerations are most often seen after dystocia. The condition may result

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in adhesions and a nonpatent cervix or in failure to seal the uterus during diestrus or pregnancy. Cervical adhesions in combination with endometritis are a common cause of pyometra in the mare.

Clinical Signs and Diagnosis

Cervical lacerations can be diagnosed by vaginoscopy and digital examination of the cervix. A digital examination of the cervix is often necessary to evaluate the degree and severity of the laceration. Evaluation of the ability of the cervix to close adequately is best performed during diestrus.

Treatment and Prognosis

If cervical lacerations are diagnosed shortly after parturition, antimicrobial ointment should be applied frequently to the lesion. Early signs of adhesions should be broken down until the tissue is healed. If the laceration results in an incompetent cervix, it should be corrected surgically. Although surgical repair of cervical lacerations has resulted in restored fertility in many mares, the condition is likely to recur at the time of the next parturition. Embryo transfer should be considered if allowed by the breed registry.

Vaginal Abnormalities

Pneumovagina

Mares.

Pneumovagina is characterized by aspiration of air, often containing microorganisms, into the vagina. Pneumovagina is secondary to changes in perineal conformation, which include cranioventral displacement of the reproductive tract, loss of integrity of the vestibulovaginal sphincter, and loss of integrity of the vulvar labia. These changes occur more commonly in older, multiparous mares and those that have had perineal lacerations. Pneumovagina is a common antecedent to infertility.

Clinical Signs and Diagnosis

In the normal mare, the anus is positioned directly dorsal to the vulva. The perineal body between the dorsal vulva and the anus is thick, muscular, and well

formed. The vestibulovaginal sphincter is well formed, and the vulva has a vertical alignment, with 80% of the vulval labia situated below the floor of the pelvis. The vulvar labia form a seal in the normal mare.

Mares prone to pneumovagina are those in which the vulva tilts horizontally at its dorsal aspect, the perineal body is thin, the vulval labia do not form a seal, and the anus lies cranial to the vulva. A scoring system has been developed to evaluate the perineal conformation in mares.[1] The system uses Caslick's index, which equals the distance (in cm) between the dorsal commissure of the vulva and the pelvic floor multiplied by the degrees of declination of the vulvar lips. Mares with a Caslick's index above 150 were found to have subnormal pregnancy rates. Affected mares aspirate air on exercise or when the vulval labia are parted. Aspirated air may be noted on transrectal palpation or vaginal speculum examination. Signs of secondary changes such as vaginitis, cervicitis, or endometritis may be apparent.

Treatment and Prognosis

Treatment of pneumovagina should be directed toward correcting defective perineal conformation. Cranioventral displacement of the reproductive tract in aged mares may be irreversible. Perineal confirmation in thin mares is often improved by increasing the mare's body condition. Pneumovagina is often successfully corrected by surgical closure of the dorsal vagina via Caslick's surgery. Secondary changes should be treated as described elsewhere. Prognosis for correction of pneumovagina is excellent; however, prognosis for fertility depends on the extent of secondary changes.

Urovagina

Mares.

The normal vagina in young mares slopes craniodorsally and is largely contained within the pelvis. With aging and repeated pregnancy, the cranial vagina may slope cranioventrally and fall below the level of the pelvic floor. Under these conditions urine collects in the anterior vagina. Urine is spermicidal, and the condition is often associated with subfertility.

Clinical Signs and Diagnosis

In mild cases, a history of infertility may be the only indicator of urovagina. In

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more severe cases, urine dribbles from the vulva at rest or during exercise and may accumulate on the skin of the hindlimbs. Speculum examination reveals a cranioventral slope of the vagina, variable inflammation of the cranial vagina and cervix, and a pool of urine in the ventral vaginal fornix. Urovagina may occur intermittently or only during estrus.

Treatment and Prognosis

Surgical procedures to prevent the anterior flow of urine include urethral extension[2] and vaginoplasty.[3] Prognosis depends on the severity of secondary endometritis and the success of surgery.

Vaginitis

Vaginitis may occur as a result of ascending infection or exposure to irritants, or secondary to pneumovagina, urovagina, perineal laceration, rectovaginal fistulas, breeding, endometritis, abortion, parturition, or dystocia. Occasionally, traumatic wounds may be infected with clostridial or anaerobic organisms; however, most infection is nonspecific.

Clinical Signs and Diagnosis

Signs may vary from hyperemia evident on speculum examination to mucopurulent exudation from the vulva. Severe trauma and infection may be followed by necrotic vaginitis with tenesmus, fetid discharge, elevated tail, swollen vulva, and systemic signs. Rapid formation of adhesions follows necrotic vaginitis. Metritis, RFMs, and uterine tears also may show systemic signs and vaginal discharge.

Treatment and Prognosis

The inciting cause should be treated. Animals with mild vaginitis may recover spontaneously, whereas moderate cases require lavage with dilute antiseptic or antibiotic solutions. Fertility is unaffected in mild vaginitis without extension, and prognosis is good. Severe, necrotic vaginitis is treated with systemic antibiotics, analgesics, and antiinflammatory agents. Caslick's surgery may be necessary to prevent aspiration of air. Local application of antibiotic and steroid-impregnated ointments may help prevent adhesions. Prognosis for severe vaginitis is guarded. Vaginal stenosis and adhesions may follow vaginitis.

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Prevention and Control

Nonspecific vaginitis may be prevented by reducing trauma to the vagina during foaling. Clinicians should elect appropriate methods for relief of dystocia and apply extractive force to fetuses judiciously.

Infectious Pustular Vulvovaginitis

Cows.

Infectious pustular vulvovaginitis (IPV) affects cattle and is caused by bovine herpesvirus 1, also the cause of infectious bovine rhinotracheitis (IBR), although the two strains are genetically distinct.[4] Therefore the respiratory and genital forms of the disease rarely occur concurrently, and abortions usually do not follow an outbreak of the genital form of the disease. IPV is spread by coitus and mechanical means and may affect unbred heifers. The incubation period of IPV is short (1 to 3 days), and the infection spreads rapidly through the herd, affecting 60% to 90% of the animals.

Clinical Signs and Diagnosis

Early in the course of the disease, IPV is characterized by a mucopurulent vaginal discharge, inflammation of the vaginal and vulvar mucosa, and painful urination. Pustules develop over lymphoid follicles and progress from small (<3 mm) ulcers to coalescing erosions. The virus also causes inflammation of the penis and prepuce (balanoposthitis), leading to considerable pain. Therefore animals of both sexes with IPV are reluctant to mate. The clinical signs subside in 10 to 30 days, leaving the recovered animals with transient immunity. Early in the course of IPV, lesions may be similar to those of granular vulvitis (see later section), but the lesions of IPV rapidly become more severe. Vulvovaginitis caused by *Histophilus somni* (formerly *Haemophilus somnus*) should be a differential diagnosis.

Treatment and Prognosis

Treatment of IPV is usually not required, although lavage of the vagina with dilute antiseptic solutions and emollients has been recommended. Mating among infected animals should be suspended until the disease subsides. The prognosis for recovery is excellent.

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Prevention and Control

Vaccination against IBR is not likely to be beneficial in the face of an outbreak, but cattle may be protected if they are vaccinated before exposure. The IPV virus may survive in cryopreserved semen used for AI; therefore semen donors and semen should be free of the virus. Genital carriers may be responsible for sporadic outbreaks of IPV.

Vaginal Varicose Veins

Mares.

Vaginal varicose veins are common in older mares. In most cases the condition is not associated with clinical signs, but affected mares may exhibit vaginal hemorrhage. A thorough examination of the reproductive tract is necessary to determine the origin of the bleeding.

Clinical Signs and Diagnosis

Clinical signs of varicose veins vary from no signs to persistent and profuse vaginal hemorrhage. Vaginoscopy or fiber endoscopy of the vagina reveals varicose veins in the vagina or the vestibulovaginal transverse fold. Fiberoptic endoscopic examination may be necessary to diagnose lesions that are present in the cranial aspect of the vestibulovaginal transverse fold. Vaginal hemorrhage from varicose veins should be differentiated from vaginal trauma and premature separation of the placenta in periparturient mares.

Treatment and Prognosis

Most mares with vaginal varicose veins do not require treatment. Surgical ligation, treatment with phenylephrine HCl cream,[5] or laser surgery of the veins may be necessary in cases of severe bleeding. The short-term prognosis after surgery is good, but the condition often recurs.

Vestibular and Vulvar Abnormalities

Coital Exanthema

Mares.

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Coital exanthema is caused by equine herpesvirus 3 (EHV-3) and is a venereally transmitted dermatitis of the genital region of mares and stallions.[6,7]

Clinical Signs and Diagnosis

The disease is recurrent, is usually mild and transient, and affects the vulva and perineum of mares and the penis and prepuce of stallions. Lesions are initially small papules that rapidly progress to pustules and then ulcers. Lesions may rarely appear on the conjunctiva, lips, nares, and mucosa of the upper respiratory tract. Rare secondary bacterial infection and systemic signs occur. Intranuclear inclusion bodies are apparent in epithelial cells on histologic sections taken from the active edge of ulcers. Coital exanthema does not affect fertility in mares, but libido may be decreased in affected stallions because of pain during coitus.

Treatment and Prognosis

Lesions usually heal spontaneously within 14 days, leaving depigmented spots. Treatment is not necessary unless secondary bacterial infection occurs. There is no available vaccine for EHV-3. Sexual rest until the lesions are healed is recommended to prevent further spread of the disease. The prognosis is excellent.

Granular Vulvitis

Cows.

Granular vulvitis may occur in females of all domestic species but is most often seen in cattle. The disease is characterized by development of granules or papules in the vulvar mucosa accompanied by genital discharge. Infertility may or may not be a feature of the syndrome. Vulvitis may be secondary to nonspecific vaginitis. *H. somni*[8] and *Mycoplasma bovigenitalium* have been isolated from cattle with vulvitis, but their role in infertility is not well defined, and there may be differences in pathogenicity among strains of the organisms. *Ureaplasma diversum* has been isolated from cases of granular vulvitis in cows and ewes and may be associated with infertility when the organism is transferred into the uterus during AI.[9]

Clinical Signs and Diagnosis

Granular vulvitis is characterized by the formation of raised granules or papules

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in the vulvar mucosa and around the clitoris with variable amounts of mucopurulent exudate. In the mild form of granular vulvitis associated with *U. diversum*, only a few granules develop and the infection has minimal effect on fertility. However, acute severe cases are characterized by hyperemia of the vulva, a profuse mucopurulent discharge, and depressed fertility. Purulent discharge during the acute phase persists for 3 to 10 days, after which the disease becomes chronic. In chronic cases the lesions are reduced in severity, and there is little or no purulent discharge. The chronic form may persist for several months, and the disease may become enzootic in some herds. The clinical signs of granular vulvitis may be similar to the early signs of IPV.

Clinical Pathology

Samples for microbiologic culture should be obtained from the vulva, cervicovaginal mucus, and uterus. Use of a transport medium for submission of samples to a laboratory is mandatory. The organisms may be eliminated before the samples are obtained, yielding false-negative results. Conversely, microorganisms incriminated as causing granular vulvitis may be isolated from the genital tracts of normal animals.

Treatment and Prognosis

Most cases of nonspecific vulvitis resolve spontaneously. Infertility associated with *U. diversum* infections is treated by preventing transfer of organisms to the uterus by using double-sheathed AI instruments. Natural breeding should be suspended. In addition, infusion of 1 g of tetracycline or spectinomycin in a nonirritating vehicle into the uterus 24 hours after breeding has been recommended to reduce the population of organisms that may have been transferred to the uterus. Local treatment of vulvar lesions with tetracycline or spectinomycin has also been suggested.

Prevention and Control

In chronically infected herds, fertility rates may approach normal if double-sheathed AI instruments are used and affected cows are treated with appropriate antibiotics.

Ulcerative Dermatosis Genital Lesions

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Small Ruminants.

Ulcerative dermatosis is a venereal disease of sheep caused by a parapoxvirus similar to but distinct from the virus that causes contagious ecthyma.[10] The disease is characterized by ulceration of the skin and mucous membranes of the vulva of ewes and the penis and prepuce of rams. Lesions also occur on the lips, nares, feet, and legs. The lesions are painful, and affected animals avoid coitus. The disease subsides in 7 to 10 days.

Because of its viral cause, no specific treatment is available for ulcerative dermatosis. Symptomatic treatment with local astringent and antiseptic ointments has been suggested. Mortality is low if the animals are otherwise healthy.

No vaccine is available. Males with the disease should not be used for breeding.

Abnormal Labial Approximation

Mares and Cows.

The most common anatomic defect of the vulva of mares and cows is abnormal labial approximation, which leads to pneumovagina and subsequently to infertility. The defect may be the result of imperfect conformation or traumatic insult to the vulva. Abnormal labial approximation is treated with Caslick's surgery or one of its modifications.

Persistent Hymen

In the developing embryo, failure of cannulation of the urogenital sinus by the mesonephric duct system results in absolute or partial occlusion of the vestibulovaginal junction. Total occlusion causes accumulation of endometrial and cervical secretions cranial to the obstruction, and occasionally the membrane may appear at the vulva. Partial occlusion may be noted only as an obstruction to breeding or during speculum examination. The membrane may be manually ruptured or incised. Prognosis is excellent.

Clitoral Hypertrophy

Clitoral hypertrophy may be a feature of intersex conditions, may occur in filly foals whose dams received progestins during pregnancy, or may follow administration of anabolic steroids.[11] Hypertrophy may persist after cessation of

steroid treatment. In cows it may be associated with freemartinism.

Vulvar wattles in cattle may superficially appear similar, but the elongated epithelial structure does not involve the clitoris.

Neoplasia

Melanomas and squamous cell carcinomas (SCCs) are the most common neoplasms affecting the perineum, anus, and vulva of gray- and light-skinned horses, respectively. Lesions are usually proliferative and may have surface ulceration, hemorrhage, and infection. Lesions should be differentiated from habronemiasis, granulation tissue, and sarcoids. Treatment is surgical removal. Sarcomas and melanomas may metastasize. Viral fibropapillomas are the most common tumors affecting the vulva of cattle. SCCs may be seen in all species and may be more common in white-skinned animals exposed to long periods of solar radiation.[12]

Vulvar neoplasia is characterized by variable degrees of tissue proliferation. The surface of SCCs and fibropapillomas may be ulcerated, necrotic, and fly-blown. In cows, squamous metaplasia of the nonpigmented skin of the vulva is frequently a precursor of SCCs of the vulva. Vulvar neoplasia must be differentiated from other causes of tissue proliferation, habronemiasis in mares, and ectopic mammary tissue in does. Neoplasia of the vulva and vestibule is diagnosed by biopsy of the tumor.

Surgical excision is the treatment for most neoplasms of the vulva. Viral fibropapillomas regress spontaneously after a period of several months. Recurrence and metastasis may occur.

Ectopic Mammary Tissue

Ectopic mammary tissue has been described in does and is characterized by swelling of the vulvar lips. The abnormal enlargement begins before each parturition and persists for approximately 2 months. The condition is benign unless the tissue enlarges sufficiently to interfere with evacuation of feces or urine. Milk may be aspirated from the mammary tissue, and the condition may be confirmed by biopsy; however, this may introduce infection and lead to complications.

Abortion

Mares

Information on the major causes of abortion in horses is summarized in Table 43.7.

TABLE 43.7
Major Causes of Infectious Equine Abortion

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Equine herpesvirus 1 (EHV-1)	Seventh month to term	Pulmonary edema, multifocal hepatic and pulmonary necrosis, intranuclear inclusions	Histopathology, virus isolation, fluorescent antibody test, fetal serology, PCR
Equine viral arteritis (pestivirus)	5-10 months	Myocardial arteritis	Histopathology, virus isolation, PCR, serology
Nocardioform actinomycetes, *Crossiella equi*, *Amycolatopsis* spp.	Mid to late gestation	Characteristic placentitis located ventrally in the uterine body and at the base of the uterine horns	Culture, PCR
Streptococcus zooepidemicus	Any stage	Placentitis with or without inflammation in fetal tissues	Histopathology, culture
Mycotic abortion, *Aspergillus*, and other species	Latter half (often near term)	Placentitis, fetal bronchopneumonia	Histopathology, fungal culture
Leptospirosis	Seventh month to term	Icterus and autolysis	Culture, immunofluorescence, serology, PCR

PCR, Polymerase chain reaction.

Noninfectious Causes

Twin Pregnancy

Despite the overall decrease in the number of twin-related abortions, twinning remains an important noninfectious cause of abortion in the mare.[1] The mare is unable to successfully support two fetuses to term and only in rare cases (<2%) is able to carry both fetuses to term and deliver without dystocia.[2] It is much

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more common for the mare to have a natural reduction to a singleton pregnancy during the embryonic stage or to abort the pregnancy after the fetal stage.[3,4] Some breeds are more commonly diagnosed with twins during the embryonic stage (e.g., Thoroughbreds have 20% to 30% double ovulations and 10% to 15% diagnosed twin pregnancies).

Clinical Signs and Diagnosis

Mares should be evaluated with transrectal ultrasound 13 to 15 days after documented ovulation during a breeding cycle. The ovaries should be examined for more than one active CL, and the uterus should be carefully scanned from the tip of one horn to the other and along the uterine body to the cervix. Equine embryos at this stage are highly mobile within the uterus and may be located anywhere within the uterus. Twin pregnancy should not be ruled out until the entire uterine tract has been scanned for the presence of embryos. After one embryo is found, the remainder of the uterus still must be visualized to ensure the absence of a twin. The embryo proper per se is not visible at this stage of pregnancy, but the embryonic vesicle is easily visualized. Care must be taken not to confuse endometrial cysts with embryos, which sometimes can look deceptively similar. It is helpful to have scanned the mare's uterus using ultrasound before breeding to document the size and location of endometrial cysts.

Treatment and Prognosis

If twins are confirmed before 16 days of pregnancy, the best way to treat the mare is to manually crush one of the vesicles. This is done by visualizing the twins using transrectal ultrasound and spatially separating them from each other within the uterus. One twin is moved away from the other to the tip of a uterine horn, where it is crushed manually. The remaining embryo should be evaluated 1 to 2 days later to determine its status. Manual reduction of an embryo fixed in the contralateral horn from its twin between days 16 and 20 should be performed at the base of one uterine horn, because embryos are typically “fixed” at this site after day 16. Survival of the remaining embryo is greater than 90% when twin reduction is performed in this manner before day 20.[5]

It is the established practice of some veterinarians to treat mares with a nonsteroidal antiinflammatory agent (e.g., flunixin) and/or altrenogest after a twin-crush procedure. The reasoning behind this practice is that manual

stimulation of the uterus may cause a release of oxytocin, signaling a prostaglandin cascade that will result in luteolysis and complete pregnancy loss. No studies have been performed to support this theory; to the contrary, other studies have shown that the release of prostaglandin after the routine twin-crush procedure does not cause a drop in progesterone and that supplementation with antiinflammatory drugs or progesterone makes no difference in the outcome.[5,6]

Twins fixed next to each other at the base of the same horn between days 16 and 20 cannot be separated from each other. Manual reduction can still be reliably performed at this stage but will result in the loss of both embryos and the need to breed the mare again on a subsequent cycle. If twins are discovered fixed ipsilaterally between days 16 and 20, the practice of "benign neglect" may be followed for a short time. Since most of these situations will resolve naturally with the resorption of one twin and the persistence of the other, it is a responsible practice to simply monitor the situation to note if one twin regresses. If both twins continue to develop approaching the formation of endometrial cups (day 37 to 38), a decision must be made either to terminate the pregnancy or to refer the mare for advanced, selective twin reduction, which includes transvaginal, ultrasound-guided fetal aspiration[7]; transcutaneous, ultrasound-guided fetal intracardiac injection of procaine penicillin or potassium chloride[8]; or craniocervical dislocation.[9] The success of these techniques is lower than that of manual crush, and they are performed later in gestation, after the window for manual crushing has been missed. These are all specialty techniques and are beyond the scope of this chapter.

Other Noninfectious Causes of Equine Abortion

In a survey of causes of equine abortion in the United Kingdom from 1988 to 1997, nearly 39% were caused by umbilical cord pathology.[10] Most of the cases (35%) resulted from torsion of the umbilical cord. Twisting of the umbilical cord is common in equine fetuses and often is not pathologic. A diagnosis of abortion caused by umbilical torsion should be made only if localized swelling and discoloration accompany the twisting. Congenital abnormalities may cause abortion. The most common congenital abnormality in equine fetuses is contracted tendons, accounting for 5% of abortions in a study from the United States.[1] Fetuses that implant in the uterine body instead of the base of one of the horns develop placental villous atrophy and usually abort, accounting for 2% of abortions in the same study.

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Infectious Causes

Placentitis

Placentitis is the leading cause of equine late-term pregnancy loss in the United States.[1] Bacterial organisms most commonly cultured from aborted fetuses include *Streptococcus* spp., *E. coli, Pseudomonas* spp., *Klebsiella* spp., *Staphylococcus* spp., and *Leptospira* spp. Nocardioform actinomycetes are an important cause of placentitis in central Kentucky and have also been reported in Florida.[11-13] *Aspergillus fumigatus* and *Mucor* spp. are the most commonly diagnosed causes of mycotic abortion in mares, causing 5% to 30% of infectious equine abortions.

The route of placental infection is believed to most commonly be ascending via the cervix, which results in loss of chorionic villi around the cervical star. In addition to loss of chorionic villi, additional allantochorionic lesions may include nodular cystic allantoic masses, edema, necrotic areas of chorion, and necrotic mucoid exudate coating the chorion. Hematogenous placentitis shows a more generalized, diffuse loss of villi.[1] Infection of the placenta results in subsequent infection of the fetus and release of proinflammatory cytokines and prostaglandins from the inflamed placenta, which ultimately leads to mid- to late-term abortion or delivery of a premature foal.[14] The distribution of the avillous chorionic lesion classically noted in mares with ascending or hematogenous placentitis does not fit the pattern noted with nocardioform placentitis. Mares with nocardioform placentitis classically show a loss of chorionic microvilli, covered by brownish, thick, and tenacious exudate in a focal area around the ventral aspect of the uterine body and base of the uterine horns.

The pathogenesis of nocardioform placentitis is still unresolved. It has been hypothesized that the pathogen is present in the environment or introduced into the mare at the time of breeding and settles in the ventral aspect of the uterus, where infection ensues. Various nocardioform organisms have been reported in soil across the globe, although the pathogenicity of most of these organisms has not been determined. Nocardioform organisms isolated from equine placentas include *Amycolatopsis* spp. and *Crossiella equi.*[11,13,15,16] These bacteria have been diagnosed only from clinical cases of placentitis and not from the environment.[17] Nocardioform placentitis often results in abortion or premature

delivery.[1] Bacteria and resulting inflammation are limited to the interface between the chorion and the endometrium. Because no bacterial invasion or signs of inflammation have been observed in the placental and fetal tissues, the abortion is postulated to be due to nutritional deprivation of the fetus resulting from separation between the chorion and endometrium.

Clinical Signs and Diagnosis

Premature udder development and vaginal discharge are common signs of pending abortion caused by ascending placentitis. However, when these signs are present, the prognosis is poor even when mares are treated. Transrectal ultrasonography of the allantochorion in an area close to the cervix is useful to detect early signs of placentitis and impending abortion (Fig. 43.6).[18] Ultrasound evaluations may reveal hyperechoic fetal fluids, placental separation, increased or decreased fetal heart rates (normal range 75 ± 7 bpm[19]), and thickening of the combined thickness of the uterus and placenta (CTUP). Consistently low or high fetal heart rates are associated with fetal stress. Foals experiencing fetal distress often become bradycardic initially and then become tachycardic in the terminal phase of life.[20,21] Serial examinations should be performed to verify fetal well-being or distress. Mares considered “at risk” for pregnancy loss are often examined daily. Fetuses experiencing distress are often evaluated several times a day. Normal measurements of CTUP have been established (Fig. 43.7).[18,22] Mares with placentitis may show increased CTUP, edema of the allantochorion, and separation from the endometrium. A 5-MHz linear transducer should be used for transrectal ultrasonography. The transducer should be positioned 1 to 2 inches cranial to the cervical-placental junction and then moved laterally until a major uterine vessel is visible at the ventral aspect of the uterine body.[22] The CTUP should then be measured between the vessel and the allantoic fluid (see Fig. 43.6). It is important to obtain all CTUP measurements from the ventral aspect of the uterine body, because physiologic edema of the dorsal aspect of the allantochorion has been noted in normal pregnant mares during the last month of gestation.[22] In addition, care should be exercised to be certain that the amniotic membrane is not adjacent to the allantochorion because this may result in a falsely increased CTUP. To examine the placenta from a transabdominal approach, a 3.5-MHz sector transducer is used most frequently. All four quadrants of the placenta should be examined: right cranial, right caudal, left cranial, and left caudal. Measurements of the CTUP can be made with this

technique if the fetus is not in close apposition with the uterine wall. Mares with normal pregnancies should have a minimum CTUP of 7.1 ± 1.6 mm and a maximal CTUP of 11.5 ± 2.4 mm.[23] Pregnancies with an increased CTUP have been associated with the delivery of abnormal foals.[23] False-positive results have been reported, and clinical judgment should be exercised before treatment is implemented. Placental separation and purulent material at the ventral aspect of the base of the gravid horn and the uterine body can be observed in mares with nocardioform placentitis. This finding can be identified only by using transabdominal ultrasound.

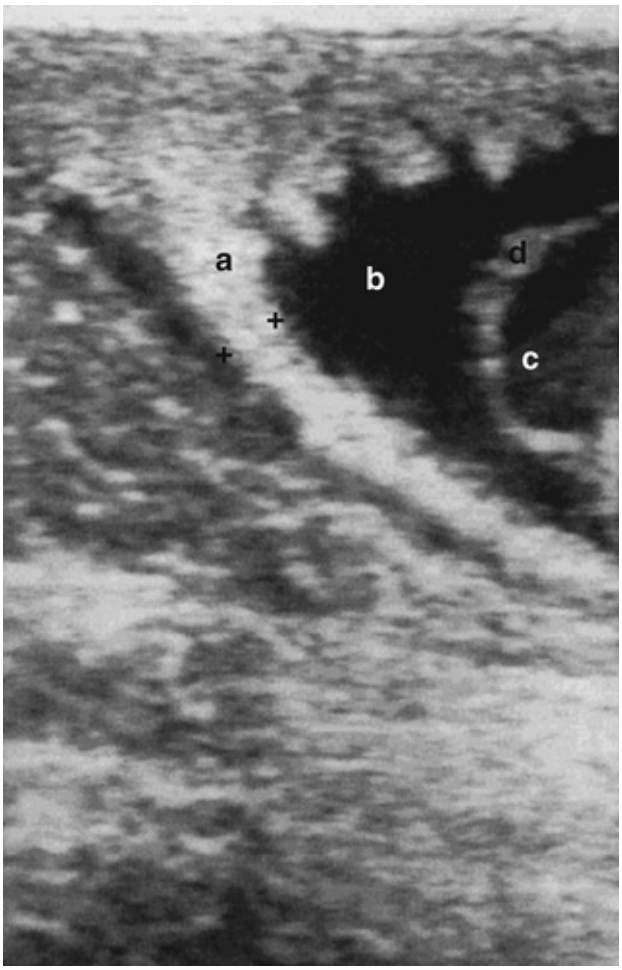


FIG. 43.6 Transrectal imaging of the combined thickness of the uterus and placenta (CTUP). Measurements of the CTUP (distance between + and +) were recorded from the ventral part of the uterine body, close to the cervix. *a,* Placenta adjacent to the cervix; *b,* allantoic fluid; *c,* amniotic fluid; *d,* the amnion. (Modified from Renaudin CD, Troedsson MH, Gillis CL, et al.: Ultrasonographic evaluation of the equine placenta by transrectal and

transabdominal approach in the normal pregnant mare. *Theriogenology*, 47:559, 1997.)

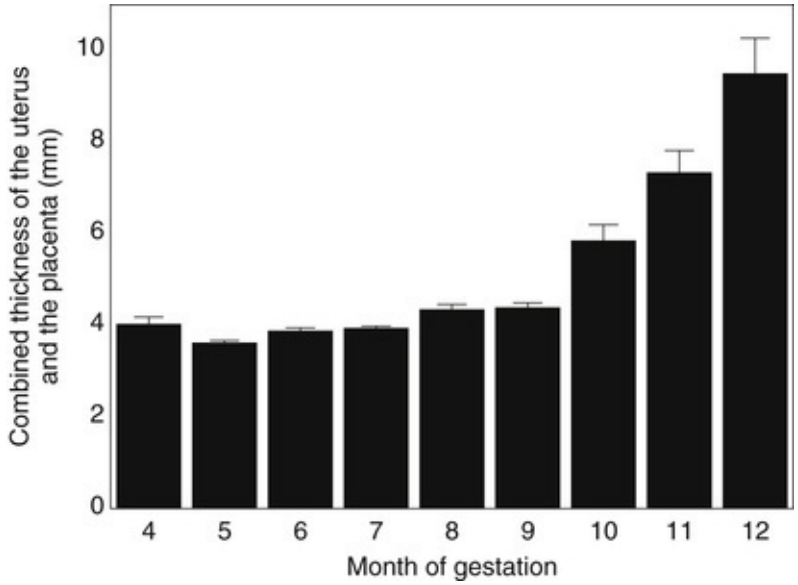


FIG. 43.7 Monthly recordings of transrectal ultrasonographic measurements of the combined thickness of the uterus and placenta (CTUP) in normal mares from 4 months of gestation and throughout the pregnancy. Month 4 is 91 to 120 days; month 5 is 121 to 150 days; month 6 is 151 to 180 days; month 7 is 181 to 210 days; month 8 is 211 to 240 days; month 9 is 241 to 270 days; month 10 is 271 to 300 days; month 11 is 301 to 330 days; month 12 is 331 to 360 days. (Modified from Renaudin CD, Troedsson MH, Gillis CL, et al.: Ultrasonographic evaluation of the equine placenta by transrectal and transabdominal approach in the normal pregnant mare. *Theriogenology* 47:559, 1997.)

The gross lesions of the fetus are not specific. An increased amount of fluid in the thoracic and abdominal cavities and an enlarged liver are frequently observed in aborted fetuses. Placental lesions in cases of ascending placentitis are most severe on the chorionic surface at an area from opposite the cervix (“cervical star”) to the body of the placenta. The affected area is edematous, thickened, and discolored or brown with a mucoid or fibronecrotic exudate on the surface. The placenta is characteristically thickened and leathery in cases of mycotic placentitis, with lesions well demarcated from the rest of the chorionic surface. Microorganisms can be isolated from the placenta and several fetal organs, most consistently from the stomach.

Mares with nocardioform placentitis may have premature mammary

development but will not have vulvar discharge, owing to the location of the infection. Placental lesions in mares infected with *Amycolatopsis* spp. and *C. equi* are located ventrally in the uterine body and at the base of the uterine horns. Affected areas are avillous, thickened, and covered by thick brown or reddish exudate. Differential diagnoses for this clinical presentation include twins and *Cellulosimicrobium cellulans* placentitis.[15]

Prevalence of fungal abortions varies greatly with region. The most common route of fungal infection is ascending via the cervix, and fungal infections may be seen with a mixed bacterial infection. Abortions are observed from mid to late gestation. The chorion generally shows marked evidence of placentitis with edema, thick plaques, and a thick, mucoid exudate. In rare cases, amniotic thickening may be noted. The aborted fetus is often small and emaciated owing to chronic placental insufficiency. Culture of the chorion may be diagnostic but takes time. Culture of the fetus is rarely rewarding. Impression smears of the chorion, as well as sometimes the fetal stomach, may reveal hyphae.

Progesterone.

The equine placenta is part of an endocrine fetal-placental interaction that synthesizes and metabolizes progestagens.[24] This endocrine function of the placenta is important for maintenance of pregnancy after the endometrial cups and the secondary corpora lutea disappear at approximately day 120 to 150 of gestation. Fetal-placental progesterone is rapidly metabolized to 5α-pregnanes. Mares with placental pathology may have increased plasma concentrations of progestagens as a result of stress to the fetal placental unit.[25,26] Unfortunately, 5α-pregnanes are not readily assayed in a commercial setting, so diagnosis of placental disease using 5α-pregnane concentrations is not possible. There is cross-reactivity between 5α-pregnanes and progesterone using some commercial radioimmunoassays for progesterone. Using an experimental model to induce placentitis, it was found that mares that develop a chronic form of placentitis also develop increased plasma progesterone concentrations.[26,27] Conversely, mares that developed acute placentitis and abortion soon after infection experienced a rapid drop in plasma progesterone concentrations. It has been suggested that serial measurement of plasma progestin concentrations in mares with placentitis might be a useful method to identify mares that may abort or deliver prematurely.[26] However, in a recent prospective study of 700 mares in central Kentucky, with blood collected weekly until the end of pregnancy,

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progesterone concentrations in the sample obtained during the week preceding abortion were not significantly different from those in mares with normal pregnancy outcome.[28] Sensitivity of progesterone assays can be improved when they are combined with evidence of placental thickening as detected using transrectal ultrasonography.[27]

Estrogen.

Serum estrogen concentrations are deviated in pregnant mares between 150 and 310 days of gestation.[29] The predominant estrogens in pregnant mares are estrone, equilin, equilenin, estradiol-17β, and estradiol-17α. Douglas[29] observed that mares aborting from placentitis had serum estrogen concentrations below those normally detected in pregnant mares. These observations were supported by results from a recent prospective study, in which low estradiol-17β sulfate serum concentrations were significantly associated with abnormal pregnancy outcome.[28] Based on these findings, it was suggested that supplementation with estradiol cypionate (ECP) or estradiol-17β may prevent abortion in mares with placentitis, but this has not been supported by later research.[30]

Relaxin.

Relaxin is produced by the equine placenta and can be detected in peripheral blood plasma from day 80 of gestation and then throughout the pregnancy. The role of relaxin during pregnancy is not fully understood, but there is some evidence that placental relaxin production is compromised in mares at risk of aborting their fetuses.[31] There currently is no commercial test available for equine relaxin.

Additional Markers for Placentitis

Acute Phase Proteins.

Serum amyloid A (SAA) remains low throughout gestation but shows a significant increase within 12 hours of parturition and returns to baseline within 60 hours postpartum.[32] Interestingly, levels of SAA in peripheral blood have also been reported to increase in mares with experimentally induced placentitis.[33] However, SAA is a nonspecific marker of inflammation with significant increase observed during other sources of inflammation and even after vaccination. Furthermore, only a weak association was detected between pending abortion

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and elevated SAA concentrations in a prospective clinical study.[28]

Serum Alpha-Fetoprotein (AFP).

Elevated AFP has been associated with abnormal pregnancy outcome under clinical conditions, and this protein may be used as a marker for mares with placentitis and/or at risk of aborting.[28] In summary, no single test appears to have sufficient specificity, sensitivity, or practicality to accurately detect early subclinical cases of placentitis. A panel of estradiol-17β, AFP, and SAA may serve as the best available method to screen mares for unhealthy pregnancies as well as predict the outcome.

Treatment and Prognosis

Treatment efforts should be directed at combating infection, reducing inflammation, and controlling myometrial activity. Pregnant mares with clinical signs of placentitis should be treated with systemic broad-spectrum antimicrobials and antiinflammatories. Commonly used antibiotics such as penicillin G sodium or potassium (22,000 IU/kg IV q6h), gentamicin (6.6 mg/kg IV q24h), and trimethoprim-sulfadiazine (30 mg/kg PO bid) cross the placenta and reach therapeutic concentrations in both placental tissues and the allantoic fluid.[34] However, the duration of these elevated concentrations was short and below that in blood plasma. This may explain why more than 60% of mares that had been treated for placentitis still cultured positive on endometrial biopsy after foaling.[35] It may also explain why antibiotic treatment appears to be necessary for the remainder of gestation in mares with placentitis. Flunixin meglumine (1.1 mg/kg IV or PO q12h) and pentoxifylline (8.5 mg/kg PO bid) have been used to control proinflammatory cytokines associated with placentitis. Treatment with progestins has long been advocated to promote uterine quiescence in mares with uterine pathology. Presumably the anti-prostaglandin effect of progestins contributes to reduced myometrial activity by interfering with upregulation of prostaglandin and oxytocin receptors.[36] Altrenogest at twice the recommended dose (0.088 mg/kg PO q24h) is commonly used.

The efficacy of multimodal, long-term therapy for equine placentitis has been investigated in a large-scale clinical trial.[37] Investigators examined records of 477 mares over 6 years. Fifteen mares were diagnosed with placentitis. Criteria for treatment included increased thickness of the uteroplacental unit using transrectal ultrasound, placental separation, and/or vulvar discharge and udder

development. The average gestational age at diagnosis was 8.6 months. Mares were treated until abortion or delivery of foal with a combination of systemic antibiotics (trimethoprim-sulfa, ceftiofur, or penicillin and gentimicin); pentoxifylline; altrenogest; and nonsteroidal antiinflammatory agents. Twelve of 15 treated mares (80%) carried their foals to term, and 11 of 15 (73%) delivered live foals. Birth weights of surviving foals from mares treated for placentitis were similar to those of foals from nonaffected mares. The benefit of this treatment strategy is supported by more recent data from a controlled study on experimentally induced placentitis.[38] Therefore long-term antibiotic, antiinflammatory, and progestin treatment may positively affect pregnancy outcome in mares with placentitis.

Although most mares are capable of conceiving and successfully carrying a foal to term in subsequent breedings, reproductive performance may be negatively affected after placentitis, be it induced by the ascending or hematogenous route. Treatments for endometritis, such as uterine lavage and intrauterine infusions of appropriate antibiotics, should be implemented after abortion. Most mares affected by nocardioform placentitis do not require subsequent treatment and show no signs of infertility the following breeding season.

Equine Herpesvirus 1 Abortion

The most prevalent viral cause of equine pregnancy loss is equine herpesvirus 1 (EHV-1), which causes abortion, paresis, and neonatal foal death. EHV-4 causes abortion in rare cases. The primary route of transmission of EHV-1 is via the respiratory tract. The virus invades the respiratory epithelium and establishes a leukocyte-associated viremia. EHV-1 establishes a chronic, possibly lifelong, latent infection. During the initial infection, placental endothelial cells are infected by the virus and transiently present targets to the immune system as the cells present viral particles. The virus eventually inactivates the major histocompatibility complex 1 (MHC-1) ability of the cells to present viral particles, thus evading the immune system.[39] After respiratory infection, EHV-1 causes an episode of viremia and infects the fetus via transplacental migration of virus-bearing leukocytes. Respiratory clinical signs in infected mares may be subclinical. The time between infection and abortion varies greatly from less than 2 weeks to several months.[40] Abortion occurs as a result of a rapid separation of the placenta, causing suffocation of the fetus.[41] Near-term fetuses

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may be born alive but will die within days. Aborting mares clear the virus quickly from the reproductive tract, and subsequent fertility is often not affected by the disease. Clinical signs and fetal lesions of abortion caused by EHV-1 and those caused by EHV-4 are indistinguishable from each other.[40]

As with all herpesviruses, EHV-1 establishes a latent infection that may recrudesce after stressful events, such as weaning, translocation, introduction of a new animal, or other illnesses. It is unclear whether a reactivation event will cause an abortion, but this is considered likely.[42] Recrudescent infections are certainly transmissible. Aborted, infected fetal materials are also highly contagious. Both of these sources may be responsible for abortion epizootics. Although epidemic abortions occur, losses may be confined to only a few mares in a herd.

Clinical Signs and Diagnosis

The primary lesion of EHV-1 is necrotizing vasculitis and thrombosis resulting from lytic infection of the capillary endothelium. The fetus may become infected or remain uninfected, depending on whether the virus crosses the uteroplacental barrier. If transplacental fetal infection occurs late in gestation, a live, infected foal may be born but will not usually survive. Stage of pregnancy during which abortions may occur varies, but the vasculitis is most pronounced from the fifth to ninth months of gestation, and 95% of abortions occur in the last trimester of pregnancy.[43]

Abortions occur suddenly as sporadic abortions or “abortion storms” without maternal clinical signs. The aborted fetus is fresh, with minimal signs of autolysis. Gross lesions in the fetus include increased fluid in the thoracic and abdominal cavities; congestion and edema of the lungs; hepatomegaly with multifocal, small (~1 mm), yellow-white necrotic foci; subcutaneous edema; and icterus. Histologically, the most characteristic lesion consists of areas of necrosis in lymphoid tissue, liver, adrenal cortex, and the lung, with large intranuclear eosinophilic inclusion bodies. In addition, a hyperplastic necrotizing bronchiolitis is often found. Lymphoid tissues are most commonly affected (nodes, thymus, spleen, and Peyer's patches). Other histopathologic lesions may include mild, multifocal, necrotizing lesions in the liver and adrenal cortex and a hyperplastic, necrotizing bronchiolitis. The placenta may be grossly normal or edematous with no specific microscopic lesions.[44]

Laboratory diagnosis of EHV-1 abortion is done by either direct

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demonstration of virus (virus isolation or viral antigen) or viral nucleic acid detection (PCR) or indirectly through serologic evidence of recent infection. The placenta, lung, liver, spleen, and thymus should be collected aseptically in suspected cases of EHV-1 abortion for virus detection. Tissue samples for virus isolation should be kept at 4° C, not frozen at –20° C, until inoculated into cell culture. Samples that cannot be processed within a few hours after collection should be stored at –70° C. The identity of virus isolates recovered from tissue specimens must be confirmed by PCR, indirect immunofluorescent assays using EHV-1 specific antisera or monoclonal antibodies, or neutralization assays using EHV-1 specific antisera or monoclonal antibodies. Serologic tests are not considered reliable in EHV-1 diagnosis. It should be kept in mind that serum from mares that aborted may already contain peak levels of antibodies, and no increase in titers will be detectable in subsequently collected sera. Equine fetuses have been found to be capable of producing antibodies to EHV-1 at 200 days of gestation. Maternal serology is of limited diagnostic value because mares may abort several weeks after infection. The rise in serologic titer may have disappeared by the time of the abortion.

Treatment and Prognosis

Most studies do suggest a beneficial effect of vaccination, and the current recommendation is to vaccinate during the fifth, seventh, and ninth months of gestation.[39,43] Both killed and modified live vaccines are available. The vaccines are not fully protective, and abortion may occur in vaccinated mares. However, consistent vaccination of pregnant mares should be expected to decrease the incidence of abortion storms and sporadic abortions in a herd.

For the effectiveness of a vaccination program to be maximized, it needs to be combined with a management strategy that minimizes exposure of mares to the virus and prevents activation of a latent viral infection. All horses—young, adult, nonpregnant, and pregnant—should be vaccinated to restrict shedding of the virus. Unnecessary stress such as transportation and overcrowding should be avoided. Pregnant mares should be kept separate from other horses on the farm. Newly arrived horses should be isolated from the resident population for 3 weeks, during which time they should be monitored daily for signs of respiratory disease.

After abortion, the fetus and fetal membranes should be transported away from the area without contaminating the surrounding environment. The stall in which the mare aborted should be disinfected with a phenolic or iodinophoric

compound, and the bedding should be prevented from contaminating other areas on the farm. All pregnant mares on an infected farm should remain on the farm until they have foaled. No horse should leave the farm until 3 to 4 weeks after the last abortion.

Equine Viral Arteritis

Equine viral arteritis (EVA) is caused by equine arteritis virus (EAV). The primary target of EAV is the vascular endothelial cells and macrophages. Shortly after infection EAV can be found in the macrophages and later in the lymph nodes. The virus infects circulating monocytes and becomes systemic in distribution by 3 days after the primary infection, resulting in a carrier state (important in stallions). About a week after the primary infection, EAV infects the blood vessel endothelium and causes enough damage by 10 days after the primary infection to cause abortion. Abortion is likely caused by myometritis and vasculitis. Serum progesterone concentrations (produced exclusively by the placenta in the last half of equine pregnancy) fall to baseline levels before the abortion because of placental hypoxia.

Although the pathophysiology is not well established, fetal death may occur by fetal anoxia secondary to compression of myometrial vessels by edema and decreased progesterone production by the placenta.[45]

History and Clinical Signs

Clinical signs may be absent or highly variable and may include pyrexia, depression, anorexia, leukopenia, limb edema, stiffness of gait, rhinorrhea and epiphora, conjunctivitis, rhinitis, urticarial rash, localized or diffuse edema, and abortion. Abortion typically occurs at 3 to 10 months of gestation and follows the onset of clinical signs by several days up to 2 months. Abortion rates in outbreaks of EVA have varied from less than 10% to 71%. Less frequently, severe respiratory distress, ataxia, mucosal papular eruptions, submaxillary lymphadenopathy, and intermandibular and shoulder edema may be observed.[46] Infection is rarely fatal in adults but is more frequently fatal in neonates due to interstitial pneumonia and secondary bacterial infections. Clinical pathologic findings are variable, inconsistent, and nonspecific and include hypoxia, hypercapnia, respiratory or metabolic acidosis, lymphocytosis or lymphopenia, neutrophilia or neutropenia, thrombocytopenia, and hyperfibrinogenemia. Gross and histologic lesions differ in severity with the virulence of the viral strain.

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Edema, congestion, and hemorrhage of the subcutaneous and lymphoid tissues and viscera are the most common gross lesions. Histologic lesions may be found in the vasculature, lymphoid tissues, lungs, intestines, adrenal glands, kidneys, and skin.[46] Abortion may occur without any clinical signs in the mare, and the fetus may be fresh or autolyzed. Fetal lesions are uncommon. The infected stallions may serve as long-term carriers, and virus may be transmitted in the semen.

Laboratory Diagnosis

Laboratory diagnosis of EVA is currently based on any combination of virus isolation, viral nucleic acid or antigen detection, and serology. The most appropriate specimens for virus isolation from live horses include nasopharyngeal swabs or washings, conjunctival swabs, and citrated or ethylenediaminetetraacetic acid (EDTA) blood samples for separation of buffy coat cells. Placenta, fetal fluids, lung, spleen, and lymphoid tissues should be collected for virus isolation to confirm cases of EAV-induced abortion. Reverse transcription PCR (RT-PCR)–based assays (standard and real time) have several potential advantages over the current virus isolation procedure. Serologic diagnosis of EVA is based on virus microneutralization and is standardized by the World Organization for Animal Health (still known by the French abbreviation OIE for Office International des Epizooties) and described in the OIE manual. There are no characteristic lesions of EVA infection in the fetus, although autolysis and myocardial arteritis have been reported. An avidin-biotin complex (ABC) for immunoperoxidase staining using monoclonal antibodies to individual EAV proteins has been used successfully to detect viral antigens in formalin-fixed paraffin-embedded samples, as well as in frozen tissue sections.

Epidemiology and Control

Transmission may occur venereally from persistently infected stallions to mares. Reproductive performance of venereally infected mares is not affected, but contact transmission from venereally infected mares to late gestational mares may cause abortion. Major outbreaks of EVA were reported in 1953, 1984, and 2006 in the United States. Apart from these incidents, occasional outbreaks have occurred, with abortion occurring at low incidence.[47] Mares may be isolated after infection but usually do not become carriers. A proportion of naturally infected stallions become persistently infected with EAV and shed the virus

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constantly in semen. Incidence of seropositive animals is higher in Standardbreds than in Thoroughbreds, and regulatory guidelines may govern the use of seropositive Thoroughbred stallions. Carrier stallions may be the reservoir for the disease between outbreaks and should be isolated and bred only to immune mares. Mares bred in this way should be isolated for 3 weeks. A modified live-virus attenuated vaccine and a killed-virus vaccine are available for prevention of EAV infection in mares and stallions, although some local regulatory restrictions on use may exist. Vaccination of mares up to 3 months before foaling or in the postpartum period appears to be safe. Vaccinating pregnant mares in the final 2 months of gestation is associated with an increased risk of abortion, and decisions to vaccinate in this period must be weighed against concerns for widespread disease in naturally infected herds.[48] Control in stallions involves vaccination of seronegative stallions under the guidance of regulatory authorities.

Leptospirosis Abortion

Leptospirosis causes bacterial abortions in some areas and was reported to be responsible for 2.2% of abortions in a Kentucky study.[49] The serovar responsible shows regional variability. Serovar *Leptospira pomona* has most commonly been associated with leptospirosis abortion in mares, but *Leptospira grippotyphosa*, *Leptospira hardjo*, *Leptospira bratislava*, and *Leptospira icterohemorrhagiae* have also been isolated from sporadic abortions.[49] Wet environmental conditions are considered important in the dissemination of the disease from wildlife to horses. Infected animals shed the spirochete in their urine, which contaminates groundwater and serves as a source for further infections. Many horses are seropositive for leptospires but are subclinical.

Clinical Signs and Diagnosis

Clinical signs may include pyrexia, hemoglobinuria, jaundice, and abortion. Aborted chorioallantoic lesions are similar to those of other bacterial placentitis cases (nodular cystic allantoic masses, edema, necrotic areas of chorion, and necrotic mucoid exudate coating the chorion) but may show a diffuse pattern of distribution, indicating a hematogenous source of placental infection. Funisitis has been reported in leptospiral cases of abortion, and examination, both gross and histologic, of the umbilical cord should always be a part of every abortion investigation.[50] Serologic antibody conversion lasts for years, so serologic

diagnoses are not helpful. Gross lesions are nonspecific. Diagnosis is best done by fluorescent antibody (FA) tests or Warthin-Starry (WS) silver stain of the allantochorion and umbilical cord. Demonstration of leptospirosis could aid in rapid diagnosis and have important clinical and therapeutic indications in the case of live-born, weak foals.[50]

Treatment and Control

Horses may shed spirochetes in urine for up to 90 days; therefore affected animals should be isolated and treated with antibiotics. Aborting mares should be isolated, and the stalls should be disinfected. Infected mares may be treated with streptomycin (10 mg/kg twice daily), penicillin (22,000 to 44,000 IU/kg IM twice daily), or oxytetracycline (5 to 10 IV mg/kg) for a period of 1 week. Because *L. pomona* is the most common isolate in the United States, mares should be separated from other leptospiral hosts such as ruminants and pigs. A vaccine against *L. pomona* is available for horses. Vaccines for cattle are not effective in horses.

Protozoal Abortion

Pregnant mares with equine monocytic ehrlichiosis (Potomac horse fever), caused by the protozoa *Neorickettsia risticii*, may abort. Abortions caused by *N. risticii* have been documented in both natural and experimental cases.[51,52] Mares were infected at 90 to 180 days of gestation and aborted at around 217 days of gestation.

Clinical Signs and Diagnosis

Abortions have been observed 2 to 3 months after clinical signs of ehrlichiosis.[53] Abortions were associated with placentitis and RFMs. Fetal histologic lesions include enterocolitis, periportal hepatitis, myocarditis, and lymphoid hyperplasia with necrosis of the mesenteric lymph nodes and spleen. Recovery of the protozoan may be from fetal bone marrow, spleen, lymph node, colon, or liver.[51,52] The diagnosis can be confirmed by identifying a small number of rickettsiae by PCR assay.

Treatment and Prevention

Treatment with oxytetracycline (6.6 mg/kg IV once daily) for 5 days in pregnant

mares with clinical signs of ehrlichial colitis may prevent or reduce the incidence of abortion. Commercial vaccines against equine ehrlichiosis are available, but the protective effect of vaccines against abortion is unknown.

Neospora caninum is a known protozoal abortifacient in cattle. This protozoan has not been definitively shown to cause abortion in the mare, but its presence has been documented in aborted foals, suggesting the need for further investigation.[54]

Insect-Related Abortion

In the equine breeding season of 2001, central Kentucky horses experienced pregnancy losses estimated to have affected more than 3000 mares (>60% of mares on some farms[55]) and to have resulted in more than $330 million in losses.[56] The syndrome was named *mare reproductive loss syndrome* (MRLS). On a much smaller scale, MRLS was documented in mare abortions in north central Florida during the 2006 breeding season. Epidemiologic studies noted abnormal weather patterns (sudden freezing in mid-April followed by unusually warm springtime temperatures) and positive correlations with the presence of black cherry trees *(Prunus serotina)* and abnormally large numbers of the eastern tent caterpillar *(Malacosoma americanum)*.[57] Pregnancy loss was later linked to ingestion of the caterpillars themselves, with the toxic agent related to the larval exoskeleton.

Clinical Signs and Diagnosis

Clinical signs preceding early embryonic death or abortion are typically not observed. Both early (40 to 150 days' gestation) and late (near-term) pregnancies are affected. Hyperechoic amniotic and allantoic fluids can be noted on ultrasonographic examination, along with a dead or dying fetus (slow heart rate, <75 bpm), which would then be expelled within several days.[58,59] Characteristic histologic lesions are noted in the placenta and umbilical cord (funisitis). In many cases, endometrial cultures are positive for non-β-hemolytic streptococci and actinobacilli. *Actinobacillus* spp. identified in cases of MRLS are identical to commensal organisms found in the oral cavities and alimentary tracts of healthy horses.[60] Larval hairs (cetae) are hypothesized to migrate through the gastrointestinal system and translocate commensal organisms from the oral cavity and intestines to other sites.[57]

Treatment and Prevention

Because clinical signs are absent in the mare before fetal death, treatment is not possible. Prevention is aimed at limiting exposure to *M. americanum* larvae. Applying insecticides, physically removing caterpillar nests from trees, removing black cherry trees, muzzling mares in pasture, and supplementing hay feeding in pastures to minimize grazing have all been used.

Salmonella Abortion

Salmonella abortus equi (*Salmonella abortivoequina* or "contagious abortion") was a common cause of abortion in the early 1900s but is now rare. Non–host-specific species, including *Salmonella typhimurium,* currently cause most equine *Salmonella* abortions. Abortion caused by *Salmonella* is discussed in the Ruminants section.

Trypanosomiasis (Dourine)

The protozoan parasite *Trypanosoma equiperdum* causes a venereally transmitted genital infection that may be followed by fatal systemic dissemination in horses. Systemic illness may cause abortion. It occurs in tropical and subtropical regions and has been eradicated from North America. Dourine is diagnosed by isolation of trypanosomes in uterine discharge. Exposed animals can be detected by serology (complement fixation). Control strategies require identification and treatment or euthanasia of infected animals.

Abortion Caused by Endotoxemia

Gram-negative septicemia and endotoxemia associated with intestinal disorders that alter the integrity of the mucosal barrier (e.g., intestinal obstructions, acute enteritis, colitis, grain overload) result in the release of vasoactive metabolites including $PGF_{2\alpha}$. Endogenous release of $PGF_{2\alpha}$ during an episode of experimental endotoxemia has been shown to cause luteolysis and abortion during the first 2 months of pregnancy in mares.[61] The equine pregnancy is dependent on ovarian sources of progesterone for the first 80 days of gestation. After this time, the fetoplacental unit takes over progesterone production, which is necessary for maintenance of the pregnancy.

Clinical Signs and Diagnosis

Abortions follow a recent episode of stress induced by endotoxemic shock or gram-negative endotoxemia. Pregnancy loss at early stages of gestation may go undetected unless fetal membranes or parts are found in the stall. Abortions during later stages of the pregnancy may be observed as vaginal discharge or the detection of an expelled fetus.

Treatment and Prevention

Daily administration of a progestagen (altrenogest 0.044 mg/kg PO) has been shown to effectively prevent experimental endotoxin-induced abortion.[61] If the animal is treated while the pregnancy is still CL dependent (approximately before day 80), analysis of serum progesterone concentrations after the acute episode of the disease helps in deciding if the supplementation needs to continue. Serum progesterone concentrations of less than 1 ng/mL indicate the loss of an active CL, and supplemental progestagen treatment should continue until the fetoplacental unit is known to be capable of maintaining the pregnancy. For practical reasons, supplementation until day 100 is commonly recommended. Serum progesterone concentrations greater than 2 ng/mL are compatible with a functional CL, and the progestin treatment can gradually be discontinued. Treatments with flunixin meglumine or other prostaglandin inhibitors have not been proven to effectively prevent endotoxin-induced fetal losses unless the agents are administered before clinical signs appear.

Ruminants

Information on the major causes of abortion in cows, sheep, and goats is summarized in Tables 43.8 and 43.9.

TABLE 43.8

Major Causes of Bovine Abortion

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Bovid herpesvirus 1, IBR	Fifth to ninth months	Multifocal necrosis with intranuclear inclusions (liver, lung, spleen, kidney)	Histopathology, virus isolation, FA test of frozen fetal kidney
Bluetongue (orbivirus)	Any stage	Anomalies of skeletal and nervous systems	Pathology, virus isolation, fetal serology
BVD virus, pestivirus	Any stage	Anomalies of skeletal, nervous, cardiovascular,	Pathology, FA test on fetal tissues, fetal serology (virus neutralization, ELISA),

		respiratory, or other systems	serologic survey in herd
EBA, foothill abortion, deltaproteobacterium	Third trimester	Lymphadenopathy, splenomegaly, hepatopathy	Pathology, PCR
Brucella abortus, brucellosis, Bang's disease	Third trimester	Placentitis, fibrinous serositis, bronchopneumonia	Culture, maternal serology (card test, plate, or tube agglutination)
Campylobacter fetus subsp. *venerealis*, campylobacteriosis, vibriosis	Usually early embryonic death	Placentitis, fibrinous serositis, bronchopneumonia, hepatitis	Pathology, dark-field examination, culture (Clark media), smegma (Clark media)
Histophilus somni (formerly *Haemophilus somnus*)	Any stage	Placentitis	Histopathology, culture
Leptospira interrogans, leptospirosis	Fifth to ninth months	Icterus, edema, renal degeneration and inflammation	Fetal and maternal serology, FA in urine
Leptospira interrogans, listeriosis	Eighth or ninth month	Placentitis	Histopathology, culture
Salmonella Dublin, *Salmonella* Typhimurium	Third trimester	Placentitis	Culture
Aspergillus fumigatus and all fungal species, mycotic abortion	Third trimester	Placentitis, bronchopneumonia, dermatitis	Histopathology, fungal culture
Sarcocystis cruzi	Third trimester	Protozoa in caruncles	Histopathology or FA of caruncles
Tritrichomonas foetus, trichomoniasis	First half	Placentitis, bronchopneumonia	Microscopic demonstration of organism, culture (Diamond media), PCR
Bovine neosporosis	Mid-gestation	Similar to those found in toxoplasma-aborted sheep fetuses	Histopathology, seroepidemiology

BVD, Bovine virus diarrhea; *EBA,* epizootic bovine abortion; *ELISA,* enzyme-linked immunosorbent assay; *FA,* fluorescent antibody; *IBR,* infectious bovine rhinotracheitis; *PCR,* polymerase chain reaction.

TABLE 43.9

Major Causes of Abortion in Sheep and Goats

Cause and Common Names	Usual Stage of Gestation	Major Fetal Lesions	Diagnostic Tests
Bluetongue, orbivirus	Any stage	Anomalies of skeletal or nervous systems	Pathology, IFA, serology
Border disease, pestivirus, hairy shaker disease	Any stage	Dysplasia of skeleton, CNS, and fleece	Pathology, virus isolation, serology (cross-reacts with BVD)
Coxiella burnetii, Q fever	Near term	Necrotizing placentitis	Histopathology, microscopic demonstration of rickettsiae, complement fixation, ELISA

Chlamydia psittaci, EAE	Fourth or fifth month	Necrotizing placentitis	Histopathology, microscopic demonstration of organism, fluorescent antibody on fetal tissues or cultures, paired sera
Campylobacter fetus subsp. *fetus*, vibriosis	Last 6 weeks	Placentitis, serositis, multifocal hepatic necrosis	Pathology, microscopic demonstration of organism, culture
Toxoplasma gondii, toxoplasmosis	Any stage	Necrosis and calcification in cotyledons	Pathology, demonstration of organism, serology (e.g., agglutination, ELISA)

BVD, Bovine virus diarrhea; *CNS,* central nervous system; *EAE,* enzootic abortion of ewes; *ELISA,* enzyme-linked immunosorbent assay; *IFA,* immunofluorescent antibody.

In large commercial operations a low percentage of intermittently occurring abortions is considered acceptable; such abortions are considered “background abortions.” In beef and dairy operations 2% to 3% and 10% are considered acceptable, respectively. Abortion levels beyond these are considered abnormal and are usually investigated. When investigating bovine abortions, it is important to determine commonalities among abortion events, including stage of pregnancy affected, sire used, heifers versus cows affected, dates of new arrivals to the herd, season of year, vaccination protocols, presence of dogs, and management practices among different groups. Cows and heifers on the farm presumed to be pregnant should be evaluated to detect unobserved pregnancy losses. These examinations should document apparently normal, open animals who had previously been documented as pregnant, those with mummified fetuses, and those with pyometra. If possible, an entire fetus (or more than one) should be submitted for culture, serology, and histopathology. If the placenta is available, this should be submitted as well. If it is not practical to submit the entire animal and placenta, tissues including lung, stomach and contents, liver, spleen, and placenta should be collected and appropriately submitted for culture (chilled), viral isolation (frozen), and histopathology (formalin fixed).

Noninfectious Causes

Noninfectious causes of abortion in ruminants include the following:

- Heat stress
- Other stress
- Nitrate toxicity
- Malnutrition (rare)

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- Pine needle toxicity
- Drug induced (corticosteroids)
- Physical

Infectious Causes

Bovine Herpesvirus 1

Bovine herpesvirus 1 causes IPV and IBR. The latter disease is the major cause of bovine viral abortion.[1] IBR manifests as upper respiratory disease and abortion, and naive herds may experience abortion rates as high as 25% to 60% when exposed. The virus causes clinical signs in both dam and fetus. Immune dams exposed to the virus do not experience abortions. In naive animals the virus is carried in leukocytes and can become localized in placental tissues. Fetuses exposed to the virus usually die within 24 hours of placental infiltration. Although other stages of pregnancy may be affected, 5 to 6 months' gestation is the most susceptible stage. Fetal lesions include renal hemorrhagic edema; acute general necrosis in the liver, spleen, kidneys, lungs, and adrenal glands; widespread hemorrhage; petechia; epithelial destruction; and hepatic necrosis with intranuclear inclusion bodies. The amnion may be thickened without obvious signs of inflammation.

Diagnosis of IBR is by virus isolation from the placenta, identification of intranuclear inclusion bodies in fetal tissues, immunohistochemistry, or serum neutralization testing. If the latter is to be used, at least two samples must be taken days apart. The first must be negative and the second positive, or the first must be positive and the second titer must show a fourfold increase. Serum testing may not be helpful because the dam may have been infected months before the abortion and the titer after the abortion may actually be falling.

Prevention of disease is by vaccination (though infection and latency may occur despite vaccination). It is recommended to vaccinate heifers at 6 months and administer a booster 3 to 4 weeks before breeding. Vaccination too close to breeding can result in lowered conception rates due to normal, transient inflammation of the reproductive tract. A modified live virus is commonly used in pregnant cows from the third to eighth months of gestation, but its safety is questionable. A killed viral vaccine is available for pregnant cow use; a modified live virus vaccine labeled for intranasal administration is also available.[1]

Bovine Viral Diarrhea Virus

Bovine viral diarrhea virus (BVDV) is a pestivirus that can produce early embryonic death, fetal anomalies, or abortion (see Chapter 32 for complete discussion).[1]

History and Clinical Signs

Although fetal death is most common during the first trimester, abortion can occur at any stage of gestation.[2,3] Pathogenicity of the disease depends on gestational time of infection, the viral strain, viral biotype (cytopathic or noncytopathic), and fetal immunocompetence.[4] Often there is a history of repeat breeding and a recent episode of febrile disease in the herd before the onset of abortions.

Laboratory Diagnosis

Fetal loss generally occurs 10 to 27 days after exposure, with expulsion of the fetus up to 50 days later.[4] As a result the fetus is most often autolyzed, although in some cases it may be mummified or fresh. The aborted fetus may have a variety of dysplastic lesions, including cerebellar hypoplasia; cerebral malformations (hydrencephaly, porencephaly, microencephaly); cataracts; brachygnathia; arthrogryposis; alopecia; thymic hypoplasia; and intrauterine growth restriction.[2,5] Microscopic lesions include a mild nonsuppurative placentitis. Nonsuppurative vasculitis may be observed in the placenta, liver, or lymph nodes.

Virus isolation from fetal tissue is seldom successful, likely because of the protracted time before fetal expulsion generally occurs after infection. Viral antigen may be detected by FA test on kidney, lung, or lymph node. Virus neutralization and enzyme-linked immunosorbent assay are used to detect antibodies in fetal thoracic fluid, which indicate prenatal exposure to the virus but do not necessarily incriminate BVDV as the cause of abortion. Maternal titers are seldom of diagnostic value because a rise in titer generally occurs before abortion.

Pathophysiology

BVDV may be shed in most body secretions. The effects of exposure to BVDV vary greatly depending on the gestational time during which exposure occurred

(Fig. 43.8).[6] In seronegative cows, exposure to BVDV at the time of breeding prevents conception. Placental attachment at approximately 35 days' gestation seemingly must precede fetal infection. During the first 4 months of gestation, infection usually causes fetal death and abortion. Fetuses that survive infection with noncytopathic strains between 18 and 125 days of gestation will be persistently infected (PI), are typically seronegative at birth, and subsequently shed BVDV continuously.[4] They may develop mucosal disease later in life from superinfection with cytopathic BVDV.[7,8] Fetuses infected at between 100 and 150 days of gestation, considered congenitally infected (CI), are at risk for the development of dysplastic lesions, including teratologic defects in the brain, skin, or bronchioles. Fetuses infected after 150 days usually recover without dysplastic lesions.[2] Recent evidence, however, suggests that those fetuses born with neutralizing titers to BVDV are more likely to develop a serious illness within the first 10 months of life and less likely to conceive as heifers than those calves born without neutralizing titers to BVDV.[9,10]

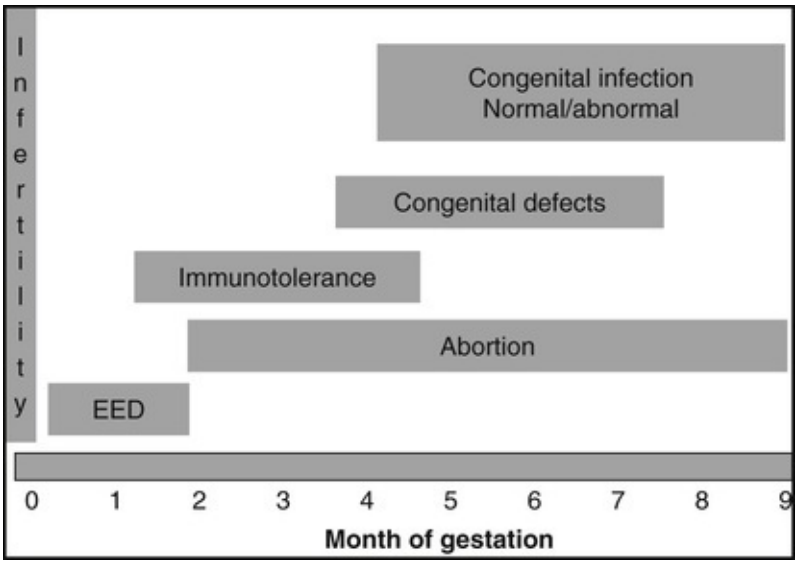


FIG. 43.8 Potential clinical reproductive outcomes after infection with bovine viral diarrhea virus. *EED,* Early embryonic death. (From Smith KC, Blunden AS, Whitwell KE, et al.: A survey of equine abortion, stillbirth and neonatal death in the UK from 1988 to 1997. *Equine Vet J* 35:496, 2003.)

Epidemiology

Most cattle have serum antibodies to the virus. The abortion rate may approach 25% with new infection of a susceptible herd.

Control

Killed and modified-live vaccines are available and are an important component of BVDV control, but BVDV is not fully controlled with vaccination. Herd health plans must focus on elimination of PI animals and prevention of new PI animals being introduced into the herd.

Leptospirosis

Leptospirosis is a spectrum of diseases caused by multiple serovars of *Leptospira interrogans*. *Leptospira hardjo* is the major serovar associated with bovine leptospiral abortion, although isolations of serovars *pomona*, *canicola*, *icterohemorrhagiae*, *grippotyphosa*, and *szwajizak* have also been reported.[11] Two serologically indistinguishable but genetically distinct types of serovar *hardjo* have been identified: *L. interrogans* serovar *hardjo* (type *hardjo-prajitno*) and *Leptospira borgpetersenii* serovar *hardjo* (type *hardjo-bovis*). Serovar *hardjo* type *hardjo-bovis* is cosmopolitan in cattle populations, whereas type *hardjo-prajitno* is isolated primarily from cattle in the United Kingdom.

History and Clinical Signs

In cattle, infection with serovar *hardjo* is associated with infertility, early embryonic death, abortions from 4 months of gestation to term, and birth of weak calves. Abortion rate is usually less than 10% but may approach 50% in some areas.[12] *L. interrogans* serovar *pomona* abortion usually occurs in the last 3 months of gestation, with an abortion rate as high as 50%. Clinical signs of leptospirosis in the cow may include icterus, hemoglobinuria, anemia, fever, and mastitis that is characterized by a flaccid udder and thick ropy secretions from all four quarters, but usually cows abort without clinical illness. Dead or weak calves may be delivered at term.[12] Abortions caused by serovar *hardjo* tend to occur sporadically rather than in storms (as may be seen with serovars *pomona* and *grippotyphosa*).

Laboratory Diagnosis

The aborted fetus is usually autolyzed, icteric, and edematous. Histologically,

renal tubular necrosis is accompanied by lymphocytic interstitial nephritis, pneumonia, and placentitis.

Leptospires are rapidly destroyed by autolysis or freezing. Isolation from fetal liver, kidney, or brain is possible but slow and impractical. Leptospires may be isolated or demonstrated by dark-field microscopy, FA staining, or histologic techniques in fetal or placental tissues or in the urine of the aborting dam within approximately 2 weeks after abortion.

Diagnosis is usually based on serology. A few infected fetuses develop microagglutination titers of 1:10 or more. It is difficult to distinguish among vaccinated, acutely infected, and recovered animals, but titers to serovar *pomona* greater than 1:12,800 in the dam suggest leptospiral abortion. Maternal titer has usually peaked by the time of abortion. Single titers of 1:800 or more in unvaccinated animals, seroconversion, or fourfold changes in titers in paired sera indicate leptospirosis in the herd. Titers to serovar *hardjo* are often less than 1:100 in affected cows and seldom exceed 1:1600.

Pathophysiology

Hematogenously spread leptospires colonize the gravid uterus up to 142 days after infection. Abortion occurs 1 to 6 weeks after acute disease with *L. pomona* infection and 1 to 3 months with *L. hardjo*. *L. hardjo* remains in the oviducts of infected cows for up to 22 days after calving.[12]

Epidemiology

Leptospira organisms are ubiquitous and an important cause of abortion in all cattle-producing regions. *Leptospira* organisms persist in the genital tract and kidneys. The organisms localized in the kidneys of infected animals are shed in the urine and serve as a source of infection for other animals. The organisms localized in the female reproductive tract are responsible for abortions. Aborted tissues are infectious to other animals and humans and should be handled with caution.[13,14]

Treatment and Control

In abortion outbreaks, pregnant cows can be vaccinated with killed bacterin and treated with oxytetracycline (antibiotic treatment can be limited to sick cows in dairy herds).[15] Aborting cows should be isolated from the rest of the herd, and aborted fetuses and placentas should be removed from the premises.[16]

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Preventing exposure to swine, rodents, and contaminated water lessens the opportunities for infection. *L. interrogans* serovar *pomona* usually has no permanent effect on fertility, but infection with serovar *hardjo* has been associated with persistent herd infection and recurring abortions.

Herd vaccination is recommended at 6-month intervals or more frequently in areas with heavy exposure to leptospires, such as dairies or beef operations with wet environments. Vaccination programs are aimed at reducing urinary shedding of leptospires and decreasing fetal loss. Vaccination is discussed in detail in the Leptospirosis section in Chapter 34.

Epizootic Bovine Abortion (Foothill Abortion)

Epizootic bovine abortion (EBA), or foothill abortion, is a syndrome of late abortions in cattle in the foothills bordering the central valley of California.[17] Once thought to be caused by *Chlamydia psittaci* or a spirochete-like organism, studies have demonstrated that EBA differs from chlamydial abortion.[17] After decades of research, a novel deltaproteobacterium, *Pajarellobacter abortibovis*, was identified as the causative agent of EBA in 2005.[18,19]

History and Clinical Signs

Late abortion or delivery of weak calves occurs in affected herds. Many fetuses in the sixth to seventh month of gestation may be aborted, especially from naive heifers that have not had natural exposure to the causative agent. Older native cows show no clinical signs of infection.

Laboratory Diagnosis

A 3-month period is required for full development of pathologic changes in the fetus. Superficial cervical lymph nodes are enlarged up to 16 g, the spleen is enlarged up to 250 g, the thymus is slightly smaller than normal, and the liver may be enlarged and nodular.[17,20] Histologically there is loss of thymic cortical lymphocytes; remaining lymphocytes are enlarged and poorly differentiated. Follicular hyperplasia, histiocytosis, vasculitis, necrosis, and pyogranulomas occur in lymph nodes and spleen. Lymphohistiocytic proliferation may also occur around vessels in the liver, lung, and meninges.

EBA has been diagnosed mainly by pathologic examination of the fetus along with a compatible clinical scenario. Studies have demonstrated high levels of

immunoglobulin G (IgG; 3 mg/mL or more) in fetal blood.[17] This deltaproteobacterium is detectable in fetal tissues with PCR, with reported sensitivity and specificity values of 88% and 100%, respectively.[18] Recent advances in real-time PCR assays are promising for diagnosis and may become the standard in the future.[21] Currently, serologic testing for EBA has promising results for identifying fetal infection, especially with fetal serum or precolostral serum in live calves. It may be difficult to distinguish immunity and recent exposure in adult cows and heifers.

Pathophysiology

Infection is transmitted by the soft-shell tick *Ornithodoros coriaceus* (pajaroello tick).[20,22] The disease can also be transmitted with fresh or frozen fetal tissue.[17] Transformation and proliferation of fetal lymphocytes and macrophages occur by 50 days but are not severe enough for diagnosis until 100 days after maternal exposure to the tick vector. IgG and IgM are deposited in vascular lesions, but an increase in fetal serum immunoglobulin is not detectable until at least 80 days after tick exposure.[17,21] Repeated superinfection may be necessary to result in fetal death.[20] Because at least 90 days are required for development of fetal lesions, infection after 6 months' gestation is not likely to result in abortion.

Epidemiology

EBA was limited to the range of the tick vector in the foothills bordering the central valley of California; however, it has also been identified in regions of Oregon and Nevada.[17,19] Of the annual calf loss in California, 5% to 10% is attributed to EBA.[22] The prevalence of infection by the spirochete is far greater than the prevalence of abortion.[20] Abortion occurs 3 to 4 months after exposure to ticks but almost always late in gestation, regardless of the time of tick exposure.[23] Older native cows from enzootic areas usually do not abort, and introduced cows and heifers generally abort only once.[17] The abortion rate may be 30% to 80% in susceptible animals.[23]

Treatment and Control

Currently no commercially available vaccine exists for EBA, but abortions can be controlled by exposing heifers to the tick vector before breeding or by changing from spring to fall calving, which takes advantage of limiting exposure

to the last trimester of gestation in some management systems. Therefore exposure of susceptible pregnant cattle to the tick only after the sixth month of pregnancy is a practical solution for ranchers using summer foothill pastures and fall calving. The tick lives in ground duff (e.g., leaves) and is not found on cattle that graze in irrigated pastures and most other areas outside of brushy foothills. Although chlortetracycline in feed has been used previously to reduce the rate of abortion,[22] such off-label use of antimicrobials in feed for cattle is no longer legal in the United States.

Brucella abortus Abortion

Brucella abortus is a gram-negative coccobacillus that is a facultative intracellular pathogen. Infection (Bang's disease) causes abortion in cattle and, less commonly, in sheep and goats.[24] Horses may be infected with *B. abortus*, which has been associated with fistulous withers, but usually experience no infertility or abortion. Bang's disease is an important zoonotic disease worldwide, particularly in developing nations.[24]

History and Clinical Signs

Abortion is the chief clinical sign of bovine brucellosis and usually occurs in the last trimester of gestation. Because of its highly contagious nature, outbreaks of abortion can occur in grouped pregnant cattle. Lameness, mastitis, epididymitis, and/or orchitis may be present in infected herds.[24] A foul-smelling, yellow to brownish exudate containing fibrin and necrotic debris may be expressed from the uterine lumen. Placentitis is a consistent finding. Cotyledons are necrotic; the intercotyledonary placenta is thickened and opaque with accumulation of odorless, flocculent, yellow-brown exudate between maternal and fetal membranes. Importantly, the affected placenta may show some normal placentomes and others with severe necrosis and hemorrhage.[24]

Laboratory Diagnosis

Histologically there is suppurative placentitis (and endometritis in the dam). Suppurative bronchopneumonia, serositis, and lymphoreticular hyperplasia are frequent histologic findings in the fetus.

Diagnosis depends on culture of *B. abortus* from fetal lung, abomasum, or placenta or from maternal uterine or mammary secretions. Organisms and

Brucella antigen can be detected in fetal tissues or placenta by immunofluorescent techniques. PCR and culture can be applied as well. Fetal abomasal fluid may be the optimal sample for PCR diagnosis.[25,26] A variety of serologic tests can be used to diagnose the disease in clinically or latently infected adults, including serum agglutination, card and buffered plate agglutination, complement fixation, and direct and indirect enzyme-linked immunosorbent assay (ELISA); the performance of these tests in infected and vaccinated herds has been reviewed recently.[26]

Pathophysiology

Initial replication of *B. abortus* occurs in regional lymph nodes. Bacteremia is followed by colonization of supramammary lymph nodes, the mammary gland, and the gravid uterus. Uterine infection occurs during the second trimester.[27] In the placenta the bacteria appear first in phagosomes of erythrophagocytic trophoblasts. Replication occurs in the rough endoplasmic reticulum of chorioallantoic trophoblasts.[27] Preferential replication in chorioallantoic trophoblasts has been attributed to their erythritol content.[24,28] The organism also occurs in fetal placental endothelial cells and capillary lumina, where it is associated with vasculitis and destruction of chorionic villi. Placental inflammation spreads along the allantochorion to involve additional cotyledons with resultant chorioallantoic ulceration, necrosis of trophoblasts, and ulcerative endometritis. Fetal death results from placental disruption and endotoxemia.[27] The fetus is frequently retained 1 to 3 days in utero. Numerous bacteria are expelled from the genital tract at parturition, but shedding usually stops by 3 weeks after abortion.

Epidemiology

Infection with *B. abortus* occurs naturally by inhalation or ingestion of bacteria present in aborted fetal membranes, fetuses, or postabortion vaginal discharge.[24] Contaminated materials are infectious for humans and should be handled with caution. Infection is not easily transmitted between cattle separated by fences or roads. Most calves infected at birth clear the infection, but persistent congenital infection has been documented.[29-31]

Bovine brucellosis has been nearly eradicated in the United States by test and slaughter of seropositive cattle and vaccination. However, a reservoir remains in

bison and elk, especially in the greater Yellowstone area.

Treatment and Control

Treatment of brucellosis is usually not effective. Combination therapy with long-acting oxytetracycline and streptomycin has been shown to reduce shedding in most cows and potentially eliminate infection in some,[32] but because eradication is typically a priority in most countries, infected cows are rarely treated. In the United States, infected individuals are destroyed, and exposed herdmates are quarantined to the herd until slaughter or the herd is recertified as brucellosis free.

In the past, strain 19 vaccine was used as part of the eradication program. However, vaccinated and field strain–infected cattle could not be differentiated. A newer vaccine for *B. abortus*, vaccine strain RB51, was developed to overcome the serologic problems associated with the strain 19 vaccine.[33] Animals vaccinated with RB51 lack antibodies to the *O*-polysaccharide chain and can thus be differentiated from field-infected cattle. Strain RB51 is also less abortifacient for cattle than strain 19, although vaccination of pregnant heifers may result in abortion and subsequent zoonotic exposure if obstetric assistance is necessary,[34] so the vaccine is to be administered only to young heifers before pregnancy.

Campylobacter fetus subspecies *venerealis* Abortion

C. fetus subsp. *venerealis* is a gram-negative flagellated bacterium that is the main cause of bovine campylobacteriosis (vibriosis, bovine genital campylobacteriosis).[35] The organism is an obligate parasite of the bovine genital tract and is not known to cause disease in other species.[35]

History and Clinical Signs

Infection with *C. fetus* subsp. *venerealis* mainly causes temporary infertility or early embryonic death, but sporadic abortions from the fourth to eighth months of gestation are possible.[1] The usual history includes a high percentage of cows exposed for the first time returning to estrus or found nonpregnant after the breeding season and cows calving late because they returned to estrus one or more times.

Laboratory Diagnosis

Autolysis is usually minimal, and the lungs of the term fetus may be partially inflated. Dehydration, fibrinous serositis, and necrotizing placentitis may be apparent grossly. Histologically, bronchopneumonia and hepatitis may also be evident. Diagnosis is based on demonstration or isolation of the organism. Using dark-field microscopy, the bacterium appears as a curved rod with darting corkscrew motility and can be differentiated from other *Campylobacter* spp. by immunohistochemistry.[1] Cows that abort may have serum antibody titers; however, they may not be diagnostic because they are not specific for *C. fetus* subsp. *venerealis*. Culture from placenta or fetal abomasal contents requires at least 72 hours. The vaginal mucus agglutination test is used to survey herds for infection. Alternatively, the penis and preputial mucosa of infected bulls may be swabbed and cultured, although culture is difficult because the organism is slow growing and often overwhelmed by saprophytes.

Pathophysiology

The bull is the primary reservoir of the organism; it resides subclinically in the crypts of the penis and prepuce.[35] Transmission is venereal. Within a week of vaginal infection the organism is established in the uterus, causing mucopurulent endometritis, which persists 3 to 4 months. Intrauterine infection either prevents conception or causes embryonic death, and infected heifers typically return to estrus by 40 days. Less commonly, abortions occur at up to 8 months of gestation.

Epidemiology

C. fetus subsp. *venerealis* is ubiquitous. Venereal transmission from infected bulls to virgin heifers approaches 100%. Cows with previous exposure to infected bulls develop immunity and therefore are less likely to experience infertility than heifers. The abortion rate can range from 10% to 50%.[35] Because persistent vaginal infection can occur, vaginal carriage into the next breeding season is possible.[35]

Treatment and Control

Infected cows usually recover spontaneously within 5 months and resist reinfection. Recovery is hastened by intrauterine infusions of streptomycin and

penicillin. Infertility may be permanent if endometritis or salpingitis is severe. Heifers should be vaccinated with a bacterin before breeding. Most vaccines are administered 1 month before breeding and require a booster vaccination 2 weeks later. Cows and bulls must be vaccinated annually. Exclusive use of *C. fetus* subsp. *venerealis*–negative semen via AI controls the disease by preventing transmission.

Histophilus somni Abortion

Histophilus somni (formerly *Haemophilus somnus*) has been associated with vulvitis, vaginitis, endometritis, weak calf syndrome, stillbirths, and occasional abortion in cattle.[36-41]

Laboratory Diagnosis

Aborted fetuses have been free of gross lesions. Necrotizing placentitis is associated with fibrinoid necrosis of placental arteries. Diagnosis is based on recovery of large numbers of the organisms in relatively pure culture from placenta or fetus, histologic evidence of placentitis, and lack of other apparent causes.

Interpretation of maternal titers to *H. somni* is difficult, and it is best to take paired serum samples. Titers between 1:256 and 1:512 in nonvaccinated herds may be the result of early active or chronic infection. Titers between 1:1040 and 1:4096 indicate recent active infection. A fourfold change in titer in paired sera is the best indicator of active infection.

Pathophysiology

Although *H. somni* can be isolated from the genital tract of clinically normal cows, the rate of isolation is higher in cows with endometritis or cervicitis.[41] Experimentally, *H. somni* can adhere to zona pellucida–intact embryos and cause degeneration.[38] Vaginitis can be induced by inoculation with *H. somni*,[39] and abortion has been induced by intraamniotic, intravenous, or intrabronchial challenge with the organism.[40]

Treatment and Control

Antibiotic treatment and vaccination anecdotally increase fertility in herds affected with *H. somni*–induced vulvovaginitis.

Listeria monocytogenes Abortion

Listeriosis is caused by *Listeria monocytogenes*, a ubiquitous, gram-positive, facultative intracellular bacterium.[42] Encephalitis, abortions, uveitis, and septicemia are other manifestations of infection in ruminants.

History and Clinical Signs

Bovine abortions usually occur in the last 2 months of gestation. Infected ewes and does typically abort in the last month. Fever, depression, RFMs, or endometritis may occur, but often the dam shows no clinical signs of infection.

Laboratory Diagnosis

In less severely autolyzed fetuses, fibrinous polyserositis may be apparent. Most aborted fetuses have gray-white hepatic foci up to 2 mm in diameter. Similar foci may be visible in cotyledons; exudation occurs between cotyledons. Abomasal erosions have been reported in aborted lambs. Histologically, suppurative placentitis and endometritis are consistent findings.

Listeria is readily cultured from abortuses without cold enrichment. *Listeria* appears in impression smears as gram-positive pleomorphic coccobacilli.

Pathophysiology

Listerial abortion can be induced experimentally in cattle 6 to 8 days after infection and in sheep 3 to 11 days after infection. Fetuses die from placentitis and septicemia and are often retained in utero several days before expulsion.

Epidemiology

Listerial abortion is usually sporadic, and incidence seldom exceeds 15%. Many outbreaks of abortion and encephalitis have been associated with feeding of silage.[42] The elevated pH of spoiled silage enhances multiplication of the organism.[42] However, nonensiled forages can be contaminated by *L. monocytogenes* originating in soil, wildlife or bird feces, or livestock manure, so exposure to silage should not be considered a necessary cause of this disease.[42] Aborted tissues are infectious for humans and should be handled with care.

Treatment and Control

The effect on fertility is usually transient, and aborting animals tend to resist

reinfection. Tetracycline may be used in remaining pregnant animals in the herd. Aborting animals should be segregated, and fetuses and placentas should be removed from the premises with strict hygienic protocols to limit human risk. Treatment and prevention of listeriosis is covered in detail in Chapter 8.

Mycoplasma Abortion

Mycoplasmal isolations from the bovine genital tract have been mainly *M. bovigenitalium* and *Mycoplasma bovis. M. bovis* is probably the more important cause of abortion.[43] *Mycoplasma mycoides* subsp. *mycoides* (see Chapter 31 for complete discussion) and *Mycoplasma capricolum* subsp. *capricolum* have been associated with caprine abortions.[44]

History and Clinical Signs

M. bovigenitalium is associated with granular vulvovaginitis and less commonly with endometritis, especially in heifers. Infertility is more common than abortion. *M. bovis* causes mastitis and abortion.[43] In goats, mycoplasmal infection is associated with septicemia, arthritis, pneumonia, mastitis, and abortion.[44,45]

Laboratory Diagnosis

Placentitis and fetal pneumonia have been associated with bovine mycoplasmal abortion.[43,45] Isolation of *Mycoplasma* from the genital tract, milk, placenta, or fetus indicates infection. However, mycoplasmosis should not be considered the cause of abortion unless placentitis or fetal inflammation is present and other more likely causes of abortion have been eliminated.

Pathophysiology

M. bovigenitalium can be isolated from the vagina in up to 12% of clinically normal cows, but *M. bovis* is isolated from less than 1%. Vulvitis can be induced by inoculation with mucosal scarification with *M. bovigenitalium;* therefore venereal transmission may be the natural route of infection.[43] Experimental inoculation with *M. bovis* induces abortion with placentitis and fetal pneumonia.[43,45] *M. bovigenitalium* is rarely isolated from abortuses or normal fetuses.

Epidemiology

Mycoplasma spp. are ubiquitous, but mycoplasmal abortions are not commonly documented.

Treatment and Control

Tetracycline, florfenicol, or macrolide antibiotics may limit losses in pregnant animals when *Mycoplasma* is implicated as the cause of abortion or granular vulvitis in herdmates.

Salmonella Abortion

A variety of *Salmonella* serotypes have been isolated from aborted fetuses of cattle, sheep, goats, and horses. A complete discussion of salmonellosis is presented in Chapter 32. Infection is acquired by ingestion or inhalation. Maternal septicemia is followed by localization of salmonellae in tissues, including the pregnant uterus, where placentitis and fetal septicemia occur. Salmonellosis accompanied by endotoxemia causes early pregnancy loss without colonization of the uterus because the infection and endotoxemia cause endogenous prostaglandin release.

History and Clinical Signs

The animal may show systemic signs before abortion. Although abortion may occur at any stage of gestation, it typically occurs in the second half and is characterized by placental necrosis, edema, and hemorrhage. RFMs and fetal autolysis may occur. Abortion may be accompanied by diarrhea, fever, or vaginal discharge, particularly in the ewe, but often infection is not clinically apparent in the dam.[46,47] Fetuses also may be lost as a result of stillbirth or perinatal septicemia.

Laboratory Diagnosis

The fetus is frequently autolyzed. Placentitis is usually present. Diagnosis is based on isolation of the organism and evidence of placentitis or inflammation of fetal tissues. Immunofluorescent techniques can identify the bacteria in impression smears or sections of placenta or fetal tissue. The dam can be tested serologically for evidence of recent active infection.

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Pathophysiology

Infected adult animals are often short-term carriers and shed salmonellae in the feces or milk. True long-term asymptomatic carriers occur mainly with the host-adapted serotypes: *Salmonella dublin* in cattle, *Salmonella abortus ovis* in sheep, and *S. abortivoequina* (or *Salmonella abortus equi*) in horses. Salmonellosis caused by *S. abortus equi* has been eradicated in the United States. Occasionally long-term carriers of other serotypes are seen; these are usually intestinal carriers and fecal shedders. Infection usually occurs by ingestion; there is no evidence of venereal transmission.[46] Maternal septicemia is followed by localization of the organism in a variety of tissues, including the pregnant uterus. The bacteria multiply in and cause necrosis of connective tissues of the cotyledon. The incubation period between infection and abortion varies from approximately 1 week to 1 month. Fetal death results from placentitis and fetal septicemia.[48] In most cases, maternal shedding of the organism in cattle ceases by 5 weeks after calving,[46] although longer-term shedding may occur with certain serotypes.

If infection and the resulting endotoxemia induce release of endogenous $PGF_{2\alpha}$, luteolysis and abortion will occur, but the fetus and placenta will not culture positive for *Salmonella* spp.

Epidemiology

Bovine abortion resulting from salmonellosis is caused mainly by *Salmonella dublin* and *Salmonella typhimurium.* Abortion is sporadic and most common in the summer and fall.[46]

Ovine abortion is associated with *S. typhimurium, S. dublin, Salmonella arizona,* and *S. abortus ovis*. *S. abortus ovis* is enzootic in parts of England and Europe but is not reported in the United States. Young ewes in late gestation are most susceptible, and the abortion rate may approach 50%.[47]

Treatment and Control

Aborting animals should be isolated; the fetus, placenta, and contaminated material should be removed from the premises. *Salmonella* spp. are infectious for humans; therefore aborted tissues should be handled with caution. Metritis is a rare complication of salmonellosis that can be fatal. Usually there is no lasting effect on fertility, but animals infected with host-adapted serotypes may become carriers and should be cultured and tested serologically and culled if positive.

Salmonellosis can be controlled by hygiene and by avoiding the introduction of carrier animals.

Ureaplasma Abortion

Ureaplasma is a small, ureolytic bacterium that lacks a cell wall. *U. diversum* has been associated with granular vulvitis and abortion in cattle.

History and Clinical Signs

Granular vulvitis appears as reddish nodules in the vulvar mucosa, with mucopurulent discharge in the early stages. The discharge is usually more copious and protracted than with IPV induced by herpesvirus.[43] Affected cows are not systemically ill. The organism has been recovered from embryo flushing media and can adhere to the zona pellucida, resisting removal by washing. It may reduce the pregnancy rate in embryo recipients when the transfer medium contains the organism.

Laboratory Diagnosis

Gross lesions include thickening of placental membranes with foci of hemorrhage and fibrinous exudate. Gross lesions are seldom apparent in the fetus. Microscopically the placenta is fibrotic, with heavy mononuclear cell infiltration, multifocal necrosis, fibrin deposition, and mineralization. Cuffs of lymphocytes surround fetal intrapulmonary airways. Diagnosis is based on isolation of the organism from genital mucosa, placenta, or fetal stomach or lung and the presence of genital or fetal inflammation.

Pathophysiology

Ureaplasma can be isolated from the genital tract of normal cows and from normal fetuses.[49] Vulvitis has been induced by inoculation of virgin heifers with *U. diversum*.[49] Intraamniotic inoculation of *U. diversum* caused placentitis, abortion, and fetal alveolitis in two of four experimental cows.[49] One cow delivered a weak calf at term. Experimental infection in ewes did not decrease fertility.[50]

Epidemiology

Bovine infection is common, but documented abortions caused by *Ureaplasma*

are rare.[43] Infertility is more common in heifers than in cows.

Treatment and Control

Nonirritating tetracyclines by intrauterine infusion are recommended for treatment. Uterine contamination can be avoided by use of the double-rod technique of AI.

Miscellaneous Bacterial Abortions

In addition to the aforementioned bacteria, other bacteria occasionally produce maternal septicemia and hematogenous abortion, as well as potential ascending infection of the gravid uterus. Many of these bacteria are ubiquitous, frequently contaminate aborted fetuses and placentas, and should not be considered the cause of abortion unless (1) they are isolated from the placenta and fetus in large numbers and relatively pure culture, (2) placentitis or fetal inflammation is evident, and (3) other more likely causes of abortion have been eliminated.

Tritrichomonas foetus

Trichomoniasis is a venereal infection of cattle caused by the flagellated protozoan *T. foetus*, which subclinically inhabits the prepuce, penis, and occasionally the urethral orifice of infected bulls; transmission to cows results in clinical disease.[51-53]

History and Clinical Signs

Infertility characterized by a high percentage of cows returning to estrus or found nonpregnant after the breeding season and cows calving late plus occasional pyometras and abortions are the most common clinical signs of trichomoniasis. Pyometra in postcoital heifers or cows suggests that trichomoniasis may be the cause and should be ruled out first. Abortions generally occur in the first half of gestation at a rate of 5% to 30%.[51] The placenta may be expelled or retained.

Laboratory Diagnosis

Diagnosis in the female is made by culturing trichomonads or using PCR to detect *Tritrichomonas* from cervicovaginal mucus, uterine exudate, placental

fluids, or fetal abomasal contents.[53] Preputial smegma collected from bulls by using a plastic pipette or commercially available sampling device run against the mucosa can also be cultured for trichomonads (sensitivity is 84% to 96% under experimental conditions[53]). Diamond's medium (or modified Pastridge medium) is recommended for cultures from cows, bulls, or aborted fetuses. The organism is sensitive to environmental conditions, and thus samples should be transported at ambient temperature, kept out of sunlight, not refrigerated, and delivered promptly to the diagnostic laboratory. The organisms are identified microscopically by their size (10 µm × 15 µm), the presence of three anterior flagellae and an undulating membrane, and a characteristic jerky, rolling motion. PCR and quantitative PCR (qPCR) are often used now for identification of *T. foetus* because of their ability to differentiate *T. foetus* from contaminant, nonpathologic trichomonads. Due to the ability of *T. foetus* to degrade its DNA postmortem, improper sample handling may lead to false-negative results on both culture and PCR testing.[54] Diagnostic testing of bulls using both culture and PCR may maximize sensitivity and specificity.[53]

There are no specific gross lesions in aborted fetuses. However, placentitis is a consistent microscopic lesion, and trichomonads can frequently be recognized in the placental stroma in histologic sections. Organisms may also be observed in the fetal lung in association with pyogranulomatous bronchopneumonia.[55]

Pathophysiology

Trichomoniasis is transmitted venereally from infected bulls to cows or vice versa. The organisms colonize the vagina, cervix, uterus, and oviducts; cervicitis and endometritis ensue. Embryonic death frequently occurs within the first 2 months of infection, followed by a 2- to 6-month period of immunity to reinfection. Clearance of infection in cows commonly occurs within 95 days; infection rarely persists for as long as 6 months.[51] However, infection in bulls older than 3 to 4 years of age is typically permanent and the main source of carryover from one breeding season to the next in beef cattle. Infection in younger bulls may be transient and related to the development of deeper mucosal folds in the prepuce as bulls age.[53]

Treatment and Control

Systemic treatment of infected animals with imidazole compounds (ipronidazole, dimetridazole) is effective, but these compounds are prohibited in

food animals in the United States.[56,57] Infected cows should be either culled or given at least 3 months of sexual rest. The use of AI with semen from *T. foetus*–negative bulls controls the disease once infected natural service bulls have been removed from the herd. In natural breeding situations, use of young virgin bulls and testing and culling of positive bulls older than 3 years of age will allow herd owners to gain control over the incidence of trichomoniasis. Vaccination of bulls and cows has shown some experimental benefit in limiting infection risk, but when all current research is evaluated extensively, vaccination appears to have very limited effect in reducing the risk of abortion.[53]

Neospora caninum Abortion

Abortion in cattle caused by *N. caninum* is relatively common and of economic importance, especially in dairy cattle. Congenital infection with limb paresis or dysfunction at birth as a result of encephalomyelitis may also occur. Canids are the definitive hosts and shed oocysts in their feces after ingestion of infected tissues from intermediate hosts (Fig. 43.9). Both the domestic dog and the coyote have been shown to transmit the oocysts in their feces.[58-60] Along with cattle, deer have been shown to serve as intermediate hosts.[60] The role of birds and wild rodents as intermediate hosts is suspected but has not yet been definitively demonstrated.[60] Aborted, infected fetal tissues ingested by canids will also result in massive shedding of oocysts in feces.[61] Transmission may be vertical (dam to fetus in utero) or via point-source horizontal transmission (ingestion of feed contaminated with feces containing oocysts).[62,63] Horizontal transmission from cow to cow does not occur. Bovine fetal lesions are distinctive and may include nonsuppurative encephalitis with foci of necrosis and gliosis, nonsuppurative myositis, hepatitis, and, most consistently, myocarditis.[37] Most abortions occur in the early second trimester, but they may occur throughout gestation. Diagnosis is based on characteristic lesions in aborted fetuses and seroepidemiologic study of an equal number of aborting and nonaborting herdmate cows if the proportion of seropositives is statistically higher in those that have aborted.[64] Finding one aborting cow to be seropositive does not confirm *N. caninum* as the cause, and cows that abort once because of *N. caninum* are not protected from future abortion caused by this organism.

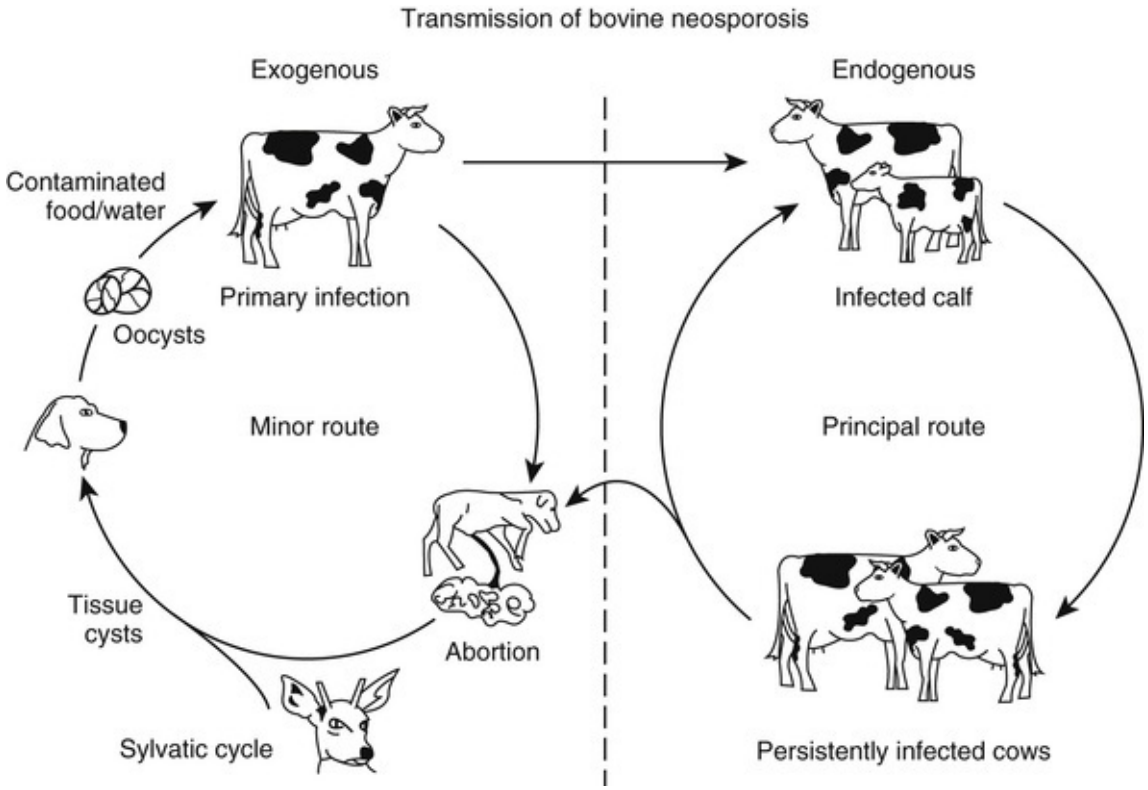


FIG. 43.9 Transmission of bovine neosporosis. Oocysts are produced by the canine definitive host, and their subsequent ingestion by a susceptible pregnant cow leads to infection of the fetus (exogenous transplacental transmission). Liveborn infected heifer calves would be expected to remain infected into adulthood, when they in turn may pass infection to their fetuses (endogenous transplacental transmission). Spread of *Neospora caninum* in this second way is the principal route whereby the parasite is propagated in a herd.

Sarcocystis Abortion

Sarcocystosis may cause abortion in cattle, sheep, and goats. Cattle are infected by *Sarcocystis cruzi*, sheep by *Sarcocystis ovicanis*, and goats by *Sarcocystis capracanis.*

History and Clinical Signs

Most cattle are infected with *Sarcocystis* but do not show clinical signs of infection; however, massive or repeated infections may elicit depression, anorexia, weight loss, lameness, hair loss, emaciation, or death. Abortions occur in late gestation, usually in severely affected animals.[65,66]

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Laboratory Diagnosis

There are no specific gross lesions in the aborted fetus. Histologically, protozoa may be observed in villi and small arteries of the cotyledon or (more likely) the caruncle but are seldom seen in the bovine, ovine, or caprine fetus. Parasites are more likely to be observed in the fetal brain than in other tissues.[65] Nonsuppurative inflammation may occur in the placenta or, less commonly, in fetal tissues, particularly the brain, heart, lung, liver, or kidney.[65,66]

FA demonstration of numerous developing protozoa in the cotyledon or caruncle is considered diagnostic. Caruncles are atrophied.[65]

Pathophysiology

The pathogenesis of abortion in sarcocystosis is unclear. Generally, numerous spores are required to induce abortion experimentally. Fetal invasion by *Sarcocystis* is rare, and abortion may result from maternal fever, anemia, or placental insufficiency.[65] Pregnant does apparently have diminished immunity to *Sarcocystis*, because low doses of *S. capracanis* result in fetal death without maternal illness if given in early pregnancy.[67]

Epidemiology

Ruminants are infected by consumption of canid feces that contain oocysts. *Sarcocystis* occurs in the skeletal and cardiac muscle of most cows without associated lesions or clinical evidence of illness.

Control

Effective therapeutic regimens for clinically ill animals have not been developed. For the life cycle of *Sarcocystis* to be broken, feeds should be kept free of dog or cat feces. These carnivores should not be allowed to eat aborted fetuses, placentas, or other ruminant carcasses.

Fungal Abortions

Mycotic Diseases That Cause Abortion

Fungal causes of bovine abortion include *Aspergillus*, *Absidia*, *Mucor*, *Rhizopus*, *Candida*, and *Mortierella*.[68,69] Mycotic abortion is uncommon in sheep and

goats.

History and Clinical Signs

Mycotic abortions usually occur in the latter half of gestation (often near term) and seldom are associated with prodromal or postabortion clinical signs in the dam.

Laboratory Diagnosis

The most consistent lesion is placentitis with necrosis and thickening of fetal membranes. In ruminants, both cotyledons and the intercotyledonary placenta are affected. Histologically, necrotizing inflammation of the chorionic villi is associated with vasculitis and thrombosis. Gross lesions may not be apparent in the fetus, but granulomatous bronchopneumonia is frequently observed histologically.[69] In bovine aspergillosis the fetus is often near term with minimum autolysis and partially inflated lungs. Emaciation and dehydration with multifocal dry, scaly skin lesions occur in approximately 25% of affected fetuses. The fungus can be isolated from the fetus and placenta or demonstrated on histologic sections with special stains.

Pathophysiology

The route of fungal infection in the bovine uterus is thought to be hematogenous.

Epidemiology

Mycotic abortion generally affects only one or two animals in a herd and is more common in the winter. Fungi cause 3% to 10% of bovine abortions.[70,71] *Aspergillus* spp. appear to be the most common fungal agent identified in mycotic abortion of cattle.

Control

The only means of control of mycotic abortion is reduction of exposure to fungal agents.

Does and Ewes

Infectious Causes

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See Table 43.9.

Bluetongue Abortion

Bluetongue is an orbivirus infection that can result in embryonic death, abortion, and fetal anomalies in sheep, cattle, or other ruminants. Twenty-six serotypes of bluetongue virus have been recognized; five of these (serotypes 2, 10, 11, 13, and 17) occur in the United States (see Chapter 32 for complete discussion).[72]

Border Disease (Hairy Shaker Disease)

Border disease or hairy shaker disease is an ovine pestivirus infection that causes embryonic and fetal death; stillbirths; dysplasia of the central nervous system, skeleton, and fleece; and birth of weak lambs with low viability.

Coxiella burnetii (Coxiellosis)

Coxiella burnetii is an obligate intracellular, pleomorphic bacterium that is related to the rickettsial family of bacteria.[73,74] It is the causative agent of Q fever, which is the disease in human beings; the disease in livestock is called coxiellosis.[74] Late-term abortions in sheep and goats, and rarely in cattle, are the primary clinical manifestation of disease. It is an important zoonosis worldwide. Subclinically infected ruminants are considered the primary reservoir of the agent.[73,74] A variety of domesticated animals, including dogs, cats, and pigs, can also be infected, most often subclinically.

History and Clinical Signs

Late-term abortions or delivery of stillborn or weak kids and lambs may occur in an affected herd or flock. Affected dams show little to no clinical signs of infection and are typically not ill prior to or after abortion. In cattle the most common manifestation of infection is conception failure and abortion.[74]

Laboratory Diagnosis

Hygienic measures, including barrier gowns, eye protection, and respiratory protection, are prudent when handling suspect animals, fetuses, fetal membranes, and contaminated bedding. There are no specific gross lesions in the fetus, but the placenta is thickened with white, chalky plaques and red-brown exudate, especially in intercotyledonary areas. Diagnosis of Q fever abortion should be

based on gross and histologic evidence of severe placentitis with large numbers of organisms visible using modified Koster stain, Stamp's modified Ziehl-Neelsen stain, or Gimenez stain. Culture of the organism is difficult; therefore PCR (ideally qPCR) can be used to detect the organism in the fetus, placenta, milk, or vaginal discharge.[73] It is important to note that *C. burnetii* can be shed in the birthing fluids of normal ruminants; however, it is present in numbers far lower than encountered when this agent causes these animals to abort.[74] Therefore, ideally, the diagnosis of *Coxeilla* abortion includes demonstration of compatible placental lesions, quantification of *C. burnetii* by qPCR, and documentation of the absence of other abortigenic agents. Serologic testing of aborting ewes and does (by ELISA, immunofluorescence assay, or complement fixation) typically shows seropositivity in aborting individuals, although titers may decline over time.[74] Importantly, both seropositive and seronegative small ruminants may shed the organism, so the use of serology in determining infection status is problematic.[74]

Pathophysiology

C. burnetii infection can be transmitted by infected ticks or by inhalation or ingestion of infected material. The organism replicates in trophoblasts, resulting in placentitis with late-stage abortion, stillbirth, or birth of weak offspring. Fetuses, fetal membranes, and uterine fluids from aborting animals contain massive numbers of the agent. The agent can persist in the environment as a durable sporelike particle called a small cell variant (SCV). These SCVs can persist in the contaminated environment and serve as a source of infection for naive animals.[74]

Epidemiology

Coxiellosis is reported in many countries worldwide. Abortions typically occur over a 2- to 4-week period and may affect 5% to 50% of the flock. Because of the agent's zoonotic potential, pregnant women, immunosuppressed individuals, individuals with preexisting illness, and those with vascular grafts should not handle *Coxiella*-infected animals or tissues or be exposed to contaminated environments, as risk of Q fever is increased in such individuals. Aerosolization and inhalation of SCVs appears to be the most common means by which humans become infected during ruminant abortion outbreaks.

Treatment and Control

As mentioned above, appropriate personal protective equipment is prudent when a suspected or confirmed abortion from *C. burnetii* is encountered. Aborting does and ewes should be segregated, and abortuses and placentas should be removed from the premises to prevent oral transmission. Farm cats and dogs should be kept out of contact with affected animals and their environment, as they may disperse the organism if allowed to feed on aborted materials. Affected animals should be situated on the premises so as to mitigate the risk of airborne transmission of SCVs to animals and people downwind of the area; an enclosed environment is ideal. Pregnant animals can be treated with tetracycline to reduce the chance of abortion, but further research on the efficacy of this measure is needed.

Vaccination of small ruminants is used in certain countries as a control measure. At present, no licensed vaccine is available in the United States or Canada, although provisional use in Canada may be allowed when the need is demonstrated.[74] In a recent meta-analysis of the scientific literature conducted by Canadian investigators, use of inactivated vaccine containing a specific phase I antigen of *C. burnetti* reduced the risk of shedding of the organism in previously exposed goats and reduced the number of organisms shed in birthing fluids in previously unexposed goats.[75] No effect on shedding risk was evident in vaccinated sheep.[75]

Cleaning and disinfection require removal of contaminated bedding and disposal by burial, burning, or composting. Soap and water scrubbing, followed by rinsing and application of an appropriate disinfectant (quaternary ammonium, 1% peroxygen, or 1:100 dilution of bleach), may reduce the environmental burden of SCVs. Appropriate personal protective equipment should be used by the personnel conducting cleaning and disinfection.

The potential for repeated reproductive loss and long-term carriage of the organism is a topic of active ongoing research. In one study goats were demonstrated to be capable of repeated reproductive failure and shedding of *C. burnetii* in two successive birthings.[76] Strategies to manage abortion and mitigate further risk of abortion in affected herds and flocks are included in a recent review.[74]

Campylobacter fetus subspecies *fetus* Abortion

C. fetus subsp. *fetus* is one agent of ovine campylobacteriosis (vibriosis) that

causes abortion in sheep and sporadic abortion in cattle and goats.[35,77]

History and Clinical Signs

Infection of ewes causes abortion in the last 6 weeks of pregnancy, stillbirths, and birth of premature lambs. Infected ewes may have fever, diarrhea, depression, and vaginal discharge several days before parturition.[35,77] In cattle the infection is not associated with infertility (unlike infection with *C. fetus* subsp. *venerealis*), but sporadic abortions can occur.[35]

Laboratory Diagnosis

Campylobacter causes necrosuppurative placentitis and multiorgan infection of the fetus. The fetus is edematous and may be pot-bellied in appearance. Multifocal, circular, pale foci—resembling donuts or targets—may be visible in the liver of roughly 25% of aborted ovine fetuses, and although these lesions are not pathognomonic, their presence is strongly suggestive of campylobacteriosis.[35,77] Diagnosis is based on culture, PCR, or microscopic demonstration of the organism. Dark-field microscopic examination of wet mounts of fetal stomach contents or placenta may demonstrate the organism, which has a characteristic corkscrew shape.[35] Histologic changes include suppurative necrotizing placentitis and pneumonia, gastroenteritis, hepatitis, and serositis in the fetus.[35]

Pathophysiology

C. fetus subsp. *fetus* is transmitted by ingestion. It then translocates across the intestinal mucosa into the bloodstream, ultimately infecting the placenta and fetus.[35] The incubation period is highly variable, ranging from 13 to 113 days (most commonly 14 to 21 days). The timing of initiation of infection appears to influence the incubation period.

Epidemiology

Infection with *C. fetus* subsp. *fetus* is important in sheep in the United Kingdom, the United States, and New Zealand. Fetal infection is most common during the last 2 months of gestation. Outbreaks of abortion tend to occur in 4- to 6-year cycles.[77] Infection is highly contagious in confined ewes, and the abortion rate may approach 70%.

Treatment and Control

Abortion outbreaks due to *C. fetus* subsp. *fetus* may be treated with tetracyclines or macrolides. Tetracycline-class antimicrobials may not be effective against North American strains of *Campylobacter jejuni*, which is clinically indistinguishable from *C. fetus* subsp. *fetus*. Thus speciation of the isolate and antimicrobial susceptibility testing are critical to appropriate antimicrobial treatment.[35,77] The efficacy of vaccination prior to the breeding season, as well as in the face of an abortion outbreak, appears to be quite variable and may depend on the degree of similarity between the vaccine and the abortigenic strain of *C. fetus* subsp. *fetus*.[35]

Campylobacter jejuni Abortion

C. jejuni is the other agent of ovine *Campylobacter (Vibrio)* abortion. *C. jejuni* is an enteric pathogen that causes enteritis and diarrhea in many species. Only in sheep is placental and fetal infection common. This organism has been associated occasionally with abortion in cattle and goats.[77-79]

History and Clinical Signs

Ovine infection with *C. jejuni* is clinically indistinguishable from that with *C. fetus* subsp. *fetus.*

Laboratory Diagnosis

Lesions in placental and fetal tissues and diagnostic testing strategies are identical to those for *C. fetus* subsp. *fetus.*

Pathophysiology

Intravenous inoculation of pregnant ewes with *C. jejuni* at 114 and 123 days of pregnancy consistently induced abortion 7 to 12 days later.[80]

Epidemiology and Control

C. jejuni is ubiquitous and can be identified in the gastrointestinal tract of normal sheep.[35] Abortion rates in excess of 25% are common, although the rate of abortion appears to vary among strains of this organism.[77] Aborted tissue is infectious for humans and should be handled with caution. Treatment and

control of ovine infection with *C. jejuni* are similar to those for *C. fetus* subsp. *fetus.* It should be reiterated, however, that most isolates of *C. jejuni* in North America are tetracycline resistant, so treatment of the remaining pregnant animals with macrolides or florfenicol is advisable.[81] The protection afforded by commercially available *C. jejuni* vaccines appears variable and is not complete.[35,81a]

Brucella melitensis Abortion

Brucella melitensis causes abortion in goats and sheep and less commonly in cattle.[81b] Infection is associated with late abortion, stillbirth, or birth of weak kids or lambs. Necropsy findings include severe placentitis and fetal serositis. The disease is diagnosed by culture or demonstration of the organism in tissue or by maternal serology, although immunization is practiced in some countries, and this can interfere with interpretation of serologic tests.[81b] Infection with *B. melitensis* is important in Mediterranean countries and in Central and South America. Suspected cases should be reported to state and federal authorities, as this is currently exotic to the United States. Human infection with *B. melitensis* can be severe.

Brucella ovis Abortion

Brucella ovis infects only sheep. Epididymitis in rams is the most common manifestation of infection.[82] Ewes seldom show clinical evidence of infection; late abortions, stillbirths, and delivery of weak lambs can occur but are very rare.[82] Fetal and placental lesions resemble those induced by *B. abortus.* Notably, *B. ovis* has not been documented to be a zoonotic pathogen.

Chlamydophila abortus Abortion (Enzootic Abortion of Ewes)

Chlamydophila abortus (formerly known as *Chlamydia psittaci*) is a gram-negative, obligate intracellular bacterium that is a major cause of abortion in sheep and goats.[77,83] Ovine chlamydial abortion is called *enzootic abortion of ewes.*

History and Clinical Signs

Late-term abortions or stillbirths with placentitis are characteristic findings.

Offspring may be born alive but weak.[77] The dam seldom shows signs of illness but may have serosanguineous vaginal discharge several days before and after parturition.

Laboratory Diagnosis

Placentitis is the most consistent necropsy finding in chlamydial abortion. The placenta is markedly thickened with necrosis in the cotyledon and intercotyledonary areas; hemorrhagic exudate may be evident at the edges of these lesions.[77] The fetus has no specific gross lesions and may be fresh, necrotic, or, rarely, mummified.[77]

Diagnosis of *Chlamydophila* abortion should be based on identification of the organism and the presence of typical placental lesions. Organisms appear in placental impression smears stained with Giemsa, Gimenez, or modified Ziehl-Neelsen stain as spheric bodies in the cytoplasm of trophoblasts. The organism can be positively identified by FA tests or by PCR.

Pathophysiology

Chlamydophila spp. reside in the intestinal tract and are also shed from the genital tract of infected animals before and after parturition. Ingestion is the main form of transmission, resulting from exposure to aborted tissues, contaminated environment, or vaginal discharge. Transmission by infected rams and bucks appears possible. The incubation period appears to be long (60 to 100 days).[77]

Epidemiology

Chlamydophila abortion has been reported in most major sheep- or goat-producing countries. The abortion rate in sheep is usually approximately 5% to 10% but may be up to 30% or more in goats. *C. abortus* also may infect other animals, including human beings.[77,83] Pregnant women or immunosuppressed individuals should not handle infected animals or tissues, and personal protective equipment appropriate for *C. burnetii* exposure should be considered for individuals handling infected animals, aborted tissues, or contaminated bedding.

Treatment and Control

Aborting does or ewes should be segregated, and abortuses and placentas should

be removed from the premises to avoid oral transmission. Oxytetracycline therapy (80 to 450 mg/head every day in feed or water) has been used where allowed by law.[84,85] Long-acting oxytetracycline injected subcutaneously at a dose of 20 mg/kg and repeated every 2 to 3 weeks may prevent further abortions.[77] Vaccination may confer variable levels of protection, with the temperature-sensitive mutant vaccine available in Europe appearing to be more promising than the inactivated vaccines currently available in North America.[77] Vaccination is described further in Chapter 48.

Toxoplasmosis Abortion

Toxoplasma gondii is a ubiquitous protozoan that is a major abortifacient in sheep and goats but only rarely causes abortion in cattle or horses. Exposure to kittens is an expected component of the history, either through direct contact or fecal contamination of feed or water. The organism is transmitted to sheep and goats by ingestion of oocysts present in feline feces.[77] Cats shed heavy numbers of oocysts in the first 2 to 4 weeks after becoming infected by ingestion of infected rodents, birds, carrion, or aborted fetuses and tissues.[77]

History and Clinical Signs

Infection does not cause clinical illness in the adult but may result in embryonic death, fetal death and abortion, stillbirth, or birth of weak, nonviable lambs or kids. Mummification of fetuses may occur, and mummified fetuses may be aborted along with stillborn or weak but live newborns.[77]

Laboratory Diagnosis

The most characteristic gross lesion of toxoplasmosis is the presence of white, chalky foci of necrosis and calcification up to 2 mm in diameter in cotyledons.[86,87] The intercotyledonary areas of the placenta are grossly normal. Specific gross lesions may not consistently exist in the aborted fetus, but histologically most have nonsuppurative encephalomyelitis,[87] and many also have pneumonia, myocarditis, or hepatitis. Tachyzoites may be found in placenta or other fetal tissues but are not numerous.[88,89] The tachyzoites are oval (2- to 4-mm × 4- to 8-mm) with a central nucleus and appear larger in impression smears than in paraffin sections. Several serologic tests, including the modified agglutination test, indirect FA test, Sabin-Feldman dye test, indirect

hemagglutination test, and ELISA, reliably detect toxoplasmosis in pleural or amniotic fluid or presuckling serum from nondecomposed fetuses.[90,91] The modified agglutination test is commercially available, safer, and more sensitive than the dye test. Fetal antibodies to *T. gondii* can be detected 35 days after infection.[86] Absence of fetal antibody does not always preclude a diagnosis of toxoplasmosis. High maternal titers are not diagnostic of toxoplasmal abortion, but lack of titer eliminates toxoplasmosis as the cause for abortion.[86] The peroxidase-antiperoxidase method for detecting *Toxoplasma* antigen in fetal tissues or placenta is reliable even in autolyzed fetuses. Fetal heart, lung, brain, spinal cord, skeletal muscle, and placenta are the preferred specimens for the peroxidase-antiperoxidase method and should not be held in formalin more than 2 days before paraffin embedding.[89]

Pathophysiology

Placental infection occurs approximately 14 days after ingestion of oocysts.[89] Infection acquired before 50 days' gestation may result in embryonic death and resorption. Infection between 60 and 100 days' gestation usually causes fetal death or birth of weak lambs. Infection during the last month of gestation often has no apparent effect on the fetus.[86] In experimental infection of ewes between 6 and 14 weeks of pregnancy, abortions occurred 1 to 2 months after inoculation.[91] In natural infections, most abortions occur 1 month before parturition.[86]

Epidemiology

Toxoplasmosis is a major cause of ovine abortion in many sheep-raising countries, including the United States.[87,88] Sheep are infected by ingestion of oocysts from feed, water, or grass contaminated with cat feces. Aborted tissues may be infectious for humans and should be handled with caution.[92]

Control

Infected ewes or does seldom abort from toxoplasmosis in subsequent pregnancies.[87] The prevalence of abortion can be reduced by avoiding contamination of foodstuffs with feline feces. Cats should not be allowed to eat placentas or carcasses that may contain tachyzoites or tissue cysts. Farm cats should be spayed or neutered to limit birth of young, susceptible kittens. In

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endemic areas, exposing replacement ewes to aborting ewes or cat feces before breeding age may induce immunity.

Camelids

The incidence of abortion in llamas and alpacas is low. Infectious causes in North America include leptospirosis, toxoplasmosis, chlamydophilosis, and other nonspecific uterine infections. Bovine virus diarrhea is considered an emerging disease in alpaca herds and may be responsible for some of the early pregnancy losses and abortions in some herds. Diagnostic work-up for abortion in camelids is similar to that described in this chapter for other species.

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▪ Male Reproductive Disorders

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Infertility Caused by Diseases of the Penis and Prepuce

Penile Injury

Stallion

Definition and Etiology

If the penis is injured while erect, it may swell rapidly and massively from vascular rupture and hemorrhage. Hemorrhage usually originates from the superficial penile vessels in the plexus external to the tunica albuginea.[1] The stallion may be kicked during mating, or hematomas may follow breeding a mare with a tightly sutured vulva or may be induced if the mare moves suddenly during mating.[2,3] Injuries can also occur during semen collection if proper techniques are not used.

Clinical Signs and Differentials

Cutaneous abrasions, lacerations, and visible hemorrhage may be present. Paraphimosis occurs when enlargement is sufficient to prevent retraction of the penis through the preputial ring.[1] Edema may extend to the scrotum and interfere with thermoregulation of the testes.[4] Venous thrombosis, lymphatic occlusion, excoriation, and swelling accompany chronic inflammation.[1] Hemorrhage from the corpus cavernosum penis (CCP) is uncommon. Rupture of the surrounding tunica albuginea, when healed, may develop fibrous adhesions that lead to penile deviation during erection.

Treatment and Prognosis

Immediate treatment is directed toward reducing edema and inflammation, as well as controlling infection. Treatment is similar to that described in the Paraphimosis section later in this chapter. Sexual rest is indicated until the lesions have healed.[5] If treatment is initiated early and paraphimosis does not occur, the prognosis for recovery is good.[1,3]

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Bull

Definition and Etiology

The penis of bulls is susceptible to injury during mating. The vigorous thrust that accompanies copulation predisposes the penis and prepuce to excoriations, lacerations, and bruising. Rupture of the tunica albuginea (penile hematoma or “broken penis”) occurs if the penis is misdirected during copulation.[6] Penile hematomas most commonly occur in young, sexually aggressive bulls. Injuries occur when these bulls attempt to breed heifers or cows that are not receptive, when females falter or collapse under the weight of the bull, or when the bull slips because of poor footing.[2] During copulatory thrusting in which the penis is bent, the tunica albuginea ruptures on the dorsal or dorsolateral surface of the penis opposite the attachment of the retractor penis muscle. Presumably, CCP pressure rapidly increases as the functionally closed system is compressed during bending to rupture the tunica albuginea. Experiments with fresh postmortem specimens indicated that a CCP pressure of 1180 to 1720 psi was required to rupture the tunica albuginea. Tearing virtually always occurred at the site described in naturally occurring cases. Mean peak CCP pressure recorded during normal coitus (275 psi) occurs when cavernous spaces fill with a relatively small volume of blood, perhaps as little as 110 mL.[6] Blood escapes from the CCP into the surrounding tissue.[1] The size of penile hematomas may be related to the number of repeated trials made by the bull before cessation of attempts at mating. Larger hematomas restrict full retraction of the penis and result in prolapse of the prepuce from the sheath. Secondary preputial injury is common.[1]

Clinical Signs and Differentials

Diagnosis of penile hematoma is made based on the presence of a swelling immediately cranial to the scrotum. Initially it is soft, fluctuant, and painful, and it becomes firm as clot organization and fibrin formation progress.[2] The main differential diagnosis is extensive preputial laceration. If a distance of more than two handbreadths is present between the scrotum and the enlargement, the swelling is more likely to be a preputial laceration. Other differential diagnoses include rupture of the urethra, abdominal hernia, and chronic, fibrous adhesions. Dysuria usually does not occur in conjunction with penile hematoma. Other signs of urethral rupture or blockage, such as extensive preputial cellulitis and

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“water belly,” elevated blood levels of urea nitrogen and creatinine, and tissue necrosis, do not occur. Abscess formation of penile hematomas sometimes occurs. A soft, fluctuant center is characteristic of an abscess. Occasionally, differentiation between blood clot and abscess may be difficult. An aseptic tap can be done to determine the character of the fluid, but the risk of inducing an abscess in a sterile hematoma is high and a tap should be used only as a last diagnostic resort or just before surgery.

If penile hematoma has been present for longer than 2 weeks, fibrous adhesions may form that prevent penile extension. Adhesions are frequent sequelae to an abscess and have also been reported to occur secondary to infiltration of local anesthetics to block the dorsal nerves of the penis.[2] Another sequela is the development of venous shunts that communicate between the CCP and either peripenile vasculature or the corpus spongiosum penis (CSP).[1,7] Such vascular shunts result in rapid drainage of blood from the CCP and impotence caused by failure to achieve or maintain full erection. If the dorsal nerves of the penis are damaged, sensation of the distal penis is lost or deficient and results in failure of the bull to successfully seek out the female's vagina and/or ejaculate. Organization of the portion of the blood clot (thrombosis) within the body of the CCP may result in functional blockage of engorgement of the more distal cavernous spaces, preventing full erection.

Treatment and Prognosis

Treatment of penile hematomas should be aimed at not only restoring the bull to usefulness but also preventing recurrence. Approximately 50% of bulls with hematomas that are treated conservatively (i.e., nonsurgically) are reported to return successfully to breeding.[1] Some theriogenologists believe that small hematomas (less than football size) do not require surgery.[8] However, surgical correction has the advantages of (1) removing the blood clot before extensive fibrous adhesions develop; (2) permitting removal of a blood clot from within the body of the CCP itself, thereby reducing the chance of blockage of cavernous filling; and (3) suturing the tunica albuginea, which should reduce the chance of recurrence of the condition after return to service and the likelihood of developing vascular shunts that will prevent complete filling of the CCP. Surgical intervention is not recommended before coagulation of the extravasated blood. Once significant fibrin formation is present, the prognosis for successful correction is greatly reduced and should be attempted only in valuable bulls.[1]

Additional recommendations before electing surgical intervention include extending the penis manually. Cases in which the penis can be extended from 6 to 8 inches or more beyond the sheath orifice, and in which penile sensation remains, carry a better prognosis.[9] If engorgement of the distal penis does not occur after careful stimulation with the electroejaculator, blockage of the CCP should be suspected and reduces the prognosis. Finally, cases with abscesses are poor risks because severe restrictive adhesions usually develop.[1]

Regardless of whether surgical or conservative intervention is selected for a penile hematoma, the bull should be treated with high levels of systemic antibiotics in an attempt to prevent abscess formation. Penicillin is a good choice because abscesses are usually caused by *T. pyogenes*. Postsurgical complications are much the same as those that may occur without surgery, but these adverse consequences are reported to occur less frequently after surgery. Bulls should not be returned to service for 2 to 3 months after treatment.[1,2]

Ram and Buck

Adhesions of the penis and prepuce caused by trauma are uncommon in adult small ruminants. The penis does not separate from the prepuce until puberty and cannot be extended before this time (4 to 5 months of age in bucks).[10] Most traumatic lesions of the penis or prepuce in sheep and Angora goats are from shearing injuries.[11] Blockage of the urethral process by calculi can cause necrosis and sloughing of tissue that may extend into the glans penis.[11] Fighting among horned animals may result in injury to the external genitalia, including the penis. In dairy goats the intersex condition can result in congenital malformation of the penis and prepuce (hypospadias).[12]

Phimosis and Injury to the Prepuce

Stallion

Definition and Etiology

Stenosis of the preputial orifice can prevent extension of the penis. The defect is likely to be a sequela to an injury that results in cicatrix formation but may rarely be congenital.[1,2] Tumors (such as melanoma or squamous cell carcinoma) or *Habronema* granulomas may encroach on the preputial cavity, thereby

preventing penile extension.[13]

Clinical Signs and Differentials

Acute posthitis often accompanies injuries to the prepuce or infections such as equine coital exanthema and dourine.[1,2] Edema is common with acute posthitis, particularly after trauma. Gravitational effects typically worsen the preputial edema, which may induce prolapse of the external prepuce, trapping the penis in the swollen internal prepuce with a constricting preputial ring.[1] Cicatricial scar formation may follow, narrowing the diameter of the preputial orifice. Transpreputial ultrasound examination may be of benefit in differentiating tumors or abscesses from inflammatory edema or hemorrhage. Containment of the penis within the prepuce causes preputial urine accumulation, worsening balanoposthitis and secondary bacterial infection. The extended chronic inflammation leads to cicatrix formation with phimosis.

Treatment and Prognosis

Preputial edema can be relieved by administration of diuretics and exercise. Application of crushed ice in plastic bags, or preputial immersion in cold water, may reduce inflammatory edema if applied soon after injury. Subsequently, application of emollient antibiotic preparations and hydrotherapy can be used to massage injured tissues and reduce edema. Systemic antibiotics and nonsteroidal antiinflammatory drugs are indicated to control secondary infection and inflammation. Sexual rest is indicated until the lesions have healed.[5]

A biopsy can be procured from encroaching tumors to identify cell types and improve prognostic capability.[5] Cicatricial scars can sometimes be successfully removed surgically. Once inflammation and infection are resolved with local or systemic antibiotic and antiinflammatory drug treatment, incision of the ventral aspect of the preputial orifice (preputiotomy) may be necessary to enlarge the opening sufficiently to permit penile extension. Large tumors or granulomas of the prepuce can sometimes be successfully removed surgically if sufficient elastic and membranous tissue remains to permit normal penile extension and retraction.[5] The prognosis for return to breeding soundness, however, is guarded when surgery must be performed. Postsurgical adhesions may develop that result in continued phimosis or penile deviation. In cases of habronemiasis, treatment with systemic insecticides or ivermectin may be indicated to kill remaining parasitic larvae.[13] Congenital abnormalities can seldom be corrected surgically.

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Bull

Definition and Etiology

Trauma to the prepuce involving the elastic lamellar layers may prevent the required flexibility of the prepuce to permit penile extension. Breed predisposition to preputial injuries corresponds to genetic differences in pendulousness of the sheath and development of the muscles responsible for retraction of the prepuce. The polled gene is linked to weak or failed development of the preputial muscles, leading to habitual preputial eversion, which predisposes to injury. Brahman-blooded cattle have the added predisposition of a loose, pendulant sheath. With their tendency to partially evert the preputial membrane through the sheath orifice, they are at greater risk of damaging the prepuce accidentally than are those breeds of cattle in which the sheath is held in close apposition to the abdominal wall.[1,2,14]

Inability of the bull to extend the penis most commonly follows injury to the penis and prepuce that culminates in strictures or adhesions that restrict normal penile movement.[15,16]

Other causes of phimosis include congenital anomalies such as a short penis, a short retractor penis muscle, and developmental abnormalities of the reproductive tract such as occurs in pseudohermaphrodites.[2]

Clinical Signs and Differentials

The more common preputial injuries are contusions, abrasions, lacerations, and frostbite. When the injured prepuce can be retracted, the injury may not be suspected unless hemorrhage is noted from the sheath or the bull is observed having difficulty during breeding. Although minor injuries may spontaneously resolve, more extensive injuries commonly progress to abscess formation and fibrous stricture formation.[1,8,15,16] Extension and examination of the penis may result in further injury if the case is complicated by phimosis. In such cases an attempt to extend the penis to facilitate examination is contraindicated because forcibly stretching the prepuce will extend the laceration and spread infection to uncontaminated areas.[1]

Treatment and Prognosis

Treatment of preputial injuries in the bull may be either medical or surgical.

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With few exceptions, such as fresh avulsive lacerations in the fornix area, surgical intervention carries a better prognosis when medical treatment is first carried out to control inflammation and infection.[15] The healing leaves more normal tissue to be identified and salvaged during surgery. In cases in which the injured prepuce is retracted into the preputial cavity, digital, speculum, or endoscopic examination can be done in an attempt to locate lesions and determine the extent and depth of tissue involvement. Systemic administration of antibiotic is necessary to reduce the incidence of abscess formation preoperatively, and antibiotic should be administered through the surgical and postsurgical periods if surgery is elected. When the injured prepuce remains prolapsed in presented bulls, the first consideration is to attempt to return the prepuce to the preputial cavity.[1,15] The exposed epithelial covering of the prepuce is easily injured and becomes quite edematous and friable because of its pendent location. Hydrotherapy for 20 to 30 minutes may be helpful in cleansing the exposed prepuce and reducing edema. After gently cleansing the prepuce and determining the degree of patency of the lumen, a protective emollient preparation is used to massage edematous swelling upward out of the prolapse.[15] Massage for 15 to 30 minutes may be required to reduce swelling sufficiently to permit the prepuce to be returned to the preputial cavity. If the prolapsed prepuce can be returned to the sheath, a retention technique should be used to prevent reprolapse. With the prepuce in place, a tube can be inserted just beyond the swollen internal portion of the prepuce to avoid urine retention. The tube is taped in place at the external preputial orifice. Tape should not extend past the proximal end of the tube or urine retention and migration into peripreputial tissue will occur. If this technique will not retain the prepuce, a purse-string suture in the skin of the sheath orifice can be used.[1] It should be tight enough to retain the prepuce but leave sufficient space for urine to pass freely. To avoid suture abscesses and stricture formation, the sheath should be clipped and prepared aseptically for suture placement, and sutures should be removed as soon as swelling and inflammation subside. If the prolapsed prepuce cannot be returned to the preputial cavity, the prognosis for correction without surgery is guarded. After cleansing as described previously, a portion of stockinette is coated in ointment and applied over the prepuce. A diaper constructed from heavy canvas, netting, or burlap with straps and centrally located perforations for urine drainage is applied under the prepuce and tied up over the back to hold the prepuce gently next to the abdominal wall to decrease gravitational edema. It is changed daily until infection and swelling are controlled and the prepuce is

either returned to the sheath or surgery is performed. Alternatively, the prolapsed portion of the prepuce can be wrapped in medicated gauze followed by application of a gentle but firm pressure wrap around a section of tubing. The pressure wrap is left in place temporarily to reduce edema, at which time the wrap is removed and the prepuce is replaced into the sheath.[15]

Once sufficient healing has occurred, the need for surgery is determined by extending the penis.[1] Adhesions most commonly take the form of encircling cicatricial strictures that must be removed surgically. Guidelines suggested for predicting successful outcome of surgery include the following: (1) a minimum of 5 cm of normal prepuce should be present on either side of the surgical site or proper unfolding may not be possible after surgery, and (2) free prepuce remaining after surgery should be at least twice the length of the free portion of the penis or the prepuce may be too short to permit full penile extension. Presurgical and postsurgical considerations, as well as surgical techniques used to correct phimosis, are described by Walker and Vaughan.[1]

Congenital anomalies contributing to phimosis are diagnosed based on physical examination of the entire reproductive tract. Abnormal karyotypes may be helpful in determining causes. If the penis cannot be extended using the techniques described and evidence of injury or adhesions is not present, congenitally short penis or retractor penis muscles should be suspected.[2]

Accompanying history may provide information that the bull could copulate when young, but as he aged his abdomen progressively enlarged, causing the penis to be of relatively insufficient length to effect copulation.[2]

Ram and Buck

Phimosis is uncommon in small ruminants. It may be congenital or acquired as a result of adhesions or preputial scarring associated with trauma or balanoposthitis.[11] Acquired phimosis can be the result of ulcerative posthitis due to the presence of *Corynebacterium renale, Corynebacterium pilorum,* or *Corynebacterium cystitidis*. These bacteria normally inhabit the prepuce and transform urea to ammonia, which is highly irritating to the prepuce. High urine urea levels, which are noted in animals fed high-protein diets, may increase the risk of ulcerative posthitis.[17,18] This condition is diagnosed during the physical examination and/or by observing the animal during the breeding process. If phimosis is due to acute inflammation of the prepuce (posthitis), it may resolve when the preputial swelling reduces. However, the prognosis is guarded until

scarring can be evaluated.

Paraphimosis

Stallion

Definition and Etiology

When injury of the penis and the laminae of the prepuce is attended by hemorrhage and edema, paraphimosis (the inability to retract the penis into the prepuce) is likely to occur.[1] Prolonged penile prolapse, caused by debility or paralysis after the use of some tranquilizers, usually culminates in extensive penile irritation.[19,20] Protracted priapism (persistent erection) can lead to penile trauma and complications similar to penile prolapse.[21] Penile paralysis and priapism are distinctly different conditions. Penile paralysis likely develops secondary to insufficient tone of the retractor penis muscles.[22] Motor innervation of the retractor penis muscles in stallions is believed to be solely supplied by α-adrenergic fibers. When α–adrenergic blocking drugs such as phenothiazine-derivative tranquilizers are administered, paralysis of these muscles can cause penile prolapse.[23] The prolapsed penis is flaccid and cannot be maintained in the retracted position.[1,22] Priapism is a persistent erection without sexual arousal and is initially unassociated with penile paralysis. It develops from engorgement of the CCP with blood, and although the horse may not achieve a full erection, its penis is not flaccid.[24,25] When the penis fails to detumesce, CO_2 tension in the CCP increases, resulting in increased blood viscosity and subsequent venous occlusion where collecting veins join the cavernous spaces. Edematous swelling of corporeal trabeculae further reduces venous outflow, thus increasing the likelihood of irreversible venous occlusion, fibrosis of the cavernous trabeculae, and arteriolar occlusion. Disruption of the arteriovenous supply and fibrosis of the CCP prevent subsequent erections.[5,26]

Clinical Signs and Differentials

Penile paralysis has been reported in exhausted or debilitated horses, in horses with myelitis or spinal injury, and in horses with severe injury to the penis.[1,19] Traumatic inflammatory edema often results in severe swelling of preputial membranes that prevent retraction of the penis into the prepuce. The inability to

retract the penis results in further gravitationally induced edema, and, as the problem worsens, edematous fluid eventually oozes through the increasingly fragile penile and preputial integument. Cellulitis develops, and the integument becomes thickened, inelastic, desiccated, necrotic, and irreversibly damaged.[1,5] In cases of long-standing priapism, the distal end of the penis becomes cool to the touch, and the clot may become palpable in the body of the CCP as fibrin organization occurs. The organized clot may be visible on ultrasound examination.[21]

Treatment and Prognosis

Prognosis for recovery becomes guarded to grave as the chronicity of the problem increases. Principles of treatment are similar to those described for the bull. The key to success is early aggressive intervention to reduce the edema via compression so that the penis can be placed within the prepuce.[27] To maintain the penis within the prepuce, a temporary purse-string suture of heavy nonabsorbable suture can be placed near the preputial orifice; however, dehiscence is common following this procedure. Alternatively, a padded plastic bottle from which the bottom has been removed can be used to support retention of the penis within the sheath. After the injured penis is dressed, the bottle is placed over it and pushed back into the sheath. The bottle is held in place with flexible straps or tubing running over the lumbar area and on either side of the scrotum up over the tailhead. Voiding of urine occurs through the bottle. The apparatus should be cleaned and replaced twice daily until the penis can be self-retained in the retracted position. Another effective method for maintaining the penis within the prepuce is the use of a 2-inch outer-diameter probe made of polyvinyl chloride (PVC) or other plastic tubing that is secured to the stallion's abdomen using elasticated bandage tape.[28] If the penis cannot be returned into the prepuce, an external support for the prolapse should be applied. Prolonged penile prolapse may result in excess gravitational pull that damages smooth muscle cells, the retractor penis muscle, and the pudendal nerves[1,22]; such sequelae decrease the prognosis for recovery and return to a successful breeding career. Chronic, refractory penile prolapse results in severe balanoposthitis that may require circumcision or penile amputation. Surgical penile retraction (the Bolz technique) is described by Walker and Vaughan.[1] A simple amputation technique that can be performed in the standing horse, using a modified Vinsot procedure, has also been described.[29]

Medical treatment of horses with priapism has generally been unsuccessful.[5,24] In cases of drug-induced priapism seen within 2 to 4 hours of occurrence, slow IV injection of 8 mg benzotropine mesylate may cause detumescence and penile retraction to occur.[30] If not seen immediately, treatment is the same as for traumatic paraphimosis. Rapid detumescence can be induced by injecting 10 mg of phenylephrine into the CCP, even in long-standing cases. However, the detumescence may be transient, especially in chronically affected cases. Flushing the CCP with heparinized lactated Ringer's solution through 12-gauge needles to remove sludged blood has been recommended for horses with priapism of 12 to 24 hours' duration that have not responded to medical treatment.[5] If a blood clot forms in the CCP, the prognosis is poor, and amputation may even be necessary. Some stallions, if severe nerve damage does not occur, may regain the ability to breed and ejaculate when assisted with placement of the penis into either the vagina of the mare or an artificial vagina. When the stallion does not regain the ability to completely retract the penis into the sheath, continued penile trauma is likely to result in damage to the sensory nerves to the glans penis. Such horses may achieve an erection but may have difficulty in seeking the mare's vulva for intromission and ejaculation. Ultrasonography of the CCP to detect cavernosal fibrosis may be useful in assessing prognosis for recovery from priapism. Prognosis for recovery is good once penile retraction occurs, but breeding should not be permitted until healing is complete.

Bull

Definition and Etiology

Paraphimosis is less common than phimosis in the bull. Causes may be the same for both conditions, but for paraphimosis include penile tumors, parasitic invasion, traumatic or spinal disease affecting innervation of structures responsible for penile retraction, inadvertently severed retractor penis muscles, or physical trapping of the penis by a constricted prepuce after injury. Penile paralysis and paraphimosis sometimes occur as a result of spinal injury or disease and in rabies cases as well.[1,2]

Clinical Signs and Differentials

Persistent exposure of the penis results in congestion, inflammation, and necrosis

of the penile integument.[2]

Treatment and Prognosis

Management of the prepuce has been discussed. Exposed portions of the penis should be frequently cleansed and protected by a bandage soaked in oily antibiotic preparations. The prolapsed penis should be supported close to the abdomen to reduce edema. The penis should be returned to the sheath as soon as possible and mechanically restrained if necessary. If the ability to retract the penis does not return in a few days, prognosis for recovery is poor.[1]

Ram and Buck

Paraphimosis is uncommon in small ruminants. The diagnosis is obvious, although the etiology may not be. Treatment involves the same principles as in the bull. Prognosis is guarded and correlates with the degree of injury and necrosis at the time the condition is discovered.

Urethral Injury and Urethritis

Stallion

Clinical Signs and Differentials

Traumatic injuries to the urethral process are usually obvious and are characterized by hemorrhage. *Habronema* granulomas are firm and friable. Ulcers of the urethral process often become secondarily invaded with bacteria such as *Pseudomonas* spp. Parasitic lesions tend to regress during winter, but if untreated they may mineralize and result in recurrence of hemospermia during the following breeding season.[31]

Lesions can occur throughout the urethra, including the pelvic urethra in the area of the ejaculatory ducts. Diagnosis is based on demonstration of the lesions by fiberoptic examination.[5] Ultrasonography and fractionation of the ejaculate may be helpful in eliminating involvement of the accessory sex glands.[32]

Urethral inflammation and lacerations may result in fibrous strictures.[33] Strictures are often painful and may separate and bleed during urination and ejaculation. Bacteriologic culture of the urethra, urine, and semen; fiberoptic examination; and histologic examination of biopsies of lesions are helpful in

making a diagnosis.[1] Strictures in the distal urethra may be identified by contrast radiography of the extended penile urethra.[1,33]

Clinical signs of uroliths include dribbling of urine with chronic cystitis, dysuria and stranguria, occasional hematuria, recurrent colic, and a stilted, painful gait in the hindquarters. Penile protrusion is frequent or constant in cases of chronic, involuntary escape of urine.[1] Diagnosis is by urinalysis, revealing the characteristic crystals, red and white blood cells, and bacteria. Urethral calculi typically restrict the passage of urethral catheters. Bladder calculi may be palpated per rectum or visualized by ultrasonography.[1,31]

Treatment and Prognosis

Treatment of urethral injuries involves first removing inciting factors such as a tight stallion ring. Sexual rest is indicated while palliative therapy is given. The ability to void urine should also be established. Systemic treatment with antibiotics that are eliminated in the urine may be useful as a prophylactic measure or in cases in which secondary bacterial invasion has occurred. More severe cases of urethritis may be treated locally either by infusion of oily antibiotic preparations through sterile, rubber urethral catheters passed to the area of the seminal colliculus of the pelvic urethra or by inserting soluble suppositories through a perineal urethrostomy. After resolution of the urethritis, the urethrostomy is allowed to heal by granulation.[33] Lacerations or rents of the proximal urethra that result in hemospermia can be treated by perineal incision into the corpus spongiosum and underlying urethra (CSU) or by perineal corpus spongiotomy where the CSP is incised, but the incision is not extended into the urethral lumen. These surgeries are believed to prevent stretching of the urethra when engorgement of the corpus spongiosum occurs during urination or erection. Repeated tissue stretching and bleeding through the site at the time of urination are thought to prevent urethral lacerations from healing without these forms of surgery.[34]

Inflammation of the urethral process may respond to local antibiotic salves. Treatment of parasitic granulomas with ivermectin speeds resolution of these cases.[13,35,36] Larger, nonresolving granulomas with mineralization may require surgical removal.[37] The skin of the urethral process should be rolled inward when sutured to the mucous membrane to prevent eversion that predisposes it to reinjury after healing. Remaining hemorrhagic or ulcerative lesions can be lightly cauterized with silver nitrate.[31] More proximally located nonresolving

urethral strictures, prolapsed subepithelial vessels, or ulcers can be removed surgically.

Calculi lodged within the lumen of the pelvic urethra can be removed via perineal urethrostomy. Treatment for urethral calculi is described in the discussion of diseases of the urinary system (Chapter 34).

Bull

Definition and Etiology

Urolithiasis is the primary problem affecting the urinary system that may interfere with normal function of the reproductive tract of the bull. It is of less importance in bulls than in steers but occasionally occurs and may result in hematuria or urethral obstruction.[1,2] Urolithiasis is thoroughly discussed in Chapter 34.

Balanoposthitis

Stallion

Definition and Etiology

Inflammation of the glans penis (balanitis) and prepuce (posthitis) often occur together (balanoposthitis). Traumatic injury resulting in inflammation of the penis and prepuce has been discussed. Balanoposthitis may also be caused by dourine, equine herpesvirus 3 (EHV-3), miscellaneous bacteria, and parasites.[3]

Equine Coital Exanthema

Equine coital exanthema is caused by EHV-3.[38,39] The occurrence of neutralizing antibodies to EHV-3 primarily in horses of breeding age suggests that spread of this infection may be primarily by genital contact.[40] Typically an inapparently infected mare transmits the virus to a stallion at the time of breeding. The stallion then transmits the infection to other susceptible mares before developing clinical signs of the disease. Clinical signs in the stallion are sometimes more severe than those observed in the mare and may include systemic manifestations such as dullness, anorexia, and fever.[40] Vesicles up to 1.5 cm in diameter develop first on the penis and then on the prepuce 2 to 5 days

later. The vesicles progress to circumscribed pustules with raised borders and depressed centers, which slough and ulcerate.[41] Scabs are seldom noted on penile lesions because they are rubbed off by extension and retraction of the penis during breeding.[41] Some affected stallions may refuse to breed mares, whereas others breed willingly, even while extensive penile lesions are present. Healing occurs in a few weeks, often leaving depigmented spots.[41]

Some immunity to the virus is acquired, as recurrence of clinically apparent disease is uncommon. It is probable that the virus remains in the genitalia in a latent form. Recurrent coital exanthema usually occurs in aged broodmares but may also occur in stallions.[41] The relationship between viral recrudescence and recurrent coital exanthema in the equine is unknown but may mimic that which occurs in human genital herpes infections.

Diagnosis usually can be made based on the characteristic clinical signs. During the acute stage, the virus can be isolated from swabs or scrapings taken from the edge of erosions, inclusions in lesion specimens, or confirmed by using an electron microscope to visualize typical herpesvirus particles in fluid or tissue samples. Probably the most sensitive, specific, and accurate tool for the detection of EHV-3 is PCR testing. Demonstration of antibody titers in serum may be useful in establishing time of exposure to the virus.[42]

Infection with EHV-3 is self-limiting. Local treatment with antibiotic ointments will not speed healing but may minimize secondary bacterial infection and soreness.[41] Care should be taken to avoid iatrogenic transmission of the infection (e.g., through contamination of sleeves, water, and examination or insemination equipment) to susceptible animals. Attending veterinarians may choose to refrain from breeding affected stallions until the lesions heal. One method that may be helpful in circumventing transmission of the infection while still breeding the stallion is to collect semen in an open-ended artificial vagina as soon as lesions are no longer painful. Collecting the semen as it directly exits the urethra reduces the chance of viral contamination from the penile and preputial lesions.

Bacterial Infections

Stallion

The external genitals of stallions harbor potentially pathogenic bacteria, fungi, and yeasts, yet balanoposthitis caused by bacterial agents is uncommon.[43-45]

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These organisms are usually considered to be surface contaminants, and the stallion is a lesionless carrier in most instances in which venereal transmission occurs.[20] Sperm motility, however, may sometimes be adversely affected by bacteria and their products in semen.[44] Offensive odors may occasionally be associated with heavy colonization of the penis and sheath with *Pseudomonas* spp. or *Proteus* spp.[2] Documentation of a bacterial infection is dependent on serial isolation of a pathogen, preferably in large numbers and relatively pure culture.[45] A single isolation of *Taylorella equigenitalis* is considered diagnostic for contagious equine metritis.[20] Samples for bacteriologic culture should be retrieved from the fossa glandis, free portion of the penile body, and folds of the external prepuce before washing the genitals of a stallion presented to a mare in behavioral estrus.[45]

If there is evidence of horizontal transmission of *Pseudomonas* or *Klebsiella* to mares, or if longevity of sperm is reduced in association with these organisms, the preferred method of management is to breed mares artificially with semen mixed with an antibiotic-containing semen extender.[46] Antibiotic selection is based on trials comparing extended semen with and without antibiotic. Extenders containing antibiotics that control the offending bacteria and permit maintenance of sperm motility are then used to breed mares.[47] Bacteria are usually not recovered after 5 to 30 minutes of incubation at room temperature.[44,46,47] Penicillin G (1000 to 1500 U/mL), streptomycin sulfate (1000 to 1500 µg/mL), polymyxin B (100 to 1000 U/mL), reagent grade gentamicin sulfate (100 to 1000 µg/mL), amikacin sulfate (100 to 1000 µg/mL), and ticarcillin (100 to 1000 µg/mL) are usually the most suitable antibiotics.[5] Gentamicin sulfate and amikacin sulfate should be buffered with 8.4% sodium bicarbonate solution to adjust pH to approximately neutral before mixing with semen extender. A suitable volume of extender can be infused into a mare's uterus immediately before cover when natural service is necessary.[46]

Colonization of the external genitals with *P. aeruginosa* and *K. pneumoniae* can be treated by thoroughly washing the penis and prepuce, including the fossa glandis and diverticulum, daily with an iodine-based surgical scrub. The genitals are then rinsed with copious quantities of tap water with dilute disinfectants added (10 mL concentrated HCl per gallon of water for *Pseudomonas* colonization, or 40 mL of 5.25% sodium hypochlorite bleach per gallon of water for *Klebsiella* colonization). Drying of the penis can be followed by generous application of 1% silver sulfadiazine cream. The procedure is repeated daily for

1 to 2 weeks followed by serial cultures to determine if treatment was successful.[48] The clinician should be cognizant that recolonization with these organisms may occur and that routine scrubbing and disinfection may predispose to infection of the genitals with potential pathogens by displacing commensal organisms.[43] While not tested in a research setting, individual clinicians have used a tranfaunation procedure to replace normal flora by rubbing the penis and preputial areas of the affected stallion with smegma of a stallion with normal penile and preputial flora.

Bull

Balanoposthitis in the bull is caused by traumatic injury and infections. Whereas injury of the prepuce is more common, penile inflammation often accompanies the traumatic posthitis. A multitude of potentially pathogenic organisms inhabit the prepuce, and injuries predispose to infection, particularly when deeper tissues are exposed. Pain and preputial discharge may be evident. Because of the presence of the many organisms in the preputial cavity, culture to identify a specific offending organism is likely to be misleading. When injury results in infection of the penis and prepuce, sexual rest in conjunction with local antibiotic treatment is indicated; systemic antibiotics are indicated if the injury is extensive or involves the full thickness of the prepuce. Treatment should be performed as previously outlined for the penis and prepuce until inflammation is corrected.

Balanoposthitis unassociated with trauma has been associated with infections caused by infectious bovine rhinotracheitis–infectious pustular vulvovaginitis (IBR-IPV) caused by bovine herpesvirus 1 (BHV-1), tuberculosis, and screwworm infestation.[2,49] Acute lesions associated with IBR-IPV infections are numerous small pustules that progress to ulcers and erosions in a few days. Purulent preputial discharge is present, and lesions may become confluent. The prepuce and penis may become quite inflamed and swollen. Healing is commonly spontaneous and rapid, beginning in 1 week and usually complete in 2 weeks. Severe cases may take longer to resolve.[49] Virus is shed from the prepuce for 2 weeks or longer, during which time venereal spread is possible. Sexual rest for 6 to 8 weeks has been recommended to prevent spread and to avoid abrasions that may aggravate inflammation.[2] Enlargement of the lymphoid follicles may be present along with a seromucoid exudate for several weeks. Histologic changes include the transient appearance of eosinophilic intranuclear

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inclusions in degenerating epithelial cells. Infusion of the preputial cavity daily may be of benefit in treatment, particularly in more severe cases. Vaccination with attenuated intranasal products has been reported as a method to prevent viral shedding into semen in bulls from AI studs.[2] Bulls infected with BHV-1 remain infected for life, as the virus remains latent in the sacral ganglia.[50,51] Viral shedding through the ejaculate occurs intermittently. Therefore valuable serologic-positive bulls could be tested for the presence of the virus in semen. Detection of BHV-1 in semen by real-time PCR is more sensitive than virus culture isolation. Two straws of extended processed ejaculate are necessary to detect the presence of the virus.[50,51]

Ram and Buck

Definition and Etiology

Balanoposthitis (also called “pizzle rot,” “sheath rot,” and “ulcerative posthitis”) commonly affects the penis and prepuce of intact and castrated male small ruminants (see also Chapter 34).[11,12] In sheep, it is important to differentiate pizzle rot from ulcerative dermatosis. Ulcerative dermatoses, caused by a parapoxvirus, also present lesions in lips and legs, as well as in the genital area (see also Chapter 32). In goats, the caprine herpesvirus produces balanoposthitis in males and vulvovaginitis in females.[52,53] It is also a cause of caprine abortion.[54,55]

Persistent Penile Frenulum and Penile Deviations

Stallion

Definition and Etiology

Persistent frenulum is rare in the stallion. However, penile deviations can occur in older stallions, particularly those that have been subjected to semen collection through most of their breeding career. In the United States, most of the affected horses have deviations to the right. It is thought that repeated bending of the penis to the left to facilitate entry into the artificial vagina causes damage to the CCP/tunica albuginea on the right side, resulting in filling defects and fibrotic

lesions that lead to penile deviation.

Treatment and Prognosis

For most affected stallions, treatment is unnecessary, and the horse continues to ejaculate normally. Some stallions have such a severe deviation that attempts to collect semen result in pain and lack of ejaculation. For these stallions collecting semen on the side ipsilateral to the direction of deviation often alleviates the problem.

Bull

Definition and Etiology

Phallocampsis, or deviation of the erect penis, is a relatively common condition in the bull. The most common cause of penile deviation is persistent penile frenulum.[2] Other types of penile deviations include spiral, ventral, and S-curved deviations.[1] Less commonly, preputial or penile injury may result in scar tissue formation that subsequently leads to deviation of the erect penis.[1]

When the penile frenulum persists, it remains connected to the ventral surface of the tip of the penis and the prepuce and causes the penis to bend ventrally during erection by preventing complete extension.[56] Copulatory ability is interfered with except in some of the Zebu-influenced breeds that are endowed with a plentiful prepuce.[1] Diagnosis is based on physical examination of the extended penis.

Because spiraling of the penis is thought to be a normal physiologic event that occurs in the vagina during ejaculation,[57] care should be taken in making this diagnosis. Bulls affected with penile deviations often have a history of no problems in mating cows for some time, occasionally for several breeding seasons. If such bulls have been closely observed, it may have been noted that the condition did not occur on every mating attempt, but the frequency of occurrence gradually increased until bulls might require numerous mounts to successfully intromit and breed a cow in estrus.[2] Penile deviations occur at full erection when the CCP is maximally distended with blood. Caution should be exercised in diagnosing this condition during erection stimulated by electroejaculation. Such erections are not considered to be entirely physiologic and frequently result in penile deviations in bulls that have no deviations under

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natural mating conditions. The spiral deviations that occur with use of the electroejaculator may be a result of tension exerted by the retractor penis muscles.[1] Diagnosis is best based on observing occurrence of the deviation frequently in natural mating situations.

The ventral or rainbow deviation of the penis is less common than the spiral deviation and is a result of the apical ligament being too thin to support the engorged, stretched distal end of the erect penis.[1] The ventral curvature may be quite pronounced, preventing affected bulls from directing and inserting the penis into the vagina of the female.

The least common of the spontaneous penile deviations is the S-shaped curvature. It primarily occurs in older bulls with an apical ligament that is short in relation to an excessively long penis.[1] Penile deviations that result from adhesions that developed from penile or preputial injury are diagnosed by physical examination.

Treatment and Prognosis

Persistent penile frenulum is easily corrected by severing the persistent band. Owners of affected bulls should be advised of the probable genetic basis and therefore the undesirability of retaining such bulls for breeding.[1] Treatment of spiral and ventral deviations is surgical.[1]

Tumors of the Penis and Prepuce

Stallion

Clinical Signs and Differentials

The most common neoplasm of stallion genitalia is squamous cell carcinoma (SCC). Generally, it is of low malignancy.[1,58] The tumor usually involves the glans penis but may also involve the shaft of the penis and prepuce and produce a fetid discharge. Large tumors may ulcerate and bleed, resulting in hemospermia. Carcinomas may resemble *Habronema* granulomas, which are more common and are diagnosed by histologic examination of affected tissue.[2,5] Carcinomas are usually well differentiated and surrounded by eosinophils. Necrosis and calcification may occur, but parasite larvae are usually not present unless secondary habronemiasis has occurred from flies feeding on the ulcerated tissue. Carcinomas may extend into the CCP or may metastasize to the inguinal

lymph nodes or other abdominal or thoracic organs. The superficial inguinal lymph nodes lie midway between the prepuce and external inguinal ring; secondary tumors in this region often grow rapidly and develop necrotic centers with purulent sinuses that must be differentiated from bastard strangles.[1]

Tumors encountered much less frequently include melanoma, papilloma, angioma, lymphosarcoma, and sarcoid. Melanoma is a common equine tumor, especially of gray horses,[13] and occasionally involves the penis and prepuce[1,2,59] (see Chapter 40). Genital papillomas are rare in stallions but may occur on the glans or shaft of the penis. The lesions appear as multiple proliferative cutaneous growths and may become friable and result in hemorrhage during erection and ejaculation.[5] The lesions are generally thought to be caused by a papillomavirus, and papillomavirus antigens have been found in cutaneous and genital papillomas.[60] Angiomas and lymphosarcomas have occasionally been reported on the genitals of stallions.[3] Sarcoids may involve the skin of the prepuce or scrotum.[1,59]

Treatment and Prognosis

When SCCs are relatively small and noninvasively attached to the skin, neoplasms may be successfully treated by cryosurgery or hyperthermia. Hyperthermic treatment (50° C for 1 to 2 minutes) appears to be most successful for SCC when lesions are small (less than ≈2 cm). If the tumor is extensive but superficial, cryosurgery may be attempted after the tumor is debulked and hemorrhage is controlled. The remaining base of the tumor is then frozen and thawed twice; healing occurs as necrotic tissue is sloughed. Successful treatment of small lesions has been reported with topical application of 5-fluorouracil.[61] If removal of tumors is unsuccessful or if neoplasia is extensive, penile amputation may be necessary.[1,62] If superficial inguinal lymph nodes are involved, euthanasia may be required.[1]

In contrast to nongenital squamous papillomas, genital forms are generally quite refractory to treatment.[5] Surgical removal and autogenous vaccine administration to treat fibropapilloma of the penis of two stallions did not effect a cure.[31]

Bull

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Definition and Etiology

Fibropapilloma is the only tumor that frequently invades the bovine penis or prepuce. The tumor may be single or multiple and usually affects young bulls. The cause is thought to be a papillomavirus antigenically similar to the virus that causes cutaneous papillomatosis in cattle.[63] Frequent mounting among young bulls is thought to result in damage to epithelial surfaces of the penis and prepuce that serves as a route of entry for the virus.[1,2]

Clinical Signs

Small papillomas may be discovered during routine breeding soundness evaluations, but many become larger before they are discovered. Large fibropapillomas may prevent withdrawal of the penis into the preputial cavity. Fibropapillomas are pedunculated and attached at a narrow base in early cases. The surface becomes cauliflower-like and friable; hemorrhage is easily induced.

Treatment and Prognosis

Many fibropapillomas regress spontaneously within a few months. Regression may be more likely in bulls approaching 2 years of age and usually occurs within 4 months of the appearance on the penis.[63,64] Several vaccines, including autogenous preparations, have been used for treatment, but vaccines may be more successful for prophylaxis.[2] Frequently surgical removal is indicated, but the fibropapillomas may recur. If only superficial attachment is present, surgical removal is easily accomplished. Catheterization of the distal urethra before surgery is helpful in identifying its location to avoid injury. If attachment has become extensive and sessile, amputation of a portion of the distal penis may be necessary.[1] Housing of young replacement bulls in individual pens, if possible, is recommended as a method to reduce the incidence of penile fibropapillomas.

Parasitic Infestations of the Penis and Prepuce

Stallion

Definition and Etiology

Habronema muscae, *Habronema microstoma*, and *Draschia megastoma* larvae commonly invade the urethral process, glans penis, and preputial ring of

stallions.[1,13] Other terms for this condition are “genital bursatti” and “summer sores.”

Clinical Signs

Shallow irritations progress to irregular 1- to 3-cm granulomatous growths that may involve the entire circumference of the urethral process.[2] Lesions are friable and bleed when manipulated. Stretching of the infected urethral process during penile engorgement and ejaculation may result in hemospermia.[5] Pruritus associated with the lesions may be intense. Frequent micturition and dysuria may resemble urine spraying that accompanies accumulation of smegma in the urethral diverticulum (“bean”). Lesions subside during the colder months in northern areas but usually reappear and increase in size during subsequent warm weather.[2] Diagnosis is made by seeing yellowish granules (calcified larvae) in the lesion and by microscopic identification of larvae.[13]

Treatment and Prognosis

See Chapter 40 for treatment and prognosis information.

Hemospermia (Blood in Semen)

Hemospermia refers to contamination of ejaculates with blood. Stallions with overt hemorrhage into ejaculates can be subfertile. Erythrocytes, rather than serum, have been implicated for the marked depression of fertility, although the precise factors involved are not known. A small amount of sanguineous contamination is compatible with good fertility, especially if the semen is quickly diluted with a suitable extender before insemination. The addition of 5% of blood (v/v) in extended semen did not affect the fertility compared to control mares artificially inseminated with extended semen containing no blood. However, if the extended semen contained 50% blood, no pregnancies were obtained. It was concluded that the level of blood rather the presence of blood affects the fertility.[65] A disproportionate number of leukocytes to erythrocytes suggests infection of the internal genital organs. Specific causes of hemospermia include lacerations of the penis, cutaneous habronemiasis, urethritis, urethral lacerations, and infection or inflammation of the accessory genital glands, which are discussed elsewhere in this chapter.

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Urospermia (Urination During Ejaculation)

Definition and Etiology

Urospermia is an uncommon but perplexing disorder of breeding stallions. Affected stallions generally exhibit normal libido and mating ability, but semen becomes contaminated with urine during the ejaculatory process. The problem may be incessant or unpredictably intermittent; urination can occur at any time or continuously during ejaculation. The amount of urine is up to 250 mL or more.[5]

The underlying cause or causes of urospermia are speculative. Closure of the bladder sphincter and seminal emission are controlled by the α-adrenergic sympathetic nervous system, and a disturbance in this pathway might contribute to urospermia.[66] Similarly, neuropathies that result in bladder paralysis (e.g., cauda equina neuritis or nerve damage secondary to EHV-3 or sorghum/Sudan grass poisoning) can create urinary incontinence that permits voiding during ejaculation. Most stallions with urospermia do not exhibit signs of a neurologic deficit.[5] In ruminants, urine can also contaminate semen collected by electroejaculation. To reduce this risk, it is recommended to avoid water ingestion 12 to 24 hours before semen collection.

Clinical Signs and Differentials

Gross contamination of ejaculated semen with urine is easily detected by its color and odor. Contamination with significant quantities of urine adversely affects sperm motility and fertilizing capacity. Elevated concentrations (relative to serum levels) of urea nitrogen or creatinine in semen document the presence of urine in the ejaculate.[5,67]

Treatment and Prognosis

Treatment options for urospermia vary, can be arduous, and are often unrewarding. Delay of semen collection (or breeding) until immediately after the stallion has voided urine may be a helpful management policy. Urination can be stimulated by administration of a diuretic drug (e.g., furosemide). Stallions may also void urine when provided access to feces of another stallion. Some stallions can be trained to urinate on command. Alternatively, the bladder can be catheterized to aid evacuation of urine before breeding, but urethritis or cystitis may result from routine use of this procedure. Fractionation of ejaculates using

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an open-ended artificial vagina can be used alone or in combination with any of the previously mentioned measures. When an open-ended artificial vagina is used, only the first three jets of the ejaculate are collected. These jets contain a majority of the spermatozoa in the ejaculate, and urination may not occur until the end of the ejaculatory process. Dilution of urine-contaminated semen in extender can restore sperm motility.[68] Semen may be centrifuged after initial dilution and the sperm pellet resuspended in extender before insemination[5]; however, centrifugation to remove urine may not provide a significant advantage to dilution in extender.[68]

Pharmacologic agents such as bethanechol chloride or flavoxate hydrochloride have been used in an attempt to correct urospermia, but usually without success.[5] Oral administration of imipramine (100 to 500 mg twice daily) has reportedly been useful for controlling urospermia in stallions, presumably by enhancing contractility of the bladder neck during emission.[66]

Infertility Caused by Diseases of the Scrotum and Testes

Scrotal Injury, Hydrocele, and Hematocele

Definition and Etiology

Trauma to the scrotum can result in excoriation, lacerations, hemorrhage, and edema.[2] Systemic diseases such as hepatic disease and equine infectious anemia may result in scrotal edema.[2,20] Suppurative inflammation may develop as an extension of scrotal injury.[2] Adhesions often develop between the visceral and parietal tunics when inflammation, infection, or hemorrhage occurs. Adhesions are usually thin fibrous strands that become thickened with time. In such cases the testis and its tunics are not freely movable within the scrotum.

Hydrocele is an accumulation of serous fluid within the vaginal tunic. Ascites, anasarca, or local lymphedema may contribute to hydrocele because the vaginal tunic communicates with the peritoneal cavity. Accumulation of a significant volume of fluid around the testis may cause thermal degeneration and a decline in seminal quality.[69] In Texas, a seasonal hydrocele has been described in bulls submitted to breeding soundness examination during the fall and winter season.[70,71] This type of hydrocele was associated with ascites and intestinal edema and has been attributed to a hypersensitivity reaction to gastrointestinal nematodes.[71,72]

Hematocele occurs when trauma to the scrotum results in accumulation of blood within the testicular tunics. Hematoceles can be primary due to a testicular trauma or secondary to hemoperitoneum. Scrotal damage initially accompanies hematocele. Thermal degeneration of the testes follows, and a thick fibrous capsule encompasses the testis after the blood clot organizes.[73]

Clinical Signs and Differentials

Diagnosis of scrotal injury, hydrocele, and hematocele is made by physical and ultrasonic examination of the scrotum. Testes remain freely movable within the scrotum if hydrocele is present. Ultrasonographic examination reveals variable amounts of anechoic fluid present surrounding the testes and epididymides, which are easy to visualize because of their echoic nature against the fluid

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background. With hematocele, evidence of trauma is often present, with thickening of the scrotal skin. Blood surrounding the testis and epididymides becomes progressively more echogenic as the clot organizes.[5,74] Extensive edema of the scrotal fascia next to the tunica dartos may be difficult to differentiate ultrasonographically from hematocele. Abdominal paracentesis is helpful in eliminating ascites or peritonitis as causes of hydrocele. Palpation per rectum of stallions and bulls may occasionally reveal that the internal inguinal rings are enlarged, readily permitting fluid transfer into the vaginal cavity.

An aseptic tap is useful to identify the character of this fluid and must be performed with care not to contaminate or penetrate the testis or its visceral vaginal tunic.[73] A modified transudate of low cellularity is typical of fluid drained from a hydrocele.[75] Fluid usually returns after drainage unless the initiating cause is corrected.[5] Determining and treating the cause of ascites could provide permanent cure of the ascites and hydrocele.[71,72]

Treatment and Prognosis

Acute scrotal injury is treated with cold water or ice application to reduce edema (see earlier discussion on penile and preputial injuries). Lacerations and abrasions should be treated with topical antibiotic ointments. Systemic antiinflammatory drugs and antibiotics may reduce swelling, control infection, and prevent abscess formation.[5,73]

Scrotal thickening usually results in elevation of testicular temperature, causing degeneration and atrophy similar to that seen with experimental scrotal insulation.[76-78] Semen quality quickly deteriorates, and a rapid reduction in number and motility of spermatozoa occurs, with a concurrent increase in morphologic abnormalities of spermatozoa.[2,79] If swelling and edema resolve and adhesions do not develop among the testes, tunics, and scrotum, spermatozoa may gradually reappear in the ejaculate by 1 to 2 months after injury, but 4 to 5 months may be required for testes to return to normal size and sperm production.[4] One or both testes may remain atrophic and become firm because of fibrosis and loss of tubules. If only one testis is atrophied, the normal testis may eventually hypertrophy.

If hemorrhage occurs within the scrotum or testicular tunics, the prognosis for return of testicular function is poor. In unilateral cases, surgical removal of the clot and affected testis may minimize damage and speed recovery of the

remaining testis.[80,81] Hydrocele is managed by correcting the underlying cause of fluid accumulation such as peritonitis or ascites.[73] Exercise may aid in control of fluid accumulation in some horses. Some stallions and bulls with persistent minor fluid accumulations within the tunics may continue to produce sufficient normal spermatozoa.[2] Permanent testicular degeneration may result in cases with extensive fluid accumulation that are unresponsive to therapy. If the condition is unilateral, removal of the affected testis may permit the animal to remain in service.[75] Because hydrocele and associated impairment of spermatogenesis may be transient (2 to 6 months),[70] caution should be exercised in recommending castration or culling of affected animals until demonstration that the disorder is long-standing.

Scrotal Dermatitis or Abscess

The scrotal skin is delicate and vulnerable to dermatitis. Causes include nonspecific environmental contaminants, bacteria, fungi, parasites, and frostbite. Scrotal abscesses are not uncommon in small ruminants and are due to shearing injuries and penetrating wounds.[11] Treatment is directed toward removing the affected testis. Bulls affected by frostbite should be provided a warm and dry environment.[82] Systemic and local antibiotics may be indicated. Abscesses should be drained. Thermal degeneration of the testes may follow dermatitis and may be temporary or permanent.[2] Semen quality should be evaluated at periodic intervals after skin lesions have resolved to gauge prognosis for improvement and return to fertility.

Testicular Aplasia and Hypoplasia

Definition and Etiology

Complete absence (aplasia) of one or both testes is rare and usually occurs in conjunction with anomalous development of other organs.[2,83] Testicular hypoplasia may be unilateral or bilateral and affects both scrotal and abdominal testes. Testicular hypoplasia is thought to result from failure of germ cells to multiply in the gonad.[2] Causes of testicular hypoplasia may include transplacental infections and intoxications, zinc deficiency, hormonal insufficiency, impaired testicular descent, abnormal karyotype, and vascular disturbances.[11,12,79] Exogenous administration of hormones to prepubertal males

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can result in testicular hypoplasia. Testicular size of adult stallions is reduced after prolonged administration of exogenous steroids.[84-86] Scrotal circumference is diminished in bulls implanted with zeranol.[87]

Clinical Signs and Differentials

Hypoplastic testes are usually smaller than normal, but they are occasionally normal in size.[88-90] Stallions 3 years of age should have a scrotal width greater than 8 cm.[20] Yearling rams with a scrotal circumference of less than 30 cm and mature rams with a scrotal circumference of less than 32 cm are not recommended for breeding.[91] The texture of affected testes varies from normal to soft in mild or moderate hypoplasia. Severely affected small testes are firm because of the relatively increased amount of stromal connective tissue. History is an important component in the clinical assessment in order to differentiate hypoplasia from atrophy. If uncertain, reexamination needs to be performed. Factors that influence the scrotal circumference in ruminants are breed, age, body condition score, and season.[92] In bulls, the minimum recommended scrotal circumference is 30 cm for 15 months old or younger and 34 cm for 2 years old or older according to the criteria established by the Society of Theriogenology.[93] Scrotal circumference in bulls is positively correlated with the number of normal functional seminiferous tubules and is negatively correlated with pathologic seminiferous tubules in bulls.[90] In bulls the heritability for scrotal circumference is medium to high.[92] In addition, scrotal circumference is negatively correlated with age at puberty of the female offspring. Bulls with higher scrotal circumference will produce females that acquire puberty earlier than females produced by contemporaneous bulls with smaller scrotal circumference.[92]

Depending on the number of seminiferous tubules affected, ejaculates from males with testicular hypoplasia may be azoospermic or contain a low concentration of spermatozoa with numerous morphologic defects.[2]

Treatment and Prognosis

No successful treatment is available for severe hypoplasia. The useful breeding life of males with testicular hypoplasia may be shortened because affected bulls are thought to be predisposed to early testicular degeneration.[88] Because of the value of some individuals, particularly stallions, owners may elect to breed males with small testes. Effective management of such stallions is based on

breeding a book of mares limited by the number of normal, motile spermatozoa present in ejaculates.

Cryptorchidism

Definition and Etiology

Incomplete or abnormal testicular descent is thought to be a genetic abnormality. The inheritance pattern in horses is thought to be dominant,[1] although studies of offspring of some cryptorchid stallions suggest that inheritance of the condition may be multifactorial.[2] The relative risk for equine cryptorchidism also appears to be influenced by breed.[3] Other modes of inheritance have been suggested from studies of the offspring of cryptorchid rams, bucks, and bulls. These include a recessive gene with incomplete penetrance in Angora goats,[4] a dominant gene with variable expressivity in Hereford cattle,[5] and either an autosomal recessive gene or a dominant gene with incomplete penetrance in inbred sheep.[6]

Testes originate near the kidney and migrate to the inguinal rings before descending into the scrotum; the epididymis precedes the testis in descent. Retained testes are located at some point along the path of migration. Ectopic testes not associated with cryptorchidism may be found under the skin of the ventral caudal abdomen or elsewhere in bulls.

Clinical Signs and Differentials

The majority of cases of cryptorchidism in stallions are unilateral.[7] Although testicular descent can occur in horses up to 2 years of age, the testes are normally descended at birth in large animals.[8] Testes are readily palpated in the scrotum of colts at 30 days of age. Spermatogenesis is inhibited in the abdominal testis because of the elevated temperature within the abdomen. The interstitial cells remain active and secrete testosterone, enabling even bilateral cryptorchids to maintain libido and copulatory activity. The descended testis may be hypertrophic; unilateral cryptorchids are fertile but are not considered sound breeders.[9]

Deep palpation of the superficial inguinal rings may reveal the testis in the canal (“high flankers”). If the testis is not located in the inguinal canal, transrectal palpation or ultrasonography can be performed in stallions and bulls

in an attempt to locate a testis or to detect the vas or epididymis entering the superficial inguinal ring, thereby providing evidence of descent into the inguinal canal.[10]

Clinical Pathology

Equine cryptorchids have high basal concentrations of testosterone (usually >100 pg/mL) and respond to human chorionic gonadotropin (hCG) administration (10,000 to 12,000 IU IV) with a significant elevation of circulating testosterone within 30 to 60 minutes if testicular tissue is present. Geldings and “false rigs” (geldings with malelike behavior) have low basal concentrations of testosterone (<40 pg/mL) and do not respond to hCG stimulation. Stallion testes contain a high concentration of conjugated estrogens, and a single measurement of high plasma conjugated estrogens (>400 ng/mL) is reported to be almost as reliable in diagnosing cryptorchidism as hCG stimulation.[11,12] Recent data suggest that anti-mullerian hormone (AMH) serum concentrations may serve as a useful marker for the presence of cryptorchid testes in the horse.[13] In some ruminants, measurement of testosterone concentrations before and after administration of hCG has also proved helpful in identifying cryptorchidism.

Treatment and Prognosis

Stimulation of testicular descent with repeated injections of gonadotropin-releasing hormone (GnRH), sometimes combined with hCG or acupuncture, has been attempted, but the success has not been critically evaluated. Surgical removal of the abdominal and scrotal testes is often prescribed; however, many breed registries allow the breeding of stallions with unilateral cryptorchidism. Bilateral cryptorchidism results in sterility because of disrupted thermoregulation of both testes. Surgical placement of a retained testis into the scrotum is not considered an ethical procedure.

Testicular Degeneration

Definition and Etiology

Testicular degeneration is an acquired condition with multiple etiologies.[1] Infections or traumatic orchitis may progress to permanent degeneration. Degeneration may be associated with thermal factors after elevation of body

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temperature by systemic infections; prolonged increase or decrease in ambient temperature; scrotal insulation from edema, dermatitis, scrotal hernias, or hemorrhage; or abnormal conformation resulting in an incompetent heat exchange system.[2-4] Degeneration results when testicular vasculature becomes occluded in torsion of the spermatic cord.[5] Obstruction of the proximal epididymis and malformation of the efferent tubules results in degeneration caused by pressure within the seminiferous tubules.[6] A variety of chemicals and ionizing radiation are capable of inducing testicular degeneration. Administration of steroid hormones may induce testicular degeneration by inhibiting secretion of gonadotropins.[7] Gradual degeneration also occurs with increasing age.[8]

Clinical Signs and Differentials

Diagnosis of testicular degeneration is based on physical examination and semen evaluation. Testes are typically thought to be small, but they may be normal size. The testicular consistency and elasticity of the testes is also decreased. Semen examination reveals a low concentration of spermatozoa, a decreased number of spermatozoa in the ejaculate, and a high percentage of spermatozoa with morphologic defects, sometimes with premature (round) germ cells.[1] Without a history of normal testis size and function before atrophy, differentiation from testicular hypoplasia is usually not possible. Discrepancies between testicular size (measured by scrotal width in stallions and scrotal circumference in ruminants) and daily sperm output may indicate testicular degeneration.[9,10]

Clinical Pathology

The measurement of plasma hormone concentrations may be helpful in establishing a diagnosis of testicular degeneration in large animals. However, the relationship between the concentrations of various hormones and the parameters of testicular function appears to be quite variable. Measurements of hormone concentrations in subfertile stallions have demonstrated that serum gonadotropins can be abnormally low or high.[11] Hormonal criteria for confirming testicular degeneration in stallions typically include low concentrations of testosterone, with concurrent low LH concentrations in early cases of degeneration or with high FSH and low estradiol concentrations in cases of chronic (or irreversible) testicular degeneration. Less is known about hormone

concentrations in other large animal species with testicular dysfunction. Scrotal insulation of rams resulted in an increase in plasma FSH concentrations and a decrease in plasma testosterone concentrations within 1 to 4 weeks.[12]

Testicular biopsy can confirm degeneration.[13] Excision of an amount of tissue sufficient for evaluation often results in hemorrhage, pressure degeneration, and necrosis.[2] Therefore testicular biopsy is usually undertaken only as a final recourse. However, testicular biopsy in the stallion appears to be a relatively safe procedure.[14]

Treatment and Prognosis

Once testicular degeneration has occurred, treatment is usually of no benefit. However, any factors that might contribute to testicular degeneration (such as febrile conditions or systemic illness) should be corrected. Treatment of injuries of the scrotum and its contents is described earlier in this chapter.

Recent findings regarding variations in serum hormone concentrations in subfertile stallions have stimulated an interest in gonadotropin replacement therapy, including the use of GnRH. Although the hypothalamic-pituitary-testicular (HPT) axis of the stallion is remarkably refractory to GnRH-induced downregulation compared with other domestic species,[15] there are few controlled studies to evaluate the effectiveness of GnRH therapy. In one study, pulsatile or constant administration of GnRH for 20 weeks did not promote testicular growth or alter spermatozoa output in reproductively sound or unsound stallions.[16] In some cases, degeneration is temporary and improved semen quality is evident after 2 to 5 months. The prognosis for an animal recovering its fertility and the economic losses the client will sustain from treatment and decreased production must be considered when deciding whether treatment of testicular degeneration is warranted.

Orchitis

Definition and Etiology

Orchitis is most commonly caused by infection or trauma. Bacterial infections may develop hematogenously or occasionally by retrograde movement from infected accessory sex glands. Periorchitis or epididymitis may coexist.[1] Testicular enlargement is due to edema that accompanies the inflammatory reaction. Contusion and inflammation of the testes occur in racing stallions,

particularly Standardbreds. *S. zooepidemicus* is commonly isolated from infectious orchitis in stallions. In bulls, infectious orchitis is caused by *B. abortus, M. tuberculosis, T. pyogenes*, *Nocardia farcinica*, bovine herpesvirus 1 (IBR-IPV), and other miscellaneous organisms.[2] Epididymitis orchitis in rams may be associated with *B. ovis* or *Actinobacillus seminis* and *Actinobacillus*-like organisms.[3]

Clinical Signs and Differentials

Acutely orchitic testes are hot, swollen, and painful. The swollen testis is turgid because of restriction by the tunica albuginea. Edema of the testicular parenchyma and concurrent presence of periorchitis or epididymitis may be detectable by ultrasound examination. Increased testicular temperature, congestion, and interference with circulation lead to ischemia and infarction. Abscesses sometimes develop, occasionally culminating in purulent liquefaction of testicular parenchyma. Testicular atrophy and fibrosis follow as the condition becomes chronic.

Acutely affected animals may refuse to mate. Ejaculates may contain numerous white blood cells. Variable mineralization of seminiferous tubules can occur as a chronic change. Decreased sperm motility and increased sperm morphologic abnormalities are evident. Standardbreds affected by acute orchitis may switch from a trot to a pace, whereas Thoroughbreds may suddenly develop a hopping gait.

Treatment and Prognosis

Treatment consists of scrotal cryotherapy and systemic administration of antiinflammatory drugs. Bacterial orchitis is treated with antibiotics chosen by semen culture and in vitro sensitivity. Antibiotic therapy should continue for 1 to 2 weeks beyond resolution of testicular swelling and pain. Testicular atrophy and sterility are common sequelae to orchitis. Changes in the testes, including precise measurements of in situ testis size, are followed by sequential ultrasound examinations or caliper measurements. Serial semen analyses over a period of several months allow the clinician to monitor response to treatment and return of testes to normal production of spermatozoa.

Prevention and Control

Support devices may aid in preventing recurrence of traumatic orchitis in

racehorses. With *Brucella* or *Actinobacillus* orchitis in sheep, the presence of subclinical carriers in the flock must be considered.

Testicular Neoplasia

Definition and Etiology

Primary testicular tumors are uncommon in large animals but may be slightly more frequent in older bulls than in stallions or rams. Testicular tumors originate from the interstitial (Leydig) cells, Sertoli cells, and the germinal epithelium. Testicular teratomas and lipomas of the testicular surface and lymphosarcoma also occur.[1-3] Although the incidence of testicular tumors is relatively greater in retained than in scrotal testes in dogs, this predisposition has not been confirmed in large animals, perhaps because most are castrated at an early age before the time of usual onset of testicular neoplasia. Retained testes in the horse, however, are thought to be more prone to neoplasia. Teratomas in particular are found more commonly in cryptorchid than in scrotal testes, probably because they are embryonal in origin and their size prevents migration of the testis into the scrotum.

Seminomas are the most common primary testicular tumor in the descended testes of adult stallions, with the majority occurring in stallions older than 10 years of age.[4] Seminomas are not hormonally active and are usually benign, but they may be malignant and invade inguinal and abdominal tissues.[5] Seminomas are rare and benign in bulls and are rarely seen in aged rams, in which they are occasionally highly malignant. The tumor arises from the germinal epithelium, occurs in retained and scrotal testes, and grows rapidly.

Interstitial (Leydig) cell tumors have been reported in stallions and bulls and can have a negative impact on semen quality and fertility.[6] Most do not produce androgenic hormones. They may be single or multiple in one or both testes and are commonly 1 to 2 cm in diameter.

Sertoli cell tumors are reported in horses, cattle, and sheep, but they are rare. Although metastasis is uncommon, extension of neoplastic tissue into the testicular vein and lymphatics can result in hydrocele. Because of the importance of Sertoli cells in spermatogenesis, these tumors are likely to exert an adverse effect on semen quality and fertility. Tumors in newborn or young calves may be due to impaired embryogenesis.[3]

Teratomas are usually a benign tumor commonly found in cryptorchid testes

of horses.[1,7] They are rare in other large domestic species. The tumors are often cystic and vary in diameter from 10 to 25 cm or more. Structures present in teratomas arise from all three embryonic layers and include hair, nervous tissue, salivary glands, adipose tissue, cartilage, and bone.[7]

Clinical Signs and Differentials

Neoplastic testes are often larger than normal, with an affected scrotal testis often twice the size of the unaffected testis, especially in cases of seminoma. Abdominally located testicular tumors can be quite large. Neoplastic testes, particularly seminomas, are typically irregular and firm. Swelling may extend into the spermatic cord, and pain that interferes with breeding or is evident on palpation may be present. Ultrasonographic appearance of testicular tumors tends to be discrete, well-circumscribed hypoechoic areas within the usually homogeneous testicular parenchyma.[5] However, seminomas may involve so much of the testis at the time of diagnosis that differentiation between neoplastic and normal tissue can be difficult.

Swelling of the affected testis may interfere with thermoregulation of the contralateral testis, resulting in decreased sperm production. Semen examination, however, may reveal seminal parameters to be within normal limits, and fertility may be acceptable. A significant amount of normal testicular parenchyma may remain covering the tumor, and living spermatozoa may or may not be present in the epididymis on the same side.[8]

Treatment and Prognosis

Testicular tumors should be surgically removed. Although metastasis is uncommon, early identification and removal of unilateral tumors prevents spread to other tissues. If semen quality is satisfactory in seasonal breeders, removal may be delayed until the breeding season is completed to avoid the transient decrease in semen quality associated with postsurgical swelling. If neoplasia is bilateral, surgical removal may be delayed until semen quality deteriorates sufficiently to negate the use of the animal for breeding.

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Infertility Caused by Diseases of the Spermatic Cord

Torsion of the Spermatic Cord

Definition and Etiology

Torsion of the spermatic cord occurs more commonly in stallions than in other large animals, possibly because of the horizontal position of the testes within the scrotum. Torsions may be transient or permanent and typically are of 180 to 360 degrees, but rotations may be greater.[1] Abnormal elongation of the caudal ligament of the epididymis (scrotal ligament), the proper ligament of the testis, or an excessively long mesorchium may encourage spermatic cord torsion.[1,2]

Clinical Signs and Differentials

Torsion of the spermatic cord occurs in degrees that vary from those producing no pain or abnormality of semen to those involving vascular obstruction and acute colic. Torsion is often a transient condition that does not interfere with testicular function or cause pain.[2] In those cases the testis is usually rotated 180 degrees or less. If torsion is of sufficient degree to result in vascular compromise, acute pain results.[2,3] Diagnosis of torsion of the spermatic cord is aided when displacement of the tail of the epididymis and scrotal ligament is evident on palpation. The head of the epididymis is normally located craniodorsal to the testis, and the tail lies caudally, where it is attached to the testis by the proper ligament. The tail of the epididymis is most readily palpable, and its location is helpful in determining the degree of rotation. Torsions of 360 degrees or greater generally cause clinical signs that must be differentiated from strangulation of herniated contents into the scrotum. The primary method used to differentiate between the two conditions is palpation per rectum of the superficial inguinal ring to identify if herniation is present.

Clinical signs of vascular impairment with spermatic cord torsion include abdominal discomfort, elevated heart and respiratory rates, unilateral swelling and edema of the scrotum, and increased testicular temperature.[4] Affected testes are painful and quickly become soft and friable.[2,3]

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Treatment and Prognosis

Manual correction of spermatic cord torsion is sometimes possible, but recurrence is likely. To attempt manual correction, the horse is sedated and the testis is rotated in the direction opposite the torsion. Both hands are used to reposition the scrotum as the testis and its tunics are rotated. Surgical correction is indicated if manual correction is not possible. Nonsteroidal antiinflammatory drugs and analgesics may be administered to control pain.

The rapidity with which correction must occur is unknown; human testes may be salvageable if torsion is corrected within 6 hours. If hemorrhage or necrosis of the testis is evident, removal is indicated because the contralateral testis may become permanently damaged. The mechanism of the damage is probably immunologic, resulting from antibodies to spermatozoa liberated as a result of ischemia.[4]

Varicocele

Definition and Etiology

Varicoceles are abnormally distended and tortuous veins of the pampiniform plexus.[1] Varicoceles are most often recognized in rams, where dilations in vessels may reach 15 cm and discourage movement and libido. Data from slaughterhouse necropsies show an increased incidence of varicoceles with age, reaching approximately 2% in rams 3 years and older. Varicoceles have been reported very infrequently in stallions.

Varicoceles may result from insufficiency of veins draining the testis or a deficiency of the fascia and connective tissue surrounding those veins that allows backflow and stasis of blood in the vessels. Infertility associated with varicocele is thought to be due to disturbance of the local thermoregulatory mechanism, causing increased testicular temperature and subsequent disturbance in spermatogenesis. In addition, the varicose veins could affect the level of oxygenation and normal interchange of hormones between the arteries and veins. In rams, bilateral varicoceles are more common than unilateral varicoceles.[1,2] This is in sharp contrast with men, in which 70% of varicoceles are unilateral and located on the left side.[2] Concomitant atrophy of the testis is common in rams. Bilateral varicoceles and atrophied testes have been reported in the ram.[3]

Clinical Signs and Differentials

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Diagnosis of varicocele is made by palpating the dilated tortuous veins (“bag of worms”) within the spermatic cord. Confirmation of the varicocele has been accomplished by ultrasonographic examination in stallions. Large echolucent areas in the venous plexus of the spermatic cord, sometimes with concurrent distention of the central vein of the testis, are described as the identifying features. The ultrasonographic appearance of a suspected varicocele can be compared with the structures of a noninvolved contralateral testis and spermatic cord or with those of another nonaffected animal.

Thrombosis of the varicocele can occur. The large, organizing laminated thrombi can be mistaken as *Corynebacterium pseudotuberculosis* abscesses in the scrotal fascia of rams. Varicoceles might also be mistaken for sperm granulomas of the caput epididymis. Unless thrombosis has occurred, varicoceles are typically fluctuant and soft and fail to elicit pain when palpated.

Treatment and Prognosis

Surgical removal of varicocele has improved semen quality and fertility of some human patients but has not been reported in large animals. Thrombosis of a varicocele necessitates unilateral castration, with transection of the spermatic cord proximal to the thrombus. Castration is also recommended for rams because of potential heritability risks.

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Infertility Caused by Diseases of the Epididymis and Accessory Sex Glands

Epididymitis

Definition and Etiology

Epididymitis is caused by infection or trauma and may occur separately but is commonly secondary to orchitis or infection of the accessory sex glands.[1] The tail of the epididymis is commonly involved, but the head and body may be affected. *S. zooepidemicus* is commonly isolated from equine epididymitis, although a number of other miscellaneous organisms, including *Proteus mirabilis*, have been incriminated.[2] In bulls, *B. abortus*, *A. seminis*, *T. pyogenes*, and other miscellaneous organisms cause epididymitis.[1] In mature rams the disease is commonly associated with *B. ovis*, whereas in ram lambs organisms from the *Actinobacillus*, *Haemophilus*, *Histophilus*, and *Corynebacterium* groups are prevalent.[3] Routes of infection have been postulated to be hematogenous, venereal, or ascending from genitourinary passages, similar to routes of infection proposed for orchitis. Injuries, such as penetrating wounds, especially during shearing, could compromise the scrotal sac, leading to epididymitis. All routes of infection are likely to occur to some degree, depending on the pathogen and species involved. In an interesting study performed in yearling rams, conjunctival inoculation of *B. ovis* culminated primarily in localized infections of the reproductive tract, which tended to first result in lesions of the distal tail of the epididymis.[4]

Clinical Signs and Differentials

Diagnosis of epididymitis is based on detection of clinical signs that include pain when irregular swellings of the epididymis are palpated, changes in shape and texture of the organ, adhesions between the epididymis and scrotal tunics, and enlargement of the tail of the epididymis. The course of epididymitis varies from acute swelling and edema to chronic abscesses, periorchitis, and fibrosis. Granulomas may develop if sperm escape into surrounding tissue.[1,5] In rams, epididymal lesions may be palpable along the entire length. Abnormal sperm morphology (especially detached heads) and leukocytes in the ejaculate may be

seen before lesions are palpable.[6]

Animals affected with the *Actinobacillus*, *Histophilus*, and *Haemophilus* groups of organisms may acquire an epididymo-orchitis syndrome.[7] Affected rams are usually younger than 1 year of age. They may be subclinical carriers or acutely ill with pyrexia, depression, pain as evidenced by an arched back, and unilateral or bilateral swelling and tenderness of the scrotal contents. If these animals recover from the acute phase, the disease may become chronic and is characterized by an enlarged, firm, and often irregular epididymis; palpable adhesions of portions of the epididymis to the testis and vaginal tunics; atrophic testes; abscess formation; and draining fistulas to the scrotal surface. Ultrasonographic examination of the epididymis may reveal dilated ducts, fluid accumulation around the tail of the epididymis, and cystic areas within the epididymis that contain purulent material.

Clinical Pathology

Inflammatory cells may be present along with abnormal sperm in the ejaculate of affected animals. Seminal leukocytes correlate positively with epididymitis lesions and correlate negatively with seminal quality.[6] Bacteriologic culture or PCR analysis of the semen may aid in identifying specific infectious causes. Serologic tests for *B. ovis* and *Helcococcus ovis* are available and are helpful in determining exposure to the organisms.[7]

Treatment and Prognosis

Infectious causes of epididymitis are treated with systemic antibiotics selected by in vitro sensitivity. The ability of the antibiotic to gain access to the epididymides must be considered. Treatment should continue for 1 to 2 weeks after inflammatory cells disappear from the semen. In unilateral cases, removal of the testis, epididymis, and spermatic cord on the affected side may salvage some valuable animals for breeding. If unilateral castration is elected, sequential postcastration examinations are indicated to ensure that infection has not spread to remaining reproductive organs.

Treatment of ram epididymitis is usually not recommended but might be attempted in valuable animals with minimal clinical signs. Oxytetracycline 10 mg/kg and dihydrostreptomycin 25 mg/kg IM twice daily for 7 days resolved shedding of *B. ovis*.[8] Because ovine brucellosis is a reportable disease in many states and provinces, treatment of affected rams should be conducted with

appropriate regulatory oversight.

In cases of moderate or severe bilateral epididymitis, the prognosis for recovery is poor. Obstructions and granulomas usually develop, resulting in sterility. Testicular atrophy is a common sequela to epididymitis.

Seminal Vesiculitis (Vesicular Adenitis)

Definition and Etiology

Inflammation of the vesicular glands is uncommon in stallions but more likely in bulls.[1] Bacterial infections including *B. abortus* and *P. aeruginosa* are incriminated in stallions.[2-4] In bulls, a variety of microorganisms have been isolated from cases of vesicular adenitis, including *Actinobacillus actinoides, Aeromonas hydrophila, T. pyogenes, B. abortus, C. psittaci, C. renale, C. pseudotuberculosis, E. coli, H. somni, M. tuberculosis, Mycobacterium paratuberculosis, Mycoplasmas, P. mirabilis, Streptococcus, Staphylococcus, Ureaplasmas,* and *T. foetus.*[1,5-17] In bulls, the most frequent microorganism isolated is *T. pyogenes.*

Vesicular adenitis may affect bulls of all ages but is most common in young, growing bulls fed high-energy rations and housed together.[1] The prevalence may reach 20% to 30% in small groups of yearling bulls in close confinement.[18] The role of viral pathogens in outbreaks of the disease is not defined. Infections may arise by either ascending or descending routes from other areas of the urogenital tract, or hematogenously. Some bulls with vesicular adenitis submitted to necropsy presented anatomic defects at the level of the seminal colliculus, which could impair its normal opening and closing.[19] In addition, it has been suggested that spermatozoa or urine reflux into the vesicular glands could produce inflammation.[20] Frequent homosexual activity among young bulls, high nutrition, and fast growth rates may be involved in spread of the infection.[1]

Clinical Signs and Differentials

The seminal vesicles of affected stallions may be of normal size or enlarged and painful when palpated per rectum.[2,3] Stallions may refuse to cover or may be unable to ejaculate.[21] Semen contains numerous neutrophils and blood. Fertility of infected semen is reduced. Bacterial pathogens are readily recovered from semen of affected stallions, but special culturing methods may be needed

(described below).

Bulls affected with vesicular adenitis may be asymptomatic or exhibit nonspecific clinical signs other than deterioration of semen quality. In severe cases, pelvic inflammation and peritonitis result in pain reflected by reluctance to move, stiff gait, tense abdomen, difficulty on defecation, and refusal to mate. In acute vesicular adenitis the palpation per rectum of the vesicular glands produces pain, and the examination is positive for an enlarged gland with loss of its lobulation and increased consistency. Other reproductive organs, particularly the ampullae, testes, and epididymides, may be inflamed.[1] Necropsy specimens of bulls with vesicular adenitis have shown concomitant inflammation of the prostate and bulbourethral glands (seminal vesicular syndrome)[1,22]; however, these changes cannot be detected by palpation per rectum. The vesicular glands may not be significantly increased in size during the acute phase. If inflammation becomes chronic, the glands usually enlarge, eventually losing their lobularity and becoming fibrotic. Abscesses are often caused by *T. pyogenes* and may rupture into the rectum or urinary bladder. Transrectal ultrasonography can be used to determine the degree and extension of the lesion in the vesicular glands.[23,24]

Purulent exudate is present in the ejaculate, sometimes as thick clots. Neutrophils may become less evident in semen as the condition becomes chronic. The ejaculate volume could be reduced. Presence of floccules or flakes in the ejaculate can be observed, and color can vary from normal to yellow-brown. Poor sperm motility, increased morphologic defects, and an elevated pH are characteristics of semen from bulls with vesicular adenitis.

Fertility of mildly affected bulls may remain satisfactory. More extensive involvement in which semen quality is markedly affected results in subfertility or infertility.[18] Semen from bulls with vesicular adenitis freezes poorly, and antibiotics used in extenders usually do not control the high numbers of bacteria present.[18,25,26]

Clinical Pathology

Bacterial pathogens can be recovered from the semen of affected stallions. However, without other evidence of infection of the accessory sex glands, recovery of pathogens from the semen should be interpreted with caution because the bacteria could originate from another location. Repeated samples for culture should be obtained from the sheath, penis, fossa glandis, preejaculatory

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fluid, urethra (before and after ejaculation), and seminal vesicle effluent manually expressed through a sterile urethral catheter positioned at the colliculus seminalis. Prostatic fluids can be collected through a catheter by massage per rectum. The first jet of a fractionated ejaculate includes the secretions of the ampullae. Alternatively, a suitable fiberoptic endoscope can be passed in the urethra to the level of the seminal colliculus and into the seminal vesicles. Purulent material may then be aspirated for culture.

Vesicular secretions from bulls can be collected either by using a sterile artificial vagina[9] or by extending and disinfecting the penis followed by irrigation of the distal urethra with sterile saline. A sterile catheter is then passed 30 cm into the urethra, and the accessory sex glands are massaged to stimulate their secretion. Fluid is collected in sterile containers. Recently, a new aseptic technique of semen collection as an alternative of both previous methods was developed. The procedure consists of clipping the preputial hairs, urination, antisepsis of the preputial area, flushing the preputial cavity with antiseptic solution, per rectum massage of accessory sexual glands, and semen collection by electroejaculation. Preliminary studies in healthy bulls using this method showed low contamination of semen samples.[27]

Treatment and Prognosis

Accessory sex gland infections are treated with antibiotics selected by culture and in vitro sensitivity. Antibiotics are administered for 2 to 4 weeks, but treatment failures may occur. Properties of antimicrobials suitable for parenteral treatment of accessory sex gland infections include high lipid solubility, a favorable pKa (higher than the pH of the target tissue or fluid), and low or limited protein binding. The antimicrobial should have a pH that is basic relative to the accessory gland fluid into which penetration is desired.[28] Vesicular and prostatic fluids have a pH of 7.3 to 7.5. Antimicrobials that may prove suitable for treatment include the newer macrolides, which are fat soluble and have a high pKa. Because of its antimicrobial spectrum and tissue diffusion characteristics, enrofloxacin has been found to be effective for systemic treatment of some cases of seminal vesiculitis in stallions. Treatment of stallions by lavage and instillation of antimicrobials directly into the seminal vesicles via a flexible videoendoscope can be accomplished by skilled operators. Removal of the affected gland has been performed in stallions and bulls.[2,25,29,30] A technique used with fair success in stallions with localized vesicular adenitis is repeated

irrigation through a catheter guided into the vesicles by endoscopy. Antibiotics are instilled into the vesicular gland lumen after each irrigation. In bulls, some experts recommend antibiotic treatment, either oral or parenteral, for a minimum of 10 days.[31,32] In bulls, direct injection of different medications into the vesicular glands has been reported, but results are mixed.[32-35] In young bulls with vesicular adenitis, parenteral administration of antibiotics was no different than in the "no-treatment" group,[33] which is in agreement with previous reports describing spontaneous recovery.[18,35] Additional measures to treat inflammation include performing repetitive semen collections, not only for monitoring the ejaculate but to evacuate the inflammatory secretions from the seminal glands as well.[18] Massage of the seminal glands per rectum has also been proposed. The inclusion of nonsteroidal antiinflammatory drugs to reduce inflammation, pain, and fibrosis has also been suggested.[18]

Seminal vesiculectomy could be used as an alternative after lack of response to medical treatment. Different techniques have been applied with variable results and complications.[29,30,36] If the bull recovers from surgery, it can exhibit a decrease in seminal parameters such as motility, volume, sperm output, and seminal constituents, which could adversely affect the freezability of the semen.

The prognosis of vesicular adenitis is difficult to determine due to the multiple etiologic organisms. Therefore the prognosis for correction of vesicular adenitis is only fair to poor. Mild cases may recover spontaneously in 2 to 3 months. In chronic cases, glands that do not abscess become fibrotic and destroyed even though purulent material does not persist in the ejaculate. In stallions with vesicular adenitis, immediate filtration of the ejaculate in order to remove cellular debris and mixing of semen in an appropriate antibiotic-containing extender to control bacterial growth may maintain sperm motility and fertility.[21]

Blockage of the Efferent Ducts (Sperm Stasis)

Blockage of the efferent ducts between the testes and penile urethra sometimes occurs in stallions. If the condition is bilateral, azospermia results despite apparent ejaculation. The ampullae are frequently tense, and enlargement may be demonstrated by ultrasonography.[1] Massage of the ampullae per rectum followed by frequent intervals for semen collection may result in ejaculation of a semen sample with a high concentration of spermatozoa, often present as "strings" or "plugs." Large numbers of detached sperm heads, often in clumps,

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are commonly observed. Collection of semen on a regular schedule may aid in preventing recurrence once the blockage is relieved. Some refractory cases have responded to administration of oxytocin or cloprostenol prior to attempt at breeding or semen collection. Empiric treatment by blockade of β-receptors and stimulation of α-receptors has been successful in some stallions that fail to ejaculate.[2]

Sperm granulomas caused by accumulation of spermatozoa in blind efferent ducts are a common cause of infertility in the buck and ram. Granulomas have also been identified in stallions.[3]

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PART 6
Preventive and Therapeutic Strategies

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• CHAPTER 44

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Critical Care and Fluid Therapy

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Equine Fluid Physiology

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Physiologic fluid compartments consist of total body water (TBW), extracellular fluid volume (ECFV), and intracellular fluid volume (ICFV). TBW is the most clearly defined compartment because it represents the total amount of water comprising an individual. Values for TBW in adult horses have been reported to range from 0.623 to 0.677 L/kg.[1-4] Values in foals are larger than in adult horses and have been reported as 0.74 L/kg.[5] Acute changes in TBW in clinical patients can be detected with serial body weight measurements, but this becomes less accurate over longer periods of time.

ECFV represents the component of TBW that is not contained within the cells. This includes plasma volume, interstitial volume, and transcellular compartments (gastrointestinal tract, joint fluid, cerebrospinal fluid [CSF], body cavities, etc.). The ECFV has been measured using a number of techniques in horses; reported values in adult horses range from 0.214 ± 0.01 to 0.253 ± 0.01 L/kg.[1,6] Estimations of ECFV in foals are significantly larger, including 0.38 to

0.40 L/kg in newborn foals and 0.290 L/kg in foals 24 weeks of age.[5,7] Plasma volume has been determined to be 0.050 L/kg in healthy adult horses and 0.090 in foals at 2 days of age.[5,7]

ICFV is the volume of fluid contained within cells. It has been estimated as the difference between TBW and ECFV. Bioimpedance technology has also been used to estimate the volume of intracellular space in horses, whereas standard indicator dilution techniques cannot be easily applied to the ICFV.[1,2] Reported values for ICFV in adult horses range between 0.356 ± 0.01 and 0.458 ± 0.06 L/kg.[1,2] The ICFV of newborn foals is estimated to be 0.38 L/kg.[5]

Rapid changes in fluid balance and compartment volumes can occur during disease states, especially critical illness. The next section discusses the physiologic relationships between these fluid volumes.

Plasma and Interstitial Balance

Although both the plasma volume and the interstitial volume are components of the ECFV, the plasma volume is separated from the interstitial space by blood vessel walls, with constant flow of fluid and proteins into the interstitial space. The plasma and interstitial volume therefore are in constant flux, and a single equation (the Starling hypothesis) describes the flow between these two spaces as net capillary filtration:

$$\text{Net capillary filtration} = K_f([P_{cap} - P_{if}] - \sigma[\pi_p - \pi_{if}])$$

where K_f is the capillary filtration coefficient, being dependent on capillary surface area and hydraulic conductivity. The other five terms in the equation represent the primary determinants of fluid balance between plasma and the interstitium:

1. π_p is the colloid osmotic pressure (COP) within the capillary (capillary oncotic pressure).
   The COP is determined by the concentration of plasma proteins, primarily albumin, and their ability to attract ions. Normal COP in adult horses is approximately 20 mm Hg (19 to 26 mm Hg) and in neonatal foals is 18.8 ± 1.9 (15 to 22.6) mm Hg.[8,9] Hypoproteinemia with resultant decreased oncotic pressure can occur during a variety of

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diseases in horses but is most often a result of loss or decreased production. Losses most commonly occur through the diseased gastrointestinal tract in large animal species (protein-losing enteropathies); losses may also occur as a result of glomerular diseases or large accumulations of protein-rich effusions within body cavities or the interstitial space. Decreased production of protein (specifically albumin) occurs in response to systemic inflammation because albumin is a negative acute phase protein.[10] Hypoproteinemia also occurs uncommonly because of liver disease.[11] Decreases in COP are also commonly observed during intravenous fluid therapy in horses undergoing general anesthesia.[12]

2. π_{if} is the COP within the interstitium.

   Interstitial COP is more difficult to measure than plasma COP, but estimates of this number include 12 to 15 mm Hg in other species under experimental conditions.[13] Changes in total plasma protein concentration are likely to also affect the interstitial protein concentration and therefore alter both oncotic pressure components in Starling's equation. This may explain why some horses with significant hypoproteinemia do not show clinical signs of interstitial fluid accumulation (i.e., edema). That is to say, the gradient between capillary and interstitial oncotic pressure is only minimally affected when both have decreased proportionally, especially with time. It has been speculated that acute changes in plasma total protein concentration, however, may lead to edema formation more often than chronic hypoproteinemia; this is because of a relatively larger decrease in plasma protein concentration as compared with that in the interstitium with acute disease. Conversely, administration of hyperoncotic intravenous fluids (fluids with a COP greater than 20 cm H_2O) can potentially shift the balance of oncotic pressure back to the vascular space by raising plasma COP. However, the colloid molecules from these fluids must remain within the vascular space to have this effect, which may be negated by significant alterations in capillary permeability.

3. P_{cap} is the hydrostatic pressure within the capillary.

   Vascular hydrostatic pressure represents the pressure of plasma within the vessels pushing out toward the interstitium. A number of factors

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influence this pressure, including blood volume, vascular tone, and central venous pressure (CVP). This outward pressure on the vessel walls serves as the driving pressure for the continuous flux of fluid and protein out of the vessels into the interstitium. Pathologic increases in hydrostatic pressure can be caused by right-sided heart failure or other obstructive processes, such as venous thromboses, which can lead to edema formation. Pulmonary capillary hydrostatic pressure increases with left-sided heart failure and significant pulmonary vasoconstriction. Administration of intravenous fluids can also increase capillary hydrostatic pressure. Fluid losses resulting from diuretic administration and acute blood loss are examples of changes that result in decreased capillary hydrostatic pressure.

4. P_{if} is the hydrostatic pressure within the interstitium.
   The hydrostatic pressure of the interstitium varies in different tissues but often is overlooked as a significant contributor to fluid balance between the vascular and interstitial spaces. The importance of the interstitial hydrostatic pressure as it pertains to fluid balance has been reviewed by Reed and Rubin.[13,14] Degeneration of the interstitial collagen network may cause a decrease in interstitial hydrostatic pressure, resulting in a shift of fluid into the interstitium. Inflammatory cytokines have been implicated as a cause for these changes in interstitial hydrostatic pressure. Severe burn injury can also result in marked negative pressures within the interstitium, causing a draw of fluid into the interstitial space and subsequent edema formation. In the future there may be practical therapeutic options to manipulate interstitial hydrostatic pressure and alter fluid balance.
5. σ is the capillary reflection coefficient for proteins.
   Changes in capillary permeability can dramatically increase the flux of fluid and protein from the intravascular space into the interstitium.[15] If this increase in flow cannot be balanced by a corresponding increase in lymphatic return, edema results. Increased vascular permeability has been regarded as a major mechanism of edema formation; however, it may be only one component of the significant fluid shift that results from a systemic inflammatory response syndrome (SIRS). Adult horses and neonatal foals may have significant differences in interstitial composition and vascular permeability. It has also been proposed that foals have an increased capillary filtration coefficient as compared with

adults.[16] These hypotheses may explain the propensity of neonatal foals to form edema relatively easily in response to overzealous fluid administration. Because of this increased risk, careful monitoring and serial assessment of the balance between plasma volume and the interstitium are warranted when treating neonatal foals with fluid therapy.

Extracellular to Intracellular Fluid Volume Relationship

There are three main determinants of net movement of fluid between the ECFV and ICFV: tonicity of the ECFV, tonicity of the ICFV, and cellular membrane permeability.

Tonicity of the ECFV.

The tonicity (or effective osmolality) of the ECFV is estimated by the following equation[17]:

$$\text{Effective extracellular fluid osmolality} = (2 \times \text{Na}) + \frac{\text{Glucose}}{18}$$

Under normal circumstances, sodium and chloride are the primary determinants of ECFV tonicity; the equation doubles the sodium concentration rather than including the concentration of specific anions, some of which may not be easily measured. It should be noted that blood urea nitrogen (BUN) is not included in the tonicity formula because BUN is an ineffective osmole. Other effective osmoles can be added to the ECFV, thereby increasing tonicity and inducing a shift of water from the ICFV to the ECFV. The tonicity of the ECFV is primarily regulated by vasopressin (antidiuretic hormone, or ADH). Administration of fluids with a tonicity greater or less than ECFV tonicity is a means to manipulate the balance of fluid between the ECFV and the ICFV. This explains why hypertonic saline causes a shift of water from the ICFV to the ECFV. Recent mathematic models have been used to predict the influence of tonicity on the absolute volumes of these fluid compartments.[18] Similarly fluid loss that has a tonicity different from the ECFV will also alter the ratio of fluid between the ECFV and the ICFV.

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Tonicity of the ICFV.

The tonicity of the ICFV is primarily determined by the intracellular concentration of potassium and its related anions. The tonicity of the ICFV and ECFV are the same at any given time, a homeostatic mechanism meant as a safeguard to prevent acute changes in cell volume. Any imbalance in tonicity between the two fluid spaces will result in a rapid shift of fluid in order to maintain osmolar equality. The tonicity of the ICFV can be altered over time by the cells in response to changes in ECFV tonicity; an example of such a response is the production of idiogenic osmoles during hypernatremia.[19] Significant changes to ICFV tonicity during disease (resulting from damaged cell membranes) can result in accumulation of intracellular potassium, calcium, or cellular debris.

Cellular Membrane Permeability.

Cell membranes are selectively permeable to water and ions. Changes in this permeability usually do not cause large alterations in global fluid balance during healthy states. However, cell membrane damage during disease states can result in significant fluid shifts. In fact, a shift of fluid from the ECFV to the ICFV is an indicator of cellular membrane damage.

Effects of Fluid Physiology on Clinical Fluid Therapy

Specific disease states dictate individualized fluid plans. However, with intravenous therapy the administered fluid enters the vascular space. From there, the characteristics of the administered fluid will determine its movement from the vascular space into the interstitium and from the ECFV to the ICFV. Hyperoncotic or hypertonic fluids result in the greatest relative expansion of plasma volume, with a corresponding reduction in ICFV. Hypotonic fluids result in the smallest increase in ECFV but add volume to the ICFV, resulting from a decrease in the tonicity of the ECFV. Estimates of the volumes of the different fluid spaces (whether based on clinical or laboratory values) before and during fluid therapy will allow for evaluation of the physiologic response in the clinical setting. The standard and universal administration of isotonic and hypo-oncotic fluids (such as lactated Ringer's solution [LRS] or physiologic saline) to all patients regardless of disease condition ignores the available research and clinical insight to suggest otherwise.

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General Principles for Fluid Therapy in Critical Care

K. Gary Magdesian

Current guidelines for replacement fluid therapy in human critical care emphasize the “fluid challenge” method, believed to be more effective and safer than traditional estimates of percent dehydration.[1] The author's protocol of fluid administration in horses follows this same algorithm. Considerations for the fluid challenge technique incorporate four primary decision phases: (1) type of fluid, (2) rate and volume, (3) goals or end points of fluid therapy, and (4) safety limits to fluid therapy.

1. Types of fluids include crystalloids (isotonic, hypotonic, and hypertonic) and natural and synthetic colloids. There is much controversy and no consensus as to whether crystalloids or colloids are more effective or advantageous in human critical care.[1] The advantages of both fluid types are capitalized on by using them together in the treatment of some cases of hypovolemia that have concurrent hypoproteinemia. Otherwise, because of cost differences and lack of demonstrated benefit of colloids as compared with crystalloids in terms of mortality for fluid resuscitation in critically ill human patients, the use of colloids cannot be recommended over crystalloids.[2] Recent publications have suggested increased mortality and complication rates in humans receiving hetastarch as compared to crystalloids. See the Fluid Therapy for Diarrhea and Colitis in Horses section later in this chapter. Table 44.1 lists the composition of several commercially available crystalloids that are used in equine practice.

TABLE 44.1

Composition of Commercial Replacement and Maintenance Fluids

Crystalloid	Sodium (mEq/L)	Potassium	Chloride	Calcium	Magnesium	Osmolarity (mOsm/L)	Organic Salt
Replacement							
Lactated Ringer's solution	130	4	109	3	0	272-273	28 lactate
Saline	154	0	154	0	0	308	0

(0.9%)							
Ringer's solution	147-148	4	156	4.5	0	310	0
Plasma-Lyte 148 or Plasma-Lyte A	140	5	98	0	3	294	27 acetate
							23 gluconate
Normosol-R	140	5	98	0	3	294	27 acetate
							23 gluconate
Maintenance							
Plasma-Lyte 56	40	13	40	0	3	111	16 acetate
Normosol-M	40	13	40	0	3	110	16 acetate
45% NaCl + 2.5% dextrose	77	0	77	0	0	280	0
5% dextrose	0	0	0	0	0	252-253	0

2. The rate of fluid therapy for replacement (i.e., treatment of hypovolemia) is based on the “fluid challenge” principles, whereby a 30- to 60-minute bolus of 10 to 20 mL of isotonic crystalloid per kilogram is administered with subsequent reassessment of perfusion parameters.[1] This rate would be faster for animals dying of hypovolemic shock, with pressure bags sometimes being used for rapid delivery. This fluid challenge method assumes that uncontrolled hemorrhage is not present because that would warrant hypotensive resuscitation instead, where the goal is a mean arterial pressure of 60 mm Hg and just enough perfusion pressure to perfuse organs. Perfusion parameters on the physical examination of horses and foals include mentation, heart rate, mucous membrane color, capillary refill time, jugular fill, extremity temperature (limbs, ears), and pulse quality. Blood or plasma lactate concentration, arterial blood pressure, urine output, and urine specific gravity are additional monitoring tools that aid in assessment for further fluid challenges. After the initial bolus, additional boluses—over 30 to 60 minutes depending on the degree of hypovolemia present—would be administered if perfusion parameters dictate a need for more fluid volume. These are repeated until signs of shock abate, a lack of improvement is noted with subsequent boluses, or fluid limits are reached (see later). Most animals

require one to three of these boluses, and rarely are four required. Alternatively, or in addition to isotonic crystalloids, hypertonic saline (7% to 7.5%) can be administered at a rate of 4 mL/kg intravenously (IV) once. Plasma sodium concentration should be monitored, as hypernatremia can result. Because of their distribution that is limited to the central compartment, colloids are bolused at lower volumes than isotonic crystalloids, such as 3 to 5 mL/kg for hetastarch. Up to 10 mL of hetastarch per kilogram may be administered per day, being limited by development of dose-dependent coagulopathies, although concerns over a mortality rate increase and renal injury in human patients has markedly reduced the use of hetastarch in those patients.

If after reassessment of the perfusion parameters additional resuscitative fluids are deemed necessary, another similar bolus is given, although each subsequent bolus is usually provided at a slightly slower rate unless the patient is markedly hypovolemic. This is repeated until signs of hypoperfusion resolve (end points are achieved) or safety limits are reached and there is no further positive clinical response to fluid bolus administration, at which point inotrope and/or vasopressor therapy is indicated if hypoperfusion persists.

3. The goals or end points of fluid therapy include both replacement and maintenance of fluid balance. *Replacement* refers to the replenishment of fluid deficits, primarily referring to those in the extracellular fluid compartment. *Maintenance fluid therapy* refers to the provision of maintenance fluid requirements to account for metabolism, insensible losses, growth, and ongoing losses. In general terms, *replacement* refers to replenishment of circulating volume and secondarily of interstitial fluid deficits; *maintenance* refers to provision of fluids after hypovolemia and dehydration have been corrected. Maintenance fluid therapy maintains both circulating volume and hydration status, including that of the intracellular compartment. In this section, replacement fluid is emphasized; the goals of replacement fluid therapy include rapid correction of hypovolemia by reversal of the signs of shock, including improvement or correction of seven perfusion parameters: tachycardia (except in some neonatal foals, which may not demonstrate tachycardia as a manifestation of hypovolemia), pale mucous membranes, prolonged capillary refill time, cold extremities, poor pulse quality, depressed mentation, and, in horses, reduced jugular

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fill time. Urine production is another positive sign indicating correction of fluid deficits and subsequent perfusion of the kidneys. Dehydration, or the extravascular fluid deficit, is corrected more slowly than hypovolemia and is marked by reduced skin turgor (increased skin tent), dry mucous membranes, and dry corneal surface (reduced tear production). Additional goals of volume replacement include correction of hypotension, tachycardia, oliguria, and blood lactate concentration.[1] A decrease in urine specific gravity (in the absence of renal failure), an increase in arterial blood pressure and CVP, and improvement in venous oxygen saturation are specific end points. The goals of maintenance fluid therapy are different than those of replacement fluid therapy; they are to maintain a normal degree of hydration by providing for ongoing losses, including insensible losses (respiratory, cutaneous evaporative losses) and any abnormal ongoing losses such as diarrhea or reflux. Maintenance fluid rates for horses vary with ambient temperature, use, diet, and metabolic status. In general, a reasonable starting point for maintenance fluid requirements includes 2 to 3 mL/kg/h for adult horses (possibly slightly lower if off feed) and 4 to 6 mL/kg/h for neonatal foals.[3,4]

4. The safety limits to fluid therapy are indicators of intravascular volume overload, including supranormal CVP, a decrease in arterial oxygen saturation (Pa_{O_2}), and clinical indicators of volume overload and overhydration. Once maximal CVP is achieved (10 to 12 cm H_2O in neonatal foals and 15 cm H_2O in adult horses), replacement bolus fluid therapy must stop; if continued, edema may form as systemic and capillary hydrostatic pressures increase in response to further fluid boluses. A decrease in oxygen saturation in serial arterial blood samples, or in SpO_2 measured with pulse oximetry, in a horse receiving fluid boluses may be consistent with the possible development of pulmonary edema; this may precede development of tachypnea, increased respiratory effort, or frank edema in large airways or nostrils. Although no published reports address fluid overload in clinical equine patients, one experimental study evaluating hyperhydration before moderate-intensity exercise in horses suggested the development of arterial hypoxemia during exercise.[5] These animals were administered oral fluids equivalent to 6% of body weight (approximately 26 L of isotonic

fluid by nasogastric tube). Hyperhydration resulted in arterial hypoxemia, suspected to be caused by pulmonary edema associated with hyperhydration, during moderate-intensity exercise.[5] Clinical indicators serving as limits to fluid therapy include visible subcutaneous edema and tachypnea; with optimal monitoring, fluid therapy will not be allowed to continue to this point. Another end point or limitation to fluid therapy is a lack of further improvement in perfusion parameters despite repeated fluid boluses. This would indicate that hypoperfusion is not solely due to hypovolemia and may require inotropes and/or pressor agents (e.g., dobutamine and norepinephrine, respectively). If safety limits are reached before the goals of fluid therapy are achieved, the next step is also to turn to inotrope and vasopressor therapy.

Prevention of fluid overload should be emphasized to the same degree as provision of fluid therapy. Fluid overload and tissue edema are very detrimental to tissue and organ health, as are dehydration and hypovolemia.

See the Fluid Therapy for Diarrhea and Colitis in Horses section later in this chapter.

Critical Care and Fluid Therapy Monitoring Techniques

K. Gary Magdesian

Monitoring tools provide for advanced critical care in the large animal intensive care unit. Several of these tools are pertinent to fluid therapy and provide guidance, end points, and safety limits. Many of these tools allow for direct monitoring of critical patient status during administration of therapy, whereas others provide indirect information through hemodynamic data. Both of these factors are important to overall case management of the critically ill equine patient.

Central Venous Pressure

Central venous pressure (CVP) is the pressure within the vena cava; the term most commonly refers to that within the cranial vena cava in most species. It is determined by blood volume, venous tone, and cardiac contractility. Increases in

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blood volume or venous tone increase CVP, as does suboptimal cardiac function. The use of CVP as a measure of adequacy of fluid resuscitation has been much debated, but less controversial is its utility as a limit on fluid administration. With serial measurements CVP can provide a limit to the administered volume of fluid. Normal CVP is approximately 2 to 12 cm H_2O (1.5 to 8.8 mm Hg) in foals and 5 to 15 cm H_2O (3.7 to 11 mm Hg) in adults.[1-4] Subnormal to negative CVP values indicate hypovolemia; however, normal values do not necessarily imply euvolemia. This is because CVP is affected by compensatory responses such as venoconstriction and by cardiac contractility and intrapleural pressures, among others.

CVP is easily measured in neonatal foals using 20- to 30-cm central venous catheters, including long-term single- to triple-lumen polyurethane intravenous catheters placed in the jugular vein. Placement can be easily confirmed through thoracic radiography, with the radiopaque catheters being visualized in the cranial vena cava just cranial to the cardiac silhouette. Measurements can be obtained in adult horses with the use of 55-cm commercial CVP catheters placed in the lower jugular vein. CVP can also be measured by passing a smaller gauge polyurethane catheter or polyethylene tubing through a 14-gauge, $5\frac{1}{4}$-inch standard intravenous catheter placed in the jugular vein. The actual measurement can be recorded with a disposable water manometer (for spot or intermittent readings of the CVP value) or using a pressure transducer for continuous waveforms. Interpretation of CVP waveforms requires knowledge of component waves and descents, including the “a,” “c,” and “v” waves, and the “x” and “y” descents. The “a” wave represents atrial contraction. The mean of the “a” wave is the appropriate point at which to measure CVP (during end-expiration in a spontaneously breathing patient). The “c” wave is associated with tricuspid valve closure and a bulging of the valve into the right atrium, and the “v” wave is caused by atrial filling from venous return. The “x” descent occurs after the “a” wave and represents the fall in pressure associated with atrial relaxation. The “y” descent occurs after the “v” wave, representing a drop in CVP caused by ventricular relaxation and reopening of the atrioventricular valves.

High CVP readings occur with fluid overload, as well as with pericardial tamponade, pleural effusion, or pneumothorax. False increases may result from catheter occlusion and air within the lines. For accurate and consistent serial results, a zero reference point should be selected and used for each measurement. The top of the sternal manubrium is a good reference point for the level of the

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pressure transducer or water manometer. The pressure transducer or water manometer can be taped to a fluid pole, providing a fixed zero point for repeated measurements in standing horses. Precision and reliability are limited by variable zero reference points, the effects of afterload and ventricular compliance, and alterations in intrathoracic pressure.[5]

It should be noted that adequacy of intravascular volume cannot be guided by any one CVP level. There is not a linear relationship between intravascular volume and filling pressures, and CVP should be regarded as only an indirect estimate of volume. Serial measurements and trends over time are more useful than single numbers. CVP can be used on a clinical level for monitoring fluid therapy as follows: If the patient responds to fluid boluses without increases or with only minor increases (2 to 3 cm H_2O) in CVP, it is appropriate to continue infusions until signs of hypoperfusion are reversed or improved, as long as other signs of fluid overload are not present.[5] Additional guidelines used in human patients are as follows: If the CVP increases to 3 to 7 cm H_2O (2 to 5 mm Hg), the infusion should be paused and perfusion reevaluated after a 10-minute wait. If the change in CVP was an increase of 7 cm H_2O or greater (≥5 mm Hg) after the fluid bolus, the infusion is stopped.[5] In this regard CVP is a better “upper limit” to fluid therapy rather than an actual goal to strive for, other than normalization of CVP in horses with subnormal values.

Arterial Blood Pressure

Arterial blood pressure measurements provide some insight into perfusion status, particularly when used in conjunction with clinical signs and lab work, such as blood lactate concentration. It can be measured either directly by using arterial catheters or indirectly with a blood pressure cuff on the tailhead. Arterial lines can be placed in the great metatarsal artery of recumbent foals and the transverse facial artery in standing adult horses for direct measurements. Indirect measurements are best performed with oscillometric blood pressure monitors that provide systolic, diastolic, and mean arterial pressure (MAP). Cuffs are provided by the manufacturer and vary in width and length with the size of the patient.

Arterial blood pressure in healthy neonatal foals is highly variable and depends on breed, gestational age, and size of foal. Reported mean arterial blood pressure (direct) in neonatal foals has been reported to be 84.4 ± 3.7 mm Hg at 1 day of age and up to 101.3 ± 4.4 mm Hg at 14 days of age.[2] Indirect blood

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pressure readings in Thoroughbred foals has been reported as 144 ± 15, 74 ± 9, and 95 ± 13 mm Hg for systolic, diastolic, and mean pressures, respectively.[6] Direct blood pressure has been reported for adult horses: 126 to 168 (systolic)/85 to 116 (diastolic) with a range for the mean arterial pressure of 110 to 133 mm Hg.[7-10] Indirect blood pressure in adult horses is reported as 111.8 ± 13.3 mm Hg for systolic pressure and 67.7 ± 13.8 mm Hg for diastolic pressure.[11]

Blood pressure values should not be regarded as the sole criteria for intervention. Rather, they should be used in conjunction with perfusion parameters, blood lactate concentration, and urine output in deciding whether there is need for further fluid administration or inotrope and vasopressor support. The exact blood pressure value that should trigger intervention in horses and foals is unknown and likely varies with the individual patient; however, end-organ perfusion requires a mean arterial pressure of 60 mm Hg, thereby making that a reasonable general minimal target.

Blood or Plasma Lactate Concentration

Blood or plasma lactate concentration is very useful in monitoring fluid support, as well as perfusion and metabolic status. Increased blood lactate concentration may be a result of hypoperfusion and reduced oxygen delivery (hypovolemia, hypotension, anemia, hypoxemia, heart failure). Other considerations for hyperlactatemia should include SIRS, sepsis, catecholamine surges, liver or renal failure, thiamine deficiency, alkalosis, hyperglycemia, exercise, seizure activity, and the action of drugs such as salicylates and theophylline.[12-15] Sepsis and SIRS may increase circulating lactate concentrations independent of perfusion status; inflammatory mediators and cytokines activate pyruvate dehydrogenase kinase, an inactivator of pyruvate dehydrogenase, resulting in reduced activity of the citric acid cycle. Normal lactate concentrations in horses are less than 2 mmol/L, with most horses having concentrations less than 1 mmol/L.[16-18] Neonatal foals have decremental values after birth, with reported concentrations of 4.9 ± 1.02, 2.25 ± 0.6, and 0.89 mmol/L at birth, 12 hours of age, and 24 hours of age, respectively.[18-20] In a study performed by the author, foals had values of 2.4 ± 1.0, 1.2 ± 0.3, and 1.1 ± 0.3 mmol/L at 0 to 2, 24, and 48 hours of age, respectively, compared with 0.6 ± 0.2 mmol/L in adult horses.[21]

Cardiac Output

Advanced monitoring in equine critical care includes cardiac output

measurement. A number of methods of cardiac output monitoring have been described in horses, including the Fick principle, indicator dilution methods (such as lithium dilution), Doppler and volumetric echocardiography, pulse contour analysis, and partial carbon dioxide rebreathing. The most practical of these include lithium dilution and echocardiographic techniques.[22-26]

Lithium dilution precludes the need for placement of cardiac catheters. A small bolus of lithium chloride is injected into a peripheral vein or the cranial vena cava (via a central line). Arterial blood is sampled using an arterial catheter at a constant rate and passes through a lithium electrode to generate a lithium concentration-time curve. Cardiac output is calculated from the area under the curve for lithium over time. Advantages of lithium dilution include only moderate invasiveness, good accuracy, and requirements for only small volumes of injectate. Disadvantages include the need for continuous arterial blood and limitations on repetitive measurements owing to lithium accumulation.[25-27]

Noninvasive cardiac output measurements can be made using the Bullet method through volumetric echocardiography.[24] McConachie and colleagues[28] reported that the Bullet method provided an accurate estimate of cardiac output in anesthetized foals. The Bullet method, as well as the four-chamber area-length, Simpson, and right ventricular outflow Doppler methods, had reasonable agreement with lithium dilution in adult horses.[28] For the Bullet method, cardiac output is calculated using heart rate and stroke volume (CO = HR × SV), where stroke volume is estimated as follows:

$$SV = \left(\frac{5}{6} \times LVAd \times LVLd\right) - \left(\frac{5}{6} \times LVAs \times LVLs\right)$$

where *LVAd* is the left ventricular area in diastole (short-axis view), *LVLd* is the left ventricular length in diastole (long-axis view), *LVAs* is the left ventricular area in systole (short-axis view), and *LVLs* is the left ventricular length in systole (long-axis view).

Cardiac output in healthy adult horses (400 to 500 kg) is 32 to 40 L/min.[22] Normal cardiac index, which is cardiac output expressed per unit of body weight, is 72 to 88 mL/kg/min. In the neonatal foal, cardiac output has been reported to be 7.1 ± 0.4 L/min (cardiac index = 155.3 ± 8.1 mL/kg/min) in 2-hour-old foals.[2] At 24 hours of age, cardiac output was determined to be 9.0 ±

0.5 L/min (cardiac index = 197.3 ± 12.0 mL/kg/min). This increased further to 15.7 ± 1.5 L/min (cardiac index = 222.1 ± 21.6 mL/kg/min) at 14 days of age.[2] A general guideline for normal cardiac index is 100 to 300 mL/kg/min in neonatal foals.[24]

Blood Glucose

Blood glucose concentration has been the focus of much study in human critical care in recent years. A number of initial studies demonstrated improved survival and reduced complications with tight glucose control using intensive insulin therapy in critically ill humans.[29,30] Maintenance of euglycemia (80 to 110 mg/dL) resulted in reduced mortality in surgical intensive care unit patients as compared with hyperglycemia (180 to 200 mg/dL). Hyperglycemia may be associated with detrimental effects in pediatric intensive care patients as well.[31] However, after these initial studies, additional studies, including meta-analyses, did not document similar benefits and revealed some adverse events with tight glycemic control, especially development of severe hypoglycemia.[32,33] Current guidelines therefore are more relaxed and recommend using a glucose concentration of 180 mg/dL or less as the target.[34] How these findings relate to critically ill horses is unknown, but prevention of hyperglycemia is likely warranted, and its effects in the equine intensive care unit require further study. In one study evaluating blood glucose in horses with acute abdominal disease, hyperglycemia in the first 48 hours of hospitalization was associated with a worse prognosis for survival to hospital discharge.[35] A study in hospitalized neonatal foals showed that foals with blood glucose concentrations less than 50 mg/dL or greater than 180 mg/dL at admission were less likely to survive.[36]

Monitoring Urine Analytes

Urine indices are useful for monitoring responses to fluid therapy. Successful production of urine output in response to fluid administration is a primary goal of fluid therapy, and measurement of urine production allows determination of “fluid balance” (input–output). Another important means of assessing the response to fluid loading is measurement of urine specific gravity and/or osmolarity. In the absence of renal failure, progressively dilute urine is a positive response to fluid administration. Horses on feed and water should be making 0.4 to 2.0 mL/kg/h urine, whereas those off feed and water will produce far less

(0.13 to 0.5, up to 1 mL/kg/h depending on duration).[37,38] Horses on fluids should therefore be producing a minimum of 0.5 but optimally 1 to 2 mL/kg/h of urine.

Urinalysis should be performed, and fractional excretion of electrolytes, particularly of sodium, provides information regarding tubular function and can aid in differentiation of prerenal and renal azotemia. Normal fractional excretion is less than 1% in adult horses and 0.31% ± 0.18% in neonatal foals.[39-42]

Fluid Therapy for Specific Diseases and Disorders in Horses

Fluid Therapy for Liver Dysfunction and Hepatic Failure in Horses (Box 44.1)

K. Gary Magdesian

Box 44.1

Fluid Considerations for Liver Failure

1. A combination of balanced, polyionic crystalloids and colloids is optimal.
2. Acetated fluids, rather than lactated Ringer's solution, should be used whenever available.
3. Colloids, particularly plasma, can be beneficial if hypoalbuminemia is present and to minimize third space accumulation of fluids.
4. Potassium supplementation (20 to 80 mEq/L) may aid in reducing hyperammonemia (<0.5 mEq/kg/h total).
5. Dextrose supplementation (1 to 2 mg/kg/min) should be provided for energy support. Blood glucose should be monitored and hyperglycemia should be avoided.

Acute liver disease may result in hypovolemia due to lack of water intake, third space losses into the gut and peritoneal cavity, and possibly pooling of blood in the portal circulation. Portal hypertension may result in gut edema with subsequent fluid loss. Considerations of fluid therapy in cases with hepatic

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dysfunction include reduced metabolic capacity as well as compromised synthetic ability of the liver. Because lactate clearance primarily occurs in the liver, fluids containing lactate optimally should be avoided in horses with significant liver failure when other options are available. Isotonic replacement fluids containing acetate rather than lactate as the alkalinizing anion, such as Normosol-R (Abbott Laboratories, North Chicago, Ill.) and Plasma-Lyte A or Plasma-Lyte 148 (Baxter Healthcare Corporation, Deerfield, Ill.), and acetated Ringer's solution are preferred over LRS. One millimole (mmol) of acetate yields 1 mmol of bicarbonate during metabolism and is therefore alkalinizing.[1] These balanced, polyionic fluids are optimal as compared with physiologic saline (0.9% sodium chloride) because of the propensity of the latter to produce a mild hyperchloremic metabolic acidosis (HCMA), and many horses with liver dysfunction have acidemia already.[2] Hyperchloremic acidosis has potentially adverse effects, including renal afferent arterial constriction, and has negative effects on organ function, including gastrointestinal, central nervous system, and coagulation.[3,4]

Provision of dextrose, even in the face of normoglycemia, should be considered unless enteral nutrition is adequate. The addition of dextrose to fluids will minimize gluconeogenesis demands on the liver as well as catabolism of endogenous tissues with subsequent increases in nitrogen turnover (and increased ammoniagenesis). With dextrose administration, the risk of hypoglycemia from liver dysfunction is also minimized, since patients may have insufficient liver and muscle glycogen reserves and impaired hepatic gluconeogenesis in order to maintain normal blood glucose concentrations. A common dextrose supplementation rate used by the author for adult horses is 1 mg/kg/min. This equates to 3% dextrose in fluids if 1 L/h of crystalloid is administered to a 500-kg horse. The author often begins with 0.3 to 0.5 mg/kg/min of dextrose and gradually advances the rate of administration as the horse tolerates the dextrose (aiming to keep the blood glucose concentration <160 to 180 mg/dL, or lower for horses that are prone to laminitis). The addition of B vitamins, diluted in the fluids, can be helpful for anorectic horses because they are required cofactors for oxidative metabolism. In addition, many of the B vitamins are stored in the liver. Injectable vitamin C is usually included by the author, at a rate of 20 mg/kg/day diluted in the fluids. Horses that remain anorectic for longer than 24 to 72 hours should be considered candidates for parenteral nutrition, with the addition of amino acid supplementation as the next step in nutritional support. If amino acids are administered, blood ammonia

concentrations should be monitored in horses with liver dysfunction, as they may be intolerant of the additional nitrogen.

Horses with liver dysfunction should be monitored closely for hyperammonemia as a marker of hepatic encephalopathy. Fluids can be tailored to minimize the risks of hyperammonemia. Provision of potassium, even in the presence of normokalemia, enables an electrolyte draw of hydrogen atoms from intracellular stores, thereby lowering pH and promoting ionization of ammonia to its less diffusible form, ammonium ion, which is not able to cross the blood-brain barrier.[5] Hypokalemia also promotes metabolic alkalosis and may compound hepatoencephalopathy due to increased urinary losses of hydrogen ion (H^+) and increased tubular absorption of ammonia, and therefore should be avoided in liver failure cases. For similar reasons, sodium bicarbonate should be used judiciously and with caution in horses with a propensity for hepatic encephalopathy. Increases in the pH of plasma will result in conversion of ammonium ion to ammonia; unfortunately this facilitates the brain uptake of ammonia with subsequent intracerebral trapping of ammonium ion.

The rate of fluid administration for horses with liver dysfunction will vary with the volume and hydration status of the individual. In general, rates should exceed maintenance requirements to account for hypoperfusion and produce some degree of diuresis of ammonium and other toxins, such as conjugated (direct) bilirubin that would otherwise have been metabolized or eliminated by the liver. Volume of fluid administration should be monitored closely in horses with ascites or portal hypertension resulting from severe liver disease because of the propensity of these patients for third space fluid accumulation. Other considerations for horses with liver disease include hypoalbuminemia, hyponatremia, hypokalemia, coagulopathies, and hyperlactatemia. Monitoring CVP will aid in preventing rises in hydrostatic pressure that would contribute to transudates or ascites.

Fluid support, for “maintenance fluid therapy,” can be modified in horses with preexisting ascites or edema to reduce the administered sodium load. These are hypotonic and should never be administered as a rapid bolus. Commercially available solutions with restricted sodium concentrations (maintenance crystalloids), such as Plasma-Lyte 56 or Normosol-M, can be used in foals. Because of their availability in only small volumes (1-L bags), combinations of isotonic crystalloids and sterile water or 5% dextrose in water (D_5W) can be used as maintenance fluids in larger patients (half isotonic fluid and half water or D_5W). If sterile water is selected, it should be allowed to mix with the isotonic

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fluid before entering the patient; administered alone, water could cause osmotic hemolysis. Another option in such horses is to restrict the volume of crystalloid administered through concurrent administration with colloids. Colloids expand the intravascular volume, limit the requirement for crystalloids, and may reduce the propensity of edema formation by raising oncotic pressure. However, consumptive coagulopathies would be contraindications to the administration of synthetic colloids.

Colloids are indicated in horses with significant hypoalbuminemia (<1.5 g/dL). Hetastarch previously has been recommended at doses up to 10 mL/kg/day unless coagulopathies are present, as these are a potential dose-dependent side effect of hetastarch. Liver failure may result in decreased production of clotting factors or antithrombin and can initiate disseminated intravascular coagulation (DIC). Because hetastarch can induce decreased activity of von Willebrand factor and factor VIII, as well as interfere with platelet function, it is contraindicated in horses with bleeding tendencies (after consumption of factors).[6] In addition, there has been much debate as to the safety of hetastarch and risks of acute kidney injury in humans, and some early evidence in dogs as related to number of days of hetastarch administration, which has markedly reduced the use of hetastarch in these patients.[7,8] Plasma is a colloid that has potential benefits for horses with hepatic failure, except perhaps for horses with virus-associated hepatitis (serum hepatitis). Coagulopathies associated with liver disease can be addressed through provision of exogenous antithrombin and clotting factors in plasma products. Plasma should probably not be administered to horses with serum hepatitis (Theiler's disease), since this disease is poorly understood and associated with prior administration of equine-origin biologics. Recently, viruses (e.g., flavivirus, parvovirus) have been associated with serum hepatitis.[9,10] Replacement of albumin is beneficial not only for oncotic pressure support but also for drug and toxin binding and as an endogenous buffer. If hypoalbuminemia is a result of hepatic dysfunction, and not urinary or gastrointestinal losses, colloids will have a longer retention time in the circulation.

Fluid Therapy for Diarrhea and Colitis in Horses (Box 44.2)

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Box 44.2

Fluid Considerations for Horses With Diarrhea or Colitis

1. A combination of crystalloids and colloids has many benefits in horses with colitis.
2. Colloids are indicated when concurrent hypoproteinemia and hypovolemia are present.
3. Potassium, calcium, and magnesium should be supplemented as necessary.
4. Hypertonic saline has several potential benefits for horses with acute colitis, including volume expansion, immunomodulation, antiinflammatory effects, anti-edema effects, and positive inotropic effects.

Horses with acute colitis are often presented in a state of severe SIRS with endotoxemia, hypovolemia, and malperfusion of tissues. Fluid therapy is the cornerstone of hemodynamic support for these horses. Not only is low circulating volume an indication for fluid therapy in these cases, but acid-base and electrolyte derangements also warrant treatment with fluids. In addition to hypovolemia, horses with colitis often have both organic and inorganic acidoses as well as hyponatremia. Organic acidosis primarily results from hyperlactatemia, whereas inorganic acidosis is usually a result of relative hyperchloremia (or hyponatremia) from loss of sodium bicarbonate.

Because of the poor sensitivity of physical examination in detecting hypovolemia in horses, estimates of percent dehydration and water deficit are not very accurate.[1] A more structured means of providing fluids to sick horses is through the “fluid challenge” method described in the previous sections as adopted from human critical care.[1] In this protocol a bolus dose of 10 to 20 mL/kg of isotonic crystalloid is administered over approximately 30 to 60 minutes to horses with hypovolemia, with subsequent reassessment of perfusion parameters. Horses with marked fluid deficits may require the initial bolus to be administered as rapidly as possible, using a pressure bag. Perfusion parameters consist of mentation, peripheral pulse quality, heart rate, mucous membrane color, capillary refill time, and extremity temperature. Lactate, arterial blood pressure, and central venous oxygen saturation are monitoring tools that are used

with the clinical examination in serial assessments to determine the best course of fluid therapy and serve as end points to replacement fluid therapy. Urine output is another clinical indicator of improvement in perfusion in response to fluid loading, and once urine production is present (as evidenced through ultrasonographic findings or urine collection) the rapid boluses can cease or slow in rate. Fluid challenge should continue as repeat boluses, albeit at progressively slower rates for each subsequent bolus, until perfusion parameters normalize or plateau in terms of improvement. No further improvement of perfusion parameters in response to boluses of fluids, with persistence of clinical indicators of hypoperfusion, suggests that inotrope or vasopressor support may be required and that further fluid therapy will not be of aid. Fluid overload is very detrimental to tissue oxygenation and cell function, and care should be taken to avoid it. A safety upper limit to fluid loading includes detection of a high normal CVP value, which should serve as a ceiling to fluid bolus administration.

Crystalloid fluid choices for horses with colitis include isotonic, balanced replacement fluids, such as Normosol-R, LRS, Hartmann's solution (compound sodium lactate solution), and Plasma-Lyte A or Plasma-Lyte 148. Normosol-R and Plasma-Lyte 148/A are slightly advantageous over LRS or Hartmann's solution from the standpoint of providing a wider strong ion difference (sodium-chloride difference). The sodium-chloride difference in these acetated fluids is 42. In contrast, LRS has a sodium-chloride difference of only 21 and Hartmann's solutions have a difference of 19 to 20. These lactated fluids have a chloride concentration greater than that of equine plasma (109 mEq/L in LRS, 111 to 112 mEq/L in Hartmann's solutions versus approximately 96 to 105 mEq/L in equine plasma), and this chloride excess can potentially compound an inorganic acidosis with large volume or duration of administration. Physiologic saline (0.9%) is even greater in its chloride concentration and produces a mild strong ion acidosis on administration of large volumes.[2] There is emerging evidence in human medicine that saline may be associated with adverse effects as compared to balanced electrolyte fluids such as LRS or Plasma-Lyte. A meta-analysis investigating the effect of different fluid therapies on mortality in septic patients suggested that balanced crystalloids were associated with an increased survival rate in septic patients compared to normal saline.[3]

In addition, Normosol-R and Plasma-Lyte 148 or Plasma-Lyte A contain acetate (and gluconate) rather than lactate as the alkalinizing salt. This may be an advantage in horses with hepatic dysfunction because the liver is the primary site of lactate metabolism, whereas acetate and gluconate are metabolized by many

tissues.

Colloids may be adjunctive to crystalloid therapy, particularly for horses with hypoproteinemia such as those with acute colitis. In human critical care medicine there is no consensus as to whether crystalloids or colloids provide more successful fluid resuscitation.[1] A combination of both is likely optimal.[1] Colloids may be useful for horses with hypoproteinemia, such as those with colitis. Concurrent hypovolemia and hypoproteinemia warrant administration of colloids, because the use of crystalloids alone could result in dilutional hypoproteinemia.[4] Plasma may be considered the optimal colloid for use in horses with colitis at this time because of concerns over possible adverse effects of hetastarch on kidney function and mortality rates in humans and dogs, although the debate about possible negative versus positive effects of hetastarch is ongoing.[3]

Hypertonic saline (7% to 7.5%) is a rapid plasma volume expander that can be used in the early volume replacement period of volume resuscitation of the horse with colitis and acute diarrhea. Hypertonic saline increases plasma volume by three to four times the volume administered. In comparison, crystalloids increase plasma volume by only 0.25 to 0.33 mL for each milliliter administered. Hypertonic saline has additional advantages beyond volume expansion, particularly for the horse with endotoxemia. These include immunomodulatory, anti-inflammatory, anti-edema (particularly of the endothelium and erythrocytes), and inotropic effects.[5-7] Microvasculature effects enhance microcirculatory perfusion, which is often disturbed during sepsis and endotoxemia. Reduction of endothelial and erythrocyte edema, two processes that contribute to multiple organ dysfunction during sepsis, results in reduced vascular resistance and blood viscosity.[6,7] The hypertonicity created by hypertonic saline evokes vasodilation, which also contributes to microperfusion when coupled with an increase in cardiac output caused by contractility-enhancing effects of hypertonic saline. The antiinflammatory and immunomodulatory effects include anti-apoptosis, free-radical scavenging properties, inhibition of leukoactivation, and prevention of immunosuppression after sepsis.[5-7] In an experimental model of hemorrhagic shock in horses, hypertonic saline resulted in improved cardiac output, stroke volume, cardiac contractility, and blood pressure as compared with isotonic saline.[8] Hypertonic saline has demonstrated attenuation of cardiovascular derangements in equine endotoxemia models as compared with isotonic saline.[9]

The dose for hypertonic saline is 4 mL/kg once, and it should be followed with, or administered concurrent to, isotonic crystalloids to replace the "borrowed" water from the intracellular space. Hypertonic saline is generally safe but should be avoided in horses with uncontrolled hemorrhage when hypotensive resuscitation is indicated. In addition, horses with marked sodium derangements should not be administered hypertonic saline. It should also be used with caution in neonatal foals.

Fluid Therapy for Sepsis (Peritonitis, Pleuritis, Pneumonia, Metritis, etc.) in Horses (Box 44.3)

K. Gary Magdesian

Box 44.3

Fluid Considerations for Horses With Sepsis

1. Crystalloids are the mainstay of fluid therapy in sepsis.
2. A combination of crystalloids and colloids may have advantages in patients with sepsis when hypoproteinemia is present.
3. Fluid challenge, consisting of 10- to 20-mL/kg boluses with reassessment of perfusion parameters and monitoring tools, is a safe and effective means of determining volume to be administered.
4. Monitoring of fluid therapy increases safety, especially in patients prone to edema. Monitoring should consist of measurement of central venous pressure, arterial blood pressure, and urine output.
5. Metabolic acidosis is very common among patients with sepsis.

The optimal fluid for resuscitation of patients with sepsis remains an area of investigation, although recent work supports the use of balanced electrolyte solutions over hetastarch or normal (0.9%) saline.[1-4] A rational approach to fluid therapy in patients with sepsis is to optimize hemodynamics (increase oxygen delivery, blood pressure, and urine output) while attempting to limit fluid overload and edema formation.[1,5,6] There is no evidence to support the use of synthetic colloids over balanced crystalloids.[1] Older meta-analyses of clinical

studies comparing crystalloids and colloids in human patient populations showed no outcome difference, but more recent studies point to a mortality decrease in patients receiving balanced crystalloids over normal saline or synthetic colloids.[1-4,6-8]

Fluid therapy is a keystone in the management of severe sepsis and septic shock. This is because septic shock is associated with both absolute and relative hypovolemia. Relative hypovolemia is the result of vasodilation and peripheral blood pooling in the face of cytokinemia. Volume repletion allows for increases in cardiac output and subsequently in systemic oxygen delivery.[7]

The recommendations for fluid therapy in septic horses are extrapolated from those in human medicine and similar to those for horses with acute enterocolitis discussed earlier in this chapter; both conditions are examples of a SIRS. In fact, enterocolitis can be thought of as a form of sepsis. Sepsis incites a host of hemodynamic derangements that challenge fluid therapy. It causes a myriad of microperfusion and hemodynamic abnormalities; these include hypovolemia, myocardial depression, vascular permeability derangements, vasodilation, DIC, and cellular changes resulting in abnormal membrane potential and membrane pump or channel function.[8] These pathophysiologic processes must be considered when a fluid plan for horses with sepsis is designed.

Sepsis is a form of documented or suspected infection.[9,10] More recently, human medical organizations have redefined sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection and septic shock as persistent hypotension after fluid therapy (vasopressor dependency) and an increased lactate concentration in the absence of hypovolemia.[11] Many equine cases, including horses with peritonitis, pneumonia, pleuritis, enterocolitis, meningitis, and metritis, fall into this category. Sepsis and SIRS are states of cytokine milieu in which cytokines and inflammatory mediators predominate. Aside from antimicrobials, the fundamental therapy is hemodynamic support, consisting of fluid and vasopressor therapy.

Initial fluid resuscitation centers on isotonic (or near isotonic) replacement-type fluids such as LRS, Hartmann's solution, or Plasma-Lyte 148 or Plasma-Lyte A, with some indications for colloids or hypertonic saline. These have been associated with improved outcomes in human patients versus normal saline or synthetic colloids.[1] Horses with sepsis often are presented with negative fluid balance resulting from both hypovolemia and dehydration. Fluid choices are the same as for horses with enterocolitis, and a combination of crystalloids and

colloids, especially plasma, may have advantages in sepsis.[5] Such a combination would address both blood volume and interstitial deficits, with plasma expanding the vascular space, providing albumin, antibodies, endogenous anticoagulants and clotting factors, and crystalloids that address both fluid spaces. The use of synthetic colloids such as hetastarch has decreased in recent times due to the possible adverse effects noted with its use.[1] Hypertonic saline may have some advantages during sepsis, including immunomodulatory, antiinflammatory, anti-edema, vascular, and inotropic effects.[12-14] A dose of 2 to 4 mL/kg of hypertonic saline may be added to the combination of isotonic crystalloids and administered during or just before administration of isotonic crystalloids.

Care should be taken to avoid overexpansion of the extracellular fluid compartment with excessive fluid administration. Horses with sepsis have a predilection for edema because of the presence of concurrent hypoalbuminemia and increased vascular permeability. Therefore careful monitoring of fluid balance is warranted. *Fluid balance* refers to input and output of fluids, and it can be monitored with urinary collection systems. Under normal circumstances urine output should represent 50% or more of input, with the remaining output caused by fecal and evaporative losses (skin and pulmonary). CVP is also useful in monitoring for safety limits in this group of patients; maximal normal CVP (10 cm H_2O [8.8 mm Hg] in foals; 15 cm H_2O [11 mm Hg] in adults) should not be exceeded. Serial ultrasonography and arterial blood gas analysis can be used to detect pulmonary edema from relative or absolute fluid overload, before the development of gross signs (froth, crackles, and tachypnea) of edema.

Because of thrombotic risks associated with sepsis-induced coagulopathies, these patients should be instrumented with minimally thrombogenic catheters, such as long-term polyurethane catheters. Attention to asepsis and cleanliness is paramount.

In human critical care, “early goal-directed therapy” has been advocated by some clinical trials, although there is ongoing debate as to its universal effectiveness.[15] These studies have used goal-oriented therapeutic adjustments of preload, afterload, and contractility to achieve a balance between oxygen delivery and demand. End points have included normalization of central venous oxygen saturation (70%), blood lactate, CVP (8 to 12 mm Hg in humans), urine output (0.5 mL/kg/h or greater), and MAP (65 mm Hg or greater in humans).[16] The therapy consisted of crystalloids and colloids for correction of CVP,

vasopressors and vasodilators for MAP, and dobutamine and red blood cell transfusions for central venous oxygen saturation. Patients receiving this early goal-directed therapy received a greater volume of fluids early (first 6 hours of treatment) and less later, as compared with patients in the conventional group. The treatment group had a lower mortality rate and less severe organ dysfunction, highlighting the importance of early identification of patients with insidious or occult malperfusion, consisting of patients with global hypoxia yet stable vital signs.[15] Whether this type of targeted fluid therapy will have a place in equine medicine remains to be studied.

Glucose should be monitored closely in horses with sepsis, as both hypo- and hyperglycemia may develop. See the previous section for glucose regulation in critically ill patients. The current goal in human patients is to maintain a blood glucose of 180 mg/dL or less.

Fluid Therapy for Renal Failure in Horses (Box 44.4)

C. Langdon Fielding • K. Gary Magdesian

Box 44.4

Fluid Considerations for Horses With Acute Renal Failure

1. Horses with acute renal failure can be polyuric, oliguric, or anuric.
2. Polyuric horses should be treated with isotonic crystalloids with the goal of diuresis. A rate of administration equal to two times a maintenance rate is a reasonable starting point, but fluid balance (input and output) should be monitored. This would equate to 4 to 6 mL/kg/h as an initial starting rate, which should be tailored (increased or decreased) to perfusion parameters, urine output, patient clinical status, and monitoring tools. Balanced, polyionic commercial electrolyte solutions, such as Normosol-R or lactated Ringer's solution, can be used in most cases.
3. Frequent reassessment of the patient's fluid status should be done to adjust rate accordingly.
4. Physiologic (0.9%) saline is mildly acidifying because of hyperchloremia and should be avoided in patients with renal failure because

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hyperchloremic metabolic acidosis may reduce renal blood flow.

5. Anuric or oliguric horses should be treated promptly. Adequacy of circulating volume and blood pressure must be ensured initially. If fluid loading with isotonic replacement crystalloids and correction of hypotension does not correct the lack of urine production, then furosemide, mannitol, and dopamine can be tried. Dialysis (hemodialysis or peritoneal) can be performed if there is potential for reversible renal injury.
6. Synthetic colloids (hetastarch, dextrans) should be avoided in horses with acute renal failure.

Fluid therapy is the major component of treatment for renal failure in horses, regardless of cause. Renal replacement therapies have been reported in horses; however, they are not widely available, further highlighting the importance of fluid diuresis.[1-3] Peritoneal dialysis is an option to complement fluid therapy, particularly if unresponsive anuria is present.[2] Development of a fluid plan for horses with renal failure begins with classification of the disease into polyuric, anuric, or oliguric renal failure. Polyuria and anuria are self-explanatory; oliguric renal failure in this section refers to a normally hydrated animal with concurrent azotemia and urine production less than 0.5 mL/kg/h.

For both oliguric/anuric and polyuric renal failure, there are two primary considerations when beginning fluid therapy: fluid type and rate. The total amount of fluid administered is usually determined by the response to treatment and does not necessarily need to be identified at initiation of therapy.

Polyuric Renal Failure.

The goal of fluid therapy in these patients is to induce diuresis, with removal of uremic toxins and maintenance of fluid, acid-base, and electrolyte balance.[4,5] The degree of renal failure that is reversible is often unknown at the onset; this is evaluated over time, particularly with response to fluid therapy. It should be noted that azotemia may not improve for up to 72 hours after initiation of fluid therapy when acute renal failure is severe. A lack of initial improvement in plasma creatinine or BUN during the first day or two of therapy should not necessarily prompt a poor prognosis or discontinuation of therapy.

The rate of fluid administration should facilitate diuresis.[5] A rate of two times the maintenance fluid rate (4 to 6 mL/kg/h, where the maintenance rate is 2 to 3

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mL/kg/h) is a reasonable starting point; however, there is a paucity of literature to recommend evidence-based rates of fluid administration for treatment of acute renal failure or other disorders. Similar fluid rates have been suggested in small animal patients with renal failure.[5] It is unknown whether increases in the fluid rate beyond this point are beneficial. Certainly, if urine output is greater than this rate, it should be matched with fluid input.

Fluid overload is a problem in renal failure and has been reported in human patients.[6,7] Excessive fluid administration may result in edema and associated morbidity and mortality. Measurement of CVP can be used to monitor excessive fluid administration and has become more practical in equine patients.[8-10] Reference ranges of less than 15 cm H_2O have been reported for adult horses; values exceeding 20 cm H_2O indicate a need to decrease the rate of fluid administration to avoid development of edema.[9] The value of CVP monitoring continues to be controversial, and CVP measurement should not be used as the sole means for monitoring fluid overload.[11]

A balanced isotonic crystalloid is suitable for diuresis while preventing significant electrolyte alterations.[5] Horses should be allowed free access to water whenever possible while intravenous fluids are administered. This allows for some degree of self-regulation of water balance and can provide free water for renal excretion of the large sodium load provided by isotonic crystalloids.

Hyperkalemia is a relatively common feature of acute renal failure.[12,13] This is often corrected when renal perfusion is optimized and diuresis is instituted. When hyperkalemia is present, anuria should be ruled out. Cardiac dysrhythmias can develop during hyperkalemia; potassium-free fluids (isotonic sodium bicarbonate; possibly normal saline, although this is controversial as noted below) should be administered to patients with dangerous hyperkalemia (>6 mmol/L), along with calcium, dextrose, and possibly insulin.

LRS has the benefit of containing a minor amount of free water (osmolarity 273 mOsm/L) and slightly less sodium than other fluids (130 mEq/L). A potential disadvantage, however, is that it contains more chloride (109 mEq/L) than equine plasma. Horses with renal insufficiency may be unable to excrete excess chloride provided by LRS diuresis. Mild hyperchloremia may result, causing a minor strong ion acidosis. LRS also contains potassium (4 mEq/L), which is a consideration in the hyperkalemic patient. However, studies in human renal transplant patients failed to demonstrate development of hyperkalemia as a result of LRS administration.[14]

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Isotonic saline (0.9%) solution has an even higher chloride content (154 mEq/L) than LRS. In fact, neither the sodium nor the chloride concentration in this fluid is similar to those of equine plasma. Isotonic saline solution has been shown to cause hyperchloremia and a mild acidosis during prolonged administration.[15-17] This hyperchloremia may make isotonic saline a less ideal fluid for long-term management of acute renal failure. Saline does not contain potassium and therefore may be warranted in horses with hyperkalemia. However, creation of a metabolic acidosis because of hyperchloremia may also pose a risk for hyperkalemia by causing an extracellular shift of potassium; this shift occurs as a result of acute changes in blood hydrogen concentration, which occur in association with hyperchloremic metabolic acidosis.[14] The effects of saline on potassium balance in horses warrant further study. Metabolic alkalosis, caused by hypochloremia or relative hypernatremia, is an indication for saline administration.

Normosol-R and Plasma-Lyte 148 (or Plasma-Lyte A) have a sodium and chloride concentration most similar to equine plasma among the commercial isotonic or nearly isotonic fluids and are excellent fluids for diuresis of acute renal failure cases. It should be noted that these contain the highest potassium concentration (5 mEq/L) of all commercial fluids described; however, this potassium content is unlikely to contribute to clinically significant hyperkalemia in polyuric animals because of urinary excretion of excessive potassium (possible exceptions are uroperitoneum and anuria).

Isotonic sodium bicarbonate solution can be made by mixing sterile water and sodium bicarbonate to create a solution with a sodium concentration of approximately 150 mmol/L. Isotonic sodium bicarbonate does not contain potassium or chloride and can be modified to contain an increased amount of free water as needed by lowering the sodium concentration. It exerts an alkalinizing effect by increasing strong cation (Na^+) concentrations without a corresponding increase in strong anions (i.e., strong ion alkalosis).

Blending of fluids with different compositions is also an option in order to correct or maintain electrolyte and free water balance. Over time, horses often develop a plasma electrolyte profile similar to that of the administered fluid, especially when large volumes are administered for prolonged periods; therefore combining or changing fluids may be necessary if derangements develop. It is also clear that monitoring of electrolytes (one to four times per day) is particularly important in renal patients.

Synthetic colloids should be avoided in horses with acute kidney disease

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because renal injury is a known complication of administration of synthetic colloids in humans.

Anuric or Oliguric Renal Failure.

Anuria and oliguria should be considered emergency medical conditions; the longer the duration of little to no urine production, the lower the chances of correcting it. Urine output in healthy horses is approximately 1 mL/kg/h, but this may decrease by 80% (to 0.2 mL/kg/h) in horses deprived of water.[18,19] In humans without significant fluid deficits, a urine flow below 0.5 mL/kg/h is one criterion used to define acute renal *injury*, whereas acute renal *failure* is associated with a urine flow below 0.3 mL/kg/h.[20] Oliguric renal failure should be suspected in azotemic horses with urine production below 0.5 mL/kg/h despite the administration of intravenous fluids. Once anuria or oliguria is suspected, a methodic approach to fluid administration and monitoring should be instituted immediately because of the associated high mortality rate. A delay in instituting treatment makes reversal of anuria less likely.

▪ Treatment of Anuria or Oliguria

1. Obtain baseline laboratory and hemodynamic parameters. These should include serum or plasma electrolyte levels, total plasma protein and blood lactate concentrations, packed cell volume (PCV), and clinical perfusion parameters. When possible, CVP, arterial blood pressure, and central venous oxygen tension should be measured as well. If possible, a body weight measurement should be obtained and recorded.
2. If CVP is not already significantly increased and there are no clinical signs of fluid overload (increased respiratory rate, peripheral edema, etc.), a fluid challenge should be initiated using 10 to 20 mL of an isotonic crystalloid per kilogram. CVP, clinical pathology, urine output, and physical examination status should be reevaluated for improvement after completion of the bolus.
3. If urine output has not increased significantly, additional fluid challenges should be given and the patient reevaluated until urine production begins or until CVP limitations are reached. A CVP value greater than 15 to 20 cm H_2O (>10 to 12 cm H_2O in foals) signifies an end point to fluid administration.

4. Arterial blood pressure should be monitored. If hypotension is present despite fluid loading, inotrope and vasopressor therapy should be considered. Dobutamine can be used as an inotrope (5 to 10 µg/kg/min). See the Fluid Therapy for Diarrhea and Colitis in Horses section earlier in this chapter.
5. Once urine flow has increased, fluids should be continued as described previously for polyuria; careful monitoring of CVP and fluid balance (measurement of serial body weight and urine output) should be done.
6. If urine flow does not begin over the next 30 to 60 minutes with fluid challenge, furosemide should be started with an initial bolus of 0.12 mg/kg IV followed by a constant rate infusion (CRI) of 0.12 mg/kg/h.[21] If CRIs are not possible, a bolus dose of 1 mg/kg IV, which can be repeated a second time 30 to 60 minutes later, can be administered instead. Furosemide may improve urine production, but there is no definitive evidence that it improves creatinine clearance or positively affects outcome in humans.[22]
7. If urine production does not begin within 30 to 60 minutes of instituting furosemide therapy, a dose of mannitol should be administered (0.25 to 0.5 g/kg bolus as a 20% solution). If still no urine is produced after an additional 30 minutes, another dose of mannitol can be administered; a total dose of 1 g/kg should not be exceeded in the anuric patient to prevent hypervolemia and edema formation. Alternatively, a CRI of mannitol (1 to 2 mg/kg/min) can be used, with a maximum cumulative dose of 1 g/kg. Plasma osmolarity should be monitored.
8. If urine output has not improved after furosemide and mannitol, the prognosis is grave without peritoneal dialysis or hemodialysis. Treatment with low-dose dopamine has been controversial in human medicine, and several large studies have failed to demonstrate a benefit.[23,24] In fact, furosemide, mannitol, and dopamine may increase urine flow but have not been shown to unequivocally improve outcome in humans with acute renal failure.[25] When dialysis is not an option for horses with anuric renal failure, dopamine can be tried in an attempt to produce urine flow (2 to 3 µg/kg/min); its proposed action is increasing renal perfusion with renal afferent arteriolar vasodilation.[26] Without urine flow, there is no opportunity to provide the patient with time to heal if the acute renal injury is reversible. If dopamine is successful at

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reversing anuria, this time can be provided.

9. Aminophylline can also be tried for reversal of anuria, at 0.5 mg/kg IV over 30 minutes. If improvement is noted, this can be repeated 2 to 3 times per day. It should be noted that aminophylline has a narrow therapeutic index, with toxicity occurring at plasma concentrations of 15 µg/mL or greater.

Hyperkalemia and metabolic acid-base disorders are common in horses with anuric or oliguric renal failure.[12] As noted earlier, hyperkalemia can be associated with life-threatening dysrhythmias. Rapid initiation of diuresis and administration of sodium bicarbonate, dextrose, and insulin are therapeutic interventions for hyperkalemia. If dysrhythmias are present, calcium should be administered to raise membrane threshold potential, thereby reducing the likelihood of abnormal rhythms.

As mentioned previously, hemodialysis has been reported infrequently in horses for clinical cases of renal failure.[1] Peritoneal dialysis has been described as a cost-effective and practical approach for horses with acute renal failure.[2] More recently, continuous venovenous hemodiafiltration was performed in experimental horses for short periods (6 hours). These therapeutic options may become more commonly used in horses that do not respond to conventional fluid therapy and medical treatments of anuria described earlier.

Fluid Therapy for Horses With Hypoproteinemia

K. Gary Magdesian

Horses with concurrent hypovolemia and significant hypoproteinemia (e.g., <4.5 g/dL) are at increased risk for edema formation with fluid therapy, making them among the most challenging to manage. The presence of concurrent hypovolemia and hypoproteinemia is a potential indication for colloids in addition to crystalloids. Administration of crystalloids alone may result in compounding of the hypoproteinemia through hemodilution.[1] With altered Starling's forces, crystalloids distribute to the extracellular fluid to a relatively greater extent than they would otherwise because of a lack of plasma oncotic force for retention. However, colloids can also extravasate due to increased vascular permeability, particularly if the endothelial glycocalyx is compromised, and therefore colloids should not be considered the definitive fluid in such cases because they too may exacerbate edema. Currently available colloids include

hetastarch, dextrans, plasma, and concentrated human albumin.[2] Because of the increased potential for side effects associated with dextrans, there is no clear indication to use them over hetastarch. Side effects of dextrans reported in horses include muscle fasciculations, swaying of the hindquarters, tachycardia, and collapse in 8 of 64 horses.[3] Potential side effects of hetastarch products include coagulopathies. Other possible side effects in humans include allergic reactions and acute kidney injury, with some studies suggesting an increase in mortality rate as compared to crystalloids.[4] Therefore the use of hetastarches has decreased in human and veterinary critical care in recent years. The author rarely uses these products any longer and primarily relies on plasma for colloid support in horses and foals.

There are newer, lower-molecular-weight, and less substituted hetastarches that may be safer than traditional hetastarches.[5] The numbers after the name of the colloid (e.g., 130/0.4) refer to the average molecular weight and degree of substitution of starch molecules with a hydroxyethyl group, respectively. Standard hetastarch has an average molecular weight of 450 kDa and a degree of substitution of 0.7 (450/0.7); the newer hydroxyethyl starch (Voluven; 130/0.4) has been modified to have more complete renal elimination and less tissue storage than the standard product, with fewer side effects such as coagulopathies. These are referred to as tetrastarches. The U.S. Food and Drug Administration (FDA) has approved a veterinary tetrastarch colloid in normal saline for treatment of hypovolemia in dogs and cats with this molecular weight and substitution (VetStarch [Abbott Animal Health, Abbott Park, Ill.]). These tetrastarches may offer lower potential complications compared with hetastarch, including coagulopathy, allergic reactions, and renal injury. VetStarch has been studied in healthy neonatal foals, at a dose of 20 mL/kg, without any observable changes in coagulation parameters, and it increased colloid osmotic pressure for 3 hours after infusion.[5] It requires further study in sick foals and adult horses over a longer period of time before side effects and safety can be evaluated.

The risk-to-benefit ratio of the hetastarches may warrant use of low doses in conjunction with plasma in horses or foals with marked hypoproteinemia in the presence of hypovolemia. An example of a case where this may be warranted is *Lawsonia intracellularis* infection in foals. Doses of 10 mL/kg/day should not be exceeded in order to avoid side effects, and the hetastarch products should be used for as few days as possible, as duration of use may also play a role in side effects. Even lower doses (e.g., 3 to 5 mL/kg) can be used in conjunction with

plasma, if plasma alone is not enough.

Numerous commercial equine plasma products are currently available. Many include antibodies to salmonella, endotoxin, and clostridial organisms; these are unlabeled claims and are largely unstudied in terms of efficacy. Another advantage of plasma, especially for the hypoproteinemic horse, includes provision of albumin, antithrombin, and additional clotting factors. Because albumin has multiple functions, including as a carrier protein (drugs, toxins) and physiologic buffer, plasma cannot be entirely replaced with synthetic colloids. Concentrated albumin has been used in neonatal foals, but its use in adult horses may be limited by cost.[2] The potential side effects of human plasma products in horses are largely unknown and require further study. For horses with continual protein losses, such as with protein-losing enteropathies (e.g., acute enterocolitis), a continuous low rate infusion of plasma (e.g., 0.4 to 0.5 mL/kg/h) can be used.

In one study evaluating the response of hypoproteinemic horses with gastrointestinal disease to hetastarch, it was determined that the oncotic benefit lasted 24 hours; in contrast, hetastarch raised the oncotic pressure of healthy horses for up to 5 days.[1,6] Nevertheless, in some cases even a short-term benefit in oncotic pressure may be preferable to the further dilutional effects of crystalloids.

Fluid Therapy for Hemorrhagic Shock (Box 44.5)

K. Gary Magdesian

Box 44.5

Fluid Considerations for Horses With Acute Hemorrhage

1. For horses with controlled hemorrhage, a combination of hypertonic saline and balanced isotonic crystalloids can be used.
2. Because of experimental evidence of proinflammatory effects of racemic lactated Ringer's solution (LRS) in severe trauma, use of this solution should be questioned in cases of severe trauma until further studies are

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available. Non-racemic LRS (with L-lactate) should be used when LRS is desired.

3. Hypertonic saline exhibits antiinflammatory effects and may have benefits for horses with severe trauma, especially when LRS or synthetic colloids are used for resuscitation, and after hemorrhage has been controlled.
4. For controlled hemorrhage, a volume three to four times the estimated blood loss should be administered in isotonic crystalloids.
5. For uncontrolled hemorrhage, hypotensive resuscitation should be used; small volumes of fluids are administered to maintain organ perfusion and a mean arterial pressure of 60 mm Hg until the hemorrhage can be controlled.

With the exception of prompt hemorrhage control, the key component to early trauma care is adequate fluid resuscitation. Traditionally, replacement with isotonic crystalloids of three times the volume of shed blood has been the approach in human trauma patients. Up to eight times the blood loss volume has been administered in severe shock states, because isotonic crystalloids distribute throughout the extracellular fluid compartment by volume, such that only 25% of the administered volume will remain within the circulating plasma volume.

Despite its importance, high-volume resuscitation is not innocuous; acute respiratory distress syndrome (ARDS) has been described in patients that received massive crystalloid resuscitation after trauma.[1] Severe trauma patients enter a phase of SIRS, with some patients developing multiple organ failure and others entering a compensatory antiinflammatory response syndrome (CARS). This latter syndrome causes immune suppression and increased susceptibility to infections. Commercial LRS brands used to contain a racemic mixture of L- and D-lactate. Those solutions, along with artificial colloids, namely dextrans and some hydroxyethyl starches, had proinflammatory effects.[2] Nonracemic LRS contains only the L-lactate form and does not share in the proinflammatory effect. It appears that the D-lactate (nonmammalian form) is largely responsible for the inflammatory reaction to racemic LRS because removing it from the solution eliminates this effect.[3] These fluids, both artificial crystalloids and colloids, can also cause neutrophil activation and upregulation of adhesion molecules.[4] Most currently available forms of LRS contain only the L-isomer form of lactate. Hypertonic saline, on the other hand, has been shown to be immunomodulatory and causes suppression of neutrophil oxidative burst activity

and neutrophil-endothelial adhesions.[5-8] Hypertonic saline counteracts the inflammatory effects of dextrans when used in combination.[9] Therefore hypertonic saline has potential advantages for early fluid resuscitation of patients with significant blood loss, after the source of hemorrhage has been controlled. This should be followed with isotonic crystalloids, perhaps acetate-containing fluids, such as Normosol-R, or physiologic saline rather than racemic LRS. Hypertonic saline should not be used in cases of uncontrolled hemorrhage because it may raise blood volume and pressure too quickly. Plasma similarly does not result in inflammatory cell activation. If hetastarch is used in patients with acute blood loss, hemorrhage must be controlled before its administration because of rapid volume expansion as well as dose-dependent induction of coagulopathies.[10-15]

Aggressive fluid resuscitation in the face of uncontrolled hemorrhage cannot be justified. Such fluid protocols can exacerbate bleeding as a result of increases in blood pressure, disruption of clots, and hemodilution of clotting factors. Instead, a protocol of hypotensive resuscitation should be followed when bleeding cannot be stopped directly.[16] With hypotensive resuscitation, low volumes of crystalloids or whole blood should be administered to maintain organ vitality without normalizing pressures. A goal of maintaining a MAP of 60 mm Hg will still allow end-organ perfusion while allowing for hemostasis.

Fluid Therapy in Acute Neurologic Injury (Box 44.6)

Darien J. Feary

Box 44.6

Fluid Guidelines for Horses With Acute Neurologic Injury

1. The clinical outcome of large animal patients with brain and spinal cord injury may be improved by the prompt recognition and treatment of systemic and central nervous system hypoperfusion.
2. Isotonic crystalloid solutions appear to be the most appropriate fluids for resuscitation in acute neurologic injury, followed by careful

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administration of hyperosmolar therapy with mannitol or hypertonic saline if evidence of cerebral edema is present.
3. Diligent monitoring of clinical and laboratory measures of perfusion, osmolarity, and electrolyte concentrations is important for optimizing patient care and the likelihood of recovery in these patients.

The approach to fluid therapy in horses and ruminants with acute brain or spinal cord injury is aimed at maintaining oxygen delivery, cerebral perfusion, and energy supply to meet the metabolic demands of the neuronal tissue, and fluid therapy is a fundamental part of preventing or minimizing secondary neuronal injury, ischemia, and irreversible damage.

The primary goals of fluid therapy for both brain and spinal cord injury follow similar principles and include prevention or prompt recognition and treatment of hypovolemia and hypotension, intracranial hypertension (or cerebral edema), and glucose and electrolyte abnormalities. There is a large body of evidence in the human critical care literature that indicates hypoxemia (PaO_2 <60 mm Hg) and hypotension (systolic blood pressure <90 mm Hg) are independently associated with worse neurologic outcomes in traumatic brain injury (TBI).[1-7] Addressing hypoxia and hypotension should be a priority in large animal patients with neurologic injury, as soon as it is practical and safe to do so. Although both brain and spinal cord injuries are potentially life threatening in large animals, acute brain injury is likely to be the most influenced, either negatively or positively, by the fluid therapy plan that is instituted. This is mainly because the cranial vault is a closed space, composed of brain (approximately 80%), blood (approximately 10%), and CSF (approximately 10%). An increase in one component must result in a compensatory decrease in another. The presence of the blood-brain barrier, intact or not, is another important factor in the selection of the most appropriate fluid for management of acute brain injury.

The most important consideration in the management of cerebral injury is the maintenance of cerebral blood flow (CBF), which is often reduced post injury. The major determinant of CBF is cerebral perfusion pressure (CPP), which is the difference between MAP and intracranial pressure (ICP) as defined by the following equation: CPP = MAP – ICP. In the normal brain, cerebral autoregulation maintains a relatively constant CBF despite wide variations in perfusion pressure, within the range of 50 to 150 mm Hg (in humans). In the injured brain, autoregulation may be impaired, often with concurrent traumatic shock and hypotension, and CBF becomes directly dependent on CPP. Therefore

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it becomes critical to prevent hypotension by maintaining MAP above 80 mm Hg and to avoid increases in ICP that result from cerebral edema or hemorrhage. ICP is not routinely measured in large animal patients, limiting its use in guiding fluid therapy. However, neurologic signs suggestive of elevated ICP (e.g., obtunded mentation, mydriasis) indicate the need for specific treatment to reduce ICP, with frequent reassessment of neurologic status being important in determining response to treatment.

Fluid management in large animal patients with acute neurologic injury is essentially based on the principles and guidelines established in human medicine from extensive laboratory and clinical studies. The ideal fluid for these human patients remains controversial and is a topic of ongoing research. When presented with a large animal patient with central nervous system injury, the clinician should formulate a fluid therapy plan tailored to the individual animal, based on findings of thorough physical and neurologic examinations and assessment of laboratory data. The author suggests the following goal-directed approach:

- Goal 1: Treat hypovolemia and hypotension with adequate fluid replacement therapy to attain a normovolemic and normotensive state.
- Goal 2: Treat signs of cerebral edema or intracranial hypertension with hyperosmolar therapy.
- Goal 3: Use fluid additives to normalize glucose and electrolyte values, and provide thiamine supplementation.

Replacement Fluid Therapy for Neurologic Trauma Cases.

Although fluid restriction historically has been advocated for patients with TBI under the premise that intravenous fluids increase cerebral edema formation, this recommendation has been replaced by prompt restoration of adequate intravascular volume using the fluid challenge approach, with the goal of achieving and maintaining euvolemia, normal blood pressure, and tissue oxygenation.[8] This is best achieved and controlled through the intravenous route

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in injured horses. Overhydration should be avoided, particularly in neonates, which are more susceptible to volume overload than adult horses.

Balanced isotonic crystalloid fluids are traditionally used for volume resuscitation, although there may be a role for hypertonic saline during resuscitation, as well as for specific treatment of intracranial hypertension (see later).[8] Selection of the appropriate fluid for replacement therapy requires an understanding of the role of the blood-brain barrier. Because of its unique properties, the development of cerebral edema is fundamentally different from edema formation in other organs or tissues.[9] Briefly, the normal blood-brain barrier functions as a semipermeable membrane, separating the brain from the intravascular space. In the normal animal the blood-brain barrier is impermeable to large molecules (plasma proteins) but is only minimally permeable to most ions. It is freely permeable to water, however. The tonicity of the intravascular fluid, determined by its sodium concentration, influences the movement of free water across the blood-brain barrier by creating an osmotic pressure gradient between the brain interstitium and the intravascular space. In TBI the blood-brain barrier may be damaged, often producing heterogeneous regions of varying degrees of blood-brain barrier integrity and permeability. Unfortunately, demonstrating and predicting the extent of such injury in clinical patients is very difficult; the clinician often likely must assume the presence of normal brain and functional blood-brain barrier regions for certain principles of fluid management, such as osmotherapy, to be effective.[10]

Hypotonic crystalloids, such as 5% dextrose in water or 0.45% saline solutions, are contraindicated in patients with TBI. They lower plasma osmolarity and result in excess free water diffusion into the brain, with subsequent cerebral edema formation. Hypotonic fluids should be avoided for rapid volume replacement in patients with brain injury.

Isotonic crystalloids, such as LRS, Plasma-Lyte 148 or Plasma-Lyte A, and Normosol-R, create a minimal to no osmotic gradient across the blood-brain barrier, are readily available and inexpensive, and are therefore the current fluids of choice for replacement and maintenance therapy in patients with brain and spinal cord injury. Hypertonic crystalloids, such as 7.5% saline, create an osmotic gradient across the blood-brain barrier in favor of free water movement out of the brain, thereby reducing ICP. Hypertonic fluids have traditionally been recommended only after adequate provision of intravascular fluid volume in horses with signs of elevated ICP or deteriorating neurologic status. However, hypertonic saline has been increasingly advocated for initial fluid resuscitation in

TBI in humans because of its ability to rapidly expand intravascular volume while simultaneously decreasing ICP.[11] The recent Brain Trauma Foundation's Guidelines for Prehospital Management of TBI recommend hypertonic resuscitation as a treatment option for patients with severe TBI (however, this is based on weak evidence).[12] It should be noted that in pediatric patients with TBI, the recommendation is to treat hypotension with isotonic fluids only.[12]

Colloids—such as plasma, human albumin, and the synthetic agents hetastarch, pentastarch, and dextran—exert variable oncotic pressures and are very effective for intravascular volume expansion and maintenance. The use of colloid solutions in neurologic injury is debatable, mainly because the major determinant of fluid flux across the blood-brain barrier is plasma osmolarity; because colloids contribute only a small number of particles in plasma, even large changes in plasma colloid oncotic pressure only minimally influence water movement across the normal blood-brain barrier. This is in contrast to the effectiveness of even small changes in plasma osmolarity.[13] In addition, the relatively higher cost of colloid solutions and the greater risk of development of hemostatic abnormalities and allergic reactions suggest little benefit of colloid solutions over crystalloids in cases of TBI. Furthermore, findings from the saline versus albumin fluid evaluation (SAFE) study showed an increased mortality in a subgroup analysis of human patients with TBI who were treated with albumin.[14]

Hyperosmolar Therapy in Brain and Spinal Cord Injury.

Hyperosmolar therapy is the pharmacologic induction of supraphysiologic serum osmolality with either hypertonic saline or mannitol and is the mainstay of medical management of patients with intracranial hypertension (ICP >20 mm Hg) associated with TBI and intracranial hemorrhage.[13] If clinical evaluation of the equine patient with TBI suggests that the patient has or is at risk for developing intracranial hypertension, then osmotherapy may be indicated. Clinical signs such as obtunded mentation, progressive mydriasis, or any deterioration of neurologic status may indicate increased intracranial hypertension. Hyperosmolar solutions exert their effect of reducing ICP by creating an osmotic gradient across the blood-brain barrier of at least 10 mOsm/L. It is advisable to measure plasma osmolarity in large animal patients, at least before administration of hyperosmolar solutions, to avoid excessive increases in plasma osmotic pressure. Osmotherapy should be instituted only

after restoration of adequate intravascular volume and blood pressure if CPP is to be optimized.

The two most commonly used and available hyperosmolar solutions for use in large animals are mannitol (20%) and hypertonic (3% to 23.4%) saline. Both agents have been shown to be effective in lowering ICP in human patients with TBI, although some studies suggest greater efficacy and fewer side effects with the use of hypertonic saline,[15,16] whereas other comparative studies have shown no benefit of hypertonic saline over mannitol in controlling ICP when multiple doses are administered over 5 days.[17] A proposed reason for this lack of benefit is an increased urinary loss of sodium with hypertonic saline and consequent inability to achieve higher serum sodium concentrations and osmolarity.

Although it is widely established that both mannitol and hypertonic saline are effective in acutely lowering ICP when it is increased, the recent Brain Trauma Foundation guidelines failed to find any evidence meeting current standards on which to base recommendations regarding osmotherapy.[12]

It is challenging to relate outcomes from research in human medicine to large animal patients because the etiology, type of brain injuries, and frequency of surgical intervention in human patients with TBI make them a very different patient population. Until ICP can be measured in the clinical setting, large animal veterinarians must use their frequent neurologic assessments, blood analysis (including osmolarity), judicious use of osmotherapy when indicated (neurologic evidence of increased ICP), and response to therapy.

Mannitol (20%) is a six-carbon sugar with an osmolarity of 1098 mOsm/L. The recommended dose is a 0.5 to 1 g/kg IV bolus administered over 20 to 30 minutes, every 6 to 8 hours. It is important to avoid rapid mannitol infusion (<5 minutes), since this can lead to transient hypotension. The ICP-reducing effects of hyperosmolar solutions are believed to be biphasic in nature. After bolus dose administration, an initial plasma-expanding effect reduces blood viscosity and hematocrit and improves rheologic properties of red blood cells, resulting in reduced ICP and improved CBF. After this immediate hemodynamic effect is a delayed osmotic diuretic effect resulting from the decreased reabsorption of sodium and water by the renal tubules, which also contributes to ICP reduction. Onset of effect of mannitol therapy is 15 to 30 minutes after bolus administration. Mannitol should not be administered as a continuous infusion for the purpose of treating cerebral edema, since it loses its plasma-expanding effects and increases the likelihood of development of side effects.[18]

The detrimental effects of mannitol are more likely to develop and become

clinically significant with excessive or prolonged use (>2 to 3 days). Side effects include hypovolemia and hypotension caused by excessive diuresis, electrolyte disturbances (e.g., hyponatremia, hypochloremia, hypokalemia, hypocalcemia), acidosis, acute renal failure, and a rebound increase in ICP associated with reversal of the osmotic gradient, a phenomenon most likely explained by accumulation of the osmotic agent in brain tissue after movement across regions of a damaged blood-brain barrier.[18] A threshold level of serum osmolarity of 320 mOsm/L is often used as an indicator for decrease or withdrawal of mannitol therapy. However, serum osmolarity is not a sensitive indicator of mannitol-induced renal failure, and the osmolar gap (the difference between calculated and measured serum osmolarity) is more reflective of serum mannitol accumulation. Based on this, an osmolar gap threshold of 55 mOsm/kg has been suggested for monitoring mannitol therapy in TBI.[15] There is insufficient evidence to support the dogma that mannitol is contraindicated in the presence of intracranial hemorrhage.

Hypertonic (7.5%) saline has an osmolarity of 2400 mOsm/L and, similar to mannitol, effectively reduces ICP primarily through an immediate hemodynamic effect, followed by a delayed osmotic effect. Hypertonic saline (7.5%) can be administered as an intravenous bolus dose (4 mL/kg) or as a CRI. There are no clear guidelines as to the optimal concentration (3% to 23.4%) or dose of hypertonic saline in human patients with TBI. However, effective CRI dosing has been achieved in human patients using 3% hypertonic saline at 0.1 to 2.0 mL/kg/h, titrating to serum sodium concentrations of 145 to 155 mmol/L, and not exceeding serum osmolarity of 360 mOsm/L.[15] Hypertonic saline may have additional beneficial effects over mannitol in TBI because of rapid augmentation of cardiac output, contractility, and MAP with administration of smaller volumes. In addition, hypertonic saline is theoretically less likely to cross the blood-brain barrier than mannitol because the reflection coefficient of NaCl is 1 (not permeable), compared with 0.9 for mannitol (more permeable). Additional benefits of hypertonic saline on the injured brain include sodium-related stabilization of cell membrane electrochemical gradients and modulation of the inflammatory response.[19]

Laboratory studies investigating the effects of hypertonic saline in resuscitation after spinal cord injury have also shown promising results, with increased spinal cord blood flow, downregulation of the inflammatory response, and attenuation of spinal cord injury.[20] Further clinical studies are needed.

Complications of hypertonic saline are uncommon and include hypernatremia and theoretical development of central pontine myelinolysis.[15] Hypokalemia can occur because of kaliuresis in response to reabsorption of large amounts of sodium in the distal tubule, as well as hyperchloremic acidosis, emphasizing the importance of regular assessment of hemodynamic and plasma electrolyte and acid-base status. Coagulopathy and bleeding complications could occur as a result of dilutional effects but are of greater concern in the actively bleeding patient. Risks of hypovolemia and acute renal failure are not reported for hypertonic saline in TBI, although renal insufficiency is a relative contraindication to all hyperosmolar therapy. Rebound elevations in ICP can occur with withdrawal of therapy; therefore slow, gradual weaning of hypertonic saline infusions is recommended.[15]

Osmotherapy is likely to be most effective if initiated early following significant TBI in cases with clinical evidence of increased ICP, and with duration determined by response to therapy, limited to 24 to 48 hours, with close observation and monitoring of neurologic status, serum electrolytes, acid-base status, osmolarity, and renal function, to minimize development of side effects. Because measurement of ICP is not practical to perform routinely in equine patients with TBI at this time (it has been measured in a research setting), the efficacy of and optimal recommendations for hyperosmolar therapy in equine patients with TBI remain unknown and are based on the human medical literature.

Fluid Additives in Neurologic Injury

Glucose.

It has been widely recognized that hyperglycemia is a common occurrence in acute brain injury in humans.[21] Hyperglycemia is believed to worsen neuronal injury and is associated with increased mortality and neurologic outcomes after TBI.[21,22] Consequently, glucose supplementation during large-volume fluid replacement should be avoided unless the patient is hypoglycemic. As noted below, hypoglycemia should be avoided in patients with TBI.

Recommendations regarding glucose control in the critically ill patient have varied significantly in the last decade. Tight glycemic control (80 to 110 mg/dL) with the use of insulin was suggested for critically ill human patients, but these recommendations have been relaxed more recently because of associated incidences of hypoglycemia when centers resort to such tight glycemic control.[23]

In addition, the human critical care literature suggests that hypoglycemia may be particularly detrimental to an acutely injured brain. The brain has limited ability to compensate for low glucose concentrations, and the addition of impaired cerebral autoregulation with fluctuations in cerebral blood flow after TBI may cause increased susceptibility to hypoglycemia.[24] Although there are no studies in horses with TBI to enable recommendations regarding the best management of blood glucose, recent human medical studies have shown that tight glycemic control after TBI is potentially detrimental due to increased regional glucose metabolism in the brain, leading to enhanced metabolic crisis, and increased markers of cellular distress (elevated lactate/pyruvate ratios and glutamate).[25] Therefore limiting the brain's glucose supply during a period of high metabolic demand after TBI may actually contribute to secondary injury. It is currently suggested that delivery of more glucose through mild hyperglycemia (120 to 150 mg/dL) may be necessary following TBI.[26]

These factors should be considered in the monitoring and fluid therapy plan for any large animal with neurologic injury, particularly neonates, since they are more susceptible to hypoglycemia.

Thiamine.

Thiamine (vitamin B_1) is a water-soluble B vitamin synthesized only by plants and microorganisms. Most animals have a nutritional requirement for this vitamin, although adult ruminants and horses normally can obtain adequate quantities produced by bacteria in the rumen or cecum.

Thiamine, in its active form (thiamine pyrophosphate), plays a very important role in glucose metabolism and energy production, where it functions as a required cofactor for certain enzymes (pyruvate dehydrogenase, α-ketoglutarate dehydrogenase, branched-chain ketoacid dehydrogenase, transketolase) involved in glycolysis, the citric acid cycle, and the pentose phosphate pathway. Thiamine is also important in nerve and muscle function, where it plays a role in neurotransmission and excitation.

Thiamine deficiency is known to be associated with neurologic disease in humans and in ruminants (polioencephalomalacia). Determination of thiamine status of an animal requires measurement of red blood cell transketolase activity; therefore measurement and documentation of thiamine deficiency in clinical cases is not routinely reported. Whether or not supplementation of thiamine in acute traumatic neurologic injury is indicated is not currently supported by

published evidence. However, given the increased susceptibility of damaged neuronal tissue to inadequate energy production and supply, the practice of thiamine supplementation in neurologic injury in large animals appears justified. In addition, recent experimental investigation suggests a potential neuroprotective role of thiamine in reactive oxygen species–induced neuronal injury.[27] The author has used a dose of 5 to 10 mg/kg of thiamine diluted in crystalloid fluids. Thiamine should be protected from light.

Electrolytes.

Sodium disturbances can have serious consequences in brain injury and should be corrected promptly if they are acute (<24 hours' duration). Isotonic fluid administration is appropriate in most cases. Glucose and mannitol cause translocation of water into the extracellular fluid, and excessive amounts can lead to a clinically significant reduction in sodium concentration, as can free water administration with hypotonic fluids. If hyponatremia (Na^+ <125 mEq/L) is believed to have been present for longer than 24 hours, slower correction (0.5 mEq/L/h or 10 mEq/day) is needed to avoid development of central pontine myelinolysis.

Calcium is essential in maintaining cell membrane potentials and promoting neurotransmitter release. Excessive intracellular calcium accumulation is also well recognized as one of the most important pathways of secondary neuronal damage. During conditions of cerebral or spinal cord ischemia, inadequate energy supply in the form of adenosine triphosphate (ATP) leads to widespread neuronal depolarization and alterations in ion channel permeability, ultimately resulting in excessive intracellular calcium concentrations and cell death.

Serum total and ionized calcium concentrations are measures of extracellular calcium, and so the goal of targeting intracellular calcium homeostasis is limited to maintaining normal extracellular fluid concentrations at this time. Because of the known toxic effects of excessive calcium in neuronal injury, a conservative approach to calcium supplementation may be justified in the acute fluid management of large animal patients. To prevent the detrimental effects of hypocalcemia, one approach may be to avoid the addition of calcium to the intravenous fluids over the initial 24 to 48 hours unless the ionized calcium concentration is ≤1.0 mmol/L or clinical signs of hypocalcemia are present.

Magnesium is an important cofactor in many enzymatic reactions and for the regulation of sodium and potassium transport across cell membranes through activation of the Na^+/K^+-ATPase pump. Magnesium is essential for central

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nervous system cellular energy metabolism, modulation of excitatory amino acid transmission, and calcium channel antagonism. After neurologic injury, disruptions in the blood-brain barrier may impair regulation of CSF magnesium concentrations, and hypomagnesemia is commonly recognized in human patients with brain injury.[28] Experimental and clinical evidence suggests that a depletion of CSF magnesium concentrations is associated with the risk of secondary neurologic injury.[29] Animal studies also suggest a neuroprotective effect of intravenous magnesium administration after traumatic brain injury.[30] However, studies in human patients with TBI have failed to show a consistent therapeutic effect of magnesium supplementation.[29] Although magnesium supplementation for the treatment of TBI in equine patients cannot be recommended at this time, it is important to monitor serum total and ionized magnesium concentrations to prevent and treat hypomagnesemia after neurologic injury. Selection of intravenous fluids containing magnesium, such as Normosol-R or Plasma-Lyte 148 or Plasma-Lyte A (Mg^{2+} = 3 mEq/L), may be beneficial.

Other electrolyte disturbances identified commonly in patients with neurologic injury include hypokalemia and hypophosphatemia. A combination of decreased dietary intake and increased renal loss as a result of diuretic therapy is a likely explanation. Because of the important role of potassium in establishing normal resting membrane potential and nerve conduction, among other functions, regular monitoring and intravenous fluid supplementation if serum potassium concentration decreases to less than 3.0 to 3.2 mEq/L is indicated in large animal patients with neurologic injury.

Serum phosphate concentrations are not as routinely monitored as other electrolytes in large animal patients, and so deficiency is rarely reported. Clinical signs of hypophosphatemia usually do not manifest until serum concentrations fall below 1 mg/dL in humans and animals. It is important to recognize phosphate deficiency in patients with recent neurologic injury because it can cause or contribute to altered mental status, muscle weakness, seizures, respiratory insufficiency, and ventricular dysrhythmias. Because clinical manifestations of hypophosphatemia have not been reported in horses, it is difficult to make recommendations for supplementation. The author has used a dose of 0.01 mmol/kg/h of sodium phosphate when marked hypophosphatemia has been present in horses.

Fluid Therapy for Horses With Rhabdomyolysis (Box 44.7)

K. Gary Magdesian

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Box 44.7

Fluid Considerations for Horses With Rhabdomyolysis

1. Horses with acute myopathies often exhibit hypochloremia and may have concurrent hyponatremia, hyperkalemia, and hyperphosphatemia, especially when the rhabdomyolysis is severe.
2. Lactated Ringer's solution is a fluid with a physiologic basis for use with rhabdomyolysis.
3. Horses with acute myopathies should be administered fluids at a rate greater than maintenance requirements in order to provide for dilution and diuresis of myoglobin.

Horses with severe rhabdomyolysis are at risk for renal failure from both myoglobinuria and hypovolemia. Myoglobin causes formation of tubular casts (with resultant tubular obstruction) by precipitation with secretory proteins from the tubular cells. It is also directly toxic through release of iron and formation of free radicals. Finally, myoglobin leads to release of platelet-activating factor and endothelins that lead to renal arteriolar vasoconstriction. In addition, horses and foals with severe rhabdomyolysis may develop marked electrolyte derangements from cell lysis, including hyponatremia, hypochloremia, hyperkalemia, and hyperphosphatemia.[1,2] In a study evaluating the electrolyte changes in horses with acute rhabdomyolysis, the most consistent abnormality was hypochloremia.[1] These changes have been reported in foals with rhabdomyolysis as a consequence of selenium deficiency, possibly combined with increased oxidant stress resulting from sepsis or hypoxia and reperfusion injury after parturition.[2] Three of four foals developed cardiac arrhythmias characterized by spiked T wave and decreased P wave amplitude on electrocardiographic analysis. Destruction of the major intracellular fluid compartment through extensive myonecrosis, combined with myoglobinuric renal insufficiency, produces major fluid shifts and electrolyte derangements. In that report, foals

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with hyperkalemia caused by rhabdomyolysis were effectively treated with mineralocorticoids, loop diuretics, and ion exchange resins to enhance elimination of potassium. Intravenous calcium, glucose, insulin, and sodium bicarbonate were also administered to help redistribute potassium back to the intracellular fluid.[2]

Metabolic acidosis is not common in horses with acute rhabdomyolysis, and alkalosis associated with hypochloremia may be more of a concern.[1] In fact, fluids with relatively higher chloride concentration as compared with horse plasma may be optimal when hypochloremia is present. These include LRS (chloride, 109 mEq/L) or Hartmann's solution (111 mEq/L). If LRS is used, attention should be paid to serum or plasma potassium concentrations because LRS contains potassium chloride in the amount of 4 mEq/L of potassium (see Table 44.1). LRS or Hartmann's solution might be preferable over acetate-containing fluids such as Normosol-R or Plasma-Lyte 148 or Plasma-Lyte A in acute rhabdomyolysis cases, because the liver is the primary organ of lactate metabolism, whereas the muscle tissue plays a larger role in metabolism of acetate. In addition, the chloride concentration of these acetated fluids is lower than that of LRS, which may be a slight disadvantage if horses have metabolic alkalosis resulting from hypochloremia. Lactate in LRS does not preclude its use in hyperlactatemic horses with muscle disorders, because hepatic metabolism of lactate occurs rapidly once plasma volume is expanded. In addition, lactate is not necessarily markedly increased in horses with rhabdomyolysis.[3]

LRS is preferred over normal saline for treatment of humans with rhabdomyolysis.[4] In a randomized blinded study of humans with rhabdomyolysis, urine and plasma pH was higher in the LRS group, whereas serum sodium and chloride concentrations were higher in the saline group.[4] Unlike the saline group, the LRS group needed little supplemental sodium bicarbonate and did not develop metabolic acidosis. Acidic urine favors formation of myoglobin-induced tubular casts and tubular obstruction. Therefore LRS is considered by many to be the fluid of choice to maintain adequate urine flow in patients with rhabdomyolysis. One potential disadvantage of LRS in treatment of rhabdomyolysis is the presence of a low concentration (3 mEq/L) of calcium. Calcium influx plays a role in cell lysis after lipoperoxidation of muscle cells. How these data apply to adult horses, which generally have alkaline urine at baseline, requires further study. Because 0.9% saline is mildly acidifying in horses as well, it likely is not the optimal fluid choice for horses with

rhabdomyolysis either. Because foals often have acidic urine, LRS may be a good fluid choice for foals with rhabdomyolysis as well.

In addition to crystalloid support, sodium bicarbonate is recommended for human rhabdomyolysis only if necessary to correct a systemic metabolic acidosis.[5] Mannitol is administered to maintain urine output (300 mL/h or greater urine output in adult humans).[5]

Hereditary causes of rhabdomyolysis in horses include polysaccharide storage myopathy, glycogen branching enzyme deficiency, and recurrent exertional rhabdomyolysis (RER).[6-8] Because an alteration in muscle cell calcium regulation is a primary feature in the pathophysiology of RER, calcium supplementation of fluids administered to affected horses should be avoided.[9] Serum potassium concentrations should be monitored frequently in horses with rhabdomyolysis because of risks associated with hyperkalemia.

Because horses with acute rhabdomyolysis are at risk for renal failure, rates of fluid administration should exceed maintenance requirements to provide diuresis and dilution of urine myoglobin concentration. In adult human patients with rhabdomyolysis, the goal of urine production is greater than 300 mL/h.[5] Myoglobin is nephrotoxic directly to renal tubular epithelium; as well, it indirectly causes renal arteriolar vasoconstriction and secondary hypoperfusion. Rates of fluid administration vary with individual fluid balance and renal function, but 1.5 to 2 times maintenance requirement is a reasonable starting point. The rate can be adjusted based on the rate of creatine kinase (CK) decline and resolution of myoglobinuria.

Fluid Therapy for Hyperkalemic Periodic Paralysis (Box 44.8)

K. Gary Magdesian

Box 44.8

Fluid Guidelines for an Acute Hyperkalemic Periodic Paralysis Episode

1. 4 to 20 mL of 0.9% saline per kilogram, depending on severity and

duration.
2. 2% to 5% dextrose (2% to 2.5% if ≥5 L are administered; 5% if 2 L are administered to a 500-kg horse)
3. 0.2 to 0.5 mEq/kg of calcium (0.2 to 0.5 mL/kg of 23% calcium gluconate total, diluted in fluids); calcium should be administered early (along with dextrose), since it is protective against arrhythmias. Dilution of 23% calcium gluconate should be to a final ratio of no more than 50 mL of calcium gluconate/L of fluid.
4. 0.5 to 1 mEq/kg of bicarbonate in second bag of normal saline, along with dextrose. Note that sodium bicarbonate and calcium should not be mixed in the same bag.
5. For refractory cases, insulin can be added to dextrose supplementation (regular insulin, 0.005 to 0.1 unit/kg/h).

Hyperkalemic periodic paralysis (HYPP) is caused by a genetic defect in the sodium channel on the sarcolemma, resulting in intermittent signs of sweating, muscle fasciculations, stridor, and weakness.[1] Stressors such as anorexia, anesthesia, concurrent illness, trailering, and cold environmental temperatures can precipitate hyperkalemia and onset of clinical signs. Fluid therapy for horses with hyperkalemia should be low or free of potassium. Physiologic (0.9%) saline and isotonic sodium bicarbonate (1.3%) are both potassium-free options that have been used. Note that these two fluid types have potential effects on acid-base physiology, with saline producing a mild strong ion acidosis and sodium bicarbonate a metabolic alkalosis. There is some evidence in human medicine that the strong ion acidosis induced by the chloride excess in saline can actually increase potassium concentrations by causing shifts from the intracellular space. There are small studies to suggest that the use of balanced crystalloids in the presence of mild hyperkalemia is safe. However, larger studies are needed before balanced crystalloids can be recommended.

Horses experiencing stressors such as forced withholding of feed before surgery or being off feed because of concurrent illness should be administered fluids with dextrose and/or calcium supplementation prophylactically at a maintenance rate. Supplementing with dextrose (2.5% to 3% dextrose at 1 L/h for an average-size horse, or 0.8 to 1 mg/kg/min of dextrose) may minimize the development of hyperkalemia and subsequent HYPP episodes. Calcium does not decrease serum potassium concentrations significantly but rather protects the heart from its adverse effects by raising threshold potential for the action

potential on the sarcolemma.

Horses experiencing an active episode of hyperkalemia or showing clinical signs of HYPP should be administered 0.9% saline as the fluid choice, with the additives of calcium (0.2 to 0.5 mEq/kg of 23% calcium gluconate total, diluted as ≤50 mL 23% calcium gluconate/L of fluid) and dextrose (5% if 2 L of fluids are administered, or up to 2% to 2.5% if 5 L are administered). If signs persist, a second bag with sodium bicarbonate (0.5 to 1 mEq/kg of bicarbonate empirically) and dextrose should be added. Calcium and sodium bicarbonate should not be administered concurrently in the same fluid administration set because of a potential for precipitation. LRS also contains calcium, and therefore sodium bicarbonate should not be added directly to it.

Administration of two 5-L bags of saline to a 500-kg horse, with 2% to 2.5% dextrose, with the first bag containing calcium (0.5 mL/kg of 23% calcium gluconate total) and the second containing sodium bicarbonate (0.5 to 1 mEq/kg of bicarbonate) is a reasonable approach to treating an acute and severe episode. Each of these bags would be given sequentially. Some horses may not require this volume of crystalloid and can be treated with less; if less volume is desired, 4 to 6 mL/kg of normal saline can be administered. In this case, dextrose, calcium, and sodium bicarbonate can be added to 1-L bags; the sodium bicarbonate and calcium must be kept separate from one another. In this case, 5% dextrose and 0.2 mL/kg of 23% calcium gluconate would be administered in the first 1-L bag, and 5% dextrose and 0.5 mEq/kg of bicarbonate can be used in the second 1-L bag.[1]

Long-term management of horses with HYPP consists of a low-potassium diet, regular exercise, attempts to minimize stressors, and medications such as acetazolamide and phenytoin.[2] Horses undergoing chronic acetazolamide therapy could theoretically develop hyperchloremia and a tendency toward metabolic acidosis because of the effects of long-term inhibition of carbonic anhydrase. Administration of large volumes of 0.9% saline can compound hyperchloremia[3]; to minimize acidemia, it can be coadministered with isotonic sodium bicarbonate or other alkalinizing crystalloid when such horses require large-volume or long-term fluid therapy devoid of or low in potassium. Phenytoin can mask the clinical signs of HYPP, even when hyperkalemia is present; it must be emphasized that phenytoin should not be the sole prophylactic medication in these horses, because hyperkalemia may be left unchecked.[2]

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Fluid Therapy for Competitive Endurance Horses

C. Langdon Fielding

Approximately 4% to 9% of endurance horses are eliminated from competition for metabolic reasons that include colic, rhabdomyolysis, synchronous diaphragmatic flutter, and exhaustion.[1,2] Veterinarians are responsible for the emergency treatment of horses with metabolic derangements, and fluid therapy is an essential component of the therapeutic management of critically ill endurance horses.

General Approach to Fluid Management of Endurance Horses.

Endurance horses experience significant fluid losses during competition; even horses that successfully complete rides lose approximately 5% of body weight in water.[3,4] Horses presented for treatment of metabolic problems often exhibit clinical signs of hypoperfusion. In evaluating sick endurance horses, the following seven clinical perfusion parameters should be evaluated:

1. Mentation
2. Heart rate
3. Pulse quality
4. Mucous membrane color
5. Capillary refill time
6. Extremity temperature
7. Jugular fill

Urine production, when apparent, can be used as an additional perfusion parameter. In the absence of polyuric renal failure, urine output signifies renal perfusion, which is one means of assessing organ perfusion. Horses with altered mentation, persistent tachycardia (>60 bpm), poor peripheral pulse quality, pale mucous membranes, capillary refill time greater than 2 seconds, cool extremities, or lack of urine production should be considered candidates for fluid therapy. Laboratory parameters consistent with dehydration, such as increased PCV, increased total protein, and increased serum creatinine, have been identified in endurance horses at risk for metabolic failure.[5]

The rapid administration of large volumes of crystalloids is the basis of treatment at many ride events. Volume loading increases preload, thereby enhancing stroke volume, cardiac output, and subsequent oxygen delivery. One

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suggested protocol for fluid resuscitation of hypovolemic endurance horses is the fluid challenge method described earlier; this consists of a bolus dose of 20 mL/kg of isotonic crystalloid (10 L for an average, 500-kg horse) followed by reassessment of the seven perfusion parameters. If the parameters have not improved in response to the initial bolus, another 20 mL/kg bolus should be administered and followed by clinical reassessment. Approximately 1 hour is required to administer a 10-L bolus through a 14-gauge intravenous catheter and standard administration set; multiple catheters or those with large bores (10 gauge) can be used for more rapid administration. Most endurance horses requiring emergency intravenous fluid administration during competition typically require 20 to 30 L of fluids.[6,7] However, more severely affected horses may require up to 40 to 60 L of crystalloids to address hypovolemia.

Several types of intravenous crystalloids are available for administration to endurance horses. LRS and Normosol-R are balanced polyionic crystalloids commonly administered to treat hypovolemia in these horses. Specific electrolyte abnormalities may dictate the use of isotonic saline (when hypochloremic alkalosis is present) or fluid additives (potassium chloride or calcium gluconate when hypokalemia or hypocalcemia is identified, respectively). However, in one study, 0.9% sodium chloride resulted in hyperchloremia when administered to eliminated endurance horses.[6] The electrolyte and serum biochemistry profiles of endurance horses that fail to finish a race are not necessarily markedly abnormal and allow the use of commercial fluids such as LRS and Normosol R.[4] A range of electrolyte abnormalities has been identified in competing endurance horses and includes hypokalemia and an increased strong ion difference (SID).[8,9] Calcium supplementation is common during fluid therapy of eliminated endurance horses. However, results of studies examining the concentration of total and ionized serum calcium in horses during endurance rides have been equivocal as to calcium status.[3,4,10] If calcium is used, it can be added to fluids through calcium gluconate (1 mL/kg of 23% calcium gluconate at a rate of ≤50 mL/L of crystalloid). Calcium supplementation is required in horses with synchronous diaphragmatic flutter and should be administered until clinical signs resolve.[11] Excessive use of calcium in endurance horses may not be warranted, since it plays a role in cell death and apoptosis, particularly with reperfusion injury; supplementation of calcium in humans with rhabdomyolysis is controversial.[12]

Endurance horses with prolonged ileus or anorexia may benefit from dextrose

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supplementation of fluids. A dose of 0.5 to 1 mg/kg/min of dextrose is well tolerated by most adult horses and is equivalent to 1.5% to 3% dextrose in fluids administered at a rate of 1 L/h for a 500-kg horse. Ideally, blood glucose concentrations should be monitored in horses administered dextrose to avoid hyperglycemia.

Medications commonly used in the treatment of endurance horses with metabolic derangements may affect fluid balance and should be considered in horses receiving fluid therapy. Sedatives and tranquilizers such as α_2-adrenergic agonists (xylazine, detomidine, romifidine) and phenothiazines (acepromazine) have deleterious effects on cardiac output and/or blood pressure.[13,14] Drugs such as dimethyl sulfoxide (DMSO) and α_2-adrenergic agonist sedatives also affect urine output and can therefore alter fluid balance.[15,16]

The following metabolic conditions are common metabolic disorders of endurance horses.

Exertional Myopathy.

Intravenous fluid therapy is the most important feature of treatment for rhabdomyolysis. See the Fluid Therapy for Horses with Rhabdomyolysis section earlier in this chapter. Fluids should be administered in 10-L (20 mL/kg) boluses until urine output is achieved and the urine is grossly clear. Low doses of flunixin meglumine (0.5 mg/kg IV) are indicated for inflammation once hypovolemia is resolved and diuresis (i.e., urination) is achieved. Adequate fluid resuscitation is indicated before release of affected horses, because exertional rhabdomyolysis has been associated with severe renal failure in both humans and horses.[17,18] Horses with myopathies should be monitored closely and reevaluated within 48 hours for azotemia and progress of increased muscle enzymes.

Failure to Recovery.

Horses that are eliminated from ride events because of persistent tachycardia warrant close monitoring. Such horses often require treatment at a later time. The seven clinical perfusion parameters should be evaluated thoroughly, and any animal with equivocal circulatory or hydration status should be reevaluated frequently to make sure that it is improving through voluntary eating and drinking, rather than deteriorating further. Those with clear hypovolemia or failure to improve with rest should be administered intravenous fluids as

described earlier.

Synchronous Diaphragmatic Flutter (Thumps).

Synchronous diaphragmatic flutter is typically associated with hypocalcemia, and concurrent metabolic alkalosis, hypochloremia, and hypokalemia are often also present and have been implicated in its development.[19] Many affected horses are otherwise stable hemodynamically and meet all the criteria for adequacy of perfusion. Despite these findings, horses with thumps often require treatment with intravenous fluids supplemented with calcium for resolution of hypocalcemia and clinical signs. Calcium gluconate can be added to 5-L bags of crystalloid (0.5 mL/kg of 23% calcium gluconate per 5-L bag for a 500-kg horse), and fluids with dilute calcium can be administered as a bolus. Adverse effects of rapid calcium administration include bradycardia, and therefore calcium warrants slow administration. Many mildly affected horses would likely resolve synchronous diaphragmatic flutter with oral electrolytes and/or the consumption of feed (particularly alfalfa).

Colic.

Colic is a common problem identified in eliminated endurance horses and can result in significant mortality.[20] All horses exhibiting signs of colic should have a nasogastric tube passed, as nasogastric reflux (likely resulting from ileus) is a common finding in these horses.[20] Intravenous fluids should be administered as outlined previously until the horse is no longer producing gastric reflux and it is passing manure regularly. Flunixin meglumine (0.5 to 1 mg/kg) can be administered intravenously once hydration is restored. Calcium gluconate can be added to 5-L bags of crystalloid (0.5 mL/kg of 23% calcium gluconate per 5-L bag for a 500-kg horse), and fluids with dilute calcium can be administered as a bolus. Managing endurance horses with colic can be challenging because many show significant levels of pain. It is important to remember that endurance horses with colic rarely have a surgical lesion and typically respond to aggressive medical therapy.[9,20]

Fluid Therapy for Burn (Thermal) Injury in Horses (Box 44.9)

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Box 44.9

Fluid Guidelines for Burn Injury Patients

1. Hypertonic saline can be used in the resuscitative phase of burn patients but should be followed with isotonic crystalloids.
2. Isotonic crystalloids are often necessary because of tremendous sodium losses through burn wounds.
3. Plasma is an important component of fluid therapy in the severely burned patient because of the potential for protein loss.
4. Administration of excessive volumes of fluids should be avoided because edema is a common complication of burn injuries.

Horses with severe burn injuries develop hypovolemic shock and require large volumes of balanced electrolyte replacement fluids.[1] Hypertonic saline and colloids (primarily plasma) may also be used but should be followed with isotonic crystalloids. In humans with burn injuries, the guidelines for rate of administration of isotonic fluids is 2 to 4 mL/kg for each percentage of surface area burned (Parkland formula).[2] A retrospective study found that significantly larger volumes of fluid (i.e., 5.58 mL/kg per percent total body surface area affected) were administered to patients during the first 24 hours of hospitalization than was predicted by the Parkland formula.[3]

If significant smoke inhalation has occurred, the affected horse is at risk for pulmonary edema. In this case, fluid deficits should be corrected carefully so as not to overhydrate the animal and compound the edema. Administration of excess crystalloids or high rates of fluids after resolution of hypovolemic shock can result in exacerbation of tissue and pulmonary edema, which is detrimental to the healing of burned tissues and smoke-injured lungs, respectively. Once hydration is adequate, fluid therapy should be discontinued (if drinking) or administered at a rate necessary only to maintain hydration status. If maintenance rates of fluids are required, patients with severe burns may require more sodium than provided for by commercial hypotonic maintenance fluids owing to the tremendous sodium losses through wounds.[4] In these cases, isotonic crystalloids may be required, and therefore monitoring of serum sodium concentrations is important in burn patients.[5] Excess free water should be

avoided in these patients, since it can promote intracellular tissue edema.[5]

An important component of fluid therapy of the patient with thermal injury is the administration of plasma. Significant amounts of plasma proteins are lost through cutaneous burns.[4] In addition, burn patients are at risk for coagulopathies, although this has been reported to be rare.[6] Plasma transfusions are an effective source of albumin, as well as antithrombin for coagulopathies. Horses with significant burns can require large volumes of plasma in the first 2 to 3 days. A CRI of plasma can be provided when ongoing losses are present.

Fluid Therapy for Acute Respiratory Distress Syndrome in Horses (Box 44.10)

K. Gary Magdesian

Box 44.10

Fluid Guidelines for Acute Respiratory Distress Syndrome

1. The ideal initial resuscitative fluid choice for acute respiratory distress syndrome (ARDS) patients is unknown, but crystalloids rather than colloids should probably be used because of the risk for compounding pulmonary edema as colloids leak into lungs. The exception would be the hypoproteinemic patient, in which plasma should be used to correct albumin deficits.
2. Hypovolemia and dehydration should be corrected, but excessive fluid volume should be avoided to minimize worsening of edema. A conservative long-term fluid plan is warranted.
3. Fluid balance in patients with ARDS should be assessed frequently; central venous pressure is a useful means of monitoring fluid balance to prevent large increases in capillary hydrostatic pressure.

ARDS presents a therapeutic challenge; because of altered Starling's forces (increased vascular permeability) in the pulmonary capillaries, affected horses and foals often have significant pulmonary edema, with protein-rich fluid.[1]

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Pulmonary capillary hydrostatic pressure becomes the main determinant of edema in these patients due to the increased permeability of pulmonary capillaries.[2] Despite this propensity toward edema formation, horses and foals with ARDS should not be allowed to develop dehydration. Maintenance of normal blood volume and hydration status is critical to tissue oxygenation, including the diseased pulmonary tissue. The goal in therapy of ARDS patients is to reduce extravascular lung water while still maintaining hemodynamic stability and perfusion. In a human clinical trial, conservative fluid management in patients with acute lung injury (ALI) improved lung function and shortened duration of mechanical ventilation and intensive care as compared with patients managed with a liberal fluid strategy, although there was no difference in mortality.[3] The conservative management did not increase nonpulmonary organ failures.[3] It should be noted that the patients in this study were volume replete and relatively stable hemodynamically. Conservative fluid therapy therefore applies to the postresuscitation phase of these patients, when administration in excess of physiologic needs can be detrimental.

Large swings in pulmonary vascular pressures should be avoided to minimize increases in pulmonary hydrostatic pressure. To avoid these wide fluctuations, intravenous fluids should be provided as a continuous infusion rather than as intermittent boluses in horses with respiratory distress.[4] The ideal type of fluid for volume replacement at the time of initial therapy of ARDS patients is unknown; however, colloids should be used judiciously due to the theoretical risk of potentiating pulmonary edema through extravasation of colloids across the leaky pulmonary vasculature. This concern warrants further study; one study demonstrated no increase in transmicrovascular flux of radiolabeled colloids when COP was raised with albumin administration in human patients with pulmonary edema.[5] Isotonic crystalloids, administered at a modest rate and only to effect in normoproteinemic patients, and replacement of plasma proteins in hypoproteinemic patients with the use of plasma are probably the safest fluid guidelines for these patients with the current level of understanding.

Patients with ALI or ARDS should therefore be monitored closely for hypoproteinemia. Correction of hypoproteinemia in human patients with ALI benefits from concurrent administration of albumin.[6] Hypoproteinemic patients receiving both furosemide (as a CRI) and albumin had improved oxygenation, increased net fluid loss, and better maintenance of hemodynamic stability compared with those receiving only furosemide.[6] In addition, 50% of patients in

the treatment group achieved resolution of the ALI or ARDS, compared with only 11% of controls. Consideration should be given to correction of hypoproteinemia in foals and horses with ARDS or ALI. An additional benefit of albumin is its antioxidant properties. Albumin can also reduce microvascular permeability and endothelial cell apoptosis.[7-9]

Monitoring of fluid therapy in these patients is especially important in order to avoid marked increases in pulmonary hydrostatic pressure. This can be accomplished through measurement of pulmonary capillary wedge pressure; however, this requires placement of an intracardiac catheter. Alternatively, CVP can be measured. This is easily performed through central lines—those placed in the cranial vena cava. In a study comparing the use of pulmonary artery catheters with that of central venous catheters in guiding treatment of ALI in humans, it was found that pulmonary catheter–guided therapy did not improve survival or organ function and was associated with more complications than central venous catheter–guided therapy.[10] The predominant catheter-related complication was development of arrhythmia. It was concluded that pulmonary catheters should not be routinely used for the management of ALI.[10]

Fluid Therapy for Horses With Metabolic Acidosis (Box 44.11)

K. Gary Magdesian

Box 44.11

Fluid Guidelines for Metabolic Acidosis

1. The two primary forms of metabolic acidosis in horses are organic acidosis, most often resulting from hyperlactatemia, and inorganic acidosis, often resulting from relative or absolute hyperchloremia.
2. Treatment of hyperlactatemia consists of addressing the underlying cause. In many cases, lactic acidosis is caused by hypovolemia.
3. Commercial acetated fluids, such as Normosol-R or Plasma-Lyte 148, and lactated Ringer's solution are good fluid choices for hypovolemia, although volume rather than type of fluid is the most important component of treatment.

4. The use of sodium bicarbonate is controversial in lactic acidosis and may be contraindicated.
5. Sodium bicarbonate is the treatment of choice for inorganic acidosis (hyperchloremia).
6. Sodium bicarbonate can be administered as a fluid in the form of an isotonic solution.

Both organic and inorganic acidoses are found in horses with critical illness. A common cause of organic acidosis in horses is lactate (lactic acidosis). Hyperlactatemia occurs with hypovolemia, sepsis, and SIRSs such as endotoxemia, marked hypoxemia, heart failure, cytopathic hypoxia, and liver failure.[1-4] Volume resuscitation can be performed with a combination of crystalloids and colloids, and possibly hypertonic saline. Acetated crystalloids (such as Normosol-R or Plasma-Lyte 148/Plasma-Lyte A) do not contain lactate; however, even LRS (which contains sodium lactate) will correct hyperlactatemia when it is caused by hypoperfusion. Providing for hepatic perfusion will allow for clearance of the lactate previously accumulated. The exception is in liver failure, where fluids devoid of lactate should be administered because metabolism will be reduced. Other less common causes of organic (high anion gap) acidosis include ethylene glycol, salicylate toxicity, and uremic acidosis. The treatment of lactic acidosis is correction of the underlying pathogenesis. If the cause is hypoperfusion, reversal of that state should be the goal of therapy; this is accomplished through restoring blood volume, cardiac output, and finally systemic vascular resistance through the administration of fluids, dobutamine, and vasopressors, respectively. Sodium bicarbonate is therefore not a part of the routine treatment of lactic acidosis; its use in lactic acidosis is in fact controversial.[5,6] In a canine model of lactic acidosis, the administration of sodium bicarbonate actually caused a decrease in pH and bicarbonate concentration and an increase in lactate.[7] Similarly, in a model of endotoxemia in ponies, administration of sodium bicarbonate resulted in an increased blood lactate concentration.[8] Despite these controversies with sodium bicarbonate and lactic acidosis, when the pH of the patient's blood is below 7.2, administration of sodium bicarbonate until the pH reaches 7.2 is justified in order to prevent the detrimental effects of severe acidemia, even when the acidosis is a result of lactate. Severe acidosis can lead to life-threatening cardiovascular complications such as impaired contractility, sensitization to ventricular arrhythmias, and

impaired responses to pressors.[9] Small doses of sodium bicarbonate should be administered slowly to increase the pH to 7.2, at which point increasing perfusion should be the goal and sodium bicarbonate can be discontinued.

Inorganic acidoses occur because of strong ion acidosis associated with electrolyte derangements. In horses these commonly result from hyperchloremia or hyponatremia, both of which decrease the strong ion difference. Common diseases associated with these metabolic abnormalities include enteritis, colitis, renal failure, and renal tubular acidosis (RTA). In these cases the acidosis is often caused by renal or gastrointestinal dysfunction of electrolyte homeostasis, whereas perfusion may be normal (i.e., normal plasma lactate). Chronic administration of carbonic anhydrase inhibitors, such as acetazolamide, is another cause of hyperchloremia. The fluid of choice for patients with hyperchloremic metabolic acidosis is one containing only strong cations without strong ions. Because sodium bicarbonate contains only strong cations (sodium), it is an ideal choice for patients with normal anion gap (hyperchloremic) acidosis. Sodium bicarbonate should be administered slowly to allow time for distribution and evaluation of its effects. As a fluid choice, rather than as a supplement, isotonic (1.3%) sodium bicarbonate can be used; this formulation contains 150 mEq each of sodium and bicarbonate ion per liter. Potential side effects of rapid or large-volume sodium bicarbonate therapy include hypernatremia, hypokalemia, ionized hypocalcemia, vasodilation, metabolic alkalosis (if in excess), and an increased affinity of hemoglobin for oxygen (left shift of the oxygen dissociation curve).[8]

Fluid Therapy for Heart Failure (Box 44.12)

K. Gary Magdesian

Box 44.12

Fluid Guidelines for Heart Failure

1. Horses with heart failure are intolerant of significant changes in central venous pressure.
2. Fluid boluses should be avoided, and fluids should be administered at a slow, continuous rate.

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3. Consideration of the amount of sodium administered should be a priority.
4. Conservative fluid rates are warranted.
5. Concurrent and careful use of diuretics may be indicated.
6. Central venous pressure should be monitored.

The cardiac patient represents a unique challenge to fluid therapy. Volume expansion poses significant risk to the horse with heart failure by raising venous pressures (edema risk) and potentiating sodium retention. Administration of sodium-containing fluids can lead to or compound edema and body cavity effusions. Despite these risks, patients with heart failure sometimes require fluid therapy, such as when they develop anorexia, renal failure, or diarrhea. Monitoring of CVP should be performed in these patients at a referral center in order to aid in prevention of edema. Initial fluid therapy should consist of conservative rates, with frequent reassessment of the effects of fluids on the patient. Continuous, slow administration of fluids, rather than boluses, should be used to avoid rapid swings in CVP. Any rise in CVP should be avoided in horses with heart failure.

The choice of fluid depends largely on concerns over sodium retention in the patient with heart failure. Fluids with lower sodium content may be preferable for maintenance fluid therapy, such as maintenance fluids (0.45% NaCl/2.5% dextrose, Plasma-Lyte 56, or combinations of isotonic replacement fluids mixed with sterile water in a 1 : 1 ratio).[1] As soon as the patient is able to drink water, the intravenous fluids should be discontinued.

Because of sodium retention in heart failure, these horses are often treated with diuretics such as furosemide, which aid in minimizing edema formation.[1] A fine balance between fluid therapy and diuretics is required.

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Fluid Therapy in Ruminants

Marie-Eve Fecteau

General Principles

In addition to its obvious use for correction of dehydration, fluid therapy in ruminants can be instrumental in the treatment of a variety of disorders, including sepsis, electrolyte and acid-base disturbances, gastrointestinal disease, liver disease, and renal disease. Although enteral fluid therapy is commonly used in adult cattle, parenteral fluid therapy is often regarded as impossible in field situations because of practical and/or economic reasons. In many cases of severely debilitated ruminants, targeted fluid therapy is the key treatment aiding in the recovery from a disease process. This section addresses some key principles of fluid therapy in ruminants, for both field situations and hospital setting, focusing on a variety of commonly encountered disease processes.

In adult ruminants, estimation of dehydration can be based on several factors, including eyeball recession, upper eyelid skin tent, heart rate, and mucous membrane moistness (Table 44.2). Once the degree of dehydration is determined, maintenance fluid requirements (2 to 3 mL/kg/h for adults and 4 to 6 mL/kg/h for neonates), as well as ongoing losses, also need to be considered. The amount of water an adult dairy cow needs just to make up for lactation is often underestimated. The daily water requirement of a 600-kg cow eating a corn silage–based diet in a thermoneutral environment, and milking 45 kg of milk per day, is at least 140 L of water per day.[1] Although laboratory measurements are necessary to confirm and quantify electrolyte and acid-base derangements, those derangements can be predicted on the basis of the suspected disease process. For example, cattle with abomasal volvulus typically suffer from a hypochloremic, hypokalemic, metabolic alkalosis, whereas ruminants with acute grain overload are typically acidotic and often hypocalcemic.[2] Patient-side biochemistry analyzers can be very useful during the initial evaluation of the patient and for monitoring fluid therapy in field situations. An attempt should be made to match fluid composition (either oral or parenteral) to the (suspected or confirmed) electrolyte and acid-base deficits of the animal. However, one should remember that restoration of kidney function alone (by providing fluid volume) may represent the most effective step in addressing the metabolic derangements of the

patient.

TABLE 44.2
Guide to Estimation of Dehydration in Adult Ruminants

Percentage of Dehydration	Eyeball Recession	Upper Eyelid Skin Tent	Mucous Membranes
Mild (6%-7%)	Slight	Slightly prolonged (2-3 seconds)	Moist
Moderate (8%-9%)	Obviously sunken	Obviously prolonged (3-6 seconds)	Tacky
Severe (10%-12%)	Severely sunken into orbits	Remains tented indefinitely	Dry

Adapted from Smith GW: Supportive therapy of the toxic cow. *Vet Clin North Am Food Anim* 21:595, 2005.

Oral fluids are practical and economical and can be useful in correcting mild to moderate dehydration and metabolic disturbances in ruminants. In the adult ruminant, the rumen should be viewed as a large reservoir capable of absorbing large volumes of water and electrolytes.[3] The main force for water movement across the rumen wall is the gradient of osmolality between ruminal fluid (normally isoosmotic) and blood perfusing the ruminal epithelium.[4] Studies in adult cattle have shown that net flow of water from rumen to plasma occurs whenever plasma osmolality exceeds rumen osmolality by at least 20 mOsm/kg,[5] which means that to optimize free-water absorption, rumen osmolality should be hypoosmotic. The opposite situation is best represented during an episode of acute grain overload when the rumen quickly becomes hyperosmotic and water is drawn to the rumen from the extravascular space, leading to severe dehydration in those animals.[6] Therefore the practitioner should take advantage of the ruminal capacity for water and electrolyte absorption by administrating hypoosmotic oral electrolyte solutions to mildly and moderately dehydrated ruminants that do not suffer from preexisting abdominal distention or ileus. Enteral fluids should contain Na^+, K^+, and Ca^{2+}. Because most dehydrated adult ruminants are alkalotic, nonalkalinizing fluid formulations are preferred.[2]

Intravenous fluids are preferred in patients that are severely dehydrated (≥8%) and/or that suffer from severe metabolic disturbances or sepsis. An intravenous catheter is typically placed in a jugular vein, although the use of an auricular vein has also proved useful in calves and adult cattle.[7] The animal should be restrained in a tie stall or box stall and given enough length of fluid

administration set to allow him or her to lie down. Large-bore coiled intravenous fluid administration sets are useful for this purpose because they have a lesser tendency to become entangled when the animal moves around the stall.

Commercially available crystalloid solutions such as LRS, Normosol-R, Plasma-Lyte 148/Plasma-Lyte A, or 0.9% NaCl may be used, although homemade solutions can also be prepared cheaply on the farm or in a hospital setting. For example, a 0.9% NaCl solution can be prepared by adding 180 g of table salt to 20 L of filtered water using large plastic carboys. Additional recipes for homemade electrolyte solutions for cattle are included in Table 44.3. If tap (unfiltered) water is used in the mixing of the fluids, the author recommends that the animal not be kept on those fluids for extended periods (<48 hours) and that parenteral antimicrobials be used concurrently to minimize the risks of bacteremia and sepsis in the patient.

TABLE 44.3

Homemade Electrolyte Solutions

	0.9% NaCl	Ruminant Electrolyte Solution	D_5W	0.45% NaCl + 2.5% Dextrose
NaCl	180 g	140 g		90 g
KCl		25 g		
$CaCl_2$		10 g		
50% dextrose			2 L	1 L
Water	20 L	20 L	18 L	19 L

Response to fluid therapy should be closely monitored and adjusted as needed. Correction of electrolyte and acid-base imbalances should be based on laboratory results when available. For additional fluid therapy monitoring techniques, see the Critical Care and Fluid Therapy Monitoring Techniques section earlier in this chapter.

Fluid Therapy for Specific Ruminant Diseases and Disorders

Fluid Therapy for Abomasal Disorders and Upper Gastrointestinal Obstructions

Ruminants with simple abomasal displacements that are managed promptly usually do not require aggressive fluid therapy. Because simple displacements

(left or right) of the abomasum do not constitute a complete gastrointestinal obstruction, they rarely cause severe electrolyte and acid-base derangements in the adult cow. In cows that appear mildly dehydrated, enteral fluids (10 to 20 L) consisting of water and electrolytes usually suffice. Older, high-producing dairy cows often have some degree of subclinical hypocalcemia, especially in the early postpartum period, and should therefore be supplemented with calcium. If present, ketosis should be treated with intravenous infusion of dextrose or oral administration of propylene glycol.

Ruminants with abomasal volvulus, abomasal impaction, or other forms of upper gastrointestinal obstructions such as intestinal volvulus or intussusception typically have more severe metabolic derangements as a result of the trapping of fluid and electrolytes within the gastrointestinal compartments proximal to the obstruction. Those animals are typically moderately to severely dehydrated and require a more aggressive approach to fluid and electrolyte therapy, usually intravenously. The acid-base and electrolyte abnormalities of ruminants with upper gastrointestinal obstructions typically include hypokalemia, hypochloremia, metabolic alkalosis (although reduced perfusion of peripheral tissues may lead to metabolic acidosis terminally), hypocalcemia, and prerenal azotemia.[8-9] To replenish fluid losses and improve the circulating blood volume, an initial fluid bolus of 15 to 20 L (20 to 25 mL/kg) of isotonic crystalloid solution should be administered prior to or during surgery. It is the author's opinion that the best crystalloid fluid choice for cattle with hypochloremic metabolic alkalosis is 0.9% NaCl because of the relative chloride excess in normal saline, although other balanced crystalloid solutions such as LRS, Hartmann's solution, Normosol-R, and Plasma-Lyte may also be appropriate. Following the initial bolus, fluid therapy should be continued with an additional 30 to 40 L (3 to 5 mL/kg/h) of 0.9% NaCl or another balanced crystalloid solution, supplemented with at least 20 to 40 mEq/L of potassium chloride. In metabolic alkalosis, hypokalemia may result from redistribution of potassium from the extracellular to the intracellular compartment.[10] Ruminants with severe hypokalemia may also have to be supplemented orally (10 g KCl per 100 kg body weight [BW], twice daily [bid])[11] through stomach tube or in gelatin caps, especially if the intravenous fluids are supplemented with dextrose, which may cause a shift of potassium intracellularly.[12] When potassium chloride is supplemented, 1.0 g yields approximately 14 mEq. Care must be taken to never exceed 0.5 mEq/kg/h of potassium in order to avoid cardiotoxicity.[11]

Multiparous cows in the postpartum period may also benefit from calcium supplementation at a rate of 25 mL/L of 23% calcium borogluconate.

Hypertonic solutions (7.2% to 7.5% NaCl), at a rate of 2 to 4 mL/kg, can also be used to rapidly expand the intravascular volume in severely dehydrated cattle.[11] Ideally, the infusion of hypertonic solution should be followed by intravenous infusion of an isosmotic crystalloid solution, as stated previously. Cattle should also have access to a supply of fresh water and electrolytes or be administered oral fluids through stomach tube if intravenous fluid administration is not possible. Oral fluid administration should be used only following surgical correction of the abomasal volvulus because a large volume of orally administered fluids may worsen abdominal distention before surgery.

Fluid Therapy for Metabolic Acidosis (Acute Rumen Acidosis and Diarrhea)

In ruminants, severe metabolic acidosis may be encountered in a variety of cases including acute grain overload (rumen acidosis) and severe enteritis with profuse diarrhea. Severe ketosis, pregnancy toxemia, and sepsis can also lead to the development of a metabolic acidosis in the affected ruminants. Fluid therapy for ruminants with severe ketosis and sepsis is discussed later in this chapter.

Animals with acute rumen acidosis are typically severely debilitated and need aggressive medical and surgical therapy. Acute ruminal acidosis is discussed in detail in Chapter 32. The rapid accumulation of lactic acid in the rumen osmotically draws water into the rumen, resulting in marked dehydration.[6] In addition, the chemical damage to the rumen mucosa allows bacterial transposition into the peritoneal cavity and portal circulation, resulting in the development of endotoxemia.[13-14] Moreover, the fermentation of larger amounts of carbohydrates induces an increased concentration of organic acids that leads to a decrease in intraluminal pH. This decrease in pH favors the overgrowth of bacteria that are able to produce high quantities of D- and L-lactate, also contributing to the acidosis. Finally, third spacing of proteins in the rumen as well as in the abdominal cavity can result in profound hypoproteinemia in the affected animals, which further compounds their precarious hemodynamic state by its negative impact on the animal's oncotic pressure. Moderate to severe hypocalcemia is also common in these cases.

Fluid therapy in calves with diarrhea is discussed at length in Chapter 20. Adult ruminants with severe enteritis and diarrhea, such as those with

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salmonellosis, often require intravenous fluid therapy if they are completely anorectic, depressed, and significantly dehydrated. Oral fluids and electrolytes may be helpful in ruminants that are mildly to moderately dehydrated, but the effectiveness of those fluids may be compromised by malabsorption and ileus resulting from the enteritis. Similar to ruminants with acute rumen acidosis, cattle with acute diarrhea will suffer from varying degrees of metabolic acidosis, which is a result of the loss of bicarbonates in the diarrhea and from the enteric bacterial production of D-lactate. The poor perfusion of peripheral tissues that is sometimes seen in severe cases of hypovolemia may lead to the development of a lactic acidosis, which may also contribute to the overall acidosis in these patients. Also, similar to ruminants with acute grain overload, ruminants with severe enteritis and diarrhea can develop hypoproteinemia from gastrointestinal losses and third spacing within the abdominal cavity. Finally, although a lesser concern in adult ruminants, sepsis caused by severe enteritis may pose an additional problem that should be addressed by the use of intravenous fluids. Intravenous fluid therapy for sepsis is discussed further later in this chapter.

The goals of fluid therapy in ruminants with severe acute rumen acidosis or acute enteritis with profuse diarrhea should be (1) volume repletion, (2) correction of acid-base and electrolyte disturbances, (3) addressing the endotoxemia or sepsis, and (4) providing colloid support. Fluids should be provided in the intravenous form, especially in the case of rumen acidosis, to avoid exacerbating the abdominal distention and because most animals suffer from severe ileus. The choice of crystalloid solution should be based on the documented or suspected metabolic disturbances. Therefore nonacidifying solutions such as LRS and Plasma-Lyte should be preferred over 0.9% NaCl solutions. In cases of severe acidemia (blood pH <7.20), a sodium bicarbonate solution (1.3% to 5%) may be preferred until the blood pH is closer to normal range. The amount of sodium bicarbonate required to correct metabolic acidosis can be calculated by the following formula: $NaHCO_3$ (mmol) = BW (kg) × base deficit × 0.3. If laboratory data are not available, a clinician may choose to alternate between fluid solutions (e.g., between LRS and bicarbonate solution) in order to avoid overcorrection of the metabolic acidosis. An initial bolus of 25 to 50 mL/kg of crystalloids (without additives) should be followed by a CRI of crystalloid fluids containing potassium (20 to 40 mEq/L) and calcium (25 mL/L of 23% calcium gluconate solution). Fluids containing potassium and/or calcium should not be bolused in order to avoid cardiotoxicity. Care should also be taken not to fluid-overload the patient, especially small ruminants and young cattle, as

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excessive fluid administration may result in edema, including pulmonary edema. Animals known to have hypoalbuminemia (<2.0 g/dL) before the start of intravenous fluid therapy should be monitored carefully for development of edema. To address the hypoproteinemia and the poor oncotic pressure, colloids (whole blood, plasma, or hetastarch) should be considered if finances allow. Colloids are substances with a high molecular weight that are too large to pass through a semipermeable membrane and are therefore restricted to the plasma compartment and provide sustained plasma volume expansion.[11] Details for collecting, harvesting, storing, and administrating whole blood and plasma are available elsewhere.[15] Hetastarch, a high-molecular-weight glucose synthetic polymer, is supplied as a 6% concentration in 0.9% NaCl and can be administered at a rate of 5 to 20 mL/kg/d.[11] This may be more feasible in small ruminants or young cattle, because the use of colloids may be cost prohibitive in a full-size cow.

Fluid Therapy for Sepsis (Toxic Mastitis, Metritis, Peritonitis)

Endotoxemic shock, which often accompanies disease processes like coliform mastitis, toxic metritis, and septic peritonitis, can lead to marked hypovolemia necessitating aggressive fluid therapy in affected animals. For the septic patient, expanding the effective circulatory blood volume in order to improve tissue perfusion and counteract the decreased cardiac output and hypotension is crucial. Fluid therapy in ruminants with sepsis is similar to that recommended for ruminants with severe enteritis or acute rumen acidosis (see previous section).

Oral fluids can be useful in ruminants that are mildly dehydrated; however, in animals that are moderately to severely dehydrated and that have signs of endotoxemia, intravenous fluids are preferred. If intravenous fluid therapy cannot be achieved because of practicality or costs, the combination of intravenous hypertonic saline (7.2% to 7.5%) and oral water and electrolytes should be considered. Following administration of hypertonic saline, the increase in plasma osmolality results in movement of water from the extravascular space to the intravascular space.[11] In adult ruminants, the rumen represents the major reservoir from which the animal can draw water. For this reason, the administration of intravenous hypertonic solution alone, without following with oral or isotonic intravenous fluids, is insufficient and inadequate at addressing the hypovolemia. For a typical adult cow, 1 to 2 L of hypertonic

saline (2 to 4 mL/kg)[11] intravenously is followed by the administration of approximately 20 L (5 gallons) of water orally. If intravenous fluid administration is an option, isotonic fluids should be continued at a rate of 4 to 5 mL/kg/h for a total of at least 40 to 60 L (for a typical adult cow) during the first 24 hours. Care should also be taken not to overload the patient with fluids, especially small ruminants and young cattle, as excessive fluid administration may result in edema, including pulmonary edema. As discussed earlier in the Fluid Therapy for Metabolic Acidosis section, a combination of crystalloids and colloids may also have advantages in treating patients with sepsis, because colloids may attenuate capillary leak associated with sepsis.[16] In addition, some animals with severe sepsis may suffer from coagulation disorders such as DIC and may benefit from plasma or hetastarch administration.[17]

Whether fluid resuscitation is performed orally or intravenously, calcium supplementation (25 mL/L of a 23% solution) should also be considered, because hypocalcemia is often encountered in toxic cattle.[18,19] The reason for the decrease in calcium concentrations in endotoxemic cattle is not fully understood.[18,19] Ruminants that are anorectic should also be supplemented with potassium chloride (20 to 40 mEq/L). Although septic adult ruminants rarely become hypoglycemic (as opposed to neonates), dextrose supplementation (2.5% to 5%) may be beneficial in anorectic patients with concomitant ketosis and/or hepatic lipidosis. The animal's blood glucose concentration should be monitored and kept between 80 to 110 mg/dL to avoid a hyperglycemic state.

Fluid Therapy for Negative Energy Balance Disorders (Hepatic Lipidosis, Ketosis, Pregnancy Toxemia)

The vast majority of cattle and small ruminants with type 1 (primary) ketosis respond quickly to simple treatments that usually involve the administration of glucose precursors (such as propylene glycol) and/or a single administration of intravenous dextrose. However, cattle and small ruminants with severe ketosis, hepatic lipidosis, or advanced pregnancy toxemia may need more aggressive treatment, which usually involves the use of a CRI of intravenous fluids containing dextrose. Ruminants with liver dysfunction or failure have a decreased ability to perform normal metabolic functions such as gluconeogenesis, to synthetize proteins, and to clear a variety of metabolites, including lactate.

The main goal of treatment of hepatic lipidosis, severe ketosis, and pregnancy

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toxemia is to limit the mobilization of fat by increasing the availability of glucose or glucose precursors and promoting uptake of glucose by the cells. It is important to note that providing dextrose is critical in such cases, even in the face of normoglycemia, because it will minimize gluconeogenesis demands on the liver and prevent further production of ketone bodies. A CRI of isotonic fluids such as Normosol-R or Plasma-Lyte, containing 2.5% to 5% dextrose, is preferred over the use of D_5W because the latter contains too much free water. Because lactate clearance primarily occurs in the liver, and may be impaired in those animals, LRS should be avoided. In ruminants with suspected or confirmed metabolic acidosis, saline solutions (0.9% NaCl) should also be avoided, since they will compound the acidemia through hyperchloremia. Small ruminants with severe pregnancy toxemia may require an initial bolus of fluids containing 10% to 50% dextrose to break the cycle of negative energy balance. The rate of glucose administration should be approximately 1 to 2 mg/kg/min, which for a typical adult cow equates to approximately 1 L/h of a fluid solution containing 3% to 6% dextrose. The animal's blood glucose ideally should be monitored and kept between 80 to 110 mg/dL to avoid hyperglycemia. Insulin (e.g., zinc protamine) can be used subcutaneously every 24 to 36 hours to promote glucose uptake by the peripheral tissues and inhibit lipolysis. The addition of B vitamins to the fluids may also be useful in anorectic ruminants.

Fluids should also contain potassium chloride (20 to 40 mEq/L), since most ruminants with severe liver disease are partially or completely anorectic and may also experience a shift of potassium intracellularly in response to dextrose administration.[12] Special caution should be taken to monitor plasma potassium concentrations closely in cows receiving mixed glucocorticoid-mineralocorticoid drugs to aid in the treatment of hepatic lipidosis, since their chronic use has been associated with the development of severe hypokalemia.[20] As discussed earlier, cows with marked hypokalemia should receive oral and intravenous supplementation with potassium chloride. Calcium supplementation (25 mL/L of a 23% solution) is also important, since most cows with hepatic lipidosis are in the peripartum period and may also suffer from subclinical hypocalcemia; in addition, clinical signs of pregnancy toxemia may resemble those of preeclampsia in small ruminants. Plasma or serum phosphorus concentrations should also be monitored in ruminants receiving repeated infusions of intravenous dextrose because this can cause significant decreases in plasma phosphorus concentrations.[21,22]

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Fluid Therapy for Obstructive Urolithiasis

Most ruminants with obstructive urolithiasis are presented with azotemia, which is usually postrenal in origin, although prerenal azotemia from dehydration and renal azotemia from renal injury are also possible. Metabolic disturbances typically include metabolic alkalosis, hyperkalemia, hyponatremia, and hypochloremia.[23] Hypophosphatemia is another common biochemical finding in goats presenting with acute urolithiasis.[23] If a rupture in the urinary tract is present on admission, the degree of hyperkalemia may be severe. Ruminants with urinary tract obstruction, particularly those with severe electrolyte disturbances, often need to be stabilized before surgery.

Although it may not be advised to administer large volumes of intravenous fluids prior to relieving the obstruction, most patients' hemodynamic state will benefit from a fluid bolus prior to surgery. In very unstable patients with severe electrolyte disturbances (K^+ >6 mmol/L), draining the bladder (or the uroabdomen) prior to surgery by performing a cystocentesis or by placing a self-retaining suprapubic cystic catheter (Bonnano catheter [BD, Franklin Lakes, N.J.]) can be beneficial. The suprapubic catheters can stay in place for up to 24 hours in most small ruminants and allow for urine egress from the bladder while the patient is receiving intravenous fluid therapy. It should be emphasized that the ultimate goals of preoperative fluid therapy are to improve the patient's hemodynamic state and to address its most severe electrolyte abnormalities (usually hyperkalemia) so that the patient can more safely undergo general anesthesia. It should be noted, however, that surgery should not be delayed until the animal's azotemia is completely resolved, as azotemia may persist for several days following surgery in some animals.

Much has been written about the best fluid composition to use in hyperkalemic animals. The most common recommendation is to administer fluids that do not contain potassium, such as physiologic saline, D_5W, or isotonic sodium bicarbonate solution. However, others may argue that balanced electrolyte solutions such as LRS also represent a valid option, even in the face of hyperkalemia.[24] Insulin may also be used to help correct the hyperkalemia, especially preoperatively. If insulin is used, blood glucose concentrations should be monitored closely, especially in young ruminants, since they are at greatest risk of becoming hypoglycemic. Potassium plasma concentrations should also be monitored closely following the combination of insulin and diuresis, since many ruminants will become hypokalemic postoperatively, especially if they remain

anorexic for some time.

The fluid rate should be tailored to the patient's hydration needs, level of azotemia, and urine production. Although overhydration is rarely a concern in adult cattle with normal kidney function, small ruminants with acute renal failure should be monitored closely to avoid pulmonary edema. An initial rate of administration of 1.5 to 2 times maintenance is usually used until the azotemia is resolved.

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• CHAPTER 45

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Rational Antimicrobial Therapy

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Antimicrobial Stewardship

The dearth of antimicrobial drug development with the advent of increasingly resistant bacteria necessitates that we use these drugs in a judicious manner that prolongs their effectiveness. Not only does inappropriate use of antimicrobial drugs result in the emergence of resistance to these drugs, appropriate or inappropriate use also can have such an impact on the normal microbiota that severe and sometimes fatal gastrointestinal disease can develop. Furthermore, there is the potential for transmission of resistant zoonotic pathogens to humans. Hence veterinarians have an obligation to use antimicrobial drugs in a responsible manner.

Antimicrobial stewardship is defined as “an activity that includes appropriate selection, dosing, route, and duration of antimicrobial therapy” so that a positive clinical outcome can be achieved with a minimum of unintentional consequences.[1,2] The American Veterinary Medical Association (AVMA) defines antimicrobial stewardship for the veterinarian as follows: “Antimicrobial stewardship refers to the actions veterinarians take individually and as a profession to preserve the effectiveness and availability of antimicrobial drugs through conscientious oversight and responsible medical decision-making while safeguarding animal, public, and environmental health.”[3] Although a number of other definitions exist, the central concept of antimicrobial stewardship is to use antimicrobial drugs in a rational and responsible manner to have a positive clinical outcome while minimizing the emergence of resistance and adverse reactions.[4-7] The details regarding implementation of an antimicrobial stewardship program will vary according to an individual practice or hospital needs; however, certain elements should be incorporated.

Many antimicrobial stewardship guidelines describe the use of the “3 Rs” for antimicrobial stewardship. These are (1) reduction of the use of antimicrobial drugs whenever possible, (2) refinement of the use of an antimicrobial agent that considers dosing and antimicrobial choice based on pathogen, pharmacokinetics and pharmacodynamics, and host factors so that the emergence of resistance is minimized while clinical efficacy is maximized, and (3) replacement of antimicrobial agents with evidence-based alternatives. Page and Prescott advocated for the use of the “5 Rs” approach to antimicrobial stewardship that incorporates the aforementioned reduction, refinement, and replacement and

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adds the responsibility of the veterinarian to commit to antimicrobial stewardship and review of stewardship programs with the aim of continuous improvement, including compliance with policies and incorporation of new evidence-based best practices.[8]

The AVMA has established core principles for antimicrobial stewardship and judicious use of antimicrobials that incorporates many of the ideas found in the 5 Rs.[3,9] Judicious use principles can include attention to disease prevention strategies and biosecurity to prevent introduction or spread of pathogens, veterinary oversight of antimicrobial use, use of antimicrobials only after careful review including evidence provided by culture and susceptibility results, use of narrow-spectrum drugs when possible, and use of regimens of antimicrobial treatment based on evidence and scientific principles including pharmacokinetic data. Other veterinary associations and government agencies have advocated or provided guidelines for antimicrobial stewardship or prudent use of antimicrobials, including the American Association of Bovine Practitioners, American Association of Equine Practitioners, American Association of Swine Veterinarians, and the Center for Veterinary Medicine (CVM) of the U.S. Food and Drug Administration (FDA).[3,9-12]

Antimicrobial therapy is the cornerstone for treatment of infectious diseases. Therapy depends on appropriate identification of the infectious agent, determination of antimicrobial susceptibility of the causative organism, and application of pharmacokinetic and pharmacodynamic principles to achieve therapeutic levels of drug at the site of infection. Often this is referred to as the five rights: right drug, right dose, right route, right time, and right duration.[6] Additional factors such as adverse effects, cost, compliance with administration, penetration of the drug of interest to the site of infection, host factors, and development of resistance must be considered when choosing an antimicrobial drug regimen (Box 45.1). Avoiding the development of resistant pathogens or commensal flora is also desirable. This chapter focuses on the use of antimicrobial drugs directed toward bacterial pathogens; however, similar principles apply when choosing antifungal, antiparasitic, or antiviral therapies. The ultimate goals of antimicrobial therapy are to provide effective treatment, with the fewest adverse events and at the lowest cost, and to prevent development of resistance. Indiscriminate or inappropriate use of antimicrobial agents leads to development of resistance in the targeted pathogen as well as in the host microbiota. The consequences of resistance are manyfold, including the inability to treat certain infections, superinfections, and transfer of resistant

organisms to humans.[13] As veterinarians, we have an ethical obligation to protect both animal and human health and well-being through judicious use of antimicrobial drugs. Consensus statements published by the American College of Veterinary Internal Medicine provide guidance for use of antimicrobial drugs and raise important considerations for the veterinarian regarding their use.[13,14]

Box 45.1

Considerations for Antimicrobial Choice

Agent present
Agent factors
Antimicrobial susceptibility of the agent
Compliance with the regimen prescribed
Cost
Extralabel use
Host factors
Penetration of antimicrobial drug to the site of infection
Route of administration
Severity of the infection
Withdrawal time

One recommendation is that veterinarians develop standardized antimicrobial drug use guidelines for different types of cases (e.g., wounds, respiratory infections) that are appropriate for their hospital or clinical practice.[13-15] Often this requires some knowledge of likely pathogens and their antimicrobial susceptibility. Development of a hospital or regional antibiogram consisting of antimicrobial susceptibility data on the most common pathogens over a period of a year or two can be very helpful in devising empirical antimicrobial use strategies.

Antimicrobial therapeutics may also be categorized into tiers for use: primary, secondary, and tertiary drugs and those that are either restricted or have been elected to not be used by the practice. Primary drugs are those that are reached for most commonly, often either before or while awaiting culture and susceptibility testing results. Often these are older antimicrobials that may have a

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narrower spectrum of activity for pathogens (e.g., penicillin, older tetracyclines, sulfonamides). Secondary drugs generally are reserved for more serious infections or for when susceptibility data indicate resistance to primary drugs. Frequently these second-line drugs are also important in human medicine, thus avoidance of resistance development is important. Examples of these drugs include fluoroquinolones and third-generation cephalosporins. Tertiary drugs are those that are often effective against resistant bacteria and are also important drugs used for human patients, such as carbapenems. These tertiary drugs should be reserved for serious infections with confirmed resistance to all primary and secondary drugs. Thus use of higher-level drugs should always be directed by antimicrobial susceptibility testing. Finally, an example of a drug that may be used only after approval by an institutional committee (i.e., restricted) or prohibited is vancomycin.

In addition to establishing tiers of drugs for antimicrobial use, it is important to follow a logical approach when deciding on the type of antimicrobial drug to use. The goal is to use an antimicrobial drug to which the organism is susceptible and that will reach adequate concentrations at the site of infection, has little to no host toxicity, and is economically suitable for the owner and/or producer. This starts with establishing whether an infection is present, identifying the organism(s), determining antimicrobial susceptibilities, and considering host factors. Once therapy has been initiated, assessment of the patient is essential to decisions regarding length of treatment and whether antimicrobial therapy should be altered. In addition, adjunctive therapies such as surgical interventions should be considered.

Is There an Infection?

This is a frequently overlooked step when determining what type of antimicrobial therapy should be instituted. Too often, antibacterial drugs are used “just in case” there is an infection, without proper examination for the signs of infection. A number of clinical signs and clinical laboratory findings can be evaluated that may point to the presence of an etiologic agent. The old saying that redness, swelling, and heat are cardinal signs of infection and inflammation still holds true. Certainly, one frequently encountered finding is elevation of body temperature. However, inflammation for reasons other than the presence of an infectious agent may result in fever. Swelling and redness are frequent indicators of a localized infection. Development and appearance of purulent

material is further evidence of infection.

Clinicopathologic findings are also important supportive evidence for an infectious disease. Elevated or depressed peripheral white blood cell counts frequently accompany significant infections. In large animal species, fibrinogen elevations are observed in bacterial infections. Serum biochemistry values may also inform the decision to use antimicrobial therapy. For example, elevations in globulin may indicate production of excess immunoglobulin as seen in subacute to chronic infectious, primarily bacterial, processes. Decreases in serum albumin may develop as a negative acute phase protein in response to inflammation accompanying an invasive pathogen.[16] If possible, cytologic examination of material from the site of suspected infection should be performed. The presence of neutrophils, particularly with features of degeneration, is indicative of a septic process. Observation of infectious agents, ideally intracellularly, helps to confirm the presence of an infection.

What Organism Is Present?

Once the presence of an infection is determined, the next step is to decide what organism might be present. Ideally, samples should be collected prior to initiating therapy so that an etiologic diagnosis can be made and susceptibility testing can be performed. In the case of a serious or life-threatening infection, therapy must be initiated prior to receipt of culture and susceptibility results. Empirical therapy often relies on clinical judgment and knowledge regarding the likely organisms present, depending on the body system affected and its likely susceptibility patterns. Additional findings such as results from cytologic examination help to inform the antimicrobial choice.

Sample Selection and Transport to the Laboratory

Appropriate collection and transport of samples to the microbiological laboratory are essential to detection of the causative agent. The site of the infection should be sampled. This may seem obvious; however, a surprisingly large number of inappropriate samples are submitted to the microbiology laboratory. In general, sterile sites are the best regions to sample. For example, sampling of nasal discharge is almost never the appropriate choice when faced with purulent nasal discharge. Identification of the large number of normal bacteria and interpretation of the findings are difficult when normally colonized sites are sampled. The actual source of the discharge, such as the sinus, guttural

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pouch, or lung, should be determined and sampled directly. An exception to this rule is in the case of equine *Streptococcus equi* subsp. *equi* infections. Lesions such as a draining tract are problematic. Frequently they have superficial contamination of the opening of the tract that is inadvertently sampled. When possible, underlying soft tissue or bone should be collected rather than inserting a swab into the tract. Drains or urinary catheter tips are also inappropriate for samples. Too often they carry a biofilm of contaminating bacteria that may or may not be indicative of the disease process.

If anaerobic culture is deemed necessary, it is important that adequate volume of tissue or fluid be collected to preserve the anaerobic environment. If possible, at least a milliliter of fluid or a square centimeter of tissue should be collected. Swabs are inappropriate for anaerobic culture because air can be trapped between the fibers, leading to death of nonaerotolerant obligate anaerobes. If the sample is smaller and not taken immediately to the laboratory, it should be placed in some sort of anaerobic transport medium that will maintain an anaerobic environment. These anaerobic systems will maintain the presence of aerobic and facultative anaerobes as well.

Samples for microbiological culture should be transported to the laboratory as soon after collection as possible. The sample should be refrigerated if it cannot be delivered quickly, and it should be kept cool or cold but not frozen for transport to the laboratory. An exception to this rule is when anaerobic transport medium (e.g., Anaerobe Systems, Morgan Hill, Calif.) is used. These vials should be maintained at room temperature. It is possible that samples that are not kept adequately chilled can have overgrowth of contaminating bacteria, which can obscure detection of the “true” pathogen.

It is best if samples are collected prior to initiation of therapy. However, if antimicrobial treatment has already been instituted, the clinician should consider withdrawing therapy for a short period before sampling. Waiting between 24 and 36 hours after the last administration of drugs is advisable, and 99% of the drug should be eliminated after 7 half-lives. In seriously ill animals such as the septic foal, delaying antibiotic therapy for any amount of time to collect samples may be detrimental. In such cases, samples should be collected just prior to the next administration of drug. Some blood culture systems contain resins that bind or inactivate antimicrobial drugs and have proven to increase the ability to detect bacteria within the sample.[17]

Microscopic Examination of Sample

Initial examination of a sample provides important clues to the type of organism present. A Wright-Giemsa–type stain is frequently used to examine cytologic preparations made from samples. This staining technique can provide much information on the bacterial or fungal organism present. Identification of coccoid or rod-shaped bacteria along with the site of infection will often result in a differential diagnosis list of organisms to consider. An examiner with a practiced eye may be able to make an educated guess about the genus of the organism observed. A Gram stain provides additional information. Although many veterinarians do not use this stain in their clinical practice, the technique is rapid and, with a little practice, easy to perform and interpret. Identification of an organism as gram-negative or gram-positive further informs the practitioner of the likely organisms present and helps to guide empirical antimicrobial choice (Box 45.2).

Box 45.2

Gram-Stain Reaction and Morphology of Commonly Encountered Large Gram Stain of Animal Bacterial Pathogens

Gram-Positive Cocci

Enterococcus spp.
Staphylococcus spp.
Streptococcus spp.
Peptostreptococcus anaerobius (anaerobe)

Gram-Positive Rod or Filamentous

Actinomyces spp.
Corynebacterium spp.
Listeria spp.
Trueperella pyogenes (formerly *Arcanobacterium pyogenes*)
Clostridium spp. (obligate anaerobe)

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Gram-Negative Rods

Actinobacillus spp.
Brucella spp.
Bordetella spp.
Escherichia spp.
Haemophilus spp.
Histophilus spp.
Klebsiella spp.
Mannheimia spp.
Pasteurella spp.
Pseudomonas spp.
Bacteroides spp. (obligate anaerobe)
Fusobacterium spp. (obligate anaerobe)

What Is the Severity of the Infection?

One of the first decisions to be made when considering antimicrobial therapy is the severity of the infection. The clinician needs to decide if therapy must be initiated immediately or whether the patient can wait for results of culture and susceptibility testing before initiating therapy. Obviously, life-threatening infections require immediate and aggressive antimicrobial therapy. Infections of sites such as joints or other orthopedic structures may necessitate empirical therapy while awaiting the results of microbiological testing. In these cases, samples should be taken for identification and susceptibility testing before initiating therapy. In cases of serious infection, empirical therapy may include use of a bactericidal drug or a combination of antimicrobial agents (see section on Combination Therapy). On the other hand, an animal with a chronic, mild, or moderate infection may wait to receive antimicrobial drugs until testing has been completed.

What Is the Likely or Confirmed Antimicrobial Susceptibility of the Organism?

In a perfect world, the clinician should have laboratory-generated antimicrobial susceptibility results to guide therapy. However, frequently therapy must be initiated prior to receipt of culture and susceptibility results. Empirical therapy

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should be based on knowledge of the inherent resistance of suspected agents and the antimicrobial susceptibility patterns observed in the practice region. Susceptibility data should be compiled regularly by the regional microbiology laboratory and used by the practitioner in the hospital setting.

The microbiology laboratory should be proficient in antimicrobial susceptibility testing and follow guidelines established by the Clinical and Laboratory Standards Institute (CLSI) or similar institution.[18] Quality assessment testing should be performed regularly. A number of methodologies are used to examine susceptibility to different antimicrobials. Two frequently used methods for antimicrobial susceptibility testing are disk diffusion, also known as Kirby-Bauer test, and broth dilution or broth microdilution, which uses a 96-well plate.

Disk diffusion is a relatively straightforward testing methodology that can be performed with little specialized equipment. It involves creating a lawn of bacteria using a standardized concentration, placing disks containing a set amount of antimicrobial drug on top of the bacterial lawn, incubating, and measuring the zone of inhibition around the disk. This zone diameter determines whether the bacterium should be considered susceptible, intermediately susceptible, or resistant to a particular drug. The advantages of this method are that it is rapid and easy to perform provided strict protocols are followed. The disadvantages are that it cannot be used for slow-growing bacteria and it provides only an interpretation rather than information about the specific concentrations of drug that inhibit growth. Consequently, knowledge about the pharmacokinetics of a particular drug cannot be fully used to develop a treatment regimen to deliver optimal dose of the drug to the site of infection.

The broth dilution or microdilution method involves inoculation of a standard amount of bacteria into tubes or wells containing an antimicrobial drug. Most clinical laboratories use twofold dilutions of drug centered on the concentration of drug found systemically using typical dosing strategies. The inocula are subsequently incubated, and then the wells are examined for visible growth. The lowest concentration of drug that inhibits visible growth is called the minimum inhibitory concentration (MIC). Sometimes the wells are subcultured to a nonselective agar and then incubated, and this agar is examined for growth. The lowest concentration of drug that results in no growth is the minimum bactericidal concentration (MBC). For cost reasons, most clinical laboratories do not determine the MBC for each organism.

The MIC is unique for each bacterium-drug combination. The resulting MIC

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guides interpretation of the bacterium as susceptible, intermediately susceptible, or resistant to a particular drug. The concentration of drug at which the interpretation of testing changes from susceptible to intermediate or resistant is called the *breakpoint*. For example, *Enterobacteriaceae* isolated from adult horses are considered susceptible to amikacin if the MIC is 4 µg/mL or less; they are deemed resistant if the MIC is 16 µg/mL or greater. If the MIC is 8 µg/mL, the isolate is considered intermediately susceptible.[18] Generally, the clinician needs to use the interpretation only when deciding which drug to choose for therapy. However, the MIC can be used to refine therapy, by altering the dose of drug or frequency, to optimize treatment.

Interpretation breakpoints for susceptibility testing of a bacterium as susceptible or resistant are set by the CLSI. This body bases interpretation on three major factors: the epidemiologic breakpoint of a population of bacteria, pharmacokinetic data, and (when available) clinical outcome from treatment of animal or human patients.[19] A graph showing MICs of a population of a single species of bacterium frequently has a bimodal distribution. The trough between the two peaks is the epidemiologic breakpoint; those bacteria with higher MICs have acquired some sort of resistance determinant. The pharmacokinetic information used to assist with determination of the breakpoint includes the peak concentration of drug, the area under the pharmacokinetic curve, and time the drug is above a particular MIC. A simplified way to think about how these data are used is to look at a bacterium with a high MIC. It would be considered resistant because the amount of drug that would have to be administered to exceed the MIC would be considered toxic to the animal host. Generally, the highest concentration of drug tested is near or a bit above the highest concentration of drug that can be achieved with recommended dosages.

Antimicrobial therapy should be directed to achieve levels that are above the MIC for a particular isolate. Ideally, the “best” antimicrobial drug to use depends on many factors other than the susceptibility result. Obviously, the organism should be susceptible to the drug chosen, but other considerations should be included, such as route of administration, penetration to the site of infection, toxicity, cost, and convenience. All of these factors being equal, the optimal drug is one for which the organism's MIC is several dilutions below the breakpoint. However, further refinement is possible when one understands the pharmacodynamic properties of the drug and bacterium.

Bactericidal and Bacteriostatic Antimicrobial Drugs

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The terms *bactericidal* and *bacteriostatic* refer to the in vitro observation that a drug kills or merely inhibits growth of a particular bacterium, respectively. If one examines the relationship between the MIC and MBC, these two values are close or nearly identical for bactericidal drugs. In contrast, the MBC is several twofold concentrations above the MIC for bacteriostatic drugs. To be clear, it takes a higher drug concentration to kill bacteria with a static drug. The in vivo consequence of this relationship means that more drug must be delivered to the site of infection to kill the bacteria with a bacteriostatic drug. Often this is not achievable given the toxicity and pharmacokinetics of the drug. In the case of bacteriostatic drugs, the clinician must rely on the host immune responses to clear the inhibited organisms. Accordingly, bactericidal drugs should be used in an immunocompromised patient. Some drugs are concentrated in areas of infection. For example, drugs undergoing renal clearance are found in high concentrations in urine. Thus drugs that show in vitro bacteriostatic activity may achieve concentrations high enough to kill bacteria in the bladder. The converse is also true; use of a bactericidal drug at inadequate dosages or that has poor penetration to the site of infection may not achieve high enough concentrations to kill the offending organism. Thus some drugs can be considered either bactericidal or bacteriostatic. In practical terms, in an immunocompetent host without an overwhelming bacterial burden, the differing impact of a bacteriostatic versus bactericidal drug is minor provided that adequate concentration of the drug reaches the site of infection.

Concentration and Time-Dependent Antimicrobial Drugs

Pharmacokinetic (PK) and pharmacodynamic (PD) principles can also be used to guide antimicrobial therapy. Pharmacokinetics refers to drug absorption, distribution, metabolism, and elimination. Pharmacodynamics examines the effect of the drug concentration on the microorganism at the site of infection over time. The relationship between PK and PD principles describes the relationship between the drug concentration and the effect on the pathogen and clinical response.[20] Parameters that explore relationships between PK and PD principles, such as the peak concentration relative to the MIC, are reflected in the PK/PD index.[21] The relationship between the MIC and PK parameters may determine the outcome of therapy.

There are two categories of antimicrobial drugs: concentration-dependent drugs and time-dependent drugs. This categorization is primarily based on in

vitro work but is supported by clinical data in animals and humans.[22] Concentration-dependent drugs are those whose antimicrobial activity is best predicted by the relationship between peak drug concentration and the MIC of the organism. Drug classes that are considered concentration-dependent drugs include aminoglycosides and fluoroquinolones. The ratio between the peak drug concentration and the MIC should equal at least 8 to 10.[23] Using the example of amikacin given earlier, if the bacterium had an MIC of 2 µg/mL, the drug should be dosed to reach a peak concentration of 20 µg/mL. The time that the drug concentration is above the MIC appears to be less important for concentration-dependent drugs. Accordingly, many concentration-dependent drugs can be administered infrequently (e.g., once daily). This dosing strategy can be advantageous with certain drugs with toxicity. For example, nephrotoxicity of the aminoglycosides is best determined by trough concentrations of drug. These antimicrobials may be administered at high dosages once daily to achieve the high peak concentration, well above the MIC, while having prolonged low trough levels. Many concentration-dependent drugs have prolonged postantibiotic effect, meaning that the effect of the drug to inhibit growth of the organism is apparent for some time after the drug is removed.

Fluoroquinolone efficacy is best predicted by the area under the concentration curve (AUC) in relation to the bacterial MIC. The AUC/MIC ratio should be 125 or greater for gram-negative organisms.[22-25] This ratio should be 60 or greater for gram-positive bacteria.[22] Some studies indicate that ratios that approach 250 or greater be used to avoid development of resistance.[22]

Time-dependent drugs are those whose antimicrobial activity is best predicted by the time the drug concentrations are above the MIC. Many drug classes are considered time dependent, including the β-lactam drugs and tetracyclines. These drugs should remain above the MIC for at least 50% of the time. These antimicrobial drugs generally are dosed more frequently or via continuous rate infusion for those with short half-lives.

Knowledge of the PK and PD principles can guide the practitioner in appropriate dosages and frequencies for an individual drug. Monitoring of drug levels can further aid development of the therapeutic plan. Table 45.1 summarizes the PK and PD parameters and activities of some antimicrobial drugs.[26,27]

TABLE 45.1

Antimicrobial Drugs, Classifications, Activities, Postantibiotic Effect, and Pharmacodynamic Index

Drug	Activity	Bacterial Effect	Postantibiotic Effect[a]	PK/PD Index[b]
Aminoglycosides	Bactericidal	Concentration-dependent	Yes	AUC_{24}/MIC, Cmax/MIC
β-Lactams	Bactericidal	Time-dependent	No, gram negative; yes, gram positive	T > MIC
Fluoroquinolones	Bactericidal	Concentration-dependent	Yes	AUC_{24}/MIC, Cmax/MIC
Glycopeptides (Vancomycin)	Bactericidal	Time-dependent	Yes	AUC_{24}/MIC
Macrolides	Bacteriostatic	Time-dependent	No	T > MIC
Sulfonamides	Bacteriostatic	Time-dependent	No	
Tetracyclines	Bacteriostatic	Time-dependent	Yes	AUC_{24}/MIC
Trimethoprim	Bacteriostatic (unless combined with sulfonamide)	Time-dependent	No	

[a] *Yes,* Prolonged effect longer than 6 hours; *no,* less than 1 hour.

[b] *AUC_{24}/MIC,* Area under the concentration curve over 24 hours/minimum inhibitory concentration; *Cmax/MIC,* maximum concentration/minimum inhibitory concentration; *T >MIC,* time drug concentration is greater than the MIC.

Adapted from Martinez M, Toutain PL, Walker RD: The pharmacokinetic-pharmacodynamic (PK/PD) relationship of antimicrobial agents. In Giguere S, Prescott JF, Baggot JD, et al., editors: *Antimicrobial Therapy in Veterinary Medicine*, ed 4, Ames, IA, 2006, Blackwell Publishing, pp 81-106; and Martinez M, Toutain PL, Turnidge J: The pharmacodynamics of antimicrobial agents. In Giguere S, Prescott JF, Dowling PM, editors: *Antimicrobial Therapy in Veterinary Medicine*, ed 5, Ames, IA, 2013, John Wiley and Sons Inc., pp 79-103.

Where Is the Infection?

Too often the question of where the infection is located is not considered when choosing an antimicrobial drug. Penetration of the drug to the site of infection is essential for successful therapy. Remember that the MIC and interpretation of the MIC are focused on systemic (plasma) levels of drugs and rarely include information on drug penetration to various anatomic locations; CLSI is increasingly providing site-specific interpretations of MICs.[18] Some anatomic locations are particularly difficult to enter, such as the central nervous system, ocular fluid, and bone. Abscesses are another structure that is difficult for antimicrobial drugs to penetrate; they are surrounded by a thick capsule with

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poor blood supply and lack of oxygen, which can limit penetration into the abscess and offer poor entry into the bacteria. The pH is generally low, which may inactivate some agents, and there is abundant protein present to bind antimicrobial drugs. A further complication is the presence of purulent debris that can provide metabolic precursors for bacteria to bypass inhibitors of metabolism, such as trimethoprim-sulfonamide combination drugs. In general, lipophilic drugs will be better able to penetrate these difficult-to-reach anatomic locations. Highly polar or charged molecules have difficulty reaching these sites.

If the causative organism is found intracellularly, as seen with rhodococcal pneumonia or *Corynebacterium pseudotuberculosis* infections, the host cell membranes are additional impediments to drug penetration. Fortunately, some drugs penetrate cells well, such as macrolides, rifampin, chloramphenicol, fluoroquinolones, and trimethoprim-sulfonamide combinations.

Empirical Versus Definitive Therapy

Empirical therapy is used for severe infections prior to obtaining culture and susceptibility results. The choice of antimicrobial drug depends on the clinician's knowledge of the likely agents present at the site of infection and their predicted susceptibilities. Knowledge of the Gram stain results can further guide therapy. Generally, empirical therapy is broad spectrum to cover multiple possible etiologies. Eventually, once the etiologic agent and its susceptibility have been identified, definitive therapy, using a drug or drugs with narrower spectrums, can be initiated. Definitive therapy should be directed to best result in a cure, using the narrowest spectrum of drug therapy, and have limited toxicity for the patient. The goal is to de-escalate the spectrum of activity of the drug as much as possible with definitive therapy in order to minimize the impact on commensal bacteria and development of resistance.

Combination Therapy

Many infections can be treated effectively with a single antimicrobial drug; however, in some instances, combination therapy may be chosen. Some drug combinations have been demonstrated to be synergistic based on both in vivo and in vitro studies. Synergy occurs when the ability of the combination to kill bacterial growth is greater than the mere additive effect of each drug. Drug combinations can also be indifferent, where each drug's effects are merely

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additive. Finally, a drug combination may be antagonistic, where the drug combination's effectiveness is less than the sum of the independent effects. Synergistic antimicrobial drug combinations are best used to treat resistant organisms. A common synergistic pair of antimicrobial drugs is the combination of trimethoprim and a sulfonamide. Either agent alone would be considered bacteriostatic, but since each of these drugs inhibits sequential steps in folic acid metabolism, they are considered bactericidal.

A combination of antimicrobial drugs might be chosen for empirical therapy before the agents and their susceptibilities are known in order to provide broad-spectrum therapy. The combination of a β-lactam drug with an aminoglycoside is frequently chosen as empirical therapy in serious infections in equine patients. This combination is synergistic as well as broad spectrum. It is important to remember that in these cases, therapy should be reduced to a single agent or a less broad spectrum of activity as soon as testing results become available.

The presence of a polymicrobial infection is another reason why combination therapy may be used when a single agent will not be able to treat all bacteria present. For example, intraperitoneal infections are frequently caused by more than one agent. It is difficult to find a single antimicrobial drug to treat all possible bacteria present, such as *Enterobacteriaceae*, gram-positive bacteria, and anaerobes. Individual drugs that are sufficiently broad spectrum are available for use in humans; however, many of these would be cost prohibitive in large animal patients. The clinician should be cautious, however, of isolation of multiple agents from a single site such as a wound. Superficial samples taken from these sites may have contaminating bacteria, often with highly resistant antimicrobial patterns, that are not truly part of the infectious process.

Combined antimicrobial drug therapy can be used to prevent emergence of resistant bacteria. Certainly, for serious or difficult-to-treat infections such as those caused by *Pseudomonas* spp., avoiding development of resistance is important not only to the patient receiving treatment but also to others who come in contact with the bacteria. The best illustration of this principle is in the treatment of human patients for *Mycobacterium tuberculosis*, in which combination therapy is always used to prevent development of resistance.[28] Resistance to certain antimicrobial drugs, such as rifampin, can emerge quickly when they are used alone; thus these drugs are best used in combination.

There are some drawbacks to using combination therapy. One is the possibility of antagonism between antimicrobial drugs. Most instances of antagonism have been demonstrated in vitro, although in vivo reports have

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appeared.[28,29] Interestingly, combination therapy of penicillin with chlortetracycline was found to be inferior to penicillin alone in survival rates in human pneumococcal meningitis.[29] Antagonism was also seen with the combination of chloramphenicol with gentamicin used to treat immunocompromised mice with a *Proteus mirabilis* infection and in a rabbit model. Interestingly, this antagonism was not evident in immunocompetent mice, suggesting that the effect of antagonism was evident only with a diminished immune response.[28,30] Use of antimicrobial drug combinations also represents an increased cost to the client. Finally, there is an increased possibility of adverse effects of and/or hypersensitivity reactions to the drugs when used together. Antimicrobial drug combinations that may be detrimental include penicillin with tetracyclines and chloramphenicol with erythromycin. Combination therapy should not be chosen merely to provide comfort to the clinician, but rather clinicians should have specific reasons for their choice.

Drug Incompatibility

Drug incompatibility or antagonism can be the result of direct incompatibility, meaning that the drugs should not be mixed together for administration or that they should not be used together therapeutically. For example, certain penicillin or cephalosporin drugs should not be mixed with an aminoglycoside in the same vial because of inactivation of the aminoglycoside and formation of precipitates. Examples of therapeutic antagonism in vivo are harder to find. The few that have been well documented have been described in humans or animal models of disease rather than in spontaneously occurring veterinary patients. Still, these antagonistic effects are worth noting, as they may someday be demonstrated to be important in veterinary patients.

Host Factors That Influence Antimicrobial Choice or Dosage

Age

The age of the animal may influence many aspects of antimicrobial therapy. Bioavailability of certain drugs varies with age where some drugs can be used orally in neonatal or young animals but are poorly absorbed in mature animals.[31] The drug distribution may also vary with age because young animals generally have a larger volume of distribution than adults due to their larger percentage of

total body water.[32] Drug biotransformation in neonates may vary from that in adults as well.[32] Therefore drug dosages and/or frequencies may have to be adjusted in young animals to provide adequate levels of drug at the site of infection and to minimize toxicity.

Fluoroquinolone use in young and adult animals should be considered carefully. This class of antimicrobial drug has been documented to cause cartilage damage in several species of young animals, and ciprofloxacin has been associated with tendinopathies in humans.[33-35] Of interest is the observation that fluoroquinolones are capable of having chondrotoxic effects on equine and canine chondrocytes in vitro,[36,37] whereas a lamb model failed to demonstrate chondrotoxicity.[38] Unfortunately, specific guidelines for the safe use of fluoroquinolones in young animals are lacking. If fluoroquinolone use is necessary in young animals, it is important to limit the duration of therapy in order to minimize the chance of damage to developing cartilage. Along the same line, tetracyclines should also be avoided in young patients to avoid discoloration of enamel of developing permanent teeth.

Reproductive Status

Antimicrobial drugs may have deleterious effects on reproduction and the developing fetus. Depending on the drug, type of placentation, and stage of gestation, some drugs are able to reach the fetus. For example, use of potentiated sulfonamides in pregnant mares has been associated with anemia, fever, and abortion.[39] Administration of pyrimethamine and trimethoprim-sulfamethoxazole to stallions has been associated with weakness and abnormal copulatory form and function.[40]

The lactating large animal must also be considered. Many antimicrobial drugs can be found in milk and may be transferred to the lactating animal or human who consumes the milk. Some drugs reach the milk in high concentrations, whereas others are found in low amounts relative to plasma. Regardless, almost all antimicrobial drugs may be found in milk. Such adulteration may make the milk unsuitable for human consumption, and appropriate withdrawal times should be adhered to before milk enters the human food chain.

Treatment of bacterial mastitis presents several challenges and is covered in more detail elsewhere in this book. Treatment should be initiated early and be based on susceptibility of the causative agent. If individual milk culture and susceptibility testing are not feasible, treatment should be based on historical

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information from the affected herd. Penetration into milk is also an important consideration when using systemic drugs to treat mastitis. Many drugs, such as the β-lactams and sulfonamides, are found in much lower concentrations in milk. Others, such as the macrolides, can be concentrated into milk. Because of the low concentrations found in milk for many of the drugs used systemically in food production animals, intramammary administration is preferred, although systemic administration can also be used and is probably indicated in the systemically ill animal or when intramammary abscesses preclude delivery of the drug via the intramammary route. As for systemic administration, withdrawal times should be closely followed with intramammary infusions.

Renal and Hepatic Function

As for all drugs, metabolism of antimicrobial drugs takes place in the liver and/or kidney, and excretion follows these routes. Therefore compromised renal or hepatic function should be considered when choosing an antimicrobial drug. Aminoglycosides are well known for their nephrotoxicity and should be avoided in cases with elevations in serum blood urea nitrogen or creatinine. If their use is still warranted despite renal dysfunction, the frequency of administration or, in some cases, the dose should be altered. Therapeutic monitoring of aminoglycoside levels should be performed to guide therapy. Macrolides and rifampin are metabolized and excreted via the hepatic route, and liver enzymes should be monitored for elevation during use. Knowledge of the route of excretion of active drug can be used to concentrate drugs at the site of infection. In the case of bacterial pyelonephritis or cystitis, renal excretion of many antimicrobial drugs can be used to the clinician's advantage during treatment.

Immune Status

The effectiveness of the immune response is important for successful antimicrobial therapy. Many drugs only reach bacteriostatic levels at the site of infection, therefore only inhibiting growth of the offending agent. In these cases, the immune response is essential for clearing the infection. Bactericidal concentrations of drugs at the site of infection should be used in cases of immunocompromise. Immunodeficiency, whether primary or secondary, may be an indication for use of combination therapy.

Duration of Therapy

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Unfortunately, there are few guidelines in veterinary medicine that direct duration of therapy. Certainly, serious or deep-seated infections such as endocarditis, pyelonephritis, and osteomyelitis warrant prolonged antimicrobial administration. However, a meta-analysis of human infection outcomes in critically ill patients demonstrated that shorter duration of therapy for infections such as urinary tract infections, ventilator-associated pneumonia, or community-acquired pneumonia had no impact on mortality.[41] In addition, prolonged antimicrobial use can be associated with adverse effects and emergence of resistant secondary infections. In veterinary medicine we must frequently rely on response to therapy. Resolution of pyrexia, decreases in white blood cell count or fibrinogen, or resolution of abnormal radiographic and ultrasonographic findings are important parameters to monitor when deciding to cease therapy. In some cases, sampling and culture of the previously infected site may be warranted to demonstrate microbiological cure. For simple infections, treatment for a few days past resolution of clinical abnormalities and clinicopathologic findings may be adequate. For complicated infectious processes or chronic infections, treatment may be needed for weeks or longer after apparent cure.

Route of Administration

The route of administration varies depending on the patient species, age, severity of the infection, bioavailability of orally administered drugs, and site of the infection. Intravenous delivery of antimicrobials is indicated for serious life-threatening infections in which high levels of drug at the site of infection are indicated. Many drugs with good oral bioavailability in small animals, such as β-lactams, cannot be administered orally in large animal patients, necessitating parenteral administration. Oral administration of antimicrobials should be used cautiously in large animal species to minimize disruption of ruminal or colonic microflora in ruminants and horses, respectively. The route of administration may also be influenced by client or patient compliance and the drug label. Intramuscular administration may be difficult for some clients and patients, resulting in inadequate duration of therapy and possible development of resistance by microorganisms. Guidelines for therapeutic use of antimicrobial drugs in feed are provided later in this chapter.

Monitoring of Therapy

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The response to treatment should always be monitored throughout antimicrobial drug administration. It helps to guide decision making regarding duration of therapy and effectiveness of the chosen antimicrobial regimen. As mentioned, clinical and clinicopathologic findings are useful guides to judge therapeutic success. Failure to respond to therapy could indicate that the organisms present in the infection are resistant to the chosen drug, particularly if the drug was chosen empirically. It may also indicate development of resistance during therapy or that there is poor penetration of drug to the site of the infection. Monitoring drug levels may be indicated to determine whether dosage and/or frequency is adequate in cases of treatment failure. A positive response to therapy may be an indication that antimicrobial treatment can be de-escalated in the case of broad-spectrum administration or that the patient can be switched from parenteral to oral administration.

Prophylactic and Metaphylactic Use of Antimicrobial Drugs

Antimicrobial drugs for prophylactic or metaphylactic use should be used only for cases or situations that are deemed high risk for infection and in which clinical data have demonstrated that this use is effective for preventing infection or decreasing morbidity or mortality.[13] Prophylactic use of antimicrobial drugs is therapy directed toward preventing infection in which the risks or consequences of development of an infection are great and outweigh the risks of adverse outcome from the drug used. Its most frequent application is in the surgical setting to prevent surgical site infections. The decision to use prophylactic antimicrobials depends on the type of surgery and the possibility of entering nonsterile sites such as the gastrointestinal or genitourinary tract, the length of the surgical procedure, the use of surgical implants, and the degree of tissue damage. It is important that the antimicrobial drug be present at therapeutic levels at the time of contamination to be effective in preventing surgical site infections.[42] The therapy should be directed toward the pathogens likely to cause the infection. In the case of surgical site infections of large animals, these include *Enterobacteriaceae*, *Staphylococcus*, and *Streptococcus*.[43-45] Generally, the drug should be administered 30 to 60 minutes before the surgery begins.[46,47] If the surgery is prolonged, repeated administration of the antimicrobial drug should be performed. However, the timing of surgical antimicrobial prophylaxis

should be tailored to the drug used to ensure adequate concentrations at the surgical site at the time when contamination might occur.[48] Perioperative administration is what is important to prevent surgical site infections, and continued use after completion of surgery is unnecessary as determined in human patients.[48,49] Therapy beyond this point will not appreciably reduce the incidence of surgical site infections and may predispose to development of resistance or superinfections and increase the likelihood of adverse reactions.[42]

Prophylactic antimicrobials should be drugs other than those used therapeutically so that treatment options remain available should an infection develop. It has been recommended that older drugs be used so that newer drugs may be used therapeutically.[50] Prophylaxis should never be used in the place of good aseptic technique and is not indicated for use to prevent infection of intravenous catheters or other similar indwelling devices. Antimicrobial use in these instances only increases the likelihood that if infection develops, it will more likely be resistant.

Metaphylaxis is use of antimicrobial drugs after exposure to an infectious agent but before development of clinical signs. Examination of parenteral treatment of calves at high risk for infection in the bovine respiratory disease complex prior to or upon entry to the feedlot has shown decreased morbidity and mortality.[51,52] However, more recent studies have demonstrated either no benefit or mixed results.[53,54] Furthermore, multidrug-resistant *Mannheimia haemolytica* has been isolated from calves receiving prophylactic or metaphylactic antimicrobials.[55] It is important to note that metaphylactic use of antimicrobial drugs will not eliminate all infections and may have a greater impact on the severity or duration of the illness. Metaphylactic administration may not always be practical for large groups of animals, and labeling may preclude antimicrobial use in this manner.

Biosecurity and Infection Control

A cornerstone of effective antimicrobial stewardship is to prevent infections in the first place through biosecurity and infection control measures on the farm and in the veterinary hospital or clinic. Segregating animals coming onto a farm, eliminating predisposing factors for bacterial disease, and vaccinating for viral diseases can limit infections and the need for antimicrobial drugs. The single most important step to control spread of disease in the clinic or hospital or from farm to farm is frequent hand washing and attention to personnel hygiene.

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Isolation or segregation of animals with contagious or highly resistant organisms and control of movement of animals can go a long way toward decreasing infection rates. Infection control and hygiene plans are important for any premises where animals are managed, not just for veterinary hospitals or clinics.[13,14]

Microbial Factors Affecting Therapy

Resistance

A number of microbial factors may influence the success of therapy. Resistance of the agent to the chosen therapeutic is a common occurrence in therapeutic failure. Resistance can result from the inherent properties of the microbe. For example, mycoplasmas lack a cell wall and are impervious to the effects of cell wall–targeting drugs like the β-lactams. Other drugs may not be able to penetrate the bacteria, as is seen in the inability of anaerobes to take up aminoglycosides in the anaerobic environment. A major contribution to resistance is acquisition of resistance determinants. Resistance may result from alteration of the antimicrobial target, gain of genes capable of degrading the drug (e.g., β-lactamases), or acquisition of genes encoding efflux pumps (e.g., tetracyclines, aminoglycosides, fluoroquinolones) that pump antimicrobials out of the bacterial cell. Bacteria can develop resistance through mutation of the gene encoding the protein target of the drug (e.g., fluoroquinolones and DNA gyrase). These events are not frequent, occurring once every 10^{10} to 10^{14} cell divisions. However, the rapid multiplication rate of a large number of bacteria makes this a real possibility. These events are often random, and their appearance is generally not influenced by the presence of a particular antimicrobial drug. However, if a drug is present, bacteria with the mutation will have a selective advantage and will rapidly outcompete nonresistant bacteria.

Alternatively, bacteria can acquire genes encoding a resistance determinant. Bacteria can obtain resistance genes through several mechanisms. Movement of plasmids, a type of extrachromosomal DNA, through conjugation between bacteria of the same or different species is a major means by which resistance develops. Other mobile DNA elements can move resistance genes between bacteria. Resistance genes are frequently associated with transposons, DNA capable of excision from host genomic DNA to plasmids and subsequent transport to other bacteria. Bacteriophages (bacterial viruses) may also move resistance genes between bacteria through a process called *transduction*. Finally,

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resistance genes can be taken up as naked DNA in the bacterial environment through a process known as *transformation*.

The simple act of using antimicrobial drugs will result in selection of bacteria that are resistant. Survey of gastrointestinal microbes, such as *Escherichia coli,* after initiation of antibiotic therapy has shown that resistance will develop in normal flora.[56-59] The most effective way to avoid resistance is to minimize the use and duration of antimicrobial drugs and, when they are used, to be sure that they are delivered to the site of infection at adequate levels to kill the bacteria.

Biofilms

Bacteria can move from existing as individual cells, also known as planktonic growth, to develop into a population that functions more as a multicellular organism known as a biofilm. The definition of a *biofilm* is "aggregated microbial cells surrounded by a polymeric self-produced matrix, which may contain host components."[60] Biofilms are notoriously difficult to treat with simple antimicrobial therapy and are known to form on a variety of surfaces, including catheters, orthopedic implants, and bone. Biofilm bacteria are different from planktonic organisms in several ways. First, they are less susceptible to antimicrobial agents. Second, they persist in the animal despite a vigorous immune response. Unfortunately, effective treatment of the biofilm-associated infection necessitates removal of the infected implant or bone.

Adverse Reactions

Adverse reactions to antimicrobial drugs certainly occur, although hundreds or thousands of doses may have to be given before they are observed. A report from Switzerland indicated that 20% of adverse reactions to drugs were to antimicrobial agents.[61] Adverse events associated with antimicrobial use can range from a hypersensitivity reaction to direct toxicity to disruption of normal microbiota. Fortunately, antimicrobial agents are directed toward the prokaryotic structures of bacteria that generally differ to some degree from the eukaryotic equivalent of the host. Consequently, they are less likely to result in direct toxicity in the patient. Some drug toxicities are predictable based on their mechanism of action or accumulation in certain cells of the host. Hypersensitivity reactions are the result of immunologic stimulation by the drug or carriers in the drug formulation. One frequently observed adverse event

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associated with antimicrobial use is the development of severe gastrointestinal disturbances. These may be the result of changes in the gut microbiota and/or proliferation of pathogenic bacteria such as *Clostridioides difficile* or *Salmonella*. Adverse reactions to antimicrobial drugs should be reported to the manufacturer and to the Food and Drug Administration Center for Veterinary Medicine.

Adjunctive Therapy

In some cases, antimicrobial drugs alone are unable to clear the infection. In these cases, adjunctive therapy should not be overlooked. Surgical débridement of necrotic material and reestablishment of an adequate blood supply help to remove bacteria and allow better antimicrobial penetration. Sometimes simple drainage of an abscess is all that is necessary to treat certain infections, obviating the use of antimicrobial drugs.

Topical treatment may be possible in some instances. Superficial skin infections may be treated with either topical antimicrobial drugs or antiseptics. Deep or severe infections may need both systemic and topical treatment. Most ocular infections are successfully treated topically where high drug concentrations can be delivered.

Local treatment of severe internal infections can also be used as an adjunct to systemic therapy. Intraarticular administration of antimicrobials and/or regional perfusion are frequently used to treat joint and bone infections in large animals. These routes deliver high levels directly to the site of the infection. Although efficacious, adjunctive therapy, including débridement and lavage, are important to remove the bacterial burden and inflammatory substances that may be detrimental to joint structures. In these instances, systemic administration is indicated.

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Medication Use in Food-Producing Animals

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Abbreviations	
AMDUCA	Animal Medicinal Drug Use Clarification Act
ANADA	Abbreviated New Animal Drug Application
ANDA	Abbreviated New Drug Application
AOAC	Association of Official Analytical Chemists
AVMA	American Veterinary Medical Association
CFR	Code of Federal Regulations
CPG	Compliance Policy Guide
CVM	Center for Veterinary Medicine
ELDU	Extralabel Drug Use
EPA	Environmental Protection Agency
FAO	Food and Agriculture Organization
FARAD	Food Animal Residue Avoidance & Depletion
FDA	U.S. Food and Drug Administration
FDA-CVM	U.S. Food and Drug Administration Center for Veterinary Medicine
FSIS	Food Safety and Inspection Service
GFI	Guidance for Industry
JECFA	Joint FAO/WHO Expert Committee on Food Additives
MRL	Maximum Residue Limit
MUADP	Minor Use Animal Drug Program
MUMs	Minor Use and Minor Species Animal Health Act
NADA	New Animal Drug Application
NDA	New Drug Application
NRP	National Residue Program
ONADE	Office of New Animal Drug Evaluation
PAMTA	Preservation of Antibiotics for Medical Treatment Act
USDA	United States Department of Agriculture
VCPR	Veterinarian-Client-Patient Relationship
VFD	Veterinary Feed Directive
WDI	Withdrawal Interval
WDT	Withdrawal Time
WHO	World Health Organization

Medicating animals that are used to produce food for human consumption is a worldwide phenomenon. Medications can be used to increase production, treat illnesses, produce healthier animals, or prophylactically and/or metaphylactically prevent or reduce morbidity and/or mortality caused by diseases. In recent years the potential impacts of drug residues have become of increasing concern for consumers, regulators, and legislators. To maintain public safety, it is important for veterinarians to educate themselves and work closely with their clients to

help minimize drug residues in the human food chain.

Definition of Food-Producing Animal Species

For the purposes of this chapter, a food animal is any animal whose tissues or products have the potential to enter the human food chain. In the United States, food animals are further categorized as major or minor food animal species. The Food, Drug, and Cosmetic Act defines the major food-producing species of animals to include cattle, swine, chickens, and turkeys. The CVM, a branch of the FDA, has a list of definitions for bovine, swine, and poultry species and classes, which can be found in Table 45.2.[1] Furthermore, in addition to these definitions, the Code of Federal Regulations (CFR) has defined dairy cattle to include all female cattle of a recognized dairy breed over 20 months of age.[2] Both dry and lactating dairy cattle are in this category. "Minor" food animal species are defined by exclusion, meaning that the "major" animal species have been identified and all others are considered "minor." Examples of "minor" food animal species are goats, sheep, and cervids.

TABLE 45.2

U.S. Food and Drug Administration's Definitions of Species and Classes of Major Food Animals[1]

Species	Class		Definition
Cattle	Beef Cattle (cattle intended for meat production)	Suckling Calves	Immature, preruminant cattle (including *dairy breeds* intended for meat production), maintained with and dependent on their dam for nourishment. Veal calves are not considered suckling calves.
		Pasture Cattle (stocker, feeder, slaughter, and sometimes replacement beef heifers)	Weaned cattle (including dairy breeds) maintained on pasture and receiving most of their diet from grazing. The term *pasture cattle* is intended to refer to cattle considered to be stockers, feeders, and/or slaughter cattle. Therefore parenthetical reference to *stocker, feeder,* or *slaughter cattle* is typically included in labeling. *Stockers* refers to weaned calves grazing pasture to enhance growth prior to finishing and slaughter; they are usually younger, weigh less, and are of lower condition (finish) than "feeders." *Feeders* refers to weaned calves grazing pasture and of sufficient weight and maturity to be placed on high-energy rations for finishing; they are generally older, weigh more, and carry more condition (finish) than stockers. *Slaughter* refers to cattle grazing pasture and suitable for

				slaughter. Sex differentiation (e.g., heifers, steers, and/or bulls) should be indicated on product labeling. *Replacement beef heifers* may be added to the Pasture Cattle class if the drug has been shown to have no negative impact on reproduction in female cattle during the period from weaning until first calving and the female cattle are intended for reproduction to produce calves intended for meat production.
		Cattle Fed in Confinement for Slaughter		Cattle (including dairy breeds) confined in group pens and fed a high-energy diet ad libitum until slaughter. Sex differentiation (heifers, steers, and/or bulls intended for slaughter) should be indicated on product labeling.
		Growing Cattle on Pasture or in Dry Lot (stocker and feeder)		Weaned cattle (including dairy breeds) maintained on pasture or in a dry lot and receiving most of their diet from forage.
		Lactating Beef Cows		Lactating beef breed female cattle nursing calves intended for meat production; their milk is not intended for human consumption.
		Non-Lactating Beef Cows		Female beef breed cattle that previously nursed calves intended for meat production but are not currently producing milk.
		Replacement Beef Bulls		Intact male beef breed cattle intended for reproductive purposes.
	Veal Calves			Immature cattle (including dairy breeds) lacking a functional rumen and intended for meat production. They are recognized as a separate class from suckling calves because of their handling, housing, and proximity to slaughter.
	Dairy Cattle (cattle intended for production of milk for human food)	Lactating Dairy Cows		Female dairy breed cattle that are producing milk.
		Dry Dairy Cows		Female dairy breed cattle that previously lactated but are not currently producing milk (cows between two lactations).
		Non-Lactating Dairy Cattle	Replacement Dairy Heifers	Female dairy breed cattle from weaning until first calving.
			Replacement Dairy Bulls	Intact male dairy breed cattle intended for reproductive purposes.
			Dairy Calves	Female or male dairy breed cattle being fed a ration that includes milk or liquid milk replacer and that are not intended for veal production.
Swine	Boars			Intact, sexually mature, male pigs intended for breeding purposes; generally not intended for slaughter in the United States.
	Barrows			Castrated male pigs intended for slaughter.
	Gilts			Female pigs intended for slaughter or breeding purposes; have not yet farrowed a litter.
	Replacement Gilts			Breeding female pigs that have not yet farrowed a litter; usually weigh 220 to 300 lb (100 to 135 kg).
	Sows			Female pigs that have had at least one litter.
	Nursing Pigs			Pigs from birth until weaning and still nursing.
	Starter or Nursery Pigs			Boars, barrows, and gilts from approximately 2 to 4 weeks of age and approximately 50 to 60 lb (23 to 27 kg).
	Growing			Barrows and gilts from approximately 50 to 60 lb (23 to 27

	Pigs			kg) to 120 to 150 lb (55 to 68 kg).
	Finishing Pigs			Barrows and gilts from approximately 120 to 150 lb (55 to 68 kg) to market weight for slaughter.
Chickens	Egg			From in ovo until hatching.
	Laying Hens (or layers)			Hens that produce eggs for human consumption.
	Chicks			Chickens from day of hatch until they are able to survive in ambient temperature (no longer brooded).
	Broiler Chickens (or fryers or frying chickens)			Meat-type chickens normally grown to a market age of 35 to 49 days and market weights between approximately 4 and 7 lb (1.80 and 3.2 kg).
	Roasters (or roasting chickens)			Meat-type chickens grown to market weights between approximately 6 and 9 lb (2.7 and 4.1 kg).
	Replacement Chickens			Chickens intended to become laying hens or breeding chickens.
	Breeding Chickens			Sexually mature male and female chickens of any type intended for the production of fertile eggs; the eggs are not intended for human consumption.
Turkeys	Egg			From in ovo until hatching.
	Laying Hens (or layers)			Hens that produce eggs for human consumption.
	Poults			Turkeys from day of hatch until they are able to survive in ambient temperature (no longer brooded).
	Growing Turkeys			Turkeys grown for meat purposes to a market age of approximately 17 (female) or 22 (male) weeks; may be further divided into heavy or light turkey strains.
	Finishing Turkeys			Turkeys intended for meat production during the last 2 to 4 weeks of growth.
	Replacement Turkeys			Turkeys intended to become laying hens or breeding turkeys.
	Breeding Turkeys			Sexually mature male or female turkeys intended to produce fertile eggs; their eggs are not intended for human food use.

On-Label Drug Use

In food animal medicine, medications can be administered to an individual animal or a herd or flock depending on numbers of animals needing treatment, disease, and/or overall management practices. Practitioners treating food-producing animals in the United States can use FDA-approved veterinary products according to the label. Using medications according to the label directions is called *on-label drug use*, where all of the drug label specifications (animal species and class, administration route, dose, dosing frequency or interval, indication, limitations, and withdrawal time) are fulfilled and the FDA-approved withdrawal time (WDT) is observed. The FDA-approved WDT is the amount of time that must be observed after the last dose is administered and

before the food product intended for human consumption can enter the human food chain. There are multiple databases where label information for FDA-approved veterinary medications is accessible and can be consulted. Table 45.3 lists a few resources.

TABLE 45.3
Useful Internet Links for Online Resources on Drug Use and Drug Residues in Food Animals

Website	Description	Website Address
U.S. Drug Information		
Drugs @ FDA	FDA's searchable database of approved human drugs	http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm
Animal Drugs @ FDA	FDA's searchable database of approved animal drugs and tolerances	https://animaldrugsatfda.fda.gov/adafda/views/#/search
VetGRAM	FARAD's searchable drug database for food animal drugs and tolerances. Approved VFD combinations are also listed.	http://www.farad.org/vetgram/
Bayer Animal Health	Site provides a link to the searchable U.S. compendium of veterinary products; use charts tab for summarized label information	http://bayerdvm.com/ or http://bayerall.naccvp.com/?m=chartindex_main&type=wt
Drugs.com	Searchable database of veterinary drugs	http://www.drugs.com/vet/
International Drug Information		
CABI's Animal Health and Production Compendium	List of international animal drug databases	https://www.cabi.org/ahpc/more-resources/drug-databases/
Canadian	Searchable	http://bam.naccvp.com/?m=chartindex_main&type=wt

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Compendium of Veterinary Products presented by Bio Agri Mix Total Solutions	Canadian compendium of veterinary products and summarized label information	
Australian Pesticides and Veterinary Medicines Authority	Pubcris is a searchable database of registered pesticides and veterinary drugs	https://portal.apvma.gov.au/pubcris
National Office of Animal Health	UK site with searchable drug compendium of approved drugs	http://www.noahcompendium.co.uk/Compendium/Overview/
Irish Medicines Board	Searchable compendium of approved drugs in Ireland	http://www.imb.ie/
European Medicines Agency Database	Public database providing online access to information about human and veterinary medicines available to EU citizens	http://www.eudrapharm.eu/eudrapharm/
USDA Foreign Agricultural Service	Veterinary drug and pesticide tolerance and MRL searchable database	https://www.fas.usda.gov/maximum-residue-limits-mrl-database
FAO/WHO Food Standards Codex alimentarius	Definitions of terms used in discussing veterinary drug residues in food animals	http://www.fao.org/fao-who-codexalimentarius/codex-texts/dbs/vetdrugs/gloss
Joint FAO/WHO Expert Committee on Food Additives (JECFA)	Description of JECFA and links to publications	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/en/
JECFA, “Residues of some veterinary drugs in foods and animals”	Searchable database of maximum residue levels for veterinary drugs as recommended by JECFA that	http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-vetdr

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	includes pharmacokinetic data summaries	
Codex alimentarius international food standards	Homepage for codex alimentarius	http://www.codexalimentarius.org/about-codex/en/
European Medicines Agency European Public MRL Assessment Report	Summary report on the established MRL and the data supporting the MRL	http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/vet_mrl_search.jsp&mid=WC0b01ac05800648
U.S. Regulatory Links		
USDA/FSIS Residue Chemistry Page	Includes FSIS sampling plan (Blue Book) and results (Red Book)	http://www.fsis.usda.gov/wps/portal/fsis/topics/data-collection-and-reports/che
USDA Food Safety and Inspection Service (FSIS)	Homepage with contact information and links to resources	http://www.fsis.usda.gov/
FDA Center for Veterinary Medicine	Homepage with contact information and links to resources	http://www.fda.gov/AnimalVeterinary/default.htm 240-276-9300 AskCVM@fda.hhs.gov
U.S. Environmental Protection Agency (EPA)		http://www.epa.gov/
Centers for Disease Control and Prevention (CDC)	CDC's Food Safety Program	https://www.cdc.gov/vitalsigns/food-safety.html
AMDUCA and ELDU Links		
FDA-CVM Compliance Policy Guide	AMDUCA	http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/Acts
AVMA: Animal Medicinal Drug Use Clarification Act (AMDUCA)	Reviews components of AMDUCA and includes list of prohibited drugs	https://www.avma.org/KB/Resources/Reference/Pages/AMDUCA.aspx
AVMA ELDU FAQ	AVMA's guidance for ELDU FAQs	https://www.avma.org/KB/Resources/FAQs/Pages/ELDU-and-AMDUCA-FA
FDA-CVM Compliance Policy Guide	Extralabel use of medicated feeds for minor	http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceM

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	species	
FARAD	U.S. site where ELDU withdrawal requests may be made online and other resources for food animal veterinarians	http://farad.org/
Canadian gFARAD	Canadian program providing information on residue avoidance	http://www.cgfarad.usask.ca/home.html
FARAD	List of restricted and prohibited drugs in food animals	http://www.farad.org/eldu/prohibit.asp
Compounding Links		
FARAD regulatory information	Details of the published law on compounding and AMDUCA	http://farad.org/amduca/amduca_law.asp
AVMA Compounding	AVMA resources on veterinary compounding	https://www.avma.org/KB/Policies/Pages/Compounding-from-Unapproved Animals.aspx http://ebusiness.avma.org/files/productdownloads/Vet_Compounding.pdf
Society of Veterinary Hospital Pharmacists statement on compounding	Position statement on the compounding of drugs for use in animals	http://svhp.org/position-statements/
Miscellaneous Links		
FARAD Species Pages	Provides guidance for species categories regarding drug use and links to resources.	http://www.usfarad.org/
FARAD VFD Resource	Provides information regarding VFD with links to other VFD resources	http://farad.org/veterinary-feed-directive.html
CA SB 27	CA Senate Bill 27	https://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=201520160
CDFA AUS	California Department of Food and Agriculture	https://www.cdfa.ca.gov/ahfss/aus/

	Antimicrobial Use and Stewardship resources	
National Pesticide Information Center (NPIC)	NPIC provides objective, science-based information about pesticides and pesticide-related topics	http://npic.orst.edu/
Minor Use Animal Drug Program (MUADP)	Searchable database for drugs approved in minor food animal species and MUMs and MUADP information	http://www.nrsp7.org/
American Association of Veterinary Laboratory Diagnosticians (AAVLD)	Listing of AAVLD labs in the United States by state	https://www.aavld.org/accredited-laboratories

Modified from U.S. Food and Drug Administration: Animal & Veterinary. 2009. Appendix III, Species and Classes of Major Food Animals. In CVM's Guidance for Industry (GFI) #191: Changes to Approved NADAs–New NADAs vs. Category II Supplemental NADAs. [WWW page]. https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIr (Accessed 20 July 2018).

Extralabel Drug Use and the Animal Medicinal Drug Use Clarification Act of 1994

Prior to the enactment of the Animal Medicinal Drug Use Clarification Act (AMDUCA) in 1994, veterinarians could legally treat food animals with on-label medications only. Passage of AMDUCA legalized most instances of extralabel drug use (ELDU) in food animals by or on the order of veterinarians.[3] Extralabel drug uses include prescribing or administering a human or veterinary drug at a higher or lower dose, frequency, or duration; by a different route of administration; in a different species or production class; or for a different indication than described on the product's label. For food animal practitioners, with this privilege comes the weighty responsibility of protecting the health of consumers of animal products. Veterinarians must meet very specific conditions before they may legally use or prescribe drugs in an extralabel fashion. Under

AMDUCA, ELDU is limited to cases in which the health of the animal is threatened or suffering or death may result from a lack of treatment. ELDU may not be used to enhance production or for nontherapeutic reproductive cycle manipulation in healthy animals and can occur only on the order of a veterinarian within the context of a veterinarian-client-patient relationship (VCPR), as described in Box 45.3. ELDU may be considered in food-producing animals only when no approved drug is available that contains the same active ingredient in the required dose, form, and concentration or when the veterinarian finds that there is no approved drug that is clinically effective for the intended use. ELDU in or on animal feed is also expressly prohibited.

Box 45.3

Conditions Necessary for Extralabel Drug Use

1. Extralabel drug use (ELDU) is permitted only by or on the order of a veterinarian.
2. The veterinarian judges on-label treatments to be unavailable or ineffective.
3. ELDU uses only U.S. Food and Drug Administration (FDA)–approved animal and human drugs, not drugs imported from foreign countries or compounded from bulk sources. When treating food animals, approved food animal drugs should be used before approved animal drugs, which should be used before approved human drugs.
4. A valid veterinarian-client-patient relationship (VCPR) exists in which the veterinarian:
    - Oversees medical treatment decisions on the farm
    - Is familiar with animal care through appropriate and timely visits
    - Has sufficient knowledge to initiate a diagnosis
    - Is available for follow-up care as needed
5. ELDU is for therapeutic or humane purposes only, not to increase production or manipulate reproductive cycles in normal animals.
6. ELDU applies only to administration to individual animals and in water, not in feed.
7. Animal identification and treatment records are sufficient to identify

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treated animals and their treatment history and are maintained for 2 years.
8. The veterinarian establishes an extended drug withdrawal period protective of human health supported by scientific evidence. ELDU resulting in violative or dangerous food residues is not permitted.
9. Drug labels list the name and address of the prescribing veterinarian, animals to be treated, and the drug name, disease indication, dose, frequency, duration, cautions, and withdrawal periods associated with treatment.
10. Certain extralabel uses specifically prohibited by the FDA are not used (see Box 45.4).

AMDUCA stipulates that ELDU applies only to FDA-approved human and veterinary medications. It does not legalize the extralabel use of Environmental Protection Agency (EPA)–regulated pesticides or U.S. Department of Agriculture (USDA)–regulated biologics. New animal drug application (NADA) or abbreviated new animal drug application (ANADA) numbers are a good indication of whether a drug is FDA approved. The presence of a NADA or ANADA number on the product label is an indication that the veterinary drug has FDA approval. Similarly, for human drugs, every approval has a unique new drug application (NDA) number for pioneer drugs or abbreviated new drug application (ANDA) number for generic drugs. Approval status of both animal and human drugs can be found on the FDA-CVM (http://www.fda.gov/AnimalVeterinary/) and FDA (http://www.fda.gov) websites, respectively.

When veterinary products are used in an extralabel manner, a withdrawal "interval" must be estimated based on scientific evidence and extended beyond the FDA-approved WDT regardless of the dose, route, or indication. This ensures that there are no illegal residues, another stipulation in AMDUCA. A residue is considered either the parent compound or a metabolite of that parent compound that may accumulate, deposit, or otherwise be stored within the cells, tissues, organs, or edible products (e.g., milk, eggs) of an animal after its use to prevent, control, or treat animal disease or to enhance production.[4] As stipulated by AMDUCA, veterinarians' obligations regarding ELDU are listed in Box 45.3.

Veterinarians who violate state or federal laws regulating the transport, sale, or use of drugs may face a variety of sanctions, including warning letters, fines, temporary or permanent revocation of license, and incarceration.

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Veterinary Feed Directive

To help combat antimicrobial resistance and protect human safety, the FDA took action by eliminating claims for production use of medically important antimicrobials (MIAs) and by increasing veterinary oversight by transitioning MIAs from over the counter (OTC) to Veterinary Feed Directive (VFD) or Prescription (Rx). MIAs for use in or on feeds that were previously OTC now require a VFD, while MIAs as a water additive became prescription only. A list of MIAs is provided in Appendix A of the FDA's Guidance for Industry #152 (https://www.fda.gov/downloads/AnimalVeterinary/GuidanceComplianceEnforce Drug classes not affected by these changes include ionophores, bacitracins, and coccidiostats. These changes became effective on January 1, 2017.

A VFD is a written statement issued by a veterinarian with a valid VCPR for the use of a VFD drug or VFD combination drug in or on animal feed. A list of sponsor applications being affected by the FDA rulings can be found at https://www.fda.gov/AnimalVeterinary/SafetyHealth/AntimicrobialResistance/Ju A list of drugs and approved VFD drug combinations can be found on the FARAD website (http://www.farad.org/vfd-drug-combinations.html). For a veterinarian to write a VFD, the veterinarian must be licensed to practice in the state the animals reside in, have a valid VCPR, and issue the VFD in compliance with the drug's approved labeling and conditions. Extralabel use of VFD drugs is prohibited.

California Senate Bill 27

In the state of California, Senate Bill 27 (SB 27) became effective on January 1, 2018. SB 27 was created to address antimicrobial resistance. It is similar to the federal regulations on judicious use of MIAs, but it extends veterinary oversite of MIAs further. For animals being treated in California, all forms of MIAs, including oral, injectable, topical, and intramammary, now require a prescription from a veterinarian. This means that MIA formulations that are designated as OTC at the federal level will be designated as prescription in the state of California. The prescription status for medications affected by this ruling can be found on VetGRAM on the FARAD website. In addition to increasing veterinary oversite of MIAs, SB 27 requires the California Department of Food and Agriculture to collect data on MIA drug sales and usage, antimicrobial resistant bacteria, and livestock management practice.

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Extralabel Drug Use of Medicated Feeds in Minor Species

Even though AMDUCA prohibits the extralabel use of medications in feed, a Compliance Policy Guide (CPG) 615.115 for extralabel use of medicated feeds for minor animal species does exist.[5] The AMDUCA prohibition of extralabel use of medications in feed was generated because of concerns of antibiotic resistance. AMDUCA's Section 530.11 specifically prohibits the “extralabel use of an approved new animal drug or human drug in or on an animal feed.” As a matter of enforcement discretion, the CVM generally has not objected to mixing a drug with an individual animal's feed, but extralabel mass medication in feed is prohibited “without limitation or exception.” Veterinarians may, however, be called on to treat minor food animal species such as farmed exotic ruminants, fish, or game birds. The CVM has found that for many of these species, very few approved drugs exist. In addition, the CVM recognizes that some minor food animal species (such as fish and game birds) cannot be practically medicated in any way other than through the use of medicated feeds. In such situations, a veterinarian may determine that extralabel use of medicated feeds (approved for use in other species) can prevent suffering and death in these minor species.

Although AMDUCA prohibits ELDU in feed, in the previously described circumstances the CVM “ordinarily will not consider regulatory action” against the veterinarian or animal producer provided that certain criteria listed in Box 45.4 are met.[5] The CVM policy being implemented in these cases is akin to that of ELDU by veterinarians before the 1994 passing of AMDUCA. The drug use is still illegal, but the CVM will apply regulatory discretion relative to taking enforcement action. A critical aspect of the CVM's regulatory discretion in this practice is that labeled treatment alternatives are not available. The best resource to aid practitioners in determining what treatments are approved for minor food animal species is the Minor Use Animal Drug Program website (http://www.nrsp-7.org).

Box 45.4

Conditions Necessary for Extralabel Use of Medicated Feed in Minor Species

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1. Extralabel use of medicated feed is only for treatment of minor species, defined by exclusion as animals other than cattle, horses, swine, chickens, turkeys, dogs, and cats.
2. Extralabel use of medicated feed is limited to farmed or confined minor species but not unconfined wildlife.
3. Extralabel use of medicated feed is limited to situations in which the health of an animal is threatened and suffering or death may result from failure to treat.
4. There is no alternative therapeutic dosage form (besides feed) that can be practically used under legal extralabel use.
5. Only feeds formulated and labeled for use in a major species animal are used.
6. Extralabel use of medicated feed in aquaculture is limited to medicated feed products approved for use in aquatic species.
7. The medicated feed is used within 3 months of a veterinarian's written recommendation. Recommendations, feed labels, and invoices are kept for at least 1 year. Adverse reactions are reported to the U.S. Food and Drug Administration within 10 days.
8. All other Animal Medicinal Drug Use Clarification Act requirements are complied with, including a valid veterinarian-client-patient relationship, lack of label alternatives, treatment records, animal identification, and extended withdrawal times (see Box 45.3).
9. The medicated feed is used in accordance with federal, state, and local environmental regulations and approval. This is particularly important for aquaculture uses.
10. The producer has followed worker safety provisions in the approved product labeling.

Prohibited Drugs and Drug Classes Prohibited From Extralabel Drug Use in Food Animals

Certain drugs may not be prescribed or used even under the auspices of AMDUCA.[6] Under statutory authority provided in AMDUCA, the FDA-CVM has prohibited approximately a dozen drugs or drug classes, making their extralabel use in food animals illegal. Other compounds not specifically listed in AMDUCA are prohibited because no approved animal or human products are commercially available. Last, extralabel use of treatments is also regulated by

the Pasteurized Milk Ordinance (PMO). The extralabel use in food animals of the compounds listed in Box 45.5 represents one of the FDA's highest priorities for regulatory attention. It is advised that the FDA-prohibited drug list be checked on a regular basis for updates, as it is subject to change. FARAD and AVMA websites both list prohibited drugs.[7,8] Alternatively, 21CFR530, the section of the CFR pertaining to ELDU, may be accessed directly.[9]

Box 45.5

Drugs or Drug Classes Prohibited From Extralabel Drug Use[a]

Diethylstilbestrol (DES)
Chloramphenicol
Nitroimidazoles (including dimetridazole, metronidazole, and ipronidazole)
Sulfonamide (other than sulfadimethoxine) in adult dairy cattle[b]
Clenbuterol
Fluoroquinolones (e.g., enrofloxacin, danofloxacin)
Glycopeptides (e.g., vancomycin)
Nitrofurans (including nitrofurazone, furazolidone; topical use prohibited as well)
Phenylbutazone in adult dairy cattle[b]
Adamantane and neuraminidase inhibitors in poultry
Cephalosporins (not including cephapirin) in cattle, swine, chickens, or turkeys:
- (i) For disease prevention purposes
- (ii) At unapproved doses, frequencies, durations, or routes of administration
- (iii) If the drug is not approved for that species and production class

[a]Extralabel use of some drugs or drug classes (not specifically addressed in the Animal Medicinal Drug Use Clarification Act) are prohibited because these

drugs are not available as approved animal or human products, by U.S. Food and Drug Administration (FDA) policy or in the Pasteurized Milk Ordinance (see chapter text).

[b]Defined by the FDA as dairy cattle (lactating or dry) older than 20 months of age.

If any of these prohibited drugs are mistakenly used in a food-producing animal, that animal and its by-products should never be allowed to enter the human food chain and ideally that animal should be isolated from other food animals.

Drugs Prohibited From Use in Food Animals

1. Diethylstilbestrol: From the 1940s to the 1970s, U.S. physicians prescribed diethylstilbestrol (DES, a potent nonsteroidal synthetic estrogen) to pregnant women to prevent miscarriage and other reproductive diseases. In 1971 a link between in utero exposure to DES and a rare vaginal cancer (clear cell adenocarcinoma) was established. In the same year the FDA published an alert advising doctors against the use of DES during pregnancy. The USDA banned the use of DES in food animals in 1979.
2. Chloramphenicol: An estimated 1 in 10,000 to 50,000 people exposed to chloramphenicol will develop a non-dose-related aplastic anemia. Because of concerns that this idiosyncratic and frequently fatal complication could be triggered by residues, chloramphenicol use in food animals was prohibited in 1984. The prohibition extends to all formulations of chloramphenicol, including ophthalmic ointments. Florfenicol, a synthetic member of the chloramphenicol family, lacks the p-NO_2 group thought to be responsible for inducing the aplastic anemia. Florfenicol may be used extralabel in food-producing species. However, veterinarians should be aware that extralabel use of florfenicol in dairy cattle older than 20 months of age requires extended withdrawals to allow depletion of drug residues in the liver to a level below detection by the Food Safety and Inspection Service (FSIS).
3. Nitroimidazoles: Historically, dimetridazole and ipronidazole have been approved for the treatment of histomoniasis (infectious enterohepatitis,

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blackhead) in turkeys. Ipronidazole and the human drug metronidazole have been used off-label to eliminate the carrier state of trichomoniasis in bulls. Laboratory studies of members of this drug class demonstrated mutagenicity and carcinogenicity, leading to the prohibition of their use in food animals. Because there are no approved veterinary nitroimidazole labels, the use of any member of this drug class in food animals is illegal.

4. Nitrofurans: In the past, nitrofurazone and furazolidone were approved for a variety of protozoal and bacterial infections in poultry and swine. Topical formulations (sprays and “puffer” products) have also historically been marketed for wounds and ocular infections in livestock (“pinkeye”). Based on laboratory evidence of carcinogenicity and the absence of a reliable detection method, the FDA withdrew approval for systemic animal nitrofuran products in 1991 and prohibited all extralabel treatment (including topical use) in 2002. Because nitrofurans have no approved food animal uses, the use of any member of this drug class in food animals is illegal.
5. Clenbuterol: Marketed in the United States as an equine bronchodilator, this synthetic sympathomimetic has been used illicitly to increase weight gain and lean body mass in food animals, particularly show animals. Because muscle depletion and fat redeposition commences after drug withdrawal, producers may be tempted to market animals with little or no withdrawal interval. Cooking temperature only minimally denatures the compound, and toxicity from residues has resulted in hundreds of emergency hospitalizations in consumers of tainted beef in Spain and Italy.[10,11]
6. Glycopeptides: Vancomycin, the only glycopeptide antibiotic available in the United States, is often the therapy of last resort for methicillin-resistant *Staphylococcus aureus* (MRSA) infections in humans. Demonstration of vancomycin-resistant *Enterococcus* in the feces of poultry and swine fed the glycopeptide avoparcin led the CVM to prohibit extralabel use of glycopeptides in food animals in 1997.
7. Phenylbutazone in adult dairy cattle: The use of phenylbutazone, a nonsteroidal antiinflammatory drug, in humans has been associated with various adverse drug reactions, including fatal blood dyscrasias. After USDA reports of a high incidence of phenylbutazone tissue residues in cull dairy cows, the CVM prohibited its use in female dairy cattle older

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than 20 months of age. Anti-inflammatory therapy for lactating dairy cattle is available as flunixin meglumine. Flunixin should be used only on-label (intravenously) because intramuscular or subcutaneous administration can greatly extend withdrawal times.[12]

8. Antiviral drugs in poultry: Concern exists that use of antiviral drugs in poultry could promote drug resistance in zoonotic pathogens, particularly avian influenza H5N1 (“bird flu”). These concerns led the CVM to prohibit extralabel use of two drug classes used in treating human influenza in 2006. Adamantanes and neuraminidase inhibitors may not be used in chickens, turkeys, and ducks. Aside from compounds specifically prohibited through AMDUCA, there are several compounds that the CVM has reminded veterinarians cannot be legally obtained as finished animal or human products and therefore have no legal extralabel uses.
9. Dipyrone: At one time approved for humans and animals, dipyrone was withdrawn from the market because of concerns of adverse events in humans associated with its use, including teratogenicity, prolonged bleeding times, and agranulocytosis.
10. Estradiol cypionate: Before 2003, estradiol cypionate (ECP; a synthetic estrogen) was commercially marketed as reproductive therapy in food animals. ECP had not undergone a formal approval process, however, and discretionary marketing was discontinued for lack of food safety and efficacy data. Use in or compounding of ECP for food animals remains illegal.
11. Gentian violet: Gentian violet was originally used as an additive to poultry feed as a mold inhibitor. However, the FDA has never approved the use of this product as a feed additive or as an animal drug, and the impact of any residues on human health is unknown. Therefore any use in feeds constitutes extralabel use of a medicated feed and unapproved animal drug. In addition to medicated feeds, topical formulations containing gentian violet are currently being marketed. However, in 2007, the FDA issued a warning advising veterinarians of the illegal nature of using topical products containing gentian violet in food-producing animals.
12. Hormone implants in veal calves: Although growth-promoting hormone implants have been marketed for ruminating cattle, these products never underwent regulatory approval for nonruminating veal calves. Concern

existed in the CVM that nonruminating calves may eliminate the hormone contained in the implants differently than ruminants. In 2005 a new warning statement was added to the label of all growth-promoting hormone implants, reminding producers and veterinarians that their use in veal calves is illegal.

13. Dimethyl sulfoxide and colloidal silver: Besides AMDUCA, the Grade A PMO also directs how drugs will be used and stored on dairy farms. Dimethyl sulfoxide (DMSO) and colloidal silver may not be used in or on dairy animals and, if found during a dairy inspection, can result in "debits."

Drug Classes Prohibited From Extralabel Drug Use in Food Animal Species

In addition to the aforementioned specific drugs that the FDA has prohibited, there are drug classes for which some drugs may have FDA approval for use in food-producing animals, but these drug classes are prohibited from any ELDU. Drug classes with an ELDU prohibition include the following:

1. Cephalosporin-class antibiotics: On April 5, 2012, in hopes of preserving their effectiveness for human populations and decreasing the likelihood of the emergence of cephalosporin-resistant strains of foodborne bacterial pathogens, the extralabel use of cephalosporins in cattle, swine, chickens, and turkeys was prohibited. This prohibition does not include (1) the extralabel use of cephapirin in food-producing animals; (2) use of a cephalosporin to treat an extralabel indication, provided that all other label directions are followed, including species, dose, route, duration, and frequency; and (3) extralabel use in minor food-producing animal species (i.e., species that do not include cattle, swine, chickens, or turkeys).
2. Sulfonamides in adult dairy cattle: The observed carcinogenicity of sulfonamides in laboratory animals, coupled with the frequent finding of sulfonamide residues in milk, led to the prohibition of extralabel use of these compounds in adult dairy cattle. The FDA defines a lactating cow as any dairy cow (milking or dry) older than 20 months of age. The use of any sulfonamide in adult dairy cattle other than approved uses of sulfadimethoxine (SDM), sulfabromethazine, and

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sulfamethoxypyridazine is illegal. This would include using a higher dose of SDM or slow-release formulation SDM boluses.

3. Fluoroquinolones: Uncertainty exists related to the magnitude and significance of human pathogen resistance resulting from antibiotic use in animals. Fluoroquinolones are mainstay treatments of antibiotic-resistant *Salmonella* and anthrax infections in humans. Concern that fluoroquinolone use in food animals was promoting human pathogen resistance prompted the CVM to prohibit extralabel use of these compounds in 1997. Any deviation from a fluoroquinolone product label (altering species use, dosage, route of administration, or disease indication) is illegal. In the case of the approved beef cattle formulation of danofloxacin, this prohibition extends to use in all non-beef-production animals, including lactating and nonlactating dairy cows, heifer replacements, bulls, and veal calves. The same applies to enrofloxacin, with the exception of nonlactating dairy cattle, defined by the FDA as dairy cows younger than 20 months of age, for which there is a label indication.

Considerations for Treatment of Companion Food Animal or Pack Animal Species With Prohibited Substances

The previously detailed FDA-prohibited drug and drug class lists pertain to food-producing animals only and not to companion species such as dogs and cats. Veterinarians treat companion animals belonging to a food-producing species, but the FDA does not make a distinction between food-producing and companion status. Even if the food-producing species with companion status are not to be slaughtered, consideration for why the prohibition exists should be carefully examined and prudent pharmacovigilance should be used. Practitioners who have used a prohibited substance in a companion or pack animal that subsequently enters the food supply are subject to enforcement actions under the Food, Drug, and Cosmetic Act. In choosing to use a prohibited drug in a companion or pack animal, the practitioner is accepting a certain amount of liability because the fate of such treated animals is often beyond their control. Practitioners may choose to have owners sign an agreement (entered into the medical record) not to introduce the animal into the human food chain.

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Compounding of Medications for Food Animals

Compounding is defined as a manipulation to produce a dosage form of a drug other than that provided for in the labeling, such as reconstitution. The CVM recognizes the need for compounding within certain areas of veterinary practice, such as mixing or dilution. Because of the absence of safety, efficacy, and food safety data for compounded drugs, the potential exists for adverse reactions in treated animals or consumers of their products. In addition, if there are not sufficient scientific data to estimate a withdrawal for a compounded medication, it is the responsibility of the veterinarian to ensure that the animal and any food products that result from that animal do not enter the human food chain. Under AMDUCA, it is legal for veterinarians (or pharmacists on the order of a veterinarian) to compound from U.S.-approved animal and human drugs if the conditions listed in Box 45.6 are met.[3]

Box 45.6

Requirements for Compounding in Veterinary Practice

1. No approved animal or human drug can be used in its available dosage form and concentration.
2. Only approved animal or human drugs are used in the compounding, specifically not foreign or bulk drugs.
3. Compounding is performed by a licensed pharmacist or veterinarian in compliance with state pharmacy laws.
4. Adequate procedures are in place to ensure the safety and effectiveness of the product.
5. Withdrawal intervals are set by the veterinarian, not by the pharmacist.
6. The scale of the compounding operation is commensurate with the established practice needs.
7. All other Animal Medicinal Drug Use Clarification Act requirements are met (see Box 45.3).

Overall, when treating a food-producing animal, the use of compounded

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medications should be only a last resort because safety of the food chain should be the veterinarian's priority.

Antidotes Compounded From Bulk Drug

Despite the prohibition, several chemicals commonly recommended as food animal antidotes are available only through compounding from bulk drug. As described in the previous section, compounding veterinary medications from bulk drugs is illegal. However, analogous to its policy concerning ELDU in feed for minor species, the CVM will not normally consider regulatory action against veterinarians compounding certain antidotes from bulk sources if certain conditions are met, essentially those listed in Boxes 45.3 and 45.6. The FDA is currently developing a new guidance document on compounding animal drugs from bulk drug substances (https://www.gpo.gov/fdsys/pkg/FR-2015-05-19/pdf/2015-11982.pdf). Inquiries can be directed to the FDA-CVM, Division of Compliance, at 240-402-7002 or via email at AskCVM@fda.hhs.gov. It is critical that veterinarians recognize that in toxicity cases, withdrawal periods will need to be established not only for the antidotes but also the toxicants. Some antidotes require substantially extended withdrawals, which may affect the decision to treat.[13] As a practical matter, toxicity cases are frequently resolved based on testing in state or federal laboratories. Because of these complexities, practitioners are advised to consult the diagnostic laboratories and/or FARAD when dealing with such cases in food animals.

FARAD: The Food Animal Residue Avoidance and Depletion Program

One of the regulatory requirements for legal ELDU is that the attending veterinarian recommend a scientifically based withdrawal interval before the producer can market the milk, meat, eggs, or other edible products. Commonly, the most efficient way for a food animal practitioner to meet these requirements is to consult FARAD. Veterinarians, producers, students, or regulatory personnel may obtain free consultation with specialists by contacting 1-888-US-FARAD or accessing the FARAD website at http://www.farad.org and submitting a request. Recommendations are made on a case-by-case basis depending on the individual variables of each exposure, changing tolerances or FDA withdrawal times, and new information in the literature. FARAD also advises on pesticide exposure and

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accidental contaminations (biotoxins, heavy metals, radionuclides, unintended feeding of medicated feed).

FARAD maintains a database of all food animal products approved in the United States, with thousands of pharmacokinetic citations describing depletion for numerous chemicals in various species. The FARAD website now has a portal for searching what citations are included in the FARAD bibliographic database. FARAD collects, analyzes, and evaluates scientific data to provide withdrawal intervals when drugs are used in an extralabel manner. The FARAD website contains a database of approved food animal drugs searchable by drug, trade name, and species, known as VetGRAM (http://www.farad.org/vetgram/). A mobile version of VetGRAM is also available on the FARAD website. Veterinarians may also find downloadable copies of published summary recommendations as well as a quick review of past recommendations there.

Published techniques for estimating a withdrawal interval (WDI) after ELDU in food animals are available.[14-16] Information that FARAD considers when estimating a WDI includes the following:

1. General factors affecting pharmacokinetic parameters and drug residues, such as conditions affecting drug absorption and elimination as well as dose, duration of treatment, and administration route.
2. Existence of an FDA-established withdrawal time. AMDUCA stipulates that a substantially extended withdrawal should be applied for any ELDU. Therefore doses that are less than the labeled dose will still require a withdrawal that is longer than the labeled WDT.
3. Physiologic factors and compromised health conditions affecting pharmacokinetic parameters and drug elimination (e.g., dehydration, renal dysfunction, gastrointestinal disease).
4. Published pharmacokinetic parameters (i.e., time versus concentration data, including drug residue serum, tissue, or milk data).
5. The existence of an established tolerance or maximum residue limit (MRL).
6. Analytical testing method and limits of detection.
7. Foreign drug approval data.

Testing for Drug Residues

If a practitioner or producer/owner wants to confirm that edible products (i.e.,

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meat or milk) are at or below the tolerance, they can consider testing for drug residues. A number of commercial rapid tests exist for drug residue testing using a milk, serum, or urine matrix. Examples of manufacturers of these tests include IDEXX Laboratories, Inc.; Charm Sciences; DSM Food Specialties; Neogen Corporation; and Silver Lake Research Corporation. Care should be taken to ensure that the test used detects residues to a level at or below the FDA-established tolerance to be certain that the food product is safe to enter the human food chain. Alternatively, samples or carcasses can be submitted to a commercial laboratory or state veterinary diagnostic laboratory for residue testing. Processing plants may be willing to test milk. FDA-established tolerances can be found on the FDA animal drugs website or FARAD's VetGRAM website.

Regulatory Monitoring of Drug Residues in Animal Products

Once products begin the process of entering the human food chain, they may undergo residue testing as part of the National Residue Program (NRP). The FSIS, EPA, and FDA cooperate to regulate animal drug residues, pesticides, environmental contaminants, and any other chemical hazards in meat or egg products. Every year, the sampling plan, known as the “Blue book,” is released, which includes such details as the number of tissue or egg samples that will be tested and which chemical or drug residue will be tested for. Results of the testing are also made publicly available on an annual basis in the “Red book.”

After remaining unchanged for many years, in July 2012, FSIS announced that scheduling of the NRP sampling plan will be changing.[17] Sample numbers per production class will be reduced because of the adoption of new analytical methods. Analysis for more chemical residues per sample will be possible, requiring fewer overall samples than in the past.

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• CHAPTER 46

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Biosecurity and Infection Control

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Infection control, biosecurity, biocontainment, and biosafety are essential functions at all health care operations, including veterinary practices.* All veterinarians at some level recognize and act to prevent adverse outcomes in patients. However, as major outbreaks of health care–associated infections (HAIs) at veterinary hospitals have become increasingly publicized,[1-15] it has become obvious that coordinated infection control practices are a critical component of delivering high-quality care at veterinary facilities, especially those with large caseloads and those that specialize in intensive care of patients. This threat is relevant to all veterinarians and all hospitals. Two surveys of veterinary referral hospitals at American Veterinary Medical Association (AVMA)–accredited institutions reported that a majority had experienced outbreaks of HAIs in the preceding 5 years (81% and 65%, respectively, for the two surveys),[16,17] and at least 45% recognized more than one outbreak.[16] The two agents most commonly associated with outbreaks reported in both surveys were *Salmonella enterica* and methicillin-resistant *Staphylococcus aureus* (MRSA), but 12 other agents were also implicated. More than half of the participating hospitals had to restrict admissions to protect patients and allow mitigation, and a large number of the equine hospitals were temporarily closed. Even with very limited surveillance, more than half of these same hospitals recognized significant illness in veterinary personnel during the study periods. The agent most commonly implicated in human illnesses was *Cryptosporidium parvum*.[16,17]

The standard of veterinary care is changing such that sporadic occurrence and outbreaks of HAIs may no longer be interpreted as unavoidable accidents when coordinated measures are not routinely used to minimize their likelihood. Our understanding of infection control issues in veterinary medicine has also advanced significantly during the previous two decades. As such, what may have passed as sufficient for infection control in veterinary practices 10 or 20 years

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ago may often not be sufficient today. It is also important to realize the important part that infection control and biosecurity must play in ambulatory practices and on our clients' premises. Inherently, healthy animals with lower contagious disease risks represent a smaller proportion of hospital populations than they do among populations in their home environments. However, veterinarians are obviously called on to contact those animals most likely to be shedding contagious pathogens regardless of whether this is in hospitals or in the field. In addition, there are several examples in which patients discharged from hospitals were the likely source of viral and bacterial infections for animals in their home environments.[6,9] The magnitude of this potential hazard is perhaps best illustrated by the equine herpesvirus 1 (EHV-1) outbreak, which occurred in association with the National Cutting Horse Association Western National Championship in Ogden, Utah, in May 2011.[18,19] It is likely that exposure to a single horse that was shedding EHV-1 at this event resulted in more than 165 horses developing clinical disease that was known or suspected to be caused by EHV-1; at least 13 of these horses were euthanized. The outbreak spanned at least 10 western U.S. states and 2 Canadian provinces. Clearly the need to apply sound biosecurity and infection control practices extends well beyond the walls of veterinary hospitals.

It is also clear that dramatic outbreaks are not the only circumstances in which HAIs affect patients. Lessons learned in human health care settings show that endemic HAIs typically create a much greater overall burden in exacerbated morbidity and mortality than do epidemics. Unfortunately, information from veterinary care settings regarding rates of endemic HAIs is limited, but there is no reason to believe that the situation would be different. Based on limited numbers of systematic studies conducted in veterinary hospitals, the burden of disease associated with sporadic or endemic HAIs is substantial in veterinary patients. A recent multicenter study performed in five academic referral hospitals reported that nosocomial events monitored as seven different clinical syndromes were recognized during hospitalization in 19.7% (95% confidence interval [CI] = 14.5% to 26.7%) of equine patients admitted for gastrointestinal (GI) disease at a rate of 3.9 events per 100 days of hospitalization (95% CI = 2.9 to 4.3 events per 100 hospitalization days).[20] Other studies reported in equine patients have principally focused on HAIs related to surgical site infections.[21,22] These rates are not dissimilar from rates reported for HAIs among humans in critical care settings. Thus these notable outbreaks of HAIs and the emerging awareness of the importance of endemic occurrences should create an acute awareness that

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dramatically sharpens our focus on preventing all types of HAIs, including those that seem sporadic. Although the discussions in this chapter are mostly framed in the context of hospital settings, the concepts and issues apply much more broadly to ambulatory practices and animals' home premises.

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How Much Is Enough? How Much Is Too Little?

Exposures to contagious disease threats, HAIs in patients, and zoonotic infections in care providers are undeniable risks in every veterinary practice. Because veterinarians have ethical and legal obligations to take reasonable protective actions to prevent their patients and employees from foreseeable harm associated with their actions (and inactions), it is clearly possible to not pay sufficient attention to infection control efforts. The consensus opinion of veterinary infection control experts is that there is a recognizable standard of practice for infection control in veterinary medicine and appropriate effort must be given to the control and prevention of infectious disease transmission in all animal populations.[23] The implication that should be recognized is that it is possible to commit malpractice by not paying enough attention to infection control while caring for patients. There are key areas that must be addressed in all comprehensive infection control programs, including patient contact, hygiene, surveillance, communication, and education (Box 46.1).[24] However, we cannot determine whether we are meeting an acceptable standard of care for infection control by listing the specific prevention strategies that are used. Rather we must evaluate the occurrence of HAIs in a veterinary practice along with how we respond to the identification of these HAIs. Few prevention practices for HAIs are universally considered applicable and efficacious for preventing HAIs in all settings. Rigorous attention to hand hygiene would meet these criteria, but many other common control methods such as the use of disinfectant footbaths or protective clothing (e.g., coveralls, barrier nursing gowns) do not. Thus it is not possible to judge whether a control program is sufficiently rigorous solely by cataloging procedures, protocols, and policies. Recognition of the risks for legal liability undoubtedly gives reason for pause, but a better motivation for emphasizing infection control practices should be to provide the best care possible within the scope of a practice's specialization. The implications of suboptimal infection control may not always be apparent, but both sporadic/endemic infections and outbreaks can have a significant effect on patient morbidity, patient mortality, hospital economics, personnel health, personnel morale, and facility reputation.

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Box 46.1

Principal Goals and Major Action Areas for Infection Control Programs in Veterinary Medicine

- Four principal goals for infection control programs:
    - Decreasing the likelihood of exposure to infectious agents among patients and personnel
    - Decreasing the intrinsic risks for health care–associated infections (HAIs)
    - Maximizing participation of personnel in infection control activities
    - Optimizing the efficiency of infection control procedures and policies
- These goals are achieved through five major actions:
    - Decreasing direct and indirect patient contact
    - Optimizing hygiene
    - Using proven directed actions that decrease risks or are protective against HAIs, as well as actions that have a reasonable likelihood of efficacy based on biology, principles of pathogen transmission, and data from other species
    - Identifying high-risk patients and HAIs through efficient surveillance strategies
    - Optimizing communication and education among all personnel

Although HAIs are an undeniable hazard associated with caring for patients, and although it is possible to reduce the risk of infections through a variety of prevention strategies, it is important to note that not all HAIs are preventable using practical and cost-effective control programs. Even impractical and cost-prohibitive programs would not eliminate HAIs, since an undefined but undeniably significant “nonpreventable” fraction of infections will occur despite any infection control practices. To be most successful, it is important that over time administrators and personnel responsible for infection control programs

strive to better understand and target prevention efforts at the preventable fraction of all HAIs.

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Principles of Infection Control

In general, all comprehensive infection control programs center on the four principal goals and five major actions listed in Box 46.1, but each operation must tailor programs to optimally fit their specific practice. When initiating an infection control plan, it is important to make a global assessment of the contagious disease hazards in a practice, the level of risk aversion, and the resources that can be expended on infection control efforts. If a veterinary practice predominantly works in preventive health care under extensive field conditions, the contagious disease hazards may be less common and less severe than those encountered by a practice that concentrates on intensive care of patients in a hospital. Further, an ambulatory practice will need to integrate their infection control efforts with on-farm biosecurity practices to provide maximum benefit to owners. The specific disease hazards will also vary with the types of patients being managed (e.g., sick neonates versus patients with acute GI disorders versus reproduction cases, equine versus bovine versus camelid). Risk aversion relates to how much a person or business is unwilling to accept or allow a negative event to occur. The inverse of risk aversion can be thought of as risk tolerance. The more risk averse a person is, the more it may be reasonable for him or her to initiate and maintain a rigorous infection control program. In contrast, a more risk-tolerant veterinarian may recognize the potential for contagious disease hazards in his or her practice but may not believe it is necessary to engage in preventive strategies that are considered extreme. However, the risk tolerance of an individual or facility cannot be the sole deciding factor; a baseline level of risk aversion must be present as an ethical imperative. As our understanding of risks for HAIs advance, the bar for expectations in all practices is being raised, resulting in professional and legal risks should veterinarians fail to ensure that they are adequately pursuing infection control in their daily practices. The third component of this internal inventory is to assess the resources that will be available for infection control activities. The term *resources* in this context is intended to broadly encompass monetary resources, personnel time, and effort.

While considering this assessment of mindset and resources, the next step in developing an infection control program is to elaborate the specific goals for the program. Managers can then tailor their infection control program to meet their specific practice needs using a systematic process for evaluation of disease

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hazards and design of control systems. This systematic approach allows design of control systems that triage efforts to optimize efficiency. One systematic approach that the authors have used successfully is hazard analysis and critical control points (HACCP) methodology.[25] After identifying which specific hazards (contagious disease) are most likely to occur, as well as when and where in the systems these events might occur or be prevented, the next step is to define specific control measures. As mentioned, most of these prevention efforts are effective because they decrease the likelihood of exposing patients to infectious agents (i.e., by optimizing hygiene in the environment, personnel, or patients or by decreasing direct and indirect contact among patients). A few other prevention practices are effective because they reduce the inherent susceptibility to infection. To identify control measures of greatest importance, it is critical to consider the life cycle and methods of transmission for the specific agents of concern. Among the questions that should be asked: Is the agent most transmitted through direct contact, or are respiratory aerosols or contaminated surfaces and fomites also important sources of exposure? Is there a subclinical carrier state associated with agent shedding, or is shedding mostly restricted to clinically affected patients? Does the agent persist well in the environment, and can common disinfection procedures readily inactivate organisms?

Each infectious disease may be considered individually in this evaluation process, but it is useful to remember that control measures that are effective against one agent are usually effective against others, particularly if they share common routes of transmission or have common risk factors in patients. Design of infection control programs should focus on practical actions for known problems, but it is important not to ignore the potential for newly recognized and re-emerging diseases.[26-28] The general strategy used in infection control protocols should be sufficiently rigorous to protect against most emerging issues, at least at a basic level. However, infection control programs should also be adequately fluid so that they can be modified to address new issues.

Another critical aspect in the practice of infection control is effective targeting of efforts. Taken to hypothetical extreme, the most rigorous infection control methods would prescribe that *every* patient be handled in complete isolation using barrier precautions verging on those used by “hazmat” personnel. Clearly this is not practical or needed in most situations, yet in a few rare circumstances this level of precaution is warranted. In many more situations, some lesser level of precaution is warranted beyond that used in casual encounters with animals in their home environments. By their very nature, these extra control measures will

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inevitably inconvenience caregivers and clients in addition to increasing costs associated with care. These measures could also affect the quality of patient care and result in a corresponding *increase* in morbidity when taken to the extreme. The challenge is to target prevention efforts to just those patients that warrant increased concern and to use the most appropriate, albeit inconvenient, methods for controlling risks to personnel and other patients.

Another side effect of the inconvenience created by infection control efforts is that people by their very nature gravitate to the most convenient methods for daily activities. As such, the more personnel are inconvenienced through infection control efforts, the less likely they are to follow prescribed policies unless they understand and believe that procedures are needed and have value. Thus a critical component of any effective infection control program is maximizing awareness of personnel and educating them on potential hazards and the value of established control measures. Establishing interactive communication regarding risks and concerns coupled with logical, objective, evidence-based presentations is clearly an important approach for convincing personnel of the need to fully participate in infection control efforts. Feedback from surveillance efforts will also provide important objective information regarding the significance of specific disease risks in a practice.

Informed Consent and Implications for Infection Control

The principle of informed consent, as it applies to veterinarians caring for animals, implies that owners have the right to receive adequate information prior to treatment to allow them to appropriately weigh risks and benefits when making decisions for their animals and themselves.[29,30] As professionals with specialized training, veterinarians can be assumed to have knowledge about the health and care of animals that goes beyond that of people without this training. An agreed-upon component of the informed consent process is the disclosure to owners of potential risks that may be associated with a veterinarian's management of animals, particularly in situations in which there is greater than average risk for a particular adverse consequence.[31] As such, it is reasonable and prudent for veterinarians to routinely disclose the potential for HAIs as part of the informed consent process for all patients. This is especially true for patients with an enhanced risk of acquiring HAIs (e.g., because of required invasive procedures or because patients are compromised), but can also be applied to

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risks for all patients. For example, if there is a known or suspected increased risk of nosocomial infections for patients at a facility, there is likely an ethical and legal obligation to disclose *prior* to admission how this risk pertains to new patients. It is extremely prudent to document the informed consent process in writing with clients. Sometimes there is reluctance to do so based on concerns that it may deter clients from using a facility, but this process can also provide an opportunity to educate clientele (and thereby increase their overall understanding) and highlight measures that are being used to mitigate risks.

Paying for Infection Control Activities

As mentioned previously, procedures used to decrease risks of HAIs inherently increase labor and material costs related to patient care. Infection control activities are an essential part of delivering veterinary care, and it is reasonable to pass on these costs to clients. It should not be expected that these costs reduce profits or be paid by veterinarians or hospitals. Remembering that only a portion of HAIs are preventable, if veterinarians have met an expected standard of care for infection control, it is reasonable to assume that costs incurred for treating complications associated with HAIs are paid by the client. Knowing that HAIs are an expected risk, veterinarians and hospitals should develop financial plans to address these risks. Consider how expenses for infection control efforts will be assessed and tracked, as well as how a practice might recover these costs from clients. The costs could be passed on to clients by directly accounting for each item, which is most reasonable when specific charges can be attributed to a specific patient (e.g., increased nursing or materials costs associated with care of a specific patient in isolation). However, this is less applicable when costs relate to care and protection of more than one patient (e.g., costs related to cleaning and disinfecting the hospital environment). In these situations, it may make more sense to compensate for costs by aggregating expenses into a general fee category related to infection control (such as a daily surcharge) or to include these costs in overhead that is compensated by general admission or hospitalization fees. It is also wise to have a contingency fund that will allow veterinarians to address special circumstances, such as when it is necessary to investigate or mitigate against suspected outbreaks of infections.

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Environmental Hygiene

Much attention is paid to the possible role of the inanimate environment in HAIs of large animals. Contamination of the hospital environment by microorganisms is inevitable and entirely expected, and detection of microorganisms in a hospital environment does not, by itself, indicate anything of clinical relevance. A variety of factors are likely involved in the potential clinical relevance of contaminants, including the organism, numbers present, likelihood of contact with susceptible hosts, degree of susceptibility of potential hosts, environmental effects (temperature, ultraviolet exposure, humidity), and routine infection control protocols. Many microorganisms grow well on environmental surfaces, provided there is adequate moisture and organic debris, and may survive for very long periods. Even with relatively inhospitable conditions, many organisms persist for extended periods. If environmental pathogens can contact the appropriate body site of a susceptible individual in adequate numbers, disease could result. Environments where patients are housed or veterinary care is delivered can be expected to have greater numbers of environmental microorganisms than corresponding areas with less animal and human traffic.[32]

The relevance of environmental contamination is often difficult to determine. Even recovery of genetically indistinguishable organisms from the environment and from a patient does not confirm that exposure to an environmental reservoir was the source of infection, since it can be difficult to distinguish cause versus effect. However, environmental contamination is of concern for both direct (e.g., oral inoculation from a reservoir of microorganisms in a stall) and indirect (e.g., transmission of an organism from an environmental reservoir to the hands of a care provider and then to an animal) transmission. Measures should be used in all veterinary care environments to reduce the environmental pathogen load. This involves cleaning and disinfecting environmental sites.

Cleaning

Cleaning is defined as the removal of all visible debris[33] and is arguably the most important step in decontaminating animal environments. Even the best disinfectants will be minimally effective when used in the presence of moderate volumes of dirt and organic debris such as feces and bedding material. Dirt and debris hamper disinfection by inactivating many chemicals, acting as a physical

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barrier between disinfectants and microorganisms, and providing a nutritional source for microorganisms. Not only does cleaning enhance the efficacy of the disinfection process by providing optimal conditions for desired biochemical reactions, but it can actually remove a majority of microorganisms so that fewer need to be killed by disinfectants. Therefore removal of as much organic debris as possible is required for optimal disinfection. This involves manual labor, consisting of removal of all bedding and feces and scrubbing surfaces to remove adherent debris and biofilms. Detergents should be used to loosen organic debris, emulsify oils and fats, and remove biofilm. The disinfectant to be used must be considered when choosing a detergent because there can be interaction between chemicals in detergents and disinfectants.

Because of the effort required to clean and scrub stalls and other large areas, less labor-intensive methods are often sought. For example, high-pressure (>120 psi) washers are frequently used in barns and hospitals. There are theoretical advantages that seemingly justify use of high-pressure washers, especially when they are designed to dispense high-temperature water and steam. Although power washing can be quite helpful in removing organic debris, this process can also exacerbate infection control problems by aerosolizing and widely dispersing infectious agents. Further, when used indiscriminately, they can damage surfaces, which then impairs subsequent cleaning and facilitates survival of pathogens. The true risk related to the use of high-pressure washers is unclear. However, the convenience of using high-pressure systems must obviously be balanced with more intensive manual cleaning methods in order to minimize unwanted consequences. Using high-pressure systems on surfaces with large amounts of gross contamination should be avoided.[34] In areas likely to be contaminated with important contagious pathogens (e.g., isolation facilities), it is logical to use high-pressure systems minimally or at least only as a secondary cleaning process on surfaces that have already been manually cleaned and disinfected.

Disinfection

Disinfection is the process of substantially reducing the burden of microbial contaminants on inanimate objects in order to reduce the likelihood of transmission of infectious agents. This should be contrasted with sterilization, which is the inactivation of all microbial agents on an object, typically performed only on materials used in invasive procedures. Disinfectants are

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biocidal chemicals that must be used at appropriate concentrations, allowing for adequate contact time to achieve the intended effect. Even with proper cleaning and selection of an appropriate disinfectant, disinfection errors can occur. It is also important to remember that microbial responses to disinfectant exposures are not uniform. There is tremendous variation in the ability of microorganisms to tolerate cleaning and disinfection. Most enveloped viruses are easy to eliminate, whereas protozoal oocysts, nonenveloped viruses, and bacterial spores may be difficult or impossible to kill with surface disinfectants.[35]

For disinfection to be effective, a few key factors must be considered: the presence of organic debris, disinfectant concentration, temperature, and contact time. Organic debris inactivates disinfectants to varying degrees, emphasizing the need for careful cleaning. Most disinfectants are available as concentrates and must be diluted prior to use. Excessively dilute disinfectant solutions may have little or no effect, whereas excessively concentrated solutions can be dangerous to use in addition to being wasteful of resources. Dilution of disinfectants is an important process and must be performed by measurement, not estimation. One method to easily ensure that disinfectants are appropriately diluted is to use metered dispensing units that can be either wall mounted or attached to the end of a hose. For some disinfectants, different concentrations may be recommended for different situations. Test strips that can commonly be purchased from a variety of vendors can also be used to verify appropriate dilution and activity disinfectant solutions. This is especially important when stock solutions are prepared for use over time. Cleaning personnel must be informed of the importance of disinfectant dilution and trained in proper methods. Contact time is critical, particularly for certain disinfectants and difficult-to-kill microorganisms. If disinfectants are applied and immediately rinsed away, there is little chance that they can be effective. Most disinfectants require 10 to 30 minutes of contact time to provide maximal microbial reduction. Chemical reactions that produce disinfection are slowed in cold temperatures, which should be considered when determining the amount of contact time required. Disinfectants should never be combined because of the potential for inactivation and production of noxious or toxic gases.

Disinfectants

It is critical to be aware that all disinfectants do not have the same effectiveness. As with antimicrobial drugs, disinfectants have a spectrum of activity that can be

highly variable between disinfectant classes (Table 46.1). Choosing the most appropriate disinfectant can be complex, involving a variety of factors including spectrum of activity, relative efficacy in the presence of organic debris, toxicity to animals and humans, potential damaging effects on certain surfaces, cost, and potential environmental effects. There is no standard disinfectant that can be used in all situations in large animal facilities, although oxidizing agents such as accelerated hydrogen peroxide and potassium peroxymonosulfate are increasing in popularity because of their broad spectrum of activity, acceptable performance in moderate amounts of organic material, relatively rapid action at room temperature, relative safety for personnel, and environmental friendliness. Other options may be appropriate in certain situations. When disinfectants with a narrower spectrum of activity are used as the primary disinfectant, protocols should be in place to use alternative products should situations that require a higher level of activity be encountered. There is no evidence that rotation of disinfectants is useful.

TABLE 46.1

Disinfectants Commonly Used in Veterinary Medicine[a]

Disinfectant	Activity in Organic Debris	Spectrum	Comments
Bleach (sodium hypochlorite)	Rapidly inactivated	Broad, including nonenveloped viruses and bacterial spores. No activity against *Cryptosporidium*.	• Used to disinfect clean environmental surfaces. • Sporicidal activity is particularly useful. • Efficacy decreases with increasing pH, with decreasing temperature, and in the presence of ammonia and nitrogen. • Varying concentrations can be used; 1:64 dilution of standard commercial (4% hypochlorite) bleach is most common. Higher concentrations, up to 1:10, can be used but should be reserved for infrequent use in special situations. • Inactivated by cationic soaps/detergents and sunlight. • Chlorine gas can be produced when mixed with other chemicals. • Bleaches fabrics and is corrosive to concrete.
Quaternary	Moderate	Variable. In general, effective against	• There are differences among types

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ammonium		gram-negative bacteria and enveloped viruses, variably effective against gram-positive bacteria, limited activity against enveloped viruses, and no activity against bacterial spores or *Cryptosporidium.*	of quaternary ammonium compounds. • Commonly used primary environmental disinfectant, although the spectrum is not necessarily optimal. • In general, low toxicity. • Inactivated by anionic detergents. • Some residual activity after drying. • Less effective in cold temperatures and low pH. • Stable in storage.
Phenols	Very good	Relatively broad spectrum, with limited activity against nonenveloped viruses and no activity against bacterial spores or *Cryptosporidium*.	• Main advantage is better activity in organic debris. • Can be irritating to skin and mucous membrane surfaces. • Reportedly toxic to cats and pigs. • Some residual activity after drying. • Noncorrosive.
Peroxygen/accelerated hydrogen peroxide	Very good	Broad spectrum, including bacterial spores and nonenveloped viruses. Some activity against *Cryptosporidium*.	• Excellent choice for routine environmental disinfection, footbaths, and environmental fogging. • Rapid action makes it a good choice for footbaths. • Low toxicity except at high concentrations. • Environmentally friendly. • Peryoxygen products can be corrosive to plain steel, iron, copper, brass, bronze, vinyl, rubber, and concrete. • More expensive than most other disinfectant options.
Alcohols	Rapidly inactivated	Moderate to no activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*.	• Not appropriate for environmental disinfection. Can be used to disinfect certain medical and patient care items, but better options are available. • Flammable. • Minimally toxic. • Fast acting.
Chlorhexidine	Rapidly inactivated	Moderate. Limited activity against enveloped viruses. No activity against nonenveloped viruses, bacterial spores, and *Cryptosporidium*.	• Not appropriate for environmental disinfection. • Appropriately diluted solutions are suitable for use on tissues or on materials that contact skin or mucous membranes. • Minimally toxic. • Bactericidal activity on skin is more rapid than many other compounds, including iodophors. Residual effect on skin diminishes regrowth.
Povidone iodine	Rapidly inactivated	Moderate. Limited activity against enveloped viruses. No activity against	• Not appropriate for environmental disinfection.

		nonenveloped viruses, bacterial spores, and *Cryptosporidium*.	• Appropriately diluted solutions are suitable for use on tissues or on materials that contact skin or mucous membranes. • Minimally toxic but some people can become sensitized to skin contact. • Appropriate dilution is important to maximize activity.

[a]It is critical to handle disinfectants and other chemicals using appropriate safety precautions. Refer to the Material Safety Data Sheet (MSDS) for each product to obtain recommendations on appropriate handling and recommended personal protective equipment.

Effect of Surface Material on Cleaning and Disinfection

The material to be cleaned and disinfected can also have a tremendous impact on efficacy. Many surfaces found in large animal clinics and farms are not amenable to thorough cleaning and disinfection. These include unsealed wood surfaces, unsealed block, dirt flooring, and areas that are difficult to clean. For stalls, solid walls with a sealed surface are optimal for disinfection. This may be difficult to achieve; however, certain procedures can be performed to facilitate disinfection.[34] Cement block walls can be reasonably well sealed with at least two coats of good-quality enamel. Wood walls can be sealed using two or more coats of marine epoxy. Regular maintenance of stalls is required to seal defects that result from kicks or chewing.

The optimal floor surface, in terms of cleaning and disinfection, is a smooth, solid, completely sealed surface. However, surfaces meeting these criteria are not all amenable to animal housing, so a compromise may be required. Finding the right balance of floor cushion, traction, durability, ease of cleaning, and cost is difficult. Regardless, certain key factors should be considered. The floor should be completely sealed so that water (and pathogens) cannot seep underneath, since this creates an obvious environmental reservoir and prevents adequate contact with disinfectants. Damaged stall matting has been cited as the likely environmental reservoir associated with serious outbreaks of HAIs.[1] If obtaining a seamless, water-impervious floor surface is not possible, floor coverings should be completely removable (i.e., rubber mats over sealed concrete floor) and must be removed regularly for disinfection. Dirt, sand, and other organic materials cannot be disinfected and are therefore unsuitable for

permanent flooring in hospital stalls or other veterinary care facilities. If sand is required for care of orthopedic patients, this material should be completely removed and discarded between every patient.

Animal Contact Items

For items that are used in patient care, disinfection processes are sometimes divided into three categories: high, intermediate, and low level. High-level disinfection involves eliminating all viruses and vegetative bacteria but is not expected to inactivate bacterial spores, fungal spores, or protozoal oocysts. High-level disinfection is difficult to attain and uncommonly used. Intermediate-level disinfection involves eliminating all vegetative bacteria but not necessarily all viruses (especially nonenveloped viruses), spores, or oocysts. Low-level disinfection results in elimination of most but not all potentially pathogenic bacteria and enveloped viruses. Items requiring disinfection should be classified according to the level of disinfection required; Table 46.2 shows examples of these.

TABLE 46.2

Examples of Items Requiring Different Levels of Disinfection

Level of Disinfection	Example Items
High level	Endotracheal tubes
	Tonometer tips
	Urinary catheters
Intermediate level	Dental equipment
	Endoscopes
	Thermometers used on multiple patients
	Vaginal specula
Low level	Thermometers used on individual patients
	Feeding instruments
	Muzzles
	Nasogastric tubes
	Oral specula
	Stethoscopes
	Twitches

After use, all items in a patient's stall should be considered to be potentially contaminated with pathogens that the animal might be shedding. Thus for patients suspected or known to have contagious diseases, every item in the stall should be treated as a source of infectious material and must be appropriately decontaminated or discarded. Many stall items may be difficult to disinfect, or it

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may not be possible to be confident in the ability to fully decontaminate them. If it is cost effective, disposal of these items is ideal. Otherwise, standard principles of cleaning and disinfection apply. It must be recognized that rough, damaged, and permeable surfaces may be very difficult to adequately disinfect. Particular attention should be paid to disinfecting surfaces that patients contact orally, such as feeders and water bowls, as well as surfaces likely to be contacted by hands of personnel. Appropriate decontamination of water bowls can be problematic. Ideally, the water supply should be turned off, and the bowl should be drained, cleaned, and applied with disinfectant for an appropriate time before it is rinsed and the water is turned on again. Nets used to hold hay have a high likelihood of contamination and are difficult to disinfect without use of gas or plasma sterilization techniques. As such, their use should be avoided if possible.

Certain items may be at particular risk for contamination. For example, thermometers used on animals with salmonellosis are almost assuredly contaminated, and complete disinfection of digital thermometers is very difficult. It is reasonable to dedicate thermometers to individual patients and discard them when they are no longer required. An alternative is the use of disposable temperature strips, which are sometimes used in human medicine. These have not been specifically validated but are routinely used in some large animal hospitals.[36]

Twitches and muzzles have a high potential for contamination with pathogens such as *Streptococcus equi* and MRSA. Rope used for twitches is extremely difficult to disinfect, apart from removing the rope for autoclaving. Chain twitches are easier to disinfect, but many find them less desirable to use. The ideal twitch material is easy to disinfect, is atraumatic, and provides good grip on the nose. It is debatable whether the ideal material is available at this time. Twitches should be routinely disinfected, to the best of the ability considering the material. Consideration should be given to regularly changing or autoclaving rope used for twitches and routinely decontaminating twitches with the understanding that complete disinfection may not be possible. Twitches used on animals that are known to harbor or are likely harboring nasal or upper respiratory tract pathogens should be considered contaminated and the material discarded or disinfected.

Few areas show a greater difference in approach to infection control between human and veterinary medicine than the handling of hypodermic needles after use. In human medicine, recapping needles is strictly forbidden because of the potential for needlestick injuries and subsequent exposure to life-threatening

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bloodborne pathogens. In veterinary medicine, recapping needles is very common, and needlestick injuries are often not perceived to be a significant health threat to veterinary personnel. Currently, there are minimal risks to veterinary personnel in almost all situations regarding bloodborne transmission of infectious agents from large animals. However, infectious disease hazards clearly continue to emerge, and it is prudent to develop safe practices that minimize the potential for exposure to bloodborne pathogens that might be transmitted from domestic large animals. In addition, physical trauma from the needle and accidental inoculation of some vaccines (e.g., RB51 modified-live *Brucella abortus* vaccine), medications (e.g., hormones, cancer chemotherapeutic drugs), or the person's own skin microbiota can lead to serious outcomes.

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Hand Hygiene

Rigorous use of hand-hygiene procedures is one of the oldest recognized infection control measures, and it is perhaps the single most important infection control practice. Unfortunately, extremely poor compliance with best practices in human and veterinary hospitals as well as in the community negates much of the potential benefit. Centers for Disease Control and Prevention (CDC) guidelines suggest that health care workers in human hospitals should wash their hands or use hand-sanitizing products before and after every contact with patients, as well as prior to eating and after using the restroom. It is hard to argue that less stringent procedures are warranted in veterinary hospitals.

Numerous indications for hand-hygiene procedures in health care settings have been identified as part of guidelines for human medicine. As shown in Box 46.2, hand hygiene is needed frequently in a clinical situation, something that may be problematic in typical settings where veterinary care is provided to large animals. Maintaining optimal hand hygiene can be especially important for ambulatory clinicians, yet can also be particularly difficult to achieve because of logistical difficulties. A variety of options exist for decontaminating hands.[37,38] The most common practices are handwashing and use of waterless hand-sanitizing solutions. Both are acceptable methods in most situations, and each has individual benefits and drawbacks. There are a variety of commercially available products that have documented efficacy for use as topical antiseptics and hand sanitizers; the most common ingredients of these products include ethanol, isopropanol, povidone-iodine, benzalkonium chloride, benzethonium chloride, and chloroxylenol.[37,38] Recently, products containing triclosan and a variety of other active compounds used in hand washes and rubs have been deemed to be unsafe for repeated human exposure by the U.S. Food and Drug Administration, and health care workers should be aware that additional investigations have been called for to support the general expectations of safety and efficacy of other active ingredients.[38]

Box 46.2

Indications for Hand Hygiene in Medical

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Practice

- When hands are visibly dirty or contaminated with proteinaceous material, blood, or other body fluids.
- Before direct contact with patients.
- Before donning sterile gloves for invasive procedures (e.g., suturing wounds).
- Before inserting an indwelling urinary catheter, peripheral vascular catheter, or other invasive device that does not require a surgical procedure.
- After contact with a patient's intact skin.
- After contact with body fluids or excretions, mucous membranes, nonintact skin, and wound dressings.
- After contact with an inanimate object in the immediate vicinity of a patient.
- After removing gloves.
- Before eating and after using a restroom.

Adapted from Centers for Disease Control and Prevention: Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR* 51(No. RR-16), 2002. http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf. (Accessed August 14, 2018.)

Handwashing

Washing with antibacterial soap has been a standard method of decontaminating the hands of health care workers for more than a century. However, the potential benefits of this practice generally are not realized because of failure to use appropriate methods or failure to wash hands at all.[39,40] Common errors include inadequate duration of handwashing, inadequate thoroughness, failure to use soap, use of contaminated items to dry hands, and contamination of hands immediately following handwashing (e.g., through contact with contaminated faucets or door handles). An appropriate technique for handwashing is outlined in Box 46.3.

Box 46.3

A Recommended Technique for Handwashing

- Wet hands first with water and then apply an appropriate amount of disinfectant soap (as recommended by the manufacturer).
- Vigorously rub hands together for *at least* 15 seconds, covering all surfaces of the hands and fingers. Make sure to scrub fingertips and clean under fingernails.
- Rinse hands with water and dry thoroughly with a disposable paper towel. Multiple-use towels of any type are not recommended.
- Use towel to turn off the faucet (and open doors when exiting a restroom).
- Avoid using hot water because repeated exposure to hot water may increase the risk of dermatitis.

Adapted from Centers for Disease Control and Prevention: Guideline for hand hygiene in health-care settings: recommendations of the Healthcare Infection Control Practices Advisory Committee and the HICPAC/SHEA/APIC/IDSA Hand Hygiene Task Force. *MMWR* 51(No. RR-16), 2002. http://www.cdc.gov/mmwr/PDF/rr/rr5116.pdf. (Accessed August 14, 2018.)

The importance of the type of soap used in handwashing is also often overlooked. Plain soaps, those without antibacterial agents, have minimal direct antibacterial activity. The main benefit of these is assistance with removal of dirt and organic debris, although efficacy data are conflicting. The use of plain soap can slightly decrease bacterial numbers on hands, but studies in human medicine have failed to demonstrate effective removal of significant pathogens from the hands of hospital personnel.[41] Also, the routine use of plain soap can at times be associated with *increases* in numbers of bacteria carried on hands if use of these products results in skin damage and irritation through drying.[42] Plain soaps are preferable to not washing hands in the absence of suitable alternatives (such as in field settings) but should be avoided whenever possible in health care situations.

Most soaps used in hospital settings contain biocides such as chlorhexidine,

which produce greater decreases in skin contamination compared with plain soap.[40] Iodine and iodophors have been used as skin antiseptics and have a broader antibacterial spectrum. However, both (particularly iodine) can be irritating to skin and are less commonly used for routine handwashing and skin disinfection in medical personnel. In addition, some people become sensitized to skin contact with these products.

Compliance with handwashing protocols is often poor for a variety of reasons. The time required is a major factor, particularly in situations in which contact with many patients is likely. Although handwashing requires less than a minute to complete, if it is indicated 100 times in a day, this represents a significant amount of time cumulatively committed to this activity. Lack of convenient access to proper handwashing facilities is also frequently a problem. If access to sinks with running water, soap, and disposable towels is not convenient (i.e., not adjacent to where animal contacts occur), it is less likely that handwashing protocols will be rigorously followed. Regardless of the type of soap used, frequent handwashing leads to skin irritation and damage, which compounds compliance problems by making people reluctant to wash their hands; as well, skin damage associated with handwashing increases the potential for colonization or transient carriage of potential pathogens.[42-45]

Nail care and jewelry can also be significant impediments to achieving optimal levels of hand hygiene.[46] Colonization with higher bacterial numbers, colonization with bacterial pathogens, and outbreaks of infectious disease have been reported in human hospitals in association with effects related to long fingernails and artificial nails.[47] Studies have shown that these hamper effective hand disinfection, and many health care facilities, particularly intensive care units, prohibit their staff from having long (¼ inch or longer) or artificial nails. The role of these factors in risks to patients in veterinary settings is unclear, but some veterinary facilities have developed similar protocols and restrictions.

Waterless Hand Sanitizers

Waterless hand sanitizers have proliferated in health care facilities and in the community because of their low cost, ease of use, and efficacy. The CDC has concluded that hand sanitizers are the preferred method for cleaning hands that are not visibly dirty in comparison to handwashing.[39] Most waterless hand sanitizers use varying concentrations of alcohol (isopropanol, ethanol, n-

Propanol, or a combination), although a few products contain alcohol plus biocides or biocides (e.g., benzalkonium chloride) alone. Alcohol products are most commonly available, with concentrations ranging from 60% to 95%, although lower concentration products can sometimes be encountered and should be avoided. Concentrations greater than 95% should also be avoided because the presence of water is important for the bactericidal activity. They may be in liquid, gel, or foam preparations.

Alcohols have excellent effect against gram-positive and gram-negative bacteria but not bacterial spores or protozoal oocysts.[39,40] Antiviral effects are variable, with less reliable effects against nonenveloped viruses. Alcohol-based products have been shown to have good effect on reduction of hand contamination of health care workers and have been shown to be more effective than standard handwashing.[48] Frequent contact with alcohol can lead to significant drying of skin, so most commercial products contain emollients, humectants, or similar skin-conditioning agents. Alcohol-impregnated towelettes are also commercially available but contain a small volume of alcohol and are no more effective for hand decontamination than washing with plain soap.[49]

In human health care, hand-hygiene efforts are focused on increased use of waterless hand sanitizers. One concern that is sometimes expressed in large animal practice about waterless hand sanitizers is their activity in the presence of organic debris. However, a study of the efficacy of hand sanitizers on hand disinfection after performing physical examinations in horses reported that both alcohol and alcohol/chlorhexidine hand sanitizers were more effective for decreasing bacterial contamination than washing hands for 15 seconds with antibacterial soap.[50] This level of disinfection was noted even though the culture fluid collected off the hands was visibly dirty, indicating that there was a reasonable amount of gross contamination. Thus waterless hand sanitizers are likely to be effective under normal large animal practice situations. However, when contamination of the skin is readily apparent, handwashing is probably required for optimal effect. It is important to remember that alcohol-containing products are flammable. Although very rare, fires have been associated with exposure to open flame. Common sense and ensuring that hands are rubbed together until all alcohol has evaporated should greatly minimize any risks.

While most available products contain only alcohol as a sanitizing agent (in addition to humectants or emollients), some commercial products contain alcohol plus other biocides such as chlorhexidine. These are sometimes present because of a purported residual effect; however, evidence of residual activity of

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chlorhexidine has been challenged.[51]

One of the main advantages of waterless hand sanitizers is their portability. Although it is difficult to make the water source needed for handwashing portable or always accessible, these products can be easily placed in ambulatory vehicles, carried by individual staff, and easily placed throughout hospitals. As such, there is a greater likelihood of obtaining compliance by facilitating access. Unfortunately, regardless of the types of products used, compliance with hand hygiene is often a major problem.[52,53] Infection control programs need to address hand-hygiene compliance through a variety of means to increase use of this critical infection control tool.

Surgical Hand Antisepsis

Scrubbing the hands and forearms with disinfectant solutions has been a standard practice prior to surgery, but there is increasing movement to the use of waterless products. Recommended techniques for presurgical scrubbing vary somewhat but typically involve a systematic 2- or 3-minute scrub of all hand and forearm surfaces.[54] One concern with repeated surgical scrubbing is the potential for skin irritation and subsequent increases in bacterial contamination. This has led to increasing use of brushless techniques, especially with the use of waterless hand sanitizers containing 1% chlorhexidine gluconate and 61% ethanol, which has been shown to be equal or superior to brush application of 4% chlorhexidine soap.[55] These can be directly applied to the hands and arms as the sole preoperative skin antisepsis method, or if there is concern about the degree of gross contamination, hands can be washed and dried, followed by application of the waterless product.

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Barrier Protocols and Protective Attire

Barrier nursing techniques are an important infection control tool. The basic premise for their use is that placing some type of barrier between caregivers and patients prevents skin or clothing from being contaminated, whereas the contaminated outer barrier item can be discarded or left in the contaminated environment. Prevention of contamination of personnel's skin, regular clothing, personal items, and medical instruments can substantially reduce the risk of transmission of pathogens between animals, contamination of the general environment, and zoonotic transmission.

Use of Barrier Precautions

Basic barrier techniques should be used in all veterinary hospitals. Standardized, clean, protective outwear should be worn over hospital-dedicated attire for any patient contact, regardless of the anticipated nature of contact or the assumed infectious disease status of the patient. The need for other barrier items varies with circumstances and is often dictated by the type of disease syndrome being managed (e.g., diarrhea or GI disease, respiratory disease, wound infection, fever of unknown origin) as opposed to documentation of specific infections or diseases. Other factors that might indicate a need for additional barriers include farm of origin (e.g., farms with endemic *S. equi* or rotavirus infections) or a patient that is considered to have an increased risk of infection (e.g., compromised neonates). Gloves, gowns, and overboots are the most commonly used items for additional barrier protection, but masks, caps, and eye protection may also be required at times. In some facilities, overboots are not used in all areas, but personnel are required to wear footwear that can be readily disinfected. Disinfection of this footwear is required after exiting potentially contaminated areas.

Limitations to Barrier Precautions

The greatest limiting factors associated with use of barrier precautions in infection control are poor compliance and improper use. Written protocols that document practical use of barrier precautions should be developed. They should specifically state when additional barriers are required; it is not possible to

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achieve consistent results if protocols are ambiguous or suggest too much discretionary interpretation. In addition, it is critical to educate personnel on the need for barrier nursing precautions and on proper application. Many human hospitals require physicians and nursing staff to undergo practical training in the proper use of barrier precautions to avoid inadvertent spread of contaminants, and this type of active training may help to ensure uniform understanding and application of protocols. It is also important to regularly monitor compliance with protocols.

Protective Outerwear

Standard protective outerwear for large animal veterinary personnel should include clean coveralls, lab coats, scrubs, or other dedicated clothing (hospital uniforms), in addition to easily cleanable footwear. Protective outerwear should be worn for every animal contact and should be changed regularly. This includes any time outerwear becomes visibly soiled or otherwise contaminated with body fluids perceived or known to be contaminated with potential pathogens (e.g., feces, blood, nasal exudates, urine, or uterine fluid). In addition, outerwear should be changed frequently (at least daily) because gross contamination does not need to be present for pathogen contamination to have occurred. Hospital personnel should change their hospital outerwear before leaving the building to decrease the risk of transfer of infectious agents from the hospital to the community. To facilitate this control measure, it is optimal from an infection control perspective for veterinary practices to provide laundry services or laundry facilities. Clothing that is potentially contaminated with biohazardous material should be handled appropriately so that personnel handling laundry are aware of the hazards and how to reduce risks for exposure.

Gloves

Gloves are an important component of barrier precautions if used properly. The CDC recommends glove use by health care workers to reduce the risk of transmission of infections from patients to personnel, to prevent health care workers' skin flora from being transmitted to patients, and to reduce transient contamination of the skin on the hands of personnel by microorganisms that can be transmitted from one patient to another.[56] The same concepts apply to veterinary medicine. In certain situations, glove use has been shown to be an

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effective means of reducing pathogen transmission in human medicine.[57] However, incorrect use can negate these effects or even be harmful. Common errors with glove use include failing to wear gloves when needed, not changing gloves after contact with infectious items, touching items (e.g., cell phones, computers, pens, medical supplies) while wearing contaminated gloves, contamination of hands or clothing while removing gloves, and failing to wash hands after glove removal.[58] Although gloves are used to prevent contamination of hands, the potential for inadvertent contamination through microbreaks in the glove surface or contamination during glove removal necessitates use of handwashing or application of hand-sanitizing solutions in conjunction with glove use.[56]

There are no widely accepted standards in veterinary medicine for when gloves must be used, apart from the use of sterile gloves during surgical procedures. Examination gloves that are clean but not sterile are often used when handling wounds or infected body sites and for contact with animals known or suspected to be shedding contagious pathogens. Despite relatively widespread use of examination gloves in a variety of circumstances in veterinary medicine, it is quite unusual for practices to have formal protocols regarding how and when they should be used.

Gowns

Although protective gowns have traditionally been used during surgery, their use as a barrier garment when contacting high-risk patients is increasing in both human and veterinary medicine. The CDC has produced guidelines for human medicine stating that “gowns should be worn by personnel during the care of patients infected with epidemiologically important microorganisms to reduce the opportunity for transmission of pathogens from patients or items in their environment to other patients or environments.”[56] In general, gowns should be worn whenever direct or indirect contact with patients or their environment may result in contamination of caregivers’ clothing or skin that facilitates transmission of pathogens.

The ideal barrier gown would cover all areas of the body that might become contaminated, prevent penetration of liquids, be of adequate strength to resist tearing and puncture under normal activities, be comfortable to wear for long periods, be available in appropriate sizes for all personnel, be easy to put on and remove without contamination of regular attire, be nonabrasive to skin, be

unlikely to startle patients, and be of acceptable cost. Unfortunately, a product with all of these characteristics does not currently exist, and facilities must prioritize the relative importance of different gown properties. This is often difficult because neither the overall effectiveness of gowning nor the effectiveness of different gowns in veterinary situations has been adequately evaluated. The problem most likely to be encountered with barrier gowns in veterinary practice is poor resistance to liquids, especially under direct contact or pressure. In large animal practice, there is a greater likelihood of contact with relatively large volumes of fluids (e.g., with diarrheic animals) or direct contact with patient surfaces that have moist secretions or excretions (e.g., animals with nasal discharge or large infected wounds). The types of anticipated activities may also have an impact on the required size of gown. Gowns that do not completely cover the legs and feet may be useful in some circumstances but ineffective in situations with prolonged direct contact, such as assisted neonatal nursing.

In human medicine, there are conflicting data regarding the efficacy of gowning for prevention of HAIs.[57,58] Gowns may be more effective for reducing infection of personnel. It is possible that the most significant advantage in some situations is not the protective effect of gowns or other protective outerwear, but rather the raised awareness of the potentially infectious nature of the patient, which may in turn encourage concurrent application of other important infection control practices.

Footwear, Footbaths, and Footmats

Contaminated footwear has been shown to be an important factor in transmission of contagious pathogens in intensive agriculture settings,[59-62] but the role of footwear contamination in spread of contagious diseases in veterinary hospitals or human health care facilities is less clear.[63] A few investigations have noted the dissemination of *Salmonella* on floors in veterinary hospitals, indicating a potential for transmission via this route, but these have not directly linked disease transmission to environmental contamination.[1-4,64] Regardless, use of disposable shoe covers or footwear that is dedicated for use in isolation areas is a commonly implemented control strategy in veterinary hospitals, as is the use of footbaths or footmats containing disinfectants. Use of disinfectant footbaths or footmats does not affect total numbers of bacteria found on floor surfaces,[32,65] nor do these products completely sterilize footwear. It must be remembered that

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disinfection is a chemical process affected by time, temperature, and the presence of organic debris, whereas footbaths are frequently used with an unreasonable expectation of immediate sterilization. However, broad-spectrum, rapidly acting disinfectants such as peroxygens and accelerated hydrogen peroxide products have been shown to decrease bacterial counts on footwear surfaces if adequate time is allowed for action and if surface contamination such as manure is routinely removed from footwear.[66-71] Implementation of requirements for change of footwear or use of footbaths or footmats should not be undertaken lightly, as enforcing uniform compliance with these policies can be difficult and the cost for implementing can be significant. Further, a substantial effort is required to ensure that reusable footwear is kept clean and that disinfectant solutions are frequently changed (at least daily, but typically more frequent changes are warranted when solutions become dirty, as this significantly decreases the activity of disinfectant solutions). Still, it is our impression that rigorous use of disposable or dedicated footwear in isolation areas, in addition to the best-practice use of disinfectant footbaths or footmats, provides a useful adjunct in the control of diarrheal agents such as *Salmonella*. It is less clear that they provide substantive benefit in control of highly resistant agents such as rotavirus, respiratory agents, or contact-transmitted agents such as MRSA. Regardless, easily cleanable, closed-toe footwear should be mandatory for working in large animal health care environments.

Eye and Face Protection

The use of protective eyewear, including goggles and face shields, is common in human medicine during procedures that generate aerosols or airborne droplets of blood, body fluids, and secretions[72] but often overlooked in veterinary medicine.[73] Face shields have the advantage that they decrease the potential for facial mucous membrane exposures in addition to ocular exposures. Inexpensive disposable face shields are commonly available and are generally quite comfortable for people with varying face shapes and sizes, and thus would seem to have great potential for use in all large animal practices. Despite the current low prevalence of bloodborne zoonotic pathogens in large animal species, it would be prudent to consider the use of some type of eye protection whenever generation of small particulates or aerosols of liquids or secretions is likely to occur, including when motorized equipment is being used for dental procedures, foot trimming, or orthopedic surgery. Situations in which eye protection should

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be seriously considered include examination of animals with suspected viral encephalitides or draining abscesses and working with a struggling animal with a respiratory or skin/soft tissue infection where infectious agents might be aerosolized during movement. Although not studied, face protection may also help protect against zoonotic disease involving fecal-oral transmission, such as *C. parvum*, which has an extremely small infectious dose, most likely through prevention of inadvertent hand-mouth contact.

Respiratory Protection

Masks and respirators are often used to reduce the risk of respiratory and oral exposures to infectious agents, to reduce the risk of contamination of patient sites with organisms from personnel, and in some situations to prevent contamination of hands with nasal or oral microflora. Standard surgical masks may be effective against the spread of large-particle droplets that are transmitted by close contact and travel only short distances (up to 3 feet) from infected patients.[74] However, the overall effectiveness of surgical masks in hospital situations has recently been questioned.[75]

Airborne transmission of zoonotic pathogens is of minimal concern in most veterinary settings, and mask use is uncommon in veterinary hospitals apart from during surgical procedures. One exception that has been frequently overlooked is the risk of zoonotic *Coxiella burnetii* transmission when handling periparturient ruminants, especially during obstetrical procedures in small ruminants.[28] The actual reduction in zoonotic disease risk that might be associated with the use of surgical masks during routine patient contact is unclear. However, increased awareness of risks of specific zoonotic diseases and infections in immunocompromised personnel and others with special disease risks has prompted reconsideration of recommendations regarding personal protective equipment in some circumstances. For example, although clinical Q fever is considered relatively rare, it has become abundantly clear that people working with small ruminants are very commonly infected with *C. burnetii*, and the significant health consequences of these rare clinical infections may warrant mandatory use of respiratory protection when handling high-risk patients, especially if people have a higher risk for serious infection sequellae (e.g., pregnant women). In addition, although airborne transmission is not considered an important route of exposure for MRSA, the hospital personnel primarily become colonized in the nasal passages, and hand-to-nose contact is frequent.

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Thus mask use may prevent direct contact of hand and nose, thereby decreasing hand contamination or decreasing the risk of inoculation of the nose following contamination of the hands during animal contact. Mask use may be particularly important for prevention of MRSA exposure when working in barns containing many MRSA-positive animals and high dust burdens. This is most relevant for swine veterinarians but could include clinicians entering veal calf units in some regions. Masks capable of filtering non-oily particulate aerosols with 95% capability (N95 masks) are recommended in human medicine for dealing with airborne contagions such as the severe acute respiratory syndrome (SARS) coronavirus. Although there is currently little indication for routine use of these masks, except in regard to periparturient small ruminants,[28] it is reasonable to expect facilities to at least have a plan in place to implement N95 masks if required. A critical aspect of the use of N95 masks is fit testing and training in their use, since improperly fitted or used masks may confer little or no benefit over surgical masks. Use of powered air-purifying respirators (PAPRs) has become increasingly common in large veterinary teaching hospitals in situations where risks for small-particle transmission of zoonotic agents are recognized.[28,36] PAPRs require a larger initial investment, but they do not require fit testing, and minimal training is required for effective use in controlling airborne hazards.

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Animal Movement and Housing

Housing and movement can have a profound effect on the likelihood of exposure of patients to pathogens. Ideal facilities have no contact between inpatients and outpatients, allow for grouping and segregation of animals with different risks for contagious diseases, prevent direct contact with adjacent animals, reduce the potential for indirect exposures through contact with contaminated environments, and have adequate space so that there is time to properly disinfect all housing and handling environments between use with different animals. This, of course, is completely dependent on early recognition and effective management of patients with higher risks of transmitting contagious diseases.

One major problem frequently encountered in large animal facilities, particularly older facilities, is that construction and design factors often hinder infection control activities. Infection control issues were often not given high priority when designing many older facilities, so a variety of problems are often encountered. These include patient traffic flow problems, requisite mixing of inpatients and outpatients, inability to segregate different cohorts in the population, heavy traffic around important areas (e.g., surgery, isolation), inadequate stall numbers, inadequate isolation facilities, poor ventilation, improper drainage, use of materials that are difficult to clean and disinfect, and design issues that hinder adequate cleaning and disinfection. A variety of challenges come with designing an optimal facility. Many measures used to enhance infection control are inherently inconvenient, and designs that optimize infection control often have a significant impact on building costs and efficient use of the facility. It can be difficult to reconcile ease of operation with the level of infectious disease risk that is desired. However, development and rigorous use of sound infection control protocols can overcome most deficits in design and construction to achieve an acceptable practice standard for minimizing HAIs.

Outpatient Areas

In general, outpatients tend to have a lower contagious disease risk, in terms of both likelihood of shedding infectious agents and their susceptibility to infectious disease. However, “lower” risk does not mean “no” risk, and it is important to design holding areas that minimize contact with other animals while clinicians obtain histories and initial examinations to more clearly categorize

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patients relative to their contagious disease risk. Ideally, outpatients should have little or no contact with inpatient animals and minimal contact with areas visited by inpatients. However, this is often not entirely possible. For example, it is often impractical to build separate areas for diagnostic imaging of inpatients and outpatients. However, the general principle of separation of inpatients from outpatients should be adhered to as much as possible.

Holding stalls in admission and outpatient examination areas may need to house many animals every day. As such, it is important that a sufficient number of stalls is available to allow appropriate cleaning between use, that there are established mechanisms to allow admitting clinicians to identify high-risk cases, and that this information is promptly conveyed to relevant personnel so that extra precautions can be taken with that patient and the environment with which it has been in contact. Environmental precautions may range from routine cleaning and disinfection to restricting use pending high-level cleaning and disinfection, stall cultures, or patient cultures.

Inpatient Areas

Inpatients pose greater challenges than outpatients because they often have significant risk factors for infectious disease acquisition such as comorbidity, dietary changes, antimicrobial treatment, disruption of natural defense mechanisms, surgery, and placement of invasive devices. Compromised inpatients, particularly certain patient groups (e.g., those with GI disease), may be more likely to shed infectious agents such as *S. enterica*. Thus infection control protocols should emphasize the need to reduce the risk of transmission of infectious agents from inpatients to other hospitalized animals and hospital personnel and to minimize risks related to contamination of the hospital environment. A variety of methods can be used to manage this risk, which needs to be balanced with levels of risk aversion and available resources to support infection control efforts.

One method of reducing the risk of disease transmission between individuals and groups (i.e., between animals in different wards or those assigned to different services) is to assign animals to different cohorts and then create physical and procedural separation among the different groups. It is important to group animals based on known or suspected infectious disease status or infectious disease susceptibility, as well as to group and separate animals with different disease syndromes (e.g., respiratory disease or GI disease). It is also

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logical to group and segregate animals that are managed by different clinical services in order to decrease the probability of transmitting infectious agents through indirect contact and to increase the ability to contain a cluster of infections related to one clinical service. Examples include segregating patients managed by surgery and medicine services to help reduce risks for transmission of different contagious agents and managing cattle separately from other large animal patients (especially horses) to reduce risks for *Salmonella* transmission. In general, managing inpatients as smaller cohorts helps to contain transmission risk, thereby decreasing the likelihood of a widespread outbreak in the entire patient population. Creating smaller cohorts of patients with different risks for contagious disease also facilitates the use of varying levels of infection control precautions for different groups.

The design of some facilities does not allow for the separation of different cohorts in different buildings or wards. When physical separation of inpatient groups (excluding isolation cases) is impossible or impractical, animals with different disease risks can still be managed differently in a common ward system. One approach is to designate areas within large wards for different cohorts. Another is to identify animals in different risk categories, applying different levels of infection control precautions, but to allow interspersing of animals from different risk categories in the same area. This is similar to the approach for patient isolation used in most human hospitals, but it is only effective for diseases that are not transmitted by aerosols (i.e., it is not generally effective for contagious respiratory diseases such as influenza or EHV) and where there is a reasonable ability to prevent direct (e.g., nose-to-nose contact over stall walls) or indirect (e.g., cross-contamination from stall cleaning supplies) transmission. Physical separation within a ward can be enhanced by the use of chain or rope barricades to identify and minimize access to patients with elevated contagious disease risk status. A key for successful infection control using this type of system is the absolute need for prominent identification of different groups, having defined protocols for each group, and maintaining effective communication about the disease status of these patients. One system that has been used is color labels to indicate infection control status. For example, colored adhesive dots can be placed on stalls or stall cards of all patients; red dots might indicate animals with a known highly contagious disease, yellow dots might indicate that animals are suspected of having an infectious disease or may have increased risk of acquiring infectious disease, and green dots might indicate that animals are considered to have an average or low

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risk of carrying or acquiring contagious disease agents. This type of system is easy to apply and easy to understand. In addition, more prominent signs can be used to more clearly indicate certain concerns (e.g., *Salmonella,* MRSA, rabies suspect) to all personnel. One consideration with these more specific labels, however, is whether visitors could obtain confidential and sometimes prejudicial information from visible notices.

Isolation of Highest Risk Patients

The most rigorous control of contagious disease hazards requires that transmission potential be absolutely minimized for patients suspected or known to be infected with highly contagious pathogens or pathogens associated with highly consequential diseases. In general, this means that these patients should have no direct or indirect contact with other animals or areas used in the routine care of patients via personnel, fomites, aerosols, or other materials. It also means that human access to these patients and their care environment should be tightly controlled. In general, to achieve this level of isolation, these patients will require housing in a separate, specially designed unit.

Most isolation protocols in large animal medicine focus on a limited number of pathogens. Protocols for large animal facilities tend to focus heavily on animals clinically affected by *S. enterica,* viral respiratory pathogens, and *S. equi,* and more recently on horses with neurologic disease because of the risks related to EHV-1. Whether these protocols are adequate or excessive for control of other pathogens is debatable, and a broader scope is likely required in many facilities. That said, protocols that reduce the risk of transmission of one agent generally reduce the transmission potential of other agents, particularly if there are similarities regarding transmission routes or risk factors for exposure and infection.

Large animal isolation protocols need to consider a variety of issues, including indicators for isolation, cleaning and disinfection, personnel movement and barrier precautions, patient contact and movement, manure disposal, and supply stocking. Defining methods for identifying animals that need to be isolated and establishing specific criteria for handling these animals are critical steps, and these methods must be properly communicated to all individuals associated with patient or facility care. Developing protocols for rapid identification of patients that represent a contagious disease hazard is critical to the success of any infection control program. The best isolation units are not effective if

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unoccupied. Specific disease and syndrome criteria for isolation should be developed to facilitate prompt isolation of appropriate individuals, typically in advance of confirmation of the presence of an infectious agent. Isolated animals should be kept physically separate from the rest of the hospital population at all times if possible. This means that isolation units should be designed so that animals will rarely if ever need to leave the unit, except for an emergency procedure such as surgery. Stocks, examination areas, and scales should be available. A major deficiency of many large animal isolation facilities is the inability to use mechanical hoists and slings to safely manage recumbent, profoundly ataxic patients, which is important because of concerns regarding herpesvirus myeloencephalitis resulting from EHV-1 infections. Ideally, there should be minimal contact of personnel with isolated animals and their stall environment. The ability to monitor patients in isolation using viewing windows or by remote electronic means (e.g., web cameras, closed-circuit video) facilitates the ability to deliver excellent patient care while minimizing risks associated with direct contact.

These units must be strictly managed with specific predetermined protocols in order to reliably manage the risk of transmission. Isolation protocols should be comprehensive and clearly documented in writing. Proper training of all staff, particularly lay staff that may have no background in infectious diseases and infection control, is critical. Standardized protocols for management of isolation units in human health care settings have been published by the CDC.[74] However, similar standardized guidelines have not been established for veterinary medicine, and protocols used at veterinary facilities are highly variable because they are tailored to specific operations and different facility and logistic resources. It is logical for veterinary facilities to consider guidelines that have been developed at other veterinary facilities and in human health care settings when developing their own isolation protocols.

In some situations, housing of potentially infectious animals in an isolation unit is not possible because of patient care issues or limitations in isolation space. As a result, consideration needs to be given to management of higher risk patients within the general hospital environment. This can be done in a few different ways, including grouping those with general risk and applying intermediate isolation techniques to cases that are considered at higher risk of being infectious but not deemed candidates for housing in an isolation unit. In-hospital isolation protocols allow for an increased level of protection but are not a replacement for a proper isolation unit and should not be used solely for

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clinician convenience. Protocols should be developed regarding the handling of animals, the stall, and the area around the stall. Animals that are isolated in the hospital should not leave stalls unless they are being moved for required procedures. If movement is necessary, feet should be cleaned and disinfected using appropriately diluted chlorhexidine solutions. The potential for environmental contamination can be reduced by having a person follow the animal with a bucket to collect any feces that may be passed during transit. Traffic areas should be promptly cleaned and disinfected. Protective barrier clothing such as full waterproof coveralls or full-length waterproof gown, gloves, and dedicated footwear or boot covers should be worn for any contact with the patient or its environment. The area around the stall entrance should be considered potentially contaminated and disinfected routinely (at least three to four times per day). Disinfectant footbaths or footmats used at stall doors can reduce bacterial contamination of footwear.[66-68] Attention should be paid to the pattern of water drainage from the stall and in the area. If water runs from the stall to the breezeway or runs down the breezeway past the stall, then housing potentially or known infectious animals in the stall may be inappropriate. Animals should not be allowed contact with neighboring animals. Barriers may be required if solid walls are not present on all sides. Specific protocols should be developed for cleaning in-hospital isolation stalls. These stalls should be cleaned last, personnel cleaning the stalls must wear protective gear, and items used to clean the stalls must be disinfected immediately after use.

Isolation guidelines for human medicine target the prevention of five different types of transmission: contact transmission, droplet transmission, airborne transmission, common vehicle (fomite) transmission, and vector-borne transmission.[56-58,72-74]

- Contact transmission is typically the most important mode of transmission and involves transmission of infectious agents to patients by caregivers or directly between patients. In large animal medicine, this could include situations such as transfer of MRSA from a colonized person to an animal under his or her care, transmission of *S. equi* between horses by personnel,

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or direct transmission of viral respiratory pathogens between horses in adjacent stalls that can have nose-to-nose contact.

• Droplet transmission involves transmission of infectious agents in relatively large fluid droplets generated by coughing, snorting, or vocalizing. These large droplets do not remain suspended in the air for long periods, nor are they transmitted long distances; therefore special air handling is not required. An example of this is transmission of bacterial agents from a coughing horse to another horse stabled in relative proximity. An extrapolation to veterinary context might also include transmission of surface contaminants during environmental cleaning processes with water under high pressure.

• Airborne transmission involves agents that can be transmitted effectively in small particles (5 μm or smaller) that can remain suspended in air and travel greater distances. Special air handling is required to control this route of transmission. Equine influenza can be spread through a barn via the airborne route over extended distances.

• Common vehicle or fomite transmission involves infection caused by contact with contaminated items such as feed bins, muzzles, twitches, thermometers, and other medical equipment.

• Vector-borne transmission involves vectors such as

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mosquitoes, flies, and rodents. This may be of particular concern in some areas with reportable vector-borne diseases such as equine infectious anemia.

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Surveillance

HAIs occur in all veterinary facilities; if HAIs are never recognized, it is because surveillance has been ineffective at detecting them. All comprehensive infection control programs should have a surveillance component because the information collected serves as sensory input to guide ongoing efforts so that they are focused and efficient. Without surveillance information, infection control programs will be guided more by emotions and opinions than by data and evidence. Infection control programs will have much greater acceptance and utility if, in the long term, decisions are based on objective information about infection and disease occurrence at a specific hospital. Useful surveillance goals for infection control programs include developing a system to allow prompt identification of contagious disease threats, evaluating the effectiveness of infection control practices, measuring personnel compliance with infection control procedures, providing a basis for logical infection control decisions, and stimulating efficient and economical use of resources.

Surveillance Options and Strategies

Theoretically, an optimal surveillance system would allow real-time detection of all HAIs. However, pursuing this goal would be unrealistic for reasons of practicality and would be an inefficient use of resources. Although all HAIs are important relative to patient well-being, some are more common and more important than others. This is because the impact on patient health is much more significant for some diseases, as well as because highly contagious diseases are more likely to affect a larger number of patients. Further, regardless of whether there is a contagious etiology, HAIs that affect a large number of patients can have a tremendous impact on the cost of care and the overall burden of morbidity for patients. Focusing surveillance on these high-impact HAIs is logical, as a greater proportion of these occurrences are also likely to be preventable in comparison to more sporadic problems. Further, experiences with infection control in human health care settings have shown that it is possible to be more cost and effort efficient if high-risk, high-frequency, and high-cost problems are targeted.

Determining which specific HAIs were likely preventable is a difficult and potentially contentious task. Rather than focusing on individual infections,

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infection control efforts in human hospitals have benefited by focusing on comparing rates of infection and estimating the proportion that might be preventable by referencing some accepted standard. During the past 30 years, human hospitals have made great efforts to characterize rates of HAIs that can be expected even under the best of circumstances. By estimating rates for these "nonpreventable" infections, it has then been possible to identify hospitals with higher-than-average rates for HAIs. Because of the tremendous differences among hospitals and patient populations, it has become standard to focus on more restricted, high-risk patient groups for which there is better comparability (e.g., neonatal or cardiac intensive care patients). It is also far more feasible to perform surveillance for HAIs in these high-risk patient subgroups than it is in the general population, which has much lower risks of HAIs. Performing surveillance with standardized case definitions[20] over time allows identification of specific risk factors, which could then be used to prospectively refine management of patients (i.e., a high-risk patient could be identified and subjected to more aggressive control measures as a preventive strategy). Unfortunately, there is very limited information available on rates of disease related to HAIs at individual hospitals let alone estimation of rates in multiple hospitals; this information would be required in order to obtain interhospital comparisons that would be useful in identifying latent problems at specific facilities. Although making standardized comparisons between hospitals would require tremendous cooperative effort, individual facilities could make significant progress in identifying important changes in rates for HAIs if efforts were made to benchmark their infection rates over time.

When designing a formal surveillance effort to aid infection control programs, it is important to tailor efforts to a specific facility or practice. A wide variety of design possibilities are available for hospital surveillance systems, and the specific focus and methods should be carefully matched to the needs and resources of each establishment. Diseases that are the highest priority for surveillance must be specified along with standardized case definitions that will be used to identify these cases. Efforts may target disease caused by HAIs that are related to specific procedures or organ systems, or just as commonly they may target specific infectious agents of interest. For example, systems might be established to look for surgical or intravenous catheter site infections, methods may target surveillance for respiratory tract infections, or efforts may specifically target detection of infections with specific etiologic agents such as *Salmonella* or MRSA. It must also be determined whether clinical disease will

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be the outcome of interest or whether it is important to look for animals with subclinical infections. This will generally vary by disease and likely will be determined by the natural history or pathophysiology of the disease (i.e., Does shedding occur in the absence of clinical signs? Is there a chronic carrier state? What risk factors are related to the likelihood of shedding?). Further, if clinical disease is the outcome of interest, it is important to consider whether the case definition will include some type of etiologic confirmation, or whether diagnoses will be syndromic in nature and based on clinical signs (i.e., surgical site infections could be defined based on recovery of a bacterial agent in the presence of clinical disease, or it could be defined solely on the presence of a predetermined combination of clinical signs such as erythema and drainage). As discussed, another consideration is whether surveillance will target specific subgroups of the population or include all patients. The major benefit of targeted surveillance is that it decreases the cost and effort of data collection, but the trade-off is the inability to detect potential problems in the patients that are not being monitored. However, increasing awareness of infection control methods for common or more important diseases generally has the effect of increasing awareness and compliance with control measures that relate to other potential HAIs. It also must be determined whether surveillance will be active (i.e., patients with HAIs will be actively sought out) or whether passive surveillance (i.e., reporting is voluntary) is acceptable and appropriate. In general, active surveillance will be used only in targeted subpopulations and only to look for more common and more important diseases, and syndromic surveillance should be more heavily relied on when the targeted population is larger or as a supplement to culture or etiologically based surveillance efforts.

Another important consideration is how data will be gathered for this effort. Significant personnel compliance is needed for active culture-based surveillance of large numbers of patients. Similarly, any type of chart review system for benchmarking expected rates of HAIs requires a significant time commitment. Surveillance efforts are greatly aided by computer-based search mechanisms, and it is strongly recommended that practices consider using electronic medical record systems to maximize the ability to perform surveillance and that medical record systems be designed to facilitate collection and recovery of infection control–related data. For example, something as simple as being able to monitor the number of febrile or leukopenic patients daily could be extremely powerful as an aid to infection control efforts. Even financial databases can be useful in surveillance efforts. For example, they may be very useful for benchmarking

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antimicrobial prescriptions or specific procedures, such as intravenous catheterization, surgeries, or submission of samples for diagnostic tests.

Generalized, nontargeted surveillance to look for potentially pathogenic bacteria that can be found in health care environments is widely considered of no real benefit to infection control efforts. This includes sampling surfaces in surgical theatres to catalog the different bacteria that can be found. However, there is utility in targeted environmental cultures where there is biological plausibility as to their relevance and a plan to act on the results (and where the action differs if results are positive or negative). For example, monitoring for contamination of veterinary hospitals with *Salmonella* has been a useful adjunct to patient surveillance in comprehensive infection control programs at veterinary hospitals.[36,64,76,77] In addition, in some situations, such as when attempting to control ongoing outbreaks, there is no substitute for culturing the hospital environment to detect important environmental reservoirs.[1,3,4] Use of electrostatic household wipes has been extremely useful for sampling to detect *Salmonella* in routine surveillance as well as in the face of outbreaks.

The use of rapid and sensitive diagnostic tests is particularly important for the management of highly contagious diseases. As such, polymerase chain reaction (PCR) and antigen detection tests, which can be much more rapid than traditional culture systems for bacteria and viruses, have become more widely used for both patient and environmental surveillance efforts. However, these tests cannot fully replace culture-based assays because analysis of microbes is essential to fully understand the epidemiologic implications for each recovery. For example, if on a single day three patients were found to be shedding *Salmonella* after use of PCR testing, it would not be possible to know whether these were unrelated events. In contrast, if shedding were detected using culture and the *Salmonella* isolates were then shown to be from different serogroups, this would make it unlikely that shedding was related to exposures from a single source. In some situations, it may be logical to use both a rapid and a culture-based assay to maximize both speed and ability to perform epidemiologic investigations. Availability of qualified laboratories, rapidity of testing, and costs all have to be considered and balanced.

Monitoring Personnel Compliance

Success of an infection control program depends on universal participation within a hospital or other animal care facility that is born from a well-developed

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sense of responsibility among individuals. Actively engaging all personnel in infection control programs becomes increasingly difficult as organizations become larger and more complex. Unfortunately, the most cautious actions of a majority of personnel can be for naught if even one individual neglects to take appropriate precautions under just the right (wrong) circumstances. Although it is very important for administrators to engage in surveillance to detect systematic noncompliance with policies, it is just as important to empower and expect all personnel to monitor for individual acts of noncompliance. Remembering that most noncompliance is born from a natural tendency for people to revert to the most convenient practices, which are not necessarily the most “safe” practices from the infection control perspective, it is important to couple surveillance efforts with education so that all personnel fully understand why they are being inconvenienced. In addition, providing useful feedback and communication about issues that arise in the hospital will help to reinforce the need for compliance. For example, monitoring and reporting bacterial shedding or environmental contamination detected as a part of surveillance programs can help to keep hospital personnel aware of the potential hazards of reduced infection control efforts.

Measurements Related to Health and Disease

Although outcomes for individual animals may be the most important bottom line for many clinicians, it is important to remember that infection control by its very nature often has a larger population-based perspective. Thus although diagnostic test results for an individual animal obviously have great relevance for that animal, for the population a positive test result may not have great meaning unless it is interpreted contextually. It is therefore critical to remember that in addition to tracking numerators (e.g., numbers of infections or animals with disease caused by HAIs), some type of denominator information is needed to provide relevance over time or among different subpopulations. Examples of relevant denominators are patient admission totals for a given period, patient-days of hospitalization, numbers of procedure events such as surgeries or catheter placements, and numbers of samples submitted for culture.

Developing a Comprehensive Surveillance Strategy

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As mentioned, it is unrealistic to expect to detect all occurrences of HAIs or all animals shedding agents of interest through any hospital surveillance system. Rather, veterinarians should work toward developing strategic surveillance programs that will allow reliable estimation of rates for important events if they occur with any significant frequency, as well as rapid detection of unexpected important events. It is likely that a mix of strategies described previously will be used for the various agents and disease problems. For example, if *S. enterica* shedding occurs at some low-level yet regular frequency in a hospital (e.g., 3% of all hospitalized equine patients) and is considered an important potential hazard for other patients, it is reasonable to develop an active surveillance program that allows detection of clinical and subclinical shedding of *Salmonella* as a patient management tool and detection of important trends over time so that outbreaks of HAIs can be rapidly identified and stopped. In contrast, *Clostridium difficile* or EHV-1 may not have been detected with any regularity in patients at a particular hospital or may be more difficult to actively monitor because of available testing methodologies, yet they may still be considered important because of their significance as pathogens and their potential for contagious spread. For these pathogens, it may be more reasonable to use a reliable passive surveillance strategy to call attention to patients when clinical signs or diagnostic testing indicates that these agents may be present. In addition, maintaining some level of surveillance for compliance with infection control procedures and policies is necessary to ensure that an infection control program is functioning properly.

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Education and Awareness

Education of all personnel regarding infectious disease hazards to themselves, patients, and veterinary practices is essential to the long-term success of any infection control program. Successful programs are critically dependent on all personnel knowing and following procedures and policies used for control of contagious disease transmission in a practice. Although this type of information can be acquired over time through personal experience, this is an inefficient and unreliable method for disseminating critical information.

Written Protocols

The first step to ensuring that necessary information is disseminated to all personnel is to document policies and protocols in writing. This effort is valuable for all veterinary practices but is especially critical in larger and more complex veterinary hospitals. This relatively simple step has many benefits. First, documenting procedures requires a thorough review, which by itself is beneficial. Second, documenting policies and protocols in writing imbues the infection control program with a sense of purpose and commitment. Third, documenting procedures helps to ensure consistency in application across all personnel as well as over time. As discussed, all infection control procedures are inherently inconvenient, and the natural tendency is for personnel to drift toward more convenient ways of performing activities that may not provide an adequate degree of protection against HAIs. Fourth, documenting policies demonstrates a degree of due diligence, which is useful from a legal liability standpoint relative to the occurrence of HAIs or zoonotic infections.

Once these protocols have been documented, it is important to require their use as a reference and to make a specific effort to educate personnel about the policies and procedures. A written document serves no purpose if it is not used. Veterinarians and other personnel are busy people, and the immediacy of caring for patients and clients can easily overwhelm seemingly mundane tasks such as studying written protocols. A valuable aid in this process is to have some type of training program. This does not necessarily mean formal presentations; it is valuable to organize a meeting of all personnel for the sole purpose of discussing infection control issues. Although this seems logical, training in infection control practices is not a universal occurrence even in teaching hospitals. In a survey of

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teaching hospitals at AVMA-accredited institutions, only 42% (16 of 38) of responding institutions reported that they required personnel (students, technical staff, veterinarians) to participate in some type of formal training program regarding infection control and biosecurity, and only 7 of these institutions provided more than a single training exposure.[16]

Training Programs

It is also important to consider the differences in training and experience among personnel. By their nature, infection control programs are dependent on adherence to important protocols by all personnel regardless of their position description. Nonveterinarians are invaluable members of most veterinary practice teams, and even personnel who may never touch patients but instead serve as receptionists or have the single specific task of cleaning are absolutely critical for the success of infection control programs and may be exposed to infectious agents on periodic or routine bases. Veterinarians sometimes underappreciate how their specialized training has provided them with a broad appreciation for basic principles of contagious disease transmission and control. Without the experiences of a veterinary education, many personnel simply do not have the same understanding of contagious diseases. Telling people to follow certain rules without them understanding why the rules are necessary leads to inevitable compliance problems. Without a thorough understanding of why inconvenient infection control practices are needed, these practices will be discarded over time as seeming illogical. To help ensure uniformity of education among all personnel, some hospitals have developed training documents and require that new employees pass a written evaluation before they are permitted to begin work. Regardless of the type of training program, documentation of that training (and ideally an outcome measure such as a quiz) is important from a due diligence standpoint. Simply telling people to read a manual does not likely constitute adequate training.

Another important aspect of education and awareness is to instill a need to lead by example and to empower all personnel to hold anyone else in the practice accountable for their actions. The hierarchy in authority that is often used in the delivery of patient care (e.g., veterinarians at the top of the hierarchy, personnel without formal training at the bottom) can interfere with optimal infection control. A common non sequitur related to infection control is that those with the most training can be the persons least likely to adhere to important

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policies. This is true in both human and veterinary medicine, as has been repeatedly shown relative to hand hygiene.[39,40] In numerous studies conducted in a variety of settings, physicians and residents have been shown to be significantly less likely than nurses to adhere to appropriate hand-hygiene protocols. Observations in the veterinary setting suggest that the same trends are true for hand hygiene as for appropriate use of barrier nursing precautions. All people pick up cues for behavioral expectations from their surroundings. If personnel who clearly understand the importance of preventive measures (physicians and veterinarians) such as handwashing fail to routinely follow best infection control practices, there is little hope that trainees and laypersons will routinely trouble themselves to habitually use an important albeit inconvenient practice. Further, it seems that the more respected position a person holds in a practice, the more likely it is that acts of noncompliance by that individual will be influential on the actions of others. Students in teaching hospitals can watch classmates correctly follow infection control policies throughout the day yet be more influenced to be noncompliant by observing the single time a senior clinician ignores a practice guideline.

One way to improve compliance and counter the influences noted previously is to use disseminated enforcement by actively encouraging all personnel to call attention to noncompliance. Once it has been determined which procedures are required for a particular situation and this has been documented, there is no reason why nontechnical staff should be any less capable than a veterinarian in determining whether a procedure has been followed correctly. It is important that this community enforcement be empowered by all in a spirit of friendly camaraderie and team building. Some hospitals have noted significant improvements in compliance using this method of enforcement and have even used competitions among “teams” with the incentive of agreeing that the loser must pay a reward to the other team (e.g., pizza lunch).

Zoonosis Awareness

Every patient, healthy or sick, carries multiple potentially zoonotic pathogens in their commensal microbiota. Some patients pose higher risks because of additional pathogens, shedding of higher levels of common opportunists, or disease or behavior factors that increase the risk of transfer of pathogens.

One of the most important objectives for an infection control program is to protect personnel and clients from illness associated with zoonotic pathogens.

This is another area in which veterinarians sometimes forget that not all personnel understand hazards or how to take appropriate actions to protect themselves. Without this knowledge, personnel may take inappropriate risks or may overreact to perceived hazards in a low-risk situation. Most of the zoonotic disease prevention program focuses on routine practices that should be used on all patients because of the potential for shedding of pathogens by any patient, the potential for shedding of certain pathogens prior to the onset of clinical signs, and the fact that routine practices form the core preventive measures. Understanding and complying with those practices, and knowing when and how to use enhanced practices, are the main areas of emphasis for zoonotic disease prevention. Table 46.3 provides a summary of some zoonotic pathogens that may be transmitted from domestic large animals through occupational activities of veterinary personnel.

TABLE 46.3

Zoonotic Diseases of Domestic Large Animal Species That Are Transmissible Through Occupational Exposures to Veterinary Personnel[a]

Agent/Disease	Susceptible Animal Species	Clinical Signs in Humans	Methods of Transmission to Humans	Personal Protection for Veterinary Personnel
Bacillus anthracis (Anthrax) • Gram-positive, spore-forming, anaerobic bacterium	All species	There are three clinical forms of anthrax in humans: cutaneous, pulmonary, and gastrointestinal. Cutaneous infections manifest as skin papules and vesicles with associated cellulitis that evolve into a characteristic black eschar (scab). Pulmonary anthrax initially resembles upper respiratory infection and can evolve into severe respiratory compromise and death. The gastrointestinal form results in gastroenteritis with vomiting and dysentery.	Cutaneous transmission occurs through direct contact. Respiratory transmission occurs through inhalation of bacteria or spores. Gastrointestinal transmission results from eating undercooked contaminated meat.	Enhanced barrier precautions, including eye protection and respiratory protection using a minimum of an N95 mask, should be used when handling affected animals or working in their environments. Blood and secretions from anthrax suspects should not be allowed to contact skin. Necropsy should not be performed on animals that have died from anthrax.
Bordetella bronchiseptica	Pigs, dogs, cats,	Disease is rare in humans and occurs predominantly	Respiratory infection through	Immunocompromised individuals should avoid

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• Gram-negative bacterium	rabbits, horses	in immunocompromised individuals, resulting in pneumonia and upper respiratory tract infections.	contact and droplet routes.	contact with mucous membranes and nasal discharges of susceptible animal species. Barrier precautions and adherence to good hand-hygiene protocols reduce the risk of exposure.
Brucella melitensis, *Brucella abortus*, *Brucella suis*, *Brucella canis* (Brucellosis) • Gram-negative bacterium	Cattle, sheep, goats, camelids, pigs, horses, dogs, other species	Flu-like illness, gastrointestinal signs occur frequently in adults but less often in children; irritability, insomnia, mental depression, and emotional instability sometimes develop. Recurrent fevers are the hallmark of chronic infections in addition to fatigue, arthritis, and cardiac and other complications.	Contact, droplet, or aerosol exposure to infected fetuses, placenta and placental fluids, or infected tissues; contact with contaminated fomites. Ingestion of unpasteurized milk or milk products.	Avoid contact with fluid or tissues from abortions. Use of barrier precautions. including gloves, protective eyewear, and a minimum of N95 respiratory protection. is recommended when performing obstetric procedures or performing necropsies on high-risk animals.
Burkholderia mallei (Glanders and Farcy) • Gram-negative bacterium	Horses and other equid species	Flu-like symptoms, photophobia, lacrimation, diarrhea, septicemia, pneumonia, ulcerative and suppurative cellulitis, lymphadenopathy, splenic and hepatic abscesses.	Direct contact or droplet exposures to skin or mucous membranes; prolonged contact with infected animals is generally required for infection.	Enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are warranted when working with infected animals.
Campylobacter jejuni and *Campylobacter coli* • Spirochete bacterium	Cattle, sheep, goats, camelids, pigs, poultry, dogs, cats, other species	Disease varies from mild gastrointestinal distress that resolves within 24 hours to fulminating or relapsing colitis. Signs may include watery diarrhea, fever, nausea, vomiting, abdominal pain, headache, and muscle pain. Feces may contain frank blood. The acute symptoms usually diminish in 2-3 days and resolve in 7-10 days. Complications are rare but include Guillain-Barré syndrome, a disorder of the nervous system.	Fecal-oral transmission after contact with infected animals or their environments is a suspected but not well-documented risk factor. Ingestion of contaminated water and food, including undercooked poultry or meat, raw milk.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.
Clostridium difficile • Gram-positive, spore-forming, anaerobic bacterium	Pigs, horses, cattle, dogs, cats, other species	Colitis leading to fever, abdominal cramps, diarrhea or dysentery, dehydration, and electrolyte imbalances. Rarely, severe colitis can lead to life-threatening	Oral-fecal exposure through contact or droplet exposure to infected animals or their environments.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments; personnel should use respiratory

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		complications such as toxic megacolon, peritonitis, and colonic perforation.		protection when cleaning practices may produce droplet exposure. Avoid eating or drinking near animals or their environments.
Clostridium perfringens • Gram-positive, spore-forming, anaerobic bacterium	All species	Wound infections can result in gas gangrene with accompanying fever, swelling, and erythema of affected area, systemic signs as disease progresses. Oral exposure is associated with abdominal cramps, diarrhea, and in rare cases necrotic enteritis and septicemia.	Wound contamination through contact or droplet exposure, ingestion of food contaminated with large numbers of bacteria, potentially oral-fecal exposure through contact or droplet exposure to infected animals or their environment.	Routine use of protective outer garments or dedicated attire when working with animals or their environments. Strict adherence to good hand-hygiene protocols and appropriate cleaning and management of wounds.
Coxiella burnetii (Q fever) • Gram-negative, spore-forming, intracellular bacterium	Primarily sheep, goats, cattle, but also camelids, horses, dogs, cats, other species	Symptoms of Q fever include fever, chills, headache, fatigue, and chest pains. Pneumonia and hepatitis can occur in serious cases. In pregnant women, infections can cause premature delivery, abortion, and infection of the placenta. In people with preexisting heart valve disease, endocarditis may occur.	Contact, droplet, or aerosol exposure to urine, feces, milk, and especially fetuses and placental tissues from infected animals. Respiratory exposure to contaminated dust, occasionally ingestion of unpasteurized milk or milk products.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Caution is warranted when handling tissues or fluids of infected animals or aborted fetuses. Consider use of respiratory protection when performing obstetric procedures on high-risk animals. Enhanced barrier precautions, gloves, a minimum of N95 or powered air-purifying respiratory protection and strict adherence to good hand-hygiene protocols are warranted when working with periparturient small ruminants.
Cryptosporidium parvum (Crypto) • Apicomplexan protozoan parasite	Ruminants, pigs, horses, poultry, dogs, cats, other species	Gastrointestinal disease, including signs of abdominal pain, nausea, anorexia, and profuse watery diarrhea. Severe infections can require hospitalization for fluid therapy and electrolyte imbalances. The disease is usually self-limiting but may be chronic and debilitating in immunocompromised individuals.	Oral-fecal transmission primarily through contact with infected animals or their environments, but also through droplet exposures during cleaning.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments; personnel should use respiratory protection when cleaning practices may produce droplet exposure. Avoid eating or drinking near animals or their environments.
Dermatophilus	Cattle,	Pustular desquamative	Direct contact with	Use gloves when handling

congolensis • Gram-negative, actinomycete bacterium	sheep, goats, camelids, horses, rarely pigs, dogs, cats, other species	dermatitis.	lesions on affected animals.	affected animals; strict adherence to good hand-hygiene protocols.
Erysipelothrix rhusiopathiae (Erysipelas in pigs, erysipeloid in humans) • Gram-negative, facultative anaerobic bacterium	Pigs, other species	Characteristic cellulitis with raised red lesions, edema, and intense pruritus. Skin infections can progress to involve other cutaneous sites and also rarely to systemic infections with flu-like illness, septicemia, and arthritis.	Primarily via direct contact with infected animals, contamination of skin wounds. There are rare reports of transmission through ingestion of undercooked pork.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be used when working with clinically affected animals. Avoid eating or drinking near animals or their environments.
Shiga toxin–producing *Escherichia coli* (STEC, including O157:H7 and other serogroups) • Gram-negative bacterium	Cattle	Fever, enteritis, diarrhea, or dysentery. In children under 5 years and the elderly, infections can cause hemolytic uremic syndrome (hemolysis and kidney failure).	Oral-fecal transmission via contact or droplet exposure through exposure to cattle or their environment or through ingestion of contaminated water and food.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.
Francisella tularensis (Tularemia) • Gram-negative bacterium	Sheep, rabbits, cats, other species	Flu-like illness, rashes, nausea, splenomegaly, papular or ulcerative lesions at site of cutaneous exposure, lymphadenopathy and ulcerative lymphadenitis, pleuropneumonia from inhalation or hematogenous spread; ingestion is associated with enteritis, stupor, and delirium.	Contact, droplet, or aerosol exposure to tissues or secretions of infected animals, ingestion of tissues from infected animals.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments are warranted when handling tissues or fluids of infected animals or aborted fetuses. Gloves, eye protection, and a minimum of N95 respiratory protection should be used when performing obstetric procedures on high-risk animals.
Foot-and-mouth disease virus • Nonenveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, pigs, other species	Infection in humans is very rare; headache, fever, vesicular lesions on the hands or feet or in the mouth.	Contact, droplet, or aerosol exposure to infected animals.	When working with infected animals, enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols.
Giardia duodenalis • Flagellated protozoal	Ruminants, pigs, poultry, dogs, cats,	Gastrointestinal disease, including signs of diarrhea, intestinal gas, stomach cramps, and	Oral-fecal transmission through contact with infected	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire

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parasite	other species	nausea. A significant proportion of patients develop lactose intolerance while infected. The illness usually lasts 1 to 2 weeks, but chronic infections can last months to years.	animals or their environments or through ingestion of contaminated water or food.	when working with animals or their environments. Avoid eating or drinking near animals or their environments.
Hendra virus • Enveloped, single-stranded RNA virus	Horses, other species	Fever, lethargy, respiratory distress, neurologic signs including headache and disorientation.	Occupational contact with infected horses or their tissues.	Classified as a Biosafety Level 4 agent; contact with infected animals or their tissues should be avoided unless personnel are specifically trained to work with this agent.
Influenza virus • Enveloped, single-stranded RNA virus	Pigs, aquatic fowl; influenza viruses are generally host restricted.	Cross-species infection with influenza strains is unusual under normal circumstances but has been rarely documented with swine and avian influenza viruses resulting in fever, malaise, upper respiratory illness, and pneumonia.	Close contact with infected pigs leading to respiratory exposure through contact, droplet, and aerosol routes.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. When working with infected animals, use enhanced barrier precautions, gloves, eye protection, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols.
Leptospira spp. (Lepto) • Spirochete bacterium	All mammals appear to be susceptible to at least one species of *Leptospira*.	Severity of illness varies greatly; signs include flu-like illness with fever, chills, headache, and severe myalgia. Aseptic meningitis can occur, and 5% to 10% of cases may be associated with multiple organ failure.	Skin or mucous membrane contact with urine or less commonly with blood and tissues of infected animals, ingestion in contaminated water or food.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. A minimum of N95 respiratory protection may be appropriate if droplet exposure to urine is likely. Avoid eating or drinking near animals or their environments.
Listeria monocytogenes • Gram-positive bacterium	All species	Contact can result in papular lesions on hands and arms. Most commonly, flu-like illness and gastroenteritis. Less commonly, infections can result in a mononucleosis-like syndrome (glandular listeriosis) or in fetal infection, abortion, stillbirth, neonatal septicemia, or meningoencephalitis. Meningoencephalitis is also noted in the elderly	Immunosuppression greatly increases the risk of infection. Direct contact of skin or mucous membranes with infectious material, feces, or contaminated soil. Respiratory exposure to secretions from infected animals via droplet or aerosol routes. Oral-fecal	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments, especially among immunocompromised people. Avoid eating or drinking near animals or their environments. Enhanced barrier precautions, gloves, eye protection, a minimum of N95 respiratory protection, and strict adherence to good hand-hygiene protocols are

		and immunocompromised.	exposures through contact, droplet, aerosols, or ingestion of contaminated foods.	warranted when performing obstetric procedures on high-risk animals or when handling aborted fetuses or tissues and fluids of infected animals.
Mycobacterium tuberculosis, *Mycobacterium bovis*, *Mycobacterium avium* complex, non-tuberculous mycobacteria • Acid-fast bacterium	All species	Signs depend on the organ system involvement. General signs of infections include anorexia, weight loss, fatigue, fever, and chills. Signs of pulmonary infection include coughing and hemoptysis. Skin lesions are characterized by ulcers, papular lesions, and suppurative lesions. Signs of other organ involvement relate to the specific system.	Inhalation and oral exposure through respiratory droplet and aerosol transmission from infected animals, oral or cutaneous exposure through contact with infected tissues or contaminated surfaces, ingestion of raw or unpasteurized milk and milk products.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. A minimum of N95 respiratory protection may be appropriate if working with infected animals with clinical pulmonary disease or if performing necropsy.
Nipah virus • Enveloped, single-stranded RNA virus	Pigs, other species	Fever, neurologic signs including drowsiness, headache, disorientation and confusion, shortness of breath, and coughing.	Occupational contact with infected pigs.	Classified as a Biosafety Level 4 agent, contact with infected animals or their tissues should be avoided unless personnel are specifically trained to work with this agent.
Parapox viruses (Orf virus and bovine papular stomatitis virus [BPSV]) • Enveloped, double-stranded DNA virus	Sheep and goats (Orf virus), cattle (BPSV)	Papular lesions at areas of contact (usually hands or arms). Lesions can be 1 cm in diameter, and surrounding tissues often become swollen and painful.	Contact with lesions on animals, scabs, or contaminated objects.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be worn when examining mouths of animals suspected of being infected.
Rabies virus • Enveloped, single-stranded RNA virus	All mammals	Encephalitis with accompanying behavioral and physical signs.	Bite injuries from infected animals, contact with infected animals, and contact with bats or their habitats are the most common methods of human exposure. Contact, droplet, and aerosol exposure to saliva and respiratory secretions of infected livestock is also thought to be a possible method of infection but is not	Complete isolation of animals suspected of infection, minimizing contact with personnel. When necessary to examine or manage suspect animals, use enhanced barrier precautions, gloves, a minimum of N95 respiratory protection, eye protection, and strict adherence to good hand-hygiene protocols. Personnel that may be exposed to rabies should be vaccinated in accordance with CDC recommendations.[60]

			well documented.	
Rift Valley fever virus • Enveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, other species	Flu-like illness, photophobia, neck stiffness, and vomiting, which may progress in severe cases to one of three characteristic syndromes: eye disease, meningoencephalitis, or hemorrhagic fever. Retinal lesions are the prominent sign associated with eye disease.	Contact with blood, other body fluids, or tissues of infected animals. Accidental inoculation through sharps injuries or by inhalation of droplets or aerosols. People may also become infected by mosquitoes or possibly from ingestion of raw milk.	Extreme caution should be taken when working with animals during epidemics. An inactivated vaccine has been used experimentally to protect veterinary and laboratory personnel at high risk of exposure. Enhanced barrier precautions, gloves, eye protection, and a minimum of N95 respiratory protection are strongly recommended when working with high-risk animals or their tissues. Universal precautions should be taken when obtaining and processing specimens from patients. Samples should be handled only in laboratories by trained staff and processed in suitably equipped laboratories. Control of the mosquito vectors and use of personal protection are important.
Rhodococcus equi • Gram-positive facultative intracellular bacterium	Horses, also found in feces of sheep and cattle	A problem with growing recognition, infections in immunocompromised people commonly lead to life-threatening chronic, progressive, granulomatous pneumonia. In contrast, infections are very rare in immunocompetent people and are typically less severe.	Regular contact with horses is a documented risk factor for infection, presumably through oral-fecal exposure via direct contact or droplets, although there is often no documented direct exposure to horses.	Immunocompromised people working with horses should adhere to good hand-hygiene protocols and routinely use protective outer garments or dedicated attire when working with animals or their environments. Avoid eating or drinking near animals or their environments.
Ringworm (*Microsporum* and *Trichophyton* spp.) • Fungi	Cattle, horses, dogs, cats	Characteristic circular, well-circumscribed, red lesions that are pruritic. In immunocompetent people, infection is limited to the keratinized layers of the skin and hairs. In immunocompromised people, infections may extend to deep tissues or become systemic.	Direct contact with lesions on affected animals or objects that have contacted affected areas.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or their environments. Gloves should be worn whenever working with animals known to have dermatophytosis.
Salmonella enterica • Gram-negative bacterium	All species	Flu-like illness, gastroenteric disease, diarrhea or dysentery, septicemia.	Oral-fecal transmission through contact with infected animals, their	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with animals or

			environments, contaminated items or through ingestion of contaminated water or food.	their environments. Enhanced barrier nursing precautions are needed when working with clinically affected animals. Avoid eating or drinking near animals or their environments.
Staphylococcus aureus (methicillin resistant, MRSA) • Gram-positive bacterium	Horses, pigs, dogs, cats, other species	*S. aureus* commonly colonizes the anterior nares and other sites without causing clinical signs. Infections most commonly involve skin and soft tissues, either as a primary infection or by infecting cuts or other skin injuries, including sites of intravenous injection or catheterization. Infections of the respiratory tract and urinary tract are also noted. The risk of infection may be increased in immunocompromised people. Skin infections most commonly result in swollen, painful, erythematous lesions that can often be purulent.	Direct contact with colonized or affected animals; droplet or aerosol exposure to discharge from infected sites.	Strict adherence to good hand-hygiene protocols and routine use of protective outer garments or dedicated attire when working with horses or pigs. Enhanced barrier nursing precautions and gloves should be required when working with animals known to be colonized or infected. Cuts and abrasions should be kept bandaged and disinfected regularly.
Streptococcus suis	Pigs	Meningitis, septicemia, hearing loss, endocarditis, and arthritis.	Contact with pigs or their environments; infection risk is likely enhanced via skin wounds, mucous membrane exposure to blood or secretions from infected pigs, eating raw or undercooked pork products.	Protective clothing and gloves should be used when handling live pigs or carcasses. Strict hygiene should be observed when butchering pigs. Skin wounds should be kept clean, covered, and protected when working with pigs or carcasses. Avoid eating undercooked pork, especially in regions where *S. suis* zoonoses are common.
Vesicular stomatitis virus • Enveloped, single-stranded RNA virus	Cattle, sheep, goats, camelids, pigs, horses, other species	Infections in humans are very rare and typically result in flu-like symptoms. Less commonly, oral vesicles and cervical lymphadenopathy can be noted.	Mucosol exposure via direct, droplet, or aerosol exposures with clinically infected animals.	Enhanced barrier nursing precautions and gloves can be used when working with animals known to be colonized or infected. Eye protection and N95 respiratory protection may also be warranted when examining or treating lesions.

[a]This is not a complete list of all zoonotic diseases; less common diseases and those with vector-borne or solely foodborne routes of transmission are not included.

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Personnel With Increased Risk of Infection

All personnel are at some risk of zoonotic infection, through being at increased risk of either disease following exposure to a pathogen or serious disease compared to lower risk individuals. Some individuals may be at increased risk because of concurrent disease (e.g., immunosuppressive disorders, skin diseases or lesions), treatments (e.g., immunosuppressive therapy, antimicrobial therapy), age, or pregnancy. Being “immunocompromised” or “high risk” is not a single state, and there can be marked differences in the degree of increased susceptibility as well as the risk posed by particular pathogens. Quantifying the degree of risk is difficult, and specific information about risks posed by certain conditions and the effect of preventive measures is generally lacking. In general, preventive measures are the same for high-risk individuals, as strict compliance with core infection control practices is likely the most important factor. In some situations, use of enhanced barriers, avoiding certain procedures, or avoiding specific patients might be indicated, but these are uncommon.

One potential weak link in the management of higher risk personnel is identification. Some individuals do not realize their increased risk, highlighting the importance of general infection control training to ensure that individuals can self-identify as higher risk. Higher risk individuals also need to be able to take precautions while reducing any concerns about stigma, privacy, and job security. Involvement of the person's physician (or an Occupational Health or Infectious Disease physician) may be indicated.

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Intervention and Investigation of Outbreaks of Health Care–Associated Infections

An outbreak is defined as an increased occurrence of infection or disease above the expected baseline (endemic) level. Outbreaks are an ever-present risk in all health care facilities, veterinary or otherwise, and outbreaks will occur despite rigorous infection control protocols. As stated regarding surveillance, if HAIs are not being identified in health care settings, then methods are not sufficient to detect their occurrence. It follows that you cannot manage what you have not detected. The general principles of outbreak management are to contain the outbreak and reduce the overall impact on individual animals and the facility. It is critical to note that despite the stigma often attached to outbreaks, an outbreak of disease does not necessarily indicate poor management or malpractice. Making no attempt to identify HAIs, neglecting signs of a developing outbreak, or responding inappropriately to the spread of HAIs could all be construed as poor management and even malpractice. Thus there are many reasons why plans for a logical, aggressive, organized, and cooperative response should be developed before outbreaks have ever been identified. Consultation with internal and external experts in epidemiology, infectious diseases, microbiology, and infection control can be useful. It is unlikely that the person involved in coordinating the outbreak response will be an expert in all areas. Consulting others does not indicate a lack of ability on the part of the response team; rather, it indicates a logical approach to typically complex problems. It makes sense to consult with those who, through interactions at multiple facilities, have gained experience that usually cannot be obtained while concentrating on primary responsibilities as a clinician at a single institution. Ideally, these individuals are consulted early in the outbreak, and it may be prudent to develop contingency plans and contact consultants in anticipation of potential problems. The use of external consultants can be particularly useful because they can examine a situation and facility without the same degree of inherent bias that develops through experience and habit of regular daily practice in a facility.

One of the most important factors in outbreak intervention is early recognition of “clusters” of cases that may be related. Ideally, laboratory testing, clinical

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disease reporting, or syndromic surveillance will be used to aid in systematic efforts for early identification of suspicious clusters of cases. First-generation transmission—that is, transmission from the index case (directly or indirectly) to other animals—can be difficult to detect, particularly in situations where the index case is infectious prior to developing clinical disease. The most important control aspect related to the first generation of cases is prompt identification so that an outbreak can be recognized early enough to implement measures to reduce the risk of further transmission to a second generation of cases. Often outbreaks are not identified or addressed until multiple generations of transmission have occurred, thereby increasing the overall morbidity and mortality and complicating the response.

General principles of outbreak response include identification of the infectious agent, identification of infectious animals, identification of animals that have likely been exposed, determination of the mode of transmission, and prevention of further transmission by means such as isolation, implementation of barrier precautions, active surveillance, environmental surveillance, increased environmental disinfection, restriction of animal and personnel movement, and under extreme conditions minimizing new exposures through restricting admission of new patients.

While useful, initial intervention measures do not require definitive identification of the etiologic agent. In the absence of a confirmed etiology (i.e., recognizing a cluster of patients with diarrhea of unknown cause), outbreak intervention can still be performed using general infection control practices combined with knowledge of appropriate response regarding the most likely causes. General principles such as isolation of infected or affected animals and their direct contacts, use of barrier precautions, close attention to personal hygiene, restriction of animal and human movement, regular examination of animals and careful attention to cleaning and disinfection are important measures that are useful for most types of infectious disease outbreaks. Indeed, these measures alone will often constitute the full response even after an etiologic agent is identified.

Identification of animals likely to be shedding the agent responsible for the outbreak is critical. Definitive confirmation is not required, and a syndromic response is often better. For example, amid a *Salmonella* outbreak, it is wise to consider all animals with diarrhea, depression, or fever as likely to be infected and shedding bacteria even if culture results have been negative for some. The same is true for horses that develop fevers when others suspected of having

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herpesvirus myeloencephalitis or influenza are hospitalized in the same facility. This will result in some misclassification, but erring on the side of being overly sensitive in identifying infectious animals is more appropriate when trying to halt the spread of disease. The main problem with this type of response is imposing excessive strain on available resources (e.g., isolation stalls, personnel time) because of excessive misclassification.

Identification of potentially exposed animals is also critical. Depending on the pathophysiology of disease, these animals may or may not require segregation or isolation. For some pathogens, clinical disease precedes development of the infectious state, so exposed animals can be monitored and isolated if required. For example, horses exposed to *S. equi* consistently develop fever prior to shedding the organism;[78] as such, regular monitoring of body temperatures of exposed animals and prompt isolation of animals developing fever may be sufficient to prevent propagation of an outbreak. For many pathogens, screening of all potentially exposed animals can be useful. In particular, the use of rapid screening techniques that can provide a turnaround time of a few hours (e.g., antigen detection test for equine influenza, *S. equi* PCR) can be very useful. However, testing strategies should also include some use of culture so that whole organisms will be available to aid epidemiologic investigations. Sampling should be based on the pathophysiology of infection and disease (i.e., sampling when shedding is most likely to occur). Widespread screening of hospitalized animals will often be required to determine the extent of the outbreak and facilitate removal of infectious animals from the population. Therefore if imposed as a response to suspected spread of HAIs, it is essential that screening not be an elective procedure. As such, it is prudent for facilities to have previously considered how costs for diagnostic testing will be distributed in the event of suspected HAIs. Surveillance for shedding of specific contagious agents at the time of admission can facilitate prevention of outbreaks as well as intervention responses. In situations in which recently exposed animals do not necessarily develop consistent overt clinical signs or rapid diagnostic testing is not available, it may be necessary to segregate all potentially exposed animals, either in an isolation unit or in the main hospital.

Determination of the likely mode(s) of transmission is also required for initiation of an effective response. This is usually relatively clear based on the identity of the known or suspected pathogen. Regardless, all agents of concern for HAIs can generally be spread through contact and common vehicle (fomite) transmission, and thus controlling all methods of contact exposure to patients

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will be critical in response to suspected outbreaks. Although droplet transmission might be most important for respiratory agents, practicalities of cleaning hospital environments for large animals usually necessitates use of large volumes of water, which can also create hazards related to droplet transmission for other agents such those with oral-fecal transmission. As such, the potential for droplet transmission should also be tightly controlled in response to suspected outbreaks. Generally, only highly contagious viral respiratory agents such as influenza virus pose a true hazard for airborne transmission. However, in situations in which routes of transmission are not clear, it is prudent to assume the worst and manage the outbreak as if the pathogen is highly transmissible by multiple routes until proven otherwise.

Prevention of further transmission is obviously one of the most important goals of outbreak response. A variety of factors need to be considered to achieve this. In addition to identification of infectious animals, measures need to be established to prevent direct and indirect contact of these animals with other animals and the general hospital environment. Isolation and the use of barrier precautions can achieve this. The response to implemented infection control measures should be monitored closely to determine their adequacy, with an understanding that there is an inherent lag time from implementation of measures to control of the outbreak that is proportional to the incubation period for infectious diseases.

At times, partial or complete closure of the facility may be useful or necessary to protect patients that would be admitted in the future. Restricting new admissions decreases the number of newly susceptible individuals that might promote propagation of an outbreak. Further, if new infections appear to be occurring despite implementation of best control efforts, it is important to consider whether it is prudent or ethical to continue admitting new patients. It is also critical to consider the tremendous burden that can be necessitated by the need to deal with infection control measures and the possible effects on patient care. During outbreaks, stall space, particularly isolation space, may become limited, and decreasing the number of admissions facilitates depopulation of the facility for proper cleaning and disinfection. Clinical personnel are often overworked during outbreaks because of the number of ill animals, and excessive workload can contribute to breaches in disease prevention protocols. Although there may be reluctance among some people to restrict hospital admissions because of potential negative impacts related to public relations and finances, early, short-term closure of a facility to stem a small but developing

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outbreak is much better than a subsequent longer closure in response to a larger outbreak with more affected animals. A key component of facility closure is proper communication to staff and the public, emphasizing the proactive approach that is being taken to protect patients and clients and to prevent a major problem from developing. Regardless of whether it is deemed necessary to restrict admission of new patients, as described previously, whenever outbreaks of HAIs are suspected, it is critical to consider whether standard informed consent procedures suitably convey the risks associated with hospitalization to clients.

If environmental contamination is suspected of being widespread, complete depopulation of a ward or even the entire hospital may be necessary to allow for thorough cleaning and disinfection. The availability of multiple wards can facilitate this process, as individual problem wards can be closed and disinfected while allowing the hospital to remain functioning. Assuming that sensitive culture or other antigen detection methods are available, postdisinfection environmental screening may be indicated for certain pathogens (e.g., *S. enterica*) prior to reopening.

Although vaccination is often perceived as a cornerstone of infection control, the indications and limitations of vaccination must be considered. No vaccine confers protection to all vaccinated animals, and vaccination should never be used as a replacement for good infection control practices. A more appropriate perspective is that vaccination is principally useful when methods used to prevent exposures to infectious diseases have failed. Requiring vaccination prior to hospital admission is an area that has received limited consideration in large animal practices. Although vaccination requirements are difficult to enforce in animals admitted for emergency procedures, it may be reasonable for facilities to consider encouraging or requiring vaccination against relevant pathogens prior to admission for elective procedures. For example, requiring vaccination for influenza in horses or bovine viral diarrhea (BVD) in pregnant cattle prior to admission could decrease the risk of infection and transmission in hospitals. Problems that might be encountered with such an approach include the lack of relevant efficacy data for many vaccines, potential concerns regarding adverse effects with some vaccines, difficulty ensuring compliance, and competitive issues if all competing practices do not have the same standards.

Vaccination may be a useful intervention measure during some outbreaks, but the time lag between vaccination and protective immunity limits the potential role of most vaccines. Further, the efficacy of vaccines typically have not been

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evaluated in the face of outbreaks. It is important to remember that three possible outcomes are associated with any intervention, including vaccination: it may help, it may have no effect, or it may be harmful. For vaccination during an outbreak to be helpful in control efforts, the vaccine must be given to susceptible animals prior to exposure, must initiate a protective response before natural exposure, and must not be harmful when administered to animals that are incubating disease. These criteria are often difficult or impossible to meet during an outbreak. The greatest potential use for vaccination during an outbreak is likely intranasal influenza vaccination, since this type of vaccine can provide a rapid and effective immune response and is not contraindicated in exposed animals.

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Infection Control Issues Related to Specific Pathogens

Although all contagious diseases have the potential to be important hazards for the health of individual patients, there is more empirical evidence on the importance of some diseases. Further, while safeguarding the health of veterinary personnel must be a priority for all veterinary practices, some zoonotic diseases have been shown to be of greater concern. Information follows on control of diseases of particular importance as hazards for HAIs and zoonotic disease.

Salmonella

S. enterica is the agent most commonly reported in association with outbreaks of HAIs and closure of large animal hospitals. In two different surveys of teaching hospitals at AVMA-accredited institutions, 20 of 38 (65%) and 6 of 20 (30%) participating institutions reported identifying epidemics of *Salmonella*-associated HAIs during the previous 5 years.[16,17] Many of these institutions had to restrict admissions or even close completely to facilitate management of the outbreaks. *S. enterica* is recognized as a pathogen around the world, and HAIs have been identified in many countries. However, the average risk among large animal patients varies tremendously among species, production practices, and even geographically within a country. In North America, the general risk of shedding is very low among animals raised in the northernmost regions and can be very high in warmer latitudes. All species are susceptible to infection, but large, intensively managed populations generally often have the highest prevalence of shedding, and the likelihood of shedding in patients while hospitalized is greatly influenced by the prevalence of infection in animals at home premises. Cattle and swine from large populations often have a higher likelihood of shedding compared with horses, camelids, and small ruminants. Given these factors that affected variability in infection rates, it is prudent for large animal hospitals to objectively assess the risk of shedding among their specific patient populations in order to appropriately adjust the rigor of surveillance and control efforts.

A notable number of patients shed *Salmonella* without evidence of associated

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illness, but infected patients are significantly more likely to shed if they show signs of GI illness or are systemically ill. Numbers of organisms shed per gram of feces are generally much greater in clinically affected animals. Animals known or suspected to be infected with *Salmonella* generally should be managed in isolation with strict barrier precautions and hand-hygiene protocols. Shedding tends to be more commonly detected in the summer and fall and may also be more common in warmer climates. Whereas outbreaks of HAIs are usually detected because of clusters of clinical disease, subclinical infections can be more common than clinical infections during outbreaks. Zoonotic infections in veterinary personnel have been commonly detected in association with outbreaks of HAIs. There is apparent variability among strains in virulence, infectivity, and ability to persist in the environment, and this strain variability may be a very important determining factor regarding outbreaks of HAIs. Environmental contamination near infected patients is the rule rather than the exception,[64] and active surveillance has shown that contamination can become disseminated to quite distant areas of the hospital from only a single infected patient. In one study, 12% of 452 environmental samples collected over 10 weeks in a nonepidemic period using electrostatic household wipes were positive for *Salmonella*.[76] Experience has shown that environmental contamination is even greater during outbreaks. In nonepidemic situations, there tends to be great variability in phenotypic markers (serogroup, serotype, and antimicrobial susceptibility) among isolates recovered from patients over time, which often makes it possible to differentiate isolates in epidemiologic investigations. In other situations, especially when certain strains are circulating actively in the region of a hospital, genetic analysis may be necessary in order to differentiate strains of *Salmonella* for purposes of epidemiologic investigations. Methods used in diagnostic laboratories for culture and molecular diagnostics are highly variable, which can significantly affect the reliability of assays. As such, veterinarians should seek out laboratories that are known to have optimized laboratory methods for use in diagnostic situations. PCR assays for *Salmonella* are available commercially at a number of laboratories. However, because of the importance of phenotypic and genotypic comparisons of isolates for epidemiologic investigations conducted as part of prevention and control efforts, PCR assays are not recommended for sole use in surveillance programs without parallel analysis using culture. Active surveillance programs are commonly used in large hospitals as a management tool to detect clinical and subclinical infections in large animal patients. In addition, environmental surveillance is

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sometimes used as an adjunct to detect environmental contamination. All common disinfectants are effective against *Salmonella* organisms under optimal conditions. However, the common association of *Salmonella* with fecal material, other organic matter, and dirt requires careful adherence to good cleaning (physical disruption of surface matter using detergents) and disinfection procedures in order to minimize the likelihood of environmental persistence. Mitigation in response to outbreaks of HAIs requires thorough decontamination of all environmental surfaces, which may be possible only after closure to new admissions, although disinfectant misting may be a useful alternative in some situations.[79,80]

Clostridium difficile

Although less commonly implicated in hospital outbreaks of diarrheic disease than *S. enterica, C. difficile* can be an important pathogen in horses and is often associated with outbreaks of neonatal diarrhea on breeding farms. *C. difficile* should be considered a differential diagnosis in horses with diarrhea and duodenitis-proximal jejunitis. Standard infection control methods used for salmonellosis should be adequate to control transmission of *C. difficile,* with the exception of disinfection. Because *C. difficile* is a spore-forming bacterium, sporicidal disinfectants (e.g., accelerated hydrogen peroxide, bleach) should be used after thorough cleaning. An additional albeit unsubstantiated concern is the potential for zoonotic transmission of *C. difficile* from horses or cattle to humans. The strains of *C. difficile* isolated from animals are often indistinguishable from those that cause disease in humans. Therefore animals infected with *C. difficile* should be considered potential sources of zoonotic infections in humans.

Cryptosporidium parvum

Cryptosporidiosis may be the most common zoonotic disease affecting large animal veterinary personnel. Although it usually causes self-limiting diarrhea in healthy individuals, cryptosporidiosis can be severe (including life-threatening) in certain immunocompromised populations.

Animals of all ages in a variety of host species have been shown to shed *C. parvum* oocysts, but the shedding prevalence is much greater in young animals, and the primary infection control hazard involves shedding by diarrheic

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neonates, especially calves. This is because of the extraordinary numbers of oocysts shed by affected young animals, the small infectious dose, and the hardiness of organisms. Affected calves can shed more than 10^7 oocysts per gram of feces during peak shedding, whereas humans and other animals can be clinically infected with fewer than 100 oocysts, although there does appear to be some difference among individuals as well as among strains. While there has been less study, *Cryptosporidium* also infects foals, and foal-human transmission has been documented in a veterinary hospital.[81] To further complicate control, oocysts are profoundly resistant to all disinfectants that can be regularly used in hospitals.

Because of the high prevalence of *Cryptosporidium* in calves, all calves should be considered a source of exposure, with additional concern about diarrheic calves because of the likely greater level of shedding. While less is known about foals, some degree of risk should be considered. It is very prudent to house diarrheic neonates in isolation and handle them with strict barrier precautions and hand-hygiene protocols. Personnel cleaning these housing areas should avoid using high-pressure water to minimize the risk of aerosol and droplet exposure. This is complicated by the inherent resistance of coccidian parasites to all disinfectants, which necessitates reliance on vigorous scrubbing with soap and rinsing with copious amounts of water in decontamination efforts. The likelihood of inadvertent oral exposures while cleaning can be reduced by using face shields or disposable masks along with gloves and fastidious attention to hand hygiene. Strict adherence to basic practices to prevent inadvertent oral exposure (e.g., good hand hygiene; preventing contamination of items such as clothing, pens, and cell phones) is critical.

Equine Rotavirus

Although outbreaks of rotavirus are fairly common on breeding farms, outbreaks in veterinary clinics are rare. Equine rotavirus is of most concern in facilities with a large neonatal caseload. Rotavirus may be shed in the feces of affected foals, clinically normal foals, and adult horses. Thus prevention of exposure is difficult. However, it is likely that clinically affected foals are the most common source of infection, through direct contact or common vehicle exposure. As a result, isolation of affected animals and the use of barrier precautions are the most important infection control measures. With the exception of disinfectants, protocols directed at control of *S. enterica* should be adequate for rotavirus

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control. Little specific information is available regarding the relative effectiveness of different disinfectants on equine rotavirus. However, as a nonenveloped virus, equine rotavirus should be expected to be resistant to environmental degradation and many disinfectants commonly used in veterinary medicine. While phenolics have been recommended in the past because of their better activity in the presence of organic debris, use of oxidizing agents such as accelerated hydrogen peroxide is probably better because of similar to superior effectiveness and a much lower potential for toxicity.

Bovine Viral Diarrhea Virus and Border Disease Virus

The closely related members of the genus *Pestivirus* are not commonly considered disease hazards caused by HAIs, but this may be more because of a lack of detection than a lack of occurrence. The main infection control hazard is related to exposure of susceptible pregnant cattle, sheep, goats, or camelids to persistently infected animals, which continuously shed large amounts of virus. The long period between infection of pregnant females and the birth of affected offspring complicates the ability to make relevant observations about the origin and frequency of HAIs. As such, it may be important to encourage or require vaccination of valuable pregnant cattle or alpacas prior to admission. In addition, animals known or suspected to be persistently infected should be managed in isolation with barrier precautions to minimize transmission. This includes neonates showing signs of congenital infection. Increased infection control precautions should also be used with animals from herds with a recent history of disease related to these viruses. Direct contact with persistently infected animals is an efficient method of transmission, but limited research shows that calves can be infected through contact with contaminated stalls and through droplet or aerosol exposure over a distance of at least 1.5 m.[82] Appropriate use of cleaning and disinfection methods should readily decontaminate the environment, and all common disinfectants are effective against these viruses under optimal conditions.

Strangles (*Streptococcus equi* subsp. *equi*)

An important aspect of *S. equi* control is identification and management of subclinically infected animals.[78] Syndromic guidelines for isolation upon

admission (i.e., isolation when patients are admitted from farms with a recent history of clinical *S. equi* infections, or isolation of horses with fever of unknown origin or unexplained nasal discharge) can help in managing potentially infectious horses so that they can be isolated pending the results of screening. However, the ubiquitous nature of *S. equi* and the possibility that essentially any hospitalized horse could be a subclinical carrier mean that there is an ever-present likelihood of *S. equi* introduction into the hospital environment, and clinicians should be alert to history and clinical signs that may be indicative of previous infection in hospitalized horses. Screening and isolation of horses from farms with endemic *S. equi* is a reasonable control strategy. Nasal rinsing or guttural pouch lavage performed for diagnostic testing should be conducted only in facilities where drainage and aerosolized fluids can be contained, and thorough environmental cleaning and disinfection should be conducted before use with other patients. Standard infection control measures, including preventing direct contact of hospitalized animals, optimizing hand hygiene, using appropriate cleaning, and disinfection, should be useful for reducing the risk of *S. equi* transmission should a colonized horse be admitted. Prompt examination and isolation of horses developing fever of unknown origin during hospitalization can indicate which horses should be removed from the general population before the onset of bacterial shedding. Vaccination during an outbreak with vaccines that are currently available is not recommended because of a lack of proven efficacy and concerns regarding development of purpura hemorrhagica. There is also no evidence of a need to require vaccination of elective cases prior to hospital admission. *S. equi* is susceptible to all common disinfectants when used properly.

Equine Influenza

Influenza is one of the most contagious diseases affecting horses. Immunity is transient, and horses can be repeatedly affected during their lifetime. There is no carrier state, and maintenance in a population depends on transmission from one acutely infected horse to another. In horse populations aggregated at racetracks, shows, or other venues, attack rates can reach 15% to 30%.[83] The incubation period from exposure to onset of clinical signs is typically about 2 to 4 days, which commonly coincides with the onset of virus shedding, although viral shedding can sometimes start before the onset of clinical signs. Horses are often febrile and obtunded at the onset of disease. Paroxysmal coughing is a classical

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sign of influenza infection that develops in some horses as disease progresses. Because of its contagious nature, identification of multiple acutely febrile horses can be an early indication that influenza virus is spreading in the population. Rapid identification and confirmation of animals shedding virus allows initiation of efforts to minimize contagious spread. Antigen detection assays are commercially available and very useful for rapid confirmatory testing (e.g., Directigen EZ Flu A+B [BD Diagnostic Systems, Franklin Lakes, NJ]). However, this assay has limited sensitivity; virus shedding was detected in only approximately 30% of clinically affected horses during outbreaks using this assay, so tests should be performed on multiple clinically affected horses and interpreted in the aggregate for the population.[84,85] Negative test results for individual samples should be interpreted with caution because of the consequences associated with not using appropriate control measures during an outbreak of a highly contagious disease. Reverse transcription PCR (RT-PCR) tests are available and are likely more sensitive than antigen detection assays,[85] but there is limited published validation of the highly variable RT-PCR assays used in diagnostic laboratories. Influenza virus can be transmitted through aerosol, droplet, and contact transmission and can easily be transmitted over several feet in respiratory aerosols generated by coughing horses. As such, horses confirmed to be infected should be managed in complete isolation with full barrier precautions, paying strict attention to hand-hygiene protocols. Influenza virus can survive on surfaces at most for a few days in a cool, moist environment. As an enveloped virus, influenza is susceptible to damage from extreme environmental conditions and is readily inactivated by all common disinfectants if they are properly applied. Whereas clinically affected animals are the most likely to shed large amounts of virus, in nonaffected horses sampled during large outbreaks, seroconversion and virus shedding can be found in about 30% and 5% of the exposed populations, respectively.[83,84] As such, it is prudent to increase infection control precautions for all exposed but apparently unaffected horses in order to minimize risks of transmission. Early vaccination of all horses with intranasal vaccine may be of value in abbreviating the course of an epidemic. If new admissions are allowed when there is an elevated risk of influenza virus infection, horses should be required to be recently vaccinated with vaccines having proven efficacy prior to admission (preferably a minimum of 2 weeks prior to admission). Regardless of vaccination history, it is unwise to admit very young or immunocompromised horses when there is an increased risk of infection with influenza virus. Influenza virus is susceptible to all

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common disinfectants when used properly. Zoonotic risks of currently circulating H3N8 equine influenza viruses seem to be very low, but there is always some potential for infection.

Equine Herpesviruses

Equine herpesvirus types 1 to 5 are ubiquitous in horse populations and are highly contagious. EHV-1 and EHV-4 are the most widely recognized as important causes of outbreaks of disease in horses, and HAIs have been noted for both agents. EHV-4 infections are associated with contagious respiratory disease that principally affects horses under 3 years of age. EHV-1 is of greatest concern regarding HAIs. Infections are associated with respiratory disease, neurologic disease, peracute pulmonary vasculitis, abortion, and neonatal mortality in congenitally infected foals. The potential for contagious spread of herpesvirus myeloencephalitis was dramatically highlighted in 2011 when infections among horses at a horse show in Ogden, Utah, resulted in subsequent spread to documented clinical infections in 180 horses (29% with neurologic disease) on 63 premises located in 14 states and Canadian provinces, and subsequent euthanasia or death of 14 horses.[18,19] Documented spread of infections within hospitals as well as at the home premises of previously hospitalized horses further highlights the risk for HAIs with EHV-1.[8-10] Immunity is relatively short lived, and infections likely occur throughout the lives of horses. Many if not most of these infections are undetected or occur with only mild clinical signs. The most common clinical sequela of infection is mild respiratory disease during the first 2 years of life. More infrequently, EHV-1 infections can result in more severe complications such as abortions in pregnant mares or paralysis. All EHV-1 and EHV-4 infections originate in the respiratory tract, but epidemiologic evidence suggests that contact and droplet transmission among horses in relative proximity is much more common than aerosol transmission over greater distances. Fever is commonly the initial clinical sign exhibited by infected horses, and identification of multiple acutely febrile patients can be an early indication of nosocomial spread of equine herpesvirus in the population. Most horses can be shown to be latently infected with EHV-1 and EHV-4 by the time they reach adulthood, and subsequently any hospitalized horse might serve as a source of infection for other patients by recrudescing virus in response to stresses of disease, hospitalization, and transport. However, clinical experience suggests that EHV-associated HAIs most commonly originate

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from clinically affected horses. As such, rapid identification of animals suspected of being infected, isolation of affected horses with complete segregation of materials used in their care, and use of barrier precautions with appropriate hand-hygiene protocols are generally effective for minimizing risks for HAIs. All horses exhibiting ascending weakness, paresis, or paralysis should be suspected of EHV-1 infection and managed in isolation until the animal can be proven to have stopped shedding or another diagnosis is confirmed. Herpesvirus infection should also be promptly ruled out in horses with upper respiratory disease or fever of unknown origin. Use of PCR testing as an adjunct to thorough clinical investigation is often extremely useful for this purpose. Herpesviruses are enveloped viruses, and routine cleaning and disinfection procedures should be adequate for decontamination of surfaces, assuming that appropriate protocols are followed. PCR testing of nasal secretions is the most useful assay for rapid confirmatory testing. Serial testing of horses is useful for establishing that shedding has stopped because field data and study involving experimental infection have shown that shedding can be intermittent and negative results for individual tests must be interpreted with caution.[10] Although many laboratories offering PCR testing now provide information about the ORF30 genotype (D versus N, or sometimes labeled as “neurotropic” and “non-neurotropic” genotypes), both genotypes can cause neurologic disease, both genotypes of virus are contagious, and both genotypes can cause epidemics of disease. As such, this information should not affect the level of caution taken with infected or exposed horses.[86] Without adjunctive testing, infected horses should be quarantined for a minimum of 28 days after cessation of disease.[9,10] Using serial testing as a confirmatory adjunct, this quarantine period might be shortened to 14 days after cessation of disease.[10,86] Field data from one outbreak suggest that about 60% of horses can be shedding virus at the onset of clinical disease irrespective of the severity of clinical signs, and shedding can persist for 10 to 14 days after disease onset.[10]

EHV-3 is less commonly considered a problem regarding HAIs, but it has been noted to spread through contact with contaminated materials during reproductive procedures as well as between horses during coitus. As such, it is a notable hazard for practices that specialize in reproductive services. EHV-3 causes coital exanthema, a pustular disease affecting the vulva and vagina of mares and the penis and prepuce of stallions. Appropriate cleaning and disinfection of materials used in reproductive examinations, avoiding the use of

examination sleeves and gloves with multiple horses, and rigorous adherence to sound infection control precautions for breeding populations should control the spread of EHV-3. The prevalence of latent EHV-3 infections is not well documented.

EHV-5 has been associated with equine multinodular pulmonary fibrosis (EMPF); however, the epidemiology of this disease has been poorly described. The risk posed by horses with EMPF is unclear, and healthy horses may also shed this virus, so optimal hospital preventive approaches are unclear.

Enveloped viruses, including all herpesviruses, are susceptible to all common disinfectants when used properly.

Methicillin-Resistant *Staphylococcus aureus*

MRSA is emerging as an important veterinary and zoonotic pathogen. In large animals, MRSA infections have been most commonly identified in horses, veal calves, and pigs. Transmission of MRSA between these species and attending personnel can occur, and MRSA colonization and infection appear to be an emerging occupational risk associated with large animal veterinary practice, particularly in northern Europe where livestock-associated clones (e.g., sequence type 398) are more common and nonzoonotic MRSA infections are rare. Transmission of MRSA is thought to mainly occur through direct or indirect contact between infected or colonized people or horses and hospitalized horses. Aerosol transmission from MRSA-contaminated dust is a concern in intensive indoor housing situations, particularly swine barns. The potential for droplet and airborne transmission in less intensive situations is unknown and may be limited. The largest problem related to HAIs with MRSA in large animals has been the infection and colonization of equine patients. Infections are principally noted at surgical sites and wounds, whereas colonization predominantly occurs in the nasal passages, although GI colonization has also been noted. If not identified by active surveillance, colonized horses can be silent yet prolific reservoirs for infection of humans and horses. Prevention of MRSA transmission requires careful attention to practices that prevent contact and common vehicle transmission, including use of good hand-hygiene practices, restriction of horse contacts and isolation of infected or colonized animals, and use of specific measures aimed at identifying carriers. All colonized or infected horses should be treated as infectious, housed in isolation, and handled with strict attention to contact barrier precautions. Screening by culture of nasal swabs collected at the

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time of admission can help control MRSA in areas where it is endemic in the community or the horse population; however, the need for routine screening varies depending on the facility, the MRSA prevalence in the patient population, and other factors. Although colonized personnel can be a source of infection of patients, staff screening is fraught with complex issues (e.g., privacy, occupational health) and is difficult to justify in the absence of an ongoing outbreak that is uncontrolled with improvement in routine infection control practices. Various studies have demonstrated high rates of MRSA carriage among equine veterinary personnel, so it is reasonable to assume that all equine facilities regularly have one or more colonized staff. For this reason, good attention to standard hygiene and infection control practices is critical. *S. aureus* is susceptible to most disinfectants if used properly.

Coxiella burnetii

C. burnetii is the causative agent associated with Q fever in people and coxiellosis in animals. Although most infections in humans are subclinical, personnel who contact livestock have a greater risk of infection and disease that can be severe and even fatal in a small portion of cases. It is also highly infectious, has a low infective dose, and can be transmitted through contact as well as by droplet and airborne routes. *C. burnetii* can be found in a variety of animal species, but zoonotic transmission is most commonly associated with periparturient ruminants (especially small ruminants) and aborted fetuses. Serum antibody tests, antigen detection assays, and PCR can be used to identify infected animals, but the sensitivity of these assays has been questioned. Because of the potential significance of clinical infections in humans, all attending personnel should be appropriately aware of the zoonotic potential and risks associated with Q fever.[28] The risk of serious clinical consequences should be noted by pregnant women, people with valvular heart disease, and those who are immunosuppressed. Medical histories for individuals and flocks should be considered to determine if there is an indication that *C. burnetii* may be a greater than average risk. Infection control measures that can be used to minimize hazards to people with a high risk of clinical infection include isolating periparturient small ruminants, paying strict attention to hand-hygiene protocols, using respiratory protection and barrier nursing precautions when handling potentially infected animals, and even excluding periparturient small ruminants from care. Particular care should be taken during parturition and when handling

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aborted fetuses and newborn small ruminants. For animals known to be infected, care should be used when cleaning and disinfecting stalls or other housing environments, and contaminated bedding and other materials should be handled cautiously. *C. burnetii* is susceptible to most disinfectants if used properly.

Antimicrobial Resistance and Antimicrobial Stewardship

Although antimicrobials are undoubtedly required for proper management of a significant percentage of hospitalized large animals, any use of antimicrobials creates some degree of selection pressure for antimicrobial resistance. This can be relevant on multiple levels, including resistant infections in individual patients, outbreaks of infections caused by resistant pathogens, and increasing the pool of resistant organisms and resistance genes in the horse population.[87,88] Of additional concern is the potential transmission of resistant pathogens to people or the less well understood potential for transmission of resistance genes from animal-associated pathogens or commensals to human pathogens.

Antimicrobial use is a required part of management of many veterinary patients. The need for access to a range of antimicrobials is critical for maintenance of the health and welfare of animals, economic production of food, food safety, and food security. However, the potential consequences of antimicrobial resistance on human and animal populations cannot be ignored in this era of antimicrobial resistance. There has been (and will continue to be) increasing scrutiny of antimicrobial use in animals, particularly livestock. All of these factors highlight the need for “antimicrobial stewardship,” which is a coordinated approach to optimizing the use of antimicrobials and maximizing patient care while also minimizing the risk of resistance, toxicity, or other adverse events. It involves a multifaceted approach to determine *when* to prescribe antimicrobials; *what* drug, dose, and duration is appropriate, *how* antimicrobials are administered, and *whether* other approaches (e.g., surgery, wound care, management of underlying disease) can be used to complement or replace antimicrobials.

Veterinarians have practiced some form of antimicrobial stewardship for decades when making decisions about how and when to use antimicrobials, as well as through efforts to reduce the need for antimicrobials (e.g., preventive medicine). However, a more formal and comprehensive approach to antimicrobial stewardship is required.

Although veterinarians have practiced some form of stewardship, the overall field of antimicrobial stewardship is in its infancy in veterinary medicine. Fortunately, most aspects of antimicrobial stewardship are not complex, costly, or time consuming. There is no standard approach to antimicrobial stewardship, in part because of a lack of data but also because of the marked differences in needs, threats, and practical aspects between facilities. Some facilities may require few components while others (e.g., larger, tertiary care, greater prevalence of antimicrobial resistant pathogens) may require a more comprehensive program. Examples of potential stewardship practices are outlined in Box 46.4.

Box 46.4

Prescribing and Other Practices That Can Be Used to Promote Stewardship of Antimicrobial Drugs

Antibiogram data collection and use	Automatic stop orders
Cascading microbiology susceptibility reporting	Checklists (e.g., surgical)
Computerized decision support systems	De-escalation and streaming
Disease-specific treatment guidelines	Surgical prophylaxis guidelines
Dose optimization	Formulary restriction
Formulary restriction with preauthorization	Formulary restriction with authorization
Computer-based identification of inappropriate pathogen-drug combinations	Improved antimicrobial documentation Intravenous to oral conversion
Improved diagnostics	User (owner) education
Prescriber education	Promotion of timely and appropriate microbiological sampling
Prevention of treatment of noninfectious conditions	Scheduled antimicrobial reassessments (antibiotic time-outs)
Prospective audit with feedback (clinician/service/facility)	Targeted review for redundant therapy or therapeutic duplication
Strategic microbiology results reporting	
Therapeutic drug monitoring	

Management of Donor Animals

It is increasingly common to use animals owned by hospitals or veterinary personnel as donors for blood and ingesta (e.g., rumen fluid, equine feces) transfer to patients. Animals used for this purpose should be known to have a

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very low risk for contagious diseases (e.g., by virtue of their age, clinical status, facility origin), should be housed away from hospitalized patients, should be clinically healthy at the time of specimen recovery, and should be screened periodically for diseases that could be transmitted by use of transfer products. Diseases of concern that might be transferred by blood products from ruminants include bovine leukemia virus, bovine viral diarrhea and border disease viruses, and anaplasmosis; similarly, horses should be screened for equine infectious anemia infection. Bovine ingesta donors should be screened for Johne's disease *(Mycobacterium avium* subsp. *paratuberculosis)* and *S. enterica*, and equine fecal donors should be screened for *Salmonella* and potentially for other pathogens, such as *C. difficile*, equine coronavirus, and fecal parasites.

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*Throughout this chapter, the terms *infection control* and *biosecurity* are used interchangeably to encompass all practices related to the prevention of introduction and spread of infectious diseases in populations of animals or their human caregivers.

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• CHAPTER 47

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Prevention, Detection, and Response to Transboundary (Foreign) Animal Diseases

Pamela J. Hullinger, Consulting Editor, Danelle A. Bickett-Weddle

One of a private veterinary practitioner's most critical responsibilities is his or her role as the nation's front line of defense for detecting emerging, exotic, and transboundary animal diseases (TADs). TADs are important, transmissible diseases of livestock that are not present in the United States. If introduced, they would cause significant adverse economic or national animal, public, or environmental health consequences. Although many of these disease threats are known, new or “emerging” diseases may also impact the United States and affect human, animal, or ecosystem well-being. The U.S. Department of Agriculture (USDA) Animal and Plant Health Inspection Service (APHIS), Veterinary Services (VS) has primary responsibility for addressing foreign and emerging diseases of livestock and poultry and works closely with state animal health officials (SAHOs), private veterinary professionals, and the livestock industry to monitor for and to detect, control, eradicate, and mitigate the impacts of TADs on the livestock industries and the public. Box 47.1 shows a list of the diseases successfully eradicated from the United States. The *Code of Federal Regulations* (CFR), Title 9, part 53[1] details the federal government's list of reportable diseases of livestock and poultry and its policies and procedures for the diagnosis, appraisal, destruction, and disinfection of livestock and poultry infected with these diseases. The list specifically includes “Foot-and-mouth disease, rinderpest, contagious pleuropneumonia, Newcastle disease, highly pathogenic avian influenza, infectious salmon anemia, spring viremia of carp, or any other communicable disease of livestock or poultry that in the opinion of the Secretary constitutes an emergency and threatens the livestock or poultry of the United States.”[1] In addition to the CFR reportable disease list, many states

require the reporting of additional specific disease conditions. Additional diseases may include those of public health importance, such as equine encephalomyelitis, or other endemic diseases of industry concern, such as bovine trichomoniasis. Licensed veterinarians are responsible for maintaining a familiarity with the federal reportable disease list, as well as those of the states in which they practice. The reportable disease list for each state can be obtained through the office of the SAHO. States may also have more specific policies and procedures for the diagnosis, appraisal, euthanasia, and disinfection of livestock and poultry infected with such reportable diseases. Box 47.2 lists some reportable diseases of horses.

Box 47.1

Years When Foreign Animal Diseases Were Eradicated From the United States

1892—Contagious bovine pleuropneumonia
1929—Foot-and-mouth disease
1929—Fowl plague
1934—Glanders
1942—Dourine
1943—Texas cattle fever
1959—Vesicular exanthema
1959—Screwworm (southeastern United States)
1966—Screwworm (southwestern United States)
1971—Venezuelan equine encephalitis
1973—Sheep scabies
1974—Exotic Newcastle disease
1978—Classical swine fever
1985—Highly pathogenic avian influenza (H5N2)
1999—*Brucella melitensis*
2003—Exotic Newcastle disease
2004—Highly pathogenic avian influenza (H5N2)
2006—Bovine spongiform encephalopathy
2008—Turkey rhinotracheitis

2010—Rabbit hemorrhagic disease
2015—Highly pathogenic avian influenza (H5N2, H5N8)
2016—Vesicular stomatitis virus (New Jersey serotype)
2016—Highly pathogenic avian influenza (H7N8)
2017—Highly pathogenic avian influenza (H7N9)
2017—New World screwworm (Florida)

Box 47.2

Reportable Diseases of Horses[a]

African horse sickness
Contagious equine metritis *(Taylorella equigenitalis)*
Dourine (*Trypanosoma equiperdum)*
Equine encephalomyelitis (Venezuelan, Eastern, and Western)
Equine herpesvirus myeloencephalopathy
Equine infectious anemia
Equine piroplasmosis (*Babesia caballi* or *Theileria equi*)
Glanders *(Burkholderia mallei)*
Hendra virus *(Equine morbillivirus)*
Japanese encephalitis
Piroplasmosis
Vesicular stomatitis virus
West Nile virus

[a]This list will vary by state.

In an effort to create a standardized list of animal diseases, the U.S. National List of Reportable Animal Diseases has been proposed. This list, available at https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/program-overview/ct_national_list_reportable_animal_diseases, is based on the OIE list while complementing the state reportable disease lists.

The World Organization for Animal Health or Office of International

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Epizootics (OIE)[2] is an international organization, representing more than 180 member countries, that seeks to provide leadership and guidelines to ensure transparency and solidarity in the management of the global animal disease situation. The OIE publishes health standards for international trade in animals and animal products, as well as criteria for the validation and certification of diagnostic assays. Policies and procedures that the federal government implements to manage the intrusion of TADs into the United States are often aligned with the OIE health standards and guidelines to help ensure the most rapid and efficient recovery of U.S. exports. Another equally important function of the OIE is to provide an early warning system for member countries to have rapid situational awareness and to act quickly to protect themselves when outbreaks of OIE-reportable diseases are confirmed in other member countries. More than 115 animal diseases are reportable to the OIE. It is important to remember that some of the domestic diseases that are present in the United States, such as bluetongue, are reportable to the OIE and have implications on U.S. trade with countries that are free of those diseases.

To protect the long-term overall health and viability of U.S. animal agriculture, any incursion of a TAD must be rapidly identified and controlled. In the United States, the goal is controlling the TAD outbreak with ultimate eradication and return to preoutbreak disease status. These TAD eradication efforts present significant short-term costs to affected industries, as well as the government and the public. In some cases these effects become long term, lasting for years, and industries may never fully recover. Most TAD incursions have significant economic costs associated with disease control and eradication efforts. Direct costs of disease control include paying personnel to manage and control the outbreak, indemnity costs (to buy diseased animals from producers for destruction), and the cost of necessary supplies and equipment for euthanasia, carcass management, and disinfection. In addition to these direct control costs, one of the most immediate consequences of a TAD occurrence in the United States would be the loss of export markets and disruption of normal industry business continuity in the United States. Indirect costs of TAD outbreaks result from control measures such as livestock movement restrictions and biosecurity that disrupt normal business continuity. These are likely to be the most significant economic costs. An example is the reduction or loss of income for a dairy producer who is no longer able to ship raw milk across state lines to a milk processor due to movement restrictions. For all TADs, early detection and rapid application of situational awareness to assess the extent of the outbreak,

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followed by efficient implementation of necessary controls to limit further spread, will minimize the overall impact of the outbreak on the affected producers, the affected industries, and the U.S. economy as a whole.

The risk of a TAD incursion into the United States today is much greater than it has been in the past, for two main reasons. First, there has been a rapid expansion of international trade and travel. With a greater volume of people, animals, and animal products entering the United States on a daily basis, the opportunity for a TAD to be unintentionally introduced is much higher than previously. Second, in the wake of the terrorist attacks in the United States on September 11, 2001, there is heightened awareness and concern about the possibility of agroterrorism, or the deliberate introduction of a biologic agent targeting livestock for the purposes of inflicting economic damage and societal instability in the United States. Whether a TAD is intentionally or unintentionally introduced, the detection of the first case as soon as possible is critical to minimizing the overall impact of the resulting outbreak.

Private veterinary professionals need to be familiar with the clinical signs associated with TADs, especially those that can be easily confused with clinical signs of domestic or endemic diseases. When veterinary professionals are concerned about the possibility of a TAD in clients' animals, they need to contact a federal or state animal health official, who will consult with them on the history of the herd or flock. A Foreign Animal Disease Diagnostician (FADD) may be sent to examine the suspect animals and take and submit samples for testing at no expense to the producer or veterinarian. Testing will be prioritized by disease and level of concern. Both the livestock producer and private veterinarian should be contacted with regular updates as test results become available. Hundreds of TAD investigations occur annually in the United States, and fortunately most lead to the determination that a TAD is not involved. The TAD that goes undetected or unreported for some time because of lack of vigilance or reluctance to report will cause major economic harm to the livestock industry and the nation. Veterinary practitioners are encouraged to report a suspected TAD. It is better to investigate and rule out concerns. This not only tests the animal disease emergency response system to ensure that it is as efficient and effective as possible but could also prevent a catastrophic TAD outbreak.

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U.S. Department of Agriculture National Veterinary Accreditation Program[3]

The USDA officially established the National Veterinary Accreditation Program (NVAP) in 1921 to provide a mechanism to enable private veterinary practitioners to work on behalf of the federal government to certify animals for certain types of interstate and international movement and to assist in controlling damaging animal diseases. The current mission of the NVAP is to provide accredited veterinarians with the information they need to ensure the health of the nation's livestock and animal population and to protect public health and well-being. NVAP's goal is to maintain the effective cooperation and use of private veterinary practitioners for regulatory work in a manner that is consistent with international trade requirements and enables the safeguarding of animal health. USDA's APHIS administers the NVAP. Participation in NVAP is voluntary and is not mandated by the federal government. Box 47.3 provides the eligibility requirements for a veterinarian planning to become accredited by the USDA. Accredited veterinarians participating in NVAP must carry out their duties according to the Standards for Accredited Veterinarian Duties described in CFR Title 9, Part 161.4. USDA veterinary accreditation is specific to a given state, so one needs to contact the USDA APHIS Veterinary Services District Office with oversight for the state(s) where he or she is practicing to obtain accreditation in that specific state. One requirement of the USDA for accredited veterinarians is prompt reporting of all suspected foreign animal and communicable animal diseases to state or federal animal health officials. Box 47.4 lists some of the clinical signs that should alert a private veterinarian that a TAD should be considered.

Box 47.3

U.S. Department of Agriculture (USDA) NVAP Accreditation Eligibility Requirements

- Graduate with a doctor of veterinary medicine or equivalent degree.

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- Licensed or legally able to practice veterinary medicine in the state in which accredited duties will be performed.
- Complete Initial Accreditation Training approved by Animal and Plant Health Inspection Service (APHIS).
- Complete an orientation program approved by the USDA Assistant Director for the state in which accredited duties will be performed, and document the training.
- Submit a signed application (VS Form 1-36A).
- Complete a state-specific orientation (if required by the state).
- Wait to perform accreditation duties until APHIS provides written approval.

Box 47.4

Clinical Signs or Observations That Indicate a Foreign Animal Disease Should Be Considered

- Vesicles in oral cavity or around coronary bands
- Central nervous system signs
- Mucosal diseases
- Hemorrhagic septicemias
- Larvae in wounds
- Unusual (ornate) ticks
- High morbidity or mortality
- Unusual or unexplained illness or symptoms

Accredited veterinarians are the backbone of U.S. regulatory programs for livestock and poultry diseases in the United States. The responsibilities of an accredited veterinarian are extraordinary. In fact, the United States depends extensively on accredited veterinarians for many official functions (e.g., inspecting, testing, and certifying animals for movement). Livestock producers who move animals domestically or internationally rely on the expertise of accredited veterinarians to help ensure that animals meet the requirements of the destination and will not introduce diseases into the receiving state or country.

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The NVAP has served the animal industry well for many years and remains integral to the U.S. ability to trade internationally. There are currently more than 68,000 active accredited veterinarians in the national database, and these accredited veterinarians are instrumental in providing national capability to perform competent health certifications and to maintain extensive disease surveillance and monitoring. Today, more than 80% of all U.S. veterinarians are accredited and work cooperatively with federal and state animal health officials in NVAP.

The NVAP underwent changes to its overall process following the publishing of the Final Rule in the CFR in December 2009. As of 2010, NVAP has two species-based accreditation categories. Category I includes all animals except food and fiber species, horses, birds, farm-raised aquatic animals, all other livestock species, honeybees, and zoo animals that can transmit exotic animal diseases to livestock. Category II allows veterinarians to perform accredited duties on all animals. Category I veterinarians must complete three APHIS-Approved Supplemental Training (AAST) modules every 3 years; Category II veterinarians must complete six in the same time frame. Official AAST modules are offered free online (https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/nvap/ct_aast), through presentations at state, regional, and national veterinary meetings (registration costs vary), or purchased as PDF files on a USB drive. Details about the NVAP can be found on the USDA APHIS website (http://www.aphis.usda.gov).[3]

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Overview of Foreign Animal Disease Investigation and Response

Protecting the nation's livestock and poultry industries, and therefore a large segment of the U.S. agricultural economy from TADs, involves four basic principles or phases of emergency management: prevention, preparedness, response, and recovery. To be effectively executed, these phases require planning, cooperation, and communication among individuals, groups, and organizations at the local, state, tribal, regional, and national levels. Livestock and poultry owners; veterinarians in private clinical practice; industry groups; federal, state, tribal, and local governments; universities; veterinary diagnostic laboratories; and the consideration of public opinion and perception must all be included in emergency response preparation and planning. A response to a TAD outbreak will be carried out in accordance with the guidelines established by the National Response Framework (NRF) and using the National Incident Management System (NIMS) and the Incident Command System (ICS). Veterinarians who are interested in participating in either TAD emergency response or animal disaster response efforts, as either temporary employees or volunteers, must be familiar with these systems before an event occurs, in order to be effectively integrated into the response effort. There are both online and classroom-based training programs offered by federal, state, and local emergency response agencies to provide basic ICS training and certification. The Federal Emergency Management Agency offers several web-based, self-paced courses.[4]

Although the details of the clinical signs and epidemiology of the TADs themselves are discussed in detail in other sections of this book, many additional references and resources are available to practicing veterinarians to help them keep apprised of the clinical presentation and importance of these diseases, as well as to whom to report suspected cases. In the United States, veterinary students have access to the *Emerging and Exotic Diseases of Animals* web-based course that provides actual disease incursions, visual depictions of diseases, and the role of agencies involved in response. A portion of this course meets the USDA NVAP Initial Accreditation Training requirements. USDA also provides every U.S. graduating veterinarian with a copy of the "*Transboundary and Emerging Diseases of Animals*" text. The course and website are offered by the

Center for Food Security and Public Health at Iowa State University,[5] along with a multitude of other resources available at: http://www.cfsph.iastate.edu. Another excellent resource is the text *Foreign Animal Diseases: "The Gray Book,"* revised in 2008[6] (available at http://www.usaha.org/upload/Disease%20Info/FAD.pdf).

Prevention and Preparedness

Early recognition of a TAD may be difficult because some domestic diseases seen by veterinarians have similar clinical signs or presentations (e.g., foot-and-mouth disease [FMD]). Some TADs may have mild clinical signs that could allow them to spread undetected for a period of time. Examples of both domestic and transboundary vesicular or ulcerative diseases, which may be difficult to distinguish clinically in cattle, are presented in Box 47.5. A similar list for small ruminants is provided in Box 47.6. The increased likelihood and severe consequences of an introduction of a TAD into the United States requires private veterinarians to be continually vigilant for unusual emerging animal health conditions or situations. This requires veterinarians understanding how TADs may manifest and what clinical signs they may possess. Participation in continuing education programs aimed at increasing awareness of the clinical signs and presentations of TADs can facilitate this necessary awareness. Education and awareness should also be extended to livestock producers and their employees who will likely be the first individuals to recognize an unusual problem in the herd or flock they work with daily.

Box 47.5

Diseases of Cattle That Are Difficult to Clinically Distinguish and May Resemble Foot-and-Mouth Disease[a]

Foot-and-mouth disease
Vesicular stomatitis
Rinderpest

Bovine viral diarrhea
Malignant catarrhal fever
Bovine herpes mammillitis
Bovine papular stomatitis
Pseudocowpox
Infectious bovine rhinotracheitis

[a]Reportable diseases are highlighted in bold.

Box 47.6

Diseases of Small Ruminants That Are Difficult to Clinically Distinguish and May Resemble Foot-and-Mouth Disease[a]

Foot-and-mouth disease
Vesicular stomatitis
Malignant catarrhal fever
Peste des petits ruminants
Bluetongue—certain serotypes
Contagious ecthyma (orf)
Epizootic hemorrhagic disease

[a]Reportable diseases are highlighted in bold.

An important component of the prevention programs for TAD incursions is USDA's implementation of policies and procedures related to the importation of live animal species or products into the United States. These import rules vary by animal and product, as well as by country of origin. USDA monitors the OIE reports of the world animal health status and continually updates these importation requirements accordingly. These requirements may dictate the

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quarantine and possible testing of specified animal species for specific periods before animals are allowed to enter the United States. As of 2018, there were three animal import centers, located in New York, Miami, and Los Angeles, through which animals could legally enter the country. USDA port veterinarians at the importation stations are responsible for the examination of the animals, their identification, and evaluation of health certificates and permits for accuracy. If the requirements are not met or the animals are found to be diseased, the animals may be refused entry, sent back to their country of origin, or humanely destroyed. Once it has been determined that an animal is healthy, all the test results are negative, and all the requirements have been met, then the animal can be released to its owner and the state of destination is notified of the animal's movement into that state.

Detection

Historically, border controls and import procedures have been largely effective in keeping TADs out of the United States. There is always the possibility that a TAD could appear in the United States by either unintentional or intentional means. Illegal importation of animals and animal products via other channels poses a significant risk to U.S. agriculture. The responsibility for rapidly detecting, confirming, and effectively responding to incursions of TADs is primarily that of USDA APHIS in cooperation with livestock and poultry owners, veterinarians in private clinical practice, and SAHOs. An additional challenge for early detection of TADs is that few ongoing active surveillance programs exist that routinely test for TADs in targeted, high-risk livestock populations or in conjunction with screening for clinically indistinguishable domestic diseases in state or regional veterinary diagnostic laboratories. Because many of the TADs can mimic domestic diseases, a TAD may not be properly identified for some time if the condition is believed to be a domestic disease problem and if it is investigated with only that limited differential in mind. Even a single day's delay in identifying a TAD can result in significantly greater disease spread or economic impact owing to the large amount of daily livestock movement in the United States. Prompt reporting, investigation, and diagnosis can prevent a TAD from spreading further, can reduce the overall economic impact of the event, and can reduce the likelihood that the disease may become endemic in a wildlife or arthropod reservoir.

The most likely person to initially suspect a TAD is the producer or private

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veterinarian called by the producer to investigate an unusual disease condition. It is critical that any time a TAD is suspected, it is reported to state or federal animal health officials for expedited investigation and testing as needed. The SAHO and federal veterinarians working for the USDA routinely work to increase awareness of such conditions and reporting information among the state's private veterinarians and livestock producers. These activities require the support and assistance of state and university veterinary diagnostic laboratories, the Cooperative Extension Service, state and federal meat and poultry inspection services, universities, animal scientists, market operators, livestock and poultry producers, and private veterinarians.

For TAD outbreaks to be detected quickly, any suspicious signs or situations indicative of a TAD must be promptly reported to a state veterinarian and the USDA federal veterinarian for the state where the animal resides so that a TAD can be confirmed or ruled out. Private veterinarians are knowledgeable regarding the occurrence of various domestic animal diseases in their practice area and the history of such diseases on their clients’ farms and ranches. This type of historical information and a herd's vaccination and animal movement history are critical to assessing the likelihood of a suspected TAD. Working with the herd veterinarian and the producer, the investigating state or federal, specially trained, FADD will use the herd history and clinical investigation to assess the likelihood that the situation involves a TAD and to determine the appropriate sample(s) to collect, the method of sample delivery, and what precautions must be taken at the site while test results are pending. Samples are submitted to the National Veterinary Services Laboratories (NVSL) in Ames, Iowa, or to the Foreign Animal Disease Diagnostic Laboratory (FADDL) at Plum Island, New York, to confirm the presence or absence of a TAD. On the basis of initial TAD investigation findings, often before the laboratory has completed testing of the samples, state and federal officials in the affected state may take action to quarantine affected animals at the site of the suspected case, increase surveillance in the area, and initiate steps to gather further information to assess the situation and characterize and control the outbreak if necessary.

In the United States, select laboratories that are members of the National Animal Health Laboratory Network (NAHLN) under USDA Veterinary Services Memorandum 580.4 have been trained and proficiency-tested to run tests for TADs. With the permission of the NVSL Director, the SAHO, and the USDA Assistant District Director, these select NAHLN laboratories may run designated tests in parallel with NVSL or FADDL. When approved, this parallel testing

process can provide more timely “preliminary” results, which may facilitate local decision making. At present, assays for FMD, HPAI (highly pathogenic avian influenza), and END (exotic Newcastle Disease) have been successfully deployed to some NAHLN laboratories for use in national surveillance programs.

Response, Management, and Control

A TAD response will be conducted according to the guidelines set forth in the NRF. This response framework incorporates best practices and procedures from various emergency management disciplines. It integrates them into a unified structure that forms the basis of how the federal government coordinates with state, tribal, and local governments and the private sector during all national response incidents including animal disease outbreaks. Under the NRF, the USDA is the lead agency coordinating the protection of agriculture and natural resources. All national responses are conducted in accordance with NIMS, which established a national emergency response framework to allow local, state, tribal, and federal agencies to more efficiently and quickly work together in an emergency. The NIMS uses the ICS to organize the response. The ICS is designed to be expandable and to meet the needs associated with incidents of all sizes, to allow individuals from a variety of agencies to meld more efficiently into a common management structure, to be cost-effective by reducing duplication of effort, and to provide needed logistic, administrative, and operational staff. There are five main management functions in the ICS: incident command, operations, planning, logistics, and finance. Most veterinarians work in the operations or planning sections during a TAD response. The operations section is where the bulk of the tactical field work is conducted, such as diagnosis, biosecurity, surveillance, disinfection, and depopulation.

Once a TAD has been confirmed by the USDA, the notification and coordination process for all involved parties begins. This includes international, federal, state, tribal, local, industrial, and public stakeholders. Conference calls, electronic notification, and press conferences may be used to communicate key messages. In addition, if agroterrorism is suspected, the Federal Bureau of Investigation and the Department of Homeland Security will be involved in the response efforts. If a zoonotic disease is suspected, the Centers for Disease Control and Prevention and state and local public health departments will also be involved. Federal officials will notify the OIE of the situation so that the

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international communities are made aware of the change in the nation's animal health status. Throughout the response, the goal will be to maintain accurate, timely communications regarding the status and progress of the eradication efforts.

Once the diagnosis of the initial case is confirmed, more information must be gathered to determine the true magnitude and extent of the situation. The species affected, history of the diseased herd or flock (including recent animal movements), and stage of disease in the affected animals will provide valuable information regarding the likely extent of disease. Outbreaks can be large or small, simple or complex, and localized or widespread. Timely development of situational awareness will be critical for mobilizing the necessary resources to effectively respond to the situation.

Tactical measures or procedures used to control an outbreak may include quarantine and/or animal movement restrictions; biosecurity; epidemiologic investigations; surveillance for disease in surrounding areas; vaccination, depopulation, or treatment of affected animals; carcass disposal; disinfection; vector control; and education campaigns. The exact approach to control will vary by disease, affected region, and extent of the outbreak. In rare cases, federal and state resources will be sufficient to respond to and control the situation quickly. However, if the outbreak is large or widespread, it will require the use of additional personnel resources.

In the past, when APHIS VS required temporary personnel to assist with disease eradication, it used the National Animal Health Emergency Response Corps (NAHERC),[7] a roster of preregistered private veterinarians and animal health technicians, to assist with the control efforts. USDA plans to phase out NAHERC, but there are numerous opportunities at the local and state level to become trained and part of a response. Private veterinarians may be enlisted to examine herds or flocks for clinical disease, vaccinate animals, collect laboratory samples, perform necropsies, collect epidemiologic data, and euthanize infected animals. During the United Kingdom's 2001 FMD epidemic, many private veterinarians found that their practices had little business because their clients stopped using routine services as a precaution to reduce the chances that their farms would become infected. In other situations, veterinarians found that their clients’ animals were lost (depopulated) as a result of disease control efforts. In many cases, these private veterinarians joined the U.K. FMD task force as temporary veterinary inspectors (TVIs) working on behalf of the British government to assist in the control of the epidemic. Veterinarians in the United

States who may be interested in participating in an animal health emergency should contact the office of the SAHO for more information.

Business Continuity

TADs can have devastating effects on the animals, livestock industry, and U.S. economy. Eradicating the disease without destroying the industry is complex. The goals of a USDA response are to detect, control, contain, and eradicate the TAD in a manner that stabilizes animal agriculture, the food supply, and the economy while protecting public health and the environment. Another goal is to facilitate business continuity for noninfected animals and their products. The 2014-2015 highly pathogenic avian influenza demonstrated how science and risk-based approaches could be used to achieve this using the guidance in the Secure Poultry Supply Plans. Similar plans have been developed for FMD response for the dairy, beef, and pork industries. More information about the livestock Secure Food Supply Plans can be found at www.securemilk.org, www.securebeef.org, and www.securepork.org. Opportunities exist for veterinary practitioners to help their clients prepare ahead of an outbreak to protect their animals and livelihood.

Recovery

The goal of recovery is to return the nation to a status equal to or better than what existed before a TAD outbreak. Full recovery can be a long and arduous process. Recovery activities include payment for animals and materials destroyed for disease control purposes, successful decontamination, clean-up and restocking of affected premises, renegotiation and reestablishment of international trading status, and government and industry's reassurance to consumers and the public that the outbreak has been managed successfully. The OIE's Terrestrial Animal Health Code sets the minimum standards that guide when a country may recover its disease-free status. The OIE standards, which are a key component to the resumption of international trade, serve to reassure the international community that trading with a previously affected country is now safe.

The ultimate cost of an outbreak for a country, its producers, affected industries, and the public can be quite high. Many indirect costs and impacts beyond those to the directly affected industries can be significant yet difficult to

quantify.

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Future of Foreign Animal Disease Detection and Response

A comprehensive review of the national framework for addressing animal diseases was conducted by a committee assembled by the National Academies and published in 2005.[8] The committee's findings and recommendations support the compelling need for significant changes to create a new future for animal health in the United States. Some of the key findings included the need for new tools for detection, diagnosis, and risk analysis and the expansion of the NAHLN's capabilities for both routine and emergency diagnostics. A report by the National Academies in 2012 described the many accomplishments of NAHLN as a timely surveillance and diagnostic component of early transboundary disease detection since its creation in 2002.[9] Another improvement to diagnostic capabilities and research is the National Bio and Agro-defense Facility (NBAF), which is currently under construction, with the goal of being operational in December 2022.[10] This state-of-the-art laboratory will replace the aging facilities at Plum Island and further enhance laboratory and discovery capabilities.

In 2005, the National Academies committee concluded that animal health has broad implications, ranging from the health of individual animals and the well-being of human communities to issues of global security and the adequacy of the global food supply. Planning carefully for the future is a significant need. That remains unchanged today. Given the changing nature of the risks to animal health in this country, it is unlikely that the current philosophy on how to protect animal health will be adequate in the future.

Extraordinary changes including continued globalization will continue to present new threats to U.S. agriculture and necessitate the continued vigilance of the veterinary and agricultural communities. Although state and federal governments are working to provide more targeted, active surveillance programs, private veterinary practitioners, who on a daily basis provide health care to the national herd, will remain the core of the nation's early warning system for TAD surveillance. Therefore their awareness of TADs and willingness to serve in the critical role of being part of the nation's early warning system for TADs will continue to be a cornerstone of national defense against the intrusion and devastating impact of such diseases.

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Other Valuable Foreign Animal Disease–Related Web Resources

USDA Foreign Animal Disease Preparedness and Response Plan Training and Educational Materials. [WWW page] https://www.aphis.usda.gov/aphis/ourfocus/animalhealth/emergencymanagement/ct_fad_prep_training_materials.

Center for Food Security and Public Health at Iowa State University. [WWW page] http://www.cfsph.iastate.edu/.

Institute for Infectious Animal Diseases. [WWW page] http://iiad.tamu.edu/.

Center of Excellence for Emerging and Zoonotic Animal Diseases. [WWW page] http://ceezad.org/.

National Agricultural Biosecurity Center, Kansas State University. [WWW page] http://www.k-state.edu/nabc/.

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• CHAPTER 48

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Use of Biologics in the Prevention of Infectious Diseases

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Current Concepts in Equine Vaccination and Infectious Disease Control

Nicola Pusterla • W. David Wilson

General Considerations

Programs for controlling infectious diseases are important components of management practices directed toward maximizing the health, productivity, and performance of horses.[1] Infectious disease in an individual horse or outbreaks of infection in a group occur when horses experience challenge with an infectious agent at a dose sufficient to overcome resistance acquired through previous natural exposure to the disease or through vaccination. For this reason, programs for controlling infectious diseases should have the following three goals:

1. To reduce exposure to infectious agents in the horses' environment
2. To minimize factors that diminish resistance
3. To enhance resistance through the use of vaccines (vaccination alone cannot be expected to prevent disease; management practices must reduce the challenge from infectious pathogens)

The incidence of infectious disease in horse populations tends to rise with an increased number and stocking density of susceptible horses at a facility, with movement of horses on and off the facility, and with favorable external environmental and management influences. Other factors that influence the risk of acquiring infection and developing disease include the age, type, breed, gender, and use of the animals; geographic, climatic, and other environmental factors; facilities' layout and management practices; and history of exposure to or vaccination against individual diseases.

The conditions on breeding farms, in performance and show horse barns, and at racetracks are ideal for introduction and transmission of infectious diseases, particularly those of the respiratory tract. On breeding farms, the introduction and commingling of horses of various ages and origins and the high proportion of young susceptible horses and pregnant mares create a situation that poses special problems and demonstrates some important considerations in the practice

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of disease control. The risk of acquiring infection can be reduced by maintaining distinct groups by age and function. Resident mares and foals should be kept separate from weanlings, yearlings, horses in training, and visiting mares. Visiting mares and other horses entering the farm should have a negative test result for equine infectious anemia (EIA) virus, either by enzyme-linked immunosorbent assay (ELISA) or the Coggins AGID test, and should be appropriately vaccinated and dewormed before arrival. They should be received and maintained in barns and paddocks separate from the resident farm population. Preferably, a specific group of caretakers should attend to incoming horses, and footbaths, separate equipment, and a clean change of coveralls and boots should be used.

New arrivals should be quarantined for 30 days and monitored for signs of contagious disease. The rectal temperature should be recorded at least once daily, and any prophylactic procedures not done before arrival should be performed. Foaling mares being sent to a distant breeding farm for breeding should be transported 6 to 8 weeks before foaling; this permits timely exposure to resident pathogens at the destination farm, which allows the mare's immune system to mount a response and concentrate antibodies in the colostrum to improve passive protection to specific pathogens of the foal. Mares being shipped short distances for breeding can be transported during estrus and returned to the farm on the same day to reduce the risk of the foal acquiring infection.

Regardless of the type of equine facility, any horse that becomes ill with a possibly contagious disease should be isolated, preferably in an air space separate from the remainder of the herd, for at least 10 days beyond complete abatement of clinical signs. Separate equipment should be used, and if a separate group of caretakers is unavailable for these animals, workers should always complete their work with healthy horses before handling sick horses. Caretakers should wash their hands and boots thoroughly between horses and wear different outer clothing or coveralls. Stalls that have housed sick horses should be cleaned thoroughly, disinfected, allowed to dry, and left empty as long as possible. This approach is particularly important in dealing with organisms such as *Streptococcus equi* subspecies *(S. equi)* that can survive in a protected moist environment for several weeks.[2]

In most equine enterprises, vaccination is important to the overall management program for controlling infectious diseases. No “standard” vaccination program can be recommended for all horses; each situation must be evaluated individually by weighing the risk of acquiring infection and the

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medical and economic consequences of infection against the cost and expected efficacy of the product or products being considered for inclusion in the program, as well as their potential for inducing adverse reactions. Cost should include expenses incurred and money lost during the time the horses are out of competition, labor and medication expenses if the animals develop clinical disease and require treatment, and the expenses in time, labor, and vaccines required for proper immunization. The client's expectations should be realistic, and the veterinarian should explain the following points carefully:

- Vaccination minimizes the risk of infection but does not prevent disease in all circumstances.
- The primary series of vaccines and booster doses should be administered appropriately before likely exposure.
- Horses in a population are not all protected equally or for an equal duration after vaccination.
- Whenever possible, all horses in a herd should be vaccinated on the same schedule; this simplifies record keeping, minimizes replication and transmission of infectious agents in the herd, and optimizes herd immunity by protecting those animals that responded poorly to vaccination.

A properly administered licensed product should not be assumed to provide absolute effective protection during any given field epidemic. Copies of the vaccination and health maintenance records should accompany each horse leaving the facility for sales, training, or breeding. Similarly, owners of equine facilities should establish prerequisites for vaccination of all horses entering the facility and request that copies of the vaccination records accompany those horses.

Client expectations and the goals of disease control programs vary considerably. In performance horses, the general goal is to minimize time spent

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out of training and thereby maximize earning potential. In this case, an enforced period of rest owing to infectious disease has much more profound economic consequences than a similar recommendation for a barren broodmare or backyard horse. On the other hand, many owners of backyard horses diligently vaccinate against even low-risk diseases, despite the expense involved, to keep their horses healthy.

Only federally licensed vaccines should be used, and strict attention must be paid to the manufacturer's recommendations for storage, handling, and routes of administration to maximize the product's efficacy and safety. However, research or clinical experience may support alternate protocols for vaccination that will improve the vaccine's efficacy without increasing adverse effects. The length of time necessary to induce a protective immune response should be considered in relation to expected exposure. When inactivated (killed) vaccines are administered by intramuscular (IM) injection, for example, optimal protection is generally not achieved until 2 to 3 weeks after completion of the primary series, or 1 or more weeks after administration of a booster dose. Inactivated vaccines administered intramuscularly generally induce a greater serologic response when an initial series of three doses is given rather than the two-dose series recommended by most vaccine manufacturers. Whereas a 3- to 4-week interval between the first and second doses of vaccine is generally appropriate, a longer interval of 3 to 5 months between the second and third doses appears to optimize priming of the immune system and protection.

The primary role of authorities charged with licensing vaccines in North America has traditionally been to ensure vaccine purity and safety, with less emphasis placed on documentation of efficacy.[3-5] Consequently, little published information was available in the past documenting the efficacy of most vaccines licensed in North America. The situation has improved substantially in recent years, to the extent that published efficacy data are available for almost all equine vaccines licensed in North America since 1999. Field experience and some experimental evidence suggest that the efficacy of vaccines directed against different diseases varies considerably and that efficacy also varies among the vaccines from different manufacturers directed against the same disease.[6-8]

Vaccination is unlikely to confer protection more durable than that produced by recovery from natural disease, especially when the route of vaccination (usually IM) is different from the route of natural infection; this is because vaccines frequently do not evoke the full array of protective immune responses induced by natural infection.[9,10] For example, the efficacy and durability of

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protection induced by parenteral vaccines against respiratory tract pathogens are frequently questioned.[4,5,10] In part, this reflects the fact that parenterally administered vaccines are generally poor inducers of the local mucosal immune responses that are important for effective protection against infection of the respiratory tract.[4,9,10] In addition, immunity achieved after natural infection with some respiratory tract pathogens is short lived.

Considerations for Use of Vaccines in Broodmares

The primary goals of vaccination programs for broodmares are (1) prevention of diseases that pose a risk to the mare or her fetus and (2) maximizing the level of colostral antibodies that will be passively absorbed by the neonatal foal after nursing, thus providing it with protection against diseases that pose a risk during the first few months of life. Additional considerations in selecting vaccines for use in pregnant mares include (3) safety to the mare and fetus, (4) the potential for interference between multiple vaccines administered simultaneously, and (5) the influence of pregnancy on vaccine responses.

Protecting the Mare Against Diseases That Pose a Risk to the Mare or Her Fetus.

Broodmares are at risk of exposure to the same diseases as performance and pleasure horses, so they should be regularly vaccinated against all core and specific risk-based diseases according to published recommendations. The high horse traffic and high concentration of foals and young horses that typify many breeding farms contribute to a high risk of exposure to contagious respiratory diseases, including equine herpesvirus (EHV)-4, EHV-1, influenza, and strangles. Inclusion of influenza in vaccination protocols for broodmares is routinely recommended, and addition of EHV-4 and strangles vaccines is frequently recommended when conditions of significant risk are anticipated. Vaccination of mares against equine viral arteritis (EVA) before breeding may be indicated when they are to be bred to a known or suspected EAV carrier stallion, by either natural cover or artificial insemination. Whereas protection of the broodmare, fetus, or herdmates against the abortifacient effects of EHV-1 or EAV is the primary goal underlying inclusion of these antigens in vaccination protocols for broodmares, the goal of protecting the foal features at least as prominently in the rationale for vaccinating mares against tetanus toxoid, West Nile virus (WNV), eastern equine encephalitis (EEE) virus, western equine

encephalitis (WEE) virus, rabies virus, equine influenza virus, equine herpesvirus-1 (EHV-1), EHV-4, and *S. equi*. Inclusion of rotavirus and botulism vaccines in protocols for pregnant mares is directed almost exclusively at protecting the young foal against these diseases.

Maximizing Maternally Derived Antibody Transfer.

Maintaining consistent broodmare vaccination protocols, which typically include administration of booster doses of vaccines during the last 2 months of gestation, will not only protect the mare but also maximize the likelihood that a uniformly high level of maternally derived antibody (MDA) transfer and passive protection will be achieved within the foal crop. This is particularly important for diseases that pose a risk to the foal during the first few weeks of life. Whereas intranasally administered vaccines may afford good protection to the mare, they are typically less effective than parenterally administered inactivated vaccines in stimulating high levels of circulating immunoglobulin (Ig)G, the isotype that is passively transferred to the foal in highest concentration. Parenterally administered vaccines are preferred over intranasally administered vaccines for vaccination of mares during late gestation.

Vaccine Safety in Broodmares.

Consideration of vaccine safety in broodmares must take into account risks to the pregnancy and safety to the fetus. Potential adverse effects of vaccines on pregnancy are difficult to document even when large numbers of mares are used, unless obvious problems occur. Because fetal organogenesis occurs early in gestation, and this period is also characterized by substantial embryonic loss, even in normal mares it is sound practice to avoid administering vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail. Few vaccines carry specific label recommendations for use in pregnant mares, and little published data exist to specifically document the safety of equine vaccines during pregnancy. Licensed vaccines that carry label recommendations for use in pregnant mares include two inactivated EHV-1 vaccines (Pneumabort-K+1b [Zoetis, Parsippany, NJ] and Prodigy [Merck Animal Health, Madison, NJ]) marketed for use in pregnant mares as an aid in prevention of EHV-1 abortion, the Calvenza line of inactivated influenza (Calvenza-03 EIV [equine influenza virus]), EHV-1 (Calvenza EHV), and influenza/EHV-1 combination (Calvenza-03 EIV/EHV) vaccines from

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Boehringer Ingelheim (Ingelheim am Rhein, Germany), one multivalent vaccine (Vetera Gold) from Boehringer Ingelheim containing Eastern and Western Encephalomyelitis virus, WNV, tetanus toxoid, EHV-1, EHV-4 and equine influenza virus, one inactivated *Neorickettsia risticii* vaccine (Equine Potomavac [Merial, Lyon, France]), one vaccine licensed for prevention of type B botulism in foals (BotVaxB [Neogen, Lansing, Mich.]), and one *Leptospira pomona* vaccine (LEPTO EQ INNOVATOR [Zoetis]) for the prevention of leptospiremia. One conditionally licensed vaccine (Equine Rotavirus Vaccine [Zoetis]) for prevention of rotavirus infection in foals is labeled for use in pregnant mares. Although not specifically labeled for administration during pregnancy, widespread use in practice over many years has failed to document that any of the inactivated vaccines currently marketed for use in horses pose an unacceptable risk to pregnant mares. Therefore pregnant mares are routinely vaccinated with inactivated vaccines directed against tetanus toxoid, EEE virus, WEE virus, WNV, equine influenza virus, EHV-4, *Streptococcus equi* and, to a lesser extent, *Neorickettsia risticii*, rabies virus, and Venezuelan equine encephalitis (VEE) virus. Similarly, adverse impacts on pregnancy have not been documented for modified live, intranasally administered *S. equi* (Pinnacle I.N. [Zoetis]) and equine influenza virus (Flu-Avert [Merck Animal Health]) vaccines or the modified live, parenterally administered EHV-1 vaccine (Rhinomune [Boehringer Ingelheim]). Safety of the recombinant WNV and influenza vaccines (Recombitek [Merial]) should not be a significant concern, because the modified live canarypox vector lacks the ability to infect mammalian cells. In addition, the equivalent canarypox-vectored influenza vaccine (ProteqFlu [Merial]) marketed in the United Kingdom is labeled for use during pregnancy. Although the *Flavivirus* chimera WNV vaccine (PreveNile [Merck Animal Health]) was not specifically labeled for use during pregnancy while it was on the market, more than 300 pregnant mares were vaccinated during safety trials for licensing, without apparent adverse effects on the conceptus. In contrast, modified live virus (MLV) VEE vaccines and live anthrax spore vaccines should not be used in pregnant mares. Protection of mares against the potential abortigenic effects of EVA infection is best accomplished by completing the primary immunization series before the mare enters the broodmare band and by administering subsequent boosters during the open period before rebreeding.[11]

The practice of booster vaccinating mares against multiple equine pathogens to maximize colostral transfer of antibodies to the foal results in the typical broodmare receiving multiple doses of many vaccine antigens and adjuvants

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during her lifetime. In addition to stimulating high levels of antibody against a range of antigens, this practice may also predispose these mares to a higher rate of local and systemic adverse reactions, an issue that not only warrants further investigation but may force horse owners and veterinarians to carefully consider strategies for revaccination.

Potential Interference Between Multiple Antigens Administered Concurrently.

The possibility that “competition” between multiple antigens will compromise the response to some or all of the administered antigens should be considered. When administration of multiple vaccines late in gestation is indicated, it is good practice to administer no more than four antigens at one time and to allow an interval of 3 to 4 weeks between administering different vaccines.

Influence of Pregnancy on Vaccine Responses.

It is widely assumed that pregnant mares are fully capable of mounting appropriate cellular and humoral immune responses to vaccines, but this issue has received little research attention. Mares that have been primed before breeding appear to mount appropriate anamnestic responses to vaccines, but preliminary data suggest that the humoral response to primary vaccination with several inactivated vaccines, including WNV and rabies virus, may be downregulated during gestation, resulting in failure of some vaccinated mares to passively transfer specific antibodies to the foal via colostrum.

Vaccination of Foals and Influence of Maternal Antibodies on Vaccine Responses

MDAs and perhaps other immune effectors (e.g., lymphocytes) that are concentrated in colostrum and are passively transferred to the foal play a crucial role in defense against pathogens encountered during the first few months of life while endogenous immune function continues to mature. Passive transfer of MDAs should therefore be exploited in immunization programs for foals by consistently administering booster doses of selected vaccines to mares 4 to 8 weeks before foaling and by ensuring that foals ingest adequate amounts of high-quality colostrum within 24 hours of birth. Besides passively protecting the foal, MDAs may also exert a profound inhibitory effect on the active immune response of the foal to antigens, including those contained in vaccines. This

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phenomenon is known as *maternal antibody interference*.

Several studies reported during the 1990s brought this issue into focus by demonstrating that foals younger than 6 months of age consistently failed to mount serologic responses to inactivated influenza vaccines.[12-18] Of potentially greater concern was the finding that a high proportion of foals vaccinated under the cover of MDAs not only failed to seroconvert in response to the recommended primary series of two or three doses of influenza vaccine but also failed to respond to multiple additional doses administered during the next year, suggesting induction of a potentially detrimental immunotolerance-like phenomenon.[15,16,19] Our studies confirmed an apparent lack of response of foals to multiple doses of inactivated influenza vaccines when the hemagglutination inhibition (HI) test was used to detect serologic responses, but responses were detected when the same samples were assayed using a sensitive isotype-specific ELISA. Rather than representing true tolerance, it appears MDAs may cause misdirection of the immune response away from the more important virus neutralizing IgGa and IgGb subisotypes in favor of the less effective IgG(T) subisotype of IgG.[12] Subsequent studies in which titers of total rather than antigen-specific IgG subisotypes were determined documented that the age-related increase in concentrations of IgGb lagged significantly behind increases in concentrations of other isotypes and remained below adult levels beyond 6 months of age.[20]

Maternal antibody interference has now been documented to be a significant issue for many other antigens, including tetanus toxoid, EEE virus, WEE virus, EHV-1, and EHV-4, contained in vaccines administered to foals.[12,21-25] Even low levels of antibody below those detectable by many routine serologic tests and below those thought to be protective can completely block the serologic response to some vaccines, resulting in a potentially prolonged period of susceptibility before the foal is capable of responding appropriately to vaccines.[24] These findings also indicate that it is not typically feasible to serologically test samples from foals to predict whether they will respond to particular vaccines. We now recommend that primary immunization with most vaccines containing inactivated antigens should be delayed until foals are 6 months of age or older, and with the exception of the rabies vaccine, three doses of vaccine should be included in the primary series rather the two doses routinely recommended by vaccine manufacturers. Typically, the third dose stimulates a serologic response of greater magnitude and durability than two

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doses and may also contribute to a higher “set point” for the response to subsequent booster doses.[12,24,26,27] In contrast to the results cited, maternal antibodies do not appear to exert a marked inhibitory effect on the immune response of foals to the inactivated, live recombinant, live chimera, or DNA WNV vaccines, thereby permitting antibody-positive foals as young as 3 months of age to be immunized successfully.[26,28,29] Similarly, the canarypox-vectored recombinant influenza vaccine has been shown to efficiently prime foals in the presence of MDA.[30]

Study results should be interpreted with caution because only humoral responses are typically assessed in MDA interference studies, and infectious challenge is not performed to confirm that lack of serologic response equates to lack of protection. Lack of a serologic response may correlate well with lack of protection for some diseases and some vaccines, whereas for others this may not be the case. In contrast, the presence of a serologic response may not correlate well with protection, as is frequently the case for respiratory tract pathogens. Because many commercially available vaccines are inactivated, adjuvanted, and administered by IM injection, they have limited potential to stimulate cellular and mucosal responses, so serologic responses induced by these vaccines likely correlate well with their potential to induce protection. In turn, MDA interference with serologic responses to inactivated vaccines likely equates to failure to induce protection. In contrast, failure to detect a serologic response to a modified live, vectored, DNA, or mucosally administered vaccine may not equate to lack of protection, because vaccines of these types induce a broader array of systemic and local responses that may not be affected by MDAs.

If MDA interference were not an issue, the approach to vaccination of foals would be greatly simplified because primary vaccination against all of the important diseases could be completed before MDAs had declined to nonprotective levels. In effect, the “window of susceptibility” would be eliminated. In reality, an attainable goal is to maximize the beneficial effects of MDAs while minimizing their negative impact on primary immunization. To best meet this goal, it is necessary to decide which one (or both) of the following is the primary focus: (1) to protect the foal and weanling against specific high-risk infectious diseases that affect this age group and have the potential to cause significant disease, either directly or by predisposing to other secondary infections, or (2) to initiate primary immunization to protect against disease later in life.

Assessing risk takes into account both the likelihood the foal will become

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infected and the risk of serious sequelae or death if the horse does become infected and does develop disease. If the disease affects the foal early in life, such as is the case with rotavirus (RV) infection, there is usually insufficient time to induce a protective immune response by actively immunizing the foal. Under these circumstances, the approach should be to maximize the degree of protection passively transferred from the dam via colostrum. Other diseases like rabies can affect horses of all ages, but the risk of acquiring infection is generally low.

Diseases of Moderate to High Risk to Young Foals but Low Risk to Adults

Diseases of moderate to high risk to young foals but low risk to adults include equine rotavirus infection (on certain breeding farms in certain years) and, in geographic areas such as Kentucky and some other Eastern states, type B botulism. For these diseases, the following approach is appropriate:

- Booster-vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Introduce management practices to reduce exposure to the infectious agent.
- Vaccinate the foal if risk continues beyond the first few months of life.

Diseases of Moderate to High Risk for Weanlings and Older Horses but Lower Risk to Young Foals Born to Vaccinated Mares

Diseases of moderate to high risk for weanlings and older horses but lower risk to young foals born to vaccinated mares include EHV-4, EHV-1, strangles, influenza, tetanus, EEE, and WNV infection. For these diseases, the following approach is appropriate:

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- Vaccinate the dam before foaling to maximize uniformity of passive transfer.
- Ensure good passive transfer of maternal antibodies.
- Start foal vaccination after the risk of maternal antibody interference is no longer present in most foals. When several vaccine types are available for a particular disease, the vaccine that is least subject to MDA interference should be used. Introduce management practices to reduce exposure to the infectious agent while primary vaccination is being completed.
- If a two-dose primary series is recommended for adult horses, use three or more doses of vaccine in the primary series to improve the chances that foals that do not respond to earlier doses will respond to additional doses administered later.

Diseases of Low Risk to Foals

Diseases of low risk to foals in most circumstances include rabies, equine neorickettsiosis (EN), WEE, and EVA. For these diseases, the following approach is appropriate:

- Vaccinate the dam before foaling if the disease is a significant risk to adult horses and a vaccine shown to be safe for use in pregnant mares is available. If the available vaccines are not considered safe for use in pregnant mares, administer boosters before breeding.
- Ensure good passive transfer of maternal antibodies.

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- Start foal vaccination after the risk of maternal antibody interference is no longer present in any foal (typically 9 months to 1 year of age)

Adverse Reactions to Vaccines

Though uncommon, the possibility always exists for adverse reactions (including anaphylaxis) associated with vaccine administration, so vaccines should be administered by or under the direct supervision of a veterinarian. Adverse reactions should be reported to the vaccine's manufacturer and the U.S. Department of Agriculture (USDA) (1-800-752-6255) or the U.S. Pharmacopeia (USP) Veterinary Practitioners Reporting Program (forms may be obtained or reports submitted by calling the USP at 1-800-487-7776). Anaphylaxis constitutes a life-threatening emergency requiring prompt treatment with epinephrine (1 mg/mL; equivalent to 5 to 10 mL of a 1 mg/mL dilution IM for a 450-kg horse). Repeated doses of epinephrine can be administered at 15-minute intervals if necessary. It has recently been shown that horses vaccinated with viral vaccines can develop IgE responses to nontarget antigens, including bovine serum albumin (BSA), suggesting that subsequent administration of another viral vaccine containing the same component could elicit an adverse response, including anaphylaxis.[31]

Local irritant tissue reactions occur more frequently, particularly when polyvalent combination vaccines and injectable strangles vaccines are used. These reactions are usually self-limiting, but resolution can be promoted by parenteral or oral (PO) administration of nonsteroidal antiinflammatory drugs (NSAIDs), topical application of warm compresses or the cutaneously absorbed NSAID diclofenac (Surpass [IDEXX Pharmaceuticals, Greensboro, N.C.]), and gentle exercise. Significant reactions in the neck muscles may make the horse reluctant to lower or raise its head; feed and water buckets should be positioned accordingly. Occurrence of externally visible local reactions can be reduced by administration of the vaccine deep in the semimembranosus and semitendinosus muscles of the hindleg rather than in the neck and by allowing the horse to exercise after vaccination. Horses that repeatedly react to polyvalent vaccines may benefit from the administration of NSAIDs or antihistamines before vaccination, administration of the individual antigenic components separately in different sites, use of a different brand of vaccine, use of a vaccine that can be

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administered by a route other than IM, or use of a vaccine that contains a different adjuvant or no adjuvant at all.

Some horses develop transient self-limiting systemic signs that may include fever, anorexia, lethargy, colic, diarrhea, tachycardia, and congested mucous membranes after IM administration of vaccines. Systemic signs are perhaps more common with certain vaccines but can be associated with any vaccine.[32,33] In addition, inactivated Immune Stimulating Complex (ISCOM) and live recombinant vectored tetanus and influenza combination vaccines have been shown to elicit a prominent acute phase inflammatory response of several days' duration in vaccinated horses.[34] A similar response likely occurs with other vaccines. It is therefore inadvisable to give horses any injectable vaccine within 2 weeks before a show, performance event, sale, or prolonged transportation. It may also be beneficial to minimize environmental dust when vaccinating horses known to have allergic airway disease or hypersensitivity.[32]

If unacceptable reactions occur repeatedly, the need for continued annual or more frequent revaccination against individual antigens should be carefully reevaluated, taking into account risk of disease balanced against the risk of an adverse reaction. Many horses that experience adverse reactions have received numerous doses of multiple vaccine antigens, repeated over the years. In this situation, the vaccination protocol should be "pared down" so that only the most essential antigens are administered and the maximum possible interval between boosters is employed. For diseases like rabies and tetanus, for which resistance can reasonably be correlated with circulating antibody titer, one possible approach to define the maximum or optimal interval between booster doses would be to measure the antibody titer. Unfortunately, this approach is currently limited by the paucity of laboratories that offer this type of testing on a routine basis, inexpensively, and with a short turnaround time. Introduction of commercially available ELISA testing for antibodies to the SeM protein of *S. equi* (Equine Diagnostic Solutions, Lexington, Ky.) and neutralizing antibody testing for WNV virus (Cornell University, Colorado State University, the University of Florida, and the USDA Animal and Plant Health Inspection Service [APHIS] National Veterinary Services Laboratory) in recent years has made it possible to refine vaccination protocols for these diseases in horses that experience adverse reactions to vaccination. Testing for rabies antibodies is available through Kansas State University, and testing for antibodies to other pathogens may be available through state diagnostic laboratories.

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Available Vaccines and the Concept of Core and Noncore Vaccines

Fully licensed vaccines are now available in North America as aids to the prevention of tetanus; viral encephalomyelitis (EEE, WEE, VEE); WNV infection; influenza; EHV-1 and EHV-4 infection; strangles; rabies; EVA; EN; and type B botulism. In addition, conditionally licensed vaccines are available to immunize horses against rotavirus, equine rhinitis A virus (ERAV), and *Corynebacterium pseudotuberculosis*. Tetanus, rabies, and viral encephalomyelitis caused by EEE, WEE, and WNV pose a threat to horses in all geographic areas and are therefore considered to be core diseases against which all horses in North America should be vaccinated. The abortigenic potential of EHV-1 warrants inclusion of this disease in the core for all pregnant broodmares. Although influenza is not routinely included as a core disease, vaccination against this highly contagious respiratory tract infection is strongly recommended for all horses likely to be colocated with horses from other facilities during transportation or at sales, shows, trail rides, races, or other events. The remaining diseases for which vaccines are available are considered "noncore" or "risk based." Indications for use of vaccines against these diseases are discussed in relevant sections that follow later in this chapter. Table 48.1 details the types of vaccines licensed for use in horses in the United States. Tables 48.2 through 48.4 provide general guidelines for use of the most frequently indicated equine vaccines in foals, weanlings, yearlings, and adult horses under various management conditions and in various geographic locations.

TABLE 48.1

Types of Equine Vaccines Licensed in the United States

Disease	Dead Vaccines		Live Vaccines		DNA Vaccine
	Inactivated	Subunit	Modified Live	Recombinant	
Tetanus		X			
Western equine encephalitis (WEE)	X				
Eastern equine encephalitis (EEE)	X				
Venezuelan equine encephalitis (VEE)	X				
West Nile	X			X, X (chimera)	X
Equine influenza	X		X	X	
Equine herpesvirus 1	X		X		

Equine herpesvirus 4	X				
Strangles		X	X		
Equine viral arteritis			X		
Rabies	X				
Equine neorickettsiosis (Potomac horse fever)	X				
Botulism		X			
Rotavirus (conditional license)	X				
Equine rhinitis A virus (conditional license)	X				
Anthrax			X		
Leptospira interrogans serovar Pomona	X				
Corynebacterium pseudotuberculosis bacterin-toxoid (conditional license)	X				

TABLE 48.2

Guidelines for Vaccination of Adult Horses, Excluding Broodmares, Against Core and Noncore (Risk-Based) Diseases

Disease/Vaccine	Adult Horses (>1 Year of Age) Previously Vaccinated Against Disease Indicated	Adult Horses (>1 Year of Age) Not Previously Vaccinated Against Disease Indicated or Lacking Vaccination History	Comments
Core Diseases[a]			
Tetanus (toxoid)	Toxoid: annual revaccination	Toxoid: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate annually.	Booster at time of penetrating injury or surgery if last dose was administered >6 months previously
Eastern and Western equine encephalomyelitis (EEE, WEE)	Inactivated: annual revaccination in spring, before onset of vector season	Inactivated: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate annually before onset of next vector season.	Consider a 6-month revaccination interval for horses residing in endemic areas with a prolonged vector season (e.g., southeastern states).
West Nile virus (WNV)	Inactivated vaccine or live recombinant canarypox-vectored vaccine: annual	Inactivated vaccine or live recombinant canarypox-vectored vaccine: 2-dose primary series; second dose 4-6	When using an inactivated product or live recombinant product, consider a 6-month revaccination interval for: • Horses residing in endemic areas with a prolonged vector season • Juvenile horses (<5 years of age)

	revaccination in spring, before onset of vector season	weeks after first dose Revaccinate annually before onset of next vector season. Inactivated *Flavivirus* chimera vaccine: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate annually before onset of next vector season. Live *Flavivirus* chimera vaccine: 1-dose primary series Revaccinate annually before onset of next vector season.	• Geriatric horses (>15 years of age) • Immunocompromised horses For naive horses being imported into an endemic area during vector season, preferred approach is to complete primary vaccination series before importation. If this approach is not feasible, protect horses from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (canarypox-vectored or live *Flavivirus* chimera) that have most rapid onset of immunity.
Rabies	Inactivated: annual revaccination	Inactivated: 1-dose primary series Annual revaccination	Booster vaccination induces persistently elevated levels of antirabies antibody.
Noncore (Risk-Based) Vaccines[b]			
Anthrax (rarely indicated)	Live spore vaccine: annual revaccination	Live spore vaccine: 2-dose primary series; second dose 3-4 weeks after first dose Annual revaccination	Use only in endemic areas or in the face of an outbreak. Antimicrobial drugs must not be given concurrently with this vaccine. Administer subcutaneously in neck. Use caution during storage, handling, and administration. Consult a physician immediately if human exposure to anthrax vaccine occurs by accidental injection, ingestion, or otherwise through conjunctivae or broken skin.
Botulism	Toxoid: annual revaccination	Toxoid: 3-dose primary series; second dose 4 weeks after first dose; third dose 4 weeks after second dose Annual revaccination	
Equine herpesvirus (EHV)	Inactivated or modified live: semiannual (6-month interval) to annual revaccination (see comments)	Inactivated or modified live: 3-dose primary series; second dose 4-6 weeks after first dose; third dose 4-6 weeks after second dose	A 6-month revaccination interval is recommended for: • Horses <5 years of age • Horses on breeding farms or in contact with pregnant mares • Horses housed at facilities with frequent equine movement on and off the premises • Performance or show horses at high risk
Equine influenza	Modified live	Modified live cold-	

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	cold-adapted intranasal, inactivated, or live canarypox-vectored recombinant vaccine: semiannual for horses with ongoing risk of exposure Annual for horses at low risk for exposure	adapted intranasal vaccine: 1-dose primary series Revaccinate semiannually to annually. Inactivated vaccines: 3-dose primary series; second dose 4-6 weeks after first dose; third dose 3-6 months after second dose Revaccinate semiannually to annually. Live canarypox-vectored recombinant: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate semiannually to annually.	
Equine viral arteritis (EVA)	Modified live virus vaccine: annual revaccination. Stallions and teasers: vaccinate 3-4 weeks before start of breeding season. Mares: vaccinate when open.	Modified live virus vaccine: 1-dose primary series (see comments)	Before initial vaccination, intact males and any horses potentially intended for export should undergo serologic testing and be confirmed negative for antibodies to EAV. Samples for testing should be collected shortly before or, preferably, at the time of vaccination. All first-time vaccinated stallions should be isolated for 3 weeks after vaccination before being used for breeding.
Equine neorickettsiosis (Potomac horse fever)	Inactivated vaccines: semiannual to annual revaccination	Inactivated vaccines: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate semiannually to annually.	Because protection following vaccination is incomplete and short-lived, a revaccination interval of 3-4 months has been advocated in endemic areas when disease risk is high. However, strategic revaccination to maximize immunity before expected peak challenge in summer and fall is the preferred approach if vaccination is elected as an adjunct to strategic environmental control measures.
Rotavirus	Not applicable	Not applicable	
Strangles	Inactivated M-protein subunit or modified live intranasal vaccines:	Inactivated M-protein subunit vaccines: 2- to 3-dose series; second dose 2-4 weeks after first	Vaccination is not recommended as a strategy in outbreak mitigation, but vaccination may be warranted on farms with endemic strangles, with the understanding that the risk of adverse vaccine reactions is higher in exposed horses.

	semiannual to annual revaccination	dose; third dose (when recommended by manufacturer) 2-4 weeks after the second dose. Revaccinate semiannually. Modified live intranasal vaccine: 2-dose primary series administered IN; second dose 3-4 weeks after first dose Revaccinate semiannually to annually.	
Leptospirosis	Inactivated vaccines: annual revaccination	Inactivated vaccines: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate annually.	

[a]Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

[b]Noncore (risk-based) vaccines are selected for use on the basis of assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of noncore vaccines will vary among individuals, populations, and/or geographic regions.

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TABLE 48.3

Guidelines for Vaccination of Broodmares Against Core and Noncore (Risk-Based) Diseases

Disease/Vaccine	Previously Vaccinated Broodmares	Broodmares Not Previously Vaccinated or Lacking Vaccination History	Comments
Core Diseases[a]			
Tetanus	Toxoid: annual revaccination 4-6	2-dose primary series; second	Booster at time of penetrating injury or surgery if last dose was administered more than 6 months previously

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	weeks prepartum	dose 4-6 weeks after first dose Revaccinate 4-6 weeks prepartum, depending on timing of second dose.	
Eastern and Western equine encephalomyelitis (EEE, WEE)	Annual, 4-6 weeks prepartum	2-dose primary series; second dose 4 weeks after first dose Revaccinate 4-6 weeks prepartum, depending on timing of second dose.	Consider a 6-month revaccination interval for mares residing in endemic areas with a prolonged vector season (e.g., southeastern states).
West Nile virus (WNV)	Annual, 4-6 weeks prepartum	It is preferable to vaccinate naive mares when open. When risk is high, initiate primary series as follows: Inactivated vaccine or live recombinant canarypox-vectored vaccine: 2-dose primary series; second dose 4-6 weeks after first dose Revaccinate 4-6 weeks prepartum, depending on timing of second dose. Inactivated *Flavivirus* chimera vaccine: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate annually, before onset of the next vector season. Live *Flavivirus*	When using an inactivated product or live recombinant product, consider a 6-month revaccination interval for mares residing in endemic areas with a prolonged vector season. For naive mares being imported into an endemic area during the vector season, preferred approach is to complete the primary vaccination series before importation. If this approach is not feasible, protect them from being bitten by mosquitoes if possible, and vaccinate them with one of the vaccines (canarypox-vectored or live *Flavivirus* chimera) that have the most rapid onset of immunity.

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		chimera vaccine: 1-dose primary series Revaccinate 4-6 weeks prepartum, depending on timing of first dose.	
Rabies	Annual, before breeding *OR* 4-6 weeks prepartum	1-dose primary series Annual revaccination before breeding *OR* 4-6 weeks prepartum	Booster vaccination induces persistently elevated levels of antirabies antibody. This vaccine may be given post foaling but before breeding to reduce the number of vaccines given to mares prepartum.
Equine herpesvirus (EHV)	3-dose series with product labeled for prevention of EHV-1 abortion Administer during fifth, seventh, and ninth months of gestation.	3-dose series with product labeled for prevention of EHV-1 abortion Administer during the fifth, seventh, and ninth months of gestation.	
Noncore (Risk-Based) Vaccines[b]			
Anthrax	Not recommended for use during gestation	Not recommended for use during gestation	
Botulism	Annual, 4-6 weeks prepartum	3-dose series: first dose during eighth month of gestation; second dose 4 weeks after first dose; third dose 4 weeks after the second dose	
Equine influenza	Inactivated vaccines: semiannual, with 1 dose administered 4-6 weeks prepartum Canarypox-vectored vaccine: semiannual, with one	Inactivated vaccine: 3-dose primary series; second dose 4-6 weeks after first dose; third dose 4-6 weeks prepartum Canarypox-vectored vaccine: 2-dose primary series;	The MLV intranasal influenza vaccine can be used to protect pregnant mares against influenza, but its use for prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody. Administration of an inactivated or canarypox-vectored vaccine for the prefoaling booster is the preferred approach.

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	dose administered 4-6 weeks prepartum	second dose 4-6 weeks after first dose but no later than 4 weeks prepartum	
Equine viral arteritis (EVA)	Administration during pregnancy is not recommended unless risk of exposure is high.	Administration during pregnancy is not recommended unless risk of exposure is high.	Mares potentially intended for export should undergo serologic testing immediately before initial vaccination and be confirmed negative for antibodies to EAV.
Equine neorickettsiosis (Potomac horse fever)	Semiannual, with one dose administered 4-6 weeks prepartum	2-dose primary series: first dose: 8-10 weeks prepartum; second dose 4-6 weeks prepartum	Strategic environmental control measures are important for effective control.
Rotavirus	3-dose series: first dose at 8 months' gestation; second dose 4 weeks after first dose; third dose 4 weeks after second dose	3-dose series: first dose at 8 months' gestation; second dose 4 weeks after first dose; third dose 4 weeks after second dose	Check serum concentration of immunoglobulin in foal to verify adequate passive transfer.
Strangles	Inactivated M-protein subunit vaccines: semiannual, with 1 dose given 4-6 weeks prepartum	Inactivated M-protein subunit vaccines: 3-dose primary series; second dose 2-4 weeks after the first dose; third dose 4-6 weeks prepartum	MLV intranasal strangles vaccine can be used to protect pregnant mares, but its use for the prepartum booster is not recommended because it does not reliably stimulate high levels of circulating antibody. Administration of an inactivated M-protein vaccine for the prefoaling booster is the preferred approach.
Leptospirosis	Inactivated vaccines: annual revaccination	Inactivated vaccines: 2-dose primary series; second dose 3-4 weeks after first dose Revaccinate annually.	Inactivated vaccine can be used in pregnant mares in all 3 trimesters of gestation.

[a]Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

[b]Noncore (risk-based) vaccines are selected for use on the basis of assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of noncore vaccines will vary among individuals, populations, and/or geographic regions.

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TABLE 48.4

Guidelines for Vaccination of Foals, Weanlings, and Yearlings Against Core and Noncore (Risk-Based) Diseases

Disease/Vaccine	Foals and Weanlings (<12 Months of Age) of Mares Vaccinated During Prepartum Period Against Disease Indicated	Foals and Weanlings (<12 Months of Age) of Mares Not Vaccinated During Prepartum Period	Yearlings	Comments
Core Diseases[a]				
Tetanus (toxoid)	Toxoid: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 3-5 months after second dose (i.e., 10-12 months of age)	Toxoid: 3-dose primary series; first dose at 1-4 months of age; second dose 4-6 weeks after the first dose; third dose 3-5 months after second dose	Annual	
Eastern and Western equine encephalomyelitis (EEE, WEE)	Inactivated vaccine: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age, before onset of next vector season	Inactivated vaccine: 3-dose primary series; first dose at 3-4 months of age; second dose 4 weeks after first dose; third dose 4-8 weeks after second dose (shorter interval applies to foals receiving their primary series during mosquito season)	Annual in spring, before onset of vector season	Month of birth and geographic location influence risk of exposure to insect vectors at specific foal ages. Scheduling of primary immunization series may be amended by administration of EEE/WEE vaccines to foals at an earlier age if vectors are present. In the southeastern United States where vectors are present year-round, an additional dose should be added to primary series, beginning at 2-3 months of age. Fourth dose in the primary series should be administered at 10-12 months of age.
West Nile virus (WNV)	Inactivated vaccine or live recombinant canarypox-vectored vaccine: 3-dose primary series; first dose at	Inactivated vaccine or live recombinant canarypox-vectored vaccine: 3-dose primary series; first dose at 3-4 months of age; second dose 4 weeks after first	Annual in spring, before onset of vector season	Month of birth and geographic location influence risk of exposure to insect vectors at specific foal ages. Scheduling of primary immunization series may be amended by administration of

	4-6 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age, before onset of next vector season	dose; third dose 4-8 weeks after second dose (shorter interval applies to foals receiving their primary series during mosquito season)		WNV vaccines to foals at an earlier age if vectors are present. In the southeastern United States where vectors are present year-round, primary vaccination series should be initiated at 3 months of age.
	Live *Flavivirus* chimera vaccine: 2-dose primary series; first dose at 5-6 months of age; second dose at 10-12 months of age, before onset of next vector season	Live *Flavivirus* chimera vaccine: 2-dose primary series; first dose at 5-6 months of age; second dose at 10-12 months of age before onset of next vector season		There are no published data regarding use of the live *Flavivirus* chimera product in foals <5 months of age. If administered to foals <5 months of age, the recommended schedule for primary vaccination should be completed by administration of a dose of vaccine at 5 months of age or older.
Rabies	2-dose primary series: first dose at 6 months of age; second dose 4-6 weeks after first dose; next dose at 10-12 months of age	1- or 2-dose primary series: first dose at 3-4 months of age; second dose 4-6 weeks after first dose (not necessary if dam is seronegative); next dose at 10-12 months of age	Annual	For foals of mares with an unknown vaccination history, either follow approach outlined for foals of vaccinated mares or determine serologic status of foal (or mare) and use results to classify foal as either being from a vaccinated or unvaccinated mare.
Noncore (Risk-Based) Vaccines[b]				
Anthrax (rarely indicated)	Not applicable because vaccination of pregnant mares is not recommended	No age-specific guidelines are available for this vaccine. Manufacturer's recommendation is for primary series of 2 doses administered subcutaneously (in the neck) at a 2-3–week interval.	Annual, in spring	Anthrax vaccination is rarely indicated—only in focal endemic areas. Antimicrobial drugs must not be given concurrently with this vaccine. Exercise caution during storage, handling, and administration of this live bacterial product. Consult a physician immediately should accidental human exposure (via mucous membranes, conjunctivae, or broken skin) occur.
Botulism (type B toxoid)	3-dose primary series: first dose as early as 2-3 months of age; second dose 4 weeks after first dose; third dose 4 weeks after second dose	3-dose primary series: first dose as early as 1-3 months of age; second dose 4 weeks after first dose; third dose 4 weeks after second dose	Annual	Limited information suggests that maternal antibody does not interfere with vaccination, so foals at high risk may be vaccinated as early as 2 weeks of age.
Equine	Inactivated EHV-1,	Inactivated EHV-1,	Semiannual (6-	The benefit of intensive

herpesvirus (EHV)	EHV-1/4, or modified live EHV-1 vaccine: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 3-5 months after second dose (i.e., 10-12 months of age)	EHV-1/4, or modified live EHV-1 vaccine: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 3-4 months after second dose (i.e., 10-12 months of age)	month interval)	vaccination programs directed against EHV-1 and EHV-4 in foals and young horses is not clearly defined because, despite frequent vaccination, infection and disease continue to occur. It is difficult to induce active immunity before weanlings experience field challenge.
Equine influenza	Inactivated vaccine: 3-dose primary series; first dose at 6-7 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age Live canarypox-vectored recombinant vaccine: 3-dose primary series: first dose at 5-6 months of age; second dose 5 weeks after first dose; third dose at 10-12 months of age Modified live cold-adapted intranasal vaccine: 1-dose primary series: first dose at 11 months of age If vaccination earlier than 11 months is elected, use a 2-dose primary series: first dose at 6-10 months of	Inactivated vaccine: 3-dose primary series; first dose at 6-7 months of age; second dose 4-6 weeks after first dose; third dose at 10-12 months of age Live canarypox-vectored recombinant vaccine: 3-dose primary series; first dose at 5-6 months of age; second dose 5 weeks after first dose; third dose at 10-12 months of age Modified live cold-adapted intranasal vaccine: 1-dose primary series: first dose at 11 months of age If vaccination earlier than 11 months is elected, use a 2-dose primary series: first dose at 6-10 months of age second dose at 11-12 months of age	Semiannual (6-month interval) Semiannual (6-month interval) Semiannual (6-month interval)	An unusually high risk of exposure may warrant vaccination of younger foals. Because potentially interfering maternal anti-influenza antibody is likely to be present, a complete primary vaccination series should be given after 6 months of age. The modified live intranasal vaccine is licensed for administration to horses 11 months of age or older with a label recommendation of 1 dose for primary immunization. If vaccine is given before 11 months of age, a second dose should be administered at 11 months or older.

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	age; second dose at 11-12 months of age			
Equine viral arteritis (EVA)	Colt (male) foals: single dose at 6-12 months of age (see comments)	Colt (male) foals: single dose at 6-12 months of age (see comments)	Annual for colts intended for use as breeding stallions	Before initial vaccination, colt (male) foals should undergo serologic testing and be confirmed negative for antibodies to EAV. Maternally derived anti-EAV colostral antibodies can persist in foal for up to 6 months, so testing and vaccination should not be performed before 6 months of age. Keep colts isolated for 3 weeks after vaccination.
Equine neorickettsiosis (Potomac horse fever)	3-dose primary series: first dose at 5-6 months of age; second dose 3-4 weeks after first dose; third dose at 10-12 months of age	3-dose primary series: first dose at 5-6 months of age; second dose 3-4 weeks after first dose; third dose at 10-12 months of age	Semiannual to annual	If warranted by risk, vaccine may be administered to younger foals, in which case additional doses should be administered at 4-week intervals until foal is 6 months of age.
Rotavirus	Not recommended in foals	Not recommended in foals	Not applicable	
Strangles	Inactivated M-protein subunit vaccines: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after first dose; third dose 4-6 weeks after second dose Modified live intranasal vaccine: 3-dose primary series; first dose at 6-9 months of age; second dose 3-4 weeks after first dose; third dose at 11-12 months of age	Inactivated M-protein subunit vaccines: 3-dose primary series; first dose at 4-6 months of age; second dose 4-6 weeks after the first dose; third dose 4-6 weeks after second dose Modified live intranasal vaccine: 3-dose primary series; first dose at 6-9 months of age; second dose 3-4 weeks after first dose; third dose at 11-12 months of age	Semiannual	Vaccination is not routinely recommended as a strategy in outbreak mitigation but may be warranted on farms with endemic strangles, with the understanding that risk of adverse vaccine reactions is higher in exposed horses. If warranted by risk, the modified live vaccine (MLV) may be safely administered to foals as young as 6 weeks of age. However, vaccine efficacy in this age group has not been determined. If the MLV product is administered to foals <6 months of age, administration of third dose of vaccine should be timed 2-4 weeks before weaning if possible.
Leptospirosis	Inactivated vaccines: 2-	Inactivated vaccines: 2-dose	Annual	

	dose primary series; second dose 3-4 weeks after first dose Revaccinate annually.	primary series; second dose 3-4 weeks after first dose Revaccinate annually.		

[a]Core vaccines protect against diseases that are endemic to a region, are virulent or highly contagious, pose a risk of severe or fatal disease, have potential public health significance, and/or are required by law. Core vaccines have clearly demonstrable efficacy and have a sufficiently high level of patient benefit and low level of risk to justify their use in all equids in North America.

[b]Noncore (risk-based) vaccines are selected for use on the basis of the assessment of risk performed by, or in consultation with, a licensed veterinarian. Use of noncore vaccines will vary among individuals, populations, and/or geographic regions.

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Vaccination Recommendations for Specific Diseases

Tetanus

All horses are at risk for developing tetanus, an often fatal disease caused by a potent neurotoxin elaborated by the anaerobic spore-forming bacterium *Clostridium tetani*. Infection of tissues typically occurs via puncture wounds (particularly those involving the foot or muscle), open lacerations, surgical incisions, exposed tissues like the umbilicus of foals, and the reproductive tract of the postpartum mare (especially in the event of trauma or retained placenta). *C. tetani* is present in the intestinal tract and feces of horses, other animals, and human beings, and spores are abundant, as well as ubiquitous, in soil. Spores of *C. tetani* survive in the environment for many years, resulting in an ever-present risk of exposure of horses and people on equine facilities. Because tetanus is expensive to treat and has a high mortality rate, all horses should be actively immunized using tetanus toxoid as part of the core vaccination program. Active immunization reduces the need to administer tetanus antitoxin, the use of which is associated with the risk of inducing potentially fatal serum hepatitis.

Protection against tetanus is mediated by circulating antibodies; toxin binding inhibition (ToBi) antibody titers of greater than 0.2 IU/mL are considered to be protective in the horse.[27,35] The many available vaccines are formalin-inactivated, adjuvanted toxoids that are inexpensive, safe, and potent antigens

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that induce an excellent serologic response and solid long-lasting immunity when administered according to manufacturer recommendations. Primary immunization involves administration of two doses of toxoid at 3- to 6-week intervals. Titers of specific antibody increase to protective levels within 14 days after administration of the second dose in the primary series and, in adult horses, persist at detectable levels for 12 months or longer, depending on the adjuvant system used in the vaccine.[27,35-37] A recent study documented substantial differences between currently licensed combination tetanus-encephalomyelitis vaccines with regard to the magnitude of the vaccine-induced tetanus-specific IgGb and IgG(T) antibody responses.[8] The vaccine containing a Carbopol adjuvant induced substantially higher antibody titers than those containing either saponin or squaline combined with surfactants.[8] Revaccination once annually is recommended.

No published challenge studies are available to document the speed of onset or duration of protection induced by tetanus toxoid preparations currently licensed in North America. Conclusions regarding their efficacy are therefore based on the serologic response obtained in horses and laboratory animals and on field experience. However, a challenge study conducted in Europe over 60 years ago found that horses were resistant to challenge 8 days after receiving a single injection of tetanus toxoid, before antibody could be detected in their serum.[38] A second study demonstrated that a series of three doses of tetanus toxoid induced protection lasting for at least 8 years, and perhaps for life, even when antibodies could no longer be detected.[35] A recent study in Europe documented that protective levels of antibody (>0.2 IU/mL as measured by tetanus toxin-binding ELISA) persist for at least 18 months after revaccination of horses previously primed with a two-dose series of a tetanus toxoid/influenza ISCOM vaccine.[39] In contrast, tetanus has been documented in vaccinated horses in North America,[40] although survival was strongly associated with previous vaccination. Thus, it would not be prudent to recommend extension of the annual interval for revaccination with tetanus toxoid products available in North America, pending publication of data documenting duration of immunity (DOI). Vaccinated horses that sustain a wound or undergo surgery more than 6 months after receiving their previous tetanus booster should be revaccinated with tetanus toxoid immediately at the time of injury or surgery.

Annual revaccination of pregnant mares should be completed 4 to 8 weeks before foaling to protect the mare if she sustains foaling-induced trauma or

retained placenta and to enhance concentrations of specific immunoglobulins in colostrum. Colostrum-derived antibodies significantly interfere with the immune response of foals vaccinated with tetanus toxoid until they are about 6 months old.[12,36]

Primary vaccination of foals that have received appropriate transfer of colostral antibodies from a vaccinated mare should include three doses of tetanus toxoid beginning at age 6 months or older. Optimally, the interval between the first two doses of vaccine should be approximately 4 weeks, and the interval between the second and third doses should be 3 to 5 months. The three-dose primary series is recommended for foals because a high proportion of foals fail to seroconvert in response to two doses of tetanus toxoid regardless of whether maternal antibodies are detectable at administration of the first dose.[12,36] For foals born to nonimmune mares, this initial three-dose series can start at 1 to 4 months of age.

Tetanus antitoxin is produced by hyperimmunization of donor horses with tetanus toxoid. Administration of 1 vial of antitoxin (1500 IU) to nonvaccinated horses induces immediate passive protection that lasts not more than 3 weeks.[36] More prolonged protection may be accomplished with higher doses. In addition to the use of high doses of tetanus antitoxin to treat tetanus, indications frequently cited include administration to newborn foals born to unvaccinated mares and to unvaccinated horses that sustain an injury. In these cases the concurrent administration of tetanus antitoxin and tetanus toxoid at different sites using separate syringes has been advocated, followed by administration of additional doses of toxoid at 4- to 6-week intervals to complete the primary series.[41] Because a small but significant number of horses experience serum sickness and fatal hepatic failure (serum hepatitis) several weeks after receiving tetanus antitoxin,[42,43] a preferred approach to the unvaccinated horse that sustains a puncture or deep laceration is to thoroughly clean and debride the wound, initiate active immunization by administering tetanus toxoid, and institute a course of antimicrobial treatment with penicillin or alternate antimicrobial that is active against *C. tetani*.

Equine Encephalomyelitis (Sleeping Sickness)

The equine encephalomyelitis viruses (EEE, WEE, and VEE) belong to the *Alphavirus* genus of the family Togaviridae. They are transmitted by mosquitoes (and infrequently by other bloodsucking insects) to horses from wild birds or

rodents that serve as natural reservoirs for these viruses. Risk of exposure and geographic distribution of the encephalomyelitis viruses vary by season and from year to year with changes in distribution of insect vectors and wildlife reservoirs. The distribution of EEE has historically been restricted to the eastern, southeastern, and some southern states, with recent northward encroachment. WEE has caused minimal disease in horses in North America during the past 3 decades, but the virus continues to be detected in mosquitoes and birds throughout the western states. In the past, outbreaks of WEE have been recorded in the western and midwestern states, with sporadic cases in the northeastern and southeastern United States. Because EEE, WEE, or both are endemic in most areas of North America, vaccination against these diseases should be part of the core vaccination program for all horses. VEE is a reportable foreign animal disease. Epidemics of VEE occur when the virus undergoes genetic change and develops greater virulence for avian and mammalian hosts. These viral variants are able to multiply to high levels in the horse, and then the horse becomes a reservoir for infection in these outbreaks. VEE occurs in South and Central America but has not been diagnosed in the United States or Mexico for many years; routine vaccination of horses in these regions against VEE is not recommended at this time unless transportation to endemic areas is planned.

Available vaccines are formalin-inactivated, adjuvanted, bivalent or trivalent, whole-virus products containing EEE, WEE, and VEE virus, typically in combination products containing other antigens such as tetanus toxoid, influenza virus, WNV, or EHV-1/-4. Although correlates for protection against EEE, WEE, and VEE are not well established, circulating antibodies are assumed to be important because infection is acquired by vascular injection (mosquito bites), and current inactivated vaccines appear to have good efficacy.[44,45] A study evaluating the serologic response of horses to commercial encephalomyelitis-tetanus combination vaccines showed that the EEE neutralizing antibody responses to Encevac T (Merck Animal Health, Carbopol adjuvant) and Equiloid Innovator (Zoetis, squaline and surfactant adjuvant) were of greater magnitude and persistence than responses to Cephalovac EWT (Boehringer Ingelheim, saponin adjuvant).[8] However, no comparative randomized challenge studies have been performed using these vaccines to document whether differences in serologic responses equate to differences in efficacy. Early testing of bivalent (EEE/WEE) vaccines was performed by intracranial challenge with either EEE or WEE; the formalin-inactivated preparations demonstrated 100% protection.

Primary immunization of unvaccinated adult horses is accomplished by

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administering two doses of inactivated vaccine 3 to 6 weeks apart. In areas where EEE is not a threat and mosquito vectors are active for less than 6 months of the year, annual revaccination in the spring, before the peak insect vector season, is recommended. In areas like the Gulf States where EEE is endemic and mosquitoes are active virtually year-round, many veterinarians prefer to revaccinate horses semiannually to ensure more uniform protection throughout the year. Inactivated encephalomyelitis vaccines are considered safe for use during pregnancy, so booster vaccination of pregnant mares 4 to 8 weeks before foaling is routinely recommended to enhance colostral concentrations of specific immunoglobulins. Neutralizing antibodies to WEE and EEE are transferred passively to foals through colostrum and decline with an estimated half-life of 33 and 20 days, respectively. MDAs appear to confer protection and are detectable in the serum of many foals from vaccinated mares for at least 3 months and up to 7 months, depending on the postnursing titer.[23,46-48]

Several studies have shown that MDAs exert a profound inhibitory effect on the ability of foals to mount serologic responses to inactivated bivalent WEE/EEE vaccines, which likely accounts for some of the reported cases of vaccine failure and resultant clinical EEE in vaccinated horses, particularly those younger than 2 years of age.[19,23,24,46,47] Studies have shown that 3-month-old foals born to immune mares consistently failed to mount a serologic response to two doses of inactivated bivalent WEE/EEE vaccine, and the majority had not responded even after administration of a third dose.[24,26] Whereas many 6-month-old foals failed to seroconvert after administration of two doses of vaccine, most responded following administration of a third dose.[24] On the basis of these data, inclusion of a third dose in the primary series, 2 to 5 months after administration of the second dose, is strongly recommended for primary immunization of foals and yearlings.

WEE has a lower mortality rate than EEE, and prevalence of WEE in many western states is sufficiently low that the risk of foals acquiring infection during their first year of life is also low. Therefore primary vaccination of foals of vaccinated mares in areas where mosquitoes die off in the winter and the risk of infection is low is best completed when foals are 5 to 6 months of age or older in order to minimize the potential for MDA interference. Because foals born in the late spring and summer months are still younger than 6 months of age by the time the mosquito season comes to an end in many regions, primary vaccination of these foals can be delayed until the spring of the yearling year. In contrast, EEE is a highly fatal disease that poses a significant risk to foals during their

first year of life, particularly in the Gulf States where competent vectors are present year-round.[19,47,49] Most veterinarians in these regions recommend commencing primary vaccination of foals at 3 to 4 months of age using a three-dose primary series, followed by a fourth dose before the onset of the next mosquito season and semiannual boosters thereafter to maximize the chances of overcoming the inhibitory effects of MDAs and inducing protection.[47]

West Nile Virus

Only a few years after WNV infection was first diagnosed in horses in the northeastern United States in 1999, it had spread across the entire North American continent and is now considered endemic in all mainland areas of North America and Mexico, where it has become an important consideration in the differential diagnosis of horses presenting with signs of neurologic disease. Since 1999, the disease has been confirmed in more than 25,000 U.S. horses, about 35% of which have died or been euthanized. Roughly 40% of horses that survive acute illness caused by WNV exhibit residual effects (e.g., gait and behavioral abnormalities) 6 months post diagnosis.[50]

WNV, a member of the family Flaviviridae, is transmitted by mosquitoes and infrequently by other bloodsucking insects to horses, human beings, and a number of other mammals from avian hosts, which serve as natural reservoirs for these viruses. Horses and humans are considered to be “dead-end” hosts of WNV and therefore do not contribute to the transmission cycle. The virus is not directly contagious from horse to horse or from horse to human. Similarly, indirect transmission via mosquitoes from infected horses is highly unlikely because horses do not experience a significant level of viremia.[51] Risk of infection and death appears to increase with increasing age, but the disease has been confirmed in foals as young as 3 weeks of age. Although cases have been seen virtually year-round in the southeastern United States, the risk of acquiring infection is highest during those months in which mosquito activity peaks, typically July, August, September, and October in most areas of North America. WNV infection is a core disease against which all horses residing in the continental United States and Canada should be vaccinated.

As of April 2013, six WNV vaccines (West Nile-Innovator [Zoetis], Recombitek Equine rWNV vaccine [Merial], Equi-Nile [Merck Animal Health], Vetera WNV Vaccine [Boehringer Ingelheim], PreveNile [Merck Animal Health], and West Nile-Innovator DNA [Zoetis]) are licensed for use in horses in

North America. All six vaccines have met USDA requirements for safety in tests, each involving more than 640 horses. West Nile-Innovator is an inactivated whole-virus vaccine that contains a metabolizable oil adjuvant.[52] This vaccine is available as either a monovalent (single-component) vaccine or as several multicomponent vaccines containing other encephalitis virus antigens (EEE, WEE, VEE) and tetanus. Recombitek Equine rWNV vaccine is a Carbopol-adjuvanted canarypox-vectored recombinant modified live vaccine,[53-55] which is also available as a multicomponent containing inactivated EEE, WEE, and tetanus antigens. PreveNile is a nonadjuvanted chimeric yellow fever 17D-vectored vaccine.[56-59] This vaccine was voluntarily withdrawn from the market in May of 2010 after an unacceptably high number of adverse reactions were reported and has not yet been reintroduced. Merck Animal Health has since produced and tested an inactivated version of this chimera vaccine, which was released in 2011 as a single-component vaccine (Equi-Nile), as well as several multicomponent vaccines that also contain EEE, WEE, tetanus, EHV-1, EHV-4, and influenza antigens (Encevac + WNV; Encevac T + WNV, and Prestige V + WNV). Similarly, the Vetera line of vaccines from Boehringer Ingelheim includes both single and multicomponent (up to 8 components) versions containing an inactivated WNV antigen. West Nile-Innovator DNA is a plasmid DNA vaccine with a metabolizable oil adjuvant.[28] It appears that Zoetis is not currently marketing this vaccine.

Needle and mosquito challenge models have shown that West Nile-Innovator, Recombitek, and West Nile-Innovator DNA all significantly reduce the magnitude of viremia in experimentally infected vaccinated horses compared with nonvaccinated control horses for as long as 12 months after primary vaccination with two doses of vaccine.[28,52,53] Although viremia was reliably induced in nonvaccinated control horses in these challenge models, clinical disease was not. Therefore these vaccines are labeled as aids to the prevention of viremia due to WNV infection. In contrast, an intrathecal challenge model that reliably induced severe clinical disease was used to test the efficacy of PreveNile in studies for licensure.[57] In this model, a single dose of PreveNile prevented clinical disease, as well as viremia in 4- to 6-month-old horses challenged 1 year after vaccination; therefore PreveNile was labeled for protection against viremia and as an aid in the prevention of disease and encephalitis caused by WNV.[57] Subsequently, Recombitek was shown to induce a high level of clinical protection when tested using this rigorous intrathecal challenge model in a

placebo-controlled study in which horses were challenged 14 days after completion of a two-dose vaccination series.[54] The comparative efficacy of West Nile-Innovator, Recombitek, and PreveNile has now been tested in a randomized blinded, placebo-controlled intrathecal challenge study in which groups of 5 or 6 horses 6 months of age or older were challenged intrathecally 28 days after completion of the two-dose (West Nile-Innovator and Recombitek) or 1-dose (PreveNile) primary vaccination series.[60] In this study, all six unvaccinated control horses developed grave neurologic signs post challenge, whereas all vaccinated horses survived and none developed detectable viremia. Clinical disease was prevented in 100% of PreveNile-vaccinated horses, 80% of Recombitek-vaccinated horses, and 33% of Innovator-vaccinated horses.[60] These findings support the results of field studies that provide clear evidence that when used according to manufacturer recommendations, all available licensed WNV vaccines reduce the risk of disease and death after natural challenge, although clinical disease may not be fully prevented with all vaccines.[61-65]

Directions for primary immunization using inactivated whole virus, inactivated *Flavivirus* chimera, and recombinant vaccines include administration of two doses of vaccine 3 to 6 weeks apart (consult the specific label). Optimal protection cannot be expected until 2 weeks after administration of the second dose, although Recombitek has been shown to induce significant protection as early as 26 days after administration of the first dose when tested in both the mosquito challenge and intrathecal challenge models.[54,55] Primary immunization with PreveNile requires 1 dose. A challenge study in yearlings showed that 83% (5 of 6) were protected when challenged intrathecally 10 days after vaccination with one dose, indicating that onset of immunity is rapid.[57] Rapid onset of immunity is an important feature when faced with the challenge of protecting naive horses that are being introduced into an endemic area, as is the case when horses from Europe and other nonendemic countries are imported into North America.

Vaccine manufacturers recommend revaccination of previously vaccinated horses on an annual basis, or more frequently when local conditions are conducive to a prolonged period of potential exposure to infected mosquito vectors. Annual revaccination is best completed in the spring (late February through early April), before the onset of the insect vector season. In areas like the southeastern states, where the mosquito season is prolonged, revaccination twice annually, once in the spring and again in the late summer or early fall (late

July through early September), has been advocated in the past to maximize protection, although the rationale for semiannual vaccination against WNV has not been tested in controlled studies.

None of the licensed vaccines currently marketed in the United States carry label recommendations for administration to pregnant mares, so mares are best vaccinated before breeding whenever possible. It is well recognized, however, that pregnant mares are at risk of acquiring infection from infected mosquitoes. Consequently, it has become accepted practice by many veterinarians to administer vaccines to pregnant mares on the reasonable assumption that the risk of adverse consequences of WNV infection far exceeds the reported adverse effects of use of vaccines in pregnant mares. Thousands of doses of West Nile-Innovator vaccine have been administered safely to pregnant mares, and a published study failed to document vaccine-associated adverse effects in a large population of pregnant mares.[66] Although the Recombitek vaccine is a live vectored vaccine, the canarypox vector is incapable of replication in mammals and does not induce a viremia that could infect a fetus. In addition, a canarypox-vectored influenza vaccine available in Europe is licensed for use in horses during pregnancy, so the vectored WNV vaccine is unlikely to be associated with an increased risk of adverse effects in pregnant mares. As with other vaccines, it is sound practice to avoid administering West Nile vaccines to mares during the first 60 days of gestation unless conditions of imminent risk prevail.

Booster vaccination of previously primed pregnant mares 4 to 8 weeks before foaling appears to induce a strong anamnestic serologic response that provides their foals with passive colostral protection lasting at least 3 to 4 months.[26] In contrast, a significant proportion of naive pregnant mares failed to seroconvert when the primary series of WNV-Innovator vaccine was administered during the second half of gestation, perhaps reflecting pregnancy-associated downregulation of Th2 responses.[26] This observation adds further justification to the recommendation that when inactivated West Nile-Innovator vaccine is used, the primary series is best completed before breeding. In a similar study, pregnancy did not appear to suppress the response of mares to primary immunization with Recombitek (Wilson WD and colleagues, unpublished observations, 2007).

In contrast to findings with many other vaccines in the foals of immune mares, MDAs do not block the response of foals as young as 3 months of age to vaccination with the inactivated West Nile Innovator vaccine or the recombinant, chimera, or DNA WNV vaccines.[26,29] Although this finding is somewhat

surprising for the inactivated vaccine, it might reasonably have been expected for the other vaccines, because the vector systems accomplish transfection of cells and expression of the major E-peptide and M-peptide antigens of WNV on the surface of antigen-presenting cells (APCs) in association with major histocompatibility complex (MHC) class I and class II antigens. These peptide antigens are therefore not free in the tissues and circulation to be neutralized by MDAs. The impact of MDAs on the recently marketed inactivated whole virus (Vetera WNV Vaccine [Boehringer Ingelheim]) and inactivated chimera vaccines (Equi-Nile [Merck Animal Health]) is not known.

Primary vaccination of foals from properly vaccinated mares can be started by administration of the first dose of either an inactivated or recombinant vaccine as early as 3 to 6 months of age (consult the specific product label), followed by a second dose approximately 3 to 6 weeks later, and then a third dose 3 to 5 months after the second dose. This third dose increases the likelihood that foals with high MDA levels that may have attenuated the response to the first dose of vaccine will become primed and protected. Even in foals that have no maternally derived WNV antibodies after nursing, the third dose of inactivated vaccine in the primary series induces significantly higher and more persistent levels of antibody than two doses. A booster should be administered during the spring of the yearling year, after which the recommendations for vaccination of adult horses should be followed. Primary vaccination of foals from unvaccinated unexposed mares should commence at 3 months of age or younger (as early as 1 month of age), depending on month of birth and seasonal level of activity of mosquito vectors in the area. The three-dose primary vaccination protocol previously outlined should be followed. Revaccination should be performed before the onset of the next mosquito season.

The influence of MDAs on the response of foals to PreveNile was recently evaluated in 3-month-old and 5-month-old foals vaccinated with a single dose. Although significant titer responses were not observed post vaccination, sensitization of cell-mediated responses was accomplished, as evidenced by significant increases in expression of granzyme B, interleukin (IL)-2, perforin, and transforming growth factor (TGF)-β and nonsignificant increases in interferon (IFN)-γ expression in WNV-stimulated PBMC from foals vaccinated at 5 months of age.[29] Similar, although nonsignificant, trends were seen in 3-month-old foals.[29] When available, PreveNile was labeled for administration of a single priming dose to foals 5 months of age or older, primarily because 5 months was the minimum age of foals used in challenge trials for licensure.

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Results of the previously cited study suggest that foals younger than 5 months of age could be immunized successfully with PreveNile. Regardless, a second dose of vaccine should be administered before the onset of the next mosquito season. Preliminary data suggest that the plasmid West Nile-Innovator DNA vaccine is able to circumvent the potentially interfering effects of MDA, but the vaccine was labeled for use in horses 8 months of age or older.[28]

As with EEE, horses that have recovered from clinical WNV infection will likely be protected for the reminder of their lives and should not need to be revaccinated unless changes in their immune status, as might occur with prolonged corticosteroid administration, alter their susceptibility to infection.[67]

It is remarkable that in little more than 10 years after WNV disease was first encountered in the Americas, six vaccines with documented efficacy based on challenge studies were licensed for the benefit of horses, including three that apply the most modern technologies available for either animals or humans at the time.

Rabies

Rabies is an infrequently encountered neurologic disease of equids resulting from inoculation of the rabies virus through the bite of infected (rabid) wildlife. Wildlife species that serve as the natural reservoirs for rabies virus differ among regions of North America but include raccoons, foxes, skunks, and bats. Horses most often sustain bites on their muzzle, face, or lower limbs. The rabies virus then migrates via nerves to the brain, where it initiates rapidly progressive encephalitis. Even though the incidence of rabies in horses is low, the disease is invariably fatal and has considerable public health significance. All horses kept in areas where rabies is endemic in the wildlife population are at risk and should be vaccinated as part of the core vaccination program. Therefore vaccination of horses against rabies virus is recommended by, or under the direct supervision of, a veterinarian using one of the three inactivated tissue culture–derived products currently licensed for use in horses (Rabvac3 [Boehringer Ingelheim], RM Imrab3 [Merial], and EquiRab [Merck Animal Health]). These vaccines are potent immunogens that induce strong serologic responses that peak within 28 days after IM administration of a single dose.

Although correlates for protection against infection with rabies virus in horses are not well defined, it is logical to assume that protection correlates with titers of circulating antibody. In humans, postvaccination antibody titers are used to

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predict protection. In dogs, however, postvaccination serologic test results were not found to be completely predictive of resistance to challenge exposure during tests performed with certain inactivated vaccines.[68] Challenge studies demonstrating efficacy are required for licensing of all rabies vaccines, including those labeled for use in equids in the United States. The challenge studies are conducted by the vaccine manufacturers as outlined in the Code of Federal Regulations (CFR) from the USDA. These studies indicate a DOI of 12 months, and a minimum of 80% of vaccinated animals must be resistant to severe challenge with the rabies virus. A DOI of 14 months was documented in a placebo-controlled challenge study in which 4-month-old foals were vaccinated with one dose of EquiRab and challenged by masseter injection of virulent rabies virus 14 months later (see product data sheet).

For primary immunization, label directions on inactivated rabies vaccines licensed for use in horses suggest administration of one dose to horses aged 3 months or older followed by a second dose 1 year later. Thereafter, annual revaccination is recommended. Although none of the licensed vaccines carries a specific label approval for use in pregnant mares, it is important to acknowledge that only a limited number of equine vaccines are specifically licensed for use in pregnant mares and veterinarians do administer inactivated rabies vaccines to pregnant mares. Alternatively, veterinarians may recommend that mares be vaccinated against rabies before breeding in order to reduce the number and type of vaccines given in the period before foaling. Because rabies antibodies persist in serum for a prolonged period, foals born to mares that are revaccinated while open acquire substantial titers of rabies antibody after ingesting colostrum.

Documentation of rabies in supposedly vaccinated horses, most of which were younger than age 2, brought into question the efficacy of label recommendations for primary vaccination of foals against rabies.[69] Recent studies in our laboratory have shown that the serologic response of most 3-month-old foals from antibody-positive mares is completely blocked, even when a two-dose primary vaccination series is used. Although the response to the first dose of vaccine is typically blocked in 6-month-old foals from antibody-positive mares, these foals appear to seroconvert after administration of a second dose 4 weeks later. Primary vaccination of foals from vaccinated mares should therefore be delayed until they are 6 months of age or older and should include two doses of inactivated vaccine administered approximately 4 to 6 weeks apart, followed by a third dose at 1 year of age. For foals of mares known not to be vaccinated against rabies, the primary vaccination series can be started according to

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manufacturers' recommendations as early as 3 months of age and may comprise only 1 dose, followed by a second dose at 1 year of age. For foals from mares of unknown vaccinal history, either of the two following options is rational and can be used: (1) Assume the mare to be antibody positive, and follow the previous recommendation for foals from mares known to be vaccinated against rabies, starting at 6 months of age. (2) Document the serum antibody status of the foal by testing serum collected from the foal at 24 hours of age or older or from the dam during the periparturient period, and determine which of the approaches to follow on the basis of the presence or absence of rabies antibodies.

Equine Influenza

Infection of the respiratory tract of horses with the orthomyxovirus influenza A/equine/2 (H3N8) remains one of the most common causes of rapidly spreading outbreaks of respiratory disease. The influenza A/equine/1 subtype (H7N7) has not been recognized as a cause of clinical disease for many years and is likely extinct in nature. Influenza is endemic in the equine populations of the United States and much of the world. Evidence of influenza infection has never been documented in resident horses in New Zealand and Iceland. Whereas outbreaks of influenza have previously been reported in Singapore, Japan, South Africa, and Australia, rigorous control measures have apparently been successful in eliminating the virus from these countries. Rapid national and international transportation of horses facilitates spread of the virus. Concentrating young horses at racetracks, training facilities, boarding stables, breeding farms, shows, or similar athletic events increases the risk of infection, as does a low serum concentration of specific antibody.[70] Older horses are generally less susceptible to infection but may become ill when partial protection is overwhelmed by exposure to horses excreting large amounts of virus. Explosive outbreaks occur at intervals of several years when immunity of the equine population wanes and sufficient antigenic drift has occurred to generate a new viral strain. In contrast to herpesviruses, EIV is not maintained in asymptomatic carrier horses and does not circulate constantly, even within large groups of horses. Rather, the disease is introduced sporadically by a symptomatic or an asymptomatic infected horse. This epidemiologic finding and rapid elimination of the virus by the equine immune response suggest that infection can be avoided by preventing entry of the virus into an equine population (e.g., quarantine of newly arriving horses for at least 14 days) and appropriate vaccination.[71]

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EIV is highly contagious and spreads rapidly through groups of horses in aerosolized droplets dispersed by coughing. Contaminated buckets, grooming or feeding equipment, tack, and transport vehicles may serve as fomites because the virus can survive for hours on such objects. Severity of clinical signs of influenza, which include nasal discharge, fever, lethargy, anorexia, cough, and myalgia, depends on the degree of existing immunity and other factors. Infected horses shed virus for up to 10 days in their nasal secretions. Inactivated vaccines do not induce sterile immunity, so recently vaccinated horses can become infected, shed virus, and contribute to interepidemic persistence of infection within the equine population and propagation of infection during outbreaks.[6]

Immunity to the same (homologous) strain of H3N8 virus after natural infection persists for more than a year and involves both local and systemic humoral and cellular mechanisms. These include induction of large amounts of virus-specific neutralizing IgG and secretory IgA antibody in nasal secretions, high levels of circulating IgG antibodies, and genetically restricted antigen-specific cytotoxic T lymphocytes (CTLs) that kill infected cells.[72-76] Memory CTLs can be detected in peripheral blood for at least 6 months after infection, and solid immunity persists even when circulating antibody titers have declined to low or undetectable levels.[73,74,77,78] Similarly, protection induced by the licensed modified live intranasal (IN) influenza vaccine (Flu-Avert I.N. [Merck Animal Health]) is presumably mediated through induction of local immune responses in the respiratory tract because this vaccine does not typically induce high levels of circulating antibodies.[7,79] With the exception of ISCOM vaccines, inactivated vaccines administered by IM injection have limited potential to induce CTL or nasal secretory IgA responses and induce only low levels of neutralizing antibody in nasal secretions.[72,78,80,81] The degree of protection induced by inactivated influenza vaccines is highly correlated with postvaccination titers of circulating antibody, predominantly of the IgGa and IgGb subisotypes, as measured by HI or single radial hemolysis (SRH) tests.[70,82-84] SRH levels of 100 mm^2 or greater are considered to be at least partially protective, but levels above 140 mm^2 are required for successful prevention of disease.[82] The partial protection induced by inactivated vaccines is of limited duration (up to about 7 months, depending on the vaccine) and is manifested as a reduction in clinical signs and attenuation of viral shedding in horses exposed to infection.[71,72]

The magnitude of the serologic response to inactivated influenza vaccines

depends on many factors, the most important of which are the quality and quantity (mass) of the viral antigen and choice of the adjuvant.[82,85,86] Carboxypolymer-based compounds (carbomer, Carbopol) and ISCOMs are contained in some of the most efficacious inactivated influenza vaccines, whereas some commonly used adjuvants (e.g., alum) have been associated with induction of a nonproductive immune response.[72,85] History of previous vaccination or infection, interval since the last dose of vaccine, antibody titer at the time of vaccination, age, maternal antibody status, and relatedness of the vaccine strain to circulating field strains of influenza virus are other important determinants of efficacy, at least for inactivated influenza vaccines.[84,87,88]

Antigenic drift of the A/equine/2 subtype has resulted from point mutations in the genes encoding the amino acid sequences of the hemagglutinin (H) and neuraminidase (N) glycoprotein antigens on the surface of the virus. The result is emergence of viral strains representing two antigenic lineages, American and Eurasian, of the H3N8 virus. Further antigenic drift within each lineage has generated variants that, as with the prototypical strain A/equine 2/Miami 63, are named according to the location and year in which they were first isolated. The American lineage further evolved during the 1990s into Kentucky, Florida, and South American sublineages.[89] For the Florida sublineage, two clades have been identified: clade I, represented by Ohio 03 and South Africa 03, and clade II, represented by Richmond 07. According to the 2017 report of the OIE expert surveillance panel on EIV, only clades I and II Florida sublineage EIV strains are circulating worldwide. Clade I representatives of the Florida sublineage are present in North America, Europe, South Africa, and Japan, and clade II representatives are present in Europe, India, and China.[89]

Antigenic drift, by generating antigenically heterologous viruses, reduces the degree and duration of protection conferred by previous infection or vaccination because of the specificity of immunoglobulins, and it allows horses with high titers to become infected and develop clinical signs of disease if the vaccine strain is not closely related to the drifted infectious field strain.[90] Although antigenic drift of EIV is slower than that of human influenza viruses, it is recommended that inactivated equine influenza vaccines include viral antigens from isolates obtained within the most recent 5 years. An expert surveillance panel meets annually to recommend strains that should be included in influenza vaccines in subsequent years (www.equiflunet.org.uk). In the past, federal U.S. regulations made updating of equine influenza vaccines through inclusion of

recently isolated strains so costly and time-consuming that vaccines typically lagged more than the recommended 5 years behind the antigenic drift of field viruses, resulting in suboptimal protection. Recent changes in vaccine licensing regulations should make more frequent updating of equine influenza vaccines feasible. Even though Flu-Avert I.N. contains only a 1991 H3N8 strain of North American lineage, it has been shown to be protective against challenge with Eurasian strains and recently isolated North American strains.

The short-lived immunity after vaccination with inactivated equine influenza vaccines was the impetus for past recommendations for frequent revaccination, at intervals as short as 2 months. However, too short an interval may compromise efficacy because an optimal anamnestic response to influenza vaccination is inhibited in horses with a high antibody titer.[91] An additional consideration that potentially limits the efficacy of influenza vaccines is the phenomenon termed *original antigenic sin,* whereby horses exposed to a drifted field A/equine/2 virus will mount an anamnestic immune response directed more strongly against the strain with which they were vaccinated initially than against the drifted field virus.[86]

A considerable amount of published efficacy data based on both challenge studies and field epidemiology studies has been available for many years in Europe to support the use of influenza vaccines. In contrast, information regarding the efficacy of influenza vaccines marketed in North America has remained sparse until recently. Furthermore, studies conducted in North America during the late 1990s showed that the inactivated influenza vaccines in use at the time failed to provide much benefit in terms of reducing the risk of infection and clinical disease during field outbreaks.[6,70] Serologic testing performed during these and other studies indicated that vaccine failure was caused by failure of the influenza vaccines in use at the time to induce protective antibody titers.[6,70,92]

Fortunately, vaccine manufacturers in North America have responded to the challenge of producing more efficacious equine influenza vaccines during the past 15 years by incorporating more relevant recent viral strains, increasing antigenic mass of relevant strains, eliminating the seemingly irrelevant H7N7 strain, modifying adjuvant systems, and introducing novel technologies. An important advance occurred in 1999 when Heska Corporation marketed an attenuated live cold-adapted influenza vaccine (Flu-Avert I.N. [Merck Animal Health]) for IN administration. This vaccine, which contains a Kentucky/1991 strain of North American lineage, was found to be highly efficacious in blinded controlled challenge studies conducted 5 weeks, 6 months, and 1 year after

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administration of a single dose to naive horses.[7] Subsequently, Flu-Avert I.N. was shown to cross protect against European H3N8 strains, as well as against North American strains isolated during the late 1990s and early 2000s, and to induce a rapid onset of protection within 7 days of administration of a single dose to naive horses.[79,93] Although horses challenged 1 year after administration of a single dose showed a significant but only partial reduction in severity of clinical signs and virus shedding, a more marked reduction in clinical signs and viral shedding was found when the challenge was performed 6 months after vaccination.[7] On the basis of these results, revaccination at 6-month intervals is recommended. Field experience indicates that this regimen induces solid clinical protection after natural challenge. Currently, Flu-Avert I.N. is licensed for use in nonpregnant horses 11 months of age or older, primarily because this was the youngest age of the horses used in the challenge studies for licensing. Horses may shed small amounts of vaccinal virus for several days after vaccination with Flu-Avert I.N., but the amount of virus shed is so low that in-contact horses will not generally become infected or immunized with vaccinal virus shed by recently vaccinated horses, and the likelihood of reversion to virulence is extremely low.[94]

In recent years, several vaccine manufacturers in North America have updated their inactivated vaccines and demonstrated efficacy in challenge studies. Inactivated influenza vaccines containing one or more relevant H3N8 strains are currently marketed by Boehringer Ingelheim (Calvenza EIV), Zoetis (Fluvac Innovator), and Merck Animal Health (Prestige II). These companies also market a large number of multicomponent combination vaccines that contain the same inactivated influenza antigens as in their single-component products but also contain tetanus, WEE and EEE virus, EHV, or WNV antigens.

A study in which naive 9-month-old horses were challenged by aerosol with a recent influenza H3N8 strain (KY/99) 16 weeks after the last dose of a three-dose vaccination series (0, 4, and 16 weeks) documented that Calvenza EIV and two EIV/EHV combination vaccines (Prestige II and Fluvac EHV-4/1) reduced clinical signs and viral shedding in vaccinated horses compared with nonvaccinated control horses.[96] The group vaccinated with Calvenza EIV developed significantly higher serum antibody titers after vaccination and experienced less fever, nasal discharge, and viral shedding than horses vaccinated with either Prestige II or Fluvac EHV-4/1. On the basis of these findings, the authors concluded that Calvenza EIV, a vaccine developed,

formulated, and efficacy tested according to European Union guidelines, was the most effective inactivated influenza vaccine available in North America at that time. This vaccine is adjuvanted with Carbopol and contains the KY/95 and Ohio 03 North American strains and the Newmarket 93 Eurasian H3N8 strains. The initial two doses of this vaccine are administered intramuscularly; subsequent doses may be administered intramuscularly or intranasally. It is proposed, but not proved, that administration of booster doses by the IN route may provide a stronger local mucosal immune response. This vaccine is licensed for use in horses older than 6 months of age, including pregnant mares. Only two commercially available EIV vaccines commercially available in North America (Vetera 2^{XP} [Boehringer Ingelheim] and Prestige II [Merck Animal Health]) do follow the OIE recommendations by including contemporary relevant clades I and II EIV strains. Vetera 2^{XP} contains representatives of both clade I (A/eq/Ohio/03) and clade II (A/eq/Richmond/1/07) Florida sublineage EIV, as well as an American lineage EIV strain (A/eq/Kentucky/95). The newly formulated Prestige II is the most recently updated EIV vaccine available in North America and contains A/eq/Florida/13 (Florida sublineage clade I), A/eq/Richmond/1/07 (Florida sublineage clade II), and A/eq/Kentucky/02 (American lineage). The metabolizable oil (MetaStim) adjuvanted Fluvac vaccine evaluated in the challenge study mentioned previously contained the KY/92 strain of the H3N8 virus. This strain has since been replaced with a KY/97 strain, and the product is now named Fluvac Innovator.

In 2006, Merial was granted a North American license to market an injectable canarypox-vectored recombinant equine influenza vaccine that has been used with success in Europe for several years. This vaccine, Recombitek Equine Influenza Virus vaccine, has been shown to induce strong protection in challenge studies and has the potential to positively impact influenza prevention in North America.[95] The vaccine incorporates the HA gene from the Ohio 03 and Newmarket 93 H3N8 strains into the same vector delivery platform as the efficacious WNV virus vaccine (Recombitek) and contains a carbomer polymer adjuvant in the diluent.[95] Consequently, this vaccine invokes a broad array of humoral and cellular immune responses. Challenge studies document onset of protection as soon as 2 weeks after completion of a two-dose primary series and persistence of solid protection for at least 5 months. Administration of a booster dose at 5 months induced a strong anamnestic response that provided solid protection persisting for at least 12 months.[96] This vectored influenza vaccine

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can circumvent the inhibitory effect of maternal antibodies, an issue that significantly impacts primary immunization of foals using inactivated influenza vaccines.[30] Recombitek Equine Influenza Virus vaccine is licensed for vaccination of healthy horses as young as 5 months of age.

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Vaccination Protocols for Influenza.

Influenza should be considered a core vaccine on all facilities that are not totally closed so as to preclude contact with “outside” horses from other locations. As with other diseases, the full benefit of vaccination against influenza can be realized only if the primary vaccination series is completed, or if booster doses of vaccine are administered, several weeks before anticipated exposure. The following issues should be considered when planning an influenza vaccination program: (1) primary vaccination of adult horses, (2) routine revaccination, (3) vaccination of pregnant mares, (4) primary vaccination of foals, and (5) vaccination in an outbreak.

Primary Vaccination of Adult Horses

The following are options for primary vaccination of adult horses that have not previously been vaccinated:

- Flu-Avert: administer a single dose intranasally. A second dose administered 3 months later may be beneficial, particularly for horses vaccinated at younger than age 11 months.
- Inactivated intramuscularly administered vaccines: administer two doses 3 to 6 weeks apart according to label directions. Although not specifically recommended by some manufacturers, administration of a third dose of vaccine 3 to 5 months after the second dose is indicated because it significantly enhances the magnitude of the primary response and duration of persistence of antibodies at protective levels.
- Recombitek Equine Influenza Virus vaccine: administer two doses 4 to 6 weeks apart, and

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revaccinate 5 months later.

Routine Revaccination

Improvements in injectable vaccines and introduction of new vaccine types during the past 10 years has extended the duration of clinical protection achievable through vaccination. A routine revaccination interval of 6 months appears to be appropriate for most of the influenza vaccines currently marketed in North America. This routine protocol should be customized by adjusting timing of boosters or inclusion of an additional booster to achieve maximum protection during periods when the risk of exposure is high. For example, strategic revaccination 1 month before being placed at high risk of exposure, such as at a show or sale or being transferred to a training or boarding facility, is justified to maximize protection.

Vaccination of Pregnant Mares

For the mare to produce colostrum that contains a high level of antibodies against equine influenza, she should be revaccinated 4 to 8 weeks before foaling with a vaccine that stimulates a robust serologic response. Although the intranasally administered Flu-Avert I.N. vaccine induces good protection, it does not routinely stimulate high levels of circulating antibody, at least when used for primary immunization. An inactivated injectable vaccine is therefore recommended for prefoaling booster vaccination of pregnant mares at this time.[26]

Vaccination of Foals

The antibody status of a mare at the time of foaling is the main determinant of the postnursing circulating antibody titer in her foal and therefore has a profound impact on the ability of the foal or weanling to respond to influenza vaccines administered during the first year of life. Foals born to seronegative nonvaccinated mares respond appropriately to influenza vaccines, so primary vaccination can commence at 3 months of age or younger if significant risk of exposure to influenza exists. In contrast, maternal antibodies have been shown to completely block the serologic response of foals to a primary immunization series comprising two or more doses of inactivated influenza vaccines when the first dose is administered at 6 months of age or younger.[12-18,24] Interference from

MDA may persist until 9 months of age or beyond for foals with high antibody titers post nursing.[12-18,24,26] Studies in Newmarket, United Kingdom, have shown that influenza virus infection is rare in Thoroughbred yearlings before they enter training, suggesting that the risk of influenza is low in horses younger than age 1 year born to mares in herds that are well vaccinated.[88,97,98] There appears to be little justification to vaccinate young foals from vaccinated mares against influenza, as was recommended in the past.[48,99,100]

The IN modified live vaccine (Flu-Avert I.N.) is licensed for vaccination of horses 11 months of age or older. Whereas this vaccine has been shown to be safe in foals as young as 2 months of age,[101] published data regarding the potential for MDAs to interfere with the response are lacking. Unpublished observations suggest that MDA interferes with the response of foals between 3 and 6 months of age, whereas foals with maternal antibody vaccinated at 7 months of age were protected against virulent challenge (Holland and Chambers, personal communication). Pending publication of well-controlled studies, it is recommended that if the first dose of Flu-Avert I.N. vaccine is administered before 11 months of age, a second dose should be administered at 11 months of age or older.[102]

The European-licensed live canarypox-vectored recombinant influenza is labeled for use in pregnant mares and foals as young as 4 months.[78] The North American–licensed Recombitek EIV vaccine has been shown to be safe in foals as young as 4 months, but the minimum age recommended for vaccination of foals from immunized dams is 5 months. The recombinant vaccine has been shown to efficiently prime foals aged 10 to 20 weeks that had detectable MDA at the time of vaccination.[30] These foals showed clear evidence of an anamnestic antibody response when a secondary vaccination with the same vaccine was performed. The canarypox-vectored recombinant influenza vaccine therefore offers a unique opportunity to overcome the limitations of early-life vaccination in the face of maternally derived immunity in foals.[30] If the foal experiences failure of passive transfer of maternal antibodies, or if the mare is seronegative for influenza, the manufacturer recommends commencing vaccination at 4 months of age and including an additional dose in the primary series.

Vaccination in an Outbreak

Definitive diagnosis of equine influenza infection should be pursued during outbreaks of suspected viral respiratory disease because specific measures can

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then be instituted to contain spread of the disease. Rapid (same-day) diagnosis of influenza can be accomplished using the highly sensitive and specific polymerase chain reaction (PCR) or antigen-capture ELISA tests. In addition, virus isolation should be pursued during outbreaks to characterize new isolates and assess efficacy of current vaccines. The decision to vaccinate in an outbreak is dependent on many factors, the most important of which are the age, vaccination status, and size of the population of horses at risk; the elapsed time since onset of the outbreak; the rapidity with which a diagnosis can be confirmed; the layout of the physical facilities; and availability of personnel. Outbreaks of influenza at racetracks and similar large facilities typically take 1 month or more to spread through the entire population. Therefore sufficient time exists to enhance immune protection of many at-risk horses while implementing other management strategies to minimize disease spread.[93] It is prudent to booster-vaccinate those horses that have been on a regular influenza vaccination program but have not been revaccinated within the previous 3 months. It is also important to induce protection as quickly as possible in horses that have not previously been vaccinated. Of the vaccines currently available, Flu-Avert I.N. induces protection most rapidly, within 7 days of administration of a single IN dose. This is currently the product of choice for vaccination of naive horses and those of unknown vaccination status in the face of an outbreak.[93] Adverse effects have not been reported when Flu-Avert I.N. is administered to horses that are incubating infection, although vaccination of horses that are already clinically ill is not recommended. Alternatively, an accelerated vaccination schedule using the canarypox-vectored vaccine with a primary intervaccination interval of 14 days and booster at 105 days has been shown to quickly confer long-lasting protective antibody levels.[103] All 14 vaccinates demonstrated high SRH antibody titers 14 days following V2, thereby achieving 100% herd immunity to homologous viral challenge. Rapid induction of high levels of acquired herd immunity is critical in containing an outbreak of such a highly contagious pathogen as EIV.[103] In addition to reducing clinical and economic impacts, early vaccination clearly played an important role, together with biosecurity measures and movement restrictions, in containing the 2007 equine influenza outbreak in Australia, as well as ultimate eradication of the disease from that country.[104]

Future Influenza Vaccines.

A recombinant modified vaccinia Ankara (rMVA) vector that delivers genetic

material encoding for relevant hemagglutinin (H) antigens of an H3N8 influenza virus has been developed.[105,106] The rMVA system is designed to focus the CTL response on the recombinant antigen and was initially tested in a prime-boost strategy in which the priming dose consisted of a DNA plasmid encoding for expression of the H antigen. The intent of this DNA prime-rMVA boost regimen was to invoke both cellular and humoral immune responses involved in protection.[106] A subsequent study showed that the rMVA system was capable of inducing virus-specific lymphoproliferative and IFN-γ messenger ribonucleic acid (mRNA) responses; antigen-specific IgGa, IgGb, and IgA antibodies; and protection from challenge, both with and without a priming dose of the DNA vaccine.[105] These data indicate that vaccination of horses with rMVA alone or as part of a prime-boost regimen is an effective means of inducing protective immunity to influenza virus infection.[105] Considerable research has been performed to document the efficacy of the DNA vaccine used in the previously mentioned studies against equine influenza. However, the delivery system used (multiple sublingual, conjunctival, and subcutaneous [SC] injections delivered with a gene gun under general anesthesia) is impractical for use in the field.[105,107] Recent licensing of a naked plasmid DNA vaccine that can be conveniently administered to horses by IM injection to prevent WNV infection clearly documents the potential for development of a DNA vaccine to prevent influenza in horses in the future. In addition, a DNA vaccine expressing the hemagglutinin protein of H3N8 influenza virus was recently shown to protect ponies against challenge when administered subdermally using a needle-free delivery system.[108]

Equine Herpesvirus (Rhinopneumonitis)

The respiratory tract is the primary route of infection for EHV-1 and EHV-4, both of which cause respiratory tract disease that varies in severity from subclinical to severe and is characterized by fever, lethargy, anorexia, nasal discharge, and cough.[109] Seroepidemiologic studies indicate that the vast majority of foals become infected with EHV-1 and EHV-4 during the first year of life, but the clinical disease syndromes resulting from these infections are not always well defined, perhaps reflecting the modulating effect of MDAs.[110-112] Recurrent or recrudescent clinically apparent infections are seen in weanlings, yearlings, and young horses entering training, especially when horses from different sources are commingled.[109,113] In contrast, surveillance studies

involving racehorses document that seroconversion to both EHV-1 and EHV-4 occurs sporadically during the course of a racing season, but these seroconversions are often not clearly associated with outbreaks of respiratory disease that follow an epidemiologic pattern consistent with an infectious agent.[114,115] EHV-1 and EHV-4 are spread by direct and indirect (fomite) contact with nasal secretions, by aerosolized secretions from infected horses, and in the case of EHV-1, by aborted fetuses, fetal fluids, and placentae associated with abortions. Management practices are therefore of primary importance for control of clinical disease caused by equine herpesviruses.

Viremia occurs frequently after infection with EHV-1, potentially leading to paralytic neurologic disease (equine herpes myeloencephalopathy [EHM]) secondary to vasculitis of the spinal cord and brain, abortion of virus-infected fetuses, or birth of infected nonviable foals. In contrast, manifestations of infection with EHV-4 (rhinopneumonitis) are generally confined to the respiratory tract, because EHV-4 does not typically infect endothelial cells or produce a cell-associated viremia.[116] As with herpesvirus infections in other species, horses typically fail to clear primary infections with either EHV-1 or EHV-4, the result being that most horses in the population remain latently infected with both viruses.[109,112,117] Latently infected horses do not show clinical signs but may experience recrudescence of infection with or without clinical signs, an increase in antibody titer, and shedding of the virus when stressed. Consequently, many horses have detectable levels of SN antibody to both EHV-1 and EHV-4 in their serum.[109,112,117] These features of the epidemiology of herpesvirus infections seriously compromise efforts to control these diseases and explain why outbreaks of EHV-1 or EHV-4 can occur in closed populations of horses. Whereas most mature horses have developed some immunity to EHV-1 and EHV-4 through repeated natural exposure and do not typically show respiratory signs when they become reinfected, horses do not appear to become resistant to the abortigenic or neurologic forms of infection with EHV-1 even after repeated exposure.[118] In fact, previously exposed mature horses are more likely than juvenile horses to develop the neurologic form of the disease.[119,120]

The genetic basis underlying the apparent increased likelihood that some EHV-1 isolates will cause EHM appears to involve a single-point mutation in the DNA polymerase *(DNApol)* gene.[121] This mutation results in the presence of either aspartic acid (D) or an asparagine (N) residue at position 752 of the DNA polymerase. More than 80% of EHV-1 isolates associated with EHM are of the

D_{752} genotype, whereas less than 20% are of the N_{752} genotype.[121] Isolates of the D_{752} genotype have been designated as "neuropathogenic strains" in recent publications, lay articles, and laboratory PCR result reports, whereas N_{752} isolates have been designated as "wild-type," "abortigenic," or "non-neuropathogenic" strains. The latter terminology is unfortunate because both the D_{752} and N_{752} isolates are capable of inducing all syndromes (i.e., respiratory disease, abortion, neonatal death, and EHM).

Correlates for protection against EHV-1 and EHV-4 infection have been investigated extensively but are not yet fully defined. Infection with EHV-1 induces a strong humoral response, but protection from reinfection is short-lived and is not achieved until the horse has experienced multiple infections with homotypic virus.[109,116] No clear relationship exists between protection from EHV-1 or EHV-4 infection and concentrations of circulating antibody induced by vaccination or infection, but clinical manifestations of disease and the duration and amount of virus shedding from the nasopharynx are reduced in animals with high levels of circulating neutralizing antibody.[116,122-126] Mucosal immunity and cell-mediated responses likely play a role at least as important as circulating neutralizing antibodies in protection against EHV-1 infection[127] because the presence of MHC class 1–restricted CTL precursors in peripheral blood is correlated with protection.[116] Because EHV-4 replication is largely confined to epithelial cells of the upper respiratory tract, mucosal immunity is likely important in protection.[116]

Currently available vaccines include inactivated vaccines containing only EHV-1 or both EHV-1 and EHV-4 and one MLV EHV-1 (Rhinomune [Boehringer Ingelheim]). Several inactivated products are licensed only for protection against respiratory disease; currently, all contain a low antigen load. Two inactivated products (Pneumabort-K + 1b [Zoetis] and Prodigy [Merck Animal Health]) that contain a high antigen load are licensed for protection against both abortion and respiratory disease. Performance of the killed low-antigen-load respiratory vaccines is variable, with some vaccines outperforming others. Performance of the killed high-antigen-load abortion/respiratory vaccines is superior, resulting in higher antibody responses and some evidence of cellular responses to vaccination. This factor may provide good reason to choose the high-antigen-load abortion/respiratory vaccines when the slightly higher cost is not a decision factor. Alternatively, the Calvenza EIV/EHV (Boehringer Ingelheim) respiratory vaccine induces high titers of VN antibody comparable

with those induced by the high-antigen-load abortion/respiratory vaccines.[8] The MLV EHV-1 vaccine (Rhinomune [Boehringer Ingelheim]) has been shown to induce a level of clinical protection and reduction in viral shedding of similar magnitude to that provided by an inactivated high-antigen-load vaccine (Pneumabort-K + 1b) and of greater magnitude than is provided by one of the killed low-antigen-load respiratory vaccines.[128] Whereas vaccination with either EHV-1 or EHV-4 can provide partial protection against the heterologous strain, vaccines containing EHV-1 may be superior in this regard.

The principal indication for use of equine herpesvirus vaccines is prevention of EHV-1−induced abortion in pregnant mares and reduction of signs and spread of respiratory tract disease (rhinopneumonitis) in foals, weanlings, yearlings, and young performance and show horses that are at high risk of exposure. Many horses do produce postvaccinal antibodies against EHV, but the presence of those antibodies does not ensure complete protection. Consistent vaccination appears to reduce the frequency and severity of herpesvirus-induced disease. Although convincing evidence is lacking, field experience suggests that whereas the incidence of sporadic EHV-1–induced abortion in individual mares has not changed, the incidence of abortion storms caused by EHV-1 has declined significantly since the introduction and widespread use of EHV-1 vaccines in the United States.[117,118] Outbreaks of abortion and associated perinatal foal death, however, do continue to occur on occasion in herds of vaccinated mares.

Of the vaccines currently licensed for use in pregnant mares in North America, only inactivated monovalent EHV-1 vaccines (Pneumabort-K + 1b [Parsippany-Troy Hills, NJ] and Prodigy [Merck Animal Health, Madison, NJ]) containing abortigenic strains of EHV-1 carry a label claim for preventing abortion, whereas at least one bivalent EHV-1/4 vaccine is licensed for prevention of abortion in Europe (Duvaxyn EHV-1/4 [Intervet]). One of the vaccines available in North America, Pneumabort-K + 1b, incorporates both the 1p and 1b subtypes of EHV-1 to reflect the documented increase in the proportion of EHV-1 abortions caused by the 1b subtype that occurred during the 1980s as compared with earlier years.[129] Pregnant mares should be vaccinated during the fifth, seventh, and ninth months of gestation. Some veterinarians also recommend a dose during the third month of gestation. Similarly, vaccination of mares with an inactivated EHV-1/-4 vaccine at the time of breeding and again 4 to 6 weeks before foaling is commonly practiced to enhance concentrations of colostral immunoglobulin for transfer to the foal. However, no published reports document the effectiveness of this approach in raising titers of specific antibody

in mares that have already been vaccinated against EHV-1 3 times during the previous 5 months. Vaccination of barren mares and stallions with either a bivalent EHV-1/-4 vaccine or a monovalent EHV-1 vaccine before the start of the breeding season and thereafter at 6-month intervals is recommended, with the goal of increasing herd immunity in an attempt to reduce viral shedding and challenge to pregnant mares on breeding farms.[117]

An MLV EHV-1 vaccine (Rhinomune) has been used as an aid in prevention of EHV-1 abortion by some practitioners for many years,[130] even though this vaccine is not currently labeled for this use. Several recent developments have created renewed interest in the potential for use of MLV vaccines to protect horses against manifestations of EHV-1 and EHV-4 infection. Sequencing of the EHV-1 genome has made it possible to document the nature of the mutation encoding for attenuation, mediated through truncation of the gp2 glycoprotein of the KyA strain.[131] Similar studies may soon yield information regarding the mutation underlying attenuation of the RAC-H strain from which Rhinomune was derived.

Because currently available inactivated vaccines do not block infection with equine herpesviruses, the most we can hope for when using inactivated vaccines is reduction of severity of clinical signs and attenuation of virus shedding to help protect herdmates. Challenge studies in weanlings aged 5 to 8 months have clearly demonstrated the efficacy of an inactivated whole virus EHV-1/-4 vaccine in reducing clinical manifestations and virus shedding induced by virulent EHV-1 challenge administered 2 weeks after completion of the two-dose primary series.[125] Efficacy was clearly correlated with vaccine-induced antibody levels at the time of challenge in this study.[125]

Specific antibodies against both EHV-1 and EHV-4 are passed in colostrum.[22,25,132-134] Field studies with EHV-1 MLVs indicate that colostral antibodies exert a profound inhibitory effect on serologic responses to vaccination up to at least 5 months of age.[21,135,136] However, a cytotoxic cellular immune response to both EHV-1 and EHV-4 was induced in a substantial percentage of foals vaccinated with an EHV-1 MLV in the presence of maternal antibody, even though humoral responses were often absent.[137] It is uncertain whether these responses would provide protection against natural challenge. Recent studies with two different commercially available inactivated bivalent EHV-1/-4 vaccines and one inactivated EHV-4/EIV vaccine have shown that the majority of foals from EHV-vaccinated mares do not mount a detectable

neutralizing antibody response to vaccines administered at 3 and 4 months of age, even when three doses are administered in the primary series.[22,24,25] An increased proportion of foals responded when vaccinated with a three-dose series starting at 5 or 6 months of age, but a substantial number still failed to seroconvert.[24,25] Some foals with low or undetectable levels of SN antibody at the time of vaccination failed to mount a serologic response, suggesting that low levels of antibody, below the lower limit of detection of the SN test based on EHV-1 antigen, are capable of inhibiting the serologic response to inactivated EHV-1/-4 vaccines.[25] The failure of a large proportion of foals younger than 6 months of age to mount serologic responses to inactivated EHV-1/-4 vaccines and the influence of antibody titer at the time of vaccination on failure to respond has been confirmed using sensitive gD and gG ELISAs in studies on commercial stud farms in Australia.[138] In parallel studies, these researchers concluded that mares were the source of infection for foals, and intensive use of inactivated EHV-1/-4 vaccines on breeding farms in Australia had a minimal impact on the infection rate of young foals and weanlings with EHV-1 and EHV-4.[110,112,139]

Considering the uncertainty regarding the role of EHV-1 and EHV-4 as causes of clinically important respiratory disease, the lack of published data regarding the efficacy of available vaccines in preventing infection and establishment of latency, and results of a recent study documenting the poor serologic responses of naive horses to a number of killed low-antigen-load EHV respiratory vaccines currently marketed in North America,[8] there appears to be little rationale to support the common practice of frequent revaccination of foals, weanlings, yearlings, and young performance horses against EHV-1 and EHV-4.[5] Furthermore, an obvious dilemma in designing a vaccination strategy to prevent EHV-1 and EHV-4 infection in foals and weanlings is that if primary immunization is delayed until 6 months of age or older to reduce the likelihood of MDA interference, foals are likely to encounter field infection before the three-dose primary series can be completed. It is therefore unreasonable to expect a high degree of efficacy for vaccination programs designed to protect foals and weanlings against EHV infection using available vaccines. Despite these uncertainties, many practitioners elect to vaccinate against both EHV-1 and EHV-4. Under these circumstances, a reasonable compromise would be to start foal vaccination at 4 to 6 months of age using two doses of an inactivated bivalent vaccine or an EHV-1 MLV administered 3 to 4 weeks apart, followed by

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administration of a third dose 2 to 5 months later. Revaccination at 4- to 6-month intervals, thereafter using either an inactivated bivalent EHV-1/-4 vaccine or a modified live EHV-1 vaccine, appears appropriate for yearlings and young performance or show horses that experience contact with other horses. Frequent vaccination of nonpregnant mature horses (except those on breeding farms) with EHV vaccines is generally not indicated.

Available vaccines make no labeled claim to prevent EHM, and there is no evidence that current vaccines can prevent EHM in the field. Frequent revaccination of mature horses to help prevent EHM is not justified in most circumstances because EHM is a relatively rare disease from a population standpoint, and most mature horses have previously been infected with EHV-1 and are latent carriers. Currently available vaccines do not reliably block infection, development of viremia, or establishment of latency, and EHM has been observed in horses vaccinated against EHV-1 regularly at 3- to 5-month intervals with inactivated or modified live vaccines.[119,120,140,141]

On the basis of the presumed similar pathogenic mechanism between EHV-1 abortion and neurologic disease,[142,143] parallels likely exist in terms of the requirement for immunologic protection. The control of cell-associated viremia is thought to be critical for preventing EHV-1 abortion and, presumably, neurologic disease. Therefore the goal of any vaccination program aimed at the prevention of EHV-1 abortion or neurologic disease is to stimulate those immune responses that can reduce or eliminate cell-associated viremia. Two recent studies have investigated the protective effect of commercially available killed and MLV vaccines against experimental challenge with neurotropic EHV-1 strains 24 or 29 days after completion of a three-dose vaccination series.[122,123] A significant reduction in the level of viremia was noted in ponies challenged after vaccination with either Calvenza or Pneumabort-K + 1b, both of which are inactivated vaccines.[122,123] Reduction in viremia post challenge was not observed in ponies vaccinated with another inactivated vaccine (Prodigy) or the MLV vaccine (Rhinomune).

A challenge study performed almost 30 years ago to test the efficacy of Pneumabort-K + 1b in preventing abortion and a recent study to test the efficacy of Rhinomune against challenge with a “neuropathogenic” strain of EHV-1 provided some evidence that these vaccines may have a place in control of outbreaks of EHM.[126,128] Interestingly, the Army 183 EHV-1 strain used as the challenge virus in the Pneumabort-K + 1b efficacy study has now been shown to

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carry the D_{752} mutation, as has the Findlay 03 strain used in the Rhinomune study. However, the low numbers of horses used in these studies, the failure of either vaccine to prevent infection or significantly reduce the level of viremia, the lack of statistical significance of results pertaining to prevention of neurologic signs, and the well-known difficulties encountered in accomplishing a consistent and reproducible challenge model for neurologic EHV-1 infection justify caution in interpretation.

The significant reduction in viral shedding observed in vaccinated horses provides reasonable justification for booster vaccination of nonexposed horses at risk for infection to reduce viral shedding in the event they do become exposed to EHV-1. By enhancing herd immunity, it is hoped that the level of infectious virus circulating in the at-risk population will be reduced, and in turn the risk that individual horses in the population will develop disease may be reduced.[140] This approach also relies on the assumption that the immune system of most mature horses has already been "primed" by prior exposure to EHV-1 antigens through field infection or vaccination and can therefore be "boosted" within 7 to 10 days of administration of a single dose of vaccine. Although the validity of this approach has not been critically evaluated for prevention of EHV-1 neurologic disease, its implementation seems rational when faced with one or more horses with confirmed clinical EHV-1 infection (any form) at a particular facility. Whereas booster vaccination of horses likely to have already been exposed is not recommended, it is rational to booster vaccinate nonexposed horses, as well as those that must enter the premises, if they have not been vaccinated against EHV-1 during the previous 90 days. Use of the Rhinomune MLV or one of the inactivated EHV-1 vaccines known to stimulate high circulating titers of neutralizing antibody appears justified for this purpose. Horse owners must develop an understanding of the concept of boosting herd immunity to help protect the group of horses rather than focusing on the as yet unattainable expectation that the veterinarian can reliably protect an individual horse from developing potentially fatal EHM by administering one of the vaccines currently marketed as aids to prevention of clinical manifestations of EHV-1 infection. Ultimately, enforcement of strict biosecurity measures and hygiene practices are likely to be more effective than widespread vaccination in reducing the risk of acquiring infection.

Future Vaccination Strategies to Prevent Herpesvirus Infection.

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To be completely effective in blocking primary infection and establishing a lifelong carrier state with EHV-1 and EHV-4, future vaccination strategies should be directed at inducing a strong mucosal immune response in the upper respiratory tract during the first few weeks of life, at a time when high levels of maternal antibodies are present. Promising progress toward this goal was reported by Patel and colleagues,[144] who documented that IN administration of a single dose of temperature-sensitive modified live EHV-1 vaccine to maternal antibody-positive foals aged 1.4 to 3.5 months afforded partial but significant protection against febrile respiratory disease, viremia, and virus shedding after IN challenge with virulent EHV-1 performed 8 weeks after vaccination. This vaccine has also been shown to provide significant protection against abortion in challenge studies, and because it is capable of preventing the development of viremia, it shows potential to prevent EHM.[127,145] Recent studies with vaccinia and canarypox-vectored recombinant vaccines and DNA vaccines have generated promising results, but more research is necessary to identify the immunodominant protective antigens of EHV-1 and their interaction with the equine immune system before these approaches will be applicable for use in the field.[146-150]

The recent Third International Havemeyer Workshop on Equine Herpesvirus Type 1 highlighted the need to improve vaccines, with MLV being identified as the vaccine type most likely to be successful in inducing a protective immune response.[151] The identified goals of future vaccine candidates will be to stimulate both humoral and cell-mediated immunity, differentiate infected from vaccinated animals (DIVA), provide minimal gaps in immunity, induce a rapid onset and long-lasting immunity, be effective in the presence of MDAs to prevent infection early in life, provide a wide clinical and virologic cross-protection, be safe and effective against the development of EHM, suppress reactivation of latent EHV-1 infection, and be safe when used in the face of an outbreak.[151]

Streptococcus equi subsp. *equi* Infection (Strangles)

Strangles is a highly contagious disease caused by the bacterium *Streptococcus equi* subsp. *equi (S. equi)*. Strangles primarily affects young horses (weanlings and yearlings), although horses of any age can become infected if not protected by previous exposure to the organism or vaccination. The organism is transmitted by direct contact with infected horses or subclinical carriers or

indirect contact with water troughs, feed bunks, pastures, stalls, trailers, tack, or grooming equipment contaminated with nasal discharge or pus draining from lymph nodes of infected horses. The organism survives for several weeks in the environment, particularly in aquatic locations and when protected from exposure to sunlight and disinfectants, and can be a source of infection for new additions to the herd. Because *S. equi* is a clonal organism, there is minimal antigenic variation between different isolates even though isolates vary in their pathogenicity.

Most horses develop a solid immunity during recovery from strangles, which persists in over 75% of animals for 5 years or longer,[152] indicating that induction of durable protection through vaccination is biologically feasible if the protective antigens can be identified and presented in an appropriate manner.[153] Although the basis for acquired resistance to strangles is not completely understood, the finding that recovered horses rapidly clear intranasally inoculated *S. equi* despite not making circulating antibody to its surface proteins indicates that to be highly effective a strangles vaccine must stimulate local nasopharyngeal tonsillar immune clearance responses and that serum antibody is of lesser importance.[154] This conclusion is further supported by the finding that ponies with high levels of circulating antibody to multiple unique surface-exposed and secreted proteins after systemic vaccination remained susceptible to challenge with *S. equi*.[154] The cell wall M protein of *S. equi* (SeM) is recognized in the acquired immune response to *S. equi* infection, a response that involves both production of local antibodies in the nasopharynx and circulating opsonophagocytic antibodies.[155-157] The predominant opsonophagocytic antibodies are of the IgGb subisotype but also include IgGa and IgA, whereas IgGb and later mucosal IgA predominate in nasopharyngeal secretions.[156,158]

Strangles vaccines licensed and marketed for use in North America include one inactivated adjuvanted M-protein cell wall extract (Strepvax II [Boehringer Ingelheim]) and one attenuated live vaccine (Pinnacle I.N. [Zoetis]) derived from a nonencapsulated mutant of *S. equi* for IN administration.[159] Infection of horses with *S. equi* continues to cause troublesome outbreaks of strangles throughout North America, despite the availability and widespread use of these vaccines, indicating that their efficacy is suboptimal.[160] M-protein vaccines induce a good opsonophagocytic antibody response in serum but a minimal mucosal IgA response, which likely accounts for the incomplete protection observed when they are used in the field.[156,161] However, data do exist to

document that vaccination using injectable SeM vaccines reduces the attack rate and severity of strangles in herds with endemic infection.[161-163] The live IN vaccine has been shown to induce a relevant mucosal immune response and partial or complete protection but may do so without inducing a strong serologic response.[160,164] Because vaccinal organisms in the IN vaccine must reach the inductive sites for immunity in the pharyngeal and lingual tonsils, accurate vaccine delivery is critical to vaccine efficacy.

Vaccination against *S. equi* is not routinely recommended for pleasure or performance horses kept in low-risk situations, but it is a consideration for horses that are resident on or being transported to premises like breeding farms, where strangles is a persistent endemic problem or where a high risk of exposure is anticipated. The bacterial MLV is generally preferred over the inactivated injectable vaccine for primary vaccination of foals and weanlings and for routine use in older horses at high risk for infection. On breeding farms, efforts should be concentrated on preventing infection of foals and weanlings by booster-vaccinating broodmares 4 to 6 weeks before foaling to maximize colostral content of antibodies. Whereas the IN vaccine has been shown to be safe for use in mares at all stages of pregnancy and can be used in mares in the face of an outbreak, it does not reliably stimulate high levels of circulating antibody. For this reason, the intramuscularly administered inactivated SeM product is preferred for prefoaling booster immunization of mares. Antibodies of the IgG and IgA class recognizing the SeM are passively transferred to the foal through colostrum and are also present in the milk of immune mares.[165] Antibodies of predominantly the IgGb isotype are absorbed from colostrum and redistribute to the nasopharyngeal mucosa.[158] These IgGb antibodies, along with the SeM-specific IgA antibodies that are present in milk and passively coat the pharyngeal mucosa of nursing foals, provide protection to most nursing foals up to the time of weaning.[157,158,165] Resistance of nursing foals to strangles during the first few months of life appears to be mediated by IgGb antibodies in nasal secretions and milk and not by IgA.[165] Serologic (ELISA) responses to M-protein vaccines are poor in foals, most likely owing to the inhibitory effect of maternal antibodies.

Whereas the IN MLV may be less susceptible than the inactivated extract vaccines to MDA interference, this issue has not been investigated and the manufacturer does not recommend administration of this vaccine to horses younger than 9 months of age. Considering that on farms where strangles is endemic, foals often become infected around the time of weaning (age 4 to 8

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months), it is difficult to protect them if vaccination is delayed until age 9 months. A reasonable compromise on breeding farms where the risk of strangles infection is high and mares are on a regular vaccination program would be to begin primary vaccination of foals using the IN live vaccine as early as 4 months of age. The recommended two-dose primary series administered 2 to 3 weeks apart should be followed by a third dose 3 to 4 months later and boosters at 6- to 12-month intervals thereafter, depending on risk of infection. The IN vaccine has been administered to foals as young as 5 or 6 weeks of age during outbreaks. If a vaccine is used in this manner, a third dose of the vaccine should be administered 2 to 4 weeks before the foal is weaned to optimize protection during this high-risk period. Although there are few reports of adverse effects attributable to use of the IN strangles vaccine in young foals, the inability of foals to mount an adequate mucosal IgA response during the first month of life and the potential for interference by maternal antibodies suggests that foals are unlikely to fully benefit from IN strangles vaccine administered before 4 months of age. When an inactivated M-protein vaccine is used for primary vaccination of foals, it is recommended that the initial series begin at 4 to 6 months of age, using three doses administered at 4- to 6-week intervals, followed by semiannual boosters for as long as high-risk conditions prevail.

Strangles vaccines should be administered only to healthy, nonfebrile horses free of nasal discharge and should not be administered to those that are known to have had recent direct exposure to clinically ill animals.[153] However, outbreaks of strangles generally persist for several months to more than 1 year, particularly on breeding farms where each foal crop adds new susceptible animals to the population. Thus, strangles vaccines are frequently administered in the face of an outbreak as an adjunct to management practices designed to bring outbreaks under control, and it is not always possible to accurately determine the exposure status of each horse. Under these circumstances, the likelihood of preventing strangles is greatest for horses that have not yet been exposed and can be kept isolated from infected horses until 2 weeks after the vaccination protocol can be completed. Horses that have been vaccinated previously will generate a response more rapidly than naive horses. Similarly, the IN MLV is preferred over inactivated vaccines for immunization of naive horses in an outbreak because it is likely to generate a protective immune response more rapidly.

Injectable strangles vaccines tend to cause local reactions at the site of injection more often than other equine vaccines. Injection in the gluteal muscles is not recommended because gravitational drainage along fascial planes can

prove troublesome in the event an abscess develops at the injection site. In addition, purpura hemorrhagica, a serious and sometimes life-threatening systemic immune complex (Arthus-type) vasculitis manifested as edema with or without petechial hemorrhages on mucosal surfaces, has been observed with low frequency in the weeks after administration of strangles vaccines. Inactivated extract vaccines are implicated more often than the IN MLV, but all strangles vaccines have the potential to induce purpura hemorrhagica. The antigen present in immune complexes is SeM, along with antibodies of the IgA class. Because a high serum IgG titer against *S. equi* appears to be associated with an increased risk of developing purpura, routine testing for specific IgG antibodies using a commercially available ELISA test has been recommended as a means of preventing vaccine-associated purpura hemorrhagica.[160] Horses with titers of 3200 or greater in the SeM ELISA and those known to have had strangles during the previous year should not be vaccinated.[160] Recent studies investigated the factors associated with likelihood of horses having a high serum *S. equi* SeM-specific antibody titer.[166,167] This study indicated that older horses, horses other than Thoroughbreds and warmbloods, and horses that had been vaccinated with an attenuated live IN *S. equi* vaccine between 1 and 3 years previously had an increased likelihood of having a serum SeM-specific antibody titer of 3200 or higher. Recommendations of when to vaccinate horses after an *S. equi* outbreak largely depend on how long horses maintain a serum SeM-specific antibody titer of 3200 or higher, which can range from 9 to 27 months. Therefore the recommendation is to wait at least 1 year after an outbreak before vaccinating horses against *S. equi* and to test for *S. equi* SeM-specific antibody titer 12 to 24 months following the outbreak.[167]

The bacterial modified live vaccine for IN administration will cause injection site abscesses if inadvertently injected intramuscularly. To avoid inadvertent contamination of other vaccines, syringes, and needles, it is advisable and considered good practice to administer all parenteral vaccines before handling and administering the IN strangles modified live vaccine. Other reported adverse responses after administration of the IN modified live vaccine include nasal discharge, submandibular or retropharyngeal lymphadenopathy with or without abscessation, limb edema, internal abscesses (bastard strangles), and purpura hemorrhagica. The overall frequency of adverse events is low but appears to be higher than reported to the manufacturer (4.8 per 10,000 doses). The majority of reported adverse events, including the development of nasal discharge, lymph node abscesses, and purpura hemorrhagica, occurs in horses on farms with

endemic or epidemic strangles, so it is often uncertain whether the adverse event was caused by the vaccine or by a wild strain of *S. equi*.

Recent Developments in Strangles Vaccines.

The nonspecifically attenuated Pinnacle strain of *S. equi* was produced by chemical mutagenesis to induce random mutations throughout the bacterial genome.[157,168] Because the point mutations responsible for attenuation have not been specifically defined, the potential exists for back mutation and reversion to full virulence.[168] In contrast, the live attenuated vaccine strain TW 928 contained in a strangles vaccine (Equilis StrepE [Intervet]) formerly licensed in Europe was stably attenuated by targeted deletion of the *aroA* gene.[169] This allowed development of a companion PCR test that was used in molecular epidemiologic studies to determine whether strangles in vaccinated horses was caused by the vaccine or wild-type strains.[170] Although this development proves that targeted gene deletion is a promising route for generating stable candidate mutants for inclusion in future vaccines, the high residual virulence, unconventional route of administration (submucosal in the upper lip), and short duration of immunity induced by Equilis StrepE limited its use to the extent that the vaccine was recently withdrawn from the market.

The incomplete protection afforded by bacterins and SeM extracts administered parenterally or by attenuated live vaccines administered intranasally or submucosally, as well as the undesirable side effects associated with some of these products, has prompted research to investigate other potential vaccine antigens and vaccination strategies. Promising results have recently been achieved in challenge studies involving horses vaccinated intramuscularly and intranasally with combinations of up to seven recombinant antigens including EAG (a protein that binds α_2-macroglobulin, albumin, and IgG), CNE (a collagen-binding protein), SclC (a collagen-like protein), and two IgG endopeptidases, IdeE and IdeE2.[171,172]

Equine Neorickettsiosis (formerly termed *Potomac horse fever*)

Equine neorickettsiosis (EN), formerly known as *Potomac horse fever* (PHF), is caused by *Neorickettsia risticii* (formerly *Ehrlichia risticii*). Originally described in 1979 as a sporadic disease affecting horses residing in the northeastern United States near the Potomac River, the disease has since occurred in horses in 43

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U.S. states, three Canadian provinces (Nova Scotia, Ontario, Alberta), South America (Uruguay, Brazil), Europe (The Netherlands, France), and India. The disease does not appear to be directly contagious, and it now appears that accidental ingestion of aquatic insects harboring metacercaria infected with *N. risticii* is at least one documented mode of transmission.[173] EN is seasonal, occurring between late spring and early fall in temperate areas of the northern hemisphere, with most cases in July, August, and September at the onset of hot weather. The disease may sporadically affect individual horses or cause outbreaks involving multiple horses. Foals appear to be at low risk for the disease. If EN has been confirmed on a farm or in a particular geographic area, cases will likely occur in future years. Documentation of the involvement of operculate freshwater snails and aquatic insects like caddis flies and mayflies in the life cycle of *N. risticii* has permitted formulation of focused control measures directed at minimizing exposure of horses to the habitats occupied by these species during the summer and fall months, when disease risk is highest in endemic areas.[173] Risk reduction is best accomplished by turning off barn lights at night, covering hay or storing it indoors, preventing horses from drinking at natural water sources like ponds or streams, and staying informed about local hatches of aquatic insects.[174]

Recovery after natural infection with *N. risticii* induces a strong antibody response and durable protection from reinfection lasting 20 months or longer. However, the presence of antibodies does not necessarily correlate with protection, and cell-mediated responses likely play a crucial role.[175] A β-propiolactone inactivated host cell-free *N. risticii* vaccine protects mice against homologous challenge.[176] Only one inactivated vaccine against *N. risticii* for IM administration (Equine Potomavac [Boehringer Ingelheim]) is licensed and available for use in horses as an aid in prevention of PHF. The high rate of serious complications and mortality associated with this disease has been considered adequate justification for vaccinating horses residing in or traveling to endemic areas. In a series of studies in which ponies were challenged intravenously with *N. risticii* approximately 4 weeks after completion of the two-dose primary vaccination series using a formalin-inactivated aluminum hydroxide–adjuvanted vaccine (PHF-Vax [Schering-Plough, Union, N.J.]) that is no longer marketed, Ristic's group (1988) reported that 78% of experimentally infected ponies were protected against all clinical manifestations of disease except fever and 33% were protected against all signs including fever.[177] A

published noncontrolled field study involving the same vaccine documented induction of serologic responses in most vaccinated horses and a substantial reduction in disease prevalence, morbidity, and mortality compared with data collected in a previous year when horses were not vaccinated.[175,178]

In contrast to the results of the studies cited, epidemiologic investigations involving a large number of horses failed to demonstrate any clinical benefit from annual vaccination with currently available vaccines in the states of New York, Indiana, and Kentucky.[179,180] Failure of a substantial number of individual horses to mount an immune response to inactivated vaccines against *N. risticii*, heterogeneity of *N. risticii* isolates, the presence of only one *N. risticii* strain in vaccines, and much more rapid waning of immunity after vaccination than after natural infection likely account for the observed failure of vaccines to provide protection against field infection.[175,181] Despite the lack of documented efficacy of approved vaccines to prevent infection in the field setting, many practitioners who work in endemic areas believe that severity of disease is attenuated and mortality is reduced in vaccinated horses when vaccines are administered at 4- to 6-month intervals, with administration of one booster timed to precede the anticipated period of peak challenge.

If vaccination is elected, a primary series of two doses should be administered 3 to 4 weeks apart. The manufacturer recommends revaccination at 6- to 12-month intervals, but some veterinarians encourage a shorter revaccination interval. Because the disease has a distinct seasonal pattern, revaccination in the late spring, about 1 month before the first cases are expected, followed by a second dose 4 months later, appears to be a reasonable approach for strategic immunization to maximize the chances of protection during the period of peak challenge. The available vaccine is licensed for use in stallions and pregnant mares and can be administered to gestating mares 4 to 8 weeks before foaling to maximize passive transfer of specific antibodies to foals through colostrum. Whereas about 67% of foals from antibody-positive mares were antibody negative by 12 weeks of age, antibody was detectable in 33% of foals up to 5 months of age. On the basis of these findings, the low risk of clinical disease in young foals, and the apparent susceptibility to infection of two foals vaccinated earlier than 12 weeks of age, primary vaccination of foals from antibody-positive dams should begin with a two-dose primary series starting at age 5 months or older, followed by administration of one subsequent booster dose 8 to 12 weeks later.[178] However, the efficacy of this recommended regimen requires further study. If the primary series of two vaccinations is initiated before age 5 months,

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additional doses should be administered at monthly intervals up to 5 months of age to maximize the likelihood that an immunologic response is achieved. Vaccination of foals in endemic areas is further complicated by the distinct seasonal incidence of disease in July, August, and September, a time when most foals are between 2 and 6 months old and may be subject to maternal antibody interference with vaccination.

Botulism

Botulism is a neuromuscular paralytic disorder caused by one of eight distinct neurotoxins (A, B, Ca, Cb, D, E, F, G) produced by *Clostridium botulinum*, a soilborne, spore-forming, saprophytic, anaerobic, gram-positive bacterium.[182] Botulinum toxins are among the most potent biological toxins known and act by blocking transmission of impulses at motor end plates, resulting in weakness progressing to paralysis, inability to swallow, and frequently death. Of the seven serogroups (A through G) of *C. botulinum*, types A, B, C, and D have been reported to cause disease in horses, with types B and C responsible for most cases.[182] Three forms of botulism—toxicoinfectious botulism (shaker foal syndrome), forage poisoning, and wound botulism—have been observed in horses. Forage poisoning results from ingestion of preformed toxin produced by decaying plant material or animal carcasses present in feed, whereas wound botulism results from vegetation of spores of *C. botulinum* and subsequent production of toxin in contaminated wounds. Shaker foal syndrome, almost all cases of which are caused by *C. botulinum* type B, results from toxin produced by vegetation of ingested spores in the intestinal tract. This syndrome is a significant problem in foals between the ages of 2 weeks and 8 months in Kentucky and the Mid-Atlantic seaboard states and occurs sporadically in other areas.[183-185] Toxicoinfection with *C. botulinum* type C is currently being investigated as a cause of equine grass sickness, a largely fatal pasture-associated dysautonomia mainly affecting horses in Great Britain, continental Europe, and Australia, with reports of isolated U.S. cases.

A toxoid vaccine (BotVax-B [Neogen Corporation, Tampa, Fla.]) directed against *C. botulinum* type B is licensed for use in horses in the United States. Its primary indication is prevention of shaker foal syndrome via colostral transfer of antibodies induced by vaccination of the mare. For primary vaccination, mares should be vaccinated during gestation with a series of three doses administered 4 weeks apart, scheduled so that the last dose will be administered 4 to 6 weeks

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before foaling to enhance concentrations of specific immunoglobulin in colostrum (i.e., months 8, 9, and 10 of gestation). Subsequently, mares should be revaccinated annually with a single dose 4 to 6 weeks before foaling. A similar type B toxoid is available to protect foals in endemic areas in Australia.[186]

Passively derived colostral antibodies appear to protect most foals for 8 to 12 weeks, although foals from properly vaccinated dams can present with botulism.[184-186] Insufficient production of specific antibody by the dam in response to the vaccination, failure of passive transfer of specific immunity to botulinum toxin, overwhelming toxin production, and loss of passive immunity by the time exposure to the toxin occurs may be reasons for vaccine failure. The clinician should be aware of the status of MDA transfer of each foal.

Maternal antibodies do not appear to interfere with the response of foals to primary immunization against botulism,[187] so a primary series of three doses of vaccine administered 4 weeks apart can be started when foals in endemic areas are 2 to 3 months of age or older. Other horses can be immunized using a primary series of three doses of vaccine administered at 4-week intervals, followed by annual revaccination. No licensed vaccines are available at present for preventing botulism due to *C. botulinum* type C or other subtypes, and because cross-protection between the B and C subtypes does not occur, routine vaccination against *C. botulinum* type C is not currently practiced. A type C toxoid approved for use in mink was administered to horses under special license to protect them during an outbreak of forage poisoning caused by contaminated alfalfa cubes in southern California in 1989. The C-terminal part of the heavy chains of botulinum neurotoxin types C and D (HcBoNT/C and D) has been expressed in *Escherichia coli* and has been shown to effectively immunize horses when administered as a recombinant monovalent or bivalent vaccine.[188,189] These vaccines are not yet licensed.

Horses and foals with clinical botulism may be treated with botulinum antitoxin administered intravenously. Antitoxin is not effective against toxin that has been translocated to motor end plates, so clinical signs may progress for 12 to 24 hours after administration of the antitoxin or until all internalized toxin has attached to motor end plates. The dose of botulinum type B antitoxin recommended for treating a foal is 30,000 IU and for an adult is 70,000 IU. Foals of unvaccinated mares born in or being moved to endemic areas may benefit from transfusion with plasma from a vaccinated horse or from administration of *C. botulinum* type B antitoxin. The efficacy of these practices warrants further study. Vaccination with type B toxoid as described earlier is an

alternative to passive immunization.

Equine Viral Arteritis

Equine viral arteritis (EVA) is a contagious disease of equids caused by equine arteritis virus (EAV), an RNA virus found in the horse populations of many countries. EAV is the prototype virus in the family Arteriviridae of the genus *Arterivirus*, order Nidovirales. Although all horse breeds appear to be equally susceptible to EAV, the prevalence of infection, as determined by seroconversion, is much higher in some breeds (notably Standardbreds and warmbloods) than in others. Despite the high seroprevalence of infection in Standardbreds, clinical disease is rarely observed in this breed, indicating that subclinical infection is common.[11,190] Conversely, Thoroughbreds and most other breeds have a low seroprevalence of infection but are more likely to show fulminant clinical signs when they become infected. Most primary EAV infections are subclinical or asymptomatic. Clinical signs, if they occur, typically develop 3 to 7 days post infection and vary in severity, both within and between outbreaks, but may include some or all of the following: fever, anorexia, depression, localized or generalized urticaria, supraorbital or periorbital edema, conjunctivitis, lacrimation, serous or mucoid nasal discharge, and dependent edema involving the limbs, prepuce, scrotum, mammary glands, or ventrum. EVA is of special concern because abortion is a frequent sequel to infection in the unprotected pregnant mare. EAV can also cause life-threatening pneumonia or pneumoenteritis in young foals, and infection of the postpubertal colt or stallion may establish a long-term carrier state.[11,191] Transmission most frequently occurs through direct or aerosol contact with virus-infective respiratory secretions, leading to widespread dissemination of the virus among susceptible horses in close proximity. Indirect transmission, though less significant, can occur through contact with virus-contaminated fomites. Venereal transmission from infected carrier stallions to mares via semen during natural breeding or artificial insemination with fresh, chilled, or frozen semen can play a significant role in introduction and spread of infection on or between breeding farms or other equine facilities. The virus can persist in the reproductive tract of stallions for many years and possibly result in lifelong infection.

Historically, large-scale outbreaks of EVA have been relatively infrequent. However, the number of confirmed occurrences appears to be increasing, likely because of increased global movement of horses, increased accessibility of

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carrier stallions, and increased utilization of shipped cooled or frozen virus-infected semen. Outbreaks can be associated with serious economic consequences, as clearly exemplified by the 2006 multistate outbreak in Quarter Horses that was propagated by widespread shipment of semen from the index cases, two inapparently infected carrier stallions in New Mexico. Because the carrier stallion is widely accepted as the natural reservoir of EAV and the source of diversity among naturally occurring strains of the virus, identifying these individuals through serologic testing followed by PCR testing or virus isolation from semen forms the cornerstone of eradication measures. Vaccination also constitutes an important means of controlling spread and minimizing the consequences of infection.

A modified live vaccine based on an attenuated strain of EVA virus was developed by researchers in Kentucky in 1969.[192] This vaccine (Arvac [Zoetis]) was first used extensively in the field during the 1984 outbreak of EVA in Kentucky and proved safe and effective in bringing the outbreak under control.[11] This vaccine was developed further and licensed for use in North America. Vaccination of stallions, nonpregnant mares, and prepubertal colts has been shown to be a safe and effective means of controlling EVA. Strategic use of the MLV has formed the cornerstone of a highly successful program to control EVA in the Kentucky Thoroughbred breeding population for many years.[11] Indications for vaccination against EVA are to:

- Protect stallions against infection and subsequent development of the carrier state
- Immunize seronegative mares before being bred with EAV-infective semen
- Curtail outbreaks in nonbreeding populations. Vaccination in the face of an EVA outbreak in concentrated populations of performance horses at racetracks has been successful in controlling horizontal disease dissemination within 7 to 10 days.

Primary immunization with the modified live vaccine involves IM

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administration of a single dose, with a booster administered annually thereafter. Virus-neutralizing antibodies are induced within 5 to 8 days after vaccination and persist for at least 2 years.[11,193] Revaccination induces high VN antibody titers that persist for several breeding seasons.[194] Although the current modified live vaccine is highly attenuated and has been shown to be safe and effective in stallions and nonpregnant mares, a small proportion of first-time vaccinated horses develop mild febrile reactions and transient lymphopenia after vaccination, and vaccine virus may be isolated sporadically from the nasopharynx and buffy coat for 7 days (occasionally up to 32 days) after vaccination.[11,193,195,196] Vaccinated stallions do not shed vaccine virus in either semen or urine.[194]

Primary vaccination provides sustained clinical protection against EVA but does not prevent reinfection and subsequent limited replication and shedding of field strains of virus.[197] However, the frequency, duration, and amount of viral shedding via the respiratory tract are significantly reduced in vaccinates. Vaccinated mares may transiently shed field virus after being bred to carrier stallions, so isolation of these individuals for 21 days after breeding is recommended.[11]

Annual revaccination of breeding stallions 28 days before the start of breeding season is highly recommended as a means of preventing establishment of the carrier state.[11] Annual revaccination of mares being bred to carrier stallions should occur at least 21 days before breeding. The modified live vaccine is not recommended for use in pregnant mares, especially during the last 2 months of gestation, or in foals younger than 6 weeks of age, except in emergency situations when there is a high risk of exposure. Apparent fetal infection with the modified live vaccine strain after vaccination of pregnant mares has been documented in rare instances.[193,198] A recently published study in which 73 pregnant mares were vaccinated during midgestation to late gestation concluded that it is safe to vaccinate healthy pregnant mares up to 3 months before foaling and during the immediate postpartum period. Vaccinating mares during the last 2 months of gestation was associated with an increased risk of abortion.[199] The authors concluded that when faced with a substantial risk of natural exposure to EAV, the risk associated with vaccination must be weighed against the much greater risk of widespread abortions in unprotected populations of pregnant mares.[199]

Foals born to seropositive mares become seropositive after ingesting

colostrum. MDAs decay with a mean half-life of approximately 32 days, with the result that foals become seronegative between 2 and 7 months of age.[200,201] Maternal antibodies are unlikely to interfere with the response to vaccine administered at 7 months of age or older.[200] However, when foals younger than 6 months are vaccinated during conditions of high risk, they should be revaccinated after age 6 months. Establishment of the carrier state appears to depend on the high levels of androgens circulating in intact stallions and can be prevented by vaccinating colts, preferably before puberty and before they are used for breeding.[11] Vaccination of prepubertal colts at age 6 to 12 months is therefore central to effective control of the spread of EAV infection and should be strongly encouraged in breeds like Standardbreds and warmbloods in which EVA is prevalent and on facilities where risk of infection is high. Persistent infection has never been documented in a stallion properly vaccinated with the licensed modified live vaccine before exposure.[11]

Regulatory and Exportation Considerations With Vaccination Against Eva.

Horses vaccinated with the MLV can be expected to become seropositive for life. Titers resulting from vaccination cannot be distinguished from titers resulting from natural infection, so vaccination may complicate testing of horses for export. When planning a vaccination program against EVA, it is important to consult with state and/or federal animal health officials to ensure that any such program is in compliance with the state's control program for EVA if one exists. It is strongly recommended that before vaccination, all first-time male vaccinates be tested and confirmed negative for antibodies to EAV by a USDA-approved laboratory (http://www.aphis.usda.gov/cvbapps/Labs.jsp). Mares intended for export should be similarly tested. In instances where there is uncertainty or concern over whether vaccination against EVA could prevent export of a horse to a particular country, it is advisable to consult the federal area veterinarian (http://www.aphis.usda.gov/vs/area_offices.htm#CO) in charge in the state to determine the specific import requirements of that country. Several countries bar entry of any equid that is serologically positive for antibodies to EAV, regardless of vaccination history. Countries that do accept EVA vaccinated horses typically require stallions or colts to have a certified vaccination history and confirmation of prevaccination negative serologic status.

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Future Directions.

Development and marketing of a marker vaccine that not only affords protection but also allows vaccinated horses to be distinguished serologically from inapparently infected carriers would greatly facilitate control and even eradication of EAV from horse populations. Several new-generation EAV vaccines that potentially meet these criteria have been developed in recent years. These include an MLV DIVA vaccine with a deletion in the GP5 ectodomain,[202,203] a DNA vaccine that incorporates open reading frames (ORFs) 2b, 5, and 7,[204,205] and a subunit EAV vaccine using recombinant replicon particles derived from a vaccine strain of VEE virus that includes genes encoding both major envelope proteins (GP5 and M) of EAV.[206,207]

Rotaviral Diarrhea

Equine rotavirus (ER), a nonenveloped icosahedral RNA virus possessing a genome comprising 11 segments of dsRNA, is one of the most important causes of infectious diarrhea in foals during the first few weeks of life and often causes outbreaks involving the majority of the foal crop on individual farms.[208-210] Older foals and adult horses are more resistant to infection. Equine RV is transmitted via fecal-oral contamination and causes diarrhea by damaging the tips of villi in the small intestine, resulting in cellular destruction, maldigestion, malabsorption, and diarrhea. The genus *Rotavirus* is one of five genera of the family Reoviridae and is divided into seven serogroups (A through G) based on differences in the inner capsid protein, VP6.[210,211] All equine rotavirus isolates to date are in group A, which is further subdivided using neutralizing antibodies to the VP4 and VP7 outer capsid proteins into P (protease-sensitive, VP4-positive) and G (glycoprotein, VP7-positive) serotypes, respectively.[211] Five P serotypes (P1, P6, P7, P12, and P18) and eight G serotypes (G1, G3, G5, G8, G10, G13, G14, G16) have been identified and characterized in horses.[212-214] Molecular genome analysis strongly suggests that the vast majority of the currently circulating equine group A rotavirus strains are highly conserved, with only limited genetic diversity.[215] Most are of the P12 and G3 serotype and include two subtypes (A and B).[216]

An inactivated rotavirus A vaccine (Equine Rotavirus Vaccine [Zoetis]) containing the P12, G3 serotype (H2 strain) in a metabolizable oil-in-water emulsion is conditionally licensed in the United States and is indicated for

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administration to pregnant mares in endemic areas as an aid for preventing diarrhea in their foals caused by infection with ERs of serogroup A. Foal vaccination is not indicated; no data suggest that vaccinating the newborn foal with inactivated rotavirus A vaccine has any benefit in preventing or reducing infection severity. Label recommendations call for a three-dose vaccine series to be administered to mares during each pregnancy at 8, 9, and 10 months' gestation. This protocol has been shown to induce significant increases in serum concentrations of neutralizing antibody in vaccinated mares and in antibody concentrations of the IgG (but not IgA) subclass in colostrum and milk of vaccinated mares.[217,218] It is essential that the newborn foal receive an adequate amount of good-quality colostrum so that it absorbs sufficient anti-ER antibodies. After nursing from vaccinated mares, the concentration of passively derived ER-specific antibody of the IgG subclass in the serum of foals up to 90 days of age is significantly higher than that measured in serum of foals born to unvaccinated mares.[217,218] A field study showed this vaccine to be safe when administered to pregnant mares and provided circumstantial evidence of at least partial efficacy. An approximately twofold higher incidence of rotaviral diarrhea was found in foals from unvaccinated mares compared with those from vaccinated mares, although this difference did not prove to be statistically significant.[217] Similarly, a controlled field study in Argentina in which an inactivated aluminum hydroxide–adjuvanted vaccine containing the SA11 (G3P2), H2 (G3P12), and Lincoln (G6P1) strains of equine rotavirus was administered to 100 mares at 60 days before foaling and again 30 days later demonstrated a substantial reduction in the incidence and severity of rotaviral disease in foals from vaccinated mares compared with foals from unvaccinated mares.[219] As MDA titers wane at about 60 days of age, foals may develop rotaviral diarrhea, but the severity of diarrhea is generally milder and of shorter duration than in foals that become infected during the first 30 days of life.

Challenge studies involving two inactivated rotavirus vaccines administered in a similar manner to pregnant mares in Japan showed that their foals were not completely protected against infection but had a substantial reduction in severity of clinical signs after challenge.[214] The major correlate for protection against rotaviral infection appears to be mucosal immunity, predominantly mucosal IgA, in the gastrointestinal tract. Studies of the immunoglobulin isotype responses of mares after parenteral vaccination with inactivated ER vaccines, and of antibodies passively transferred to their foals via colostrum, indicate that this

approach is unlikely to provide foals with intestinal mucosal protection in the form of IgA.[218] Consequently, it is not surprising that current protocols do not provide complete protection. In addition, because the conditionally licensed vaccine available in the United States contains only the G3 serotype of the A serogroup, it cannot be expected to protect against infection with all field strains.

Equine Rhinitis A Virus

Two rhinitis viruses, equine rhinitis A virus (ERAV; formerly known as equine rhinovirus 1, genus *Aphthovirus*, family Picornaviridae) and equine rhinitis B virus (ERBV; formerly known as equine rhinovirus 2, genus *Erbovirus*, family Picornaviridae), have been identified in horses.[220-225] Seroprevalence studies confirm that both viruses are active in horse populations worldwide, with prevalence ranging from 20% to 90%, depending on the age group and use of the horses sampled.[221,222,226] The rhinitis viruses have been largely overlooked as potential causes of clinically apparent respiratory disease for many years, but recently investigated outbreaks of contagious respiratory disease, as well as challenge studies, suggest that ERAV and ERBV may indeed be important pathogens of horses, causing both lower and upper respiratory tract disease.[223,225,226] Clinical manifestations include pyrexia, nasal discharge, cough, lethargy, anorexia, pharyngitis, and submandibular lymphadenopathy.[223,225] It has also been suggested that ERAV may play a causative role in inflammatory airway disease.[226] A unique feature of ERAV is persistent shedding in urine but only short shedding in nasal secretions after respiratory tract infection.[220]

An inactivated ERAV vaccine (Equine Rhinitis A Vaccine [Boehringer Ingelheim]) was granted a conditional license in late 2012; efficacy and potency tests are in progress. The vaccine is labeled for vaccination of healthy horses 4 months of age or older. The manufacturer recommends a primary vaccination series of three 1-mL doses administered IM at 3- to 4-week intervals, followed by revaccination annually or before anticipated exposure. Pending publication of more data regarding vaccine efficacy, as well as the role of ERAV as a cause of respiratory disease, these authors are unable to provide recommendations regarding use of this vaccine at the present time.

Anthrax

Anthrax is a serious and rapidly fatal septicemic disease caused by proliferation

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and spread of the vegetative form of *Bacillus anthracis* in the body. *B. anthracis* is acquired through ingestion, inhalation, or skin penetration through contamination of wounds by soilborne spores of the organism. Anthrax is encountered only in limited geographic areas where moist alkaline soils, particularly those with high organic content, favor survival, germination, and sporulation of the organism. Vaccination is indicated only for horses pastured in endemic areas.

The only vaccine currently licensed for vaccination of livestock, including horses, contains viable live Sterne's strain 34F2 nonencapsulated spores in saponin (Anthrax Spore Vaccine [Colorado Serum Company, Denver, Colo.]). A primary series consisting of two doses of that vaccine should be administered SC 2 to 3 weeks apart, followed by annual revaccination. Mild to moderate swelling at the injection site is common, and adverse systemic reactions may occur occasionally, particularly in young and miniature horses. Little objective information is available regarding use of this vaccine in horses, but clinical evidence suggests that it provides protection. Vaccination of pregnant mares is not recommended.[227] Because it is a live bacterial product, appropriate caution should be used during storage, handling, and administration of the vaccine to prevent accidental inoculation of people and maintain vaccine potency. Concurrent administration of antimicrobial drugs effective against *B. anthracis* is contraindicated if the vaccine is to function as intended.

Leptospirosis

Leptospirosis is a bacterial disease with a worldwide distribution caused by spirochetes of the genus *Leptospira*. Classification of *Leptospira* spp. is fairly complex and is performed either via the traditional phenotypic classification based on serotyping or via genotypic classification based on DNA homology.[228] In North America the most prominent pathologic serovar associated with disease of equids is *Leptospira interrogans* serovar Pomona type kennewicki.[229] Opossums, raccoons, skunks, foxes, and deer are believed to be the most common maintenance host of this serovar. In horses *Leptospira* infection has most often been associated with abortion, equine recurrent uveitis, and renal and hepatic disease.[230] Horses are typically exposed to *Leptospira* by ingestion of wet vegetation or water that has been contaminated by urine of a carrier or reservoir host, after which *Leptospira* spirochetes penetrate mucous membranes or breaches of skin, although other routes of exposure include contact with

aborted fetuses, placentas, uterine discharge, or milk or with water contaminated by any of these materials.[230] A diagnosis of leptospirosis in horses can be challenging due to the difficulty in identifying *Leptospira* spp. and the high seroprevalence in the equine population.[231]A combination of serology, culture, direct detection, and qPCR testing is used to support a diagnosis of leptospirosis. A single leptospirosis vaccine (LEPTO EQ INNOVATOR [Zoetis]) is licensed for horses in the United States. The vaccine contains a whole-cell monovalent *Leptospira* bacterin with a label claim to use as an aid in prevention of leptospiremia caused by *Leptospira interrogans* serovar Pomona in healthy animals 6 months of age or older, as well as in pregnant mares in all three trimesters of gestation. The manufacturer recommends a primary vaccination series of two 1-mL doses administered IM at 3- to 4-week intervals, followed by revaccination annually.

Corynebacterium pseudotuberculosis Infection (Pigeon fever)

C. pseudotuberculosis, an agent of pigeon fever or dryland distemper, is a gram-positive, intracellular, facultative anaerobic bacterium. Flies act as a mechanical vector for this microorganism, and transmission occurs generally through abrasions or wounds in the skin or mucous membranes.[232] Pigeon fever has a seasonal incidence with the highest number of cases occurring during the dry months of the year, which is late summer and fall in the southwestern United States.[233] In recent years, pigeon fever cases have been diagnosed with increased frequency outside the western states. There are three forms of the disease, which are external infection, internal infection, and ulcerative lymphangitis. A diagnosis of pigeon fever infection is based on clinical signs, clinicopathologic data, diagnostic imaging, bacterial culture of an aspirate, and serology.[234] A conditionally licensed inactivated *C. pseudotuberculosis* bacterin-toxoid (*C. pseudotuberculosis* bacterin-toxoid [Boehringer Ingelheim]) is available in the United States. The vaccine is labeled to be used in horses 12 months of age or older for the immunization against disease caused by *C. pseudotuberculosis*. The manufacturer recommends a primary vaccination series of two 1-mL doses administered IM at 3- to 4-week intervals, followed by revaccination annually. Pending publication of more data regarding vaccine efficacy, these authors are unable to provide recommendations regarding use of this vaccine at the present time.

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Ovine and Caprine Vaccination Programs

Amanda J. Kreuder • Paul J. Plummer

Factors Affecting Vaccine Availability, Choice, and Usage

Labeled vaccines for several important diseases of sheep and goats are currently available for use in the United States, but the small market share for small ruminant vaccines has negatively affected the funding available for vaccine research and development compared with other domestic species. As a consequence of low funding and difficulties in recouping development costs, vaccines currently being produced for small ruminants in the United States, except for the modified live vaccine for bluetongue virus and the anthrax spore vaccine, are either killed bacterin products or virulent live products. These products are more basic to develop and cheaper to produce and market. Modified live products typically require increased costs related to development and production and thus are not widely available for small ruminant–specific diseases. A current list of vaccine targets available for labeled use in sheep and goats in the United States is presented in Table 48.5, and example vaccination schedules for sheep (Table 48.6) and goats (Table 48.7) are also provided. All vaccines must pass basic efficacy and safety testing by the USDA Center for Biologics; however, for the majority of vaccines currently marketed, there is an overall lack of field-based comparative vaccine efficacy data available for the practitioner's use to determine which vaccines to select. Because the value of individual animals in flocks may be low and the cost associated with vaccination for certain diseases high, a cost/benefit analysis should be performed before developing a vaccine program for a particular herd. This analysis should include not only the cost of the vaccine itself but also the high cost of labor associated with administration, as compared with the anticipated risk of infection of the herd and direct costs associated with the disease.

TABLE 48.5

Antigens and Antisera Currently Licensed in United States for Sheep and Goats

Product Type	Disease or Organism	Labeled Species
Bacterial antigens	Enzootic abortion of ewes[a] *(Chlamydophila abortus*, formerly *Chlamydia psittaci)*	Sheep
	Vibriosis[a,e] *(Campylobacter fetus* ssp. *fetus, C. jejuni)*	Sheep
	Tetanus[a] *(Clostridium tetani)*	Sheep, goats[d]
	Clostridial enterotoxemia[a] (*Clostridium perfringens* types C and D)	Sheep, goats[d]
	Additional clostridial diseases (blackleg, malignant edema)[a] *(Clostridium chauvoei, C. novyi, C. septicum, C. haemolyticum, C. sordellii)*	Sheep, goats[d]
	Anthrax[a] *(Bacillus anthracis)*	Sheep, goats
	Caseous lymphadenitis[a,e] *(Corynebacterium pseudotuberculosis)*	Sheep, goats[d]
	Ram epididymitis[a,f] *(Brucella ovis)*	Sheep
	Pasteurellosis[a] *(Mannheimia haemolytica, Pasteurella multocida)*	Sheep, goats
	Coliform mastitis[a,e] *(Escherichia coli)*	Goats
Bacterial antitoxins	Tetanus antitoxin (*Clostridium tetani* toxin)	Sheep, goats[d]
	C. perfringens antitoxin (targets a combination of *C. perfringens* toxins B, C, and D)	Sheep, goats[d]
	E. coli antitoxin (targets K99 strain)	Sheep
Viral antigens	Rabies[a] (*Lyssavirus*, family Rhabdoviridae)	Sheep
	Bluetongue[b] (type 10) (*Orbivirus*, family Reoviridae)	Sheep, goats
	Contagious ecthyma (sore mouth, orf)[c] (*Parapoxvirus*, family Poxviridae)	Sheep, goats

[a]Killed or inactivated vaccine.

[b]Modified live vaccine.

[c]Virulent live vaccine.

[d]Not all available products labeled for use in goats.

[e]Some or all products conditionally licensed.

[f]Product currently licensed but not being produced.

Information taken from North American Compendium of Veterinary Products.

TABLE 48.6

Sheep Vaccination Schedule for North America

Disease/Vaccine	Recommendation for Use	Timing for Vaccination				
		Adult Breeding Ewes	Newborn Lambs	Breeding Males	Feedlot Lambs	Replace Ewes a Rams
Clostridial enterotoxemia	Required	Yearly booster in all ewes 1 month before lambing	*Vaccinated ewe and no FPT:* first vaccine at 8-12 weeks; booster 3-4 weeks later; *Unvaccinated ewe or FPT:* first vaccine at 1-3 weeks; booster twice, 3-4 weeks and 6-8 weeks later	Yearly booster	Optional booster at weaning due to high-risk for enterotoxemia in animals fed high-concentrate diets	Optiona booster weaning before breedin
Tetanus	Required	Yearly booster in all ewes 1 month before lambing	*Vaccinated ewe and no FPT:* first vaccine at 8-12 weeks; booster 3-4 weeks later; *Unvaccinated ewe or FPT:* first vaccine at 1-3 weeks; booster twice, 3-4 weeks and 6-8 weeks later	Yearly booster	Optional booster at weaning as typically given in combination with enterotoxemia vaccine	Optiona booster weaning before breedin
Blackleg/malignant edema	Optional, depending on farm history	Yearly booster in all ewes 1 month before lambing	*Vaccinated ewe and no FPT:* first vaccine at 8-12 weeks; booster 3-4 weeks later; *Unvaccinated ewe or FPT:* first vaccine at 1-3 weeks; booster twice, 3-4 weeks and 6-8 weeks later	Yearly booster	Optional booster at weaning as may be given in combination with enterotoxemia vaccine	Optiona booster weaning before breedin
Rabies	Optional, depending on farm history and	Yearly booster; some		Yearly booster; some		Initial vaccina after 3

	use	vaccines may only require revaccination every 3 years following initial series.		vaccines may only require revaccination every 3 years following initial series.		months age
Vibriosis	Optional, depending on farm history of abortion	Yearly booster (exact timing differs based on vaccine chosen)				Replace ewes or Initial 2 series w first dos given b breedin second 2-4 mor later dependi vaccine chosen
Enzootic abortion	Optional, depending on farm history of abortion	Revaccinate annually before breeding with 2-dose series, first dose 60 days before breeding and second dose 30 days later				Replace ewes or Initial 2 series w first dos days be breedin second 30 days
Caseous lymphadenitis	Optional, depending on farm history of CL lesions	Yearly booster		Yearly booster	Initial 2-dose series following weaning with second dose given 4 weeks after the first	Initial 2 series followi weanin second given 4 weeks a the first
Contagious ecthyma	Optional, only recommended for farms with a history of lesions		Scarification and administration of vaccine to naive animals in endemic herds			
Bluetongue	Optional, depending on farm history of disease	Yearly booster at least 3 weeks before breeding and before vector season **do not use in pregnant animals**		Yearly booster at least 3 weeks before breeding and before vector season		Initial s dose vaccina after 3 months age
Pasteurellosis	Optional, depending on	Yearly booster	Initial 2-dose series given 2-4	Yearly booster	Booster at weaning, at 4-	Booster weanin

	farm history of disease		weeks apart, revaccinate after weaning if given before 3 months of age		6 months of age, or both, if initial series given before 3 months of age	4-6 mo of age, both, if series g before 3 months age
Anthrax	Limited, only recommended for use on farms with a history of disease	Yearly booster 4 weeks prior to historical timing of disease on farm		Yearly booster 4 weeks prior to historical timing of disease on farm		Initial 2 series g 2-3 wee apart st 4 weeks to histo timing disease farm

FPT, Failure of passive transfer.

TABLE 48.7
Goat Vaccination Schedule for North America

Disease/Vaccine	Recommendation for Use	Timing for Vaccination				
		Adult Breeding Does	Newborn Kids	Breeding Males	Feedlot Kids	Replace Does an Bucks
Clostridial enterotoxemia	Required	Yearly booster in all does 1 month before kidding	*Vaccinated doe and no FPT:* first vaccine at 8-12 weeks; booster 3-4 weeks later; *Unvaccinated doe or FPT:* first vaccine at 1-3 weeks; booster twice, 3-4 weeks and 6-8 weeks later	Yearly booster	Optional booster at weaning due to high risk for enterotoxemia in animals fed high-concentrate diets	Optiona booster weaning before breedin
Tetanus	Required	Yearly booster in all does 1 month before kidding	*Vaccinated doe and no FPT:* first vaccine at 8-12 weeks; booster 3-4 weeks later; *Unvaccinated doe or FPT:* first vaccine at 1-3 weeks;	Yearly booster	Optional booster at weaning as typically given in combination with enterotoxemia vaccine	Optiona booster weaning before breedin

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			booster twice, 3-4 weeks and 6-8 weeks later			
Blackleg/malignant edema	Optional, depending on farm history	Yearly booster in all does 1 month before kidding	*Vaccinated doe and no FPT:* first vaccine at 8-12 weeks; booster 3-4 weeks later; *Unvaccinated doe or FPT:* first vaccine at 1-3 weeks; booster twice, 3-4 weeks and 6-8 weeks later	Yearly booster	Optional booster at weaning as typically given in combination with enterotoxemia vaccine	Optiona booster weaning before breedin
Rabies	Optional, depending on farm history and use **no products labeled for use in goats**	Yearly booster; some vaccines may only require revaccination every 3 years following initial series.		Yearly booster; some vaccines may only require revaccination every 3 years following initial series.		Initial vaccina after 3 months age
Enzootic abortion	Optional, depending on farm history of abortion **no products labeled for use in goats**	Revaccinate annually before breeding with 2-dose series, first dose 60 days before breeding and second dose 30 days later				Replace does on Initial 2 series w first dos days be breedin second 30 days
Caseous lymphadenitis	Optional, depending on farm history of CL lesions **conditionally labeled product, not available in all states**	Yearly booster		Yearly booster	Initial 2-dose series following weaning with second dose given 4 weeks after the first	Initial 2 series followi weaning second given 4 weeks a the first
Contagious ecthyma	Optional, only recommended for farms with a history of lesions		Scarification and administration of vaccine to naive animals in endemic herds			
Bluetongue	Optional, depending on farm history of	Yearly booster at least 3 weeks		Yearly booster at least 3 weeks		Initial s dose vaccina

	disease	before breeding and before vector season **do not use in pregnant animals**		before breeding and before vector season		after 3 months age
Pasteurellosis	Optional, depending on farm history of disease	Yearly booster	Initial 2-dose series given 2-4 weeks apart, revaccinate after weaning if given before 3 months of age	Yearly booster	Booster at weaning, at 4-6 months of age, or both, if initial series given before 3 months of age	Booster weaning 4-6 mon of age, both, if series g before 3 months age
Anthrax	Limited, only recommended for use on farms with a history of disease	Yearly booster 4 weeks before historical timing of disease on farm		Yearly booster 4 weeks before historical timing of disease on farm		Initial 2 series g 2-3 wee apart sta 4 weeks before historica timing o disease farm
Coliform mastitis	Limited, **conditionally approved in California only**	2- to 3-dose series starting prekidding and continuing post kidding				

FPT, Failure of passive transfer.

Most available vaccines are bacterins, so avoiding maternal antibody interference and ensuring timely booster administration are key concepts for developing effective vaccine programs. Similar to other food animal species, proper vaccine administration and adherence to meat quality assurance are important. Vaccines should be administered subcutaneously whenever possible, either in the neck or behind the shoulder in the axillary region. Confusion over vaccine reactions that can lead to swellings that resemble lymph nodes infected with *C. pseudotuberculosis* should be kept in mind when choosing a vaccination location. Compared with sheep, goats are known to exhibit more severe vaccine reactions. If vaccines labeled for other species are to be used off label in goats, it is recommended that a small number of animals be vaccinated first to observe for reactions before vaccinating the entire flock.

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Clostridial Vaccines

The only vaccine currently recommended for routine use in all small ruminants is yearly administration of a *Clostridium perfringens* C and D plus tetanus toxoid. Vaccination or protection via passive immunity (colostrum or antitoxin administration) is particularly important before common husbandry tasks like tail docking and castration (tetanus), as well as introduction to high-grain diets (*C. perfringens* type D). Ideally, all ewes and does should receive a booster vaccination 3 to 4 weeks before parturition; previous research in sheep indicates that passive immunity acquired from properly immunized ewes confers protection for up to 12 weeks in lambs.[1] Current recommendations for vaccination include an initial series of two doses 3 to 4 weeks apart, followed by yearly boosters. Appropriate timing of the booster in the first series of immunizations is essential in the formation of an adequate immune response for the remainder of the animal's life. When to initiate the first series of vaccinations is a topic of debate because there is little evidence-based literature on which to form a decision. The following guidelines are used by the authors in clinical practice. Lambs and kids from vaccinated dams with no evidence or suspicion of failure of passive transfer (FPT) may be vaccinated starting at 8 to 12 weeks of age. In animals born to unvaccinated dams or those with suspected FPT, we recommend earlier use of the initial dose; these animals should be vaccinated starting at 1 to 3 weeks of age, with a booster in 3 to 4 weeks and consideration for an additional booster 1 month later. It is relatively common for producers to vaccinate ewes/does before parturition and then still initiate the vaccination of kids/lambs at 1 to 2 weeks of age. In such cases the practitioner should discuss the implications of passive maternal immunity on the immune response elicited by the kid/lamb and should consider either additional boosters (after the period of maternal antibody wane) or delaying initiation of the vaccines. In cases of puncture wounds or injury, a tetanus booster should be administered if it has been longer than 6 months since the last vaccination. An additional booster may also be given to animals entering a feedlot or to those on a high-grain ration year-round (e.g., dairy animals) to aid in prevention of enterotoxemia.

Multiple combination commercial products are available, including *C. perfringens* C/D only, stand-alone tetanus toxoid, and seven-way or eight-way clostridial combination products. There is little evidence that vaccination with multivalent clostridial products is routinely beneficial, but these may frequently be chosen to decrease cost or in herds with a history of disease caused by other

Clostridial species. If multivalent clostridial vaccines are selected, care should be taken to ensure the vaccine contains a tetanus toxoid; in some vaccines, *C. sordellii* may be substituted in place of *C. tetani*.

Rabies Vaccines

Highly efficacious vaccines for the rabies virus are commercially available for sheep in the United States. Vaccination for rabies is recommended in endemic areas, especially in animals with increased human exposure, such as pets, show animals, and petting zoo exhibits. Vaccination of valuable animals is also recommended. Despite the availability of highly effective vaccines, administration to all small ruminants is not routinely recommended, owing to the high cost associated with vaccination and the overall low rates of infection. In addition, unlike rabies vaccination in cats and dogs, previous vaccination of small ruminants does not necessarily constitute protection in regard to quarantine versus destruction of exposed animals. None of the currently available vaccines are labeled for goats, but they are considered relatively safe to use in this species in similar instances as with sheep. Initial vaccination after 3 months of age, followed by yearly revaccination, is recommended; after the initial yearly booster, vaccination frequency can be decreased to every 3 years in some cases, depending on vaccine label.

Foot Rot Vaccines

Commercial bacterin vaccines labeled for foot rot in sheep and targeting 10 strains of *Dichelobacter nodosus* and *Fusobacterium necrophorum* were once available in the United States. These vaccines are no longer commercially available in the United States, but the *D. nodosus* vaccine may be imported with USDA approval on a case-by-case basis. Localized vaccine reactions were common in both sheep and goats, and vaccine efficacy on a large scale has long been debated. Available evidence suggests that antigenic competition may reduce the effectiveness of simultaneous vaccination against multiple serogroups of *D. nodosus*.[2,3]

Current research performed in regions other than North America suggests newer approaches to vaccination for this disease may be more beneficial. In areas or flocks where only one or two strains may be present, targeted use of monovalent or bivalent autogenous vaccines in combination with culling of

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nonresponders may be of benefit in eradicating the disease.[4-6] However, it is considered uncommon for only one or two strains to be present; instead, multistrain infections are thought to more commonly occur.[7] Use of multiple bivalent autogenous vaccines with sequential administration staggered every 3 months may help avoid antigenic competition while allowing for prolonged protection against multiple serotypes.[8] Development of a "universal" vaccine through comparative genomics, transcriptional profiling, and serologic screening for potential candidate antigens has also shown promising results.[9] When these newer technologies will be commercially available in the United States remains to be seen. Given the difficulties and limited availability of vaccines for foot rot, veterinary practitioners are encouraged to consider alternate management strategies that include antibiotic therapy and potentially footbaths.

Reproductive Disorder Vaccines

Commercial vaccines are currently available for sheep only to aid in control of some of the important infectious abortion diseases and contagious epididymitis in the United States. Again, many of these vaccines lack comparative or published field efficacy data, so blanket recommendations for use cannot be made. For additional information on vaccination strategies in reproductive diseases, two excellent reviews have recently been written with a more in-depth discussion of each of the following diseases.[10,11]

An inactivated *Brucella ovis* vaccine is licensed in the United States for use in rams to aid in prevention of epididymitis, but at this time it is no longer being produced by the company other than on a special order basis. Inactivated vaccines are not believed to confer protective immunity to this organism but are known to interfere with serologic testing to detect carrier animals; therefore it is not recommended for routine use. In countries where *Brucella melitensis* is present, the Rev-1 live mutant vaccine may be useful in controlling both diseases; however, in *B. melitensis*–free countries like the United States and Canada, its use is prohibited.

There are currently two commercially available bivalent bacterin vaccines for abortion due to *Campylobacter fetus* subsp. *fetus* and *C. jejuni* in the United States. In general, there is minimal cross-protection between these organisms, and sheep appear to be much more susceptible than goats to abortions caused by these agents. Recommendations for use on farms with diagnosed abortions due to *Campylobacter* spp. include an initial series of two doses in ewe lambs,

followed by administration of an annual booster; exact timing varies on the basis of the vaccine chosen. Recently a new tetracycline-resistant strain of *C. jejuni* (sheep abortion clone IA3902) has emerged in the United States and is now thought to be the leading cause of *Campylobacter*-associated abortion in sheep.[12] Studies in guinea pig abortion models suggest that vaccination with certain commercial vaccines may be more beneficial than others in providing cross-protection to prevent abortion associated with this sheep abortion strain.[13] Following an abortion storm, herd immunity may initially be high, and in future breeding seasons the extent of disease may be limited to naive animals. Over time, immunity may wane, and infections may reoccur.

Chlamydophila abortus (formerly *Chlamydia psittaci*) is a common cause of abortion in both sheep and goats worldwide. Following abortion, ewes and does will develop immunity to future abortion but will often continue to shed the organism and infect other naive animals. Currently, only an inactivated culture vaccine (bacterin) is available in North America for use in sheep. Some producers have used this vaccine in goats, and it appears to be generally safe in this species. Vaccination with this type of vaccine will not prevent shedding of the organism but may decrease the rate of abortions. Vaccine efficacy is unpredictable, owing to variation in the amount of antigen present and loss of antigenicity following in vitro culture during vaccine production. Strain variation from farm to farm may also play a role in perceived vaccine failures. An attenuated live vaccine is available in other countries and is thought to be more efficacious in preventing abortion and shedding but is not without drawbacks. Live attenuated *C. abortus* organisms can be infective to humans handling the vaccine, and the vaccine strain has recently been identified in aborted placentas in the United Kingdom.[14] Newer vaccine technologies such as DNA vaccines or bacteriophage-delivered DNA may eventually offer a solution to the problems identified with current vaccine strategies.[15,16]

Vaccines for other important reproductive diseases like Q fever *(Coxiella burnetii)* and toxoplasmosis *(Toxoplasma gondii)* are not available in the United States even though they remain important causes of abortion in sheep and goats. A phase I inactivated *C. burnetii* vaccine is commonly used in many areas of Europe, with observed reductions in shedding and decreased abortion rates. This vaccine is currently part of the mandatory vaccination program in The Netherlands.[17] This vaccine is neither marketed nor approved for importation into the United States at present by the USDA. A modified live toxoplasmosis

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vaccine consisting of freeze-dried tachyzooites is available in Europe and New Zealand; it provides excellent long-term immunity. Both of these vaccines are potentially zoonotic and therefore must be handled carefully. Licensing of the *C. burnetii* vaccine has been considered in North America but may be hindered by licensing cost and market size. A vaccine for toxoplasmosis is not likely to become available in the United States in the near future, owing to the small market compared with overseas.

Caseous Lymphadenitis Vaccines

Vaccination for *C. pseudotuberculosis* has been attempted with a number of different vaccine modalities; all currently marketed products in the United States are bacterin-toxoids sold as either separate or combination products. Experimental trials have demonstrated a decrease in the occurrence of both internal and external abscesses following inoculation in vaccinated animals.[18] On the basis of these and other data, the vaccine may have a place in some herds to decrease disease prevalence. Although a large amount of research into vaccines has been done overseas,[19,20] little other U.S. vaccine research for this disease has been done. The available vaccines will not prevent all animals from developing abscesses, and animals must be vaccinated before exposure. Vaccine reactions (lameness, lethargy, depression) may occur and can be significant. Despite frequent use in goats, the fully licensed vaccine is not labeled for use in this species and may result in severe injection site reactions that can lead to decreased milk production and poor appetite. Recently, a new conditionally licensed vaccine specific for goats has come on the market. At the time of this writing, little data are available regarding its clinical use. It is not approved for use in all states, so practitioners should consult their state veterinarian or the manufacturer for more information. Initial vaccination requires a two-dose series 2 to 4 weeks apart, with annual revaccination required. Producers must be aware that vaccination will lead to a positive result on serologic testing.

Contagious Ecthyma Vaccines

Virulent live virus vaccines are available in the United States and labeled for use in both sheep and goats to decrease the severity of disease caused by contagious ecthyma virus (soremouth, orf). Use of these vaccines should be limited to herds where endemic disease is present or in outbreak situations where the disease has been newly introduced to the farm. Use of the vaccine on a farm without

previous evidence of infection will result in contamination of the farm with live virulent vaccine virus. The goal of vaccination is to induce mild disease while creating immunity to future exposure. An area free of wool or hair is selected (axilla, flank, inner thigh) and a 1-in^2 area is scarified with a provided instrument, followed by application of vaccine. Development of a scab in the region of scarification is an indication of successful vaccination. The vaccine is a virulent live virus, so care should be taken with administration as it poses a zoonotic risk of infection. Vaccination failures are known to occur, and it has been suggested that the increased occurrence of vaccine failures, particularly in goats, may be due to strain variation between sheep and goat isolates. Efforts are under way to develop goat-specific vaccine strains.[21]

Respiratory Vaccines

Despite the long list of bacterial and viral organisms thought to play a role in respiratory disease in small ruminants, the only available labeled vaccines for sheep and goats in the United States for respiratory disease are combination killed bacterins of *Mannheimia haemolytica* and *Pasteurella multocida*. Most vaccine strains of these organisms are derived from bovine isolates; small ruminant strains, particularly for *M. haemolytica*, are not the same as those found in bovine cases.[22] Cross-reactivity among strains is variable, so the efficacy of these vaccines in small ruminants is inconsistent. In addition, many previously reported cases of *P. multocida* may instead have been caused by the newly classified *Bibersteinia trehalosi* (formerly *P. multocida* type T). None of the currently labeled respiratory vaccines for sheep and goats (or cattle) contain any strain of *B. trehalosi* at this time, and experimental results investigating the efficacy of vaccination for *M. haemolytica* and/or *P. multocida* in controlling disease cause by *B. trehalosi* are mixed at best.[23,24] There are currently no labeled vaccines for viral agents of respiratory disease in small ruminants, and there are no published studies evaluating the safety and efficacy of the use of bovine vaccines in these species.

Other Vaccines

An MLV vaccine is available for bluetongue virus in the United States, but it is thought to be of limited efficacy in the field because it contains only one of the six serotypes known to circulate in North America. Cross-protection among serotypes is thought to be limited, so vaccination will only offer protection

against the vaccine strain (serotype 10). The vaccine is known to cause fetal malformations in pregnant ewes and has the potential to be transmitted to unvaccinated animals during vector season.

An avirulent live culture anthrax vaccine is available for domestic livestock including sheep and goats in the United States. Although rare, sporadic outbreaks and epizootics do occur among U.S. livestock, and premises with previous diagnosis of anthrax are considered susceptible to future outbreaks when soil and weather conditions are appropriate, such as during the 2005 epizootic in North Dakota. In endemic areas, vaccination in the spring of all livestock within 3 miles of a diagnosed case is recommended for a minimum of 5 years following the last diagnosed case.[25]

A conditionally approved (California only) endotoxin vaccine is labeled for use in milking goats to decrease the severity of toxic mastitis caused by *E. coli*. In other areas of the country, some of the endotoxin vaccines commonly administered in dairy cattle are used off label in milking goat herds. Because of the low incidence of toxic mastitis in this species, routine use is not recommended. If these vaccines are used, administration will not prevent infection but will decrease disease severity.

At present, there are no additional vaccines licensed for mastitis in milking sheep or goats in the United States. However, there is a vaccine currently licensed in multiple European countries for reduction of the incidence of subclinical mastitis cause by *Staphylococcus aureus* (sheep and goats) and coagulase-negative *Staphylococcus* (goats only) and the company is currently exploring approval for this vaccine in the United States. This vaccine is an inactivated product derived from a biofilm-expressing strain of *S. aureus*. Internal research reports by the company suggest efficacy in decreasing the incidence and severity of mastitis associated with staphylococcal infections, but no peer-reviewed research has been published to date. Previously published research has demonstrated that bacterins derived from strong biofilm producing strains of *Staphylococcus* provided the highest protection against intramammary infection and subsequent mastitis in sheep.[26] As mastitis caused by *Staphylococcus* species remains a major cause for production loss in milking sheep and goat herds, approval of an efficacious vaccine for this purpose in the United States would be beneficial.

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Bovine Vaccines and Herd Vaccination Programs

Victor S. Cortese

With the increasing size of today's cattle operations and the extensive movement of cattle, disease exposure continues to occur at a high rate. These exposures often put pressure on the efficacy of the vaccines used and may give field experience as to how well they can protect cattle. The wide diversity in uses of cattle and management practices makes a single vaccination protocol impossible for all cattle production systems. Today it is even more important to scientifically choose a vaccine or design a vaccination program based on good information. When designing programs, several variables must be considered[1]:

- The presence and degree of challenge of the particular diseases on the farm or ranch (Boxes 48.1 and 48.2)

Box 48.1

Bovine Vaccines Seldom Needed on Most U.S. Ranches and Farms[a]

Anthrax vaccine
Clostridium septicum (malignant edema) bacterins
Leptospira grippotyphosa bacterins
Leptospira icterohaemorrhagiae bacterins
Leptospira canicola bacterins
Clostridium botulinum toxoids
Clostridium novyi bacterins
Rabies vaccine
Tetanus toxoids
Erysipelas bacterins
Clostridium sordellii (malignant edema) bacterins

[a]These vaccines are not cost-effective.

Box 48.2

Bovine Vaccines for Ranch- and Farm-Specific (Soilborne) Diseases

Blackleg bacterins
Clostridium haemolyticum (redwater) bacterins
Anthrax vaccine
Clostridium novyi (infectious necrotic hepatitis) bacterins

- Management practices on the facility that support or hinder vaccination programs
- The times or ages when disease problems occur and whether the diseases are associated with any stressors
- The immune system components necessary to afford protection against various diseases
- Some basic immunologic concepts
- The information available on products being considered and the source and quality of the information
- Required vaccines for a particular use of the animal (e.g., 4-H shows)

Challenge

The level of disease challenge and degree of protection continually fluctuate. Biological variability makes the degree of protection different in every vaccinated animal. The same is true for the level of exposure to a pathogen. Overwhelming challenge can override immunity and lead to disease even in

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well-vaccinated animals.[2]

Timing of Disease

On many farms, certain diseases occur at consistent times. Timing may give some insight into stresses that occur in the management of the cattle. Correcting these stresses can have a positive impact on vaccination and lessen animals' susceptibility to disease. This type of history is also helpful in determining the timing of vaccinations, a concept that is often underused in veterinary medicine. Knowing when a problem historically has occurred allows vaccinations to be scheduled when they will induce maximum immune responses in preparation for expected challenges.

Assessing Vaccine Efficacy

The efficacy of a vaccine can be extremely difficult for the practitioner to assess. Traditionally, serologic data showing prevaccination and postvaccination titers have been equated with protection. For many diseases, however, the correlation is poor between the antibody measured and the protection generated by the vaccine in the animal.[3] Recently a study comparing BVDV protection showed an inverse relationship between antibody levels and the ability of the vaccines to prevent development of persistently infected calves.[4] Cell-mediated immune function tests have been added to show a more complete stimulation of the immune response after vaccination.[5] Although these tests provide more information about the vaccine, they still do not answer the basic question of how well a vaccine truly protects. This question can be answered only by well-designed challenge studies. Many examples of well-designed studies involve both viral[6,7] and bacterial[8,9] agents. To assess a challenge study, the following information is necessary:

1. Trial design, including animal characteristics
2. Statistical analysis of the results
3. Determination of whether statistical differences are biologically important
4. Route of administration of the challenge
5. Characteristics of the challenge organism

6. Consistency of the challenge model with the desired protection sought (e.g., respiratory vs. reproductive protection)
7. Method of clinical score assignment
8. Level of disease seen in the control unvaccinated cattle
9. Publication of the results in a peer-reviewed article

Unfortunately, the challenge model is not well established for many diseases. Field trials are even harder to assess but are valuable for judging the effectiveness (i.e., efficacy in a particular situation) and efficiency (i.e., cost-effectiveness) of a vaccine[10] (Boxes 48.3 to 48.12; also see Boxes 48.1 and 48.2). Several good references on field trial analysis are available.[11,12] Recently the Center for Veterinary Biologics (CVB) began giving vaccines different labels depending on the strength of the efficacy data submitted to them in the licensing trials.

Box 48.3

Vaccines Recommended for Use in Adult Beef Cows

Vaccines Highly Recommended for All Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii var. *hardjo*
Leptospira pomona bacterins
Campylobacteriosis bacterins[a]

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Tritrichomonas foetus vaccine
Anaplasmosis vaccine (inactivated)
Rotavirus-coronavirus (calf scours) vaccine (inactivated)

Fusobacterium necrophorum (foot rot) bacterin
Escherichia coli bacterins
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Clostridium perfringens type C (enterotoxemia) toxoids
Anthrax vaccine
Clostridium novyi bacterins

[a]Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, and/or "bull-proof" perimeter fencing).

Box 48.4

Vaccines Recommended for Use in Adult Beef Bulls

Vaccines Highly Recommended for All Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii serovar *hardjo*
Campylobacteriosis bacterins[a]

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Tritrichomonas foetus vaccine
Anaplasmosis vaccine (inactivated)
Leptospira pomona bacterins
Fusobacterium necrophorum (foot rot) bacterin
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine

Clostridium novyi bacterins

[a]Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, and/or “bull-proof” perimeter fencing).

Box 48.5

Vaccines Recommended for Use in Beef Calves[a]

Highly Recommended Vaccines

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Parainfluenza type 3 (PI-3) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins
Brucellosis vaccine[b]

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins
Moraxella bovis (pinkeye) bacterins
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Anaplasmosis vaccine[c] (modified live)
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine
Fusobacterium necrophorum (foot rot) bacterin
Clostridium novyi bacterins

Mannheimia haemolytica vaccines (new)

[a]Under 12 months of age.

[b]Heifer replacements only.

[c]Heifer and bull replacements only.

Box 48.6

Vaccines Recommended for Use in Stocker Cattle

Highly Recommended Vaccines

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Parainfluenza type 3 (PI-3) vaccines
Mannheimia haemolytica vaccines (new)
Leptospira pomona bacterins

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Moraxella bovis (pinkeye) bacterins
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine
Fusobacterium necrophorum (foot rot) bacterin
Clostridium novyi bacterins

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Box 48.7

Vaccines Recommended for Use in Beef Replacement Heifers

Vaccines Highly Recommended for Use in All Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins
Campylobacteriosis bacterins[a]

Vaccines That May Be Useful or Necessary in Specific Herds or Geographic Locations

Blackleg bacterins
Tritrichomonas foetus vaccine
Anaplasmosis vaccine (modified live)
Rotavirus-coronavirus vaccine (inactivated)
Escherichia coli bacterins
Fusobacterium necrophorum (foot rot) bacterin
Moraxella bovis (pinkeye) bacterins
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Clostridium perfringens type C toxoids
Anthrax vaccine
Clostridium novyi bacterins

[a]Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, or “bull-proof” perimeter fencing).

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Box 48.8

Vaccines Recommended for Routine Administration to Cattle Entering Feedlots

Essential Vaccines

Infectious bovine rhinotracheitis (IBR) vaccine (modified live)
Bovine virus diarrhea (BVD) vaccine (modified live)
Bovine respiratory syncytial virus (BRSV)

Highly Recommended Vaccines

Mannheimia haemolytica vaccine[a]
Leptospira pomona bacterins

Vaccine That May Be Needed in Some Groups of Cattle in Feedlot

Clostridium haemolyticum (redwater) bacterins

Vaccines Necessary Only in Specific "Problem" Feedlots

Blackleg bacterins
Bovine respiratory syncytial virus (BRSV) vaccines
Fusobacterium necrophorum (foot rot) bacterin

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[a]Some commercial modified live cytopathic virus BVD vaccines trigger severe fatal BVD in cattle that are chronically infected with noncytopathic strains of BVD virus and immunologically tolerant as a result of prenatal infection.

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Box 48.9

Vaccines Recommended for Use in Adult Dairy Cows

Vaccines Highly Recommended for Use in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV)
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins

Vaccine Highly Recommended for Cows in Specific Infected Herds

Core endotoxin vaccines

Vaccines Highly Recommended for Dairy Cows Grazing in Specific Endemic Areas

Clostridium haemolyticum bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccines That May Be Useful in Controlling Specific Disease Problems in Individual Dairy Herds

Escherichia coli (calf scours) bacterins
Rotavirus-coronavirus (calf scours) vaccine (inactivated)
Fusobacterium necrophorum (foot rot) bacterin
Clostridium septicum (malignant edema) bacterins
Clostridium sordellii (malignant edema) bacterins

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Box 48.10

Vaccines Recommended for Use in Adult Dairy Bulls

Vaccines Highly Recommended for Bulls in All Commercial Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Leptospira borgpetersenii serovar *hardjo*
Campylobacteriosis bacterins[a]

Vaccines Highly Recommended for Bulls Grazing in Specific Endemic Areas

Anaplasmosis vaccine (inactivated)
Clostridium haemolyticum (*Clostridium novyi* type D, redwater) bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccines That May Be Useful in Specific Herds or Geographic Locations

Leptospira pomona bacterins
Fusobacterium necrophorum (foot rot) bacterin

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[a]Highly recommended except in herds from which this disease can be reliably excluded (by virtue of the closed status of the herd and by isolation from other potentially infected herds by distance, terrain, or “bull-proof” perimeter fencing).

Box 48.11

Vaccines Recommended for Use in Dairy Calves[a]

Vaccines Highly Recommended for Calves in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Parainfluenza type 3 (PI-3) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins
Brucellosis vaccine

Vaccines Highly Recommended for Calves Grazing in Specific Endemic Areas

Blackleg bacterins
Clostridium haemolyticum bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccine Highly Recommended for Calves in Herds With Adult Cows Grazing in Specific Endemic Areas

Anaplasmosis vaccine (modified live)

Vaccines That May Be Useful in Controlling Specific Disease Problems in Individual Dairy Herds

Mannheimia haemolytica vaccines (new)
Histophilus somni (formerly *Haemophilus somnus*) bacterins
Moraxella bovis (pinkeye) bacterins
Fusobacterium necrophorum (foot rot) bacterin

[a]Up to 12 months of age.

Box 48.12

Vaccines Recommended for Use in Yearling Replacement Dairy Heifers

Vaccines Highly Recommended for Use in Heifers in All Dairy Herds

Infectious bovine rhinotracheitis (IBR) vaccines
Bovine virus diarrhea (BVD) vaccines
Bovine respiratory syncytial virus (BRSV) vaccines
Leptospira borgpetersenii serovar *hardjo*
Leptospira pomona bacterins

Vaccines Highly Recommended for Dairy Heifers Grazing in Specific Endemic Areas

Blackleg bacterins
Anaplasmosis vaccine (Anavac[a] or Anaplaz)
Clostridium haemolyticum (*Clostridium novyi* type D [redwater]) bacterins
Anthrax vaccine
Clostridium novyi bacterins

Vaccines That May Be Useful for Controlling Specific Disease Problems in Individual Groups of Dairy Heifers

Fusobacterium necrophorum (foot rot) bacterin
Moraxella bovis (pinkeye) bacterins

Vaccines Administered to Springing Heifers That May Be Useful for Controlling Specific Disease Problems in Specific Dairy Herds

Gram-negative core antigen (coliform mastitis) vaccines
Escherichia coli (calf scours) bacterins
Rotavirus-coronavirus (calf scours) vaccine (inactivated)
Clostridium septicum (malignant edema) bacterins
Clostridium sordellii (malignant edema) bacterins

[a]Anavac (BioLOGIC Laboratories, Davis, Calif. 95616) is the preferred vaccine for use in dairy herds where adult cows are grazing in an endemic area.

Cattle Vaccines

Bovine vaccines tailored for use against 8 viral diseases, more than 28 bacterial pathogens, and 1 protozoal disease (trichomoniasis) are currently federally licensed in the United States (Table 48.8). These vaccines have been designed to aid in preventing a myriad of diseases in cattle, including reproductive, respiratory, generalized septicemic, and toxic (endotoxic and exotoxic) diseases. The vaccines have demonstrated some degree of protection against the pathogen for which they were designed, but they may not have proved protective against all the various syndromes known to be caused by a specific infectious agent. The challenge models for each pathogen and the release requirements for each vaccine are monitored by the Veterinary Biologics division of the USDA's Animal and Plant Health Inspection Service (USDA/APHIS) and can be found in Book 9 of the Code of Federal Regulations.

TABLE 48.8

Antigens Available in Currently Licensed[a] Cattle Vaccines

Antigen Type	Common Name of Disease or Vaccine	Pathogen
Virus	BRSV	Bovine respiratory syncytial virus
	Rednose	Bovine herpesvirus type 1, infectious bovine rhinotracheitis virus (IBRV)
	BVD-MD	Bovine virus diarrhea virus (types 1 and 2)–mucosal disease
	PI-3	Parainfluenza type 3 virus
	Rabies	*Lyssavirus* spp.
	Warts	Bovine papillomavirus, bovine rotavirus, bovine coronavirus

Bacteria	Anthrax	*Bacillus anthracis*
	Bangs	*Brucella abortus*
	Vibriosis	*Campylobacter fetus* subsp. *veneralis*
	Blackleg	*Clostridium chauvoei*
	Redwater disease (bacillary hemoglobinuria)	*Clostridium haemolyticum*
	Black disease	*Clostridium novyi*
	Enterotoxemia	*Clostridium perfringens* type C
	Foot rot	*Fusobacterium necrophorum*
	Heel warts	*Treponema bacteria*
	Haemophilis, TEME	*Histophilus somni*
	Hemorrhagic bowel syndrome	*Clostridium perfringens* type A
	Overeating	*Clostridium perfringens* type D
	Malignant edema	*Clostridium septicum, Clostridium sordellii*
	Mycoplasma pneumonia and mastitis	*Mycoplasma bovis*
	Tetanus	*Clostridium tetani*
	Endotoxin vaccines	J5 *Escherichia coli*
		R mutant *Salmonella* vaccine
	Coliform scours	*E. coli* K99 and non-K99
	Food safety	*E. coli* O157 (SRP—conditionally licensed)
	Foot rot	*Fusobacterium necrophorum*
	Pinkeye	*Moraxella bovis*
	Leptospirosis	*Leptospira borgpetersenii* serovar *hardjobovis*
		Leptospira interrogans serovar *hardjobovis*
		Leptospira interrogans serovar *cannicola*
		Leptospira interrogans serovar *icterohaemorrhagiae*
		Leptospira interrogans serovar *grippotyphosa*
		Leptospira pomona
	Johne's disease	*Mycobacterium avium* subsp. *paratuberculosis*
	Salmonella	*Salmonella* Dublin, *Salmonella* Typhimurium
		Salmonella sideophore vaccines (SRP—conditionally licensed)
	Shipping fever	*Mannheimia haemolytica (Pasteurella haemolytica)*
		Pasteurella multocida
	Endotoxin vaccines	R *Salmonella,* J5 *E. coli*
	"Staph" mastitis	*Staphylococcus aureus*
Rickettsiae/protozoa	"Trich"	*Tritrichomonas foetus*
	Anaplasmosis	*Anaplasma marginale* (not federally licensed)

[a]Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

TEME, Thromboembolic meningoencephalitis.

Modified from Bayley AJ: *Compendium of veterinary products*, ed 5, Iowa City, IA, 1999, Iowa State University Press.

During gestation the bovine reproductive system, with its multilayered placenta, leaves the fetus in a naive environment susceptible to infection. Abortions may be due to infection of the placenta, inflammation of the ovary, death of the fetus, or disruption of the cervical plug. It is therefore difficult to achieve protection against reproductive diseases. Vaccination must minimize the

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amount or duration (or both) of the viremia or septicemia, or it must prevent the pathogen from moving through the cervix or crossing the placenta. Only a few currently licensed vaccines have proved protective against the reproductive forms of various diseases, and the duration of immunity they afford has not been established.

Each manufacturer's development and production of cattle vaccines is different, so the composition of vaccines varies substantially among manufacturers. Outlines of production are proprietary for each manufacturer, but some information can be found in technical and marketing materials. For example, some viral vaccines are grown on bovine-derived kidney cell lines and others are grown on porcine-derived kidney cells. Some vaccines are grown only on calf serum, whereas others are grown on both calf and fetal calf serum. Variability is seen in the strain or strains chosen for the vaccine, number of growth cycle passages chosen for attenuation, growth medium, and number of viral or bacterial particles in the vaccine.

Three types of vaccines represent the basic technologies currently available in cattle viral and bacterial vaccines[2,13-17]:

1. *Modified live (attenuated) vaccines* contain living bacterial or viral organisms. These organisms usually are collected from a field disease case and then grown in abnormal host cells (viruses) or media (bacteria) to change or attenuate the pathogen. Each completed replication cycle is known as a *passage,* and the changed pathogen is then administered back to the animal to determine if it is still virulent. After several passages the pathogen begins to lose virulence factors because it cannot cause “disease” in the unnatural host cells. Once the pathogen can no longer cause “disease” in the target species, it is tested to see if it can confer protection. The final vaccine is usually passed a number of times beyond the passage where virulence disappears in order to reduce the risk of reversion to a virulent pathogen. These vaccines require good quality control to reduce the risk of a contaminant entering the vaccine.
2. *Inactivated (killed) vaccines* are easier to develop because virulence after growth is not a problem. The same pathogen is isolated from a disease outbreak. The pathogen is grown and then chemically or physically killed. The inactivation is usually achieved by either adding a chemical to the pathogen or using ultraviolet rays. The major concern with inactivation is the potential loss of important epitopes. An adjuvant is

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normally added to inactivated vaccines to heighten the immune response. The vaccine is then tested for efficacy.

3. *Genetically engineered vaccines* have been genetically altered, usually through a mutation. This mutation may be induced by several different methods, but the resulting bacterium or virus has different properties that may alter virulence or growth characteristics. Most of these vaccines are modified live mutants (e.g., temperature-sensitive viral vaccines or streptomycin-dependent *Mannheimia/Pasteurella* vaccines), but inactivated marker vaccines are also genetically engineered. These vaccines have been engineered to delete a gene and cause an immune response deficient in antibodies to a certain epitope; this allows diagnostic methods to distinguish between vaccine and natural exposure responses (e.g., gene-deleted infectious bovine rhinotracheitis [IBR] vaccines).

Once its efficacy has been established, the vaccine is put through a series of experiments to determine the minimum dose required to achieve adequate protection, called the *minimum immunizing dose* (MID). The vaccine will contain more than the MID to ensure that it contains at least the MID at the expiration date found on the label. In effect, a vaccine's efficacy is not determined by the final product used by the veterinarian, but at a reduced level of immunogens from the amount contained in the final vaccine.

Autogenous Vaccines

In addition to the vaccines licensed by the USDA, several companies will make autogenous vaccines for use by veterinarians and cattle owners. These vaccines do not fall under any particular USDA/APHIS guidelines and are usually derived from cultures (e.g., viral or bacterial) isolated from specimens submitted by the particular farm. Such vaccines can be used only on that particular facility and cannot be sold for use on other farms. These vaccines are not tested for efficacy or safety, and the components found in the vaccines may vary from batch to batch; this adds some element of risk when they are used. Nevertheless, this type of vaccine may be an option to consider when federally licensed vaccines are unavailable for a specific farm problem.

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Maternal Antibody Interference Revisited

It is an accepted belief that maternal antibodies can block immune responses from vaccination. This belief has been based on a procedure of vaccination followed by a titer evaluation in the vaccinates. Many studies have shown that vaccinated animals may not display increased antibody levels if high levels of maternal antibody to that antigen are present. However, recent studies have shown that both B-cell memory responses and cell-mediated responses can be stimulated despite high maternal antibody for the same antigens.[18-20] Seropositive calves vaccinated at a young age with modified live (MLV) bovine herpesvirus type 1 (BHV-1), parainfluenza type 3 (PI-3), and/or bovine respiratory syncytial virus (BRSV) vaccines have shown higher antibody responses on revaccination than control calves vaccinated only at the second date. These young vaccinates typically do not show increased antibody responses after the initial vaccination in the presence of high maternal antibody. Cell-mediated immune responses, as indicated by antigen-specific T-cell blastogenesis, have been demonstrated in the face of high maternal antibody levels[21] when attenuated BRSV and BHV-1 vaccines were used. Similar responses have been reported in laboratory animals as well.[22-24] One study also demonstrated higher levels of protection at challenge if calves were vaccinated with a modified live BRSV vaccine.[20] It is clear from these studies that maternal antibody interference with vaccines is not as absolute as once thought. The animal's immune status, specific antigen, and presentation of that antigen should be considered when designing vaccination programs in which maternal antibody may be a factor.

Impact of Stress

Stress affects the immune system of all cattle, as can a number of other factors. The release of corticosteroid that occurs during the birthing process has a dramatic impact on the newborn's immune system. Newborns also have a higher number of suppressor T cells than adults.[2] These factors and others dramatically diminish systemic immune responses for the first week of life.[25] Other stresses should be avoided at vaccination time to maintain the integrity of the immune system. Procedures like castration, dehorning, weaning, and movement have to be considered as stressors in cattle, and all have the potential to temporarily diminish immune system functioning.[26-28]

Systemic vaccinations should be avoided during high-stress times because of these diminished responses and because vaccination at such times may even have undesired effects.

Booster Importance

It is important to follow the label directions for administering vaccines. Many inactivated vaccines and some modified live BRSV vaccines require a booster before protection is complete. The first time an inactivated vaccine is administered, the primary response occurs. This response is not strong, is fairly short-lived, and is predominantly composed of IgM antibodies (Fig. 48.1). The response seen after a booster vaccination is called the *secondary* or *anamnestic response*. This response is much stronger, of longer duration, and is primarily composed of IgG antibodies.[2,12] If the booster is given too early, the anamnestic response does not occur, and if too much time elapses before the booster is given, it acts as an initial dose, not as a booster.

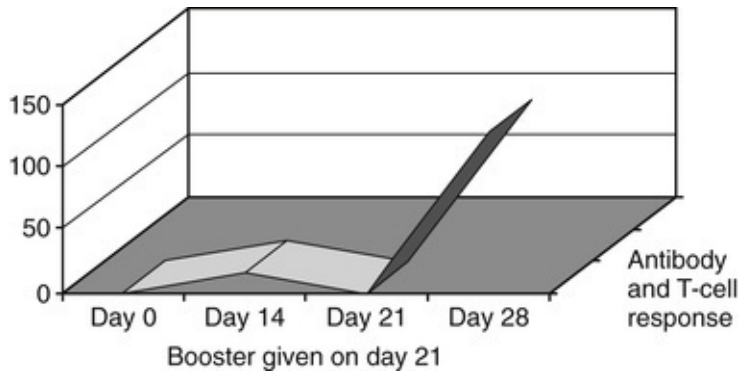


FIG. 48.1 Anamnestic response seen after booster dose is administered to vaccinates.

With most MLV vaccines (except for some BRSV vaccines), the primary vaccination also stimulates the secondary response without the necessity of a booster because the virus or bacterium is replicating in the animal.

Adverse Reactions

Adverse reactions are a risk with any vaccination and can be categorized as one of the following two primary types of hypersensitivities[2,4,29-34]:

1. *Type I (immediate) hypersensitivity* is mediated by IgE stimulation and release of granules from basophils and mast cells. This reaction is seen within minutes of vaccination and often begins with shaking or sweating. Most of these animals respond to intravenous (IV) injection of epinephrine. Every vaccine can occasionally elicit an anaphylactic reaction. Cattle should always be kept under observation for at least 30 minutes after administration of a vaccine. Epinephrine should be administered at a dosage of 1 mL of 1 : 1000 solution per 50 kg of body weight, preferably by IV injection, at the first sign of weakness, staggering, or dyspnea. With most vaccines, anaphylactic reactions occur no more often than 1 case per 5000 to 10,000 doses administered. The rate of occurrence may be much higher after administration of *Salmonella*, *E. coli*, and some *Moraxella bovis* bacterins, which may have high levels of endotoxin.
2. *Type III (immune complex) hypersensitivity* is mediated by attachment of an antibody-antigen complex to complement and the ensuing activation of the complement cascade. The resultant reaction may occur locally or systemically. The reaction may be delayed, as the complexes form and the cascade begins, or subsequent, as products begin to exert their effects. The signs are similar to those of an immediate hypersensitivity reaction, and the treatment is administration of epinephrine.

One of the more common reactions seen in cattle has been associated with the endotoxin and other bacterial components found in most gram-negative vaccines.[32-35] Currently, there are no requirements for monitoring or reporting the amount of endotoxin found in cattle vaccines, and the level of endotoxin may vary dramatically between vaccines and between serials of the same vaccine. Furthermore, the potency of endotoxin varies among different gram-negative bacteria. This type of reaction is seen primarily in Holsteins because of a genetic predisposition and may be seen after administration of any gram-negative bacterin. The signs vary depending on the farm's or individual's sensitivity to gram-negative bacterial components. The number or potency of the gram-negative fractions in vaccinations administered simultaneously are also instrumental in causing these reactions. As a general rule, no more than two gram-negative vaccines should be administered to dairy cattle on the same day because of the possibility of adverse reactions, which may include anorexia and transient decreases in milk production, early embryonic death, abortion, and

gram-negative bacterial shock (endotoxic shock), which requires treatment with flunixin or ketoprofen, steroids, antihistamines, and fluids.

Site reactions are common sequelae to many vaccines. These granulomas are usually caused by overreaction to the adjuvants, but they may also be directly aimed at the antigen or antigens. This has been a major focus of beef quality programs and has generated a push to have all vaccines labeled and to have them administered subcutaneously to avoid damaging the muscle.

Finally, some vaccines may affect appetites post vaccination. This impact continues to be an area of concern and active research, particularly in stressed cattle and neonates.[36-41]

Read the Labels

The vaccine label is a wealth of information that is approved by the CVB/APHIS. The CVB evaluates the supportive efficacy data supplied by the vaccine manufacturer and decides whether the vaccine can be licensed or not. They also determine what type of efficacy claim can appear on the vaccine labels and in advertising. Included are dosage, route of administration, precautions, timing, indications, storage information, withdrawal period, and shelf life. As found in Veterinary Services Memorandum 800.202 (June 2002), the CVB also does some preliminary rating of vaccine efficacy by granting one of five level of protection statements (in order of highest efficacy to lowest): Prevention of Infection, Prevention of Disease, Aid in the Prevention of Infection, Aid in Disease Control, and Other Miscellaneous Claims. The label can be a good starting point for comparing vaccines.

Newer Immunologic Concepts in Cattle Vaccination

The terms *dominant antigen*, *antigen interference*, and *immunodominance* have been used interchangeably to describe a unique phenomena of the immune system. The term *immunodominance* has become the accepted term in human immunology, and textbooks have been written on the subject.[42] Immunodomination is defined as the process whereby immune expression or recognition of one epitope or antigen influences the recognition of a second distinct epitope or antigen.[43] This prioritization of epitopes by the immune system has been widely studied, and many articles have been published. Although most studies have focused on the occurrence of immunodominance in

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immune responses to the multitude of epitopes within a specific antigen (virus or bacteria), there are continued studies on the interactions between different antigens. On any bacteria or virus, only 0.2% of the possible epitopes have any measurable immune response.[44] This also extends to interactions between concurrent administration of different vaccines.[45,46]

Immunodominance has been shown to occur via several different mechanisms. These include:

1. Dominant epitope processing block antigen presenting cells from the antigen presentation of subdominant epitopes[43]
2. Dominant epitope T cells block expansion of subdominant T cells (CD4+ and CD8+)[3]
3. Dominant epitope processing using T-cell synaptic molecules to be used and exhausted and/or the release of defective synaptic molecules, thereby blocking attachment of subdominant T cells[42]
4. Shifting of subsets of CD4+ subsets toward antiviral or antibody formation[45,46]

One of the first published cattle studies demonstrating the potential for interactions between cattle vaccines was published in the *Canadian Journal of Veterinary Medicine* in 1992.[47] The authors demonstrated that vaccination with a modified live bovine herpesvirus 1 (infectious bovine rhinotracheitis virus, BHV-1) vaccine blocked the *M. haemolytica* vaccine response. The same phenomena of modified live BHV-1 vaccine over *M. haemolytica* vaccine response was observed in a vaccine field trial performed by Kansas State University.[48] More recent studies that have compared the serologic responses to *M. hemolyica* bacterins with coadministration of attenuated BHV-1 (MLV and temperature sensitive [TS]) supported the earlier findings; however, immunodominance was not shown if the BHV-1 vaccine was administered intranasally or on subsequent vaccination.[49-50] Antigen interaction has been shown with several other vaccines as well.[51-53] More research is necessary to continue to understand these interactions and how they pertain to developing vaccine program strategies.

Another new immunologic concept that also started in human immunology and is now being researched in veterinary immunology is the prime boost

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vaccine strategy. This concept involves priming the immune system to a target antigen delivered by one vector, route, or mechanism and then selectively boosting this immunity by readministration of the antigen in the context of a second and distinct method.[54] This is considered heterologous versus traditional homologous boostering.

Several papers have highlighted the power of prime-boost strategies in eliciting protective cellular immunity to a variety of pathogens and have demonstrated efficacy in humans.[55] The key strength of this strategy is that greater levels of immunity are established by heterologous prime boost than can be attained by a single-vaccine administration or homologous boost strategies. Recent studies in veterinary medicine have demonstrated the prime boost concept.[56-59] These and other studies indicate that this area of vaccination strategy is poised to make tremendous progress.

Summary

Designing a vaccination program requires a good history of the individual farm and a basic understanding of the immune system. Vaccines that should be considered for routine or optional use in various classes of pastured beef cattle, feedlot cattle, and dairy cattle are listed in Boxes 44.3 to 44.12. The vaccines chosen should be supported by good, solid efficacy studies (and by effectiveness and efficiency studies if possible) to ensure that the product can fulfill the needs of the farm or ranch (see Table 44.8). Management decisions that do not maximize the potential of the product chosen may be made, and realistic expectations of all products should be well explained to the producer before the vaccines are administered. The owner should be involved in the vaccine decision-making process, and all information on the product should be shared.

Establishing good baseline immunity of replacement heifers and the foundation vaccination program can have dramatic effects on the health and profitability of the herd, so such programs must be well planned.

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Bovine Herpesvirus Type 1: Infectious Bovine Rhinotracheitis Virus

Bovine Herpesvirus Type 1 Vaccines

Robert W. Fulton

In 2018 more than 100 vaccines against BHV-1 were available in the United States for use in cattle.[1] These vaccines were either monovalent or in combination with other viral and/or bacterial immunogens. Vaccination protocols for beef and dairy cattle in the United States routinely incorporate use of one or more vaccines against BHV-1. These vaccines are classified into four types: (1) MLV vaccines for parenteral administration (IM and/or subcutaneous); (2) MLV, IN administered vaccines; (3) chemically altered, live virus, TS vaccine for parenteral use and/or IN use; and 4) inactivated viral (killed [KV] vaccines for parenteral use. These vaccines may be single-component (monovalent) vaccines (e.g., BHV-1 alone) or may contain several immunogens, including various combinations of bovine viral diarrhea (BVD) viruses types 1 and 2; bovine parainfluenza type 3 (PI-3) virus, bovine respiratory syncytial virus (BRSV), *Leptospira* spp., *Histophilus somni, M. haemolytica, P. multocida*, and/or *Campylobacter* spp.[1] BHV-1 vaccines in the United States are principally derived from the Cooper/Colorado 1 strain, and in some cases the temperature sensitive mutant, RLB106.[1] The characteristics of the BHV-1 vaccines are described as follows.

BHV-1 MLV parenteral vaccines induce both B-cell (humoral) and T-cell (cell-mediated) active immune responses after administration of MLV vaccine.[2,3] Calves born to dams with circulating BHV-1 antibodies may absorb the colostrally derived maternal antibodies to BHV-1 and other viruses.[4] The mean half-life of viral antibodies to BHV-1 in calves receiving maternal immunity was 21.2 days.[4] Potentially, calves receiving passive immunity to BHV-1 may have a reduced response to BHV-1.[5] Calves seronegative to BHV-1 were given BHV-1 neutralizing antibody intramuscularly and subsequently given MLV BHV-1 intranasally. The passive BHV-1 immunity via BHV Ig had a reduction on the efficacy of MLV BHV-1.[5] The passively administered BHV-1 antibodies protected against viral shedding in viral-challenged calves.[5]

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Modified Live Virus Parenteral Vaccines

The MLV parenteral vaccines were the initial vaccines licensed for use in cattle for protection against BHV-1.[6] Vaccines are attenuated by multiple passages in cell culture and often retain their ability to replicate in a susceptible animal, possibly causing viremia. MLV parenteral vaccines are relatively inexpensive, offer a convenient route of administration, and stimulate a rapid onset of immunity (i.e., within 3 to 5 days of administration).[7-12] In general, one dose given to a susceptible animal stimulates protective immunity, which varies in duration depending on the clinical form of the disease challenge.[3,12] Duration of immunity studies are important to determine length of protection after initial vaccination. Calves receiving a combination MLV vaccine with BHV-1 were protected for at least 126 days after vaccination as measured by protection against infection.[13] Licensure of BHV-1 vaccines in the United States requires efficacy studies using a standard challenge with the BHV-1 USDA Cooper strain. In addition, administration of a combination modified live BHV-1 vaccine yielded protection against virulent field strains of BHV-1.[14] The MLV parenteral vaccines may cross the placenta and infect the fetus, causing abortion.[15] Most MLV BHV-1 parenteral vaccines are not approved for use in pregnant heifers/cows or nursing calves.[1] However, companies have received label claim for BHV-1 and BVDV MLV vaccine use in pregnant cows providing they were vaccinated before breeding initially with that line of vaccines and within 12 months thereafter and to nursing calves provided their dams were vaccinated within 12 months as described earlier.[1,16] The impact of MLV BHV-1 and concurrent *M. haemolytica* vaccines has potential negative interactions. Administration of an MLV vaccine containing BHV-1 and PI3V in combination with a *M. haemolytica* vaccine reduced the efficacy of the *M. haemolytica* vaccine in preventing respiratory disease morbidity, respiratory disease mortality, and fibrinous pneumonia mortality and reduced the antibody response to *M. haemolytica* leukotoxin antibody response in a feedlot study.[17] In another study, coadministration of MLV BHV-1 and *M. haemolytica* immunogen interfered with the serologic response to *M. haemolytica* leukotoxin serum antibody response.[18]

Modified Live Virus Intranasal Vaccines

MLV IN vaccines generally can be divided into two types, based on the attenuation process: (1) those modified by passage in a cell culture[19,20] and (2) those modified by treatment such that they become "temperature sensitive"[21] (i.e., they do not replicate at internal body temperature). MLV IN vaccines stimulate protection in susceptible animals with only one dose, in contrast to chemically altered MLV parenteral vaccines. Calves receiving a temperature-sensitive IN BHV-1 vaccine were protected against virulent BHV-1 challenge.[22] The label directions for selected, but not all, MLV IN vaccines may indicate that they can be safely used in pregnant cattle.[1] These vaccines induce a rapid onset of protection (within 3 days of administration), possibly through interferon in the nasal secretions.[19] One benefit of the MLV IN vaccines is that they stimulate immunity at the upper respiratory tract, the portal of entry of the virus. Another benefit is their potential to immunize calves that are already seropositive because of maternal (humoral) antibodies passively transferred through the colostrum.[22,23] Animals vaccinated with the MLV IN vaccines may transiently shed virus in the nasal secretions and therefore might infect susceptible contact animals.[22,24]

Chemically Altered Live Virus Vaccines

The chemically altered BHV-1 vaccine strain was modified by nitrous acid treatment, which caused changes in the viral genome that resulted in a strain (RLB 106) that is TS, meaning that it has limited replication at internal body temperature.[25] Presumably, because of the limited viral replication, the vaccine requires two doses to stimulate immunity. Because it is TS, the vaccine can be used in pregnant cattle.[1,25,26] This vaccine containing the TS protected cattle against respiratory disease in challenged calves and abortions and stillbirths in challenged females.[26] In one study heifers received two doses of the vaccine and were challenged with BHV-1 seven months later (at 6 months' gestation). These heifers showed a significant reduction in the number of abortions and stillbirths compared with controls.[26]

Inactivated Viral Vaccines

Inactivated viral vaccines are prepared by growing virus in cell cultures and then inactivating them with chemicals. An adjuvant is added to the inactivated strain

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to help stimulate an immune response. Inactivated BHV-1 vaccines require two doses (14 to 28 days apart) when used for the initial vaccination of susceptible cattle. Historically it has been thought that inactivated vaccines against viruses did not induce as long duration of immunity as the MLV vaccines, nor did they confer protection against mucosal infections. Experiments have shown inactivated BHV-1 vaccine protected calves against BHV-1 in a respiratory disease study and also against against BHV-1 experimentally induced abortions.[27-29] Controlled studies should be performed to determine the duration of immunity induced by inactivated BHV-1 vaccines and MLV vaccines, both for respiratory disease and fetal infections. A disadvantage of inactivated vaccines is that the onset of protection may not be as rapid as with MLV parenteral or MLV IN vaccines. An advantage of the inactivated vaccines is that they can be used in pregnant cows and nursing calves.

Use of Vaccines to Prevent and Control BHV-1 Diseases

Many vaccines are available for preventing and controlling the different forms of BHV-1 disease, and each vaccine has certain characteristics that should be considered when designing a vaccination program. Each vaccine also has both benefits and limitations. Probably more important is management of the cattle for which the vaccines are used.

Pregnant Animals or Animals Nearing Breeding Season

The MLV parenteral vaccines may infect the fetus if pregnant susceptible heifers or cows are vaccinated. Abortions have been reported subsequent to vaccination with MLV parenteral vaccines.[15] In many cases the abortions may have occurred to the inadvertent use of the MLV vaccines in pregnant cows.[30,31] However, there has been a report of BHV-1 abortions in pregnant cows after MLV BHV-1 in late gestations in cows vaccinated according to the label (three doses including two as calves and one before breeding).[32] This study indicates that some animals may not develop required immunity despite following protocol. At the time of the diagnosis there was no way to differentiate field from vaccine BHV-1 strains. In recent years using modern genomic testing including PCR and

sequencing the products, MLV vaccines have unique single nucleotide polymorphisms (SNPs) for each virus strain in the vaccine. The isolates from aborted fetuses can be differentiated from field strains on the basis of the SNP profile. In recent years BHV-1 isolates from aborted fetuses have been identified as MLV vaccine strains.[31,33-35] The MLV vaccine virus may also result in corpus luteum infection or disease.[30,36,37] Experimental studies have indicated a reduced conception rate in susceptible cattle that received an MLV parenteral vaccine 3 to 4 days before or 14 days after breeding.[36,37] It has been reported that pregnant cattle raised in contact with calves recently vaccinated with MLV parenteral vaccines had a greater incidence of BHV-1 abortion than those that did not have contact with vaccinates.[38] Consequently, the labels of MLV parenteral vaccines have usually stated that the vaccine should not be used in calves nursing pregnant cows. Recent studies have shown that calves given an MLV parenteral vaccine did not shed virus in their nasal secretions, nor did contact animals become infected with the vaccine virus.[39-41] However, in a recent study of calves pulled for BRD treatment in feedlots, the BHV-1 vaccine strains were isolated from nasal secretions and necropsy tissues of calves within 35 days of vaccination.[42] Similar duration of isolation of field strains of BHV-1 was noted (35 days). Multiple companies have received label claim from the MLV vaccine containing BHV-1 and BVDV for pregnant cows provided the cows had received the same line of vaccines with the MLV BHV-1 and BVDV before breeding and within 12 months thereafter.[1] Likewise, that vaccine could be used in nursing calves if cows were previously vaccinated with that line of vaccines within 12 months.[1] Another concern is that the MLV vaccine virus may recrudesce, with resulting shedding of virus in cattle either stressed or receiving corticosteroids.[43] Realistically, concern about transmission of BHV-1 to animals in contact with those receiving MLV parenteral vaccines would be negligible if the contact animals were properly immunized and immune to BHV-1.

Until the vaccine labels on many MLV parenteral vaccines are changed, MLV IN vaccines or the inactivated or chemically altered live virus vaccines are usually recommended for pregnant cattle or those near breeding. The exceptions are the approved vaccines cited.[1] Vaccine recommendations should be weighed, with the benefits of vaccination as a guide and especially with the realization that properly vaccinated cattle are better protected when exposed to either field (virulent) or vaccine strains shed by vaccinated animals. In a meta-analysis of publications to determine efficacy of BHV-1 vaccination to prevent abortion in

pregnant cattle, both inactivated and MLV vaccines decreased abortion risk.[44] Because of the potential of some vaccinated animals to not respond to MLV vaccines used according to label and being susceptible to MLV vaccine causing abortion if given in late gestation, a recent study indicated protection if the previously MLV-vaccinated cows were given an MLV strain with the temperature-sensitive strain at late gestation.[45] A recent publication indicated that large-scale field studies demonstrated that conception was highest in animals previously vaccinated and revaccinated with inactivated vaccine compared with animals revaccinated with MLV.[30]

Rapid Onset of Immunity

Cattle that are susceptible and likely to be exposed to BHV-1 should receive either an MLV parenteral vaccine or MLV IN vaccine because both types induce immunity within 3 days of the initial dose. Rapid onset of immunity is desirable in such situations as stocker calf and feedlot operations, in which calves are transported long distances to pastures or feedlots, which stresses the animals and makes them more susceptible to infection. Such calves also are exposed to infection with BHV-1 from contact cattle in the markets. The drawback to inactivated vaccines is that two doses are required to obtain good immunity.

Duration of Immunity

Controlled studies on the duration of immunity are limited, and there was variation of the duration of immunity. A degree of protection against challenge existed at 6 to 9 months after vaccination with an MLV IN vaccine or an inactivated vaccine.[46,47] A parenteral MLV BHV-1 MLV vaccine provided protection up to 126 days after vaccination.[13] In a subsequent study, a parenteral BHV-1 vaccine provided protection in calves after 97 days' vaccination when challenged with virulent field BHV-1 strains and the antibodies induced by the MLV vaccine neutralized the field BHV-1 strains.[48] An additional study reported that BHV-1 MLV vaccination provided a 1-year-long duration of immunity following vaccination of seronegative calves, and the challenge was by the respiratory route.[49] Challenge studies for licensure are usually performed on calves within days of vaccination, at the time of peak immunity. Also, the challenge may be for only one form of disease, usually the respiratory type and

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often with the USDA virulent Cooper strain as challenge. Such challenges may detect only protection against a severe form of the respiratory disease. However, an MLV vaccine containing BHV-1 administered 8 or 13 months before challenge provided significant protection against fetal infection resulting from a severe challenge (intravenous challenge with the USDA Cooper strain).[50] BHV-1 manifests itself in other forms, such as abortions, neonatal disease, genital disease (male and female), and conjunctivitis. Yet little or no data are available about the efficacy of vaccines against these other forms of disease. For example, in one case the genital form of BHV-1 disease (infectious pustular vulvovaginitis) occurred in heifers that had received an MLV parenteral vaccine 5 months earlier.[51] Given the lack of duration of immunity studies for all BHV-1 vaccines individually and the cost of vaccines, breeding animals are usually vaccinated at least annually. In selected feedyards the animals may be revaccinated during the feeding period. In these feedlot cattle processing protocols, cattle receive a monovalent BHV-1 or multivalent viral combination MLV parenteral vaccine at reimplant time at approximately 100 days after arrival. There have been field reports of BHV-1 respiratory disease (IBR) in feedlot cattle after a few months of entry/processing at which time they received MLV vaccines containing BHV-1.[52]

Vaccination of Calves With Maternal Antibody

The possibility exists that maternal BHV-1 antibodies acquired by the calf through ingestion and absorption of colostrum may interfere with vaccination. The level of these serum BHV-1 antibodies in the calf depend on the amount in the colostrum, the amount absorbed, and the half-life of the particular antibody —for BHV-1, this is 21.2 days.[4] Some calves receive no BHV-1 antibodies through the colostrum, or they may lose them within 1 month. Some calves, however, may have serum BHV-1 antibodies for up to 6 months after birth.[4,43]

Vaccination recommendations for neonatal calves include use of multiple doses of an MLV parenteral, an inactivated, or a chemically altered live TS virus vaccine or administration of an MLV IN vaccine. The maternal antibodies may block the parenterally administered MLV or inactivated vaccine. However, the MLV IN vaccine may induce BHV-1 antibody immunity.[23] Calves given a TS IN MLV vaccine and possessing maternal antibodies were able to override the maternal antibody when later challenged by the respiratory route with virulent

virus.[22] To date, there are limited if any studies on the use of parenteral MLV BHV-1 in challenge studies to determine efficacy of the parenteral MLV BHV-1 to override maternal antibody in the calves. However, in studies on calves with BVDV maternal antibodies, BVDV MLV stimulated protective immunity when the calves were later challenged with BVDV.[53] Calves often are revaccinated at 6 to 8 months of age regardless of their prior vaccination history.

Advances in Vaccines

Molecular techniques of biotechnology have been applied to the study of vaccines and the response to vaccination (vaccinology). These advances are especially noted for herpesviruses, including BHV-1. In addition to conventional vaccines manufactured via propagation of MLV and inactivated BHV-1 strains, current and future technologies offer opportunities for other vaccines.[54,55] These include subunit vaccines with a portion of the virus, deletion mutants with specific viral genomic fragments deleted, live vectored strains, DNA vaccines using plasmids, and plant-based vaccines. DNA vaccines comprising combinations of plasmids encoding for genes along with immunostimulatory CpG motifs have been evaluated for safety and efficacy in vaccinated cattle.[56] Deletion mutant BHV-1 vaccines as marker vaccines with selected glycoprotein genes deleted along with diagnostic tests for the deleted genes may permit identification of vaccinates under control programs.[57,58] Needle-free delivery of vaccines has been developed and implemented.[55] By high-pressure gas delivery, vaccines may penetrate the skin and be administered intradermally, subcutaneously, or intramuscularly.[54] Such delivery is designed to minimize damage resulting from IM injections. Two studies compared needle-free intramuscular injection of multivalent MLV vaccine containing BHV-1 with conventional subcutaneous injection via syringe in dairy calves and feedlot cattle. In both studies antibody titers to BHV-1 were higher at day 21 postvaccination than conventional needle injection.[59,60]

Vaccination Programs

The best possible vaccine provides protective immunity in the host against infection (viral replication) when challenged; protects the animal against all forms of disease, including multiple organ and systemic forms; and provides

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lifelong mucosal and systemic immunity. Ideally, the vaccine recommendations would incorporate the results of field trials that are carefully designed to show the efficacy of the vaccine against a pathogen. Information is available, as can be seen by a review of the literature, for evaluating the field efficacy of the respiratory disease vaccines.[61,62] The summary of results was mixed for BHV-1 vaccines and for other respiratory viral and bacterial vaccines. Such studies use reduction in general BRD production measures such as morbidity, mortality, reduction of clinical signs, and economic benefit without regard to immunity to a specific agent. However, vaccines evaluated under field conditions may be used in cattle already incubating the virulent infectious agent at time of vaccination or that may be stressed and unable to mount an effective immune response. Animals receiving vaccines before commingling and before feedlot entry developed immunity, which provided protection against respiratory disease, resulting in less morbidity and mortality and treatment costs, and often resulted in greater economic return to the producer.[63,64]

Veterinarians therefore must make recommendations based on (1) experimental studies of vaccination followed by challenge under controlled laboratory conditions apart from the field conditions of normal cattle management and (2) clinical experience with vaccines. Data from challenge studies often are under the control of universities, the federal government, or a biologic manufacturer and may not be published. Government licensure studies require efficacy and safety evaluations, but these studies may not be available in scientific publications for review by those making recommendations. For these reasons, the veterinarian may not have access to all the data needed to make a good decision on vaccines.

The veterinarian's dilemma is confounded by other factors. First, licensure may be granted for vaccination efficacy that demonstrated protection against one form of disease, such as respiratory type. However, the virus may be just as important a pathogen of other organs, such as the developing fetus, as is the case with BHV-1. Second, information is not available or limited about the duration of immunity induced by each BHV-1 viral vaccine commercially available. Licensure studies may use challenge of vaccinated animals within 2 to 4 weeks of initial vaccination, yet cattle may be in feedyards (months) or breeding herds (years) after vaccination. Third, vaccines may induce a strong parenteral immunity, yet the surface mucosal defenses at the portal of entry may still be susceptible to infection even in presumably well-vaccinated animals. Thus, it is entirely possible that natural infections could still occur in these vaccinated

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animals. Ecologically this point is reinforced because viruses, for which there are good immunization products, are still circulating in cattle populations after years of vaccination.

The veterinarian therefore must weigh both the benefits provided by vaccines and their limitations. This is probably best done by focusing on the real economic effects of certain disease manifestations, including morbidity, mortality, and treatment and prevention costs. Historically, this approach has been applied to two important forms of BHV-1 disease: the respiratory form, singularly or in combination with pneumonic bacterial diseases; and the fetal disease (abortions). As a result, most vaccine regimens focus on preventing respiratory disease in both young and adult animals and on protecting the pregnant breeding herd of cows and heifers against abortions. Another fact to be considered is that many vaccines may have multiple viral or bacterial components (or both), which may require multiple doses for an immunogen mixed with one that requires only one dose.

Guidelines

Calves.

Calves may be vaccinated at branding, weaning, or 30 days before weaning. Calves vaccinated before 6 months of age should be revaccinated because the earlier vaccination may have been blocked by maternal antibodies. The MLV parenteral and IN vaccines require only one dose in susceptible calves, whereas the chemically altered live virus or inactivated vaccines require two doses. Although the labels for most MLV parenteral vaccines state that the vaccine should not be used if the calf is nursing a pregnant cow, the likelihood of infection of the pregnant cow may be minimal, especially if she is already immune. Yet as described earlier, MLV parenteral vaccines are available for use in pregnant cows and nursing calves.

Breeding Cows and Heifers.

Yearling heifers (12 to 14 months of age) should be vaccinated at least 1 month before breeding. Any of the vaccines may be used, but if two doses are required, the second dose should be given at least 1 month before breeding.

Pregnant cows may be vaccinated with a vaccine that has a label description warranting such use; these include MLV IN vaccines, chemically altered live

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virus vaccines, inactivated vaccines, and approved MLV parenteral vaccines. Generally one dose is used, primarily because of management considerations. However, following the vaccine label for number of doses and safety for pregnant cow use is important. Administering booster doses of the BHV-1 vaccines may have two conflicting outcomes as a result of booster dose stimulation of an increase in colostral BHV-1 antibodies, which are transferred to the newborn calf in the colostrums; consequently, (1) it may be beneficial to the calf to have increased BHV-1 serum antibodies for protection against BHV-1 disease, or (2) the calf may have longer duration of BHV-1 antibodies, which may block BHV-1 immunization. There are no published multiyear duration of immunity studies in vaccinated cattle challenged with virulent BHV-1. Because of the relatively low cost of BHV-1 vaccines and the need to vaccinate against other pathogens, many breeding cows are given a BHV-1 vaccine annually.

Stocker and Feeder Cattle.

Cattle to be shipped to forage pasture after weaning (wheat pasture or native grass) or to feedyards should be vaccinated 2 to 3 weeks before shipment. However, management practices and marketing may only permit vaccination at initial collection point, market site, or stocker/feedlot delivery. All the major types of BHV-1 vaccines may be used, but those that require only one dose have two advantages: rapid onset of immunity and less handling required (one dose vs. two).

Cattle presented for purchase immediately before shipment, with no known vaccination history, pose a challenge. Presumably healthy cattle may be candidates for the 1-dose MLV parenteral or MLV IN vaccines because these calves may benefit from rapid immunity. Cattle already infected with BHV-1 may not be protected by vaccination.

Cattle entering the feedyard usually receive either the MLV parenteral or MLV IN vaccine, particularly for the rapid onset of immunity.[65] Cattle are often revaccinated during the feeding period in some operations to ensure protection against BHV-1 disease later in the feedyard.[52] Recently studies have shown that delaying MLV vaccination (BHV-1, PI3V, BVDV1, BVDV2, and BRSV) 30 days after processing in stressed auction market calves resulted in a significant decrease in the number of calves requiring additional treatment for BRD.[66]

Breeding Services

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Veterinarians should consult the breeding bull center for vaccination requirements for bulls, especially relating to export shipment and collection for artificial insemination (AI). MLV IN vaccines have been used in AI bulls because these vaccines are less likely to cause latent infections than MLV parenteral vaccines.[67,68] The MLV parenteral vaccines cause latent infections that may recrudesce with stress after administration of corticosteroids, which means the virus may be present in semen.[43,65]

Advances in Diagnostic Medicine and Future Research

In recent years, diagnostic laboratories have moved to newer technologies including immunohistochemistry and genomic tests for infectious agents including viruses.[69] The genomic tests focus on real-time PCR (RT-PCR) and sequencing of the viral genome by whole genomic testing and/or sequencing of PCR products. Reliance on genomic testing has often replaced traditional isolation attempts in cell culture, which are more laborious and time consuming. Sequencing of the viral nucleic material permits the differentiation of field strains from vaccine strains due to the SNPs' pattern. This is important as BHV-1 strains are often isolated from cattle with prior MLV vaccination. BHV-1 parenteral MLV strains may migrate to other sites such as the respiratory tract (nasal passage and lung) with shedding and the fetus from the injection site. The MLV and field strains may initially be identified by RT-PCR; however, the primers for the PCR do not differentiate field from MLV strains. Thus, genomic sequencing is required to differentiate the strains.

Future research should include developing live virus seed stocks for BHV-1 vaccines that are nonabortifacient and do not induce latency in vaccinated animals. Possibly MLV BHV-1 latent infections may remain in the herd for some time (years perhaps) and then be shed, exposing other susceptible animals including susceptible heifers/cows resulting in BHV-1 fetal disease (abortions).

Bovine Virus Diarrhea Virus Vaccines

Victor S. Cortese

Our knowledge of the different vaccines' ability to protect against infection with BVDV is rapidly increasing. Currently, three kinds of BVDV vaccines are available: MLV vaccines, temperature-sensitive vaccines (available only in Europe), and inactivated virus vaccines (Table 48.9). MLV BVDV vaccines have demonstrated advantages over the newer inactivated vaccines. Most of these advantages are common to all MLV vaccines[1,2]: (1) MLV vaccines are less expensive, (2) postvaccination anaphylactic reactions occur less often than after administration of some inactivated vaccines, (3) immunity is achieved more rapidly after administration of a single dose (within 7 to 10 days), (4) MLV vaccines produce much higher levels of serum-neutralizing antibodies,[3] (5) immunity lasts longer,[4-6] (6) MLV vaccines are effective against a broader spectrum of viral strains,[3] and (7) MLV BVDV vaccines are better able to protect the developing fetus from infection.[7]

TABLE 48.9

Currently Licensed Vaccines for Bovine Virus Diarrhea Virus

Product	Company	Type of Vaccine	BVDV[a]	BVD Type 1 Strain	BVD Type 2 Strain
Arsenal	Novartis	MLV	M	1b–GL760–nCP	
Bovi-Shield GOLD FP[b]	Zoetis	MLV	M	1a–NADL–CP	2–53637–CP
Breed-BackTM FP	Boehringer Ingelheim	MLV	M	1a–Singer–CP	2–296–CP
CattleMaster	Zoetis	Hybrid (TS-IBR & PI3, Killed BVD)	K	1a–5960–CP 1a–6309–nCP	
CattleMaster GOLD	Zoetis	Hybrid (TS-IBR & PI3, Killed BVD)	K	1a–5960–CP	2–53637–CP
Elite	Boehringer Ingelheim	Killed	K	1a–Singer–CP	
Express[b]	Boehringer Ingelheim	MLV	M	1a–Singer–CP	2–296–CP

Herdvac	Zoetis	MLV	M	1a–NADL–CP	
Jencine	Merck	MLV	M	1b–WRL–nCP	
Master Guard	Intervet/AgriLabs	Hybrid (Killed IBR, BVD)	K	1a–C24V–CP	2–125C–CP
PregGuard GOLD FP 10[b]	Zoetis	MLV	M	1a–NADL–CP	2–53637–CP
Prism	Boehringer Ingelheim	Hybrid (Killed BVD)	K	1a–NADL–CP	2–5912–CP
Pyramid 4 Pyramid 8 Pyramid 9	Boehringer Ingelheim	MLV	M	1a–Singer–CP	
Pyramid 5, Pyramid 10[b]	Boehringer Ingelheim	MLV	M	1a–Singer–CP	2–5912–CP
Reliant	Merial	Hybrid (Killed BRSV)	M	1a–NADL–CP	
Reliant Plus	Merial	Hybrid (Killed BRSV)	M[c]	1a–Singer–CP	
Respishield	Merial	Killed	K	1a–Singer–CP	
Resvac 4/Somubac	Zoetis	MLV	M	1a–NADL–CP	
Surround	Novartis	Killed	K	1a–Singer–CP 1b–NY–NCP	
Titanium	AgriLabs	MLV	M	1a–C24V–CP	2–296–CP
Triangle+Type II BVD	Boehringer Ingelheim Vetmedica	Killed	K	1a–Singer–CP	2–5912–CP
Vira Shield 61	Novartis	Killed	K	1a–KY22–CP 1b–????–nCP	2–TN131–nCP
Vista	Merck	MLV	M	1a–Singer–CP	2a–125A–CP

[a]M = modified live BVDV component(s); K = killed BVDV component(s).

[b]MLV licensed for use in pregnant cattle when used according to label.

[c]Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture.

On the other hand, MLV BVDV vaccines have certain disadvantages compared with inactivated BVDV vaccines: (1) some MLV vaccines can produce mild immunosuppression for brief periods after administration,[5] (2) some have been associated with what is usually a rather low incidence of a highly fatal disease syndrome, postvaccinal mucosal disease[8,9] (see later), and (3) until recently, MLV vaccines were not ordinarily recommended for routine use in pregnant cattle.

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Studies have shown that the duration of cross-neutralizing antibodies stimulated by inactivated BVDV vaccines depends on the antigenic similarity between the vaccine strain and the wild-type virus to which the cow is exposed.[10,11] If there are few common proteins, the ability to neutralize can be as short as 4 months; if there are many common antigenic sites, neutralization may last a year. MLV BVDV vaccines stimulate cross-neutralizing antibodies that can still be detected 18 months after vaccination.[3] This longer duration was further demonstrated by a modified live BVDV vaccine receiving a USDA label containing a 1-year duration of immunity against the birth of both type 1 and type 2 persistently infected calves.[12]

Recent studies have demonstrated the ability of both modified live[13,14] and inactivated type 1 vaccines[15] to provide protection against type 2 BVDV strains, although the protection afforded by the MLV vaccine was more complete. The USDA/APHIS has established a licensing protocol for BVDV vaccines to obtain a type 2 BVDV protection claim. Most of the vaccines licensed against both BVDV type 1 and type 2 contain BVDV type 1 and type 2 isolates. The question of current vaccines' ability to cross-protect against BVDV type 1b strains has been raised,[16] and further studies are needed to determine the level of protection afforded by current vaccine strains.

Vaccination and Mucosal Disease

Mucosal disease (MD) is seen when an animal that is persistently infected is exposed to another closely related cytopathic strain of BVDV. Also, theoretically a noncytopathic BVDV strain can mutate spontaneously into a cytopathic strain, resulting in MD without any subsequent exposure. High stress and immunodepression may be involved in this mutation.[17,18]

A major concern with the MLV vaccines is whether they can cause MD.[10,19,20] For MD to occur, the cytopathic strain in the MLV vaccine must be closely related to the noncytopathic strain in the persistently infected animal. With the degree of attenuation of MLV vaccines today, an animal must be nutritionally deficient or severely stressed, or both, to face an increased likelihood of developing MD from the vaccine. This suggests that a specific set of circumstances is required and that MD caused by vaccination, when it occurs, is rare.

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Bovine Virus Diarrhea Virus Vaccines and Reproductive Control

Control of BVDV centers on prevention of persistent infection and elimination of persistently infected cattle; this means identifying and removing persistently infected animals and continued vaccination to prevent persistent infection are necessary for effective control. Persistent infections occur through in utero infection of the fetus (up to roughly 125 days' gestation) with a noncytopathic strain of BVDV.[3,17] Although the mechanism of transplacental transfer of BVDV is unknown, small amounts of virus in the dam's bloodstream appear to be sufficient to produce these immunotolerant cattle. Protection of the dam may or may not correlate with protection of the fetus from subsequent persistent infection if viremia of the dam occurs. To break the cycle of in utero infection and persistent infection, it is essential that vaccination provide fetal protection.

Several studies have been performed to assess the ability of vaccines to protect the fetus against either natural or artificial challenge. Results of these studies showed that most inactivated vaccines failed to provide much fetal protection,[7,10,21-26] except for one experimental vaccine, which is reported to give a high level of fetal protection. With the experimental vaccine, inability to isolate the virus from offspring of vaccinated animals indicated good protection.[27] However, the challenge of controls resulted in only about a 50% rate of persistent infection. Only one inactivated vaccine has demonstrated a high level of fetal protection and was given the appropriate label by the USDA (see Table 48.8). Other published reports demonstrated that MLV BVDV vaccines were more effective at protecting the fetus[7,28-30] and that inclusion of a type 2 vaccine broadened the strains against which vaccinates were protected.[31] To date, vaccines licensed in the United States have not been required to provide fetal protection. However, label indications are being granted by the USDA to vaccines that demonstrated the ability to prevent development of persistently infected calves. Several vaccines have achieved this label claim (see Table 48.8).

Bovine Virus Diarrhea Virus Vaccination Programs

Because BVDV infections can cause severe death loss and immunosuppression, all herds of cattle should be vaccinated against BVDV. Although it was once thought that BVDV vaccines would not immunize calves that were passively immune to BVDV,[32,33] recent studies have shown that immunization can occur

with certain inactivated vaccines[34] and with MLV vaccines (when the passive antibody titer against BVDV is ≤1 : 64).[13,35] When required, BVDV vaccines can be administered to young calves, with the possibility of gaining some degree of protection. In most calves the maternal antibodies against BVDV drop below the 1 : 64 level by 5 to 6 months of age. If an early BVDV problem does not exist, waiting to administer the first BVDV vaccine until at least 6 months of age increases the number of animals that respond to vaccination.

Among cows given MLV BVDV vaccines in the last trimester of pregnancy, 86% of the calves from seronegative cows[36] and some calves (0[36] to 52%[37]) from seropositive dams were actively immune at birth. In addition, the calves' level of passive immunity to BVDV was enhanced, in that seronegative cows seroconverted and serum antibody titers were boostered in 52% of the seropositive cows. The rate of occurrence of BVD in neonatal calves was reduced.[38] Administration of an MLV BVDV vaccine to seronegative cows after day 118 of gestation did not result in adverse effects.[38,39] However, vaccination with an MLV noncytopathic virus vaccine before day 118 resulted in fetal resorption, abortion, congenital defects, and the birth of undersized, weak, persistently infected calves. Several authors have recommended vaccination of cows with an MLV BVDV vaccine during the last trimester of pregnancy.[22] Three MLV BVDV vaccines are now labeled for use in pregnant animals. To ensure the safety of these vaccination schedules, label directions must be adhered to.

It is important to consider the epidemiologic nonresponse rate to any vaccine when designing a BVDV vaccination program. Therefore even though MLV BVDV vaccines do not require a booster dose, a second dose may be advised to stimulate protection in animals that did not respond to the initial vaccination. BVDV vaccination programs should include the following features:

1. A virus isolation and cull program should be instituted, along with a vaccination program that includes administration of at least one dose of an MLV BVDV vaccine to all replacement animals.
2. Vaccination with killed vaccines should be increased to 2 or 3 times a year, or an MLV BVDV vaccine should be given to open cows 3 weeks before breeding or turning in the bull.
3. The vaccines used should have been proved to stimulate protection against BVDV type 1 and type 2.

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Bovine Respiratory Syncytial Virus Vaccines

John A. Ellis

Bovine respiratory syncytial virus (BRSV) is a pneumovirus in the paramyxovirus family that endemically infects cattle populations worldwide. Although the virus can cause disease in all ages of cattle, it primarily occurs in recurrent seasonal outbreaks in calves with decayed concentrations of maternal antibodies.[1-3] Resulting respiratory disease is characterized by pyrexia, coughing, and tachypnea, which can progress rapidly to severe expiratory dyspnea.[2,4] BRSV is also considered one of the viral agents that predisposes animals to secondary bacterial infections in the bovine respiratory disease complex (BRDC); however, secondary infections are often absent in fatal BRSV-associated respiratory disease.[2,5,6] Subclinical BRSV infection or mild respiratory disease due to BRSV infection in dairy cattle may have a negative impact on milk production.[7]

Parenteral Vaccines

MLV and inactivated parenteral BRSV vaccines have been commercially available since the 1980s.[8] Most of these vaccines are formulated in combination with other viral respiratory pathogens, including PI-3, BHV-1, and BVDVs. The efficacy of commercial MLV nonadjuvanted and adjuvanted combination BRSV vaccines in conferring significant disease sparing subsequent to experimental infection with a virulent field isolate has been demonstrated[8], despite a meta-analysis that reported no differences in morbidity or mortality comparing vaccinees with unvaccinated controls.[9] Most vaccinated calves shed virus, but the peak virus titer was suppressed compared with unvaccinated controls, indicating immunity is not sterilizing. Viral clearance was coincident with the simultaneous appearance of mucosal antibody, cytotoxic T cells in the lungs, and anamnestic or primary serum antibody responses. In contrast, virus clearance in unvaccinated calves was coincident with the appearance of BRSV-specific cytotoxic cells before mucosal antibody was detected.[8]

The efficacy of parenterally delivered MLV vaccines in calves with MDAs,

the most relevant candidates for vaccination in the field, remains controversial and incompletely resolved.[8,10] In classical studies conducted in small numbers of calves in the 1980s, administration of attenuated BRSV by the IM route to passively immune calves reportedly did not elicit mucosal memory IgA or serum antibody responses or even prime for such responses.[11] In contrast, several studies have documented a variety of BRSV-specific T-cell responses after parenteral vaccination in passively immune calves.[8] However, it has not been determined in a challenge experiment whether these in vitro responses are associated with a protective cell-mediated memory response once maternal antibodies have decayed. Available data from one challenge study conducted with a representative commercial combination parenteral MLV BRSV vaccine given to young BRSV-seropositive calves indicated that priming for protective immunity was blocked by MDA concentrations typical of good passive transfer.[12] Although the ability of parenteral modified live BRSV vaccines to prime for protective immunity in the context of MDAs is likely to vary with the concentration of MDA, the antigenic mass of the vaccine, and/or vaccine formulation,[13] it is probably most prudent, in the absence of serologic data on individual calves, to assume that a biologically significant amount of inhibition of priming will occur in the face of MDA and use mucosal (IN) vaccines in young BRSV-seropositive calves.[14]

Disease-sparing efficacy similar to that demonstrated for parenteral MLV BRSV vaccines has also been documented in the case of some combination inactivated vaccines containing BRSV formulated with different adjuvants[8] when tested in a disease-producing challenge model in young BRSV-seronegative calves. Clinical protection was associated with serum concentrations of BRSV-specific IgG as determined by ELISA,[8] and in one case[8] the presence of IFN-γ–secreting BRSV-specific $CD4^+$ T lymphocytes in the blood of vaccinated calves. There are conflicting data concerning the ability of commercial inactivated BRSV vaccines to override maternal antibodies and stimulate protective responses after parenteral immunization, which may be related to the vaccine formulation and adjuvant, as well as whether disease was produced in the challenge model used in testing.[8,10] Relevant to the importance of vaccine formulation in affecting efficacy in the context of MDAs, some studies with experimental vaccines have demonstrated clinical protection following experimental challenge of seropositive calves[8]; however, whether or not these or future novel vaccines will become commercialized remains to be

determined.

Most experimental studies concerning the efficacy of commercial BRSV vaccines are consistent with previous field trials, demonstrating the safety and efficacy of parenterally administered vaccines.[8] In addition, one study suggested the usefulness of combination vaccines in reducing the impact of subclinical BRSV infections.[7]

As alluded to, protection against BRSV infection and disease is immunologically multifactorial. Certainly, IgA is part of that response,[1-3,8] but serum IgG acquired from either passive or active immunization can significantly reduce the severity of clinical respiratory disease that results from BRSV infection.[8] Several studies have reported that the incidence and severity of disease in calves were inversely related to maternal antibody titers.[2,8] In the case of herd immunity, passive antibodies were detectable in 50% of the calves for 3 months after birth and were present in some calves until 7 months of age.[15] Therefore administration of BRSV vaccines to cows in late gestation to booster colostral antibody titers is a rational strategy to deal with BRSV-induced respiratory disease in young calves (1 to 3 months of age) in problem herds, without having to be concerned about the immunizing potential of particular parenteral vaccines in young seropositive calves.

Intranasal Vaccines

Because BRSV is an endemic infection in most cow herds, most young calves will have BRSV-specific maternal antibodies unless there is failure of passive transfer. Given the endemic nature of BRSV, many calves are likely exposed to BRSV early in life and will contract BRSV-associated respiratory disease if their passive protection is poor or has waned. These biological factors, together with the mixed results with parenteral administration of BRSV vaccines to young seropositive calves, stimulated interest in IN vaccines for BRSV. Combination IN vaccines containing ML BRSV are commercially available in North America and Europe.[8]

Conceptually, it was demonstrated in the late 1980s that IN inoculation of tissue culture–attenuated BRSV to passively immune calves primed the calves for immunologic memory, as evinced by anamnestic local IgA and systemic IgG responses after challenge.[16] Subsequent studies with culture-attenuated BRSV, then with single-component and combination parenteral BRSV vaccines

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administered intranasally and, finally, with commercial IN BRSV vaccines confirmed these phenomenona. Importantly, in addition, these studies documented an association between immunologic responses and significant disease-sparing.[8]

As epidemiologic studies suggest is the case in nature,[1,2,8] iatrogenic mucosal exposure to BRSV IN vaccines is capable of "overriding" MDA, resulting in effective priming of young calves.[8] This has been confirmed by experimental challenge studies and documenting enhanced BRSV-specific antibody responses, compared with nonintranasally vaccinated controls, following parenteral administration of commercial vaccines at approximately 2 months of age to commercially reared beef calves.[8] However, the duration of immunity to neonatal IN vaccination is apparently short, probably less than 4 months.[14] Therefore the current focus of applied research in BRSV vaccines is determining an optimal protocol for boosting of neonatally, mucosally primed immunity. One study[17] suggests that parenteral inactivated BRSV vaccines, used in a "heterologous prime-boost" protocol[18] at 2 months of age, may be superior to similar modified live vaccines, used in the same way, in conferring clinical immunity. Further data are required to provide a better evidence-based foundation for recommendations on the use of BRSV vaccines.

Adverse Reactions to Bovine Respiratory Syncytial Virus Vaccines

A major factor hampering development of a vaccine for human respiratory syncytial virus (HRSV) is the dramatic HRSV vaccine failure in the 1960s, in which vaccination with a formalin-inactivated (FI), alum-adjuvanted HRSV predisposed children to more severe disease after subsequent HRSV infection.[1] Historically, deriving primarily from these observations, there has been a concern about the use of inactivated BRSV vaccines in cattle.[8] Although this same disease-enhancing phenomenon has been demonstrated in some studies of experimental FI-BRSV vaccines in cattle,[8] it is unlikely that modern manufacturing practices would use formalin inactivation of BRSV or other viral vaccines in cattle. Moreover, there are documented cases of apparent enhancement of BRSV-associated respiratory disease in cattle that received *either* inactivated *or* MLV vaccine in the field, indicating that some commercial vaccine formulations may stimulate potentially pathogenic immune responses in

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some cattle, but that it is not necessarily a strict function of inactivation per se.[8] The immunologic mechanisms responsible for vaccine-associated disease enhancement in pneumovirus infections are not completely understood; it may have more to do with the timing between vaccination and BRSV infection than being completely a function of vaccine formulation.[8] However, it is unlikely that the current hypothesis applied in studies of vaccine enhancement of disease in HRSV infections, namely a strict dichomotization between protective T-helper cell (Th1)-like responses versus pathogenic Th2-like responses involving IgE and/or “hypersensitivity “ reactions in response to BRSV vaccines, is particularly relevant to cattle.[8] Nevertheless, given the history of adverse reaction to RSV vaccines in humans and, to a lesser extent, cattle, care should be taken in making assumptions about the efficacy and safety of BRSV vaccines. Data from the laboratory and field use situations should be evaluated before using a particular BRSV vaccine to best avoid adverse reactions.

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Parainfluenza Type 3 Virus Vaccines

John A. Ellis

Parainfluenza virus type 3 (PI-3V) is a ubiquitous paramyxovirus in cattle populations worldwide.[1] In uncomplicated experimental PI-3V infections, clinical signs of coughing, tachypnea, and fever have been observed from 4 to 12 days after infection.[1] Although the virus was originally detected in calves with respiratory disease (often in the absence of other agents), it has been used to experimentally reproduce respiratory disease, and exposure to the virus has been detected by seroconversion in animals with BRD complex, its importance as a pathogen has been somewhat controversial.[1,] Generally PI-3V has been viewed as a potentiating agent in mixed infections, predisposing the animal to bacterial pneumonia by altering bacterial clearance in the upper and lower airways and infecting both respiratory epithelia and alveolar macrophages.[1] Although, as originally described,[1] the PI-3V quasispecies exists as one serotype, recently three serologically distinct genotypes of the virus have been molecularly defined.[2-4] This has raised unresolved questions about differences in virulence among PI-3V isolates, as well as possible genotype-specific variation in vaccine efficacy.[2-4]

Five types of PI-3V vaccines are currently available commercially: (1) MLV IM vaccines, (2) MLV temperature-sensitive IM vaccines, (3) MLV IN vaccines, (4) MLV temperature-sensitive IN vaccines, and (5) inactivated virus vaccines. All PI-3V vaccines available in North America are combined with at least a BHV-1 vaccine.[1] A single-antigen MLV PI-3V IN vaccine that was available in Europe had demonstrated efficacy in a challenge model that produced severe disease typical of that reported in the original descriptions of the virus.[1,5] However, generally, the challenge models previously and currently used result in minimal if any clinical disease, making it difficult to assess the clinical immunity induced by PI-3V vaccines.[1] In most vaccine efficacy studies, the use of attenuated virus resulted in minimal disease,[1] yielding a lack of differences in morbidity and mortality between vaccinees and controls in a meta-analysis of published vaccine studies.[6] This probably contributes to the impression that PI-3V is not a significant pathogen. The latter assumption was also commonly made about BRSV before more robust challenge models were developed and used.[7]

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Opinions have been divided as to the relative importance of mucosal versus systemic immune responses in achieving protection from PI-3V–associated respiratory disease and, by extension, the comparative efficacy of IN and IM vaccines.[1] Some comparative studies reported that IN vaccination resulted in better protection against experimental challenge; others were unable to demonstrate any advantage to the use of one vaccine or route of administration over the other.[1] A notable exception, however, was young calves with maternal antibodies, in which IN administration was thought to produce a more effective immune response. Passive antibodies may persist in calves until 8 months of age and may interfere with active immunization.[1] Consequently, calves vaccinated parenterally before 6 months of age should be revaccinated after reaching 8 or 9 months of age.[1]

Although not experimentally documented, as in the case of BRSV, it is likely that given the similar biology of PI-3V infection, a mucosal (IgA) response is necessary to prevent PI-3V infection, but that passively (maternal) or actively acquired serum IgG is likely to mediate significant sparing of clinical disease subsequent to infection. The cell-mediated (cytotoxic T-cell) response in the clearance of PI-3V is a poorly documented but probably important effector mechanism stimulated by MLV vaccines, as is the case with BRSV.[1]

There is debate about the overall utility and economic benefit of using PI-3V (and BRSV) vaccines in the field.[1,6] Much of the uncertainty is undoubtedly related to the difficulties involved in determining the relative importance of a particular agent in a multifactorial disease process such as BRD complex.[8] Few studies[1] address the economic impact of subclinical paramyxovirus infections in cattle. No recent studies (in the past 5 years) directly address the economic impact of inclusion of PI-3V in combination vaccines. There are conflicting data from studies conducted under commercial feedlot conditions as to the economic benefit of including PI-3V in a vaccination program.[1] One study found no decrease in morbidity or mortality when two versus one dose of a combination viral vaccine containing PI-3V was used in a feedlot environment.[1] A limitation of these studies and such studies in general is the difficulty in obtaining, or failure to attempt to obtain, specific etiologic diagnoses, making it difficult to determine whether an immune response against one or more antigens was responsible for any disease sparing. Although an increased use of PCR[9] can partially address this, it does not directly associate a particular pathogen with actual lesions in affected organs.

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Mannheimia haemolytica, Pasteurella multocida, Histophilus somni, and *Bibersteinia trehalosi*

Jared D. Taylor

Mannheimia haemolytica Vaccines

M. haemolytica, serotype 1 (formerly *Pasteurella haemolytica* A1) is the main bacteria responsible for the clinical signs and lesions of severe bovine fibrinous pleuropneumonia (shipping fever).[1,2] The bacterium is a gram-negative commensal of the bovine upper respiratory tract (URT), whose presence in the nasopharynx is not predictive of impending disease.[3,4] Historically, it has been hypothesized that immunosuppression resulting from stress or viral infections permits the bacterium to proliferate initially in the URT, evade clearance by normal protective mechanisms, and subsequently establish infection within the lungs. It is now recognized that the lower respiratory tract (LRT) is not sterile, and *M. haemolytica* and other pathogenic bacteria can be present in the lung in the absence of disease.[98,99,101] Processes and factors that allow the organisms to proliferate and progress to induction of disease are not fully understood. Regardless, once *M. haemolytica* initiates a disease process, it stimulates a series of pathologic events leading to acute, severe fibrinopurulent inflammation and necrosis. The bacterium was renamed *M. haemolytica* due to substantial genomic differences between it and other members of the *Pasteurella* genus; however, commercial vaccines may still refer to by its previous name, *P. haemolytica*.[5]

Immunity to *Mannheimia haemolytica*

Twelve serotypes of *M. haemolytica* occur (A1, A2, A5, A6, A7, A8, A9, A12, A13, A14, A16, and A17), and only partial cross-serotypic protection is seen following vaccination.[6] Serotypes A1, A2, and A6 are the most prevalent.[7-9] Because *M. haemolytica* is strictly an extracellular organism, humoral immunity is far more important to controlling infection than is cell-mediated immunity. Indeed, there is substantial evidence that cattle entering a feedlot with preexisting serum antibody titers to *M. haemolytica* have less respiratory disease

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and fewer deaths than do those without serum antibodies.[10,11] Maternal antibodies to *M. haemolytica* and *P. multocida* can be found in both dairy and beef cattle but decline to undetectable levels between 30 and 90 days of age.[12] Most calves subsequently and spontaneously develop antibodies to these bacteria due to natural exposure to the nasal flora.[12] Unfortunately, this antibody response is typically short lived, and calves seem to become more susceptible to disease following their decline. Antibody responses following natural exposure target numerous cellular components and secreted products. Those with the most potential for stimulating immunity include capsular polysaccharide, lipopolysaccharide (LPS), outer membrane proteins (OMPs), iron-regulated OMPs, a secreted leukotoxin (LKT), a serotype-specific antigen, and several other secreted enzymes including neuraminidase, a sialoglycoprotease, and bovine immunoglobulin-specific proteases.[13,14] The central dogma of *M. haemolytica* vaccination is that immunity to the organism requires stimulation of antibodies that neutralize LKT and antibodies that bind to surface antigens, allowing for complement-mediated killing and/or phagocytosis of the bacterium.[15] There is no agreement as to what are the most important surface antigens. However, OMPs and iron-regulated OMPs are the major candidates based on many in vitro and in vivo studies.[16-20] Capsular polysaccharide is theoretically an important surface antigen because it is the first surface molecule encountered by cellular and humoral components of the immune system, and its presence enhances *M. haemolytica* resistance to phagocytosis and complement-mediated killing.[21] However, antibody responses to *M. haemolytica* capsular polysaccharide do not always correlate with resistance, and vaccination with purified capsular polysaccharide failed to protect against challenge.[22,23] LPS is also a surface antigen; however, antibodies to *M. haemolytica* LPS failed to correlate with resistance to experimental challenge, and passive antibodies to *M. haemolytica* LPS were not protective in experimentally challenged calves.[24,25]

Use of *Mannheimia haemolytica* Vaccines in Beef Calves

Several studies have examined how rapidly various commercial *M. haemolytica* vaccines induce antibody response and how long after vaccination antibodies remain detectable. Antibody responses reach their maximum quickly (typically within 14 days after vaccination) and abruptly wane (significantly lower by day 28, and sometimes returning to baseline by day 42).[26-28] Revaccination an

extended period after the initial vaccination (140 days in one case) may stimulate rapid anamnestic responses.[27] However, it is unclear if this suggests efficacy in protecting against disease.

When designing a vaccination program for prevention of bovine respiratory disease, four questions should be addressed: (1) Should calves be vaccinated for *M. haemolytica*? (2) What type of *M. haemolytica* vaccine should be used? (3) How many doses of *M. haemolytica* vaccine should be given? And (4) When should the vaccination be administered? We will attempt to provide a basis for answering some of these, but the clinician ultimately must make decisions in consideration of the type of operation (cow-calf, stocker, dairy, or feedlot); management practices; interpretation of published literature; consultations with colleagues; and personal experience.

1. Should an *M. haemolytica* vaccine be used?
   This may be the most difficult question for the practitioner to answer. Vaccine efficacy has been demonstrated primarily with experimental models of pneumonia using one of several challenge methods including direct *M. haemolytica* challenge via intratracheal, intrabronchial, or transthoracic routes or using a combination viral (usually BHV-1) and *M. haemolytica* challenge.[13] The majority of published reports examining vaccination efficacy through experimental challenge have used experimental vaccines and not commercial ones. There are few published reports of efficacy of individual commercial vaccines against experimental *M. haemolytica* challenge. Nonetheless, the studies published have, in general, supported efficacy of commercial vaccines, although not in all cases.[29-31] Of course, one must consider the potential of bias favoring publication of positive results accounting for some or all of this difference (either because of simple publication or due to influence of pharmaceutical companies over dissemination of information related to their product).
   Clinical studies examining field efficacy of vaccines are abundant and frustratingly inconsistent. Numerous studies have found a protective factor from vaccinating.[32-36] Similar numbers of studies found vaccination to be ineffective or inconclusive.[37-39] Perino and Hunsaker[40] reviewed 10 published studies of several commercial live and subunit *M. haemolytica* vaccines with respect to their efficacies in field studies of

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feedlot cattle. Their report concluded that commercial *M. haemolytica* vaccines available at the time did not consistently reduce morbidity or mortality or increase weight gains. Of those studies, five showed positive outcomes based on reduced morbidity, mortality, or increased weight gain, whereas five studies demonstrated no positive outcome. Three of those studies demonstrating positive outcomes involved the same *M. haemolytica* bacterin-toxoid given at arrival in the feedlot; however, two clinical trials with the same vaccine showed no significant differences when given at arrival and/or 3 weeks before shipment. A more recent, rigorous review of *M. haemolytica* vaccines trials using feedlot cattle found that conclusions remain conflicting at times. However, their meta-analysis determined vaccination against *M. haemolytica* offers a modest reduction in morbidity but not mortality.[41] An observational trial also found vaccination at the ranch of origin to be associated with decreased morbidity.[96] It is important to note that the study was performed in Australia, and the vaccine examined is only available in that country.

When examining efficacy of vaccines in field trials, it is relevant to note that diagnosis and treatment in such studies is based on undifferentiated BRD (rather than disease solely attributable to *M. haemolytica*). Although *M. haemolytica* is the predominant bacterial isolate associated with BRD, it is not the sole pathogen. In order to conclude that an *M. haemolytica* vaccine is efficacious in reducing BRD, a study would need to have a high power (large number of cattle enrolled), a relatively high incidence of BRD, and a large proportion of that disease attributable to *M. haemolytica*. This may play a role in the lack of definitive evidence of vaccine efficacy. Given these considerations, if a clinician chooses to recommend vaccination, questions 2 to 4 from earlier need addressed.

2. What type of *M. haemolytica* vaccine should be used?

Numerous commercially available bovine biologicals contain *M. haemolytica* antigens.[42] *M. haemolytica* vaccines are often in combination with viral vaccines, *H. somni* or *P. multocida* bacterins, and occasionally *Clostridium* spp. biologicals. Despite the various licensed *M. haemolytica* biologicals available, formulations of *M. haemolytica* vaccines fall into one of nine categories, seven of which are nonliving vaccines. These are described by their manufacturers as follows: (1) bacterin with aluminum hydroxide adjuvant, (2) bacterin with water-in-

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oil adjuvant, (3) outer membrane extract, (4) bacterin-toxoid (leukotoxin toxoid), (5) toxoid-cell-associated antigen, (6) adjuvanted toxoid (culture supernatant), (7) recombinant leukotoxin-extracted OMP vaccine, (8) autogenous (herd-specific) bacterins produced from isolates submitted by practicing veterinarians, and (9) live streptomycin-dependent mutant. The latter vaccine is the only currently licensed live *M. haemolytica* biological. In the past, several live *M. haemolytica* vaccines were commercially available, and those vaccines showed potential efficacy; however, untoward side effects such as severe local and systemic reactions often occurred after vaccination. Studies have occasionally compared commercially available vaccine products under field conditions.[43,44] Unfortunately, they often are supported by industry funding (creating a potential conflict of interest) and typically do not include a negative control group. Thus, the significance and validity of the findings from these studies are unclear.

Most studies comparing commercial vaccines have relied on antibody titers (typically to LKT and/or whole bacterial cell preparations) as outcome of interest. Although antibodies appear important to protection, it is unclear what antigens are most important, what titer is sufficient for protection, or if a higher titer is always better. Therefore conclusions from those studies are difficult to interpret. Direct comparisons of two or more commercial *M. haemolytica* vaccines against experimental or natural challenge have rarely been published. In one such comparison between a commercial *M. haemolytica* bacterin-toxoid and the live streptomycin-dependent mutant vaccines, the bacterin-toxoid elicited the greatest serologic responses and significantly reduced lung lesions after experimental challenge.[31] Calves receiving the live mutant vaccine had lesions that were not significantly lower than for control cattle. Demonstration of protection against experimental challenge, however, may not necessarily indicate that the vaccine will be efficacious against natural disease under field conditions.

3. How many doses of *M. haemolytica* vaccine should be given?

Although many of the currently available *M. haemolytica* biologicals are licensed for only one injection, manufacturers recommend a booster if possible. Of course, administration of two doses of a *M. haemolytica* vaccine is not practical for most cow-calf operations. Shewen[45] demonstrated that one of the reasons one dose of *M. haemolytica*

vaccine often stimulates adequate antibody response is because most cattle carry *M. haemolytica* in their nasopharynx and have a primed immune system that can produce a rapid anamnestic response to vaccination. However, as mentioned earlier, it is unclear if this suggests continued efficacy in protecting against disease.

4. When should an *M. haemolytica* vaccine be given? Given the short persistence of elevated titers following vaccination, administering a *M. haemolytica* vaccine at the appropriate time becomes critical.[46-48] Manufacturers of *M. haemolytica* biologicals usually recommend vaccination between 15 and 21 days before "weaning, shipping or exposure."[42] If vaccination was more than 2 to 3 weeks before time of greatest risk, a booster should be given before shipment. This protocol is incompatible with routine management of most cow-calf operations, making it difficult to recommend vaccination as a standard practice in this segment of the industry. Further adding to the challenge of identifying an optimal time for vaccination is the possibility that concurrent administration of MLV vaccines may interfere with response to *M. haemolytica* vaccination. Cortese and colleagues[28] examined serologic response to vaccination with four commercially available *M. haemolytica* vaccines in calves naïve to bovine herpesvirus 1 (BHV-1) and *M. haemolytica*. When the vaccines were given concurrent with an MLV product, the antibody response against LKT was consistently lower than when the *M. haemolytica* product was administered alone. It is unclear whether this would impact the efficacy of the vaccines in reducing disease, although previous work with an experimental vaccine suggests it could.[49] Work examining different products found no evidence of BHV-1 interference with response to a bacterin product,[100] but this study examined response to *P. multocida* vaccination, not *M. haemolytica*. Moreover, assessments were directed at CMI response to vaccination, not antibody titers.

A negative effect of BHV-1 vaccination on anti-LKT titers was not seen with IN administration of an MLV vaccine, although only one product was examined in this study.[50] Concurrent vaccination with IN MLV and *M. haemolytica* vaccines resulted in an initial anti-LKT titer equivalent to that produced by the *M. haemolytica* vaccine alone. Moreover, a robust anamnestic response occurred

when a booster of the *M. haemolytica* vaccine was given 90 days later, in conjunction with a parenteral MLV. Similarly, no negative effect on response to *P. multocida* vaccine was observed to result from concurrent IN BHV-1[100] (although, as mentioned earlier, there was also no negative effect from parenteral administration of BHV-1, either). Thus, it appears that some of the negative effect of concurrent MLV vaccination may exist. This effect may be muted if calves are not naïve for BHV-1 and/or other viral agents or if an IN route is used.

Vaccination of cattle against pneumonic mannheimiosis on arrival at the feedlot is somewhat controversial, for numerous reasons. Most importantly, it may not allow enough time for development of adequate protection before the period of highest morbidity.[51] Secondly, if cattle have been vaccinated 2 to 3 weeks before shipment and had an appropriate immunologic response, antibody titers may be adequate, making revaccination not cost effective. Finally, vaccination with an MLV vaccine at arrival is nearly universal, which may interfere with response to the *M. haemolytica* vaccine, if the calves have not previously been vaccinated or exposed to respiratory viruses.[28] Since the vaccination history is rarely known for cattle entering a feedlot, it may be impossible to make an informed decision regarding these considerations. Nonetheless, vaccination with a *M. haemolytica* product on feedlot entry is often practiced.[46-48] Results in several field trials indicate that this practice can potentially afford some protection against shipping fever during the first 14 days in the feedlot.[46] Selective use of *M. haemolytica* vaccines has also been advocated. Some feedlots designate cattle as high risk and low risk for respiratory disease. Managers may be more willing to vaccinate low-risk cattle because high-risk cattle are either sick on arrival or can break with disease soon after entry into the feedlot.[47] Therefore high-risk cattle would not have time to mount an immune response to vaccination before disease. However, low-risk cattle are less likely to break with disease soon after entry into the feedlot, and when they are vaccinated there is often adequate time for immunity to develop before a respiratory outbreak occurs.[47] While this is arguably rational, research to support or refute its effectiveness is lacking. As stated earlier, a meta-analysis of vaccination for *M. haemolytica* in feedlot cattle found a modest reduction in morbidity (relative risk 0.93, 95% confidence interval of 0.89 to 0.98), but no significant reduction in mortality (RR 0.75, 95% CI 0.56 to 1.04).

In summary, there is some evidence that use of *M. haemolytica* vaccination can be beneficial. However, *M. haemolytica* vaccination is not warranted or

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appropriate in all situations. It would likely provide the most benefit when employed by cow-calf producers, but doing so correctly would require administration at an appropriate time (2 to 3 weeks before shipping). It would also be preferable to not perform MLV vaccination concurrently (unless an IN product is used or the MLV is a booster of previous administration). It would be questionable whether the additional cost and effort are justified, as weaning for at least 40 days seems more important in reducing disease than is vaccination.[52] For stocker/backgrounder and feedlot operations, use of *M. haemolytica* may offer less benefit. Usage is particularly questionable in lightweight, high-risk calves. These calves are likely to develop disease before vaccination could produce an immune response, and the resulting inflammatory response to endotoxin and other innate immune stimulators may have negative effects, including decreased feed intake. Usage may be justified in backgrounded or yearling cattle that are more likely to respond to vaccination before the period of greatest risk for disease.

Use of *M. haemolytica* Vaccination in Dairy and Veal Calves

Management differences between dairy and beef calves could be expected to impact disease incidence and severity, as well as immune status in these two classes of cattle. In addition, evidence suggests that purebred Holstein calves may not respond immunologically as well as beef or Holstein crossbred cattle.[53] Thus, it would seem prudent to consider this population separately. Unfortunately, studies of *M. haemolytica* vaccination in dairy and veal calves have been published less frequently than those in beef calves. In general, vaccination of young dairy calves has failed to produce significant antibody responses.[54,55] This is probably due to interference by colostral antibodies. As passive immunity wanes, calves develop anti–*M. haemolytica* antibodies as a result of natural exposure.[55] In terms of protection against natural disease, vaccinated calves had similar incidences of respiratory disease as did unvaccinated controls.[56,57] In another study, a *M. haemolytica* bacterin-toxoid was found to be less effective than a commercial streptomycin-dependent mutant *M. haemolytica* and *P. multocida* vaccine in reducing respiratory disease in veal calves.[58] Failure of *M. haemolytica* vaccines to provide protection in dairy and veal calves could be because *P. multocida* is usually the most common isolate from dairy calf pneumonia.

Vaccination for *Pasteurella multocida*

P. multocida, particularly serogroup A, serotype 3 isolates, is the second most common bacteria associated with pneumonia in beef cattle and the most common isolated from pneumonia in dairy calves.[2] Although *M. haemolytica* has traditionally been the major pathogenic bacterium associated with shipping fever, some studies have suggested that the incidence of *P. multocida* in BRD has increased in beef cattle.[1,48,99]

The antigenic makeup of nonliving *P. multocida* vaccines presently available are proprietary and are described in the *Compendium of Veterinary Products* as bacterial extracts, cell-associated antigens, soluble antigens, and/or bacterins. Conventional formalin-inactivated, whole-cell, aluminum hydroxide-adsorbed bacterins have been the industry standard and are not considered highly efficacious.[42] A commercial live streptomycin-dependent mutant *P. multocida* and *M. haemolytica* vaccine is available. One study that examined this product found no difference in immune response compared with nonvaccinated controls.[100] However, only CMI responses were assessed rather than antibody levels.

The immune mechanisms involved in resistance to *P. multocida* lung infections in cattle are poorly understood. Antibodies are presumed to be important in protecting against disease, and serum antibody levels have been correlated with severity of lesions following challenge,[59,60] as well as decreased risk of natural disease.[10] However, there are few peer-reviewed studies examining efficacy of vaccination in field conditions, and those that have been published suffer from severe shortcomings (typically sponsored by a manufacturer and often lacking a nonvaccinated control group). A meta-analysis[41] reported three trials of vaccination of feedlot cattle with products containing *P. multocida* along with *M. haemolytica*. The results of these trials were not examined separately but instead were combined with results of studies examining only *M. haemolytica*. Nonetheless, the reported results are not compelling (one reduced BRD, one increased BRD, and one trial showed no effect). Little work has been done regarding commercial *P. multocida* vaccines in dairy calves, despite the prevalence of *P. multocida* in respiratory disease in that population. In the one trial identified, a combined *M. haemolytica–P. multocida* vaccine was no better than control.[56] There is more published work related to vaccines against *P. multocida* serogroups B and E, which cause hemorrhagic

septicemia in cattle and water buffalo,[61] but those have limited or no relevance to BRD.

Studies suggest that *P. multocida* OMPs or iron-regulated OMPs could be important immunogens for protecting cattle against pneumonia, and vaccination of calves with outer membrane preparations substantially enhanced resistance against experimental challenge.[13,62,63] Work on specific OMPs and cell surface antigens continues, but results have not been incorporated into commercial vaccines as of yet. Although the *P. multocida* toxin, which is produced primarily by serogroup D isolates, is an important virulence factor and immunogen for *P. multocida* in atrophic rhinitis of swine, there is no evidence that this toxin is important in pneumonia of cattle, nor would it be beneficial to include the toxin in a cattle vaccine.[13]

In summary, significantly less is known about the immunogenicity and vaccinology of *P. multocida* than for *M. haemolytica*. Products currently available are generally unrefined and have limited evidence of efficacy. As such, it is difficult to make recommendations regarding their usage. It seems reasonable to presume that these products will work no better than *M. haemolytica* vaccines and suffer from many of the same challenges. Thus, their usefulness (if any) is likely restricted to vaccination at least several weeks before maximum risk. Vaccination of lightweight, high-risk calves is probably of limited benefit and should be avoided due to the potential negative impact of innate immune system stimulators (such as endotoxin) contained within vaccine preparations. Inadequate information exists to comment on potential usefulness of *P. multocida* vaccination in dairy and veal calves.

Vaccination for *Histophilus somni (Haemophilus somnus)*

Histophilus somni (formerly *Haemophilus somnus*) is the cause of thrombotic meningoencephalitis (TME), septicemia, and reproductive disorders in cattle. In addition, it is the third most common bacterial isolate from beef cattle pneumonia in most epidemiologic surveys.[1,2] Cases of *H. somni*–induced pneumonia are often associated with concurrent myocardial necrosis. Potential immunogens have been experimentally studied in *H. somni* and consist of lipooligosaccharide (LOS),[64] several OMPs including immunoglobulin-binding proteins that bind the Fc receptor of bovine immunoglobulin and are associated

with serum resistance of pathogenic strains,[65,66] and iron-regulated OMPs.[67] As in most gram-negative bacteria, *H. somni* LOS is a dominant antigen that stimulates an antibody response to the polysaccharide moiety following natural or experimental exposure. Interestingly, *H. somni* LOS has been demonstrated to exhibit phase variation in its epitopes (i.e., antigenic drift), thus allowing the bacterium to escape the immune response.[64] Currently, there is no evidence that those anti-LOS antibodies are protective.[68] Likewise, several OMPs and iron-regulated OMPs have been shown to be immunogenic in cattle. The major *H. somni* outer membrane protein (MOMP) is weakly immunogenic and shows strain antigenic variability.[69] Given the weak immunologic reactivity and its antigenic variability, MOMP is likely of limited utility in diagnostics or subunit vaccine development. Immunoglobulin-binding protein A (IbpA) not only binds immunoglobulins but is cytotoxic for bovine alveolar type II epithelium.[70] In addition, vaccination of calves with recombinant subunits of IbpA enhanced resistance against experimental intrabronchial *H. somni* challenge.[71] Unfortunately, sera from calves that received a commercially available vaccine showed no antibody reactivity to IbpA, suggesting a bacterin vaccine does not stimulate a response to this important virulence factor.[97]

Several approved *H. somni* biologicals are available, often in combination with respiratory viruses or other bacterial pathogens (*Clostridial* spp.). Currently licensed *H. somni* biologicals are formalin-killed bacterins with aluminum hydroxide as adjuvant. Efficacy of *H. somni* bacterins has been generally favorable in stimulating protection against experimental pneumonia, against intravenous and intracisternal *H. somni* challenge as a model of TME, and against natural TME. Overall, vaccine-induced immunity has been best against experimental and natural TME.[41,51,72,73] Using an experimental challenge model of *H. somni*-induced pneumonia, significant protection was afforded calves vaccinated twice with an *H. somni* bacterin.[74] Resistance correlated with a high serum antibody response to the bacterium. One study demonstrated a reduced risk for respiratory disease in cattle that had high antibodies titers to *H. somni* on arrival in a feedlot.[75] Therefore the potential would appear to exist for stimulating resistance to *H. somni*–associated pneumonia. Unfortunately, commercial *H. somni* vaccines can stimulate IgE antibodies and thus potentially increase the risk for type I hypersensitivity.[76] Administration of a commercial *H. somni* vaccine concurrent with a formalin inactivated bovine respiratory syncytial virus (BRSV) vaccine resulted in increased morbidity and pathology

following co-infection, compared with vaccination with experimental subunit vaccines.[94] The authors attributed this negative outcome to IgE response to both agents. The negative outcomes were despite a strong IgG1 and IgG2 response in calves receiving the commercial *H. somni* vaccine. However, the co-vaccination/co-infection nature of the study precludes conclusions about effects of the *H. somni* vaccine alone.

Under field conditions, commercial *H. somni* bacterins have had limited success in inducing a protective immune response against respiratory disease.[40] In the three trials reviewed by Perino and Hunsaker, *H. somni* vaccination resulted in reduced treatment rate,[77] an increased rate of cattle being treated for respiratory disease,[78] and no significant difference from nonvaccinated controls.[79] In a more recent study, partial reduction in feedlot respiratory disease was associated with vaccinating for *H. somni*, whereas a significant reduction in respiratory disease was associated with *H. somni* vaccine in combination with *M. haemolytica* or *M. haemolytica* vaccine alone.[80] Ribble and colleagues[81] demonstrated reduced steer mortality following *H. somni* vaccination but not heifer mortality. A meta-analysis demonstrated no benefit associated with *H. somni* vaccines in beef cattle,[41] but the authors acknowledged that the few published trials offered little power to find a benefit, if it existed.

Vaccination for *Bibersteinia trehalosi*

B. trehalosi was originally classified as *Pasteurella haemolytica* Biotype T and consists of four serotypes (T3, T4, T10, and T15).[6,82] In 2007, Blackall and colleagues[82] proposed the new classification of the bacterium using phenotypic and molecular characteristics of 43 European isolates, of which 14 were from cattle and 9 of those were isolated from lung (the authors did not indicate if those isolates were from pneumonic lungs). Traditionally, *B. trehalosi* has been associated with diseases of sheep, primarily septicemia in domestic sheep and fatal pneumonia in Bighorn sheep.[83] In recent years, *B. trehalosi* has been isolated from bovine pneumonia, and there is concern among cattlemen, dairymen, and veterinarians that the bacterium is an emerging pathogen.[84] *B. trehalosi* has been isolated sporadically from bovine pneumonia as early as 1971 with occasional subsequent descriptions of isolations.[85-89] Much of the currently available information about prevalence of *B. trehalosi* in bovine pneumonia is anecdotal and not well documented in the scientific literature. What little data

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are documented, however, indicate a low prevalence of the bacterium. The Veterinary Laboratories Agency (VLA) laboratories in the United Kingdom documented 65 isolates of *B. trehalosi* from bovine pneumonia cases since four initial cases were recorded in 2003.[90] Isolations ranged from 0 (2005) to 22 (2009) with over two thirds of the isolates occurring in the last 3 years of the study. Isolates have been from both beef and dairy cattle, and all ages have been affected. In 72% of the cases, *B. trehalosi* was isolated in combination with one or more other bacterial or viral respiratory pathogens. From 2007 and 2009, *B. trehalosi* was isolated from approximately 20 to 45 cases of respiratory disease in dairy cattle annually.[84] That report also documented multiple case of respiratory disease in two dairies and one beef cattle operation. A challenge study evaluated clinical disease and lung lesions following experimental challenge with multiple strains of *B. trehalosi* isolates (including leukotoxin positive and leukotoxin negative strains) found little evidence of pathogenicity of *B. trehalosi*.[95] There were no clinical signs observed following inoculation with only *Bibersteinia,* and lung lesions were no different from negative control calves. The findings were notably different from challenge with *M. haemolytica* or combination of *B. trehalosi* and *M. haemolytica,* which produced clinical signs and mortality. These authors concluded that *B. trehalosi* may not be a primary pathogen of respiratory disease in cattle.

Little is known about immunity against *B. trehalosi,* and commercial vaccines specifically targeting this agent are not currently available. There is only approximately 35% homology between the genomes of *B. trehalosi* and *M. haemolytica*.[91] Some *B. trehalosi* strains are hemolytic and produce leukotoxin that is antigenically related to *M. haemolytica* leukotoxin and can be neutralized by anti-*M. haemolytica* leukotoxin antibodies.[45] This suggests that vaccination of cattle with a *M. haemolytica* vaccine that stimulates antileukotoxin antibodies may provide some level of immunity against leukotoxin-positive *B. trehalosi* strains. Indeed, one study found that a commercially available *M. haemolytica* toxoid reduced clinical signs, mortality, and lung lesions to intratracheal challenge with *B. trehalosi* isolate with leukotoxin genes.[93] The authors of this study referred to unpublished findings of leukotoxin genes being present in up to 45% of *B. trehalosi* isolates. However, an earlier publication found only approximately 15% of the bovine isolates produce leukotoxin.[82] Other potential antigens, such as outer membrane proteins, appear to be substantially different from those of *M. haemolytica*.[92] Thus, while there is some evidence for use of

commercial *M. haemolytica* vaccine for protection from *B. trehalosi,* the resulting immunity may well be inadequate for complete protection.

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Bovine Reproductive Disease Vaccines

Victor S. Cortese • Carole A. Bolin

As discussed earlier, cows have a multilayered placenta that leaves the fetus susceptible to infection. Infection of the placenta, inflammation of the ovary, death of the fetus, or disruption of the cervical plug all may cause abortion. Reproductive disease is therefore the most difficult disorder to achieve protection against. Vaccination must minimize the amount or duration (or both) of the viremia or septicemia, or it must prevent the pathogen from moving through the cervix or crossing the placenta.

Reproductive diseases and protection against them through vaccination are areas of active research. With current research, a vaccination program can be designed to help control reproductive diseases, but there is little or no research on the efficacy of many vaccines currently used to prevent reproductive disease. Given that the causes of reproductive failure are so numerous (infectious agents account for only a small percentage), vaccination to prevent infectious reproductive losses may not appear to be effective. This is often because diagnostic testing has not been attempted or has not determined the cause of reproductive inefficiencies. A vaccination program may be inappropriately instituted when the cause is not infectious, or the current program may unfairly be deemed ineffective. Use of viral vaccines to help prevent reproductive diseases was discussed earlier in the chapter.

Brucella abortus Vaccine

Brucella vaccination has best shown the effectiveness of vaccination in controlling a reproductive disease. Successful control and even eradication of *Brucella abortus* in many areas of North America are a testament to the ability of a program involving testing, culling, and vaccination to control a reproductive disease with zoonotic consequences; vaccination with either strain 19 or strain RB51 *Brucella* has proved to be effective. However, many herd owners have stopped vaccinating against this disease as states have been declared *Brucella* free.

Abortions caused by *B. abortus* are usually seen after 5 months' gestation. Retained placentae and subsequent metritis usually follow. The abortion is due to severe placentitis. *Brucella* infections have also been associated with a decrease

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in conception rates and an increase in services per conception. A higher number of dead and weak calves has also been demonstrated in infected herds. Orchitis, seminal vesiculitis, or both may characterize infections in bulls.

Only heifer calves can be vaccinated for brucellosis. Both of the two licensed *B. abortus* vaccines are modified live bacterins, and vaccination of bulls may lead to orchitis.[1] Legal use of the vaccines is usually confined to heifer calves 4 to 12 months of age, because vaccination of older animals with the strain 19 vaccine may lead to false-positive results on routine *Brucella* screening tests. Because the strain 19 vaccine may cause septicemia, clinical illness, and occasionally death,[2] sick, unhealthy, or stressed cattle should not be vaccinated. The RB51 strain vaccine is an O antigen–deficient mutant of the *B. abortus* strain 2308. The RB51 vaccine has three primary advantages:

1. Antibodies induced by this vaccine do not react with the serologic tests routinely done to diagnose *Brucella* infections.
2. The vaccine can be used in adult cattle at a lower dosage under special circumstances and with USDA permission.
3. The vaccine tends to cause less postvaccination fever and stress than the traditional strain 19 vaccines.

The long-term immunity conferred by *Brucella* vaccination is the cell-mediated type.[3,4] Calfhood vaccination does not prevent a herd of cattle from becoming infected with *B. abortus*, but it does largely prevent abortions and protects 65% to 75% of the cattle in the herd from infection while infected reactors are identified and slaughtered.[5] For these reasons, in addition to vaccination, a control program should include testing and culling of all animals that test positive.

Leptospira Bacterins

Leptospirosis occurs worldwide and is caused by infection with the spirochete *Leptospira*. The pathogenic leptospires were formerly classified as members of the species *Leptospira interrogans;* the genus has recently been reorganized, and pathogenic leptospires are now identified in seven species of *Leptospira*.[6] As part of this reclassification, the serovar names have remained the same, but some of the common leptospiral pathogens of cattle have different species names than

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before. The key changes for this discussion include (1) *L. interrogans* serovar *grippotyphosa* is now *L. kirschneri* serovar *grippotyphosa*; and (2) the two types of serovar *hardjo* have been formally split into two species: serovar *hardjo* type *hardjobovis* (found in the United States and much of the world) is now *L. borgpetersenii* serovar *hardjo,* and the less common serovar *hardjo* type *hardjoprajitno* (found primarily in the United Kingdom) is now *L. interrogans* serovar *hardjo.*

Although traditionally associated with abortions, infection with various serovars of *Leptospira* is associated with a variety of clinical signs, including severe systemic disease (most often in young animals), decreased milk production, birth of weak calves, and infertility. In addition, infected cattle are known to present a risk of zoonotic transmission of the infection to humans. Many different serovars of *Leptospira* have been shown to cause reproductive failure and abortions in cattle. Of these serovars, *hardjo*, *pomona,* and *grippotyphosa*[7-10] are more common, with serovars *canicola, icterohaemorrhagiae,* and *bratislava* occasionally implicated. The epidemiology of infection of cattle with these serovars differs with cattle serving as the reservoir or maintenance host for serovar *hardjo* and as an incidental host for the other serovars. In general, maintenance host infections are associated with a high prevalence of infection, a poor immune response, and long-term infection and shedding, whereas incidental host infections are characterized by low overall prevalence of infection with epidemics recognized, a vigorous immune response, and short-term infection and shedding. These differences in the epidemiology of leptospirosis caused by different serovars of *Leptospira* require different strategies for prevention.

Leptospirosis can cause abortion storms in which a high number of cattle may abort within a short period. There may also be an increased number of stillbirths and births of premature and weak calves during these periods.[11] Although serovars *pomona* and *grippotyphosa* tend to cause abortions in the last trimester of pregnancy, serovar *hardjo* can cause abortions at any stage of pregnancy. Abortions are usually due to fetal infection and subsequent fetal death, although placentitis may also occur. Serovar *hardjo* can also colonize the oviducts and uterus,[8,2-13] diminishing fertility. After an initial serovar *hardjo* infection, cattle may remain infected and shed the spirochete for long periods,[14-15] whereas infection and shedding of the other serovars is relatively brief.

Current bacterins generally contain combinations of leptospiral serovar *pomona, grippotyphosa, canicola, icterohaemorrhagiae,* and either *L.*

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interrogans serovar *hardjo* type *hardjoprajitno* or *L. borgpetersenii* serovar *hardjo* type *hardjobovis.* A monovalent *L. borgpetersenii* serovar *hardjo* type *hardjobovis* vaccine is also available. There has been considerable debate in recent years regarding the efficacy of leptospiral bacterins for cattle. The bacterins have label claims that indicate they are to be used as an "aid in the prevention of disease." These bacterins should therefore be expected to decrease the severity of clinical signs, including abortion, associated with infection. In general, the evidence supports such claims for serovars for which cattle are an incidental host (i.e., serovars *pomona*, *grippotyphosa*, *canicola*, and *icterohaemorrhagiae*). Protection mediated by bacterins for these serovars is thought to occur because of induction of antibodies directed against the LPS on the surface of the *Leptospira*.[16] However, vaccination does not always prevent infection and leptospiruria caused by serovar *pomona*.[17-19]

The efficacy of bacterins for prevention of infection, leptospiruria, and clinical signs associated with serovar *hardjo* infection is significantly more controversial. Evidence that the efficacy of traditional serovar *hardjo* vaccines is less than optimal includes induction of a relatively poor antibody response in vaccinated animals, the common presence of *hardjo* infection in herds despite routine vaccination, and experimental trials that did not demonstrate protection afforded by these traditional vaccines for prevention of infection, colonization of the renal or genital tract, or transplacental infection on challenge with *L. borgpetersenii* serovar *hardjo* type *hardjobovis*.[20-22] In these studies, cattle were not protected from infection despite the induction of antibody directed against serovar *hardjo* LPS. Further investigation and evaluation of other serovar *hardjo* bacterins has led to a hypothesis that cell-mediated immunity may play a role in protective immunity against serovar *hardjo* in cattle.[23-27] Newer serovar *hardjo* bacterins have been introduced in monovalent and polyvalent formats, and there is evidence these bacterins provide significant protection of cattle against infection, tissue colonization, shedding, and transplacental infection.[23,28,29] Other new bacterins for serovar *hardjo* are also entering the marketplace, but as of this writing, extensive data regarding the performance of these products for reproductive protection are unavailable in the literature.

Some *Leptospira* bacterins are labeled as single initial dose products, but a booster dose is recommended approximately 1 month after the first dose.[18] *Leptospira* bacterins must be administered by IM or SC injection. Although some manufacturers specify revaccination at 12-month intervals, this duration of

immunity has been questioned and more frequent revaccination is often necessary to control *Leptospira* abortions.[19-21] A 1-year duration of immunity has been documented for two of the newer serovar *hardjo* bacterins, but this duration has not been documented for other *hardjo* vaccines or for the other serovars, making vaccination every 6 months a reasonable recommendation in many circumstances. Nevertheless, because leptospiral abortions are uncommon during the first half of pregnancy, it may be possible to use an annual vaccination schedule (serovar *hardjo* excepted) in seasonally calving herds like beef herds. Cattle in such herds can be vaccinated when they are 2 to 4 months pregnant, usually at the time pregnancy is diagnosed, and protected through the remainder of the pregnancy with a single annual dose.[19]

Prevention of leptospirosis caused by serovar *hardjo* requires a somewhat different approach. Prebreeding vaccination of heifers that is effective in managing reproductive sequelae of other types of leptospirosis may be too late to prevent the consequences of serovar *hardjo* infection. Heifers exposed early in life may remain infected well into the time of breeding. Therefore efforts to control serovar *hardjo* infection should be targeted at preventing the initial infection and are best done by vaccinating young stock well before the time when they are mixed with older animals. In addition, bulls can carry serovar *hardjo* and transmit the infection quite readily during breeding.[29] Therefore bulls should be fully included in efforts to control serovar *hardjo* infection by vaccination.

Bovine Genital Campylobacteriosis Vaccines

Originally classified as *Vibrio, Campylobacter fetus* subsp. *veneralis* causes a venereal infection of cattle. The bacteria are introduced during natural breeding by infected bulls or artificial insemination (AI) with infected semen. Bulls are usually infected by breeding with infected cows, but contact with infected bedding may also be a cause. Older bulls (>4 years of age) are more likely to be infected. After deposition in the vagina, the bacteria rapidly colonize the vagina and cervix and in 25% of these cows are found in the oviducts. The organism can persist for months after infection of these sites. It has been shown that fertility never returns to normal in some infected animals, and some may be permanently sterile because of the damage caused by salpingitis.

Vaccination with *Campylobacter* vaccines has been shown to be effective in protecting heifers even when vaginal cultures test positive for the bacteria.[30] It

appears that the uterus is resistant to the bacteria after vaccination. Studies have demonstrated improved breeding efficiency in vaccinated herds.[30] Vaccination of bulls with oil-adjuvant vaccines not only prevents infection of bulls for up to 1 year[31] but also aids in prevention of mechanical transfer of organisms during natural service.[32] Vaccination with two doses has been shown to be effective at clearing infections from carrier bulls.[33,34]

Vaccination

Use of *C. fetus* bacterins is recommended in all breeding herds that use bulls, even if only on selected cows. In heifer herds using virgin bulls or in 100% AI-bred herds, vaccination against *Vibrio* organisms is not necessary.

Several different *C. fetus* vaccines are available, including oil-adjuvanted and aluminum hydroxide–adsorbed types. Oil-adjuvant *C. fetus* bacterins have proved to be more effective[35] and provide longer lasting protection after a single dose.[36] Unfortunately, oil-adjuvant vaccines cause localized granuloma formation and fibrosis at the site of injection. This may cause visible blemishes, which may be objectionable in registered stock or show cattle. Administration no earlier than 4 months before the breeding season is preferred.[36] When aluminum hydroxide–adsorbed *C. fetus* bacterins are used, a priming dose should be administered at least 6 weeks before the immunizing (booster) dose and the booster should be administered 10 days before the beginning of the breeding season.[37] After administration of an aluminum hydroxide–adsorbed bacterin, serum antibody concentrations peak rapidly and decline precipitously, falling to susceptible levels by 4 weeks after one dose or 11 weeks after two doses.[39] Some aluminum hydroxide–adsorbed bacterins do not require an initial booster.

Campylobacteriosis (vibriosis) is most effectively controlled when all breeding-age animals, including bulls, are included in the vaccination program.[32] Vibrin (Zoetis) is the only *C. fetus* bacterin available in the United States that has been evaluated in bulls.[30] Two 5-mL doses are administered to breeding bulls at 4-week intervals beginning 8 weeks before the start of the breeding season.[30] In subsequent years, a single booster dose is administered 4 weeks before the start of the breeding season.[33] This dosage is 2.5 times that recommended for vaccination of cows.

Bovine Trichomoniasis Vaccines

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Bovine trichomoniasis is a venereal infection of cattle caused by the protozoal agent *Tritrichomonas foetus*. Early in the course of the disease, abortions with pyometra may be seen in 5% of infected cows; these abortions occur early in gestation.[38] However, infertility is the most common sign, with long interservice intervals.[39,40] Early embryonic death is followed by a period of conception failure. Some natural resistance develops after infection, but carrier cows may be an important component of the epidemiology of this disease. In rare cases, uterine destruction may leave a cow sterile after an infection.[41]

The efficacy of *Tritrichomonas* vaccines is questionable,[42-45] but the vaccines do appear to reduce actual reproductive losses.[46] Heifers, cows, and breeding bulls should be vaccinated twice at 2- to 4-week intervals, the second dose given 4 weeks before the beginning of the breeding season[46]; SC administration is recommended. In subsequent years a single annual booster vaccination should be given 4 weeks before the beginning of the breeding season.

In a problem herd, trichomoniasis vaccination must be coupled with other control measures like culturing, culling, and treatment to effectively control the disease.

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Neonatal Calf Enteric Disease Vaccines

Gerald E. Duhamel

Neonatal calf enteric diseases (NCEDs) can have a devastating impact on the profitability of beef cow-calf and dairy operations. In addition to mortality, medical, and labor costs, NCED can significantly reduce body weight of beef calves at weaning and performance of replacement dairy heifers.[1]

Several well-characterized infectious causes of NCED have been described.[2] Some of the more common infectious agents are group A RVs, coronavirus (CV), enterotoxigenic *E. coli* (ETEC), salmonellae, and *Cryptosporidium* spp.[3-9] Sporadic outbreaks of necrohemorrhagic enteritis affecting 3- to 10-day-old calves have been associated with infection with *C. perfringens* type C.[10] Other less well-characterized viruses (group B RV, calicivirus, torovirus, astrovirus); bacteria (enterotoxigenic *Bacteroides fragilis,* attaching-effacing enteropathogenic and enterohemorrhagic *E. coli, Enterococcus durans*); and protozoans *(Giardia duodenalis)* have also been associated with NCED.

Because of the continuous calving and constant introduction of replacement heifers on dairy farms and the continuous flow of susceptible calves on veal calf operations, infections caused by more than one agent should be suspected in these types of operations.[3-9,11-13] In addition to different infectious agents, mixed infections with different groups and serotypes or genotypes of viruses and bacteria can also occur. Consequently the severity, duration, and spread of clinical disease associated with complicated infections are usually greater than with a single agent, and control may be more challenging. When scours occurs in a herd that has been vaccinated against enteric diseases, possible contributing factors should be considered, including concurrent infection with pathogens not present in the vaccine (e.g., *Cryptosporidium* spp., salmonellae, nongroup A RVs, other pathogens), suboptimal management of colostrum feeding, and poor control of environmental contamination. Under these conditions, strategic improvement in husbandry practices might be sufficient to reduce the infectious threshold for NCED and obtain the full benefit of pathogen-specific vaccination. In any situation, thorough laboratory diagnostic investigation is essential to identify the primary cause of NCED and any other possible contributing factors and to serve as a basis for implementation of appropriate control strategies for present and future calf crops.[14]

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Management practices and risk factors associated with development of NCED are sufficiently different between dairy and beef herds that control measures can be tailored according to the type of production. For example, in dairy herds, high turnover of older cows and continuous introduction of replacement heifers pose a higher risk of introducing new enteric disease pathogens in a susceptible population than in closed beef herds. Similarly, continuous calving and proximity of susceptible calves on dairy farms creates an ideal environment for recirculation of enteric disease agents back into the adult population. This in turn may increase and broaden herd immunity such that the efficacy of a vaccine might be enhanced partly because of the booster effect vaccine can have on preexisting immunity. Beef cattle herds, in contrast, are generally relatively closed, and a susceptible calf population is present only for a relatively short period annually during the calving season. Introduction of new pathogens or new strains of enteric disease agents, particularly during the calving season, can have a devastating effect because of the potential for exposure of a high number of susceptible animals over a relatively short period of time. Conversely, after an outbreak, herd immunity might be more stable and the occurrence of NCED might be reduced during the following calving seasons.

Under both types of production systems, vaccination for NCED is rarely successful without reasonably good management programs aimed at providing adequate intake of high-quality colostrum and minimizing environmental contamination through effective sanitation. General herd health management steps that can affect the success of a vaccination program for NCED should include a calving cow-calf care plan aimed at minimizing exposure of newborn calves to infectious agents that can overwhelm innate or passively acquired immunity. This is accomplished by careful monitoring of colostrum intake, eliminating all potential means of NCED transmission, and reducing the load and duration of exposure to pathogens present in the calving environment. The following are eight simple recommendations to accomplish these goals:

1. Establish a sound biosecurity program, including purchase of replacement animals only from reputable sources and a complete ban on the introduction of foster calves, which pose a high risk of introducing new NCED agents.
2. Provide adequate protein and energy feed, including proper concentrations of vitamin and micronutrients (e.g., copper and selenium) and abundant clean drinking water throughout gestation and calving to

ensure heifers and cows have optimal body condition scores at calving, produce adequate volume of high-quality colostrum and milk, and deliver healthy and vigorous calves at birth that have a fully developed and functional immune system.[15]

3. Avoid crowding and keep the calving area and equipment clean, dry, and protected from the elements, particularly cold winter wind or wet muddy conditions. Provide sufficient bedding in calving pens so that calves are not born in a wet, manure-contaminated environment. Separate feeding and bedding grounds should be available in the calving area. Similarly, to minimize infectious disease transmission, use separate equipment for feeding and manure handling.
4. Limit the spread of infectious disease agents from younger, more susceptible, and potentially shedding animals to the main herd by segregating first-calf heifer pairs from the mature cow herd during the calving season until the youngest calf is at least 4 weeks old. Because of potential problems associated with nursing in first-calf heifers, newborn calves in this group should be monitored closely for colostrum intake and early detection of failure of passive transfer so that rapid intervention can be implemented.[15-17] Because first-calf heifers are at a competitive disadvantage with mature cows, segregation of pregnant first-calf heifers also ensures free access to feed and water at all times.
5. Ensure that each calf ingests roughly 10% of its body weight (at least 4 L [1 gallon]) of colostrum divided into half as soon as possible and preferably within the first 2 to 3 hours of birth, then the rest 4 to 6 hours later, but always before the calf is 24 hours old. Consider heat-treating colostrum at 60° C for 60 minutes to reduce total coliform count, and thus, reduce risk of illness (including scours) as a function of improved passive transfer of maternal immunity.[18] In dairy herds, do not rely on the calf nursing the dam for adequate colostrum intake; instead, routinely use nipple/bottle or bucket feeding and esophageal tubing. If a calf is unable to suckle or is at risk for failure of passive transfer of maternal immunity, force-feed fresh or freshly thawed frozen colostrum from the calf's dam or from a mature cow in the same herd or a neighboring herd. First-milking colostrum is optimal for passive transfer of immunity to the calf; however, feeding calves colostrum from day 1 and day 2 milking can provide long-term health benefits.
6. Thoroughly rinse and soak with hot water, and vigorously scrub and

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disinfect all equipment with detergent and bleach, and let them completely dry between uses for feeding colostrum and treating sick calves. This includes such items as nipple bottles, esophageal tubes, buckets, balling guns, and calf carts. For more difficult pathogens to kill such as *Cryptosporidium* spp., consider using chlorine dioxide (ClO_2) disinfectant.

7. Move cow-calf pairs away from the calving area as soon as possible after birth in dairy herds. In beef herds, segregate calves by age by scheduled movement of dams that have not calved to new calving pastures—the so-called Sandhills Calving System (http://veterinaryextension.colostate.edu/menu2/Cattle/Calf%20Scours%
8. Develop a calf-care program including rapid identification and isolation protocols for scouring calves from healthy calves in dairy herds, or sick cow-calf pairs from healthy pairs in beef herds, to minimize environmental buildup of infectious disease agents.[15]

Giving calves a healthy start maximizes their genetic potential and reduces costs and labor associated with treating sick animals while minimizing production losses.

Rotavirus and Coronavirus Vaccines

RVs and CVs are ubiquitous in the cattle population; most adult cattle have VN serum antibodies.[19-23] RV infections are widespread in both dairy and beef cow-calf production systems, whereas infection with CV most often occurs as sporadic outbreaks of severe diarrhea in beef cow-calf herds or chronic low-grade diarrhea in dairy and veal calf operations. In addition to causing NCED, infection with CV causes winter dysentery in adult cattle[24] and respiratory tract infection in calves,[25] and it also contributes to BRD complex in feedlot cattle.[26] Fecal shedding of RV and CV is common among adult cattle,[27-30] providing a constant source of challenge for naive newborn calves and allowing persistence of these viral agents at the herd level.

Although only one type of CV is known to cause NCED,[31] different subtypes of CVs can be identified on the basis of minor genomic and antigenic differences.[31-35] On a herd basis, however, affected calves can display a range of clinical signs from enteric only to mixed enteric and respiratory signs. A

molecular epidemiologic investigation based on comparative analyses of a gene encoding a major structural protein of bovine CV revealed (1) identical CV strains in different animals from the same herd and from paired nasal and fecal samples from the same animals, suggesting herd outbreaks are associated with a single strain circulating among susceptible cattle; (2) identical CV strains in affected cattle from different herds in the same region, suggesting transmission between herds; and (3) different CV strains in cattle affected during different outbreaks occurring over several years in the same herd, suggesting herd outbreaks are associated with the introduction of new strains in a recovered herd.[36]

Currently, RVs are classified into at least eight distinct groups, A through H.[37] Although RVs that belong to groups A, B, and C naturally infect cattle,[30,37-41] members of group A RV are by far the most prevalent.[39,41] The group A RVs are further classified according to sequence differences in two genes encoding the corresponding outer protein layer of the virus, namely viral protein 7 (VP7) or G (for glycoprotein) serotype and the protease-activated attachment protein VP4 or P (for protease sensitive) serotype.[42-44] Because both the G and the P proteins are involved in neutralization of virus infectivity in vitro and protection in vivo,[45-47] and each protein can segregate independently in progeny viruses during mixed infections leading to wide variations in relative frequency of individual G/P antigenic combinations according to geographic locations and individual farm, consideration of the G/P configuration of RVs is critical to development of effective vaccination programs for prevention of NCED.

Although a good correlation between the antigenicity of the G proteins and their corresponding gene sequences is well established, a similar relationship has not been found for the P proteins. Nevertheless, the binary G/P serotyping of group A RVs classification has largely been replaced by a G/P genotyping system based on nucleotide sequence of the corresponding genes.[48] Globally, 27 different G genotypes (G1 to G27) and 35 P genotypes (P1 to P35) are found among group A RVs infecting animals and humans.[48] At least eight distinct G types (G1, G2, G3, G6, G8, G10, G11, and untypeable) are known to infect cattle in the United States[49,50]; however, G6 appears to be the most widespread, while G8 and G10 account for fewer infections.[23,50-55] Similarly, RVs with any of four P types (P1, P5, P11, and untypeable) are known to infect cattle in the United States, but P5 appears most prevalent.[50,53,56]

The genome of RVs is composed of 11 gene segments that can be exchanged

among RV strains when animals are infected by more than one virus differing in G/P types at the same time.[43] Therefore mixed infections produce progeny RV with a genetic makeup derived from either parental strain by a mechanism called *gene reassortment.* Because the G and P proteins are independently involved in generation of specific VN antibodies, reassortment of the genes encoding these proteins during mixed infections can generate new progeny viruses that can evade what once was a protective immune response.[55] Genetic reassortment is a well-characterized mechanism of immune evasion that allows persistence of RVs in susceptible populations but can also promote interspecies transmission.[57] Some RV strains appear to be host specific; however, zoonotic spread of bovine RVs to humans is increasingly recognized.[57-60] In the case of bovine group A RVs, the potential for emergence of virus strains carrying any of 36 possible antigenic configurations (4 Ps × 8 Gs = 32 potential types) underscores the limitation of vaccination programs and also the importance of sound management practices designed to minimize exposure by limiting environmental contamination.

Vaccination Programs

Two approaches are widely used in an attempt to protect calves against RV and CV infection and diarrhea. The most common approach involves passive protection of the suckling neonate by transfer of high levels of specific VN colostral antibodies induced by parenteral vaccination of the pregnant dam.[21,61-69] The mechanism of passive protection with this approach is due to the continuing presence of an amount of specific VN antibodies in the intestinal lumen sufficient to neutralize infectious virus before infection of the intestinal villous enterocytes.[19,66,70-74] The continuous presence of VN antibodies in the gut lumen may also reduce the severity of the disease if infection has already developed. In addition, some of the VN colostral antibodies that are absorbed into the bloodstream are secreted onto mucous membranes and may provide local immunity later in life.[75] However, colostral transfer of immunity is less efficient in ruminants than in other species; high concentrations of maternal antibodies are present for less than 3 days postpartum, and these concentrations often fall below protective levels within 1 week of parturition.*

A delicate balance exists between passive protection afforded by lactogenic immunity and development of the calf's own innate and adaptive local immunity to RV and CV. Because most calves' level of resistance to the adverse clinical

effects of RV and CV infection increases with age, disease caused by these agents can be controlled under certain circumstances by continuous hand-feeding of fresh, frozen, or fermented colostrum from vaccinated cows throughout the first 3 to 4 weeks of life.[†] The goal with this approach is to allow development of subclinical infection while the milk VN antibody concentration is partially protective.[63,74,79] Conversely, lactogenic immunity might interfere with development of adaptive immunity, or some calves might not be exposed to RV and CV infection until after milk antibody concentrations have fallen below protective levels, leaving the calf fully susceptible to infection.[61,63,80]

There are currently five safe and effective USDA-approved vaccines on the market for prevention of neonatal calf diarrhea caused by group A RV and CV. The first RV and CV vaccine for parenteral administration to pregnant cows (Calf-Guard [Zoetis]) became commercially available in 1979. This vaccine contains a single live attenuated G6:P1 strain of group A RV. However, because precalving parenteral vaccination of cows with this vaccine resulted in low VN antibody concentrations in the colostrum and milk,[21,22,63,81] this product was later reformulated to a more potent parenteral preparation that contains inactivated G6 and G10 strains of group A RV and CV (ScourGuard 4KC [Zoetis]). Other inactivated vaccines that contain either three strains of group A RV and a strain of CV (Scour Bos 4 and 9 [Elanco U.S. Inc., Larchwood, Iowa]) or two strains of group A RV and two strains of CV (Guardian [Merck Animal Health, Madison, N.J.]) have also been licensed for use in pregnant cattle in the United States. The latter product can also be combined with a modified live CV vaccine (Bovilis [Merck]) for IN administration to healthy calves 3 days of age or older.

Vaccination of pregnant cows with inactivated RV and CV vaccine can raise the level of VN antibodies in the colostrum.[21,61-70,82] Although there are reports of successful protection of calves against NCED by parenteral vaccination of pregnant cows with RV and CV,[‡] negative results have also been reported. Failure of this vaccination strategy is generally attributed to failure of passive transfer of colostral antibodies to the calf or overwhelming virus challenge. An alternative explanation might be that the serotypic specificity of the passively transferred maternal antibodies may affect the protective efficacy of the RV vaccine.[91]

Information on protective immunity against infection of calves with group A RVs having the same or a different G/P serotype configuration as the vaccine

strain is incomplete.[51,82,92-96] Although immunity to RV appears to be G/P serotype specific with some strains,[51,82,92,95] there is some indication that immunity directed against certain strains can neutralize in vitro[51,96] and protect challenge-exposed calves in vivo[51,95] against RV strains with different G/P configurations. Also, parenteral vaccination of seropositive cows with a single strain of RV can elicit serum VN antibodies to a broad spectrum of RV serotypes and genotypes, suggesting that this strategy may provide a means of enhancing passive protection against other potential RV serotype challenges.[83,93,95] However, a difference in the P protein of a vaccine RV and the infecting RV was suggested as the basis for failure of an inactivated monovalent RV and CV vaccine in beef cow-calf herds.[97,98]

Although antigenic and genotypic variations are documented among bovine CVs,[31-35] reduced protection of nursing calves after challenge with a strain of bovine CV different from the vaccine strain has not been demonstrated. Consequently, addition of more than one strain of bovine CV in certain vaccines might not be justified at this time.

Another approach for preventing NCED caused by RV and CV involves oral vaccination of calves with an MLV vaccine that contain attenuated G6:P1 strain of group A RV (Calf-Guard) or IN vaccination with an MLV attenuated CV vaccine (Bovilis).[99-109] The mechanism of disease prevention with these vaccines is unknown, but interference with infection by virulent virus, followed by development of secretory IgM and IgA and/or CMI in the intestinal mucosa, has been proposed for the group A RV vaccine.[80,102] To achieve adequate protection, the manufacturer recommends that the group A RV vaccine be given immediately after birth, before the calf has nursed. This regimen might be applicable to calves whose dams have not been vaccinated. However, because the colostrum of most heifers and cows contains some level of VN antibodies arising from natural exposure,* administration of colostrum should be delayed for several hours after vaccination to avoid inactivation of the vaccine virus. Under commercial conditions, it is nearly impossible to administer vaccine within minutes of birth or to effectively regulate colostrum intake in relation to the time of vaccination. Therefore infection before vaccination, neutralization of the vaccine virus by colostral antibodies, and overwhelming challenge with infectious RV shed by unvaccinated diseased calves might explain a lack of field efficacy with this approach.[64,104-107] This is evident from the data obtained in vaccine efficacy evaluation studies in which only a portion of the calves on a

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farm or a ranch are vaccinated in double-blind or odd/even-day vaccination trials.[76,108,109] When all calves are either vaccinated or not vaccinated in sequential comparisons, morbidity and mortality rates from NCED are significantly reduced by this vaccination strategy,[70,99-101,108,109] but the design and statistical validity of the latter kinds of trials have been questioned.[90,105]

Although not recommended by the manufacturer, the oral attenuated RV vaccine has been administered to calves with unknown immune status that were raised as veal calves or replacements in heifer development operations.[6] Under these circumstances, vaccination might provide active immunity and protection against potential virus challenge when calves from several different sources are commingled.

The manufacturer recommends administration of the IN MLV attenuated CV vaccine in calves 3 days of age and older, after colostrum intake on the first day of age.

Rotavirus and Coronavirus Vaccination Products

ScourGuard 4KC

ScourGuard 4KC consists of inactivated bovine G6 and G10 strains of group A RV and a bovine CV strain combined with K99 *E. coli* bacterin and *C. perfringens* type C toxoid. For first-calf heifers and mature cows that have not previously been vaccinated, a two-dose series of vaccine should be administered by IM injection into the neck of pregnant cows and heifers 3 weeks apart, starting 6 to 9 weeks precalving. The second dose should be given 3 to 6 weeks before the expected calving date. A single annual booster dose should be administered 3 to 6 weeks before each subsequent calving.

Scour Bos 9

Scour Bos 9 consists of inactivated bovine group A RV strains G6, G8, and G10 and a CV strain combined with bacterins from four *E. coli* K99 serotypes and *C. perfringens* type C toxoid. The first vaccine should be administered by IM injection into the neck of pregnant cows and heifers 8 to 16 weeks before the expected calving date, with a booster dose of vaccine 4 weeks before the expected calving. Only one annual dose at 8 to 10 weeks before calving is required thereafter.

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Guardian

Guardian consists of inactivated bovine group A RV G6 and G10 strains together with type 1 and type 3 bovine CV strains combined with cell-free extract of enriched K99 pili from *E. coli* and bacterin-toxoid from *C. perfringens* types C and D. The vaccine should be administered by SC injection of pregnant cows and heifers up to 12 weeks before the expected calving date. A booster dose of vaccine is given approximately 3 to 6 weeks following initial vaccination. One annual dose administered 5 to 7 weeks before expected calving is required thereafter.

Bovilis

Bovilis is a modified live bovine CV recommended for IN administration to calves 3 days of age and older.

Calf-Guard

Calf-Guard is a modified live bovine G6 strain of group A RV and bovine CV recommended for oral vaccination of newborn calves. The vaccine should be administered immediately after birth, before the calf has nursed. As indicated earlier, interference by maternal antibodies may limit the efficacy of the vaccine, so vaccination of calves older than 1 day may be ineffective.

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Bacterial Scours Vaccines

Gerald E. Duhamel • Victor S. Cortese

Enterotoxigenic *Escherichia coli* (Calf Scours) Bacterins

Neonatal calf diarrhea associated with enterotoxigenic *E. coli* (ETEC) usually occurs within the first 72 hours of life. The majority of ETEC-associated NCEDs are associated with strains that produce the F5 (K99) fimbrial adhesin mediating adherence to specific receptors located on the brush border of small intestinal villous enterocytes, thereby resisting normal peristaltic clearance mechanisms, and thus, promoting bacterial colonization of the intestinal mucosa.[1-3] Adherent ETEC produce enterotoxins that stimulate water and electrolyte loss into the intestinal lumen, leading to dehydration and electrolyte imbalance that can be fatal. These ETEC strains may also express other types of fimbriae, including F41 and F1 (type 1), sometimes in combinations with the same strain of ETEC.[1,4] Intestinal colonization and villous attachment by strains of ETEC expressing adhesive fimbriae can be prevented by precalving vaccination of the dam with a bacterin that contains a single fimbrial antigen in common with the challenge strain.[1,4] However, disease may occasionally be caused by ETEC expressing fimbrial antigens different from the most common, $F5^+$; therefore typing of *E. coli* isolates obtained from diarrheic calves can assist with proper selection of an ETEC fimbriae-based vaccination program.[5,6]

Because calf scours associated with ETEC strains occurs so early in life, there is not enough time for a newborn calf to mount a protective immune response through vaccination. Therefore control of ETEC-induced calf scours is aimed at (1) limiting calf exposure to bacterial pathogens, (2) vaccinating dams to provide high levels of fimbriae-specific colostral antibodies (i.e., usually against the F5 antigen), and (3) providing adequate volume of colostrum as soon as possible after birth to prevent bacterial colonization of the calf intestinal tract.[3] Pregnant cows are vaccinated in late gestation to ensure high concentrations of anti-F5 colostral antibodies. When colostrum from vaccinated cows is fed to newborn calves, the antibodies prevent bacteria expressing fimbrial adhesin from binding to specific host cell receptors located on the brush border of small intestinal

villous enterocytes, mostly in the jejunum and ileum.[1,8] Unbound ETEC bacteria are passed into the feces by intestinal peristalsis and, thus, prevented from colonizing the small intestine and causing disease. By 72 to 96 hours of age, calves are highly resistant to ETEC infection and will rarely show clinical signs of diarrhea.[1,9] Thus, feeding calves colostrum with a high concentration of antibodies against F5 fimbrial antigen, even though restricted to the first day of life, is often sufficient to prevent severe diarrheal disease.[4] Passive circulating serum antibodies that are absorbed into the bloodstream from the intestinal tract are thought to play little or no role in protective immunity against NCED caused by ETEC.[1] However, for maximum efficacy of ETEC vaccine programs, a concurrent well-managed colostrum program should be in place.

Nearly all strains of ETEC that have been isolated from neonatal calves have F5 fimbriae. Currently there is no evidence that a bacterin with multiple types of fimbrial antigens is more effective than products with only F5, so long as the vaccine and challenge strains share a common fimbrial antigen.[1] However, vaccines with multiple fimbrial antigens are more likely to have at least one of the antigens expressed by the challenge ETEC strain. Besides non-F5 ETEC strains potentially causing calf scours, a lack of efficacy of fimbriae-based ETEC vaccines may be due to *E. coli* belonging to a pathotype other than ETEC, including attaching and effacing *E. coli* (AEEC) and Shiga toxin–producing *E. coli* (STEC), which cause hemorrhagic enterocolitis in 1- to 6-week-old calves. Given that AEEC and STEC strains do not produce fimbrial adhesins, fimbriae-based ETEC bacterins will not protect against these strains.[6,7] Unfortunately, commercially available vaccines for prevention of calf scours associated with AEEC and STEC are not currently available.

Escherichia coli Vaccination Programs

The general recommendations for use of fimbriae-based ETEC vaccines (bacterins) are summarized in Table 48.10. ETEC bacterins are offered as single-antigen vaccines and in combination with other antigens designed to protect against other diseases in addition to ETEC infection. Oil-adjuvanted ETEC bacterins are administered by IM injection in a single dose 2 weeks to 6 months before calving, and administration is repeated annually.[10] Non–oil-adjuvanted ETEC bacterins are recommended for IM or SC injection in two doses administered at a 2- to 4-week interval, with the second dose given 3 to 6 weeks before calving. In subsequent years a single booster dose should be administered

3 to 6 weeks before calving. ETEC bacterins do not protect calves that do not ingest adequate amounts of colostrum soon after birth. Also, because this protection is based on passive immunity, high environmental challenge levels may overwhelm the limited amount of antibodies present in the lumen of the calf's small intestine. This is consistent with the higher prevalence and severity of clinical ETEC infections in the offspring of replacement dairy heifers kept in overcrowded closed confinement than in less intensive cow-calf beef operations. Environmental control of bacterial contamination is paramount to effective NCED management.

TABLE 48.10

Currently Licensed[a] *Escherichia coli* Bacterin Toxoids, *Salmonella* Bacterins, and Core Endotoxoid Vaccines

Antigens	Vaccine	Vaccination Regimen	Manufacturer
Escherichia coli			
K99	Pili Shield	1 dose 2 weeks before calving	Novartis Animal Health (Larchwood, IA)
K99	ScourGuard 3(K)	*Year 1:* 2 doses 6 weeks and 3 weeks before calving *Subsequent years:* 1 dose 3-6 weeks before calving	Zoetis (Florham Park, NJ)
Salmonella			
Salmonella Typhimurium	POLY-BAC B SOMNUS	2 doses 2 weeks apart	Texas Vet Lab (San Angelo, TX)
Salmonella Dublin and *S.* Typhimurium	Salmo-Shield TD	2 doses 2-4 weeks apart	Novartis Animal Health (Larchwood, IA)
	SDT-Guard	2 doses 2-4 weeks apart	Boehringer Ingelheim (St. Joseph, MO)
	Salmonella Dublin/Typhimurium Bacterin	2 doses 2-3 weeks apart	Colorado Serum Company (Denver, CO)
Salmonella Dublin	*Salmonella* Dublin Modified Live EnterVene-d	2 doses 2 weeks apart; start at age 2 weeks or older	Boehringer Ingelheim Vetmedica (St. Joseph, MO)
Salmonella			
Core Antigens			
J-5 *E. coli* mutant endotoxin core	J-VAC	*Year 1:* 2 doses 2-4 weeks apart *Subsequent years:* 2 doses 2-4 weeks apart	Merial (Iselin, NJ)
	ENVIRACOR J-5	*Year 1:* 3 doses starting 8 weeks and 4 weeks before calving and 2 weeks after calving	Zoetis (Florham Park, NJ)

[a]Licensed by the Animal and Plant Health Inspection Service, U.S. Department of Agriculture, as

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Salmonella Vaccines

Salmonellosis is due to infection by various pathogenic *Salmonella enterica* serotypes (see Chapter 32). Disease severity varies according to serotypes and strain-specific virulence determinants, but also according to the number of infective organisms, route of entry, and host natural and acquired resistance mechanisms. Bovine salmonellosis is caused predominantly by *S. enterica* serotypes Typhimurium (*S.* Typhimurium) and Dublin (*S.* Dublin), and although both serotypes can cause enteritis, clinical disease associated with each serotype is different.[11] Disease caused by *S.* Typhimurium, a ubiquitous group B *Salmonella* serotype, is most often associated with enteritis resulting in diarrhea in young calves. The host-restricted serotype group D *S.* Dublin most often causes systemic infections that may result in asymptomatic shedding or abortion in pregnant cows. Consequently, commercially available *Salmonella* vaccines contain single or combinations of *S.* Typhimurium and Dublin. Because *Salmonella* serotype Newport and other group C *Salmonella* have increased in prevalence, serotyping of *Salmonella* is critical to implementing an effective vaccination program. All currently licensed products are formalin-inactivated, whole-cell, aluminum hydroxide–absorbed bacterins, except for a genetically altered, stable, nonreverting, aromatic-dependent (*aroA* mutant) modified live *S.* Dublin vaccine (Entervene-D [Boehringer Ingelheim Vetmedica Inc., St. Joseph, Mo.]) and a siderophore receptor protein (SRP)-based vaccine (SRP *S.* Newport Vaccine, Conditional USDA License [Zoetis, Parsippany, NJ]). One *S.* Typhimurium and three *E. coli* mutant lipopolysaccharide (LPS) core antigen vaccines can provide protection from morbidity and mortality associated with salmonellosis.

A modified live and genetically altered (via deletion of *aroA*) *S.* Dublin vaccine marketed for parenteral use is effective in 2-week-old calves against challenge with *S.* Dublin, but it also provides cross-protection to challenge with *S.* Typhimurium.[12,13] As with many gram-negative bacterial vaccines, adverse reactions to this vaccine have been reported. Anecdotal reports of effective oral use in calves younger than 2 weeks old indicate that this route may help avoid some adverse reactions associated with injection of an endotoxin-containing product. Killed *Salmonella* bacterins can produce measurable serum antibody responses to bacterial proteins in calves and adult cattle. However, calves

vaccinated with a killed bacterin are unable to produce anti-LPS antibodies until 12 weeks of age,[14] and optimum responsiveness does not occur until a year old.[15] Most controlled studies in which calves were vaccinated with a killed *Salmonella* bacterin and orally challenged have reported a lack of protection.[16-18] One small study that reported good protection after vaccination of 3- to 6-week-old calves with two doses of killed bacterin used IM challenge.[19] Another study in 6-month-old cattle found that a single intradermal dose of heat-killed *S.* Dublin protected against IV challenge.[20] Vaccination of cattle 3 months of age or older with two doses of killed *Salmonella* bacterins can prevent salmonellosis. Although little has been published on the efficacy of a conditionally USDA-licensed SRP *S.* Newport vaccine, the clinical impression is that it is safe and effective at reducing fecal shedding of *Salmonella* but also capable of controlling disease caused by different serotypes of *Salmonella.*

Vaccination of adult cows, with passive transfer of antibody to calves through colostrum, is frequently used in dairies to control salmonellosis in neonates. Controlled trials evaluating passive protection have produced mixed results, with some indicating a lack of protection[18,21] and others demonstrating some protection in 5-day-old calves.[22] Vaccination of dry cows may be useful for control of salmonellosis in calves younger than 3 weeks of age but is minimally effective for controlling salmonellosis in calves older than 3 weeks. There are anecdotal reports of protection against salmonellosis by repeated vaccination of calves with an *S.* Typhimurium mutant LPS core antigen vaccine (ENDOVAC [IMMVAC Inc., Columbia, Mo.]). A J-5 *E. coli* Rc-mutant LPS core antigen–based bacterin (J-VAC [Merial Ltd., Athens, Ga.], ENVIRACOR J-5 [Zoetis], and Hygieia [Biological Laboratories, Woodland, Calif.]) improve survival and reduce morbidity rate from naturally occurring bacterial infections in dairy calves vaccinated at 3 and 17 days of age.[23]

Gram-Negative Mutant Lipopolysaccharide Core Antigen Bacterins

All genera and species of gram-negative bacteria share a common set of LPS core antigens that are present within the inner layer of the bacterial cell wall.[24] Endotoxin from gram-negative bacteria is thought to play an important role in producing clinical signs, biochemical and hematologic alterations, and lesions associated with a wide variety of bovine diseases caused by gram-negative

bacteria,[24] including salmonellosis and coliform mastitis, variously caused by *E. coli, Klebsiella* spp., *Enterobacter aerogenes,* and *Serratia* spp. Vaccines based on *S.* Typhimurium or *E. coli* with mutated LPS core antigen are designed to provide broad protection against related gram-negative infections by reducing the severity of clinical signs associated with sepsis and endotoxemia.

General Considerations

Several gram-negative mutant LPS core antigen oil-adjuvanted vaccines are currently marketed. Three vaccines use a J-5 Rc-mutant strain of *E. coli* that lacks the serotype-specific O-chain LPS components that ordinarily prevent deeper cell wall antigens from eliciting adaptive host immune response and production of antibodies against gram-negative core antigens.[24] Another commercial vaccine uses an Re-mutant strain of *Salmonella* Typhimurium.

Theoretically, gram-negative mutant LPS core antigen vaccines are expected to reduce the severity of disease, but not the rate of occurrence of infection. In four different clinical trials, however, the incidence of clinical coliform mastitis in dairy cows was reduced by 69%, 72%, 80%, and 82%, respectively, by vaccination with a J-5 *E. coli* vaccine.[25-27] Data are consistent with the hypothesis that antibodies induced against gram-negative LPS core antigens assist in either the control of bacterial infection, neutralization of bacterial endotoxin, or a combination of both. In the trial where clinical coliform mastitis was reduced by 82%, however, vaccination did not reduce the incidence of subclinical intramammary coliform infections that were present at the time of calving.[27]

Vaccination Programs

Recommendations for use of bacterins to prevent disease associated with salmonellosis are summarized in Table 48.11. Cows should not receive other vaccines containing gram-negative organisms (*Pasteurella, Salmonella, Brucella, Campylobacter [Vibrio], Histophilus somnus, E. coli,* or *M. bovis* bacterins) within 5 days of vaccination with J-5 *E. coli* bacterin.

TABLE 48.11

Currently Licensed Vaccines for Prevention of Calf Scour Associated With F5 (K99) Enterotoxigenic *Escherichia coli*

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Infection and Disease Associated With *Salmonella enterica*

Antigen	Vaccine Name	Vaccination Regimen	Manufacturer
***E. coli* F5 (K99) Vaccines**			
F5 (K99 [bacterin])	Bovine Pili Shield	*Year 1:* 1 dose 8-16 weeks before calving	Novartis Animal Health (Larchwood, IA)
		Subsequent years: 1 dose before calving	
F5 (K99 [cell-free extract])	Guardian	*Year 1:* 2 doses up to 12 weeks and approximately 3-6 weeks before calving	Intervet Inc./Merck Animal Health (Omaha, NE)
		Subsequent years: 1 dose up to 5-7 weeks before calving	
F5 (K99 [bacterin])	ScourGuard 4KC	*Year 1:* 2 doses 6-9 weeks and 3-6 weeks before calving	Zoetis (Florham Park, NJ)
		Subsequent years: 1 dose 3-6 weeks before calving	
F5 (K99) (4 strains [bacterin])	Scour Bos 9	*Year 1:* 2 doses 8-16 weeks and 4 weeks before calving	Novartis Animal Health (Larchwood, IA)
		Subsequent years: 1 dose up to 8-10 weeks before calving	
***Salmonella* Vaccines**			
Salmonella enterica serotype Typhimurium (bacterin-toxoid)	POLY-BAC B SOMNUS	2 doses 2 weeks apart	Texas Vet Lab (San Angelo, TX)
S. enterica Dublin/Typhimurium (bacterin)	*S.* Dublin-Typhimurium bacterin	*Adults:* 2 doses 2-3 weeks apart before placement on feed, and pregnant cows 4-6 weeks before calving	Colorado Serum Company (Denver, CO)
		Newborn calves >7 days of age: 2 doses 2-3 weeks apart	
S. enterica Dublin/Typhimurium (bacterin)	SDT-Guard	*Adults:* 2 doses 2-4 weeks apart	Boehringer Ingelheim Vetmedica, Inc. (St. Joseph, MO)
S. enterica Newport (siderophore receptor protein [SRP]; conditional USDA license	*Salmonella* Newport Bacterial Extract	6-month-old and older: 2 doses 2-4 weeks apart	Zoetis (Florham Park, NJ)
S. enterica serotype Dublin (modified live)	EnterVene-d	*2 weeks of age and older:* 2 doses 12-16 days apart	Boehringer Ingelheim Vetmedica, Inc. (St. Joseph, MO)
***Salmonella/E. coli* Mutant LPS Core Antigen Vaccines**			
S. enterica serotype Typhimurium (bacterin-toxoid)	ENDOVAC-Dairy	*Cows during dry period and heifers during third trimester of pregnancy:* 2 doses 2-3 weeks apart	IMMVAC Inc. (Columbia, MO)
		Subsequent years: 1 dose	
	ENDOVAC-Beef	*Year 1:* 2 doses 2-3 weeks apart	
		Subsequent years: 1 dose	
J-5 *E. coli*	J-VAC (bacterin-toxoid)	*Year 1:* 2 doses 2-4 weeks apart	Merial LTD (Athens, GA)
		Subsequent years: 2 doses 2-4 weeks apart	
		Pregnant cows: 2 doses starting at 7 months of gestation or at dry off and 1-3 weeks before calving	

ENVIRACOR J-5 (bacterin)	*Cows or heifers:* 3 doses starting at 7 and 8 months of gestation and 2 weeks after calving	Zoetis (Florham Park, NJ)
E. coli bacterin	3 doses 4-6 weeks apart	Hygieia Biological Laboratories (Woodland, CA)
BOVILIS J-5 *E. coli* bacterin	3 doses 4-6 weeks apart	Merck Animal Health (Madison, NJ)

A J-5 *E. coli* bacterin has also successfully reduced morbidity and mortality in experimental *S.* Typhimurium infection in calves.[28] However, because of the short half-life of passively acquired antibodies stimulated by mutant LPS core antigen vaccines,[29] vaccination of dry cows is unlikely to be an effective control measure for salmonellosis in calves except when calves are exposed to and infected with *Salmonella* in the first week or two after birth. Salmonellosis in dairy calves often occurs after 2 weeks of age. However, when vaccinated at age 3 and 10 days with an oil-adjuvant J-5 *E. coli* bacterin, calves do develop strong antibody responses by 17 days of age; this strong antibody response occurs even in the presence of passively acquired antibodies to LPS core antigens.[30] Consequently, a combined program in which both dry cows and neonatal calves are immunized against LPS core antigens might be a useful approach for reducing the severity of salmonellosis in neonatal dairy calves.

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Clostridial Vaccines

Francisco A. Uzal and J. Glenn Songer

Clostridial infections cause mostly acute and frequently fatal disease in cattle. The pathogenesis of most clostridial diseases is mediated by powerful toxins,[1,2] and prevention is therefore based on immunoprophylactic amelioration of the effects of these molecules. Unfortunately, the ready availability of mostly inexpensive and efficacious bacterins, toxoids, and bacterin-toxoids has not eliminated clostridial infections, mainly because these immunoprophylactic products are sometimes used poorly or not at all. Duration of immunity is poor in some cases, and frequent revaccination is required if adequate immunity is to be achieved. Accurate diagnosis remains an important component in management of clostridial diseases as it provides vital information on type of vaccines to use in a given area or herd.[3-5] Immunization of cattle against clostridial diseases can be complicated by the development of site reactions, leading to trimming at slaughter.[6] These problems are exacerbated with some of the multivalent modern clostridial vaccines and have stimulated the biologics industry to seek a new paradigm for preparation and delivery of vaccines. Approaches have included concentration of the antigen into smaller doses and use of alternate adjuvants. Recombinant proteins delivered by conventional means, application of slow-release media, in vivo expression from attenuated bacterial delivery systems, and production in vivo by replicon particles from alpha viruses will likely be a major focus of effort.

Clostridium chauvoei (Blackleg) Bacterins

Blackleg occurs frequently despite long-term availability of generally effective bacterins.[10] The most common route of exposure in cattle is likely ingestion, and dormant spores seeded within macrophages in the skeletal or cardiac muscle germinate when muscle damage provides appropriate conditions of lack of oxygen. Signs in affected animals, when observed, include fever, anorexia, depression, and lameness. Sudden death is common. Lesions are characterized by extensive, dry, and emphysematous to edematous, hemorrhagic, and necrotic myositis with or without subcutaneous edema. In diagnosis, differentiation between blackleg and gas gangrene edema is important as both clinical signs and lesions may overlap.[7]

Vaccination against blackleg is universally advocated, especially in cattle younger than 2 years. Dogma holds that protection arises from the immune response to a heat-labile soluble antigen, but *C. chauvoei* produces alpha toxin and several other toxic factors that may be equally important targets.[8-11] Recommendations for immunization are summarized in Table 48.12.

TABLE 48.12

General Considerations for Use of Clostridial Seven-Way and Eight-Way Bacterin-Toxoids[a]

	Coverage Designation[a]	
Protection, by Species	**Seven-Way**	**Eight-Way**
Clostridium chauvoei	x	X
Clostridium septicum	x	X
Clostridium novyi B	x	x
Clostridium sordellii	x	x
Clostridium perfringens type C	x	x
Clostridium perfringens type D	x	x
Clostridium perfringens type B[b]	x	x
Clostridium haemolyticum (novyi type D)	x	
Dose (mL)	2-5	5
Recommended boosters	After 2-4 weeks for *C. sordellii* and *C. perfringens* C and D; after 5-6 months for *C. novyi* type B and *C. haemolyticum.* Calves initially vaccinated at <3 months of age should be revaccinated at 4-6 months (or at weaning).	
Comment	No use <21 days preslaughter	

[a]Note that many combinations are available commercially, including some that also contain immunogens against nonclostridial diseases. Some of these combinations also include tetanus toxoid.

[b]No currently licensed product is produced by use of cultures of *C. perfringens* type B, but protection against type B infection is implied by the inclusion of toxoid prepared against type C (beta toxin) and type D (epsilon toxin) strains.

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Gas Gangrene Bacterins

Gas gangrene, historically called *malignant edema,* is a wound infection most frequently caused by *C. septicum,*[12,13] although other microorganisms, including *Clostridium novyi* type A, *Clostridium chauvoei*, *Clostridium sordellii*, and more rarely *C. perfringens* type A can also be involved. The infection usually follows direct contamination of a wound, including accidental trauma, iatrogenic injuries, and genital tract lacerations during delivery. Infection spreads mostly along fascial planes, and lesions that are initially warm and pitting become crepitant and cold. The clinical signs and lesions are similar to those of blackleg, except that subcutaneous and interstitial tissue is more frequently involved than muscle.[13] "Braxy" or "Bradsot" is a form of *C. septicum* alimentary infection characterized by necrotizing abomasitis, which occurs most commonly in calves and lambs.[14]

Cattle are protected by two initial doses of the corresponding bacterin, 4 to 6 weeks apart, followed by an annual booster. Vaccination is recommended in areas with a substantial incidence of the disease[13] (see Table 48.9). Vaccines elicit antibody responses to both somatic and toxin antigens, and research findings suggest a central role for *C. septicum* alpha toxin.[11,15,16] Several bacterins contain immunogens to most or all the components of the gas gangrene complex.

Clostridium haemolyticum (formerly called *Clostridium novyi* type D) (Bacillary Hemoglobinuria) and *Clostridium novyi* type B (infectious necrotic hepatitis or black disease) Bacterins

Bacillary hemoglobinuria, also called *redwater,* is caused by *Clostridium haemolyticum* and it occurs mostly in cattle, although occasional cases in sheep have been reported. *C. novyi* type B causes infectious necrotic hepatitis (black disease) of sheep, with occasional cases being reported in cattle.[17,18]

The hallmark lesion of both diseases is acute focal or multifocal liver necrosis. Dormant spores in Kupffer cells germinate when liver injury provides appropriate anaerobic conditions, most frequently associated with migration of larvae of *Fasciola hepatica* through the liver parenchyma, although cases of both diseases may occur in animals free of this parasite.[17,18]

Beta toxin, a homolog of *C. perfringens* alpha toxin (CPA), mediates the

pathogenesis of bacillary hemoglobinuria, and *C. novyi* alpha toxin seems to be the main virulence factor involved in the pathogenesis of infectious necrotic hepatitis. Both diseases usually occur in well-nourished animals, with bacillary hemoglobinuria occurring mostly in animals 1 year of age or older,[17,18] and infectious necrotic hepatitis affecting mainly adult animals.[19] Tissue damage caused by migrating liver fluke larvae or other less understood factors allows germination of dormant spores in Kupffer cells. Vegetative growth yields focal or multifocal hepatic necrosis with local production of a large amount of toxins. In cattle with bacillary hemoglobinuria, systemic dissemination of beta toxin via the bloodstream results in intravascular hemolysis, hemorrhage, and hemoglobinuria.[17] When urine takes on the color of port wine, about 50% of the red cells have lysed and death ultimately results from anoxia. Because the pathogenesis of infectious necrotic hepatitis is thought to be mediated mostly by *C. novyi* alpha toxin with much less involvement of beta toxin, jaundice and hemoglobinuria are not usually observed in animals with this disease.[19]

A vaccination program is essential for herds pastured in endemic areas. When heavy exposure to fluke metacercariae is expected, an initial double dose, 4 to 6 weeks apart, of bacterin-toxoid should be administered to all cattle older than age 6 months, before they are pastured in the spring. This should be followed by a single annual booster a few weeks before the season when heavy exposure to flukes is expected. Liver fluke control also helps prevent cases of both bacillary hemoglobinuria and infectious necrotic hepatitis.

Clostridium botulinum (Botulism) and *Clostridium tetani* (Tetanus) Toxoids

Botulism is caused by *C. botulinum* neurotoxins, which block acetylcholine release from cholinergic nerve endings.[20] Cattle in the United States are most commonly affected by type C, and this is commonly associated with an infected animal carcass in the feed. Clinical signs include incoordination, flaccid paralysis, and difficulty in swallowing; respiratory paralysis causes eventual death.[20,21]

Toxoids of botulinum toxins can be employed for immunoprophylaxis, but vaccination is usually practiced only in populations at immediate risk, such as beef cattle grazed on phosphorus-deficient range land, where cattle tend to chew on bones of carcasses left in the field, increasing the risk of contamination.[22] Feeding of poultry litter poses a similar problem, in that it may contain animal

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remains, but this practice has now been suspended in the United States.

Spores of *C. tetani* are found in soil, and animal hosts are usually infected in association with some traumatic event. Spores introduced to tissue under proper conditions of anaerobiosis germinate and produce tetanus neurotoxin.[23] Tetanus can develop after several different interventions in cattle including, but not limited to, calves after castration by the elastrator method.[24,25] Cases may also occur in postparturient dairy cows.[23] Toxin moves retrograde, binding to presynaptic axonal terminals and resulting in muscular tremor and increased stimulus response; continued motor neuron hyperactivity causes sustained tetanic spasms in the innervated muscles and then permanent rigidity. Death is due to respiratory failure.[23]

Acquired resistance to tetanus is based on circulating antitoxin, and widespread vaccination with toxoid in populations at risk has dramatically lessened the impact of tetanus on animal production. Neonatal passive immunity acquired from the dam is followed by active immunization with toxoid at 2 to 3 months of age followed by a booster 4 to 6 weeks later. Single annual boosters are commonly recommended at 1- to 5-year intervals. Passive immunotherapy is intended to neutralize preformed toxin, although it is much more effective when used prophylactically than therapeutically. Vaccination is recommended in endemic areas, but universal vaccination is not usually recommended as a cost-effective means for control of tetanus.

Clostridium perfringens Toxoids

C. perfringens causes various diseases in domestic animals, and those of greatest importance affect the gastrointestinal tract[4] (Table 48.13) (see ruminant section of Chapter 32). This organism has been historically classified into 5 types (A, B, C, D, and E) on the basis of the production of one or more of the following toxins: alpha, beta, epsilon, and iota. Two additional types (i.e., F and G), have been recently added on the basis of the production of enterotoxin and and necrotic B-like toxins (see Table 48.13).[26]

TABLE 48.13

Classification Schedule of *Clostridium perfringens* Based on Production of 6 Toxin

C. perfringens

Toxin Type	alpha	beta	épsilon	iota	enterotoxin	NetB
A	+	−	−	−	−	−
B	+	+	+	−	−	−
C	+	+	−	−	−/+	−
D	+	−	+	−	−/+	−
E	+	−	+	−	−/+	−
F	+	−	−	−	+	−
G	+	−	−	−	−	+

C. perfringens type A is present in the intestine of most clinically healthy animals. Although this microorganism has been associated with gastroenteric syndromes in many mammals including, among others, cattle, final proof of involvement of *C. perfringens* type A in these syndromes is lacking and there are currently no accepted criteria to establish a diagnosis of *C. perfringens* type A enteritis in cattle.[4]

Type B disease is a rare disease that affects mostly sheep, and it has not been diagnosed in the United States. Pathogenesis is thought to be mediated by beta and epsilon toxins.[27] Type C strains affect several mammalian species including cattle. Because beta toxin, the main virulence factor of *C. perfringens* type C, is exquisitely sensitive to trypsin and other intestinal proteases, type C disease occurs mostly in neonatal animals in which trypsin is naturally inhibited by colostrum present in the intestine. In the absence of trypsin activity, beta toxin accumulates and produces local hemorrhage and necrosis, as well as systemic effects.[28,29] Type D produces enterotoxemia in sheep and goats and rarely in cattle. Epsilon toxin is the main virulence factor of type D strains; this toxin facilitates its own absorption through the intestinal wall and, in circulation, damages the central nervous system and other systems distant from the gut.[30] *C. perfringens* type E has been associated, albeit infrequently, with cases of enterotoxemia in lambs, calves, and rabbits. However, the few diagnoses of this condition reported so far were based on isolation of *C. perfringens* type E from the intestinal content of sick animals, which is not considered a diagnostic criterion for *C. perfringens* intestinal diseases because this organism is found in most healthy animals.[4]

C. perfringens types F and G are not involved in diseases of cattle.[26]

Although a few commercial vaccines including type A toxoid are currently available, because type A disease has not been definitely proved to occur in cattle, the use of such vaccines has not been fully evaluated.

Vaccination against type C enterotoxemia is recommended only in herds where the disease has been documented. Because the disease affects mostly

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neonates, vaccination of all dams before calving is required, and immunity is provided to calves via immune colostrum. Initial immunization should be followed by a booster after 3 to 4 weeks, with the second dose (and subsequent boosters precalving) administered approximately 2 to 3 weeks before parturition.

Type D enterotoxemia occurs sufficiently infrequently in cattle that vaccination may not be cost-effective. No commercial products are licensed in the United States for use against infections by strains of type E. Although production of autogenous toxoids or bacterin-toxoids have been used, these have not been scientifically evaluated and information about their efficacy is lacking.

Miscellaneous Bovine Rickettsial, Bacterial, and Viral Disease Vaccines

Derek A. Mosier

A number of bovine vaccines are available for anaplasmosis, infectious bovine keratoconjunctivitis, staphylococcal mastitis, anthrax, interdigital necrobacillosis (foot rot), papillomatous digital dermatitis (foot warts), rabies, and fibropapillomas. These are discussed individually next and summarized in Table 48.14.

TABLE 48.14

Recommendations for Use of Some Bovine Disease Vaccines: *Anaplasma, Moraxella, Staphylococcus,* Anthrax, *Fusobacterium necrophorum,* Papillomatous Digital Dermatitis, Rabies, and Papillomas

	Pathogen					
Characteristic	***Anaplasma marginale*[1]**	***Anaplasma marginale*[2]**	***Moraxella bovis*[3-8]**	***Staphylococcus* Species[9]**	***Bacillus anthracis*[10]**	***Fusobacterium necrophorum*[11-1]**
Passive antibodies protective			Yes	NA	?	NA
Duration of colostral immunity (months)			4-6	NA	?	NA
Type of vaccine	Modified live	Inactivated	Bacterin	Bacterin	Sterne nonencapsulated avirulent spore	Bacterin
Immunizes in the presence of passive immunity	No		No	NA	7	NA
Earliest recommended age for initial vaccination (months)	1-4[a]		1[a]-5	6	Any	6
Site of administration	IM	SC	IM[6,7] or SC	IM	SC	IM or SC
Doses required for protection	1	2	1[b]-2[c]	2	1-2	2

Interval between priming and immunizing doses (weeks)	NA	3-4	3	2	2-3	3-4
Interval from first dose to protection (days)	42	35	21[b]-42[c]	28	8	35
Duration of vaccinal immunity (months)	Lifelong	12	<9	5-6	12	?
Recommended booster interval (months)	NA	12	12	5-6[d]	12[f]	12
Contraindications	Do not use in cattle over 2 years of age or in the last 4 months of pregnancy; do not administer tetracyclines	—	—	—	Avoid simultaneous administration of antimicrobials; do not use in sick animals	—
Side effects	Illness, anemia, abortion, death	Anaphylaxis	Anaphylaxis	Anaphylaxis	Mild illness, fever, decreased milk production	Anaphylaxis
Withdrawal time (days before slaughter)	—	60	21, 60[6,7]	21[e]	42	21

[a]Calves vaccinated before the age at which passive immunity no longer exists should be revaccinated on reaching that age.

[b]Oil-adjuvant vaccines.

[c]Aluminum hydroxide-adjuvant vaccines.

[d]Give booster 3 to 6 weeks before calving.

[e]No milk withdrawal required.

[f]Booster can be given sooner in heavily contaminated areas.

[1]Anavac, PHL Associates, Davis, CA.

[2]Anaplasmosis Vaccine, University Products LLC, Baton Rouge, LA.

[3]I-Site, AgriLaboratories, St. Joseph, MO.

[4]Maxi/Guard Pinkeye bacterin, Addison Biological Laboratory, Fayette, MO.

[5]Ocu-Guard MB and Alpha-7 MB, Boehringer Ingelheim, St. Joseph, MO.

[6]Piliguard Pinkeye-1 Trivalent and Piliguard Pinkeye + 7, Merck Animal Health, Summit, NJ.

[7]Pinkeye Shield XT4, Novartis Animal Health, Larchwood, IA.

[8]Vision 7 20/20 with Spur, Intervet Inc., Merck Animal Health, Summit, NJ.

[9]Lysigin, Boehringer Ingelheim Vetmedica, St. Joseph, MO.

[10]Anthrax Spore Vaccine, Colorado Serum Co., Denver, CO.

[11]Volar, Intervet, Millsboro, DE 19966.

[12]Fusogard, Novartis Animal Vaccines, Larchwood, IA.

[13]Serpens species bacterin, Hygieia Biological Laboratories, Woodland, CA.

[14]Defensor 3, Zoetis, Florham Park, NJ.

[15]Rabdomun, Schering-Plough Animal Health, Union, NJ.

[16]Imrab 3 and Imrab Large Animal, Merial, Duluth, GA.

[17]Wart vaccine, AgriLaboratories, St. Joseph, MO.

[18]Wart vaccine, Colorado Serum Co., Denver, CO.

?, Unknown; *IM,* intramuscular administration; *NA,* not applicable; *SC,* subcutaneous administration.

Anaplasmosis

Anaplasmosis is a vectorborne or mechanically transmitted disease caused by the rickettsia *Anaplasma marginale*.[1,2] The disease occurs worldwide and is most prevalent in tropical and semitropical areas. Anaplasmosis is the only major tickborne disease of cattle in North America, being enzootic in the southeastern and some midwestern and western states and sporadic in the northern states and Canada.[1-3] In enzootic areas with adequate numbers of arthropod vectors, most adult cattle become naturally immune through repeated exposure. Maternal antibodies protect calves until they also become subclinically infected and develop immunity. Disease is more severe in older cattle than in calves, and nonimmune older cattle are particularly at risk when they are moved into an endemic area.[1,4] Susceptibility to disease occurs when there is a lack of arthropod vectors to maintain natural infection and immunity or when a nonimmune adult is introduced into an enzootic area. In these situations or when vector or environmental conditions suggest an increased risk of disease, vaccination can be beneficial.

No widely marketed commercial vaccines against anaplasmosis were available as of 2012 in North America. A killed vaccine (Anaplasmosis Vaccine, University Products LLC, Baton Rouge, La.) is available in some states, including Arkansas, California, Florida, Indiana, Illinois, Iowa, Kansas,

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Kentucky, Louisiana, Mississippi, Missouri, Nevada, Oklahoma, Oregon, Tennessee, Texas, and Wisconsin, and in Puerto Rico. The vaccine consists of an emulsion of concentrated inactivated *A. marginale* antigens and adjuvant suspended in 10% oil, similar to the last widely available commercial vaccine that was discontinued in 1999 (Plazvax [Schering-Plough Animal Health]). The killed vaccine is not USDA licensed, but it is USDA approved for use as an experimental vaccine. The vaccine has reportedly been used successfully in cows at all stages of pregnancy without an episode of neonatal isoerythrolysis. In endemic areas the vaccine is recommended for use just before the onset of the vector season. Vaccine-induced immunity does not generally occur until 2 weeks after administration of the second dose of an initial series or 2 weeks after a booster dose in previously immunized cattle.[5,6] Vaccination does not prevent infection or clinical disease and does not eliminate *A. marginale* from a herd, but it does reduce the severity and incidence of disease.[1,6] Inactivated vaccines could be used in conjunction with oxytetracycline in the face of outbreaks to provide both temporary and more prolonged protection.

A sheep-passaged modified live vaccine (Anavac [PHL Associates, Davis, Calif.]) has been used in California and Latin America.[7] Because this vaccine causes mild clinical disease, it has limited use for vaccination of mature susceptible cattle.[1,7] If the vaccine is administered to cattle older than 2 years of age, anemia, severe clinical disease, and death may occur, especially in bulls and heavily lactating cows.[7] The vaccine is recommended for use in healthy cattle between age 1 month and 2 years and is most commonly administered to 7- to 24-month-old cattle in herds in endemic areas. Concurrent use of certain antibiotics or other live or MLV vaccines is contraindicated.

A live vaccine (Frozen Anaplasmosis [Tick-borne gallsickness] vaccine for cattle [Onderstepoort Biological Products, Onderstepoort, South Africa]) composed of *A. marginale* subsp. *centrale*, a less pathogenic species or subspecies of *A. marginale*, is used in some countries including Africa, Australia, Israel, and Latin America but not in North America.[6,8,9] This vaccine consists of standardized and frozen red blood cells from splenectomized cattle that were infected with *A. marginale* subsp. *centrale.* The vaccine is recommended for use in 4- to 9-month-old cattle; older cattle have an increased risk of severe vaccine-induced disease. The vaccine produces mild disease but protects against subsequent severe disease caused by *A. marginale.* Immunity is considered long term or possibly for life if subsequent natural exposure occurs to

ensure development of durable immunity.

Immunity to *A. marginale* is proposed to involve humoral responses to a variety of major surface proteins and enhanced macrophage phagocytosis and killing, both mediated by IFN-γ–producing $CD4^+$ T lymphocytes.[1,10,11] Inadequate protection from vaccines during field use can result from antigenic variability of the organism, geographic differences in the organism that result in a lack of cross-reactivity between *A. marginale* strains, and weak immune responses to protective *A. marginale* antigens.[1,4,12-14] Purified native, recombinant, and tick culture–derived *A. marginale* immunogens and DNA vaccines are being investigated for possible commercial use in the future.[6,9,12,13,15-17]

Infectious Bovine Keratoconjunctivitis

The most common infectious agent associated with infectious bovine keratoconjunctivitis (IBK) is *M. bovis*.[1] Vaccination is most effective when done before fly season in herds with a history of problems. Certain breeds (e.g., Herefords, Hereford crosses) are particularly susceptible and may benefit from vaccination.[1,2] Commercial vaccines used to help prevent the disease consist of inactivated cultures of various strains of *M. bovis*.[3] Some products recommend two doses given 3 weeks apart for initial vaccination, beginning as early as 3 weeks of age to no earlier than 5 months of age. Other products recommend a single dose administered 3 to 6 weeks before the predicted onset of the disease season, with annual vaccination thereafter. *M. bovis* bacterins are also available in combination with seven-way clostridial bacterin-toxoids.[4] Although multivalent *M. bovis* bacterins can provide some protection in field use, efficacy varies depending on the *M. bovis* strains present in the bacterin and those responsible for disease.[1,5-7] Seven different disease-producing serogroups of *M. bovis* are recognized on the basis of differences in pili, and there is variable cross-reactivity between serogroups.[3] Pilin gene rearrangements and pilin-type switching can allow *M. bovis* to switch from expression of one type of pilus antigen to another, making it difficult to predict what serogroup(s) may be necessary for protection.[2,3,6] Monovalent bacterins are generally ineffective in field use, and multivalent bacterins provide neither consistent nor reliable protection.[3,5-7] Vaccines must incorporate pili from all major serogroups or conserved immunogenic portions of all serogroups to provide optimum

protection.[3,6,7] Experimental recombinant vaccines containing cloned pili of various serogroups have demonstrated some promise for future vaccines.[5,6] Another immunogen considered important for protection is *M. bovis* β-hemolytic corneotoxic and leukotoxic cytotoxin.[1-3] Experimental vaccines containing hemolytic cytotoxin preparations alone or in combination with pilus antigens have shown some efficacy in experimental trials.[1,3,8-10] Other potential immunogens include iron-regulated OMPs, proteases, fibrinolysins, and phospholipases.[1-3] Vaccine-induced protection is correlated predominantly with a suitable lacrimal immune response (predominantly IgA but also IgM and IgG) and not with serum antibody levels to *M. bovis* antigens.[1-3] Therefore an antigen delivery system that enhances lacrimal and mucosal immunity is an important feature of an effective vaccine.[11] The presence of other agents contributing to IBK (e.g., *Moraxella [Branhamella] ovis, Mycoplasma bovoculi,* or BHV-1) should also be considered when there is poor *M. bovis* vaccine efficacy.[12] Autogenous *M. bovis* or *M. bovis* plus *M. bovoculi* vaccines have not been consistently effective against the disease.[1,13,14] Use of MLV vaccines for IBR is contraindicated in the presence of an outbreak of IBK because it may exacerbate the IBK.[1]

Staphylococcal Mastitis

S. aureus is considered one of the most important causative agents of bovine mastitis.[1] Vaccination against *S. aureus* may be beneficial in dairy herds that have an existing mastitis problem,[1,2] but vaccination in well-managed dairy herds with a low level of staphylococcal mastitis may not provide much economic benefit.[2] Staphylococcal bacterins contain conserved antigens or antigens from multiple strains or serotypes of *S. aureus*.[3-5] The typical recommended vaccination protocol is two doses given 2 weeks apart, followed by revaccination at 6-month intervals. Vaccination can start at 6 months of age, and one of the semiannual doses should be given 3 to 4 weeks before calving. Vaccination with *S. aureus* bacterins does not generally eliminate disease but can substantially reduce clinical mastitis and the incidence of subclinical and chronic staphylococcal infection.[1,2,5,6] Vaccination may be more effective in heifers because of their initial lower basal immunity compared with older cows.[6] The benefits of immunity induced early in life include the abilities to clear the organism and resist chronic infection on initial natural exposure. Vaccination

during the dry period may be more effective than vaccination during lactation. In some but not all studies, vaccination has reduced somatic cell counts in milk.[5,6] Vaccination in combination with antimicrobial therapy has been successfully used to eliminate chronic staphylococcal mastitis.[7]

In considering the use of staphylococcal vaccines, the prevalence of various pathogens that can cause mastitis must be considered. For mastitis caused by *S. aureus*, differences between the *S. aureus* strains in vaccines and the strains specifically responsible for the disease may diminish vaccine efficacy.[1,4,8] Both long-standing bacterins and some newer-technology vaccines have achieved positive results.[1,9] Experimental trials suggest that more effective vaccines may be derived by stimulating immune responses to combinations of *S. aureus* capsular polysaccharide.[10] A vaccine based on technologies used for human staphylococcal vaccines that incorporates capsular polysaccharide from the three *S. aureus* serotypes most commonly associated with mastitis stimulated immunologic parameters necessary for protection.[11] Other vaccines have used highly conserved membrane proteins, iron-regulated proteins, a staphylococcal superantigen conserved by many mastitis strains, and DNA vaccines directed against adhesin proteins in attempts to achieve the "universal" *S. aureus* vaccine.[5,12-14]

In herds where other pathogens are a major cause of mastitis, *S. aureus* vaccines may be of minimal benefit.[2] Other important causes of bovine mastitis include *Streptococcus* spp. (e.g., *Streptococcus uberis*, *Streptococcus dysgalactiae*, and *Streptococcus agalactiae*) and coliform bacteria (e.g., *E. coli*). Recombinant vaccines containing *S. aureus* and *S. agalactiae* have shown some promise in experimental models.[15] Experimental vaccines composed of bacterial proteins derived from *S. uberis* and *S. dysgalactiae* reduced somatic cell counts compared with controls after challenge.[16,17] *E. coli* J5 vaccines have also been used to successfully reduce the severity of mastitis (reviewed elsewhere in this section).

Anthrax

Anthrax is an acute, highly fatal disease caused by *Bacillus anthracis*.[1] Vaccination has proven to be an effective means of controlling the disease in endemic areas and in the face of outbreaks.[1-3] Bovine anthrax vaccines are derived from the live toxigenic, nonencapsulated spore vaccine developed by

Sterne and consist of spores suspended in a diluent containing saponin and glycerin.[1] Annual vaccination of livestock in areas of endemic anthrax is recommended 4 weeks before outbreaks are expected, typically in the spring to provide protection during the summer months.[1] A single dose generally provides adequate immunity for about a year, but a second dose given 2 to 4 weeks after the first is sometimes recommended. Cattle should not be vaccinated within 42 days of slaughter. Antibiotics should not be administered within 7 days of vaccination to avoid interference with in vivo growth of the vaccine organism. Outbreaks can occur sporadically but often occur in areas with a history of flooding followed by drought.[4,5] Vaccination in the face of an outbreak does not protect all cattle, but the spread of infection and the number of new cases generally declines within 10 days.[3,5] Localized subcutaneous edema can develop at the injection site within 24 hours; it may last for several days and is sometimes severe.[2] Since the intentional release of *B. anthracis* via the mail system in 2001, there has been increased interest in technologies for the development of an efficacious long-acting human vaccine for anthrax.[2,6-8] Some of these technologies could hold promise to reduce some of the localized side effects of the current bovine vaccine,[9] but it is unlikely a new bovine vaccine will match the safety, efficacy, and cost-effectiveness of the Sterne strain vaccine in the foreseeable future. All anthrax outbreaks should be reported to local regulatory and public health officials, and appropriate guidelines for vaccination should be followed, including quarantine and vaccination of all susceptible livestock on affected and surrounding premises.

Interdigital Necrobacillosis (Foot Rot)

Interdigital necrobacillosis (foot rot) in cattle results from interdigital infection with *Fusobacterium necrophorum*, with lesser contributions from *Porphyromonas levii* (previously classified as a subspecies of *Prevotella [Bacterioides] melaninogenica*) and sometimes *Dichelobacter (Bacterioides) nodosus* (the most common cause of foot rot in sheep) and other bacteria.[1-3] Commercial *F. necrophorum* bacterins to aid in the prevention of foot rot (and hepatic necrobacillosis) are available for use in cattle. Recommendations for initial vaccination are two doses given 3 to 4 weeks apart, followed by annual revaccination. Vaccination is also recommended when endemic conditions exist or when exposure is imminent. The efficacy of *F. necrophorum* vaccines is unclear because hepatic abscesses are sometimes the study focus, but some

benefit for foot rot has been demonstrated in experimental studies and field trials.[4] Vaccination is especially recommended in herds with a high incidence of disease. Protective immunity most closely correlates with the level of antileukotoxin antibodies.[5] In experimental models, truncated recombinant leukotoxin proteins provide protection and presumably would have some benefit against interdigital *F. necrophorum* infection.[6,7] Most foot rot infections involve single rather than multiple strains of *F. necrophorum,* so a vaccine that targets the specific strain involved should be effective.[8]

Papillomatous Digital Dermatitis (Foot Warts)

Papillomatous digital dermatitis, or foot warts, can be a serious problem in dairy cattle.[1] The disease is characterized by ulcerative to proliferative digital lesions that most often occur in replacement heifers and younger cows after introduction into a milking herd.[1,2] Risk is greatest in larger dairy breeds in herds of greater than 500 head. *Treponema* spp. are most commonly isolated from lesions and are considered the most important cause of foot warts. A wide variety of *Treponema* are incriminated, including *T. phagedensis, T. denticola, T. vincentii/T. medium,* and *T. pedis*.[3-5] No virus was seen in biopsies from multiple warts from dairy cattle in two herds.[6] Several bacterial species have also been isolated from lesions, including *Fusobacterium necrophorum*, *Serpens* spp., and *Porphyromonas levii*.[7,8] However, the precise combinations of these agents necessary to produce disease remain unclear. Commercial bacterins are available for use as preventives and/or aids to treatment and consist of killed cultures of *Serpens* spp. or *Treponema* spp. organisms. Recommendations are for three doses administered SC at 3- to 4-week intervals, followed by revaccination every 4 to 6 months. Company field trials report reduced onset of new infections and sometimes more rapid resolution of existing infections in vaccinated cattle. However, some trials failed to show significant improvement in vaccinated cows compared with unvaccinated ones.[8,9] The requirement for frequent boosters and the high recurrence rates of natural infection suggest that immunity to the disease is short lived or weak.[2]

Rabies

Rabies is a highly fatal zoonotic neurologic disease caused by a rhabdovirus.[1] Bovine rabies in North America is generally uncommon, and routine vaccination

of cattle is not recommended in most situations.[2] However, vaccination may be a consideration in rural areas of Latin America, where vampire bats are important sylvatic vectors, or Africa, where exposure to infected dogs is a major cause of bovine rabies.[3,4] In endemic areas, vaccination of valuable cattle or herds may be a reasonable precautionary measure. This is particularly true in situations where cattle are in frequent contact with human beings, in order to reduce the anxiety of animal workers and minimize the likelihood of human exposure. Currently licensed rabies vaccines for cattle contain inactivated cell culture–derived virus.[5] The recommended regimen is initial vaccination at 3 months of age followed by annual vaccination thereafter. Because the duration of protective neutralizing antibody levels after initial vaccination can vary, some experts have suggested that a second booster dose be given either 1 month after initial vaccination or at 6 months of age.[6] Subsequent annual revaccination induces strong anamnestic responses that persist for 1 year or longer.[6] In Latin America, modified live vaccines are sometimes used but do not stimulate the same level of immunity as inactivated virus vaccines. A Capripoxvirus vector expressing rabies virus glycoprotein has shown promise in providing long-term protection against rabies (and lumpy skin disease) and may be a cost-effective mechanism for rabies control in cattle in some developing countries.[7,8]

Fibropapillomas (Warts)

Fibropapillomas (warts) are manifested in a variety of forms and locations, each caused by 1 of over 13 different types of bovine papillomaviruses (BPV).[1,2] Lesions associated with papillomaviruses can occur in the epidermis of the head, face, neck, and legs (BPV-1 and BPV-22); upper alimentary and urinary tracts (BPV-4); teats and udder (BPV-1, BPV-3, BPV-5, and BPV-6); and genital epithelium (BPV-1).[1,2] Immunity after infection or vaccination is virus type specific and is induced by viral structural proteins.[1] Therefore the efficacy of both autogenous and commercial vaccines depends on which viral antigens are incorporated into the vaccine and which virus type is responsible for the disease. Vaccines containing BPV-1 and BPV-2 are generally effective for prevention, with some reports that BPV-2 also aids in regression of existing lesions.[1,3] Vaccines are usually ineffective for treatment or prevention of disease caused by BPV-3 and BPV-5.[3] Vaccination with structural capsid proteins of BPV-4 generally induces long-lasting immunity and is effective in preventing

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papillomas caused by BPV-4.[1] However, in immunocompromised cattle (e.g., those ingesting bracken fern), papillomas may spread and can progress to squamous cell carcinoma.[2,4] Interpreting the response to vaccination against fibropapilloma can be complicated by spontaneous regression of some lesions. Lesions associated with BPV-1, BPV-2, and BPV-4 usually regress spontaneously within 1 to 12 months, whereas lesions caused by BPV-3 and BPV-5 do not normally regress spontaneously.[2,3]

Commercial vaccines consist of inactivated virus-laden tissue extracts derived from bovine papillomas.[5] The recommended regimen is an initial dose divided and given in at least two different sites, followed by a second dose in 3 to 5 weeks. Vaccination should continue for at least 1 year after elimination of disease from the herd. Autogenous vaccines can be made by homogenization and inactivation (0.3% formalin) of excised wart tissue, followed by dilution of the homogenate in physiologic saline and filtration through gauze. Three 1- to 5-mL intradermal injections given at 1-week intervals are recommended. Because autogenous vaccines generally contain the virus type associated with the disease, these often provide favorable results for both regression and prevention.[6] Vaccination is most commonly used with valuable animals destined for competitive shows or overseas sale.[3] Recombinant or native BPV proteins derived from multiple virus types have shown promise in experimental studies and could form the basis for a vaccine that protects against all BPV types.[7]

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• CHAPTER 49

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Parasite Control Programs

Sherrill A. Fleming, Consulting Editor, Martin K. Nielsen, Lora Rickard Ballweber

The traditional approach to parasite control programs has focused on using the appropriate anthelmintic at appropriate intervals. Parasitic disease in domestic animals was assumed to be the result of not dosing the animals often enough with anthelmintics. Scant consideration has been paid to the interaction of the parasite with the host and the environment because of the reliance on anthelmintics. These drugs have been placed directly into the hands of the livestock owner because the expertise of a veterinarian did not seem necessary in the control of parasites. However, reports of resistance to anthelmintics and emergence of new manifestations of parasitism are surfacing throughout the world. It has become increasingly apparent over the past 25 years that this approach to parasite control is no longer sustainable.

Secondary to the notion that parasitism is under control is the decrease in research to develop new anthelmintics. There has been little pharmacologic development other than in variations on the current anthelmintics. Recently two new anthelmintic classes have been developed but are not commercially available internationally. Research programs in parasitology of domestic animals are facing funding reductions as research priorities shift to other diseases. As producers and owners struggle to deal with the realities of anthelmintic resistance, veterinary medicine must reassess traditional approaches to parasite control programs. Veterinarians need to reeducate themselves away from the traditional tools of deworming, anthelmintic rotation, and pasture rotation. Integrated and holistic management strategies incorporating selective use of anthelmintic agents, enhancement of host immunity to parasitic infection, and grazing and environmental management have become increasingly important in the design of sustainable parasite control programs.

The impact of parasitic infection varies widely with geographic area and management system. General guidelines may be suggested for parasitic control,

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but it is inadvisable to adhere to any rigid anthelmintic schedules or even management recommendations. The best parasite control programs are those designed with the goals of the producer in mind, as well as the costs and returns of treatment. Other factors that must be considered include the animal's environment, climatic variations, and geographic location. Although many producers and owners would like a “cookbook” approach to parasite control, these are rarely effective across the various management conditions. It is unfortunate that an epidemiologically and economically sound parasite control program designed for animals in one geographic area may be neither efficient nor effective in another location.

The most important concept in the design of sound parasite control programs is the interaction of the parasite with the host and the environment. An understanding of the life cycle and epidemiology will suggest the most effective methods for parasite control. In this chapter, parasite factors, host factors, and environmental factors affecting transmission and disease expression are discussed for each major class of parasites in each host species (horses, cattle, small ruminants). The methods of monitoring parasite infections and anthelmintic resistance are presented in detail. Coccidiosis in cattle and small ruminants is summarized and, finally, the classes of anthelmintics and their modes of action are discussed at the end of the chapter.

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Equine Parasitic Disease

Martin K. Nielsen

The changed approaches being promoted for control of equine gastrointestinal helminths are based on the scientific concepts outlined in the following section. The recommendations given today are based on our best knowledge of parasite and host biology as well as mechanisms of anthelmintic resistance. Some of these recommendations are likely to change as new information is generated. In essence, the traditional strategies used for equine parasite control were based on the best scientific evidence available at the time, and the recommendations now given are merely a response to the experiences gathered over the past decades. The concepts underlying the modern approaches for equine parasite control are presented here.

Anthelmintic Resistance

Anthelmintic resistance can be defined as “the loss of treatment efficacy of a given anthelmintic formulation that used to have efficacy against the same parasite species and stage in the same host animal, at the same dosage, and by the same route of administration.” From this sentence, we can learn several things: (1) If a drug formulation never had efficacy against the parasite and stage in question, we are not facing resistance. (2) In cases of nonlabeled use of anthelmintics, we cannot make any conclusions regarding resistance because we have no information about the expected level of efficacy. (3) Horses are always infected with several different species of parasites at the same time, and resistance often occurs in some but not all of these species. (4) The expected level of efficacy needs to be defined for each parasite species for each drug in order to evaluate the possible presence of resistant parasites.

The current levels of anthelmintic resistance in equine parasites are presented in Table 49.1. Resistance has been widely documented in cyathostomins (small strongyles) and *Parascaris* spp. It is worth noticing that as a general pattern, the resistance profiles are almost completely complementary between the two parasite categories. The drugs that seem to still work well against *Parascaris* spp. often have no or little efficacy against cyathostomins, and vice versa. However, levels of anthelmintic resistance are constantly developing, and this pattern therefore may very well be shifting. As described in the following

section on egg reappearance periods, signs of emerging ivermectin and moxidectin resistance have been reported in cyathostomins,[1-4] and total drug failure is a realistic possibility in this parasite group. No new anthelmintic formulations with new modes of action are expected to be introduced to the equine market in the foreseeable future.

TABLE 49.1

Current Levels of Resistance by Major Nematode Parasites to the Three Anthelmintic Classes in Managed Horse Herds

Drug Class	Cyathostomins	Large Strongyles	*Parascaris* spp.
Benzimidazoles	Widespread	None	Early indications
Pyrimidines	Common	None	Early indications
Macrocyclic lactones	Early indications	None	Widespread

The only available method for evaluating anthelmintic efficacy in horses is the fecal egg count reduction test (FECRT). This method is outlined in Box 49.1 along with some suggested cutoff values for determining anthelmintic resistance.

Box 49.1

Fecal Egg Count Reduction Test (FECRT)

The FECRT evaluates the efficacy of an anthelmintic drug based on its ability to reduce the fecal egg output after treatment. Fecal egg counts (FECs) are performed just before (or at the time of) and 14 days after treatment. The fecal egg count reduction (FECR) is calculated for each individual horse according to the following formula:

$$\%\ \text{FECR} = \left(\frac{FEC_{pre} - FEC_{post}}{FEC_{post}} \right) \times 100\%$$

It is recommended to use an egg counting technique with a detection limit of less than 25 eggs per gram (EPG). Always use the same technique consistently. Include horses with the highest possible pretreatment egg counts, and never use horses with counts below 200 EPG.

The FECRT should be established on the farm level by calculating the FECR for a number of individual horses and then calculating the average FECR for the treated group. It is recommended to include at least 5 to 10 horses on each farm if possible.

Suggested cutoff values for resistance depend on the drug tested and the number of horses investigated, but the following cutoff values are recommended as general guidelines for strongyle and ascarid nematodes:

Benzimidazoles:	95%
Pyrantel:	90%
Ivermectin:	95%
Moxidectin:	95%

If the farm average FECR falls below these values, anthelmintic resistance should be suspected. However, it is important to rule out other causes of decreased efficacy, such as misdosing, inadequate storage, etc. One must also consider how many horses were tested and how high the starting FECs were. Due to inherent variability in the measurement of FEC when performing FECRT, interpretation of the data can sometimes be difficult when results fall into the borderline zones. In such cases, it is recommended to repeat the FECRT.

There are currently no available methods for diagnosis of anthelmintic resistance in equine tapeworms.

Egg Reappearance Period

Egg reappearance periods (ERPs) are defined as the period of time from anthelmintic treatment until parasite eggs are found in the feces again. Although ERPs could potentially be established for a number of different parasite categories, they are most often referred to for strongyle (i.e., cyathostomin) parasites. The ERPs were initially defined for each anthelmintic class to help identify the optimum interval between anthelmintic treatments, and this was the basis for launching the so-called interval dose program in the 1960s.[5]

Nowadays, ERPs are used for an entirely different purpose. It has been observed that the first sign of developing anthelmintic resistance to a given drug is often a gradual shortening of the ERP until reduced efficacies can finally be found with the FECRT. This concept is highly relevant for monitoring the efficacy of ivermectin and moxidectin against cyathostomin parasites. Initially ERPs were reported to be at least 9 and 16 weeks for ivermectin and moxidectin, respectively,[6-8] but recent publications reported egg reappearance at around

week 4 to 5 for both drugs.[1,4] Necropsy-based studies have suggested that these observations were due to survival of luminal yet premature stages of cyathostomin larvae.[2,3]

Prepatent Period

Prepatent periods (PPPs) should not be confused with the egg reappearance periods defined above. Although the latter defines a response to anthelmintic treatment, PPPs are defined in the absence of anthelmintic intervention. The PPP for any given parasite is defined as the time elapsed from the uptake of the infective stage of the parasite until it reaches patency and starts shedding eggs to be detected in the feces. Thus the PPP represents the duration of the parasitic part of the life cycle. Table 49.2 presents PPPs for some of the most important equine helminth parasites. It should be noted that although the PPPs for cyathostomin parasites generally are relatively short, they can undergo arrested development for up to several years, which thereby dramatically lengthens the PPP.[9]

TABLE 49.2

Prepatent Periods of Some Important Equine Parasites

Species	Prepatent Period	Reference
Cyathostomins	2–3 months[a]	113
Parascaris equorum	2½–3 months	114
Anoplocephala perfoliata	1½–4 months	115
Strongylus edentatus	11–12 months	116
Strongylus equinus	8 months	117
Strongylus vulgaris	6–7 months	116

[a]Encysted larval stages can remain dormant for years.

Information about PPPs can be considered when identifying optimal times for routine collection of fecal samples and anthelmintic intervention.

Parasite Distributions

Regardless of parasite and host species, distributions of parasites among their hosts always seem to follow the same pattern. Hosts of similar age and breed and kept under identical management grazing in the same pasture can have widely different parasite burdens. Parasites never follow a symmetric normal distribution but are rather said to be overdispersed.[10] Technically speaking, this

means that the variance is larger than the mean, but in practical terms this has been translated to the so-called 20/80 rule.[11] This refers to the observation that about 20% of the host animals harbor approximately 80% of the parasites. Similarly, about 20% of horses are shedding 80% of the total strongyle egg output. This phenomenon is most pronounced in adult horses, where a large majority is shedding low numbers of strongyle eggs and very few individuals can be observed with very high counts. This pattern has been found to be consistent in individual horses over time, and the tendency is particularly strong among horses with zero or low strongyle egg counts.[12-14] Taken together, these observations have become the foundation for the selective therapy principle discussed later in this chapter.

Parasite Refugia

The term *parasite refugia* has become generally accepted as an important factor affecting the rate of development of anthelmintic resistance in large animal parasites.[15] Parasites in refugia are the parts of any given parasite population (including all stages, both internal and external) that are not exposed to the anthelmintic drug at the time of treatment. It can be said that these parasite stages in a way "escaped" the drug and can be viewed as refugees, hence the terminology. Logically, all stages on pasture, such as eggs and preinfective larvae, are always in refugia. In addition, animals left untreated are contributing significantly to the refugia, and some parasitologists therefore distinguish between "pasture refugia" and "animal refugia." Finally, some anthelmintic formulations have no efficacy against some parasite stages within the horse, and these can be regarded as part of the refugia as well. Examples of this include pyrantel formulations that have no efficacy against parasite stages present outside the gastrointestinal lumen and ivermectin, which has no documented efficacy against encysted cyathostomin larvae.

The parasites in refugia are hypothesized to play a role in diluting out resistant parasites whenever the animals are dewormed. A simplistic explanation of this concept is the larger the refugia, the more the dilution of resistant parasites, and the slower the development of resistance. In a theoretical example, let us consider a horse herd that is dewormed with a drug that has efficacy against all parasitic stages of the parasites, and the treatments are carried out at time of the year when no eggs or larvae are present on pasture. This would represent a scenario with no parasite refugia. Because no anthelmintic treatment is 100%

efficacious, there will always be a few parasites surviving and passing their genes to the next generation. In a situation with low or even no refugia, all eggs being passed in the feces after deworming will be progeny of resistant parasites mating in the intestinal tract. However, if some of the horses in the herd were left untreated or treatments were carried out under circumstances with eggs and larvae present on pasture, then the few resistant worms surviving treatment would be diluted out by the many nonresistant worms, eggs, and larvae, and the progression of resistance in the parasite population would be much slower.

The role of parasite refugia in the development of anthelmintic resistance was initially shown in a sheep study,[16] and recent work with a combination of computer simulations and field studies with ruminants has provided solid evidence behind the concept.[17-19] Most recently, computer simulation models have been established for *Parascaris* spp. and cyathostomin parasites,[20-21] and studies confirm the value of parasite refugia in these parasites.

Important Parasites Infecting Horses

Over the past five decades the emphasis has shifted several times in terms of which parasites are considered the major targets of the control programs. When the first modern paste dewormers were introduced in the 1960s, the large strongyle *Strongylus vulgaris* was considered the most important threat to equine health and was therefore identified as the main target for the interval dose program.[5] As time went on and new anthelmintic drug classes were introduced, this parasite went from being present in virtually all horses to becoming very rare.[22-23] At the same time, cyathostomins were recognized as major pathogens and identified as the new primary target of parasite control programs.[24] More recently, the tapeworm *Anoplocephala perfoliata* has been associated with an increased risk of specific colic types.[25] In addition, *Parascaris* spp. are identified as the major parasitic pathogens in foals.[26-27] These are the four major parasite pathogens, but others can play a role as well. Less important but widely occurring parasites include *Strongyloides westeri*, *Oxyuris equi*, and the bot larvae of *Gasterophilus* spp. Finally, the insect-borne nematodes *Thelazia* spp., *Habronema* spp., and *Setaria* spp. can occur at significant levels in certain habitats and are included in this chapter.

Parascaris Species

Recent work has recognized the presence of two *Parascaris* spp. infecting horses: *Parascaris equorum* and *Parascaris univalens.* These two species are morphologically identical but can be differentiated by karyotyping and counting the number of chromosomes. Available data suggest that *P. univalens* is the predominant species, while *P. equorum* may be extremely rare.[28]

The equine roundworm has gained status as perhaps the most significant parasitic threat to equine health in managed horse populations. The major reason for this shift of emphasis is the high level of ivermectin and moxidectin resistance observed worldwide (see Table 49.1). *Parascaris* spp. are the primary parasites in foals until about the time of weaning. Between 6 and 12 months of age, most horses clear infection with this parasite, and the strongyles become the predominating parasite group instead. However, a smaller second wave of ascarid infections can be observed around 8 to 10 months of age.[29] Equine ascarids are ubiquitous in foaling operations, although prevalence differences can be observed between individual farms.[30-31] Patent infection is not uncommon in adult horses, particularly brood mares that are highly exposed to infection.

The life cycle is classic ascarid. Eggs are often claimed to be highly resilient to environmental influences, but very little evidence exists to substantiate these claims. Work with eggs of the pig roundworm, *Ascaris suum,* has substantiated this, but very little work has been done with *P. equorum* eggs. The infective stage is the embryonated egg, which hatches in the stomach and small intestine of the horse. Larvae then penetrate the mucosal lining and migrate the classical hepatotracheal route. Passing through the lungs has been associated with airway symptoms in young foals,[32] but the major pathogenic role is played in the small intestine. Here, the parasites compete with their hosts for nutrients, which can result in ill-thrift, weight loss, rough hair coat, and pot-bellied appearance.[26,32] The major clinical impact is associated with verminous small intestinal impactions.[26] Surgery is often required to relieve the condition, and prognosis for long-term survival is guarded with only 11 of 37 published cases surviving beyond 1 year after the colic incident.[26] Rather ironically, anthelmintic treatment has been shown to be a significant risk factor for this condition.[26] The instant paralysis elicited by most dewormers can cause the worms to aggregate in the lower parts of the jejunum and ileum. Benzimidazole-type drugs are not acting through paralysis of the worms and appear to be less associated with this condition.[26] Given that benzimidazoles have maintained efficacy against

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roundworms, they appear to be a good first choice for this parasite in most instances.

Cyathostomins

Historically, this group is also referred to as small strongyles. It consists of 50 different species belonging to 14 different genera.[33] However, some of these species and genera have been described as infecting equids other than horses, such as donkeys and zebras. Horses are always infected by multiple species, and there currently is limited knowledge about the pathogenic role of individual cyathostomin species. Cyathostomins are truly ubiquitous, and all grazing horses are exposed to infection.

The cyathostomins all follow the same basic strongyle life cycle. Strongyle eggs are passed in the feces, where they will hatch, and larvae develop through the first (L_1) and second (L_2) stages until they finally reach the third, infective stage (L_3). Hatching and subsequent larval development is highly temperature-dependent. At temperatures below 6° C, eggs do not hatch but remain viable. Hatching and larval development occurs at increasing rates up to about 40° C. At temperatures above this level, eggs and larvae quickly die out. Optimal conditions for development of eggs and larvae are in the temperature range of 25° to 33° C, where L_3 is reached within 3 to 4 days. In comparison, this takes several weeks at around 10° C. When molting from L_2 to L_3, the larvae retain their L_2 cuticle on the outside of the new sheath. This makes L_3 particularly resistant to environmental influences such as desiccation and freezing. Thus, for this stage, the widespread notion of the “killing frost” is a myth. In addition, intact fecal balls provide excellent protection of larvae, enabling them to further withstand desiccation and freezing temperatures well.[34] Due to the double-layered cuticle, L_3 cannot uptake feed and thus live on carbohydrates and lipids stored in their cells. The more active these larvae are, the shorter they live. As larval activity is highly temperature dependent, it can be deduced that the higher the temperature, the shorter the survival. Dry conditions, as achieved with freezing or desiccation, limit larval movement and therefore facilitate their survival. However, repeated cycles of frost and thaw have a deleterious effect on most free-living stages of strongyle, although this can be mitigated by snow cover, which tends to stabilize temperatures right at the freezing point, which is optimal for survival of eggs and L_3.[34]

Inside the horse, the L_3 exsheath in the stomach and subsequently reach the colon and cecum. Here, they enter the glands of Lieberkühn and penetrate cells at the base. From here, some species appear to penetrate deeper into the submucosa, while others remain in the mucosa. A fibrous capsule is formed around each larva, and then a fluid-filled cyst is formed. Larvae can remain encysted for several years,[9] but encystment appears to be a strategy for the parasites to make it through the winter, where conditions on pasture are unfavorable for parasite transmission. Interestingly, in warmer climates, encystment appears to occur over the hot summers. Horses can harbor several hundred thousand encysted cyathostomin larvae without showing any sign of discomfort. The major clinical consequences are associated with the process of excystment, where the L_4 penetrate their cysts and migrate the short distance back to the intestinal lumen. This causes a small local inflammatory reaction around the vacated cyst. In rare cases, synchronous emergence of large numbers of larvae from their cysts can cause a severe generalized acute typhlocolitis, called larval cyathostominosis.[24] This condition is characterized by profuse watery diarrhea and pronounced dehydration as well as protein loss and ventral edema. The case fatality rate is reported to be 50%.[24] Identified risk factors for larval cyathostominosis include horses aged 1 to 4 years, anthelmintic treatment within 14 days prior, and late fall, winter, or early spring in temperate climates.[35] The luminal worm burden appears to elicit some sort of a repressive signal, which prevents the encysted stages from resuming development. If the luminal burden is removed by anthelmintic treatment, this repressive signal disappears abruptly, and a synchronous emergence is triggered. Treatment of acute larval cyathostominosis involves intensive fluid therapy, which can be combined anti-inflammatory drugs and antibiotics. The anthelmintic drug of choice is a single dose of moxidectin (400 µg/kg PO) because of its efficacy against encysted larvae. The 5-day elevated dose of fenbendazole (10 mg/kg PO once daily) is also labeled for treatment of encysted cyathostomins, but larvicidal resistance has recently been reported to this regimen, making it unlikely to have maintained full efficacy once adulticide resistance has been documented to the single dose.[36]

Chronic cases of larval cyathostominosis also occur. These are typically characterized by weight loss and loose feces or intermittent diarrhea, often over an extended period. Plasma protein and albumin levels can be lowered, and ventral abdominal edema can be observed. Horses usually recover, although it may take time for them to regain full body condition.

Tapeworms

Three species of tapeworm infect horses: *A. perfoliata, Anoplocephala magna,* and *Anoplocephaloides (Paranoplocephala) mamillana*. Of these, *A. perfoliata* is by far the most common, and it is the only species that has been associated with clinical disease. Being a cestode, the life cycle involves intermediate hosts, which are oribatid mites that feed on the organic material present in the feces. During this process, the mites can ingest tapeworm eggs present in the feces. Inside the mite, eggs develop to infective cysticercoids over a period of approximately 2 to 4 months. Horses inadvertently ingest these mites during grazing. In the gastrointestinal tract, the cysticercoids are liberated from the mites, and the scolexes attach to the mucosal lining around the ileocecal valve in the cecum.

Prevalence of *A. perfoliata* has been reported to vary widely between farms and regions, often ranging between 20% and 80% of horses.[25] Prevalence appears to be habitat-dependent, and it is likely associated with conditions favoring survival of the oribatid mites. However, the most significant factor appears to be access to pasture. The longer the time spent on pasture, the higher the tapeworm exposure seems to become.[37] Horses younger than 2 years and older than 15 years of age have been reported to have significantly larger *Anoplocephala* burdens than horses between these ages.[38-39] While this could be explained by the assumed incomplete levels of immunity in these age groups, it is equally likely that these age groups simply spend more time on pasture. Tapeworm burdens appear to be accumulating through the grazing season to reach their highest point in the fall and winter.[38-43]

An increasing number of case-control studies has associated *A. perfoliata* infection with colics originating from the ileal region.[25] These include ileal impactions and ileocecal intussusceptions, which are sometimes complicated by intestinal rupture.[44-45] Taken together, these studies indicate that tapeworms can play a role in the development of colic, but this is often largely confounded by the multifactorial nature of colics and regional differences in climate and management.

Two anthelmintics are labeled for treatment of equine tapeworms: praziquantel and pyrantel pamoate. Praziquantel is a sole tapeworm drug that has no efficacy against nematodes. For this reason, it is most often formulated in combination with ivermectin or moxidectin, although it exists in a standalone formulation for horses in Europe. Pyrantel, on the other hand, is widely acting

against luminal stages of nematodes as well as cestodes. At the dosage labeled for nematode treatment (6.6 mg/kg), the efficacy of pyrantel pamoate is greater than 80% against *A. perfoliata*.[46] A double dosage of pyrantel pamoate (13.2 mg/kg) is a substitute for tapeworm treatment, and the efficacy of this has been found to be greater than 95%.[47]

Strongylins (Large Strongyles)

The strongylin group comprises the three *Strongylus* species—*S. vulgaris, Strongylus edentatus,* and *Strongylus equinus*—as well as *Triodontophorus* spp., *Craterostomum acuticaudatum*, and *Oesophagodontus robustus*. As mentioned, large strongyles have generally become quite rare in managed equine establishments. The most common of these nowadays is probably *Triodontophorus* spp., but the *Strongylus* species, particularly *S. vulgaris,* are considered the most pathogenic of helminths infecting the horse.

The development of the external stages of the strongylins is virtually identical to what is already described for the cyathostomins. Inside the horse, larval migrations are widely different. The three *Strongylus* species all have PPPs of 6 months or more, and they spend several months migrating in various tissues and organs of the horse. Major pathologic lesions have been ascribed to these migrations, whereas the adult worms are found to do little harm to their hosts. The lesions caused by migrating stages of *S. vulgaris* are classic in equine parasitology and very well described.[48] L_3 invade the mucosa of the small intestine, cecum, and colon. They then molt to L_4 before they enter local arterioles. Inside these, they migrate beneath the endothelium toward the root of the cranial mesenteric artery, leaving characteristic fibrous tracts on the intimal surface. Upon reaching their destination about 14 days post infection, they enter the lumen of the vessel and remain there, embedded in thrombus masses. Here, they grow in size and molt to L_5, while causing a pronounced verminous endarteritis with roughened intima, fibrosis of arterial walls, and increased diameter of the vessels. After about 4 months, the L_5 are transported by the bloodstream to the walls of the ventral colon and cecum, where pus-filled nodules are formed around them in the submucosa. These nodules eventually open into the intestinal lumen, and the young adult worms emerge. After another 6 weeks, the worms become sexually mature and start shedding eggs. Although the lesions are pronounced, they are relatively rarely accompanied by disease. A classical syndrome of thromboembolic colic has been described,[49] where

thrombi detach from the arteritis lesions and are carried distally until they reach a terminal branch sufficiently small to become occluded. This causes ischemia and infarction of intestinal segments, which is very painful to the horse. However, the primary manifestation in many cases appears to be peritonitis due to bacterial overgrowth of the devitalized intestinal segment, and the prognosis for survival is reserved.[50]

Larvae of *S. edentatus* migrate via the portal system to the liver, where they molt to the fourth stage within the parenchyma. They migrate within the liver, and then migrate sub- and retroperitoneally via the hepatorenal ligament to the adipose tissue in the abdominal walls. Larvae can also be found in the perirenal fat tissue. Here, larvae eventually molt to L_5 and migrate retroperitoneally back to the intestinal walls. Described lesions include a filamentous peritonitis, especially around the liver and diaphragm, as well as hemorrhagic and inflammatory lesions in the abdominal wall.[51] The third *Strongylus* species, *S. equinus*, is probably the rarest, at least in managed horses on the northern hemisphere, where it is hardly encountered at all. As opposed to *S. edentatus*, it migrates within the peritoneal cavity and passes through the pancreas, where it can cause significant damage.[52] Despite their obvious pathologic impact, neither *S. edentatus* nor *S. equinus* have been associated with defined clinical syndromes.

None of the strongylins have been reported as resistant to any of the anthelmintic drug formulations available. Treatment efficacies against *S. edentatus* appear to be more variable than in the other species,[53] but this seems to always have been the case and thus cannot be concluded to be resistance.

Other Parasites

Other parasites frequently infect equines but are generally considered of lower importance. For completion, they are briefly covered here.

S. westeri, or the equine threadworm, parasitizes the small intestine of suckling foals. This parasite is remarkable because it is able to maintain a full life cycle outside its host, and only female worms seem to infect the foals. Infection occurs via three possible routes: skin penetration by L_3, ingestion of these larvae from the environment, or lactogenic transmission from the mare.[54] Infection usually occurs within the first weeks of life, and infected foals are usually asymptomatic. However, one study reported an association between diarrhea and high *Strongyloides* egg counts (>2000 eggs per gram [EPG]),[55] and

another study described a “frenzy” syndrome in foals exposed to apparent percutaneous penetration of L_3 from the environment.[56] Because of *S. westeri*, it has become a widely used practice to deworm mares at or just before foaling. However, it remains unclear how effective this measure is, as *S. westeri* prevalence has been observed to increase in managed equine populations in recent years.[57]

O. equi, the equine pinworm, is widely prevalent, but eggs are rarely encountered in fecal samples, as they are laid outside the digestive tract. Adult worms live in the dorsal colon. The female worm migrates through the descending colon and rectum to protrude from the anus and deposit her eggs in patches on the perianal skin. When these egg patches dry up, they become very itchy to the horse, and horses begin rubbing their tails against various objects. This serves as an excellent means to spread eggs in the environment. The infective stage is the embryonated egg, which is inadvertently ingested from the contaminated environment. Besides the tail-rubbing, *O. equi* does not cause disease or discomfort to the horse, and there is no justification for routinely targeting this parasite in the parasite control program. Recent studies have reported apparent resistance to ivermectin in isolates of *O. equi*.[58,59]

Gasterophilus spp. are the widely occurring botflies, whose larval stages overwinter in the intestinal tract and then pass in the feces during the spring. They then pupate in the loose soil for a couple of months until the adult flies emerge. The two most common species are *Gasterophilus intestinalis* and *Gasterophilus nasalis*. Eggs are glued onto the hair coat, and larvae make their way into the oral cavity either by crawling on the skin *(G. nasalis)* or when the horse grooms itself or another herd member *(G. intestinalis)*. In the mouth, the larvae spend several weeks burrowing into the tongue and subsequently spend time in the interdental spaces before reaching the stomach.[60] In the stomach, *G. intestinalis* attaches to the mucosal lining by the margo plicatus, whereas *G. nasalis* can be found in the pyloric region. Characteristic lesions have been described at the attachment site,[61] but these have not been consistently associated with disease. With the emergence of equine dentistry over the past decades, the lesions in the oral cavity are gaining more attention, as *Gasterophilus* spp. can cause oral discomfort.[62]

The equine eye worm, *Thelazia lacrymalis*, is transmitted by muscid flies and can be found within the conjunctival sac of horses, where they generally appear to do very little or no harm to the eye. However, abscess formation and

inflammation of the lacrimal glands have been described.[63] Prevalence rates in the range of 20% to 42% have been reported in managed horses.[64,65]

The group of stomach worms comprises *Habronema* spp., *Draschia* spp., and *Trichostrongylus axei*. *Habronema* and *Draschia* spp. have very similar life cycles. Like *Thelazia* spp., they are both transmitted by muscid flies. The flies acquire the infective larvae while feeding on the feces. Horses get infected by accidentally ingesting infected flies. Here, the larvae eventually reach the stomach, where *Habronema* larvae apparently cause no gross lesions, but adult specimens of *Draschia* spp. can be found embedded in large tumor-like fibrous masses around the margo plicatus.[66] Common to both of these species is that the larvae can be deposited by the flies in or near wounds or mucocutaneous junctions. For the parasite, this represents a dead-end pathway, from which the life cycle cannot be completed.[67,68] When larvae are deposited in this manner, they cause a condition usually referred to as cutaneous habronemiasis or draschiasis, or "summer sores." This is characterized by persistent, eosinophilic granulomatous lesions with eosinophilia and fibrosis. A rare, pulmonary form of habronemiasis has been described as well.[69] Anthelmintic resistance has not yet been reported in *Habronema* or *Draschia* spp., but several veterinary practitioners from subtropical and tropical regions report that skin lesions consistent with cutaneous habronemiasis do not resolve upon treatment with a macrocyclic lactone (ivermectin or moxidectin). The prevalence of *Draschia* spp. seems to have decreased dramatically after the introduction of ivermectin.[70]

T. axei possesses the rare capacity of infecting both ruminants and monogastrics such as pigs and horses. The external part of the life cycle is similar to that of the strongyle parasites described in this chapter. Inside the horse, it develops within the gastric glands, where it can cause hypertrophy of the mucosa.[71] In horses, *T. axei* has not been found to affect pH or levels of plasma pepsinogen.[72] The parasite is a rare finding in horses, but prevalence has been found to increase when horses are co-grazed with sheep.[73,74]

Setaria and *Onchocerca* spp. are filarial nematodes infecting horses. Infective L_3 are transmitted by blood-sucking arthropods feeding on the horses. The larvae then migrate to their predilection site, which is the connective tissues (*Onchocerca* spp.) or the abdominal cavity *(Setaria equina)*. Here, they develop into adult worms, which then release microfilariae intro the bloodstream. These microfilariae in turn will enter the blood-feeding arthropods, and the cycle is complete. The intermediate hosts for *Onchocerca* spp. are biting midges

(*Culicoides* spp.) and black flies (*Simulium* spp.), whereas the hosts for *S. equina* are mosquitoes. The latter parasite is regarded as nonpathogenic, whereas *Onchocerca* spp. have been associated with pronounced skin reactions. Microfilariae of *Onchocerca cervicalis* tend to congregate in certain regions of the body, including the ventral midline and face, where they are ingested when *Culicoides* feed in these regions.[75] This results in a verminous dermatitis characterized by intense pruritus.[76] Lesions can be effectively treated with macrocyclic lactones.[77] However, there is no known therapy to eliminate adult *O. cervicalis* from the connective tissue around the ligamentum nuchae of horses. Therefore infected horses will need periodic retreatment with ivermectin or moxidectin to prevent or control recurrence of clinical signs.[78,79] Treatment of the skin-dwelling microfilariae has been associated with an inflammatory reaction to the dying parasites,[80] which can be confused with the widely occurring *Culicoides* hypersensitivity (summer eczema, sweet itch).

Adult *Parafilaria multipapillosa* is another filarial nematode that occurs in subcutaneous and intermuscular connective tissue of horses outside North America. Nodules form in the overlying skin and may rupture and bleed or leak tissue fluids. This condition is often referred to as "summer bleeding,"[81] not to be confused with the "summer sores" described with cutaneous habronemiasis or draschiasis. L_1 are present in the exudate from bleeding lesions and ingested by feeding horn flies *(Haematobia irritans).* Larvae develop to the infective third stage within the fly and are transferred to horses when flies feed on lachrymal secretions or skin wounds. The larvae then migrate in the subcutaneous tissues and develop to the adult stage within a year. Eggs and microfilariae can readily be identified in smears taken from lesion exudates.[82] Little is known about anthelmintic efficacy, but lesions have been observed to recur after treatment with macrocyclic lactones.

The equine lungworm, *Dictyocaulus arnfieldi,* is covered in the Lungworm Infection in Large Animals section later in this chapter.

Halicephalobus gingivalis (formerly *Micronema deletrix*) is a free-living nematode belonging to the order Rhabditida. It is widely present in the soil and humus but possesses a capacity to also invade living tissues. Infection appears to occur through soil-contaminated wounds or nasal mucosal membranes with apparent predilection in the head region,[83-86] but penile infection has also been described.[87] Inside the host, the nematode reproduces tremendously, and the larvae invade deeper into the tissues. Larvae appear to have a special affinity for

the central nervous system (CNS) and the kidneys.[85] Lesions are multifocal, eosinophilic, and pyogranulomatous. Once the CNS is affected, symptoms often slowly progress into a very grave state. Symptoms include blindness, ataxia, loss of proprioception, head pressing, coma, recumbency, and death.[85,88,89] Treatment options are very limited. Surgical debulking can be combined with repeated high doses of fenbendazole (50 mg/kg) or ivermectin (0.55 mg/kg),[90] but the overwhelming majority of published cases had a fatal outcome. Similarly, *Halicephalobus* spp. infection has been reported to be extremely rare but fatal in humans.[91-93]

Diagnostics

The cornerstone of diagnostics in equine parasitology remains the fecal egg counting methods. Before these are discussed, it should be emphasized that egg counts can be performed for at least three purposes: (1) evaluation of anthelmintic efficacy with the FECRT (see Box 49.1); (2) identification of low, medium, and high strongyle egg shedders for a targeted treatment approach; and (3) diagnosis of parasite infection in clinical cases. When discussing the usefulness of fecal egg counts, it is important to note that this largely depends on the purpose. In other words, fecal egg counts are not equally useful for all three purposes.

Numerous techniques exist with various names such as Stoll,[94] Wisconsin,[95] or McMaster,[96] but they are all based on the same simple principle. A flotation medium is usually constructed with some sugar or chemical salt solution to have a specific density higher than most parasite eggs but lower than the fecal matter. Examples of components used in flotation media include glucose, sucrose, sodium nitrate ($NaNO_3$), sodium chloride (NaCl), magnesium sulfate ($MgSO_4$), and mercury chloride (HgCl). Very frequently used media are saturated glucose-NaCl and Sheather's sugar solution, which are relatively cheap and easy to compose. The numerous different egg counting techniques and the even more modifications of these can appear confusing, but in reality there are only three factors to consider when the choice of method has to be made: (1) the level of accuracy and precision associated with the technique, (2) the detection limit of the technique, and (3) the equipment requirements and time consumption in the laboratory.

The accuracy of a given technique is a measure of how close the determined egg counts are to the true egg count in a given sample. All of the different

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available techniques are associated with a certain degree of egg loss in the process of mixing, filtering, and flotation, so the eggs counted are only a subset of the true number of eggs per gram of feces. Similarly, precision is a measure of repeatability between repeated counts from the same sample. As a general rule of thumb, the simpler and perhaps more user-friendly methods come with lower accuracy and precision, whereas the more refined techniques that use centrifugation-enhanced flotation and larger counting chambers usually have higher precision and accuracy. The McMaster technique, for example, comes with low to moderate accuracy and precision,[97] whereas the FLOTAC system is very accurate and precise.[98] However, the FLOTAC is much more time consuming and includes a centrifugation step. A recently developed modification of the FLOTAC principle, the Mini-FLOTAC, is relatively user friendly as it does not involve centrifugation and has been found to have better precision and accuracy than the McMaster method.[97] These features are important when interpreting the FECRT. Low precision allows for high levels of variability in the FECRT. This is the reason why the FECRT always must be performed by averaging values across several horses on each farm.

The choice of detection limit will depend on the purpose of the egg count. If FECRTs are performed, it is crucial to be able to detect low egg counts in the posttreatment samples to possibly discover early signs of reduced anthelmintic efficacy. A crude McMaster, which is performed by many practice laboratories, usually comes with a detection limit of 25 or 50 EPG, which makes it very unsuitable for the FECRT, unless the pretreatment levels are very high. The FLOTAC technique mentioned above comes with a detection limit of 1 EPG. While this can also be achieved by a more traditional technique such as the Wisconsin, FLOTAC has been shown to have much higher precision.[98] For identification of high strongyle shedders for a targeted treatment approach, the detection limit is not important, and McMaster methods can be used.

Until recently, there were no published studies evaluating egg counts as a diagnostic test for horses. From the database generated over 50 years of equine parasitology research at the University of Kentucky, fecal egg counts were related to total intestinal worm counts from close to 700 horses.[99] Results indicated a high positive predictive value, indicating that an egg count–positive horse is very likely to also harbor worms in the intestine. However, the negative predictive value was low, emphasizing that 0 EPG does not necessarily indicate zero worms. Further, there were no direct linear correlations between strongyle

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and ascarid egg counts and the corresponding intestinal worm burdens. Thus higher egg counts do not necessarily equate to larger worm burdens. However, strongyle egg counts in the range of 100 to 500 EPG did correspond to significantly smaller strongyle burdens than egg counts above this level.[99] Taken together, this information illustrates that fecal egg counts can be used to qualitatively detect presence of strongyle or ascarid burdens, but that there are considerable limitations to these techniques as quantitative diagnostic tools. Furthermore, it should be borne in mind that much of the parasitic disease observed in horses is caused by migrating or encysted larvae that are not shedding any eggs. Detecting eggs in the feces cannot be used to estimate the probable presence of larval burdens. Also, strongyle eggs are practically ubiquitous in equine fecal samples, and their mere presence cannot be used to suggest parasitic disease. In foals and weanlings, egg counts can be very useful for determining whether parasite burdens are dominated by strongyles or ascarids, which is crucial information for selecting the right anthelmintic (see Table 49.1).

Another weakness of strongyle fecal egg counts is that up to 50 strongyle species have been described infecting horses,[33] and it is not possible to morphologically distinguish between their eggs. Larval cultures can be performed to differentiate large and small strongyles and for species-specific detection of the three *Strongylus* species.[100,101] In a retrospective validation, larval cultures were found to have high positive and moderate negative predictive values with no direct linear correlation between larval counts and worm counts.[99] Thus larval cultures should be interpreted with the same caution as egg counts. A pragmatic approach has been to pool feces from several horses into one pool, but this cannot be recommended, as diagnostic sensitivity is greatly lost with this approach and the negative predictive values are likely to be much lower.

Diagnosing tapeworm infection is a particular challenge despite the availability of several different techniques. Anoplocephalid eggs may show up on routine egg counts from time to time, but validation studies have shown that the diagnostic sensitivity of the simple McMaster is less than 10%.[25] The reason for this is believed to be the uneven distribution of tapeworm eggs in the feces. Eggs are released in clumps often retained within a tapeworm segment, which then disintegrates on its way through the cecum and colon. The eggs remain in their clumps, and egg counting methods examining just a few grams of feces can

easily miss detecting these eggs. A modified egg counting technique that analyzes 40 g of feces has been found to have a diagnostic sensitivity and specificity of 0.61 and 0.98, respectively.[102] However, this was based on detection of cestode burdens comprising only a single worm. If the threshold were adjusted to detect 20 or more tapeworms, the sensitivity was improved to about 90%.[25] Thus the tapeworm infections most likely to not be detected with this method are small burdens unlikely to cause clinical disease. Several enzyme-linked immunosorbent assays (ELISAs) have been made commercially available for detecting anti-*Anoplocephala* antibodies.[25] These assays have been found useful for evaluating the level of tapeworm exposure on the herd level. Optical density (OD) values correlate positively with worm burdens, and the assays can be helpful for generating information to help balance the level of tapeworm-directed treatments on each farm. It should be emphasized that serology is generally less useful for diagnosis on the individual level. Antibody levels are too variable, horses remain titer-positive for months after tapeworm treatment,[103] and one recent study suggests cross-reactivity with the less common *A. magna*.[104] In the United States, the diagnostic laboratory at the University of Tennessee, College of Veterinary Medicine, offers a modified version of the *Anoplocephala* ELISA, but no information is available on the performance of this test. There are currently no available methods for diagnosis of anthelmintic resistance in equine tapeworms.

Integrated Parasite Control

It is often said that a “one size fits all” parasite control program does not exist. There is no simple chart to hang on the wall in the horse barn, and follow the same guidelines for all of the horses. To the frustration of many horse owners, farm managers, and veterinary practitioners, it is much less straightforward to identify what to do. This section outlines the elements to incorporate in a modern evidence-based equine parasite control program.

The most important evidence to incorporate on each farm is the efficacy of the anthelmintic drugs used. Although Table 49.1 can be used to predict the drugs more likely to still have efficacy on a particular farm, the only way to really know is to evaluate the efficacy with the FECRT, as described in Box 49.1. Ideally, all drugs used should be tested on every farm each year. Regardless of the deworming program incorporated, it is very important to know the efficacy of the drugs used. Veterinary practitioners who provide recommendations on the

choice of anthelmintic should realize that these recommendations cannot be given without knowing the efficacy on the given farm. For ivermectin and moxidectin, the efficacies measured on day 14 post treatment should still be 100% in the large majority of instances, but the ERP may be shortened considerably on some farms. Thus it may be a pragmatic solution to perform the posttreatment egg counts in week 4 or 5 after treatment to evaluate whether there is evidence of a shortened ERP. A shorter ERP should not necessarily discourage people from using the drug, as there may not be valid alternatives, but it provides useful information about the level of parasite control achieved by using these drugs.

Egg counts can also be used for two other purposes. In foals, they can readily tell whether parasite burdens are predominantly *Parascaris* spp. or strongyles. This is crucial information, as the drugs that are likely to work against *Parascaris* spp. would not have efficacy against strongyles on many farms, and vice versa. In adult horses, a few egg counts repeated over time can be used to identify horses that are consistently shedding low, moderate, and high egg numbers.[11,105,106] This can then be used in a targeted selective approach, where the consistent high shedders can receive more anthelmintic treatment and horses consistently shedding low numbers can receive less treatment. Simulations have shown that treating all horses shedding 200 strongyle EPG or more with a drug with a 99.9% efficacy yields an overall reduction of the strongyle egg shedding of 94%.[11] However, when using 200 EPG as a treatment threshold, only about 50% of adult horses will need treatment, so with just half as many treatments, close to the same overall egg count reduction can be reached. This selective approach increases parasite refugia, slows down the development of anthelmintic resistance, and is widely implemented in some countries.

Recent studies have illustrated that in a system basing all anthelmintic treatments on fecal egg counts, some horses will not be dewormed for years.[107] This gives room for the large strongyle species, particularly *S. vulgaris,* to reemerge, which has been documented in Denmark.[107,108] Here, about 80% of farms using selective therapy had at least one horse infected with *S. vulgaris,* which was twice as much as in farms not using selective therapy. Although none of the horses showed clinical signs of disease, the pathogenic potential of *S. vulgaris* does suggest that horse populations would benefit from a basic foundation of anthelmintic treatments applied to all horses. Given the long life cycles and no apparent development of resistance in large strongyle species, just one or two yearly treatments with ivermectin or moxidectin would effectively

reduce the occurrence. Further treatments beyond this basic foundation should be directed at high strongyle shedders in a selective approach as described above.[109]

Tapeworms need to be considered in every parasite control program. They should be assumed to be present under most circumstances, although large regional differences in prevalence can occur.[25] As indicated in the previous section, the serum ELISA could be useful for generating information about the level of tapeworm exposure in a herd. If OD values are consistently high (i.e., many horses above the level of 1.0 to 2.0) or if confirmed clinical cases have occurred, a more aggressive treatment approach can be taken. In most cases, however, annual treatments in the fall appear to be of greatest benefit to minimize burdens and prevent the development of gravid forms that will otherwise contaminate pastures in the coming season. With an ivermectin-praziquantel combination formulation, this could easily be incorporated into the basic treatment foundation described above.

It has been a widely used strategy to regularly rotate between anthelmintic drugs when deworming horses. The theoretical basis for this strategy all makes good intuitive sense; parasites carrying genes that enable them to survive treatment with one drug can be killed by applying another drug with a different mode of action. Unfortunately, there is no evidence to support this hypothesis. In fact, one equine study clearly suggested that rotating drugs with each treatment did not appear to slow development of resistance.[110] Computer modeling studies with both ruminant and equine parasitology data have convincingly shown that rotating drugs does not prevent accumulation of resistant genetic alleles and therefore does not slow down the development of resistance.[111,112] Besides, rotation would only make sense if several anthelmintic drugs to which no resistance had already developed were available. As shown in Table 49.1, there are only three drug classes to choose from. Thus it will be difficult to find many horse farms without resistance already developed to one or maybe even two of them. Further, when rotation is carried out blindly without testing the efficacy of all drugs used, alternating between drugs may very well mask resistance so that it takes longer for it to be discovered. In summary, drug rotation does not appear to prevent or reduce the development of resistance, and it may create a false sense of security for the horse owner, who will believe that a solid strategy is in place.

Foals and young horses require specific consideration with regard to parasite control, as they are the most susceptible to infection, often shed the highest egg

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numbers, and are more at risk for parasitic disease than their older counterparts. As a rough guideline, most foals should require approximately five anthelmintic treatments during their first 15 months of life. Higher treatment intensity can be justified in cases of on high infection pressure or documented clinical problems in the herd. Less than four treatments would be considered inadequate unless low parasite transmission levels or absence of *Parascaris* spp. can be consistently documented.

The major helminth pathogen in foals younger than 6 months of age is *Parascaris* spp. Treatments targeting this parasite should be timed around the age of 2.5 to 3 months of age, when the first worms will have reached the intestine and started shedding eggs. Considering the increased risk of impactions from paralytic anthelmintics, benzimidazoles may be the best choice at this time. If this treatment is delayed just a couple of months, the worms will have grown much larger and increased in numbers, posing an increased threat of verminous impaction. A second deworming treatment should be targeted around or preferably just before the time of weaning. This is a stressful period for the foal, and large parasite burdens are undesired. At weaning, the main parasitic threat is still likely to be *Parascaris* spp., but strongyle parasites may start to play a role as well. Therefore fecal egg counts yield useful information about the presence of ascarids and strongyles and help guide the veterinarian to select the right anthelmintic.

Benzimidazoles are unlikely to be effective against cyathostomins on many farms, so other drug classes should be considered. Similarly, ivermectin has lost efficacy against *Parascaris* spp. across the world. Again, it is crucial to routinely evaluate the efficacy of the anthelmintics chosen with the FECRT. A third treatment should be considered for the weanlings or yearlings at about 8 to 10 months of age, which would be in the late autumn or early winter in most cases. This should target strongyles and tapeworms, while ascarids should be considered only in the case of positive egg counts. The next treatment could coincide with the fecal testing and treatments that are carried out in the spring for adult horses on many farms. In areas with defined grazing seasons, a fifth treatment should be considered about midway through the grazing season. Yearlings are considerably more susceptible to parasitic infection than older horses, and leaving them untreated for an entire grazing season of 5 to 9 months' duration puts them at risk of acquiring large parasite burdens.

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Gastrointestinal Nematode Infections in Cattle

Lora Rickard Ballweber

Cattle are hosts to numerous species of gastrointestinal nematodes (GINs) that, together, cause parasitic gastroenteritis (PGE).[1-3] Within the strongyle-type nematodes, *Ostertagia ostertagi* and species of *Cooperia* have been the most prevalent parasites across the United States, followed by species of *Haemonchus, Trichostrongylus,* and *Oesophagostomum*. Other species within the genera *Nematodirus* and *Trichuris* complete the GIN population in the United States. The various GINs do differ somewhat with respect to their site of infection and pathologic effects, but their general life cycle patterns are quite similar. The hookworm *Bunostomum phlebotomum,* the threadworm *Strongyloides papillosus,* and the roundworm *Toxocara vitulorum* are not widely distributed within the United States and not considered a part of the "normal" GIN population.

Life Cycle

Adult female nematodes produce eggs that pass out of the host with the feces. Under optimal conditions in the external environment, first-stage larvae (L_1) can develop and hatch from eggs within 24 hours. L_1 grow and develop to second-stage larvae (L_2), which in turn grow and develop into third-stage larvae (L_3). In general, the third stage is the infective larval stage. After ingestion, L_3 develop into fourth-stage larvae (L_4), which then develop into immature adults. Sexually mature adult nematodes develop within 2 to 4 weeks after ingestion of the L_3 unless arrested development occurs. The life cycle of *Nematodirus* is the same except that development to infective L_3 occurs within the egg before hatching. For *Trichuris,* development to the infective L_1 occurs within the egg, which does not hatch until ingested by the animal. Approximately 8 weeks are required before sexually mature *Trichuris* are present.[1,3]

Climate and management of pastures and animals are among the numerous factors that influence the level and extent of parasitism. Although temperature is considered the driving force behind larval development, larval development can

proceed only in the presence of adequate moisture. Larvae of all stages can be killed by extremely low or high temperatures, desiccation, and/or direct sunlight. Larval development and transmission tend to occur in predictable seasonal patterns based in part on regional climatic differences.[1-4] In the southern United States, infective L_3 persist longest when conditions are cool and wet (October to May), but die off quickly during the summer after rain-induced liberation from the fecal pat.[5,6] Nematodes acquired by grazing cattle during the summer months come from eggs recently deposited on pasture. In the northern United States, infective L_3 may be on pasture year-round. Significant numbers of *Cooperia* and *Nematodirus* may be acquired for up to 12 months after deposition of eggs on pasture, with acquisition of fewer numbers for up to 24 months. Acquisition of low levels of *Ostertagia* can occur for at least 14 months after deposition of eggs. In subtropical climates, seasonality may be much less marked and pasture infectivity may follow the rainfall pattern. In arid climates, large numbers of larvae may be present on the pasture whenever local conditions permit lush grass growth.[2,7-9] Sufficient moisture, usually in the form of rainfall, is also of critical importance to transmission, to release larvae from the fecal pat and provide a film of moisture for migration onto vegetation.[1,4]

Not only can larvae survive on pasture, but some species can arrest development within the host. This usually occurs when adverse environmental conditions would decrease larval survival in the external environment. Best known for this phenomenon is *O. ostertagi*. In northern temperate climates, pasture larval populations peak in the summer and early fall, and L_4 tend to overwinter in the host, resuming development in the spring. In warmer climates with hot, dry summers, the highest numbers of infective larvae may be found in the late spring to early summer, and L_4 tend to oversummer in the host, resuming development in the fall.[2,10,11]

Pathophysiology

Of all the cattle nematodes, *O. ostertagi* has long been considered the most pathogenic nematode in temperate regions. The pathophysiology of ostertagiasis centers on the development of larvae within the gastric glands of the abomasum. As the larvae develop within the lumen of the glands, hyperplasia and intense eosinophilic infiltration occur. Mucosal glandular cells lose their differentiation, and cell junctions are weakened. Albumin is lost into the lumen. Parietal cells

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cease to function, causing a decrease in hydrogen chloride (HCl) production. The change in pH stimulates overproduction of gastrin, which initiates cell proliferation and hyperplasia. Alkalinity also decreases the bacteriostatic activity of the abomasum. When the pH exceeds 5, the conversion of pepsinogen to pepsin is inhibited. As a result, pepsinogen is released into the blood through permeable cell junctions. Initially, cellular changes occur within the parasitized glands, but as the glands distend due to nematode growth, the changes encompass the surrounding, nonparasitized glands as well. Widespread hyperplasia creates the typical “Moroccan leather” appearance of the abomasum. In experimental models, *Ostertagia* infection in calves is also associated with elevated peripheral eosinophil counts and decreased lymphocyte counts.[1,3,12]

Populations at Risk

Although infections with some GINs readily induce immune responses that limit future populations of nematodes within the gut, cattle remain susceptible to *O. ostertagi* for many months. Protective immunity is usually not evident without prolonged exposure and may not occur until the animals are 2 years of age or older.[1] Consequently, clinical type I ostertagiasis occurs primarily in young cattle (up to ≈18 months of age) during their first grazing season (primary exposure), and type II disease is present in older animals (2 to 4 years of age). Adult cattle, after the second grazing season, rarely show signs of nematode infection or require anthelmintic treatment. Although mature cattle ingest infective larvae, fewer larvae establish infections, so parasite numbers and the magnitude of fecal egg shedding are generally decreased. Most preventive and treatment strategies therefore are directed at young grazing stock, primarily beef calves and dairy replacement heifers.

Clinical Manifestations

In young animals, GINs may simply cause poor growth and ill thrift, or they may cause serious clinical illness and even death. Inappetence, a common feature of PGE, contributes to reductions in weight gain, growth, and possibly onset of puberty.

The synchronous development and maturation of inhibited larval *O. ostertagi* can result in severe clinical disease, called *type II ostertagiasis.* Usually seen in cattle months after their first grazing season on contaminated pastures, it is

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characterized by intermittent profuse watery diarrhea accompanied by thirst, anorexia, ill thrift, and hypoproteinemia. Fever, anemia, and submandibular edema may also be present. Conversely, *type I ostertagiasis* results from the rapid acquisition of large numbers of larvae that complete development to the adult stage within the usual 3-week time frame. The primary physiologic change is appetite suppression. Although the underlying mechanism for the two types is the same, the seasonal occurrence of each type varies in accordance with the epidemiologic patterns of the area.[1,3]

For both types I and II ostertagiasis, reduced feed intake and diarrhea have a negative effect on animal weight; however, leakage of endogenous protein into the gastrointestinal tract has greater impact on the loss of production. The need to replace these proteins (e.g., albumin, immunoglobulins) occurs at the expense of muscle proteins and fat deposition.[1,3]

Compounding the effects of *O. ostertagi* are the other GINs. Larval and adult *Haemonchus* parasites inhabit the abomasum and are avid bloodsuckers, capable of producing severe anemia. *T. axei* inhabits the abomasum, producing local and systemic changes like those produced by *O. ostertagi* with similar clinical signs. *Cooperia* species live in the small intestine, inducing tissue changes resulting in fluid, electrolyte, and protein losses and reduced feed intake. Infection with *Oesophagostomum radiatum* produces structural and functional changes, including anemia, hypoproteinemia, diarrhea, anorexia, and weight loss.[1,3,13,14]

Control of Gastrointestinal Nematodes

GINs affect ruminants in one of two ways—economically or clinically. Clinical disease is the manifestation of abnormal signs resulting in severe morbidity or mortality. In contrast, economic disease is the level of parasitism preventing an animal from reaching its genetic potential, which translates into loss of milk or meat production. Most parasite losses are economic rather than clinical.[1] The goal of any control program should be to decrease the chances of acquiring large numbers of GINs. Control programs must consider the expected species present, the environment, host nutrition, husbandry, and time of year. Given the higher stocking rates today versus 30 years ago, the concomitant reduction in alternative control practices, and the widespread availability of inexpensive, safe, and effective dewormers, maintaining acceptable levels of animal production in the face of GINs has relied heavily on the use of anthelmintics. Management, however, provides a much cheaper and more effective means for

controlling GINs than anthelmintics alone.[1,15,16]

Anthelmintics.

Anthelmintics and their doses used in cattle are given in Table 49.3. Animals benefit from the removal of the parasites, as well as from preventing immediate reestablishment of infections by those compounds with persistent activity. Macrocyclic lactones and benzimidazoles are currently the most popular compounds in use. Levamisole and morantel tartrate are less commonly used, and availability in some areas is limited. Drug withdrawal times must always be considered, and the manufacturers' recommendations must be followed.

TABLE 49.3

Efficacy of Various Anthelmintics Against Gastrointestinal Nematodes in Ruminants Without Resistance Issues

	Dose (mg/kg)[a]				Hypobiotic Larvae
Drug	**Sheep**	**Goats**	**Cattle**	**Adults**	
Benzimidazoles					
Albendazole	5–7.5	20	10	+	+
Febantel	5		7.5–10	+	±
Fenbendazole	5	10	5–10	+	±
Mebendazole	15–20			+	±
Netobimin	7.5		7.5	+	+
Oxfendazole	5		7.5	+	+
Oxibendazole	15		15	+	±
Levamisole, Morantel and Pyrantel					
Levamisole	5–7.5	12	5–7.5[b]	+	−
Morantel	5–12.5	10	10	+	−
Pyrantel	25			+	−
Macrocyclic Lactones					
Ivermectin	0.2	0.4	0.2[c]	+	+
Doramectin	0.2[d]	0.2[d]	0.2[c]	+	+
Eprinomectin			0.5–1.0[e]	+	+
Moxidectin	0.2	0.4	0.2[c]	+	+
Other Drugs					
Closantel	5–10			+[f]	−
Nitroxynil	10			+[f]	−

[a]All doses are for oral administration unless otherwise indicated.

[b]10 mg/kg for topical administration.

[c]0.2 mg/kg for oral, subcutaneous, or intramuscular administration; 0.5 mg/kg topically as a pour-on.

[d]Injectable not recommended for use in sheep and goats by injection or pour-on.

[e]0.5 mg/kg for topical administration; 1.0 mg/kg in extended-release formula for injectable administration; not recommended for sheep.

[f]Effective against *Haemonchus contortus* only.

+, Highly effective; ±, moderately effective or effective according to some authors; −, ineffective.

Note: Administration of some of these products may constitute extralabel use in sheep and goats; follow manufacturers' guidelines for meat and milk withdrawal in cattle; not all compounds are available in all countries.

Historically, anthelmintic-resistant GINs have been far less of a problem in cattle than in sheep or goats. Unfortunately, this situation has changed. Anthelmintic-resistant nematodes of cattle have been confirmed in the United States and elsewhere, with resistance reported in all classes of compounds currently available.[1,16-20] Species of *Cooperia,* which are the dose-limiting parasites for the macrocyclic lactones, are most commonly associated with these reports; however, resistant species of *Ostertagia*, *Haemonchus,* and *Trichostrongylus* have also been documented.[15-18] Regrettably, producer concerns regarding anthelmintic resistance remains secondary to the production benefits gained by their use.[21] Even where anthelmintic resistance is identified as a problem for the beef cattle industry, the preventive steps taken actually contribute to the selection for anthelmintic resistance alleles.[22] Such strict reliance on anthelmintics without regard for good pasture parasite management will lead to more rapid selection of nematodes with resistance alleles.

Producer concerns may also be influenced by the fact that *Cooperia* species are most commonly associated with anthelmintic resistance, and these species are considered of minor pathogenic importance.[1] Thus resistance in *Cooperia* would be a less severe problem than resistance in the highly pathogenic *O. ostertagi.* Recently, though, negative production effects associated with *Cooperia punctata* have been demonstrated,[23] as has an increased pathogenicity of an isolate of macrocyclic lactone-resistant *Cooperia oncophora*.[19] In addition, single-species infections are uncommon in cattle entering feedlots, and production losses where anthelmintic-resistant *Cooperia* was a component of the GIN population have been documented.[24]

Simultaneous administration of anthelmintics with a similar spectrum of activity but different mechanisms of action has been suggested as a means of providing GIN control in the face of single- or multiple-drug resistance while prolonging the effective life of available compounds. The expectation is that

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GINs surviving one anthlemintic will likely be killed by the second.[25,26] Computer simulation models also indicate that reversion toward susceptibility is more likely to occur when drugs were used in combination rather than in rotation.[27] Although combination anthelmintic products are available elsewhere in the world, licensure in the United States has not yet occurred.

Treatment Intervals.

The choice of drug and treatment interval should be formulated for an individual herd or farm, as part of an overall GIN control program. Factors to consider include the geographic location, time of year, and grazing management.[1] There are several options for preventing clinical disease and maximizing gains in first-season grazing calves using strategic anthelmintic treatments. It should be noted, however, that these recommendations reflect the practices currently in use and assume anthelmintic resistance is not an issue on the farm in question. Recommendations are based on the calendar in the northern hemisphere, and not all products are available in every country.

- *Prophylactic anthelmintic use*. (1) Two or three treatments between turnout and midsummer to minimize the number of eggs deposited on pasture. For calves turned out in early May, two treatments 3 and 6 weeks later are used. For calves turned out in April, three treatments at 3-week intervals are recommended. If using parenteral or pour-on macrocyclic lactones, the interval is extended to 5 (ivermectin) or 8 (doramectin, eprinomectin, moxidectin) weeks due to the residual activity against ingested larvae.[3,20] (2) Use of an intraruminal bolus at turnout or weaning. This provides either the sustained release of anthelmintic drugs or pulse release of therapeutic doses of anthelmintic at 3-week intervals.

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This strategy may be most cost-effective on farms where pasture infectivity is high. However, evidence suggests that young cattle protected with these products are more susceptible to infection in their second year at grass.[3] Likewise, the use of extended-release injectibles at turnout provides the ability to treat existing infections while preventing new infections with anthelmintic-susceptible GINs for approximately 120 days.[28]

• *"Dose-and-move" strategy.* This strategy consists of treating calves with a single dose of anthelmintic, then moving them to a "safe" pasture (risk of infection is low) just before the anticipated peak in pasture infectivity (e.g., early to midsummer in temperate climates). This strategy minimizes the number of anthelmintic treatments during the grazing season. However, it is effective only on farms where such pastures are available. Furthermore, any residual nematodes left behind will likely possess resistant genes; therefore contamination of the "safe" pasture will be with resistant nematodes. This must be considered when planning for the future use of the pasture (discussed later). Also, sufficient numbers of overwintering L_3 *O. ostertagi* may be present in the spring in some years, resulting in heavy infections and clinical disease.

• *Targeted strategic treatment.* This strategy relies on

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> the selective use of anthelmintics by targeting individual animals within a herd rather than using whole-herd treatments. Promoted for sheep and horses, this strategy has not been embraced by the beef cattle industry. However, a recent investigation of dairy cows indicates that selective treatment strategies can compete economically with whole-herd treatment strategies.[29]

Integrating effective pasture management can reduce the number of anthelmintic treatments necessary[1,30]; however, there currently is no realistic alternative to the continued use of available compounds in intensive production systems. Therefore it is imperative that the efficacy of these compounds be maintained for as long as possible. Recommendations designed to promote this in beef cattle include the following: (1) do not treat second-year (unless not previously pastured) or adult cattle to maintain a population of unexposed nematodes (refugia) on the farm; (2) do not graze first-year calves on the same pasture each year (avoids exposure to larvae produced from resistant nematodes); and (3) do not use the same family of anthelmintic year after year in calves.[31]

Adult Cattle.

In general, the cattle most at risk for clinical disease and production losses are beef calves and dairy replacement heifers in their first season at pasture.[2] Development of immunity should protect the animals during their subsequent grazing seasons. Treatment of adult beef cattle is generally unnecessary, unless immunity is inadequate or pasture infectivity is exceptionally high. Anthelmintic treatment may be warranted in first-calf heifers and newly acquired cows that may not have been pastured as heifers. In some situations it may be beneficial to treat beef cows after spring calving. Despite these recommendations, a recent survey showed that approximately 86% of U.S. beef cow and calf producers routinely treat their cows one or more times per year.[22] Benefits of treating adult dairy cattle depend on a variety of factors, including grazing management

options and levels of GINs.[1,27]

Other Strategies.

Alternate grazing of cattle and sheep is promoted as an effective control measure. Ideally, a 3-year rotation of cattle, sheep, and crops is used. Few GINs cross-infect cattle and sheep. Adding this to the infective L_3 life span on pasture of less than 1 year, this scheme could provide good control of bovine ostertagiasis. Annual rotation of beef cattle and sheep in marginal areas has been reported to provide adequate parasite control.[3] However, in areas where *Haemonchus* is prevalent or where *Haemonchus contortus* cycles in cattle,[15,17,24] co-grazing these two species may be dangerous. Rotational grazing of calves with adult cattle has been shown to be an effective control practice.[2,3]

Vaccination for the control of *O. ostertagi* has been an ongoing area of research for many years with mixed results.[32,33] Given that it has taken more than 20 years for development of a commercially available vaccine against *H. contortus,* it is unlikely that a viable *O. ostertagi* vaccine will come to market in the near future.

Evaluation of Control Programs.

Success of control programs is based on the producer's expectations. Because most control programs are based on anthelmintic use, the response to treatment is the criterion by which control programs are currently evaluated.[15,22] As long as animal production meets producer expectations, the control program is considered to be a success. Fecal egg counts are most useful as a tool to evaluate pasture contamination and assess treatment efficacy; however, most U.S. producers do not have this done. In fact, most cow and calf producers do not even involve a veterinarian in the diagnosis or treatment of PGE.[22]

Lack of expected response to anthelmintic treatment may be the first indication of program failure in the form of a resistance problem.[15,17] However, inappropriate administration or underdosing of the anthelmintic may also be responsible, and determining the root cause of the treatment failure is vital for future control efforts. Detection of anthelmintic resistance currently depends on the FECRT. This test only detects clinical resistance or when less than an expected response to treatment occurs. This usually occurs only when the frequency of resistant alleles in the population reaches 25%.[34] The FECRT

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estimates anthelmintic efficacy by comparing pretreatment and posttreatment fecal egg counts. Fecal samples are collected immediately before or at the time of treatment and then 10 to 14 days later. Although guidelines for using FECRT in cattle were proposed in 1992, they lack detail, particularly in interpretation of data.[19,35] Comparing FECRT with controlled efficacy studies showed FECRT results to be reliable for detecting ivermectin-resistant *C. oncophora* and *O. ostertagi* and moxidectin-resistant *O. ostertagi*. However, due to reduced fecundity of moxidectin-resistant female *C. oncophora*, FECRT results were equivocal, with day 7 results showing efficacy but day 14 results indicating resistance.[36] Thus, for cattle, waiting the full 14 days before collection of the second sample is vital. A method for using composite fecal samples in the FECRT has been described with the aim of reducing costs to the producer; however, it still requires the collection of individual fecal samples.[37] Because cattle tend to have lower fecal egg counts than sheep, use of appropriate flotation techniques capable of handling low fecal egg counts is important.[1]

Clinical Management

Diagnosis.

Antemortem diagnosis of ostertagiasis in young animals is primarily based on clinical signs of inappetance, weight loss, and diarrhea at a time of the year that is consistent with the parasite's epidemiology.[3] In temperate areas, type I disease usually occurs in fall, and type II occurs in the late spring. Grazing history is important because clinical disease can develop in older animals that have not previously grazed pastures. Affected farms usually also have a history of previous outbreaks. Plasma pepsinogen levels are useful in animals up to 2 years old; however, the test is less reliable in older cattle.[1]

The most reliable method for diagnosis of ostertagiasis or PGE is necropsy. The “Moroccan leather” abomasal lesion is pathognomonic for *Ostertagia.* For PGE, casual examination of the lumen of the gastrointestinal tract is unlikely to find any of the strongyle-type nematodes because the worms are small and easily overlooked. Adult *Nematodirus* are larger and may be more readily seen, but alone they are unlikely to be the cause of PGE. Nodules associated with larval *Oesophagostomum* can be found in the wall of the lower small intestine, as well as the upper large intestine, and adults can be found in the contents of the large

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intestine. *Trichuris* will be partially embedded within the cecum; removing the contents is necessary in order to see them. Abomasal wall digestion techniques can be used to identify the presence of larval *Ostertagia*.[2,3]

Treatment.

Animals with type I ostertagiasis can be expected to respond well to treatment with the standard dose of any of the current anthelmintics, as long as resistance is not an issue. These animals should also be moved to a less contaminated pasture. Because any parasites not removed by proper administration of the drug will have resistance alleles, targeted strategic treatment, rather than whole-herd treatment, may be beneficial in keeping the population of resistant nematodes low.

Successful treatment of animals with type II ostertagiasis requires compounds that are effective against arrested larvae, as well as the developing larvae and adults. Only the modern benzimidazoles and macrocyclic lactones are effective at standard doses. Even though the larvae may be killed, the damage to the abomasal mucosa may limit complete recovery. Animals with profound hypoproteinemia and dehydration respond poorly compared with those showing only mild diarrhea and slight hypoalbuminemia. Severely affected animals may need supportive treatment to survive. Recovered animals often fail to thrive.

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Gastrointestinal Nematode Infections in Sheep and Goats

Sherrill A. Fleming

Gastrointestinal nematode (GIN) infections in sheep and goats are responsible for severe clinical syndromes and profound production and death losses. Young animals, periparturient ewes and does, and animals on substandard planes of nutrition are most susceptible to outbreaks of parasitic disease. The GINs of small ruminants include *H. contortus, Teladorsagia circumcincta* (formerly *Ostertagia*), *T. axei, Nematodirus* spp., and *Cooperia* spp.[1] The proportions of each of these nematodes in small ruminant populations vary according to geographic location. *H. contortus* is usually the most significant pathogen in wet, temperate climates such as the southeastern United States. *T. circumcincta* may be the predominant infection in northern or arid climates such as England. *H. contortus* and *T. circumcincta* represent the majority of parasite burdens seen in small ruminants.[2] Anthelmintic resistance is present in all these parasites, but the prevalence is highest for *H. contortus,* making it the most economically important GIN of sheep and goats.[3]

The problem of anthelmintic resistance in GINs of small ruminants has been reported in South Africa, Australia, New Zealand, Malaysia, Spain, France, Denmark, the United Kingdom, Brazil, and the United States.[4-7] In the United States, resistance to all classes of anthelmintics has been documented.[5,7] Resistance to two and three classes of anthelmintics was found on 14 of 15 farms and 6 of 18 farms, respectively, in a survey of 18 goat flocks in Georgia and South Carolina.[5] The first report of total anthelmintic failure was made on a meat goat farm in Arkansas in 2005.[7] It is no longer acceptable to plan parasite control programs solely on the basis of the use of anthelmintics. Veterinarians and producers must customize programs to control exposure to infection and reduce the use of anthelmintics. A thorough knowledge of the biology of GINs is necessary to plan effective control programs.

Life Cycle and Epizootiology[8,9]

The life cycle of a GIN is direct and consists of a host phase and a free-living

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phase. Worms mate in the host, and females lay eggs that pass in the feces. Eggs hatch and develop to infective larvae while remaining in the fecal mass. Infective larvae then move from the fecal mass onto the surrounding forage, where they can be consumed during grazing, thus completing the cycle. The time from ingestion of infective larvae to egg-laying adults, the prepatent period, is about 3 weeks. The time for development from egg to infective larvae can be as short as 4 to 10 days (especially during the summer months); therefore transmission (reinfection) and continual pasture contamination can be rapid. During the colder months, development is delayed and may take 1 to 2 months to reach the infective larvae stage, so pasture contamination and reinfection are minimized. The infective larvae have a protective sheath, making them relatively resistant to adverse environmental conditions, and they can survive for months, thus extending transmission potential. As long as the temperature and moisture conditions remain favorable, development and survival continue; conditions that are too hot, too cold, and/or too dry threaten parasite survival.

The life cycle of a GIN has four phases.

Phase 1—Symbiotic/Parasitic Phase.

Phase 1 is the interaction between host and parasite. During this phase, the parasite must develop and survive in the host. After ingestion, infective larvae lose their protective sheath and invade the mucosa of the abomasum, small intestine, or large intestine depending on the GIN species involved. While in the mucosa, larvae develop to the next larval stage and then return to the surface of the gut mucosa, where they become adult worms. The host defense mechanism is immunity. When the infectious agent enters the body, the immune system reacts to mobilize various components (antibodies, killer cells, etc.) to inhibit or kill the invaders. These components act on larval stages in the mucosa and the adults in the lumen. The strength of the immune response depends on the age of the host, nutritional status, and concurrent stressors. The immune system matures with age with young naive animals susceptible to infection and older animals more resistant. As a result, young animals usually harbor the highest GIN populations and suffer the most severe consequences, whereas adult animals have lower infection levels. Under poor nutrition and/or stressful conditions, the immune system is compromised and cannot respond adequately, regardless of the age of the animal.

The prepatent period of most worms is about 3 weeks, but this period can be extended for worms that can enter a period of delayed development called

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hypobiosis. This occurs during the season of the year when the environmental conditions are unfavorable for development and survival of the free-living larval stages. Depending on the worm and the environment, this happens during either summer or winter.

Phase 2—Contamination Phase.

Phase 2 involves eggs being passed in the feces. The magnitude of this phase is affected by stocking rate, age of the animals, season of the year, and hypobiosis. The higher the stocking rate, the more feces are deposited on the grazing area, thus the more eggs are passed, and vice versa. More eggs are also passed from young versus older animals. Most worms have a definite seasonality, resulting in higher egg production and deposition during different times of the year. Of particular note is the periparturient rise (PPR) in fecal egg count (FEC). This occurs at or around parturition and extends through most of the lactation period because these are stressful conditions when the dam's immune system is compromised. The existing female worms increase the number of eggs deposited in the feces. If a worm species undergoes hypobiosis, the development time to the adult stage is extended. This will result in fewer adult worms over time and fewer eggs deposited in feces. However, when these hypobiotic larvae resume development, massive numbers become mature adults over a short period of time, and the resultant egg production and deposition in the feces can be high.

Phase 3—Free-Living Phase.

Phase 3 involves larval development and survival, which depend on prevailing environmental and nutritional conditions. The development and survival from egg to L_1, then to L_2, and finally to L_3 or infective larvae occur within the fecal mass. L_1 and L_2 are unprotected and require oxygen and energy (feeding on nutrients and microorganisms) to grow. L_3 are enclosed in a protective sheath and do not feed. Temperatures conducive for normal development and survival are between 65° and 85° F. With lower or higher temperatures, development and survival are reduced. Moisture is also crucial for development and survival. Because the initial development and survival occur within the fecal mass, moisture is usually adequate to allow development to the infective larvae; however, if the fecal mass dries out quickly due to high temperatures and/or physical disruption of the fecal mass, the L_1 and L_2 are susceptible to desiccation and will die. Generally, L_3 can survive very low temperatures, but sustained

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temperatures above 95° F are usually lethal. When infective larvae migrate out of the fecal mass, they are relatively resistant to environmental conditions encountered due to their protective sheath. Temperature is usually the only factor that may adversely affect L_3. The moisture conditions at ground level under forage cover are usually adequate for L_3 to move around and survive. Because they do not feed, length of survival depends on how fast they use energy reserves. The hotter it is, the faster they move and use up energy stores, which decreases survival. Infective larvae move up and down the forage when there are moist condiitons (i.e., advancing and receding dew). Rain also provides a moisture medium for larval movement on forage. For the most part, infective larvae do not move much past 30 to 50 cm from the fecal mass or 5 to 6 cm up the forage. Therefore the lower the animals graze and the closer they are to the fecal mass, the greater the consumption of L_3.

Phase 4—Infection Phase.

Phase 4 occurs when available L_3 are consumed during grazing. This phase is affected by stocking rate in two ways. The stocking rate determines how many eggs initially contaminated the pasture and, consequently, how many L_3 will be available to consume. If the initial contaminating animals are removed and replaced by new animals, the new stocking rate will determine the level of exposure each animal has to infective larvae during grazing (i.e., the higher the stocking rate, the more chance of exposure, and vice versa). Grazing animals usually do not graze close to fecal masses, so the greater the distance between masses, the less the exposure. Eventually fecal masses disintegrate, forage grows well with the fertilization, and animals will graze over the area where exposure can be high. Natural sources of water, such as streams, ponds, or lakes, provide moisture along the banks, where forage can grow readily. When animals congregate to drink and consume the attractive forage, defecation in these areas usually leads to increased contamination and eventually to more L_3. Essentially, a high stocking rate has been artificially created in a relatively small area. The same can be said for areas where supplements, especially hay, are fed if conditions are favorable. Once L_3 are consumed, phase 1 is repeated.

Pathophysiology of Gastrointestinal Nematode Parasites

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The damage done by *H. contortus* is the result of the blood sucking by L_4 and adult parasites. The pathogenesis of *Teladorsagia* in sheep is similar to that described for *Ostertagia* in cattle and is a result of destruction of abomasal mucosa. *T. axei* causes abomasitis, whereas *Trichostrongylus colubriformis* and other *Trichostrongylus* spp. penetrate beneath the duodenal mucosa and result in generalized enteritis, including hemorrhage and plasma protein loss into the intestinal lumen.

Clinical Signs of Gastrointestinal Nematode Parasites

Most animals acquire mixed infections of nematodes. Clinical signs may therefore reflect the effects of more than one species of parasite. There appears to be some synergism between *T. circumcincta* and *T. colubriformis,* which makes the effect of the combined infection more severe than that of either alone. Although mixed infections with GINs are assumed, the actual population of parasites in small ruminants varies depending on the geographic location. In general, most clinical illnesses results from *H. contortus* infections. Most parasitic infections in small ruminants are associated with altered gut function, anorexia, ill-thrift, weight loss, and hypoproteinemia. Diarrhea is a variable sign (black scours). Animals may die suddenly without overt clinical signs or may exhibit chronic wasting. Clinical signs of *H. contortus* infection can vary from peracute to chronic and result from decreased nutrient use and anemia/hypoproteinemia. The most common signs are failure to thrive, weight loss, and decreased appetite. Weakness, bottle jaw, pale mucous membranes, poor capillary refill time, and possibly diarrhea develop with more severe or long-term infections. Following sudden exposure to large numbers of L_3, animals can die acutely, even before the infection is patent. Other diseases such as pneumonia and heat stress may result secondarily.

Anemic Crisis and Patient Management

The anemia created by *H. contortus* is due to blood consumed by the parasite and is usually chronic. Parasitized patients present with lethargy and weight loss and often have hematocrits of less than 10%, yet many are still capable of rising and walking. Addressing the anemia by blood transfusion must be weighed carefully against stress to the patient caused by restraint, jugular catheterization,

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and blood administration, as well as by the hemolysis of these same cells several days later. Obviously, in life-threatening circumstances (a patient unable to stand), administration of whole blood can be critical. In a chronic situation (patient rising and/or eating), treatment with an effective anthelmintic should eliminate the parasite and halt blood loss. Because *H. contortus* consumes blood, the affected animal actually loses substrates essential to erythrocyte production (iron, cobalt, copper). Providing supplemental iron and B-complex vitamins should speed reversal of the anemia. Assuming blood loss has been halted, a 1- to 1.5-point rise in the hematocrit per day is expected when the bone marrow is maximally stimulated. In most parasitized patients, a rise of one half of this value is a more realistic expectation.[10]

If blood is to be given, it is essential to be certain that the donor has a normal packed cell volume (PCV). Blood collected from animals in the same environment may be as anemic as the patient, but the individual is more capable of dealing with the anemia. In lambs weighing less than 45 kg, 1 unit of whole blood (≈450 mL) is often sufficient to survive a crisis, provided *H. contortus* has been controlled.

Populations at Risk

Young animals are most susceptible to infection and clinical manifestations of disease. Lambs and kids may become heavily infected with parasites and shed large numbers of nematode eggs. In sheep, some degree of immunity develops as the animal approaches 1 year of age. Adult animals typically have complete immunity against *Nematodirus* and variable resistance to *Trichostrongylus* spp. Some immunity to *Haemonchus* and *Teladorsagia* spp. develops with age; compared with lambs or kids, adults are more resistant to infection with these species. However, even mature animals may succumb to parasitic infection when malnourished or challenged with heavily contaminated pasture. A periparturient rise in fecal egg production is seen in ewes and does.

Goats are more susceptible to GIN infections than are sheep. The difference lies in part in the host's immunologic responses to nematode antigens. Goats prefer to browse on brush and trees and only graze grass when forced to by management. Under natural conditions, goats would have a low level of exposure to infective larvae, and this may explain their lower level of natural immunity compared with sheep.[11,12]

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Refugia

Most parasitologists now consider levels of refugia (see Parasite Refugia section earlier) as the single most important factor in selection for anthelmintic-resistant parasites.[13,14] Worms in refugia provide a pool of genes susceptible to anthelmintics, thus diluting the frequency of resistant genes. For many years parasitologists and veterinarians have recommended that all animals on a premise be treated with an anthelmintic at the same time. However, this strategy has proven problematic, and a selective approach is now recommended. Only those animals in danger of severe parasitism should receive medication. This selective approach is highly compatible with host-parasite dynamics because 20% to 30% of animals harbor about 80% of the parasites.[15] Animals with low worm burdens are an important source of refugia, are not in danger of the negative effects of parasitism, and should not be treated.

Management of Gastrointestinal Nematodes in Small Ruminants

The traditional approaches of deworming often, rotating class of anthelmintics, and moving to clean pastures has ensured development of anthelmintic resistance to all classes of drugs and disseminating these resistant parasites over a wide area. It is obvious that drastic changes in the management of GIN in sheep and goats are long overdue. Several countries have developed websites and/or companies that make recommendations for specific geographic areas.[16] WormBoss in Australia and SCOPS in Great Britain are two good examples that attempt to give specific management advice.[16,17] A New Zealand company sells a system of record keeping and testing complete with a computer system for keeping farm records.[18]

FAMACHA or Smart Drenching Method.[19]

To maintain adequate levels of refugia, it is necessary to leave a portion of the herd or flock untreated. FAMACHA is a selective approach for *H. contortus* that targets the portion of the herd or flock with high worm burdens, including those animals that are poorly resilient to worm infections.[20] This approach will successfully control parasites in the entire group and delay the development of anthelmintic resistance. Failure to observe animals closely for clinical signs may

result in the death of some individuals. It is necessary to know which anthelmintics are effective before beginning this system. The differences among farms in overall quality of management, stocking rates, breeds of animals, preexisting levels and spectrum of anthelmintic resistance, presence of nematode species other than *H. contortus*, and production targets need to be considered before implementing FAMACHA on individual farms. This system was developed in South Africa for identifying sheep that are anemic, and it has been extended to use in goats.[21] In this method the ocular mucous membranes of sheep and goats are categorized by comparison with a laminated color chart bearing pictures of sheep conjunctivae classified into five categories ranging from red (A/1; normal) to practically white (E/5; severe anemia). Because anemia is the primary pathologic effect from infection with *H. contortus*, this system can be an effective tool for identifying animals that require treatment (but only for *H. contortus*). FAMACHA has been tested extensively and validated in both sheep and goats in South Africa and in the southern United States.[22,23] In all studies, the numbers of false negatives were low, suggesting that when using FAMACHA according to recommended guidelines, death from anemia would be rare.

Based on the results of recent studies in the United States and numerous studies performed in South Africa, guidelines for using FAMACHA have been developed, and it is suggested that these guidelines be read in their entirety before FAMACHA is practiced.[20] Individual animals are scored 1 to 5 by comparing their mucous membrane color with a laminated chart. It is recommended that treatment be withheld until animals score a 4 or 5 as long as animals are in good body condition and good overall general health, animals are examined frequently (e.g., every 2 weeks), and good husbandry is used to identify animals in need of treatment (e.g., unthrifty, anorexic, lagging behind, bottle jaw) between FAMACHA examinations. Using this approach, the number of anthelmintic treatments administered will be reduced greatly, resulting in significantly diminished selection pressure for resistance and therefore a reduction in drug costs. Due to the increased handling of animals, labor costs will be increased. *Only adult animals should be managed with this system.* Lambs and kids have comparatively small blood volumes, poor immunity, and poor resilience and can progress rapidly from moderate to severe anemia. This precaution should also be extended to ewes and does during the periparturient and early lactation period because these animals have decreased immunity to GINs.[19,24-26] These and other animals that may be stressed by disease or in poor

body condition should always be treated if scored as 3. Alternatively, in the northern parts of the country where *H. contortus* is an important problem but resistance prevalence is much lower, it may be reasonable to be more liberal when making treatment decisions (i.e., treat all 3, 4, and 5). Many more treatments are given when all animals with scores of 3 and higher are dewormed, but a significant number of animals will remain untreated to supply refugia. These refugia combined with a relatively short transmission and treatment period are likely to produce a slow evolution of resistance, but the more intensive treatment protocols will improve animal productivity.

On farms where low to moderate levels of resistance have been diagnosed to one or more drugs (60% to 90% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these "less effective" drugs either singly or in combination on all animals scored as 3. There is evidence that using dewormers with different modes of action in combination has greater efficacy and does not cause a more rapid development of resistance.[27] Using drugs that are less effective in this group is unlikely to lead to clinical problems because the few 3 scores that are moderately anemic and in need of treatment should receive a sufficient reprieve from infection until the next FAMACHA examination, and the majority of the 3 scores that are not anemic do not need to be treated. This strategy helps to preserve the efficacy of the drugs that are still fully effective by saving them only for the 4 and 5 categories and also helps to decrease egg contamination of pastures.

Training of producers is critical when using this method. It is the responsibility of veterinarians and other animal health professionals to ensure that standards of training are maintained by using the "Train the Trainer" seminars through the American Consortium for Small Ruminant Parasite Control (ACSRPC, formerly Southern Consortium or SCSRPC) at www.acsrpc.org or www.wormx.info. When using FAMACHA, it is extremely important that efficacy of anthelmintics is known because animals are not treated until they become anemic. Treating anemic animals with a drug that has moderate to poor efficacy due to worm resistance may result in animal deaths. Other important precautions when using FAMACHA include but are not limited to (1) the card is an aid in the control of *Haemonchus* spp. only; (2) the system should be used by producers only where technical assistance is available from a veterinarian or other animal health professional; (3) other management-based worm control practices must be maintained; (4) smart drenching principles should be used; (5) paleness or reddening of the conjunctivae may have other causes; (6) animals

should always be scored with the help of the chart, not from memory; (7) animals are examined at least every 2 to 3 weeks at the beginning of the expected period of *Haemonchus* spp. challenge in climates where a seasonal incidence of infection occurs, and during critical periods weekly examinations may be necessary; (8) the card is protected from light when not in use and replaced after 1 year of use.[4,28]

Maintaining records of treatments that are included with the FAMACHA kits gives the owner the ability to rate the genetic merits of individuals on the premises. Host resistance to infection with *H. contortus* measured on the basis of FEC and PCV is a moderately heritable trait, and it has been demonstrated that the same animals tend to exhibit the highest FEC and lowest PCV on each occasion they are measured.[29-31] Importantly, data from recent investigations examining the heritability of resistance and resilience of Merino sheep to infection with *H. contortus* indicate a high heritability for the clinical estimates of FAMACHA scores.[22] Removing the most susceptible animals from the breeding pool each year will have the long-term effect of improving the overall innate genetic resistance and/or resilience of the herd or flock to *H. contortus*.

Five-Point Check.[32]

Because FAMACHA is based on anemia and focuses on parasitism by *H. contortus*, a combined system that could identify problems with a variety of other potentially pathologic parasites (*Oestrus ovis*, *Teladorsagia* spp., *Trichostrongylus* spp., *Nematodirus* spp., and *Oesophagostomum columbianum*) has been proposed. This is the Five-Point Check, which includes checking for nasal discharge, submandibular edema, back body condition scoring, and fecal staining of perineum in addition to ocular membrane color. Anthelmintic recommendations were made based on the points that identified poor scores. Pilot studies showed good acceptance and usefulness of this system, but further studies need to be completed to determine the efficacy and economy of this approach.

Grazing Strategies.

The goal of pasture management is to provide safe pastures for grazing by reducing the exposure of susceptible hosts to infective larvae.[33,34] A safe pasture is one that has had no sheep or goats grazed on it for 6 months during cool or cold weather or for 3 months during hot, dry weather. Weaning sheep and goats

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at 2 months of age and rotating them through pastures ahead of the adults while forage is longer will minimize the exposure of susceptible animals to infective larvae. Pastures should be subdivided into smaller lots to allow longer rest periods between grazings. Pastures that are overgrown provide a good environment for larval survival because ultraviolet light and dry conditions are effective in killing larvae. Keeping pastures clipped will also assist in weed and parasite control and improve forage quality. Short-duration grazing carries pasture rotation to a level that maximizes forage production and harvesting by controlled animal grazing. It is management intensive but can be effective in controlling parasite burdens. Tilling and reseeding heavily contaminated pastures will convert them to safe pastures and provides an opportunity to improve the forage quality. Taking a cutting of hay from a pasture assists in reduction of infective larvae, but one report indicates GINs and tapeworms developing in "worm-free" lambs after feeding hay from heavily infected pastures. During the most dangerous part of the grazing season, it may be necessary to dry lot the flock and feed hay and grain from elevated feeders.

Stocking rate is an important consideration in parasite control because it affects the exposure to infective larvae and the contamination of the pasture. It is impossible to make a general recommendation on stocking rate because this will vary according to the type of pasture, time of year, current weather conditions, and type of animal being grazed. Thumb rules include five to seven goats or five sheep being the equivalent of one cow and suggest five to seven goats per acre. Goats prefer to browse brush and trees, whereas sheep prefer to graze near the ground. Pasture management must include monitoring the condition of herbage to ensure that overgrazing does not occur and to maintain a productive pasture.

In the early spring or at the onset of the rainy season, reduced pasture contamination is the most important aspect of control. The ewe or doe in the periparturient relaxation of resistance, even if she has the genetic capacity for resistance, will be a source of eggs for the environment. Strategic deworming to remove arrested or recently emerged larvae before they contaminate the pasture will have a great impact on pasture contamination. Treatment 2 weeks after a rain that removes recently acquired worms before they can begin passing eggs will also decrease pasture contamination. Providing sufficient dietary protein is vital during the periparturient period and during rapid growth so that animals will tolerate the worm burden better, as well as increase resistance to infection.[35-37] A strong link between nutrition and parasitism has been illustrated between protein intake and resistance to GIN infection. The most dramatic has

been the abolishment of the periparturient egg rise in lambing ewes by providing protein at 130% of requirements. Immunity is closely related to protein repletion. GINs increase the demand for amino acids by the sheep. Lambs will voluntarily select a higher protein diet when infected with GINs compared with uninfected lambs. There is conflicting documentation that sheep will decrease feed intake when initially infected with GIN. Some authors hypothesize that the decrease in intake may be due to stimulation of the immune system or that the host is becoming selective in its diet.

Pastures may be used for hay cropping and grazed during the last half of the grazing season to effectively reduce GIN challenge. When plants high in condensed tannins are grazed, incoming larvae are adversely affected, and these plants provide bypass protein for the host.[38-40] There is growing evidence in work from New Zealand and Europe that grazing or feeding of plants containing condensed tannins (CTs) can reduce FEC, larval development in feces, and adult worm numbers in the abomasum and small intestine. Preliminary tests with *Sericea lespedeza* (also known as *Lespedeza cuneata*), a perennial warm-season legume, have shown positive effects of reduced FEC in grazing goats, and in sheep and goats in confinement when the forage was fed as hay. In addition, an effect on reducing worm burden has also been reported. *S. lespedeza* is unfortunately considered to be an invasive exotic species in the United States. Similar results have been observed using quebracho extract for small intestinal worms, but not abomasal worms. In addition to its potential use in controlling worms, *S. lespedeza* is a useful crop for limited resource producers in the southern United States. It is adapted to hot, dry climatic conditions and acid, infertile soils unsuitable for crop production or growth of high-input forages, such as alfalfa. It can be overseeded on existing pasture or grown in pure stands for grazing or hay. In addition to hay, *S. lespedeza* is being evaluated in the form of meal, pellets, and cubes to be fed as a supplement to grazing animals, or as a deworming method under temporary short-term confinement. The physical structure of some plants may challenge larvae to ascend vegetation or may provide protection from adverse pasture conditions. If animals are allowed to browse, their chances of acquiring larvae diminish as the distance from the ground increases. Most infective larvae are found within 2 inches (50 mm) of the soil surface.

Alternate grazing or co-grazing with other species of livestock may harvest *Haemonchus* larvae from the pasture. Small ruminants can graze after cattle, and this is considered a safe pasture, assuming adequate parasite control in the cattle.

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For the most part, each livestock species harbors its own parasite fauna except for overlap between sheep and goats. Only *T. axei*, a minor abomasal worm, is found in all livestock species. In general, the *Haemonchus* in sheep and goats do not do well in cattle, and vice versa. However, some populations of *H. contortus* may thrive in calves. If practical, cattle and small ruminants can be grazed together where each consumes the parasites of the other, which reduces available infective larvae for the preferred host species.

Anthelmintic administration should be coordinated with the weather. During hot, dry weather, there will be little or no exposure to L_3. As soon as there is significant rainfall (0.5 to 1 inch), larvae exposure goes up exponentially as previously inactive larvae become active and new larvae are hatched. Producers should be trained to plan deworming within 3 weeks of significant rain after a dry spell. Similar strategies can be used during cool weather. Once ambient temperatures drop below 50° F, the flock can be dewormed and no further treatments are necessary until temperatures become favorable to larval development and activity.

Alternative Therapies

1. *Copper oxide wire particles (COWPs)* have been marketed for years as a supplement for livestock being managed in copper-deficient areas.[41] COWPs come in adult cattle, calf, and ewe boluses (25, 12.5, and 4 g, respectively). Only the cattle boluses are available in the United States. Due to potential toxicity in sheep, only one dose per year is recommended. It is also well known that copper has some anthelmintic activity against abomasal worms but not other gastrointestinal worms. That makes COWP a narrow-spectrum product. However, in view of anthelmintic resistance by *H. contortus*, recent work has revisited the possibility of using COWP to specifically target *H. contortus*. Such work has shown that as little as a gram or less and 2 g may remove substantial numbers of *H. contortus* in lambs and ewes, respectively. Similar work in goats has not been tested adequately to establish what is needed, but similar doses may be appropriate. As mentioned, copper must be used cautiously in sheep because toxicity can develop due to liver accumulation. Toxicity may not be an issue in goats because they have been reported as not being as sensitive to excess copper intake. Thus higher doses and/or more treatments during haemonchosis season

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may be useful in goats.

2. *Other nutritional considerations* include phosphorus, cobalt, and molybdenum.[42] Supplementation with phosphorus has been shown to prevent worm establishment. Cobalt deficiency has also been associated with reduced immunity to GINs. The addition of molybdenum at 6 to 10 mg/day decreased worm burdens in lambs. This effect was not attributable to the expected copper deficiency. Molybdenum may have a role in increasing jejunal mast cells and blood eosinophil numbers.
3. *Nematode-trapping fungi* included in feed or supplements have demonstrated potential for biological control of the free-living stages of GIN parasites under experimental and natural conditions.[43-45] These fungi naturally inhabit soil throughout the world where they feed on a variety of free-living soil nematodes. These fungi capture nematodes by producing sticky traps on their growing hyphae. Of the various fungi tested, *Duddingtonia flagrans* possesses the greatest potential for survival in the gastrointestinal tract of ruminants. After passing through the gastrointestinal tract, spores germinate and looped hyphae trap the developing larval stages in the fecal environment. This technology has been applied successfully under field conditions and is an environmentally safe biological approach for control of worms under sustainable, forage-based feeding systems. The major drawback is that the fungal spores must be fed daily. Daily feeding, which ensures that all animals consume an equivalent amount of feed, is necessary. For adequate control of larvae during the transmission season, spores must be fed for a minimum of 60 days. This can be expensive and time consuming. A bolus prototype that would allow a single administration where spores would then be slowly released over a 60-day period is being developed. This product is not available in the United States at this time.
4. *Vaccines* have been explored for management of the negative consequences of parasitism.[46-48] Successful vaccines have been developed for lungworms in cattle and tapeworms in sheep. The most promising vaccine for small ruminant worms has been what is called a “hidden gut” antigen and specifically targets *H. contortus*. This antigen is derived from the gut of the worm, and when administered to the animal, antibodies are produced. When the worm ingests blood during feeding, it also ingests these antibodies. The antibodies then attack the

target gut cells of the worm and disrupt the worm's ability to process the nutrients necessary to maintain proper growth and egg production. This vaccine is currently available in Australia and has been shown to alleviate losses from *H. contortus* in sheep when used according to directions (Barbervax®). Multiple vaccinations are required prior to and during the active parasite season.[49] There are also reports of successful use in goats.[50,51] Vaccines for other worms that do not feed on blood have focused on using antigens found in worm secretory and excretory products. Protection has been variable, and marketing of such products has not been pursued.

5. *Genetic improvement in resistance* to nematode infection is most likely based on inheritance of genes that play a primary role in expression of host immunity.[52-54] Based on survival of the fittest management conditions, several breeds around the globe are known to be relatively resistant to infection. Such breeds include Scottish Blackface, Red Maasai, Romanov, St. Croix, Barbados Blackbelly, and the Gulf Coast Native. Katahdin sheep have been considered more parasite resistant, but studies to document this are few and not conclusive. Using such breeds exclusively or in crossbreeding programs would certainly lead to improved resistance to worm infection, but some level of production might be sacrificed. Selection of more resistant stock can be accelerated by identifying sires that produce relatively resistant offspring. Computer programs have been used in New Zealand and Australia to rank sire genetics based on resistance to GIN infections, but change takes up to 8 to 10 years. Heritabilities for FEC, a common measurement for assessing parasite burden, range from 0.22 to 0.40, which is relatively high. Thus selection for resistance using a measurement such as FEC has been moderately successful.
6. *Replacement of resistant nematodes with susceptible parasites.* Genomic studies and identification of resistance genes are working on inserting susceptible genes to create susceptible populations that can be introduced to contaminated pastures to compete with resistant parasites.[55-58]

Anthelmintic Use.

Anthelmintics have deliberately been left to the end of this section because drugs

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cannot be considered the most important aspect of a parasite control program. Guidelines for drug dosages are contained in Table 49.3. At this time, only oral administration of anthelmintics is recommended in small ruminants. In general, goats require 1.5 to 2 times the dosages of sheep, with the exception of levamisole, due to more rapid gastrointestinal transit times. It is critical that producers accurately assess weights of individual animals and dose appropriately. If an approximate dose is going to be used in all animals, that dose should be for the heaviest animal in the group.

The challenge of anthelmintic resistance is life threatening in small ruminants. There is no point in repeatedly deworming with expensive drugs if that drug is no longer effective. See the following section, Evaluation of Parasite Control Programs, for information on detecting anthelmintic resistance. On farms where low to moderate levels of resistance have been diagnosed to one or more drugs (60% to 95% reduction in FEC), a useful strategy to help gain the full benefits of both treatment and resistance prevention could be to use these “less effective” drugs either singly or in combination. Drugs in the benzimidazole family may be effective if multiple-day dosing regimens are used.

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Evaluation of Parasite Control Programs

Sherrill A. Fleming

The efficacy of a given parasite control program should not be assumed; it should be assessed on a regular basis. The routine performance of quantitative tests for parasite burdens allows veterinarians to identify the development of anthelmintic resistance. Although fecal flotation is useful in identifying the presence of parasites, the use of the McMaster technique allows an estimation of the numbers of parasites. Both procedures are relatively simple and can easily be performed in the practice setting. Alternatives to the McMaster technique include FLOTAC, Mini-FLOTAC, and smartphone automated parasite egg counting systems to determine fecal egg counts (FECs).[1] Once resistance has been documented, it is important to identify the species involved through larval identification.

FEC and FEC Reduction Tests[2-6] (Box 49.2)

Determining numbers of nematode eggs in feces is the simplest and least invasive way to evaluate a parasite control program. Fecal examination may be of limited value in an individual animal because animals dying of parasitic infection may have no eggs in the feces, whereas animals with high FECs may be clinically normal. Nevertheless, FECs can provide information on the level of infection present in an individual animal, particularly when egg counts are repeated over the course of 2 to 3 weeks. Herd average FECs are more useful and provide an accurate reflection of the degree of environmental contamination and rate of infection. Pretreatment and posttreatment FECs can also be used to establish the efficacy of an anthelmintic in a particular group of animals. A quantitative McMaster or Stolley technique, rather than simple flotation, is crucial for accurate monitoring.

Box 49.2

Modified McMaster Technique (Fecal Egg Count)

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This is one method for performing a McMaster fecal egg count. Similar protocols are used routinely in many laboratories, so you may see a slightly different procedure recommended elsewhere. The important point is to use the same procedure each time.

The first step is to collect freshly passed feces uncontaminated by soil or bedding. The best way to accomplish this is to wear a rubber glove and extract feces directly from the rectum. Alternatively, feces can be picked up off the ground if done soon after deposition. The collection container should be labeled with the identification of the animal and the date of collection. Fresh samples work best, but accurate results can be obtained if the sample is refrigerated during the interim. If samples are not refrigerated, the eggs will hatch within 12 to 24 hours. Once hatched, eggs cannot be counted.

Materials

Compound microscope
Scale
Saturated sodium chloride (table salt)
50-mL centrifuge tube, with screw cap and marked with milliliter increments
Pipette (1-mL syringe or eye dropper works well)
McMaster egg counting slide (Chalex Corporation, Issaquah, Wash.)
Paper towels
A fresh fecal sample, refrigerated until tested

Procedure

1. Weigh out 2 g of feces into a 50-mL centrifuge tube and fill to 30-mL line with salt solution. It is recommended to weigh feces on a small scale, but if you do not have a scale you can still get a close estimation by putting 28 mL of salt solution into a 50-mL centrifuge tube first and then adding feces until a volume of 30 mL is achieved.
2. Pour off approximately 25 mL of the salt solution into another small container, keeping feces in the tube (use tongue depressor).
3. Soak feces for a few minutes and mix (soft feces) or break up (fecal pellets) with tongue depressor.
4. Add back approximately one half of the salt solution and mix well,

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breaking up any remaining feces as well as possible.

5. Add back the remaining salt solution and screw the cap back onto the tube.
6. Shake tube vigorously for approximately 1 minute to disrupt any remaining feces as much as possible.
7. Set tube aside for a few minutes to let bubbles dissipate.
8. Wet McMaster chamber with water and dry top and bottom on paper towels.
9. Rock (do not shake) tube several times to thoroughly mix solution without causing large air bubbles to form.
10. Immediately pipette (using 1-mL syringe or eye dropper) a sample of the suspension and fill both sides of counting chamber. Work quickly. If it takes more than a few seconds to load the first chamber, mix the fecal solution again and refill pipette before loading the second chamber.
11. Let the sample stand for 1 to 2 minutes to allow eggs to float.
12. Count all eggs inside of grid areas (more than one half of eggs should be inside grid) using low-power (10×) objective. Focus on the top layer, which contains small air bubbles (small black circles; if numerous large air bubbles are visible, remove the fluid and refill).
13. Count only trichostrongyle and strongyle eggs (oval shaped, approximately 80 to 90 microns long). Do not count *Strongyloides* species (oval, ≈50 microns long), tapeworm eggs (triangular or D shaped), or coccidia (various sizes). Note the presence of other species but count only the trichostrongyle and strongyle eggs.
14. Once filled, the chambers can sit for no longer than 60 minutes before counting without causing problems. After 60 minutes, drying and crystal formation may begin.
15. Total egg count (both chambers) × 50 = EPG (eggs per gram).

Notes

This is a dilution technique, and theoretically this ratio of feces to flotation solution will not detect infections with fewer than 50 EPG of feces (one egg seen on slide), so it is not accurate for samples with low numbers of eggs. On a practical level this is not important because from a clinical standpoint, slight differences in results when egg counts are low do not matter.

Fairly soon after counting is complete, thoroughly rinse out the McMaster

chamber with warm running water. Doing so will keep the chamber clean and ready to be used again. If fecal solution dries in the chamber, do not soak in soapy water for long periods because this will cause the chamber to become cloudy. If the chamber gets dirty, soak for only a few minutes in water containing dish soap and then rinse completely with tap water.

It is suggested that guidelines published by the World Association for the Advancement of Veterinary Parasitology (WAAVP) be used to perform and evaluate data from an FECRT, applying practical modifications to fit the situation on the farm.[3] Briefly, groups of 15 animals that have not been treated within the past 8 weeks are randomly allocated to treatment groups, and FECs are performed using a modified McMaster technique 10 to 14 days after treatment. An untreated control group must be included. If fewer than 12 to 15 animals per group are available, treatment groups should be balanced by performing a pretreatment FEC. Animals are then stratified by FEC from highest to lowest, blocked by number of treatment groups, and then within each block randomly assigned to treatment. Alternatively, where *Haemonchus* is the primary parasite, animals may be scored using the FAMACHA method as they come through the chute, blocked by FAMACHA score, and then randomly assigned to treatment within blocks. This approach is a bit more complicated but will result in groups that are balanced, which will result in a more accurate test. Calculations are performed using the following formula:

$$\mathrm{FECR\%} = 100 \times \left(1 - \frac{X_{t2}}{X_{t1}} \frac{X_{c1}}{X_{c2}} \right)$$

where X_c and X_t are the geometric mean or arithmetic mean EPG for control (c) and treated (t) groups before (1) and after (2) treatments, respectively.[6] Free software that performs all calculations and gives data interpretation is available.[7] If the RESO calculator is used, the assignment of resistance status is based on both percent reduction and the 95% confidence intervals. If the RESO calculator is not used, the following guidelines can be applied: reductions of greater than 98% indicate high efficacy, reductions of 90% to 98% indicate efficacy, reductions of 80% to 89% indicate moderate efficacy, and reductions of less than 80% indicate insufficient efficacy. FECRTs yield reliable data only if FECs are

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sufficiently high to properly measure a reduction from treatment. If the control group's mean FECs are below 150 EPG, objective assessment of resistance will not be reliable. Group mean FECs of less than 150 EPG can be common in adult sheep; therefore when FECRT is performed on a sheep farm, it is preferable to use weaned lambs if available. With goats, low FECs are usually not a problem.

Larval Identification

Ideally, if there is less than a 90% egg count reduction, the eggs should be hatched and the larvae species identified. In the majority of cases these will be *H. contortus*, but other species, especially *Trichostrongylus* species, readily develop resistance as well. One can sometimes be fooled into an improper interpretation of egg count reduction results if mixed species are present and only one is resistant.

Egg Hatch Assays and Larval Development Tests[3]

Eggs from feces are incubated with concentrations of the anthelmintic to be tested and the eggs hatched. A dose-response curve is generated (DrenchRite test from Horizon Technology, Sydney, Australia).[4] The advantage of this test is that a single fecal sample can be tested for all available classes of anthelmintics simultaneously. The cost of this test has recently increased and may discourage owners from pursuing this diagnostic. However, when compared with the cost of using anthelmintics that are ineffective, it is easy to justify the use of this test. It is important to read instructions for submitting this test and scheduling a testing date before the samples are collected.

Larval Culture

Larval cultures can be used to distinguish between large and small strongyles in horses and to identify the various nematode species in ruminants. Most parasitology laboratories can perform this examination. It requires submission of 200 to 400 g of fresh feces. Pooled samples from several herd members are often used.

Pasture Larval Counts[8]

Counts of parasitic larvae on herbage are useful to indicate the level of exposure experienced by the grazing animal. This examination is somewhat tedious but can be performed by many university laboratories. A 2-kg sample of forage is

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gathered for submission to the laboratory. The grass is sampled by walking a V pattern across the acreage and stopping every three paces to sample grass. The samples are subsequently washed and passed through screening to isolate and identify larvae.

Necropsy Evaluation

The nature and magnitude of parasitic infections can be established by necropsy examination. Gross examination and an estimate of adult worm population in the gut lumen are often sufficient. Many worms detach from the mucosa as the carcass cools; however, the damage done by the parasites can be seen on gross or histologic examination. Occasionally it is necessary to use digestion techniques or histologic examination to document the presence of hypobiotic larvae.

Future Evaluation Techniques

Research is developing to make identification procedures more rapid. Validation and refinement of automated smatrphone apps for performing egg counts and identifying egg species has been reported and is expected to improve with continued use.[1] The use of deep amplicon sequencing (rDNA ITS-2) has great potential for improving the identification of populations of nematodes, the “nemabiome” that will identify the species present and their population percentages.[9] These approaches have been validated for cattle and small ruminants. These techniques have great potential for being able to identify the populations present, the anthelmintic resistance level, and response to treatments more quickly.[9,10]

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Lungworm Infection in Large Animals

Lora Rickard Ballweber

Traditionally, lungworms are those nematode parasites that reside in the lung as adults. In domestic ruminant and equine species, most clinical cases of lungworm involve the genus *Dictyocaulus.* Species of *Dictyocaulus* tend to be host specific, with *Dictyocaulus viviparus*, *Dictyocaulus filaria,* and *Dictyocaulus arnfieldi* found in the bronchi of cattle, small ruminants, and equids (horses, ponies, donkeys), respectively. Sheep and goats may also be infected with *Protostrongylus rufescens* and *Muellerius capillaris*.[1,2] This section focuses on *Dictyocaulus* infection, with a brief discussion of other lungworm parasites found in small ruminants.

Because verminous pneumonia requires specific treatment, it is important to distinguish it from diseases caused by other infectious agents. Often the role of lungworm in the cause of respiratory disease is obscured by a parasite-induced hypersensitivity response or by superimposed secondary bacterial infections.

Life Cycle

The life cycle of *D. viviparus* is direct, with no intermediate host involved. Adults produce embryonated eggs that hatch shortly after oviposition. L_1 migrate up the trachea, are swallowed and passed in the feces, where they develop to L_2 and infective L_3 within a week under optimal environmental conditions. After the L_3 are ingested, they exsheath within the abomasum and migrate through the wall of the intestine to the mesenteric lymph nodes, where they molt to the L_4. The L_4 then migrate through the lymphatics and bloodstream to the lungs, arriving as early as 7 days after infection. L_4 may then develop to sexually mature adult worms, or they may arrest development as late L_4 or molt to immature adults and then arrest. Arrested development can prolong the normal prepatent period from 3 to 4 weeks to approximately 5 months.[1,2]

Most problems with cattle lungworms in North America occur in areas of moist climates or areas of intense irrigation where larvae on pasture are protected from desiccation and larval dispersal away from the fecal pat onto herbage is facilitated. Under favorable conditions, infective L_3 can survive on

pasture for as long as 11 months.[1] These larvae, plus the larvae produced from carrier animals harboring small numbers of adults or adults that developed from arrested larvae, can result in high levels of contamination on spring pastures. In subtropical climates, larvae are virtually absent during the hot summers; larval contamination of pastures peaks in the autumn because of carrier animals.[2]

The life cycle of *D. filaria* is similar to that of *D. viviparus*, including the ability of the larvae to arrest development. The prepatent period is approximately 26 days, with peak larval output occurring 39 to 57 days post infection. As with *D. viviparus, D. filaria* is more prevalent in moist climates, and larvae can survive on pasture throughout the winter. Spring pastures contaminated with overwintering larvae and larvae produced from adults developing from arrested larvae in carrier animals are sources of infection for susceptible lambs or kids.[1,2]

The life cycle of *D. arnfieldi* is similar to that of other species of *Dictyocaulus*, except that larvated eggs are passed in the feces with the L_1 hatching almost immediately thereafter. The prepatent period is 2 to 3 months.[2,4]

Unlike species of *Dictyocaulus, M. capillaris* and *P. rufescens* have indirect life cycles that involve molluscan intermediate hosts. Adults, occurring in the parenchyma *(M. capillaris)* or small bronchioles *(P. rufescens)*, produce eggs that develop and hatch. L_1 are passed with the feces; once on pasture, larvae invade the foot of a susceptible species of snail or slug and develop to infective L_3. Sheep and goats become infected when ingesting the mollusk while grazing. The larvae penetrate the intestine and migrate to the lung in much the same manner as *Dictyocaulus.* Early L_4, developing L_4, and adult *M. capillaris* become embedded in fibrous nodules within the parenchyma. *Protostrongylus* larvae mature in the alveoli and enter the bronchioles as adults. The prepatent period for both species is 5 to 6 weeks, although arrested development may prolong the prepatent period of *M. capillaris.* Patency for both species is very long (>2 years).[2-4]

Pathophysiology

Clinical bovine dictyocaulosis is characterized by bronchitis and pneumonia. The disease process is divided into four phases: penetration, prepatent, patent, and postpatent. In the penetration phase (days 1 to ≈7), no clinical sign or significant respiratory pathology occurs as the larvae migrate to the lungs. The prepatent phase (days 7–8 to 25) starts with the arrival of larvae in the alveoli

and ends with immature adults in the bronchi. An eosinophilic infiltrate blocks bronchioles; excess mucus production and alveolar collapse occur. Respiratory failure resulting from severe interstitial emphysema and pulmonary edema can lead to the death of heavily infected animals beginning about day 15 onward. The patent phase (days 25–26 to 55–60) is associated with egg-laying adults in the bronchi and trachea. Bronchial and tracheal epithelial damage occurs, air passages are blocked by exudate, and consolidation of lobules results from aspiration of eggs and L_1 into bronchioles and alveoli. Bronchitis, tracheitis, and pneumonia follow. The postpatent phase (days 61 to 90) is normally the recovery phase and is associated with the expulsion of adult nematodes. Clinical signs begin to diminish; however, peribronchial fibrosis and epithelialization of alveoli may remain. A frequently fatal syndrome, called *postpatent parasitic bronchitis,* can occur in about 25% of heavily infected animals during the postpatent phase. This syndrome is characterized by proliferation of type 2 pneumocytes in the alveoli, impaired gas exchange at the alveolar surface, interstitial emphysema, and pulmonary edema and is thought to result from the aspiration of dead and dying worm material into the alveoli. Fatal secondary bacterial infections, resulting from weakened pulmonary defenses, may also occur.[1,2]

Goats tend to be more susceptible to infection with *D. filaria* and more severely affected than sheep, although individual susceptibility to infections does occur. Heavy infections in both species produce bronchitis, pulmonary edema, atelectasis, and emphysema, although death is uncommon. As with *D. viviparus,* secondary bacterial infections can occur.[1]

The characteristic lesions of dictyocaulosis in horses and donkeys are similar. Pathologic changes include discrete circular areas of overinflation (not emphysema) surrounding affected bronchi primarily in the caudal lung lobes. Histologically these areas contain a small bronchus packed with nematodes. The small airways are often occluded with exudate. Adult worms may also be found in the main bronchi surrounded by small amounts of mucus with little cellular reaction; however, if L_1 are present, they are surrounded by an intense mucopurulent reaction. In horses, in addition to these types of lesions, many immature nematodes are present in smaller bronchi, accompanied by bronchial epithelial hyperplasia with large amounts of mucus and pus. Many areas of alveolar hemorrhage and edema are also present.[2,4]

Pathologic changes caused by *P. rufescens* result from occlusion of small bronchioles by mature worms, resulting in clogging of lesser branches with eggs,

larvae, and cellular debris. Other changes include desquamation of alveolar and bronchial epithelium and cellular infiltration and proliferation of connective tissue. The results are small areas of lobular pneumonia that appear as gray to yellowish conical lesions whose base is on the surface of the lung. In sheep and goats infected with *M. capillaris,* distinct subpleural nodules containing adults and L_1 are common. However, infections in both hosts may be more diffuse with interstitial pneumonia, bronchopneumonia, or fibrinous pleuritis. Secondary bacterial infections can also occur.[1,2,5]

Populations at Risk

Clinical dictyocaulosis occurs most frequently in pastured calves, lambs, and kids in the first grazing season. Clinical disease is also reported in adult cattle as a result of primary exposure as adults, exposure of a previously immune animal whose immunity has waned due to lack of reinfection, or exposure of an immune animal to a massive challenge of infective larvae *(reinfection syndrome).*[1,2,6-8] Although dairy or dairy-cross calves are most frequently affected, beef calves are also susceptible to *D. viviparus*.[2,9,10] Many infections with either *M. capillaris* or *P. rufescens* are subclinical; however, goats do appear to be affected clinically more often than sheep with *M. capillaris*.[1,2]

Immunity to *D. viviparus* occurs after first exposure and can develop before the end of the first grazing season. However, it is variable in both degree and duration. Cattle may be immune for 7 to 12 months after infection. In subsequent infections most larvae are either killed before reaching the lung or are inhibited from maturing into adults. Usually the immunity developed during the first grazing season is boosted by reinfection in subsequent years and prevents manifestations of disease. However, without reexposure to infective larvae or vaccination, immunity wanes and disease can occur in adult cattle.[1,2,8]

Occasionally, outbreaks of acute lungworm disease are seen in adult cattle on pasture whose immunity is overwhelmed by ingestion of large numbers of larvae. This condition is called the *reinfection syndrome.* Although most ingested larvae are killed or fail to mature, some reach the lung and incite an acute, immune-mediated reaction.[2]

Both sheep and goats develop a strong immunity to *D. filaria.* Thus disease is more common in young animals. As with cattle, the strength and duration of immunity depend on the level of and number of reinfections, as well as the

length of time between events.[1] Although not common, cattle can be infected with *D. filaria.* Patent infections do not establish, but clinical disease may occur.[1,11]

Individual horse or pony susceptibility to infection with *D. arnfieldi* is evident, with infections occurring during any time in the life of the animal. Patent infections can establish in foals (<5 months old) without accompanying clinical signs. Patent infections are rarely established in older horses, where clinical disease is more common. Donkeys apparently do not develop an immunity to infection, with larval excretion increasing with age.[2-4]

Although immunity to *M. capillaris* appears to be incomplete (adult nematodes can live for up to 4.5 years), responses to subsequent infections do limit the numbers of adults that will develop and the numbers of larvae shed in the feces. However, reinfections may be cumulative, resulting in older animals harboring larger numbers of worms.[1]

Clinical Manifestations

Clinical disease (“husk”) caused by *D. viviparus* in cattle can occur within 1 or 2 weeks of the introduction of susceptible animals onto contaminated pasture. However, disease most often occurs 2 to 4 months into the grazing season. Severity of disease depends on the number of larvae ingested, the animal's level of immunity, and the number of larvae reaching the lungs. Within an affected group, differing degrees of clinical severity will occur. Coughing, dyspnea, and loss of condition are typical. Slight increases in respiratory rate may progress to severe tachypnea and dyspnea characterized by the classic “air-hunger” position of head and neck extended with open-mouth breathing. Auscultation of the lungs reveals vesicular murmurs and bronchial tones that progress to moist rales as fluid accumulates. Emphysema may occur with crackling noises heard on auscultation. Mild pyrexia may be present. Milk production is usually depressed in adult dairy cattle. Morbidity rates are high, with most animals gradually recovering. Secondary bacterial infections can lead to recurrence of clinical signs during the postpatent phase, leading to acute interstitial pneumonia.[1,2,7] Acute dictyocaulosis in calves, resulting from a massive primary infection, can occur during the prepatent period with sudden onset of severe dyspnea followed by death within 24 to 48 hours.[2] Reinfection syndrome in adult cattle shows frequent coughing and slight tachypnea and, for dairy cattle, a sudden drop in

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milk production starting approximately 2 weeks after being placed on heavily contaminated pastures. Deaths rarely occur.[2]

Coughing and unthriftiness are the usual signs of infections with *D. filaria*. In severe cases, dyspnea, tachypnea, and nasal discharge can occur. Death is uncommon.[1,2]

In horses, lungworm infection may or may not cause clinical signs. When present, the typical syndrome is similar to chronic obstructive pulmonary disease and includes persistent coughing, nasal discharge, and increased respiratory rate; death is uncommon. Donkeys tend to remain asymptomatic, although hyperpnea and harsh lung sounds may be present on close examination.[2-4]

Infections with *M. capillaris* are generally asymptomatic; however, impaired pulmonary gas exchange, reduced weights and breeding performance, and increased mortality have been reported.[1,12,13]

Control of Lungworm Infection

Control of dictyocaulosis in cattle has depended on vaccination and/or prophylactic use of anthelmintics, whereas management strategies designed to decrease numbers of infective larvae ingested are more common recommendations for sheep and goats. These strategies include providing dry pastures to decrease larval development and survival; grazing older, clinically immune animals that shed larvae away from susceptible lambs and kids; and grazing lambs on pastures that have not been grazed by adults during the previous year. Treating or culling infected adults can also help reduce pasture contamination. Limiting contact with intermediate hosts and providing mollusk-free housing will decrease infections with parasites that require these intermediate hosts. Treatment of animals before the start of the grazing season has also been suggested to reduce subsequent infection levels in the intermediate hosts.[1,2]

For cattle, leaving contaminated pastures ungrazed for at least 6 weeks during the summer in temperate regions can reduce pasture infectivity because larvae will not survive dessication. Young, susceptible stock may be given a prophylactic treatment in midspring or early summer to prevent or limit clinical disease. Housed animals, in particular 1- to 2-year-olds with subclinical but potentially patent infections, should be treated before being turned out to pasture in the spring. All early clinical cases should be treated in an effort to limit

disease severity and decrease pasture contamination.[1,2,14,15]

Control of lungworms in horses and ponies depends on control in donkeys. Co-grazing with donkeys should not occur. If it does, donkeys should be monitored for L_1 and treated to reduce larval output and pasture contamination.[2]

Anthelmintics.

Several anthelmintics are effective against lungworms (Table 49.4).[1,3,4,16-20] The macrocyclic lactones are particularly effective against both adult and developing L_4 stages and have prolonged residual activity that prevents appearance of larvae in the feces for at least 60 days.[21,22] Concerns that such highly efficacious anthelmintics would prevent induction of immunity in first-season grazing animals by killing ingested larvae, before they can penetrate the intestine and thus stimulate an immune response, appear to be largely unfounded. The immune response may be attenuated, but exposed animals still develop some degree of immunity to lungworm infection despite prophylactic treatment with these drugs.[22-26] The exception to this may be sustained-release intraruminal devices containing ivermectin, levamisole, or a benzimidazole or long-acting injectables. Although their use can prevent clinical disease for several weeks or months during the grazing season,[26-31] some studies have shown that use of these delivery systems impaired the development of immunity in treated calves.[26,30] Other studies, however, showed that treated calves can develop immunity during the grazing season.[32] Regardless, vaccination of treated animals before their second grazing season may be advisable.[2,8]

TABLE 49.4

Drugs Used to Control Lungworm

Drug	Dose[a]
Macrocyclic Lactones	
Cattle: ivermectin, abamectin, doramectin, eprinomectin, moxidectin	0.2 mg/kg PO, 0.5 mg/kg topical
Sheep: moxidectin, ivermectin	0.2 mg/kg PO, SC
Goats: ivermectin	0.2-0.3 mg/kg PO, SC
Equids: ivermectin, moxidectin; eprinomectin	0.2 mg/kg, 0.4 mg/kg PO; 0.5 mg/kg topical
Others	
Albendazole	7.5-10 mg/kg PO (O, C, B)
Fenbendazole	7.5 mg/kg PO (O); 15-30 mg/kg PO (C); 5 mg/kg PO (B)

Mebendazole	15-20 mg/kg PO (O, C)
Oxfendazole	4.5 mg/kg PO (B), 7.5-10 mg/kg PO (O, C)

[a]Dose depends on the product and species; follow manufacturers' recommendations; multiple treatments may be warranted depending on host species; sheep and goats should be dewormed by mouth; be aware that some recommendations constitute off-label use.

B, Bovine; *C,* caprine; *O,* ovine; *PO,* by mouth; *SC,* subcutaneously.

Vaccines.

An effective vaccine has been developed against *D. viviparus* in cattle and is available in the United Kingdom and parts of western Europe. Two doses of live, irradiated larvae are administered by mouth 4 weeks apart. The larvae migrate to mesenteric lymph nodes and provoke an immune response but die before they reach the lung. Management considerations associated with use of the vaccine include the following: (1) calves must be at least 2 months old; (2) vaccinated calves should not be placed on pasture for at least 2 weeks after the second dose; (3) vaccinated calves must not be placed onto heavily infected pastures, nor should they be mixed with animals showing signs of lungworm disease or with unvaccinated calves; (4) animals should not be treated with an anthelmintic during vaccination or the larvae in the vaccine will be killed; (5) immunity is not long-lasting, so animals must continue to ingest low levels of infective larvae to maintain immunity; and (6) the vaccine has a short shelf life and is relatively expensive. Farms with contaminated grazing areas and a history of lungworm disease benefit most from vaccination.[8,14,33]

Evaluation of Preventive Programs

The efficacy of preventive programs is best assessed by evaluating the number of susceptible animals that demonstrate signs of infection. Because total eradication of the lungworms is difficult and low numbers of parasites produce minimal problems and maintain immunity, a useful goal is the control of clinical signs and achievement of production goals.

Clinical Management

Diagnosis.

Presumptive diagnosis of clinical lungworm infection is based on clinical

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presentation, farm history, seasonal prevalence, and response to treatment.[1-4] Verminous pneumonia may mimic respiratory diseases caused by other agents that require specific treatment. Although definitive diagnosis is difficult, it is important.

To document the presence of lungworm infection, it is necessary to demonstrate larvae or adult worms. In cattle and small ruminants, the presence of specific L_1 in fresh feces indicates lungworm infection.[1,14,34] The Baermann technique is the technique of choice for detection of L_1 in feces and is considered to be very sensitive for the diagnosis of patent primary bovine lungworm infections beginning about 3.5 weeks after infection, provided a sufficient number of animals are sampled.[34] Antibody detection tests have also been developed and are commercially available for use in cattle. Evaluation of their application for testing bulk milk tank samples indicates these tests appear to be most useful in diagnosing suspected dictyocaulosis in moderate to severe outbreaks. In mild outbreaks where just a few animals are coughing or on farms where prevalence is low (<20%), examination of serum and/or feces from individual animals is preferred.[35,36]

Although examining donkeys co-grazing with horses has been the standard recommendation for the antemortem diagnosis of *D. arnfieldi*,[4] diagnosis of lungworm infection in horses is often presumptive and usually based on resolution of clinical signs after treatment.[2,3]

Transtracheal wash may demonstrate a large number of eosinophils, which is supportive of verminous pneumonia, and eggs or larvae are occasionally seen with patent infections. This procedure can also help rule out bacterial pneumonia. Finding nematodes at necropsy is definitive. Adult *Dictyocaulus* are usually found in the bronchi or bronchioles, whereas adult *P. rufescens* tend to be in the bronchioles and adult *M. capillaris* are found in subpleural nodules on the dorsal aspect of the diaphragmatic lobes. Nematodes and the eggs may also be found in histologic section of the lung.

Treatment.

Animals that are only coughing and/or tachypneic usually have small numbers of *D. viviparus,* and their treatment should result in a rapid recovery. For animals that are dyspneic and anorexic with or without a fever, lung damage is likely severe and anthelmintic treatment is unlikely to result in complete recovery. In some animals, anthelmintic treatment worsens clinical signs, and some heavily

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infected animals may die. In severely affected individuals, hydration status should be monitored, particularly if the animal is not drinking. Antihistamines and antibiotics may also be included in the therapeutic regimen. Goats infected with *M. capillaris* may need multiple treatments; even so, pathologic changes can still be evident 3 months after parasite elimination.[2,8,14,37]

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Coccidiosis in Food Animals

Lora Rickard Ballweber

Coccidiosis causes serious economic losses in a variety of food animal species. Regular infections with a mixture of species generally occur throughout the life of the animal. Infections tend to be asymptomatic and self-limiting unless management or other factors allow the abnormal concentration of oocysts in the environment or when host defenses are compromised. Kids are especially susceptible to coccidiosis and may develop chronic diarrhea as a consequence. In many production operations, coccidiosis is an annual event.

Life Cycle

Coccidiosis in ruminants is caused by intracellular parasites of the genus *Eimeria.* They are strictly host specific, developing within cells at species-specific sites along the intestinal tract. The life cycle is complex, involving both sexual and asexual phases within the same host. Unsporulated oocysts (noninfective) are passed in the feces and subsequently sporulate (in as little as 1 to 4 days under ideal conditions) under suitable conditions of oxygen, moderate temperatures, and high moisture. The now infective sporulated oocysts are ingested by the host with contaminated food or water. Digestive enzymes activate the sporozoites within the oocysts, which excyst in the intestine and enter intestinal cells. The asexual phase of development, in which two or more cycles of merogony occurs, is then initiated. Asexual fission results in the production of merozoites. Mature meronts rupture (along with the host cell), releasing merozoites, which enter other cells and repeat the cycle or progress to the sexual phase of development (gamogony). In this phase, merozoites enter new cells and produce macrogametes and microgametes. Microgametes are released by cellular rupture and fertilize a macrogamete to form a zygote. A cyst wall then forms around the zygote, resulting in the next generation of oocysts. Once again the host cell ruptures, releasing oocysts into the lumen of the intestine, where they are then passed with the feces. The prepatent period is generally 1 to 4 weeks, depending on the particular species of *Eimeria.*[1-4]

Pathophysiology

Most intestinal *Eimeria* develop exclusively in the intestinal epithelial cells, although a few exceptions (e.g., *Eimeria bovis*) do exist. As a result of the developmental cycle, infected host cells are destroyed. However, the degree of damage depends on the species of *Eimeria* involved; the site of infection (discussed later); the number of oocysts ingested; and various host factors, including age, physical condition, and premunition.[1-4] If the number of oocysts ingested is low, nonimmune healthy animals may tolerate infection and show no signs of disease. However, if nonimmune animals ingest many oocysts, widespread rupture and exfoliation of intestinal cells alter gut function, allowing loss of blood, fluid, albumin, and electrolytes into the gut. Secondary bacterial invasion can also occur. Sections of sloughed intestinal mucosa and fibrin casts may be seen in the feces, which may be blood tinged.

The most pathogenic species of ruminant coccidia are those that destroy the cells of the large intestinal mucosa (*Eimeria alabamensis, E. bovis,* and *Eimeria zuernii* in cattle; *Eimeria crandallis* and *Eimeria ovinoidalis* in sheep; *Eimeria ninakohlyakimovae* and *Eimeria caprina* in goats) or involve deeper layers of the lower small intestine (*Eimeria christenseni* in goats).[3] Because the ruminant small intestine is very long, providing many host epithelial cells, enormous parasite replication can occur with minimal damage. If nutrient absorption is compromised, the large intestine can compensate to a certain extent. Conversely, the rate of cell turnover in the large intestine is much lower than that in the small, it is much shorter in length, and other regions of the gut cannot compensate for its impaired function.[3]

A condition called nervous coccidiosis has been described, primarily in weaned beef cattle.[4-8] The pathophysiology of this manifestation has never been definitively established, and conflicting theories have been proposed, including copper imbalance, plasma electrolyte imbalances, a neurotoxin, and a combination of stressors in which coccidia are only one factor.[4,8]

Populations at Risk

Infections with mixtures of pathogenic and nonpathogenic species of *Eimeria* occur throughout the life of most ruminants and usually do not cause clinical signs because species-specific immunity is acquired quickly and maintained by continuous reinfection. The net effect of the immune response is a reduction in clinical signs and a decrease in oocyst production.[3] Therefore adults help

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maintain the parasite but are not usually the source of heavy environmental contamination; rather, nonimmune animals, whose initial infections result in excretion of massive numbers of oocysts, are primarily responsible.[3,4] Clinical coccidiosis is therefore a disease of young, nonimmune animals that ingest large numbers of sporulated oocysts from heavily contaminated environments.[1-4] Calves 6 to 12 months of age are most susceptible to infection, as are lambs and kids 1 to 6 months of age; however, most clinical disease in lambs and kids occurs at 4 to 8 weeks of age. Conditions favoring coccidiosis include overcrowding, housing multiple age groups together, and pens that are not cleaned regularly.[1-4,9] Thus coccidiosis is a disease of management. Although stress, such as from shipping, weaning, dietary changes, and/or adverse weather, appears to facilitate outbreaks, the mechanisms are not fully understood.[1-4,10]

Even though reported in range animals, coccidiosis is chiefly a disease of confinement leading to heavily contaminated environments. Clinical disease can occur in cattle at any age but is evident most often in calves from 3 weeks to 6 months of age.[3,4,11] In dairy cattle, coccidiosis is most common in calves when they are taken from hutches into group calf pens or mini–free-stall barns. In beef cattle the disease is most prevalent in feedlot calves. In sheep, disease is usually limited to lambs younger than 6 months old. Coccidiosis is most common in intensively reared lambs, although suckling lambs on pasture in constant use at high stocking rates are also at risk. Young kids appear particularly susceptible to coccidiosis, with clinical disease especially prevalent 2 to 3 weeks after weaning. Occasionally, adult animals develop coccidiosis either from impaired cellular immunity or when stressed (moved into a new herd, prolonged travel, extreme weather conditions).[3,4]

Clinical Manifestations

The destruction of epithelial cells and subsequent loss of blood, albumin, fluid, and electrolytes typically cause a profuse, sometimes bloody, diarrhea. Despite the blood loss, anemia is not usually apparent. Death is usually from dehydration. Light to moderate infections in cattle may cause watery feces, poor condition, and reduced weight gain. Severe infections cause projectile, bloody diarrhea with mucus, rectal tenesmus, inappetence, dehydration, and weight loss. Clinical signs last approximately 1 week. In lambs, clinical signs are similar to those of cattle except blood and tenesmus are less common than cattle. In kids,

clinical signs include pasty, watery diarrhea and dehydration.[1] Sudden death can occur in both lambs and kids, but the case fatality rate is usually low in most outbreaks. After recovery from the disease the gut does not return to normal function for several weeks, and concurrent appetite suppression leads to poor growth and/or stunting.

Cattle considered to have nervous coccidiosis exhibit muscle tremors, hyperesthesia, nystagmus, and seizures. Interictal periods are normal or near normal. The mortality rate is high.[2,4-6]

Control of Coccidiosis

The presence of coccidiosis depends on the amount of environmental contamination; thus the level of infection is directly related to the level of fecal contamination. Houses and pens used for sequential groups of young animals often become highly contaminated and serve as the source of infection for subsequent groups. Therefore minimizing exposure of susceptible animals to infective oocysts depends on management techniques that focus on either sanitation to avoid the buildup of environmental contamination or elimination of environmental conditions conducive to oocyst survival (or both).[3,4,9] Decreased stocking rates, proper manure disposal, elevated feed bunks, and routine cleaning of water troughs will help reduce contamination and exposure to oocysts. Sunlight and low humidity will kill oocysts, as does disinfection with formaldehyde, ammonia, or methylbromide; however, proper cleaning is a prerequisite for efficient disinfection.[4,9] Prophylactic use of coccidiostats is inevitable if conditions of animal husbandry cannot or do not improve.

Drugs.

The various drugs that have been used to prevent or treat coccidiosis in ruminants are listed in Table 49.5.[2-4,12-19] Be sure to pay strict attention to local regulations surrounding the use of any drug in food or farm animals.[2] Therapeutic anticoccidials are used in acute outbreaks; particularly useful here in calves are the benzeneacetonitrile compounds (diclazuril, toltrazuril), which currently are not labelled for use in food animals in the United States.[4] Scouring calves should be removed from the group, and supportive therapy, including electrolytes, glucose, and antidiarrheals, may help to improve survival.[3]

TABLE 49.5

Drugs Used for Treatment and Prevention of Coccidiosis in Ruminants

Drug	Treatment[a]	Prevention[a]
Amprolium	10 mg/kg for 5 days (B)	5 mg/kg for 21 days (B)
	25–40 mg/kg for 5 days (O, C)	50 mg/kg for 21 days (O)
	65 mg/kg once (O, C)	
Decoquinate		0.5 mg/kg for 28–30 days
Diclazuril		1 mg/kg once; a second dose can be given 14 days later
Lasalocid		1 mg/kg continuously (B)
		25–400 mg/ton feed, continuously (B, C)
		80 mg/kg milk replacer (neonatal calves)
		Free choice in salt at 0.75% total salt mixture
Monensin	2 mg/kg for 20 days (O)	1 mg/kg for 28 days
		10–20 ppm in feed, continuously
		16–33 g/ton of feed, continuously
Nitrofurazone[b]	15 mg/kg for 5–7 days	33 mg/kg for 14 days
	In feed at 0.04% or in water at 0.0133% for 7 days	In feed at 0.04% for 21 days
Salinomycin		10 ppm in feed (O)
Sulfadimethoxine		50 mg/kg for 5 days (O)
Sulfamethazine	247 mg/kg day 1, 123 mg/kg days 2–5	35 mg/kg for 15 days (B)
	140 mg/kg for 3 days	25 mg/kg for 7 days (O)
	140 mg/kg once, then 70 mg/kg for 5–7 days	55 g/ton of feed (C)
Sulfaquinoxaline	10–20 mg/kg for 5–7 days	
Toltrazuril	20 mg/kg	20 mg/kg once, timing depends on production system

[a]Oral administration; dose or regimen may vary among references.

[b]No published data, and extralabel use prohibited in cattle in the United States.

B, Bovine; *C,* caprine; *O,* ovine.

Note: Coccidiostats used in poultry feeds may be toxic to ruminants.

Often outbreaks of coccidiosis can be predicted based on farm history. Addressing husbandry issues that promote contamination with and survival of oocysts should be addressed first; however, where these issues cannot be improved, it is best to use drugs prophylactically or metaphylactically rather than therapeutically to prevent losses. Administration of anticoccidials during this time does not completely prevent infection but prevents clinical disease without interfering with the production of protective immunity.[4] Timing is also crucial, as improper metaphylactic use could result in wasted money or increased susceptibility to massive infections later in life.[18] Preventive measures are best used during periods of highest risk, such as in calves after weaning or in

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crowded conditions. If coccidiosis occurs in nursing calves, addition of anticoccidials to creep feed may be necessary. In contrast, lambs and kids are most at risk while still nursing. Thus administration of anticoccidials for 30 days prior to lambing or kidding has been recommended to reduce environmental contamination of the lambing or kidding areas.[2] Resistance to anticoccidials can occur and is a problem in the poultry industry; however, evidence for resistance in livestock is mostly circumstantial and unproven.[2]

Other Strategies for Minimizing Clinical Infections.

No vaccine for ruminant coccidiosis exists. Immunization of calves with a "trickle dose" of oocysts before turnout onto infected pasture attenuates the effects of natural challenge[20] but is not commonly used. Use of growth implants containing estradiol and progesterone can attenuate the effects of high oocyst challenge in dairy calves but is not used for this purpose.[21] It has been reported that oocysts of *E. alabamensis* may survive the hay-making process,[22] and hay from infected pastures should not be used to feed susceptible calves. However, whether all species of *Eimeria* can survive the hay-making process or how common survival is with various types of hay production is unknown.

Concerns regarding the potential impact of anticoccidial drug use within the food chain and on the environment has sparked increasing interest and efforts to find novel agents characterized by low risks for consumer health and better environmental compatibility as well as sustainability.[23] Evaluations of secondary plant metabolites, including polyphenols, flavonoids, tannins, and saponins, show promise in animal models (mice) or poultry,[23] but few efforts have addressed livestock. Because much effort has focused on the anthelmintic properties of tannin-containing legumes and their use in controlling GINs of ruminants,[24] particularly where anthelmintic-resistant populations of these parasites occur, some efforts evaluating their use as anticoccidials have occurred.[25-31] The primary focus has been on small ruminants. Although all studies varied in their design (e.g., plus/minus concurrent GIN infections) and some lack certain information (e.g., species of *Eimeria* present), these data do indicate an overall reduction in oocyst excretion, which would aid in reducing environmental contamination.

Evaluation of Preventive Programs

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Evaluation of any coccidiosis prevention plan is based on the presence and extent of clinical disease. Herds or flocks that require preventive strategies do so because they usually have a history of prior disease. Program efficacy therefore is evaluated on the basis of a decrease in prevalence of clinically ill animals.

Clinical Management

Diagnosis.

Diagnosis is presumptive and based on history (which may include a stressful event), thorough knowledge of the herd or flock management, and clinical signs of severe diarrhea (usually young animals). Postmortem findings of inflammation, hyperemia, and thickening of the cecum with masses of gamonts and oocysts in mucosal scrapings will be confirmatory. Because pathogenicity varies by species, the value of fecal oocyst counts is debated. In general, fecal oocyst counts alone are not helpful *if the species of coccidia present are not identified.* The mere presence of oocysts does not itself indicate disease, as high numbers of nonpathogenic species can be present in animals with other causes of diarrhea. Clinical signs can also develop in the early stages of the life cycle before oocyst shedding. If fecal examinations are done during a suspected outbreak, multiple animals should be sampled. Due to the short life cycle, oocyst counts are highest in early patency and drop quickly after about 1 week. Thus fecal samples should be collected when diarrhea starts. Any standard fecal flotation method can be used to find oocysts.[2-4]

Treatment.

Drugs used in the treatment of coccidiosis are listed in Table 49.5. Supportive therapy, when indicated, is primarily directed at replacing fluid losses and supporting the animal until the gut epithelium regenerates.

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Anthelmintic Use[1]

Sherrill A. Fleming

An anthelmintic is defined as an agent that acts to destroy or expel parasitic intestinal helminths. Anthelmintic drugs are used to treat animals that are suffering the adverse effects of a parasitic burden. They may also be used to prevent and minimize the economic losses associated with parasitic infection. Anthelmintics may be used on individual animals or a group of animals.

Drug Action

To use an anthelmintic properly, it is necessary to consider its mode of action, spectrum of activity, and duration of effect. The pharmacodynamics of an anthelmintic is specific for each species that is treated. Efficacy for a given drug may be defined as its ability to kill adult or larval parasites, suppress parasitic egg production, or promote the expulsion of worms from the gastrointestinal tract.

The emergence of drug-resistant strains of nematodes has necessitated the use of each class of anthelmintic to be customized to the premise where it will be used. Package inserts should be regarded as guidelines rather than gospel. Refer to the Anthelmintic Drugs and the Evaluation of Parasite Control Programs sections for particulars on anthelmintic performance. Readers should refer to the sections on horses, cattle, and small ruminants for more specific recommendations.

Anthelmintic Drugs (see Table 49.4)[1,2]

Avermectins and Milbemycins

The avermectins and milbemycins are macrocyclic lactones. They act by increasing the permeability of parasite cell membranes to chloride ions, which results in nonspastic paralysis and death of the parasite. These drugs may also act by potentiating presynaptic release of γ-aminobutyric acid (GABA), an inhibitory neurotransmitter, although this theory has been challenged.

These products have a high level and broad spectrum of activity against adult and larval nematodes. They are also effective against various ectoparasites such as mites, lice, ticks, bots, and cattle grubs; however, they are ineffective against flukes and tapeworms. These drugs suppress nematode egg production for longer than other anthelmintics. Because of its long duration of effect, moxidectin suppresses fecal egg counts and protects against reinfection for longer than ivermectin. Concern has been expressed about the environmental impact of these long-acting anthelmintics in grazing animals.

Several products have been developed for use in animals. The avermectins include ivermectin, abamectin, doramectin, and eprinomectin. The milbemycins include nemadectin and moxidectin. Oral (drench, sustained-release intraruminal device), topical (pour-on), and injectable formulations are available, depending on the drug. Ivermectin is safe to use during pregnancy, but currently it is not approved for use in lactating dairy animals or females of breeding age. Similarly, doramectin and moxidectin are not approved for use in female dairy cattle of breeding age. Eprinomectin is unique in that it has no withholding period for milk or meat, so there are no restrictions on its use in cattle. At labeled doses, moxidectin is a safe drug; however, accidental overdosage has caused neurologic signs in foals and miniature horses. Some of these products have extended efficacy periods but run the risk of having subtherapeutic periods, which increase the selection for resistant nematodes.

Benzimidazoles

The benzimidazoles (BZDs) comprise a large class of anthelmintics that interfere with parasitic carbohydrate metabolism by inhibiting the enzyme fumarate reductase. Many BZDs have been developed and marketed. They include

albendazole, fenbendazole, mebendazole, oxfendazole, oxibendazole, parbendazole, ricobendazole, thiabendazole, triclabendazole, and the probenzimidazole drugs febantel and netobimin.

BZDs are widely used in horses and ruminants. In general, they exhibit a high degree of safety and a broad spectrum of activity against GINs and lungworms. Some members of this class (e.g., albendazole) are also active against liver flukes and certain cestodes in ruminants. Albendazole and netobimin can cause teratogenicity and embryo toxicity in sheep when given during early pregnancy. Fenbendazole, oxfendazole, and oxibendazole are considered safe for use in pregnant animals.

Resistance to BZDs has been documented in certain equine, ovine, and caprine parasites (see species-specific sections). In general, a strain of parasite resistant to one BZD drug quickly develops resistance to other BZDs or pro-BZDs, a phenomenon known as *side resistance*.

Levamisole (Imidazothiazoles)

Levamisole acts by causing neuromuscular depolarization and paralysis of the parasite. It has been widely used in ruminants to treat GINs and lungworm infections. However, levamisole resistance has become a problem in many areas. Levamisole is the only anthelmintic that has shown resistant parasites reverting to sensitivity if not used for several years. Recurrence of resistance will develop fairly rapidly with reuse of levamisole.

The dose of levamisole should be calculated carefully because toxic doses are only one to two times therapeutic doses. Signs of toxicity may mimic those of organophosphate (OP) toxicity, including muscle fasciculations around the lips and eyelids, hypersalivation, spastic movements, depression, and diarrhea. In ruminants, muzzle foam may develop after oral administration of the drug but usually disappears within a few hours after administration. In horses, transitory excitement has been seen after treatment. Levamisole is not recommended for use as an anthelmintic in horses. Concurrent administration of morantel, pyrantel, diethylcarbamazine, or OPs could enhance the toxic effects of levamisole.

Morantel and Pyrantel (Tetrahydropyrimidines)

The tetrahydropyrimidines morantel and pyrantel are cholinergic agonists that exert their anthelmintic effect by depolarizing neuromuscular junctions and

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causing irreversible paralysis of susceptible parasites, similar to the action of imidazothiazoles. Morantel is slower in its onset of action but much more potent than pyrantel. These products are effective against many species of adult nematodes but do not appear to be active against larval stages. Pyrantel is also effective against tapeworms in horses when given at twice the recommended dose. The margin of safety is relatively wide, and there is no contraindication to using morantel or pyrantel with other cholinergic drugs. However, it is recommended that morantel and pyrantel not be used concurrently and that neither be given with levamisole. Piperazine antagonizes the effects of morantel and pyrantel, so it should not be used with either of these drugs. Resistance to morantel and pyrantel has been documented in strains of *H. contortus* and in some cyathostomes (equine small strongyles).

Organophosphates

OPs block neurotransmission by inhibiting acetylcholinesterase. Various formulations of OP drugs are available for treating gastrointestinal nematodiasis. Commonly used OPs include haloxon, coumaphos, trichlorfon, and dichlorvos. Toxicity occurs with these products in a dose-related manner, so dosages should be calculated with care. In addition, the potential danger to humans administering these products should not be overlooked. Atropine is recommended in cases of overdose in livestock.

Phenothiazine

The mode of action of phenothiazine (PTH) has not been clarified; it is thought to interfere with anaerobic metabolism of nematodes. The various formulations of PTH differ in purity and particle size. The purified product (99% PTH) with small particle size (2 µm) is the most effective.

Although PTH is effective against a wide spectrum of GINs, resistant strains of parasites have emerged in several species. The drug is synergistic with piperazine; combinations of these drugs have effective activity against PTH-resistant nematodes. PTH used in combination with piperazine can be administered at a much lower dose.

PTH toxicity has been reported. Toxic reactions include corneal inflammation, abortion, ataxia, hemolytic anemia, photosensitization, and nephrotoxicity. The drug should not be administered to debilitated or anemic animals or to animals in the last month of pregnancy.

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Piperazine

Piperazine salts block neuromuscular transmission, resulting in paralysis of susceptible GINs. The worms are then passively removed from the gastrointestinal tract by intestinal peristalsis. Piperazines have low toxicity and are safe in young or pregnant animals. However, their spectrum of activity is limited, in practical terms, to ascarids. Piperazine must be used with caution in horses heavily infested with ascarids because the paralyzed ascarids can cause an impaction that may culminate in bowel rupture. Diethylcarbamazine is a piperazine derivative that has been used to control lungworm infection in sheep and cattle.

Monepantel

Monepantel is a new amino-acetonitrile derivative (ADD) compound that has a unique mode of paralyzing nematodes and is intended to be used as an oral drench. This product has been released for use in New Zealand but is not available in the United States at this time. The countries that do have this drug available are beginning to report resistance in nematode populations.[3,4]

Combination Dewormers

Combination dewormers have been shown to extend the effectiveness of anthelmintics. Many of the newer products reaching the market contain two or more classes of anthelmintics, but to date none of these products is available in the United States. One study showed that not only did combination anthelmintics not increase resistance development but there was some evidence of reversion to susceptibility in *T. circumcincta* populations.[5]

Other Anthelmintics

Praziquantel is a cesticidal drug that causes spastic paralysis, decreased glucose uptake, and disruption of the tapeworm's tegument. Although not approved for this use, praziquantel is effective for treating tapeworm infestation in horses. It has also been used to control various cestodes in small ruminants. Nitroxinil is a halogenated phenol that has flukicide activity *(Fasciola hepatica)* and some nematodes and is available in some countries as an injection. Salicylanilides are a chemical class of antiparasitic active ingredients with efficacy against certain roundworms, tapeworms, and/or flukes. The class includes closantel (flukes and some nematodes), niclosamide (tapeworms and rumen flukes [*Paramphistomum*

spp.]), oxyclozanide (some flukes), and rafoxanide (some flukes and nematodes).

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• CHAPTER 50

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Nutrition of the Sick Animal

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Introduction

Horses, cattle, and other large animal species evolved as grazing herbivorous animals, meeting energy and nutritional needs with forage, salt, and water. In most cases, feeding based on teleologic principals is best, unless the individual is unwilling or unable to eat. There are little data on feeding critically ill or hospitalized large animal species and its association with or effect on morbidity and mortality or hospital stay.

Protein/Calorie Malnutrition

It is generally agreed on that feed can be withheld from healthy, “nonstressed” adult individuals for 2 to 3 days. The average, healthy adult horse or ruminant can apparently tolerate food deprivation (protein/calorie malnutrition [PCM] or simple starvation) for 72 hours with few systemic effects. In humans a decline in blood glucose concentration results in a fall in insulin concentration. During the first hours to days of starvation, glycogen stores are mobilized from various tissues (liver, kidney, muscle) for glucose production. As glucose becomes limited, many body tissues begin to rely on fatty acid oxidation and the production of ketone bodies as energy sources. Glycerol produced from lipid degradation, lactate from the Krebs cycle, and amino acids provided from muscle tissue breakdown continue to be used for gluconeogenesis to provide energy to glucose-dependent tissues (central nervous system and red blood cells). This response to starvation correlates with an increase in circulating levels of growth hormone, glucagon, epinephrine, leptin, and cortisol and a decrease in insulin and thyroid hormones. During PCM there is an increased drive to eat and a decrease in energy expenditure. Metabolism slows in an effort to conserve body fuels, and the body survives primarily on fat stores, sparing lean tissue until refeeding occurs.

Although similar adaptive responses to PCM can occur in the healthy older foal, the neonate has limited body reserves. The healthy newborn foal should have enough liver glycogen to support energy needs for several hours of life. However, glycogen stores at birth can vary significantly with illness or prematurity. Lack of early nutritional support can result in hypoglycemia or hypothermia and quickly affect the ability to maintain functions and behavior.

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Catabolic Response to Injury

During illness or after trauma, food intake frequently falls. However, despite this decline in intake, the adaptive responses to starvation do not occur. In contrast to PCM, in humans and laboratory animals, the metabolic response to injury (critical illness, sepsis, trauma, surgical manipulation, etc.) is characterized by an increased metabolism and the onset of a catabolic process leading to excessive breakdown of tissue proteins. There is a preference to use amino acids from the breakdown of skeletal muscle proteins as a metabolic fuel, in contrast to PCM in which fat is the principal source of energy. The adaptive switch to fat utilization is limited due, in part, to increased concentrations of circulating insulin. Insulin resistance develops, and hyperglycemia may occur despite the absence of food intake. This metabolic state is the result of a complex interaction of inflammatory cytokines, circulating hormones, and neurotransmitters and is designed to provide endogenous substrates for gluconeogenesis, wound healing, immune cell replication, and synthesis of acute-phase proteins.[1] Although this response is beneficial, long-term muscle breakdown results in loss of muscle strength, visceral organ dysfunction secondary to loss of structural and enzymatic proteins, impaired wound healing (due to loss of precursors for wound healing), immunosuppression, and compromise to the patient's overall health.

As sodium retention and water retention are components of this response, weight loss and muscle wasting frequently go unnoticed. Food deprivation during this hypermetabolic/catabolic state results in a much greater loss of lean muscle mass and visceral protein than would be expected during simple starvation. The metabolic adaptations to starvation in a healthy human can result in a 75% decrease in protein loss, whereas the metabolic responses to critical illness result in an increase in energy expenditure and protein metabolism.

Although nutritional supplementation can reverse the catabolic processes occurring during simple starvation, it will not completely reverse those occurring during metabolic stress because as long as tissue injury persists, catabolic processes are maintained.

Summary

In malnourished or debilitated individuals, nutritional supplementation (calories and/or protein) has been shown to be beneficial in improving survival, immune

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function, wound healing, and gastrointestinal function in humans and animal models.[2-5] Catabolism of lean muscle during critical illness and the resultant weakness have been the rationale for recommendations to increase amino acid supplementation in critically ill humans.[6-10] However, indiscriminate nutritional supplementation in patients without a history of malnutrition has not been clearly linked to improved outcomes and in some studies is associated with increased complications. Anorexia is part of the acute stress response and may be beneficial during illness as it activates autophagy, a cellular process that results in removal of damaged organelles, protein aggregates, and microorganisms. The autophagic response has been linked to improved outcomes in critical illness.[11] Nutrients (particularly amino acids), growth factors, and insulin suppress autophagy and may ultimately have a negative impact on morbidity and mortality. Recent randomized controlled trials have failed to show a clear benefit to early nutritional support (whether caloric or amino acid supplementation) in critical illness, and some have even found potential harm.[12-19] In human medicine recommendations are to determine nutritional risk factors in both baseline nutritional status and disease severity, as well as complication risks.[18-20] This information is then used to determine route (enteral vs. parenteral), type (standard formulations vs. supplementation of additional components), and rate of nutritional support.[21]

Thankfully, it is rare for large animal veterinarians to have to manage patients with the same severity and types of illnesses and comorbidities found in human intensive care units (ICUs). Exactly when and how much nutritional supplementation is ideal is not known, but extrapolation from human studies would suggest that meeting complete nutritional needs should not be the goal. However, the combination of an increased catabolism and the altered metabolic processes seen with injury and illness do cause significant loss of lean body mass and can impact the return to performance of a competitive athlete. Recently, research in nutritional therapy in humans and laboratory species has been focused on attenuating the metabolic response to stress, preventing oxidative cellular injury and favorably modulating the immune response with the ultimate goal being to reduce disease severity, complications, and length of stay, as well as to improve outcome.[21]

The goals for this chapter are to provide guidelines to help maintain muscle mass, provide essential nutrition, and decrease morbidity associated with illness. While nutritional support recommendations continue to be debated in the human

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intensive care unit, some tenets are likely to continue to hold true:

1. Hyperglycemia has been shown to negatively impact immune function and may increase the risk of infection. Control of blood glucose with a goal of avoiding severe hyperglycemia without risking hypoglycemia is recommended. At times, an insulin infusion may be necessary to prevent severe hyperglycemia, though careful blood glucose monitoring is recommended to avoid hypoglycemia.
2. Meeting 100% of our patients' nutritional needs is unnecessary and often unrealistic, as volume restrictions for enteral supplementation and costs for parenteral nutrition (PN) frequently limit our ability to provide the calculated requirement in large animal species.
3. Nutritional supplementation can have benefits in minimizing the severity of protein loss, providing both essential and conditionally essential amino acids, vitamins, and minerals, and in decreasing morbidity associated with illness.

Lastly, the approach to nutritional support of the large animal patient should be considered on an individual-case basis. This includes evaluating preadmission nutritional status and activity level, comorbidities that could impact recovery and metabolic response to illness, as well as illness severity and likely recovery time.

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Assessment of Nutritional Status

Although the healthy adult horse or ruminant with an adequate body condition score (see Chapter 9) and minor injury or illness rarely requires nutritional supplementation, early nutritional support should be strongly considered in patients with increased metabolic demands, such as young growing animals or lactating dams, individuals presenting with a prior history of malnutrition or hypophagia, patients with underlying metabolic abnormalities that could worsen with feed deprivation, and individuals with an illness such as severe trauma, sepsis, or strangulating bowel obstructions that may result in an increased metabolism and excess losses (e.g., albumin loss through a compromised gastrointestinal tract). Underweight horses with a BCS less than 3.5 out of 9 (though this depends on the breed and individual characteristics) should ideally receive nutritional support early in the disease process rather than waiting to see if the individual will begin to eat on his or her own volition. Obese or overconditioned individuals, particularly pony breeds, miniature horses, donkeys, and camelids, as well as lactating mares, are at risk for developing hyperlipemia and should receive nutritional support, especially if their serum triglycerides are above normal reference values. Lactating dairy cattle or pregnant sheep or goats should also receive early nutritional support to minimize the risk of developing ketosis, fatty liver, or pregnancy toxemia. Patients with pituitary pars intermedia dysfunction (formerly known as equine Cushing's disease) or equine metabolic syndrome are insulin resistant and may also be at greater risk for developing hyperlipemia and fatty infiltration of their liver. Depending on the severity and type of underlying disease process and individual characteristics (breed, body condition), some animals may develop severe hyperlipemia (triglycerides > 500 mg/dL) or ketosis within days of onset of anorexia. The combination of illness and metabolic effects of hyperlipemia or ketosis can worsen the individual's inappetence, creating a vicious cycle. Consequently, if feed deprivation is prolonged (in some cases as little as 1 to 2 days of anorexia can result in moderate to severe hyperlipemia) or there is a concern regarding the individual's desire or ability to eat, early intervention is indicated to prevent more severe metabolic complications.

A list of BCS descriptions for different species is provided in Chapter 9. Changes in weight or BCS are often easily overlooked on day-to-day observations of the patient if a concerted effort is not made at detecting them.

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Palpation of the animal (ribs, dorsal vertebral processes) is necessary in sheep with a heavy fleece, camelids with long fiber, and horses with a thick winter hair coat.

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Nutritional Needs of Sick or Injured Large Animals

Energy Requirements

While the energy requirements of large animal species of various ages, stages of growth, and activity levels have been determined and equations are available to calculate these needs, the energy and protein requirements for the hospitalized, sick patient are not known and likely vary depending on disease state, environment conditions, and level of fitness of the individual. Historically, multipliers have been used to estimate the energy requirements in certain conditions including severe sepsis, trauma, and burn injuries. However, the increased metabolic demand of illness or surgical trauma and recovery is likely to be balanced by the inactivity and decreased metabolic demands of digestion of the patient during hospitalization. Consequently, these multipliers likely overestimate the caloric requirement of certain illnesses. Studies in the human ICU and in sick neonatal foals suggest that the metabolic energy needs may fall more closely within the range of the resting to maintenance energy requirements of the normal, healthy animal.[22-24] The exceptions to this are individuals with extreme trauma, burns or severe sepsis, surgical conditions that require intestinal resection, and patients with large areas of devitalized tissue (such as clostridial myositis patients undergoing multiple fasciotomies). When estimating the energy requirements of the majority of other patients, resting energy requirements (DE_r) are an acceptable target. Resting energy requirements are defined as the amount of energy needed to maintain an individual (no weight gain or loss) in a *thermoneutral environment without the metabolic demands of digestion*. Maintenance energy requirements (DE_m) include the demands of digestion in this equation and are approximately 30% higher than resting energy requirements. Resting energy requirements will vary slightly depending on the size of the horse but can be estimated using approximately 22 to 23 kcal/kg/day for the average full-size horse. Maintenance energy requirements can be estimated using 30 to 35 kcal/kg/day. If a patient tolerates nutritional supplementation at resting energy requirements, the feeding rate (i.e., calories/kg/day) can be gradually increased if needed.

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Protein Requirements

The maintenance protein requirement of the healthy adult horse is estimated at approximately 0.5 to 1.5 g/kg/day. The needs of a growing foal are higher and may approach 7 g/kg/day during maximum growth periods. In addition, the lysine requirements of growing horses are higher than for mature horses.[25] During critical illness or severe injury, protein catabolism and utilization of amino acids as a source of fuel continue despite the presence of other energy stores. Consequently, when calculating protein requirements in human patients, it is recommended to provide the higher end of the estimated need.[22,26] Another consideration is supplementation of nonessential amino acids that may improve outcome in illness. Glutamine is considered a conditionally essential amino acid and is used as a fuel for enterocytes and other rapidly dividing cells.[27] In periods of inappetence the majority of glutamine is produced by mobilization of muscle stores.[28] Glutamine release during critical illness may act as a cell signaling molecule regulating the inflammatory and immune response; however, in periods of illness when glutamine requirements may actually increase, endogenous sources may be inadequate, resulting in relative glutamine deficiency.[29] Glutamine has been shown to be critical in maintaining gut wall integrity, immune function, and antioxidant supplies.[29] In a large-scale review of published meta-analyses and systematic reviews of glutamine supplementation's effect on outcomes, glutamine supplementation was associated with decreased infection complications, length of hospital stay, and mortality, suggesting it may be worth adding to supplementary diets.[30] Other recommendations for amino acid supplementation include branched chain amino acids and arginine supplementation. Arginine, a nitric oxide precursor, is an important vasodilating agent, it upregulates immune function, and may reduce ischemia reperfusion injury.[31-32]

The amount and ideal route of glutamine or arginine supplementation has not been determined in the horse. In one in vitro study, glutamine supplementation improved mucosal restitution in an oxidant-injured equine colon model.[33] Currently the American Society of Parenteral and Enteral Nutrition guidelines do not recommend addition of immune-modulating amino acid supplements due to a lack of evidence for outcome improvement in patients in the medical ICU and concerns about cardiovascular risks associated with modulation of nitric oxide.[9] In actuality, many commercially available parenteral and enteral products

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contain nonessential amino acids. When feeding by the enteral route, protein needs can be met by feeding a complete feed (which generally contains nonessential or conditionally essential amino acids) or by addition of specific amino acids to a component diet. Alternatively, glutamine can be purchased separately and added to a diet, though recommendations for amounts are currently not available.

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Nutritional Support of the Neonate

The healthy, full-term neonate is born with enough body fat and glycogen reserves to provide energy supply for approximately 12 hours. Premature or systemically compromised neonates (such as in-utero sepsis) may lack these minimal reserves, making them at increased risk for hypoglycemia, hypothermia, and organ dysfunction.

While a healthy, normal foal ingests approximately 15% of its body weight in milk per day during the first few weeks of life (increasing to as much as 30% during the first month), the metabolic demand of a sick, recumbent neonate is likely closer to 5% to 10% (50 to 100 kcal/kg/day).[23] Ten percent body weight in milk/day is typically adequate for growth and activity in neonatal calves. Neonatal small ruminants typically ingest between 10% and 15% of their body weight in milk per day. An example of a feeding schedule and volumes for a 50-kg foal can be found in Table 50.1.

TABLE 50.1

Milk Intake Requirements for a 50-kg Foal

Body Weight in Milk/Day	Liters/Day	mL/2-Hour Feedings
5%	2.5	208
10%	5	420
15%	7.5	630

A healthy average-size foal (50 kg) is expected to gain between 0.5 and 1 kg/day. Failure to gain weight can be a sign of an uncontrolled illness (such as a focus of infection) or the result of insufficient nutritional support.

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Enteral Routes of Nutritional Supplementation

The choice whether to use the enteral or parenteral route of feeding can be summarized by the simple statement, “if the gut works, use it.” While there are conflicting data regarding the pros and cons of parenteral feeding versus enteral feeding, it is clear that enteral feeding has some distinct benefits. Enteral nutrients provide the majority of nutrition to the gut, which is responsible for 15% to 35% of the total body oxygen consumption and protein turnover.[34] Enteral feeding offers the advantage of maintaining the gastrointestinal tract and is generally less expensive. Enteral feeding has been shown to improve gut barrier integrity, gut mass, protein content, motility, and function in piglets.[35] The complete absence of enteral nutrition results in mucosal atrophy, increased gut permeability, and enzymatic dysfunction in critically ill human patients.[36] Even small amounts of enteral feeding may provide benefits. In a neonatal piglet model, provision of 5% to 10% of nutritional needs by enteral feeding resulted in improved intestinal motility and lactose digestion and decreased mucosal permeability. Enteral provision of 20% of energy and nutrient needs for normal growth prevented loss of gut protein mass, whereas 40% to 60% of nutritional needs were needed to maintain normal gastrointestinal growth.[35]

The enteral route of nutritional support is simpler as there is less concern of fluid and electrolyte overload, and this route allows fiber feeding, which cannot be achieved parenterally. That said, clinicians are often hesitant to use the enteral route in patients with gastrointestinal disorders. In the critically ill patient with poor perfusion and decreased oxygen delivery to the tissues, the gastrointestinal tract is one of the most vulnerable organs to ischemia. Decreased oxygen delivery has been shown to increase mucosal permeability, resulting in increased translocation of bacteria and absorption of bacterial toxins.[37,38] Inflammatory mediators, produced in the gut as a result of ischemia, are absorbed across the damaged mucosa and enter the portal and systemic circulations; this absorption has been implicated in the onset of septic shock or multiorgan failure.[39] Inflammation and enterocyte injury can result in decreased motility and nutrient absorption. In this situation, institution of forced enteral feeding may result in colic, bloat, bacterial overgrowth, diarrhea, and other complications. Because

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digestion increases the metabolic activity of the enterocytes, enteral feeding during states of poor oxygen delivery may actually worsen the oxygen debt and ischemic injury. In contrast, enteral nutrition has been shown to increase total hepatosplanchnic blood flow in healthy patients, resulting in greater oxygen delivery to the mucosa, suggesting that enteral feeding may be beneficial in the poorly perfused gut.[39] In a rat *Escherichia coli* sepsis model, enteral feeding of glucose resulted in improved intestinal perfusion rates.[40] Given this conflicting information, the decision on the route of administration of supplemental nutrition must be determined on a case-by-case basis, with consideration of the primary disease condition, the status of the gastrointestinal tract, and individual clinician experience. The enteral route is always preferred when the gastrointestinal tract is functional. However, patients with overwhelming bowel ischemia, inflammation, and high risk of ileus or intestinal resection may not always be the best candidates for EN and may be better off started on PN while they are gradually reintroduced to enteral nutrition.

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Liquid Diets for Horses

In equids with decreased appetite or complete anorexia, enteral diet choices are limited to those that can be administered through a nasogastric tube. Types of liquid enteral diets include slurry diets composed primarily of normal feedstuffs (Table 50.2), commercial equine enteral diets, liquid component diets that allow the clinician to tailor the feeding regimen adding fiber, vitamins, minerals, and amino acids separately (Table 50.3), and commercially available liquid diets for humans (Table 50.4).

TABLE 50.2

Equine Feeds Suitable for Use in Liquid Enteral Diet

Feed	Digestible Energy (kcal/kg)	Crude Protein (%)	Crude Fat (%)	Crude Fiber (%)	Nonstructural Carbohydrate (%)	Ethanol-Soluble Carbohydrate (%)	Starch (%)
Equine Senior[a] (Purina Mills)	2695	14.0	4.0	13.0	20	8	9
Strategy Healthy Edge[a] (Purina Mills)	2860	12.5	8.0	18.0	18	5	12
Senior[a] (LMF)	2341	14.0	4.0	20.0		5.9	22
Senior[a] (Triple Crown)	3401	14.0	10.0	17.0	11.7	5.3	6.4
Low Starch[a] (Triple Crown)	3142	13.0	6.0	18.0	13.5	3.1	10.4
Alfalfa pellets[b]	2190	16.7	2.3	24.7	9.3	7.0	2.1
Grass pellets[b]	2050	13.1	2.6	22.1	12.1	6.8	3.3
Oat hay pellets[b]	1790	7.74	2.1	26.2	20.1	9.9	4.4

[a]As fed, manufacturer analysis.

[b]As fed, average values, Equi-Analytical Laboratories, 2013.

TABLE 50.3

Composition of and Feeding Schedule for Naylor Diet

Constituents	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Electrolyte mixture	230	230	230	230	230	230	230
Water (liters)	21	21	21	21	21	21	21
Dextrose (grams)	300	400	500	600	800	800	900

Dehydrated cottage cheese (grams)	300	450	600	750	900	900	900
Dehydrated alfalfa meal (grams)	2000	2000	2000	2000	2000	2000	2000
Energy (nonprotein calories), kCal	7400	8400	9400	10,400	11,800	11,800	12,200

From Naylor JM, Freeman DE, Kronfield DS: Alimentation of hypophagic horses. *Comp ContEducPract Vet* 6:S93, 1984.

TABLE 50.4
Nutritional Content of Selected Liquid Diets

	Vital HN[a]	Osmolite[a]	Critical Care Meals/Packet
Cal/L	1000	1008	1066
Protein	41.7 g/dL	40 g/dL	12%
Fat	10.8 g/dL	34 g/dL	1%
Carbohydrate	185 g/L	135.6 g/L	73%

[a]Product formulated for human use.

Complete pelleted feeds offer several advantages—they are relatively inexpensive, meet the maintenance nutrient requirements, and contain sources of fiber. Fiber is beneficial in increasing colonic blood flow, enzymatic activity, and ruminal and colonic mucosal cell growth and absorption.[41]

Both human and equine liquid formulations are available and have been used as enteral nutrition support in horses.[42-45] The use of human products (Osmolite and Vital HN) in the mature horse can be expensive and has been associated with diarrhea and laminitis (though cause and effect are not clear); consequently they are rarely used and not currently recommended, having been largely replaced by equine-specific formulations.[46,47] WellSolve Well Gel (Purina Mills, LLC, St. Louis, Mo.) and Enteral Immunonutrition Formula (Platinum Performance, Inc. Buellton, Calif.) are two diets currently available for use. The major disadvantage of these products over complete pelleted diets is their cost.

Component diets have been described for use in equids.[47] Corn oil may be added to the diet to increase the caloric content but should be added gradually (increasing the intake by ¼ cup or 60 mL daily not to exceed 2 cups or 600 mL total daily intake) to prevent diarrhea.

Liquid diets can be given by continuous flow through an indwelling small-bore (18-French) nasogastric feeding tube (Mila International Erlanger, Ken.) or via periodic passage of a nasogastric tube and administration of larger meals. When using pelleted diets in equids, the authors recommend that 1 kg of a pelleted complete feed be soaked in approximately 4 L of water. Once this water

has been absorbed, an additional 2 L of water are added to form a slurry that can be administered via a large-bore (external diameter 305 cm) nasogastric tube. Slurry diets made from complete pelleted feeds may not pass through a nasogastric tube using gravity alone. Instead, the slurry can be administered by use of a marine supply bilge pump. If a bilge pump is not available or a large-bore tube cannot be passed, pulverizing the pellets before adding water may improve gravity flow. The horse should be checked for the presence of gastric reflux before administration, and the slurry should be pumped slowly with attention paid to the animal's attitude and reaction. As the stomach volume of a mature, 450-kg horse is approximately 9 to 11 L, the volume of each feeding should not exceed 6 to 8 L per feeding. The volume fed should be adjusted for smaller horses. Long-term placement of nasogastric tubes in horses is not without the risk of complications.[47] Small-bore, 18-French, softer (polyurethane) tubes (Mila International, Erlanger, Ken.) are recommended if intubation is prolonged, as they are better tolerated by the patient but generally preclude the use of slurry diets. Alternatively, intermittent placement of a nasogastric tube is effective in decreasing complications but can be difficult, and at times traumatic, for the patient. When instituting enteral feeding, particularly in a patient with prolonged anorexia, it is best to start gradually increasing the amount fed over several days (Table 50.5). A maximum of 50% of calculated requirements should be fed in the first 24 hours; if the patient tolerates this level of supplementation, the amount can be increased over the next few days until the target feeding rate is achieved. Rapid changes in feed amount such as feeding 100% of required intake the first day in an animal that has not eaten for 3 to 5 days can be associated with colic, regurgitation, or diarrhea, particularly with liquid diets made for humans or high-fat diets.

TABLE 50.5

Enteral Feeding Schedule for Adult Horses (450-Kg Horse)

Day 1	Day 1	Day 2	Day 3	Maintenance (1%-1.5% Body Weight)
Number of meals	2-3	3-4	4-6	4-6
Complete feed (kg)/meal	0.5 kg	0.75	0.75-1.0	1.0-1.25
Water (L)/meal	4-6	4-6	6-8	6-8

Creation of an esophagotomy should be considered when prolonged enteral nutritional support is likely to be required or when medical or surgical conditions prevent passage of a nasogastric tube. Esophagotomy can be performed in a

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standing, sedated animal and, once in place, allows frequent intubation and feeding while avoiding the trauma and discomfort associated with repetitive nasogastric intubation. Once the animal has recovered and its appetite has returned, tube feeding can be discontinued to allow the esophagotomy incision to heal by second intention.

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Liquid Diets for Ruminants

In most cases the most practical and least expensive way to force-feed ruminants is the blender-type or slurry diet. Hypophagic adult cattle and other ruminants may be force-fed a suspension of alfalfa meal and/or slurry made from soaked complete pelleted feeds. Some classic examples where force-feeding may be indicated include cows with hepatic lipidosis, cattle with balling gun injuries/retropharyngeal trauma, mandibular fractures, tetanus, or listeriosis where oral feeding is either impossible or contraindicated. Administration of the enteral feedings can be achieved simply by passing an ororumenal tube (adequate for patients who may only necessitate enteral feeding for a short period of time) or placing a temporary rumen cannula (for patients necessitating enteral feeding for extended periods of time. An additional advantage of rumen cannula feeding is that the clinician is no longer limited to a strictly liquid diet as grain and finely chopped hay can be administered through the rumen cannula. Administration of ruminal liquor obtained from a healthy donor cow provides a good source of microflora, as well as volatile fatty acids and essential amino acids as an energy source in hypophagic cows, and is felt to be beneficial in all ruminant species.[48]

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Enteral Supplementation in Neonates

Enteral Support of the Neonate

The enteral route of nutrition is always preferred over parenteral, as enteral feeding has been shown to increase gastrointestinal mass and function compared with the parenteral route. Small volumes (1% to 2% body weight in 24 hours divided into q2h feedings) are recommended when initiating enteral feeding in foals, particularly if there is concern regarding the health of the gastrointestinal tract. Over time, one can gradually increase the volume fed, paying careful attention to changes in intestinal motility, residual volumes of gastric milk, and signs of colic or diarrhea. An example of a gradual feeding schedule for a sick neonatal foal can be found in Table 50.1.

Enteral feeding should be avoided in severely hypotensive or hypothermic neonates. Those with enteropathy, whether secondary to oxygen deprivation or infection, may be unable to absorb nutrients and develop colic and diarrhea when fed. A detailed history and careful repeat assessments of the neonate's gastrointestinal tract (including ultrasound examination if possible) are critical to ensure that the patient can tolerate enteral feedings. Enteral supplementation should be avoided in individuals with a dilated small intestine or ileus or other signs of enteritis. Sequential measurement of abdominal size can be useful to assess gastrointestinal distension and intolerance to feeding. Colic signs in foals are often subtle; foals may appear fussy or agitated and show an increase in heart rate and respiratory rate. If deterioration is noted, enteral feeding should be discontinued or decreased until resolution.

Foals, beef calves, and neonatal small ruminants normally nurse relatively small amounts of milk frequently throughout the day, whereas dairy calves drink larger volumes less frequently. When foals are fed less frequent meals, hunger may cause them to rapidly ingest larger volumes, overloading the small intestinal ability to digest the nutrients, which can result in bloating, colic, and diarrhea. If this occurs, feeding cold milk may help limit large-volume ingestion. An acidified milk replacer is also available; this product is less likely to become rancid when left out for long periods of time during the warmer season.

Generally, a neonate that is too sick to stand is also unlikely to have an adequate suckle reflex. Bottle or syringe feeding is strongly discouraged when supplementing sick or recumbent neonates. These individuals often have a weak

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or absent suck, putting them at high risk for aspiration. Small soft nasogastric tubes (MILA International Erlanger, Ken.) that may be sutured in place for longer-term use are available for use in foals and have also been used in neonatal calves. Many of these tubes come with a guide wire, which helps stiffen the tube to make insertion easier. Before feeding, it is important to determine if the tube is in the stomach or abomasum. A radiograph can be helpful to identify the radiopaque strip within the tube. Alternatively, tubes can be detected by ultrasound or careful palpation of the esophagus during passage. Alternatively, calves can be fed using esophageal feeders to ensure milk is deposited in the abomasum and not the immature rumen. In neonatal small ruminants, red rubber catheters are often used for esophageal feeding.

When introducing a foal to nurse, it is often beneficial to milk the mare first and feed the foal via the nasogastric tube. This decreases the risk of aspiration due to large-volume let-down by the mare or extreme hunger by the foal. Auscultating the foal's trachea while nursing can help determine if aspiration is occurring. Bucket feeding allows the foal to nurse with its head down, decreasing the risk of aspiration. Once the foal is trained to the bucket, it can be hung in the stall, allowing them to drink at will. Clinicians should also remember to provide other foodstuffs, as a foal will begin mimicking their dam eating hay and concentrates within the first few days of life.

Enteral Feeds for Neonates

Natural species milk and colostrum are ideal enteral feeds for neonates. When mare's milk is limited, supplementing with goat's or cow's milk is generally recommended at least through the early neonatal period (first 2 weeks of life). Many neonatologists prefer goat's milk as a better replacement to mare's milk. Although comparison of the fat, protein, and calories content among goat, sheep, and cow milk does not seem to reveal any significant benefit of one over the other, the major whey protein in both goat and mare milk is β-lactoglobulin, while the major whey protein in cow's milk is α-lactoglobulin.

If necessary, gradual transition from one type of milk or replacer is recommended, as rapid changes may result in colic, diarrhea, or constipation. If constipation develops, a small amount of mineral oil (5 mL) may be added to tube-fed meals. The fluid characteristics of mineral oil make it unsafe to administer orally, as it will not stimulate a cough reflex if aspirated. Even a small amount of aspirated mineral oil can result in significant pulmonary consolidation

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and dysfunction.

Unlike calves, long-term supplementation of a foal typically requires switching to milk replacers due to cost and accessibility issues of whole milk products. If using a milk replacer, it is strongly recommended to choose a replacer developed for foals rather than one designed for all large animal species to ensure adequate protein, fat, and carbohydrate concentrations. Replacers that contain whey protein are recommended over other protein sources due to digestibility concerns. In contrast to milk replacers, milk is high in potassium and low in sodium and chloride. When feeding milk replacers, it is important to provide a freshwater source to prevent hypernatremia.

Key Points

- Enteral nutrition provides intraluminal nutrition to the gastrointestinal tract and has been shown to improve gut barrier integrity, gut mass, protein content, motility, and function.
- Enteral feeding needs to be increased gradually with careful assessment of gastric residuals before bolus feeding.
- Enteral nutrition can be tailored using complete feeds or specific components diets.

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Parenteral Nutrition

PN' major advantages are its abilities to supply nutrition when the enteral route is unavailable and tailor the types of nutrition provided for each individual animal. PN has been shown to decrease weight loss, particularly lean body mass, and improve wound healing, immune function, and outcome in human and animal studies when the enteral route cannot be used.[49] PN can be used to provide partial nutritional support or total nutritional support. In the adult horse it is most commonly used to supply partial nutrition when oral intake is insufficient or the oral route cannot be used. Horses with proximal enteritis, colitis, postoperative ileus, esophageal lacerations, or obstructions can receive nutritional support until resolution of the underlying problem allows reinstitution of adequate enteral feeding (1.5% body weight or ~23 kcal/kg day). Recumbent or dysphagic animals at risk for aspiration pneumonia and individuals with preexisting protein calorie malnutrition; increased energy demands (late gestation, early lactation, and young, growing animals); metabolic derangements resulting in hyperlipemia; and completely anorexic animals or those with prolonged decreased feed consumption (<25% maintenance for several days) should also be considered as candidates for partial or total PN.

There has been a significant amount of information published in recent years evaluating the pros and cons of PN. Much of the impetus has come from the desire to determine if there is a negative effect of relying on PN as the sole nutritional source. Although the results of studies vary, it appears that the major disadvantage lies in the loss of the beneficial effect of enteral nutrition on maintaining gut function and mass. PN is more expensive than enteral feeding in terms of supplies and time. In humans, the parenteral route may also be associated with an increased risk of infection, although results are contradictory.[49,50] Published reports of PN use in horses primarily consist of case reports with little information evaluating the benefits and risks of PN.[51-55]

In a retrospective study examining 79 equine cases of gastrointestinal disease treated with PN, the most common complication was hyperglycemia.[46] Four horses developed thrombophlebitis. Because no comparison was made between PN-treated individuals and controls, the authors were unable to determine if PN affected outcome.[46]

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Dextrose

The simplest and least expensive form of PN is the supplementation of intravenous crystalloid fluids with dextrose. This represents a short-term solution for boosting caloric intake and preventing secondary metabolic derangements when a rapid return to normal feed consumption is anticipated. Dextrose can be added to make a final solution with a concentration that ranges from 2.5% to 5%. If the fluid is infused at a rate to meet maintenance fluid requirements (1 to 2 mL/kg/h), the patient's renal threshold of glucose (10 mmol/L or 180 dL for adult horses; 121 mmol/L or 216 dL for foals) will usually not be exceeded. The energy provided may be calculated on the basis of 3.4 kcal/g of dextrose. A 450-kg horse treated with fluids supplemented with 2.5% dextrose and infused at a rate of 1 L/h (24 L/day) will receive 2040 kcal from the dextrose (close to 20% of the patient's DE_{rest}). Although protein is not provided with the dextrose therapy, the supplemental energy will blunt the catabolism of endogenous lipid and protein stores. Patients treated with dextrose should have their blood glucose monitored closely.

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Complex Parenteral Nutrition

Depending on the desired goals and duration of supplementation, solutions containing various amounts of carbohydrate, amino acids, lipids, vitamins, electrolytes, and minerals can be formulated. Carbohydrates and lipids are used to meet the patient's energy needs, minimizing breakdown of endogenous protein for energy and allowing the administered amino acids to be used for wound healing and immune functions. Carbohydrate is commonly provided using 50% dextrose solutions. These solutions are hyperosmolar (2525 mOsm/L) and should be infused through a central line or large peripheral vein (jugular vein) to reduce the risk of thrombophlebitis. Dextrose provides 3.4 kcal/g or 170 kcal per 100 mL (50 g) of 50% dextrose.

Lipids are recommended to provide the remainder of nonprotein calories. Lipids are isotonic and can be infused separately in a peripheral vein or combined with other components. Lipids come in 10% and 20% emulsion and are composed principally of safflower and soybean oil, egg yolk phospholipids, and glycerin. Lipids should be added to the solution last to avoid destabilization of the emulsion due to an acidic environment. Some clinicians mix PN solutions in isotonic crystalloids to provide both fluid support and nutritional support. When doing so, it is best to separate the lipid component, as the presence of divalent cations can result in destabilization of the emulsion. Some clinicians are reluctant to use lipids in PN solutions due to the costs and risks associated with destabilization, as well as metabolic consequences that may develop (hyperlipemia, fatty liver, lipid thromboembolism). It can be difficult to provide total energy requirements without lipids, especially in insulin-resistant patients or patients with systemic inflammation, as these individuals appear to have a harder time regulating blood glucose. Lipids are calorie dense, containing 9 to 11 kcal/g. Although recommendations vary, lipids can be added to provide 30% to 60% of the nonprotein calories in a PN solution. The addition of lipids to PN is beneficial in patients with persistent hyperglycemia or hypercapnia, reducing the dependency on glucose as the principal energy source. Lipids should be avoided in horses with known hyperlipemia or in horses suspected of being lipid intolerant. Lipid intolerance can be seen in patients with systemic inflammation, sepsis, or underlying metabolic derangements, and triglyceride levels should be monitored regularly.

Amino acid preparations are available in several concentrations; 8.5% and

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10% solutions are most commonly used in veterinary medicine. They are approximately twice the osmolarity of plasma and are acidic. Amino acid preparations should be mixed with dextrose before adding the lipid component to prevent destabilization of the lipid emulsion. Solutions containing both essential and conditionally essential amino acids, including glutamic acid, would seem to be preferable, though no data on the benefits of conditionally essential amino acids in horses are available. As already discussed, while resting energy requirements should be used when calculating caloric needs for adult animals, protein requirements should be determined using maintenance requirements of approximately 0.7 g/kg/day or higher. Although there are no clear data on the benefits of a higher protein supplementation, current recommendations in humans are to provide protein in excess of the normal daily requirement because of the higher protein catabolism seen with injury or inflammation. The ratio of nonprotein calories to nitrogen (in the final solution) is recommended to be 120 to 150 : 1 in healthy humans and 80 to 90 : 1 in acutely ill humans to limit the use of protein as an energy source. The ideal ratio in equids is unknown; consequently, human targets are typically used. This can be calculated using the conversion of 1 g nitrogen to 6.2 g protein. Protein provides ~4 kcal of energy/g protein, and 100 mL (10 g) of 10% amino acid solution contain 40 kcal.

Additional components may be added to PN or given separately including electrolyte solutions and vitamin and mineral supplements. The vitamin and mineral requirements of the critically ill horse are unknown, but published recommendations for healthy horses (NRC 2007) can be used when determining feeding rates. Multivitamin supplements for humans are available and can be added directly to PN solutions. If possible, however, it is best to limit the amount of additives to PN solutions to avoid contamination or lipid destabilization. On the basis of information in humans, it is strongly recommended to supplement water-soluble B vitamins daily as deficiencies can exacerbate problems associated with refeeding.[56] Though horses and ruminants synthesize some of the B vitamins in their gastrointestinal tract, chronic inappetence or disruption of the normal flora may affect synthesis. Parenteral B vitamins are light sensitive; when added to crystalloids, the fluids need to be protected from sunlight. Some vitamins are best given orally (vitamins C and E) or added to separate crystalloid solutions (B vitamins). Vitamin C is also produced by the horse, and a need for supplementation has not been documented. However, some authors recommend oral supplementation in sick horses with recommendations of 10 to 20 g/horse/day.[57] Fat-soluble vitamins such as E, D, and A are stored in body tissue

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and generally do not need daily supplementation. However, the antioxidant benefits of vitamin E may make it worth providing oral supplementation early in illness. Doses of oral vitamin E vary significantly from 500 international units (IU)/horse/day to 40 IU/kg/day. Minerals, if required, are best supplemented in separate crystalloid solutions because divalent cations may destabilize lipid emulsions. Although trace mineral requirements for sick animals are not known, trace mineral supplementation is rarely performed except in patients receiving PN as their sole nutritional source for prolonged periods (>7 days). See Table 50.6 for a PN formulation for adult horses.

TABLE 50.6

Parenteral Nutrition Formulation for Adult Horses

Ingredient	Dosage Rate	Volume/Day (450-kg Horse)
50% Dextrose	2.8 g/kg/day	2500 mL
10% Amino acids[a]	1.3 g/kg/day	6000 mL
10% Lipid[b]	0.8 g/kg/day	3500 mL

[a]FreAmine III, Braun Medical Inc., Irvine, CA.

[b]Liposyn III, Hospira Inc., Lake Forest IL, or 20% Lipid solution: Nutrilipid B, Braun Medical Inc., Irvine, CA.

Ratio of dextrose−amino acids−to-lipid is 1 : 2.4 : 1.4.

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Parenteral Nutrition in Ruminants

Because of cost, use of PN is usually limited to calves, and little information exists on the use of PN in the adult bovine or ovine and caprine species.

Parenteral Nutrition for Foals and Calves

Because of their poor energy stores, early nutritional supplementation is critical in inappetant neonates. A dextrose infusion can be instituted initially while determining the health and function of the gastrointestinal tract. The placenta is reported to supply approximately 4 to 8 mg/kg min of glucose (~25% to 50% DE_r), and this is a useful target when providing short-term parenteral support with dextrose.[58] This would equate to 4 to 8 mL of a 5% dextrose solution per minute. Glucose infusion alone is inadequate as a long-term nutritional source; therefore more complete PN is needed for prolonged intolerance to enteral feeding.

The initial target energy intake for a critically ill neonatal foal or calf is 40 to 50 mg/kg. Hypertriglyceridemia (>200 mg/dL) has been associated with higher mortality in neonatal foals.[46] To limit complications, lipid calories should comprise less than 50% of the nonprotein calories in a PN formulation.

A PN formulation designed with 8.7, 3.0, and 1 g of dextrose, amino acid, and lipid, respectively, per kilogram body weight (BW) per day provides a total energy of 50 kcal/kg BW/day, a calorie-to-nitrogen ratio of 104 : 1, and an osmolarity of 1260 mOsm/L (Table 50.7). The PN formulation contains 21% calories from protein, 20% calories from lipid, and 59% calories from dextrose, with lipid comprising 25% of the nonprotein calories. If the foal or calf tolerates the full infusion rate, more calories can be added from all ingredients to achieve a recipe that provides 70 to 100 kcal/kg BW/day. An anabolic state can be achieved solely with PN therapy, but because enteral feeding is the desired goal, EN or oral milk consumption should begin as soon as possible. Changes in the rate of infusion and the PN formulation should be made to prevent hyperglycemia, but insulin can be administered if necessary to maintain blood glucose in a normal range.

TABLE 50.7

Parenteral Nutrition Formulation for Foals (50 kg)

Ingredient	Dosage Rate	Volume/Day (50-kg Foal)
50% Dextrose	8.7 g/kg/day	870 mL
10% Amino acids	3.0 g/kg/day	1500 mL
10% Lipid	1 g/kg/day	500 mL

The most common indication for the use of PN in calves is diarrhea, particularly in chronic cases accompanied by weight loss.[59] In such cases, if sufficient milk is fed to meet the calf's nutritional needs, the diarrhea is often exacerbated and PN allows the quantity of milk to be reduced without compromising the nutritional status of the patient. The PN regimen provided for foals in Table 50.7 would also be suitable for calves. However, because amino acids and lipids are the most expensive components of PN, a modified formula based on a 10 : 2 : 1 glucose-to–amino acid–lipid ratio has been used with success.[26] For a 50-kg calf, this would allow the quantity of milk to be reduced without compromising the nutritional status of the patient. B vitamin or multivitamin products may be added to the formula (≈1 mL of supplement/L PN), but trace minerals are not usually necessary for the short-term administration that is most common in calves.

Preparation and Administration of Parenteral Nutrition (Box 50.1)

Preparation of PN should be performed under a laminar flow hood (or a clean surface away from drafts or excessive dust) using aseptic techniques. Lipids should be added last to prevent destabilization of the emulsion in acidic amino acid solutions. Parenteral solutions are an excellent media for growth of bacteria and ideally should be used within 24 hours of preparation. Before use, they should be kept in a dark, cool area away from direct sunlight to minimize degradation and loss of vitamins (when these have been added to the solution). Over time, lipid emulsions will destabilize and oxidize, so they should not be stored for prolonged periods. The shelf life of a lipid solution will vary depending on the type of lipids and size of the emulsion, so manufacturers' recommendations should be used when determining shelf life. Because PN solutions are hyperosmolar, delivery through a central venous or jugular catheter is recommended. Because of the increased risk of sepsis associated with parenteral feeding, a separate catheter or portal should be designated for PN only. In the authors' clinic, a 14-gauge double-lumen catheter (Arrow Catheter,

Reading, Pa.) is used with one port designated for administration of PN. Catheter placement and line maintenance should be performed using strict aseptic technique, and it is currently recommended that all lines be changed daily and that connections should not be broken after changes. Administration of PN solutions should not be stopped suddenly; if the animal needs to be moved, it is best to continue administration during the transfer. Gradual introduction of PN is recommended to decrease the risk of complications. It is recommended to use an intravenous infusion pump to ensure that the rate of infusion is consistent. We generally start with an infusion rate targeting approximately 25% of the daily requirement. The most common complication associated with PN is hyperglycemia, and blood glucose concentrations should be determined before increasing the rate of infusion. If blood glucose levels are within reference ranges, then the rate can be increased by an additional 25% every 4 to 8 hours. In the authors' experience most patients will develop mild hyperglycemia that corrects without treatment. Patients with persistent hyperglycemia may require insulin infusions to control the hyperglycemia and allow continued infusion.

Box 50.1

Instructions for Compounding a Parenteral Nutrition Solution

1. Compound the solution in a laminar flow hood, if available. Use a clean room in the hospital if a laminar flow hood is not available.
2. Clean the preparation area well, using alcohol as a final preparation on the counter.
3. Wear a gown, mask, and sterile gloves when compounding the parenteral nutrition (PN) solution.
4. Wipe off all injection sites and infusion ports with alcohol before connecting the infusion lines.
5. Use a new transfer set for each PN ingredient.
6. Add the dextrose and amino acid solution to the compounding bag or container. Mix gently.
7. Add the lipid solution *after* the dextrose and amino acid solutions have been mixed together.

8. Gently swirl the solution to mix the ingredients.
9. Add any vitamin or mineral supplements to the solution *after* the macronutrients (dextrose, amino acid, lipid) have been added. Ensure that there are no incompatibilities with the supplemental additives.
10. The PN formulation can be stored in the refrigerator for 24 hours, followed by 24 hours of storage at room temperature. Shield the solution from sunlight.

Complications Associated With Parenteral Nutrition

Hyperglycemia both at admission and during hospitalization has been associated with an increased risk of complications including infections and renal failure, longer hospital stays, and reduced survival in humans and horses with critical illness or injury.[60,61] In a landmark prospective, randomized, controlled clinical trial of humans admitted to the ICU, tight glycemic control using intensive insulin therapy during hospitalization was associated with a significant improvement in morbidity and mortality compared with the more traditional, less stringent glycemic control.[62] Tight glycemic control (maintained between 80 and 110 mg/dL compared with 180 to 200 mg/dL) decreased the incidence of infections, acute renal failure, and days of mechanical ventilation and improved neurologic outcome in brain injury patients.[63] Additional studies using less stringent glucose control have found similar results.[64,65] As previously mentioned, hepatic gluconeogenesis is upregulated during the acute phase of critical illness. Insulin resistance and loss of exercise-associated uptake of glucose, as well as the increased production of glucose, are thought to result in hyperglycemia. Normal cells downregulate glucose transporters during periods of hyperglycemia to protect against glucose toxicity.[66] During inflammation this protective response is lost, allowing glucose to enter the cell along a steep concentration gradient.[67,68] Elevated intracellular glucose concentrations have been associated with increased oxidative stress, mitochondrial dysfunction, and altered energy metabolism.[69] The use of insulin therapy to maintain blood glucose levels within the normal range has been shown to have the added benefit of correcting dyslipidemias.[70] Additional reported beneficial effects of maintaining euglycemia include improved immune function due to improved phagocytosis, decreased glycosylated nonfunctional immunoglobulin, and

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blunting of the catabolic process.[71-74]

While extrapolation to a different species with different underlying diseases should always be performed cautiously, it would seem prudent to try to maintain blood glucose concentrations within or close to normal range. It is unclear at this time if strict glycemic control is better than a less stringent control. In cases where hyperglycemia persists, the use of intensive insulin infusions is recommended to attempt to normalize the blood glucose concentration.

Lipid infusions have been associated with allergic reactions, hyperlipemia, alterations in liver function, and fat embolism. The risk of fat embolization is higher in larger droplet emulsions or in emulsions that have been stored too long and have begun to destabilize. Although solutions containing lipids are useful in providing additional calories, their use needs to be determined on a case-by-case basis. Lipids should be avoided in patients with a predisposition to or preexisting hyperlipemia or underlying liver dysfunction. Thrombocytopenia, coagulopathy, fat embolization, and alterations in cellular immunity are reported with lipid infusions. Triglyceride levels and platelet counts should be monitored regularly when lipids are added to PN solutions.

Additional complications reported with PN include hyperammonemia and elevations in serum urea nitrogen due to excess protein catabolism, hypercapnia due to excess carbohydrate metabolism, thrombophlebitis due to hypertonicity, pulmonary embolism (thought due to destabilized lipid emulsions), and sepsis.[46,51,75-77]

Monitoring

It is recommended to monitor blood glucose at least every 4 to 6 hours when starting PN and to adjust the rate to try to maintain blood glucose within or close to the established normal ranges. If significant hyperglycemia (>180 mg/dL) develops and persists for more than 2 to 4 hours, the infusion should be slowed or insulin infusion begun. If costs are a concern, blood values may be monitored less frequently once steady state has been achieved. In addition, daily assessment should include serum electrolytes (especially potassium and phosphorus), TCO_2, blood urea nitrogen, triglycerides (depending on species), and ammonia and liver function during the acclimation period. If possible, the patient should be weighed daily. Once a steady state has been reached, the frequency of blood monitoring can be decreased. The same approach should be used when discontinuing PN.

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The most common reason for instituting PN is the unwillingness or inability of a patient to ingest feed. For patients with decreased appetite, palatable feeds should be offered even during PN therapy to try to stimulate appetite. Once a patient has begun to readily ingest and tolerate a reasonable amount of food (25% normal intake or more) and has a steady appetite, PN can be gradually discontinued. Decreasing the supplement by 25% every 4 to 8 hours is generally well tolerated. Frequent monitoring of blood glucose during withdrawal (every 4 hours) is warranted, particularly in foals due to the risk of transient hypoglycemia.

Key Points

- PN allows provision of nutritional support when the enteral route is unavailable.
- PN allows supplementation to be tailored to the individual animal.
- PN must be handled with strict aseptic technique and should be gradually introduced and discontinued to prevent metabolic consequences.

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Conclusions

It is clear that nutritional support is an important adjunct to medical therapy in the sick, injured, or debilitated large animal patient. What is not clear is the optimal route, composition, or amounts of support. The enteral route should be chosen whenever possible to maximize the benefits to the gastrointestinal tract, as well as the patient as a whole. Complete or partial PN is most useful as a bridge during recovery and transition to enteral feeding in the horse. Although the exact caloric requirement for sick, debilitated animals is unknown, estimates are available to use as a target for nutritional supplementation. Research in humans and laboratory animals suggests that even a little nutritional support is beneficial, and the reader is encouraged to consider nutritional support, whether enteral or parenteral, in any anorexic, chronically debilitated, or sick large animal patient.

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PART 7
Congenital, Hereditary, Immunologic, and Toxic Disorders

OUTLINE

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• CHAPTER 51

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Genetic Disorders

Angela M. Hughes, Kari J. Ekenstedt, Consulting Editors

Inherited diseases and congenital defects are structural or functional abnormalities that may or may not be obvious at birth. There are a wide range of possible defects, from a single structural change (e.g., leg length) to the involvement of multiple organs or systems (e.g., storage diseases, chromosomal abnormalities), depending on the type and extent of toxic exposure during gestation or genetic mutation. It is important to identify animals with genetic or congenital disorders because of the economic and emotional impact on clients, but many disorders can be difficult to recognize and trace, particularly if they lead to embryonic or fetal death, abortion, dysmaturity, premature birth, or full-term stillbirth.

It is important to remember that not all congenital defects are genetic in origin, and making the distinction between conditions caused by an environmental factor or by a genetic cause will help clients make appropriate changes to prevent the disorder in the future. To determine the cause of a disorder, it is vital that each case be examined thoroughly. Each case should be subjected to a full, careful description of the disorder including a complete necropsy. The environment and management conditions should be investigated for potential causative agents, and all available genetic information for the affected animal(s) and unaffected herdmates should be collected including sex, birth date, and breed. Environmental teratogens affecting large animals include toxic plants, drugs, viruses, and physical agents (e.g., hyperthermia, irradiation). Although it may be difficult to identify inciting teratogens, analysis of affected herds will reveal patterns that follow seasonal or management changes or stressful events.

This chapter focuses on the essential genetic information that veterinarians require to inform their clients about genetic diseases, make breeding recommendations, and find information on diseases and traits with a genetic component.

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Genetic Information

The basic blueprint for life in most organisms, the genetic material, is deoxyribonucleic acid (DNA). DNA is composed of two strands of *nucleotides:* adenine (A), thymine (T), guanine (G), and cytosine (C). These nucleotides, or bases, align to form complementary pairings such that A always pairs with T and G always pairs with C. These strands can be completely separated and replicated in preparation for cellular division. Alternatively, they can be temporarily partially separated and transcribed into ribonucleic acid (RNA), which is then translated into functional proteins.

The DNA sequence of a mammalian genome is divided into autosomes and a pair of sex chromosomes, X and Y. Each chromosome contains a variety of genes and "filler" DNA that does not code for proteins but may determine where and to what degree each gene is expressed. Genes on each chromosome code for the various structural and enzymatic proteins required for life. One set of chromosomes, and thus one set of genes, is inherited from each parent. As a result, a mammal generally has two copies, or alleles, of any given gene. Simple traits or diseases involving these genes can be inherited in dominant or recessive patterns and involve the autosomes or sex chromosomes. Not all traits or inherited diseases are simple; many involve multiple genes and interactions between genes and the environment, which can unfortunately make it difficult to diagnose and understand a complex disease or trait.

Recessive Inheritance

Traits or diseases with a recessive mode of inheritance require two affected alleles of the gene to express that trait or disease. These conditions can be *autosomal,* involving genes on the autosomes, or *sex-linked,* caused by genes on either the X or Y chromosome. Generally, autosomal recessive traits or diseases are caused by loss-of-function mutations in which the gene product has decreased ability or no ability to perform its original function. When an animal inherits the affected allele from both parents, it is *homozygous* for the affected alleles and is unable to make functionally normal copies of that specific protein. *Heterozygous* individuals inherit only one copy of the affected allele, and they have a "backup" copy of the normal or wild-type allele to provide the functional protein. These heterozygous individuals are carriers of the trait or disease allele

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and can produce affected offspring if bred to another heterozygous or homozygous affected individual.

The hallmarks of autosomal recessive traits include 1) all offspring of two affected parents are affected, 2) approximately equal numbers of males and females are affected, and 3) unaffected carrier parents can produce affected offspring, and thus the trait or disease can skip generations. In addition, mating an affected individual to a noncarrier (homozygous normal) produces only offspring that appear normal but carry the affected allele. Breeding two carrier individuals results in approximately 25% normal, 50% carrier, and 25% affected offspring.

An example of an autosomal recessive trait is spider lamb syndrome, or hereditary chondrodysplasia. Lambs affected with this syndrome display several skeletal abnormalities including disproportionately long “spider” legs, curvature of the spine, facial deformities, rib and sternum deformities, lack of body fat, and muscular atrophy. The causative mutation is a single base-pair substitution, from a T to an A, altering a highly conserved and nonpolar valine amino acid to a polar glutamate in the critical tyrosine kinase II region of the fibroblast growth factor receptor 3 *(FGFR-3)* gene. This prevents the receptor from functioning to limit endochondral ossification and thus bone growth.[1] Genetic testing for the causative mutation has helped limit the prevalence of affected lambs; however, they are still occasionally observed, particularly where genetic testing has not been routinely used.[2]

Dominant Inheritance

Traits or diseases with a dominant mode of inheritance only require one affected allele to express the trait or disease, also known as the affected *phenotype*, and there is no distinguishable difference in the affected phenotype of a heterozygote and homozygote (homozygous for the affected allele). Again, the genes that are responsible for these traits or diseases can be on the autosomes or sex chromosomes. Dominant traits or diseases may be caused by gain-of-function mutations that enable the mutant protein to have an altered structure or function. Alternatively, a single, functional copy of a gene may not be enough to achieve normal levels of function (“haploinsufficiency”), resulting in the need for two normal copies of the gene to achieve a normal phenotype.

The main feature of an autosomal dominant trait or disorder is that affected individuals must have at least one affected parent (unless it is a new mutation),

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and thus the disorder does not skip generations. There is no sex bias with an autosomal dominant trait, and approximately half the offspring of a heterozygous affected individual bred to a normal individual will be affected. Breeding two heterozygous affected individuals will result in 75% affected (one third of which are homozygous and two thirds of which are heterozygous) and 25% normal offspring.

An example of an autosomal dominant disease is myotonia in goats. When startled or when making sudden, forceful movements, these goats can develop severe, acute muscle stiffness causing immobility and sometimes falling over, resulting in descriptions such as “fainting,” “nervous,” “stiff-legged,” or “epileptic” goats. A single nucleotide change, from a G to a C, was identified that substituted a proline amino acid for a conserved alanine in the *CLCN1* gene, a chloride channel in the muscle fibers. This alteration in the chloride channel causes a diminished channel-open probability at voltages near the resting membrane potential of skeletal muscle, resulting in decreased chloride conductance and a significantly decreased electrical threshold for firing action potentials. Ultimately, this altered chloride channel allows conduction of repetitive impulses that result in sustained muscle fiber contraction and stiffness.[3] Far from selecting against this trait, these myotonic or “fainting” goats are purposely bred in some scenarios, where they are generally used for meat production; in fact, they are considered by some to be a breed in their own right.

Codominant Inheritance

The codominant (or semidominant) pattern of inheritance is distinguished by the fact that homozygotes can be differentiated from heterozygotes on the basis of clinical features. A well-known example of a codominant disease is hyperkalemic periodic paralysis (HYPP) in Quarter Horses. In HYPP the voltage-gated sodium channels in the muscle fibers have a mutation, specifically a C to G change that substitutes a leucine residue for a highly conserved phenylalanine, which increases sodium permeability across the skeletal muscle cell membrane. This causes increased muscle mass but also drooling, prolapse of the nictitating membrane (“third eyelid”), respiratory stridor, and weakness. Homozygous HYPP horses experience more frequent and severe clinical signs of disease than heterozygous horses.[4,5] Thus it is important to counsel breeders to avoid producing homozygous affected horses by not mating two heterozygous horses, since approximately 25% of their offspring would be expected to be

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homozygous affected and 50% would be heterozygous, while only 25% would be homozygous normal. Breeding a heterozygous horse to an unaffected horse will also result in approximately 50% of the offspring being heterozygous with no possibility of producing a homozygous affected foal. It should be pointed out that HYPP heterozygous horses are still considered affected; however, their disease is easier to manage environmentally (via nutrition and management practices) compared with HYPP homozygous−affected horses.

Sex-Linked Traits

Sex-linked traits and diseases involve genes located on either the X or Y chromosome. Males have only one copy each of the X and Y chromosomes, so they are *hemizygous*. As a result, males are particularly susceptible to sex-linked conditions because if they have a mutant allele for one of the genes on either of the sex chromosomes, they lack a “backup” copy of the normal allele and will express the affected phenotype. Females generally are less likely to demonstrate sex-linked recessive traits or diseases because they have two copies of the X chromosome. However, because of random X inactivation in each cell during fetal development, some females may express an affected phenotype. To achieve this, the X inactivation must be skewed such that the unaffected chromosome is inactivated more often than the X chromosome carrying the affected allele. In rare cases in which the inactivation is significantly skewed, females may be mildly to severely affected, depending on the level of expression for the affected chromosome.

Key characteristics of X-linked recessive traits are 1) the trait appears with much greater frequency in males than females, 2) half the sons of carrier females will be affected, 3) half the daughters of carrier females will be carriers, and 4) all of the daughters of affected males will be carriers. Hemophilia A, characterized by a strong tendency to bleed resulting from mutations in the clotting factor VIII gene on the X chromosome, is an example of an X-linked recessive disorder.

X-linked dominant traits are characterized by the following: 1) affected offspring must have at least one affected parent, 2) the disorder does not skip generations, and 3) an affected male mated to normal females will transmit the mutation to all his daughters but not to his sons.

Few Y-linked diseases are recognized in any mammalian species because of the small number of genes on the Y chromosome. In addition, the majority of the

genes contained on the Y chromosome are involved in male fertility; thus mutations in these genes generally render the animal sterile, resulting in no transmission of the mutations to future generations.

Polygenic Traits

In addition to the single-gene traits and diseases, numerous conditions are the result of two or more genes and may also involve genetic and environmental interactions. In fact, entire biological pathways can be involved and interconnected, influenced by gene-gene interactions and/or gene-environment interactions; such pathways can turn genes, or groups of genes, on or off. Many of these polygenic traits are economically important. For example, a large number of genes may be contributing a small portion to the overall milk production of a dairy cow,[6] and endocrine fertility traits in dairy cattle are likewise driven by multiple genetic loci.[7] In beef cattle, at least eight genes have been significantly associated with stature and thus the physiology of growth.[8] Other highly polygenic beef cattle traits include carcass and meat quality.[9]

Now that the major large animal species have had their genomes sequenced, cattle and sheep livestock associations and producers are increasingly using whole-genome approaches for genetic evaluation, in an effort to tackle polygenic traits, as well as overall genetic value. For example, dairy cattle geneticists are now using single nucleotide polymorphism (SNP) markers spanning the entire genome, combined with progeny test data, in order to predict genetic merit for polygenic traits for any animal. This can be done before the animal produces any offspring. The swine industry is also using genome-wide data; however, much of these data are proprietary to specific corporations, so they may be difficult to access.

Fueled by decreasing costs, whole-genome sequencing is now becoming broadly available; this allows identification of additional forms of genetic variation such as copy number variations and short insertions and deletions. With data now consisting of entire genomes, more accurate breeding values can be attained, a better biological understanding of the genome can be achieved,[10] and areas of the genome that impact production—even if the physiology is unknown—can be taken into consideration.

Teasing out the details of a complex polygenic system, such as assigning a specific gene and a measure of its contribution to a polygenic trait like milk production or meat quality, is difficult; however, research is ongoing to identify

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the exact genes involved and the role each gene plays for many economically important traits and diseases. Thus it is anticipated that our understanding of polygenic traits in large animals will continue to increase in the next few years. Companies are already beginning to explore the value of genetic predictions for disease susceptibility and offer products that assist in genetic selection of, for example, dairy heifers, based on various health and disease traits. The full utility of such products is still being evaluated.

Penetrance and Expressivity

For many simple traits, there is an obvious difference between the two phenotypes that can be translated to the alleles involved, or *genotype,* with 100% certainty. A good example of this is albinism, which is considered to be 100% penetrant, with *penetrance* defined as the percentage of individuals within a given genotype that actually show the phenotype associated with that genotype. Influences such as modifying genes or environmental interactions can alter the expression of certain genes such that the exact genotype is not expressed in the outward phenotype. Alternatively, the function of a gene may be subtle, making it difficult to measure distinctions adequately between genotypes. Genotypes that may not be expressed in every individual are considered to be “incompletely penetrant.”

Another measure of genetic expression is the concept of *expressivity*. Modifier genes and environmental influences can affect the degree to which a genotype is expressed. For example, “variable expressivity” may be involved in pigment intensity when two individuals have the same genotype at the gene responsible for red pigmentation, but one has clearly darker red hairs than the other.

Incomplete penetrance and variable expressivity can greatly complicate analysis of genetic traits and diseases. These factors can also make breeding decisions more difficult because it may not be possible to classify an animal's genotype solely on the basis of a phenotype. In these more ambiguous cases, genetic testing will play a vital role in the unequivocal determination of genotypes, allowing appropriate and informed breeding decisions.

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Chromosomal Abnormalities

Occasionally, problems arise during mitosis, meiosis, or fertilization, resulting in chromosomal, or *karyotype*, abnormalities such as a chromosome missing from a pair *(monosomy)* or an extra chromosome *(trisomy)*. Many karyotypic abnormalities have been identified in all large animal species, but not every chromosomal abnormality has been associated with an overt disease phenotype.[11,12] Some examples of common chromosomal abnormalities include the absence of an X chromosome, called *XO Turner syndrome*, which results in female infertility. An additional X chromosome in *XXY Klinefelter syndrome* causes underdeveloped males with poorly developed male sexual behavior. In addition to abnormal numbers of sex chromosomes, rare trisomies of autosomal chromosomes have been observed in mammals; however, monosomies of autosomes are generally not compatible with life in mammals. An additional chromosomal abnormality can occur when two chromosomes unite into a single large chromosome, called a *Robertsonian translocation,* or centric-fusion translocation, leading to reduced reproductive capacity in some species and early embryonic death in cattle. Because of possible chromosomal abnormalities, several countries have instituted mandatory karyotype examination of some breeding cattle. In addition, clinicians should consider karyotyping any animal that presents for reduced fertility or has multiple abnormalities.

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Breeding Schemes

As a result of numerous advances in the field of genetics, the genetic causes of many diseases and traits are known and can be tested before using an animal in a breeding program. As research continues, more DNA-based tests are expected; however, clients may be interested in testing for a disease or trait that does not yet have a known genetic cause. For these situations, sires can be tested using breeding trials, as described in Table 51.1. For example, if a sire is bred to carrier females for a disease of concern, he would have to produce 10 normal offspring to ascertain that he is not a carrier with 95% confidence, 16 normal offspring to have 99% confidence, and 24 normal offspring to have 99.9% confidence that he is not a carrier for the disease of concern. The time required to complete test mating can be significantly shortened using superovulated affected females, insemination, and embryo transfer (two per recipient) followed by early cesarean section at 60 days and examination of the offspring for the genetic defect(s) of concern.

TABLE 51.1

Test Mating Schemes to Examine Males for Genetic Traits or Diseases at Various Confidence Levels

Females Used for Test Matings	Normal Offspring Needed to Reach Probability Level of:		
	0.05	0.01	0.001
Affected[a]	5	7	10
Normal carriers[a]	10	16	24
Sire's daughters[b]	22	35	52

[a]Tests for only one trait.

[b]Tests for all undesirable recessive traits.

It has historically been common practice for artificial insemination (AI) studs to conduct such test matings for recessive genetic diseases. However, now that many of the deleterious mutations are known, genetic testing, rather than test mating, is the current preferred approach. As mentioned previously, the dairy and beef cattle, swine, and sheep industries are aggressively pursuing whole-genome genetic testing, often in combination with offspring data. Test matings are thus largely relegated to the arena of historical interest, although there may

be unique situations or other species in which a test mating may still be a legitimate approach.

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Positive and Negative Selection

Breeders can improve their breeding stock by selecting for or against specific traits and diseases. These processes are known as *positive* and *negative selection*, respectively. A breeder may choose to breed an animal because it has desirable genes or qualities (positive selection). Alternatively, someone may choose not to breed an animal that has been shown, through either genetic or breeding tests, to carry an undesirable trait or disease (negative selection). Ultimately, both scenarios will achieve the goal of improved breeding stock.

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Recommendations for Breeding Programs

When a genetic disease has been identified, it is recommended that parentage be verified by DNA analysis and the extended pedigree be confirmed. In addition, a pathologist should make appropriate examinations of tissues for an accurate diagnosis, and a certified statement detailing the condition should be written by a veterinarian or other third-party witness. The final decision with regard to the status of a particular animal should be withheld until all reasonable doubt has been removed; for bulls, this is usually at least two thoroughly documented cases or a positive genetic test, if available. The AI organization and breed registry should be informed of the status of each animal because disease information is important in future breeding decisions. Many AI organizations list any undesirable recessive alleles in their advertising, and some also remove carrier animals from service (see Box 51.1 for a discussion on genetic counseling recommendations).

Box 51.1

Genetic Counseling for Single-Gene Autosomal Recessive Diseases

From the standpoint of conserving as much genetic diversity as possible within the closed gene pool of registered purebred animals, regardless of species, it is recommended by veterinary geneticists to retain heterozygotes (carriers) of autosomal recessive diseases as breeding animals, assuming they are otherwise good breeding candidates and the disease has a known, genetically testable mutation. If the animal has many other desirable traits, the genes underlying those traits can still be retained in the gene pool by breeding the carrier individual only to homozygous normal (clear) animals for the recessive disease in question. All offspring will be either homozygous normal or, at worst, carriers; no affected offspring will be produced. All offspring should be genetically tested for the gene in question. Exceptional offspring (again, regardless of carrier status) should be retained and used for breeding. Only

slowly, and over several generations, using genetic testing, should the carriers be removed from the gene pool. Consider the example of an autosomal recessive hydrocephalus in Friesian horses; this disorder has been associated with a nonsense mutation in *B3GALNT2*, where homozygotes for the affected allele exhibit hydrocephalus, while heterozygotes (carriers) are normal. The frequency of heterozygous individuals in the Friesian breed is ~17%.[13] Immediate removal of 17% of the gene pool, based on carrier status of this one gene, could create catastrophic new genetic bottlenecks. The recommendation in this scenario is to continue breeding heterozygotes, but only to homozygous-clear mates, therefore producing no foals with hydrocephalus but maintaining as much genetic diversity in the breed as possible. Ultimately, veterinary genetic counseling needs to consider which individuals should be bred and to whom they should be mated, keeping both short-term (individual offspring of this mating) and long-term (genetic health of the breed) perspectives. Finally, note that this recommendation is not appropriate in dominant genetic mutation scenarios; heterozygous individuals with dominant mutations are considered affected and typically should not be bred, depending on the severity of the condition.

Depending on the value of the animal in question, a breeder may choose to remove the animal from the breeding program at the first sign of a potential genetic problem. In these cases, documentation of the abnormal conditions should still be conducted for completeness and for comparison with other cases that may be found in the future.

In some cases, a breed association may choose to formally regulate both testing and registration of individuals with genetic diseases. For example, the American Quarter Horse Association no longer registers Quarter Horse foals born on or after January 1, 2007 that test homozygous positive for HYPP (two affected alleles), and all foals coming from bloodlines known to carry the HYPP affected allele are required to be genetically tested for HYPP and to have genetic parentage verification testing performed.[14]

Caution should be exercised before drastic changes are made in breeding populations. Inbreeding and extreme narrowing of the gene pool, such as by excessive use of a small number of sires, are results that should be avoided. Maintaining diversity in the herd and overall breeding population is important in order to avoid inbreeding depression and the increase of recessive diseases. In some industries, such as swine, where crossbreeding is common, this is less of a

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concern. In other industries, such as dairy cattle, producers are increasing their utilization of crossbreeding over and above the historical standard. Most commercial AI studs and/or breed association mating programs in the dairy industry are now designed with an option to limit inbreeding, typically accomplished with simple pedigree analysis but increasingly using genomic data; however, the producer must choose to apply that option. Breed associations may eventually need to intervene by actively soliciting and providing incentives for outbred animals. Producers, as well as the commercial stud owners, must carefully balance the short-term gains that may come from inbreeding with the long-term consequences of the overall narrowing of the gene pool.

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Obtaining Genetic Information

Because of the ever-increasing wealth of genetic information, the most complete and current information can be found using online resources. There are now hundreds of recognized single-gene traits and diseases across all large animal species; descriptions of each one is beyond the scope of this chapter. Because it is difficult for the practitioner to be familiar with all of them, online resources become vital. It is recommended that clinicians use websites produced by reputable institutions to obtain the most accurate and referenced information available (Box 51.2). Alternatively, clinicians are encouraged to contact the Veterinary Genetics services available at many veterinary schools if they are unable to locate the information they require.

Box 51.2

Recommended Websites for Large Animal Genetics

OMIA—Online Mendelian Inheritance in Animals: horse, cattle, sheep, goat, pig, various other species
http://omia.angis.org.au/

U.S. Department of Agriculture, Agriculture Research Service, Animal Genomics and Improvement Laboratory: dairy cattle, dairy goat
http://aipl.arsusda.gov/

Veterinary Genetics Laboratory at the University of California, Davis: horse, cattle, sheep, goat, pig, various other species
http://www.vgl.ucdavis.edu/services/index.php

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• CHAPTER 52

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Genetic Tests for Large Animals

Danika L. Bannasch, Consulting Editor, Carrie J. Finno

Genetic testing based on deoxyribonucleic acid (DNA) involves the analysis of an animal's DNA to determine its genotype for an inherited disorder, trait, or anonymous marker. Genetic testing can be used for positive or negative selection in a population, depending on whether it is being used to identify a disease (negative) or a trait (positive). Genetic testing can also be used for permanent individual identification and parentage determination. Many breed registries require parentage verification to ensure the accuracy of their pedigrees.

Using genetic testing results for selection requires an understanding of the mode of inheritance of the disease or trait. Most often, a genetic test will be performed for a recessive disorder to determine if an animal is a carrier. Carriers are asymptomatic but have the potential to produce diseased progeny. Because they have no outward manifestation of disease, a genetic test is extremely valuable for managing their breeding appropriately. Carrier animals can be bred to noncarriers if needed to retain valuable characteristics while not producing diseased offspring. In the case of positive selection for a trait of interest, carrier animals may have higher breeding values because they can produce a trait if bred to other carriers or to animals with the trait. Genetic tests may also be used for dominant disorders if the disease/trait has a late age of onset or if it is inherited in a codominant manner. DNA testing for traits that are controlled by more than one locus (polygenic) may also be used for selection for economically important traits. In these cases, one particular genotype may confer a slight advantage over another and therefore, in a large population, can have a significant effect on production.

Box 52.1 defines key genetic terms; see also Chapter 51.

Box 52.1

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Definitions of Genetic Terms

Allele One of the variant forms of a gene at a particular locus, or location, on a chromosome.

Base pairs Two bases that form a "rung of the DNA ladder." A DNA nucleotide is made of a molecule of sugar, a molecule of phosphoric acid, and a molecule called a "base." The bases are the "letters" that spell out the genetic code. In DNA the code letters are A, T, G, and C, which stand for the chemicals adenine, thymine, guanine, and cytosine, respectively.

Genotype Genetic makeup, either at a single locus or at all loci.

Genome wide association study A study that uses genome-wide markers, typically microsatellites or single nucleotide polymorphisms (SNPs) to determine an association between a phenotype and region of particular chromosome.

Linked Association of genes and markers that lie near each other on a chromosome; linked genes and markers tend to be inherited together.

Locus Place on a chromosome where a specific gene is located; a type of "address" for the gene.

Marker Segment of DNA with an identifiable physical location on a chromosome, the inheritance of which can be followed. A marker can be a gene or some section of DNA with no known function. Also known as a *genetic marker.*

Microsatellite Repetitive stretches of short sequences of DNA used as genetic markers to track inheritance in families.

Phenotype Observable traits or characteristics of an animal (e.g., coat color, weight, presence or absence of a disease).

Recombination Genetic transmission process by which the combinations of alleles observed at different loci in two parental individuals become shuffled in offspring individuals.

Single nucleotide polymorphism (SNP) Differences in a single base pair of DNA (A, C, T, G) often used as genetic markers for linkage and association studies

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Individual Identification and Parentage Testing

Researchers use genetic markers distributed along all the chromosomes as tools to identify regions associated with diseases or traits. One type of marker used for individual identification and parentage testing is composed of small nucleotide repeats and is called *microsatellite* markers or *short tandem repeats* (STRs). These markers have a feature that makes them extremely useful to geneticists; the markers have been chosen to be “polymorphic” (show differences) between individuals. In other words, individual animals will have different lengths of the nucleotide repeats for each of these markers. The high level of polymorphism of this type of marker makes them useful for “mapping” (identifying the chromosomal location of diseases and traits).

The microsatellite markers are assayed by polymerase chain reaction (PCR) amplification using fluorescent-labeled primers. Primers are short (20 base pairs), single-strand lengths of DNA that are complementary to a specific region of the genome. PCR is the amplification of a section of DNA contained between two primers designed to complement the unique sequence flanking the STR. The PCR products are then resolved by electrophoresis on the basis of their length. Markers with many different alleles are said to be polymorphic and would be a useful marker for individual identification or parentage. Because the markers show differences between individuals, a collection of these markers can be used as a form of identification of an animal. High statistical significance can be obtained with as few as 10 markers, depending on the species and breed. The DNA type of an animal will not change over its lifetime and can therefore be used as a form of permanent identification.

Many purebred registries require parentage verification for registration purposes. To accomplish parentage verification, a DNA sample must be available from both parents, as well as the offspring. DNA samples are taken in the form of hair, blood, or buccal swabs (depending on the species and registry) and submitted at the time registration is requested. Each animal inherits one copy of each marker from its sire and one copy from its dam, so the markers can also be used to verify parentage. The most useful marker has a high polymorphism rate because that type of marker will be most likely to show differences not only between the sire and the dam but also between the two

copies (alleles) of the marker. A set of polymorphic markers (10 to 20) is used to verify parentage to ensure a high probability that the parentage is correct. Table 52.1 shows the allele sizes for a set of markers in a parentage case. For marker *A* the offspring inherited a 122 allele and a 126 allele. The 122 came from its dam, so the 126 came from the sire. Because sire 1 does not have a 126 allele, it has been excluded. In this example, sire 1 is excluded as the sire of the offspring and sire 2 is verified on the basis of the results for all three markers.

TABLE 52.1

Parentage Verification Using Microsatellite Markers

	Allele Sizes for 4 Markers			
Individuals	**A**	**B**	**C**	**D**
Dam	122/124	110	131/133	80/82
Offspring	122/126	110/112	133	82/86
Sire 1	128	112/114	131	84
Sire 2	126	112/114	131	86/90

Genome Sequence

Whole-genome sequencing and genome assembly of large animal species was completed in the early 2000s (horse September 2007, cow October 2011, sheep February 2010, goat February 2013). The whole-genome sequence of an organism provides the exact base pairs along each chromosome of the individual animal that was sequenced. This “assembly” of DNA sequence then becomes the reference assembly for each organization, and genetic variation is compared with that reference providing a frame of reference for all DNA sequencing. In the horse, a Thoroughbred mare (Twilight) was selected for sequencing because of her low heterozygosity rate (1/1380 base pairs). In 2010, a Quarter Horse mare underwent whole-genome sequencing and was aligned to Twilight.[1] In cattle, a single partially inbred Hereford cow was selected to contribute 6× whole-genome shotgun (WGS) reads and another 1.5× came from individual animals of the Holstein, Angus, Jersey, Limousin, Brahman, and Norwegian Red breeds for detection of single nucleotide polymorphisms (SNPs). Following sequencing of each species, over 20,000 protein-coding genes were annotated on the sequences by virtue of previously sequenced cDNAs and also by prediction software that compared known genome sequences in other species with newly sequenced genomes. Since these initial assemblies, revisions have occurred within species.

These initial and updated annotated genome databases are publicly available (Table 52.2).

TABLE 52.2
Map Status and Genomic Resource for Large Animal Species

	Horse	Cattle	Sheep	Goat
Chromosome (2n)	64	60	54	60
Most recent assembly	EquCab3.0[a]	Bos_taurus_UMD_3.1.1[b]	Oar_v4.0[c]	ARS1[d]
SNP-chip available (# SNPs)	3 chips: 54,602[e] 65,157[e] 670,796[f]	7 chips: 2900[e] 6909[e] 6912[e] 7931[e] 54,001[e] 54,609[e] 648,875[f] 777,962[e]	2 chips: 54,241[e] 606,006[e]	2 chips: 52,295[e]

[a]Available from http://www.ncbi.nlm.nih.gov/genome/145.

[b]Available from http://www.ncbi.nlm.nih.gov/genome/82.

[c]Available from http://www.ncbi.nlm.nih.gov/genome/83.

[d]Available from http://www.ncbi.nlm.nih.gov/genome/10731.

[e]IlluminaInc., San Diego, Calif.

[f]Affymetrix, Inc., Santa Clara, Calif.

With the advent of whole-genome sequencing and assemblies, there has been a rapid expansion in the number of SNPs discovered in the genomes of large animal species. SNPs are single base pairs of DNA with differences between individuals. They generally have only two alleles and are therefore less informative than the STR markers mentioned earlier. They have distinct advantages, however, when it comes to ease of genotyping. Very large numbers of SNP markers can be genotyped for a fraction of the cost of microsatellite markers. SNPs are now considered the next generation of markers to conduct breed diversity and to map disease-causing traits. The availability of such a tool as an SNP chip facilitates rapid mapping of diseases to specific chromosomal regions and analysis of candidate genes. SNP arrays are currently available on many large animal species (Table 52.2) and are currently being used in mapping

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studies of various complex disorders. Haplotype structures are being identified across species with targeted resequencing and, most recently, whole-genome next-generation sequencing, of animals from different breeds.

In addition to genomic mapping, functional genomic tools have become more readily available and affordable to researchers. More recently, sequencing of the transcriptome, through technologies such as RNA-Seq, have allowed researchers to evaluate gene expression differences among tissues and between animals of different disease states.

Identifying Genetic Mutations

Initial genetic mutations in large animal species were discovered through the use of comparative genomics. Genes involved in a specific disease were targeted because of equivalent diseases in other species, namely humans. In the horse, the genetic mutations for many diseases that have genetic tests currently available, including hyperkalemic periodic paralysis (HYPP)[2] and severe combined immunodeficiency (SCID),[3] were uncovered by evaluating candidate genes that had been associated with similar diseases in humans (Table 52.3). With the sequencing and annotation of whole genome maps, other diseases were discovered through whole-genome linkage mapping (hereditary equine regional dermal asthenia [HERDA][4]), genome-wide association studies with microsatellites (Type I polysaccharide storage myopathy [PSSM][5]) and genome-wide association studies using SNP array technology (Lavender foal syndrome[6]).

TABLE 52.3
Genetic Tests for Horses

Disease/Trait	Gene	Mode of Inheritance	Reference
Androgen insensitivity syndrome (AIS)	*AR*	X-linked recessive	18
Cerebellar abiotrophy (CA)	*TOE1/MUTYH*	Autosomal recessive	19
Curly coat	*KRT25*	Autosomal dominant	20
Dwarfism, *ACAN* related	*ACAN*	Autosomal incompletely dominant	21,22
Dwarfism, Friesian	*B4GALT7*	Autosomal recessive	23
Hereditary regional dermal asthenia (HERDA)	*PPIB*	Autosomal recessive	4
Junctional epidermolysis bullosa (JEB)	*LAMA3*	Autosomal recessive	24
JEB	*LAMC2*	Autosomal recessive	25
Foal immunodeficiency syndrome (immunodeficiency of Fell ponies)	*SLC5A3*	Autosomal recessive	26
Gaitedness	*DMRT3*	Multifactorial	27
Glycogen storage disease IV (glycogen branching enzyme deficiency)	*GBE1*	Autosomal recessive	28
Hoof wall separation disease (HWSD)	*SERPINB11*	Autosomal recessive	29
Hydrocephalus	*B3GALNT2*	Autosomal recessive	30
Immune-mediated myositis	*MYH1*	Autosomal semidominant	31
Incontinentiapigmenti	*IKBKG*	X-linked semidominant	32
Lavender foal syndrome (LFS)	*MYO5A*	Autosomal recessive	6
Malignant hyperthermia (MH)	*RYR1*	Autosomal dominant	33
Megacolon (ileocolonicaganglionosis or lethal white foal syndrome)	*EDNRB3*	Autosomal semidominant	10–12
Multiple ocular defects	*PMEL17*	Autosomal semidominant	34

Myotonia	*CLCN1*	Autosomal recessive	35
Naked foal syndrome	*ST14*	Autosomal recessive	36
Night blindness, congenital stationary	*TRPM1*	Autosomal recessive	37
Occipitoatlantoaxial malformation (OAAM)	*HOXD3*	Autosomal recessive	38
Ocular squamous cell carcinoma	*DDB2*	Autosomal recessive	39
Ovotesticular disorder of sexual development	*SRY*	Y-linked	40
Periodic paralysis II (hyperkalemic periodic paralysis; HYPP)	*SCN4A*	Autosomal semidominant	2
Polysaccharide storage myopathy type I (PSSM I)	*GYS1*	Autosomal dominant	5
Severe combined immunodeficiency	*DNAPKcs*	Autosomal recessive	3
Skeletal atavism	*SHOX*	Autosomal recessive	41
Thrombasthenia (Glanzmann thrombasthenia)	*ITGA2B*	Autosomal recessive	42,43
Warmblood fragile foal syndrome	*PLOD1*	Autosomal recessive	44

A similar theme is evident in cattle. Initial genetic mutations were discovered based on sequencing of candidate genes known to cause similar disease in humans (bovine leukocyte adhesion deficiency [BLAD][7]). Later studies used microsatellite markers and performed linkage analysis (complex vertebral malformation[8]) and, most recently, the use of SNP-based genome-wide association studies has identified recessive defects (congenital muscular dystony types 1 and 2[9]). At the time of publication, there are 147 genetic tests available in cattle (Table 52.4). It is worth noting that the majority of genetic tests currently available are for diseases/traits that are inherited as autosomal recessive traits. With the current technologies available through SNP-association mapping and next-generation sequencing, we should expect to further our understanding of polygenic traits and diseases.

TABLE 52.4
Genetic Tests for Cattle

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Abortion/Stillbirth	*MIMT1*	Maternally imprinted	45
Abortion	*ANXA10*	Autosomal incompletely dominant	46
	EXOSC4	Autosomal recessive lethal	47
	MED22	Autosomal recessive lethal	47
	MYH6	Autosomal recessive lethal	47
	OBFC1	Autosomal recessive lethal	47
	RABGGTB	Autosomal recessive lethal	47
	RNF20	Autosomal recessive lethal	47
	RPIA	Autosomal recessive lethal	47
	SNAPC4	Autosomal recessive lethal	47
	TTF1	Autosomal recessive lethal	47
	APAF1	Autosomal recessive lethal	48
	CWC15	Autosomal recessive lethal	49

	SLC39A4	Autosomal recessive	50
	EDA	X-linked recessive	51
	TUBD1	Autosomal recessive lethal	52
	SUGT1	Autosomal recessive lethal	53
	SMC2	Autosomal recessive lethal	54
	GART	Autosomal recessive lethal	55
	TFB1M	Autosomal recessive lethal	56
	PFAS	Autosomal recessive lethal	57
	SLC37A2	Autosomal recessive lethal	55
	RNASEH2B	Autosomal recessive lethal	58
Achondrogenesis, type II	*COL2A1*	Autosomal dominant	54,59,60
Acrodermatitisenteropathica	*SLC39A4*	Autosomal recessive	50
Anhidrotic ectodermal dysplasia	*EDA*	X-linked recessive	51,61–64
	EDAR	Autosomal recessive	60
Arachnomelia (spider limbs)	*MOCS1*	Autosomal recessive	65
	SUOX	Autosomal recessive	66
Arthrogryposis	*AGRN*	Autosomal recessive lethal	67
	CHRNB1	Autosomal recessive	68
	MYBPC1	De novo	69
	PIGH	Autosomal recessive	70
Axonopathy (Demetz syndrome)	*MFN2*	Autosomal recessive	71
Brachyspina	*FANCI*	Autosomal recessive	72
Caprine-like generalized hypoplasia	*CEP250*	Autosomal recessive	73
Cardiomyopathy and woolly haircoat syndrome	*PPP1R13L*	Autosomal recessive	74
Cardiomyopathy, dilated	*OPA3*	Autosomal recessive	75
Cataract	*CPAMD8*	Autosomal recessive	76
	NID1	Autosomal recessive	77
Chediak-Higashi syndrome	*LYST*	Autosomal recessive	78
Chondrodysplasia	*EVC2*	Autosomal	79
Citrullinemia	*ASS1*	Recessive	80
Complex vertebral malformation	*SLC35A3*	Autosomal recessive	8
Congenital muscular dystonia 1	*ATP2A1*	Autosomal recessive	9
Congenital muscular dystonia 2	*SCL6A5*	Autosomal recessive	9
Contractural arachnodactyly (Fawn calf syndrome)	*ADAMTSL3*	Autosomal recessive	81
Curly hair, karakul-type	*KRT27*	Autosomal dominant	54
Deficiency of uridine monophosphate synthase (DUMPS)	*UMPS*	Autosomal recessive	82
Depigmentation with microphthalmia	*MITF*	Autosomal dominant	83
Developmental duplications	*NHLRC2*	Multifactorial	84
Dominant white with bilateral deafness	*MITF*	Autosomal dominant	83
Dwarfism Angus	*PRKG2*	Autosomal recessive	85
Fleckvieh	*GON4L*	Autosomal recessive	86
ACAN-related	*ACAN*	Autosomal recessive lethal	87
Growth hormone deficiency	*GH1*	Autosomal recessive	88
Proportionate, with inflammatory lesions	*RNF11*	Autosomal recessive	89
Ears crop	*HMX1*	Autosomal dominant with variable expressivity	90
Ehlers-Danlos syndrome Holstein variant	*EPYC*	Autosomal recessive	91
Type VII (dermatosparaxis)	*ADAMTS2*	Autosomal recessive	92
Epidermolysis bullosa Dystrophic	*KRT5*	Autosomal dominant	93
	ITGB4	Autosomal recessive	94
	LAMA3	Autosomal recessive	95
	LAMC2	Autosomal recessive	96

	COL7A1	Autosomal recessive	97
Facial dysplasia syndrome	*FGFR2*	Autosomal dominant	98
Factor XI deficiency	*F11*	Autosomal recessive	99
Fanconi syndrome	*SLC2A2*	Autosomal recessive	100
Forelimb-girdle muscular anomaly	*GFRA1*	Autosomal recessive	101
Glycogen storage disease II (Pompe's disease)	*GAA*	Recessive	102
Glycogen storage disease V	*PYGM*	Autosomal recessive	103
Goiter, familial	*TG*	Autosomal	104
Gonadal hypoplasia	*KIT*	Autosomal recessive	105
Hairy	*PRL*	Autosomal dominant	106
Hemophilia A	*F8*	X-linked	107
Holstein cholesterol deficiency	*APOB*	Autosomal recessive lethal	108
Hydrallantois	*SLC12A1*	Autosomal recessive	109
Hypotrichosis	*HEPHL1*	Autosomal recessive	110
Streaked	*KRT71*	Unknown	111
	TSR2	X-linked semidominant	112
Ichthyosis congenital	*ABCA12*	Autosomal recessive	9
Lethal multiorgan developmental dysplasia	*KDM2B*	Autosomal recessive	113
Leukocyte adhesion deficiency, type I	*ITGB2*	Autosomal recessive	7
Male subfertility	*TMEM95*	Autosomal recessive	114
Mannosidosis alpha	*MAN2B1*	Autosomal recessive	115
Mannosidosis beta	*MANBA*	Autosomal recessive	116
Maple syrup urine disease	*BCKDHA*	Autosomal recessive	117
Marfan syndrome	*FBN1*	Autosomal dominant	118
Mucopolysaccharidosis IIIB	*NAGLU*	Autosomal recessive	119
Multiple ocular defects	*WFDC1*	Autosomal recessive	120
Muscular hypertrophy (double muscling)	*MSTN*	Autosomal recessive	13–15
Myasthenic syndrome, congenital	*CHRNE*	Autosomal	121
Myoclonus	*GLRA1*	Autosomal recessive	122
Myopathy of the diaphragmatic muscles	*HSPA1A*	Autosomal recessive	123
Neurocristopathy	*CHD7*	Autosomal dominant	60
Neuronal ceroid lipofuscinosis 5	*CLN5*	Autosomal recessive	124
Osteogenesis imperfecta, type II	*COL1A1*	Autosomal dominant	60
Osteopetrosis	*SLC4A2*	Autosomal recessive	125
Osteopetrosis with gingival hamartomas	*CLCN7*	Autosomal recessive	126
Ovotesticular disorder of sexual development	*SRY*	Y-linked	127
Perinatal weak calf syndrome	*IARS*	Autosomal recessive	128
Polled	*POLL*[a]	Dominant	129,130
Progressive degenerative myeloencephalopathy (Weaver syndrome)	*PNPLA8*	Autosomal recessive	131
Protoporphyria	*FECH*	Autosomal	132
Pseudomyotonia, congenital	*ATP2A1*	Autosomal recessive	133
Ptosis, intellectual disability, retarded growth and mortality (PIRM) syndrome	*UBE3B*	Autosomal recessive	134
Renal dysplasia	*CLDN16*	Autosomal recessive	135
Resistance/susceptibility to Mannheimia hemolytica leukotoxin	*ITGB2*	Autosomal recessive	136
Retinitis pigmentosa 1	*RP1*	Autosomal recessive	137
Scurs, type 2	*TWIST1*	Autosomal dominant	138
Slick hair	*PRLR*	Autosomal dominant	106,139
Sperm, short tail	ARMC3	Autosomal recessive	140
Spherocytosis	*SLC4A1*	Autosomal incompletely	141

		dominant	
Spinal dysmyelination	*SPAST*	Autosomal recessive	142
Spinal muscular atrophy	*KDSR*	Autosomal recessive	143
Spongiform encephalopathy	*PRNP*	N/A	144
Syndactyly	*LRP4*	Autosomal recessive	145,146
Tail, crooked	*MRC2*	Autosomal recessive	147
Tibialhemimelia	*ALX4*	Autosomal recessive	67,149
Tricho-dento-osseous-like syndrome	*DLX3*	De novo autosomal dominant	150
Thrombopathia	*RASGRP2*	Unknown	151
Trimethylaminuria	*FMO3*	Autosomal recessive	152
Vertebral and spinal dysplasia	*T*	Autosomal incompletely dominant	153
Xanthinuria, type II	*MOCOS*	Autosomal recessive	154,155
Yellow fat	*BCO2*	Unknown	156
Zinc deficiency-like syndrome	*PLD4*	Autosomal recessive	157
A2 milk	*CSN2*	Autosomal codominant	158
Beta-lactoglobulin, low expression	*PAEP*	Autosomal	159
Milk yield and composition	*GHR*	Polygenic	160
Milk yield and composition Meat tenderness	*DGAT1*	Polygenic	161
Milk yield and composition Meat tenderness	*Leptin*	Polygenic	162,163
	Calpastatin	Polygenic	164,165
	μ-Calpain	Polygenic	166,167

[a]Considered a locus and not a gene.

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Disease Testing

Clinicians can use DNA testing in disease diagnosis or to determine an animal's potential for producing diseased progeny. Generally, disease diagnosis is based on clinical signs and other diagnostic tests, but occasionally DNA testing is used, in particular for later-onset diseases or diseases for which diagnosis by traditional methods is difficult or invasive. To offer a genetic test, the gene responsible must be known. Ideally, the actual mutation that causes the disease has been identified. Rather than knowing the exact gene or mutation, only a region of a chromosome may have been implicated in a particular disease. DNA tests can be divided into two categories: mutation tests and linked-marker or haplotype tests. *Mutation* tests are based on an actual mutation that causes disease, whereas the *linked-marker* or *haplotype* test is based on the region of the chromosome that is known to cause disease but not necessarily the actual mutation. Usually, haplotype tests are offered instead of a mutation test because the mutation has not yet been identified. With the current tools available in large animals, the identification of disease causing mutations is so efficient that marker-based tests are rarely used.

Mutations that cause disease appear in many different forms. A change of a single base pair from one base to another can cause a disease by changing an amino acid (“missense” mutation), truncating the amino acid chain (“nonsense” mutation), or altering expression or proper splicing. For example, missense mutations have been shown to cause lethal white foal syndrome in the American Paint horse.[10–12] Insertions or deletions of a single base pair (bp) can cause mutations in the coding sequence by altering the translational frame, which ultimately causes protein truncation. An 11-bp deletion in the myostatin gene causes a frameshift mutation and protein truncation in Belgian blue and Peidmontese cattle with the double-muscle phenotype.[13–15] Large deletions or insertions that remove hundreds and thousands of base pairs can also cause disease. For example, the polled intersexuality mutation in goats is caused by an 11.7-kilobase deletion that removes a regulatory element that controls the expression of two genes.[16] This endless array of possible changes in the DNA that result in disease makes each individual DNA-based genetic test different.

The basis for DNA testing is PCR. Primers can be designed specifically to amplify either the disease-causing allele or the normal allele. Alternatively, the

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PCR product can be digested with a restriction enzyme that cleaves the DNA at a particular sequence of bases. A restriction enzyme is chosen that shows a different cleavage pattern between the mutant and the normal version of the PCR product. Direct sequencing of a section of DNA can also be used to determine the animal's genotype. Many different methods are available to assay changes in DNA that lead to disease. Each company that offers a test may choose a different type of assay for the same mutation.

There are limits to all genetic testing. For mutation tests, the specific mutation being assayed is the only factor being evaluated. An animal may have a different mutation in that gene or a mutation in a different gene that causes the same phenotype (phenocopy). It is therefore correct to state that an animal has been "DNA tested negative" for this specific mutation rather than "DNA tested clear" of the disease. In addition, more complicated modes of inheritance do not provide a direct disease or trait prediction. For example, some loci have incomplete penetrance and not all animals with the affected genotype will get the disease or trait. Other genetic tests are for susceptibility loci and merely confer a disease risk.

No association or committee evaluates quality control of DNA tests that are available in animals. Most tests are published in the scientific literature not as tests but as articles describing the discovery of the mutation. Because some cases involve patent issues, some tests are offered before publication. Much of the research done to identify the mutations involved in the tests is performed at universities and funded by granting agencies that have both financial and intellectual interest in patenting the tests.

Tables 52.3, 52.4, 52.5, and 52.6 list available genetic tests for traits and diseases other than coat color in horses, cattle, and sheep and goats, respectively. Only tests published in peer-reviewed journals are listed. Additional tests available in cattle for various forms of the milk proteins also are not listed in Table 52.4. The breeds of cattle are not listed because rapid changes in testing mean that tests are always being validated for new breeds. It is therefore recommended that a search be performed for the availability of a test for a particular breed each time the need arises. Coat color genetic tests are listed in Table 52.7, with each particular species in which the genetic mutation has been identified referenced.

TABLE 52.5

Genetic Tests for Sheep

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Achromatopsia-2	*CNGA3*	Autosomal recessive	168
Ataxia, familial episodic spinocerebellar	*FGF14*	Autosomal incompletely dominant	169
Chondrodysplasia (spider lamb)	*FGFR3*	Autosomal recessive	170
Chondrodysplasia, Texel	*SLC13A1*	Autosomal recessive	171
Ehlers-Danlos syndrome, type VII (dermatosparaxis)	*ADAMTS2*	Autosomal recessive	172
Epidermolysis bullosa, junctionalis	*LAMC2*	Autosomal recessive	173
	ITGB4	Autosomal recessive	174
Fecundity Barbarine	*BMP15*	X-linked	175
Belclare	*BMP15*	X-linked	176
Belcalre/Irish Cambridge	*GDF9*	Autosomal	176
Booroola	*BMPR1B*	Autosomal semidominant	177-179
Embrapa	*GDF9*	Autosomal	180
Galway	*BMP15*	X-linked	176
Grivette	*BMP15*	X-linked	181
Hanna	*BMP15*	X-linked	182
Inverdale	*BMP15*	X-linked	182
Lacaune	*B4GALNT2*	Autosomal codominant	183
	BMP15	X-linked	182
Norwegian	*GDF9*	Unknown	184
Olkuska	*BMP15*	X-linked	181
RaseAragonesa	*BMP15*	X-linked	185
Small tail Han	*BMPR1B* *BMP15*	Autosomal	186
Thoka	*GDF9*	Autosomal	187
Vacaria	*GDF9*	Autosomal	188
Fleece variation	*IRF2BP2*	Not reported	189
Gangliosidosis, GM1	*GLB1*	Autosomal recessive	190
Gangliosidosis, GM2, type 1	*HEXA*	Autosomal recessive	191
Gaucher disease, type I	*GBA*	Autosomal recessive	192
Glycogen storage disease V	*PYGM*	Autosomal recessive	193
Hemophilia A	*F8*	X-linked	194
Hypophosphatemic rickets	*DMP1*	Autosomal recessive	195
Hypotrichosis	*HR*	Autosomal recessive	196
Lissencephaly and cerebellar hypoplasia	*RELN*	Autosomal recessive	197
Microphthalmia	*PITX3*	Autosomal recessive	198
Motor neuron disease, lower	*AGTPBP1*	Autosomal recessive	199
Muscular hypertrophy (double muscling)			
Callipyge	*DLK1*	Polar overdominant	200
Texel	*MSTN*	Autosomal	201
Myotonia	*CLCN1*	Autosomal recessive	202
Neuronal ceroid lipofuscinosis			
10	*LOC443060*	Autosomal recessive	203
5	*CLN5*	Autosomal recessive	204
6	*CLN6*	Autosomal recessive	205
Polled/Horns	*RXFP2*	Autosomal	206
Porphyria cutaneatarda	*UROD*	Autosomal recessive	207
Resistance/susceptibility to lentivirus	*TMEM154*	Multifactorial	208
Spongiform encephalopathy (scrapie	*PRNP*	Autosomal recessive	209

susceptibility)			
Waardenburg syndrome, type 4A	*EDNRB*	Autosomal recessive	210
Yellow fat	*BCO2*	Autosomal recessive	211

TABLE 52.6
Genetic Tests for Goats

Disease/Trait	Gene	Mode of Inheritance	Reference(s)
Casein, α-S1, reduced concentration	*CSN1S1*	Autosomal	212
Casein, α-S2, null allele	*CSN1S2*	Autosomal recessive	213
Casein, β, null allele	*CSN2*	Autosomal	214
Goiter, familial	*TG*	Autosomal recessive	215
Horns/Polled	*PISRT1, FOXL2*	Autosomal	16,216
Mannosidosis, β	*MANBA*	Autosomal recessive	217
Mucopolysaccharidosis IIID	*GNS*	Autosomal recessive	218
Myotonia	*CLCN1*	Autosomal dominant	219

TABLE 52.7
Genetic Tests for Coat Color

Coat Color	Gene	Species	Reference(s)
Albinism	*TYR*	Cattle	220
Albinism (oculocutaneous type IV)	*SCL45A2*	Cattle	221
Albinism (oculocutaneous type VI)	*SLC24A5*	Horse	222
Agouti	*ASIP*	Horse	223
		Cow	224
		Sheep	225
Appaloosa	*TRPM1*	Horse	37
Brown (Dun)	*TYRP1*	Cow	226
		Sheep	227
Champagne	*SLC36A1*	Horse	228
Cool gray	*MLPH*	Cattle	229
Cream dilution	*SLC45A2*	Horse	230
Dilution	*PMEL*	Cow	231
Dominant red	*COPA*	Cow	60
Dominant white	*KIT*	Horse	232
		Cow	233
Extension	*MC1R*	Horse	234
		Cow	235
		Sheep	236
		Goat	237
Gray	*STX17*	Horse	238
Macchiato	*MITF*	Horse	239
Roan	*KITLG*	Cow	240
Silver	*PMEL17*	Horse	241
White belt	*TWIST2*	Cow	242

White spotting	*MITF* (Horse, cow)	Horse	239
	PAX3 (Horse)	Cow	233
	EDNRA (Goat)	Goat	243

The diseases or traits that are tested can be divided into two categories: those that have straightforward Mendelian inheritance patterns (recessive, dominant, and sex-linked) and those that are more complicated because many genes are involved with conferring the phenotype (polygenic). *Quantitative trait loci* (QTL) are the genes that contribute to a polygenic disease. In cattle, a vast number of QTL have been placed in specific regions of chromosome for quantitative traits such as dairy form, milk production, and fertility.[17] Selection for these traits can be done with DNA testing (Table 52.4). Because so many different QTL exist, however, selection can be challenging, and trade-offs need to be made.

Genetic testing relies on advances made in the field of genomics. Veterinarians and owners are fortunate that large animal species were chosen as economically important species for whole-genome sequencing. With the tools currently available, the number of disease-based or trait-based tests available in the future will markedly increase.

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• CHAPTER 53

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Immunologic Disorders

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Equine Immunologic Disorders

Overview of Immunologic Disorders in Horses*

Lais R.R. Costa

The immune system is composed of primary or central organs (bone marrow and thymus) and secondary or peripheral organs (spleen, lymph nodes, and mucosa-associated lymphoid tissues). Immune cells of myeloid and lymphoid lineages are generated (produced and developed) in central organs, subsequently populating the peripheral organs where they carry out their functions of immunosurveillance and mounting immune responses to defend the body from microbial invasion. Many immune cells are not static; instead, they are constantly circulating, migrating into various tissues, and capable of performing their functions of immunnosurveillance, inflammation, and tissue repair in organs outside the immune system. Functionally, immune cells traditionally have been classified into two branches: innate and adaptive immune cells. Cells of the innate branch of the immune system mostly comprise cells of the myeloid lineages—including granulocytes (neutrophils, eosinophils, basophils, mast cells), monocytes and macrophages, dendritic cells (DCs)—and subsets of cells of the lymphoid lineage—including natural killer (NK) cells, plasmacytoid DCs, B1 cells, and gamma delta T cells. Cells of the adaptive branch of the immune system primarily comprise cells of the lymphoid lineages expressing antigen-specific receptors, including B lymphocytes, T lymphocytes (alpha beta T cells of either CD4 and CD8 subpopulations), and regulatory T cells. The various components of the immune system work in unison to bring about broad defense throughout the body. Detailed review of the cellular and molecular components of the immune system and the mechanisms involved in the immune response of horses can be found elsewhere.[1-3]

Normal Immune Response in Horses

The immune response results from an intricate network of innate mechanisms of resistance and complex adaptive immune defense. The innate immune mechanisms are the first line of defense and do not require previous exposure to the invader. Cell-associated molecules and soluble factors of the innate system

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are capable of recognizing a number of common microbial structures or patterns and respond quickly to an invasion by promoting inflammatory reaction and chemotactic stimuli for leukocyte trafficking, thus serving as the first immune barrier to invading organisms. Cells and soluble factors of the innate system also provide co-stimulatory signals and antigen presentation to cells of the adaptive lymphoid lineage. Once mounted, the adaptive host defense confers antigen-specific anamnestic response following the initial encounter with an antigen or invader. The adaptive immune response can recognize nearly an infinite array of antigenic determinants or epitopes, distinguishing self from those that are nonself. As well, the adaptive immunity has memory that leads to increased effectiveness upon antigenic reexposure. Thus the innate and adaptive mechanisms work together to identify and eliminate offending molecules and organisms that invade the body.

Innate recognition of invaders involves detection of alarm signals generated exogenously (invader patterns) or endogenously (patterns of damaged cells or tissue). Several cells of the innate immune system, including cells of the macrophage lineage, DCs, mast cells, neutrophils, NK cells, and gamma delta T cells, as well as B cells can recognize exogenous and endogenous alarm signals. Sentinel cells scattered throughout the body, especially at sites likely to be invaded (skin and mucosal surfaces), serve the primary function of invasion recognition. Exogenous invasion signals (called pathogen-associated molecular patterns [PAMPs]) and endogenous markers of danger (called damage-associated molecular patterns [DAMPs]) are recognized by pattern recognition receptors (PRRs) expressed on macrophages, DCs, and mast cells. Typically PAMPs are conserved structural molecules that are abundant and commonly found in different organisms. Examples of extracellular and intracellular PAMPs are depicted in Fig. 53.1, *A*. Alarmins, another name for DAMPs, may be of intracellular origin when released upon cell death or of extracellular origin when released upon damage of connective tissue (Fig. 53.1, *B*). PRRs are generally expressed on cell membranes (for recognition of extracellular pathogens) or within the cytosol and cytoplasmic vesicles (for recognition of intracellular pathogens), but some PRRs circulate in blood as soluble factors (Fig. 53.1, *C*). A number of families of PRRs have been identified, with Toll-like receptors (TLRs) being one of the most important families. The binding of a signature PAMP or DAMP to a particular PRR activates a signaling pathway that results in transcription and translation of specific genes characteristic of an appropriate response against the triggering pathogen. Some of the known PRRs and the

corresponding PAMPs and DAMPs they recognize and their signaling cascade are discussed in Chapter 32 and found elsewhere.[2,4-7]

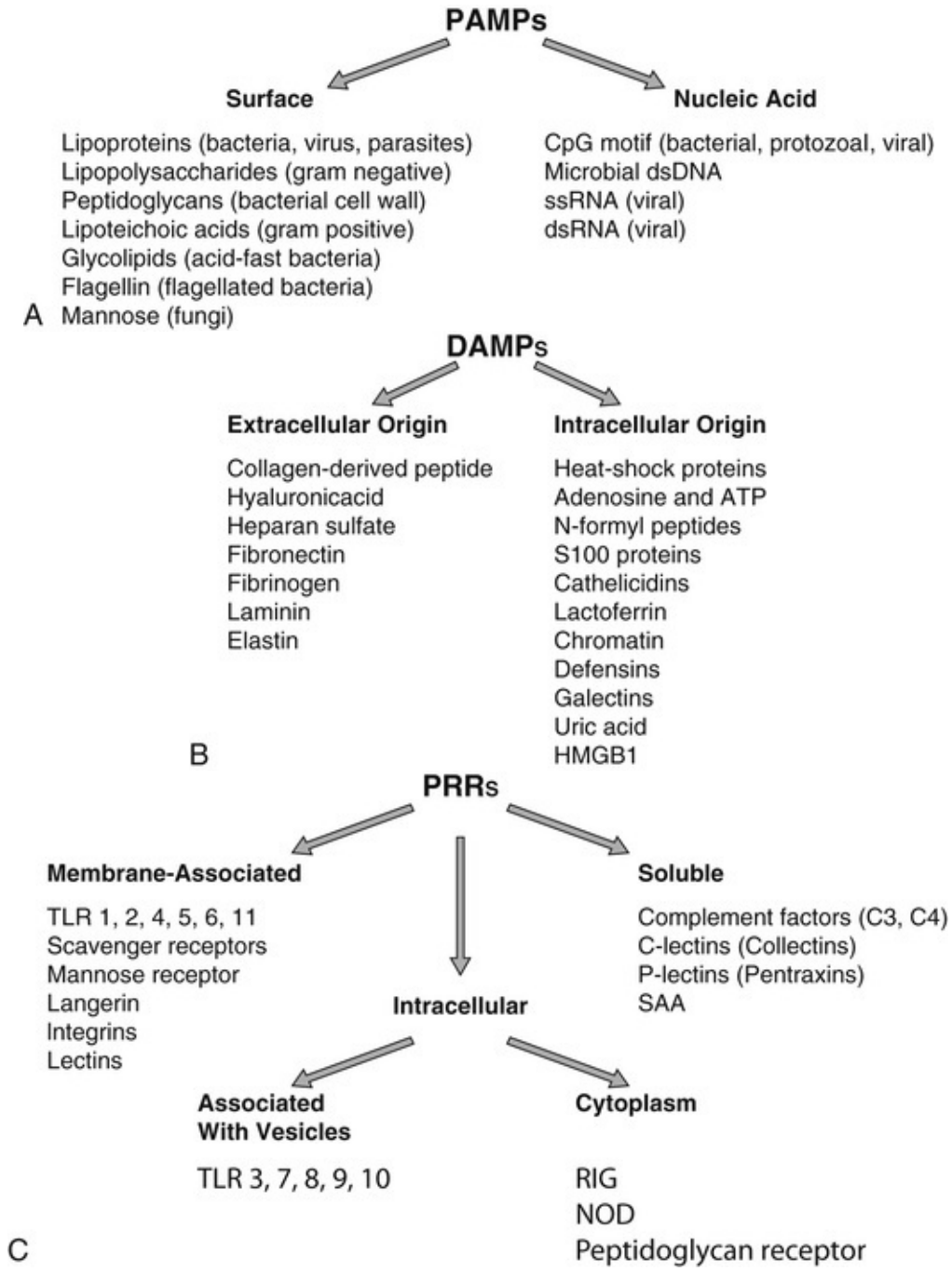


FIG. 53.1 **A,** Pathogen-associated molecular patterns *(PAMPs)* are exogenous invasion signals that comprise conserved and essential molecules abundantly and commonly found in many different organisms. *CpG,* Unmethylated cytosine-phosphate-guanine deoxynucleotide; *dsDNA,*

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double-stranded deoxyribonucleic acid; *dsRNA,* double-stranded ribonucleic acid; *ssRNA,* single-stranded ribonucleic acid. **B,** Danger-associated molecular patterns *(DAMPs)* are endogenous invasion signals that are released upon cell death or damage of connective tissue. *ATP,* Adenosine triphosphate; *HMGB1,* high mobility group box 1 protein. **C,** Pattern recognition receptors *(PRRs)* recognize pathogen-associated and damage-associated molecular patterns as signals of invasion and danger. *NOD,* Nucleotide-binding oligomerization domain-like receptor; *RIG,* retinoic acid–inducible gene 1 protein; *SAA,* serum amyloid A; *TLR,* Toll-like receptors.

Once alarm signals are recognized and cell signaling is activated, a cascade of events leads to development of an inflammatory reaction characterized by increased blood flow, increased vascular permeability, and leukocyte migration and activation. Inflammatory response is reviewed in detail in the Endotoxemia and Sepsis section in Chapter 32. Soluble mediators of the innate immune mechanisms include acute-phase proteins, proinflammatory cytokines, chemokines, vasoactive mediators, antimicrobial peptides, and protease systems (Table 53.1). Of note is the complement system activated upon specific immunologic recognition by antibodies (classical pathway), upon association of soluble factor C3b to microbial molecules (alternative pathway), or upon binding of soluble PRRs (lectins) to microbial carbohydrates. Complement activation leads to an amplifying cascade of sequential proteolytic cleavages, resulting in enhancement of phagocytosis (opsonization) and release of potent proinflammatory factors (C3a and C5a) that increase vascular permeability, exert chemoattraction of leucocytes, and amplify inflammation. The final product of the complement sequential proteolytic cleavage is the formation of lytic multiprotein complex, the terminal complement complex, or membrane attack complex.

TABLE 53.1

Examples of Soluble Mediators of the Innate Immune System and Their Main Functions

Categories of Mediators	Examples of Soluble Mediators	Functions
Acute-phase proteins	C-reactive protein	Opsonization, complement activation, soluble PRRs
	Serum amyloid A	Leukocyte recruitment and activation, soluble PRRs

	Cerulloplasmin Ferritin	Iron sequester (limiting nutrients required by microorganisms)
	Fibrinogen	Hemostasis
	Complement C3b Complement C4b	Factors of complement, involved in activation of leukocytes, soluble PRRs
Protease systems	Complement	Mediate inflammation, opsonization and MAC formation
	Kinins	Mediate inflammation
	Clotting and fibrinolysis proteins	Hemostasis
Host defense peptides and enzyme	Equine beta defensin Equine neutrophil antimicrobial peptide Equine cathelicidin Lysozyme	Antimicrobial (bacteriostatic and bactericidal) actions
	Type I interferons (IFN-α, IFN-β)	Antiviral glycoproteins mainly produced by macrophages, DCs, and fibroblasts
Vasoactive mediators	Biogenic amines (histamine, serotonin) Peptides (kinins) Lipids (PGs, TX, PAF, LTRs)	Vascular smooth muscle relaxation (vasodilation) and endothelial cell contraction (leakage of plasma into tissues)
Proinflammatory cytokines and chemokines	CXCL8 (formerly known as IL-8) CCL2 (formerly known as MCP-1)	Chemoattractants for cells of both innate and adaptive branches of the immune system
	IL-1 IL-6 TNF-α	Mediate a variety of cellular responses such as chemotaxis of leukocytes, activation of leukocytes (including T and B cells), upregulation of iNOS and COX-2, and induction of fever
Prostanoids	PGs LTRs PCs	Mediate and modulate acute inflammation
Lectins	P-lectins (pentraxin)	Bind microbial glycoproteins and polysaccharides
	S-lectins (galectins)	Mediate binding of leukocytes to extracellular matrix
	C-lectins (dectins)	Surface PRRs

COX, Cyclooxygenase; *DCs,* dendritic cells; *IFN,* interferon; *IL,* interleukin; *iNOS,* inducible nitric

oxide synthase; *LTRs,* leukotrienes; *MAC,* membrane attack complex; *MCP1,* monocyte chemoattractant protein-1; *PAF,* platelet-activating factor; *PCs,* prostacyclins; *PGs,* prostaglandins; *PRRs,* pattern recognition receptors; *TNF,* tumor necrosis factor; *TX,* thromboxane.

Neutrophils and macrophages take the center stage in innate immunity, as they are capable of destruction of offending organisms by phagocytosis, oxidative burst activity, and production of lytic enzymes. Neutrophils (polymorphonuclear granulocytes) are abundant and the predominant circulating leukocyte in horses. They are produced in the bone marrow at a very high rate; circulate for a short time (average of 12 hours); exit the bloodstream into capillaries of the liver, spleen, lungs, and bone marrow; and eventually migrate into tissues where they undergo apoptosis. Apoptotic neutrophils are removed by macrophages. Upon inflammatory stimulation, circulating neutrophils are mobilized via diapedesis, and production of new neutrophils in the bone marrow is induced in order to fulfill the recruitment demands, as neutrophils are terminally differentiated and do not divide. Neutrophils have three major types of enzyme-rich granules in their cytosol. Upon stimulation, granules containing complex mixtures of bactericidal molecules are exocytosed. Release of enzymes mediates not only microbial destruction but also tissue damage. Once activated, neutrophils are the most abundant first line of phagocytes at sites of acute inflammation or infection.

Macrophages originate from monocytes and become specialized phagocytic cells resident in various tissues, collectively called the mononuclear phagocyte system (formerly known as the reticuloendothelial system). Macrophages are named according to the tissues they home: microglial cells in the brain, histiocytes in connective tissue, Kupffer cells in the liver, splenic macrophages in the spleen, alveolar macrophages in alveoli of the lungs, pulmonary intravascular macrophages in capillaries of the lungs, and osteoclasts in bones. The mononuclear phagocyte system plays a critical role in removal of bloodborne pathogens and particles and of parasitized and aged red blood cells (RBCs) from the bloodstream when the blood passes through capillary beds lined by macrophages in the liver, spleen, and lungs. The mononuclear phagocyte system is also responsible for the removal of apoptotic cells in tissues. Macrophages also function as sentinel cells responsible for recognition of invaders, release of alarmins, and production of mediators that amplify inflammation and promote neutrophil recruitment. Macrophages serve as a backup to neutrophils, being slower responders with greater phagocytic and antimicrobial abilities, particularly effective against intracellular organisms.

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Macrophages have other critical immune functions, including antigen processing and presentation to T cells, secretion of cytokines that stimulate lymphocytes and shape the adaptive immunity, and modulation and suppression of the immune response. Hence subpopulations of macrophages exert different immunologic functions. For instance, after exposure to PAMPs and interferon gamma (IFN-γ), macrophages differentiate into M1 cells that are potent amplifiers of inflammation, secreting large quantities of proinflammatory cytokines and producing large amounts of lysosomal enzymes and mediators involved in oxidative burst. In contrast, differentiation into M2 cells occurs after exposure to interleukin (IL)-4, IL-10, and IL-13, leading to anti-inflammatory response characterized by modulation of inflammation and promotion of tissue repair.

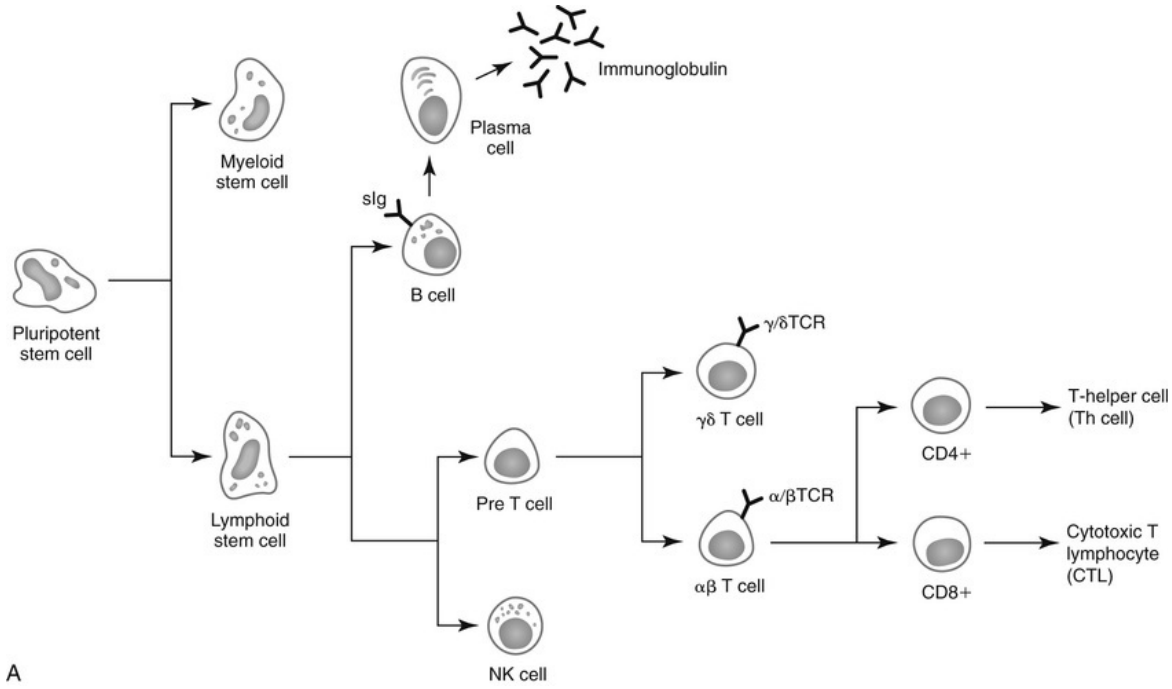
DCs comprise a heterogeneous population of immune cells, originating from either myeloid or lymphoid precursors and exerting three main immune functions: serving as sentinel cells for the detection and recognition of invaders; providing antigen presentation to T cells, thus initiating the adaptive immune response; and guiding the type of adaptive response by regulating the milieu of co-stimulatory cytokines. Sentinel DCs are prominent at skin and mucosal surfaces. With respect to their origin, DCs are classified as DC1-type cells, which include myeloid-DC and Langerhans cells, originated from monocytes; or DC2-type cells, the plasmacytoid DCs that originate from lymphoid precursors. Myeloid DCs can convert to macrophages, and vice versa, and are considered part of the mononuclear phagocyte system. Plasmacytoid DCs are specialized in secreting type I interferons (IFN-α and IFN-β) upon viral infections, which activate lymphocytes and NK cells. DCs, along with macrophages, are the principal antigen-processing cells providing stimulation of T cells. Antigen processing and presentation in the context of major histocompatibility complex (MHC) classes I and II are critical functions linking the cells of the innate immune system and those of the adaptive immune system.

NK cells, gamma delta T cells, and B1 cells are lymphoid cells considered to be in the interface between innate and adaptive immunity. NK cells recognize cells under stress, including viral-infected or tumor cells that do not express antigenic epitopes in the context of MHC class I. Many viral-infected and tumor cells actively promote downregulation of MHC class I expression, which allows them to evade detection by cytotoxic T cells, also known as $CD8^+$ alpha beta T lymphocytes (see below). In the absence of MHC class I molecule expression, the NK cells become activated and secrete perforins and granzymes that destroy

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the target cells. Another mechanism used by NK cells to destroy viral-infected and tumor cells is called antibody-dependent cell-mediated cytotoxicity (ADCC), which involves binding of receptors for the gamma heavy chain of immunoglobulin G (IgG) (Fc-gamma receptor) on NK cells to IgG bound to viral-infected or tumor molecules expressed on target cells. Once activated, NK cells release cytotoxic granules, containing granzymes and pore-forming protein perforin, onto the surface of the target cell, causing programmed cell death of the target cell. Gamma delta T cells comprise a heterogeneous population of T cells that express gamma delta T-cell receptors (TCRs) and exert a wide range of immune functions, including response to heat shock proteins, cytokine production, activation independent of MHC, and participation in delayed hypersensitivity reaction. In horses, the role of gamma delta T cells has not been well described. A subpopulation of B cells known as B1 cells has been partially described in the horse, and they are abundant during fetal and neonatal periods; with age, these cells concentrate in the peritoneal cavity. Equine B1 cells have diverse immunoglobulin light chain repertoires but more frequently express a receptor that binds to phosphorylcholine commonly present on bacteria, helminths, apoptotic cell membranes, and oxidized lipids; B1 cells are known to become activated, differentiate, and secrete antibodies in a T cell–independent manner but their origin and function still need to be determined in the horse.[8,9]

The adaptive (antigen-specific, clonal) immune response involves two major populations of lymphocytes, B cells and T cells (Fig. 53.2, *A*). B lymphocytes populate germinal centers of the spleen and lymph nodes and comprise 15% to 30% of the peripheral blood lymphocytes. Alpha beta T lymphocytes populate the periarteriolar regions of the spleen and the paracortical regions of lymph nodes and comprise about 70% to 80% of peripheral blood lymphocytes of horses.


Immunoglobulin
Plasma cell
Myeloid stem cell
sIg
B cell
Pluripotent stem cell
γ/δTCR
γδ T cell
T-helper cell (Th cell)
CD4+
Pre T cell
α/βTCR
Cytotoxic T lymphocyte (CTL)
αβ T cell
CD8+
Lymphoid stem cell
NK cell

A

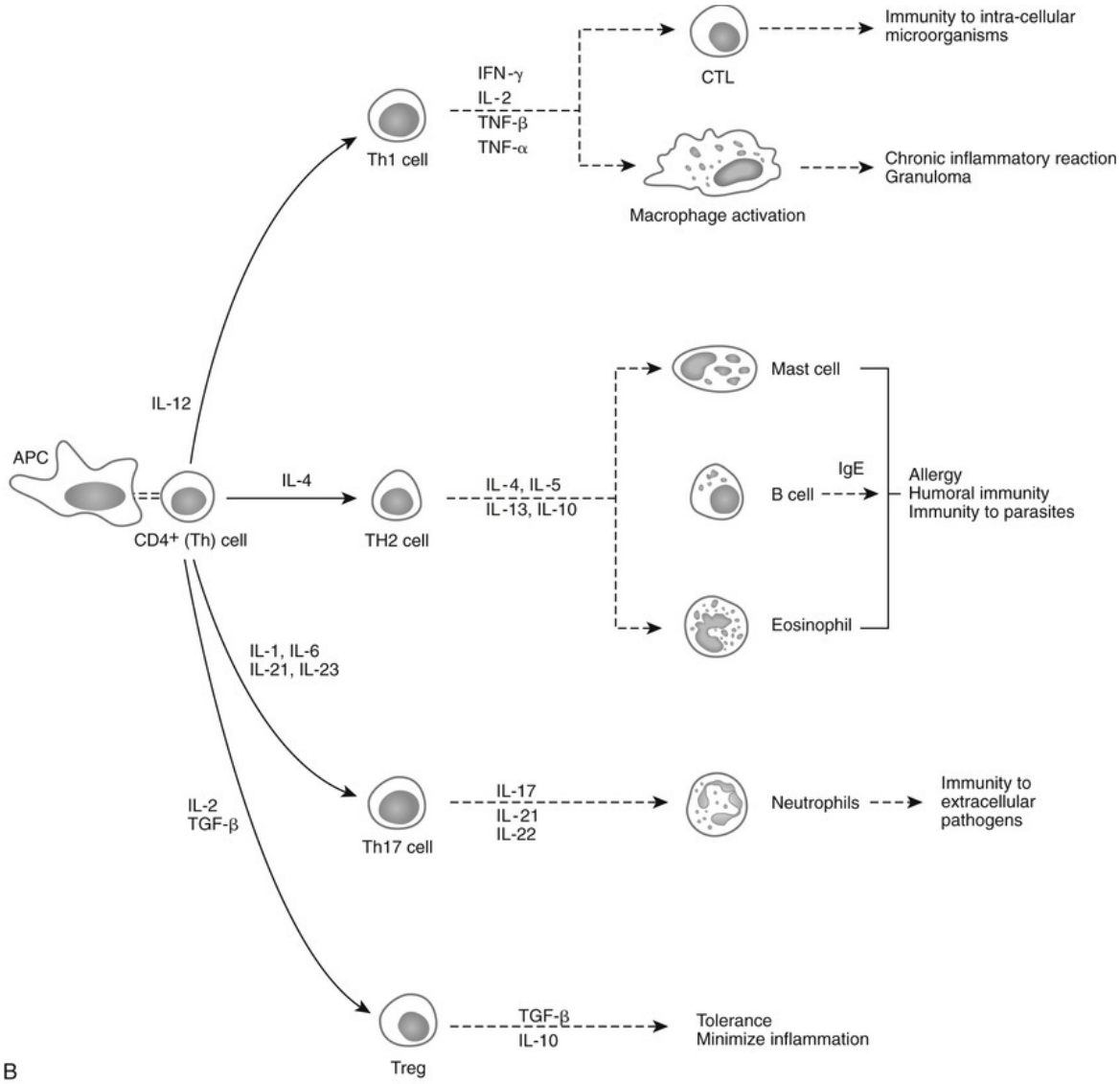


FIG. 53.2 **A,** Ontogeny of the lymphoid cell lineage. *NK cell,* Natural killer cell; *sIg,* surface immunoglobulin; *TCR,* T-cell receptor. **B,** Simplified functional differentiation of T-helper *(Th)* cells. CD4+ Th cells can be divided into subsets of Th cells based on their cytokine profile. Antigen-presenting cell *(APC)* interaction with Th cells via antigen presentation, co-stimulatory molecules, and cytokine milieu leads to the functional differentiation of subsets of Th cells. The cytokine milieu by APCs that leads to the functional differentiation of individual Th cells is listed. The known roles of the various functional subtypes of Th cells are also listed. *CTL,* Cytotoxic T cell; *IFN,* interferon; *Ig,* immunoglobulin; *IL,* interleukin; *TGF,* transforming growth factor; *TNF,* tumor necrosis factor; *Treg,* regulatory T cell;

In the adaptive immune response, the highly specific antigen recognition is mediated by B-cell immunoglobulin receptors (BCRs) on B lymphocytes and by alpha beta T-cell receptors (TCRs) on T lymphocytes. The diversity of these

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receptors, both BCRs and TCRs, that allows recognition of an enormous number of antigenic epitopes is generated by several mechanisms, including DNA recombination of different gene segments V, D, and J encoding the antigen-binding region, addition of nucleotides during the recombination process (junctional diversity), and point hypermutations. Both BCRs and TCRs are heterodimers, which in turn provides yet another mechanism to increase antigen-recognition diversity.

The B lymphocytes produce and express antibodies or immunoglobulins (Igs) on the cell surface and are the precursors of plasma cells, which secrete Igs. B cells mediate humoral immunity, which classically provides defense against toxins, extracellular bacterial infections, parasites, and certain viral infections. There are several isotypes of Igs, classified according to their heavy chain constant region—IgA (alpha), IgD (delta), IgE (epsilon), IgG (gamma) and IgM (mu heavy chain)—and each isotype confers special functions.[10] For instance, dimeric IgA (joined by J chain) produced in mucosa-associated lymphoid tissues is the most abundant Ig isotype in body secretions, whereas monomeric IgA is present in serum; the main IgA functions are antigen neutralization and opsonization. IgD is a surface receptor of naive mature B cells, and its function is not well determined. IgE is present in small amounts in serum, and it is mostly found bound to Fc epsilon receptors on the surface of mast cells and basophils; when two or more IgE molecules bind to the antigen or allergen, it promotes cell degranulation. IgM is the original surface receptor of developing B cells and is present in naive and some activated and memory B cells; when secreted by plasma cells, IgM circulates as pentamer, and it promotes antigen neutralization and complement activation. IgG is the main Ig isotype in plasma and serum; IgG's main functions are neutralization and opsonization, and some subclasses promote complement activation. The characteristics and immunologic functions of the equine Ig isotypes and subclasses are summarized in Table 53.2.[11-15] Besides antibody production, B cells function as important antigen-presenting cells (APCs) by recognizing, internalizing, processing, and finally presenting antigens in the context of MHC class II to T cells. A less appreciated function of subsets of B cells is the production of cytokines. Subsets of B cells are now recognized as regulators of the immune responses during inflammation and autoimmunity.

TABLE 53.2

Characteristics and Immunologic Functions of Equine Immunoglobulin (Ig) Isotypes IgM, IgG, IgA, and IgE and Subclasses IgG1 to IgG7

Ig Isotype		**Ig Mu**	**Ig Gamma**								**Ig Alpha**	**Ig Epsilon**
Original Ig designation		**IgM**	**Total IgG**	**IgGa**		**IgG (T)**		**IgGb**		**IgGc**	**IgA**	**IgE**
Current Ig designation		**IgM**	**IgG**	**IgG1**	**IgG2**	**IgG3**	**IgG5**	**IgG4**	**IgG7**	**IgG6**	**IgA**	**IgE**
Agglutination		++	Yes	+	U	+		+		U	No	No
Precipitation		++	Yes	+	U	+		+		U	No	No
Opsonization		++	Yes	+++	U	+++		+++		U	+	No
Neutralization		++	Yes	+++	U	+++		+++		U	+++	No
Complement fixation		++++	Variable	Yes	No	Yes	No	No		No	+	No
ADCC by NKs		No	Yes	+++	U	No		No		?	No	No
Mucosal protection		++	No	No		No		No		No	++++	No
MC sensitization		No	No	No		No		No		No	No	Yes
Immunity to parasites		No	Yes	No		++		++		No	No	Yes
Mean concentration (mg/mL)	Serum	1.1 ±0.4	18.4 ± 2.8	3.4 ± 2		3.8 ± 0.2		15.6 ± 6.5		0.2 ± 0.1	1.35 ± 09	0.11 ± 0.07
	Colostrum	1.23 ± 0.32	360 ± 107	82 ± 44		44 ± 25		183 ± 38		0.3 ± 0.1	9 ± 3	0.19 ± 0.0
	Milk on day 1 postpartum	NA		1.6 ± 1		0.8 ± 0.6		3.1 ± 1.6		0.06 ± 0.06	0.3 ± 0.1	NA

Summary of data compiled from several authors (see references).

Concentrations of Ig isotypes and subclasses are approximated with the goal of highlighting the differences between the various isotypes.

Note that the Ig concentrations are given in mg/mL. Most laboratories report Ig concentrations in mg/dL. Conversion from mg/mL = 100 × mg/dL.

ADCC, Antibody-dependent cell-mediated cytotoxicity; *MC,* mast cell; *NA,* not applicable; *NKs,* natural killer cells; *U,* unknown.

T lymphocytes expressing alpha beta TCRs orchestrate the adaptive immune responses and provide cell-mediated immunity for protection against fungal, protozoal, intracellular bacterial, and viral infections. Unlike B lymphocytes, alpha beta T lymphocytes only recognize antigen fragments associated with the MHC molecule. The alpha beta T lymphocytes are categorized according to the expression of cluster of differentiation (CD) as CD4 or CD8. Functionally, CD4+ T lymphocytes comprise the T-helper (Th) cells, whereas CD8+ T lymphocytes comprise cytotoxic T cells (CTLs). The CD4+ T lymphocytes recognize antigenic epitopes in the context of MHC class II, which means that endocytosed antigens (e.g., extracellular pathogens) are processed and presented by APCs via the exogenous pathway. The CD8+ T lymphocytes recognize antigenic epitopes

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in the context of MHC class I, which means that the antigens are derived from intracellular proteins (e.g., intracellular pathogens) via the endogenous pathway. Activation of CD8+ T lymphocytes to become effector CTLs requires specialized APCs to be capable of cross-presentation, where antigen peptides that originated from exogenous foreign proteins are presented on MHC class I molecules.[16] Specific subsets of DCs have adapted their endocytic and phagocytic pathways to acquire exogenous antigens from infectious agents and present them in the context of MHC class I, without being infected by the infectious agent.

Based on the profile of cytokine expression, CD4+ Th cells are classified into distinct functional subsets of Th cells that modulate the humoral and cellular immune responses. Fig. 53.2, *B* illustrates a simplified version of the functional differentiation of Th cells. APC interaction with Th cells via antigen presentation, co-stimulatory molecules, and cytokine milieu leads to the functional differentiation of particular subsets of Th cells. The secretion of IL-12 by APCs leads to the generation of the T-helper type 1 (Th1) cell subset, which produces primarily IFN-γ and functions in cell-mediated immunity, immunity to intracellular organisms, chronic inflammation, and delayed-type hypersensitivity (DTH) reactions. The cytokine IL-4 generates the T-helper type 2 (Th2) cell subset, which secretes IL-4, IL-5, IL-10, and IL-13 and interacts with B cells for the production of antibodies. The subset designated Th17 is induced by a cytokine milieu that includes IL-1, IL-21, IL-23, and IL-6; Th17 cells secrete proinflammatory cytokines IL-17, IL-21, and IL-22, which promote immunity to extracellular pathogens (bacteria and fungi).[17,18] The immunomodulatory cytokine milieu based on IL-2 and transforming growth factor beta (TGF-β) promotes differentiation to the subset designated regulatory T cells (Tregs), which secrete the immunosuppressive cytokines TGF-β and IL-10. A number of other Th subsets have been described in human and animal models of disease, demonstrating the complexity of adaptive immune response.

Factors Associated With Adequacy of the Immune Response

Many factors influence the adequacy of the immune response of an individual animal to potential environmental organisms. Important factors to consider in the horse are age; genetic predisposition; exercise fitness; stress associated with exercise or transportation; state of health, including nutritional status; and the

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presence of concurrent diseases, including viral infections, tumors, and autoimmunity. Moreover, increased concentrations of corticosteroids can result in varying degrees of immunosuppression and may exacerbate preexisting infectious diseases or decrease resistance to environmental pathogens.[19] The increase in endogenous corticosteroids may be associated with stress or disease; the most common condition in horses is caused by pituitary pars intermedia dysfunction (PPID).[20] In addition, corticosteroid treatment is the most common iatrogenic cause of immunosuppression (see the Drug-Induced Immunosuppression section later in this chapter).[21]

Age has been shown to affect immune function in multiple species. Altered immune function has been identified at both ends of the age spectrum, in foals and older horses. Detailed overviews of the immune responses in young horses and older horses have been reviewed recently, and they are discussed in detail later in this chapter.[22-29] At birth foals have no circulating Igs of their own, and they normally receive maternal transfer of colostral antibodies soon after birth. Colostrum is critical for neonatal immunologic protection. Although foals are immunocompetent at birth, their immune system is naive. Heathy neonatal foals appear to have neutrophilic phagocytocytic ability and killing capacity via oxidative burst activity comparable to that of mature horses.[29-31] Differences in adaptive immune responses between foals and adult horses are not completely understood.[32-35] Despite the apparently adequate preparedness of the immune system in young foals, their ability to develop a humoral immune response is believed to be affected by the maternal-derived antibodies. As the foals age, the maternal antibody levels decline and no longer provide comprehensive protection, but at the same time they may interfere with the foals' ability to mount an immune response. Aging is associated with changes in immunologic status, in particular a decline in the functionality of the immune system characterized by a chronic, low-grade proinflammatory state and a decreased antigen-specific immunity or clonal exhaustion.[20,28] The aging process affecting the immune response is often referred to as immunosenescence.

Nutritional status is well recognized to exert a major impact on immune function, and nutritional deprivation produces impairment of the immune response.[36] Collectively called nutritionally acquired immunodeficiency syndrome (NAIDS), these immunologic dysfunctions include protein-calorie malnutrition and deficiencies of single nutrients. Protein-calorie malnutrition and deficiencies of single nutrients that assist in nucleic acid metabolism lead to

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dysfunction of the adaptive immune response, especially the T-cell functions, and result in atrophy of lymphoid tissues. In these individuals, the cell-mediated immunity and humoral response to T cell–dependent antigens are subnormal. Deficiency of single nutrients can impair production of key proteins by lymphocytes as well as phagocytic cells. Inadequate nutritional status may result from (1) increased and unmet nutritional requirement, including during growth, pregnancy, lactation, aging, and intense work; (2) disease state associated with altered nutrient intake, such as conditions leading to hypophagia or anorexia; and (3) disease state associated with altered absorption of nutrients.[37] Young, growing animals are most likely to develop NAIDS, followed by geriatric patients, contributing to the greater risk of infections in both age groups.

Exercise represents not only an increased nutritional requirement but also a physiologic stress that can significantly alter the immune response. However, defining the precise effects of exercise on the equine immune system and susceptibility to disease has been difficult because of the complexity of the immune system, host factors (e.g., age, level of fitness), and the variable nature of exercise. In general, it appears that exercise may have both positive and negative effects on the immune response.[38-45] Suppressive effects, such as a decline in the CD4+/CD8+ ratio of T cells, decreased lymphoproliferative responses, and suppression of the innate immune system, have been associated with strenuous high-intensity exercise, prolonged exhaustive exercise, or overtraining. In contrast, moderate exercise tends to have beneficial effects on the host defense mechanisms. Data in horses directly linking exercise-induced immunosuppression and increased susceptibility to infectious disease are limited. However, the potential immunosuppressive effects of exercise need to be recognized. Influenza infection in trained horses subjected to moderate exercise led to increased signs of clinical disease, but the duration of disease was unaffected.[46] Unconditioned ponies vaccinated with a killed influenza vaccine and subjected to 5 days of strenuous exercise had an increased susceptibility to clinical influenza after challenge exposure compared with rested ponies.[47] However, ponies with exercise-induced immunosuppression responded to the administration of an intranasal modified-live equine influenza vaccine and were protected from challenge.[48]

Immunologic Disorders Resulting From Compromised or Deficient Immune Responses

Increased susceptibility to infections, because of recurrence, chronicity, or severity of infectious illness beyond what is considered "normal," raises the suspicion of inadequate immune response. Inadequate immune protection may result from immunodeficiency disorders or a state of immunosuppression.[49-53] General clinical features associated with immunodeficiency disorders or immunosuppression include (1) repeated episodes of infections that respond poorly to standard therapy or return following discontinuation of antibiotic therapy; (2) infections associated with opportunistic or low pathogenicity organisms rarely observed in immunocompetent individuals; (3) systemic illness after administration of attenuated live vaccines; (4) failure to respond to vaccination; and (5) persistent marked abnormalities in leukocyte numbers. Pathogens most often associated with immunodeficiencies in horses include *Pneumocystis jirovecii*, *Candida* spp., *Aspergillus* spp., adenovirus, *Cryptosporidium*, and *Rhodococcus equi* in adult horses. The type of organism causing infection often suggests the type of defective immunity. When inadequate immune response is suspected, it is important to determine if there is a primary immunodeficiency disorder or a secondary state of immunosuppression.

Primary immunodeficiency disorders recognized in horses are characterized mainly by defects of components of the adaptive immune response and are outlined in Table 53.3. Yet it is possible that many forms of impaired or inadequate immune response in foals and mature horses are not clinically recognized or still poorly defined. Detailed information on the diagnosis and management of immunodeficiency disorders in horses are provided later in this chapter and found elsewhere.[54]

TABLE 53.3

Features of Immunodeficiency Disorders Affecting the Adaptive Immunity of Horses

Immunodeficiency Disorder	Age of Clinical Onset[b]	Breed and Gender	Peripheral Lymphocyte Count	B cell Count and Function	Serum IgM Concentration	Serum IgG Concentration	Se C
Failure of passive transfer of maternal immunity (partial or total)	Neonate (0 to 3 weeks)	Any	Normal	Normal count; normal function	Low	IgG <800 mg/dL	L

SCID	1-3 months	Arabian, Arabian cross, Caspian[b]	Severe absolute lymphopenia (< 1000 cells/μL)	Low count; absent function	Undetectable[a]	Only from passive transfer (incapable of producing any Ig)	U
Foal immunodeficiency syndrome (FIS)	3-5 weeks	Fell pony Dale pony	Normal at birth, then progressive lymphopenia	Count declines over time; no function	Undetectable[a]	Only from passive transfer (incapable of producing any Ig)	U
X-linked agammaglobulinemia	2-6 months	THB, STB, QH Males only	Normal or low	Absent	Undetectable[a]	Undetectable[a]	U
Juvenile selective IgM deficiency	2-18 months	Any; especially Arabian, QH, THB, STB, Paso Fino	Normal	Normal count	Undetectable or low	Normal	N
Transient hypogammaglobulinemia of the young	2-18 months	Any; especially Arabian, THB	Normal	Normal	Persistently low (detectable)	Persistently low (delayed onset of Ig synthesis for variable period of time)	L
Transient CD4+ T cell lymphopenia of the young	2-18 months	Any	Normal to low	Normal count; normal function	Low or normal	Low or normal	L
Common variable immunodeficiency	Older than 2 years; average 10 years	Any;especially THB, QH, WB, pony, Arabian, Paint	Normal or low	Low count or absent	Undetectable or low	Low	N gr de ti

[a]Values depend on concentration of passively transferred maternal antibodies and age.

[b]Report of clinical and postmortem findings of SCID, but negative for SCID genetic testing.

Onset of signs listed in this table is in face of adequate colostral transfer of maternal immunity, except for partial or total failure of passive transfer of maternal immunity.

ID PHA, Intradermal phytohemagglutinin; *Ig,* immumoglobulin; *NR,* not reported; *QH,* Quarter Horse; *SCID,* severe combined immune deficiency; *STB,* Standardbred; *THB,* Thoroughbred; *Vx,*

vaccine; *WB,* warmblood.

Inherited forms of complement dysfunction or factor deficiency have not been reported in the horse. However, depletion of complement component C3 associated with chronic infections, such as equine infectious anemia, has been reported. Moreover, the foal is born with low serum complement activity, and colostrum is not a significant source of complement. Therefore foals are transiently deficient in serum opsonic capacity and rely on their own production of complement after birth. In sepsis, complement component C3 is rapidly consumed, which delays the physiologic age-dependent increase observed in healthy foals.[31] Neutrophil dysfunction, characterized by decreased neutrophilic phagocytocytic ability and killing capacity via oxidative burst activity is reported in septic neonates.[29-31]

Pelger-Huet anomaly of neutrophils is an inherited disorder described in Arabian horses, characterized by a reduced number of nuclear segmentation and bilobed dumbbell-shaped nuclei, making mature neutrophils resemble band forms.[55,56] Immunophenotyping of Pelger-Huet neutrophils of horses revealed normal expression of myeloid-specific markers and adhesion molecules, and evaluation of phagocytosis and oxidative burst via flow cytometry revealed normal neutrophil function. Despite the morphologic anomaly revealed during the evaluation of blood smears, the functions of Pelger-Huet neutrophils are virtually normal, and clinical signs of immunodeficiency are not observed; however, their inflexible nuclei restrict their ability to emigrate from blood vessels.[53]

Immunologic Disorders Leading to Immune-Mediated Injury

Inappropriate or exaggerated immunologic responses can directly injure bodily tissues. The clinical manifestation of immune-mediated injury depends on the nature and sites of tissue injury. Immune-mediated tissue injury can be from humoral or cell-mediated immune responses, or a combination of both. Immune-mediated tissue or organ damage, often referred to as hypersensitivity reaction, has been classified according to the nature of the immunologic pathway involved. The basic framework of disease mechanisms involving the adaptive immunity proposed by Gell and Coombs consisted of four types of immunopathologic reactions: type I (also referred to as immediate hypersensitivity) encompassing those mediated by IgE; type II encompassing cytotoxic mechanisms mediated by antibodies, generally of the IgG and IgM

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isotypes; type III encompassing those mediated by immune complexes, which mostly involve IgG and IgM isotypes; and type IV, which are delayed reactions mediated by sensitized T cells. The four types of hypersensitivity reactions are discussed in more detail below. Comprehensive reviews of hypersensitivity disorders may be found elsewhere.[2,3,57,58]

Immediate or type I hypersensitivity reactions are mediated by antibodies of the IgE isotype; hence they manifest after a primary exposure (sensitization) to antigen or allergen and subsequent B-cell differentiation, antibody production, and memory development. These reactions typically occur within 15 minutes to a few hours after the time of exposure to the antigen or allergen, depending on the need for metabolic processing of the triggering molecule. Binding of the antigen or allergen to at least two IgE molecules bound to the surface of mast cells via high-affinity IgE receptors (Fc epsilon RI) leads to degranulation of mast cells and release of mediators such as histamine, serotonin, leukotrienes, prostaglandins, various chemokines, and cytokines. These inflammatory mediators cause vasodilation, edema, smooth muscle contraction, and chemotaxis; this immediate inflammatory reaction occurs locally and potentially systemically. Of clinical significance, localized reactions may propagate to systemic reactions known as anaphylaxis. In horses, anaphylaxis may manifest with fever, hypotension, bronchoconstriction, dyspnea, tachypnea, coughing, sweating, piloerection, diarrhea, and abdominal pain, as the respiratory and gastrointestinal (GI) tracts are the shock organs.

Antibody-mediated hypersensitivities reactions include (1) reactions to self cell-associated antigenic epitopes, referred to as type II hypersensitivity, and (2) reactions involving soluble antigen-antibody (Ag-Ab) complexes, referred to as type III hypersensitivity. Antibodies of the IgG, IgM, and IgA isotypes can trigger severe inflammation via opsonization for enhanced phagocytic function and complement activation with deposition of C3b and iC3b that lead to destruction of antigen-bearing cells. In addition, Igs also mark the cell target for ADCC by NK cells. Activation of C5a potently recruits neutrophils that release proteolytic enzymes (including acid phosphatases, acid hydrolytic enzymes, cathepsins, elastase, collagenase) and oxidative agents with further tissue destruction. Target cells may be circulating or be part of tissues. In type II hypersensitivity, the binding of Ig to antigenic epitopes on cells that are fixed in a tissue or on tissue structural elements, such as basement membrane, results in damage to the respective tissue. For instance, direct antibody binding to self-antigens of the keratinocyte desmosome are responsible for damage that results

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in acantholysis, blistering, and desquamation in the pemphigus complex. If the antigen-bearing cell is circulating (e.g., erythrocyte, platelet, neutrophil), the cell may be destroyed in circulation but more typically is removed by the mononuclear phagocyte system. Examples of hypersensitivity to antigenic epitopes on circulating cells include alloimmune reactions (such as neonatal isoerythrolysis, neonatal alloimmune thrombocytopenia, and neonatal allogeneic neutropenia) and drug hypersensitivities (such as penicillin-induced hemolytic anemia). In the case of type III hypersensitivity, antibodies bind to soluble antigens (e.g., pathogens) that are not cell associated, resulting in Ag-Ab complexes that deposit in a variety of vascular beds, including lymph nodes, kidneys, joints, and skin.[59] Tissues in the vicinity of the precipitated Ag-Ab complexes are also damaged by the ensuing immune reaction. An important condition characterized by hypersensitivity reaction to soluble antigens in horses is purpura hemorrhagica.

Delayed hypersensitivity reactions, also referred to as type IV hypersensitivity, consist of exaggerated cell-mediated immune responses within 24 to 48 hours from the time of exposure to the antigen. This condition also requires previous sensitization to the antigen, with a previous exposure that leads to APC processing and presentation of the antigens to T cells in the context of MHC and the cytokine milieu. The cytokine milieu, dictated by the APCs, leads to the differentiation of Ag-specific T cells into specific subsets of Th cells or CTLs and development of memory. Classically, the sensitization phase of cell-mediated hypersensitivity involves antigen processing and presentation in the context of MHC accompanied by IL-12 as co-stimulatory signal by the APCs, leading to differentiation of the T cells into Th1 cells. Upon reexposure to the same antigen, APCs activate the antigen-specific Th1 cells that proliferate and produce large amounts of Th1 cytokines (IFN-γ, IL-2, tumor necrosis factor [TNF]–α, and TNF-β). This cascade of cytokines activates macrophages and recruits nonspecific circulating leukocytes, including monocytes and lymphocytes, to infiltrate the site; there is amplification of the inflammatory reaction and development of epithelioid macrophages and multinucleated giant cells, leading to a chronic inflammatory reaction that mediates tissue damage or granuloma formation. If during sensitization the cytokine milieu by APCs includes IL-4 and IL-5, the T cells differentiate into Th2 cells. Upon reexposure, the sensitized Th2 cells produce large amounts of the Th2 cytokines (IL-4 and IL-5), leading to IgE production and nonspecific eosinophilic activation. If the sensitized T cells differentiate into CTLs, upon reexposure, the sensitized CTLs

proliferate and mediate cytotoxicity and tissue damage. Examples of DTH in horses include (1) contact dermatitis to heavy metals and aniline dyes found in tack, bedding, soaps, and blankets; (2) granulomatous diseases; and (3) hypersensitivity to insect bite. Table 53.4 summarizes some disorders caused by immune-mediated injury in the horse; detailed discussion of these and other conditions can be found elsewhere.

TABLE 53.4

Immune-Mediated Conditions and the Immune Mechanism Mediating Tissue Injury in the Horse

Organ/Tissue	Condition	Proposed Immunologic Mechanism Mediating Injury
Systemic	Systemic anaphylaxis	• Abs of IgE isotype bound to mast cell surface via high-affinity Fc epsilon receptor I lead to degranulation and release of vasoactive and inflammatory mediators. • Type I hypersensitivity reaction.
	Systemic lupus erythematosus (SLE)	• Autoantibodies against nuclear structures, including nucleic acids and ribonucleoproteins, mediate tissue injury. Antinuclear Abs (ANAs), combine with Ags and deposit in basement membranes of skin, glomeruli, synovial membranes, and lymph nodes. • Type II hypersensitivity reaction.
	Multisystemic eosinophilic epitheliotropic disease (MEED)	• Chronic IgE-mediated hypersensitivity reaction against undefined Ags characterized by eosinophilic infiltrate involving multiple tissues/organs, including skin, lungs, GI tract (leading to malabsorption and enteric protein loss), GI-associated lymph nodes, liver, and pancreas (resulting in maldigestion).
	Serum sickness	• Generalized hypersensitivity reaction resulting from formation of large quantities of immune complexes to circulating Ags and deposition in disseminated vascular beds. • Type III hypersensitivity reaction.
	Equine sarcoidosis	• Idiopathic systemic granulomatous disease, affecting most commonly skin, lymph nodes, and lungs, and less commonly spleen, intestinal tract, liver, and endocardium. • Characterized by multifocal infiltrates of macrophages, lymphocytes, plasma cells, multinucleated giant cells, and epithelioid macrophages. • Unknown triggering agent. • Type IV hypersensitivity reaction.
Respiratory system	Recurrent airway obstruction (RAO) or equine asthma	• Hypersensitivity to inhaled organic dusts characterized by neutrophilic infiltrate. • Complex immunopathologic mechanisms: (1) increased expression of IL-4 and IL-5, with development of allergen-specific Th2 response, Ag-specific IgE bound to mast cells and basophils; and (2) concurrent upregulation of cytokines of Th17 and Th1 immune responses.
	Hypersensitivity pneumonitis	• Lymphocytic/plasmacytic bronchiolitis and lymphocytic interstitial pneumonia, sometimes accompanied by granuloma formation and fibrosis, associated with inhalation of organic antigens such as chicken dust and fungi.
Alimentary	Chronic	• Malabsorptive and maldigestive disorders characterized by infiltration of

system	inflammatory bowel disease	the GI mucosa and submucosa with immune cells. • Phenotypic characterization according to infiltrate: (1) predominance of eosinophils (eosinophilic entiritis, MEED, and segmental eosinophilic enteritis), (2) lymphocytes and plasma cells (lymphocytic-plasmacytic enteritis and premalignant lymphoma), and (3) macrophages and epithelioid macrophages (granulomatous enteritis and sarcoidosis).
Renal system	Glomerulonephritis	• Disease resulting from deposition of Abs leading to activation of complement, vasculitis, influx of inflammatory cells (particularly neutrophils), and possibly proliferation of mesangial and endothelial cells. • Mechanisms include: (1) antibodies to the glomerular basement membrane (type II hypersensitivity reaction), or (2) circulating immune complexes in glomerular vascular endothelium (type III hypersensitivity reaction).
Nervous system	Polyneuritis equi (PNE)	• Progressive, insidious radiculoneuritis characterized by granulomatous inflammation of the nerve roots, hemorrhages, demyelination, axonal degeneration, and fibrosis. • Inflammatory infiltrate of the perineurium consists of lymphocytes (including T cells and B cells), plasma cells, macrophages and giant cells, eosinophils, and neutrophils. • Cases of PNE present antibodies to myelin P2 protein.
Hematopoietic system	Autoimmune hemolytic anemia	• Antibodies directed against autologous RBC Ags activate complement, resulting in rapid destruction of RBCs or removal by phagocytic cells from the mononuclear phagocyte system.
	Neonatal isoerythrolysis	• Alloantibodies of maternal origin (absorbed from colostrum) recognize Ags on the foal RBCs that are inherited from the sire but absent in the mares. • Alloantibodies directed against RBCs' surface glycoproteins or glycolipids, known as alloantigens, mediate RBC damage and destruction.
	Drug-induced immune-mediated hemolytic anemia	• Three mechanisms: (1) drug (e.g., penicillin, sulfonamides, phenylbutazone) binds to RBC surface glycoproteins, is recognized as foreign, and is eliminated; (2) drug and Ab combine, resulting in direct activation of complement with RBCs destroyed as bystanders; (3) drug modifies RBC membranes such that Abs are passively adsorbed and the RBCs are removed by phagocytic cells in the mononuclear phagocyte system.
	Neonatal alloimmune thrombocytopenia	• Alloantibodies of maternal origin (absorbed from colostrum) recognize Ags on the neonate's (horse or mule) platelets. Ig-mediated damage and destruction ensue.
	Immune-mediated thrombocytopenia	• Primary autoimmune disorder in which Igs are directed at autologous platelet Ags, or secondary to infectious disease (e.g., equine infectious anemia) or lymphoma with foreign Ags precipitating on the platelets. Ags are recognized by Igs and Ig-mediated damage and destruction ensue.
	Neonatal allogeneic immune-mediated neutropenia	• Binding of alloantibodies of maternal origin (absorbed from colostrum) lead to destruction of foal's neutrophils.
Vascular system	Hypersensitivity vasculitis	• Immune-mediated vasculopathy, most often affecting small vessels, results from deposition of immune complexes or autoantibodies on the endothelium, leading to inflammation and damage. Vasculitides are most commonly neutrophilic (leukocytoclastic) but may be eosinophilic, lymphocytic, or mixed. • Either type III or type II hypersensitivity reaction. • Generally, lesions involve the skin, typically in dependent and nonpigmented areas.
	Equine purpura hemorrhagica	• Hypersensitivity vasculitis, most commonly post *Streptococcus equi* infection or vaccination, resulting from deposit of immune complexes of

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	(EPH)	the IgA isotype in walls of small vessels (venules and arterioles). • Type III hypersensitivity reaction. • Commonly manifested as cutaneous and mucosal involvement, but when severe, EPH leads to extensive edema and hemorrhages of dermis, subcutaneous tissue, skeletal muscles, lungs, kidney, spleen, and intestinal wall.
Eye	Equine recurrent uveitis (ERU)	• Immune-mediated ocular disease characterized by recurrent-remitting episodes of intraocular inflammation, mediated by CD4+ Th1 and Th17 responses directed against several retinal proteins, leading to destruction of intraocular structures.
	Immune-mediated keratopathy (IMK)	• Primary, nonulcerative, noninfectious keratitis (progressive or chronic) characterized by mild to moderate cellular infiltrate (predominantly lymphocytes and plasma cells), corneal vascularization, and corneal edema.
Skin	Pemphigus complex (pemphigus foliaceus and vulgaris)	• Autoimmune vesiculobullous disorders of the skin or mucous membranes mediated by Abs to components of keratinocyte desmosome (i.e., desmogleins), leading to destruction of keratinocyte adhesion (acantholysis). • Horses are commonly systemically ill (depression, anorexia, weight loss, and fever).
	Bullous pemphigoid	• Autoimmune vesiculobullous and ulcerative disorder of the skin and oral mucosa mediated by antibodies to glycoprotein (BPA2 = bullous pemphigoid Ag II and collagen XVII) in the lamina lucida of the cutaneous basement membrane (BM), with complement activation leading to chemotaxis of neutrophils, eosinophils, and mononuclear cells, and consequent damage of the BM. • Horses often appear systemically ill (depression, anorexia, weight loss, and possibly fever).
	Cutaneous (discoid) lupus erythematosus	• Autoantibodies against nuclear structures combine with Ags and attach to keratinocytes, leading to ADCC. Injured keratinocytes release IL-2, resulting in lymphohistiocytic infiltrate. • Lesions may be induced or exacerbated by UV light.
	Erythema multiforme	• Immunologic reaction (triggered by various insults such as infections, drugs, food, neoplasia, or idiopathic) leading to apoptosis of keratinocytes and resulting in formation of macules, papules, urticarial lesions, or vesicular bullous lesions.
	Cutaneous adverse drug reactions	• Immune-mediated condition triggered by a drug (e.g., sulfonamides, penicillins, phenylbutazone, ivermectin, diuretics, phenothiazine, antipyrectics) can be of any of the four types of hypersensitivity reactions. Reaction is typically noted 1 to 3 weeks after beginning of therapy.
	Hypersensitivity to insect bite	• Salivary Ags are introduced by bites from *Culicoides* spp. (or possibly *Simulium* spp., *Stomoxys calcitrans*, and *Haematobia irritans*), triggering an immediate and delayed responses leading to pruritus. (1) IgE-mediated reaction (type I hypersensitivity). (2) Cell-mediated hypersensitivity reaction associated with Th2 lymphocyte response and nonspecific eosinophilic activation (type IV hypersensitivity).
	Feed-related allergies	• Mixed hypersensitivity reactions mediated by IgE, immune complexes, or cellular responses to foodstuffs (including malt, beet pulp, buckwheat, wheat, alfalfa, red or white clover, barley, bran, oats, etc.).
	Atopic dermatitis	• Genetically predisposed inflammatory and allergic skin reaction mediated by allergen-specific IgE, leading to degranulation of mast cells and release of inflammatory mediators that cause erythema, vascular leakage, and pruritus.

	Allergic urticaria	• Hypersensitivity reaction mediated by one or a combination of (1) IgE, (2) immune complexes, or (3) cytotoxins, leading to activation of tissue mast cells or blood basophils and resulting in release of mediators and formation of wheals.
	Allergic contact dermatitis	• Cutaneous delayed reaction to nonirritant agents (heavy metals and aniline dyes) that alter skin self-proteins, transforming them into antigenic targets. • Type IV hypersensitivity.
	Granulomatous dermatoses	• Chronic inflammatory dermatoses characterized by the presence of macrophages, histiocytic giant cells, and occasionally eosinophils. • Examples of granulomatous dermatoses include noninfectious (equine nodular collangenolytic granuloma, amyloidosis, sterile granuloma) and parasitic/infectious (habronemiasis, bacterial granulomas, pseudomycetoma, fungal granulomas, pythiosis, sporotrichosis).
	Neonatal ulcerative dermatitis, thrombocytopenia, and neutropenia	• Multifocal ulcerative skin disease of neonatal foals associated with profound thrombocytopenia and mild neutropenia suspected to be caused by alloantibodies of maternal origin (absorbed from colostrum). Immunologically mediated damage and destruction ensue.
Muscle	Immune-mediated myositis (IMM)	• Rapid onset of muscle atrophy associated with mononuclear infiltrate of macrophages and lymphocytes (mostly CD4+ cells, lesser CD8+ cells, and clusters of B cells) and no evidence of IgG deposition.
	Infarctive purpura hemorrhagica (IPH)	• Severe infarctive vasculitis associated with deposition of Ag-Ab complexes (i.e., atreptococcal M protein bound to IgM or IgA) along the vessels and activation of complement leading to leukocytoclastic vasculitis and vascular necrosis in skeletal muscles as well as skin, GI tract, and pancreas vessels.
	Rhabdomyolysis associated with *Streptococcus equi*	• Severe, generalized rhabdomyolysis during *S. equi* infection. • Proposed mechanisms: (1) streptococcal superantigen causing nonspecific, polyclonal T-cell activation, massive cytokine release, uncontrolled inflammatory response, tissue necrosis, and multiorgan dysfunction; (2) bacteremia, multiplication of *S. equi* in skeletal muscles, release of bacteria proteases causing myodegeneration.
	Systemic calciniosis or calciphylaxis	• Severe muscle atrophy associated with elevated calcium and phosphorus, leading to fatal systemic dystrophic calcification. • Proposed mechanism: strong systemic inflammatory process and synergistic effect of inflammatory cytokines (TNF-α and IL-6).
Synovial	Immune-mediated polysinovitis/ polyarthritis	• Nonerosive polyarthritis and effusion of other synovial sheaths, such as tendons and bursae, with deposition of immune complexes and mild lymphocytic/plasmacytic infiltrate of synovial tissue: (1) associated with remote infectious processes (*Rhodococcus equi* pneumonia) or (2) without concurrent infectious process.

Ab, Antibody; *ADCC,* antibody-dependent cellular cytotoxicity; *Ag,* antigen; *GI,* gastrointestinal; *Ig,* immunoglobulin; *IL,* interleukin; *RBCs,* red blood cells; *Th,* T-helper cell; *TNF,* tumor necrosis factor; *UV,* ultraviolet.

Evaluation of Immunologic Response in Horses*

Lais R.R. Costa

Assessment of immune response encompasses in vivo, in vitro, and ex vivo measurements of immune function and can be divided into three categories: (1) assays for characterizing the adequacy of the immune response when an

immunodeficiency or immunosuppression is suspected (e.g., assays to assess humoral, cellular, and innate immune responses)[1-5]; (2) assays for identifying inappropriate or exaggerated immunologic responses when immune-mediated injury is suspected (e.g., antinuclear antibody titer, assay for platelet surface–associated IgG, isotype-specific antibodies coating erythrocytes)[6-9]; and (3) assays of immunologic recognition of pathogens (e.g., antibody titer to specific antigens or pathogens) and protection against infectious agents.[10] The aspects of immune response evaluation discussed in this section include only assays for characterizing the adequacy of the immune response when immunodeficiency or immunosuppression is suspected. Assays for identifying inappropriate immunologic responses when an immune-mediated condition is suspected and assays of immunologic recognition of pathogens and protection against infectious agents are discussed in this book under body systems or found elsewhere. Genetic tests are also available to diagnose inheritable conditions, and those are discussed under their respective diseases in this book.[11,12]

Characterizing the Adequacy of the Immune Response

Assessment of the adequacy of a patient's immune response is warranted when there is an increased recurrence, severity, or chronicity of infectious illness above and beyond what is considered normal, especially if the possibility of enhanced virulence of the pathogen involved has been ruled out. Because true immunodeficiency disorders are uncommon, they should be considered only after more common causes of recurrent infection have been excluded. It is important to remember that inadequate immune response may occur in association with malnutrition, neoplasia (especially leukoproliferative disorders), autoimmune diseases, immunosuppressive therapy, and the presence of underlying diseases such as PPID. In addition, immunosuppression and immune evasion mediated by the infectious agent itself should be considered. Therefore the diagnostic plan should include evaluating the patient's immune response as well as ruling out conditions that may account for the inadequate immune response of the patient.

In case of increased recurrence, severity, or chronicity of infectious illness above and beyond what is considered normal, the type of infectious agent involved may provide clues that will guide the choice of diagnostic plan. For instance, when the recurrent, severe, or chronic infection is caused by encapsulated bacteria such as *Staphylococcus aureus*, *Streptococcus*

zooepidemicus, Klebsiella spp., or *Actinobacillus equuli,* it raises the suspicion of compromised B-cell function, complement deficiency, or phagocytic dysfunction.[4,13-16] Assays for humoral immunity and phagocytic function should be investigated first. When the recurrent, severe, or chronic infection is caused by an intracellular organism such as *R. equi, P. jirovecii, Candida albicans,* or *Aspergillus* spp., compromised cellular immunity should be considered.[5]

Evaluation of humoral immunity is assessed readily by measurement of Igs. A comprehensive approach to the evaluation of humoral function in horses can be found elsewhere.[4] Tests to evaluate humoral immunity include (1) determination of total serum concentration of each Ig isotype, namely IgG, IgM, and IgA[17-20]; (2) humoral response to vaccination by measurement of antigen-specific antibody titers prior to and at 15 to 21 days post vaccination[4,10]; (3) evaluation of gamma globulins by serum electrophoresis to determine the nature of gammopathies (monoclonal or polyclonal); (4) characterization of peripheral blood B-cell distribution by immunophenotyping and flow cytometry (FCM)[4,21]; and (5) detection of deficiencies of the CD4+ Th cell function that co-stimulates and helps B-cell differentiation and survival, leading to secondary humoral disorders.

Assessment of cellular immunity is more challenging, and in vitro assays may fail to demonstrate dysfunction in cellular immune response. A comprehensive approach to the evaluation of cellular immune function in horses can be found elsewhere.[5] Tests available to evaluate cellular immunity include (1) immunophenotyping and FCM of circulating lymphocytes, including determination of CD4+ and CD8+ T lymphocytes,[22,23] (2) determination of cytokine profiles,[24,25] (3) mitogen-induced lymphocyte proliferation or blastogenesis,[21] and (4) mitogen-induced cytokines and expression of co-stimulatory markers.[5]

Table 53.5 lists assays used to assess and characterize the adequacy of adaptive (humoral and cell-mediated) and innate immune responses.

TABLE 53.5

Assays to Assess and Characterize the Adequacy of Immune Response in Horses

Assay	Sample	Description	Purpose	Comments

Complete blood cell count (CBC)	Whole blood preserved in EDTA	Standard hemogram, focusing on leukogram and evaluation of cell morphology.	Identification of abnormalities in number and morphologic changes of lymphocytes, monocytes, neutrophils, and eosinophils.	Part of the initial assessment patients. Equine CBC can l laboratories. Absolute, persistent lymphop immune mechanisms.
Serum protein electrophoresis	Serum	Separation of serum proteins by gel electrophoresis.	Evaluation of gamma globulins, which are primarily Igs, and determination if they are monoclonal or polyclonal.	In horses with repeated infec and polyclonal in nature. Mo evidence of lymphocyte mali are supportive of Ig deficien pathology laboratories.
Semiquantitation of Igs	Serum	Precipitation of Igs using serial concentrations of specific salts (e.g., zinc sulfate, sodium sulfite precipitation, glutaraldehyde coagulation).	Semiquantitative tests measure IgG to predict failure of transfer of passive immunity after colostrum ingestion.	Tests based on these principl (1) Zinc sulfate precipitati (2) Glutaraldehyde coagul Precipitation of Igs can be us easy to perform.
	Serum or whole blood preserved in EDTA or heparin	Species-specific tests based on antigen-antibody (Ag-Ab) reactions, either enzyme-linked-immunosorbent assay (ELISA) or latex bead agglutination.		Examples of commercially a (1) Species-specific equin Idexx) (2) Latex bead agglutinati Centaur)
Radial immunodiffusion (RID) for quantitation of Igs	Serum	RID quantitates Igs of specific isotypes using a precipitation reaction where the diameter of the reaction corresponds to a certain concentration of Ig.	Quantitation of specific classes of equine Igs (e.g., IgG, IgM). RID requires incubation for 24 hours. RID can be used to evaluate foals for failure of transfer of passive immunity after colostrum	RID is a species-specific qua standard for Ig quantitation. commercially available. RID veterinary clinical immunolo is not currently available.

			ingestion or testing humoral competence at any age.	
IgG turbidimetric immunoassay (TIA) for quantitation of Igs	Serum or plasma (blood collected in EDTA or heparin) harvested after centrifugation	TIA is based on the principles of immunologic agglutination and light scattering of the agglutination products. The automated TIA is performed on chemistry analyzer, and results are available within hours.	Quantitation of equine IgG results are available within less than 15 minutes. TIA can be used to evaluate foals for failure of transfer of passive immunity after colostrum ingestion or to test humoral competence at any age.	TIA is a species-specific qua specificity and very good co TIA are commercially availa equipment.
Equine Ig ELISA kits for quantitation of various Ig isotypes	Serum or plasma (blood collected in EDTA or heparin) harvested after centrifugation	Various platforms of ELISA: sandwich ELISA, competitive ELISA.	Quantitation of specific classes of Igs (e.g., IgG, IgM, IgA, IgE) is considered of reasonable accuracy.	ELISA is a species-specific c commercially available ELIS IgA, IgM, and IgE manufact spectrophotometric equipme
Measurement of specific Ab responses pre and post vaccination	Serum	Paired serum samples, pre and 15-20 days post vaccination are tested to measure Ag-specific Abs. Samples can be stored in the refrigerator or frozen.	Determination of B-cell function by evoking an anamnestic response to a protein Ag.	Choice of Ab titers dependin Several laboratories provide which vaccines are used. Re and postvaccination titers us
Equine cytokine multiplex assay	Serum or body fluid	Detects soluble equine IL-4, IL-10, IL-17, IFN-γ, and IFN-α in biological samples using monoclonal Abs specific for each cytokine and fluorescent bead/microspheres that are color coded.	Quantitation of cytokines as pg/mL of biological sample.	Offered at the Animal He University, http://ahdc.vet.cornell.ed Results may be difficult t
Equine cytokine ELISA	Serum	Detects soluble cytokines and chemokines in biological samples using various platforms of ELISA.	Quantitation of specific equine cytokines and chemokines.	ELISA is a species-specific c commercially available ELIS cytokines and chemokines m requires spectrophotometric Results may be difficult to in
Immunophenotyping of peripheral blood	Whole blood preserved in	Enumeration of specific subsets of	Determination of circulating	Flow cytometry is a qualitati horses, about 10% ± 4% of c

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lymphocytes	EDTA or heparin	lymphocytes using fluorescent antibodies to cell surface markers and flow cytometry.	lymphocyte types—B cells (CD19+-like, CD20+, CD21+, sIgM+), total TCD3+ cells, CD4+ T cells and CD8+ T cells—and determination of CD4/CD8 ratio.	64% ± 6% are CD4+ T cells CD4/CD8 ratio is 3.5 ± 1.0.
Immunophenotyping of leukocyte populations in body fluids	Body fluid (e.g., CSF, pleural fluid peritoneal fluid) and apirates (e.g., bone marrow, lymph node) preserved in EDTA or heparin	Evaluation of leukocyte types and subsets using fluorescent Abs to cell surface markers and immunocytochemistry.	Determination of B cells (sIgM+), total CD3+ T cells, CD4+ T cells, CD8+ T cells, and myeloid cells (CD172a).	Immunocytochemistry is a q for cell distributions or coun
Immunophenotyping of leukocyte populations in tissues (e.g., lymph node, spleen, bone marrow)	Biopsy specimen preserved in formalin or fresh frozen	Evaluation of leukocyte types and subsets using Abs to cell surface markers and immunohistochemistry.	Determination of B cells (sIgM+), total CD3+ T cells, CD4+ T cells, CD8+ T cells, and myeloid cells (CD172a).	Immunohistochemistry is a q availability of Ab reagents w
Histologic evaluation of lymph node	Biopsy specimen preserved in formalin	Evaluation of lymphoid tissue morphology using histology, histochemistry, and immunohistochemistry with specific antibodies to cell markers.	Determination of the presence or absence of B cells (sIgM+) and germinal centers.	Useful to evaluate humoral d diagnosis. Offered at most di Health Diagnostic Center, Co
Peripheral blood phagocytic functions of opsonization capacity, phagocytosis, and oxidative burst	Whole blood preserved in heparin	Peripheral blood leukocytes are incubated with oxidative-sensitive dye dihydrorhodamine (DHR), and/or fluorescent-labeled inactivated bacteria (e.g., *Staphylococcus aureus*, *Escherichia coli*). Bacterial opsonization can be performed with pooled or autologous serum; heat-inactivated serum or no serum can be used as controls.	Evaluation of functions of the innate immune response: (1) opsonization capacity by serum complement components and Igs; (2) phagocytosis by neutrophils and monocytes; and (3) oxidative burst by neutrophils and monocytes. Oxidation of DHR generates	Currently performed for rese immunology laboratories to immunodeficiencies.

			green-fluorescent rhodamine 123 (rho). Two-color flow cytometric analysis can be performed for oxidative burst and phagocytosis.	
Intradermal skin testing with the plant lectin phytohemagglutinin (PHA)	Direct patient skin testing	Measure the thickness of a skin fold before injection, then intradermal injection of 50 µg of PHA dissolved in 0.5 mL saline. At a different site 10 cm (4 inches) away, 0.5 mL of saline is injected as control. After 24-48 hours, the skin thickness of both injection sites is measured.	Evaluation of lymphocyte response to stimulus in vivo. PHA elicits an immune response without requirement of prior sensitization. Increase in skin thickness should be greater than 0.6 mm, otherwise there is a defect in cell-mediated immunity.	The intradermal testing with confirmation with in vitro as
Mitogen-induced lymphocyte proliferation (blastogenesis) assay	Whole blood preserved in EDTA or heparin	Lymphocytes are isolated, labeled with CFSE, and incubated in vitro with mitogens, including pokeweed mitogen (PWM), phorbol mistrate acetate (PMA), PHA, and concavalin A (ConA).	Measurement of proliferating cells by reduction (division) of fluorescent-labeled cellular proteins using flow cytometry. PWM and PMA stimulate blastogenesis of B and T cells; PHA and ConA stimulate T cells.	Currently performed for rese immunology laboratories to immunodeficiencies.
Mitogen-induced cytokine and co-stimulatory cell marker expression	Whole blood preserved in EDTA or heparin	Lymphocytes are isolated and incubated in vitro with mitogens, including PWM, ConA, PHA, and PMA. Measurement of cytokines and cell markers via flow cytometry, multiplex assay, or molecular assay.	Measurement of cell function and response based on cytokine production (e.g., IFN-γ) and expression of co-stimulatory molecules (e.g., CD40 ligand, CD28, MHC class II)	Currently performed for rese immunology laboratories to immunodeficiencies.

Severe combined immunodeficiency (SCID) genetic testing	Collect sample from a convenient source of DNA: (1) swab the inside of the mouth with a mucosal brush and submit the brush containing mucosal cells (2) blood sample in EDTA or ACD anticoagulant (3) Pulled mane or tail hair placed in a clean bag	A DNA-based carrier test for the genetic mutation affecting the DNA-dependent protein kinase (DNA-PK) located in chromosome 9.	Genetic tests that detect carriers of the recessive genetic trait; information can be used to select mating pairs and avoid producing affected foals. Recessive genetic traits, requiring two copies of the mutated gene to produce an affected foal. These conditions are fatal, and animals homozygous for the mutation do not survive to reproductive age. Horses that have one copy of the mutated gene are normal.	Laboratories offering SCID t (1) VetGen, Ann Arbor, M (2) Veterinary Genetics La https://www.vgl.ucdavis (3) Animal Genetics, http://www.animalgenet
Foal immunodeficiency syndrome (FIS) genetic testing		A DNA-based carrier test for genetic defect affecting the sodium/myo-inositol cotransporter gene *(SLC5A3)* located in chromosome 26.		Laboratories offering FIS tes (1) Animal Health Trust, N http://www.aht.org.uk/c (2) Animal Genetics, http://www.animalgenet (3) LABOKLIN Laborato UK, http://www.labokli testID=8454

ACD, Acid citrate dextrose as anticoagulant; *CFSE,* carboxyfluorescein succinimidyl ester; *CSF,* cerebrospinal fluid; *EDTA,* ethylenediaminetetraacetic acid; *IFN,* interferon; *Ig,* immunoglobulin; *IL,* interleukin; *MHC,* major histocompatibility complex.

Immunity at Birth and the Immune Development of the Foal

Angela I. Bordin

Despite a lengthy development of the innate and adaptive immune systems in the equine fetus, the foal is born with a relatively immature and naive adaptive immune system. In addition, the epitheliochorial placentation in the mare precludes transfer of immunoglobulins in utero, and foals are born hypogammaglobulinemic.[1] At birth they rely heavily on colostral IgG for protection against infection but also on colostral soluble molecules and cells for stimulation of the immune system. In horses, colostrum absorption occurs within the first 24 to 36 hours after birth (with a peak around 8 hours) through specialized enterocytes that allow absorption of macromolecules. After this period, these specialized cells mature, and absorption of immunoglobulins

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ceases. Consumption of antibody-rich colostrum therefore is essential for protection against pathogens not only immediately after birth but also during the period until foals can produce their own antibodies at protective levels, which may require 2 to 3 months. Therefore in foals with low or inadequate transfer of colostral IgG, hypogammaglobulinemia increases the susceptibility to infections during the first few months of life. The knowledge of the actual (rather than an estimated) IgG concentration in the foal's blood after ingestion of colostrum could be used for clinical planning and monitoring of risk of infection in the initial months of life, and tests are repeated as needed during this phase. Besides antibodies, other factors are possibly transferred to the foal via colostrum, including the cytokines IFN-γ, IL-4, IL-6, and TNF-α.[2-4] Maternal lymphocytes in colostrum can also be absorbed through the GI tract and participate in adaptive immune responses of the equine neonate. Equine colostrum contains primarily CD4+ and CD8+ T cells and few B cells. These cells can express inflammatory cytokines (IFN-γ and IL-17) upon stimulation.[5]

There is evidence that the immune system of foals actively develops during the fetal period. For instance, the detection of Igs in the fetus and presuckle foal, despite their low levels, suggests antibody production in utero.[6] Indeed, antigen-specific antibody production and antigen-specific IgG isotype switching have been measured in the equine vaccinated fetus or potentially in the foal born to naturally infected dams.[7-9] In addition, functional lymphocytes and lymphoid tissue organization have been detected in the fetus by 100 (T cells) and 200 days (B cells), and presence of IL-8 in presuckle foals suggests endogenous production.[2,10] Despite maternal antibodies, foals have been shown to produce endogenous serum IgM and IgG at protective values by 2 ± 3 months of age, regardless of colostrum ingestion.[11-15] Although foals can make their own antibodies despite colostrum consumption, prepartum vaccination of mares is important because Ig levels in mares' serum correlate with levels in mammary secretions, and foals with inadequate transfer of passive immunity through colostrum are more susceptible to infections, particularly to those pathogens that cause septicemia and are challenging in the first few months after birth.[16]

The development of the immune system continues intensively after birth with the exposure to both pathogenic and nonpathogenic microorganisms in the environment. In individuals not exposed to microbes, such as germ-free mice and rabbits, both innate and adaptive immunity are not as well developed as those exposed to environmental microbes and present many immunologic

defects.[17] Although research of the microbiome of horses and foals is still a developing area, it has been demonstrated that it changes significantly with age.[18-21] By 1 month of age, the microbiome of foals is significantly more diverse than at birth, and both changes and increases in bacterial communities in the gut likely reflect the replacement of milk diet by available forage and concentrate fed to the mare.[18-21] It has been shown that diversification of the microbiome in neonates of all species influences various developmental processes such as immunity to infection.[22,23]

Absolute peripheral blood lymphocyte counts in healthy equine neonates are somewhat comparable to adult horses, but prematurity or immaturity is often characterized by lymphopenia.[15,24] Therefore a rapid increase in the blood lymphocyte count (at least two times) is expected in the initial few months of life in a normally developing immune system responding to microorganisms.[15] Hence both B and T lymphocyte subpopulations increase with age.[12,15,25] In addition, B-cell markers such as B29A+ and CD21+, as well as MHC class II, also increase with age, whereas the proportion of CD8+ lymphocytes decrease with age.[25]

Innate immune cells are fundamental for protection against infections soon after birth and a crucial link between innate and adaptive immune systems. In foals, phagocytic function by innate immune cells is particularly important for protection against disease because of the lack of developed adaptive immunity.[26] Neutrophils are the most abundant effector cells of innate immunity in blood and the first line of defense by containing the infection via phagocytosis and subsequent killing of invading pathogens, as well as producing both cytokines and chemokines that recruit and activate other effector cells.[27,28] In general, studies report comparable neutrophil function in foals and adult horses; however, some studies showed decreased bactericidal activity in individual foals relative to adults, including during sepsis.[15,29-31] Phagocytosis and killing of yeasts by neutrophils increase with age, being lower in newborns before colostrum ingestion and reaching adult levels by 1 month of age.[32-34] Neutrophil chemotaxis also increases with age.[35] Macrophages are another important type of phagocytic cells: they ingest and kill intracellular pathogens and recruit other phagocytes to the site of infections; in addition, they function as APCs. In a study comparing newborn, 3-month-old foal, and adult alveolar macrophages and monocyte-derived macrophages, the authors observed a similar capacity of

R. equi intracellular killing in newborn and adult horses.[36]

Opsonization of pathogens with antibodies plays an essential role in their uptake by phagocytes through antibody Fc receptors and subsequent bactericidal capacity; therefore hypogammaglobulinemia markedly limits phagocytic activity and protection.[29,30,32,37,38] The complement system is also important for the defense against pathogens, but colostrum is not a reliable source of this protein, and foals depend on their own production for protection.[39] Complement activity in foals increases with age, being 13%, 64%, and 85% of that in adult horses in the first week after birth, at 1 month, and at 5.5 months of age, respectively.[34]

DCs are APCs to T lymphocytes for the generation of cell-mediated responses. There are functional differences between DCs of adult horses and foals, in which cells from young foals are less able to produce cytokines in response to stimulation (e.g., lipopolysaccharide [LPS], cytosine-phosphate-guanosine oligodeoxynucleotide [CpG-ODN]) and are considered less mature than cells in adult horses.[40] DCs from foals have reduced expression of MHC class II and co-stimulatory molecules, meaning that their potential for interaction and ability to stimulate naive T cells is limited.[15,41] In addition, foals' APCs also express less CD1, which is a surface cell molecule involved in the presentation of lipid antigens to subsets of T cells, in comparison to adult horses' cells.[42]

Under physiologic conditions, serum IgM concentration of 25 mg/dL but less than 20 mg/dL for IgG may be measured in presuckle foals.[10,13] Nevertheless, endogenous synthesis of IgG_b ($IgG_{4/7}$) cannot be detected until 63 days old.[43] IgG_b ($IgG_{4/7}$) is the most common isotype in serum of both adult horses and foals, as well as in colostrum, and IgA is the major isotype found in nasal secretions of adult horses and milk. In nasal secretions of foals, however, IgG_a and IgG_b are the major isotypes.[43] Maternal antibodies decline within the first 3 months of age, with an IgM half-life of 6 ± 16 days and an IgG half-life of 28 ± 32 days.[11,43] Serum half-lives of Ig isotypes in foals are 17.6, 32, 21, and 3.4 days for IgG_a (IgG_1), IgG_b ($IgG_{4/7}$), IgGT ($IgG_{3/5}$), and IgA, respectively.[43] Yet the equine fetus and newborn can respond to vaccination with antibody production, indicating that the humoral response is in place at early life. Two important studies demonstrate that early intramuscular vaccination of newborns can elicit specific yet modest antibody responses to antigens.[44,45] However, the development of a long-lasting immune response with memory cells is limited at this age. The current recommended age for vaccination of foals born from mares

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vaccinated in the prepartum period is 4 to 6 months for most vaccines with the exception of botulism, for which the first dose can be administered at 2 to 3 months of age (according to American Association of Equine Practitioners [AAEP] guidelines). This recommendation aims to especially avoid maternal antibody interference, assuming adequate transfer of passive immunity.

CD4+ Th1 responses (or Th1-associated cytokine response) are thought to be essential for protection against intracellular pathogens, whereas Th2 responses with a shift to antibody production are thought to be important for extracellular pathogens and parasites. Foals are known to have reduced IFN-γ responses at birth.[46,47] Although foal peripheral blood lymphocytes respond to nonspecific stimulation with a mitogen, foals produce less cytokine compared to adult horses, and this response increases with age in vivo and in vitro.[48] Bronchial lymph node lymphocytes of foals produce lower levels of IL-4 (a hallmark for Th2 response) than those of adult horses.[49]

Despite being considered partially immature and naive, both innate and adaptive immune systems of foals can be stimulated to generate an immune response. Parapoxvirus ovis (PPVO) and inactivated *Propionibacterium acnes* (PA) were used as immunostimulants in foals: PPVO increased phagocytosis in neutrophils, and PA reduced intracellular replication of *R. equi*.[50] In addition, due to the expression of TLR9 by foal neutrophils, CpG-ODNs have shown to stimulate cytokine as well as reactive oxygen species (ROS) production both in vitro and in vivo.[27,51-53]

Failure of Passive Transfer of Maternal Immunity*

M. Julia B. Felippe • Debra C. Sellon

■ Definition and Etiology

Normal foals are immunocompetent at birth and capable of mounting an immune response. However, they are immunologically naive: they have had no exposure to foreign antigens and have not yet mounted any type of protective immune response or accumulated significant levels of immunoglobulins. Although the equine fetus is capable of producing antibodies, newborn foals are essentially devoid of Ig at birth, with the exception of small amounts of IgM normally produced in utero. Without being able to rely on their acquired immunity in the

first encounter with pathogens, foals are indeed more susceptible to infectious diseases during the neonatal period. Foals begin mounting immune responses and producing their own Igs immediately on exposure to antigens after birth, and Igs produced by the foal are detectable within 1 to 2 weeks of life and reach significant levels by 2 to 3 months of age.

Immunologic protection of the newborn foal therefore relies on the transfer of maternal immunity through the colostrum. Under normal circumstances, temporary protection against infection in the first 1 to 2 months of life is provided to the foal in the form of passively transferred antibodies, cytokines, immune mediators, and a small number of mononuclear cells from the dam (Fig. 53.3; Table 53.6). Because of the diffuse epitheliochorial nature of the equine placenta, no transplacental transfer of Igs occurs in horses. Instead, ingestion and absorption of Ig-rich colostrum within the first day after birth are the sole means of passive transfer of immunity in foals. Serum IgG concentration in healthy foals after ingestion of colostrum under natural conditions varies between 500 and 6000 mg/dL.[1-3] In a properly functioning system, maternal antibodies wane as levels of endogenous antibodies increase, and thus the foal should be protected during this transition period (Fig. 53.4; Table 53.7).

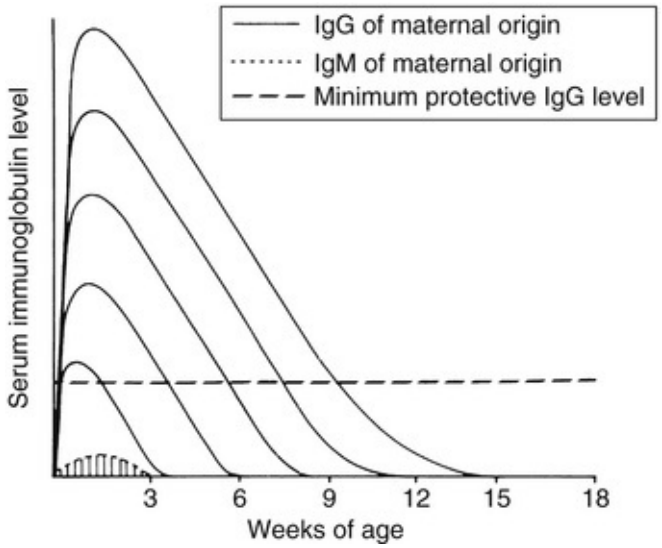


FIG. 53.3 The duration of protection provided by colostral immunoglobulins (Igs) in the foal varies with the isotype of immunoglobulin (e.g., IgG, IgM) and the quantity absorbed during the first 24 hours of age.

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TABLE 53.6

Immunoglobulin Concentration (mg/dL) in Equine Colostrum, Milk, and Normal Serum[a]

Sample	Breed	Total IgG	IgM	IgA
Colostrum	STB	2700-15,000	50-200	10-2050
	QH	21,000-32,000	ND	600-1200
Milk	QH	30-75	ND	50-90
Newborn presuckle	Arabian	1-10	5-15	ND
	QH	0-30	ND	ND
1 day of age	STB	300-3500	5-65	16-100
	QH	3300-4500	ND	26-64
	Mixed	1300-1900	ND	45-65
1 week of age	QH	2500-4000	ND	6-36
1 month of age	QH	1250-2300	ND	2-10
	Mixed	900-1450	ND	30-50
2 months of age	QH	1450-3100	ND	0-28
3-5 months of age	Mixed	1000-1700	ND	30-50
4 months of age	Mixed	250-950	40-90	ND
10-15 months of age	Arabian/THB	1500	50	ND
Adult horses	THB, QH	1500-2400	70-150	ND
	Mixed	1400-3200	ND	10-70
Adult ponies	Shetland	1000-1700	110-140	ND
	Welsh	1600-2750	ND	ND

[a]Low and high values were calculated from mean and standard deviation reported (see references in text).

Ig, Immunoglobulin; *ND,* not determined; *QH,* Quarter Horse; *STB,* Standardbred; *THB,* Thoroughbred.

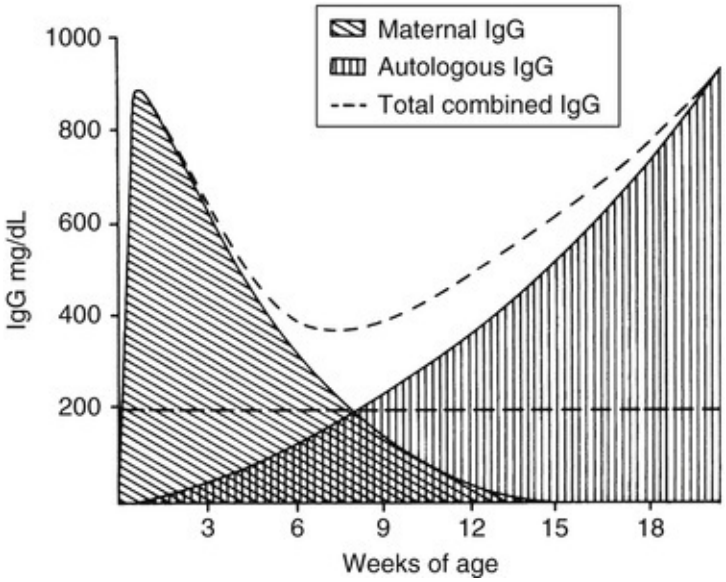


FIG. 53.4 Maternal immunoglobulin *(Ig)* wanes, whereas the production of autologous immunoglobulin increases during the first several months of life. The combined total amount of immunoglobulin ideally remains above the level considered the minimum for maintenance of good health.

TABLE 53.7

Approximate Half-Life (in Days) of Immunoglobulin Classes in Large Animals

Species	IgG	IgM	IgA	$IgG_{(T)}$ ($IgG_{3/5}$)
Equine	11.5-23	4-5	NA	20
Bovine	G1: 17	2.8	4.8	—
	G2: 22			
Sheep	G1: 14.5	1.8	4.1	—
	G2: 10.6			
Goat	G1: 13.2-17.2	NA	NA	—

Ig, Immunoglobulin; *NA,* not available.

From Perryman L: Personal communication, Department of Veterinary Microbiology and Pathology, Washington State University, Pullman, Wash., 1988.

Failure of the foal to ingest or absorb sufficient quantities of colostrum to provide adequate absorption of IgG is called *failure of passive transfer* (FPT). *Complete* FPT is defined as a foal with a serum IgG concentration of less than 400 mg/dL at 24 hours of age. *Partial* FPT is defined as a foal with a serum IgG concentration of 400 to 800 mg/dL at 24 hours of age. The reported incidence of complete or partial FPT in foals varies from 3% to 37.8%.[4-11] Risk factors for

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FPT include month of foaling, adverse health events for mare or foal in the periparturient period, age of the dam, and colostral immunoglobulin content. Low total Ig content in colostrum is associated with breed (e.g., Standardbred), age of dam (e.g., older mares), and low total solar radiation (i.e., shorter days).[5,10,12]

Immunoglobulins are selectively concentrated from the mare's sera into colostrum in response to hormonal changes that occur in the last 2 weeks of pregnancy; local production in the mammary gland is also possible. The predominant Ig isotype in equine colostrum is IgG, followed by IgA and smaller quantities of IgM.[13] The reported amount of total IgG in equine colostrum is variable among different studies (see Table 53.6), but overall a good-quality colostrum should contain 2500 to 5000 mg/dL. The reported amounts of IgA often range between 500 and 1500 mg/dL, whereas IgM generally ranges between 100 and 350 mg/dL. At birth the neonate has specialized enterocytes in the GI tract that can absorb large molecules such as immunoglobulins intact by pinocytosis.[14] Absorbed proteins pass through the intercellular spaces and lacteals into the systemic circulation via the lymph. The window of gut absorptive capacity for Igs is narrow, lasting from birth until about 18 to 24 hours of age. Maximal absorptive efficiency occurs immediately after birth, declining to only 22% efficiency at 3 hours after birth and then to less than 1% by 20 hours.[15,16] The decline in Ig absorption is accompanied by transient proteinuria that peaks at 6 to 12 hours of age and declines by 24 to 36 hours of age. This proteinuria most likely reflects absorption and excretion of low-molecular-weight milk proteins.[16]

Diminished Ig absorption over the first 12 to 24 hours of life is the result of shedding of specialized enterocytes capable of pinocytosis and replacement by more mature cells that are incapable of absorbing immunoglobulins.[15,17] It has been hypothesized that delayed ingestion of macromolecules may prolong the duration of intestinal permeability to Igs. In one study, however, the type of fluid administered to foals before the ingestion of colostrum did not influence subsequent IgG absorption, suggesting that the process of gut closure is not mediated by a finite capacity for the uptake of macromolecules.[18]

The half-life for maternal IgG in the foal's circulation varies between 20 and 30 days.[19-21] Concentrations decline as a result of normal protein catabolism, gradual dilution associated with an increasing plasma volume as the foal grows, and transfer of functional antibody into the mucosa. Most maternal antibodies

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are present in only negligible concentrations by 6 months of age, although antibodies to some infectious agents have been detected for up to 12 months after birth. As passive antibody concentrations decline, endogenous antibody production increases. There is a nadir in serum Ig concentrations in colostrum-fed foals at approximately 1 to 2 months of age, followed by gradually increasing concentrations until adult levels are reached at 5 to 10 months.[22,23] Serum Ig concentrations are similar in colostrum-fed and colostrum-deprived foals by 3 to 4 months of age.

In addition to antibody, other colostral factors may be important for optimal immune protection of foals. For example, colostrum influences cell-mediated immunity and activates granulocytes. Colostrum contains many constituents of innate immunity and immunomodulating agents, such as cytokines, growth factors, hormones, enzymes, CD4 and CD8 T lymphocytes, macrophages, neutrophils, and epithelial cells.[24-26] The cellular components of colostrum are likely to play an especially important role in local GI immunity in the neonatal foal. Maternal cells are found in a variety of blood and tissues in the neonate after absorption of colostrum, suggesting that these cells may also play a role in systemic immunity.[24]

In foals, FPT may occur because of ingestion of poor-quality colostrum with a low Ig content, failure to ingest a sufficient quantity of colostrum, or failure to absorb colostral Igs from the GI tract.[27] Colostrum may have an insufficient quantity of Ig because of prelactation (lactation before parturition), premature foaling, a defect in the mare's ability to concentrate Ig in the colostrum, ingestion of endophyte-contaminated fescue grass or hay, or other factors. Premature lactation is most commonly associated with twin pregnancies, placentitis, and premature placental separation but occasionally occurs without any concurrent uterine, placental, or fetal pathology. Mares most likely to produce colostrum with low Ig content are those older than 15 years of age, those that foal early in the year, and Standardbred mares.[5,10,11] Insufficient colostral Ig concentration has also been associated with ingestion of endophyte-contaminated fescue grass or hay.[28,29]

Foals that are orphaned or rejected at birth, too weak to stand, or unable or lack the desire to suckle are unlikely to ingest sufficient colostrum to prevent FPT. Malabsorption is occasionally incriminated as a cause of FPT in foals that are observed to suckle adequate quantities of good-quality colostrum. This most often happens in premature or dysmature foals, possibly as a result of immature

GI function but may also occur in otherwise healthy and vigorous full-term foals.[30] Glucocorticoids enhance the maturation of small-intestinal epithelial cells and thus their loss of absorptive capacity, leading to speculation that endogenous corticosteroids released secondary to stress at parturition may impair Ig absorption in foals.[31,32] However, administration of adrenocorticotropic hormone (ACTH) failed to affect absorption in experimental foals, and stress has not been a consistent historical finding in foals with FPT caused by presumptive impaired Ig absorption.[8,33]

■ Clinical Signs and Differential Diagnoses

The association between FPT and infection has been investigated in numerous studies.[4,5,7,10,11] Although the results have varied somewhat, FPT is generally considered a risk factor for infectious disease. By itself, FPT produces no clinical signs of disease and cannot be detected by physical examination. Clinical presentations that strongly suggest an underlying problem with FPT include onset of bacterial infections within the first 2 weeks of life, particularly septicemia, septic arthritis, pneumonia, and enteritis. Other immunodeficiencies or simply exposure to potent pathogens cannot be ruled out solely based on the time of onset; however, even with other forms of immunodeficiency, clinical signs of infection usually do not show up for several weeks if passive transfer is adequate.

■ Clinical Pathology

FPT is diagnosed by the demonstration of low serum concentrations of IgG in the foal as early as 6 to 12 hours after birth, typically between 12 and 24 hours after birth, and probably for as long as several weeks after birth (see Table 53.6). The level of IgG considered adequate for protection against infectious disease is poorly defined and probably varies considerably with the environment. A serum IgG concentration greater than 800 mg/dL is considered to provide adequate protection for most foals in their first few weeks of life. In contrast, an IgG concentration of 400 to 800 mg/dL in a foal at high risk for sepsis because of its environment or other factors indicates the need for Ig replacement. Importantly, these figures only address *total* Ig content and not pathogen-specific antibody titers, which also play a critical role in determining risk for certain infectious diseases.

In healthy foals that nurse within 2 hours of birth, serum IgG concentrations

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become detectable at approximately 6 hours of age and peak at approximately 18 hours. Routine determination of serum IgG concentrations in apparently healthy foals is usually recommended between 12 to 24 hours of age. Foals considered to be at high risk for FPT and sepsis may be assessed as early as 6 to 12 hours of age.[34,35]

Importantly, since endogenous production of Igs in the foal takes an average of 2 to 4 months to reach protective levels, and colostrum-derived IgG concentrations decrease at a half-life of about 20 to 30 days, it is critical to ensure that minimum levels of transfer (>800 mg/dL or perhaps 1000 mg/dL serum IgG concentration) are measured after ingestion of colostrum in the foal's blood; this minimum amount of colostrum-derived IgG is expected to protect the foal beyond the first week of life, bridging this transition period in the first few months of life (see Fig. 53.3).

Described methods for IgG quantitation include turbidimetric immunoassay, radial immunodiffusion (RID), enzyme-linked immunosorbent assay, zinc sulfate turbidity, latex agglutination, and glutaraldehyde coagulation.[34,36-41] Selection of an appropriate screening test for a specific farm or foaling environment should be made after considering overall accuracy based on sensitivity and specificity, time necessary to perform the test, simplicity of the testing procedure, technical skills and knowledge of the attending personnel, and cost. Turbidimetric immunoassay and RID are the most accurate quantitative (actual value) diagnostic tests; turbidimetric tests provide immediate results, whereas RID turnaround is 24 hours, which may be impractical when an at-risk foal needs rapid diagnosis and treatment. Total serum protein is not a reliable indicator of FPT in foals (unlike calves) because of the wide variation in total serum protein in cases of adequate transfer; serum globulin values correlate better with IgG values when using appropriate cutoff points.[41-45] Many veterinarians prefer to use semiquantitative commercial kits based on enzyme-linked immunosorbent assay or glutaraldehyde coagulation technology for stall-side screening of foals.[40-43] Both types of tests have high sensitivity and negative predictive value. False-negative and false-positive results tend to be more common when attempting to accurately identify foals with partial FPT of IgG concentrations between 400 and 800 mg/dL. These tests do not provide actual values above 800 mg/dL, which prevents predicting humoral protection throughout the first few months of life, given the half-life of colostrum-derived IgG (see Fig. 53.3).

No consistent changes in the blood work are seen in foals with FPT; however, a range of abnormalities related to secondary infection (e.g., neutrophilia,

neutropenia), hyperfibrinogenemia, and hypoglycemia may be present. The presence and severity of these changes depend on the organisms and systems involved.

■ Necropsy Findings

No specific necropsy findings are indicative of FPT. Necropsy findings reflect the site and severity of secondary infectious problems that have developed. Lymphoid tissue is normally developed, unless secondary infections have caused lymphoid necrosis or atrophy.

■ Treatment and Prognosis

Treatment of FPT depends on the degree of FPT, the environment in which the foal is exposed, the foal's age at diagnosis, and the presence of secondary infectious problems. Treatment is aimed at minimizing exposure to pathogens, supplying immunoglobulins, and managing secondary infections, if present.

If FPT can be anticipated within hours of birth because of premature lactation, low-specific-gravity colostrum, or a weak or orphaned foal, treatment can include the provision of an alternative source of colostrum or antibody orally. Foals with complete colostrum deprivation require approximately 1.5 g IgG/kg body weight to achieve a peak serum IgG concentration of more than 800 mg/dL. In a 45-kg foal, administration of 1 to 3 L of colostrum with a specific gravity greater than 1.060, divided into multiple hourly feedings over the first 6 to 8 hours of life, is desirable. Mares that donate colostrum for feeding should be healthy, checked for blood type, negative for anti-RBC alloantibodies (especially anti-A and anti-Q), and appropriately vaccinated during the last 4 to 6 weeks of gestation.

If equine donor colostrum is not available, bovine colostrum, a commercial colostrum substitute, or equine plasma may be administered orally to the foal.[46-53] Because bovine colostrum is often more readily available than equine colostrum, it may be substituted in emergency situations when equine colostrum is not available. Bovine colostrum is relatively well absorbed in the foal, but bovine immunoglobulins have a much shorter half-life in foals and do not contain antibodies specifically directed against equine pathogens. It is certainly better than no colostrum and, on the basis of a small experimental study, may be used without creating adverse reactions.[4,11,48,49] Approximately 2 to 4 L should be administered orally, and many foals develop transient mild diarrhea; increased

colostrum-derived gamma-glutamyl transferase (GGT) values will be measured in the foal's blood for a few weeks.

Concentrated equine serum products such as Seramune Oral (Sera, Inc., Shawnee Mission, Kan.) are available for use in foals with FPT.[54] In one study, however, it failed to increase serum IgG concentrations in colostrum-deprived foals to adequate levels, probably because of the relatively low total IgG dose administered.[53] If the product contains 25 to 30 g of IgG/300-mL bottle, approximately three bottles may be required to increase the serum IgG concentration of a 45-kg colostrum-deprived foal to greater than 400 mg/dL.[53]

If no other sources of immunoglobulin are available for a foal, oral administration of equine plasma or serum may be considered. This is an expensive source of oral Ig, however, and approximately 2 to 4 L are required to treat a colostrum-deprived 45-kg foal.

If the foal is older than 6 hours of age, the absorption of colostral antibody is significantly decreased, although a locally protective effect of the colostrum may still be present in the intestinal tract. If the foal is older than 12 hours of age, it is unlikely that sufficient colostrum will be absorbed; therefore Ig levels should be rechecked at 24 hours and intravenous (IV) plasma transfusion given, if indicated by persistently low serum Ig levels.

Some animals with FPT, particularly partial FPT, do well without treatment if they are systemically healthy, are not heavily exposed to pathogens, and have no preexisting infections. FPT itself is not necessarily fatal. If plasma transfusions are not administered, owners should be made aware of the risks, and these foals should be maintained in an environment with minimal exposure to potential pathogens. Foals with other risk factors for septicemia (e.g., prematurity, dysmaturity, placentitis) should receive IV plasma transfusions if they have blood IgG concentrations of less than 800 mg/dL at 12 to 24 hours of age. Importantly, foals with FPT may develop recurrent infections around 1 to 2 months of age when blood IgG concentrations are below protective levels or until endogenous IgG production reaches protective values. Therefore checking serum IgG concentrations should also be a practice in foals with recurrent infections during this transition time.

If the decision is made to supplement plasma parenterally, equine plasma for transfusions can be collected and processed locally or obtained commercially. Available sources of commercial equine plasma include Plasmune (formerly Foalimmune) and HiGamm-Equi (Lake Immunogenics, Inc., Ontario, N.Y.); Equi-Plas and Polymune (Plasvacc USA, Inc., Templeton, Calif.); and Immuno-

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Glo Normal Equine Plasma (Mg Biologics, Inc., Ames, Iowa).[55] Commercial sources are convenient, save time, have been screened for anti-RBC antibody, contain minimal amounts of RBCs, are free of diseases such as equine infectious anemia, and originate from animals with known Ig levels. The major disadvantage is that plasma may not contain antibodies specific for the pathogens from the particular environment to which the foal is exposed.

Use of a local donor has the potential benefit of providing antibodies specific to the environmental pathogens to which the foal has been exposed. If a local donor is to be selected, several criteria should be met. First, the horse should be healthy, and results of agar gel immunodiffusion for equine infectious anemia should be negative. Second, no anti-RBC antibody should be detectable in the horse's serum. The donor's plasma should be screened for lysins and agglutinins by a blood-typing laboratory against a panel of cells representing all known blood groups. If plasma evaluated in this way is not available, the presence of anti-RBC antibody in donor plasma can be crudely evaluated with a minor crossmatch for agglutination using donor plasma and recipient blood cells. Lytic antibodies require an external source of complement for activity in vitro and may not be detected using this test.

Ideally, a third criterion is selection of a horse that is negative for blood group factors Aa and Qa. Even though there are dozens of blood group factors, Aa and Qa have been associated with the great majority of cases of neonatal isoerythrolysis (NI).[56-58] If plasma is collected and separated by sedimentation, it is inevitable that some RBC contamination be present. If Aa-positive (Aa+) RBCs are given to an animal that is Aa negative (Aa−) or if Qa+ RBCs are given to an animal that is Qa−, the recipients could become sensitized to these antigens. This sensitization probably would not have any immediate consequences for the recipient foal because the foal's cells would not be affected by the antibodies, but it has potentially sensitized any Aa− and Qa− females for production of a foal with NI later (see the Diseases Caused by Allogeneic Incompatibilities [Horses and Ruminants] section later in this chapter). To avoid these potential complications, the ideal donor should be Aa− and Qa− and possess no anti-RBC antibody in its serum. It is desirable to have identified this type of donor to avoid the need for immediate crossmatching in every case of plasma transfusion.

The volume of plasma needed to correct the measured IgG deficit in a foal can theoretically be calculated on the basis of the blood volume of the foal and the concentration of IgG in the foal's serum and in the donor plasma; however, these

calculations do not reliably predict the actual levels of IgG achieved after transfusion.[34,59] A 20-mL volume of plasma per kilogram of body weight administered intravenously in general raises serum IgG levels 200 to 300 mg/dL, and often two to three times this amount is necessary to bring serum IgG levels into the range considered the minimum for protection (e.g., 800 mg/dL).[34,60] If the foal is already clinically ill, additional plasma often will be required to raise IgG levels an equivalent amount.[34,40] In a newborn foal (estimated at 50 kg) with complete FPT, between 2 and 4 L of plasma is frequently necessary.

Plasma should be administered through an IV catheter placed aseptically in one jugular vein. Frozen plasma is thawed and warmed slowly to room temperature in a lukewarm water bath. Microwave thawing or thawing with high temperatures is not recommended because this may denature important plasma proteins. An appropriate in-line blood filter should be used for IV administration of any blood product to remove fibrin clumps and other debris. Initial infusion rates should be slow (0.5 mL/kg over 10 to 20 minutes) to monitor for adverse reactions. Muscle fasciculations, piloerection, increased heart or respiratory rate, fever, respiratory distress, abdominal pain, soft feces, blanching of mucous membranes, and collapse are indicative of transfusion reactions. One dose of flunixin meglumine has been used in cases of adverse reactions, and plasma transfusion may be attempted again at a slower rate. In the absence of these or other adverse effects, the remainder of the transfusion may be administered in 30 to 40 minutes. Slower infusion rates are recommended for foals that are systemically ill. If other IV fluid therapy is being administered concurrently, slower infusion rates are also indicated to diminish the likelihood of inadvertent fluid overload.

Serum IgG concentrations in the foal should be rechecked 24 hours after plasma transfusion to confirm that the desired increase has been achieved. The delay from transfusion to IgG assessment is necessary to allow for distribution of Ig into extravascular spaces. Healthy foals transfused with plasma at 1 day of age experienced a 30% decrease in serum IgG concentrations by 7 days of age.[59] This decline may be even more marked in septic foals with increased vascular permeability, increased catabolism, and increased demand for use in immune responses.

Although several equine serum-derived products are marketed for IV administration in the treatment of foals with FPT, these products have been associated with significant adverse reactions in some foals. Administration of high-quality equine plasma is preferred for treatment of foals with FPT.

■ Prevention and Control

Evaluation of colostral Ig content has proved to be valuable in predicting the occurrence of FPT and assessing the neonate's risk for FPT.[34,61] Colostrum with high Ig concentration tends to be sticky, yellow, and thick, but these subjective criteria are unreliable in assessing colostral quality. The quantity of Ig in colostrum may be more accurately estimated by single RID, refractometry, glutaraldehyde coagulation, or specific gravity.[62] Because 24 hours are required to read the results of RID, it is more practical in a field situation to assess specific gravity with the other tests. A handheld Brix 0% to 50% sugar refractometer provides a simple and cost-efficient stall-side screening test for assessing colostral quality.[63,64] A Brix reading of 20% to 30% correlates with adequate colostral quality; a reading greater than 30% indicates good-quality colostrum.[65] A commercial kit based on glutaraldehyde coagulation of immunoglobulins is the Gamma-Check-C (Veterinary Dynamics, San Luis Obispo, Calif.). Colostral specific gravity using a colostrometer such as the Equine Colostrometer (Lane Manufacturing Company, Denver, Colo.) should be at a minimum of 1.060, corresponding to an IgG concentration greater than 3000 mg/dL; levels of 6000 mg/dL or higher are desirable. Approximately 75% of foals that ingest colostrum with a specific gravity less than 1.060 will have serum IgG concentrations less than 400 mg/dL; when colostral specific gravity is greater than 1.060, foals usually attain serum IgG concentrations above 500 mg/dL.[62]

Some of the causes of FPT can be alleviated or recognized for early intervention by careful management. These include identification of mares that drip colostrum before parturition, attendance at foaling to ensure that foals suckle within several hours of birth or are supplemented artificially with colostrum, and screening of high-risk foals with doubtful nursing histories. Routine screening of foals between 12 and 24 hours of age allows early identification of FPT and potentially allows for therapy before the onset of infections. Although signs of septicemia secondary to FPT are often first observed on days 3 to 4 of life, a bacteremia may already be present at 24 hours of age or earlier.[62,65]

A colostrum bank can be established by collecting small amounts of colostrum from lactating mares (e.g., 200 to 250 mL) within the first 2 hours after foaling. This is only about 10% of the total colostrum produced by the average mare in

the first 24 hours after parturition and therefore does not adversely affect the foal suckling the donor mare. Although the volumes are quite variable, mares produce about 300 mL of colostrum per hour and about 5 L during the first 18 hours. Colostrum can be stored frozen for at least 1 year at standard freezer temperatures, approximately −20° C (−4° F). Although frozen immunoglobulins are stable for much longer, the overall quality of the colostrum may deteriorate. Ideally, banked colostrum should be screened for the presence of anti-RBC antibodies as advised for plasma. Colostrum typically has low titers of agglutinins, which are probably not of significance unless they present a dilution of one eighth or greater.

Transient Hypogammaglobulinemia*

M. Julia B. Felippe

■ Definition and Etiology

Transient hypogammaglobulinemia is a rare disorder characterized by the delayed onset of Ig synthesis in the foal.[1-4] Foals normally produce some IgM and trace amounts of IgG in utero and begin to produce significant amounts of immunoglobulins after birth following exposure to environmental antigens (see Fig. 53.4). Assuming adequate passive transfer, maternal antibody fills the void from birth until the foal has produced sufficient autologous antibody for protection (e.g., first 2 months). For unknown reasons, in transient hypogammaglobulinemia, the onset of endogenous antibody production is delayed in the first 6 months of life, but in some cases, protective levels of IgG (i.e., >800 or 1000 mg/dL) may be reached only by 2 years of age. As maternal immunoglobulins wane, the amount of endogenous antibody is transiently insufficient to be protective, making the foal highly susceptible to infections; recurrent pneumonia is a common presentation.

This disorder has been described in the literature in an Arabian foal and a Thoroughbred foal, but this author has diagnosed the condition in other foals. It is possible that this condition is underdiagnosed because testing serum IgG concentrations in older foals (i.e., beyond the first week of life) is not common practice in equine medicine. Therefore to make a diagnosis, serial samples may be required to document that autologous Ig is not increasing sufficiently as maternal Ig declines. Many cases that are not followed this closely probably occur.

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■ Clinical Signs and Differential Diagnoses

Clinical signs occur more often when passively acquired antibodies are catabolized to nonprotective levels, which may happen in the first month of life. As with other Ig deficiencies, signs consistent with the recurrent infections are seen in affected foals. The differential diagnosis list should include FPT and, if the affected animal is male, agammaglobulinemia.

■ Clinical Pathology

The cardinal features are persistently low serum Ig concentrations and recurrent bacterial infections that require antibiotic therapy.[1,2] Determining low levels or nonprotective levels of Ig in young foals is challenging because of variable amounts of passively transferred immunoglobulins, their catabolism, presence of infections in early age, environmental risks, and age-dependent developmental aspects of the immune system, among other factors. In the event of a robust passive transfer of antibodies at birth, colostrum-derived antibody concentrations are expected to wane by 3 to 4 months of age, and foals with normal immune system development will have produced measurable quantities of endogenous antibodies by then. Therefore serum IgG concentration of 500 mg/dL and serum IgM concentration of 50 mg/dL are commonly measured in affected and normal foals between 3 and 6 months of life; however, in foals with transient hypogammaglobulinemia, the concentrations of immunoglobulins, including IgG and IgM, do not increase with age at the same degree when compared with age-matched samples.

Affected foals have normal cell-mediated responses in vitro and in vivo and appear to be able to respond to immunization to some antigens. Normal numbers of B and T lymphocytes are present in blood and lymph nodes. However, some foals may present CD4 T-cell lymphopenia and low CD4/CD8 ratio distribution (<2).[5] In addition, the age-dependent increase in the expression of MHC class II molecules on lymphocytes, but not on monocytes, is delayed.[5]

Differentiation between FPT and transient hypogammaglobulinemia is based on the age of the patient at evaluation. Transient hypogammaglobulinemia must be differentiated from agammaglobulinemia. Both disorders have normal lymphocyte counts and normal responses to PHA skin testing and show waning levels of maternal IgG and IgGT if followed serially. However, transient hypogammaglobulinemia cases usually have low but detectable levels of IgM and IgA, whereas agammaglobulinemia cases usually have no detectable levels

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of these immunoglobulins. Differentiation between the two may require serial sampling to show that Ig production does ultimately increase in the patient with transient hypogammaglobulinemia. Moreover, B lymphocyte count is absent in cases of agammaglobulinemia and normal in cases of transient hypogammaglobulinemia.

■ Pathophysiology

The cause of this delayed development of the humoral immune response is currently unknown. A proposed mechanism is inadequate lymphoid tissue milieu to support B-cell differentiation.[5] Immunoglobulin is critical for neutralization and opsonization of pathogens for efficient phagocytosis and killing by phagocytes; therefore recurrent bacterial infections are common and require continued or intermittent antibiotic therapy. A syndrome of transient hypoglobulinemia of infancy has been described in children and is characterized by recurrent infections and one or more reduced serum Ig levels.[6-7] The pathophysiology of this disorder is also not completely understood.

■ Necropsy Findings

No specific gross or microscopic lymphoid changes have been associated with transient hypogammaglobulinemia. Necropsy findings would reflect the secondary infectious processes that have affected the foal.

■ Treatment and Prognosis

The goal of therapy is to minimize infections until the foal's immune system begins to function adequately. Treatment should include antimicrobial therapy and plasma transfusions for Ig replacement as needed; periodic (i.e., every 2 months) evaluation of serum IgG and IgM concentrations and distribution of CD4 and CD8 T cells and B cells in peripheral blood document trends in values and resolution of this transient condition and determine the continued need for supportive therapy. With appropriate support the prognosis is good, as the hypogammaglobulinemia resolves with time.

Severe Combined Immunodeficiency*

Melissa T. Hines

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■ Definition and Etiology

Severe combined immunodeficiency (SCID) is a group of disorders in which both T- and B-cell functions are absent.[1-4] SCID has been recognized in several species, including humans, mice, dogs, pigs, and horses.[2-10] In horses, the condition primarily affects Arabians and part-Arabians, although sporadic cases have been described in other breeds, such as Caspians and Appaloosas.[2,3,11,12] Affected foals are highly vulnerable to infections as a result of a stem cell defect that prevents maturation of T and B cells and leads to a complete inability to produce antigen-specific immune responses. In horses of Arabian breeding, the condition is transmitted as an autosomal recessive trait.[13]

■ Clinical Signs and Differential Diagnoses

Foals clinically affected with SCID are typically normal at birth, but the absence of both specific humoral and cellular immunity renders them susceptible to infections once colostral protection wanes.[2,3] Typically, affected foals develop infectious diseases between birth and 2 months of age and die before 5 months of age. The exact age of onset of infectious disease depends to some degree on the adequacy of passive transfer of maternal immunity and the degree of environmental challenge by organisms. Infections in affected individuals can be caused by a variety of bacterial, viral, parasitic, and fungal agents, some of which rarely affect animals that are not immunocompromised.[2,14-19] Many body systems may be involved, but pneumonia is particularly common. *P. jirovecii* (formerly called *Pneumocystis carinii*) pneumonia and adenoviral pneumonia are often found in SCID foals as compared with other foals. Differential diagnoses include other immunodeficiencies of foals.

SCID in Arabians and Arabian-cross horses has an autosomal recessive mode of inheritance. Thus foals of Arabian breeding that show clinical manifestations of SCID are homozygous for the defective SCID gene. Carriers of the gene are asymptomatic but can be detected by production of an affected offspring or genetic testing.[20,21] A correlation between heterozygosity for the SCID allele and the development of sarcoids has been demonstrated, suggesting that the gene may play a role in tumor suppression.[6]

■ Clinical Pathology

A consistent finding on the hemogram of affected foals is an absolute

lymphopenia, which is less than 1000 lymphocytes/µL and often much lower.[22,23] Depending on the neutrophil response, the total white blood cell (WBC) count may be low, normal, or elevated, making it essential that the absolute number of lymphocytes be determined. Septic and other compromised foals, as well as some normal foals, may have low lymphocyte counts during the first few days of life; therefore persistent lymphopenia should be established before considering a diagnosis of SCID.[24]

Concentrations of autologous serum Ig are low in foals clinically affected with SCID.[22,25-27] The presence of colostral antibody may mask these low levels of autologous Ig; therefore the degree of colostral transfer and the age of the foal should be considered when interpreting the serum Ig values (see Table 53.6). In normal foals, IgM is produced in utero, and thus some IgM should be present in presuckle serum.[28] Although not pathognomonic, the absence of IgM in presuckle serum is a feature of SCID. Also, due to the relatively low concentrations of IgM in colostrum and the short half-life of IgM (see Table 53.7), maternally derived IgM is generally absent from the circulation by about 3 weeks of age. Thus the absence of serum IgM after 3 weeks of age, although also not pathognomonic, is consistent with SCID.

Foals affected with SCID do not respond to intradermal phytohemagglutinin (PHA) by increasing skin thickness as do normal foals, nor do they respond to DTH stimulators, such as dinitrochlorobenzene.[29] In vitro tests such as blastogenesis are depressed with all mitogens.[22,23,26] The definitive diagnosis of SCID in foals of Arabian breeding is based on genetic testing demonstrating that the foal is homozygous for the defective SCID gene.[20,30] Pulled hair, whole blood in ethylenediaminetetraacetic acid (EDTA), or bristle-style cheek swabs may be submitted to VetGen (3728 Plaza Drive, Suite 1, Ann Arbor, Mich., 48108, vetgen@vetgen.com, www.vetgen.com) for DNA testing to determine if a horse is clear, heterozygous, or homozygous for the gene defect. Before the advent of genetic testing, the criteria required to confirm a diagnosis of SCID included (1) persistent lymphopenia (<1000/µL), (2) absence of serum IgM in presuckle samples or samples collected after 3 weeks of age, and (3) thymic hypoplasia along with characteristic histopathologic changes in lymphoid tissue.[27,31] These criteria were used to diagnose SCID in a Caspian filly with pneumonia that was negative for the defective gene of Arabians.[11] Therefore different mutations could be involved in some cases of SCID.

■ Pathophysiology

Foals of Arabian breeding with SCID have a mutation in the gene encoding the catalytic subunit of DNA-dependent protein kinase (DNA-PK) and thus lack activity of this enzyme.[4,7,30,32,33] The mutation results in a five–base pair deletion in the gene on equine chromosome 9. This deletion results in a frameshift and a 967 amino acid deletion from DNA-PK, making the protein unstable. Without functional DNA-PK, lymphocyte precursors are unable to complete gene rearrangement events that lead to the expression of antigen-specific receptors on lymphocyte surfaces, namely T-cell receptor and immunoglobulin. As a result, there is an absence of mature, functional T and B lymphocytes. IFN-γ, which is a cytokine primarily produced by lymphocytes, is deficient.[34]

Neutrophils, monocytes, and NK cells appear to be fully functional, and complement concentrations are normal.[2,35,36] Although these nonspecific protective mechanisms appear to be intact, the absence of both cell-mediated and antibody-mediated immunity leaves the foal vulnerable to even innocuous infectious agents.

■ Epidemiology

SCID has been reported in Arabians in the United States, Canada, Australia, Morocco, and Great Britain.[2,3,37-39] It is believed that the trait originated in a horse in Great Britain and subsequently was imported into other countries. The widespread distribution of this disease provides a significant example of the *founder effect* in population genetics.

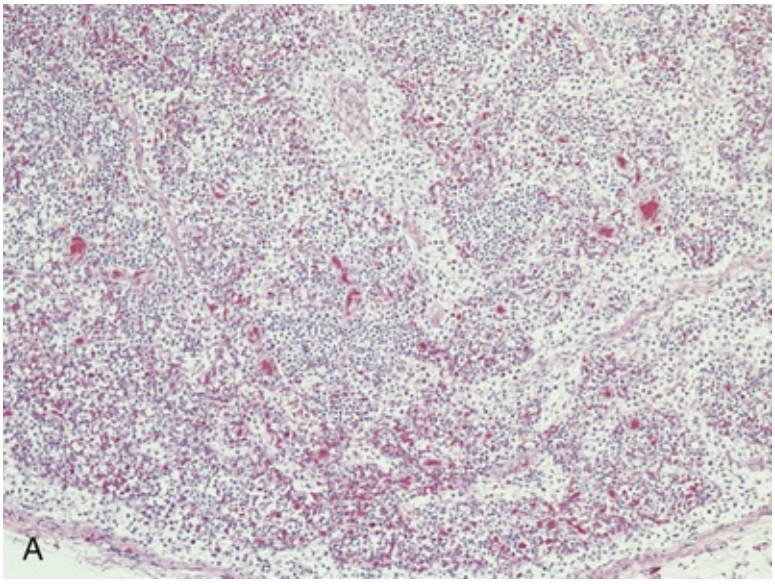
The prevalence of SCID at one time was estimated to be 2% to 3% of Arabian foals born in the United States.[40] From this estimate, it was predicted that the numbers of SCID carriers at that time could be as high as 25% of the U.S. Arabian horse population. The number of carriers appears to have decreased. Studies of Arabian horses in 1998 and 2002 found the frequency of SCID gene carriers to be approximately 8%, leading to the prediction that 0.18% of Arabian foals would be affected with SCID, assuming a random breeding population.[6,38] In a study of Arabian foals in South Africa, the carrier prevalence of SCID decreased significantly from 6.4% in the 2004/2005 foals to 3.4% in the 2009/2010 foals, and it was suggested that genetic screening may have played a role in reducing the carrier prevalence.[41] Several hereditary conditions in

addition to SCID can affect Arabians, and while studies are limited, it is suspected that these are most likely distinct conditions. A study of ten Egyptian Arabian horses with juvenile idiopathic epilepsy found no association between this disorder and SCID.[42]

■ Necropsy Findings

Lymphoid tissues should be evaluated both grossly and histologically in cases of suspected immunodeficiencies. In SCID, the thymus is small and has a fatty appearance on gross examination.[26,31,43] Because the thymus may be difficult to identify, mediastinal tissue often must be collected “blindly” for subsequent histologic evaluation and identification of thymic remnants. Histologically, the thymus is largely replaced with adipose tissue, with only islands of lymphoid cells and partially formed Hassall's corpuscles present.

The spleen and lymph nodes may not be significantly abnormal on gross examination, but they generally have microscopic abnormalities, including the absence of germinal centers and periarteriolar lymphocytic sheaths in the spleen, as well as absence of germinal centers with scarcity of lymphocytes in other areas of lymph nodes (Fig. 53.5, *A*).



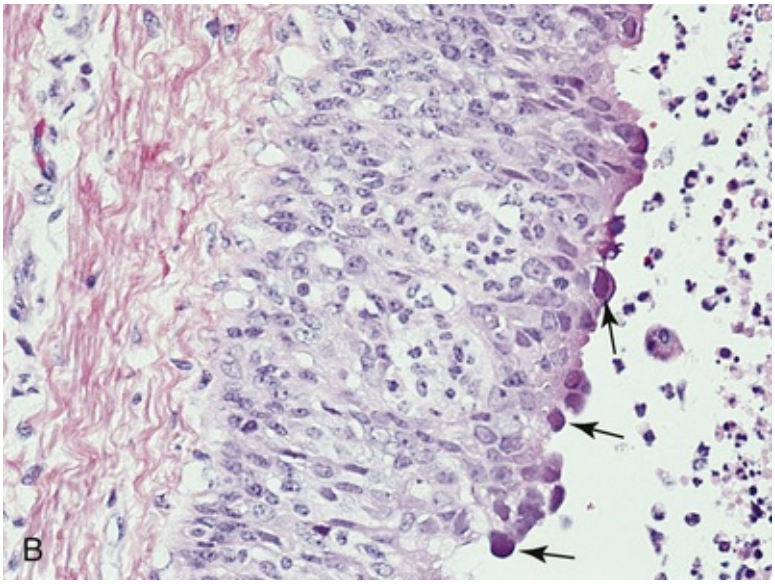


FIG. 53.5 Tissue from an Arabian foal with severe combined immunodeficiency (SCID). The foal presented at 1 month of age for evaluation of persistent pneumonia. **A,** 200× mediastinal lymph node with extensive lymphoid atrophy. The node is poorly populated with lymphocytes that fail to form lymphoid follicles, and active germinal centers are lacking. The node is predominantly composed of loosely scattered mononuclear cells and edema. **B,** 400× tracheal epithelium with adenovirus inclusion *(black arrows),* epithelial hyperplasia, and suppurative tracheitis. (Photos courtesy Sushan Han.)

Foals with SCID typically have evidence of infectious disease on necropsy, with bronchopneumonia being particularly common (Fig. 53.5, *B*). Infectious lesions in other systems, such as colitis and hepatitis, are also frequently found.

■ Treatment and Prognosis

Affected foals invariably die by about 5 months of age, despite intensive conventional therapy (e.g., antimicrobials, plasma transfusion, isolation).[44] There is no practical method of curing affected foals at this time. Successful bone marrow transplants have been performed between histocompatible full siblings in a research setting, but this option remains impractical.[45-47]

■ Prevention and Control

SCID in horses of Arabian breeding is an autosomal recessive trait, and therefore production of an affected foal identifies both sire and dam as carriers of the SCID gene.[13] Mating of two carriers is expected to result in 1 in 4 foals affected with SCID, 1 in 4 completely normal and not a carrier, and 2 in 4 asymptomatic

carriers of the SCID trait. Mating of a carrier and a normal horse (noncarrier) does not produce any affected foals, but half the offspring would be expected to be carriers.

The disease can be controlled in horses of Arabian breeding by avoiding the production of affected foals, which has been simplified now that carriers can be identified by genetic testing. Mares and stallions intended for breeding should be tested to determine whether they are free or heterozygous for the defective SCID gene. Under no circumstances should two heterozygotes be mated to each other. If an owner decides to continue breeding a heterozygote, the breeding partner should be confirmed homozygous normal. All foals from such matings should be tested to determine if they are clear of or heterozygous for the defective gene (50/50 probability). Only homozygous normal foals should be selected for future breeding purposes, whereas heterozygous foals should be used for nonreproductive purposes. The decreasing prevalence of SCID provides support for the positive effect of genetic screening.[6,38,41]

Foal Immunodeficiency Syndrome

M. Julia B. Felippe

■ Definition and Etiology

Foal immunodeficiency syndrome (FIS), previously known as *Fell Pony syndrome* and also referred to as "anemia, immunodeficiency, and peripheral ganglionopathy," is an inheritable and fatal condition characterized by profound anemia and septicemia, the latter due to a primary immunodeficiency. A genomewide study identified a mutation in the gene *SLC5A3* on chromosome ECA26 associated with the syndrome.[1] The mechanistic implications of this mutation have not been fully resolved, and a causal relationship between the *SLC5A3* mutation and FIS requires further studies to date. The presence of other mutations in that genomic region has not been ruled out as being responsible for the phenotype of the immunodeficiency syndrome.

■ Clinical Findings, Clinical Signs, and Differential Diagnoses

FIS-affected foals are born apparently healthy but rapidly fail to thrive. The fatal illness becomes clinically apparent in foals within 1 month, and death occurs

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generally by 3 months of life due to a primary, profound, nonregenerative anemia and B-cell lymphopenia, with increased susceptibility to opportunistic infections and septicemia.

The foals present with weight loss and dullness, pale mucous membranes, and signs of infection, including diarrhea and pneumonia.[2-4] Enterocolitis, bronchopneumonia, pancreatitis, and glossal hyperkeratosis are often caused by opportunistic infections (e.g., *Escherichia coli*, *Cryptosporidium* spp., adenovirus). The severe, progressive anemia results from lack of erythrocyte production in the bone marrow (nonregenerative), and it is not associated with hemorrhage or hemolysis.[2,3,5]

■ Clinical Pathology

At birth, blood work may be normal, with normal or borderline low erythrocyte counts and hemoglobin values and normal distribution of neutrophils and lymphocytes.[5] When infections are present, abnormalities in the leukogram, including regenerative neutropenia or neutrophilia, toxic changes in neutrophils, and lymphopenia, may be present, and values vary depending on the type and phase of infection. Thrombocytes are often present in the blood at normal values unless disseminated intravascular coagulopathy secondary to septicemia is present.

Severe normocytic or macrocytic anemia develops rapidly. Based on bone marrow cytology, FIS-affected foals may be born with erythroid precursors but rapidly evolve to erythrocyte hypoplasia. At birth, hemoglobin and hematocrit values may be measured in the low end of the normal reference range, and peripheral blood B-cell distribution may be equivalent to that of healthy, unaffected foals. In a few weeks, profound anemia and B-cell lymphopenia develop. In time, cytologic evaluation of the marrow reveals differentiating myeloid precursors, megakaryocytes, and/or paucity of hematopoietic precursors. When present, proerythroblasts have been described to be binucleate.[4]

■ Immunologic Findings

Absolute lymphopenia in FIS-affected foals likely reflects poor lymphocyte development in primary and secondary lymphoid tissues, as well as failure of lymphocyte population expansion with age.[6,7] B-cell distribution in blood may be within normal or low-normal values at birth but rapidly declines in the first

few weeks of life.[5,8] Although CD4+ and CD8+ T-cell distributions have been reported as normal in affected foals, T-cell dysfunction is suggested by the small thymus and opportunistic infections with cryptosporidia and adenovirus.[7,9] The expression of MHC class II molecules in peripheral blood lymphocytes may be decreased and/or fail to increase with age in FIS-affected foals when compared with healthy foals, also supporting abnormal lymphocyte development.[10] Nevertheless, when stimulated in vitro, the peripheral blood lymphocytes of affected foals respond normally to mitogens PHA, concanavalin A (ConA), and pokeweed mitogen (PWM).[4,7]

Although the B-cell lymphopenia limits the ability of FIS-affected foals to produce immunoglobulins, serum IgG concentrations are often normal when clinical signs are detected due to the presence of circulating colostrum-derived antibodies.[2-4,11] Nevertheless, serum IgM concentration (a parameter not confounded by colostrum-derived antibodies at this age) is low or not detectable in affected FIS-affected foals and strongly suggests impaired primary humoral immune response.[5,11,12] FIS-affected foals develop septicemia despite normal (colostrum-derived) serum IgG concentrations, suggesting a broad lymphocytic dysfunction.[4,5]

The distribution and function of neutrophils have been reported as normal, including the presence of bands and normal oxidative burst activity.[4]

■ Pathophysiology

Bone marrow cytologic studies performed prospectively in affected foals immediately after birth and before clinical signs became evident at a later age revealed evidence of initial erythroid hyperplasia with dysplasia, followed by a rapid and progressive hypoplasia and aplasia, as well as marked anemia.[5] In addition, a concomitant mild myeloid dysplasia could be observed, which questions the involvement of further types of cells.

The presence of erythrocytes and B cells in peripheral blood at birth suggests a limited hematopoiesis during fetal life. Nevertheless, this cell production is not sustained after birth, leading to a marked and progressive anemia and B-cell lymphopenia in the perinatal phase, corresponding clinical signs, and death. Erythrocytes and B lymphocytes are the most severely affected cell populations in FIS, and both undergo critical developmental stages in the bone marrow. The condition may be caused by independent or common genetic abnormalities that affect both cell lines. Most early B-cell differentiation essential genes and genes

associated with erythropoiesis are expressed in the affected foals, and a potential common hematopoietic genetic defect is still under investigation.

■ Epidemiology

FIS is a genetic and inheritable fatal immunodeficiency condition that occurs in male and female young foals of the Fell and Dales breeds and potentially in other breeds that include common ancestors.[13,14]

The Fell Pony breed experienced loss of genetic diversity due to the small numbers of animals and overuse of prominent stallions, which likely led to the spread of the genetic defect. Pedigree analysis of the Fell Pony breed suggests that FIS may have an autosomal recessive inheritance. Carriers are phenotypically normal. FIS was initially described in the United Kingdom and subsequently in Fell Pony foals in the United States, Czech Republic, and Netherlands.[2,4,15,16]

■ Necropsy Findings

In the postmortem, abnormal gross findings include generalized tissue pallor, thymic hypoplasia, and inflammation and lymphadenopathy associated with infections of many organs (e.g., necrotizing enteritis, pyogranulomatous bronchopneumonia, pancreatitis, myocarditis). The medullary cavities of bones often do not contain marrow but instead pale, tan, fatty tissue, a striking finding in early age. Histopathology reveals severe erythroid hypoplasia, with small numbers or absent late erythroid precursors in the bone marrow, and high myeloid-to-erythroid ratio (ranging from 16 to 32 : 1, compared with the normal myeloid-to-erythroid ratio of 0.5 to 1.5 : 1).

Despite lymphadenopathy, there is severe lymphocytic hypoplasia and lack of secondary lymphoid follicles in the lymphoid tissues; in addition, plasma cells are absent. Immunohistochemical staining detects no B lymphocytes in the bone marrow and rare or few B cells in the lymph nodes and spleen, dispersed in the tissues without forming germinal centers. In addition, peripheral ganglionopathy characterized by neuronal chromatolysis involving trigeminal, cranial mesenteric, and dorsal root ganglia has been reported.[2]

■ Treatment and Prognosis

FIS is a fatal disease, and foals die or are submitted to euthanasia soon after the initial clinical signs. Management of infections and septicemia may be

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temporarily possible with antibiotic therapy; however, the combination of infectious organisms, commonly viruses and bacteria, prevents a sustained protection. The severe, progressive anemia is a major challenge for treatment.

■ Prevention and Control

A DNA-based carrier test was developed by the Animal Health Trust (Newmarket, United Kingdom).[1,14] The genetic test offers powerful herd management planning to avoid the mating of two carriers with the genetic defect and consequently to decrease the incidence of FIS, a fatal disease to date. The use of the genetic test has been shown to reduce the number of births of affected foals.[17]

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Agammaglobulinemia*

Melissa T. Hines

■ Definition and Etiology

Agammaglobulinemia in horses is a rare primary immunodeficiency characterized by complete B-cell dysfunction with an intact cell-mediated response. The disorder is associated with a failure of B-lymphocyte maturation, absent or very low serum Ig concentrations, and failure of specific antibody production. It has been described in Thoroughbreds, Quarter Horses, and Standardbreds, and thus far it has been reported only in males, suggesting that the trait may be X-linked.[1-4] Although this linkage has not been proven in the horse, the disorder is sometimes referred to as X-linked agammaglobulinemia. The first report of an immunodeficiency in any species was agammaglobulinemia in a young boy, and it was subsequently established that the most common form of agammaglobulinemia in humans is X-linked.[5-11]

■ Clinical Signs and Differential Diagnoses

Horses with agammaglobulinemia typically develop signs around 2 to 6 months of age as transferred maternal antibodies decline. The specific signs reflect the infections that develop. Pneumonia and septic arthritis, as well as dermatitis and enteritis, have been reported. Infections often respond poorly to therapy. The differential diagnosis list should include transient hypogammaglobulinemia and common variable immunodeficiency (CVID).

■ Clinical Pathology

Total peripheral blood lymphocyte counts are within the normal range, but lymphocyte phenotyping reveals a lack of circulating B cells with normal numbers of T cells. Changes on routine laboratory evaluation are nonspecific and may reflect chronic infection. Depending on the response to infection, neutrophil counts may be normal, low, or high.

Serum concentrations of IgM, IgA, and all subisotypes of IgG are persistently low or absent. Depending on the age at evaluation, the assessment of antibody concentrations may be complicated by the presence of maternal antibody. Considering that the half-life of IgG is longer than that of IgM, serial sampling

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will demonstrate a decline in antibody concentrations, with IgM and IgA typically decreasing first, followed by a decrease in all subisotypes of IgG. In some foals, low levels of Ig may persist, possibly due to either a prolonged catabolism of antibody or some residual B-cell activity, which has been identified in human patients with X-linked agammaglobulinemia.[1-5]

Horses affected with agammaglobulinemia do not produce specific antibody in response to immunization regardless of the antigen. Cell-mediated responses are essentially normal, including lymphocyte proliferation in response to T-cell mitogens (PHA and PWM) and DTH skin testing by intradermal (ID) injection of PHA. In contrast, lymphocyte proliferation and DTH skin testing by ID injection of ConA is blunted, but the reason for this response to ConA remains unclear.[4] Total hemolytic complement activity is also normal.

■ Pathophysiology

The molecular basis of agammaglobulinemia in horses is unknown, but a defect at the stem cell level that blocks early B-cell differentiation is suspected because all classes of Ig are affected. In human patients with X-linked agammaglobulinemia, a mutation in *Btk*, a gene encoding Bruton's tyrosine kinase, accounts for the disease.[7,8] Assessment of the *Btk* gene in horses may help in understanding this disorder.

■ Necropsy Findings

Gross and histologic changes in the lymph nodes, spleen, and thymus have been observed in horses with agammaglobulinemia.[1-4] Lymph nodes are small and microscopically show as being devoid of germinal centers and follicles. Grossly, the spleen may be small and contracted and microscopically shows lack of germinal centers, periarteriolar lymphocytic sheaths, and plasma cells. The thymus may be small and difficult to locate, making it necessary in some cases to blindly sample tissue from the mediastinal region. Histologically, the thymus does not show recognizable epithelial structure and lacks defined nodules. The reason for cell-mediated functions to be normal while the architecture of the thymus is so abnormal remains unexplained.

■ Treatment and Prognosis

In the absence of production of autologous antibody, affected horses develop recurrent infections. Although antimicrobial therapy and administration of

plasma may temporarily control infections, the long-term prognosis is poor. In human patients with X-linked agammaglobulinemia, early diagnosis along with well-controlled Ig replacement therapy have allowed patients to survive well into adulthood.[9]

Horses with agammaglobulinemia illustrate that T cells make a significant contribution to immunity along with B cells. Horses with defects in both B- and T-cell functions (e.g., SCID) seldom survive to 5 months of age, whereas horses with a pure B-cell defect such as agammaglobulinemia may survive between 1 and 2 years. Agammaglobulinemia with a lack of circulating B cells was identified in a Pinto gelding that did not exhibit recurrent pyogenic infections until 3 years of age.[12] It is not certain whether this horse had agammaglobulinemia or a form of common variable immunodeficiency. Although it could not be established whether the immunodeficiency was primary or secondary, an underlying disease process was not identified.

Selective IgM Deficiency*

M. Julia B. Felippe

■ Definition and Etiology

Selective IgM deficiency is a very rare, poorly characterized immunologic disorder described based on absent or markedly decreased serum IgM concentrations with normal or elevated levels of other Ig isotypes.[1] Three presentations of the disorder have been described in horses.[2-6] The most common involves foals that have severe infectious pneumonia, arthritis, or enteritis, resulting in death before 10 months of age. The second involves foals with a history of repeated episodes of infections that respond to antimicrobial therapy but recur when treatment is stopped. These foals tend to do poorly and are stunted, although they may survive for 1 to 2 years. The third involves older horses that are usually 2 to 5 years of age at initial diagnosis. These horses do not necessarily have problems with recurrent infections, but about half ultimately have lymphosarcoma.[6] Selective IgM deficiency has been most frequently reported in Arabians and American Quarter Horses, although it affects other breeds.

It is unclear whether the selective IgM deficiencies reported in foals are primary or secondary or are a feature of other immunodeficiencies. The levels of

endogenous IgM present before the onset of infections have not been measured. The occurrence of multiple cases within groups of related horses suggests a genetic basis. However, to date, breeding trials have been inconclusive regarding the heritability of this condition. In humans, there is no described genetic or molecular mechanism as the cause of selective IgM deficiency, and this condition has been shown to manifest with infections, atopy, autoimmunity, and cancer, although it can also be asymptomatic.[7-9] Recent literature points out the importance of ruling out other humoral deficiencies and performing clinical case follow-up to confirm persistence of selective IgM deficiency.

■ Clinical Signs and Differential Diagnoses

Foals with selective IgM deficiency tend to have frequent respiratory infections, and *Klebsiella* spp. are commonly isolated. Other infections, such as enteritis and septic arthritis, have also been reported. The age of onset of clinical signs may be slightly later than in foals with SCID, and the condition may be difficult to diagnose when colostrum-derived antibodies are still circulating. The most important differential diagnosis is delayed hypogammaglobulinemia of the young, which may take several months (i.e., 6 to 24 months) to resolve.

Although low serum IgM concentration has been shown to have a low specificity, sensitivity, and positive predictive value for the diagnosis of lymphoma, older horses with IgM deficiency should be carefully evaluated for neoplasia using definitive diagnostic tests (e.g., lymph node biopsy, cytology, and histology), since the clinical signs and hematologic features of lymphoma in horses are often nonspecific[10] (see Chapter 37).

■ Clinical Pathology

Selective IgM deficiency is defined by a persistently low or absent serum IgM concentration, whereas levels for other classes of Ig are normal or elevated for age. Serum IgM concentrations are more than two standard deviations below the age-specific mean (see Table 53.6). In one study, serum IgM concentrations in adult healthy horses during a period of 5 months ranged from 50 to 242 mg/dL, and 20% of these horses had values below 60 mg/dL; based on these data, IgM deficiency was suggested at values lower than 23 mg/dL.[10] Serum IgM concentration of 10 to 22 mg/dL may be measured beyond 185 days of gestation in the equine fetus, and levels of 25 mg/dL may be measured in presuckle foals; however, there is marked individual variation in how serum IgM concentration

increases with age.[11-13] Because IgM levels may transiently decrease, especially in critically ill foals, it is essential to document that IgM levels are persistently low rather than to base a diagnosis on a single sample. Lymphocyte counts and other in vitro immunologic tests, such as lymphocyte proliferation to mitogens (including PHA, ConA, PWM, and LPS), are generally normal.[2,4] However, in one horse with selective IgM deficiency, lymphocytes failed to respond to the B-cell mitogen LPS, whereas responses to the T-cell mitogens ConA and PHA were normal.[5] The hemogram and biochemical profile may reflect infection or inflammation, depending on the underlying infectious process (e.g., neutrophilia, hyperfibrinogenemia, anemia) and the organ system involved, but no diagnostically specific changes occur.

■ Pathophysiology

The pathophysiology of selective IgM deficiency is difficult to explain when B-cell development in the bone marrow depends on IgM expression on the cell surface, as part of the B-cell receptor, and patients have normal numbers of IgM-expressing B cells.[1,7,8] Exclusive impaired secretion of IgM could be caused by intrinsic B-cell dysfunction or dysfunction of T cells during B cell–T cell interaction in lymphoid tissues, but it is curious why such deficiencies do not affect more elaborated B-cell differentiation into other isotype (e.g., IgG, IgA)–secreting plasma cells. Whether IgM is low because of decreased production, hypercatabolism, or loss is not known. In one case with lymphosarcoma, suppressor activity was identified in the neoplastic cells, suggesting that the low IgM may be a result of suppression of B-cell function by neoplastic cells.[5,14] IgM plays a role in complement activation and neutralization of antigens, but such functions can also be accomplished by IgG or IgA, which are generally within normal levels.

■ Necropsy Findings

Lymphoid tissue in affected foals is grossly and histologically normal. Other findings reflect secondary infections. Pneumonia is frequently present and is often caused by infections with encapsulated bacteria (e.g., *S. aureus, S. zooepidemicus, A. equuli, Klebsiella* spp., and *E. coli*).[2,4]

■ Treatment and Prognosis

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For the clinical cases diagnosed in the literature, selective IgM deficiency has an unfavorable long-term prognosis. Most horses eventually succumbed to infection despite appropriate antimicrobial therapy. However, some of the reported foals recovered IgM and IgG productions when yearlings.[2,4] Plasma therapy may provide transient benefit not for IgM replacement (because only small amounts of IgM are present in plasma and the half-life of transfused IgM is short) but for expansion of IgG concentration and potentially coverage (neutralization, opsonization, complement activation) against pathogens.[7] No concentrated IgM preparations are commercially available for parenteral use. If persistently low IgM levels can be documented, a poor to grave prognosis can be expected.

■ Prevention and Control

Some cases of selective IgM deficiency may be hereditary, and therefore it may be advisable to avoid repeating matings that produced an affected offspring. However, no firm recommendations can be made.

Common Variable Immunodeficiency

M. Julia B. Felippe

■ Definition and Etiology

Common variable immunodeficiency (CVID) in the horse is a rare, late-onset, clinically relevant immunologic disorder of inadequate antibody production due to impaired B-cell differentiation in the bone marrow and consequent B-cell depletion from lymphoid tissues and blood. The cause of impaired B-cell development in the bone marrow is under investigation, and a primary or secondary cause has not been resolved.

■ Clinical Findings, Clinical Signs, and Differential Diagnoses

Most patients are reported to have had a healthy life until the signs of disease manifest as late-onset recurrent bacterial infections and fevers, hypogammaglobulinemia or agammaglobulinemia, progressive B-cell lymphopenia or depletion, and poor response to protein vaccination (e.g., tetanus toxoid).[1] The most common clinical signs include recurrent pneumonia, sinusitis, meningitis and/or neurologic disorders, abnormal gait (ataxia),

peritonitis, gingivitis, hepatitis, diarrhea, susceptibility to GI parasites, uveitis, conjunctivitis, and skin abscesses.[2-4] Meningitis may clinically present with marked depression, alternated by periods of normal appetite. Weight loss and muscle atrophy are common.

The humoral feature of this immunodeficiency predisposes to infections and diseases caused by encapsulated bacteria, which requires opsonization with both antibody and complement for effective phagocytosis and bacterial killing. Therefore common pathogens involved in infections include *Staphylococcus* spp., *Streptococcus* spp., *Actinobacillus* spp., and *Klebsiella* spp. Occasionally, fungal infections, such as *Aspergillus* spp., *Bipolaris* spp., *P. jirovecii* (formerly *P. carinii*), or *R. equi* infections, have been diagnosed in a small number of CVID-affected horses that were treated with glucocorticoids or presented with a concomitant CD4+ T-cell lymphopenia.[1,5] In addition, *Borrelia burgdorferi* meningitis, cranial neuritis, and radiculoneuritis have been described in horses with B-cell lymphopenia and hypogammaglobulinemia.[6-8]

A differential diagnosis is lymphoma because some forms of this type of cancer may alter lymphocyte distribution and function, including B-cell lymphopenia and hypogammaglobulinemia. If the disease manifests before the yearling phase, differential diagnoses would include transitory hypogammaglobulinemia (in which B cells are normally present) of the young and X-linked agammaglobulinemia (in which B cells are absent).

■ Clinical Pathology

During bacterial infections, blood work may reveal leukocytosis with neutrophilia, often mature, although a left shift and toxic changes may be present. Intermittent lymphopenia (<1200 cells/µL) is common. During the period when infections respond to antibiotic therapy, both neutrophil and lymphocyte counts may be within normal reference values.

Hyperfibrinogenemia is present accordingly to active infections. An important feature is the presence of low-normal or low globulin levels despite severe bacterial infections and hyperfibrinogenemia; the hypoglobulinemia results from the hypogammaglobulinemia. Abnormal liver enzymes may also be measured when there is septicemia.[3]

In the case of meningitis, spinal fluid analysis reveals increased protein values and pleocytosis, often with nondegenerate neutrophils, lymphocytes, and monocytes.[3] Blood culture has not been routinely performed in these patients but

has resulted in bacterial growth in some cases; culture of spinal fluid may or may not result in bacterial growth.

■ Immunologic Findings

Peripheral blood lymphocyte immunophenotyping reveals persistent, severe B-cell lymphopenia (<2%) in most patients. In a subpopulation of affected horses, B cells may be persistently measured at a distribution of less than 10%. A relative increase in the percentage of circulating CD8+ T cells and occasionally in CD4+ T cells has been observed in most patients. The parameter that defines a humoral dysfunction is serum IgG concentration, which is markedly and persistently low (<800 mg/dL) in *all* affected horses. Serum IgM concentrations are markedly reduced (<25 mg/dL) in all patients, suggesting the inability to elaborate primary immune response. Serum IgA concentrations are often within low-normal values (≈60 mg/dL) in early diagnosis in most patients despite severely low serum IgM and IgG concentrations, but levels reduce with progression of clinical disease, severity of clinical condition, and proximity to euthanasia. Affected horses do not respond to tetanus toxoid vaccination with an increase in serum antibody titers, and prevaccination values are often low or undetectable. It is recommended that these values be interpreted in the context of clinical presentation (i.e., recurrent bacterial infections, infections caused by opportunistic microorganisms, septicemia in adult horse) and subsequently measured after 2 to 3 months to confirm a persistent rather than transitory immunologic condition.

Lymphocyte proliferation assays reveal normal or subnormal responses to PWM, PHA, and ConA mitogens and therefore are not useful in the diagnosis.[1] Upon stimulation with mitogens, the expression of IFN-γ and CD40 ligand in isolated lymphocytes of affected horses is comparable with control healthy horses, suggesting normal T-cell function and capacity for co-stimulation of B cells, which is required for B-cell differentiation and antibody production.

Besides the B-cell lymphopenia, a small number of CVID-affected horses may also present a concomitant CD4+ T-cell lymphopenia, leading to a low CD4/CD8 ratio (<2). In these cases, infection with intracellular organisms that require cellular immunity may be observed, characterizing a clinical relevance for this finding.

The in vitro phagocytosis and oxidative burst activity are normal and often increased in these patients, reflecting in vivo activation.

Postmortem diagnosis can be based on the presence of infections in tissues

plus the absence of germinal centers in the lymph nodes and spleen, with paucity or absence of B cells and plasma cells and no evidence of lymphoma.

■ Pathophysiology

By the time of clinical diagnosis in horses, B cells are markedly rare in primary and secondary lymphoid tissues, leading to peripheral blood B-cell lymphopenia or depletion.[3,9] It is likely that B-cell production was sustained in the affected patients for a period of time before the diagnosis of CVID, and secondary lymphoid tissues were then populated with B cells, including memory cell development; this possibility is based on the clinical evidence that all patients diagnosed to date had a normal development and no obvious susceptibility to infections prior to diagnosis. A late-onset event impairs B-cell development in the bone marrow, and the continuous population of peripheral tissues could not be sustained.[10] B cells must be continuously generated over an individual's lifetime from hematopoietic stem cells in the bone marrow to maintain adequate population and humoral function in the lymphoid tissues.

B-cell differentiation and development is regulated by a network of transcription factors and demethylation of dinucleotides at promoter sites.[11] In the bone marrow of affected horses, the expression of key early B-cell commitment genes, including *E2A* and *PAX5*, is significantly decreased in comparison with healthy horses; in addition, *PAX5* downstream target genes are also significantly reduced in CVID-affected horses, including *CD19*, *IGHM*, and *IGHD*.[12] Immunohistochemical studies confirm the absence of PAX5-BSAP protein in the bone marrow of affected horses. Through a hierarchical dependence, *PAX5* directly promotes the expression of B lymphoid–specific genes while it represses the transcription of non–B lineage genes.[13] Hence CVID in horses may be caused by impairment of B-cell development in the bone marrow at the transition between pre-pro-B cells and pro-B cells; current studies investigate epigenetic mechanisms that lead to gene silencing in earlier stages of B-cell differentiation.

■ Epidemiology

Affected patients are unrelated adult horses and ponies (average age 10 years, range 2 to 23 years) of both sexes and many different breeds (e.g., Thoroughbred, Quarter Horse, Arabian, Warmblood, Paint) living in distinct parts of the United States.[1] Cases elsewhere in the world have not been reported

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but are likely; their identification may be limited by the lack of knowledge of differential diagnosis for immunodeficiency diseases and availability of immunologic testing for the horse.

By the time the diagnosis of CVID is obtained, several months of recurrent infections and fevers may have been observed in some cases. The recurrent character of clinical signs is the most common factor that triggers the suspicion of an underlying immunodeficiency. Affected horses have been euthanized for financial reasons or due to poor quality of life either soon after the diagnosis or after a few years of antimicrobial management. Survival for several years after diagnosis is extremely rare but has been documented in a patient with marked B-cell lymphopenia (<2%) that maintained serum IgG concentrations between 500 and 900 mg/dL.

■ Necropsy Findings

Necropsy findings include organ lesions according to the infectious processes. In addition, histopathology confirms the lack of germinal cells, which affects the lymph node typical cortical-paracortical distribution and the primary and secondary follicles in the cortex.[1,3] In general, lymph nodes are small. In addition, there is absence or marked paucity of plasma cells in various lymphoid and mucosal tissues. Immunohistochemical analysis may identify occasional positive B cells dispersed or in small groups in the lymph nodes but absent B cells in the bone marrow and spleen (Fig. 53.6).

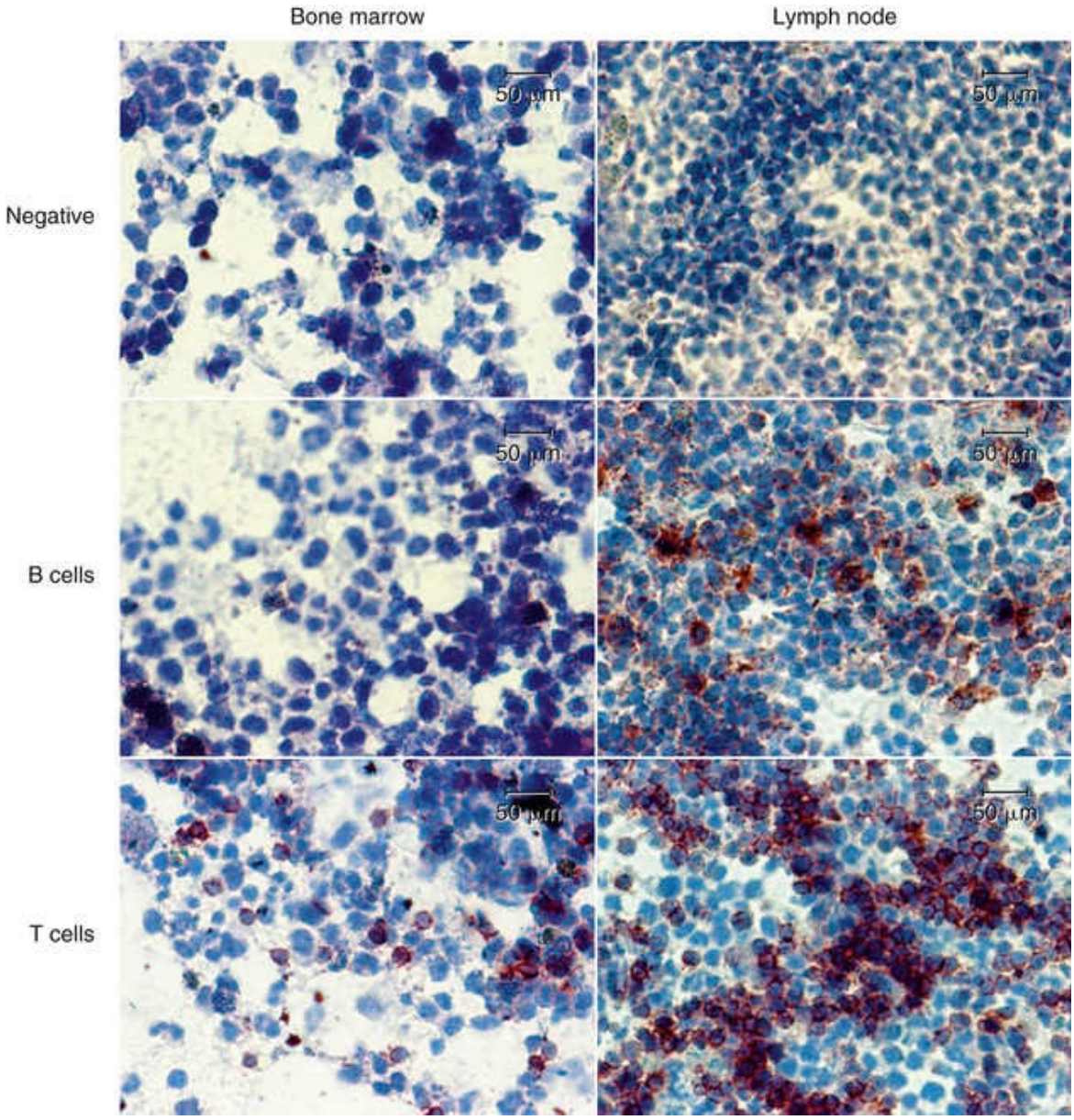


FIG. 53.6 Immunohistochemical analysis of bone marrow and lymph node microsections from a horse with common variable immunodeficiency (CVID). Bone marrow and mesenteric lymph node microsections from a horse with CVID were stained using monoclonal antibodies against equine B-cell (CD19-like) and T-cell (CD3) markers, irrelevant control (negative), and 3-amino-9-ethylcarbazole (AEC) chromogen. Note the lack of germinal centers and paucity of lymphocytes in the lymph node. B cells are not detected in the bone marrow; numerous B cells are detected dispersed in the lymph node. T cells are present in the bone marrow and lymph nodes; however, the typical cortical-paracortical regions in the lymph node are lost with the lack of germinal centers. (Photos courtesy Julia Felippe.)

■ Treatment and Prognosis

Most affected horses are subjected to euthanasia due to severe pneumonia, meningitis, and/or septicemia. When affordable, a few horses have been managed for 1 to 5 years on continuous or intermittent antibiotic and Ig therapies. Commercial equine plasma is the current available source of Ig for clinical use, and its low concentration prevents it from being a cost-effective treatment. Frequent Ig replacement therapy in human patients is possible due to the availability of IgG concentrate products, which improves quality of life. Hematopoietic stem cell transplantation has been attempted in a horse with CVID, but no replacement of B-cell population with function has been successful to date; the costs involved with the procedure discourage clinical application. When the mechanism of disease is revealed, gene therapy may be a more feasible treatment if appropriate.

■ Prevention and Control

Current studies investigate the possibility of epigenetic mechanisms that lead to the impaired B-cell differentiation in the bone marrow. Epigenetic regulation can be affected by environmental or infectious elements, yet to date, common factors have not been identified in the horse patients. At this time, prevention and control measures are not known.

Immunosenescence in Horses

M. Julia B. Felippe • Dianne McFarlane

■ Definition

Immunosenescence is the term used to describe a multitude of changes in the immune system associated with aging. Reported age-associated changes in the immune system in people include alterations in cell population composition, as well as inadequate or inappropriate immune responses.[1] Immunosenescence is considered an important risk factor for the infectious, neoplastic, and inflammatory diseases that accompany aging. However, a balanced (successful) or detrimental (pathologic) effect of aging can result in different outcomes (e.g., immunity) in different individuals depending on how biological resources are individually maintained or exhausted, respectively.[2] Although there are limited available data, evidence suggests that horses experience age-related changes in

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the immune function, some of them in agreement with and some of them contrary to elderly humans.[3]

An important consideration when investigating age-related changes of immune function is how to define “aged,” including chronologic versus biological aging.[4,5] A study population that is too old may cause one to miss age-related immune defects because the selected population may have survived to extreme old age due to exceptional immune function. It is likely that aging biomarkers may differ between very old horse populations (e.g., horses older than 30 years of age) and less old horse populations, such as horses around 20 years of age. Risk of certain diseases, frailty, or other impairments differs along the spectrum of aging. It is also important that the comparisons are made between fully mature horses and aged horses. Finally, marked variations in leukocyte composition, cell morphology, and inflammatory and anti-inflammatory cytokine release ex vivo were shown to be influenced by age, sex, breed, and individual factors, highlighting the importance of study design, analyses, and comparisons that account for this variability.[6]

■ Clinical Findings

Several important factors must be considered when evaluating age-induced changes in the immune system. First, it is important to separate age-associated functional changes from disease-induced changes. In an aged population, this can be difficult due to the high prevalence of comorbidities that contribute to chronic, low-grade, or occult inflammatory disease. Ideally, strict evaluation criteria should be used. In human immunologic research, a screening procedure known as the SENIEUR protocol has been developed.[7] This protocol combines a clinical examination, medical and lifestyle history, diagnostic blood analyses, and urinalysis to identify healthy aged individuals for study inclusion. No such standardized protocols have been adopted in veterinary gerontology. In aged horse studies, important additional factors to consider include endoparasite load and hormone profiles. The high prevalence of PPID in the aged equine population and the immunosuppressive effects of pars intermedia–derived pituitary hormones make it absolutely critical that endocrine status be reported when evaluating immunosenescence in horses and ponies.[8,9] Other important considerations when assessing immune function in aged horses include diet, medications, nutritional supplements, exercise, season, and environmental conditions of the study participants.

■ Clinical Pathology

Hematologic changes associated with aging in horses and ponies include a lower total WBC count due to a lower total lymphocyte count compared with younger counterparts.[10-13] In addition, there is a decrease in total monocyte and eosinophil counts in aged ponies.[11] The implications of these hematologic changes remain unclear.

■ Immunologic Findings

Age-associated alterations in lymphocyte subset populations have been documented in several species, including people, dogs, and rodents, although inconsistencies in outcomes exist among the various studies.[14-17] Aging has been associated with alterations in subsets of circulating lymphocytes (i.e., CD4+, CD8+, and B cells) in horses and ponies.[10-13,18] The consistent decrease in total circulating lymphocyte populations in aged horses results from a decrease in total number of CD4+ and CD8+ T cells and B cells,[10-12] although another study reported an increase in the percentage of CD4+ lymphocyte population.[18] The CD4/CD8 ratio is an indicator of whether lymphocyte populations favor an inflammatory or immunosuppressive reponse. The CD4/CD8 ratio has been reported to increase, decrease, or remain unchanged in geriatric human populations.[19-21] CD4/CD8 ratio has been reported to be increased in aged horses, suggesting a proinflammatory state known as *inflammaging*.[12] A robust decrease in peripheral naive T cells has been a consistent finding in numerous studies in people and rodents.[22-25] Thymic involution is considered a likely major contributor to the failure to maintain a naive T-cell pool. In addition, it has been suggested that the loss of naive T cells may be the result of lifelong infection by viruses, especially cytomegalovirus or other chronic antigenic stimulants that promote a bias toward the frequency of memory cells.[26,27] The effect of age on naive T-cell populations has not been explored in the horse.

Serum cytokine profiles in the aged are typically those of a proinflammatory phenotype.[28,29] Aged horses show similar cytokine profiles with increased gene expression of TNF-α, IL-6, IL-1β, IL-8, IFN-γ, IL-15, and IL-18.[12,18] In addition, there are increased proinflammatory-to–anti-inflammatory cytokine ratios such as IL6/IL10 and TNF-α/IL-10.[25] Serum cytokine concentration of TNF-α was found to be increased in aged horses in one study but not another.[18,30] Obesity also increases the frequency of mononuclear cells

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expressing inflammatory cytokines.[31] Confounding factors that might affect serum TNF-α concentration in these and other studies include concurrent illness, inflammation, or season of sample collection. A chronic, controlled, low-grade inflammation seems to play a role in improving immunity and counterbalancing the inevitable immunosenescence; however, uncontrolled inflammation leads to decreased adaptive immunity, cellular dysfunction, and increased immunosenescence.[2] Indeed, in human medicine, balanced inflammaging seems to play a role in longevity.

One of the most consistent findings in immunosenescence is a decrease in the ability of lymphocytes to proliferate. Studies in rodents and people have shown impaired lymphocyte proliferation possibly involving a decrease in serum IL-2 concentration or IL-2 receptor expression.[23,32,33] However, a decrease in lymphocyte proliferation has also been reported independent of these two factors, suggesting that defects in intracellular signal transduction may also be a consequence of aging.[34] Horses also experience an age-associated decrease in lymphocyte proliferation, which is not responsive to IL-2 supplementation and not associated with a change in lymphocyte IL-2 receptor expression.[11,18,35] This suggests that, similar to what has been observed in people, the age-associated defect in lymphocyte division in horses may be in intracellular signaling. In addition, progressive age-associated telomere shortening in equine peripheral blood mononuclear cells has been associated with decreased proliferation potential.[36]

Several studies have assessed the ability of peripheral blood mononuclear cells (PBMCs) to respond to immune stimulation. Inflammatory response after stimulation of whole blood or PBMCs from healthy aged people results in a greater release of proinflammatory cytokines than that observed in nonaged adults, a condition known as “trained innate immunity.”[2,37-39] Similar studies in aged horses have revealed an increase in TNF-α and IFN-γ production from PBMCs following stimulation.[23,37]

Although immunosenescence affects primarily adaptive immunity, changes in innate immunity occur as well. Innate immunity includes the response of neutrophils and macrophages as a first-line defense against pathogens. Age-associated changes in neutrophil function that have been reported in people and rodents include decreases in phagocytosis, oxidative burst, chemokinesis, and chemotaxis, whereas neutrophil numbers appear to be maintained.[40-43] In healthy aged horses, neutrophil adhesion, oxidative burst, and phagocytosis were all

found to be unchanged, whereas chemotaxis was increased compared with that observed in healthy adult horses.[44]

One of the major health concerns regarding immunosenescence in people is a failure of the geriatric population to develop an adequate protective titer following vaccination, particularly after influenza virus immunization.[45] As a result, morbidity and mortality due to influenza infection is greatest in the very old. The response of aged horses to influenza vaccines has also been reported to be less robust than that of young or adult horses in several studies.[11,46] Muirhead and colleagues[46] reported a decrease in Ig subisotypes IgG1 (formerly IgG_a) and $IgG_{4/7}$ (formerly IgG_b) in aged horses, although single radial hemolysis titers suggested that both adults and aged horses had adequate response that was protective. Using a different vaccine, Horohov and colleagues[11] reported a tenfold decrease in resultant titers in aged ponies compared with nonaged adults, but it is not clear if adequate titers were achieved in either group. Another study using canarypox recombinant virus vector expressing the hemagglutinin antigen of influenza in older horses slightly enhanced antibody responses but did not affect cell-mediated immune responses.[47]

Response to naive antigenic challenge has also been examined in horses older than 20 years of age. Contrary to what has been reported in primates, the magnitude of a primary antibody response did not decline with age.[46,48-50] When a rabies vaccine was administered to aged horses naive to rabies vaccine, the antibody titer after both the initial and the second immunization did not differ from that of nonaged adult horses. Nutritional factors may affect immune responses, and vitamin E supplementation of older horses enhanced humoral response to vaccination and improved phagocytic bacterial killing.[51] Further studies are necessary to clarify the ability of aged horses to respond to naive and anamnestic vaccinations, including to different types of vaccines, and to assist in the development of ideal vaccination protocols for geriatric horses.

Finally, given the importance of the gut microbiota in the function of the immune system, dysbiosis or microbiota remodeling with age may somehow affect immunosenescence and inflammaging, and the balance between proinflammatory and anti-inflammatory mediators.

Drug-Induced Immunosuppression

M. Julia B. Felippe

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Immunosuppressive therapy is required when an immune response causes excessive damage to tissues or autoimmunity develops. On the basis of their primary mechanism of action, immunosuppressants may be classified as inhibitors of gene expression or transcription (e.g., glucocorticoids); inhibitors of nucleotide synthesis (e.g., azathioprine); inhibitors of calcineurin phosphatase (e.g., cyclosporine, tacrolimus, rapamycin) and kinase (e.g., leflunomide); alkylating agents (e.g., cyclophosphamide, chlorambucil); and monoclonal antibodies (e.g., against T-cell receptor IL-2R).[1-4] In the horse, only a few of these drugs have been studied and are used clinically.

Autoimmunity results from the production of self-reactive antibodies and/or T lymphocytes. The potential mechanisms involved include lack of central negative selection of autoreactive cells; molecular mimicry of microbes and self-epitopes; or the development of new epitopes on self-proteins secondary to tissue injury caused by viruses, bacterial exotoxins, chemicals, or tumors.

The type of mechanism involved in autoimmunity (e.g., antibody-mediated and/or cellular-mediated) may require immunosuppressive therapy with corresponding cellular metabolism targets. In addition, the combination of drugs may increase the success and decrease the necessary course of immunosuppressive therapy; nevertheless, this approach has been empirical in large animals and still lacks scientific evidence. Although the goal for immunosuppressive therapy is to decrease tissue damage caused by exacerbated immune response, systemic susceptibility to infections, particularly to fungal and viral organisms, is a risk in patients under therapy.[5,6]

Glucocorticoids are potent immunosuppressant drugs.[7] The lipophilic glucocorticoids pass freely through cell membranes and bind to a cytosolic glucocorticoid receptor (GR).[8,9] This interaction allows the GR transcription factor to translocate into the nucleus; bind to glucocorticoid-responsive elements; and regulate gene transcription that promotes or represses synthesis of cytokines, chemokines, inflammatory enzymes, and adhesion molecules. Frequently used glucocorticoids in horses include hydrocortisone, dexamethasone, prednisolone, methylprednisolone, isoflupredone, triamcinolone, beclomethasone, fluticasone, and budesonide. Oral prednisolone has better bioavailability than prednisone in the horse.[10] In general, therapeutic doses are high and frequent in the initial phase of treatment, and dosage is subsequently tailored to the clinical condition. Glucocorticoids in horses have been used for the treatment of a broad range of diseases that directly involve the

immune system, including atopy or skin hypersensitivity reactions, contact dermatitis, immune-mediated hemolytic anemia, immune-mediated thrombocytopenia, immune-mediated myositis, uveitis, purpura hemorrhagica, vasculopathy, pemphigus foliaceus, inflammatory airway disease, recurrent airway obstruction, and lymphomas or lymphosarcomas, many times with limited efficacy.[11-24]

Glucocorticoids cause immunosuppression mainly by sequestration of CD4+ T lymphocytes in the mononuclear phagocyte system and by inhibition of the transcription of cytokines.[3] A single IV dose (any of 0.05, 0.1, or 0.2 mg/kg body weight) of dexamethasone has shown to induce neutrophilia and lymphopenia, a decrease in the peripheral blood CD4+ T-cell population with a concomitant increase in the CD8+ T cells, and a consequent decrease of CD4/CD8 ratio; these effects are observed at 4 and 12 hours after the drug administration and gradually decrease over time in the first 48 hours.[25] Chronic treatment with glucocorticoids may lead to susceptibility to infection, hyperglycemia, hypokalemia (particularly isoflupredone), GI ulceration, delayed wound healing, osteoporosis, growth suppression, myopathy, and hypertension.[3,22] Parenteral, oral, and aerosolized corticoids reversibly suppress adrenocortical function, while the response to ACTH stimulation remains intact.[22,26]

Aerosolized glucocorticoids have been used for the prevention and treatment of recurrent airway obstruction and inflammatory airway disease in the horse, and they were shown to decrease airway hypersensitivity, neutrophilic pulmonary inflammation, and the expression of IL-1β and IL-8 in isolated alveolar macrophages.[18,19,22,23,27,28]

Aerosolized fluticasone proprionate may be detected in plasma for a minimum of 72 hours post administration.[29] The treatment of heaves-affected horses with inhaled fluticasone at therapeutic dosages for 11 months had no significant or detectable effect on innate and adaptive (both humoral and cell-mediated) immune function assays, including response to vaccinations.[30]

Inhaled budesonide may be detected in the plasma of horses with recurrent airway obstruction at higher concentrations and at longer time points (beyond 96 hours) after administration in comparison with healthy horses.[31]

Azathioprine inhibits the de novo pathway of purine synthesis, which is essential for DNA and RNA production and consequently lymphocyte activation and proliferation. Azathioprine has been used in horse patients for the treatment

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of immune-mediated anemia, immune-mediated thrombocytopenia, vasculopathy, and pemphigus foliaceus.[32] The use of azathioprine allows reduction in the glucocorticoid dose when the two are combined in therapy. Because proliferation of many cell types can also be inhibited, adverse effects associated with azathioprine treatment include leukopenia, alopecia, and hepatotoxicity. A single IV dose (1.5 mg/kg) of azathioprine resulted in a rapid decrease in plasma drug concentration with a half-life of 1.8 minutes.[33] Oral bioavailability at 3 mg/kg was low and varied from 1% to 7%. When given daily for 30 days, and subsequently every other day for another 30 days, that oral dose did not cause clinical adverse effects or abnormal hemogram, leukogram, and serum biochemical analysis in most horses. Lymphopenia and immunosuppression were observed in one horse during the experiment.

Cyclosporine is a cyclic polypeptide that binds to the cytoplasmic receptor cyclophilin and subsequently to the catalytic domain of the cytoplasmic phosphatase calcineurin.[34] This binding inhibits dephosphorylation of transcription factors, most importantly the nuclear factor of activated T lymphocyte (NFAT), which prevents their translocation to the nucleus. Therefore the production of key elements of T-cell activation and proliferation (IL-2, IL-4, CD40L, TNF-α, IFN-γ, *c-myc*) is suppressed. Cyclosporine has been used in the horse for intravitreal treatment of recurrent uveitis and immune-mediated keratitis.[35] Potential adverse effects of cyclosporine include vasoconstriction, hypertension, nephrotoxicity, hepatotoxicity, and potential susceptibility to infectious organisms that require cell-mediated protection.

Rapamycin and tacrolimus are macrolide antibiotics that bind to the cytoplasmic FK binding protein (FKBP), and the resultant protein complex inhibits calcineurin. The effect includes cell-cycle arrest and decrease in the expression of inflammatory cytokines. Rapamycin ocular toxicity and distribution have been studied for potential clinical use in the horse.[36]

Cyclophosphamide (phosphoramide and acrolein) and chlorambucil (phenylacetic acid mustard) metabolizes alkylate DNA bases, resulting in mutagenic, cytotoxic, antiproliferative, and chemotherapeutic effects. Cyclophosphamide affects B cells and has been used in the treatment of autoantibody-mediated diseases. In horses, these drugs have been used for the treatment of lymphosarcoma.[37] Adverse effects associated with cyclophosphamide and chlorambucil therapies include anemia, leukopenia, alopecia, and secondary malignancies.

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Vincristine is a vinca alkaloid that binds to tubulin in the mitotic spindle and prevents purine synthesis. Consequently it inhibits cell proliferation, resulting in antitumor and immunosuppressive effects. In horses, vincristine has been used for the treatment of immune-mediated thrombocytopenia, pemphigus foliaceus, and lymphosarcoma.[38] Mild neurologic adverse effects (proprioceptive deficits) and ileus may occur in the horse.

The development of species-specific monoclonal antibodies and the identification of appropriate antigenic targets have contributed to the advance of their use in medicine.[39] The great advantage of monoclonal antibodies is the specificity of response, which may minimize adverse effects. Examples of use include treatment of inflammation (targeting inflammatory cytokines) and cancer.[40]

Immunosuppression Associated With Immune-Mediated Disorders*

M. Julia B. Felippe • Debra C. Sellon

Immune-mediated disorders often cause tissue or cellular damage. One of the outcomes is the potential for immunosuppression and increased risk of secondary infection through a variety of mechanisms, including loss of epithelial barriers, loss of critical immune cellular elements, hormonal imbalances, and dysregulation of immune responses. Autoimmune disorders comprise a subset of immune-mediated conditions, and self-molecules become a target in the context of an immune response. The etiology of most autoimmune diseases is uncertain but appears to be related to exposure to an antigen (e.g., infectious organism, tumoral proteins, drugs) and/or an environmental trigger (e.g., chemicals) in an individual animal or human that is genetically susceptible.

Aplastic anemia and myelodysplastic syndrome, both associated with autoimmune syndromes in humans, have been reported rarely in the horse.[1,2,3] Severe panleukopenia is seen peripherally, whereas significant bone marrow hypocellularity and myeloid maturation arrest are seen in aplastic anemia and myelodysplastic syndrome, respectively. Profound immunosuppression would be expected to occur with such pathology because immune cells involved in all aspects of innate and adaptive immunity are affected.

Autoimmune neutropenia may occur from hypersensitivity mediated by autoantibodies (or isoantibodies) that destroy circulating neutrophils or

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neutrophil precursors in the bone marrow. These antibodies may be produced as a primary autoimmune disorder secondary to drug administration, infectious disease, or neoplasia. Adult immune-mediated neutropenia has been reported in the dog, generally occurring concurrently with immune-mediated thrombocytopenia and/or immune-mediated hemolytic anemia, but no similar reports have been described in the horse.[4] Destruction of neutrophils has also been reported in alloimmune neonatal neutropenia with the absorption from colostrum of alloantibodies (produced by the dam). These alloantibodies, once in the foal's circulation, promote opsonization of neonatal neutrophils and enhanced clearance from circulation. The impaired immunity associated with profound neutropenia places these foals at significant risk for sepsis and other serious infections and must be identified early to allow successful intervention. Administration of exogenous granulocyte colony-stimulating factor (G-CSF) is usually necessary because affected foals often do not produce adequate levels of endogenous G-CSF.[5] Alloimmune neonatal neutropenia causes moderate to severe neutropenia in neonatal foals and has been reported in conjunction with alloimmune neonatal isoerythrolysis, ulcerative dermatitis, and thrombocytopenia.[5-7]

Reported occasionally in horses, immune-mediated thrombocytopenia has the potential to negatively affect immune responses.[8,9] Platelets can play both indirect and direct roles in protecting an animal from infection. They promote antiviral cytotoxic T lymphocyte–mediated responses and contain important antibacterial proteins that when released promote rapid microbial killing.[10] Diminished levels of platelet-derived cytokines may affect Th polarization and have a negative impact on bone marrow function.[11] Importantly, RBCs from thrombocytopenic mice have demonstrated an increased susceptibility to hemoparasite infection, indicating that thrombocytopenia can have an important in vivo effect on immunocompetency.[10]

Autoimmune skin disorders causing lesions that impair the skin barrier can predispose affected areas to secondary infection.[12] This is primarily a concern with the large bullae and ulceration occurring in pemphigus vulgaris or bullous pemphigoid, but the risk exists for any skin disease that breaches this important physical barrier to infection. Pemphigus foliaceus, paraneoplastic pemphigus, cutaneous (discoid) lupus erythematosus, and systemic lupus erythematosus (SLE) can all cause lesions that may predispose to secondary infection. This risk may be amplified if the lesions are painful or pruritic, leading to excoriation or

self-mutilation. Hence *Culicoides* hypersensitivity, urticaria, and vasculitis are autoimmune conditions of the skin that can also predispose to secondary infections.

In cutaneous vasculitis, most commonly seen in the horse as purpura hemorrhagica, Ag-Ab complexes are deposited in the walls of small blood vessels, and the resultant inflammation is manifested as severe edema, tissue necrosis, and ulceration. Penetration of the skin barrier under this condition may result in a secondary bacterial infection, particularly cellulitis and pneumonia. Therefore prophylactic antimicrobial therapy is often warranted in the treatment of purpura hemorrhagica.[13]

Systemic lupus erythematosus, rarely reported in horses,[14] may impair cutaneous defense to infection and compromise the adaptive immune system. In humans, SLE causes dysregulation of apoptosis that leads to premature death of PBMCs, resulting in leukopenia, particularly lymphopenia.[15] The functionality of T cells in patients with SLE is impaired, with decreased IL-2 secretion and other factors leading to weakened antiviral immunity.[15]

Most reports of diabetes mellitus (DM) in the horse have described type 2 (noninsulin-dependent) DM secondary to PPID or equine metabolic syndrome. However, type 1 DM resulting from autoimmune destruction of pancreatic beta cells and subsequent decreased insulin production has been reported.[16] In humans, DM is associated with an increased risk of lower respiratory infections, urinary tract infections, and infections of the skin or mucous membranes.[17] Abnormal function has been documented in neutrophils, monocytes, and lymphocytes, including decreased adherence, chemotaxis, and intracellular killing, as well as impaired phagocytosis and diminished lymphocyte proliferative response.[18] These negative effects have largely been attributed to the impact of poor glycemic control, and it is therefore likely that similar effects could occur with equine DM.

Immunosuppression Associated With Leukoproliferative Disorders*

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Neoplastic disease can impair cell-mediated and humoral immune responses as a result of an abnormal bone marrow environment, altered patterns of cytokine production or release, or impaired proliferative responses (anergy). In

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horses, immunodeficiency has most often been described in association with lymphosarcoma or plasma cell myeloma.

Lymphosarcoma

Immunodeficiency has been identified in some horses with equine lymphosarcoma. The immunologic abnormality most often described is a decrease in the concentrations of serum immunoglobulins, especially IgM.[1-5] Recurrent or persistent infections may occur and complicate recognition of the underlying neoplastic disorder. Neoplastic cells were suggested to be T-suppressor cells in one horse, indicating a possible mechanism for the IgM deficiency.[1] Diminished lymphocyte blastogenesis responses indicative of impaired T-cell function have been described in two horses with lymphosarcoma, one of which had concurrent IgM deficiency.[5] Some horses with lymphosarcoma have been diagnosed with concurrent bacterial infections, which may be related to immunosuppression.[4,5] Lymphosarcoma has been associated with bone marrow necrosis in people and horses, leading to pancytopenia and sepsis, presumably due to profound neutropenia.[6] Similarly, myelophthisis secondary to tumor cell infiltration of bone marrow may lead to pancytopenia and immunosuppression in horses.[7,8]

Plasma Cell Myeloma

Plasma cell myeloma has been reported in horses of several breeds.[9] Although reports of the condition are limited, there appears to be no gender predilection. Horses have ranged in age from 3 months to 22 years (median is 11 years) at diagnosis. Common clinical signs include weight loss, anorexia, fever, pneumonia, and limb edema. Both equine and human patients with plasma cell myelomas have an increased susceptibility to bacterial infections, probably as a result of a secondary immunodeficiency.[9-11] Immune suppression in human patients with myeloma is well documented and can lead to severe infection.[12] Mechanisms include abnormal Ig production, abnormal cytokine production, and dysfunctional NK cell and DC populations.[12] As a malignancy of plasma cells or lymphocytoid plasma cells, plasma cell myelomas typically produce large quantities of a homogeneous immunoglobulin or immunoglobulin fragment, resulting in a monoclonal gammopathy. In both equine and human cases of myeloma, the predominant serum globulins are generally subclasses of IgG.[9,10]

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Hyperglobulinemia is a characteristic but not invariable finding. Monoclonal gammopathies in the horse have also been reported with lymphoma and benign disorders.[13,14] The concentrations of normal polyclonal immunoglobulins are generally decreased in myeloma patients as a result of several mechanisms, including decreased synthesis and accelerated catabolism of antibody and suppressed clonal expansion of B cells.[9-11] Similar to plasma cell myeloma, certain types of B-cell lymphoma and/or leukemia can produce monoclonal gammopathies and decreased relative numbers of normal B cells and polyclonal immunoglubulins.[15] Decreased numbers and dysfunction of neutrophils and defective complement activation may also contribute to the impaired immune function.

Other Leukoproliferative Disorders

A wide variety of other leukoproliferative disorders have been described in horses, including acute and chronic granulocytic leukemia,[16-18] myeloblastic leukemia,[19] myelomonocytic leukemia,[20,21] monocytic leukemia,[22] eosinophilic myeloproliferative disorder,[23] and malignant histiocytosis.[24] Regardless of the primary cell line of origin, the end result is often myelophthisis and pancytopenia with the potential for significant immunosuppression. A horse with myelomonocytic leukemia was diagnosed with pulmonary aspergillosis.[25]

Immunosuppression Associated With Infectious Agents or Processes

M. Julia B. Felippe • Debra C. Sellon

The interrelationship between infectious agents and the host immune system is complicated. Infection, regardless of etiology, initiates a cascade of complex reactions intended to assist the host in control and elimination of the infectious agent. When the immune system is compromised, infectious agents have an increased opportunity to become established and cause significant disease in the host. This may happen because external factors suppress immune function in the host before encountering a pathogen or because the pathogen suppresses immune responses in the host.

Common Infections in the Immunocompromised Host

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Immunocompromised horses are incapable of developing a normal immune response, usually as a result of an immunodeficiency disorder, immunosuppressive therapy or endocrine dysregulation, underlying disease, or malnutrition. When an equine host has impaired immune responses for any reason, infectious agents have an increased opportunity to establish persistent infection or cause significant harm to the host. For many immunocompromised horses, the result is persistent or unusually severe disease secondary to infection with common equine pathogens. In some situations, however, the immune capabilities of the horse are so impaired as to enable normally nonpathogenic infectious agents to cause disease. Identification of such pathogens or patterns of infection in an equine patient should lead the clinician to suspect underlying immunodeficiency.

Undoubtedly, primary immunodeficiency disorders (including SCID, agammaglobulinemia, FIS, and CVID), described in detail earlier in this chapter, represent the principal cause of immunocompromise in horses.[1-8] The most commonly described pathogens in horses with severe primary immunodeficiency include adenoviruses, *Cryptosporidium parvum*, *Candida* spp., *P. jirovecii* (formerly *P. carinii*), and *R. equi* (in adult horses). These are generally considered to be pathogens of the respiratory and GI tracts, and most affected horses present with persistent or severe clinical signs associated with these body systems. Horses with less severe primary or secondary immune deficiency (e.g., selective IgM deficiency) may present with recurrent respiratory tract infections associated with a variety of bacterial pathogens.[4] The most common secondary immunodeficiency disorder of horses is FPT of immunity.[9] Affected foals commonly develop bacterial septicemia with or without localized bacterial infections.

Some foals with FPT or other forms of immunosuppression develop localized or systemic candidiasis.[10,11] This disorder appears to be most common in foals with FPT that have been treated with broad-spectrum antimicrobials for treatment of bacterial septicemia. This syndrome has some similarities to mucocutaneous candidiasis in people, which has been associated with several different subtle T-cell defects. Oral lesions range from discrete, focal, white, plaquelike lesions on the margins of the tongue to a generalized, thick, white, pseudomembranous coating covering the tongue and gingival mucosa. Most foals exhibit bruxism, ptyalism, fever, and depression. Other significant clinical problems include pneumonia, septic arthritis, and diarrhea. This syndrome should be distinguished from the glossitis caused by *Candida* infection seen in

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inappetent or debilitated neonatal foals, which is fairly common and generally resolves with amelioration of the primary disease.[12] Regardless of cause or underlying nature of the immunodeficiency, the prognosis for foals with oral candidiasis and associated bacterial septicemia is guarded to poor.

Immunosuppression may also occur secondary to corticosteroid administration, which is discussed in detail earlier in this chapter. Corticosteroid therapy results in lymphopenia, suppression of macrophage phagocytic function, impaired killing of ingested organisms, impaired secretion of monokines, and inhibited antigen processing and presentation.[13,14] Cell-mediated immunity is impaired through T-cell lymphopenia, altered cytokine production, and decreased antigen presentation, and it is reflected in the suppression of mitogen stimulation responses. Humoral immunity is impaired indirectly through altered T-cell responses, enhanced Ig catabolism, and decreased antigen presentation.[13] Horses receiving high or prolonged therapy with corticosteroids have been reported to experience exacerbations of preexisting infections or decreased resistance to newly encountered pathogens.[15,16] This may manifest as bacterial pneumonia or pleuropneumonia, candidiasis and other fungal infections, equine protozoal myeloencephalitis, or a variety of other infectious disorders.[11,16]

Infections That Cause Immune Suppression

Some infectious agents have developed strategies to elude immune defenses in hosts with otherwise normal, functioning immune systems. These strategies may downregulate immune responses to the extent that the host becomes vulnerable to secondary infection. Many viral, fungal, and bacterial infections transiently suppress specific and nonspecific immune responses, predisposing animals to secondary bacterial infections.[17] Severe endotoxemia or septicemia may suppress neutrophil numbers and bactericidal function, predisposing to secondary infection.

Equine Influenza.

Although little work has been done to specifically examine the effects of equine influenza viruses on the equine immune system, it is widely acknowledged that this viral infection predisposes horses to secondary bacterial infection.[18,19] Proposed mechanisms for increased susceptibility to bacterial infection after influenza infection include disruption of the barrier function of respiratory epithelium, exposing bacterial adhesion molecules; desensitization of alveolar

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macrophages to bacterial Toll-like receptor ligands; and alteration of immune functions in the alveolar microenvironment.[20,21]

Perinatal Equine Herpesvirus Type 1 Infection.

Infection of the fetus with equine herpesvirus type 1 (EHV-1, rhinopneumonitis) late in gestation has been associated with death or postnatal development of interstitial pneumonia, lymphopenia, marked necrosis and atrophy of the thymus and splenic lymphoid tissue, and increased susceptibility to bacterial infections.[22] Despite apparently adequate passive transfer of maternal antibody, affected foals contract a variety of infectious bacterial diseases, including colibacillosis, streptococcal septicemia, salmonellosis, and Tyzzer's disease. EHV-1 is isolated from nasal passages in about 30% of the cases. The spleen and thymus are grossly small at necropsy. Bilateral adrenocortical hyperplasia is noted in most foals. Histologically, splenic periarteriolar lymphocytic sheaths are depleted of lymphocytes, and no lymphoid follicles are detectable. Thymic alterations vary from extreme diminutions of thymocyte numbers to complete necrosis of thymic lymphocytes with disappearance of Hassall's corpuscles and disruption of the epithelial matrix. Lymph nodes also show lymphoid necrosis. An immunodeficiency secondary to the marked lymphoid damage induced by the virus is credited with allowing secondary bacterial infections to become established. Immunization of broodmares against EHV-1 would seem to be the most appropriate approach to prevention.

Equine Herpesvirus Type 5 Infection.

Equine herpesvirus type 5 (EHV-5) is an emerging pathogen linked to equine multinodular pulmonary fibrosis (EMPF).[23-26] This gammaherpesvirus has been found in bone marrow of infected horses, contributing to speculation that the virus may be immunosuppressive.[25,26] Many affected horses are lymphopenic for undetermined reasons, most are anemic and thrombocytopenic, and at least one affected horse was profoundly pancytopenic, leading to speculation that immune-mediated or direct viral destruction of mature cells and/or hematopoietic precursors in the bone marrow may play a role in diminished cell counts in peripheral blood.[23-25] Transient improvement in cell counts after initiation of corticosteroid therapy supports the possibility of immune-mediated mechanisms for destruction of hematopoietic cells.[25] One case of EMPF presented with primary lymphocytic leukemia, generalized lymphadenopathy,

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and infiltration of neoplastic lymphocytes in bone marrow, lymph nodes, and spleen.[26] Infiltrating cells were almost exclusively T lymphocytes, whereas B lymphocytes could not be detected. Depletion of B-cell lines was accompanied by hypogammaglobulinemia.[26] EHV-5 infection was demonstrated in lung, bone marrow, and lymph nodes.[26] A link between the T-cell leukemia and infection by EHV-5 was suggested.

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Diseases Caused by Allogeneic Incompatibilities (Horses and Ruminants)

M. Julia B. Felippe • Jill R. Johnson

The surfaces of cells are covered with molecular structures, the presence or absence of which is determined by genes and cell function. Some of these molecules have limited heterogeneity within a species, and all members of the species share identical forms (monomorphic). In other cases, a spectrum of minor structural variations or polymorphisms of a particular molecule occur within the population; therefore some members of the species will have one form of the molecule, whereas others will have another. If the structural variations are such that the immune system of one individual can recognize the differences in the molecules from another individual, these are known as alloantigens. Antibodies produced against these antigens are alloantibodies. Examples of alloantigens include certain molecules of RBCs, platelets, and WBCs.

In nature, because there are few situations in which tissues are exchanged, there are relatively few naturally occurring diseases that involve allogeneic incompatibilities. Neonatal isoerythrolysis (NI), neonatal alloimmune thrombocytopenia (NAIT), and alloimmune neonatal neutropenia (ANN) are three examples of such naturally occurring diseases. Blood transfusion reactions and organ transplant rejection are examples of iatrogenic diseases associated with allogeneic incompatibilities.

The same alloantibodies that mediate disease are also useful in vitro as reagents for the detection of the presence of alloantigens and serve as the basis for blood typing, for instance.

Blood Typing and DNA Profiling

The blood type of an individual is the actual composite of genetic codes determined by codominant alleles (i.e., the pair of one maternal and one paternal alleles). Several kinds of genetic markers have been used in blood typing, including RBC alloantigens, major histocompatibility complex molecules, and electrophoretic markers. Polymorphisms of the DNA have emerged as useful genetic markers and essentially replaced other genetic tests for parentage

verification.

Red Blood Cell Antigens

The blood group genes produce surface molecules that contain antigenic sites known as *factors*. More than 30 different factors have been identified. Each factor is associated with only one system, although the same factor may be associated with more than one allele within the system. The factors are named with an uppercase letter to denote the system and a lowercase letter to designate the factor within that system. Groups of factors that are produced by a single allele are called *phenogroups*.

The presence of RBC antigens is detected primarily by either agglutination or complement-mediated lysis of test cells using antibodies directed against *specific* RBC alloantigens. In some systems, antigens are detected with antiglobulin tests.

Seven independent RBC groups or systems have been internationally defined in horses under the auspices of the International Society for Animal Genetics[1-4] (Tables 53.8 and 53.9). These systems are named A, C, D, K, P, Q, and U. Additional systems are recognized by individual laboratories. Each system corresponds to a particular gene for which two or more alleles exist. Some blood groups are relatively simple and contain only two alleles, whereas other systems may have more than two dozen different alleles.

TABLE 53.8

Domestic Animal Blood Groups

Species	Blood Group Systems
Equine	A, C, D, K, P, Q, U
Bovine	A, B, C, F, J,[a] L, M, R′, S, T, Z
Ovine	A, B, C, D, M, R,[a] X
Caprine	A, B, C, M, J[a]

[a]Soluble antigens.

From Suzuki Y: Personal communication, Stormont Laboratories, Inc., Woodland, Calif., 1990.

TABLE 53.9

Blood Group Systems, Factors, and Alleles of the Horse Recognized by the International Society for Animal Genetics

System	Factors	Recognized Alleles

A	a,[a] b,[b] c, d, e, f, g	Aa, Aadf, Aadg, Aabdf, Aabdg, Ab, Abc, Abce, Abe, Ac, Ace, Ae, A−
C	a	Ca, C−
D	a, b,[b] c,[b] d, e, f, g,[b] h, i, k, l, m, n, o, p, q, r	Dadl, Dadlnr, Dadlr, Dbcmq, Dcefgmq, Dcegimnq, Dcfgkm, Dcfmqr, Dcgm, Dcdmp, Dcgmq, Dcgmqr, Ddeklqr, DeIno, Ddeloq, Ddelq, Ddfkir, Ddghmp, Ddghmq, Ddghmqr, Ddki, Ddlnq, Ddlnqr, Ddlqr, Ddno, Dq,(D−)
K	a	Ka, K−
P	a,[b] b, c, d	Pa, Pac Pacd, Pad, Pb, Pbd, Pd, P−
Q	a,[a] b, c[b]	Qa, Qab, Qabc, Qac, Qb, Qbc, Qc, Q−
U	a[b]	Ua, U−

[a]Most common factors involved in neonatal isoerythrolysis (NI).

[b]Previously reported to cause NI in at least one case.

From Cothran G: Personal communication, University of Kentucky, Lexington, Ky., 1996.

Eleven blood groups have been identified in cattle[5] (Tables 53.8 and 53.10). In cattle, groups B and J have the greatest clinical relevance. The B group is a complex system with more than 60 different antigens.[6] This complexity has been used to advantage for individual animal identification and parentage studies in the past, but it makes it difficult to closely match donor and recipient blood for transfusions. The J antigen, a lipid found in body fluid, is adsorbed to erythrocytes; thus it is not a true erythrocyte antigen. Newborn calves do not have this antigen but usually acquire it during the first 6 months of life. After acquiring it, some groups of cattle have high amounts of J antigen both in the serum and adsorbed to erythrocytes, whereas other groups have small amounts found only on erythrocytes. These latter groups, often referred to as *J negative*, actually may have anti-J antibodies and develop transfusion reactions when transfused with blood from J-positive donors.[1]

TABLE 53.10

Blood Group Factors of Cattle Recognized by the International Society for Animal Genetics

System	Factors
AA[a]	A1, A2, H, Z, a
F[a]	F, V
J	J, j
L	L, l
M	M, m
Z	Z, z
R″	R′, S′
B[b]	B, G1, G2, G3, l1, l2, K, O1, O3, OX, Pl, P2, Q, T, Y2, A′, B′, D′, E1′, E2′, E3′, G′, I1′ (I′), I2′, Jl′, J2′, K′, O′, P1′, P2′, Q′, Y′, A″, B″, G″, I″

C	C1, C2, R1, R2, W, X, X2, L′, E1, C′, C″, X′, Fl, F6, F10, Fl5
S	S1, S2, U, H′, U′, S″, U″
T	

[a]Cases of neonatal isoerythrolysis associated with production of anti–red blood cell antibodies against factors in response to anaplasmosis and *Babesia* vaccines.

[b]Additional factors are recognized by individual laboratories.

Seven blood groups have been identified in sheep (see Table 53.8). The B system is analogous to the B system in cattle and is extremely polymorphic, with more than 52 different alleles. The R system is similar to the J system in cattle in that the antigens are soluble and are passively adsorbed to erythrocytes.[5] The M-L system is involved in the genetically determined RBC potassium polymorphism found in sheep.[7]

Blood groups of goats appear to be similar to those of sheep, and many of the reagents used for typing sheep blood have been used to type goats' blood. Reagents used to detect antigens of the J system of cattle have been used to detect differences in a similar system in goats.[8]

The biological function of RBC antigens is not known for any system in any species with the exception of the M-L blood group system in sheep, which is involved in active potassium transport across RBC membranes.

Electrophoretic Markers

Many plasma and intracellular proteins have polymorphic forms. These variants have subtle biochemical differences, which for the most part do not alter the major characteristics of the molecules but can be detected using electrophoretic methods. These are not technically alloantigens because the differences are not detected immunologically. The various forms of the molecules are detected based on their different rates of migration in electrophoresis. The specific forms of any particular protein that an individual possesses are determined genetically, and those used in blood typing are usually expressed codominantly. Currently, no diseases are clearly associated with the presence or absence of particular alleles of polymorphic proteins; however, they are useful genetic markers for identification and parentage studies commonly included in the blood type (Table 53.11).[3,8-10] Electrophoretic markers were used extensively in horses because RBC antigens did not provide the same degree of discrimination among individuals in this species as they do, for example, in cattle. The current application is limited to legacy parentage verification when parental DNA is not

available for testing.

TABLE 53.11

Examples of Polymorphic Proteins Used in Blood Typing

Protein	System	Source
Alpha1 B glycoprotein	AlB	Serum
Albumin	ALB	Serum
Transferrin	TF	Serum
Carboxylesterase	ES	Serum
Vitamin D–binding protein	GC	Serum
Protease inhibitor	PI	Serum
Peptidase A	PEPA	Serum
Plasminogen	PLG	Serum
Glucose phosphate isomerase	GPI	RBCs
6-Phosphogluconate dehydrogenase	PGD	RBCs
Phosphoglucomutase	PGM	RBCs
Catalase	CAT	RBCs
Carbonic anhydrase	CA	RBCs
Acid phosphatase	AP	RBCs
Hemoglobin A	HBA	RBCs
NADH diaphorase	DIA	RBCs

NADH, Reduced nicotinamide adenine dinucleotide; *RBC,* red blood cell.

Major Histocompatibility Complex

Three systems of equine alloantigens tested using lymphocytes have been described: ELA, ELY-1, and ELY-2.[11-15] ELA is the major histocompatibility complex (MHC) of the horse. ELA is a complex system that includes several genes, each of which is polymorphic (e.g., has many different alleles). Because the MHC regulates the interactions of many cells in the immune response, a potential for the association of disease susceptibility or resistance with ELA exists. An association between a particular ELA allele and equine sarcoid has been described.[16,17] ELY-1 and ELY-2 have limited polymorphism and appear to be two allele systems.

The MHC of cattle is called BoLA, for bovine lymphocyte antigen. In sheep the MHC is called OLA, for ovine lymphocyte antigen, and is also known as SH-LA. In goats the comparable system is GLA.[18]

DNA Polymorphisms

A wide variety of approaches has been developed for detecting genetic variation

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using DNA. Certainly, DNA sequencing is the most sensitive approach, but other approaches have been used to detect DNA variants. Genetic variation of DNA can be detected among individuals based on differences in length for a section of DNA or even for differences in base composition at specific sites. DNA length variants are usually referred to as *minisatellite* or *microsatellite markers.* Minisatellite DNA markers are based on sequences, often 15 to 100 bases long, that may be repeated hundreds of times on a chromosome. The number of repetitions can vary dramatically among individuals and collectively is referred to as *DNA fingerprinting.* Although they are powerful, these tests are costly and time consuming. More recently, another type of DNA length variant has been discovered. Microsatellite DNA markers are short repetitions of nucleotides, usually ranging from 1 to 9 bases long, which may be repeated 15 to 40 times. As with minisatellites, the number of repetitions may vary among chromosomes. More than 100,000 of these markers are thought to exist in each species and to contribute to the development of genetic maps in diverse species. These markers currently form the basis for most parentage analysis.

Variation recognizable as a change in a single base of DNA is more subtle but can be detected through a variety of techniques. Single-nucleotide polymorphisms (SNPs) are variations in single nucleotides at specific positions in the genome, such as coding or noncoding sequences of genes, or between genes (intergenic). These variations may not change (synonymous SNPs) the protein sequence; however, they may change (nonsynonymous SNPs) the protein sequence or alter its expression. SNPs are used to determine haplotypes (linkage of SNPs) in a population, as well as in association studies for individual genetic background and susceptibility to certain diseases, disease severity, and effective treatments.[19,20] Examples described for horses include susceptibility to insect bite hypersensitivity, uveitis, *R. equi* pneumonia, and papillomavirus-induced sarcoids in horses, as well as variations in the immune system.[21-28] Examples described for ruminants include susceptibility to mastitis, ketosis, tuberculosis, paratuberculosis, as well as variations in the immune system.[29-35]

DNA sequence variation is often detectable using restriction enzymes. Restriction enzymes are isolated from bacteria and will cleave DNA when the sequence is specific for the enzyme. For example, the method to detect the gene defect causing hyperkalemic periodic paralysis (HYPP) in horses is based on polymerase chain reaction (PCR) amplification of the gene and then detection of sequence differences that occur between the normal and mutant gene using restriction enzyme digestion of the DNA. Other approaches to identifying DNA

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sequence differences include single-strand conformational polymorphism (SSCP), allele-specific PCR amplification, and ligase chain reaction. DNA-based testing has essentially replaced blood typing for purposes of parentage analysis.

Blood Typing and DNA Genotyping Applications

To determine an animal's blood type or DNA genotype, a battery of different tests is run on the blood or tissue to check for the presence or absence of each recognized allele in each of several genetic systems. Each system is controlled by a separate autosomal gene. These genes are inherited independently of one another.[4,15] Most genetic markers used in blood typing are expressed codominantly, which means that the alleles on both chromosomes are expressed. This often allows determination of genotype (the actual genes present) from the phenotype (the antigens actually detected). Some systems have null alleles with no detectable products that would allow inference of genotype (e.g., C, K, and U blood group systems in horses). An individual can have only two of the possible different alleles for any given gene (one on each chromosome of a pair).

Blood typing based on RBC antigens and electrophoretic markers has been used for animal identification and pedigree analysis, but currently RBC typing is used primarily for prediction of potential for NI and crossmatching for blood transfusion.

The use of genetic markers for parentage verification is based on exclusion (i.e., markers are tested until a discrepancy is found). If no discrepancy is observed after a statistically acceptable amount of testing, the probability of a match is determined.

Because genetic testing is a composite mosaic of a large number of different, largely independent genetic markers, the odds of two individuals sharing exactly the same pattern of markers, whether RBC antigens, electrophoretic markers, or DNA polymorphisms, are remote. Thus once an animal's genetic type is on record, it can be a powerful identifier of an individual animal. In this sense it is an unalterable form of identification that is present from birth to death.

These markers can be used to support or refute parentage claims because the presence or absence of markers is genetically determined and because the markers contributed by both parents are expressed in a codominant fashion (unless “blank” alleles exist). Blood typing and DNA profiling cannot prove that one horse is the parent of another; however, in certain instances it can exclude

with certainty a stated parent as the true parent. Two types of parentage exclusions can occur: type I and type II[36] (Fig. 53.7). With type I, the foal possesses a dominant or codominant marker that is not present in either parent; this result indicates that at least one of the stated parents is incorrect. If one parent (usually the dam) is known with certainty based on circumstances other than genetic type, the error lies with the other stated parent. With type II exclusions, the foal does not possess either of the dominant or codominant markers of a stated parent. Because a foal must inherit one of the two markers expressed by each parent, exclusion can be made if neither of the two markers present on the stated parent is detected in the foal. In parentage cases, each genetic system is evaluated for type I and type II exclusions. A parent can be excluded based on an inconsistency in one system. For this reason, the more systems that are used, the better genetic typing becomes as a tool for solution of parentage disputes. The calculated effectiveness of blood typing for detecting incorrect paternity using 20 internationally defined systems in horses is as high as 96%.[3,9,37] With DNA genotyping, effectiveness is as high as 99.998%.[38-40]

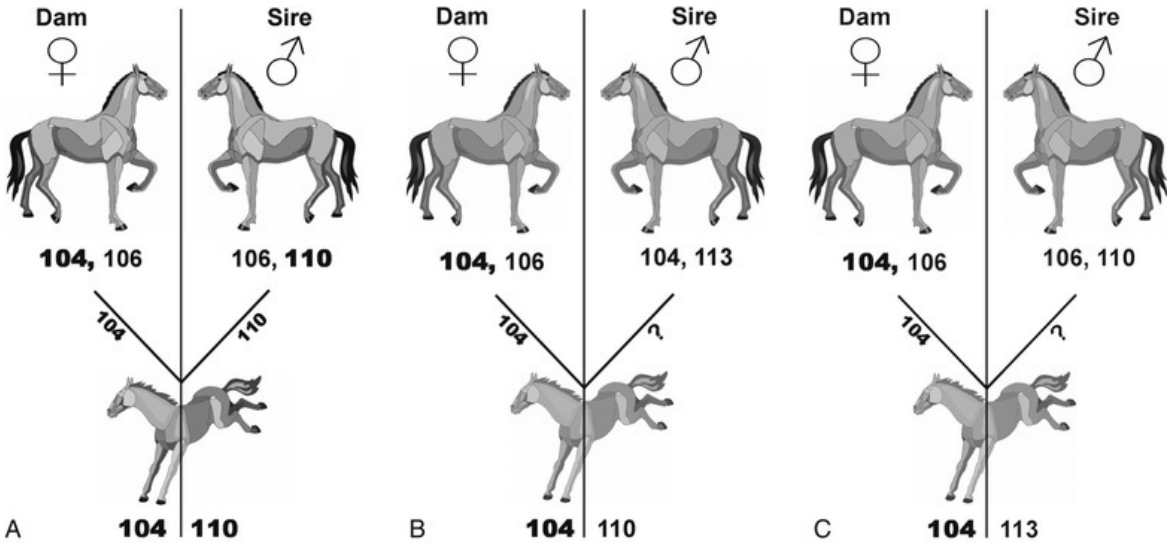


FIG. 53.7 **A,** The sire of this foal cannot be excluded as the sire of the foal based on the results for the DNA marker VHL20. **B,** The sire of this foal is excluded by a type I exclusion. The foal possesses an allele for the DNA marker VHL20 not present on either parent. Assuming that the dam of the foal is known to be correct and therefore would have contributed the 104 allele to the foal, the sire must be incorrectly stated. **C,** The sire of this foal is excluded by both a type I and a type II exclusion. The foal possesses an allele not present on either parent and also does not possess either allele expressed by the putative sire.

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Laboratories that provide DNA genotyping in North America are listed in Box 53.1.

Box 53.1

Laboratories Providing DNA Genotyping Services in North America

Animal Genetic Testing and Research Laboratory
108 Gluck Equine Research Center
University of Kentucky
Lexington, KY 40546
(859) 218-1212
www.ca.uky.edu/gluck/AGTRL.asp
(Horses)
Animal Genetics, Inc.
1336 Timberline Road
Tallahassee, FL 32312-1766
(866) 922-6436
www.horsetesting.com
(Horses)
Maxxam Analytics
Animal DNA Laboratory
335 Laird Road, Unit 2
Guelph, Ontario
N1H 6J3
Canada
(519) 836-2400
http://maxxam.ca/services/dna-testing/animal-dna-testing
(Horses and cattle)
Zoetis Genetics
333 Portage Road, Building 300
Kalamazoo, MI 49007-9970
(269) 833-4744

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www.zoetis.com/products-services/genetics
(Cattle)
Igenity
4665 Innovation Drive, Suite 120
Lincoln, NE 68521
(402) 435-0665
www.igenity.com
(Cattle)
Genetic Visions, Inc.
3220 Deming Way #160
Middleton, WI 33562
(608) 662-9170
www.geneticvisions.net
(Cattle)
Veterinary Genetics Laboratory
University of California, Davis
PO Box 1102
Davis, CA 95617-1102
(530) 752-2211
www.vgl.ucdavis.edu
(Multiple species)
Molecular Cytogenetics and Genomics Laboratory
Department of Veterinary Integrative Biosciences
Texas A&M University
Room 314B, Bldg. 1197 (VRB)
College Station, TX 77843
(979) 862-2879 or (979) 458-0520
http://vetmed.tamu.edu/vibs
http://vetmed.tamu.edu/labs/cytogenics-genomics
(Multiple species)
SRC Genserve Laboratories
125-15 Innovation Blvd.
Saskatoon, Saskatchewan
S7N 2X8
Canada
(306) 933-7700
www.src.sk.ca

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(Multiple species)

Neonatal Isoerythrolysis

■ Equine

Definition and Etiology

Neonatal isoerythrolysis (NI) is a condition characterized by the destruction of RBCs in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[2,41,42]

Production of alloantibodies can be stimulated in mares in several ways, including transfusion, exposure to blood from the foal during parturition, or as a result of placental pathology during gestation. Incompatibilities of at least some blood groups between the dam and foal are the rule rather than the exception, and yet the incidence of sensitization of the dam and occurrence of NI is relatively low. Most blood groups are not strongly antigenic under the conditions of exposure via previous parturition or placental leakage. Several blood group factors, however, are particularly immunogenic, and antibodies against these antigens have been reported to cause nearly all cases of NI. These include factor Aa in the A system and factor Qa in the Q system. In mules, a unique donkey RBC antigen called donkey factor has been associated with NI.[43,44] Antibodies to these antigens develop after the exposure of the mare to RBCs and are not naturally occurring. In humans, the absence of certain RBC antigens results in the production of natural antibodies against that antigen, presumably because of exposure to cross-reacting antigens in the diet. This does not occur in horses, with a few exceptions, and has not been associated with NI. Ca-negative (Ca−) horses frequently make anti-Ca antibody of low titer without known RBC exposure. However, anti-Ca antibody is generally not associated with NI, and mares with anti-Ca antibody appear less likely to develop certain antibodies responsible for NI.

For NI to occur, several things must happen (Figs. 53.8 and 53.9). First, the dam must be negative for the antigen in question. Mares that are Aa−, Qa−, or both are considered at risk because most cases of NI in horses are associated with either anti-Aa or anti-Qa antibodies. All horses appear to lack donkey factor; thus all mule pregnancies are considered at risk. Second, the mare must become sensitized and produce antibody to the offending antigen. Sensitization

can be caused by exposure during a previous pregnancy, blood transfusion, or transplacental contamination with fetal RBCs earlier in the current pregnancy (rare). Third, the foal from the current pregnancy must have inherited from its sire the antigens to which the mare has been sensitized. When these conditions are met, there is a significant potential that maternal antibody directed against the foal's RBC antigens will appear in the colostrum and, if subsequently ingested and absorbed by the foal, could cause loss of RBCs. The higher the anti-RBC titer is at foaling, the higher the risk. The highest titers are likely to be produced in a previously sensitized mare that is reexposed to the same RBC antigens shortly before parturition.

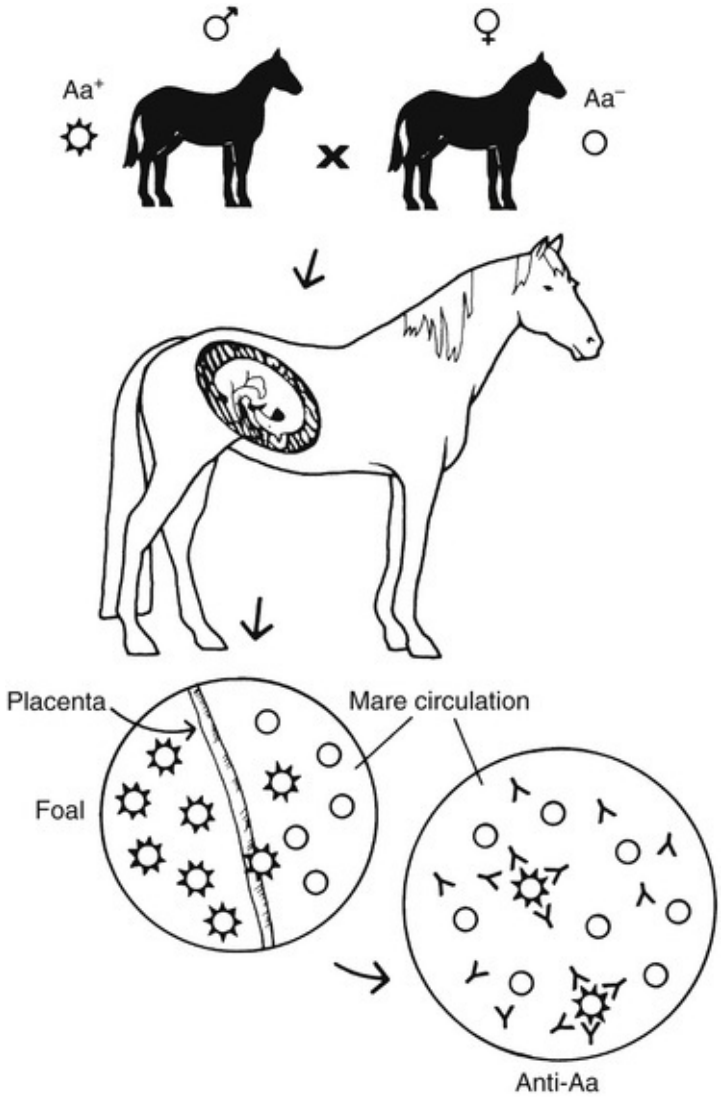


FIG. 53.8 Entrance of red blood cells of paternal antigen type into

maternal circulation stimulates the production of alloantibody and, consequently, the presence of alloantibodies in the mare's serum and in the colostrum.

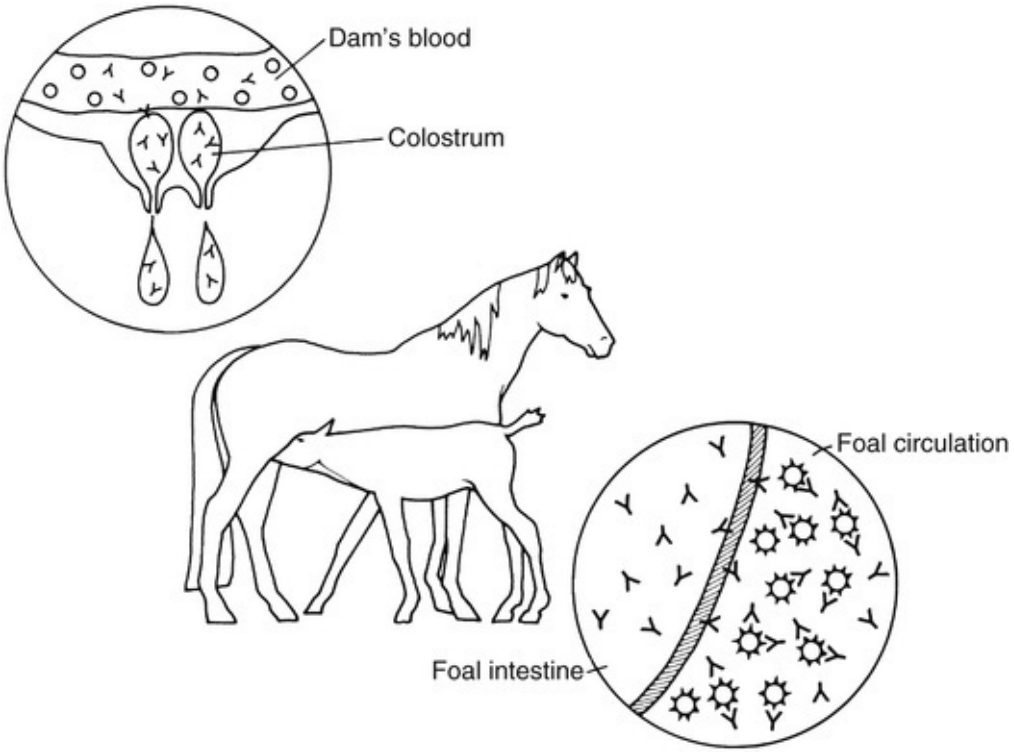


FIG. 53.9 Alloantibody in the mare's serum is concentrated in colostrum at the end of gestation. Through passive transfer, the foal absorbs immunoglobulins, including alloantibodies. The absorbed antibodies attach to the foal's red blood cells and cause either premature removal from circulation or intravascular lysis.

■ Clinical Signs and Differential Diagnoses

Foals are born healthy and usually begin to develop signs of NI at 24 to 36 hours of age, after suckling. Progressive lethargy and weakness are early signs. In acute cases, mucous membranes show initial pallor that is followed by icterus. In severe cases, hemoglobinemia and hemoglobinuria may be pronounced. In peracute cases, death may precede the development of icterus. Breathing becomes rapid and shallow, followed by labored breathing as the disease progresses. The foals may yawn repeatedly. Heart rate is elevated. Seizure-like activity may occur as the anemia becomes more severe.

■ Clinical Pathology

Affected foals are anemic. All indicators of RBC concentration (packed cell volume [PCV] hemoglobin, RBC count) show significant decreases. PCV values often decline into the teens, and values as low as 5% have been observed. Hemoglobinemia and hemoglobinuria may be present. Bilirubin (mainly unconjugated) levels will be increased as a result of accelerated RBC destruction. Total bilirubin levels may be close to 20 mg/dL in severe cases. Affected foals, especially mule foals, may also be thrombocytopenic.[4]

Demonstration of significant amounts of alloantibodies in the colostrum (or serum from the mare) that are directed against the RBC antigens expressed by the foal provides a definitive diagnosis of NI. These antibodies are most commonly demonstrated by lytic and agglutinating tests.[45,46] Lytic tests are believed to be more reliable indicators of the presence of offending antibody.[45] The presence of antibodies attached to the foal's RBCs can also be demonstrated with a direct antiglobulin test (Coombs test). The presence of antibodies in the mare's serum that attach to RBCs can be demonstrated with an indirect antiglobulin test.[2]

■ Pathophysiology

In mares sensitized to RBC antigens, most commonly Aa or Qa, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passed to the foal through passive transfer. If the foal's RBCs carry the antigen that the antibody recognizes, the cells become antibody coated. Subsequently, they are removed prematurely by the mononuclear phagocyte system (reticuloendothelial system) or lysed intravascularly by complement. A distinction has been made between antibodies that are lysins as opposed to agglutinins; however, this distinction is based on in vitro testing and may be somewhat artificial. Under appropriate laboratory conditions, offending antibodies may exhibit both abilities.[43] However, when using certain conventional agglutination tests, some alloantibodies capable of producing NI may go undetected.[10]

■ Epidemiology

The percentages of mares at risk for sensitization against the common offending antigens (Aa and Qa) vary among breeds, depending on the frequency in the population of each gene involved (Table 53.12). In Thoroughbreds the

prevalence is about 1%, and in Standardbreds the incidence is about 2%.[42] The prevalence in mules (donkey sire, horse dam) has been reported to be as high as 10%.[2] Increased numbers of mares at risk in a breed do not necessarily translate to higher numbers of NI cases. A corresponding number of stallions lack the factors in question and are therefore unable to sire foals with the offending antigen.[42] Virtually all mule pregnancies are incompatible with regard to donkey factor.[44]

TABLE 53.12

Estimate of the Percentage of Mares in Selected Breeds That Are "At Risk" for Producing a Foal With Neonatal Isoerythrolysis[a]

Breed	At Risk for Aa	At Risk for Qa
Thoroughbred	2%	16%
Standardbred—pacer	22%	[b]
Standardbred—trotter	3%	[b]
American Saddlebred	25%	88%
Quarter Horse	25%	68%
Arabian	3%	72%

[a]Based on the lack of all alleles that include factors Aa or Qa.

[b]Mares all lack factor Qa and are technically "at risk," but all Standardbred stallions also lack the factor.

Although the disease is more common in multiparous mares, NI can occur with the first pregnancy.

■ Necropsy Findings

Liver failure, kernicterus, and complications related to bacterial sepsis are the most important causes of death in foals dying from NI.[47] Pale tissues with or without icterus and splenomegaly are characteristic necropsy findings. Lesions associated with RBC destruction and anemia, such as nephrosis and centrilobular hepatic necrosis, may also be present.

■ Treatment and Prognosis

In most cases, by the time the problem is recognized clinically (e.g., when the foal is about 24 hours of age), the bulk of colostral antibody will have been depleted from the mare's milk and the absorptive ability of the foal's gut will have diminished. Withholding milk at this point is of questionable benefit.

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Stress should be minimized and exercise restricted. Affected foals have decreased exercise tolerance and can collapse and die if forced to follow their dams. Generalized supportive care should be administered as indicated by clinical parameters. Intravenous fluids are frequently indicated to promote diuresis to minimize the effects of the large hemoglobin load presented to the kidneys. Acid-base balance should be monitored and corrected if indicated.

If the anemia becomes severe (e.g., PCV = 10% to 15%), transfusions that provide RBCs should be considered. Unless the PCV drops below this level, transfusion may not be necessary if rest is enforced. The object of transfusion is to provide the affected foal with RBCs that will not be destroyed by the maternal alloantibodies that were absorbed from colostrum. The foal is immunologically naive and will not have autologous alloantibody directed against any RBCs that would have an immediate effect on transfused RBCs. Thus the key is to select an RBC donor whose cells will not be destroyed by the maternal antibody derived from colostrum. Selection of a donor with cells that will not be destroyed by the maternal antibody can be based on the results of crossmatching using mare serum, colostrum, and/or foal serum (all contain the same antibody) and the donor RBCs.

Washed RBCs from the dam are obviously the perfect choice in terms of cells that will not react with the alloantibodies present in the foal. Therefore, to avoid administering additional harmful antibody to the foal, the mare's serum (containing antibody against the foal's cells) must be removed by washing before administration. Up to 6 to 8 L of blood can be collected from the mare into containers with acid-citrate-dextrose (ACD) or sodium citrate (3.8% NaCitrate solution; 1 part NaCitrate/9 parts blood), although 3 to 4 L usually provide sufficient RBCs. The preparation of large volumes of washed cells is aided by a large-volume centrifuge, but the procedure can be accomplished by serial sedimentations. Anticoagulated blood from the mare is allowed to settle for 1 to 2 hours. The plasma is aseptically drawn off, a similar or greater volume of sterile isotonic saline (0.9% NaCI) is added to the RBCs and mixed, and the RBCs are again allowed to settle. The saline is then drawn off and discarded. At this point the RBCs can be resuspended in an equal volume of isotonic saline for administration, or the washing procedure can be repeated. The sedimentation method is less desirable than centrifugation because it is slower and does not remove as much of the offending antibody. The aim is to dilute any harmful antibody to insignificant levels.

If it is not possible to use the dam's RBCs, alternative donors can be selected.

The donor should lack the antigen to which the alloantibody is directed. Because it is generally not possible to blood type donors on short notice, a previously identified horse that has been determined by blood typing to be Aa−, Qa−, and free of alloantibody is a good choice for a donor because most cases of NI are associated with these two antigens. The odds of randomly selecting a donor that lacks the offending type (e g., Aa−, Qa−, or both) and would therefore be a suitable donor vary significantly with the breed and would mirror the percentage of the population of mares at risk. For example, the odds of finding an Aa− Thoroughbred to serve as an RBC donor would be about 1 in 50 (2%), whereas in Quarter Horses the odds would be about 1 in 4 (25%) (see Table 53.12). The sire of the foal is not the donor of choice. He shares the same RBC antigens as the foal, and his cells will react with the maternal alloantibody present, adding more of a load to the foal's mononyclear phagocyte system as they are destroyed.

In the case of mules, the same considerations in the use of washed cells would be necessary if the dam's cells were used. However, because the offending antibody is generally directed against a unique donkey antigen, it appears that RBCs from any horse would be satisfactory. Horses do not appear to make naturally occurring antibodies against donkey factor; therefore in most cases it is not necessary to wash the cells from horses that would not be likely to have been immunized by pregnancy against donkey factor.

Transfusion of RBCs that will not react with maternal alloantibody results in the introduction of an obviously incompatible cell into the foal. Transfused cells may sensitize the foal to future transfusions, causing reactions (perhaps not within hours or a few days but potentially within a week). The RBCs will probably not survive for long periods in the circulation, and such transfusions should be considered temporary measures. These possibilities must be considered when weighing the potential good versus potential harm of such transfusions.

To produce clinical improvement, 1 to 4 L of washed RBCs or whole blood are usually adequate, although some cases may require repeated transfusion if the anemia progresses. Exchange transfusions can be done whereby blood is administered via one jugular and withdrawn simultaneously from the opposite jugular and discarded, allowing administration of large volumes of blood without overloading the vascular system. There is no good evidence to suggest that this is more effective than simply providing a source of RBCs that are unaffected by the maternal antibody.

Limited transfusion studies in adult horses have suggested that transfused

RBCs do not survive long in circulation (e.g., 2 to 4 days), whereas in foals cells survived slightly longer (e.g., 4 to 6 days).[48,49] PCVs in foals with NI commonly increase following transfusion and then gradually decline. This decline is probably not great cause for concern if it is gradual because the PCV of the foal generally levels off as the offending maternal antibody is metabolized. However, even short-term survival of cells may be of benefit in severely affected foals and may allow them to survive until the titer of maternal anti-RBC immunoglobulin has declined in the circulation. Hepatic failure in foals administered blood transfusions may be the result of iron intoxication. Administration of drugs that increase iron excretion, such as deferoxamine mesylate, are of potential value.[50]

The prognosis varies depending on the quantity of antibody ingested, the rapidity of onset of signs, and the degree of anemia. Peracute cases may die before the problem is recognized, with no chance for administration of therapy. Foals that develop the condition more slowly may respond to supportive care or transfusion if the PCV continues to fall.

■ Prevention and Control

Several strategies are available for prevention of NI.[51,52] First, identify broodmares at risk for development of NI by testing them for the presence of Aa and Qa. Mares negative for either antigen, which means they could potentially make antibodies against them, should be considered at risk. One subsequent strategy would be to breed at-risk mares to Aa-negative and Qa-negative stallions, thus eliminating the possibility of the foal inheriting the offending antigens. However, in breeds in which a relatively small part of the population is negative for these antigens, identifying a stallion that is negative for both antigens and suitable based on other criteria may be difficult. The percentage of at-risk females based on the presence or absence of Aa or Qa is somewhat balanced by the number of males able to transmit the offending antigen. For example, all Standardbred mares would be considered at risk because of the absence of Qa; however, because the antigen Qa is not present in the Standardbred population, no stallions have the Qa antigen to pass on to foals.

In the circumstance of unknown or incompatible matings, sera from at-risk mares should be screened for the presence of anti-RBC antibodies within 30 days before foaling. This can be done by submitting a serum sample and an anticoagulated sample to a screening laboratory. A panel of 10 to 12 different RBCs selected to represent all major blood groups is adequate to screen for anti-

RBC antibody in the absence of blood from the sire. If results of serum testing are equivocal (e.g., low but positive titer, especially if there is anti-Aa or anti-Qa activity), the test should be repeated closer to the time of parturition because the levels of offending antibody can rise quickly late in gestation.

If anti-RBC antibody is detected in the mare before parturition, the colostrum should be checked for reactivity against the foal's RBCs before allowing the foal to ingest colostrum. An alternative source of colostrum should be provided to the foal. Most field screening tests of colostrum have not proved to be satisfactory for practical use; however, the jaundiced foal agglutination (JFA) test described in Box 53.2 has been shown to correlate well with the standard hemolytic assay, and it may detect antibody that does not react on the standard agglutination tests.[7]

Box 53.2

Jaundiced Foal Agglutination (JFA) Test

Materials

1. Centrifuge capable of spinning 300× to 600× gravity
2. Test tube rack
3. Test tubes: 13- × 100-mm disposable or blood collection tubes
4. Pasteur pipettes and rubber bulbs or other pipette system to deliver 1-mL volumes
5. Isotonic (0.9%) saline at room temperature
6. Serum or colostrum from the mare; RBCs from mare and foal, preferably in EDTA anticoagulant

Methods

1. Collect colostrum from the mare.
2. Collect an EDTA-anticoagulated blood sample from the foal before nursing.
3. Set up six tubes and add 1 mL of saline to each tube. Label the tubes Control, 1 : 2, 1 : 4, 1 : 8, 1 : 16, and 1 : 32.

4. Make serial dilutions of the colostrum at 1 : 2, 1 : 4, 1 : 8, 1 : 16, and 1 : 32 in five of the tubes. Add 1 mL of colostrum (or serum) to the tube labeled 1 : 2 and mix. Then take 1 mL from that tube and add it to the second tube labeled 1 : 4 and mix. Take 1 mL from that tube and add it to the third tube labeled 1 : 8, and so on, until all five dilution tubes have been filled. Discard 1 mL from the last tube labeled 1 : 32.
5. Add 1 drop of the foal's whole blood to each of the six tubes and mix.
6. Centrifuge the tubes for 2 to 3 minutes at a medium speed (300× to 500× gravity).
7. Invert each tube, pouring out the liquid contents; observe the status of the button of RBCs at the bottom of the tube. Complete agglutination causes the cells to remain tightly packed in the button; strong agglutination causes the cells to remain in large clumps; for weaker agglutination the cells are in smaller clumps as they run down the side of the tube. When there is no agglutination, the cells easily flow down the side of the tube. This should be the case in the control tube. If the cells in the control tube are clumped, they may be autoagglutinating and the results will have questionable validity.
8. If there is a positive reaction with the foal's cells, the test should be run with the dam's own RBCs to be certain that neither the conditions of the test nor the viscosity of the colostrum is causing the agglutination.
9. Positive reactions at 1 : 16 or greater are considered significant. At levels of 1 : 16 or greater, this test correlates well with the standard hemolytic assay. At dilutions of less than 1 : 16, the correlation is not as good, and more false-positive results will be recorded. Also, other factors such as the viscosity of colostrum make less diluted samples more difficult to read.

EDTA, Ethylenediaminetetraacetic acid; *RBCs*, red blood cells.

Horses negative for Ca frequently make anti-Ca antibody; however, this antibody is not known to produce adverse effects in the foal. It has clouded the issue of field screening tests for NI because it commonly causes positive reactions in most screening tests at low dilutions. Because these tests do not differentiate between antibody to Aa, Qa, Ca, or any other blood group, anti-Ca antibody, when present in low dilutions, is responsible for many false-positive reactions. This antibody actually appears to play a protective role in the

prevention of sensitization of mares to NI through a mechanism of antibody-mediated immune suppression. Aa− and Qa− mares that are also Ca− (and thus often produce anti-Ca antibody) become sensitized to Aa and Qa at a significantly lower rate than mares that are Ca+.[53] This is attributed to the fact that anti-Ca antibody is produced by Ca− mares. The anti-Ca antibody may more rapidly remove potentially sensitizing cells from the circulation before they stimulate production of antibody against Aa or Qa.

Uncommonly, other antigens have been associated with NI in foals. These include factors Db, Dc, Dg, Ua, Pa, Qc, and Ab.[2,4,53-58] Two other factors, R and S, have been described to be associated with NI, but they are not detected by routine hemolytic or agglutinating methods and are detected only using an antiglobulin test (direct Coombs test).[41] Because of the difficulty in testing for these antigens, there has never been sufficient agreement among laboratories to allow international designation. These antigens may not be detected using the JFA test.[25] Estimates are that 1 in 2000 pregnancies may result in sensitization against some other antigen besides Aa or Qa. Because these cases occur so infrequently, it is not practical to consider mares without these antigens to be at risk for NI. A blood-type evaluation of mares with a history of production of foals with NI should be done to identify the offending antibody or antigen.

A list of laboratories providing NI screening tests (e.g., Aa, Qa, and Ca typing and screening of sera for alloantibody) is provided in Box 53.3. Routine agglutinating crossmatch tests using mare serum or colostrum and foal or sire cells can be performed by most veterinary or human hematology laboratories.

Box 53.3

Laboratories Providing Equine Neonatal Isoerythrolysis Testing[a] in North America

Clinical Laboratory Services—Hematology
University of California, Davis
Veterinary Medical Teaching Hospital
Central Laboratory Receiving, Room 1033
One Garrod Drive

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Davis, CA 95616-8747
(530) 752-8684
www.vetmed.ucdavis.edu/vmth
Animal Genetics Testing and Research Laboratory
108 Gluck Equine Research Center
University of Kentucky
Lexington, KY 40546-0099
(859) 218-1212
www.ca.uky.edu/gluck/AGTRL.asp
Rood and Riddle Veterinary Laboratory
Rood and Riddle Equine Hospital
2150 Georgetown Road
Lexington, KY 40511
(859) 233-0331
www.roodandriddle.com/laboratory.html
Hagyard Laboratory
Hagyard Equine Medical Institute
4250 Iron Works Pike
Lexington, KY 40511-8412
(859) 259-3685
www.hagyard.com/Hagyard-Laboratory.html

[a]Serum or colostrum from the suspect mare is required to screen for the presence of alloantibody. Acid-citrate-dextrose anticoagulated blood is generally preferred for screening for red blood cell antigens.

Ruminants

NI is not a naturally occurring disease in cattle, sheep, or goats. Its occurrence in cattle has been associated with administration of vaccines derived from blood origin, such as certain anaplasmosis and babesiosis vaccines.[2] When these vaccines are used on breeding females, they may sensitize the dam to certain blood groups, most commonly in the A and F systems. Under chance circumstances, if the blood types of the sire and offspring reflect these systems and the dam has produced alloantibodies, an isoimmune hemolytic crisis may appear in the calf associated with successful passive transfer.

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Hemolytic crises are rare in sheep and are even difficult to induce experimentally.[2]

Bovine neonatal pancytopenia (BNP) is a fatal condition reported in Europe and New Zealand in a subset of neonatal calves born to cows vaccinated with a certain vaccine product (Pregsure® BVD [Pfizer, New York, N.Y.]); the vaccine has been withdrawn from the market.[59] Nevertheless, cases of BNP continue to be seen in calves born to dams that have been historically vaccinated. This vaccination-induced alloimmune condition is characterized by marked anemia, thrombocytopenia, lymphopenia, and bone marrow hypoplasia, causing severe internal and external hemorrhage. The involvement of colostrum was identified by inducing the disease in newborn calves (about 10 days when offering colostrum from vaccinated cows) and by preventing disease by colostrum substitution.[60] Studies demonstrated that the alloantibodies produced by vaccinated cows reacted with proteins from the cell line used to manufacture the vaccine. One study demonstrated that the development of BNP involves a heritable trait (19%) determined by the dams; that is, genetic differences between dams explain in part why the colostrum of some but not all vaccinated dams cause BNP in the calf or cause subclinical disease.[61] Genetic inheritable differences do not seem to involve major histocompatibility complex classes I and II genes or differences in Ig isotypes but rather unknown genes that control the amount of alloantibody produced by the vaccinated dams.[62,63]

Neonatal Alloimmune Thrombocytopenia

■ Equine

Definition and Etiology

Neonatal alloimmune thrombocytopenia (NAIT) is a condition characterized by the destruction of platelets in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[63] The syndrome has been observed in horse and mule foals.[44,64,65] The prevalence of this condition is unknown. Some cases may be asymptomatic, and the condition may be self-limiting as alloantibody is metabolized.

■ Clinical Signs and Differential Diagnoses

Few clinical signs may appear unless foals are traumatized. Affected foals may

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have prolonged bleeding from venipuncture sites. Petechial hemorrhages may or may not be present.[64] Other conditions often associated with thrombocytopenia in neonates include sepsis, disseminated intravascular coagulation, equine infectious anemia, drug-induced thrombocytopenias, and angiopathies. The challenge is to determine whether the thrombocytopenia is primarily due to allogeneic antibodies or secondary to some other disease process.

■ Clinical Pathology

Profound thrombocytopenia in the absence of other hematologic changes typifies uncomplicated NAIT. Evidence of successful passive transfer is present based on quantification of serum IgG. Affected foals are thrombocytopenic. Thrombocyte counts less than 10,000 cells/µL have been observed.[64]

Demonstration of significant amounts of antibody in the colostrum (or serum from the mare) that are directed against platelet antigens expressed by the foal provides a definitive diagnosis of NAIT; however, assays for equine platelet-bindable and platelet-associated immunoglobulins are not routinely available.

■ Pathophysiology

The pathophysiology is believed to mirror that of NI. In mares sensitized to platelet antigens, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passively transferred to the foal. If the foal's platelets carry the antigen that the antibody recognizes, the platelets become antibody coated. Subsequently they are removed prematurely by the mononuclear phagocyte system. Platelet antigens have not been characterized in horses, although platelet-associated antibodies have been recognized in affected foals. Circulating antibody is removed by attachment to platelets and rapid clearance by the mononuclear phagocyte system.

■ Treatment and Prognosis

Circulating antibody is removed relatively quickly, and treatment may not be necessary. Platelet-rich plasma may be indicated in cases of severe thrombocytopenia accompanied by clinical signs of bleeding complications; however, as offending antibody is removed, the problem will tend to be self-limiting.

■ Prevention and Control

Currently there are no screening tests to predict NAIT. Following production of an affected foal by a mare, it would be prudent to provide an alternate source of colostrum to foals born in subsequent pregnancies.

A rare condition of severe thrombocytopenia, neutropenia, and ulcerative dermatitis has been described in equine neonates, and clinical signs suggest an association with passively transferred colostral antibodies or other factors.[66]

Alloimmune Neonatal Neutropenia

■ Equine

Definition and Etiology

Alloimmune neonatal neutropenia (ANN) is a condition characterized by the destruction of neutrophils in the circulation of a foal by alloantibodies of maternal origin absorbed from colostrum.[67,68]

■ Clinical Signs and Differential Diagnoses

In the absence of secondary bacterial infections, no clinical signs are observed. Diagnosis depends on the presence of persistent neutropenia in the absence of evidence of increased consumption or decreased production of neutrophils.

■ Clinical Pathology

Persistent neutropenia in the face of normal clinical conditions has characterized reported cases.

■ Pathophysiology

The pathophysiology is believed to mirror that of NI. In mares sensitized to granulocyte antigens, alloantibodies are concentrated in the colostrum late in gestation. These antibodies are passed to the foal through passive transfer. If the foal's neutrophils carry the antigen that the antibody recognizes, the neutrophils become antibody coated. Subsequently they are removed prematurely by the mononuclear phagocyte system. Neutrophil antigens have not been characterized in horses, but neutrophil-associated antibodies have been recognized in affected foals. Circulating antibody is removed by attachment to neutrophils and rapid clearance by the mononuclear phagocyte system.

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■ Treatment and Prognosis

ANN is self-limiting in infants and typically resolves over several weeks as maternal antibodies diminish. Administration of antimicrobial drugs may provide protection against bacterial infections. Corticosteroids are not currently recommended for treatment of the condition in human infants and have not been used in equine cases. Administration of recombinant human granulocyte colony-stimulating factor (rhG-CSF) was associated with increases in neutrophil counts in one affected foal.[67]

■ Prevention and Control

Demonstration of agglutinating neutrophil antibodies or immunoglobulin coating of neutrophils using flow cytometry from the foal may be used to confirm a diagnosis.[67] Following production of an affected foal by a mare, it would be prudent to provide an alternate source of colostrum to foals born in subsequent pregnancies.

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Ruminant Immunologic Disorders

George M. Barrington, *Consulting Editor*

Immunity at Birth and the Immune Development of the Calf

David J. Hurley

At birth, calves possess the appropriate immune components needed for a protective response; however, these components lack maturity and require time to become as functional as those in adults. Although calves that do not receive colostrum within the appropriate time can still mount innate responses, they have a much greater risk of disease during the neonatal period and beyond.[1] For more on closotrum management in ruminants, see Chapter 19.

Prior to receiving colostrum, calves rely on macrophages located in tissues to manage tissue-level immune homeostasis. This includes mounting and managing the response to environmental microbes that share common antigenic determinants. The ability of macrophages to recruit monocytes, neutrophils, and other innate cells from neonatal circulation is a core component of the immediate innate immune response. Finally, in addition to macrophage activation and recruitment of circulatory innate cells, the activities of antimicrobial peptides combine to form the functional limit of immunity in calves at birth.

The earliest production of antibody by neonatal calves is reported in circulation at approximately 4 days of age. IgM can regularly be measured at 8 to 10 days of age.[2] T cell–dependent IgG is not usually observed in the circulation of calves until at least two half-life decays of maternal antibody. A large volume of research supports the role of IgG1 in the health and immune development of calves and its importance in providing protection from invading microbes. In addition, IgA in colostrum and milk play an important role in managing the colonization of the GI tract by microbes and the management of GI disease. Maternal antibody, directed against local microbes, helps protect calves during development and growth.

In calves, some B cells can be found in the neonatal organized lymphoid tissue both before and immediately after birth. These cells are widely distributed and are not organized into germinal centers (organized B-cell areas following

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immune activation). Their exact function and origin are not clear. After ingestion of colostrum containing viable maternal cells and IgG, or noncellular maternal factors and IgG, an almost complete depletion of the IgG-bearing cells in organized lymphoid tissues of the neonatal calf is observed. A small number of IgM- and IgA-positive cells are also present in these organized lymphoid tissues, and these are not affected by feeding whole colostrum or maternal colostrum without live cells.[3] Tracking of B cells in the peripheral blood of calves indicates that at birth about 5% of circulating mononuclear cells are B cells and that the number increases to about 20% by 20 weeks of age.[4] Fetal B cells are rapidly deleted from organized lymphoid tissues of very young calves. B cells are found in low numbers in the blood of young calves but are not likely to represent a sufficient pool of naive B cells to produce all the antibody required to resist pathogens early in life. Thus antibody transferred from colostrum (or whey antibody in colostrum substitutes) is required to adequately protect the calf.

Colostrum has a significant effect on the development of the neonatal GI tract.[5] Critical nutrients, vitamins, minerals and trace elements, and nonnutrient factors (Ig, growth factors, hormones, and cytokines) affect several processes, including the function of microbes; mucosal epithelial cell proliferation, migration, and differentiation; recruitment and function of innate immune cells; production of immune-active molecules; development of vascular beds and normal vascular tone; and mechanisms necessary for efficient transfer of nutrients and other components to the body. Serial microbial colonization of neonatal mucosal surfaces is critical for the development of both the innate and the adaptive immune networks.[6-8]

Norrman and colleagues compared the effects on B- and T-cell production of feeding newborn calves either colostrum or milk replacer.[9] They demonstrated that colostrum intake decreased neonatal adaptive immune responses compared with colostrum-deprived calves that lacked immune-priming assistance. The model also indicated that calves receiving colostrum were protected from the immune-suppressive effects of glucocorticoids and thus were less susceptible to infection.

Once calves ingest colostrum, immunoglobulin (primarily IgG1) rapidly crosses the gut epithelial cells and enters the circulation. Once in circulation, IgG1is distributed to the tissues by mass action, where it acts as a key element in immediate immune protection against microbial agents. Because of its structural flexibility, IgG1 readily enters tissues and enhances the response by

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macrophages, monocytes, and neutrophils.

In addition to circulating innate immune cells, both T and B lymphocytes are present as part of the adaptive response, though both are considered naive, having never been activated. Core structures such as the spleen and lymph nodes will eventually serve as foci for lymphoid maturation.

There is evidence in calves that lymphocytes can be activated as early as 2 days after birth.[10,11] Both colostrum-deprived and colostrum-fed calves produced antibody- (primarily IgM) and antigen-responsive T cells after exposure to bacille Calmette-Guerin (BCG) and ovalbumin antigens, and calves receiving colostrum had less evidence of disease over the course of the study. Both groups showed the capacity to mount adaptive responses to test antigens. Thus it appears that a full complement of experienced B and T cells and an adult-like organization of lymphoid tissues are not absolute requirements for successful production of at least some adaptive responses. However, this limited capacity is not sufficient to protect calves from disease.

It has long been established that maternal leukocytes present in colostrum successfully pass from the neonatal intestine into circulation. The exact function of these maternal cells is only beginning to be understood and is a topic of much debate. Nonetheless, while it is clear that calves can develop without the transfer of viable maternal cells, there are many reports of specific enhancements in immune function seen over the first 7 to 28 days after ingestion of colostrum with viable maternal cells.[12-24]

The induction of the adaptive response strongly depends on expression of antigen in the context of MHC antigens. At birth, calves have very low levels of MHC classes I and II antigen expression on circulating cells. However, rapid enhancement in expression of MHC classes I and II antigens is observed after ingestion of colostrum containing viable maternal cells (within 12 to 24 hours). A similar increase in cells expressing MHC classes I and II antigen requires at least 7 days in calves receiving colostrum without viable maternal cells.[25] The role of MHC class II in transmitting antigen information from tissues to lymphocytes in secondary lymphoid tissues and activating local lymphocyte and NK cell populations has been clearly established.

Maternal cells originating from colostrum appear to home to lymph nodes and mucosal lymphoid structures of calves.[26] Circulating leukocytes in calves receiving maternal colostral cells showed enhanced capacity to respond to viral and bacterial antigens that the dam had exposure to for 12 to 48 hours after

colostrum feeding.[16-18,21,27] Calves not receiving viable maternal cells from colostrum showed no response to viral antigens and suffered more severe GI disease.[16,22-24] The innate and adaptive immune responses are clearly enhanced by ingestion of viable maternal cells in colostrum.[12-15,19,20,24]

In calves the number of circulating leukocytes declines rapidly beginning around day 2 after birth and reaching a minimum between days 7 and 11.[28,29] At birth, the predominant leukocyte in neonatal circulation is the segmented neutrophil, making up about two thirds of circulating WBCs. The other third includes lymphocytes, primarily T cells. As the total number of circulating leukocytes declines and then recovers over the first 2 weeks of life, the proportion of cell types also shifts. By day 14, neutrophils make up one third of total cells, and lymphocytes (including NK and gamma-delta cells) make up more than half of total cells. In the neonate, both NK and gamma-delta cells can leave the circulation and participate in immune protection within tissues.

Once DCs and neutrophils populate organized lymphoid tissues, the lymphoid environment changes to provide enhanced capacity for homing of lymphocytes and the structural development of germinal centers in these tissues. Although lymphoid germinal centers are rarely observed in mammals younger than 21 days of age, the seeds of the network required for their development begin in the first week of life. B cells, located in functional germinal centers, are under the influence of imbedded follicular DCs and surrounded by supporting Th cells. B cells and neutrophils (carrying whole antigen) provide important components for the development of an antibody response. Slowing development are low levels of MHC class II antigen expression by B cells, monocytes, DCs, and macrophages during the first 10 days to 2 weeks of life. Expression of MHC class II antigen is a limiting factor in the development of a rapid adaptive response.[25]

The process of calf immune development to adult levels takes time. Many potential pathways can lead to successful protection. The path a calf takes will be influenced primarily by the management strategies of the farm or ranch. For example, dairy calves can have a range of contact time with the dam (0 to 4 days) and may receive fresh, frozen, or processed colostrum, which is single-source or pooled. Dairy calves may be fed waste milk or milk replacer that may not possess populations of local microbes. In contrast, most beef calves are exposed to a number of herdmates and remain with their dam and herd during development. Beef calves are typically more aggressive than dairy calves,

usually stand and nurse within 1 to 2 hours after birth, and continue to nurse ad libitum. In dairy calves the primary reason for FPT of maternal immunity involves poor-quality colostrum (low IgG1), whereas in beef calves FPT typically results from conditions that adversely affect the timely ingestion and absorption of colostral immune components.

Lethal Trait A46

Munashe Chigerwe

Lethal trait A46, also known as bovine hereditary zinc deficiency, Adema disease, hereditary thymus hypoplasia, and hereditary hyperkeratosis, is an autosomal-recessive immunodeficiency disorder with clinical presentation similar to acrodermatitis enteropathica (AE) in humans. The disease was first described in 1964 in Black Pied Friesian cattle.[1] Black Pied Friesian is a cross breed between Black Pied Jutlands from Denmark and Friesians from the Netherlands. A similar disorder has been reported in Shorthorn cattle in the United States[2] and Angus cattle in Australia.[3]

Zinc is an essential nutrient for several physiologic processes as a cofactor of many enzymes and transcription factors.[4] The molecular basis in AE in humans has been linked to an identification of a defect in a solute carrier (SLC), referred to as *SLC39A4*. A defect in a bovine ortholog of *SLC39A4* has been identified in cattle with lethal trait A46.[5] The defect has been postulated to negatively affect a pore responsible for zinc transport, leading to impaired zinc absorption.[5] Zinc is required for normal lymphocyte function. In a zinc-deficient state, lymphocyte numbers and function are reduced, and antibody responses are reduced.[6] Clinical signs associated with lethal trait A46 include skin lesions, diarrhea, and bronchopneumonia. Calves appear normal at birth but develop skin lesions at 4 to 8 weeks of age. The skin lesions are characterized by alopecia, hyperkeratosis, and exanthema. The distribution of the skin lesions includes the perineum, lower legs, head, and neck. Skin lesions of the entire body of the animal may be observed in advanced cases. Death occurs at approximately 4 months, secondary to bronchopneumonia or complicated diarrhea. Necropsy findings in affected animals include acanthosis, hyperkeratosis, thymus atrophy, gut-associated lymphoid tissue, spleen, and lymph nodes. The disease is responsive to zinc supplementation. Doses of 0.5 to 1 g/day zinc oxide[7] or 1 g/day of zinc acetate in cattle younger than 2 years of age[8] and of 45 g/day of zinc acetate in cattle older

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than 2 years have been recommended.[5]

Bovine Leukocyte Adhesion Deficiency

Bovine leukocyte adhesion deficiency (BLAD) is an autosomal-recessive congenital disease of Holstein calves characterized by chronic, recurrent bacterial infections and death. Leukocytes express cell surface glycoproteins called β_2 integrins, which mediate cell–extracellular matrix and cell-cell interactions.[9-11] The β_2 integrins include lymphocyte function-associated antigen-1 (LFA-1), complement receptor type 3 (CR3), and p150,95, and the family of these proteins is referred to as CD11/CD18 adhesion molecule.[9-11] The β_2 integrins LFA-1, CR3, and p150,95 consist of unique subunits—CD11a, CD11b, and CD11c, respectivelyand a common subunit CD18.[9,11] The CD11/CD18 adhesion molecules are essential for host defense against infections.[9-11] LFA-1 is expressed on all leukocytes and is essential for leukocyte adhesion and lymphocyte cytotoxicity.[9-11] CR3 and p150,95 are present on the surfaces of neutrophils, monocytes, macrophages, and NK cells.[9,12] Binding of CR3 and LFA-1 on the neutrophil surface with intercellular adhesion molecule 1 expressed on the vascular endothelium is required for neutrophil emigration into sites of inflammation.[12] Calves affected by BLAD lack expression of adhesion molecules of the CD11/CD18 family on the leukocyte surface.[13] The molecular basis for BLAD is a single point mutation (adenine to guanine) of the *CD18* gene, resulting in aspartic acid to glycine substitution at amino acid 128 (D128G) in the glycoprotein.[14] Calves with BLAD are homozygous to the D128G allele, whereas β_2 integrin expression in heterozygotes occurs in 56% to 90% of cattle not affected by BLAD.[15]

Clinical signs in calves appear within a couple of weeks after birth and include anorexia, fever, chronic pneumonia, chronic diarrhea, severe ulcers on oral mucosal membranes, ulcerative stomatitis, gingivitis, periodontitis, loss of teeth, impaired wound healing, chronic dermatitis, decreased growth rate, and death.[16,17] Marked and persistent neutrophilia is a consistent hematologic finding in calves with BLAD due to lack of emigration of neutrophils out of the vessels.[16] Consistent serum biochemical abnormalities include hypoalbuminemia, hyperglobulinemia, and hypoglycemia, consistent with chronic infections.[17] In the United States, 14% of bulls and 6% of cows were

reported to be carriers of the D128G allele.[18] Diagnostic tests are available to detect heterozygotes and homozygotes. The information is available from the Holstein Association USA in Brattleboro, Vermont.

Selective IgG2 Deficiency

Rana Bozorgmanesh

IgG subclass deficiencies have been reported in ruminants. Primary (partial or complete) IgG2 deficiency in Red Danish milk cattle increases their susceptibility to gangrenous mastitis, bronchopneumonia, peritonitis, and abomasoenteritis.[1-3] There is also a report of IgG2 deficiency with transient hypogammaglobulinemia and chronic respiratory disease in a 6-month-old Holstein heifer that was eventually euthanized due to lack of improvement with therapy and a poor prognosis.[4] A transient IgG2 deficiency (with no adverse consequences) has been reported in neonatal lambs that ingested colostrum resulting in delayed synthesis of IgG2 to 5 to 6 weeks of age.[2]

Chediak-Higashi Syndrome

Chediak-Higashi syndrome is an inherited disorder resulting in partial oculocutaneous albinism, photophobia, increased susceptibility to infection, and coagulopathies. The condition affects cattle, mink, cats, mice, killer whales, and humans.[5,6] The condition is characterized by enlarged cytoplasmic granules (often lysosomes) in most types of granule-containing cells and defects in the function of leukocytes, renal tubular cells, and platelets. Neutrophils demonstrate abnormal intracellular killing due to a defect in the hexose monophosphate shunt as well as defective degranulation.[6] The condition is well documented in Japanese Black cattle, where inheritance has been identified as a simple autosomal recessive trait as it is in other animals and humans.[5,7]

Combined Immunodeficiency

Both T- and B-cell deficiencies due to genetic failure result in combined immunodeficiency. This may go unnoticed until maternal antibodies wane at several weeks of age, leaving the animal susceptible to infections. There is one report of a 6-week-old Angus embryo-transfer calf that died as a result of generalized systemic mycosis. This calf was hypogammaglobulinemic and

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lymphopenic and had an absence of serum IgM. Necropsy confirmed the absence of lymphoid tissues and the diagnosis of combined immunodeficiency. Interestingly, the full sibling from the same embryo flush was healthy at 6 months.[8]

Viral and Bacterial-Induced Immunodeficiency

Bovine viral diarrhea (BVD) infection has been associated with altered immune function in infected calves and lambs.[9-11] Evidence suggests that the virus may have immunosuppressive effects on both the innate and the adaptive immune systems, making animals more susceptible to secondary infections and resulting in the establishment of persistent infection and immunotolerance.[9-10] Cattle infected with Johne's disease may show an inability to mount cell-mediated immune responses as well as the presence of humoral immunosuppressive factors contributing to chronic intracellular infection.[12] Furthermore, a state of tolerance may exist in the intestine of cows subclinically infected with Johne's disease organisms, in part due to proliferation of regulatory T cells that suppress mucosal immune responsiveness.[13]

Immunosuppression in the Periparturient Period

Barry J. Bradford • Jodi L. McGill

Introduction

In dairy cattle, the period 3 weeks prior to calving through 3 weeks after parturition, referred to as the transition period, is marked by dramatic changes in physiology, metabolism, and immunity.[1] The transition period is associated with a sharply increased incidence of metabolic and immunologic diseases, including endometriosis, mastitis, ketosis, and dystocia.[1-3] Further, the occurrence of health problems in the first few weeks postpartum is a major risk factor for continued production and reproductive performance problems.[4] It is now widely accepted that the increased incidence of both metabolic and production-related diseases is directly related to a temporary state of immunosuppression, which is known to affect the transition cow for at least 3 to 5 weeks following parturition.[2]

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Immunologic Disorders of the Innate Immune System.

The innate immune system responds rapidly and nonspecifically to insults and thus plays a critical role in protecting the cow during the early days following parturition. Neutrophil function is particularly affected during transition, demonstrating reductions in chemotaxis, phagocytosis, oxidative burst capacity,[5-9] and downregulated expression of pathogen recognition receptors.[10,11] Changes in glucocorticoid levels at or around the time of calving are thought to be a prime factor leading to impaired neutrophil functions,[12,13] and a number of studies have shown that increased circulating cortisol levels downregulate neutrophil adhesion molecules, leading to reduced neutrophil surveillance activity and immune response.[13-15] However, glucocorticoid levels are increased for only a short period post calving[16-18]; thus additional factors likely contribute to the prolonged state of immunosuppression observed during transition. The final stages of fetal development and colostrogenesis require significant quantities of calcium, causing most cows to develop either subclinical or clinical hypocalcaemia in the transition period.[19] Hypocalcemia is linked to elevated cortisol plasma concentrations,[20] and cows with decreased serum calcium concentrations have decreased neutrophil activity, delayed pathogen recognition by peripheral blood mononuclear cells, and increased susceptibility to several periparturient conditions.[21-24] Due to the high demands of early lactogenesis, transition cows also regularly enter a state of negative energy balance and mobilize adipose and other tissues for energy.[2,4,18] Increased mobilization leads to increased concentrations of non-esterified fatty acids (NEFAs) and ketone bodies, such as beta-hydroxybutyrate (BHB). BHB is clearly shown to negatively affect neutrophil functions, including formation of neutrophil extracellular traps (NETs), chemotaxis, and phagocytosis.[25-27] High circulating NEFA concentrations are associated with diseases such as hepatic lipidosis,[28] retained placenta,[29] and mastitis.[30,31] High circulating NEFA concentrations in vivo are associated with reduced neutrophil and mononuclear cell functions,[32,33] and a study by Scalia and colleagues showed in vitro that high levels of NEFAs were associated with increased neutrophil oxidative burst activity but severely reduced viability.[34]

Immunologic Disorders of the Adaptive Immune System.

Like the innate immune system, the adaptive immune system of the transition

cow is altered both qualitatively and quantitatively. Numbers of circulating lymphocytes and monocytes are reduced during the postpartum period.[35,36] Large quantities of serum IgG are transported into the mammary gland during colostrogenesis,[37] and physiologic reductions in serum IgM and IgG have been reported well into the postpartum period.[38] High levels of glucocorticoids are thought to be a primary factor in suppression of the adaptive immune system,[12] although lymphocyte blastogenesis and cytokine secretion are also adversely affected by metabolic factors such as hypocalcaemia,[22] ketosis,[39,40] and high circulating NEFA levels.[32,41]

Epidemiology

Impaired immune function during the periparturient period likely contributes to increased risk of infectious disease at that time. It is well established that mastitis incidence is greater in the first 5 weeks of lactation than during the remainder of the lactation,[41] along with high prevalence of metritis at this time.[42] Although numerous possible mechanisms could explain increased infectious disease incidence in early lactation, there is now strong evidence that impaired innate immunity is at least a contributing factor.[43]

Several functional attributes of neutrophils, including chemotaxis, phagocytosis, oxidative burst, and bacterial killing were found to be impaired prior to disease onset in cows that experienced retained placenta, mastitis, or metritis compared to healthy herdmates.[5,33,44] Mastitis and retained placenta were also associated with an increase in the proportion of immature neutrophils in circulation,[44] perhaps due to extravasion of the more mature, functional neutrophils. Shifts in monocyte populations were recently linked to postpartum disease; a high ratio of CD14+ to CD14– monocytes in the 6 weeks before parturition was associated with substantially greater risk of mastitis or metritis in early lactation.[45] Although there have been fewer studies linking adaptive immune function to transition success, a pilot study showed that cows with a weak lymphocyte proliferation response to LPS 3 weeks prior to parturition subsequently suffered from clinical infections postpartum, and this functional classification was associated with a genetic polymorphism.[46]

Interventions

A variety of approaches are being advanced to attempt to counteract

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periparturient immunosuppression and decrease disease incidence during this critical period.[19] Among the most widely adopted methods is vaccination against the J5 component of *E. coli* endotoxin, which decreases the incidence of coliform mastitis.[47] Although not commercially available, early trials are also showing promise for a multitarget metritis vaccine strategy.[48] A longer-term approach already in use by dairies is genetic selection for superior immune response, with reported benefits for periparturient disease incidence.[49]

An innate immune stimulant is now available to substantially increase circulating neutrophil populations and enhance their functionality.[50] This modified bovine G-CSF, when administered 7 days prior to and immediately after calving, decreases clinical incidence of mastitis in early lactation,[51,52] although the potential impacts on other infectious conditions are not yet known. Feed additives are increasingly investigated for impacts on immune function. Beyond the benefits of better understanding and meeting requirements for nutrients like vitamin E[53] and chromium,[54] some yeast-containing products may stimulate innate and adaptive immunity in ways that are not completely understood.[55-58] Another line of research is investigating the immune benefits of decreasing milk yield through decreased milking frequency or partial milking in the first week of lactation.[59] Ultimately, the practices with the most impact for supporting immunity during the periparturient period are likely to be already established best management practices: appropriate stocking density,[60] prevention of heat stress[61] and hypocalcemia,[62] and body condition management.[63]

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• CHAPTER 54

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Disorders Caused by Toxicants*

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Poison cases in large animals occur less often than in other species but are usually more time consuming and frustrating to manage. Generally, an animal is found dead in the stall or pasture, or a sudden outbreak of illness occurs in a herd of animals. A rapid response is necessary, especially in herd cases, to eliminate the toxicant, treat affected animals appropriately, and prevent the development of further cases. The initial history is frequently limited, yet owners, trainers, barn managers, elevator owners, and others may demand an immediate answer. Emotions often run high, especially with the death of a beloved horse or when legal and media-related issues arise. The veterinarian is left to provide immediate answers to many complicated issues while attempting to undertake a diagnostic investigation.

The simple act of finding a toxicant does not necessarily mean it is the causative agent or that it is even related to the problem at hand. Concluding thus without further evidence could skew the investigation and result in an inaccurate diagnosis and further illness in or death of other animals. A complete toxicologic investigation, including a thorough history, clinical signs, clinicopathologic testing (including necropsy if available), and analytic testing, should be undertaken in a careful and systemic manner. Internet websites can be used to provide accurate and rapid sources of toxicologic information to aid in the investigation and provide treatment options[1,2] (Table 54.1). An established working relationship with a diagnostic laboratory providing advanced testing and access to a board-certified toxicologist specializing in large animals will increase the likelihood of a positive diagnosis.

TABLE 54.1
Common Internet Websites

Type	Organization	Web Address
Animal poison control centers	ASPCA Animal Poison Control	www.aspca.org/pet-care/animal-poison-control
	Pet Poison Helpline	www.petpoisonhelpline.com
Diagnostic laboratories	American Association of Veterinary Laboratory Diagnosticians	www.aavld.org
General information	International Veterinary Information Service	www.ivis.org
	Veterinary Information Network	www.vin.com
Literature search sites	MedlinePlus	http://medlineplus.gov/
	National Agricultural Library	http://agricola.nal.usda.gov
	PubMed	www.ncbi.nlm.nih.gov/pubmed/medline.html
	Google Scholar	https://scholar.google.com/

Toxicology information	Extoxnet	http://extoxnet.orst.edu
	InChem	www.inchem.org
	MSDS Search Site	www.msdssearch.com/
	Toxnet	www.toxnet.nlm.nih.gov/

Refer to references 1 and 2 for a more complete listing of various toxicology information resources.

History

An accurate history is the starting point of any toxicologic investigation and, when done correctly, ensures that you have obtained the appropriate samples for further analysis. The investigation may vary from simple to complex but should always be done in a calm and ordered manner so that nothing is overlooked. The history should be used to provide information on circumstances surrounding the problem and may or may not identify the toxicant itself. Again, the presence of a toxicant in the environment does not necessarily mean that it is the source of the problem. Finding a toxicant is simply a starting point, as it may or may not support the clinical findings. Many other factors, including the dose and degree of exposure, need to be considered because exposure to a nontoxic dose generally does not result in a worthwhile diagnosis.

Species, breed, age, sex, body weight, and body condition are important pieces of information that should be collected for all involved animals. Current and past medications used, vaccination history, reproductive status, and illnesses in other animals are other pieces of useful data. Species identification is particularly important because some toxins are species specific or have different toxicologic profiles for different species. In addition, absorption of some toxins in ruminants, horses, and swine varies due to their specific gastrointestinal (GI) tracts. Some individual breeds may have different metabolic pathways, resulting in delayed metabolism and excretion. The presence of a P-glycoprotein transporter in the *MRD1* gene was recently identified in horses, and this may play a role in the development of breed-related toxicosis.[3,4,5] Very young and very old animals are often at increased risk for developing signs of poisoning at much lower doses. Neonatal animals absorb some metals and chemicals more readily than adults do, and nursing animals may receive toxic substances in the milk. Geriatric animals often have underlying deficiencies in liver metabolism and renal excretion that affect their ability to clear potential toxicants in a timely manner.

Initial questions often revolve around whether a known toxicant is present in

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the animals' environment. There are literally hundreds of toxicants, but many people, when questioned appropriately, often know or are suspicious of which one(s) may be playing a role. Common questions include whether medications, pesticides, herbicides, or fertilizers have recently been used or are present on the property. Is rodent control used in barns and outbuildings? Are there old junk piles on the property? What farm equipment and automotive products have been used recently? Have any old buildings been moved or torn down? Are there any known poisonous plants on the property?

Recent changes in animal management should be investigated in detail. Animal handlers should be questioned about the introduction of any new feeds, either new bags or fresh batches from a feed mill, or a complete change in feed. Feed should be examined closely for mold and the presence of any foreign bodies. Samples of feed, both as purchased and as fed, should be obtained and stored for further analysis. Hay and pasture should be examined for the presence of blister beetles, clippings from plants such as yew or oleander, other poisonous plants and weeds, foreign bodies, and mold. Again, samples should be taken and saved for analysis. Water samples from the original source and at the trough or stock tank should be taken and conserved in preserving jars for analysis if needed.

Clinical Signs

Live animals should have a complete physical examination performed and be closely examined for the presence of any unusual clinical signs. Ultimately, the conclusion of the physical examination may help to narrow the list of toxicants. Both the nature of the signs and the sequence of events should be documented. Specific abnormalities such as the color and consistency of mucous membranes, mouth lesions, blistering on pink skin areas, loss of hair around the eyes or tail, horizontal lines on hoof walls, presence of bite marks, and other abnormal findings may help determine whether the process is specific to an organ system or more generalized in nature. It is important to remember that in some instances this may not actually be an intoxication because other diseases or illnesses may result in similar generalized, nonspecific clinical signs.

The time frame from when the animal was last noted to be normal to the onset of signs should be determined, as should cessation, continuation, and duration of signs. Much of this information may need to be obtained in a historical manner from the animal caregiver because the veterinarian is often examining the animal

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at a single time point in the progression of signs and may otherwise miss valuable information.

Clinicopathologic Testing

The results of clinicopathologic tests often shorten the list of potential toxicants and may point toward a specific organ system and toxicant.[3] It is invaluable to obtain and either test or store appropriate samples at the time of the physical examination or postmortem. Blood should be examined for electrolytes, complete blood cell count (CBC), liver enzymes, blood urea nitrogen (BUN), and creatinine. Urine should be examined for specific gravity and discoloration, as well as crystals, casts, red blood cells, hemoglobin, and methemoglobin. Other body fluids (e.g., ocular, cerebrospinal), hair, and ingesta should be obtained as needed. All samples except blood and central nervous system (CNS) fluid can be frozen.[3,6,7] Blood should be centrifuged, the clot removed, and the sample stored in the refrigerator. It is important to remember that zinc and many of the trace minerals must be collected in a special tube for analysis.[6]

If possible, animals should be referred to the appropriate diagnostic laboratory for a postmortem completed by a board-certified pathologist. This is especially important if the animal is insured or legal issues are looming on the horizon. Animals sent to the diagnostic laboratory should be identified by tattoo, microchip, ear tag, or other means. Digital pictures taken before shipment can be used as a further source of identification. If a field necropsy is performed, extra samples should be taken because it is far wiser to take more samples than needed and discard them later rather than not have them at all. Often necropsy results will show specific lesions that may confirm a working diagnosis or point the veterinarian in another direction. Sometimes, the postmortem shows only generalized lesions or no lesions at all.

Analytic Testing

Analytic testing can be used to provide a definitive answer, but it must be used correctly and the results analyzed judiciously. Samples should not be sent to an analytic laboratory without some knowledge and forethought. The analytic laboratory will need guidance in terms of what they are testing for, as well as a history including the time since intoxication, dose of toxicant, and postmortem changes. Urine is the gold standard, especially for drug identification, but serum

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and plasma can also be used for analysis. Different forms of instrumentation and analyses are used for specific substances. For example, metals such as lead, zinc, arsenic, and others are analyzed with atomic absorption and spectrometry.[6] Enzyme-linked immunosorbent assay screens are generally sensitive, but the risk of cross-reaction with other substances may be large.[6] Drugs, many pesticides, and plant toxins are analyzed using gas or liquid chromatography–mass spectrometry, but unless specifically requested, the results are generally not quantitated and only demonstrate the presence of a toxicant.[3,5,6]

In summary, poisoning cases can vary from simple and direct to highly complex. It is important to investigate each one using a systematic approach, including history, clinical signs, clinicopathologic findings, and the results of analytic testing. As the veterinarian works through the investigation, each step may narrow the list of toxicants until a final answer is found. Alternatively, some investigations do not come to a conclusion, and the veterinarian is left to wonder what actually occurred. In many of these cases, environmental and management changes eliminated the toxicant before the investigation, leaving only the after effects.

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Poisonous Plants

Tam Garland

Plant Poisoning Considerations

The need for forage and therefore risk of toxicosis in both ruminants and Equidae is well established. Significant economic losses have been attributed to poisonous plants in regions and countries that rely on grasslands for raising livestock. Studies in the western United States suggest that plant poisonings adversely affect 3% to 5% of rangeland cattle, sheep, goats, and horses.[1] In China, poisonous grassland species of plants are responsible for an estimated $12.3 million of all livestock losses, including loss of performance and mortality from 2000 to 2006.[2] The estimated price of plant poisonings in Australia is $100 million (Australian dollars) per year.[3,4]

Based on these statics, poisonous plants pose significant dangers to all large animal species. Poisonings can occur for a variety of reasons. Toxic plants may be consumed inadvertently when baled into hay or processed into silage. Consequently, the animal may be unable to avoid the plant. However, hungry or thirsty animals are much more prone to eat plants that may otherwise be avoided. Naive animals, those unaccustomed to the surroundings, are more likely to consume plants that are unfamiliar to them.

The severity of toxicity may be affected by a variety of factors acting on the plant, such as season (summer versus winter) or moisture (either excessive or drought conditions). Severe heat may affect the toxicity of plants. The type of soil may be an influencing factor in the toxicity of the plants as well as the micronutrient levels in the soil. For example, some soils may be high in such nutrients as selenium, and some plants are selenium accumulators.

Investigation of possible plant poisoning on the affected premises include limited availability of forage as evidenced by animal observation and body condition scores; drought affecting plant growth, availability, and potentially high concentrations of toxins such as nitrates; recent storms having downed trees or fences or even a lightning strike; feed changes; inappropriate disposal of garden, shrub, or tree trimmings; and administration of herbal products for medicinal value. The level of toxins within a given plant species is often

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variable, even in samples obtained from the same pasture. Toxicity may be more pronounced in specific growth phases of the plant species, during times of stress or rapid growth, or after drying. Endophyte or fungal infections of the plant may also be important, either as the sole or an additional source of toxicity. These factors can be important in the timing and choice of plant specimens to identify, as well as assay for toxicity.

Individual animal factors play a role in both quantity of plant consumed and expression of clinical signs, thus making investigations more challenging. More than one type of toxic plant may have been ingested, which may lead to a wider variety of clinical signs. An individual animal may develop a taste for a plant being avoided by others in their herd or flock or be forced to eat it due to feed competition and low social order. Herbicide application may also enhance the palatability of plant species such as water hemlock.[5] Recent fertilizer application may increase nitrate concentrations in both plants and water supplies. Some plants can create a wide range of clinical signs depending on the amount consumed, either acutely or chronically. Research done on specific plants and toxins, and applied to feeding trials, has demonstrated that differences in metabolism, GI flora, and genetics may have a role in disease expression. Yet another variable is interaction between plant toxins and medications. Consumption of hay with two separate species of nightshade (*Solanum* spp.) has recently been identified as a factor in the development of clinical signs of ivermectin toxicosis in horses.[6]

Any suspicion of plant poisoning in an individual or group of individuals in a herd or flock should trigger a diligent investigation. The first step is a complete history of the affected individuals, the herd or flock, and the premises. In addition to routine health questions, emphasis should be placed on current feed, and whether any changes have been instituted; weather factors possibly affecting feed and water access or quality; fertilizer use on forage sources; differences in the management of affected and unaffected animals; and the potential for feeding errors or inadvertent exposure to garden refuse.[7] If the history yields evidence to strengthen the suspicion of plant poisoning, it may be necessary to immediately remove access to the suspected source of the clinical problems. If multiple animals have been affected, determining a timeline of events and cases may be helpful in evaluating the history and determining the cause.

The second step in the investigation should be thorough examination of affected animals to identify and characterize clinical abnormalities and lesions. Low body condition scores, particularly if accompanied by a strong appetite,

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should raise clinical suspicion of consumption of normally unpalatable plants, or lack of appropriate nutrition. Pregnant animals should be evaluated for signs of potential abortion. Quick access to a veterinary diagnostic laboratory, an animal poison control center, or an available online database where clinical signs are entered to yield potential diagnoses may help veterinarians quickly sort through potential differential diagnoses for the animal(s).[8] Symptomatic treatment is often the first line of medical response if the etiology has not been determined or a specific antidote is not available or approved for use in a particular species, especially a food animal species. Stress of treatment, particularly for ruminants, must be weighed against the benefits. Activated charcoal administration remains advisable for most acute toxicoses, if the animal can withstand the stress of administration. In monogastrics, stomach lavage followed by instillation of a slurry of activated charcoal in water may be the best option for acute cases. However, in ruminants this may be more challenging, and a rumenotomy for evacuation of contents and instillation of activated charcoal could be considered. In herd situations, rumenotomies on multiple animals may not be feasible or affordable. The cost of treatment of an animal may exceed the value of the animal, and treatment considerations for large animals and the associated cost should be discussed with owners or caregivers prior to treatment. A limited number of specific antidotes are described for a few plant poisonings, but their use may be restricted by cost and the need to avoid food residues. Enhanced excretion of toxins through laxatives or manipulation of urine or rumen pH may be applicable in specific situations where the toxic plant or principle has been confirmed.

Postmortem examination of affected animals should take place as soon after death as possible to maximize the opportunities to identify lesions and an etiology. In some plant poisonings, a specific odor may be noted, such as a bitter almond smell in cyanide poisoning (e.g., *Prunus* spp.), an acetone smell with white snakeroot poisoning, and a mousy aroma due to poison hemlock ingestion.[5]

Samples should be taken of rumen or stomach contents to look grossly and microscopically for recognizable plant fragments or seeds. An aliquot of the ingesta should be collected and labeled and a second sample frozen as soon as possible for toxicologic analysis. This is especially necessary when the possible toxin is unknown. Depending on the history and the timeline, more ingesta samples may be warranted from other segments of the digestive tract, especially the abomasums of calves. If the animal is a calf, collect contents of the

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abomasum in a similar fashion. Intact seeds may be identifiable in the distal intestinal tract or manure.

Samples of aqueous humor, amniotic fluid, and fetal stomach fluid for nitrate concentrations should be considered if clinical signs are compatible with a particular etiology. If the animal has died within a few hours, blood samples for hematologic, chemistry, and toxin profiling may be rewarding. Tissue samples are important for characterizing histologic lesions to confirm a plant toxicity or alternative etiology. All grossly affected tissues should be sampled and a piece of liver, both fresh and frozen, submitted for toxicologic analysis. If neurologic signs were observed, the brain should be removed with proper barrier precautions.[7]

Identification of the plants, foodstuffs, or water responsible for clinical signs or deaths is important for guiding treatment and further control of an offending agent. Inspection of the feed, including grain, hay, and pasture, may be necessary when dealing with suspected plant intoxications or suspected mycotoxins. Mycotoxins may be visible as moldy bits in the feed. However, the presence of mold does not ensure a mycotoxin, just as the absence of mold does not ensure the absence of mycotoxins (see the Mycotoxins section later). Several samples of the feed should be obtained for both toxic plant and mycotoxin testing. Remember as well that grasses can contain mycotoxins such as ergot. Walking the fence line looking for known toxic plants and evidence of grazing them is necessary for completeness. Samples of plants in question or unknown to you should be collected, especially if there is evidence of grazing.[8] Fresh plants may be placed in plastic bags, chilled, and shipped chilled overnight to a diagnostic lab. Additional samples can be pressed between newspaper sheets or brown paper with a board or heavy cardboard with some type of weight (e.g., books, gym weights) on top to keep them flat. The plants should remain under the weight for several days. Modern technology (smart phone) can be used to take photos of the plants and email or text them immediately to the toxicologist at the diagnostic lab. A telephone conversation with the toxicologist may assist you in finding the offending plant more quickly, perhaps even while you are on site. For identified plants known to have variable toxicity, such as larkspur (Color Plate 54.1) or selenium-accumulating plants, multiple samples should be taken of the same species, concentrating on areas where the plants have been visibly browsed or grazed.[9] Resources for plant identification include toxicology texts, the U.S. Department of Agriculture (USDA) plant identification website, the USDA Poisonous Plant Research Laboratory website and its publications, other

country-specific websites, and university or extension service plant experts.[10-16] In the United States, plant samples can be sent to the USDA Poisonous Plant Research Laboratory or Texas A&M's Veterinary Medical Diagnostic Laboratory. Other veterinary diagnostic laboratories may be able to identify the plants. Your diagnostic laboratory of choice may send the sample to one of these other labs, or you may need to request that it be sent to one of these laboratories.

Common plant poisonings often trigger a recognizable pattern of clinical signs and disease progression. These are reviewed below in more detail, with emphasis on diagnostic features, treatment options, and preventive measures. Less frequent causes of livestock morbidity and mortality are listed in tables, grouped by predominant clinical signs. Highlights of newly described toxicities that have the potential to harm multiple animals are presented in this chapter section.

Sudden Death

Poisonous plants, chemical toxins, lightning strikes, and infectious diseases are causes to consider when investigating sudden death in multiple animals. Numerous plant species have the potential to kill multiple animals within minutes to hours (Table 54.2).

TABLE 54.2

Plants With Potential to Cause Sudden Death in Large Animals[a]

Common Name	Scientific Name	Species Affected[b]	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Cyanogenic plants[1,10]	Many	O, B, C, E, P	Hydrogen cyanide	Worldwide	Cyanosis, dyspnea, muscle twitching, staggering, convulsions, coma	Sodium thiosulfate, sodium nitrite
Nitrate-accumulating plants[10]	Many	B, O, C, E	Nitrates	Worldwide	Weakness, drowsiness, chocolate mucous membranes, muscle tremors, tachycardia, tachypnea, staggering gait	Methylene blue
Copperweed[10]	*Oxytenia acerosa*	B, O	Unknown	Southwest U.S.	Appetite loss, weakness, coma, death in 1-3 days (longer in sheep)	

Death camas[10,17]	*Zigadenus* spp.	O, B, E	Zygacine	U.S., Canada	Salivation, bloody frothing, vomiting, muscle weakness, staggering, tachycardia, coma	Atropine
Dogbane[1]	*Apocynum* spp.	O, B, E	Cymarin	North America	Blue mucous membranes, tachycardia, mydriasis, progressive weakness, coma	
Easter (Atamasco) lily[10]	*Zephyranthes atamasca*	B, E	Unknown	Southern U.S., Mexico	Staggering, diarrhea, collapse	
Erva de rato[18]	*Palicourea*	B, O, C	Monofluoroacetate	Brazil	Depression, incoordination, seizures	
False hellebore, skunk cabbage[10]	*Veratrum* spp.	O, C, B	Cyclopamine, cyclopasine, jervine	U.S.	Salivation with frothing, weakness, vomiting, tachyarrhythmias, muscle tremors, coma, congenital defects	
Fitweed[10]	*Corydalis* spp.	B, E	Isoquinolone alkaloid	U.S., Canada	Tachypnea, seizures, staggering, snapping at objects, muscle tremors, depression	
Foxglove[10]	*Digitalis purpurea*	B, E	Digitoxin, digitalin, digoxin, saponins, alkaloids	U.S., Canada, Europe	Colic, melena, anorexia, polyuria, arrhythmias, seizures	
Goat's rue[19]	*Galega officinalis*	O, C, B	Galegin, hydroxygalegin	France	Asphyxia, hydrothorax	
Greasewood[1]	*Sarcobatus vermiculatus*	O, B	Oxalates	Western U.S.	Drooling, coma, crystalluria	
Jimsonweed, thornapple[20]	*Datura stramonium*	E, P, B	Tropane alkaloids	Worldwide	Colic, ileus, diarrhea, mydriasis, tachycardia, anorexia, muscle spasms, seizures, polyuria	
Larkspur[1]	*Delphinium* spp.	B, O, E	Alkaloids (methyllycaconitine)	Western U.S.	Weakness, staggering gait, muscle twitching, bloat, tachyarrhythmias, salivation, vomiting	Neostigmine
Locoweed[1,10]	*Astragalus* and *Oxytropis*	E, B, O, C	Swainsonine and other alkaloids	Worldwide	Depression, irregular gait, abnormal behavior, abortion, congestive heart failure	
Milkvetches[1]	*Astragalus* spp.	B, O, E	Miserotoxin	Worldwide	Acute signs of respiratory distress, muscle weakness, emphysema. Chronic	

					signs of goose stepping, knuckling, wheezing, drooling, collapse	
Milkweed[1]	*Asclepias* spp.	E, B, O, C	Cardenolides	North America	Depression, weakness, dyspnea, mydriasis, tachycardia, fever, spasms, bloat, respiratory paralysis	
Mistletoe[10]	*Phoradendron villosum*	E	Amines, toxic proteins	North America	Colic, diarrhea, bradycardia, hypotension	
Monkshood[10]	*Aconitum napellus*	E	Aconitine, mesaconitine, napelline, hypaconitine	U.S., Canada	Weakness, arrhythmias, salivation, bloat	
Nightshade[1]	*Solanum* spp.	E, B, P, O	Solanine and other glycoalkaloids	North America	Dypsnea with expiratory grunt, salivation, progressive weakness, trembling, paralysis	
Perilla mint[10]	*Perilla frutescens*	E, B, O, C	Perilla ketone, egomaketone, isoegomaketone	Eastern and southern U.S., Asia	Acute respiratory distress	
Poison hemlock[1,10]	*Conium maculatum*	O, B, P, E, C	Coniine, γ-coniceine, cyanapine	North America, Europe	Trembling, ataxia, salivation, incoordination, mydriasis, tachycardia, respiratory paralysis, coma, convulsions, abortion, birth defects	Atropine
Rayless goldenrod[1]	*Isocoma* spp.	E, B, O, C	Tremetol	Southwest U.S.	Muscle trembling (legs and nose), stiff gait, depression, constipation, urine dribbling, acetone odor on breath, coma	
Sweet clover[1]	*Melilotus* spp.	B, O	Coumarin converted to dicoumarol by molds	North America	Massive hemorrhages or sudden death, occasional bloat	
Tobacco[10]	*Nicotiana* spp.	E, B	Nicotine, anabasine	Southern U.S., Mexico	Muscle tremors, tachycardia, colic, dyspnea, diarrhea, congenital defects	
Water hemlock[21]	*Cicuta maculata*	B, E	Cicutoxin	U.S.	Salivation, frothing, muscle tremors, mydriasis, convulsions, coma	
White cedar,	*Thuja*	B, O, C	Thujone	Europe,	Hypersalivation,	

arbor vitae[19]	*occidentalis*			northeast U.S., Canada	colic, bloat, bloody diarrhea	
White snakeroot[1,10]	*Eupatorium rugosum*	B, E, O, C, P	Tremetol	U.S., Canada	Sluggish behavior, muscle tremors, anorexia, acetone breath odor, melena, constipation, dysphagia, tachyarrhythmias, congestive heart failure, myoglobinuria	
Yew[1]	*Taxus* spp.	B, E, O, C, P	Taxine alkaloids	Worldwide	Tremors, dyspnea, mydriasis, vomiting, diarrhea, weakness, convulsions, coma	

[a]Plant names in bold are discussed in more detail in the text.

[b]Species listed in relative order of toxicity importance: *B,* Bovine; *C,* caprine; *E,* equine; *O,* ovine; *P,* porcine.

Several groups of plants deserve greater discussion because of the frequency with which they are incriminated in the death of livestock and horses. All produce a range of clinical signs influenced by the amount consumed, time period of consumption, concentration of toxins, animal species, and in some instances, accommodation of ruminal microbes.

Larkspur (*Delphinium* spp.)

Larkspur (Color Plate 54.1) is considered one of the most important plant poisonings of range animals in the United States, second only to locoweed in its impact.[10] Cattle are most susceptible, but sheep and horses can be affected. The toxicity varies with the specific plant, stage of growth, amount eaten, and time period over which it is consumed. Numerous toxic diterpenoid alkaloids have been identified in the nine *Delphinium* spp., the most often cause of poisoning in cattle. Tall larkspur *(Delphinium barbeyi)* is considered the most problematic.[1] These alkaloids cause a curare-like blockade of neuromuscular junctions, by reversibly binding to nicotinic acetylcholine receptors. Larkspur consumption may also enhance the toxicity of another range plant, death camas (*Zigadenus* spp.).[17]

Death varies from sudden to 3 hours post larkspur consumption. Clinical signs include excitability, muscle tremors, stiffness, staggering, and a basewide stance.[10] Cattle may assume a kneeling position before collapsing. Bloat,

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regurgitation (ruminants), constipation, mild GI irritation, venous congestion, and aspiration pneumonia may be observed. There are no pathognomonic postmortem changes. A definitive diagnosis is usually reached by identifying pieces of larkspur in the upper GI tract.

If treatment is possible, bloat should be immediately addressed to relieve thoracic compression and reduce the chances of aspiration; however, the stress of treatment may hasten death. Intravenous (IV) physostigmine has been advocated at dosages of 0.04 to 0.08 mg/kg, repeated as needed over several hours.[10] Neostigmine at 0.04 mg/kg is slightly less effective. Neither drug is approved for use in food animals. An affected animal may be mistaken for a grass tetany case; however, treatment with magnesium exacerbates the effect of larkspur's toxins at the neuromuscular junction and should be avoided.

Prevention of larkspur toxicity in range cattle is challenging and requires knowledge of when the plants are most toxic and most palatable, particularly if other forage is limited. For example, early spring grazing of cattle in pastures with tall larkspur should be curtailed as soon as the flower stalks begin to elongate. Sheep are more tolerant and can be used to reduce the plant's density. Aversion to eating larkspur has been created with lithium chloride administration, a strategy that may be worthwhile on some ranches.[22] Larkspur reduction may not be cost-effective with herbicides, leading investigators to use insect control with the larkspur myrid *(Hoplomachus affiguratus)*.[10]

Cyanogenic Plants

Toxicity induced by consumption of cyanogenic plants produces sudden death, along with the characteristic signs of bright red mucous membranes and bright red venous blood.

Clinical signs are rarely observed but include obvious respiratory distress, rapid breathing, bloat, salivation, muscle twitching, staggering, mydriasis, cardiac arrhythmias, and convulsions.[10] Cyanide blocks molecular oxygen transfer in cytochrome oxidase systems in mitochondria causing tissue anoxia.[23] Ruminants are more susceptible than monogastrics because rumen microorganisms readily release cyanide from the cyanogenic glycosides. Acute, sublethal cases generally recover within an hour. Toxicities have also been reported in alpacas.[24] Chronic cyanide toxicity has been associated with sorghum consumption in pregnant horses and cattle. The foals and calves are born with arthrogryposis. Animals may also develop neurologic damage to the

brain and spinal cord resulting in weakness, ataxia, and urinary incontinence. Low doses of cyanogenic glycosides can be goitrogenic.[10]

Cherry red venous blood may be observed in fresh postmortem examinations. In ruminants, a bitter almond odor may be detected in rumen contents.[10] Tracheal, pulmonary, and muscle congestion may be observed, along with hemorrhages in multiple organs. Cyanide ion content may be measured in refrigerated samples of heart, brain, or skeletal muscle or rumen contents. Blood samples for analysis should be kept in airtight containers at 4° C until analyzed. A sensitive field test for use on forage samples or rumen content has been developed using alkaline picrate–treated filter paper strips.[11]

A number of plants have varying levels of cyanogenic glycosides, including the following trees, shrubs, crops, and grasses: acacia, African star grass, apple, arrow grass, Bahia grass, bamboo, Bermuda grass, birdsfoot trefoil, bracken fern (Color Plate 54.2), cassava, chokecherry, Christmas berry vetch, corn, elderberry, eucalyptus, flax, flowering quince, hydrangea, Indian grass, Johnson grass, lima bean, mountain mahogany, poison suckleya, reed canary grass, service berry, sorghum, South African daisy, star grass, Sudan grass (*Sorgum* spp.), tall manna grass, Texas queen's delight, and white clover.[10,23] Seeds of apples and crabapples (*Malus* spp.) and the seeds, as well as leaves of the *Prunus* spp. (bitter almond, cherry, chokecherry, apricot, peach, nectarine, plum, mock orange), may have large amounts of cyanide. Drying as hay or incorporation into silage generally decreases the toxic potential of the forage plants; most are not routinely grazed or browsed. Early growth phases of the plants are the most toxic. Poisoning is most likely if animals eat a large quantity in a short period of time. Wilting, frost, drought, or other damage to the plant enhances toxicity.[1] Toxicity is measured as cyanogenic potential. Plant material containing more than 20 mg per 100 g (200 ppm) cyanide potential is reason for concern, but this varies between species.[23] Cyanogenic potential is significantly reduced by properly curing forages for hay or ensilage.

If the diagnosis is made rapidly, some cattle and sheep may be saved by IV or intraperitoneal (IP) injection of 20 mL of a 10% solution of sodium thiosulfate mixed with 10 mL of a 10% solution of sodium nitrite.[1] However, this treatment is not approved for use in food animals. An alternative treatment has been described for ruminants using only a 30% to 40% thiosulfate solution IV at a dose of 25 to 50 g/100 kg of body weight.[11] Administration of a gallon of vinegar diluted in 3 to 5 gallons of water administered by stomach tube to help

acidify the rumen has also been recommended.[10] Preventive measures are largely focused on limiting access to highly cyanogenic plants and trees, particularly during rapid early-growth phases, and planting varieties with lower cyanogenic potential.

Nitrate Toxicity

Many plants and some water sources contain harmful concentrations of nitrates, which can cause a wide range of clinical signs from sudden death to congenital defects in ruminants, camelids, and monogastrics. Examples of plants known to accumulate nitrates are listed in Table 54.3. When photosynthesis is impaired by shade or prolonged cloudiness or excessive nitrogen is applied to plants (e.g., fertilizer), nitrate accumulation may reach dangerous levels. Other triggers for nitrate accumulation include drought, frost, hail, and herbicide application. Nitrates are water soluble and can leach from harvested forages, occasionally causing toxicosis by elevating concentrations in the lowest bales of a rained-on haystack.[25]

TABLE 54.3
Plants With Potential to Accumulate Nitrates

Type	Common Name	Scientific Name	Reference(s)
Crops	Barley	*Hordeum* spp.	25
	Beets	*Beta vulgaris*	10
	Corn	*Zea mays*	10, 25
	Flax	*Linum* spp.	10
	Kale	*Brassica oleracea*	10
	Oats	*Avena* spp.	24, 25
	Pearl millet	*Pennisetum typhoides*	10, 25
	Rape	*Brassica napus*	10
	Rye	*Secale cereale*	10, 25
	Soybeans	*Glycine max*	10, 25
	Sunflower	*Helianthus annuus*	10
	Turnips	*Brassica rapa*	10
	Wheat	*Triticum aestivum*	10, 25
Forages	Alfalfa	*Medicago sativa*	10, 25
	Barnyard grass	*Echinochloa* spp.	10
	Button grass	*Dactyloctenium radulans*	26
	Johnson grass	*Sorghum halepense*	10, 25
	Sudan grass	*Sorghum vulgare*	10, 25
	Sweet clover	*Melilotus* spp.	10
	Tall fescue	*Lolium arundinaceum*	25
Weeds	Canada thistle	*Cirsium arvense*	10
	Cheese weed, mallow	*Malva* spp.	10

	Dock	*Rumex* spp.	10, 25
	Field bindweed	*Convolvulus arvensis*	10
	Fireweed	*Kochia* spp.	25
	Goldenrod	*Solidago* spp.	10
	Jimsonweed	*Datura stramonium*	10
	Kochia (summer cypress)	*Kochia scoparia*	10, 25
	Lambsquarters	*Chenopodium* spp.	10, 25
	Nightshades	*Solanum* spp.	10, 25
	Pigweed	*Amaranthus* spp.	10, 25
	Ragweed	*Ambrosia* spp.	10
	Russian thistle	*Salsola kali*	10
	Smart weed	*Polygonum* spp.	10

In ruminants, ingested nitrates are converted to nitrites and ammonium in the forestomachs. Nitrates can cross the placenta. If excessive nitrates are ingested, absorbed nitrites can trigger oxidation of the ferrous iron in hemoglobin, producing methemoglobin. Chocolate brown mucous membranes and blood are characteristic findings. Vasodilation and hypotension may result, leading to hypoxia, dyspnea, exercise intolerance, death, fetal stress and subsequent abortion, stillbirths, and/or weak neonates.[27] In bulls, sperm abnormalities and degenerative changes within the testes have been reported.[28] If the animals are anemic or hypoxic for any other reason, methemoglobinemia will have even greater consequences. At postmortem examination, a brownish cast of the tissues due to the methemoglobinemia may be apparent.

Congenital hypothyroidism in equine neonates is most often caused by insufficient iodine intake by the broodmare but can also be caused by excessive nitrate intake. Multiple animals in the herd may be affected.[29,30] Signs of high nitrate intake may not be observed in the broodmare. Abortion may result, or more commonly a dysmature foal is produced after prolonged gestation. The affected neonates have varying degrees of signs but classically include mandibular prognathism, flexural deformities of the forelimbs, secondary rupture of the common digital extensor tendon just above the carpus, poorly ossified cuboidal bones, and poor immune function. If recognized at birth, these foals can survive to be useful animals if treated intensively with splints to address the flexural deformity, very limited weight-bearing until the cuboidal bones ossify, and measures to reduce the likelihood of infection. If an affected foal is allowed to bear weight before full ossification of the cuboidal bones in the hocks and carpi, angular limb deformities will likely result. The syndrome can be prevented by avoiding high nitrate forage or water sources and ensuring that there is adequate iodine in the mare's diet. Confirmation of nitrate toxicity is based on demonstration of elevated levels in forages, weeds, water, or body

fluids such as aqueous humor, fetal stomach fluid, and amniotic fluid.[1,10] In ruminants, plants containing more than 1.5% nitrates (measured as KNO_3) dry weight may be lethal. Sublethal effects are seen from feed containing 0.5% to 1.5% nitrates. Seeds are usually unaffected by high nitrates in other plant parts. Ruminants can adapt to higher nitrate feeds if their introduction is gradual. Reproductive effects in ruminants are linked to forage concentrations greater than 5000 ppm on a dry matter basis.[27] In adult ruminants, signs of methemoglobinemia are seen with forages containing 2000 to 10,000 ppm nitrates on a dry matter basis. Water with more than 200 ppm is excessive for pregnant ruminants; 30 ppm is the recommended limit for broodmares.[10,29,30] In nonpregnant animals, a range of 445 to 1000 ppm in water is considered dangerous for livestock.[10,26]

Treatment of nitrate toxicity in ruminants is restricted by the paucity of approved drugs. Methylene blue administration is prohibited in food animals in the United States for at least 180 days before slaughter but, if permitted in other areas, may be given IV at a rate of 4 to 15 mg/kg body weight as a 2% to 4% solution.[10] In acute ruminant cases, the adjunct therapy of the administration of either cold water or vinegar to slow nitrate reduction, and mineral oil to hasten passage of the ingested source has been used, provided the animal can withstand the stress of intubation.[10]

Forages known to have high nitrate potential should be tested prior to feeding livestock, particularly if fertilizer or poultry litter has been used on the forage. High-nitrate forages can potentially be ensiled to reduce the nitrate content by as much as 30%.[26] Nitrate levels are highest at night and in early morning, and this knowledge can be applied to the timing of pasture access and hay cutting. If high-nitrate forage is harvested, the nitrate content will not dissipate on curing. Gradual introduction of high-nitrate forage into the ruminants' diet will permit rumen microflora to adapt, but this should preferentially begin with nonpregnant adult animals to minimize the reproductive effects. Monensin in the diet may change the threshold for toxicity[31] and probiotics containing *Propionibacterium* spp. reduce nitrates, which may also be useful.[10]

Neurologic Signs

Many plant ingestions result in neurologic signs exclusively or as part of an array of signs. Plants linked to neurologic deficits are listed in Table 54.4. Many

other plants found in Australia and New Zealand also can produce neurologic signs.[3] Abnormal behavior, seizures, coma, ataxia, weakness, and muscle tremors may be associated with ingestion of poisonous plants or other medical conditions such as rabies, encephalitis, and electrolyte disorders. Perennial ryegrass infected with an endophyte, *Neotyphodium lolii*, causes perennial ryegrass staggers in all herbivores. The syndrome, caused by lolitrem B, was recently reproduced in horses demonstrating varying degrees of muscle fasciculations, tremors, truncal swaying, basewide stance, and limb edema.[35] Signs abate when the forage is changed.

TABLE 54.4
Plants Associated With Neurologic Signs[a]

Common Name	Scientific Name	Species Affected[b]	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Blown grass, Pacific bent grass[3]	*Agrostis avenacea*	B, O	Corynetoxins in nematode	Australia, New Zealand, southwest U.S.	Incoordination, weakness, muscle weakness, rocking stance, high-stepping, collapse, seizures, abortion	
Bracken fern[10]	*Pteridium aquilinum*	E, P, B, O	Ptaquiloside	Worldwide	Weight loss, progressive incoordination, depression, tremors, crouching stance with arched neck (equine), blindness (sheep), aplastic anemia (ruminants), thrombocytopenia, bladder and gastrointestinal cancer	Thiamine
Buttercup[10]	*Ranunculus* spp.	B, E	Ranunculin	North America, Europe	Salivation, depression, blindness, hematuria, oral ulcers, diarrhea, colic	
Caltrop or carpetweed[10]	*Kallstroemia* spp.	B, O, C	Unknown	Southwest U.S.	Hindlimb weakness, knuckling, seizures, posterior paralysis	
Castor bean[19]	*Ricinus communis*	E, B, O, C, P	Ricin	Worldwide	Bloody diarrhea, tenesmus, colic, trembling, incoordination, seizures	

Coyotillo[10]	*Karwinskia humboldtiana*	B, O, C, E, P	Unknown	Southwest U.S.	Hypersensitivity, muscle tremors, abnormal high-stepping gait, diminished reflexes, progressive paralysis	
Fitweed[10]	*Corydalis* spp.	B, E	Isoquinolone alkaloid	U.S., Canada	Tachypnea, seizures, staggering, snapping at objects, muscle tremors, depression	
Golden chain tree[10]	*Laburnum anagyroides*	E, B	Cystisine	Southern U.S.	Incoordination, muscle tremors, mydriasis, excitement, seizures, coma, vomiting, diarrhea, paralysis	
Hairy cat's ear, flatweed[32]	*Hypochaeris radicata*	E	Unknown	U.S., Europe, Australia	Bilateral stringhalt, depression, aggression	Phenytoin
Hairy vetch[10]	*Vicia villosa*	B, E	Unknown	U.S., Europe	Excitement, slobbering, oral ulcers, nasal discharge, cough, stiffness, anorexia, weakness, seizures, swelling of the head and neck, pruritic dermatitis, diarrhea, abortion, myocardial necrosis	
Halimium[33]	*Halimium brasiliense*	O	Unknown	Brazil, Uruguay	Transient seizures when excited, muscle tremors, ventroflexion of neck or opisthotonus, nystagmus, tetanic spasms, postictal ataxia	
Horse chestnut, buckeye[10]	*Aesculus hippocastanum*	B, O, C, E	Aesculin, fraxin, alkaloids	U.S., Europe	Muscle tremors, incoordination, depression or excitability, hopping gait, dorsomedial strabismus (ruminants), gastroenteritis (monogastrics)	
Horse nettle[10]	*Solanum carolinense*	B, E	Solanine	U.S., Canada	Falling when excited, incoordination, anorexia, emaciation, rough coat, constipation, mouth inflammation	Physostigmine
Horsetail or	*Equisetum* spp.	E, B, O	Aconitic acid, palustrine,	Worldwide	Weight loss, staggering, muscle	Thiamine

scouring rush[10]			thiaminase		tremors or rigidity, paraparesis, tachycardia, diarrhea, coma	
Jamaican nettle tree[34]	*Trema micrantha*	B, C, E	Trema toxin, ammonia	Americas	Apathy, blindness, recumbency, paddling, coma (hepatic encephalopathy)	
Jimmyweed[10]	*Haplopappus heterophyllus*	B, E	Tremetol	Western U.S., Mexico	Depression, trembling, weakness, knuckling, seizures, paralysis, congestive heart failure, acetone breath smell	
Jimsonweed, thornapple[35]	*Datura* spp.	E, P, B	Tropane alkaloids	Worldwide	Colic, ileus, diarrhea, mydriasis, tachycardia, anorexia, muscle spasms, seizures, polyuria	
Johnson grass[10]	*Sorghum halepense*	B, O, E	Hydrocyanide	Worldwide	Posterior ataxia, urinary incontinence, cystitis, weight loss	
Kochia[1]	*Kochia scoparia*	B, O, E	Thiaminase, nitrates, oxalates	Worldwide	Ataxia, muscle spasms, depression, blindness, photosensitization	Thiamine
Locoweed[36]	*Astragalus* and *Oxytropis* spp.	E, B, O, C	Swainsonine (endophyte produced)	Worldwide	Abnormal behavior, abortion, reduced fertility, skeletal malformations, weight loss	
Locust trees[19]	*Robinia* spp.	E, B, O, C	Robinin, robitin	North America, Europe	Diarrhea, anorexia, weakness, posterior paralysis, mydriasis, dyspnea, arrhythmias	
Lupines[1]	*Lupinus* spp.	O, B	Piperidine, quinolizidine	U.S., Canada	Salivation, frothing, depression, dyspnea, loss of muscle control, convulsions, coma, birth defects	
Mescal bean, Eve's necklace	*Sophora* spp.	B, O, C, E	Cystisine	Southwest U.S., Mexico	Incoordination, violent muscle tremors, falling, stiffness, respiratory paralysis	
Milkvetches[10,36]	*Astragalus* spp.	B, O, E	Miserotoxin	North America	Acute and chronic—acute: respiratory distress, muscle weakness, emphysema; chronic: goose-stepping, knuckling, wheezing, drooling, posterior	

					paresis, collapse	
Milkweed[36]	*Asclepias* spp.	E, B, O, C	Glycosidic cardenolides	North America	Depression, weakness, dyspnea, ataxia, seizures, arrhythmias	
Morning glory[3]	*Ipomoea* spp.	B, O, C, E	Calystegines	Worldwide	Ataxia of hindlimbs, staggering	
Nightshade[10]	*Solanum* spp.	B, O, C, E	Solanine	Worldwide	Fatigue, muscle tremors, head tremors, seizures, bloat, congestion of lungs, heart, spleen	Physostigmine
Oak[10]	*Quercus* spp.	B, E, O, P	Gallotannins	North America, Europe	Incoordination in horses along with weakness, ileus, mouth ulcers, mucosal discoloration, patchy sweating, abnormal feces, colic, dark urine	
Paspalum grasses[37]	*Paspalum* spp.	B, E	Ergot alkaloids	Worldwide	Staggers, muscle tremors, seizures, abortion, gangrene	
Poison hemlock[1]	*Conium maculatum*	O, B, P, E	Coniine, γ-coniceine	North America, Europe	Trembling, ataxia, salivation, incoordination, mydriasis, tachycardia, respiratory paralysis, coma, convulsions, birth defects	Atropine
Russian knapweed[1]	*Centaurea repens*	E	Sesquiterpene lactones	Western U.S.	Twitching of lips, tongue flicking, involuntary chewing, weight loss, emaciation, poor prehension, incoordination, muscle tremors, facial paralysis	
Ryegrass[38]	*Lolium perenne*	B, O, E	Lolitrem B	Worldwide	Muscle tremors, fasciculations, truncal swaying, basewide stance, slowed movement, limb edema	
Sagebrush[10]	*Artemisia* spp.	E	Unknown	Western U.S., Mexico	Abnormal behavior, ataxia, sage aroma in breath and manure	
Sneezeweed[1]	*Hymenoxys* spp.	O, B, E	Sesquiterpene lactones	North America	Equine: weakness, incoordination, foaming at the mouth, seizures; ruminants: chronic vomiting,	

					emaciation, stiffness	
Squirrel corn, Dutchman's breeches[10]	*Dicentra* spp.	B, E	Isoquinoline alkaloid	North America	Muscle tremors, seizures, extensor rigidity, dyspnea, pain	
Sudan grass[10]	*Sorghum sudanense*	B, O	Hydrocyanide, nitrates	Worldwide	Posterior ataxia, urinary incontinence, cystitis, weight loss	
Yellow jessamine[10]	*Gelsemium sempervirens*	E, B, O, C, P	Gelsemine, gelseminine	Eastern U.S., Mexico	Weakness, hypothermia, mydriasis, seizures, extensor rigidity, coma	
Yellow star thistle[1]	*Centaurea solstitialis*	E	Sesquiterpene lactones	U.S., Argentina, Australia	Twitching of lips, tongue flicking, involuntary chewing, weight loss, emaciation, poor prehension, incoordination, muscle tremors, facial paralysis	

[a]Plant names in bold are discussed in more detail in the text.

[b]Species listed in relative order of toxicity importance: *B,* Bovine; *C,* caprine; *E,* equine; *O,* ovine; *P,* porcine.

Locoweed and Milkvetch

Locoweed and milkvetch (*Astragalus* spp. and *Oxytropis* spp.) (Color Plate 54.3) are the most important plant-related toxicoses in the western United States and significantly affect animals in other areas of the world.[10] A review of poisonous plants affecting livestock in China suggested locoweeds were responsible for an estimated 80% of all livestock losses due to plant toxicoses.[2] Many species in these genera can cause four different toxic syndromes: sudden death from methemoglobinemia due to nitro compounds in cattle and sheep (milkvetch [*Astragalus* spp.]); respiratory syndrome with emphysema-like signs, most often seen in sheep (milkvetch [*Astragalus* spp.]); neurologic signs (*Astragalus* spp. and *Oxytropis* spp.); and selenium toxicosis (*Astragalus* spp.). Recent investigations have shown that the toxin swainsonine, responsible for the signs of nervous system dysfunction, is produced by an endophyte *(Undilum oxytropis)* in the plant seeds rather than by the plants themselves.[39] Swainsonine triggers clinical signs after chronic locoweed ingestion in horses and ruminants. This same toxin poisons horses and cattle consuming swainsona or darling pea (*Swainsona* spp.) in Australia.[3] The toxin creates a lysosomal storage disease in

which α-mannosidase is inhibited, resulting in swelling of axonal hillocks and growth of new dendrites and synapses in severe locoweed cases, a nonreversible change.[36]

Clinical neurologic signs of locoweed intoxication begin with depression and incoordination and progress to aberrant behavior, aggression, circling, weight loss, and eventually death if locoweed consumption continues. In affected horses, this leads to unpredictable behavior, endangering riders and handlers, so these animals are often euthanized or perhaps salvaged for breeding. Similar signs may be seen in horses forced to eat sagebrush.[10] Pregnant animals may abort or give birth to neonates with neurologic signs. In cattle and sheep, swainsonine-induced damage to the lungs and hearts may contribute to high mountain disease, characterized by right-sided heart failure.[10]

Nitro-toxins are the most common toxins found in the milkvetch species of *Astragalus* and are primarily responsible for ruminant herd and flock problems. The toxic principles are β-D-glycosides converted to 3-nitro-1-propanol (miserotoxin) in the rumen and subsequently changed to the toxic compound 3-nitropropionic acid in the liver.[36] Signs of acute toxicosis include weakness, tachycardia, respiratory distress, coma, and death. Chronic consumption results in neurologic signs beginning with weakness, incoordination, fetlock knuckling, and goose stepping, progressing to paralysis and death. Respiratory emphysema, as well as incoordination and weakness, may be observed in both acute and chronic cases, particularly in sheep.

Chronic ill-thrift is attributed to chronic locoweed consumption. Research in food animals has demonstrated a number of effects attributed to swainsonine, including reduced production of growth hormone and thyroxine, decreased intestinal absorption of nutrients, and reduced immune response to vaccinations. These can lead to poor weight gain and increased frequency of infections.[10]

Diagnosis of locoism is based on clinical signs and confirmed by measurement of swainsonine and/or α-mannosidase in serum. Vacuolation of peripheral lymphocytes may be evident in some cases. Vacuolation of many tissues, particularly brain and liver, may be seen histologically after finding little gross change at necropsy. Treatment is removal from locoweed forage.[10]

Locoweed is usually not palatable but will be eaten if more enticing forage is not available. For example, many locoweed species start growth early in the spring, attracting livestock less interested in dormant grasses. This period of preference is influenced by rainfall, so the impact of locoweed and milkvetch

species will vary from year to year even within a region. Prevention is challenging if alternative forages are not available in the spring. One innovative approach is a conditioned food aversion model that combines feeding fresh-picked locoweed to naive animals with lithium chloride administration by stomach tube. The treated animals form a strong and lasting (>3 years) aversion to locoweed following a single dose but must be pastured separate from nonaverted animals on locoweed areas to prevent social facilitation from extinguishing the aversion.[22]

Musculoskeletal Disease Attributed to Plant Poisoning

Plant poisonings may affect the skeletal system, resulting in abnormal bone growth or remodeling. Day-blooming jasmine *(Cestrum diurnum)* induces calcinosis in horses and cattle by means of calcinogenic glycosides converted to vitamin D–like compounds.[10,40] This plant is found in the southeastern United States and tropical countries. Other plants with this potential include *Solanum malacoxylon, Solanum sodomaeum, Solanum linnaeanum, Trisetum flavescens,* and *Nierembergia veitchii.*[10] Those affecting the fetus are discussed in the Reproductive and Neonatal Effect of Poisonous Plants section later.

Signs of muscle dysfunction in livestock and horses have been attributed to ingestion of a number of plants, often as part of a larger panoply of signs. Muscle tremors may be manifestations of muscle or nervous system dysfunction, as well as electrolyte disturbances or pain. The toxin tremetol (tremetone and other compounds) affects all species of livestock and horses consuming it. The effects of the toxin are cumulative and affect both skeletal and cardiac muscle. Important plants include white snakeroot *(Eupatorium rugosum),* rayless goldenrod *(Haplopappus heterophyllus),* and burrow weed *(Isocoma pluriflora).*[10] Adult cattle are relatively unaffected by consumption of white snakeroot but pass the toxin through the milk, causing clinical signs in milk-fed calves. Rayless goldenrod produces myonecrosis and cardiomyopathy at higher doses in goats.[41] Horses, cattle, and pigs may be affected by this plant. The effect of tremetol on myocardial tissue may lead to arrhythmias and congestive heart failure. Tremorgenic mycotoxins should also be considered in cases with muscle tremors, particularly in livestock grazing perennial ryegrass or *Paspalum* species such as dallisgrass or bahiagrass.[42]

Senna (previously *Cassia*) species such as coffee weed (Color Plate 54.4) and sickle pod are an important source of skeletal and cardiac muscle degeneration and gastroenteritis in cattle, sheep, goats, horses, and pigs.[10] Renal and hepatic failure may be observed in severe cases. Gossypol poisoning attributed to feeding cottonseed or its products containing a high level of gossypol is a source of muscle degeneration and significant morbidity and mortality in livestock.[10]

Summer Pasture–Associated Myositis and Equine Atypical Myopathy

Recent research defined ingestion of box elder seeds from female trees *(Acer negundo)* (Color Plate 54.5) as a cause of acute, nonexertional, severe, often fatal rhabdomyolysis in pastured horses and a donkey in the United States and Canada.[43] The syndrome of atypical myopathy seen in horses, donkeys, and zebras in Europe may also have this underlying cause because outbreaks have been linked to ingestion of maple leaves *(Acer pseudoplantanus)* covered with European tar spot *(Rhytisma acerinum)*.[44] Box elder trees are also found in Europe. In addition, European researchers have demonstrated a link between atypical myopathy and *Clostridium sordellii* toxin.[45] In both syndromes, one or multiple animals may be affected, typically on a premises having the equids for a portion of the day on a pasture with sparse grass surrounded by or with trees, which, along with any seeds or fruiting bodies, are often knocked down after a storm or high winds.[43,46] The toxic principle identified in box elder seeds is hypoglycin A, a branched-chain amino acid, which is metabolized to methylene cyclopropyl acetic acid (MCPA), a potent inhibitor of multiple acyl-CoA dehydrogenases. Lack of these enzymes damages mitochondria and impairs lipid metabolism within muscle cells, leading to lipid accumulation, thus limiting the muscle cell's energy supply and causing cell death.[43]

Clinical signs include muscle weakness, recumbency, and myoglobinuria.[43] Other reported signs include dysphagia, esophageal obstruction, or colic-like signs. In atypical myopathy, myocardial damage may be detected with electrocardiography (ventricular premature depolarizations, prolonged QT intervals); echocardiography (abnormal ventricular wall motion); and elevated serum troponin concentrations.[47] Histologically, the change in both diseases is marked myofibril degeneration with intramyofiber lipid accumulation in skeletal, respiratory, and cardiac muscles. Additional confirmation of this

etiology for rhabdomyolysis can be obtained at specialized laboratories by demonstration of increased urinary organic acids (specifically ethylmalonic and methyl succinic acids and glycine conjugates) and abnormal patterns of serum acylcarnitines.[48] Other toxic etiologies to be considered for muscle disease are white snakeroot, rayless larkspur, and monensin toxicity.

Treatment of affected cases is symptomatic but should include attention to establishing a positive energy balance. Case fatality rate is high despite treatment.[43] Preventive measures should focus on provision of sufficient forage to deter horses from consuming box elder seeds, rapid removal of downed box elder branches after high winds, and planting less toxic trees as windbreaks.

Cardiovascular and Hematologic Plant Toxicities

Ingestion of plants containing toxins affecting myocardial function may result in a wide variety of signs, including sudden death. Consumed plants most noted for producing myocardial effects are those containing cardiac glycosides. Cattle are most frequently affected. These include the pasture plants milkweed (*Asclepias* spp.), dogbane or Indian hemp *(Apocynum cannabinum),* blue-eyed grasses (*Sisyrinchium* spp.), and a number of plants possibly more likely to be found in gardens than pastures: foxglove (*Digitalis* spp.), hellebores (*Helleborus* spp.), hyacinth (*Hyacinthium* spp.), kalanchoe (*Bryophyllum* spp.), lily of the valley *(Convallaria majalis),* oleander (*Nerium* spp.), periwinkle *(Vinca major),* pheasant's eye *(Adonis microcarpa),* spindle tree (*Euonymus* spp.), squill (*Drimia* or *Urginea* spp.), and star of Bethlehem (*Ornithogalum* spp.). Digestive signs of hemorrhagic enteritis with colic may also be seen.[10] Gousiekte is a syndrome of heart failure and sudden death affecting sheep and cattle in South Africa 4 to 6 weeks after ingestion of the pavetamine-containing Rubiaceae (coffee) family of plants. Six plants in the genera *Fadogia, Pavetta,* and *Vangueria* have been implicated in significant losses. New research suggests that toxin production in the plants may be linked to their infection by *Burkholderia* spp. of endophytic bacteria.[49] The toxin inhibits myocardial protein synthesis, resulting terminally in dilated cardiomyopathy and congestive heart failure.[50]

Four important plants with toxins that damage the myocardium and cause mortality in large animals are yew (*Taxus* spp.), avocado *(Persea americana),* death camas (*Zigadenus* spp.), and summer pheasant eye (*Adonis* spp.). Avocado poisoning in horses produces edematous swelling of the head and neck and subsequent respiratory distress, which may progress to congestive heart failure.

Likewise, goats may develop signs of heart failure. The udder is affected by avocados in female horses, cattle, and goats, creating a noninfectious mastitis.[10] Summer pheasant eye consumed in hay caused signs of colic and death in horses, and pigs have died after consuming a diet containing *Adonis* seeds.[51]

Signs of anemia and hemorrhage are linked to ingestion of several groups of plants that cause methemoglobinemia, hemolysis, or thrombocytopenia. Ingestion of wilted maple leaves or bark (*Acer* spp.) (Color Plate 54.6), most often red maple, results in oxidative damage to erythrocytes and acute Heinz body anemia or methemoglobinemia in horses and zebras. Weakness, tachycardia, tachypnea, icterus, and hemoglobinuria may occur. In severe cases, laminitis, colic, or abortion may occur.[52] In ruminants, nitrate-accumulating plants that cause methemoglobinemia should be considered (see Table 54.3). Wild onions and garlic can produce hemolytic anemia, most often observed as a clinical problem in cattle.[10]

Plants containing coumarin, such as sweet clover (*Melilotus* spp.), have the potential for endogenous coumarin to be converted to dicoumarol if cut plants become moldy. Signs ranging from subtle to death may be observed, particularly in cattle, depending on the amount of dicoumarol present and any trauma to the animal causing bleeding. Transfusion and vitamin K_1 administration may be necessary in moderate to severe cases.[10]

Thiaminase enzymes in bracken fern *(Pteridium aquilinum)* and horsetail (*Equisetum* spp.) produce a thiamine deficiency most often causing neurologic signs in horses. Other signs associated with bracken fern ingestion are due to alternate toxins, particularly ptaquiloside, a sesquiterpene glycoside responsible for detrimental effects on the bone marrow and neoplastic changes in the bladder and upper GI tract. The cancerous changes in the urinary tract may manifest as enzootic hematuria in cattle. Retinal changes resulting in blindness are reported in sheep. The toxins are transmitted through milk. Protamine sulfate administration may counteract the effects on blood coagulation. In horses, bracken fern may also produce colic.[10,36]

Digestive and Hepatic Plant Poisonings

A plethora of plants have the potential to induce pathology in the digestive tract and liver. Plants causing significant impact in large animals are listed in Table 54.5. The effects of a plant may be mechanical or chemical irritation, altered

motility, or altered cell function. Depending on the toxin, plant species, animal species, and stage of intoxication, a single species of plant may produce a wide range of signs, even within the same animal. Clinical signs may include excessive salivation or slobbering, anorexia, dysphagia, colic, vomiting or regurgitation in ruminants, bloat, constipation, diarrhea, and melena. Excessive salivation may result from injury due to plant awns, irritant substances in the plant, mold infection of the plant (e.g., red clover and slaframine production), and inability to swallow. Sources of plant awns include grasses (e.g., foxtail, needle, squirrel tail, bristle, sandbur, medusahead rye, prairie threeawn, tanglehead, tickle grass), cacti (e.g., prickly pear), nettles, and many seed pods.[10,55] Substances irritating to mucous membranes are found in a number of plants and may also produce signs of diarrhea in the more distal digestive tract.

TABLE 54.5
Plants Producing Gastrointestinal (GI) Clinical Signs[a]

Common Name	Scientific Name	Species Affected[b]	Toxin(s)	Plant Habitat	Clinical Signs	Specific Therapy
Pyrrolizidine alkaloid plants[10]	See Table 54.6	P, B, E, C, O	Pyrrolizidine alkaloids	Worldwide	Loss of appetite, lethargy, diarrhea, constipation, icterus, photosensitization	
Autumn crocus[10,16]	*Colchicum autumnale*	B, E, P	Colchicine, colchiceine	Europe	Salivation, dysphagia, colic, abdominal pain, diarrhea, tenesmus, melena, cardiorespiratory failure, congenital defects	
Bitterweed[1]	*Hymenoxys odorata*	O, B	Sesquiterpene lactone	Southwest U.S.	Weight loss, poor appetite, vomiting, bloat, abdominal pain, stiff gait (lambs)	
Box or boxwood[10]	*Buxus sempervirens*	E, B, O,	Alkaloids	Worldwide	Colic, melena, respiratory failure	
Broomweed, snakeweed[1]	*Gutierrezia* spp.	O, C, E, B	Saponins	Western U.S., Mexico	Diarrhea, constipation, rough hair coat, anorexia, abortion, photosensitization	
Buffalo bur[10]	*Solanum rostratum*	E, B, O, C	Solanine alkaloids and glycoalkaloids	U.S.	Trauma to mucosal surfaces; tiredness; muscle	Physostigm

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					tremors; bloat; congestion of lungs, heart, liver, spleen	
Buttercup[10]	*Ranunculus* spp.	B, E	Ranunculin	North America, Europe	Salivation, depression, blindness, hematuria, oral ulcers, diarrhea, melena, colic	
Castor bean[10]	*Ricinus communis*	E, B	Ricin	Worldwide	Bloody diarrhea, tenesmus, colic, trembling, incoordination, seizures	
Chinaberry[10]	*Melia azedarach*	P, B, O, C, E	Alkaloids, saponin	China, southeast U.S.	Colic, vomiting, constipation, hemorrhagic diarrhea or muscle tremors, ataxia, seizures, tetraparesis	
Coffeeweed[10]	*Cassia* spp.	B, O, C, E, P	N-methylmorpholine and anthraquinone glycoside	Eastern, southern U.S.	Diarrhea, anorexia, staggering gait, myoglobinuria, renal failure, liver failure (horse)	
Colorado rubberweed (Pingue)[1]	*Hymenoxys richardsonii* var. *floribunda*	O, B	Sesquiterpene lactone	Western U.S.	Weight loss, poor appetite, vomiting, salivation, GI stasis, bloat, abdominal pain, weakness, depression, stiff gait	
Corn cockle[10]	*Agrostemma githago*	B, O, P, E	Githagenin	U.S., Europe	Colic, diarrhea	
False hellebore, skunk cabbage[10]	*Veratrum* spp.	O, B, C	Steroids	U.S., Canada	Salivation, colic, diarrhea, respiratory failure, abortion, malformed neonates	
Foxtail grass[10]	*Hordeum jubatum*	E	None	U.S., Canada	Foreign body–induced ulceration in ears, eyes, neck, face, mouth; colic; impaction	
Hairy vetch[10]	*Vicia villosa*	B, E	Unknown	U.S., Europe	Excitement, slobbering, nasal discharge, cough, stiffness, anorexia, weakness, seizures, swelling	

					of the head and neck, pruritic dermatitis, hair loss, diarrhea, abortion, photosensitivity	
Horse nettle[10]	*Solanum carolinense*	B, E	Solanine	U.S., Canada	Anorexia, emaciation, rough coat, constipation, mouth inflammation, falling when excited	Physostigm
Jimsonweed, thornapple[35,53]	*Datura* spp.	E, P, B	Tropane alkaloids	Worldwide	Colic, ileus, diarrhea, mydriasis, tachycardia, anorexia, muscle spasms, seizures, polyuria	
Kentucky coffee tree[10]	*Gymnocladus dioica*	B, O, E	Cystisine	Eastern U.S., Canada	Vomiting, colic, diarrhea, hypotension, bradycardia, seizures, muscle paralysis	
Lantana[10]	*Lantana camara*	B, O, C, E	Lantadene A and B	Worldwide	Photosensitization, anorexia, constipation, gastroenteritis	
Laurel[10]	*Kalmia* spp.	E, O, B, C	Andromedotoxin	Northern U.S., Canada	Colic, nasal discharge, salivation, odontoprisis, bloat, bradyarrhythmias, collapse, coma	
Leafy spurge[10]	*Euphorbia* spp.	B, E	Unknown	North America	Blistering of lips, tongue, skin, GI irritation, photosensitization	
Lobelia[10]	*Lobelia* spp.	B, O, C	Lobeline	U.S., Mexico	Excessive salivation, vomiting, diarrhea, mydriasis, coma, ± oral and corneal ulcers	
Locust trees[36]	*Robinia* spp.	E, B, O, C	Robinin, robitin	North America, Europe	Diarrhea, anorexia, weakness, posterior paralysis, mydriasis, dyspnea, arrhythmias	
Marsh	*Caltha*	B, O, E	Anemonin	Northern	Ulceration of skin,	

marigold[10]	*palustris*			U.S., Canada	oral cavity, salivation, diarrhea, colic, nervousness	
Mesquite[10]	*Prosopis glandulosa*	E, B	Arabinose	Western U.S.	Colic, salivation, rumen or intestinal obstruction (phytobezoars), tremors, anemia, emaciation	
Nightshade[10]	*Solanum* spp.	B, O, C, E, P	Solanine	U.S.	Fatigue, muscle tremors, mydrasis, bloat, colic, watery diarrhea, congestion of lungs, heart, spleen	Physostigm
Oak[10]	*Quercus* spp.	B, E, O, P	Gallotannins	North America, Europe	Incoordination in horses along with weakness, ileus, mouth ulcers, mucosal discoloration, patchy sweating, abnormal feces, colic, dark urine	
Oleander[10]	*Nerium oleander*	B, E	Oleandrin, neriine	Southern U.S., Mexico, Mediterranean	Tachycardia, severe gastroenteritis, diarrhea, abdominal pain, sweating, weakness	
Persimmon[10]	*Diospyros virginiana*	E	Tannins	Southern U.S.	Obstruction due to phytobezoars, colic, weight loss	
Pokeweed[10]	*Phytolacca americana*	B, O, C, P, E	Saponins, oxalates, alkaloids	Eastern U.S.	Oral irritation, excessive salivation, vomiting, colic, bloody diarrhea, depression	
Privet[10]	*Ligustrum vulgare*	E, B	Ligustrin, ligustron	U.S., Canada	Diarrhea, severe colic, hypotension, renal failure	
Rape[10]	*Brassica napus*	B, E	Glucosinolates	North America	Colic, bloat, diarrhea, pulmonary emphysema (cattle), icterus, anemia, goiter	
Red clover[10]	*Trifolium pratense*		Slaframine from mold infection	U.S.	Slobbers, bloat, stiffness, diarrhea, blindness, abortion, laminitis	

Rhododendron[10]	*Rhododendron maximum*	B, O, C, E	Andromedotoxin	U.S., Canada	Colic, nasal discharge, salivation, odontoprisis, bloat, bradyarrhythmias, collapse, coma	
Rosary pea[10]	*Abrus precatorius*	E, C	Abrin	Southeast U.S.	Anorexia, abnormal temperature, ulcers, incoordination, lung congestion, liver and urinary damage	
Sesbania or bladderpod[10]	*Sesbania* spp.	B, O, C	Saponins	North America	Severe hemorrhagic diarrhea, abomasitis, renal and hepatic necrosis	
Sneezeweed[1]	*Hymenoxys hoopesii*	O, B, E	Sesquiterpene lactone	North America	Vomiting, stiff gait, poor appetite, weakness, coughing ± aspiration, pneumonia, emaciation, ascites	
Tobacco[10]	*Nicotiana* spp.	E, B	Nicotine	Southern U.S., Mexico	Muscle tremors, tachyarrhythmias, colic, dyspnea, diarrhea, congenital defects (blindness, staggering, forelimb collapse, coma at high doses)	
Tung or candle nut tree[10]	*Aleurites* spp.	B	Saponins	China, southeast U.S.	Anorexia, atonic rumen, watery diarrhea, emaciation	
Yellow wood[3]	*Terminalia oblongata*	B, O	Tannins	Australia	Nervous signs (sheep). Colic, photosensitization, icterus, dark urine, stiffness, nephrosis (cattle)	
Yellow bristle grass[10]	*Setaria lutescens*	E	None	U.S., Canada	Ulcers in mouth, digestive tract	
Yerba de pasmo[54]	*Baccharis pteronioides*	B, O, E	Trichothecenes	Southwest U.S., South America	Anorexia, hemorrhagic enteritis	

[a]Plant names in bold are discussed in more detail in the text.

[b]Species listed in relative order of toxicity importance: *B,* Bovine; *C,* caprine; *E,* equine; *O,* ovine; *P,* porcine.

Bracken fern *(P. aquilinum)* (Color Plate 54.2) has long been recognized as a cause of enzootic hematuria and bladder cancer but more recently has been linked to upper digestive tract squamous cell carcinoma in cattle grazing pastures with high bracken content in conjunction with bovine papillomavirus type 4. In a study reviewing 40 tumors in cattle, metastasis was common (56%), predominately to regional lymph nodes.[56]

Hepatic Disease

Absorption of toxins from the digestive tract results in subsequent exposure of liver tissue where further pathologic changes may be induced. Depending on the toxin and disease syndrome, signs of liver disease may be only subtle weight loss or failure to grow but more often include icterus, photosensitization, and/or hepatic encephalopathy. For example, alsike clover can produce two syndromes in horses, either hepatic encephalopathy or photosensitization. (Plants causing primary photosensitization are listed in the Poisonous Plants Affecting Skin and Hooves section later.) A variety of plants damage biliary cells, leading to secondary photosensitization as the primary clinical sign, including agave *(Agave lechuguilla),* bear grass or sacahuista *(Nolina texana),* bog asphodel *(Narthecium ossifragum),* kleingrass and switchgrass (*Panicum* spp.), and puncture vine *(Tribulus terrestris).*[10] Mycotoxins can also produce biliary damage leading to photosensitization. Photosensitization is one of many systemic effects often seen with consumption of plants, such as black sage *(Artemisia nova)* consumed concurrently with horsebrush (*Tetradymia* spp.), *Brassica* spp., Dutchman's breeches *(Thamnosma texana),* hairy vetch *(Vicia villosa),* inkweed *(Phytolacca octandra), Kochia* spp., *Lantana* spp. (Color Plate 54.7), and yellow wood *(Terminalia oblongata).*[3,10,36,57] Plants containing pyrrolizidine alkaloids also produce photosensitization and are the most important source of widespread liver problems to both livestock and horses (see the Pyrrolizidine Alkaloids section below).

Severe hepatic disease may lead to signs of liver failure, including hepatic encephalopathy and sudden death. The pyrrolizidine alkaloid plants are the foremost plants associated with this. *Senna* (formerly *Cassia)* spp., in particular the seeds, are very toxic to multiple species. Sixty percent of a herd of broodmares died with signs of hepatic encephalopathy with histologic lesions of

pericentrolobular necrosis after ingesting seeds of *Senna occidentalis* (formerly *Cassia occidentalis*) in ground corn.[58] Cocklebur (*Xanthium* spp.) and blue-green algae should also be considered. Cocklebur most often produces signs in calves and cattle, but pigs and horses have also been affected.[10]

Pyrrolizidine Alkaloids

This large group of plants is a common source of adverse effects in livestock in many areas of the world, particularly in the southern United States, Australia, and South Africa. Plants in this category of toxins are listed in Table 54.6. Frequently the clinical syndromes are chronic, with clinical signs of liver damage observed months after the plant is eaten. Cattle and horses are most susceptible, with younger animals more easily affected. Poisoning typically occurs in overgrazed pastures but may develop when plants such as houndstongue *(Cynoglossum officinale)*, tansy ragwort *(Senecio jacobaea)*, or rattlebox (*Crotalaria* spp.) (Color Plate 54.8) are incorporated in hay or accidentally harvested with small grains.[1] In cattle, chronic consumption usually occurs for an extended time before the onset of signs. Consumption of mature pyrrolizidine alkaloid forage at a rate of 5% or more of their total daily diet for more than 15 days usually results in death in 1 to 6 months.[1] Young plant growth tends to be even more toxic. Those animals consuming less may become chronic poor doers. In horses, consumption of *Crotalaria* spp. causes liver failure and fibrosing pulmonary alveolitis.[10] Pigs are most prone to development of extrahepatic lesions.[36] There is some evidence that pyrrolizidine alkaloids pass through the placental membranes to affect the fetus. In humans, carcinogenicity is reported.[1] The pyrroles are powerful alkylating agents reacting with cellular proteins, crosslink DNA, and cause cell necrosis and abnormal mitosis.

TABLE 54.6
Plants Containing Pyrrolizidine Alkaloids

Common Name	Scientific Name	Plant Habitat	Reference(s)
Groundsel	*Senecio* spp.	Western U.S., Australia	1, 3
Heliotrope	*Heliotropium* spp.	Worldwide	3
Houndstongue	*Cynoglossum officinale*	Southwest U.S.	1
Kochia	*Kochia scoparia*	Western U.S.	1
Paterson's curse	*Echium plantagineum*	Australia	3
Rattlebox, rattlepod	*Crotalaria* spp.	U.S., Australia	1, 3
Tansy ragwort	*Senecio jacobaea*	North America, Europe	10, 19

Tarweed, fiddleneck	*Amsinckia* spp.	U.S., Mexico, Australia	10
Viper's bugloss	*Echium vulgare*	Australia, California	3

Clinical signs are variable but originate from hepatic damage induced by the ingested pyrrolizidine alkaloids. Other stressors may trigger expression of clinical signs. Photosensitization of areas of white skin, particularly on the animal's dorsum and face, may be the first sign of illness. Crusting around the muzzle and eyes may be observed. In cattle, an unpleasant sweetish odor may be noted. Lethargy, loss of appetite, and weight loss are common. Weakness is observed when the animal tries to walk. In the terminal stages, signs of hepatic encephalopathy such as blindness and belligerent or compulsive behavior may be reported. Mucous membranes and sclera can be markedly icteric. Ascites, diarrhea, or constipation may be present as well.[1] Serum chemistry analysis confirms hepatocellular and biliary cell damage. The characteristic lesion on postmortem examination or biopsy is liver cirrhosis with necrosis and fibrosis, accompanied by bile duct proliferation. Varying degrees of hepatic megalocystosis may be observed in liver tissue.[36] Gastroenteritis may also be evident.

There is no specific treatment for pyrrolizidine alkaloid poisoning. Livestock may frequently graze these plants with seeming impunity if there is abundant high-quality forage available. If pastures with these plants are unavoidable, the use of herbicides should be considered. Biological control measures have been developed for some plants, such as tansy ragwort, and may be considered as preventive measures.

Reproductive and Neonatal Effect of Poisonous Plants

Poisonous plants affecting fertility, pregnancy, fetal development, and lactation can have a large economic impact, as can plants infected with ergot or endophytes. Significant management challenges exist when livestock on pasture or on a range are affected. The effects may be as subtle as reduced conception rates or as apparent as abortion storms and multiple neonates with congenital defects. Any severe plant poisoning in a pregnant animal has the potential to precipitate an abortion. Toxins from a few plants may pass into the udder in an active form, harming the neonate or human who drinks the milk.

Ponderosa pine *(Pinus ponderosa)* needles and bark, when consumed in the last trimester, are a significant cause of abortion and premature delivery in cattle

in the western United States and Canada.[1] Junipers, lodgepole pine, and Monterey cypress evergreens and perennial broomweed (*Gutierrezia* spp.) may produce similar syndromes. A few cows or even the whole herd may be affected. Isocupressic acid, the abortifacient compound, is rapidly metabolized to agathic acid in the rumen, a process accelerated by conditioning of the cattle to pine needle consumption, thereby reducing its effect.[59] Other toxic compounds such as diterpene abietane acids are also present. A vasoconstrictive effect on uterine vessels leads to uterine inertia, abortion, and frequently dystocia and/or retained placenta. Edematous swelling of the udder and vulva may be observed before abortion. Calves are typically weak, and lactation from the dam may be impaired.[1,10] Many other plants have been identified as sources of significant abortion in other parts of the world.[3,25,60]

Phytoestrogens may accumulate in a number of commonly consumed forages, adversely affecting reproductive performance. Examples include alfalfa and some types of clovers, which can produce coumestrol, and soybeans, which may contain isoflavones. Phytoestrogen concentrations may increase in stressed or diseased legumes. Fungal infections of feed may provide an additional source of xenoestrogens such as zearalenone. These phytoestrogens interact with endogenous estrogen receptors. In swine this can create a syndrome of hyperestrogenism characterized by precocious sexual development in females and preputial swelling and testicular atrophy in immature males. Goats and sheep may be more susceptible to this syndrome than cattle. Disruption of cyclic estrogen changes in older animals has more subtle effects, resulting in reduced fertility.[25]

A number of plants with significant reproductive effects, including locoweed and those accumulating nitrates, are discussed earlier in this chapter. Locoweed is particularly dangerous to range animals, as the plant may contain excessive selenium and/or endophyte infection. Reduced fertility, abortion, fetal defects, abnormal placentas, hydrops, and weak neonates may be observed. Sperm quality is also affected.[10] Nitrate-accumulating plants (see Table 54.3) can be responsible for sudden death, abortions, stillbirths, congenital defects, and weak neonates.

Congenital defects resulting from ingestion of specific plants during pregnancy may trigger abortion or result in nonviable neonates. Skeletal deformities such as arthrogryposis, kyphosis, scoliosis, torticollis, and cleft palate can be the result of lupine ingestion during early gestation to midgestation

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in ruminants, a syndrome called “crooked calf disease,” a significant problem in range cattle. The two specific teratogens identified and studied are anagyrine, a quinolizidine alkaloid, and ammodendrine, a piperadine alkaloid, both of which reduce uterine motility. Toxin absorption and the likelihood of ingestion are affected by body condition score.[61] Anagyrine is also present in mountain thermopsis. Other plants with similar effects include locoweed, poison hemlock, and tobacco. The teratogenic effects of poison hemlock are greatest in cattle and pigs. In sheep, false hellebore and skunk cabbage (*Veratrum* spp.) ingestion in early gestation may result in abortion or birth of cyclopic lambs.[10] Cattle, goats, and llamas are also susceptible.

Congenital hypothyroidism in equine neonates can be caused by ingestion of high nitrate forages or plants with goitrogenic effect. Goitrogenic effects may be observed from plants providing excessive iodine (e.g., seaweed) or compounds such as thiocyanates (white clover) or glucosinolates (*Brassica* spp., kale, turnips, and canola seeds) interfering with iodine use. Horses are particularly susceptible to excessive iodine, as well as iodine deficiency. Excessive iodine consumption in a seaweed-based supplement led to abortion in 27 of 39 mares, goiters, and signs of congenital hypothyroidism in many of the neonates, including pathologic changes in the long bones.[62] Diagnosis is most readily based on histologic evaluation of the thyroid gland or changes of the skeletal system characteristic of congenital hypothyroidism. More commonly, this syndrome is attributable to iodine deficiency or excessive nitrate in forages or water.

Poisonous plants ingested by their dam, which may or may not show signs of toxicity, may affect milk-fed neonates depending on the chemistry of the toxin and/or its metabolites. If plant poisoning is suspected in a sick dam, an alternative milk source for the neonate should be considered, particularly if the toxin is an alkaloid. Plants affecting milk flavor, such as onions, may diminish neonatal consumption. More significant toxic plants to consider in this category include those with pyrrolizidine alkaloids (see Table 54.6), white snakeroot, rayless goldenrod, locoweed, lupines, mountain thermopsis, poison hemlock, tobacco, *Cassia* spp., and lobelia. A number of plants in the Brassica family (mustards, kale, rape, turnips, horseradish, radish, and watercress) can adversely affect thyroid function, as well as impart a bitter flavor to the milk.[10]

Ergot Alkaloids and Endophytes

Clinical syndromes ascribed to plants affected by ergot and endophytes are often included in veterinarians' thought processes when considering poisonous plant etiologies. For this reason, plants with this potential are included in the charts of predominant clinical signs. Two categories primarily affecting reproductive functions are discussed here: ergot alkaloids (ergopeptines) from ergot and those from endophyte infections. Neurologic signs and other syndromes associated with endophyte-infected locoweed are discussed in the Neurologic Signs section earlier.

Ergot-infected forages and grains have much higher concentrations of ergot alkaloids than are found in endophyte-infected forages.[25] Ergot infection (*Claviceps* spp.) of many grasses and cereal grains produces dark fungal sclerotia (ergot bodies) shaped like seeds readily visible in the plant's seed head in pasture, hay, or contaminated grains.[63] Similarly, many grass species can be infected with endophytes; the most economically important is fescue (*Lolium* spp.) infected with *Neotyphodium coenophialum.* Ergovaline is the most prevalent ergopeptine in endophyte-infected tall fescue and considered responsible for most signs associated with fescue toxicosis.[64] Infection provides fescue the advantages of increased resistance to drought, insects, parasitic nematodes, and herbivores. In contrast to ergot infections, endophyte infections are not visible to the naked eye and require microscopy for confirmation. The endophyte infects the plant's seed, ensuring its survival to germination in subsequent seasons.[64] Tall fescue can be infected with both *Claviceps* spp. and the endophyte simultaneously.[25]

Ergot alkaloids affect all livestock and horses. Species susceptibility is highest in horses, followed by cattle, then sheep, goats, and finally camelids. Different disease syndromes may be present, depending on the affected species and type of ergot alkaloids ingested. In ruminants and horses, ergot alkaloids, particularly ergovaline, have vasoconstrictive effects (α_2-adrenergic agonist) and/or depress secretion of prolactin via effects on lactotropic dopamine D_2 receptors in the adenohypophysis of the pituitary. There is a reduction in steroid genesis, including progesterone production by corpora lutea, and relaxin. Diminished relaxin production has less impact on readiness for parturition in ruminants because it is also produced by the placenta. Thermoregulatory centers are affected by diminutions in prolactin and dopamine receptor perturbation, leading to clinical problems in extreme temperatures.[64] *Claviceps cyperi* has produced signs of severe ergotism in dairy cows in the heat of South Africa.[65] In contrast,

infection of grasses with another form of ergot, *Claviceps paspali*, produces predominately neurologic signs associated with γ-aminobutyric acid inhibition.[25]

Clinical abnormalities attributable to ergot and endophyte infections of grasses are often detected in regions with warm, wet climates conducive to fungal infections, such as found in the southern portions of the United States (endophytes) and the cool, wet springs of the northwestern United States (ergot).[66] Prevalence of toxicosis will vary by season and from year to year. Deciphering toxicity attributable to these fungal infections is complicated by the fact that some species of grasses can be infected with both simultaneously and have dangerous levels of nitrates.[25] In addition, concurrent copper deficiency may augment reproductive system clinical signs, as ergopeptine alkaloids impair copper homeostasis. Heavy parasitic loads may have a similar effect.[25]

Depending on environmental conditions, the vasoconstrictive effects of the ergot alkaloids can be costly to livestock. Cold weather can result in gangrene of the distal extremities and lameness. The tongue may also be affected in sheep. Lameness can lead to decreased feed consumption and diminished natural mating. In ruminants experiencing heat stress, hyperthermia can occur due to failure of heat dissipation through the skin. Sheep with full fleeces are particularly susceptible to this syndrome. Other signs include a dull, rough hair coat and unthrifty condition. Nervousness, increased salivation, tachypnea, and delayed puberty may be seen. In some regions, this condition is referred to as "summer slump." Ergot alkaloids should also be considered in alpacas and llamas that develop heat stroke.[64] Fat necrosis or lipomatosis in cattle and goats is associated with consumption of ergot alkaloids in fescue grasses. Masses of necrotic fat in the pelvic canal can lead to dystocia.[25] Because the ruminant placenta can produce a placental lactogen during pregnancy, the suppression of prolactin and hence milk production is minor in comparison to horses. Bulls grazing endophyte-infected pastures during the summer may have altered sperm motility parameters. Cows may have changes in ovarian follicular dynamics, as well as diminished embryo quality. Reduced fertility in both unshorn ewes and rams has been reported during the summer.[25] Diminished immune function may make animals more susceptible to infectious diseases and cases with dry gangrene more susceptible to wound infections. In swine, agalactia and abortion have been reported in association with ergot consumption.[63]

Ergot *(Claviceps purpurea)* and endophytes of forages such as fescue (*Lolium* infested with *N. coenophialum*) have been extensively studied in horses.

Broodmares eating ergot or endophyte-infected tall fescue pasture or hay may exhibit failure of udder development, agalactia, prolonged gestation, placental abnormalities, dystocia, decreased milk production, and subfertility.[66] Foals may show signs of dysmaturity despite prolonged gestation and frequently suffer failure of passive transfer and secondary septicemia due to the failure of udder and colostrum development. Early embryonic death and abortion are also possible, with a higher risk of abortion associated with ergot infections than endophyte infections.[67] Ergot alkaloids may stimulate the myometrium and probably impair placental circulation.[66] Gangrene of the extremities has been seen in horses exposed to ergot, as has a syndrome characterized by staggering following consumption of *Paspalum* grass seeds infected with *C. paspali.*[68] A slightly different syndrome characterized by peripheral edema has been described in horses grazing Mediterranean tall fescue intentionally infected with a genetically modified, nontoxigenic form of endophyte, suggesting other factors may be involved and should be considered if reseeding of pastures is desired.[69]

Diagnosis of ergot alkaloid or endophyte-induced toxicity is based on recognition of clinical signs and consumption of infected feed. Diagnostic testing of suspect forages, hay, grain, or processed forages is based on observation of *C. purpurea* sclerotia or intercellular endophyte infection via feed microscopy and testing of the forages. High-performance liquid chromatography (HPLC) can confirm the presence of ergopeptine alkaloid toxins: ergovaline, ergotamine, ergocristine, ergosine, ergocornine, and/or ergocryptine.[25,64] Adverse effects are linked to total dietary concentrations greater than 100 to 200 ppb. Affected broodmares' calcium concentrations in the mammary secretions rarely exceed 50 ppm at parturition.[70]

Treatment is most effective if signs are recognized in the early stages and suspect feed is removed. If pasture is the source, and alternative grazing is not available, mowing to remove seed heads and possible ergot bodies may be helpful. Foaling should be attended due to the risk of dystocia, placental problems, and likely dysmaturity of the neonate. Domperidone (1.1 mg/kg PO q24h) can be used successfully in pregnant mares suspected of ergot alkaloid toxicosis if use is begun 10 to 14 days before expected foaling. Reserpine (2.5 to 5 mg/450 kg PO q24h) may be helpful to induce lactation if administered postpartum.[66]

Prevention focuses on replacing contaminated feed sources with safer alternatives such as legumes or endophyte-free fescue grass. Ammoniation to

degrade ergovaline in contaminated hay may be economically feasible on large cattle operations.[71] Pregnant broodmares should be removed from fescue pastures no later than day 300 of gestation. Domperidone can be used as described earlier in broodmares. Attention to mineral nutrition and other additive stressors is advised.[66]

Respiratory Syndromes Following Poisonous Plant Ingestion

Few plants are associated with the development of predominately respiratory signs in large animals. Perilla mint *(Perilla frutescens)* (Color Plate 54.9) causes significant morbidity and mortality in ruminants. Perilla contains ketones and related furan compounds. These are bioactivated in the lung, causing atypical interstitial pneumonia and acute respiratory distress. A similar syndrome is seen in cattle following ingestion of sweet potatoes *(Ipomoea batatas)* damaged by *Fusarium* spp. molds.[72] Acute bovine pulmonary emphysema and edema may occur following ingestion of forages high in tryptophan, typically immature summer grasses. Rumen bacteria convert tryptophan to 3-methylindole, a furan further metabolized to a lung toxicant. Gradually introducing cattle to these grasses or using monensin or tetracycline in the feed for a week before and 2 weeks after turnout on pasture can prevent this syndrome. However, use of antibiotics with claims not on the label may be prohibited by regulations. Also, recall the regulations regarding the Veterinary Feed Directive if considering adding an antibiotic to the feed. Peanut hay *(Arachis hypogaea)* has been linked to acute respiratory distress in beef cattle.[72]

Poisonous Plants Affecting Skin and Hooves

Skin and hooves may be adversely affected by plants causing physical trauma or those containing toxins or excessive selenium. Plants with awns or barbs capable of damaging skin may also damage the digestive tract and adjacent tissues if migration occurs.

Photosensitization and laminitis are chief complaints requiring further investigation. Photosensitization may be a primary effect of the ingested toxin or a secondary effect due to liver damage. Sunlight triggers an oxidative reaction with photoreactive, polyphenolic compounds absorbed from the digestive tract in

areas of unpigmented skin, leading to inflammation, cellular necrosis, and sloughing of affected skin, particularly in horses and cattle. Lesions are typically most severe on the face and dorsum of the animal. Common plant sources of primary photosensitization are St. John's wort *(Hypericum perforatum)*, buckwheat *(Fagopyrum esculentum)*, Dutchman's breeches *(Thamnosma texana)*, bishop's weed *(Ammi majus)*, rain lily *(Cooperia pedunculata)*, spring parsley *(Cymopterus watsonii)*, giant hog weed *(Heracleum mantegazzianum)*, and cow parsnip (*Heracleum* spp.).[10] Wild parsnips *(Pastinaca sativa)* contain furanocoumarins, which can result in contact blisters and photosensitization following ingestion.[55]

Hoary alyssum *(Berteroa incana)* (Color Plate 54.10) ingestion and black walnut *(Juglans nigra)* shavings used for bedding are known triggers of laminitis in horses.[10] Hoary alyssum, a weed often growing on the periphery of hayfields in Europe and North America, is usually avoided at pasture but remains toxic in hay for months. Clinical signs of toxicosis include limb edema, fever, and laminitis. In severe cases, intravascular hemolysis, endotoxemia, hypovolemic shock, diarrhea, abortion, and death may occur.[73,74] Black walnut shavings need not be ingested to cause limb swelling and laminitis in horses. Black walnut extracts containing the tree's heartwood and administered by nasogastric tube have been used to create a model for studying laminitis in horses. These studies suggest that oxidative stress to laminar tissues with subsequent inflammation is responsible for the predominant clinical sign, as well as a systemic inflammatory response.[75]

Selenium Toxicosis

Chronic excessive selenium ingestion produces skin and hoof abnormalities, known as “alkali disease.” It is problematic for livestock in areas with seleniferous soils, such as the Great Plains of the United States and Canada, as well as in many areas in Russia, Israel, and China.[76] Common seleniferous plant species with this potential include primary selenium accumulator plants, such as milkvetch (*Astragalus* spp.), woody aster *(Machaeranthera*, section *Xylorrhiza)*, goldenweed *(Haplopappus*, section *Conopsis)*, and prince's plume *(Stanleya pinnata)*.[1,10] Selenium can reach levels of approximately 3000 ppm, remaining water soluble and not incorporated into plant protein. Secondary selenium accumulator plants may contain up to several hundred ppm and, rarely, several thousand ppm selenium. This group includes acacia, other asters (*Aster* spp.),

beard tongue (*Penstemon* spp.), gumweed *(Grindelia),* Indian paintbrush *(Castilleja),* some milkvetch (*Astragulus* spp.), sage (*Artemesia* spp.), saltbush *(Atriplex patula),* snakeweed *(Gutierrezia),* stickleaf *(Mentzelia),* and toadflax *(Comandra).*[1,10] A third group of plants possibly endangering livestock do not accumulate selenium compounds but do incorporate it into readily absorbed plant proteins, rarely presenting with more than 50 ppm. This latter group is the most problematic because it includes grasses (e.g., Western wheatgrass), small grains, and alfalfa.[1]

Toxicity is difficult to predict because palatability and tolerance vary with animal species, individual genotype, the form of selenium in the plant, duration of consumption, and amount consumed. Ruminants tend to be more tolerant of high selenium in the forage than horses. Water sources in seleniferous areas may also contribute to excessive selenium intake.[77]

Three syndromes are ascribed to excessive selenium intake: acute toxicosis, blind staggers, and chronic alkali disease. Signs of acute selenium toxicosis are most often described after iatrogenic overdosage of selenium and rarely occur from plant ingestion. In horses, the first signs of selenium toxicity may be vesicles on oral and nasal mucosa and a straw-colored exudate at mucocutaneous junctions, followed by coronary band separation from the hooves and hair loss in the mane and tail. In the tail, the hairs tend to break at the same level, leaving a "bob" tail.[10] In cattle, abnormal posture, unsteady gait, diarrhea, abdominal pain, and elevated pulse and respiratory rate are seen. Sheep do not show the typical signs of poisoning; rather, depression, increased respiration, and sudden death are observed.[10] At necropsy, in acute cases, endocardial petechial hemorrhage, acute congestion and hemorrhage of the lungs, enteritis, and passive congestion of the liver are reported.

Animals that chronically ingest high selenium forages show signs of emaciation, rough hair coat, lack of vitality, and lameness. Reproductive efficiency diminishes. Hooves may become overgrown or cracked (including swine), and long hair may fall out. At postmortem, cardiac atrophy, hepatic cirrhosis, anemia, and erosion of the long bones may be noted.[1,78]

Serum selenium provides an accurate reflection of the body's current selenium pool, whereas whole blood selenium (glutathione peroxidase) reflects a longer period of selenium intake. Both can be useful in antemortem diagnosis. Hair and liver selenium are other options, particularly for more chronic cases and postmortem determination. Laboratories used for selenium determinations

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should provide ranges for normal values by species and sample type because these vary. Investigation of a herd or flock problem should ideally include samples from multiple animals to reduce the risk of misinterpretation based on the values of one or two individuals.

Once a selenium toxicosis is identified, producers and owners need to find alternative grazing and water sources for their animals, particularly breeding horses and cows. Consultation of soil maps may be useful, as may be looking for primary selenium accumulator species serving as indicators. Animals relocated from high-selenium areas often recover when fed lower selenium rations. Producers should also check that diets contain sufficient copper and protein to avoid enhancement of selenium's toxic effects.[10]

Plant Toxicity in the Urinary System

Urinary system damage may be the result of direct toxin damage or secondary to the toxin's effects on other systems, leading to dehydration, pigmenturia, or hypoxia. Renal damage is an important determinant of case outcome for many intoxications. This fact should focus clinical attention on hydration, urinary output, and other measures of renal function. Among common plant toxicities, renal dysfunction can be significant following consumption of bracken fern *(P. aquilinum)*, cocklebur (*Xanthium* spp.), inkweed *(P. octandra)*, oak (*Quercus* spp.), pigweed *(Amaranthus retroflexus)* (Color Plate 54.11), jimsonweed (Color Plate 54.12), and all plants rich in oxalates.[36,57,72,79] Bracken fern's toxin, ptaquiloside, is carcinogenic to bladder epithelium and responsible for the syndrome of enzootic hematuria in cattle.[36] In oak poisoning, nephritis with necrosis and renal tubular casts is observed, possibly leading to acute renal failure. Inkweed has caused acute renal tubular necrosis in calves, along with signs of photosensitization and cholangiohepatopathy.[57]

Oxalate Toxicity

Consumption of plants with high concentrations of sodium oxalate and/or potassium oxalate damages renal tissue if a large amount of plant is consumed over a short period. In addition, some contain insoluble oxalate crystals in the form of complexes called *raphides*, which cause direct damage and irritation to the mucosal surfaces of the mouth and pharynx.[80]

Clinical manifestations of oxalate poisoning are variable and depend on factors such as the form of oxalate in the consumed plant, the animal species, and the rate of consumption. Plants capable of causing oxalate toxicity are listed in Table 54.7. The balance between soluble (oxalic acid) and insoluble forms of oxalate in plants varies and is affected by GI tract pH following ingestion. Binding of calcium can occur in the GI tract lumen. Once absorbed from the GI tract, oxalates precipitate calcium from the blood, producing hypocalcemia, which may be most notable in lactating animals.[81] Oxalate crystals damage the microvasculature of the GI tract and may precipitate out on the wall of the rumen. Poorly soluble calcium oxalate crystals precipitate out in the renal tubules, causing acute nephrosis, tubular obstruction, and acute renal failure. At a cellular level, citric acid cycle of energy metabolism is inhibited, leading to cell death. In renal tubular cells, other pathways have been suggested, such as the production of phosphatidylserine, which promotes attachment of oxalates to the cell membrane, and phospholipase A2, with subsequent mitochondrial damage and cell death.[82]

TABLE 54.7
Plants That May Contain Oxalates

Type	Common Name	Scientific Name	Reference(s)
Crop	Agave	*Agave americana*	80
	Beets	*Beta vulgaris*	10
	Prickly pear	*Opuntia echios*	80
	Quinoa	*Chenopodium quinoa*	10
	Rhubarb	*Rheum* spp.	10
	Soybean	*Glycine max*	80
	Spinach	*Spinacia oleracea*	80
Grass	Beardgrass	*Brachiaria brizantha*	80
	Birdwoodgrass	*Cenchrus setigerus*	80
	Buffel grass	*Cenchrus ciliaris*	10
	Bristlegrass	*Setaria* spp.	10, 80

	Elephant grass	*Panicum* spp.	10
	Kikuyu grass	*Pennisetum clandestinum*	10
	Napier grass	*Pennisetum purpureum*	80
	Pangolagrass	*Digitaria decumbens*	80
Weed	Dock	*Rumex acetosa*	10
	Greasewood	*Sarcobatus vermiculatus*	10
	Halogeton	*Halogeton* spp.	10
	Kochia	*Kochia scoparia*	10
	Lambsquarters	*Chenopodium* spp.	10
	Nettleleaf	*Tragia urticifolia*	80
	Noseburn	*Tragia ramosa*	80
	Pigweed	*Amaranthus retroflexus*	10
	Pokeweed, pokeberry	*Phytolacca americana*	10
	Russian thistle	*Salsola* spp.	10
	Slenderleaf ice plant	*Mesembryanthemum nodiflorum*	80
	Sorrel	*Oxalis* spp.	10

Oxalate poisoning in multiple animals is most often reported in sheep. Acute toxicosis is usually evident within 24 hours. The largest outbreaks are attributed to *Halogeton* spp. consumption. Other plants blamed for multiple deaths include slenderleaf ice plant *(Mesembryanthemum nodiflorum)* and golden bristlegrass *(Setaria sphacelata)* in Australia.[80] Muscle tetany or flaccid paralysis may be observed. These clinical signs pertain to hypocalcemia and hypomagnesemia, which result from sequestration of calcium and magnesium ions. Other reported signs include anorexia, ruminal stasis, mouth froth, weakness, stiffness, tachypnea, ataxia with jerky extensor rigidity, coma, and death. At necropsy, severe rumenitis may be evident. Kidneys are pale, edematous, and enlarged. Calcium oxalate crystals are readily identified in the rumen wall and kidneys. Less commonly, chronic toxicity has been reported with signs typical of chronic renal damage: anemia, weight loss, and poor appetite. Clinical signs of oxalate poisoning in cattle are similar to those in sheep but typically less acute and attributable to hypocalcemia. These include incoordination, belligerence, excessive salivation, bloat, recumbency, coma, and death. In calves, hypersensitivity to stimulation and seizures are possible.[11]

In horses, secondary nutritional hyperparathyroidism has been attributed to chronic high oxalate consumption, resulting in calcium binding in the hindgut and therefore deficiency. This leads to signs of osteodystrophia fibrosa.[80] Acute toxicosis with oxalate nephrosis failure is less common but associated with grass species with high oxalate content.

Treatment should be symptomatic with attention to electrolyte balance and renal function, but it may be insufficient in severely affected animals. Activated charcoal may help bind oxalates remaining in the GI tract. Prevention requires

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recognition of the toxic potential of oxalate-bearing plants and management of livestock to avoid consumption of large amounts in a short period. Gradual introduction to the plants, ample alternative forage, and water are necessary to avoid deaths. In sheep, slow introduction (≈10 days) of sheep to grazing areas with high proportions of oxalate-bearing plants can result in better tolerance to the toxic effects. In contrast, a sheep acclimated to grazing other forage can be killed with as little as 12 oz (340 g) of halogeton.[1]

Cyanobacteria

Birgit Puschner

Microcystis spp., *Nostoc* spp., *Anabaena* spp., *Planktothrix* spp.: cyanobacteria that produce hepatotoxic microcystins

Anabaena spp., *Oscillatoria* spp., *Phormidium* spp., *Planktothrix* spp.: cyanobacteria that produce neurotoxic anatoxin-a

Anabaena spp.: cyanobacteria that produce neurotoxic anatoxin-a(S)

Aphanizomenon spp., *Anabaena* spp., *Lyngbya* spp., *Cylindrospermopsis* spp.: cyanobacteria that produce neurotoxic saxitoxins (paralytic *shellfish poisoning toxins*)

Aphanizomenon spp., *Anabaena* spp., *Cylindrospermopsis* spp., *Lyngbya* spp: cyanobacteria that produce cytotoxic cylindrospermopsin

Climate change can increase the frequency and intensity of cyanotoxin blooms worldwide, as blooms typically occur during warm months when water temperatures exceed 20° C and water is stagnant.[1] High nutrient concentrations, especially phosphorus and nitrogen, increase the presence of cyanobacteria and cyanotoxins.[2] Cyanobacteria are suspended in the water column and easily visible or are attached to the surfaces of stones and sediments along the bottom of lakes or rivers.[3] Currently, of the 2000 species identified worldwide, more than 80 are categorized as toxigenic. Toxigenic and nontoxigenic species and strains coexist in water; thus the potential toxicity of a given water source must be carefully evaluated not only by identification of the actual cyanobacteria population but also by measuring toxin concentrations.[4,5] George Francis first reported in *Nature* in 1878 a toxigenic bloom of a “poisonous Australian lake” with “a thick scum like green oil paint” and vividly described acute intoxications

of sheep, horses, dogs, and pigs.[6] Since Francis's publication in 1878, numerous case reports describing morbidity and mortality in animals exposed to cyanotoxins have been published.[7-13]

The most commonly reported cyanotoxin poisoning in large animals is acute hepatotoxicosis subsequent to microcystin exposure. Microcystins are produced by multiple cyanobacteria and detected in fresh and coastal waters worldwide.[14] They present a realistic threat to pastured animals because of their presence in ponds and streams and because animals readily consume contaminated water (Fig. 54.1). Acute neurotoxicosis resulting from anatoxin-a or anatoxin-a(S) can occur in large animals, but reports are rare.



FIG. 54.1 Pond with *Microcystis* bloom in Petaluma, California. Pond water contained microcystin-LR and resulted in acute deaths and photosensitization of Holstein heifers.

The frequency of cyanotoxin poisoning in animals is likely underreported due to absent diagnostic work-up of large animal mortalities and the current lack of well-established confirmatory methods in biological specimens. Diagnostic confirmation of suspect cyanotoxin poisoning cases of humans and animals requires extensive efforts from both toxicologists and clinicians, and resources are often not readily available. New cyanotoxins and expansion of existing cyanotoxins into new regions are discovered continuously, and oral bioavailability and toxicity data are often unavailable. It is probable that cyanotoxins poisonings are more common in animals than humans due to increased dependence and contact with surface waters.

Hepatotoxic Microcystins

Microcystin-poisoned animals typically die within a few hours after exposure. Severe destruction of the hepatocytes leads to hypovolemia and shock secondary to blood loss into the disintegrated liver lobules and embolism of hepatocytes into the lung. Clinical signs of nervousness, reluctance to move, recumbency, diarrhea, and pale mucous membranes are seen within 30 minutes to several hours of exposure.[15,16] Many die within hours to days, but animals exposed to nonlethal doses may survive and develop hepatogenous photosensitization (Fig. 54.2).



FIG. 54.2 Holstein heifer with hepatogenous photosensitization from microcystin-LR toxicosis; Central Valley of California.

Clinical chemistry changes of animals with microcystin toxicosis include elevated serum gamma-glutamyl transpeptidase (GGT), aspartate aminotransferase (AST), bile acids, alkaline phosphatase (ALP), hypoglycemia, and hyperkalemia. Acute hepatic damage results in a grossly enlarged and friable liver from intrahepatic hemorrhage and, histopathologically, in hepatocyte dissociation, degeneration, and necrosis. Pathologic findings should quickly lead to an environmental assessment for possible microcystin-contaminated water.[17] Necrotic hepatocytes can also be seen in the pulmonary vasculature.

Microcystis, *Anabaena*, *Planktothrix*, *Nostoc*, *Oscillatoria*, and *Anabaenopsis* genera are among the known microcystin producers.[18,19] Toxins are retained

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inside the cyanobacteria and released only upon cell damage, lysis, and death; of note, destruction of algal mats (either naturally or through the application of herbicides) may result in a pulse of microcystin release following destruction of the individual cell walls. Microcystins are cyclic heptapeptides that inhibit protein phosphatases; currently, more than 80 different structural variants have been identified. The most extensively studied congener, microcystin-LR, is found worldwide and causes acute, lethal hepatotoxicoses in farm animals.[2,16,20] Most natural outbreaks are a result of oral exposure through drinking water; microcystin-containing algae release microcystins in the acidic environment of the stomach. Recently, the risk for microcystin exposure through blue-green algae–containing dietary supplements led to deaths in horses.[21] Inhalation exposure to microcystins has been documented in humans recreationally using certain waters.[22,23] All animal species, including fish and reptiles, and humans are considered susceptible to the toxic effects.

Animals with acute microcystin poisoning may have algal material in the GI tract (Fig. 54.3) or on the skin, especially the legs. Although identification of algae material in water and gastric contents is an important component of the diagnostic work-up, it does not confirm intoxication. As mentioned, the toxicity of cyanobacteria is strain specific, and morphologic observations alone cannot predict the hazard level. Detection of microcystins in gastric contents is confirmatory, but these tests are not routinely available at diagnostic laboratories and are limited to a few structural variants.[24-26] Commercially available methods for microcystin analysis of liver and other tissues are not yet available. Consumption of milk, meat, or liver is unlikely to pose a significant health risk to humans.[27,28] However, as a tumor promoter, microcystins may pose a cumulative health risk as they become more ubiquitous.

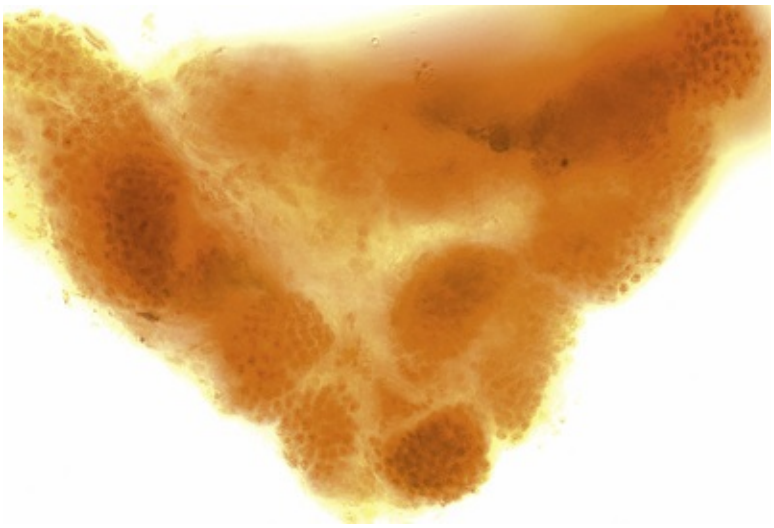


FIG. 54.3 Characteristic algal cell aggregates in rumen content of a heifer formed by *Microcystis* spp. Direct microscopic examination of rumen content in formalin (1 : 1; v/v). 60×. Rumen content was confirmed to contain microcystin-LR.

Neurotoxic Anatoxins

Anatoxins are produced by many cyanobacteria genera, such as *Anabaena, Aphanizomenon, Planktothrix, Oscillatoria, Microcystis, Cylindrospermum,* and *Phormidium.* Reports of anatoxin-a poisoning in livestock are extremely rare; most cases are documented in dogs. However, all animals are considered susceptible. Anatoxin-a poisoning leads to muscle tremor, rigidity, respiratory failure, collapse, and death within minutes to a few hours.[29-31] This is a result of anatoxin-a being a potent cholinergic agonist at nicotinic receptors.[32] Animals poisoned with anatoxin-a(S) develop acute signs of excessive salivation, lacrimation, diarrhea, and urination (SLUD) because anatoxin-a(S) is a naturally occurring, irreversible acetylcholinesterase inhibitor.[33] Animals often die of respiratory arrest within 30 minutes.

Because of the acute onset, CBC and chemistry profiles of animals with anatoxin poisoning are generally unremarkable. Furthermore, other than the possible presence of algae material in GI contents, there are no specific gross or microscopic lesions. Confirmation of anatoxin-a poisoning is by analytic detection of the toxin in urine, bile, or GI contents.[31] Diagnosis of anatoxin-a(S) toxicosis is aided by the determination of blood acetylcholinesterase activity. In any suspect cases, environmental samples should undergo a toxicologic and phycologic analysis.

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Other Cyanotoxins

Other freshwater cyanotoxins of concern to livestock include neurotoxic saxitoxins, hepatotoxic nodularins, and cylindrospermopsin, which targets multiple organs (liver, kidneys, lung, heart, GI tract).

Treatment for cyanotoxin poisoning is supportive but often unsuccessful. Efficacy of decontamination with activated charcoal is limited.[34,35] Symptomatic and supportive care to treat hypovolemia and electrolyte imbalances, as well as antioxidants such as vitamin E and selenium, may aid in the therapeutic regimen for large animals poisoned with microcystins. Animals that develop photosensitization must be protected from sun exposure. Because of the rapid onset of clinical signs in anatoxin-a poisonings, therapeutic options are even less pertinent; artificial respiration may be of benefit along with general supportive care. Administration of activated charcoal is suggested, but scientific evidence on its adsorptive capacity for anatoxin-a is lacking. Atropine can revert excessive muscarinic receptor activation in animals poisoned with anatoxin-a(S). It is important to note that pralidoxime (2-PAM) is not recommended.[36]

The frequency and extent of harmful cyanotoxins have increased with the addition of nutrients to surface freshwater ecosystems around the world. Steps must be taken to reduce fertilizer runoff and applications in fields surrounding ponds used for drinking water. Prevention of blooms is key to protecting animal and human health.

Mycotoxins

Timothy J. Evans • George E. Rottinghaus • Benjamin R. Landers

Importance of Mycotoxins

Mycotoxins are secondary fungal metabolites, which, if consumed in sufficient amounts, cause adverse health effects in animal species, including humans.[1] They can be detected in various matrices, including cereal grains and forage, and are a major concern to international agricultural production and a threat to food safety worldwide.[1-3] Individuals working within the United States swine and poultry industries are particularly cognizant of the potential for mycotoxin exposures, given the dietary dependency of those monogastric species on cultivated cereal grains. However, the globalization of agricultural commodities, climate change–related weather conditions favoring fungal growth and/or

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mycotoxin production, subsequent reductions in the availability of foodstuffs not contaminated by mycotoxins, and economic pressures from higher costs of better-quality foodstuffs all underscore the need for individuals participating in other aspects of animal agriculture in the United States to have a greater awareness of the potential for mycotoxin contamination.

In addition, the increasing risk to human and animal health posed by mycotoxins means that the veterinary profession must be vigilant in the surveillance of domesticated large animal populations as sentinels for mycotoxin contamination of agricultural products. Veterinary practitioners, regardless of whether their practices involve small companion animals or livestock, will need to be familiar with the "major" mycotoxins and the wide range of clinical signs, including subtle reductions in livestock production and food residues associated with these fungal toxins.[4] It is only through an increased awareness of these toxins that mycotoxin-related illness in food animals can be minimized and companion animal and human exposure to mycotoxins limited or prevented.

General Principles of Mycotoxin Production and Detection

Many fungi are capable of producing toxins (i.e., are toxigenic), and a given mycotoxin could be synthesized by more than one fungal species.[3] Some fungi produce more than one toxin or even multiple classes of toxins.[1,3] Although a number of relatively common mycotoxins have already been identified, it is likely that many more potentially toxic, secondary fungal metabolites have yet to be isolated and characterized.[2,3,5] Fungal colonization does not necessarily mean that a given mycotoxin is being produced.[1,3] The substrate, moisture content, pH, ambient temperature, relative humidity, and other requirements for toxin synthesis are often more stringent than those for fungal growth.[1,2] The "ideal" toxigenic conditions for the production of specific mycotoxins have been characterized, and some mycotoxins are more likely to be produced in a "field" or "storage" setting.[1-3] The mere presence of fungal growth does not necessarily correlate with toxin production, and some mycotoxin-contaminated foodstuffs might not even be visibly moldy.[3]

From a clinical perspective, the inability to accurately predict whether mycotoxins will be present in a specific foodstuff means that fungal identification and spore counts are not adequate for identifying livestock diets contaminated with mycotoxins.[1-3] High-performance liquid chromatography (HPLC), liquid chromatography–tandem mass spectrometry (LC-MS/MS),

and/or enzyme-linked immunosorbent assay (ELISA) are some of the more common analytic techniques used to directly measure mycotoxin concentrations in grains or processed foodstuffs. The use of an ultraviolet light to detect fluorescence associated with kojic acid, as an indirect indicator of aflatoxins, is outdated as the sole means of detecting these toxins.[1,6] Likewise, use of semiquantitative methods, such as thin layer chromatography (TLC), as standalone evidence of fungal toxin contamination, is also less than optimal. The consistent use of appropriate sampling techniques ensures the detection of suspected mycotoxins and guarantees that detected mycotoxin concentrations are representative of actual livestock exposure.[3,7,8] Grain "screenings" or "fines" are the grain by-products most likely to contain the highest concentrations of mycotoxins.[1,3]

One of the biggest challenges pertaining to mycotoxin contamination in livestock rations is the accurate interpretation of analytic results, especially now, when low concentrations of mycotoxins are detected by increasingly sensitive laboratory methods.[4] Table 54.8 shows "action levels" established by the U.S. Food and Drug Administration (FDA) for some mycotoxin-contaminated commodities fed to different species of livestock. These action levels (more specifically, "advisory levels" for deoxynivalenol and "guidance levels" for fumonisins) were originally intended as guidelines for "acceptable" concentrations of individual mycotoxins in common substrates being transported between states.[6,9] The mycotoxin concentrations have often been interpreted as the highest dietary concentrations of these mycotoxins considered "safe" in the denoted species. However, the definition of "safe" is a relative term that depends on the end point being measured. Some concern has recently been expressed as to whether these action levels are low enough to prevent adverse health effects, especially with respect to carcinogenesis in humans.[10]

TABLE 54.8
Summary of Mycotoxins Important to Livestock

Mycotoxins	Fungal Sources Substrates	Primary Toxic Effects	Dietary U.S. Food and Drug Administration Action Levels
Aflatoxins	*Aspergillus flavus* and *Aspergillus parasiticus*	Macromolecular binding enzymatic inhibition	Total aflatoxins[a]
B_1, B_2, G_1, G_2	Corn, nuts, cottonseed+	DNA adducts formed → hepatic	Immature 20 ppb
			Dairy/horse 20 ppb
		insult/failure cancer (1° hepatic)	100+ lb pigs 200 ppb

		All species	Feedlot beef 300 ppb Breeding 100 ppb
Deoxynivalenol (DON/Vomitoxin)	*Fusarium graminearum* (formerly *Fusarium roseum*) Corn, wheat, barley+	↓Protein synthesis, GI irritation, ↑vomiting → feed refusal, ↓nutrient absorption, ↓immunity 1° Swine Dairy cattle?	DON[b] Swine 1 ppm Horses/other 2 ppm Cattle 5 ppm
Zearalenone	*F. graminearum* (formerly *F. roseum*) Corn, wheat, barley+	Hyperestrogenism → reproductive tract Δs Pseudopregnancy Early embryonic death 1° Swine ↑Subfertility/ovary Δs Dairy cattle?	No action level determined Clinical signs Young gilts 1-3 ppm Mature sows >3 ppm Bred sows >15 ppm Heifers >10 ppm Cows >25 ppm
Fumonisins 1° B_1 and B_2	*Fusarium verticillioides* (formerly *Fusarium monilforme*) 1° Corn	Sphingolipid Δs → leukoencephalomalacia Horses Pulmonary edema Swine Hepatic disease in both	Total fumonisins[b] Horses 1 ppm Swine 10 ppm Ruminants 30 ppm or Repro/dairy 15 ppm
Ergot Alkaloids Ergopeptine alkaloids *Ergovaline* Lysergic acid+ *Ergonovine/Lysergol* Ergopeptine alkaloids *Ergotamine*+	*Epichlöe coenophiala* (genus formerly *Neotyphodium* and *Acremonium*) Tall fescue grass *Neotyphodium lolii* Perennial ryegrass *Claviceps purpurea* Small grains and grasses	1° Vasoconstriction → dry gangrene/↑temp ↓Feed intake Ruminants/camelids? 1° Hypoprolactinemia → agalactia/long gestation Horses	Ergot bodies 0.1% by weight % Ergot bodies versus ergopeptine alkaloid concentrations

[a]Based on corn action levels.

[b]Actually “advisory” levels for DON and “guidance” levels for fumonisins, based on highest allowable grain level and percent of diet.

GI, Gastrointestinal.

From references 1, 3, 6, 8, 9, 25, 33, 37, 46, and 47.

Mycotoxicoses

In discussing mycotoxin-related diseases, it is important to differentiate “mycosis” from “mycotoxicoses.” The term *mycosis* refers to a disease caused by fungal growth, rather than by the adverse effects of any toxins produced by that fungi.[3] *Mycotoxicoses*, on the other hand, are diseases caused by the adverse health effects of mycotoxins, which in most cases have been ingested.[1-3] For a specific mycotoxicosis to occur, growth conditions in substrates colonized by the appropriate fungal species must favor production of a specific toxin, and sufficient amounts of that toxin-contaminated substrate must be consumed by a

susceptible animal species.

The higher the dietary concentration of a given mycotoxin, the more likely and severe are the observed adverse effects.[1-3] Similarly, the duration of exposure to a mycotoxin affects the likelihood and severity of the observed clinical signs, with longer exposures increasing the probability of more severe intoxications.[2,3] Peracute and acute intoxications generally occur over a short period (usually days) and involve one or several “large” doses (orders of magnitude greater than “allowable” quantities) of a specific mycotoxin. In these instances, the diagnosis is often straightforward because contaminated feed is more likely available for testing. However, clinically recognized mycotoxicoses more often than not involve subacute (weeks) to chronic (months) dietary exposures to fungal toxins.[1] Depending on the dietary concentration of a given mycotoxin, clinical signs in these types of exposures may be “classic” for a mycotoxin's typical target organ (e.g., moderate to severe hepatocellular damage with sufficient amounts of aflatoxins) or more subtle in nature (e.g., immunosuppression, suboptimal growth, reproductive inefficiency, and/or carcinogenesis), reflecting impaired hepatic function.[3,4] In subacute to chronic mycotoxin exposures, affected animals could still be ingesting specific toxins, with contaminated foodstuffs readily available for testing, or the consumption of specific mycotoxins may have already ceased, especially if the observed clinical signs are more subtle in nature and/or took some time to develop. Under these circumstances, analyses of representative samples of grains or forages harvested at the same time as the suspect foodstuffs or analyses of samples of prepared rations retained by the supplier or manufacturer might be the only way to establish the definitive cause of a suspected mycotoxicosis.

Another aspect of a potential mycotoxicosis, as illustrated in Fig. 54.4, using reproduction as an example of monitored animal performance, is the role that mycotoxins may play in diminished livestock performance, such as decreased feed consumption, growth rates, and fertility. In these instances, there may not be a single, definitive “cause” but rather a multifactorial etiology. It is probably overly convenient to hold feed manufacturers and distributors wholly responsible in these instances and to forget the important role of other factors, such as environmental stressors, infectious agents, and suboptimal management. In fact, the mention of this type of diagnostic conundrum can increase the overdiagnosis or misdiagnosis of a mycotoxicosis, especially when the detected concentrations are well below established levels of concern, and should not be misconstrued as an effort to indict trace amounts of some mycotoxins as the

primary cause of clinical abnormalities in livestock.[4,6] However, although it is not practical or even possible to eliminate all measurable fungal toxins from livestock diets, one should also recognize that there is no nutritional requirement or benefit related to dietary mycotoxins. It is critical, therefore, when no clear-cut, single cause of diminished performance is evident, to take an integrated approach and objectively evaluate the relative contributions of a wide variety of enzootic variables or "stressors" to the clinical problems being observed.[4]

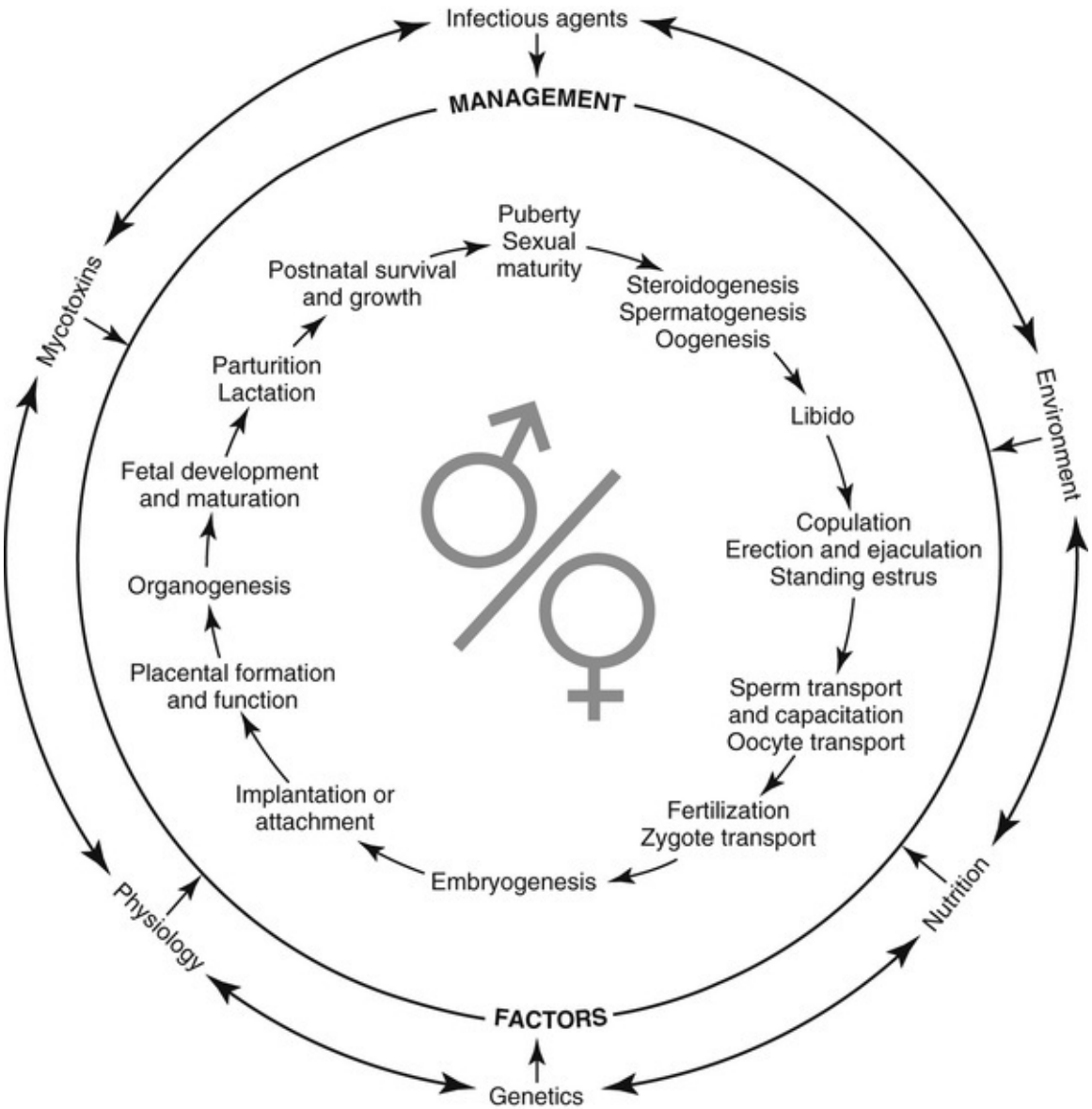


FIG. 54.4 The continuum of developmental stages and reproductive functions taking place in males and/or females, as well as the embryo and

fetus, is shown schematically and illustrates the complexity of reproduction in ruminant species. The possible influences of genetic and physiologic predispositions, as well as nutritional, environmental, infectious, and especially mycotoxin stressors, on decreased reproductive performance are also represented, along with the role “management” can play in modulating those influences on reproductive function. (Modified with permission from Evans TJ: Diminished reproductive performance and selected toxicants in forages and grains. Vet Clin North Am Food Anim Pract 27:345, 2011. Modifications and artwork courtesy Don Connor and Howard Wilson.)

Major Mycotoxins of Veterinary Importance

Aflatoxins.

Aflatoxins arguably pose the most clinically relevant, mycotoxin-related threat to the worldwide health and well-being of humans and domestic animals. A number of fungal species, in particular *Aspergillus flavus* (*A*+*fla*+toxin) and *Aspergillus parasiticus*, can produce aflatoxins under appropriate growth conditions in a variety of nuts and grains, including cottonseed, peanuts, and especially corn.[1-3] The major aflatoxins found in contaminated grains include aflatoxins B_1, B_2, G_1, and G_2 (B or G = fluorescence color), with aflatoxin B_1 (AB_1) generally being present in the highest concentrations.[3] Although aflatoxins are sometimes described as “storage” mycotoxins, there are certainly instances when they are produced under “field” conditions.[1,6] Drought and/or insect damage to corn or other susceptible plants, followed by warm (>25° C), humid (>70% humidity), ambient weather conditions, is the “classic” scenario that facilitates initial fungal invasion of compromised kernels and seeds and subsequent fungal growth with aflatoxin production.[1-3,6] In fact, drought conditions are often associated with increased scrutiny on the part of grain elevator operators, livestock producers, and regulators, with respect to possible aflatoxin contamination, particularly in corn and corn by-products.

Ingested AB_1 is metabolized by multiple cytochrome P450 subfamilies in the liver to produce several metabolites, including AB_1-8,9-epoxide and AB_1-dihydrodiol, which are toxic, and aflatoxin M_1 (AM_1), which can be found in meat as well as in milk.[1] AB_1-8,9-epoxide and other toxic metabolites bind to biologically important molecules, such as essential proteins, including enzymes involved in carbohydrate and lipid metabolism and protein synthesis.[1,3] These

AB_1 metabolites also bind to macromolecular nucleic acids, inhibiting transcription and forming DNA adducts, which can be associated with carcinogenesis, especially hepatic tumors.[1-3,8] In addition, toxic metabolites of AB_1 can bind to subcellular organelles, such as mitochondria and ribosomes.[1]

Although excretion of violative AM_1 residues (>0.5 ppb or 0.0005 ppm) in the milk is the first observed "abnormality" associated with AB_1 exposure in lactating dairy animals, the liver is considered the major target organ of toxic AB_1 metabolites in all species.[1-3,6] Clinical signs of aflatoxicosis range from prolonged prothrombin time (PT), hemorrhage, bloody diarrhea, and rapid death in peracute and acute intoxication, to anorexia, slow rumen motility, weakness, tremors, ataxia, and reproductive failure (abortion), to hepatic failure with icterus, coma, and death in subacute aflatoxicoses.[1-3,6,8,11-16] Aflatoxin-induced hepatic insult and failure are usually accompanied by many of the typical clinical pathologic abnormalities expected with hepatocellular necrosis and/or hepatic failure, and elevations in the detected activities of liver-specific enzymes in serum often precede other clinical signs.[6] Suppression of immune function, particularly those aspects related to cell-mediated immunity, have also been reported in animals following repeated exposure to moderately high dietary concentrations of AB_1.[1,6,8,15] Chronic exposure to dietary aflatoxins can be associated with decreased growth rates and feed efficiency, roughened hair coats and ill-thrift, impaired resistance to infectious disease, and hepatic fibrosis with regenerative nodules.[1,3,6] Spermatogenesis can also be adversely affected by chronic exposures of male animals to AB_1.[17] Low-level subacute to chronic exposures to AB_1 and its toxic metabolites also have the potential to be associated with teratogenesis, mutagenesis, and/or carcinogenesis, and experimentally, AB_1 in grain dusts can be present in sufficient quantities to be converted to carcinogens by pulmonary cytochromes.[3,18]

Attempts to estimate the dosages or dietary concentrations of total aflatoxins likely to be "safe" or, conversely, the concentrations that will probably be associated with clinical disease can be challenging. Anecdotal evidence and reports of clinical cases of aflatoxicosis, which provide some dose-related data, may require additional scrutiny because some of the factors known to influence the toxicity of aflatoxins might be unaccounted for or unknown.[6] However, such reports are still of value because they represent "real" clinical situations. An animal's plane of nutrition, rate of hepatic metabolism, age, and species, as well

as the level and duration of aflatoxin exposure, are all important determinants as to whether and what signs of aflatoxicosis are likely to be observed.[1,3,6,8] Animals fed a diet deficient in protein, selenium, and/or vitamin E and those with enhanced rates of hepatic metabolism are more likely to experience hepatic insult associated with dietary aflatoxin contamination.[6,8] Immature animals, particularly young swine, are the livestock populations considered most susceptible to adverse health effects associated with aflatoxins.[3,6] Weeks of exposure to total dietary aflatoxin concentrations of 200 ppb (0.2 ppm) have been associated with mild hepatic insult and suboptimal growth of piglets and decreased performance in calves.[3,6,8] Horses and more mature cattle and swine have experienced toxic insult to the liver following weeks to months of exposure to aflatoxin concentrations exceeding 400 and 600 ppb (0.4 and 0.6 ppm), respectively, and hepatic failure and death are possible in animals consuming foodstuffs that contain a flatoxin concentration exceeding 1000 ppb or 1 ppm.[3,6,8,11,12,14,15,19]

The “threshold” AB_1-induced “abnormality” usually first observed at the lowest dietary concentrations in livestock species is an actionable level of AM_1 detected in milk obtained from exposed lactating dairy animals.[3,6] The concentrations of AB_1 causing short-term, minimally violative AM_1 residues in milk are much lower than those likely to cause any liver-related adverse health effects, especially in ruminants.[3,6,8,11-16,19] The ratio of the concentration of AB_1 in the diet to the AM_1 concentration detected in the milk varies widely from less than 50 : 1 to almost 2000 : 1 (average of 300 : 1), and the proportion of dietary AB_1 excreted as AM_1 can range between 0% and 4% (average of 1%).[6] Excretion of AM_1 in the milk generally continues for 2 to 7 days after withdrawal from an AB_1-contaminated diet.[3,6]

The accurate diagnosis of clinical aflatoxicosis usually involves the detection of high AB_1 concentrations in the feed or, less optimally, the gastric contents of animals exhibiting appropriate clinical signs.[3,6,8] The detection of AB_1 and/or AM_1 in the liver and kidney, in particular, can also be indicative of recent AB_1 exposure (usually within 7 days) and may help establish the consumption of dietary AB_1 by a deceased animal, when foodstuffs are unavailable for analyses.[3,8]

Treatment of aflatoxicosis in large animals is often cost prohibitive, especially

in food-producing animals, and limited to therapy for hepatic insult and/or failure; provision of a balanced, AB_1-free diet; possible supplementation with trace minerals and vitamins (selenium and vitamin E); and most importantly prevention of further exposure.[3,6,8] Growth conditions are not conducive to AB_1 production in *Aspergillus*-infected stored grains when the moisture content is reduced to less than 15%.[8] Ammoniation has been reported to prevent fungal colonization and growth and to facilitate detoxification of aflatoxins.[1,3,8] In "emergency" situations where it is difficult to find affordable, alternative foodstuffs free of AB_1 contamination, producers may consider dilution of feeds to "safe" concentrations of AB_1.[3] However, this approach has some attendant risk, including the species of animal involved, exposure to enzootic stressors other than aflatoxins (e.g., infectious disease, poor nutrition), level of animal management and husbandry skills, willingness of the producer to thoroughly "blend" the feeds and collect frequent representative samples for AB_1 analyses, and the targeted "safe" concentration of AB_1.[3,4] One possible approach to the dilemma of which targeted AB_1 concentrations are likely to be "safe" is for producers to aim for total aflatoxin concentrations approximately one half of that shown in Table 54.8 for total dietary aflatoxin action levels, particularly in diets intended for lactating dairy cows, immature livestock, or animals used for breeding purposes.[4,9] This approach can also be used for other mycotoxins for which there are action levels.[4] Another consideration, especially for aflatoxins, may be the incorporation of clay binders in rations to prevent the absorption of fungal toxins.[3,4,6,8] Hydrated sodium calcium aluminosilicates (HSCASs) have been shown to effectively prevent violative AM_1 residues in milk and meat and to reduce livestock production indices, especially those parameters (e.g., growth and reproductive performance) likely to be affected by low-level chronic exposure to dietary aflatoxins.[3,4,6,8,20-24] Before using a given binder, there should be in vivo evidence that the binder in question is effective at reducing AB_1 absorption in live animals.[1,3,4,6]

Deoxynivalenol (DON or Vomitoxin).

Deoxynivalenol (DON or vomitoxin) is classified as a trichothecene mycotoxin and is produced in grains such as corn, wheat, and barley by toxigenic *Fusarium* species, especially *Fusarium graminearum* (formerly *Fusarium roseum*). This species is also the conidial stage of *Gibberella zeae* and associated with "head

blight" and "scab" in wheat and "Gibberella ear rot" in corn.[1-3,25] Although growth of this toxigenic fungal species occurs in the field when temperatures are warmer (20° to 25° C), DON production is favored under storage conditions when it is cooler (0° to 15° C).[1,3] Rising and falling (undulating) temperatures, especially when associated with a cool, wet fall and delayed harvest, facilitate production of DON.[1,3,26] Trichothecenes are stable compounds that persist much longer than the fungi producing them.[1] Deoxynivalenol can also be found in forages (such as corn stover and wheat straw) associated with the grains most frequently contaminated by this mycotoxin.[1,27] In addition, grains contaminated with vomitoxin are often contaminated with zearalenone (see below), which is also produced by *F. graminearum* (see Table 54.8) under similar fungal growth conditions.[1,3,25]

Deoxynivalenol is an extremely important trichothecene mycotoxin, from an agricultural perspective, because of its impact on indices of animal performance and the frequency with which it is detected in livestock diets, especially those intended for consumption by swine and dairy cattle.[1-3,8,26] This particular fungal toxin inhibits protein synthesis and induces emesis by crossing the blood-brain barrier and directly stimulating the chemoreceptor trigger zone in the medulla oblongata, hence the alternative name of "vomitoxin."[3,25] Immunosuppression has been reported in some animal species, but feed refusal and gastroenteritis are the most common clinical signs, particularly in swine.[1-3,25] Clinical pathologic abnormalities include those associated with decreased feed intake, impaired absorption of nutrients, vomiting, and diarrhea.[8,25]

Table 54.8 shows the guidance levels for DON in various species of livestock. Clinical signs of dietary exposure to DON, such as feed refusal, generally begin within 1 day of ingestion.[3,25] Dietary concentrations of DON associated with clinical disease range from 1 ppm (feed refusal) to 5 to 10 ppm (vomiting and possible gastroenteritis) in swine; ruminants have been reported to refuse eating contaminated foodstuffs containing more than 10 to 20 ppm of DON.[8,25] One dilemma often associated with DON occurs because of the low concentration frequently found in grains and their related forages. It is difficult to differentiate the direct adverse effects of the mycotoxin itself from clinical signs related primarily to reduced palatability and/or the decreased nutritional value of poorer quality foodstuffs, particularly when feed refusal and abnormalities arising from reduced feed intake are the only observed clinical signs.[4] Similarly, any

deviations from optimal dairy cattle performance should not necessarily be attributed solely to low-level mycotoxin contamination (<0.5 ppm) without taking into account the reduced palatability and nutritional value of contaminated grains and forages. Evaluation of overall diet quality, rather than just the presence or absence of low concentrations of mycotoxins such as DON, remains an important aspect of the management of livestock production systems, even when experimental data indicate improvement following the addition of "binders."[28,29] Such products may have benefits related to nutrient uptake that are completely independent of interactions with DON or any other mycotoxins.[30]

As with AB_1, appropriate clinical signs and analyses of foodstuffs and, less desirably, gastric contents can be used to determine whether there has been dietary exposure to DON.[3,8,25] However, unlike AB_1, consumption of DON is not associated with residues in milk or meat.[3,25] Treatment of DON intoxication is limited to supportive care and prevention of further exposure to foodstuffs contaminated by DON and related mycotoxins. There has been limited in vivo success in developing binders that are effective in preventing the absorption of DON in experiments involving susceptible species.[31,32]

Zearalenone.

Like DON, zearalenone (ZEA) is produced in corn and other grains and their corresponding forages by *F. graminearum* (formerly *F. roseum*) and other *Fusarium* species.[1-3,8,33] The synthesis of ZEA is facilitated by a drop in temperature to 12° to 14° C with greater than 23% relative humidity.[1,3,8,33] Under certain growth conditions, both DON and ZEA can be detected in some contaminated foodstuffs, and the diagnosis, treatment, and prevention of dietary exposures to ZEA is essentially the same as outlined for DON.[1,3,25,33]

Zearalenone is a naturally occurring, nonsteroidal xenoestrogen that binds to both the α and β estrogen receptors (ERα and ERβ). Swine, especially sexually immature, prepubertal gilts, clearly is the species most susceptible to the xenoestrogenic effects of ZEA. The enhanced sensitivity of swine to the xenoestrogenic effects of ZEA is based on several factors. The slow detoxification and enterohepatic recirculation of ZEA and its metabolites in swine certainly play important roles in the ZEA susceptibility observed in this species.[1,3,33] However, it also important to note that the porcine liver preferentially metabolizes a greater portion of ZEA into the potent

xenoestrogenic metabolite, α-zearalenol, than other animal species.[1,3,33,34] Anecdotally and perhaps more controversially, dairy heifers have also been reported to be particularly susceptible to the xenoestrogenic effects of ZEA, especially when they are being bred to produce their first calf and after entering their first lactation.[3,4,33]

Within a few days to a week after exposure to dietary concentrations of ZEA as low as 1 ppm (possibly even lower concentrations, depending on the clinical or experimental circumstances), classic hyperestrogenism, as evidenced by vulvar swelling (one of the earliest and most dramatic signs), enlarged mammary glands, possibly prolapsed rectum, and increased size and weight of the tubular portions of the female reproductive tract, can be observed in prepubertal gilts.[1,3,8,33] Nymphomania in females and feminization and decreased testicular weights in males can also be observed, especially in gilts and young boars.[33] Dietary concentrations of 3 to 10 ppm of ZEA can be associated with anestrus and pseudopregnancy in postpubertal gilts and sexually mature sows, due to the unique luteotrophic effect of estrogens in swine.[8,34] Exposure of recently bred sows (7 to 10 days after breeding or insemination) to concentrations of ZEA, exceeding 15 ppm, can result in early embryonic death and prolonged interestrous intervals.[8,33]

Although it is clear that postpubertal dairy heifers are more susceptible than mature dairy cows (>10 ppm versus >25 ppm ZEA, respectively) to adverse reproductive effects associated with ZEA, there still remains doubt as to how often ZEA-related problems are observed in dairy cattle in “real-world” situations.[4,8,33] There are reports that cattle are insensitive to ZEA, while others report a 25% lower pregnancy rate in postpubertal heifers fed 12.5 ppm of ZEA.[4,33,35,36] The disparity between these reports attests to the significance of the stage of sexual maturity, concurrent exposure to other enzootic stressors, and sensitivity of the criteria used to evaluate impaired reproductive performance in determining how ZEA affects dairy cattle fertility.[4]

Fumonisins.

Fumonisins, especially fumonisin B_1 and B_2 (FB_1 and FB_2), are produced primarily by the ubiquitous fungal species *Fusarium verticillioides* (formerly *Fusarium moniliforme*).[1-3] *F. verticillioides* grows primarily on corn, and the highest concentrations of FB_1, which is the most common and clinically

important fumonisin, are most often found in association with corn “screenings” or “fines.”[8,37,38] Although growth conditions facilitating FB_1 production are not as well defined as those for AB_1, DON, and ZEA, drought conditions during the growing season and subsequent cool, wet weather during ear development seem to correspond to higher FB_1 concentrations.[8,37]

Fumonisins structurally resemble sphingolipids, which are found in highest concentrations in the brain and liver and are essential for cell growth and differentiation, as well as vascular integrity.[1,3,8,37] One primary toxic mechanism of action proposed for fumonisins, in particular FB_1, is inhibition of the conversion of sphinganine to sphingosine, resulting in a disruption of sphingolipid biosynthesis.[3,8,37,39] Horses and swine are the two livestock species most susceptible to fumonisin intoxication.[1,3,37] The brain is generally considered the major target organ in horses, especially following more chronic, low-level exposures, but centrilobular hepatocellular necrosis, with clinical pathologic changes in the serum typical of toxic hepatic insult, can be observed in the absence of brain lesions when horses are acutely exposed to high FB_1 concentrations.[1,3,37] Subacute to chronic consumption of dietary concentrations of FB_1 exceeding 8 to 10 ppm have been associated with the sudden onset of the clinical syndrome referred to as *equine leukoencephalomalacia* (ELEM) or “moldy corn poisoning.”[1,3,8,37,40-42] Horses affected by ELEM (also see Chapter 35) exhibit altered mentation, ranging from depression to neuroexcitation, sometimes accompanied by head pressing; incoordination and apparent blindness; and finally recumbency and death, often within 5 to 7 days of the onset of clinical signs.[1,3,37,40-42] The pathognomonic lesion of ELEM is *leukoencephalomalacia*, or degeneration of the white matter of the brain, which can be grossly visible involving one or both cerebral hemispheres or subtle and difficult to detect in stained sections of brain.[1,3,37,40-42] Hepatosis of varying severity can also be observed in cases of ELEM, and transient increases in the activities of enzymes specific for hepatocellular damage might be observed under those circumstances.[37,41]

The primary clinical abnormalities associated with FB_1 exposure in swine include porcine pulmonary edema (PPE), which is thought to be secondary to left-sided heart failure, and toxic insult to the liver.[1,3,8,37] However, unlike ELEM, it is difficult to pinpoint any consistent “threshold” dietary concentrations of FB_1 likely to cause heart failure and the resulting PPE in swine

or, alternatively, histopathologic changes restricted to only the liver.[8,37,38,43,44] Some authors have suggested that FB_1 concentrations in contaminated corn or especially in contaminated corn screenings, ranging from the dietary action level of 10 ppm of FB_1 (see Table 54.8), should be considered actionable. Conversely, it is interesting to note that swine have been chronically exposed to dietary FB_1 concentrations in excess of 100 ppm, without the development of signs consistent with PPE and with hepatic fibrosis being the only observed histopathologic finding.[44] It appears that if PPE is going to develop, it will almost certainly do so within the first week of consumption of FB_1-contaminated diets.[37,43] This consistent observation suggests the role of various stressors, such as recent transport, excessive animal handling, and/or the presence of respiratory pathogens.[44,45]

The diagnosis of ELEM and PPE involves the observation of the appropriate, species-specific clinical syndromes, as well as the detection of sufficiently high enough concentrations of FB_1 in corn-based rations, especially those diets prepared using screenings from homegrown corn.[3,37] An elevated sphinganine–to–sphingosine ratio (SA/SO ratio) in the serum, urine, or tissues of animals suspected of being exposed to FB_1 can also be an accurate indication of recent (<7 days) exposure to FB_1.[3,8,37] As with DON and ZEA, treatment of fumonisin intoxication is limited to stabilization and supportive care, withdrawal from FB_1-contaminated rations, and, most importantly, prevention.[47] Unless absolutely unavoidable and only if there is concurrent and vigilant FB_1 surveillance to ensure that FB_1 concentrations remain below 1 ppm (see Table 54.8), horses should not be fed diets containing homegrown corn and/or, especially, corn screenings. A similar approach could also be used to prevent FB_1-related PPE and hepatic disease in swine.[3]

Ergot Alkaloids.

Ergot alkaloids (EAs) are a complex class of mycotoxins that play a role in several financially devastating livestock diseases (i.e., “fescue toxicosis,” “perennial ryegrass staggers,” and “ergotism”).[1,46,47] However, unlike the other “major” mycotoxins discussed in this chapter, EAs are not found in corn and the most commonly occurring intoxications involving EAs are restricted to forages (i.e., fescue toxicosis and perennial ryegrass staggers). Unfortunately, the

economic impact of these two mycotoxicoses is thought by many to be restricted to certain geographic regions.[46,47] Ergotism, on the other hand, which can be associated with the ingestion of contaminated forages or grains, has mistakenly been relegated to history because of its sporadic occurrence and is almost exclusively limited to livestock species.[46-48] Although there are several separate systems of nomenclature for EAs, an easy way to view these compounds is to divide them into clavine alkaloids, ergopeptine alkaloids (ergopeptines, ergopeptides, or EPs), and lysergic acid and its derivatives (LA+).[46,47] The LA+ have also been referred to as "ergoline alkaloids"; however, this terminology has the potential to be confused with the ergoline ring structure present in all EAs.[46-48,50,51] The most clinically relevant EAs to livestock species are EPs, which include ergovaline, ergotamine, ergocristine, ergosine, ergocryptine, and ergocornine, and LA+, such as lysergol, lysergic acid amide, and ergonovine or ergometrine (see Table 54.8).[46,47,51,52]

Most of the naturally occurring EAs have been isolated from fungal species within the *Epichlöe* and *Claviceps* genera.[46-51] *Epichlöe coenophiala* (formerly *Neotyphodium* or *Acremonium coenophialum* or *Epichlöe typhina*) is the endophyte that can grow, as part of a symbiotic grass-endophyte relationship, within the intercellular spaces of tall fescue grass, a long-lived perennial, cool-season grass most simply referred to as *Festuca arundinacea* or, more recently, *Lolium arundinaceum.* Toxigenic endophyte-infected (E+) tall fescue grass grows in humid temperate areas worldwide, including the upper southeastern and lower midwestern United States.[1,48-51] The EP present in highest concentrations in E+ tall fescue is ergovaline (≈0.2 to 0.6 ppm ergovaline in the vegetative parts of the plant and >1 ppm ergovaline in the seed heads), and LA+ are also present in this grass.[50,51-53] The livestock species most likely to consume E+ forages are ruminants, especially cattle, and horses. The primary sources of the EP compounds—ergotamine, ergocristine, ergosine, ergocornine, and ergocryptine—are the dark-colored ergot bodies or sclerotia of *C. purpurea*. Ergot sclerotia, unlike endophytic mycelia, are externally visible and replace the individual seeds of many common pasture grasses, including E+ tall fescue and small cereal grains, such as oats, barley, wheat, and especially rye and triticale, but *not* corn.[47,48,50] The cool, wet springs in the northwestern United States, the northern Great Plains, and parts of western Canada facilitate the germination and growth of *C. purpurea*.[47,48,50] Those animal species likely to consume E+ tall fescue will also be exposed to the EAs produced by *C. purpurea*, if the E+ tall

fescue or other nearby grasses are infected by this fungal species ("ergotized"). On the other hand, when small cereal grains are contaminated by ergot bodies, not only ruminants and horses but also swine, poultry, and even humans are likely to be exposed to EAs. The total concentration of EPs in *C. purpurea* sclerotia are extremely high, generally ranging from 2000 to 10,000 ppm, with LA+ also likely to be present.[47,48,50,54-57]

Although there is some overlap, the pathogenesis of clinical signs associated with dietary exposures to EAs can generally be explained in terms of vasoconstriction and/or hypoprolactinemia. Vasoconstriction involving interactions with dopaminergic, adrenergic, serotonergic, and glutamate receptors is responsible for many of the clinical signs observed in ruminants, especially cattle, and possibly in South American camelids.[46,47,51] Hypoprolactinemia-induced agalactia in late gestational mares is the most sensitive indicator of dietary exposure to EAs.[47,50,51] The stimulation of dopamine D_2 receptors by EAs dramatically reduces prolactin secretion by lactotropes in the adenohypophysis.[8,46-51,58] Abdominal fat necrosis in cattle is associated with chronic exposure to EAs in E+ tall fescue and arises from both vasoconstriction and the effects of hypoprolactinemia on lipid metabolism.[46,51] The higher the dietary concentrations of EAs, the more likely horses are to exhibit vasoconstrictive effects and the more likely agalactia will be observed in ruminants, in which a placental lactogen helps prevent abnormal lactation from the amounts of EAs often present in E+ tall fescue.[1,34,47,51] Swine exhibit vasoconstrictive effects and suboptimal reproductive performance, including agalactia, when exposed to sufficient concentrations of EAs.[1,47]

When trying to define levels of exposure to EAs, the most readily available data pertain to concentrations of EPs measured using HPLC. If animals ingest total dietary concentrations of EPs between 0.1 and 1.0 ppm, regardless of the sources, this is equivalent to low-level exposures involving only E+ tall fescue without seed heads, plus or minus other grasses.[50,51,53] Low to moderately high total dietary concentrations of EPs between 1 and 5 ppm correspond to what would be expected in pastures consisting entirely of E+ tall fescue in the seed head stage.[51,53] Moderately high dietary concentrations of total EP ranging between 5 and 10 ppm and very high dietary EP concentrations, exceeding 10 ppm, would involve contamination of foodstuffs by ergotized grains.[47,54-57,59]

Due to vasoconstriction, the toxicity of EAs can be extremely dependent on ambient weather conditions (see Table 54.8), especially with lower dietary

concentrations of EAs (0.1 to 1.0 ppm total concentration of EP), which are typical of E+ tall fescue.[51] When it is hot, a syndrome referred to as “summer slump” or “summer syndrome” is observed in ruminants, in particular cattle, grazing E+ tall fescue.[1,51] This condition is thought to arise from the limited peripheral dissipation of heat associated with vasoconstriction.[1,3,48,49,51] Regardless of the source of toxins, EA-related “heat stress” is characterized by hyperthermia, rapid breathing, lethargy, an unthrifty appearance, and reductions in feed intake and average daily gain, as well as suboptimal male and female reproductive performance.[1,3,4,46-49,60-63] When it is colder, peripheral vasoconstriction in ruminants impairs the circulation to the distal extremities, resulting in cow discomfort, lameness, and eventually dry gangrene with sloughing of ear tips, switches, and hooves referred to as “fescue foot” or “gangrenous ergotism,” depending on the source of the EAs.[1,3,8,46,47,51] Controlled experiments indicated that dietary concentrations of ergovaline between 0.4 and 0.8 ppm produced gangrenous effects in ruminants.[64] However, the ambient temperatures in those specific experiments were not below freezing, so, considering the impact of ambient temperature on the vasoconstrictive effects of EAs, lower ergovaline concentrations could be expected to possibly cause “fescue foot” at temperatures below freezing.[47,51,64] Given “average” ergovaline concentrations in E+ tall fescue and clinical signs in cattle eating other forages “free” of EAs, along with E+ tall fescue, it appears that adverse effects on production parameters can be observed in cattle, when total dietary concentrations of EP exceed 0.1 to 0.2 ppm, especially under extreme weather conditions.[47,51,53,54] In areas where cattle are commonly affected by fescue toxicosis, it stands to reason that suspected “fescue foot” or dry gangrene affecting the lower portions of the tail (“switch”) observed during the late spring or early summer tends to be more likely associated with the higher concentrations of EPs in ergotized grains or grasses (especially ergotized E+ tall fescue) rather than the lower EP concentrations in tall fescue infected only with endophyte.[51,55-57,64]

Exposure to EAs during the last month of pregnancy is the most common cause of agalactia in mares.[47,50,51,58] Hypoprolactinemia, with minimal udder development, was consistently induced in pregnant ponies treated with a semisynthetic EP, and lactational abnormalities will invariably be the first signs observed in late gestational mares consuming EAs.[50,58] Anecdotal reports suggest that dietary concentrations of ergovaline as low as 0.05 ppm can cause

agalactia in some susceptible late gestational mares.[50] Prolonged gestation, dystocia, and abortion, as well as fetal and placental abnormalities, are additional adverse effects observed in pregnant mares consuming higher dietary ergovaline concentrations (generally ≥0.1 ppm).[47,50,51] Pellets containing screenings of ergotized grains or grasses can also be associated with EA intoxication in pregnant mares.[50] The absence of normal changes in udder development ("waxing"), on which horse breeders and veterinarians are dependent to predict imminent parturition, results in unexpected and unsupervised parturition.[58]

The diagnosis of intoxications involving EAs requires the observation of appropriate clinical signs, identification of a source of EAs, and determination of EA concentrations in that source, as well as in the total diet.[1,3,46] The accurate interpretation of those analytic results necessitates a thorough understanding of the analyses being performed and the pathogenesis of EA intoxications in different species.[1,46] Using reproductive performance as an example of a monitored parameter, management factors and the stressors shown in Fig. 54.4, particularly those related to environment, should be considered when interpreting analytic results.[3]

The basic principles for the treatment and prevention of intoxications related to EA are no different than those outlined for other mycotoxicoses (i.e., removal from the source, stabilization, and supportive care). Incorporation of pasture management practices, including frequent mowing with removal of seed heads, careful use of nitrogen-containing fertilizers, dilution with legumes, production of hay, and pasture replacement with genetically modified varieties of continental tall fescue free from EAs, can provide added benefits to cattle producers and horse breeders living in enzootic areas.[47,51] Drying and ammoniation of E+ tall fescue hay, manipulation of stocking rates, physical manipulation of ergotized grasses during the haying process, use of stockpiled E+ tall fescue during the fall, and copper supplementation can also help to further minimize EA-induced effects and maximize performance parameters in cattle.[3,48,65,66] Veterinarians should also be aware of "fescue-associated edema syndrome" recently observed in horses consuming a genetically modified Mediterranean tall fescue in Australia.[67]

Provision of ample shade (also, possibly pond access) and plenty of potable water to cattle consuming low concentrations of EAs during the summer can help prevent "summer slump" or clinical signs resembling this condition, when the source of EA is not E+ tall fescue.[47,49] It is also becoming increasingly

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apparent that genetic testing has the potential to be used as a management tool in the prevention of fescue toxicosis. A single nucleotide polymorphism (SNP) in the dopamine D_2 receptor gene has recently shown promise as a biomarker for resistance to fescue toxicosis in Angus-based cattle, and it is likely to be commercially available in the very near future.[68]

Knowledge of mare breeding dates, confirmation of pregnancy, and withdrawal from any dietary sources of EAs at least 30 days before the anticipated foaling date are critical for the prevention of agalactia in pregnant mares.[3,47,49-51] Frequent evaluation of mammary development and, if deemed necessary, daily administration of the dopamine D_2 antagonist domperidone (1.1 mg/kg body weight; watch for leaking colostrum) are additional ways to facilitate adequate lactation and prevent failure of passive transfer in foals.[47,49-51] Domperidone can also be used to mitigate prolonged gestation, along with the attendant risk of dystocia.[47,50,51]

Grain or grass screenings or “fines,” in general, and/or any grains containing visible ergot bodies should *not* be incorporated into feeds intended for consumption by pregnant mares or cattle maintained under extreme weather conditions.[47,50,51] The only current FDA action level pertaining to EAs is expressed in terms of the percentage of ergot bodies (see Table 54.8) rather than concentrations of EPs.[9] On the basis of the average EP content of ergot sclerotia in barley, 0.1% ergot bodies translates to approximately 2.5 ppm, which, depending on the proportion of the diet represented by this ergotized grain, may not be very protective in many clinical instances.[47,53-57]

Snake Bites and Blister Beetle

C. Langdon Fielding

Most snakebites reported in horses and other large animal species in North America are associated with rattlesnakes, which belong to a group of venomous snakes, the pit vipers.[1-5] Other recent retrospective studies describing snakebites in horses include reports of elapid snake envenomation in Australia and viperid envenomation in Israel.[6-7]

Rattlesnake Envenomation

There are approximately 30 different species of rattlesnakes found globally, and

their venom contains various enzymes, proteins, and peptides. Mortality rates for horses envenomated by rattlesnakes may be as high as 10% to 20%, but this depends on the severity of the bite and the response to treatment.[1-3] Rattlesnake bites typically occur during the spring and summer and should be suspected only in regions where the snakes are known to exist.[2]

The muzzle is the most commonly described location for rattlesnake bites in horses, and rapid, severe swelling is common (Fig. 54.5).[2] As the nostrils become swollen and the airways narrow, respiratory distress is common. In more severe cases, swelling may continue to spread up the head and down the neck. Epistaxis is observed in many horses following rattlesnake bite, and bleeding from the ocular tissues occurs as an effect of the venom progress (Fig. 54.6). Arrhythmias have been described in horses after rattlesnake envenomation, both acutely and chronically.[1,3,4] Diagnosis of rattlesnake bite is based on the characteristic swelling in a horse from an appropriate region during the typical time of year (spring and summer). The presence of fang marks, which are difficult to find in some cases, supports the diagnosis and helps to differentiate from other causes of acute head swelling. An ELISA to detect rattlesnake venom in the bite tissue and the urine of horses has been described.[8]



FIG. 54.5 A horse with swelling in the muzzle and throatlatch area due to rattlesnake bite. (Courtesy Dr. Skip Aaroe, Trinidad, Colo.)



FIG. 54.6 A horse with bilateral epistaxis and swollen muzzle due to rattlesnake bite. (Courtesy Dr. Skip Aaroe, Trinidad, Colo.)

Thrombocytopenia and prolongation of clotting times are described hematologic abnormalities but have not been consistent across various studies in horses.[1-3] Anemia can also be observed and is suspected to be due to both hemolysis and blood loss. Increases in cardiac troponin I (cTnI) have been described in a recent study, confirming myocardial damage in horses with envenomation.[1]

Treatment of horses with rattlesnake envenomation largely depends on the severity of the clinical signs, with many animals requiring only careful monitoring for respiratory distress. Maintenance of a patent airway is the single most important aspect of treatment, and a tracheostomy may be necessary in up to 50% of animals presented for veterinary care.[2] A nasal stent (plastic tubing placed up one or both nostrils) can be used but may be challenging to place and maintain in a distressed horse experiencing pain.

Antivenin has been described for the treatment of horses with rattlesnake envenomation.[2] Although clinical trials in other species have suggested efficacy, antivenin use in horses has only been retrospectively reported.[9,10] Currently, there are three USDA-approved veterinary antivenoms, but only one (Rattler

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Antivenin [Mg Biologics, Ames, Iowa]) is labeled for use in horses. Another product labeled for use in dogs (Antivenin, a polyvalent antivenin marketed by Boehringer Ingelheim Vetmedica, Inc., St. Joseph, Mo. [formerly by Fort Dodge Animal Health, Fort Dodge, Iowa]) was rehydrated according to the label directions, diluted in saline, and administered slowly to horses over 30 minutes.[2] Horses typically required 1 to 2 vials, and beneficial effects were anecdotally observed even when given 24 hours after envenomation.[2] Antivenin polyvalent crotalidae (VenomVet [MT Venom, LLC, Canoga Park, Calif.]) is approved for use in dogs, but use in horses has not been reported. A polyvalent antivenin (Crofab [BTG International (formerly Protherics), West Conshohocken, Pa.]) is labelled for use in humans, but its use has also not been reported in horses.[9]

Wound care, particularly cleaning of the bite site, and tetanus prophylaxis are important components of treatment. Intravenous fluids are often necessary if the horse is unable to drink, but catheter placement should be performed carefully because affected animals may be prone to bleeding. Many horses may not be able to eat well immediately following a bite, but soaked pellets or mashes can often be hand fed as the swelling subsides. The use of broad-spectrum antibiotics is controversial and not recommended in other species but has been advocated by some authors due to concerns of aspiration pneumonia and infection at the bite site. Nonsteroidal antiinflammatory drugs (NSAIDs) are frequently administered to horses and may help to decrease pain and inflammation. There is no evidence to support the use of corticosteroids or antihistamines for rattlesnake envenomation.

Elapid Envenomation

A large case series of elapid snake envenomation in horses was reported from Australia, where elapids represent the most common snake envenomations.[6] Envenomations had a seasonal pattern, with the spring and summer months most common. Neuromuscular weakness was the most commonly described clinical sign, with rhabdomyolysis and hemolysis occurring less frequently (Fig. 54.7). Increased creatine kinase (CK) activity, cTnI, and coagulation times were present in some horses but inconsistent in others. Treatment with polyvalent elapid snake antivenom was common, and the overall survival rate was 86%.



FIG. 54.7 A 3-year-old Standardbred gelding with profound generalized neuromuscular weakness and mental obtundation (note inability to retract the tongue). The horse returned to normal strength within 24 hours after administration of multivalent elapid antivenom. (Courtesy Nicholas Bamford, BVSc(Hons), PhD, DACVIM, Melbourne Veterinary School, Faculty of Veterinary & Agricultural Sciences, The University of Melbourne, Australia.)

Daboia (Vipera) palaestinae Envenomation

A large cases series of *Daboia palaestinae* envenomation in horses was reported from Israel, where most envenomations are caused by this snake.[7] A seasonal pattern also existed in this study. Most horses were bitten on the head, and local swelling was common. Other frequently reported signs included tachycardia and increased respiratory effort. Laboratory abnormalities included increased CK activity, hypoproteinemia, and hyperphosphatemia. Many of the horses in the study were treated with antivenom for *Vipera palaestinae.*

Blister Beetle

Cantharidin toxicosis in horses occurs following ingestion of alfalfa hay that is contaminated with blister beetles.[11] Affected animals are typically found in the midwestern United States due to the swarming of beetles in this region and subsequent incorporation into cut hay. In one study, cases were most likely to occur during the late summer and early fall.[12] Cantharidin causes irritation to the mucous membranes and interferes with a family of enzymes called the

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phosphoprotein phosphatases.[13]

Horses with cantharidin toxicosis develop signs of GI disease (colic, diarrhea), urinary system disease (renal failures, cystitis), and cardiac disease (arrhythmias).[11,14] Affected horses may also exhibit a stiff gait.[14] With increased severity, horses may exhibit synchronous diaphragmatic flutter, hypovolemic shock, and death.[11,14] Laboratory data reflect abnormal renal function (azotemia), as well as hypocalcemia, hypomagnesemia, and hypoproteinemia.[11] Myocardial damage may be reflected in changes in myocardial enzymes; however, this has not been evaluated in horses.

Presumptive diagnosis of cantharidin toxicosis in horses can be made following the identification of the beetles present in ingested hay. Testing of stomach contents and urine for cantharidin levels has been suggested as a common means for definitive diagnosis.[12,15] It has been shown that 450 µg/kg body weight of ingested cantharadin can cause clinical signs and even mortality.[14]

Treatment of cantharidin toxicosis is primarily supportive. Administration of activated charcoal to animals with recent exposure may be appropriate. Intravenous fluid therapy is important to correct hypovolemia and dehydration. If renal failure is present, therapy should be directed toward maintaining urine production. A balanced isotonic intravenous fluid can be used for resuscitation. Electrolyte and acid-base abnormalities should be corrected using additional supplements to intravenous fluids (e.g., calcium gluconate, magnesium sulfate). GI protectants are indicated, as are pain medications to provide relief for the ulceration of the GI and urinary systems. Hay that is suspected of contamination should be removed and not fed to animals.

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Metals and Other Inorganic Compounds

Robert H. Poppenga

Metals are intrinsic to nature and ubiquitous in the environment of animals. Although the form or valence of any given metal can be changed, metals themselves cannot be destroyed.[1] Mining, industrial, and reclamation activities of humans have resulted in the large-scale redistribution of metals in the environment.

Metals can be categorized as those that play an essential role in biological processes (e.g., those that are nutritionally necessary, such as iron, copper, zinc, and selenium, among others) and those that do not (e.g., lead, mercury). It is important to point out that disease syndromes caused by deficiencies of nutritionally important metals are different in pathogenesis and clinical manifestations than those caused by exposure to excessive amounts of the same metal.

The toxicity of metals is often harder to define than that of other toxicants. One reason for this is that the form of a metal plays a critical role in its bioavailability.[1] For example, elemental mercury, when ingested, is essentially unavailable for systemic absorption. In contrast, organic forms of mercury such as methyl mercury are highly bioavailable. The interaction of metals also plays an important role in the determination of toxicity. For example, high dietary calcium can decrease absorption of lead, since lead uses calcium transport mechanisms for its uptake into the body. Other factors that can influence toxicity include animal age, gender, and the capacity of an individual for biotransformation of a metal.

The distribution and accumulation of metals in certain tissues in the body can mitigate damage. Lead can accumulate in bone where it is not available to affect target tissues such as those in the CNS. Also, metals can be sequestered in the body by cystine-rich proteins called metallothioneins that are highly inducible by metals and essential for metal homeostasis and detoxification.[1] The interaction of metals with sulfhydryl-containing groups like cystine is the basis for the efficacy of metal chelators, such as succimer or dimercaprol, which contain numerous sulfhydryl groups.

Arsenic

Historically, various forms of arsenic have been used as herbicides, insecticides, wood preservatives, growth promotants, and therapeutic agents.[2] Arsenic is found in various valences and forms. There are trivalent and pentavalent inorganic and organic forms. Pentavalent (arsenate, H_3AsO_4) and trivalent (arsenite, H_3AsO_3) forms of arsenic include sodium, potassium, and calcium salts. Paris green (copper acetoarsenite) and lead arsenate have been used as insecticides, and trivalent inorganic arsenic forms such as monosodium methanearsonate (MSMA) and disodium methanearsonate (DMSA) are used as herbicides. Historically, pentavalent organic arsenicals such as sodium arsanilate and 3-nitro-4-hydroxyphenylarsonic acid were used as feed additives for some livestock species but have been withdrawn by the FDA due to human health concerns (http://www.foodsafetynews.com/2015/04/fda-to-withdraw-approval-for-arsenic-based-drug-used-in-poultry/#.WvC5QX8h3RY). In addition, the use of arsenic as a wood preservative in the form of chromated copper arsenate (CCA) has been banned for residential use by the U.S. Environmental Protection Agency (EPA), although it is still permitted for use in commercial, industrial, and some agricultural settings.

As for most metals, the bioavailability of arsenic is variable and depends on its form (organic versus inorganic, solution versus powder). The arsenic in solutions of organic arsenicals is almost completely absorbed from the GI tract.[3-5] Alternatively, arsenic compounds of low solubility such as arsenic trioxide are absorbed less efficiently. Once absorbed arsenic is widely distributed in the body and reaches its highest concentrations in the liver, spleen, kidney, lungs, and GI tract. Persistent residues are found in keratinized tissues such as skin, hair, and nails. Clearance of arsenic from the blood is multiphasic, with the first phase having a 1- to 2-hour half-life.[4,5] Forty to seventy percent of an absorbed dose is eliminated via the urine within the first 48 hours. To a large extent, inorganic arsenic is metabolized in the liver by the addition of methyl groups prior to its elimination.

The toxicity of arsenic is variable and depends on its form, purity, solubility, particle size, and valence; the species exposed; and the condition of the exposed individual.[4,5] For example, trivalent arsenicals are 4 to 10 times more toxic than pentavalent arsenicals. Acute arsenite toxicity ranges from 1 to 25 mg/kg body weight (BW), whereas toxicity of arsenates is 30 to 100 mg/kg BW. Methanearsonate herbicides are toxic at 10 to 25 mg/kg BW over several days. Weak and debilitated animals are more susceptible to intoxication.[4,5]

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The mechanism of toxic action of arsenic also depends on its form.[1] Trivalent inorganic arsenicals (i.e., arsenites) inhibit cellular respiration. They bind to sulfhydryl compounds, especially lipoic acid and α-keto oxidases. Lipoic acid, a tissue respiratory enzyme cofactor, plays an essential role in the tricarboxylic acid (TCA) cycle. Tissues with high oxidative energy requirements (e.g., actively dividing cells such as those of the intestinal epithelium, kidney, liver, skin, and lungs) are more severely affected. Trivalent arsenic affects capillary integrity by an unknown mechanism. The GI tract is most affected; capillary dilatation is followed by transudation of plasma into the GI tract, resulting in submucosal congestion and edema. In contrast, pentavalent inorganic arsenicals (i.e., arsenates) appear to substitute for phosphate in oxidative phosphorylation. Uncoupling of oxidative phosphorylation produces a cellular energy deficit. Elevated body temperature is not characteristic of pentavalent arsenical poisoning as it is in poisonings by other oxidative uncouplers (e.g., nitrophenols).

Organic arsenicals also vary in terms of their mechanism of toxic action. Trivalent organic arsenicals appear to have a mechanism of toxic action similar to that of the trivalent inorganic arsenicals. However, pentavalent organic arsenicals (e.g, those previously used as livestock feed additives) act on nerves by an unknown mechanism. They produce demyelination and eventual axonal degeneration, leading some researchers to believe that pentavalent organic arsenicals interfere with the B vitamins essential for maintenance of nervous tissue. Alternatively, neurotoxicity may be related to effects on the cytoskeleton of axons.[6]

The clinical signs and lesions are similar for the trivalent inorganic arsenicals, whereas the organic pentavalent compounds used as feed additives cause peripheral nerve degeneration in monogastric animals. The inorganic arsenic compounds (arsenites, arsenates) cause dosage-related peracute, acute, or subacute toxicosis with cardiovascular collapse, sometimes presenting as sudden death.[7,8] Acute poisoning occurs 3 to 12 hours after ingestion. Clinical signs include ataxia, diarrhea with or without blood, recumbency, and death, with the most prominent clinical sign in acute and subacute cases being diarrhea that is frequently hemorrhagic.[7,9] Other clinical signs include anorexia, dehydration, weakness, colic, and agalactia. No specific abnormalities are noted from CBC or serum chemistry tests. Because arsenic can damage multiple organs, changes associated with liver or kidney dysfunction can be present if the animal survives for several days. Protein, red blood cells, and casts can be noted in the urine.

Clinical signs associated with organic pentavalent arsenical intoxication include ataxia, incoordination, torticollis, blindness, paralysis, and recumbency.[2]

For trivalent arsenicals, consistent necropsy lesions are present in the GI tract and may be hemorrhagic, edematous, necrotic, or eroded. The lesions may be confined to one region or spread throughout the GI tract.[3,7-9] In ruminants, the abomasum is often the most severely affected area. The gut lumen is sometimes filled with necrotic material from the sloughed lining of the GI tract. Other lesions include pulmonary edema and hemorrhage of the cardiac serosa and peritoneum.[4,5] Histopathologic examinations may reveal multifocal necrosis of the liver and proximal tubules of the kidney. Renal lesions are likely in animals that survive a subacute toxicosis. Peracute cases often have no abnormal gross findings. Pentavalent organic arsenicals cause both central and peripheral nerve lesions, including mild edema and Wallerian degeneration in optic and peripheral nerves.

An antemortem diagnosis relies on a history of ingestion of arsenic, the occurrence of consistent clinical signs, and the detection of toxic concentrations of arsenic in GI contents, whole blood, or urine. Suspect sources of exposure can also be tested to confirm the presence of arsenic. The rapid elimination of the metal from the body makes the collection of appropriate samples as early as possible an important consideration. Most veterinary diagnostic laboratories can test for arsenic. It is important to point out that low-level concentrations of arsenic in blood or urine are not unusual and do not indicate arsenic intoxication. The interpretation of a given concentration of arsenic depends on an evaluation of the entire case and the timing of sample collection in relation to exposure. Postmortem analysis of stomach contents, liver, kidney, or urine can confirm exposure. Again, the significance of detected concentrations, especially relatively low concentrations, needs to be interpreted in conjunction with other case variables. Postmortem lesions may be absent in cases of rapid death. Otherwise, severe GI lesions consisting of reddening of the gastric mucosa and proximal small intestine, watery GI contents, and blood and sloughed mucosa in the feces are commonly noted with trivalent arsenicals. Detection of compatible central and peripheral nervous system lesions is important to demonstrate after intoxication by pentavalent organic arsenicals. Other organ lesions are not specific for arsenic.

The rapid onset of clinical signs often precludes initiating decontamination procedures. Activated charcoal is unlikely to adsorb significant amounts of arsenic, although with significant exposures its administration is

recommended.[10] Symptomatic animals need to be stabilized first. This might entail treatment for circulatory shock and hypotension and maintenance of body temperature. Renal and liver failure and electrolyte abnormalities may need to be addressed. Glucose and glycogen stores should be maintained parenterally with dextrose or parenteral alimentation solutions.[10] Chelation therapy is typically indicated. Historically, dimercaprol (BAL or British anti-Lewisite) was the recommended chelator. It is a sulfhydryl-containing chelator that binds to arsenic and allows the arsenic-chelator complex to be eliminated. An alternative chelator, succimer, has several theoretical advantages over dimercaprol, including less toxicity and an oral (versus injectable) dosing form. It has been theorized that because succimer is hydrophilic, it may not remove arsenic that has escaped the extracelluar space as efficiently as dimercaprol does.[4,5] However, available studies suggest that succimer is equal to or even superior to dimercaprol in increasing arsenic elimination.[10] If dimercaprol is used, monitoring for adverse reactions, including pain at the injection site, GI signs, tremors, and seizures, is required. Succimer is likely cost prohibitive for most large animals. D-Penicillamine, another arsenic chelator used in humans, may be too expensive in livestock as well.[11,12] Ethylenediaminetetraacetic acid (EDTA) is not effective for arsenic toxicosis.[13]

Although the administration of B-complex vitamins and amino acids has been recommended, the evidence for their efficacy is lacking. Parenteral antibiotic administration might be considered to prevent secondary bacterial infections of the GI tract. The use of GI protectants may also be indicated. Recovering animals should be fed a high-quality diet in small portions that can be increased as time and circumstances permit. The prognosis in symptomatic animals is always guarded, particularly in the absence of early intervention and intensive monitoring and treatment.

Copper

Sources of copper used in livestock are widely available as sulfates, chlorides, and oxides. Concentrates of copper are found in feed premixes, fertilizers, copper footbaths, aquacides, and fungicides (Bordeaux mixture). Sheep are very susceptible to poisoning by chronic copper accumulation in feeds formulated with excessive copper and inadequate molybdenum and sulfur. Absorption in monogastric and young ruminants with a nonfunctional rumen is 75% but only

1% to 10% in cattle and sheep with normal rumen function.[14] Dietary molybdenum at 2 to 5 mg/kg diet and dietary sulfur at 0.4% of diet substantially reduce ruminant copper accumulation. High dietary zinc (>200 mg/kg diet) and iron also limit copper absorption in ruminants.[14]

Acute copper toxicosis has occurred in cattle given injections of copper disodium edetate as a therapy for copper deficiency.[15] Sheep are often poisoned when fed rations intended for cattle or horses,[16] and llamas have developed copper toxicosis when fed cattle feed.[17] Sheep have developed toxicosis on pastures fertilized with manure from swine or poultry fed copper.[18] Cattle develop copper toxicosis when supplemented with excessive copper,[19] when fields are contaminated by copper smelting,[18,20,21] or when they are fed litter from chickens supplemented with copper.[22] Excessive copper in calf milk replacers has been a source of toxicosis in both calves[23,24] and goat kids.[25] Dairy goats were intoxicated as a result of chronic feeding of a mineral mix containing high concentrations of copper.[26]

Copper poisoning can be acute or chronic. Acute toxicosis results from ingestion or administration of soluble copper salts in one of the sources listed earlier, usually from one to several large doses of copper regardless of sulfur or molybdenum status. Chronic copper toxicosis can be categorized as simple, hepatogenous, or phytogenous. Simple chronic toxicosis is caused by ingestion of excessive copper relative to molybdenum and/or sulfate in the diet. Sheep fed diets with a copper–to–molybdenum ratio greater than 10 : 1 are at high risk for developing clinical copper poisoning. Molybdenum and sulfate bind to dietary copper in the rumen and also form a copper-molybdenum complex post absorption, which decreases absorption, retention (through increased bile and urinary excretion), and eventual accumulation of copper in the liver.[27] For cattle, dietary copper–to–molybdenum ratios above approximately 40 : 1 allow chronic copper accumulation, and most clinical cases in cattle involve dietary copper in excess of 40 mg/kg diet. Hepatogenous copper toxicosis occurs when hepatotoxic plants such as *Senecio* species or *Heliotropium europaeum* damage the liver and cause copper retention.[27] Phytogenous copper poisoning occurs from prolonged grazing on plants (e.g., subterranean clover *[Trifolium subterraneum]*) with elevated copper/molybdenum ratios. In general, mature pastures have lower copper/molybdenum ratios than young, rapidly growing plants.[14] Breed differences in accumulation of copper in liver have been noted

for both sheep and cattle.[27,28]

The pathogenesis of copper toxicosis involves absorption, binding to albumin and transcuprein proteins, and transport to the liver, where it binds with ceruloplasmin, a hepatic metalloprotein. The concentration of copper in hepatic lysosomes increases over several weeks to months, leading to excess accumulation. When this occurs, there is necrosis of liver parenchymal cells and swelling of Kupffer cells, followed by sudden spontaneous or stress-related release of copper into the bloodstream.[14,27, 29,30] This acute phase includes reduced blood glutathione, increased erythrocyte fragility, hemoglobin oxidation, and methemoglobin formation. Resulting intravascular hemolysis leads to anemia, icterus, and hemoglobinuric nephrosis.

The clinical signs of copper poisoning are most prominent in sheep and include an abrupt onset of depression, anorexia, and weakness. Feces may be watery, dark, or blood tinged, especially in cattle. Evidence of a hemolytic crisis is apparent, and signs include anemia, methemoglobinemia, and hemoglobinuria. Mucous membranes are icteric, muddy brown, or a combination of both.[27,30-33] Cattle with copper toxicosis after injection of copper disodium edetate have dyspnea, head pressing, ataxia, and circling.[14]

Antemortem, the diagnosis of chronic copper toxicosis relies on measuring copper levels in serum as well as measuring serum hepatic enzymes.[19,27,30] However, serum copper is not elevated until just before or during the hemolytic crisis. Therefore animals with toxic copper levels in the liver may have normal or low serum copper values, so serum copper levels alone are not useful for judging copper status. For sheep and cattle there is typically a substantial increase in serum aspartate amino transferase (AST) and gamma-glutamyl transpeptidase (GGT) released from damaged liver before the hemolytic crisis occurs and while the animals are still clinically normal.[14] Controlled studies of serum activities for AST and GGT have been shown to be good predictive indicators of hepatic copper accumulation in sheep or cattle that are clinically normal.[34]

Postmortem copper should be measured in both fresh liver and kidney. After the liver has released copper into the bloodstream, liver copper values may fall into a nontoxic range, but kidney copper values will remain in a toxic diagnostic range. Acute toxicosis from copper disodium edetate does not consistently cause elevated copper levels in the liver or kidney.[15]

The diagnosis should correlate with histopathologic lesions in formalin-fixed

liver and kidney.[27,30] Gross lesions are present in the liver, kidneys, and spleen. The liver is yellow and friable and may be larger or smaller than normal. Hemoglobin casts in tubules cause the kidneys to appear dark red or blue-black. The spleen is enlarged and congested. Histopathologic changes in the liver include centrilobular necrosis, pigment-laden Kupffer cells, hepatic fibrosis, and bile duct hyperplasia.[19,27,30] Granules in the liver are positive for copper when stained with copper-specific rhodamine or rubeanic acid.[23]

Several treatment options are currently available but are often unsuccessful once an animal is in acute hemolytic crisis. Ammonium molybdate (50 to 500 mg PO once daily) and sodium thiosulfate (300 to 1000 mg PO once daily) for 3 weeks have been used for many years as a treatment.[14,27,30] Liver copper levels begin to decrease within 4 days of beginning therapy.[27] An unapproved treatment is ammonium tetrathiomolybdate at 3.4 mg/kg subcutaneously (SC) on alternate days for three treatments.[35] Either route of administration significantly decreases liver copper levels within 6 days. This change is accompanied by an increase of copper in the blood, bile, feces, and urine.[27] Most of this copper is bound with tetrathiomolybdate and albumin in an inert complex.[27,30] Xylazine given with tetrathiomolybdate is reported to double the amount of copper excreted in the urine as compared with tetrathiomolybdate alone.[36] D-Penicillamine (26 mg/kg PO twice daily for 6 days) results in a tenfold to twentyfold increase in urinary copper excretion in sheep,[37] but this option is expensive and may not be cost-effective for many livestock. Animals in the acute hemolytic phase of poisoning should be treated as needed for serious hemolytic anemia and potential methemoglobinemia from copper's oxidant effect.

Iodine

Iodine is used to prevent some infectious diseases and as a treatment for foot rot. Common sources of iodine include potassium iodide, sodium iodide, kelp, Chile saltpeter nitrate deposits, and ethylenediamine dihydriodide (EDDI). Oilseed proteins or their concentrates incorporated into foodstuffs contain 0.1 to 0.3 mg iodine/kg. Estimated iodine requirements are beef cattle, 0.5 mg/kg diet; dairy cattle (lactating), 0.8 to 1.0 mg/kg diet; sheep, 0.2 to 0.5 mg/kg diet; swine, 0.3 to 2.0 mg/kg diet; and horses, 0.1 to 0.2 mg/kg diet.[38] EDDI has been incorporated into animal feed and drug products for many years for both

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nutritional and therapeutic purposes. It has been formulated in salt-mineral mixtures and in liquids and powders for adding to feed or drinking water. EDDI has been used as a supplemental source of iodine and is considered generally recognized as safe (GRAS) for nutritional purposes when used at levels consistent with good feeding practices. EDDI products also have been marketed with claims for the treatment and prevention of certain diseases in several animal species but primarily for “foot rot,” soft tissue “lumpy jaw,” and “wooden tongue” in cattle. However, all such EDDI products (including feeds) bearing therapeutic claims now are considered adulterated (https://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceMa

Oversupplementation can result in toxicosis. Iodine concentrations greater than 50 mg/kg diet for calves caused reduced growth rate and greater than 100 mg/kg diet resulted in coughing and nasal discharge, as well as reduced hemoglobin and serum calcium concentrations. Previous use of EDDI as an expectorant in feedlot cattle (400 to 500 mg/head/day) or swine (250 to 500 mg/head/day) sometimes resulted in signs of excessive expectorant activity.[39] Elevated iodine intake (50 mg/day) in dairy cows will raise milk iodine to concentrations that may be unacceptable for public health reasons. One report of abortions in dairy cows was associated with excessive iodine consumption. Maximum tolerable levels based on available literature are cattle, 50 mg/kg diet; sheep, 50 mg/kg diet; and swine, 400 mg/kg diet.[40]

The clinical signs of toxicosis include a nonproductive cough, lacrimation, serous nasal discharge, scaly hair coats, and hyperthermia. Other reported signs include decreased milk production, decreased gain and feed conversion, exophthalmia, nervousness, dermatitis, alopecia, and tachycardia. Young animals appear more susceptible than other age groups. Adults may not develop toxicosis unless stress, disease, or nutritional imbalances are also present.[41] Excess supplementation in mares is associated with goiter in foals.

A diagnosis can be confirmed only with serum or milk analysis. Iodine concentrations in milk are directly related to levels of iodine in the diet.[41] Elevated serum iodine concentrations (1600 µg/mL) may be associated with mild clinical signs. Nonlactating cows have higher serum iodine concentrations than lactating cows that are eliminating iodine in milk.

Treatment is restricted to removal of the dietary source of iodine. Clinical signs associated with the respiratory tract disappear 1 to 4 weeks after the iodine source is removed.[37]

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Iron

There are a number of iron salts and formulations. Some insoluble forms of iron such as elemental iron and ferric oxide (i.e., rust) are not hazardous when ingested due to low bioavailability. One newer source of iron, a chelated iron called iron phosphate EDTA, is found in some slug and snail baits.

The kinetics of iron absorption are complex. Iron body stores are regulated at the site of absorption from the GI tract because the body is not able to actively excrete iron. From the GI tract, iron must first enter duodenal mucosal cells, possibly by a carrier-mediated process. Next the iron either is lost as the mucosal cells slough into the GI lumen or is bound to ferritin for later transfer to transferrin, a serum iron-binding transport protein. Serum transferrin concentrations greatly exceed the amounts necessary to bind iron under normal physiologic processes (normal binding capacity is three to four times the serum iron concentration). However, in intoxications, the binding capacity is exceeded, allowing free iron to cause cell damage.[42]

Free iron can cause direct or indirect tissue and cell damage. Iron acts as a free radical and can also produce free radicals. Free radicals have one or more unpaired electrons, which can initiate lipid peroxidation resulting in cell membrane damage. Tissues that have first contact with free iron are primarily affected, although all tissues are susceptible to damage if exposed. The primary targets are the GI, cardiovascular, and hepatic tissues. Iron also damages mitochondria, leading to loss of oxidative metabolism.[42] Iron may have a direct negative inotropic effect on the myocardium.[43]

Toxicosis from iron overload has occurred in neonatal foals (normally born with high iron absorption and high serum iron levels) and adult horses given ferrous fumarate orally; calves injected with ferrous gluconate and ferric ammonium citrate; neonatal swine dosed with parenteral iron; pigs born from vitamin E– and selenium-deficient sows; and young bulls injected with ferric ammonium citrate.[44-48]

The clinical signs of iron toxicosis in neonatal foals include depression, icterus, head pressing, and disorientation.[44] Adult horses develop anorexia, icterus, and sometimes petechial hemorrhages.[49] Calves with iron toxicosis exhibit trembling, vocalizing, bruxism, colic, and convulsions.[45]

Clinicopathologic findings are related to cholestatic liver failure. Animals often have elevated serum levels of γ-glutamyl transferase, alkaline phosphatase

(ALP), bile acids, and unconjugated bilirubin. Coagulopathies include abnormal coagulation profiles, thrombocytopenia, and elevated fibrinogen.[44,45,49]

Gross postmortem lesions are variable. The liver is discolored, pale tan, or mottled red-brown, and most are friable and swollen or shrunken. Hemorrhages may be present in the gastric mucosa, intestines, and urinary bladder. Microscopic lesions include bile ductile proliferation, periportal necrosis, lobular necrosis, and fibrosis.[44-47,49] Lesions in the liver tend to have a rather distinct periportal distribution since periportal regions of the liver are the first to be exposed to excessive free iron absorbed from the GI tract.

Iron toxicosis is diagnosed based on clinical signs and a history of recent iron exposure. When serum iron and total iron-binding capacity (TIBC) are evaluated, serum iron often exceeds TIBC. In dead animals, the liver iron is elevated to varying degrees in different species; iron may be above normal if the animal had hemolysis or blood congestion occurred within the liver. Although tissue iron concentrations may help support a diagnosis of iron intoxication, it is common, particularly in horses, to detect elevated liver iron concentrations unrelated to overexposure to iron. Treatment of iron toxicosis is usually limited to supportive care. Patient stabilization is a priority in symptomatic animals. Treating circulatory shock and metabolic acidosis is critical. Sucralfate might be useful to provide some GI protection. Repeated phlebotomy or chelation therapy with deferoxamine (40 mg/kg IM q4-8h) has been used to treat iron overload in humans and small animals.[48] It combines with iron to form ferrioxamine, which is subsequently eliminated via the kidneys.[43] Deferoxamine given intravenously too rapidly can cause cardiac arrhythmias; as well, it is a teratogen and should be used in pregnant animals only if the potential benefits outweigh the risks. The success rate and cost of these treatments in large animals has not been well documented. The prognosis is variable depending on the dosage ingested and availability of appropriate monitoring.

Mercury

Mercury toxicosis has been caused by application or ingestion of an inorganic mercurial product used as a counterirritant or from ingestion of seeds treated with organic mercurial fungicides, which are no longer used in most of the world.[50] If blistering agents are used with dimethyl sulfoxide (DMSO), mercury absorption is enhanced.[51,52] The kidney is the primary target and storage organ

of inorganic mercury, but mercury also localizes in the GI mucosa and is eventually excreted by the kidneys.[50-53] Organomercurials such as methyl mercury are lipophilic and can be found in adipose and brain tissue.

Mercury causes two clinical syndromes depending on its form: acute poisoning from inorganic mercury salts and chronic neurologic damage from organomercurials. Acute inorganic mercury causes ulceration of the mouth, the esophagus, and the remainder of the GI tract followed by diarrhea and anorexia. If the animal survives, acute nephrosis develops. Anorexia, gastroenteritis, weight loss, nephritis, and alopecia occur in animals exposed to chronic low doses of inorganic mercury.[52] Organic mercury fungicides and methyl mercury cause brain damage, blindness, incoordination, and proprioceptive deficits. Most neurologic signs are long term or permanent.

The diagnosis of mercury salt toxicosis is supported by elevated serum creatinine and BUN levels, as well as proteinuria, glucosuria, and isosthenuria. Necropsy findings may include an ulcerated, necrotic, edematous, and hemorrhagic GI tract and pale, swollen kidneys. Confirmatory mercury concentrations may be found in liver, kidney, brain, whole blood, and urine.[50]

Therapy should include detoxification (oral sodium thiosulfate) for recent exposure and administration of an appropriate chelator. Sodium thiosulfate or BAL can be used for chelation therapy (see the Arsenic section earlier). Residual topical mercurial products (e.g., blisters) should be washed well from the animal's skin.[50-53] Supportive care should be provided for severe gastroenteritis and kidney failure. The treatment success rate is low when poisoning is severe or progressive; the presence of oliguria indicates a poor prognosis.[50-53] Surviving food animals should be monitored closely for potential mercury residues, which may persist for extended periods in organs or muscle.[50]

Other Toxicants

Additional inorganic toxicants are covered in the following chapters:

Fluoride, Chapter 38
Lead, Chapter 35
Molybdenum, discussed under copper deficiency in Chapter 32
Selenium (see the Poisonous Plants section earlier)
Sodium, discussed under salt poisoning in Chapter 35

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Sulfate, discussed under copper deficiency in Chapter 32 and under polioencephalomalacia in Chapter 35
Zinc, discussed in the Osteochondrosis section in Chapter 38

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Medications, Therapeutic Agents, and Illicit Substances

Dionne Benson • Lynn R. Hovda

Toxic and adverse drug reactions in large animals occur with some frequency but are not as routinely reported as occurrences in small animals. Blurred lines between toxicity and adverse reactions exists in the literature and in practice. Strictly speaking, toxic effects are dose related and do not occur at normal doses, whereas adverse reactions occur at normal as well as elevated doses.[1,2] The definition of an adverse drug reaction has not changed for 30 years and technically is “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of a disease, or for modification of physiological function.”[2]

Adverse drug reactions can be classified in a variety of ways with six different presentations of the normal scheme.[2,3] A more simplified approach uses only two different types of reactions: dose related and idiosyncratic.[4] In dose-related reactions the signs move from physiologic to pharmacologic to toxic as the dose is increased. Often simply stopping the medication and allowing the drug to clear the system results in cessation of the clinical signs. Anaphylactoid reactions are included in this group because they are not immune mediated and depend on mast cell degranulation to manifest effects. Idiosyncratic reactions are generally not related to a specific dose or concentration of the medication administered. Immune-mediated reactions are included in the group.

Finding accurate information on adverse or toxic medication reactions in large animals is difficult. Preclinical studies are generally small and include a limited number of animals when, in fact, the medication will be used to treat thousands of animals and reactions may not show up until these numbers are reached.[5] Clinical trials are often helpful, but again small numbers of animals may be involved. Useful information, including preapproval medication data, can often be found on the FDA's website (http://www.fda.gov).

Treatment of adverse or toxic reactions varies for each medication and route of exposure. Few antidotes exist for large animal medications, and for the most part treatment is symptomatic and supportive.[6] The use of an offending medication should be discontinued as soon as a reaction is recognized. Bathing

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for topical exposures, gastric lavage followed by activated charcoal for most recent oral exposures, mineral oil, and intravenous fluids are all useful tools for dealing with the clinical signs.

The most commonly reported adverse or toxic drug reactions in horses are to antimicrobials (procaine benzylpenicillin), NSAIDs, anesthetic agents, sedatives, and antiparasitic drugs.[7] Reports in cattle and swine primarily implicate antimicrobials.[7] Some of these drugs are covered in separate chapters or discussed more generally throughout this text.

Antimicrobial Drugs

It is not possible in the scope of this chapter to begin to review all the antimicrobial drug adverse or toxic reactions. Two antimicrobials, however, have specific known risk factors for large animals and are covered here.

Doxycycline

Doxycycline is a tetracycline used in large animal medicine to treat a variety of illnesses. The IV use of doxycycline in horses is not recommended and has been associated with supraventricular tachycardia, systemic arterial hypertension, discomfort, collapse, and death.[8] The cause is unknown but may be concentration or infusion-rate dependent. Treatment is symptomatic and supportive.

Sudden death has been reported in calves accidentally receiving 3 to 10 times the recommended daily dose (5 mg/kg bid) of doxycycline.[9,10] There is no known breed or genetic predisposition. Clinical signs included lethargy, dullness, loss of appetite, cough, dysphagia from paresis or paralysis of tongue, tachycardia, and tachypnea. Major problems included myopathies and necrosis (tongue, myocardial, other striated muscle), acute tubular necrosis, and hepatic fatty degeneration or congestion.[9] The tongue is affected before the myocardium. The cause of acute tubular necrosis remains unknown but may be a combination of a decreased cardiac output from myocardial issues and an increase in myoglobin from muscle necrosis. Death was reported to be from myocardial necrosis, although a recent clinical study in healthy calves dosed at five times the recommended daily dose for 5 days failed to support this.[10]

Enrofloxacin

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Enrofloxacin is a second-generation quinolone metabolized in the liver to ciprofloxacin, an active metabolite. Ciprofloxacin, itself a quinolone antimicrobial, should not be used orally in horses because it causes mild diarrhea to severe colitis, laminitis, and endotoxemia.[11]

The most common adverse reactions in horses include mild diarrhea, neurologic signs, and orthopedic disorders in young animals. The neurologic signs are generally dose related (i.e., high dose, bolus route) and transient, resolving in 10 to 15 minutes after administration.[12] Diluting the drug and administering it at a slower rate prevents the development of neurologic signs. Juvenile arthropathies with associated cartilage damage have been reported in neonatal foals and other species, but the true incidence is unknown.[13]

Several other adverse or toxic reactions have been reported. Intrauterine infusion in mares resulted in acute endometrial ulceration, necrosis, and hemorrhage, as well as fibrosis with inflammation.[14] Oral ulcers developed in animals treated with a gel compounded from the injectable cattle product.[15] Finally, to prevent toxicosis, the dose in neonatal calves needs to be lowered to accommodate their lower amounts of body fat and different metabolic capacities.[16]

β_2-Adrenergic Receptor Agonists (Clenbuterol, Ractopamine, Zilpaterol)

All three of these agents have been abused in horses for their known anabolic effects.[17,18] The use of clenbuterol in food-producing animals, once similarly abused, is now completely banned due to accumulation in meat.[19] Ractopamine and zilpaterol are still allowed as feed additives and are discussed later in this chapter (see the Feed Additives section later).

Clenbuterol is labeled for the management of acute and chronic respiratory disorders in horses. The normal dosage range is 0.8 to 1.6 µg/kg bid, with a maximum recommended dosage of 3.2 µg/kg bid for 3 days.[19] The dose needed for muscle partitioning in food-producing animals is estimated to be 5 to 10 times the therapeutic dose, whereas the dosage needed for repartitioning in horses is much lower at 2.4 µg/kg bid.[20]

At normal doses clenbuterol is a moderately selective β_2-adrenergic receptor agonist; at high doses all β-adrenergic receptors are stimulated, and a wide variety of signs occur. Clinical signs are dose dependent, with nervousness and

mild agitation, sweating, and increased heart rate occurring in some horses 5 to 10 minutes after a therapeutic dose of 1.6 µg/kg.[19] Far larger overdoses, 10 µg/kg and 100 µg/kg, were used in three Quarter Horses treated with compounded, bootlegged products.[17] The horses showed excitation, profuse sweating, tachycardia, whole body muscle tremors, hypothermia, recumbency, and, in two cases, death. Laboratory abnormalities associated with these large overdoses included azotemia, elevated CK, hypocalcemia, hypochloremia, hyperbilirubinemia, hyperphosphatemia, and severe hyperglycemia. Treatment included, among other things, multiple sedatives and analgesics, GI protectants, IV fluids, propranolol (0.01 mg/kg IV diluted in 150 mL over 30 minutes), and insulin (0.22 U/kg IM).[17] It is important to note that propranolol is effective in treating tachycardia but will do little for other signs and that hyperglycemia, in these horses, did not resolve spontaneously and required multiple doses of insulin.

Long-Acting Tranquilizers

Fluphenazine Decanoate

Fluphenazine decanoate is a phenothiazine neuroleptic agent used as a powerful antipsychotic medication in human beings.[21,22] Although not approved or marketed for use in horses, it has been used for years off label to provide long-term sedation for anxious or nervous show horses and racehorses and for uncontrollable horses that need stall rest for surgical procedures.[22]

The suggested equine dose is 0.05 to 0.08 mg/kg IM, but clinical signs have occurred in horses 12 to 36 hours after doses of 25 mg to 125 mg (roughly 0.06 to 0.26 mg/kg).[22,23] Signs are consistent with development of an extrapyramidal syndrome and include extreme agitation followed by a brief quiet period, hypermetria, profuse sweating, circling, rhythmic head tossing and neck arching, violent pawing, and self-mutilation.[22,23] These signs are nonresponsive to normal means of control. Hepatitis and urticaria (multiple, raised nodules; nonpruritic) occurred in one horse but may have been due to other factors.[24]

Short-term sedation with xylazine, detomidine, or romifidine may control the animal long enough to perform a physical examination and place an intravenous catheter. Often these drugs are ineffective and a barbiturate is necessary. Diphenhydramine (0.67 to 1.5 mg/kg IV q12-24h) or benztropine mesylate

(0.018 to 0.035 mg/kg PO q12h) has been used to control the extrapyramidal signs.[22,23] They are not always effective and a barbiturate (pentobarbital or phenobarbital) may need to be used for several days until the signs resolve.

Reserpine

Reserpine, a medication infrequently used in humans to control blood pressure, is used off label in horses to provide long-term sedation.[25] Clinical signs of an adverse reaction include profuse sweating, trembling, shaking, flatulence, watery diarrhea, marked miosis, upper eyelid ptosis, and paraphimosis ranging from mild to almost irreversible.[25-27] Treatment is similar to fluphenazine decanoate, although diphenhydramine and benztropine mesylate are not effective because reserpine's mechanism of action is different.

Blood-Doping Agents—Erythropoietin and Darbepoetin

Blood-doping agents such as erythropoietin (EPO) and darbepoetin have been abused in horses, in particular those horses in endurance events such as horse racing.[28] They increase aerobic capacity and endurance by increasing red blood cell production and therefore oxygen transport.[29,30] The danger in using human products is the potential for an immune response with antibody development.[31] Clinical signs, including depression, lethargy, and anemia, can occur after a single dose or may not occur until many doses have been administered.[28,31,32] Two Standardbred racehorses developed severe anemia, elevated serum irons, and bone marrow–specific hypoplasia after receiving at least two doses of EPO (4000 IU).[28] Treatment for these horses included stopping the EPO and administering oral dexamethasone (0.05 mg/kg once daily) with tapering of the dose as anemia resolved.

Miscellaneous Medications

Isopropyl Alcohol

Isopropyl alcohol is not a problem when used topically, but toxicosis has occurred when it is inadvertently given orally. A horse accidentally received 2 L via nasogastric tube instead of mineral oil. Shortly thereafter it became dull,

depressed, and collapsed with no menace response and slow pupillary light reflexes.[33] Treatment included gastric lavage, activated charcoal, and IV fluids, with recovery complicated by surgical correction of a cecal impaction.

Dimethyl Sulfoxide

When administered intravenously in concentrations greater than 50%, dimethyl sulfoxide (DMSO) results in severe hemolysis.[34] Few issues occur with topical and oral use of DMSO without additives. DMSO-associated toxicosis occurs when it is used in combination with other products, carrying them across membranes including the skin and the blood-brain barrier. In two instances, the application of a DMSO and mercury blister to limbs resulted in the development of mercury toxicosis.[35]

Dioctyl Sodium Succinate (or Docusate)

Dioctyl sodium succinate (DSS) is frequently used as a stool softener in horses with impactions. Single doses of 0.65 to 1 g/kg have resulted in agitation, abdominal pain, dehydration, watery diarrhea, intestinal mucosal damage, collapse, and death, with signs occurring within 1 to 2 hours of administration.[36] Treatment is supportive and includes GI protectants, IV fluids, correction of electrolyte abnormalities, and pain relief.

Lidocaine

Lidocaine, when used as a continuous IV infusion for ileus, has caused muscle fasciculations, anxiety, sedation, and visual dysfunction. The targeted serum level associated with this use of lidocaine is 1 µg/mL (0.98 µg/mL), with signs occurring at levels of 1.85 to 4.53 µg/mL.[37,38] Geriatric and neonatal horses, as well as those with hypoproteinemia, may develop signs at much lower doses and serum levels. Treatment consists of stopping the infusion and waiting a short time for the signs to resolve.[38]

Menadione Sodium Bisulfide (Vitamin K_3)

Menadione sodium bisulfide (vitamin K_3) is an ineffective anticoagulant in large animal species and toxic to horses in normal doses.[39] When administered to horses, weakness, stiffness, colic, laminitis, and a depressed appetite occur within 4 to 48 hours.[39,40] Acute tubular necrosis with azotemia, proteinuria,

hematuria, hyperkalemia, hypochloremia, and hyponatremia develop.[39] Treatment is focused primarily on the renal system, with IV fluids and diuretics such as furosemide or mannitol recommended.

Propylene Glycol

Propylene glycol is used as antifreeze, a drug vehicle, and a treatment for bovine ketosis. A mature horse inadvertently received a gallon of propylene glycol instead of mineral oil and developed depression, ataxia, sweating, pain, and salivation in 10 to 25 minutes; some signs resolved. Cyanosis, respiratory distress, and sudden death occurred 24 hours later.[41] Although not effective in this case, sodium bicarbonate may be used to treat developing lactic acidosis. Cows receiving an overdose (median toxic dose of 2.6 g/kg BW) become ataxic, depressed, and recumbent 2 to 4 hours after administration; signs resolve in 24 hours with supportive care.[42]

Illicit Substances

Cobalt

Cobalt is an essential mineral for mammalian species. It is used in the creation of cobalamin (vitamin B_{12}). The dietary need for cobalt varies by species and is higher in ruminants (especially sheep) than in horses.[43-45] Toxicity in ruminants is often poorly recognized due to the lack of distinctive clinical signs.[46] Cobalt, however, has purportedly been used as a supplement to racing horses to induce erythropoietin creation by stabilizing hypoxia-inducible factor 1α.[47,48] Despite a lack of evidence-based medicine that this process occurs in the horse, there are allegations that this practice continues. Toxicity in the horse has been observed when high doses of cobalt are administered to research horses.[49] Toxicity has been documented in videos showing sweating, colic, and muscle fasciculations.[49] Signs resolved within hours without medical intervention.[49]

Glaucine

Glaucine was recently identified in several samples collected from racehorses. Glaucine is available in injectable products that can be purchased on the Internet. These are made from extracts of the yellow hornpoppy *(Glaucium flavum).*

Glaucine can also be found in bulk bedding shavings made from tulip poplar trees *(Liriodendron tulipifera).*[50] Horses bedded on these shavings may ingest them, causing them to have measurable levels of glaucine. Glaucine is a weak dopamine receptor antagonist.[51] There have been no reports of toxicologic effect from either ingestion or IV injection in horses. However, there has been one case report of apparent ischemic heart effects where glaucine and diphenylprolinol were identified in a human patient.[52] In addition, glaucine has been associated with hallucinations, weakness, and sedation in humans.[53]

Dermorphin

Dermorphin is a peptide that bonds to mu opioid receptors.[54] It has been identified in samples collected from racing horses. It is purported to be administered for its analgesic properties. In a study investigating selected pharmacodynamic effects of dermorphin, researchers identified several responses to IV administration, including headshaking, colic-type symptoms, sweating, tachypnea, and sedation.[54] These behaviors also occurred to a lesser degree in some horses receiving IM administration. Most symptoms resolved quickly and without supportive care.[54]

Nomifensine

Nomifensine was recently identified in samples collected from several racehorses. Sold as a prescription antidepressant and later removed from the United States market, nomifensine may now be used in competitive horses for its dopamine-related analgesic effects.[55] There have been no reports of nomifensine-related toxicity in horses. In a study of nomifensine in dogs, dosages in the 3 to 10 mg/kg range had slight effects on blood pressure, heart rate, and blood flow.[56] These effects were transient in nature. It was withdrawn from the U.S. human drug market due to the risk of hemolytic anemia.[57]

Gamma-Aminobutyric Acid

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter present in the CNS of mammals.[58] In show and racing horses there have been allegations of inappropriate use of exogenous GABA for its calming effects. In research, IV administration caused transient sedative effects and increased heart rate.[58] In addition, purported effects of IV injection include sudden death,

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although this claim has not been verified. Other potential detrimental effects are unknown.

Feed Additives

Robert H. Poppenga

Inclusion of a variety of chemicals in livestock feed is an efficient and cost-effective mechanism to improve animal performance and prevent disease. Livestock feed additives include growth promotants such as ionophores, partitioning agents such as ractopamine, antiparasiticides and larvicides such as tetrachlorvinphos, antibiotics, hormones such as melengesterol acetate, buffers, probiotics, nutritional agents, dietary supplements, and adsorbents such as sodium bentonite. Fortunately, most feed additives are safe when used appropriately. The following discussion is limited to those feed additives that are most commonly associated with adverse effects.

Urea and Other Nonprotein Nitrogen Sources

Nonprotein nitrogen (NPN) is converted by ruminal bacteria to ammonia by the enzyme urease. Ammonia is subsequently used by the bacteria to form amino acids and, ultimately, protein. Use of ammonia for bacteria protein synthesis depends on the availability of a highly fermentable carbohydrate source.

NPN can replace a portion of more expensive natural protein in ruminant rations, providing up to 40% of their nitrogen requirement. Rumen bacteria can effectively use ammonia nitrogen in limited quantities. However, when ammonia is produced beyond the capacity of the bacteria to use it, it will accumulate in the rumen at potentially toxic concentrations. The most commonly used form of NPN is urea, although other forms such as ammonium salts or ammoniated feed are also used. NPN is available either in a granular form that is incorporated into concentrates or range blocks or as a liquid that is incorporated into palatable vehicles such as molasses or encased (as urea) in a polymer network designed to release urea through pores in the polymer. Urea is typically recommended at a maximum rate of 3% of the grain ration or 1% of the total ration.[1]

The toxicity of NPN for ruminants depends to a certain extent on the adaptation of rumen bacteria to NPN; properly adapted animals can tolerate higher concentrations of NPN than naive individuals. Acclimation to NPN can be lost within 1 to 3 days, so maintaining a constant intake is important to prevent potential intoxication. One advantage to the use of polymer-encased urea

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is that the urea is slowly released over approximately 16 hours, which better matches NPN with carbohydrate availability. In unacclimated cattle, a toxic dose of urea is approximately 0.45 g/kg BW. In comparison, a lethal dose for acclimated cattle is approximately 1 to 1.5 g/kg BW. Younger ruminants are more susceptible than older animals to intoxication.[1,2]

Ammonia not used by rumen bacteria is absorbed systemically and can result in hyperammonemia within 30 minutes to 2 hours if it is not detoxified to urea by the liver for excretion. The amount of ammonia absorbed depends on the pH of the rumen. Normally, when rumen pH is below 7, most ammonia is in the form of the charged ammonium ion (NH_4+ versus the uncharged NH_3). As more ammonia is produced in the rumen, the pH of the rumen becomes more alkaline, with a resultant dramatic shift in the relative amounts of NH_4+ and NH_3 in the rumen. Unionized NH_3 readily crosses the rumen wall; in blood, ammonia is primarily in the form of ammonium ion.

NPN-induced ammonia toxicosis usually results from one of the following situations: (1) inadequate or improper feed mixing, (2) error in calculating the amount for inclusion in feed, (3) inadequate adaptation to NPN, (4) inclusion in carbohydrate-deficient rations, or (5) unrestricted consumption of palatable liquid NPN formulations.[2]

Clinical signs of ammonia toxicosis can occur within 30 minutes to several hours after consumption of excessive NPN. Signs include weakness; dyspnea; salivation; bruxism; bloat; excitation; belligerence; vocalizations; muscle tremors beginning with eyelids, lips, and neck and progressing posteriorly; and convulsions. Due to the rapid onset of clinical signs, it is common to find animals dead without signs being noted. There are no characteristic postmortem findings associated with intoxication. Gross or histopathologic lesions most often involve the lungs and brain and include generalized congestion, hemorrhages, and pulmonary and brain edema.

As evidenced by typical clinical signs, the CNS is a primary target of NPN intoxication. Mechanistically, ammonium ion causes a number of changes in the CNS, including amino acid disturbances, alterations in neurotransmission, cerebral energy deficits, and alteration of nitric oxide synthesis. Brain edema due to hyperammonemia is thought to occur through increased astrocyte osmolality and cytotoxic oxidative and nitrosative damage.[3]

A diagnosis of intoxication relies on a history of NPN supplementation, compatible clinical signs, and ideally measurement of elevated ammonia

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concentrations in rumen contents, whole blood, or ocular fluid. Unfortunately, ammonia is volatile, so appropriate sample handling and storage are critical for ammonia measurement. If urea is the NPN source, it can be measured in feed or, less usefully, in rumen contents. An antemortem rumen pH value greater than 8 is consistent with NPN intoxication. Postmortem pH values can be misleading depending on the time lag between death and necropsy.

Treatment is designed to decrease the amount of unionized ammonia absorbed from the rumen. Adult cattle should be given 20 to 30 L of cold water orally to reduce the ability of rumen bacteria to convert urea to ammonia by inhibiting and diluting urease. In addition, decreasing rumen pH shifts the form of ammonia to the unabsorbable ammonium ion; this is accomplished by administering 2 to 6 L of vinegar.

A number of strategies can minimize the risk of intoxication. These include a gradual adaptation to NPN, feeding readily fermentable carbohydrate sources, ensuring uniform feed mixing, maintaining a regular feeding schedule, feeding liquid supplements with phosphoric acid to maintain an acidic rumen, coating urea with fat and extruding urea with concentrates such as grain, using urease inhibitors to decrease its hydrolysis, and ensuring that mineral nutrition is adequate.[2]

Ammoniated Feed

Ammoniated feed intoxication is a hyperexcitability syndrome called “bovine bonkers” and is reported in cattle and calves fed ammoniated molasses, hay, straw, and silage.[1] The ammoniation process improves the palatability and digestibility of otherwise poor-quality roughages. Ammoniation of high-quality roughages such as wheat, Sudan grass, alfalfa, orchard grass, Bermuda grass, fescue, and sorghum containing high concentrations of soluble sugars is most often associated with the syndrome. The putative toxicants are the imidazoles, 2- and 4-methylimidazole, which are formed during the ammoniation process. The mechanism causing CNS excitation is unknown.

Hyperexcitability, either spontaneous or induced, is a hallmark of the syndrome. Affected animals will suddenly stampede and run in circles or a straight line until they collide with other animals, buildings, or fences. Other clinical signs include ear twitching, mydriasis, trembling, salivation, increased urination and defecation, and bellowing. The only postmortem lesions noted are secondary to trauma. The imidazoles can be excreted via milk, so nursing

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animals are at risk of intoxication.[4,5] Neurologic signs have been reported in nursing calves whose dams had been fed ammoniated barley greenfeed; dams were unaffected.[4]

A diagnosis of intoxication depends on a history of feeding ammoniated forages and consistent clinical signs. Treatment is nonspecific and typically limited by difficulties in handling affected animals. Sedation can be tried; acepromazine has been suggested.[5] Animals often recover once exposure is halted.

Prevention involves restricting ammoniation to poor-quality roughages that contain low concentrations of soluble sugars. The amount of ammonia used should not exceed 3% of the dry weight of the forage. In addition, the processing temperature of the forage should not exceed 70° C (158° F).[1]

Ionophores

Ionophores are commonly added to cattle and poultry feed for their growth promotant and anticoccidial properties. A number of ionophores, including narasin, salinomycin, lasalocid, monensin, semduramycin, laidlomycin, and maduramycin, are commercially available. In cattle, ionophores result in more propionic acid production in the rumen, which improves feed efficiency. They are also used to prevent rumen acidosis and emphysema. Intoxication most often occurs due to errors in feed mixing that result in overdosing of target species (cattle and poultry) or accidental inclusion in feed of nontarget species (e.g., horses, camelids).

Ionophores are potentially toxic to a variety of mammalian and avian species, although sensitivities vary between species and among different ionophores.[6,7] Intoxications have been documented for horses, cattle, goats, pigs, camelids, chickens, turkeys, quail, and ostriches. Ionophores bind and transport ions across cell and organelle membranes; the direction of movement depends on the concentration gradient of a particular ion. This results in disruption of multiple ion gradients as one or more ions move into or out of cells. Monovalent ionophores such as monensin, salinomycin, and narasin preferentially complex with either sodium (monensin) or potassium (salinomycin and narasin) ions. Divalent ionophores such as lasalocid and laidlomycin are capable of binding and transporting divalent cations such as calcium and magnesium across membranes. At a cellular level ionophores affect mitochondrial function and result in loss of aerobic energy production.

▪ Horses

Horses are the most sensitive livestock species with reported median lethal doses (LD_{50}s) of 0.6 mg/kg for salinomycin, 2 to 3 mg/kg for monensin, and 21.5 mg/kg for lasalocid.[6] Clinical signs in horses are similar irrespective of the ionophore ingested, although signs can vary among individuals within an affected group. Signs most commonly occur with 24 hours of exposure, but delayed onset can occur in some cases. Acute clinical signs are primarily due to effects on muscle cells and the nervous and digestive systems. Feed refusal is one of the earliest signs noted in horses. Other signs include weakness, ataxia or incoordination, tremors, stumbling, exaggerated stepping, hesitance to move or turn, tachycardia, congested mucous membranes, hypotension, dyspnea, hyperpnea, sweating, and recumbency. Death can occur without signs being observed. In individuals surviving acute intoxication, longer-term clinical signs result from myocardial damage and decreased cardiovascular function and include unthriftiness, poor performance, poor exercise tolerance, arrhythmias, pitting edema, and hyperpnea. Delayed sudden death can occur long after exposure.

A variety of clinicopathologic changes can occur, including elevated ALP, AST, lactate dehydrogenase (LDH), creatine phosphokinase (CPK), creatinine, indirect bilirubin, BUN, glucose, hematocrit, serum osmolality, and phosphorus. Decreased concentrations of serum Ca^{++} and K^{+} and urine osmolality occur. Myoglobinuria is often noted. Unfortunately, the usefulness of such changes is limited by significant variation among affected individuals and the timing of their occurrence. Measurement of serum cardiac troponin I has been suggested to help with the early identification of horses with cardiac damage.[8]

The most significant necropsy findings are due to direct or indirect myocardial damage. Acutely affected horses develop degeneration and necrosis of cardiac muscle, whereas horses dying later have marked cardiac myopathy and fibrosis. Lesions can be absent in horses dying peracutely.

A diagnosis of intoxication relies on a combination of consistent clinical signs, necropsy findings where death occurs, and analytic proof of ionophore exposure. Because medicolegal considerations are often encountered in cases involving horses, it is critical to try to quantify ionophore feed concentrations.[6] This is difficult if representative feed samples are not available. Testing several feed samples can be important to confirm non-uniform feed mixing. In the absence of feed testing, stomach contents and/or tissue testing (preferably heart tissue) can

be done to confirm exposure but not necessarily intoxication.[9]

There is no specific treatment for ionophore poisoning.[10,11] It is critical to quickly remove access to suspect feed and initiate decontamination (e.g., gastric lavage and/or activated charcoal) as soon as possible. The efficacy of decontamination in most cases is questionable. Supportive therapy is directed toward restoration and maintenance of cardiac output and tissue perfusion, stabilization of cell membranes, and treatment with anti-arrhythmics if unstable, life-threatening arrhythmias are present.[10] Affected horses should be rested for up to 3 months after exposure, and echocardiograms (echos) and exercising echos performed to identify evidence of chronic cardiomyopathy. Reported mortality is 60% or greater.[10]

▪ Cattle

Cattle are less sensitive to ionophores than horses. At prescribed use levels, ionophores are safe. The LD_{50} for monensin in cattle is reported to be 26.4 mg/kg, and lethal doses of lasalocid range from 50 to 100 mg/kg.[7]

In cattle, signs of acute intoxication include early anorexia, rumen atony, CNS depression, muscle tremors, watery diarrhea, tachycardia, ataxia, recumbency, and death. Animals can be found dead without clinical signs being noted. Animals surviving acute intoxication can subsequently develop congestive heart failure characterized by brisket edema, prominent jugular pulses, ascites, fluid feces, dyspnea, and tachycardia. Deaths can occur weeks to months after exposure and be precipitated by exertion such as calving. In dairy cattle, decreases in milk production are likely, with production requiring several days to a week to return to previous levels.

Clinical pathologic changes are similar to those described for horses. On necropsy, lesions include myocardial degeneration, pulmonary edema, enlargement of the heart and liver, hydropericardium, hydrothorax, and ascites.

Elements necessary for a diagnosis in cattle are similar to those for horses. However, in contrast to cases involving horses in which confirming exposure is likely to be significant, in cattle it is important to confirm exposure to feed concentrations higher than expected concentrations. Although, similar to horses, tissue testing can identify exposure to an ionophore, tissue concentrations associated with intoxication have not been definitively determined.[12] Treatment is similar to that for horses, although it is less likely to be as extensive in cases involving cattle.

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▪ Poultry

Both salinomycin and monensin intoxication have been reported in turkeys.[13] Sensitivity to salinomycin is age dependent, with younger birds being less sensitive. Clinical signs in affected birds include dyspnea, drowsiness, sternal recumbency with rear legs extended posteriorly, inability to stand, stiffness, and weakness. Extensive fragmentation and necrosis of skeletal muscle fibers occurs, and myocardial damage can also be noted.

Acute onset of feed refusal, decreased water consumption, and severe paralysis ranging from an abnormal gait to complete inability to move have been described in a chicken broiler breeder flock after monensin was included in their feed at approximately seven times the intended concentration.[14] The flock experienced high morbidity and mortality. Postmortem lesions were similar to those reported for intoxicated turkeys. Although the mortality rate returned to normal 21 days after feed removal, loss of productivity resulted in elimination of surviving birds.

β_2-Adrenergic Agonists

In livestock, β_2-adrenergic agonists have been used as repartitioning agents (i.e., repartitioning nutrients away from fat in favor of muscle). This results in increased carcass weight and ratio of muscle to fat and improved feed efficiency. β_2-adrenergic agonists approved in one or more countries for use in livestock feed include ractopamine (finishing beef cattle, swine, and turkeys) and zilpaterol (finishing beef cattle). Clenbuterol is approved for treating recurrent airway obstruction in horses but is not approved for use in food animals.[15] Due to the anabolic effects of β_2-adrenergic agonists, there is the potential for their use as doping agents in racehorses.

Horses appear to be more sensitive to adverse effects than cattle following exposure to zilpaterol. In a limited number of horses, adverse effects were noted soon after a single zilpaterol dosage of 0.17 mg/kg BW PO; this is the recommended dosage for cattle.[16] Signs included nervous behavior, profuse sweating, muscle tremors, and tachycardia within 20 to 60 minutes post dosing. Clinical pathologic changes were consistent with muscle damage and included increased serum activity of LDH, CK, and AST. Myoglobin-induced nephropathy is possible in some individuals. The duration and severity of adverse effects were unanticipated, with some signs persisting for up to 2 weeks.

Affected horses recovered completely without treatment. Widespread accidental contamination of horse feed with zilpaterol resulted in violative urine residues in 48 horses from four California race tracks (http://www.chrb.ca.gov/Board/committee_packages/Apr-2013MC.pdf). No horses were reported to be symptomatic, but the case illustrates that nontoxic concentrations of feed additives can potentially result in adverse consequences unrelated to an adverse health effect. Fortunately, because of the widespread nature of the feed contamination, no regulatory action was taken against any positive horse.

Based on human data, clenbuterol is approximately 19 times more potent than zilpaterol, and zilpaterol is approximately 125 times more potent than ractopamine. Dosages of ractopamine of up to 10 times the dose of zilpaterol given to horses have not been associated with adverse effects.[17]

Antibiotics

The erroneous addition of antibiotics to feed is of particular concern in horses. Antibiotics such as lincomycin, clindamycin, tetracycline, and erythromycin have been associated with lethal colitis in horses.[6] Adverse effects are believed to be due to disruption of the normal microbial flora, resulting in overgrowth of pathogenic bacteria such as *Clostridium* spp., *Salmonella* spp., or *Escherichia coli.* Subsequent production of endotoxins or enterotoxins causes digestive tract damage and systemic clinical effects. Treatment primarily involves IV fluid therapy and correction of acid-base and electrolyte abnormalities.

Pesticides

Tetrachlorvinphos (TCVP) is an organophosphorus insecticide fed to horses, cattle, and swine as a pass-through fly larvicide. It is a cholinesterase inhibitor, and intoxication is associated with overstimulation of muscarinic and nicotinic cholinergic receptors. TCVP has low mammalian toxicity, with an LD_{50} in laboratory animals of greater than 1 g/kg BW. However, anecdotal evidence suggested that horses receiving TCVP at recommended levels were more likely to exhibit GI problems and increased reactivity, leading to handling difficulties. In one study, six horses given the recommended dose of TCVP for 30 days were noted to have heightened reactivity to an external stimulus that correlated with a reduction in whole blood cholinesterase activity.[18] Another study demonstrated that TCVP at the recommended dose depressed plasma butyrylcholinesterase

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activity in horses but did not disrupt cholinergic neurotransmission in target tissues.[19] Although TCVP at recommended doses does not cause typical signs associated with organophosphorus insecticide overexposure, some clinicians have suggested that alternative methods for fly control be used for horses due to potential adverse effects on behavior.

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Pesticides and Rodenticides

Michelle Mostrom

Pesticides comprise a wide variety of chemicals used to control insects and parasites in agriculture, animals, and public health, as well as to control weeds, fungi, and rodents or other animals determined as unwanted by man. The toxicology of pesticides covers several different chemical classes. This section focuses primarily on insecticides and rodenticides that are more commonly associated with toxicoses in large animals. Poisoning or toxicosis in large animals generally occurs due to misuse or overdosage with a pesticide, malicious use of pesticides or baits, or occasionally from accidental exposure (e.g., drift from aerial spraying, cleanup of buildings with old stored products).

All pesticides sold and distributed in the United States must be registered by the EPA. Registration is based on scientific data demonstrating that the chemicals can be used without posing unreasonable risks to people or the environment. With advancement of science, all pesticides that were first registered before November 1, 1984, were required to be reregistered to meet the more stringent standards. General scientific data on the toxicity of pesticides can be located on the EPA website (www.epa.gov) and in numerous databases supported by the U.S. National Library of Medicine, such as ToxNet (http://toxnet.nlm.nih.gov), using search terms for the chemical, Chemical Abstract Service (CAS) number, trade name, or clinical signs. The product label can also provide data on potential toxicosis.

Unfortunately for large animals, a limited number of antidotes is available for treatment of pesticide and rodenticide toxicoses.[1,2] For example, atropine sulfate, epinephrine, and vitamin K_1 do not have New Animal Drug Approval and are not formally approved by the Food and Drug Administration/Center for Veterinary Medicine (FDA/CVM), but the labels are reviewed and on file with the FDA/CVM.[3] These drugs may be used as antidotes in food animals, but the veterinarian should contact the Food Animal Residue Avoidance Databank (FARAD; www.farad.org) regarding withdrawal times if animals or milk will be put into the food chain. Because toxicoses involving pesticides often occur in nontarget species or at high concentrations, withdrawal intervals for these chemicals in food animals are often not readily available. A reasonable place to start locating this information is through contact with your state veterinarian, the

District Office for the FDA in your region, and the U.S. Department of Agriculture Food Safety and Inspection Service (USDA FSIS; www.fsis.usda.gov). The state veterinarian may also assist with recommendations for proper disposal of chemically contaminated carcasses.

Box 54.1 outlines suggested steps to handle unknown exposure of livestock to pesticides.

Box 54.1

Approach to Unknown Exposure of Livestock to Pesticides

1. Type and number of animals exposed (age, weight, dairy or beef, pregnant, lactating, etc.).
2. Location of exposure (pasture, dry lot, aerial drift, etc.) or crops/pasture/hay land.
3. Clinical signs of exposed animals (consider taking whole blood for cholinesterase activity). If animal deaths are involved, perform necropsies and take samples for routine necropsy along with brain (cholinesterase activity and chemical analysis), fat, liver, kidney, lung, urine, and skin (if dermal exposure) for possible chemical analysis.
4. Try to obtain trade name of pesticide, particularly if accidental exposure such as aerial drift, and the wind direction if sprayed onto animals.
5. If a licensed applicator accident, the applicator will have pesticide label data and concentration, wind speed, and direction.
6. With a chemical name identified, you can access information on toxicity by several routes:
    a. Contact a veterinary diagnostic lab and toxicologist for toxicity data.
    b. Locate data on the EPA website, including “How to Search for Information about Pesticide Ingredients and Labels” (https://www.epa.gov/ingredients-used-pesticide-products/how-search-information-about-pesticide-ingredients-and-labels).
    c. Search for chemical toxicology data, which can often be located on the U.S. National Library of Medicine website, specifically the

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Hazardous Substances Data Bank (HSDB). Enter the chemical name in the HSDB and data on human and animal toxicity, emergency medical treatment, pharmacology, chemical safety and handling, and environment fate can be obtained (https://toxnet.nlm.nih.gov/newtoxnet/hsdb.htm).

7. If questions on grazing restrictions or crop use for livestock, check the pesticide label for data. In addition, some state extension bulletins can provide grazing restriction information on some chemicals.
8. Data on pesticide chemical tolerances for residues in crop commodities, meat, and meat by-products can be found in the Code of Federal Regulations (40 CFR Part 180) (https://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/index.tpl).
9. Check the electronic Code of Federal Regulations (eCFR) for updated data. Instructions for conducting an eCFR search for tolerances can be found on the EPA website: “How to Search for Tolerances for Pesticide Ingredients in the Code of Federal Regulations” (https://www.epa.gov/pesticide-tolerances/how-search-tolerances-pesticide-ingredients-code-federal-regulations).
10. Treatments for animals may be only supportive care for clinical signs. Consider using activated charcoal to bind pesticides by oral exposure; check individual chemical information for specific medications. If dermal exposure occurred, wash the animal with soap and water to decrease absorption. Clipping hair should be considered in long-haired livestock.
11. Chemical analyses for all pesticides, metabolites, and possible inert ingredients are not readily available (especially herbicide analysis in biological tissues). Chemical standards may not be available or could be expensive; laboratory methods in crop or biological matrices may have to be developed. Check with a veterinary toxicologist regarding costs and the possibility of chemical analyses.

Organophosphates and Carbamates

The introduction of newer types of external parasiticides and chemical products has significantly reduced the incidence of these toxicoses in livestock. Both organophosphate (OP) and carbamate insecticides inhibit acetylcholinesterase (AChE) at cholinergic nerve synapses and at neuromuscular junctions, causing acetylcholine to accumulate at nerve junctions and cause excessive synaptic

action. They also inhibit other cholinesterases in the body (e.g., red blood cells, serum, liver, pancreas, nervous tissue). These insecticides lack species selectivity and may pose a hazard to domestic and companion animals, wildlife, and aquatic species. The anticholinesterase compounds may adversely affect the cardiovascular, respiratory, ocular, reproductive, endocrine, dermal, and immune systems but primarily act on the nervous system and skeletal muscles.[4] Death is usually the result of respiratory failure, often with cardiovascular involvement.

Approximately 200 OPs and several dozen carbamate compounds have been synthesized for numerous purposes. They are incorporated into various products, including baits, dips, dusting powders, sprays, pour-ons, and oral anthelmintics. The OPs used as defoliants and herbicides, such as glyphosate and gluphosinate, have low acute mammalian toxicity but could induce delayed polyneuropathy.[4] Aldicarb, sold under the trade name Temik, was synthesized to mimic acetylcholine and is considered to have maximum potential for mammalian toxicity.[4]

Both OPs and carbamates inhibit the metabolism of acetylcholine at cholinergic sites. Acetylcholine is a neurotransmitter at postganglionic parasympathetic neurons in smooth muscles, cardiac muscles, or exocrine glands; at neuromuscular junctions of the somatic nervous system; at cholinergic synapses in the CNS; and between preganglionic and postganglionic neurons of the autonomic nervous system. The enzyme AChE normally breaks down acetylcholine at these cholinergic sites, but when bound by OPs or carbamates it is inactive. During toxicity, acetylcholine maintains depolarization of the postsynaptic membrane, which is initially stimulatory but may progress to paralysis. The OPs have high affinity for the cholinesterase enzyme and are considered irreversible inhibitors of AChE. Organophosphates can undergo an "aging" process, which stabilizes the OP-AChE bond and cannot be broken. Carbamates do not undergo "aging" and can be dislodged from AChE, resulting in spontaneous enzyme regeneration. These insecticides also induce toxic effects through noncholinergic mechanisms that may involve glutamate release and activation of *N*-methyl-D-aspartate receptors and the γ-aminobutergic, adenosinergic, and monoaminergic systems that are involved in seizures, which are reviewed by Gupta and Milatovic.[4]

The toxicity of OPs and carbamates varies widely, from highly toxic compounds (OP nerve gases such as Sarin, Soman, and VX, and carbamates such as aldicarb and carbofuran) to minimally toxic ones (e.g., malathion, tetrachlorvinphos). The very young, very old, and weakened animals are more

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susceptible to poisoning from these compounds. Following exposure, OPs and carbamates are rapidly distributed throughout the body and can undergo oxidation, hydrolysis, and conjugation. They are excreted in the urine and feces. The OPs tend to be more lipophilic than carbamates and are more likely to cross the blood-brain barrier; however, carbamates may cause marked CNS signs. Clinical signs can occur within minutes to hours of exposure depending on the dose, route of exposure, and toxicity of the insecticide. Death can occur within minutes with highly toxic chemicals or when large amounts are ingested. Repeated exposures can be clinically important. The insecticides may be metabolized and excreted within days of exposure, but the regeneration of AChE may require 2 weeks.[5] Clinical signs of acute toxicity due to OP and carbamate exposures result from overstimulation of muscarinic and nicotinic acetylcholine receptors because of the buildup of acetylcholine from inactivation of AChE. The clinical effect is excessive synaptic neurotransmitter activity and depolarization of effector organs.[6] Muscarinic signs include ptyalism, excessive tracheobronchial secretions and sweating, bronchospasms and laryngospasms, lacrimation, nausea, diarrhea, miosis, and bradycardia. The muscarinic clinical signs are frequently described by the term *SLUD* (salivation, lacrimation, urination, and defecation). Nicotinic clinical signs include muscle fasciculations, tremors, weakness, ataxia, flaccid paralysis, vomiting, and paralysis of respiratory muscles. Muscarinic signs generally appear first, followed by nicotinic signs, and finally by CNS effects (hyperactivity and seizures).

Not all clinical signs are observed in an OP or carbamate toxicosis. The clinical appearance of an AChE toxicosis may vary with the species exposed, toxic compound, dose, route of exposure, and timeline in exposure-response. For example, the use of methiocarb as a snail bait in Australia uncommonly causes problems in horses but can result in AChE inhibition, clinical signs, and death. A 400-kg gelding developed clinical signs of profuse sweating, hypersalivation, lateral recumbency, paralysis of a distal hindlimb, and generalized muscle tremors within a few hours after consuming almost 20 g of methiocarb in bait form (1 kg of 2% weight/volume).[7] The horse had signs of colic, ileus, and a significant amount of nasogastric reflux (total reflux volume after presentation at a veterinary clinic was 55 L) but never developed diarrhea. Because of the large volume of nasogastric reflux, activated charcoal was not given nor was atropine administered due to the lack of GI borborygmi. Gastric lavage had been performed about 6 hours post ingestion but was probably ineffective to recover ingested bait; the authors speculated that the worsening clinical signs were due

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to continued absorption of methiocarb, and the horse was euthanized about 54 hours post ingestion of the bait.

Delayed toxicosis has occurred with the use of chlorpyrifos, a chlorinated OP, as a pour-on in bulls and some exotic breeds of cattle. The toxicity appeared to be related to testosterone levels in cattle, with larger and older bulls affected. Clinical signs appeared 2 to 7 days post exposure and included weakness, muscle fasciculation, anorexia, rumen stasis and distention, and depression.[8] Decontamination of the skin and rumen, activated charcoal, and symptomatic treatment are recommended for treatment of chlorpyrifos poisoning in bulls.

Diagnosis of OP or carbamate toxicosis includes (1) history and clinical signs consistent with the toxicosis; (2) response of animals to treatment with atropine; (3) determining cholinesterase inhibition (whole blood, retina, brain), corresponding with adverse clinical effects; and (4) detection of the insecticide in biological tissues (GI contents or tissues). The diagnosis can be challenging. Clinical pathologic changes are not consistent and postmortem lesions are nonspecific. Often pulmonary edema is evident on postmortem, along with tracheal fluid and diarrhea, but these changes are not unique to AChE toxicosis.

Measurement of cholinesterase activity in whole blood and brain is commonly used to establish an OP or carbamate diagnosis. Generally, AChE activity less than 50% of normal level indicates exposure, and activity less than 25% of normal level in an animal with compatible clinical signs indicates toxicosis from an OP and/or carbamate. Use of AChE activity alone is not always diagnostic. The use of OP anthelmintics in horses at therapeutic doses decreased AChE activity to less than 25% of normal level, while no horses displayed clinical signs.[9] Interpretation of AChE activity is difficult in a carbamate toxicosis. Carbamates can spontaneously dislodge from the cholinesterase enzyme before or after sample collection; therefore AChE activity may be in the normal range even though the animal is experiencing toxicity from a carbamate compound.

Check with your diagnostic laboratory for proper collection of specimens (whole blood, brain, plasma, serum, retina) for AChE activity. With an OP exposure, AChE activity in whole blood is fairly stable for about 7 days after collection if the blood is stored under refrigeration.[9] For determination of AChE activity in the brain, submit a chilled whole or half brain because cholinesterase activity varies in different regions of the brain and the laboratory may have a preference for the brain region tested.

Identification of the insecticide can often be made on postmortem specimens, including rumen, GI contents, liver, fat, brain, and perhaps kidney. Samples

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should also be taken of the suspect source (e.g., bait, feed, water) for identification and concentration. It is not unheard of to have acute death losses in animals; finding depression of AChE in brain, whole blood, and retina; detecting the insecticide in rumen contents; but locating no source of insecticide on the farm.[10] With suspect insecticide toxicosis, check with the diagnostic laboratory for proper collection and shipment of samples. Generally, the samples are kept chilled or frozen before analysis. Management of OP or carbamate toxicosis depends on the clinical signs and time from exposure. Treatment should be initiated quickly. If the animal is having seizures, stabilize the animal and attempt to control the seizures with diazepam, which may need to be supplemented with methocarbamol, barbiturates, or general anesthesia. Oxygen therapy and ventilatory support may help with severe dyspnea. The noncompetitive antagonist for OPs and carbamate is atropine, which blocks excessive acetylcholine at synapses. It can control muscarinic signs and some CNS signs, but not nicotinic signs (e.g., muscle fasciculations, weakness, paralysis). The therapeutic range for atropine sulfate is between 0.25 and 1 mg/kg, with one quarter of the dose given intravenously and the remainder administered IM or SC.[5,6] It may be necessary to use the high end of the range in toxic situations. The dose should be repeated as needed (usually a lower dose and every 2 to 4 hours) to control bradycardia and secretions into the lungs. Avoid overtreatment with atropine, especially during prolonged treatment. Note that atropine has a low margin of safety in horses and causes GI stasis, which should be carefully monitored during use. It is recommended not to exceed a total dose of 65 mg of atropine in the average horse.[5] When atropine is used in multiple doses as an antidote for a toxicosis, check with FARAD (www.farad.org) for milk and/or meat withdrawal recommendations. Note that veterinarians must also consider the residue-withdrawal interval for the insecticide in tissues.

Acetylcholinesterases can be reactivated with oximes, such as pralidoxime chloride (2-PAM), if aging has not occurred or with the irreversible binding of an OP to AChE. The oxime attaches to the OP insecticide and dissociates the OP-cholinesterase bond. Response to oxime therapy is better when oximes are used within 24 hours after exposure to OP insecticides. Oximes ameliorate to some degree muscarinic, nicotinic, and CNS signs and work best with atropine. The dose, frequency, and route of administration of 2-PAM vary in the literature. A dose of 20 mg/kg IV q4-12h has been recommended in ruminants; its use should be stopped if no response occurs within 36 hours.[11] Excessive doses of oximes

have the capability to inhibit cholinesterase.[4] The use of 2-PAM in treatment for a large animal OP toxicosis would be very expensive; in addition, 2-PAM is not approved for use in large animals and should be used with oversight under FDA/CVM guidance. In some cases, the use of 2-PAM in carbaryl (carbamate) toxicity has been considered detrimental.

Once the animal is stabilized, decontamination should be considered. Oral dosage of activated charcoal (1 to 2 lb/500 kg in a slurry) can bind the insecticides in the GI tract and prevent absorption; this treatment may also be helpful with topical application of some insecticides. The use of activated charcoal is particularly recommended for ruminants, which have the capacity for large retention of GI contents. With topical exposure to insecticides, animals should be washed with a liquid dishwashing detergent and rinsed off to reduce absorption. Gastric lavage with water may be indicated in high-dose exposures where only a few hours have passed since ingestion. Additional therapy may include fluids to treat dehydration and electrolyte imbalances.

Several drugs are contraindicated in OP and carbamate toxicosis (with cholinesterase inhibition), including opiates, physostigmine, phenothiazine tranquilizers, neostigmine, succinylcholine, levamisole, antihistamines, aminoglycoside antibiotics, and theophylline.

Glyphosate

Although glyphosate can be chemically described as an OP compound, it is a phosphanoglycine and not recognized as a cholinesterase inhibitor. It is usually formulated as an isopropylamine, sodium, ammonium, or timesium salt and is active as a broad-spectrum, postemergent, nonselective herbicide. Glyphosate is one of the most used herbicides worldwide. It interferes with the production of essential aromatic amino acids in plants.[12] Glyphosate is not metabolized efficiently in mammals and is mainly excreted unchanged into the urine; however, it can undergo GI microbial metabolism in humans and rats.[12] Recently, the International Agency for Research on Cancer (IARC) classified glyphosate as “probably carcinogenic to humans (Group 2A)” based on limited evidence in humans and with a positive association for non-Hodgkin's lymphoma and with “sufficient evidence in experimental animals for carcinogenicity.”[12] Limited data are available in livestock. In a field study of Danish dairy cows, all cows on eight dairy farms excreted glyphosate, in varying concentrations, in their urine.[13] The authors reported increased activity of

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several serum enzymes, glutamate dehydrogenase, glutamate oxaloacetate transaminase, and creatinine kinase in cows on all farms, which could indicate a possible effect of glyphosate on liver and muscle cells. Low serum concentrations of manganese and cobalt were observed in all animals, which may be explained by the strong mineral chelating effect of glyphosate; however, the mean levels of copper, zinc, and selenium were within the normal reference range. In a recent study of glyphosate in lactating dairy cows, glyphosate residues in foodstuffs (0.8 to 84.5 mg glyphosate/day average intake in the experimental groups) were fed to cows during a 16-week trial.[14] No glyphosate residues were detected in the milk, and no adverse effects were detected in body condition score, net energy intake, net energy balance, or milk performance parameters. Given the health controversies surrounding the widespread use and exposure to glyphosate, additional animal studies are warranted.

Pyrethroids

Pyrethroids are active synthetic derivatives of natural toxins in the plants *Chrysanthemum cinerariaefolium* (or *Tanacetum cinerariaefolium*) and *Chrysanthemum cineum*. These chemicals are important insecticides used in crop protection to control insect vectors carrying infectious diseases of animals and humans and to control insects on premises. They are available as wettable powders, granules, and emulsifiable concentrates in sprays, dusts, dips, foggers, ear tags, pour-ons, and back rubbers. Pyrethrins are the naturally active insecticidal compounds from the plants; pyrethroids are synthetic analogs of the pyrethrin esters and tend to have more potent insecticidal activity, to be more stable in the environment, and to be more toxic. The pyrethroids are categorized as type I pyrethroids (a cyano group is absent) or type II pyrethroids (an alpha-cyano group that increases the insecticidal potency is present). Allethrin, bifenthrin, permethrin, resmethrin, and tefluthrin are examples of type I pyrethroids. Cyfluthin, cypermethrin, deltamethrin, and flumethrin are examples of type II pyrethroids. Often synergists such as piperonyl butoxide, propyl ethers, and sesamin are combined with pyrethroids to inhibit mixed-function oxidase and esterase enzymes in the target species and reduce detoxification of the insecticide and prolong its action in insects. Synergists may also enhance toxicity in animals. Pyrethroids interfere with conductance of nerve membranes by binding to the membrane and prolonging the sodium current. The pyrethroids act on axons in the central and peripheral nervous systems. Gamma-aminobutyric acid–gated chloride channels may also be affected by high doses of

type II pyrethroids. Compared with insect sodium channels, mammalian sodium channels are much less sensitive to pyrethroids and recover more quickly from depolarization.

Most pyrethroids are applied dermally, and there is limited absorption through this route. Pyrethroids are absorbed more efficiently across GI and pulmonary membranes. Pyrethroids are lipophilic in nature and distribute into fat, central and peripheral nervous systems, milk, and other organs. Once absorbed, pyrethroids can undergo metabolism by nonspecific esterases and microsomal mixed-function oxidases. Pyrethroids and their metabolites are excreted in feces and urine, with a majority of pyrethroids excreted within 12 to 48 hours.[15]

Following application of pyrethroid pour-on products, cattle can exhibit a paresthesia-like syndrome, thought to result from direct action of pyrethroids on sensory nerve endings.[15] Cattle may be restless and uncomfortable, and twitch the skin on their backs. Young animals are more susceptible due to a lack of metabolism of pyrethroids; death can occur due to respiratory failure and convulsions leading to paralysis. No specific clinical pathologic or histopathologic changes have been reported with pyrethroid applications. In a toxicosis, check with the veterinary diagnostic laboratory regarding analytic testing on appropriate tissues. Pyrethroids concentrate more in nervous tissue than serum or plasma.

Pyrethroids have been implicated in disrupting the endocrine system, adversely affecting reproduction and sexual development, and interfering with the immune system. Pyrethroid treatment of laboratory animals and in vitro samples has induced a decrease in epididymal sperm count and sperm motility, as well as an increase in abnormal spermatozoa.[16,17] Pyrethroid treatments of mice and rats disrupt testosterone synthesis and downregulate 17β-hydroxysteroid dehydrogenase (convert androstenedione to testosterone) and biosynthetic enzymes that have a critical role in the synthesis of testosterone in Leydig cells.[18,19] In addition, pyrethroid exposure has been shown to disrupt luteinizing hormone–responsible ovulatory genes in rats and prostaglandin synthesis in granulosa cells in vitro.[20]

Exposure of bulls in a bull stud to bifenthrin was associated with poor semen quality, including (1) decreased motility, (2) reduced ejaculate volume, and (3) spermatozoa abnormalities with a high percent of distal midpiece reflexes.[21] At 64 days post exposure, semen quality recovered to levels observed before exposure in these bulls. In this case, the use of bifenthin was apparently an

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excessive use of product in a building (bull stud) with the animals present, so that excessive exposure was dermal, inhalation, and oral; in addition, these animals were being continually monitored for semen quality for cryopreservation, and therefore clinical abnormalities in semen were easily detected (Evans, T: personal communication, August 2012). Field cases of bulls exposed to pyrethroids that subsequently developed poor sperm quality and motility, with gradual recovery to normal after about 2 to 4 weeks, have been reported.[22,23] There are few scientific data, however, with controlled studies to support observations that use of pyrethroids will alter sperm quality in bulls.

Accidental pyrethroid exposure in bulls may result in inadequate semen quality (particularly for cryopreservation) but may not impair bull fertility when bulls are used in natural settings, such as pasture breeding where several males are available to breed female cows during a breeding season. The important considerations when using pyrethroids on pastured cattle are to exactly follow the application recommendations on the label, to use a product that the cattle producer has experience with for insect control, and to avoid using close to breeding if possible. Another recommendation is to use only one method of insect control with pyrethroids on breeding cattle at a time (e.g., only spraying, only ear tags).[23]

With dermal exposure, wash and scrub the exposed area using liquid dishwashing soap and rinse well. Avoid using power washers because they may cause dermal trauma.[15] If seizures occur, the use of diazepam, methocarbamol, and barbiturates may be effective.

Neonicotinoids

A relatively new class of insecticides are the neonicotinoids, which are heterocyclic nitromethylenes used primarily in crop protection against sucking and certain chewing pests. The neonicotinoids include imidacloprid, acetamiprid, dinotefuran, thiamethoxam, and clothianidin.

The neonicotinoids act on postsynaptic nicotinic receptors located in the CNS. They act as agonists against nicotinic acetylcholine receptors in insects and mammals.[24] The insecticides initially increase the frequency of spontaneous discharge, which is followed by a complete block of nerve propagation. Neonicotinoids have been considered relatively low risk for nontarget organisms and the environment.[25] The activity in vertebrates is much lower due to different binding properties to the nicotinic receptors, and they primarily act on the α7

nicotinic receptor subtype. However, with the widespread use of neonicotinoids, an increase in acute neonicotinoid poisoning cases has been reported worldwide.[24] Increasing evidence of a variety of toxic effects in animals and humans has been identified, including altered thyroid and reproduction hormones in birds and mammals; upregulation of cytokines and suppressed cell-mediated immunity identified in rat experiments; and oxidative stress-related damage to lipids, DNA, and proteins in vertebrates and invertebrates.[24] Use of neonicotinoids can represent a health risk to wild bees and honey bees, with the European Union considering a complete ban on the outdoor use of three neonicotinoids: imidacloprid, clothianidin, and thiamethoxam.[26]

Imidacloprid has widespread use as an insecticide for dermal application on animals, as well as an insecticide for crop protection. Imidacloprid is primarily metabolized in the liver.[27] Metabolism of imidacloprid in mammals is by two routes: (1) oxidative cleavage and glutathione conjugation and (2) hydroxylation. Most of the imidacloprid is rapidly excreted in the urine. Imidacloprid is not considered carcinogenic and has a high margin of safety due to low mammalian toxicity. The neonicotinoids do not readily pass the blood-brain barrier.

Adverse effects noted in laboratory animals dosed with imidacloprid were decreased activity and tremors, impaired pupillary function (dilated or pinpoint), and uncoordinated gait; higher doses were associated with hypothermia. The no-observed-effect level (NOEL) for chronic imidacloprid exposure in dogs was 15 mg/kg PO.[27]

Treatment for overdoses of imidacloprid is symptomatic. With dermal exposure, wash the animal with soap and water; with oral exposure, use activated charcoal for adsorption and a cathartic. Generally, imidacloprid absorption and elimination are rapid, and supportive care should provide recovery.

Organochlorines

Organochlorines are chlorinated hydrocarbons. These compounds include lindane, mirex, kepone, dichlorodiphenyltrichloroethane (DDT), aldrin, dieldrin, heptachlor, chlordane, toxaphene, and endosulfan. The persistence of some organochlorines in the environment and concern for neurotoxicity and endocrine disruption have terminated the use of most organochlorines. These compounds have limited to no distribution in the United States but may occasionally cause toxicoses when stored chemicals contaminate feed or premises. Organochlorines

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are available in other countries.

The organochlorines have several mechanisms of action. The DDT-type organochlorines affect the brain and peripheral nerves by slowing sodium influx and inhibiting potassium outflow, partially depolarizing the cell and increasing firing of the neuron.[28] Several organochlorines may act by inhibiting attachment of GABA to its receptor, which stimulates the neuron. The organochlorines are absorbed orally and dermally. These compounds are highly lipid soluble and distribute to adipose tissue, brain, liver, kidney, and milk. Metabolism of organochlorines can be through dechlorination and oxidation, glucuronidation, and sulfation. More toxic epoxides can be formed by the mixed-function oxidases. The organochlorines are excreted into bile and the GI tract. They can undergo enterohepatic recycling, prolonging exposure for weeks. These compounds bioaccumulate in fatty tissue and persist in the environment. Organochlorines can act as endocrine disruptors.

Acute clinical signs include salivation, vomiting, and nervous system signs of agitation, hyperexcitability, incoordination, apprehension, nervousness, and tremors. As clinical signs progress, animals may display clonic-tonic seizures, opisthotonus, paddling, and clamping of the jaw. Cattle may walk backward, lick excessively, or have abnormal postures.[29] Seizures can persist for several days. Between seizures the animals may be depressed or normal in appearance. Clinical pathologic changes and histopathology are nonspecific.

Diagnosis is based on history, clinical signs, and analytic determination of organochlorines in blood, fat, liver, brain, or milk. Contact the veterinary diagnostic laboratory for sample submission instructions. Generally, samples for organochlorine analysis should not be submitted in plastic but wrapped in aluminum foil and/or placed in clean glass containers. Note that tissue levels of organochlorines do not correlate well with severity of clinical signs or prognosis.

Detoxification is a crucial step in treatment. Animals with topical exposure need to be washed with soap and water, and animals with long hair should be clipped to reduce organochlorine exposure. Treating personnel should wear gloves and aprons to reduce human exposure. With oral exposure, activated charcoal (1 to 2 g/kg body weight in a slurry) should be administered orally. Feeding activated charcoal, at 500 to 1000 g/day for a limited time, to large animals will reduce enterohepatic cycling.[28] General supportive care, such as the use of diazepam or barbiturates to control seizures and placing the animals in an environment to prevent trauma and keep comfortable, are important. Organochlorines typically have a prolonged residue time in body tissue. Animals

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that are lactating or losing weight generally eliminate more organochlorines due to loss of milk fat or body fat, respectively.

The state veterinarian should be contacted regarding exposure of animals to organochlorines and proper disposal of contaminated tissue or materials. The long persistence of organochlorines in tissue prevents immediate placement of food animals or milk into the food chain; proper state or federal agencies will need to be contacted for withdrawal intervals.

Paraquat

Paraquat is a bipyridyl herbicide used as a desiccant on crops. Most questions about paraquat exposure in large animals relate to aerial spray drift onto animals and/or their pasture and application to forages that will be used for livestock. Paraquat absorbed onto soil particles is biologically inactive. Animals that have access to concentrated paraquat formulations or to wet forages following paraquat application are at risk for developing clinical signs.

Paraquat is poorly absorbed (5% to 10%) from the intestinal tract but has prolonged residual time in the digestive tract. Emulsifiers or other chemicals in paraquat formulations may enhance absorption and toxicity. Paraquat is concentrated in renal tissue and is eliminated in the urine.

Paraquat forms free radicals in the body and has special affinity for the lung. The production of superoxide radicals and hydrogen peroxide results in damaged cellular membranes and tissue necrosis.

Following ingestion, the initial signs reflect the irritating action of paraquat, resulting in abdominal pain, vomiting, anorexia, and depression. By the second to third day post exposure, the onset of renal failure appears along with liver damage (hepatocellular necrosis), which is followed by delayed development of pulmonary fibrosis, respiratory dyspnea, cyanosis, and pneumomediastinum.[30] Death may occur several weeks after exposure. With topical exposure to paraquat, erythema, blistering of skin, and corneal irritation can occur and may resolve without additional complications.

Histopathologic changes from paraquat toxicosis include apoptosis or necrosis of alveolar epithelial cells, denuded alveolar basement membranes, and with a chronic response, hyperplasia of type II alveolar epithelial cells and pulmonary fibrosis.[30] Hepatic and renal lesions may be present. The diagnosis is based on history of exposure to paraquat and chemical analysis of paraquat in urine, plasma (up to 30 hours post exposure), and lung tissue (after 30 hours post

exposure).

Treatment should be initiated as soon as possible (within 24 hours) using activated charcoal, bentonite, or fuller's earth. Supportive care includes monitoring vital signs frequently, using fluids to maintain renal perfusion, treating secondary infections, and pain management. If treatment is delayed, the prognosis is extremely poor.

Rodenticides

Zinc and Aluminum Phosphide

Zinc phosphide is a rodenticide used since the 1930s. Zinc phosphide is a gray, crystalline powder that is relatively stable under dry conditions. Rodent formulations contain 2% to 5% zinc phosphide mixed with grains; therefore the baits are attractive to most species. Under wet or acidic conditions, zinc phosphide degrades to phosphine gas. Phosphine gas has the odor of acetylene or rotten fish, and poisoning can occur in people at detectable concentrations of 2 ppm. Acute, oral lethal doses of zinc phosphide were reviewed in various species.[31] The lethal dose of zinc phosphide in ruminants was approximately 60 mg/kg body weight.

Aluminum phosphide is a fumigant used in stored agricultural products to control rodents and insects. It has a high potential of acute toxicity with inhalation exposure. After application of aluminum phosphide tablets to grain, phosphine gas is released for up to 5 days. A general recommendation is that grain treated with aluminum phosphide should not be handled or fed for at least 10 days after treatment.

Phosphine gas is readily released in acidic environments and can block cytochrome c oxidase, resulting in disruption of oxidative phosphorylation within mitochondria of cells.[32] Blocking energy-producing pathways leads to cell death and eventual multiple-organ failure. Brain, heart, liver, and kidney are most affected by phosphine gas due to high metabolic rates and high demands for oxygen. Because of the higher pH of the rumen, as compared with an acidic monogastric stomach, ruminants should be more resistant to phosphide toxicants.

The onset of clinical signs occurs within 15 minutes up to 12 to 18 hours, depending on the dose and stomach contents (the more acidic, the quicker the release of phosphine gas). Death can occur within several hours after appearance

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of clinical signs. Ruminants show tympany and bloat, whereas horses can display signs of colic and abdominal pain. Horses fed a pelleted ration recently treated (within 14 hours) with aluminum phosphide showed rapidly developing clinical signs of profuse sweating, tachycardia, tachypnea, pyrexia, ataxia, seizures, and widespread tremors.[33] Clinicopathologic changes include hypoglycemia, high serum lactate and ammonia concentrations, and elevated activity of gamma-glutamyl transpeptidase, aspartate aminotransferase, and alkaline phosphatase. Several horses in this case developed clinical signs consistent with hepatic encephalopathy, and eventually 27 of 28 clinically affected horses died within 2 days after exposure. Postmortem changes were petechial and ecchymotic hemorrhages in numerous organs, widespread vascular congestion, hepatic lipidosis, pulmonary edema, and neuronal necrosis in the cerebral cortex.

Phosphine gas can be detected in gastric contents, vomitus, and possibly liver and kidney. The samples need to be packed in airtight containers and frozen immediately to prevent phosphine gas dissipation. Check with the veterinary diagnostic laboratory for analytic capability to detect phosphine gas.

The progression of clinical signs often limits treatment options. Early decontamination of the animal by emesis (if the animal vomits), gastric lavage (especially with 5% sodium bicarbonate), and products to increase gastric pH for zinc phosphide exposure is critical. Activated charcoal may be beneficial when mixed with an antacid and a cathartic (e.g., aluminum or magnesium hydroxide). No specific antidote is available for phosphine gas. Supportive therapy should be aimed at correcting acidosis, treating shock and liver failure, and controlling seizures. Horses that developed clinical signs after phosphine gas exposure were treated by gastric lavage followed by di-tri-octahedral smectite, atropine, fluids, 10% dextrose, flunixin meglumine, and sedatives.[33]

Metaldehyde

Metaldehyde is a molluscicide, usually sold in less than 5% concentrations as pelleted baits, granules, liquids, and wettable powders. Feed ingredients such as apples, molasses, rice, oats, and soybeans have been added to the baits to increase palatability to nontarget species. Most toxicoses occur in the coastal areas of the United States, where snail and slug populations can be high.

The mechanism of action of metaldehyde is unclear but may be related to alterations of neurotransmitters in the brain. Metaldehyde is toxic to all known

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animals. Oral ingestion is the most likely route of exposure. Acute, oral lethal doses of metaldehyde were reviewed in various species.[34] The lethal dose ranges for metaldehyde were 200 to 300 mg/kg body weight in ruminants and 60 to 360 mg/kg body weight in horses. Young animals appear to be more susceptible than adults.

Clinical signs of toxicosis usually occur within several hours of exposure and include salivation, restlessness, anxiety, hyperpnea, tremors, colic, ataxia, nystagmus, and convulsions. Blindness and loss of a menace reflex have been reported in cattle with metaldehyde toxicosis.[35] No specific changes in clinical pathology or histologic lesions occurred in animals poisoned with metaldehyde. Gross lesions have included congestion in renal, hepatic, pulmonary, and GI tissues and petechial and ecchymotic hemorrhages throughout the body. Demonstration of metaldehyde in GI contents (possibly serum/plasma and urine) confirms exposure. Samples should be submitted frozen to the diagnostic laboratory.

Initial therapy may involve control of seizures and tremors with diazepam and barbiturates; xylazine and acepromazine have been used in horses.[34] Decontamination by gastric lavage and activated charcoal, orally at 1 to 2 g/kg body weight, followed by mineral oil has also been recommended. Supportive care with intravenous fluids and a quiet environment may be beneficial.

Anticoagulant Rodenticides

Cases of hemorrhagic disorders reported in cattle generally involve repeated exposure to moldy sweet clover hay or sweet vernal hay (dicoumarol) over a prolonged period. Accidental ingestion of anticoagulant baits over a brief period may result in potential toxicosis in large animals. The anticoagulant rodenticides are divided into first-generation coumarin derivatives (e.g., coumachlor, coumatetralyl, warfarin), second-generation coumarin derivatives (e.g., brodifacoum, bromadiolone, difenacoum, flocoumafen), and the indanedione derivatives (e.g., chlorophacinone, diphacinone, pindone). Generally, the second-generation coumarin compounds are more toxic than the first-generation products and can poison with one feeding.

All anticoagulant rodenticides interfere with vitamin K epoxide reductase, which converts inactive vitamin K to the active vitamin. A depletion of active vitamin K may affect vitamin K–dependent clotting factors in the intrinsic, extrinsic, and common coagulation pathways. Anticoagulant rodenticides are

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well absorbed on oral exposure and are highly bound to plasma proteins. Oral availability of warfarin, chlorophacinone, and bromadiolone in sheep was estimated to be more than 79%.[36] Anticoagulants are metabolized in the liver, and some compounds may undergo enterohepatic recirculation. The half-life of anticoagulant rodenticides varies greatly with the compound and the species. The half-life of brodifacoum in horses was given as 1.22 ± 0.22 days, as compared with that of warfarin in horses at 16 hours.[36,37] The half-life of bromadiolone in cattle was reported to be approximately 20 hours.[36] As a general observation, the duration of action of anticoagulant rodenticides in large animals is about 14 days for warfarin, 21 days for bromadialone, and 30 days for brodifacoum and other second-generation coumarin derivatives. Ruminants are thought to have lower susceptibility to anticoagulants; however, a study in anticoagulant-dosed sheep revealed that the compounds were not degraded in the rumen and their bioavailabilities remained high after oral dosing.[37] The authors speculated that several factors may lower ruminant susceptibility, including the presence of a large forestomach (diluting the compound) and ruminal production of vitamin K_1, which may partially counteract the toxic effects.

Clinical signs may become apparent 2 to 10 days post exposure. Affected animals may display melena, epistaxis, hematuria, or excessive bleeding from a wound. If bleeding occurs within a body cavity, the animal may exhibit pallor, weakness, dyspnea, fever, and depression. Animals may die suddenly from excessive hemorrhage and shock. Generally, gross and histologic lesions are consistent with hemorrhage. Diagnosis is based on history, clinical signs, prolonged clotting times and anemia, and response to the antidote, which is vitamin K_1. Analytic detection of the anticoagulant rodenticide in whole blood, liver, and perhaps GI contents can confirm exposure.

Vitamin K_1 is the antidote for anticoagulant rodenticides; the duration of therapy varies with the specific compound causing the toxicosis and may last several days to several weeks. The recommended dose of vitamin K_1 in the adult horse is 2.5 mg/kg IM/SC once to twice daily.[38] The prothrombin time should return to normal within 24 hours. Vitamin K_3, although less expensive to use, is not as effective as vitamin K_1, will cause renal disease in horses,[29] and is not recommended.

Packed cell volumes should be closely monitored during clinical signs, and whole blood transfusions may be required if the animal is anemic. Decontamination of the GI tract with activated charcoal may lower absorption of

the anticoagulant. After the animal has stabilized and the appropriate time has passed, vitamin K_1 should be discontinued for 48 hours and prothrombin time retested.

1080

Sodium monofluoroacetate, fluoroacetate, or 1080 is a nonselective rodenticide that is toxic to animals and humans. The compound 1080 has been available in the United States since the 1940s but now is restricted for use as a predacide in the United States. It is used in Australia and New Zealand to kill invasive, unwanted species. Fluoroacetate naturally occurs in several plants in Africa, Australia, South America, and perhaps southern Florida. Sodium monofluoroacetate also appears to be available over the counter in the United States as foreign rodenticides or "herbal" pesticides. This compound is colorless, odorless, and water soluble.

The mechanism of action of 1080 involves a critical cycle, the Krebs or tricarboxylic acid cycle, in cellular metabolism. Many of the effects of 1080 toxicosis result from impaired oxidative metabolism and reduced energy production.[39] The oral LD_{50} for monofluoroacetate in ruminants and equines ranges from 0.22 to 0.55 mg/kg body weight.[40] Sodium monofluoroacetate is quickly absorbed from the GI and respiratory tracts and through mucous membranes but slowly absorbed through intact skin.

In general, herbivores experience cardiotoxic effects, omnivores experience cardiac and CNS effects, and carnivores experience CNS effects. Clinical signs occur within 30 minutes to several hours post ingestion. Cattle may stagger, tremble, sweat, and display signs of GI irritation; they can die of heart failure.[41] Horses can display hyperesthesia to external stimuli and have marked cardiac arrhythmias and ventricular fibrillation from 1080 poisoning. Sheep and pigs may show a combination of cardiac and CNS signs. Animals may have decreased GI movements, salivation, restlessness, apparent blindness, ataxia, frequent urination, muscular tremors, polypnea, and tachycardia. Pigs may have intermittent vomiting. Clinical pathology changes may include hyperglycemia, increased serum citrate, hypocalcemia (ionized), and acidosis. Electrocardiograms on 1080-poisoned sheep revealed S-T segment elevation and a marked increase in T-wave amplitude, suggesting cardiac ischemia.[42] Severely affected animals generally die within hours to a few days post exposure. Postmortem lesions in ruminants may involve endocardial and epicardial

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petechiae, edema of the brain, and lymphocytic infiltration of perivascular tissue. A diagnosis of 1080 toxicosis is based on clinical signs, history of exposure, and detection of 1080 in the bait, vomitus/gastric contents, kidney, and liver. Few veterinary diagnostic laboratories in the United States analyze for 1080 in tissues. Generally, the assay is by gas chromatography/mass spectrometry with a detection limit of 10 µg/kg (or parts per billion).

In a recent case of multiple episodes of 1080 intoxication in a calf-raising operation, calves were found dead or displayed a stiff gait, dribbled urine, and became recumbent and died with ecchymotic and suffusive hemorrhages on the epicardial surface with moderate to large amounts of fluid in the pericardial sac.[43] Another case of 1080 toxicosis involved high, acute death loss in ewes and lambs following transfer of the flock to a new pasture over a municipal landfill site.[44] Clinical signs observed in affected animals were disoriented running and breaking through fences, apparent blindness, weakness, and ataxia. Gross lesions included pulmonary congestion and edema and epicardial petechiae and ecchymotic hemorrhages on the ventricles. Histologic changes were acute to subacute myocardial degeneration and necrosis with neutrophilic and lymphohistiocytic myocarditis. Compound 1080 was detected in several kidney samples, but the source of 1080 was not determined. No long-term effects on health or reproductive performance were observed in ewes that survived experimental dosing with a single, near-lethal amount of 1080.[42]

Compound 1080 has no known antidote, and the rapid onset of clinical signs may prevent effective, quick decontamination of the GI tract with activated charcoal. A treatment protocol for 1080 toxicosis in dogs involves gastric lavage followed by activated charcoal, control of seizure and convulsions with barbiturates or gas anesthesia, fluid therapy including sodium bicarbonate, monitoring serum calcium and potassium, and use of acetamide if available.[45] The prognosis for most cases of 1080 toxicosis is poor.

Strychnine

Strychnine is a rodenticide often sold at 0.5% to 1% concentrations in a powder, pellets, or with grain bait for below-ground application. Strychnine-treated seeds are often dyed red or green. In several states, the use of strychnine is restricted. Storage of old containers of strychnine-laced grains can be sources of accidental toxicoses. Accidental and malicious toxicoses continue to occur regularly.

Strychnine is an alkaloid from the seeds of *Strychnos nux-vomica* and

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Strychnos ignatii. Strychnine blocks inhibitory action of glycine at the inhibitory neurons, Renshaw cells, spinal cord, and medulla. The lack of inhibition leads to rigidity and tetanic convulsions. Strychnine is quickly absorbed from the GI tract and widely distributed in the body. A small portion of the dose is excreted into urine. Hepatic enzymes can readily metabolize strychnine.

Clinical signs can appear within a few minutes to a few hours and include sweating, nervousness, incoordination, recumbency, and tonic-clonic seizures. The seizures can be induced by stimuli such as bright light, loud noises, and touch. No specific clinical pathology or histologic changes occur in strychnine toxicoses. Analytic determination of strychnine in gastric contents (and to a lesser extent in urine, serum/plasma, liver, and kidney) confirms a strychnine toxicosis.

Decontamination by gastric lavage followed by oral administration of activated charcoal, which binds strychnine, is important; however, the degree of sensory stimulation may require initial treatment to control seizures and support respiration. The use of barbiturates along with diazepam and methocarbamol may control seizures. Severe respiratory dyspnea may require mechanical ventilation. In addition, intravenous fluid therapy and a quiet environment may be beneficial. Prognosis for treatment of large animals with strychnine toxicosis is poor because of the difficulty of treating animals in the field. In one case report, several horses had access to an old bag of strychnine-contaminated barley. Clinical signs of CNS stimulation were observed in five of six horses, with two horses dying. Treatment in the field consisted of activated charcoal and mineral oil to assist decontamination of the gut and xylazine, diazepam, and pentobarbital for CNS signs.[46]

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Color Plates



COLOR PLATE 54.1 Tall larkspur *(Delphinium barbeyi).* (From Plumlee KH: *Clinical veterinary toxicology*, St Louis, 2004, Mosby, pp 337-338.)



COLOR PLATE 54.2 Bracken fern *(Pteridium aquilinum).* (From https://gobotany.newenglandwild.org/genus/pteridium/.)



COLOR PLATE 54.3 Lambert's locoweed *(Oxytropis lambertii).* (From www.opsu.edu.)



COLOR PLATE 54.4 Coffee weed *(Cassia).* (From Schilcher H: *Leitfaden phytotherapie*, Urban & Fischer, München, 2010, Elsevier.)



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PCV/HCT (%)	22-33	27-45	22-38	32-53	24-44
Erythrocytes ($\times 10^6$/µL)	5.1-7.6	9-15	8-18	6.8-12.9	5.5-9.5
Hemoglobin (g/dL)	8.5-12.2	9-15	8-12	11-19	8-14
MCV (fL)	38-50	28-40	16-25	37-58.5	—
MCHC (g/dL)	36-39	31-34	30-36	31-38.6	—
Reticulocytes	—	0	0	—	—

[a]From George JW, Snipes J, Lane M: Comparison of bovine hematology reference intervals from 1957-2006. *Vet Clin Pathol* 39:138, 2010.

[b]From Jain NC: *Schalm's veterinary hematology,* ed 4, Philadelphia, 1986, Lea & Febiger.

PCV, Packed cell volume; *HCT,* hematocrit; *MCV,* mean cell volume; *MCHC,* mean cell hemoglobin concentration.

Normal Values for Leukogram Data (Adult Animals)

	Cattle	Sheep	Goats	Horses
White blood cells (1×10^3/µL)	4.9-12	4-12	4-13	5.4-14.3
Neutrophils (1×10^3/µL)	1.8-6.3	0.7-6	1.2-7.2	2.3-8.6
Bands (1×10^3/µL)	Rare	Rare	Rare	0-1
Lymphocytes (1×10^3/µL)	1.6-5.6	2-9	2-9	1.5-7.7
Monocytes (1×10^3/µL)	0-0.8	0-0.75	0-0.55	0-1
Eosinophils (1×10^3/µL)	0-0.9	0-1	0.05-0.65	0-1
Basophils (1×10^3/µL)	0-0.3	0-0.3	0-0.12	0-0.29
Neutrophil/lymphocyte (N/L) ratio	0.4-2.34	0.3-0.7	0.6-3.6	0.8-2.8

Normal Serum Protein Values for Horses, Cows, Sheep, and Goats

	Value	Horse	Cow	Sheep	Goat

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Total	g/dL	5.2-7.9	6.74-7.46	6-7.9	6.4-7
Albumin	g/dL	2.6-3.7	3.03-3.55	2.4-3	2.7-3.9
Globulin	g/dL	2.62-4.04	3-3.48	3.5-5.7	2.7-4.1
Fibrinogen	mg/dL	200-400	200-700	200-500	200-300

From Kaneko JJ, Harvey JW, Bruss ML, eds: *Clinical biochemistry of domestic animals,* ed 5, San Diego, 1997, Academic Press (Appendix VIII, Blood analyte reference values in large animals).

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Endsheet 7

Clinical Chemistry: Normal Range for Large Animals

Component	Unit	Equine	Bovine	Ovine	Caprine
Chemistry					
Total bilirubin	mg/dL	1.0-2.0	0.01-0.5	0.1-0.5	0-0.1
Direct	mg/dL	0-0.4	0.04-0.44	0-0.27	0-0.1
Indirect	mg/dL	0.2-2.0	0-0.3	0-0.12	0-0.1
Cholesterol	mg/dL	75-150	80-120	52-76	80-130
Creatinine	mg/dL	1.2-1.9	1.0-2.0	1.2-1.9	1.0-1.8
Glucose	mg/dL	75-115	45-75	50-80	50-75
Fibrinogen	mg/dL	100-400	300-700	100-500	100-400
Haptoglobin	mg/dL	0.01-0.17	0.0-0.05	NA	NA
Serum amyloid A	mg/dL	0-2.0	NA	NA	NA
Protein (total serum)	g/dL	5.2-7.9	6.7-7.46	6.0-7.9	6.4-7.0
Albumin	g/dL	2.6-3.7	3-3.55	2.4-3.0	2.7-3.9
Globulin	g/dL	2.62-4.04	3.0-3.48	3.5-5.7	2.7-4.1
Urea nitrogen	mg/dL	10-24	20-30	8-20	10-20
Enzyme					
ALP	IU/L	143-395	0-488	68-387	93-387
AST	IU/L	226-366	78-132	60-280	167-513
CK	IU/L	108-430	44-211	64-158	104-219
GGT	IU/L	7-54	15-39	40-79	20-56
LDH	IU/L	162-412	697-1445	238-440	123-392
LDH-1	%	6.3-18.5	39.8-63.5	45.7-63.6	29.3-51.8
LDH-2	%	8.4-20.5	19.7-34.8	0-3.0	0-5.4
LDH-3	%	41-65.9	11.7-18.1	16.4-29.9	24.2-39.9
LDH-4	%	9.5-20.9	0-8.8	4.3-7.3	0-5.5
LDH-5	%	1.7-16.5	0-12.4	10.5-29.1	14.1-36.8
SDH	IU/L	1.9-5.8	4.3-15.3	5.8-27.9	14-23.6
Electrolyte					
Sodium	mEq/L	132-146	132-152	139-152	142-155
Potassium	mEq/L	2.4-4.7	3.9-5.8	3.9-5.4	3.5-6.7
Chloride	mEq/L	99-109	97-111	95-103	99-110
Calcium	mg/dL	11.2-13.6	9.7-12.4	11.5-12.8	8.9-11.7
Phosphorus	mg/dL	3.1-5.6	5.6-6.5	5.0-7.3	6.5
Magnesium	mg/dL	2.2-2.8	1.8-2.3	2.2-2.8	2.8-3.6
Osmolality	mOsm/kg	270-300	270-300	NA	NA
Anion gap	mEq/L	6-15	14-20	NA	NA
Acid-Base (Venous Blood)					
pH		7.32-7.44	7.31-7.53	7.32-7.54	NA

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Pco_2	mm Hg	38-46	35-44	37-46	NA
Bicarbonate	mEq/L	20-28	17-29	20-25	NA
Tco_2	mEq/L	24-32	21-32	21-28	26-30
Special					
Red blood cell acetylcholinesterase	IU/L	450-790	1270-2430	640	270
Ammonia	µg/dL	13-108	NA	NA	NA
BSP ($t_{1/2}$)	Min	2.0-3.7	2.5-4.0	1.6-2.7	2.1
Serum iron	µg/dL	73-140	57-162	166-222	NA
TIBC	µg/dL	200-262	63-186	NA	NA
Lactic acid	mmol/L	1.11-1.78	0.56-2.22	1.00-1.33	NA
Ketones					
Acetone	mg/dL	NA	0-10	0-10	NA
Acetoacetate	mg/dL	NA	0-1.1	NA	NA
BHB	mg/dL	NA	0-10	NA	NA

ALP, Alkaline phosphatase; *AST,* aspartate aminotransferase; *BHB,* β-hydroxybutyrate; *BSP ($t_{1/2}$),* bromsulphalein clearance halftime; *GGT,* γ-glutamyltransferase; *CK,* creatine kinase; *LDH,* lactate dehydrogenase; *NA,* not applicable; *Pco_2,* partial pressure of carbon dioxide; *SDH,* sorbitol dehydrogenase; *Tco_2,* total carbon dioxide; *TIBC,* total iron-binding capacity.

Data from Kaneko JJ, Harvey JW, Bruss ML, editors. *Clinical biochemistry of domestic animals,* ed 6, Burlington, MA, 2008, Academic Press, and the Normal Values Clinical Pathology Ontario Veterinary College and Animal Health Lab-Guelph, 2012.

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